



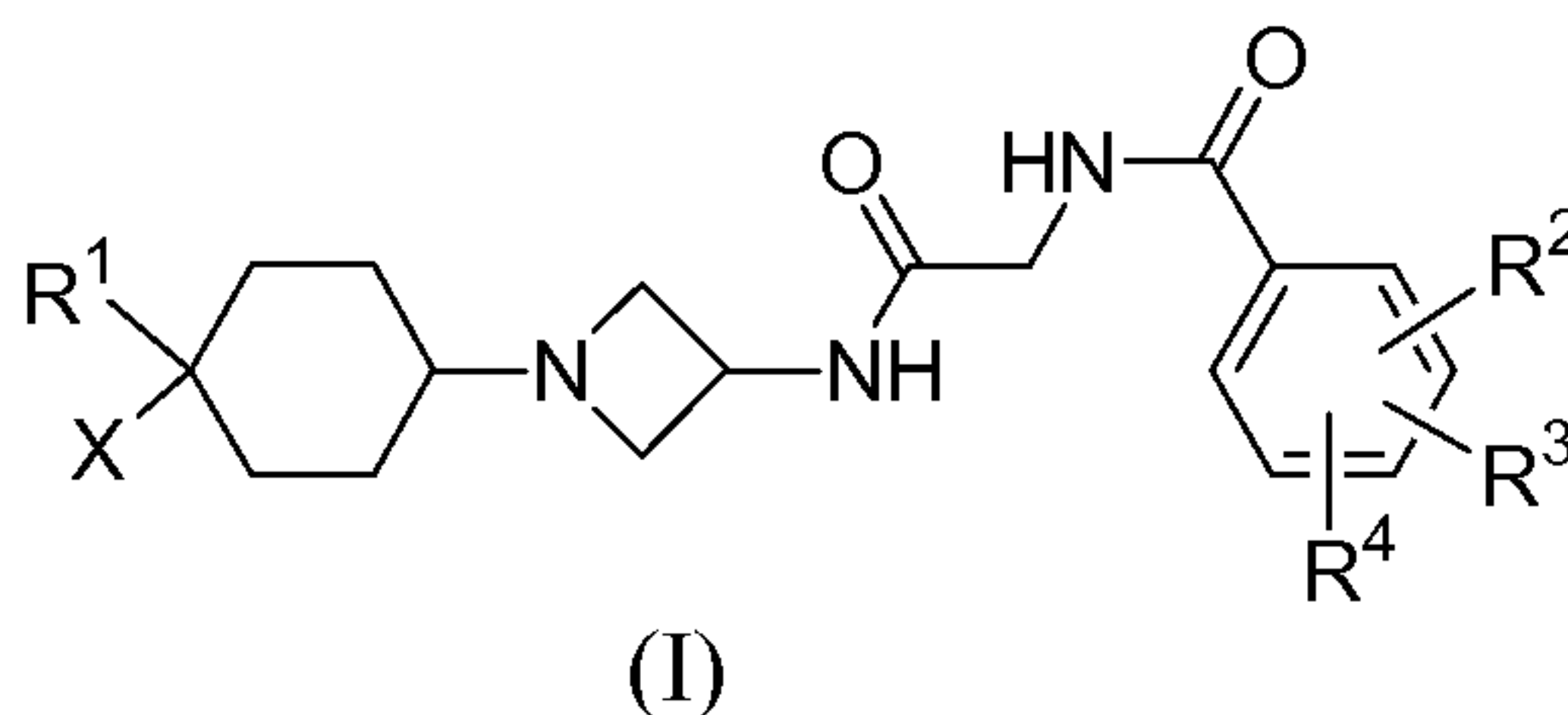
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(54) Titre : DERIVES DE 4-AZETIDINYL-1-HETEROARYL-CYCLOHEXANE EN TANT QU'ANTAGONISTES DE CCR2
(54) Title: 4-AZETIDINYL-1-HETEROARYL-CYCLOHEXANE ANTAGONISTS OF CCR2



(57) **Abrégé/Abstract:**

The present invention comprises compounds of Formula (I). Formula (I). wherein: X, R¹, R², R³, and R⁴ are as defined in the specification. The invention also comprises a method of preventing, treating or ameliorating a syndrome, disorder or disease, wherein said syndrome, disorder or disease is type II diabetes, obesity and asthma. The invention also comprises a method of inhibiting CCR2 activity in a mammal by administration of a therapeutically effective amount of at least one compound of Formula (I).

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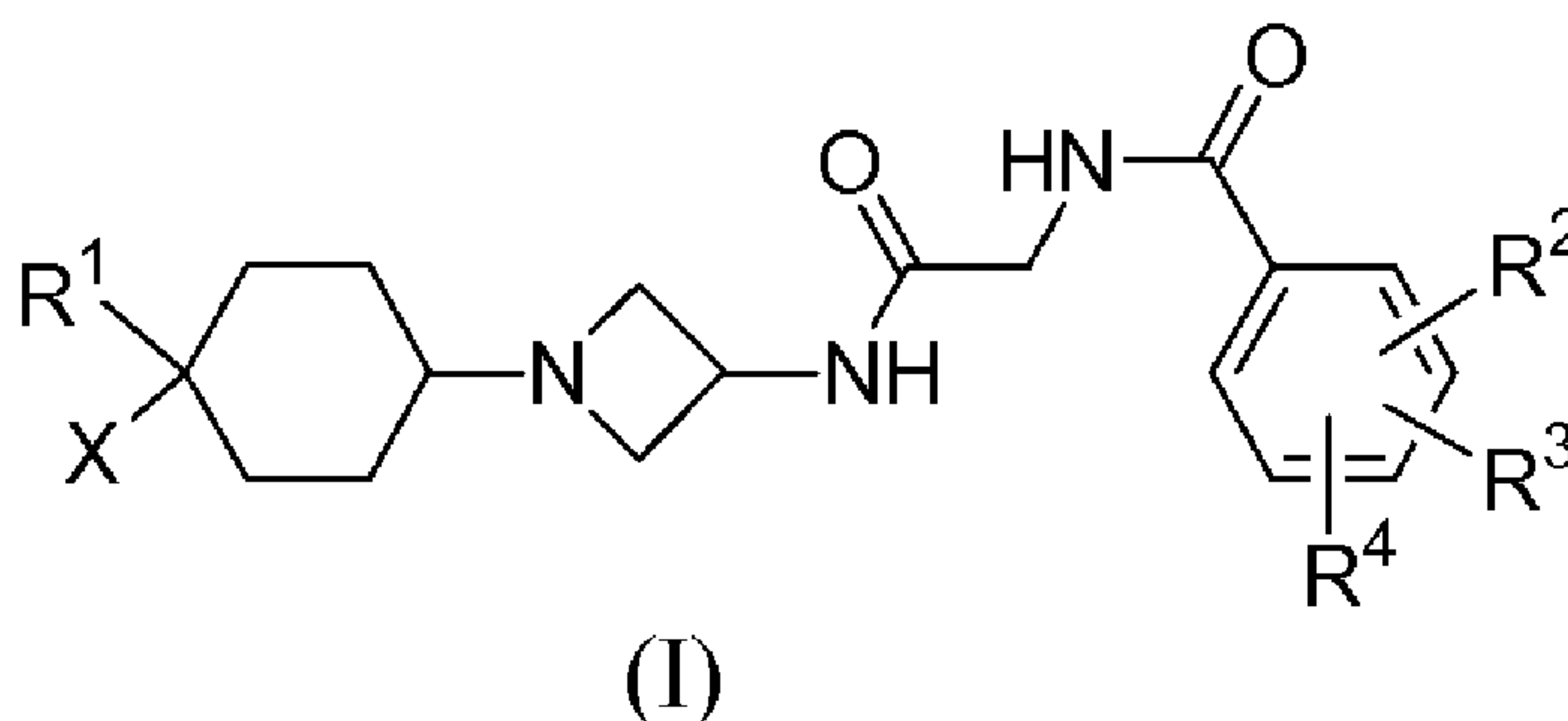
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(54) Title: 4-AZETIDINYL-1-HETEROARYL-CYCLOHEXANE ANTAGONISTS OF CCR2



(57) Abstract: The present invention comprises compounds of Formula (I). Formula (I), wherein: X, R¹, R², R³, and R⁴ are as defined in the specification. The invention also comprises a method of preventing, treating or ameliorating a syndrome, disorder or disease, wherein said syndrome, disorder or disease is type II diabetes, obesity and asthma. The invention also comprises a method of inhibiting CCR2 activity in a mammal by administration of a therapeutically effective amount of at least one compound of Formula (I).

4-AZETIDINYL-1-HETEROARYL-CYCLOHEXANE ANTAGONISTS OF CCR2**FIELD OF THE INVENTION**

The invention is directed to substituted dipiperidine compounds, which are antagonists to the chemoattractant cytokine receptor 2 (CCR2), pharmaceutical compositions, and methods for use thereof. More particularly, the CCR2 antagonists are substituted piperidyl acrylamide compounds useful for preventing, treating or ameliorating a CCR2 mediated syndrome, disorder or disease.

BACKGROUND OF THE INVENTION

CCR2 is a member of the GPCR family of receptors, as are all known chemokine receptors, and are expressed by monocytes and memory T-lymphocytes. The CCR2 signaling cascade involves activation of phospholipases (PLC β 2), protein kinases (PKC), and lipid kinases (PI-3 kinase).

Chemoattractant cytokines (i.e., chemokines) are relatively small proteins (8-10 kD), which stimulate the migration of cells. The chemokine family is divided into four subfamilies based on the number of amino acid residues between the first and second highly conserved cysteines.

Monocyte chemotactic protein-1 (MCP-1) is a member of the CC chemokine subfamily (wherein CC represents the subfamily having adjacent first and second cysteines) and binds to the cell-surface chemokine receptor 2 (CCR2). MCP-1 is a potent chemotactic factor, which, after binding to CCR2, mediates monocyte and lymphocyte migration (i.e., chemotaxis) toward a site of inflammation. MCP-1 is also expressed by cardiac muscle cells, blood vessel endothelial cells, fibroblasts, chondrocytes, smooth muscle cells, mesangial cells, alveolar cells, T-lymphocytes, macrophages, and the like.

After monocytes enter the inflammatory tissue and differentiate into macrophages, monocyte differentiation provides a secondary source of several proinflammatory modulators, including tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), IL-8 (a member of the CXC chemokine subfamily, wherein CXC represents one amino acid residue between the first and second cysteines), IL-12, arachidonic acid metabolites (e.g.,

PGE₂ and LTB₄), oxygen-derived free radicals, matrix metalloproteinases, and complement components.

Animal model studies of chronic inflammatory diseases have demonstrated that inhibition of binding between MCP-1 and CCR2 by an antagonist suppresses the inflammatory

5 response. The interaction between MCP-1 and CCR2 has been implicated (see Rollins B J, Monocyte chemoattractant protein 1: a potential regulator of monocyte recruitment in inflammatory disease, *Mol. Med. Today*, 1996, 2:198; and Dawson J, et al., Targeting monocyte chemoattractant protein-1 signaling in disease, *Expert Opin. Ther. Targets*, 2003 Feb. 7 (1):35-48) in inflammatory disease pathologies such as psoriasis, uveitis,

10 atherosclerosis, rheumatoid arthritis (RA), multiple sclerosis, Crohn's Disease, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, type II diabetes and diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, tuberculosis, sarcoidosis, invasive *staphylococci*, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, Chronic

15 Obstructive Pulmonary Disease (COPD), allergic asthma, periodontal diseases, periodontitis, gingivitis, gum disease, diastolic cardiomyopathies, cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, glomerulonephritis, solid tumors and cancers, chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, and
20 carcinomas of the bladder, breast, cervix, colon, lung, prostate, and stomach.

Monocyte migration is inhibited by MCP-1 antagonists (either antibodies or soluble, inactive fragments of MCP-1), which have been shown to inhibit the development of arthritis, asthma, and uveitis. Both MCP-1 and CCR2 knockout (KO) mice have demonstrated that monocyte infiltration into inflammatory lesions is significantly

25 decreased. In addition, such KO mice are resistant to the development of experimental allergic encephalomyelitis (EAE, a model of human MS), cockroach allergen-induced asthma, atherosclerosis, and uveitis. Rheumatoid arthritis and Crohn's Disease patients have improved during treatment with TNF- α antagonists (e.g., monoclonal antibodies and soluble receptors) at dose levels correlated with decreases in MCP-1 expression and the
30 number of infiltrating macrophages.

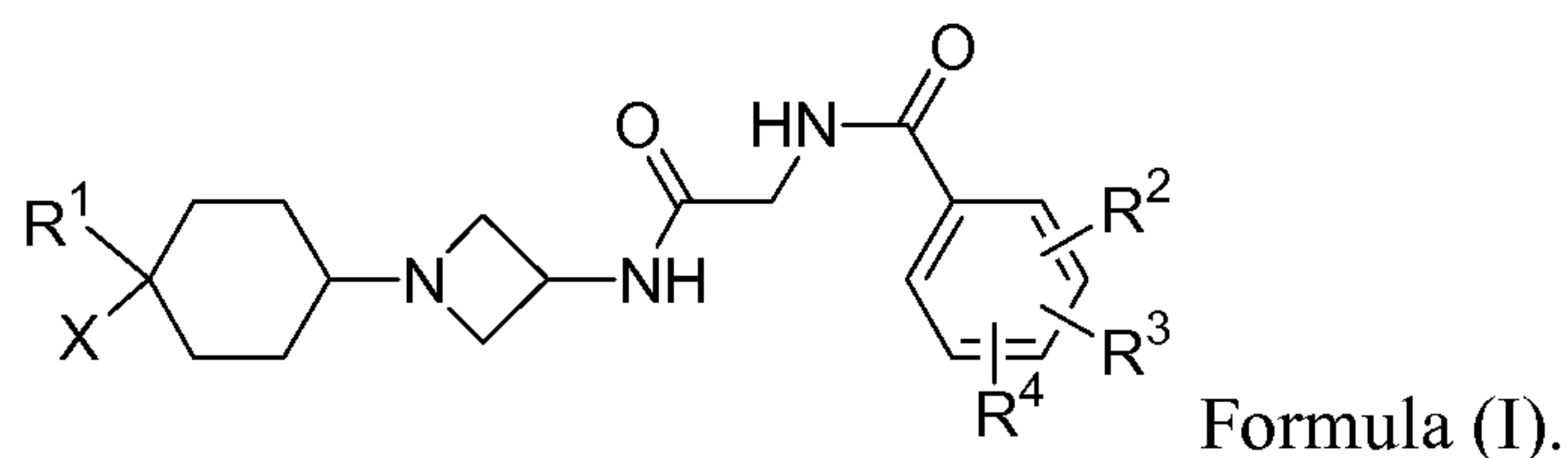
MCP-1 has been implicated in the pathogenesis of seasonal and chronic allergic rhinitis, having been found in the nasal mucosa of most patients with dust mite allergies. MCP-1 has also been found to induce histamine release from basophils in vitro. During allergic conditions, both allergens and histamines have been shown to trigger (i.e., to up-

5 regulate) the expression of MCP-1 and other chemokines in the nasal mucosa of people with allergic rhinitis, suggesting the presence of a positive feedback loop in such patients. There remains a need for small molecule CCR2 antagonists for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease resulting from MCP-1 induced monocyte and lymphocyte migration to a site of inflammation.

10 All documents cited herein are incorporated by reference.

SUMMARY OF THE INVENTION

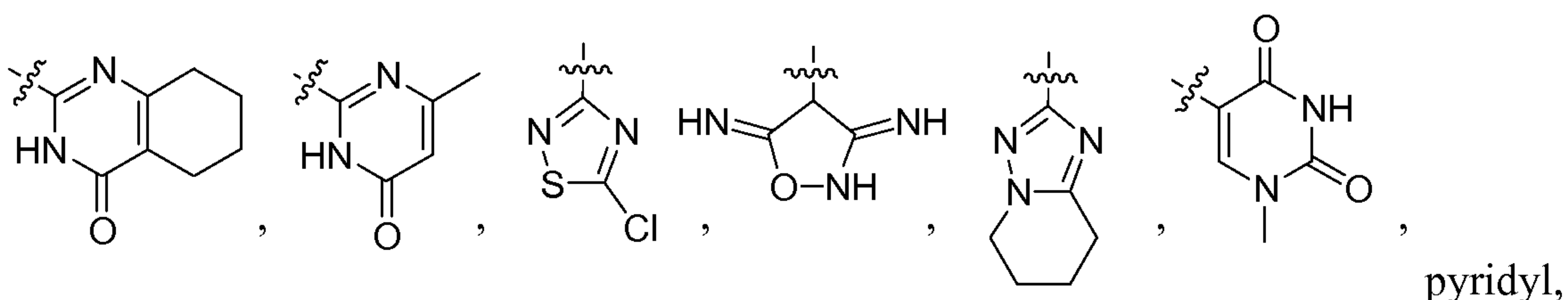
The present invention comprises compounds of Formula (I):



15 wherein:

X is F, NH₂, or H;

R¹ is



pyridyl-*N*-oxide, pyridin-2-onyl, indolyl, pyrazinyl, 3-*H*-thiazol-2-onyl, pyrimidyl,

20 benzooxazolyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, thiophenyl, furyl, [1,2,4]oxadiazolyl or [1,3,4]thiadiazolyl; wherein said pyridyl, pyridyl-*N*-oxide,

pyrimidyl, pyrazolyl, imidazolyl, thiophenyl, or thiazolyl is optionally substituted with one substituent selected from the group consisting of OC₍₁₋₄₎alkyl, OC₍₃₋₆₎cycloalkyl,

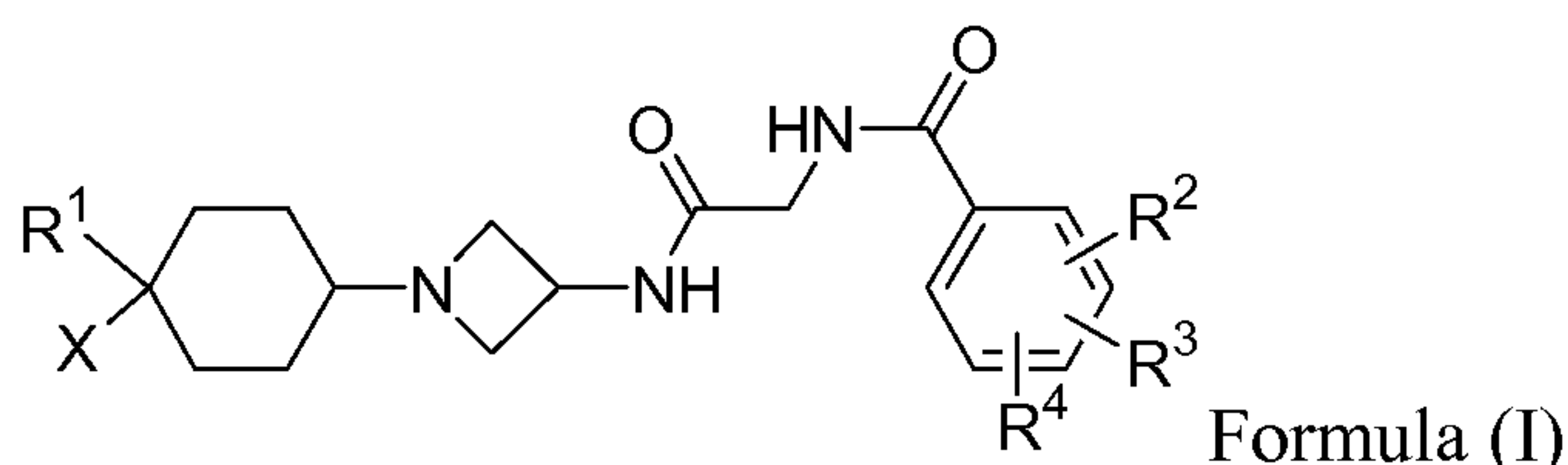
OCH₂CF₃, OCH₂Ph, F, CN, Cl, OCF₃, CF₃, CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, N(C₍₁₋₄₎alkyl)₂,

25 C₍₁₋₄₎alkylOH, Si(CH₃)₃, —C≡CH, SCH₃, S(O)CH₃, SO₂CH₃, pyrrolidinyl, OH, NH₂,

- NHCN, CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl, N(SO₂CH₃)₂, NHSO₂CH₃, NHC(O)CF₃, NHC₍₁₋₄₎alkyl, NHCO₂H, NHCO₂C₍₁₋₄₎alkyl, NHCOC₍₁₋₄₎alkyl, NHCONH₂, NHCONHC₍₁₋₄₎alkyl, and Br; or said pyridyl may be substituted with one OCH₃ group and one CH₃; wherein said pyrimidyl is optionally substituted on any carbon atom with one N(C₍₁₋₄₎alkyl)₂ group; or said pyrimidinyl is substituted on any two carbon atoms with two substituents independently selected from the group consisting of OH, OCH₃, and CH₃; wherein said thiazolyl is substituted with CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl, or OH; or said thiazolyl is optionally substituted on two adjacent carbon atoms to form a fused bicyclic system benzothiazol-2-yl, wherein said benzothiazol-2-yl is optionally substituted with Br or OCH₃; wherein said pyridin-2-onyl is optionally substituted with one substituent selected from the group consisting of CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, and CH₂CH₂OH, or said pyridin-2-onyl is substituted with 2 methyl groups; wherein said [1,2,4]oxadiazolyl is optionally substituted on any carbon atom with OH, CCl₃, or pyrrolidinyl;
- 15 R² is C₍₁₋₄₎alkyl, NH₂, NO₂, NHCH₂CH₂OH, N(C₍₁₋₄₎alkyl)₂, N(SO₂CH₃)₂, CN, F, Cl, Br, CF₃, C₍₃₋₆₎cycloalkyl, heterocyclyl, OCF₃, OCF₂H, CF₂H, or OC₍₁₋₄₎alkyl; R³ is H, F, Cl, CF₃, or OC₍₁₋₄₎alkyl; alternatively, R² and R³ may be taken together with their attached phenyl to form a benzo[1,3]dioxolyl, 2,3-dihydro-benzofuranyl, or 2,3-dihydro-benzo[1,4]dioxinyl group;
- 20 R⁴ is H, OC₍₁₋₄₎alkyl, or F;
- and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

- 25 The present invention comprises compounds of Formula (I):

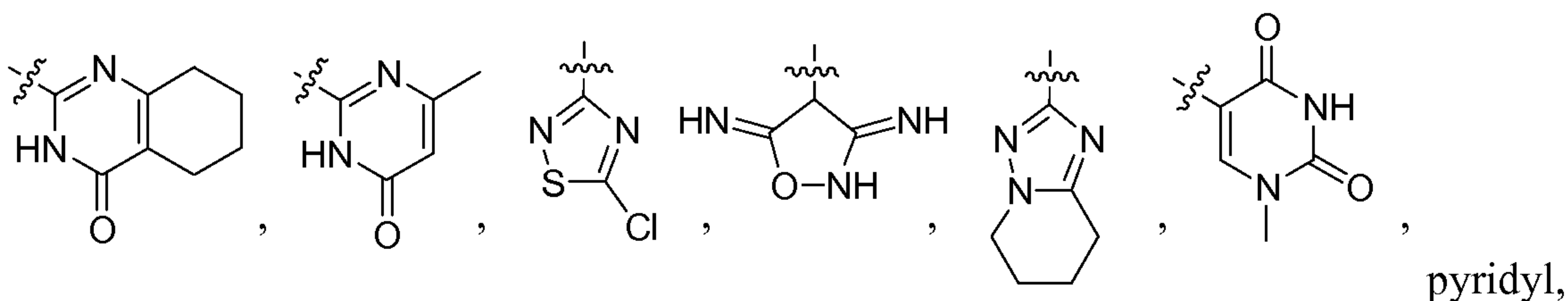


wherein X, R¹, R², R³ and R⁴ are as defined above;

Another embodiment of the invention comprises compounds of Formula (Ia):



and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

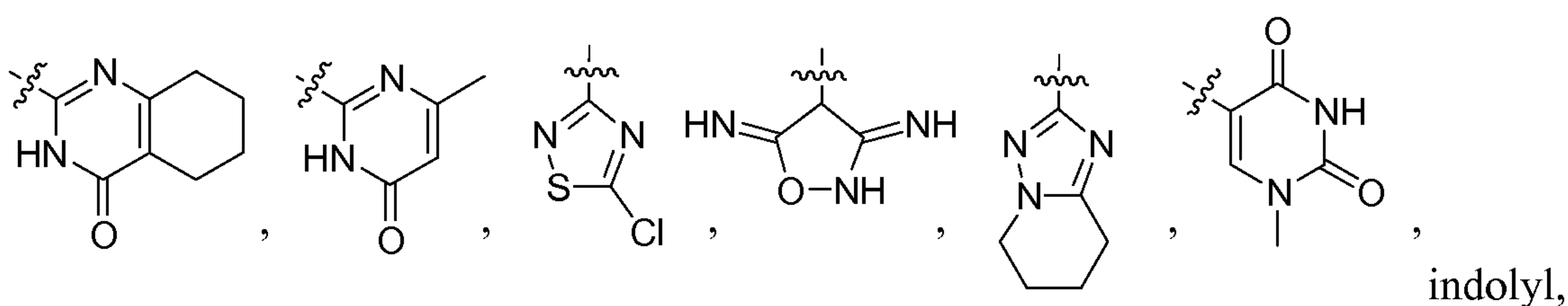
 $\mathbf{R}^1$ is

pyridyl-*N*-oxide, pyridin-2-onyl, indolyl, pyrazinyl, 3-*H*-thiazol-2-onyl, pyrimidyl, methyl substituted imidazolyl, methyl substituted pyrazolyl optionally substituted with Br, thiophenyl optionally substituted with Br, benzooxazolyl, oxazolyl, thiazolyl, isothiazolyl, [1,2,4]oxadiazolyl or [1,3,4]thiadiazolyl; wherein said pyridyl, pyridyl-*N*-oxide, or thiazolyl is optionally substituted with one substituent selected from the group consisting of OC₍₁₋₄₎alkyl, OC₍₃₋₆₎cycloalkyl, OCH₂CF₃, OCH₂Ph, F, CN, CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, N(C₍₁₋₄₎alkyl)₂, C₍₁₋₄₎alkylOH, Si(CH₃)₃, —C≡CH, SCH₃, S(O)CH₃, SO₂CH₃, pyrrolidinyl, OH, NH₂, NHCN, CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl, N(SO₂CH₃)₂, NHSO₂CH₃, NHC(O)CH₃, NHC(O)CF₃, NHC₍₁₋₄₎alkyl, and Br; or said pyridyl may be substituted with one OCH₃ group and one CH₃; wherein said pyrimidyl is optionally substituted on any carbon atom with one N(C₍₁₋₄₎alkyl)₂ group; or said

- pyrimidinyl is substituted on any two carbon atoms with one OH group and one CH₃;
 wherein said thiazolyl is substituted with CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl, or OH; or
 said thiazolyl is optionally substituted on two adjacent carbon atoms to form a fused
 bicyclic system benzothiazol-2-yl, wherein said benzothiazol-2-yl is optionally
 5 substituted with Br or OCH₃; wherein said pyridin-2-onyl is optionally substituted with
 one substituent selected from the group consisting of CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, and
 CH₂CH₂OH, or said pyridin-2-onyl is substituted with 2 methyl groups; wherein said
 [1,2,4]oxadiazolyl is optionally substituted on any carbon atom with OH, CCl₃, or
 pyrrolidinyl;
 10 R² is C₍₁₋₄₎alkyl, NH₂, NO₂, NHCH₂CH₂OH, N(C₍₁₋₄₎alkyl)₂, N(SO₂CH₃)₂, CN, F, Cl, Br,
 CF₃, pyrrolidinyl, OCF₃, OCF₂H, CF₂H, or OC₍₁₋₄₎alkyl;
 R³ is H, F, Cl, CF₃, or OC₍₁₋₄₎alkyl; alternatively, R² and R³ may be taken together with
 their attached phenyl to form a benzo[1,3]dioxolyl group;
 R⁴ is H, OCH₃, or F;
 15 and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts
 thereof.

Another embodiment of the invention comprises compounds of Formula (I) and/or
 Formula (Ia) wherein:

- 20 X is F, or H;
 R¹ is



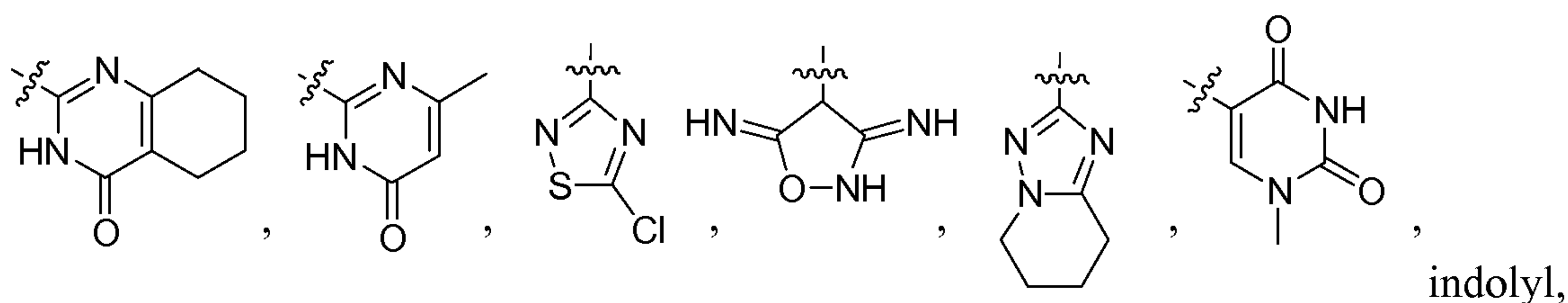
- pyridyl, pyridyl-*N*-oxide, pyridin-2-onyl, pyrimidyl, pyrazinyl, methyl substituted
 imidazolyl, methyl substituted pyrazolyl optionally substituted with Br, thiophenyl
 25 optionally substituted with Br, benzooxazolyl, oxazolyl, thiazolyl, [1,2,4]oxadiazolyl,
 isothiazolyl, or [1,3,4]thiadiazolyl; wherein said pyridyl, pyridyl-*N*-oxide, or thiazolyl is
 optionally substituted with one substituent selected from the group consisting of OH,
 OC₍₁₋₄₎alkyl, NHC(O)CH₃, N(SO₂CH₃)₂, NHSO₂CH₃, NHC(O)CF₃, NHC₍₁₋₄₎alkyl, OC₍₃₋

₆cycloalkyl, OCH₂CF₃, OCH₂Ph, F, CN, C₍₁₋₄₎alkyl, N(C₍₁₋₄₎alkyl)₂, C₍₁₋₄₎alkylOH, Si(CH₃)₃, —C≡CH, SCH₃, S(O)CH₃, SO₂CH₃, pyrrolidinyl, NH₂, NHCN, and Br; or said pyridyl may be substituted with one OCH₃ group and one CH₃; wherein said pyrimidyl is optionally substituted on any carbon atom with one N(C₍₁₋₄₎alkyl)₂ group; or
 5 said pyrimidinyl is substituted on any two carbon atoms with one OH group and one CH₃; wherein said pyridin-2-onyl is optionally substituted with one substituent selected from the group consisting of CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, and CH₂CH₂OH, or said pyridin-2-onyl is substituted with 2 methyl groups; wherein said thiazolyl is substituted with CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl, or OH; or said thiazolyl is optionally substituted
 10 on two adjacent carbon atoms to form a fused bicyclic system benzothiazol-2-yl, wherein said benzothiazol-2-yl is optionally substituted with Br or OCH₃; wherein said [1,2,4]oxadiazolyl is optionally substituted on any carbon atom with OH, CCl₃, or pyrrolidinyl;
 R² is NH₂, NO₂, NHCH₂CH₂OH, N(CH₃)₂, N(SO₂CH₃)₂, CN, F, Cl, Br, CF₃,
 15 pyrrolidinyl, or OCH₃;
 R³ is H, F, Cl, CF₃, or OCH₃; alternatively, R² and R³ may be taken together with their attached phenyl to form a benzo[1,3]dioxolyl group;
 R⁴ is H, or F;
 and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts
 20 thereof.

Another embodiment of the invention comprises compounds of Formula (I) and/or Formula (Ia) wherein:

X is F, or H;

25 R¹ is



pyrimidyl, pyridin-2-onyl, pyrazinyl, thiazolyl, [1,2,4] oxadiazolyl, or pyridyl, wherein said pyridyl is optionally substituted on any carbon atom with one substituent selected

from the group consisting of OH, OC₍₁₋₄₎alkyl, NHC(O)CH₃, N(SO₂CH₃)₂, NHSO₂CH₃, NHC(O)CF₃, NH₂, NHC₍₁₋₄₎alkyl, N(CH₃)₂, NHCN, SO₂CH₃; or said pyridyl is optionally substituted on any two carbon atoms with one OH group and one CH₃; wherein said pyrimidinyl is optionally substituted on any carbon atom with one N(CH₃)₂ group; or said

5 pyrimidinyl is substituted on any two carbon atoms with one OH group and one CH₃; wherein said pyridin-2-onyl is optionally substituted with one substituent selected from the group consisting of CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, and CH₂CH₂OH, or said pyridin-2-onyl is substituted with 2 methyl groups; wherein said thiazolyl is substituted with CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl, or OH; wherein said [1,2,4]oxadiazolyl is optionally

10 substituted on any carbon atom with OH, CCl₃, or pyrrolidinyl;

R² is CF₃, CN, F, or Cl;

R³ is H, Cl, CF₃, or F;

R⁴ is H, or F;

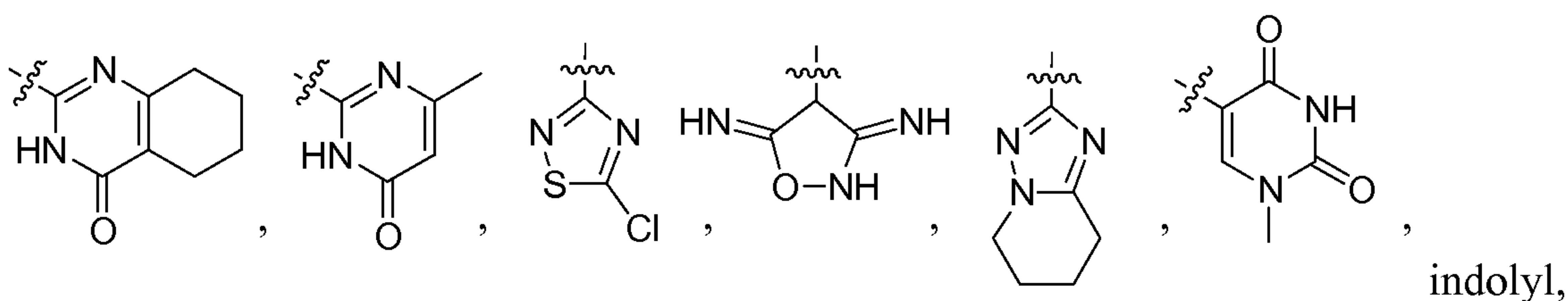
and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts

15 thereof.

Another embodiment of the invention comprises compounds of Formula (I) and/or Formula (Ia) wherein:

X is F, or H;

20 R¹ is



pyrimidyl, pyridin-2-onyl, methyl pyridin-2-onyl, pyrazinyl, thiazolyl, [1,2,4]oxadiazolyl, or pyridyl, wherein said pyridyl is optionally substituted on any carbon atom with one substituent selected from the group consisting of OH, OCH₃, NHC(O)CH₃, N(SO₂CH₃)₂, NHSO₂CH₃, NHC(O)CF₃, NH₂, NHCH₃, N(CH₃)₂, NHCN, SO₂CH₃; or

25 said pyridyl is optionally substituted on any two carbon atoms with one OH group and one CH₃; wherein said pyrimidinyl is substituted on any carbon atom with one N(CH₃)₂ group; wherein said pyridin-2-onyl is *N* substituted with one substituent selected from the

group consisting of CH_2CN , $\text{C}_{(1-4)}\text{alkyl}$, CH_2CF_3 , and $\text{CH}_2\text{CH}_2\text{OH}$, or said pyridin-2-onyl is substituted with 2 methyl groups; wherein said thiazolyl is substituted with CO_2H , CONH_2 , NHCO_2CH_3 , or OH ; wherein said [1,2,4]oxadiazolyl is optionally substituted on any carbon atom with OH , CCl_3 , or pyrrolidinyl;

5 R^2 is CF_3 ;

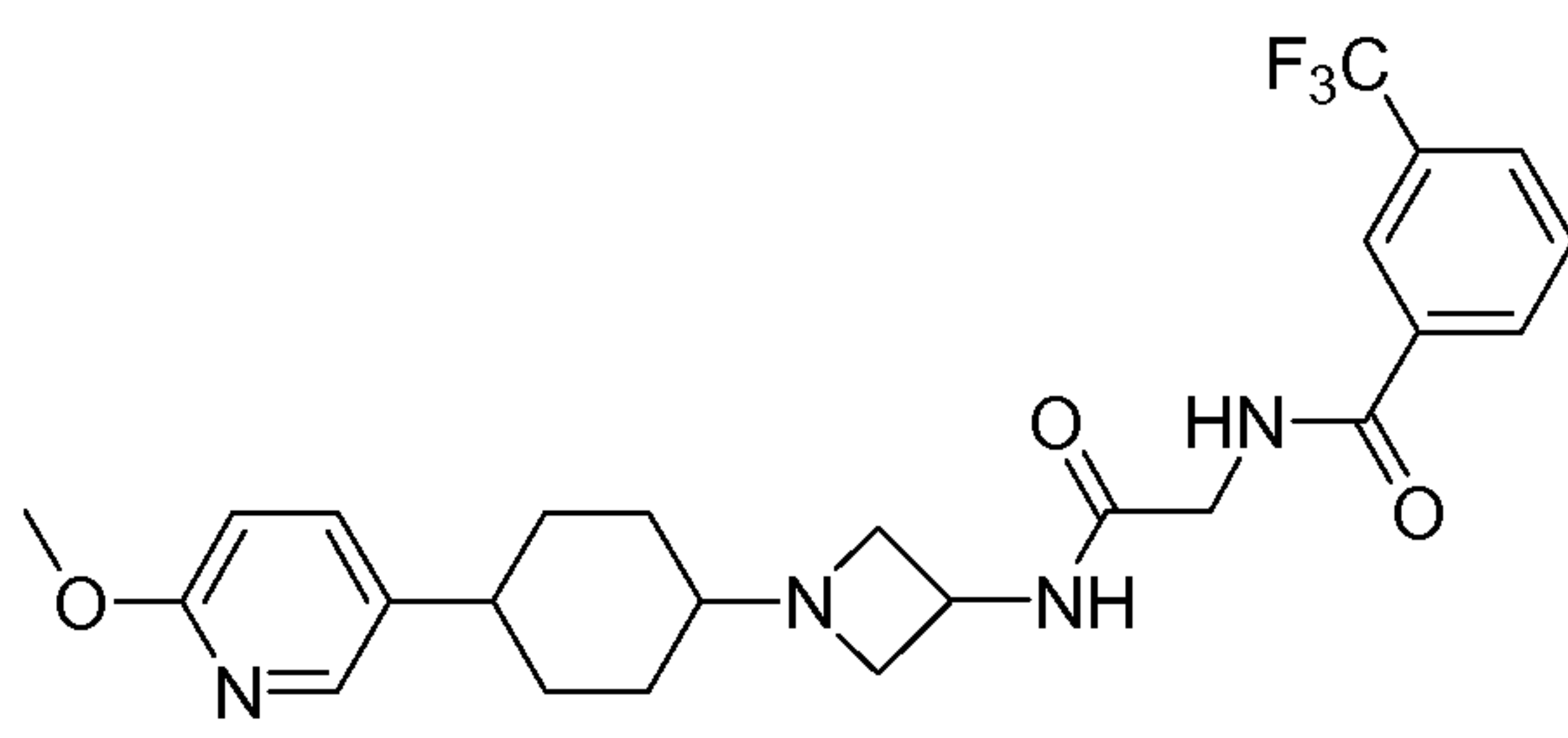
R^3 is H, or F;

R^4 is H;

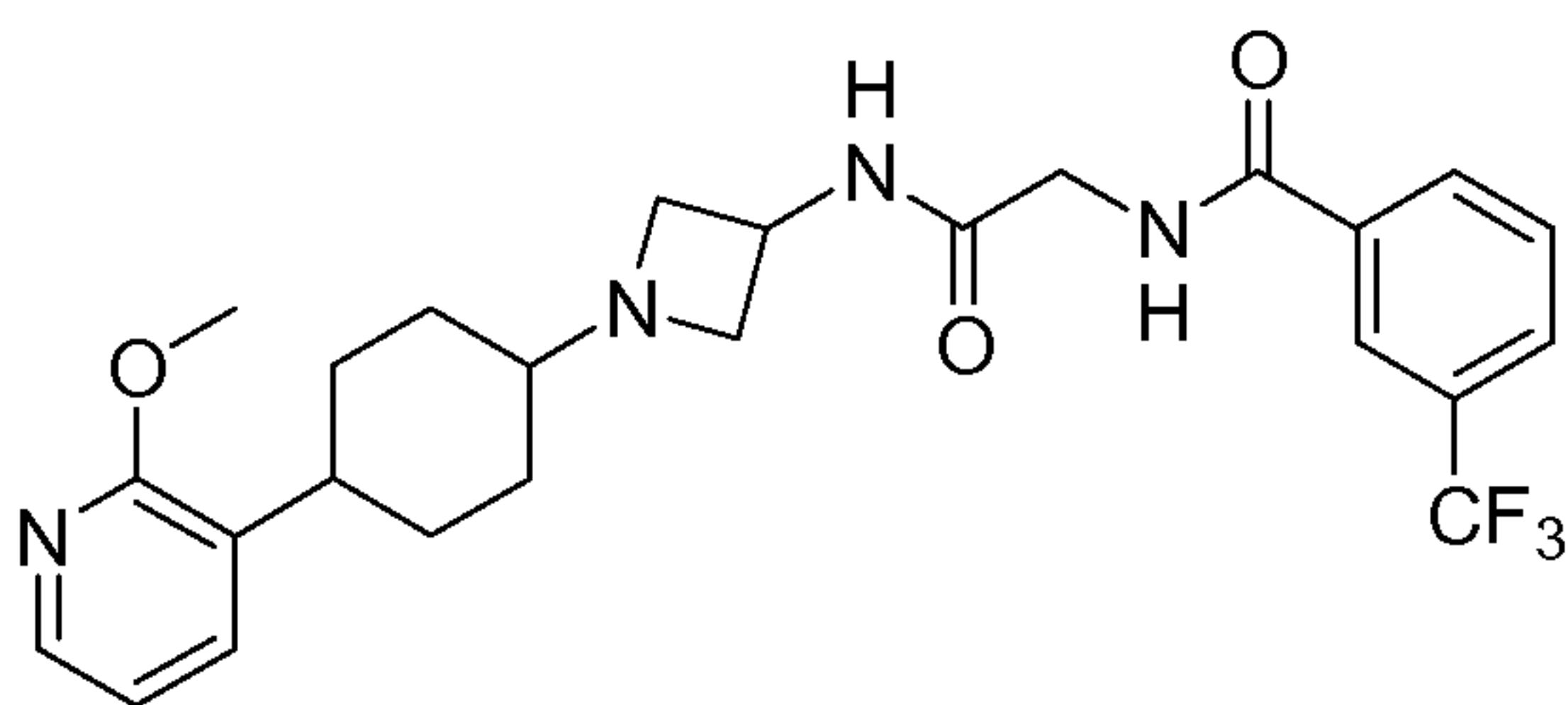
and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

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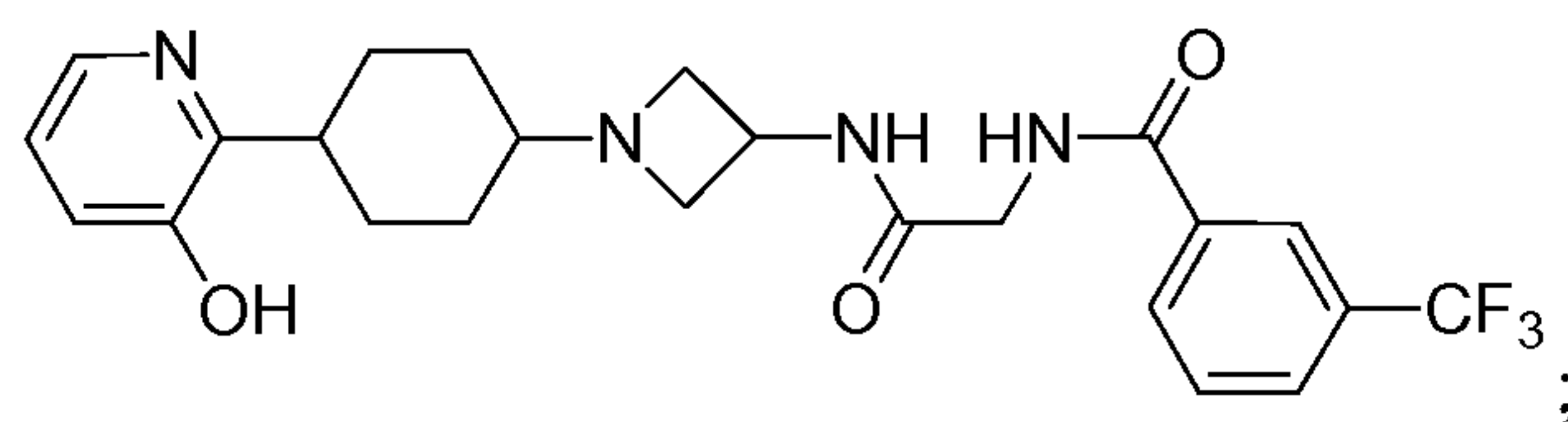
Another embodiment of the invention is a compound which is selected from the group consisting of:



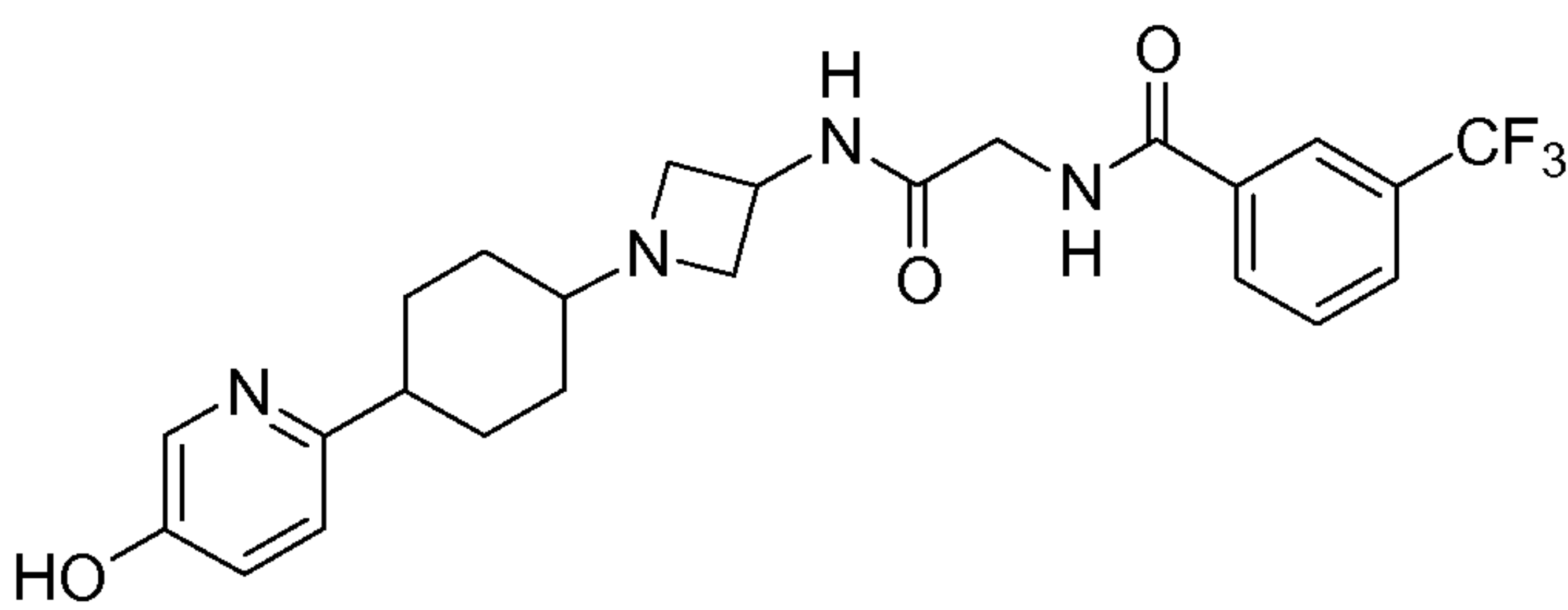
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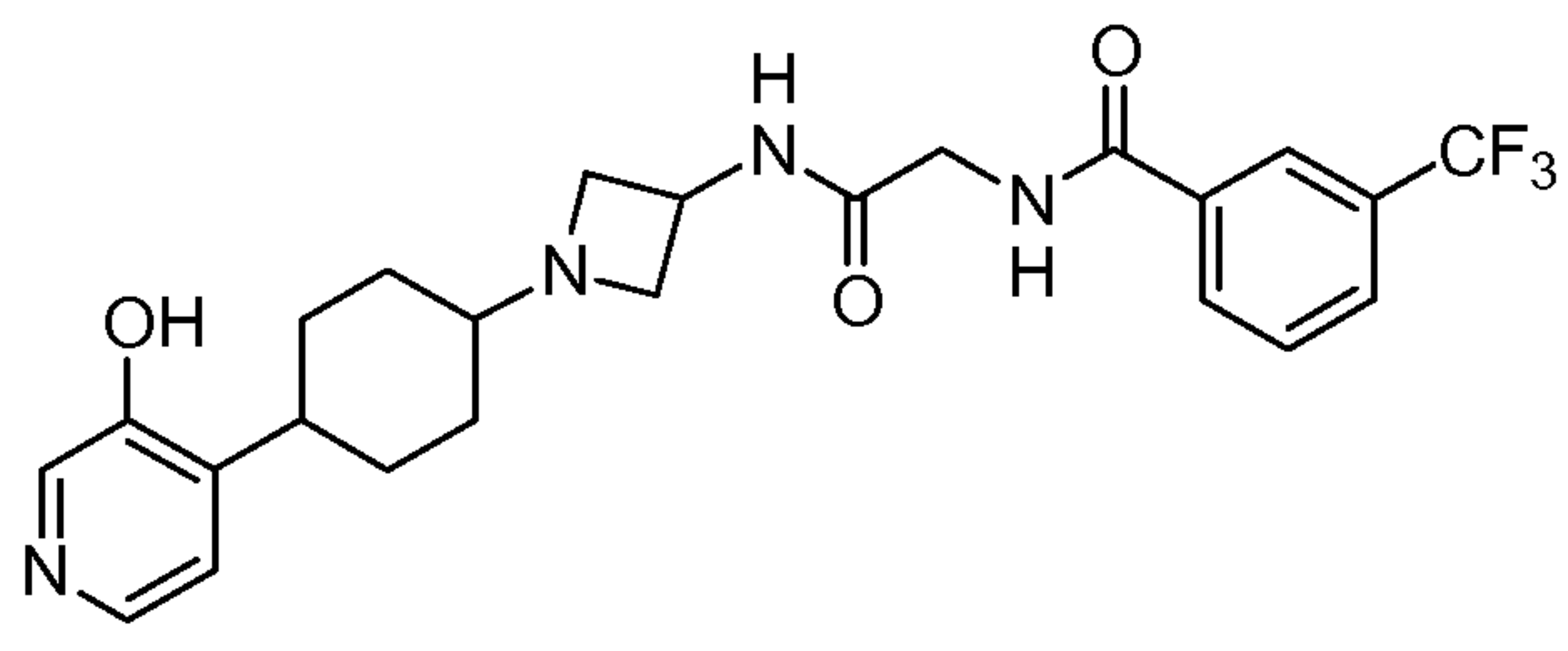
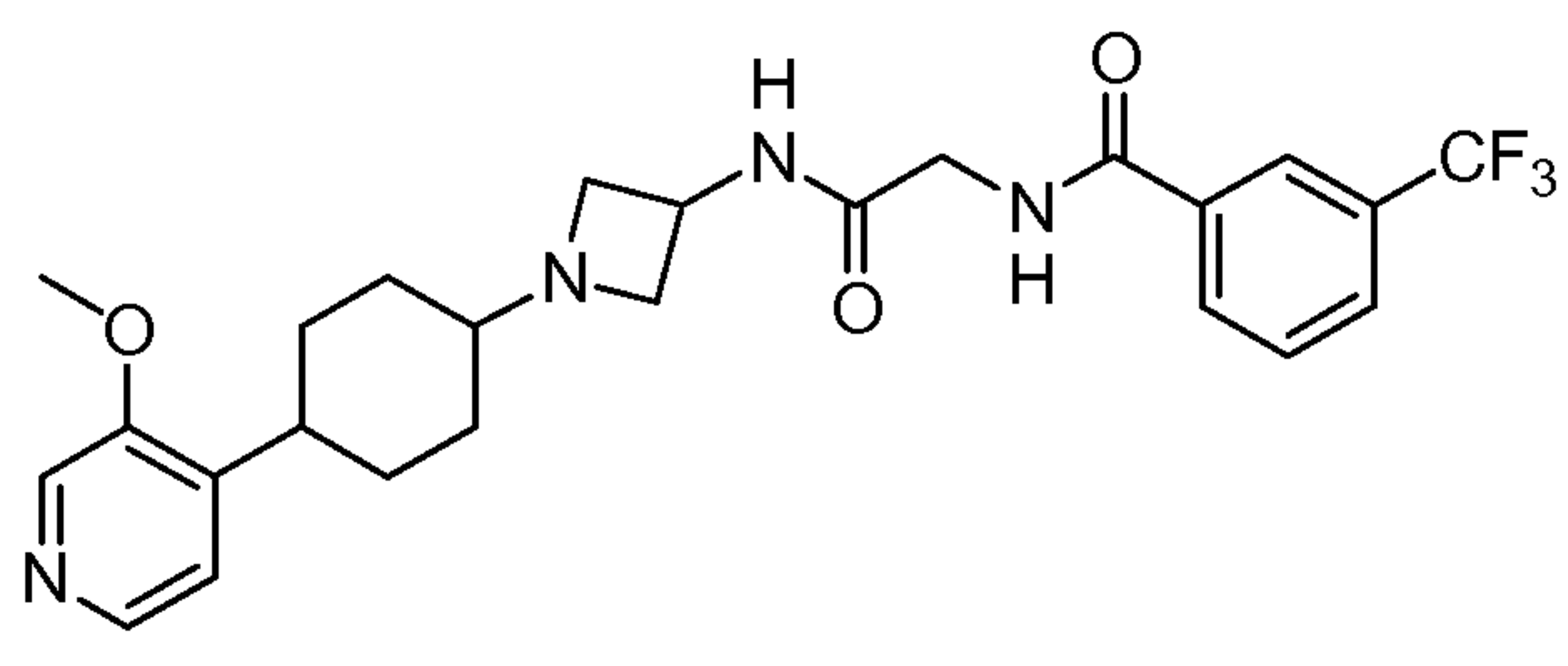
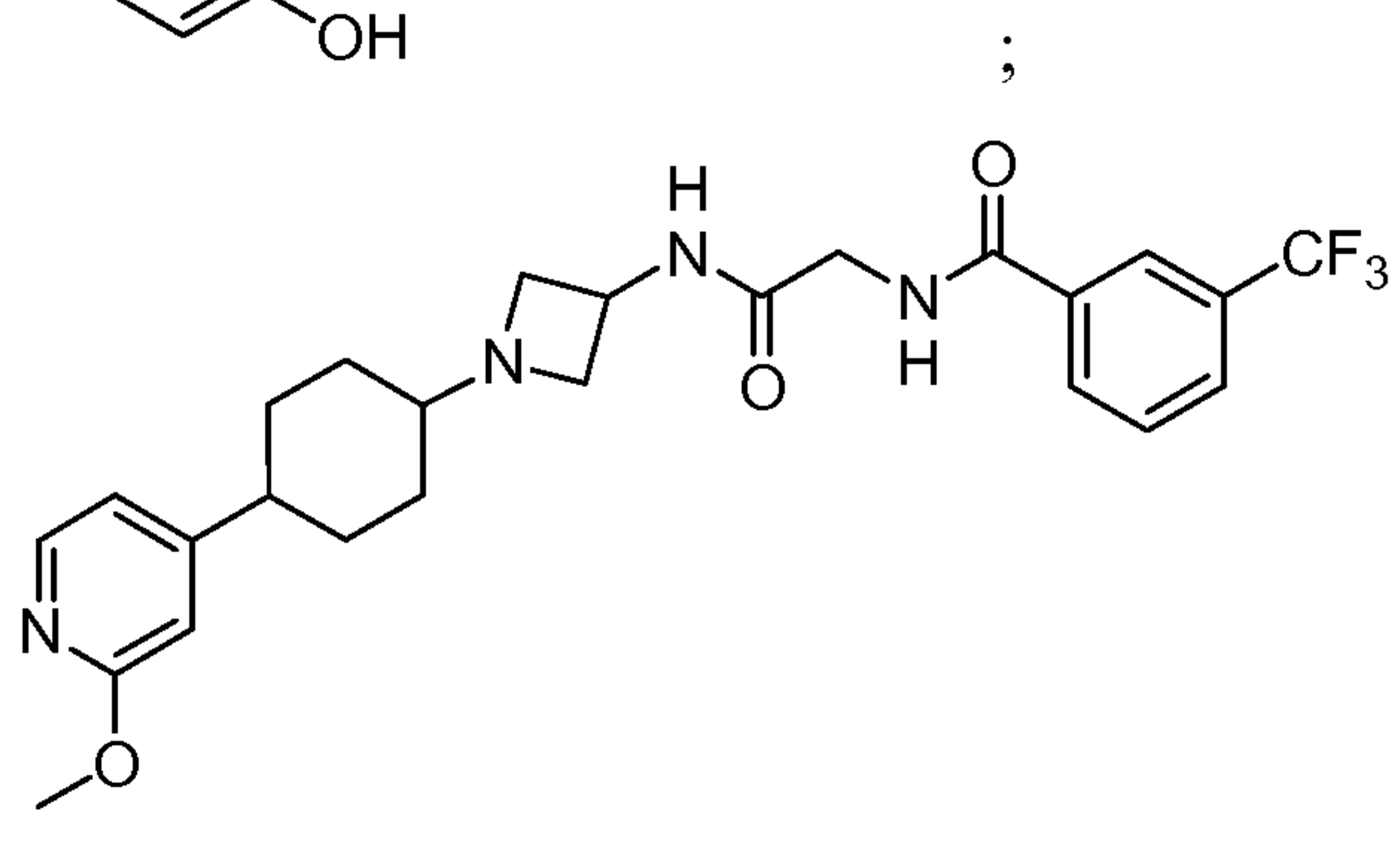
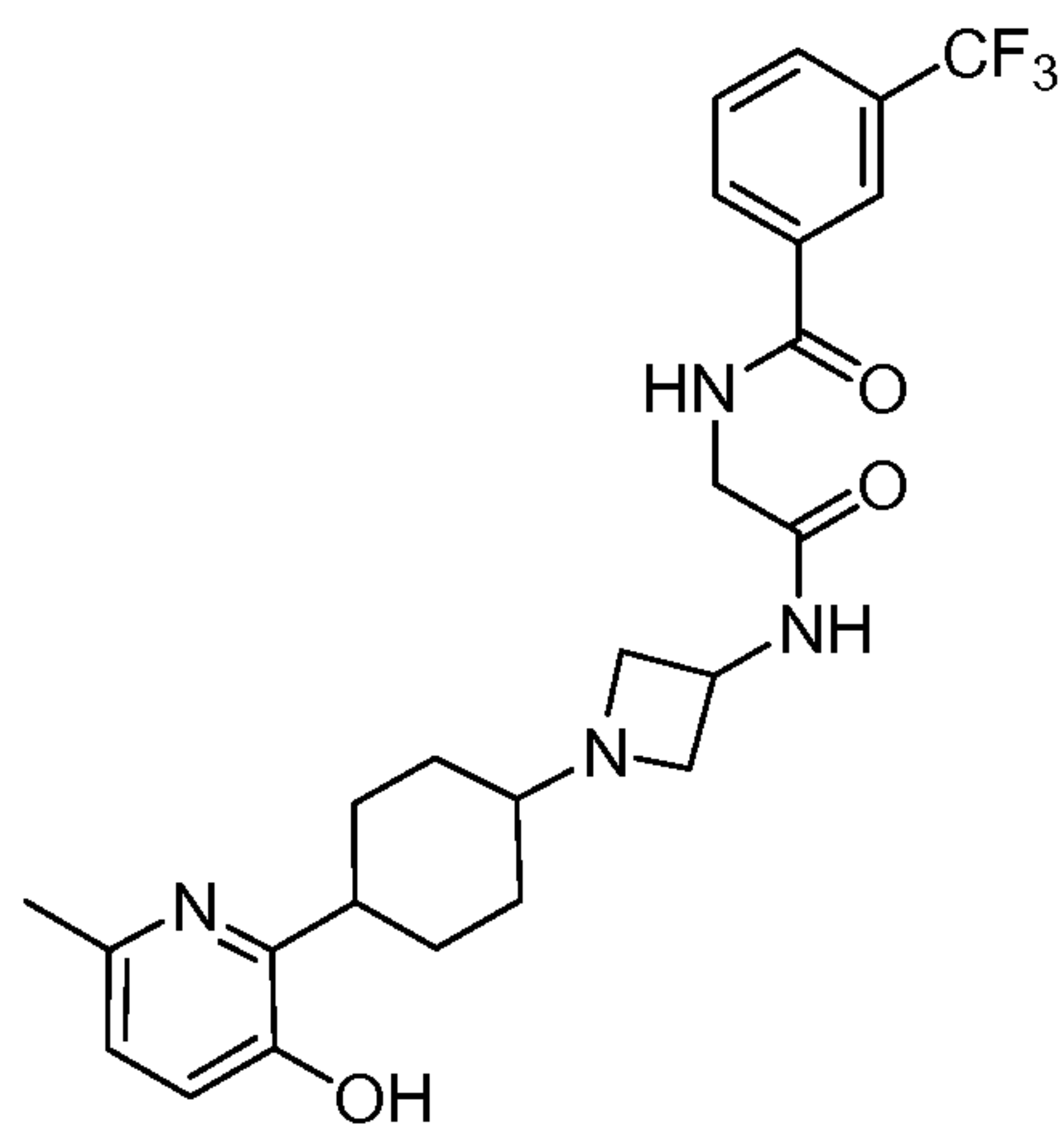
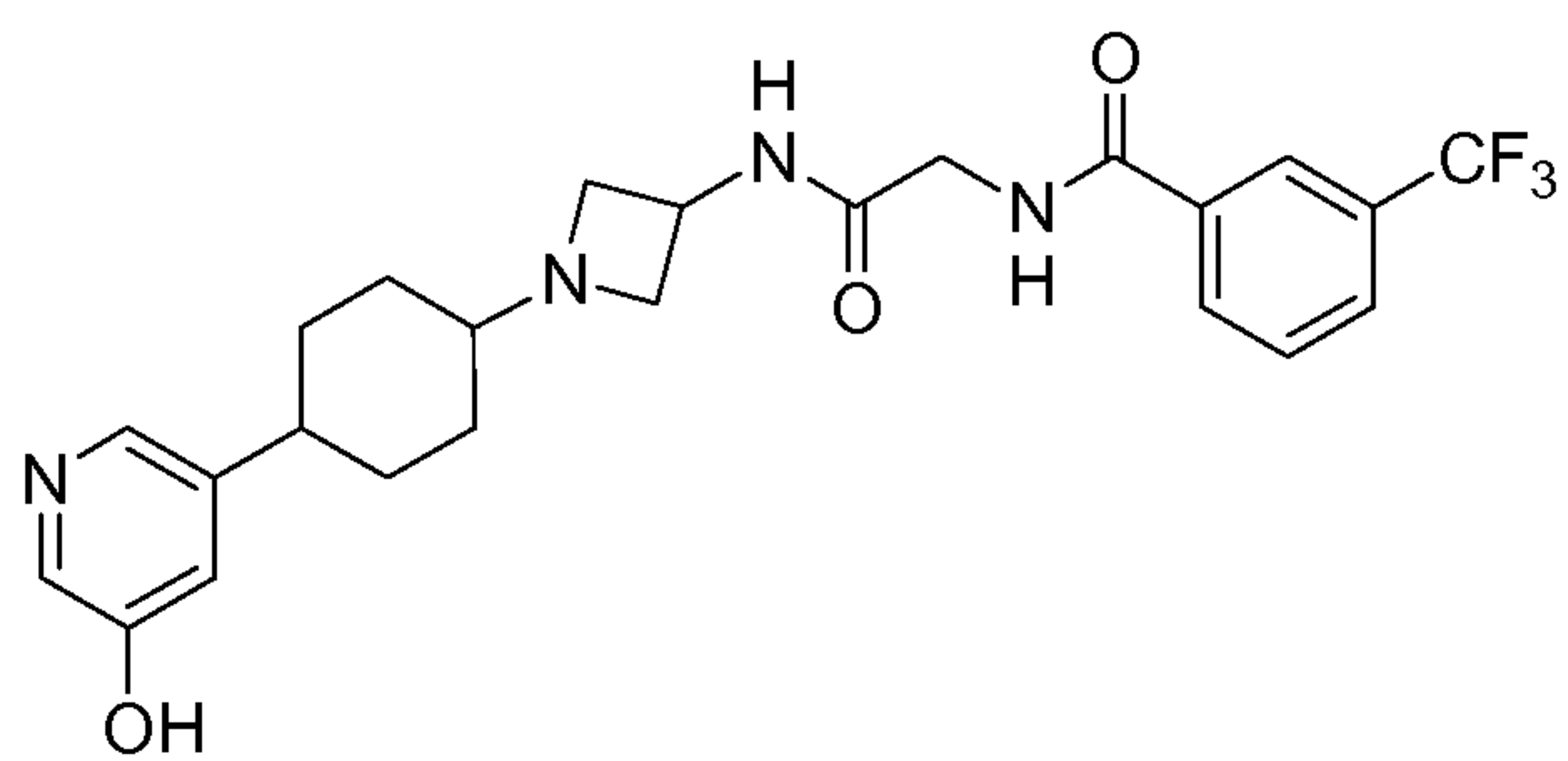


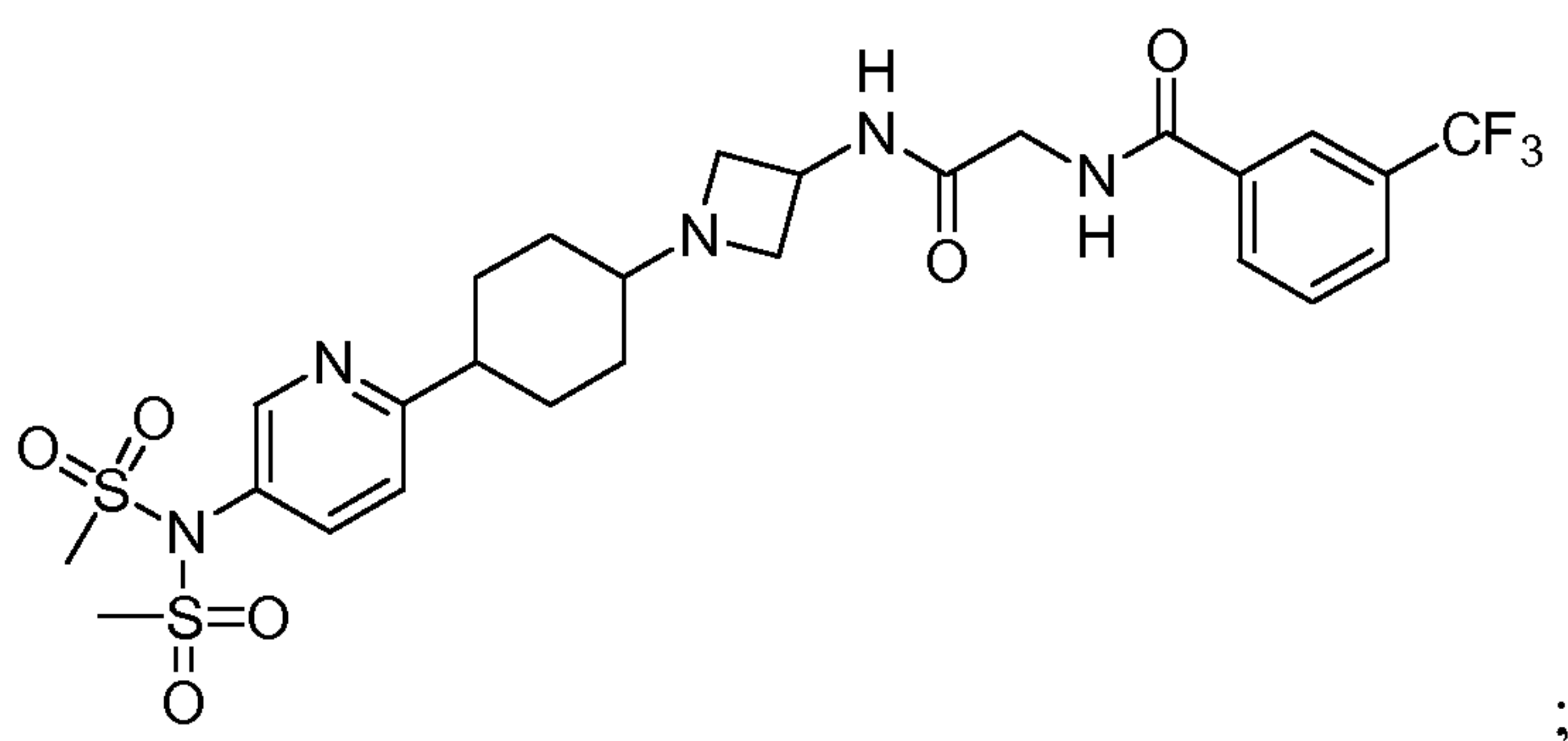
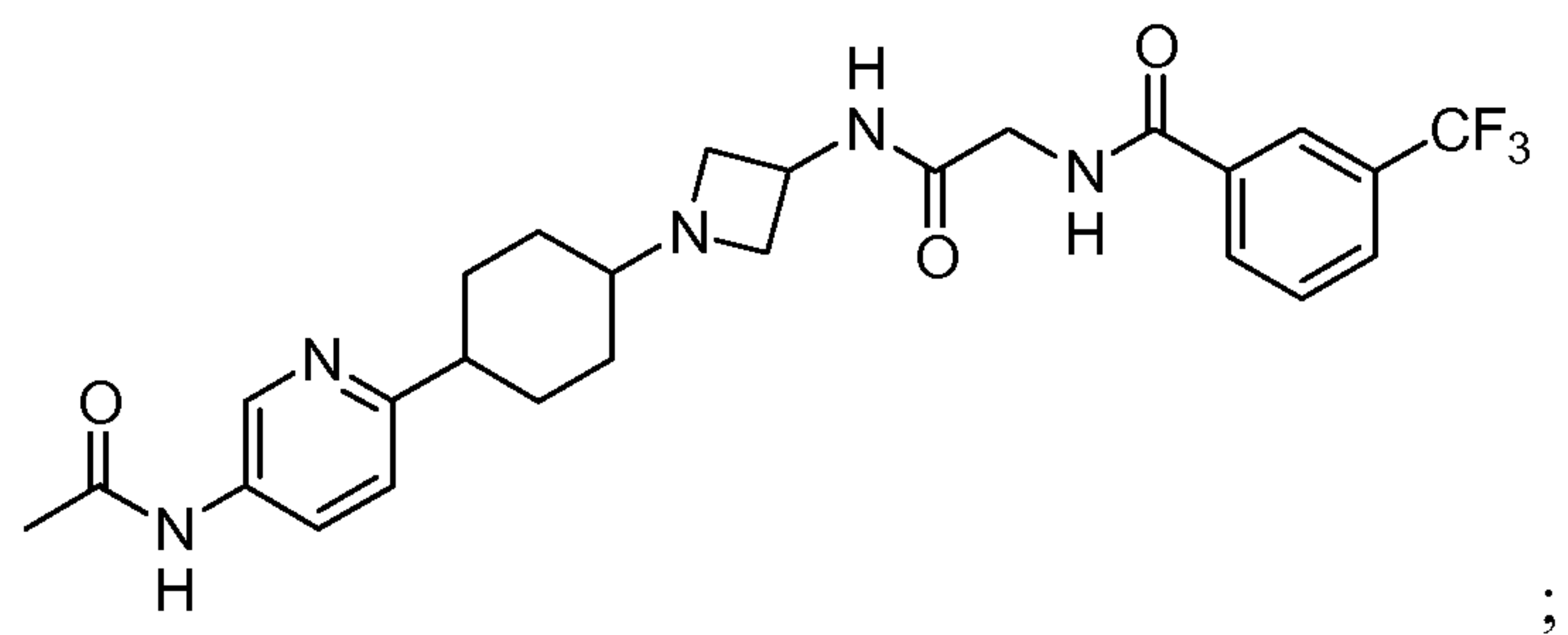
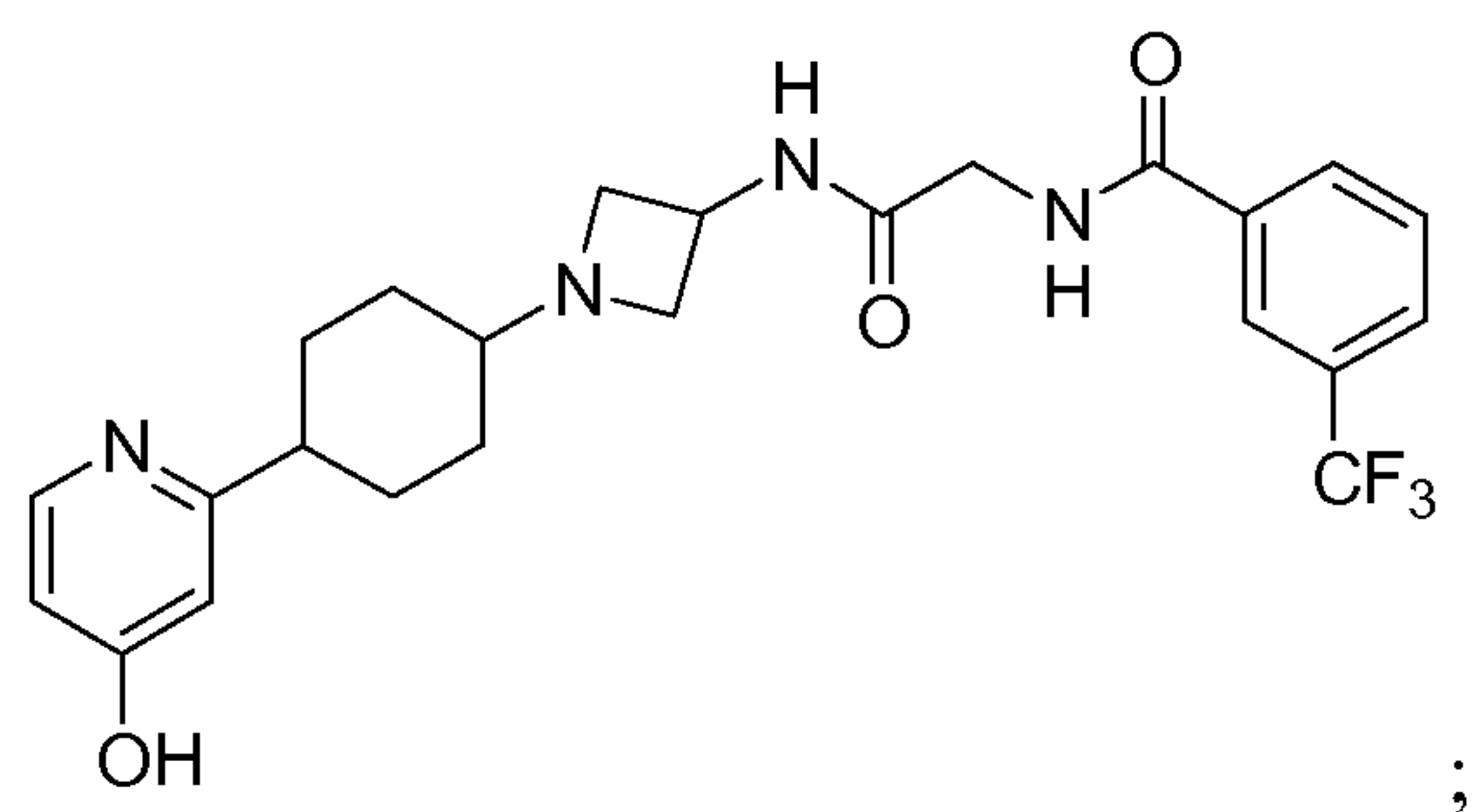
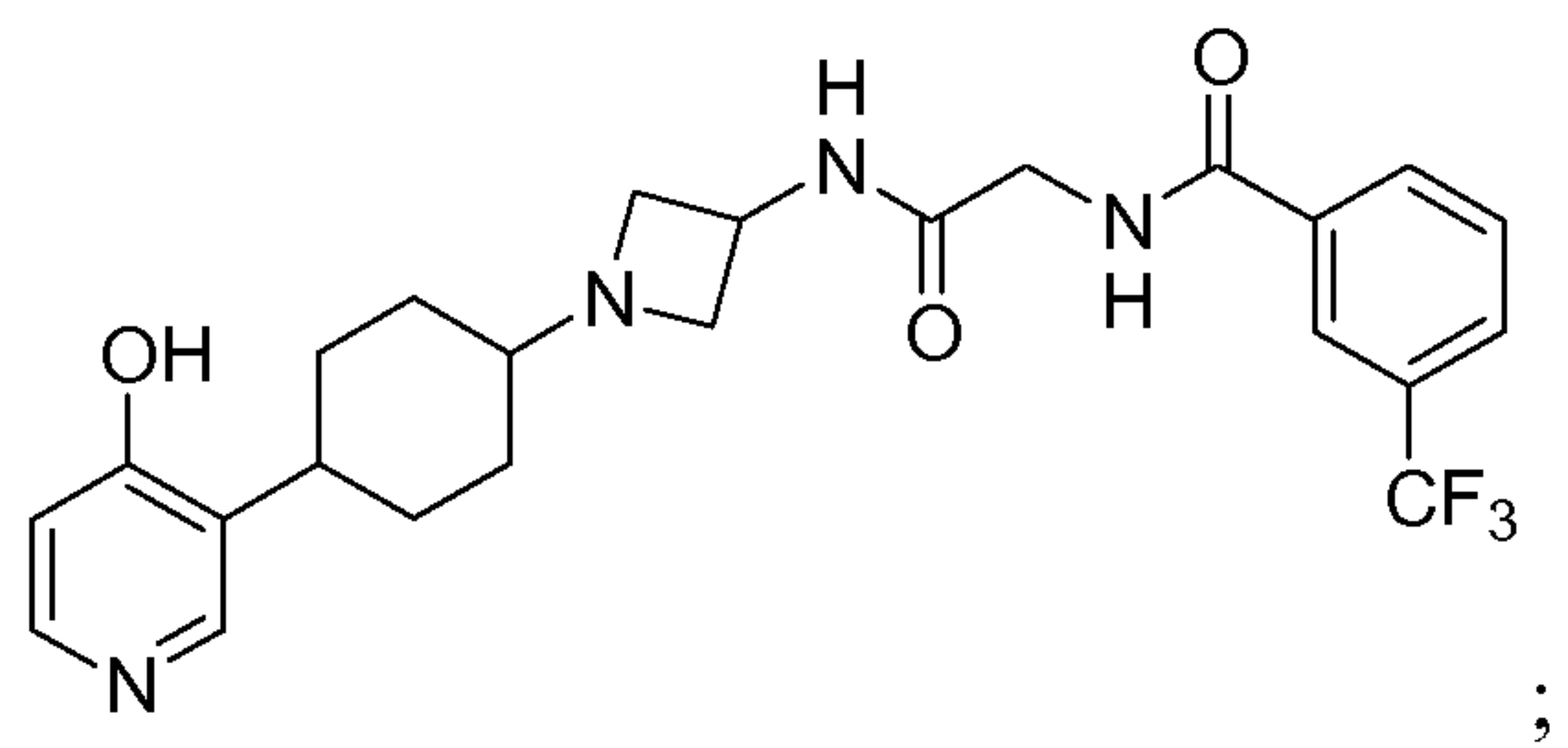
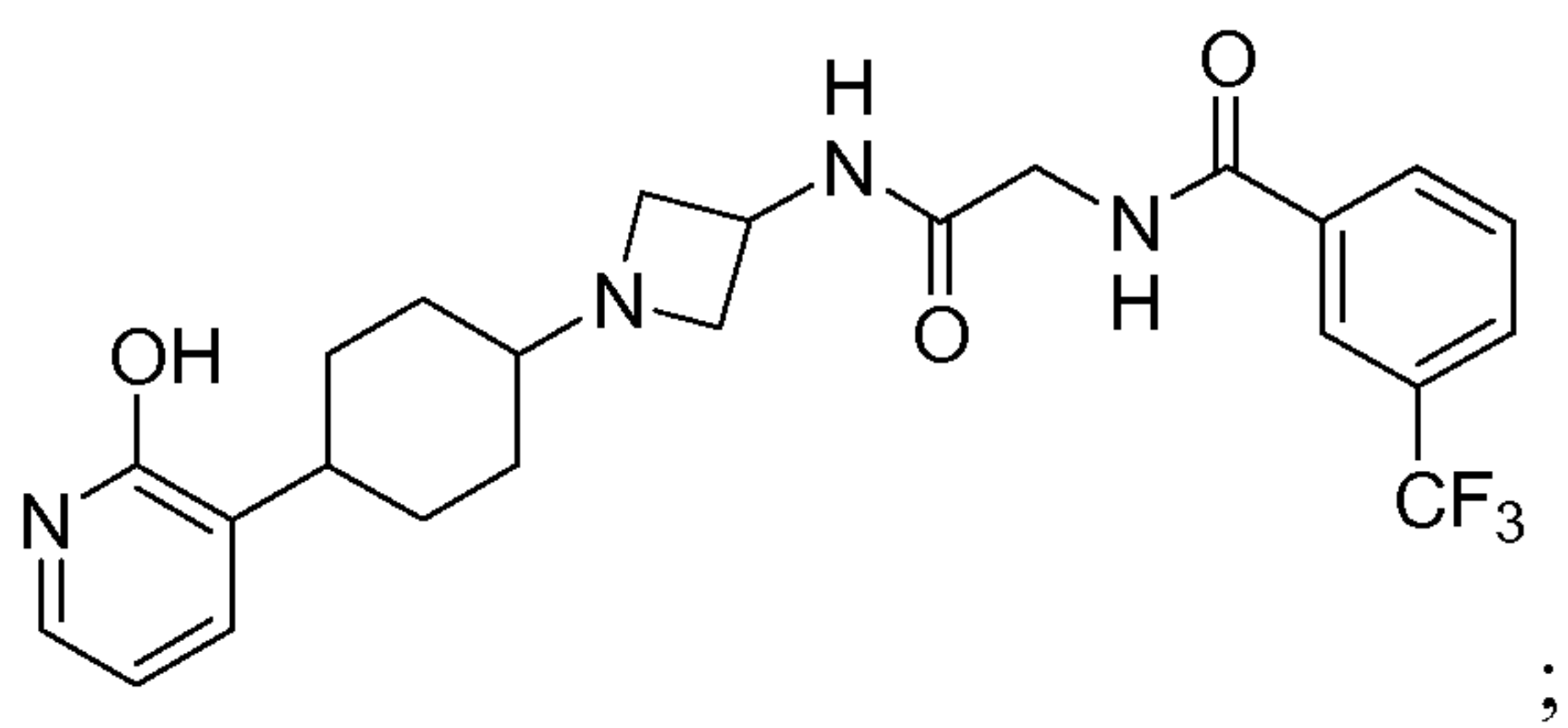
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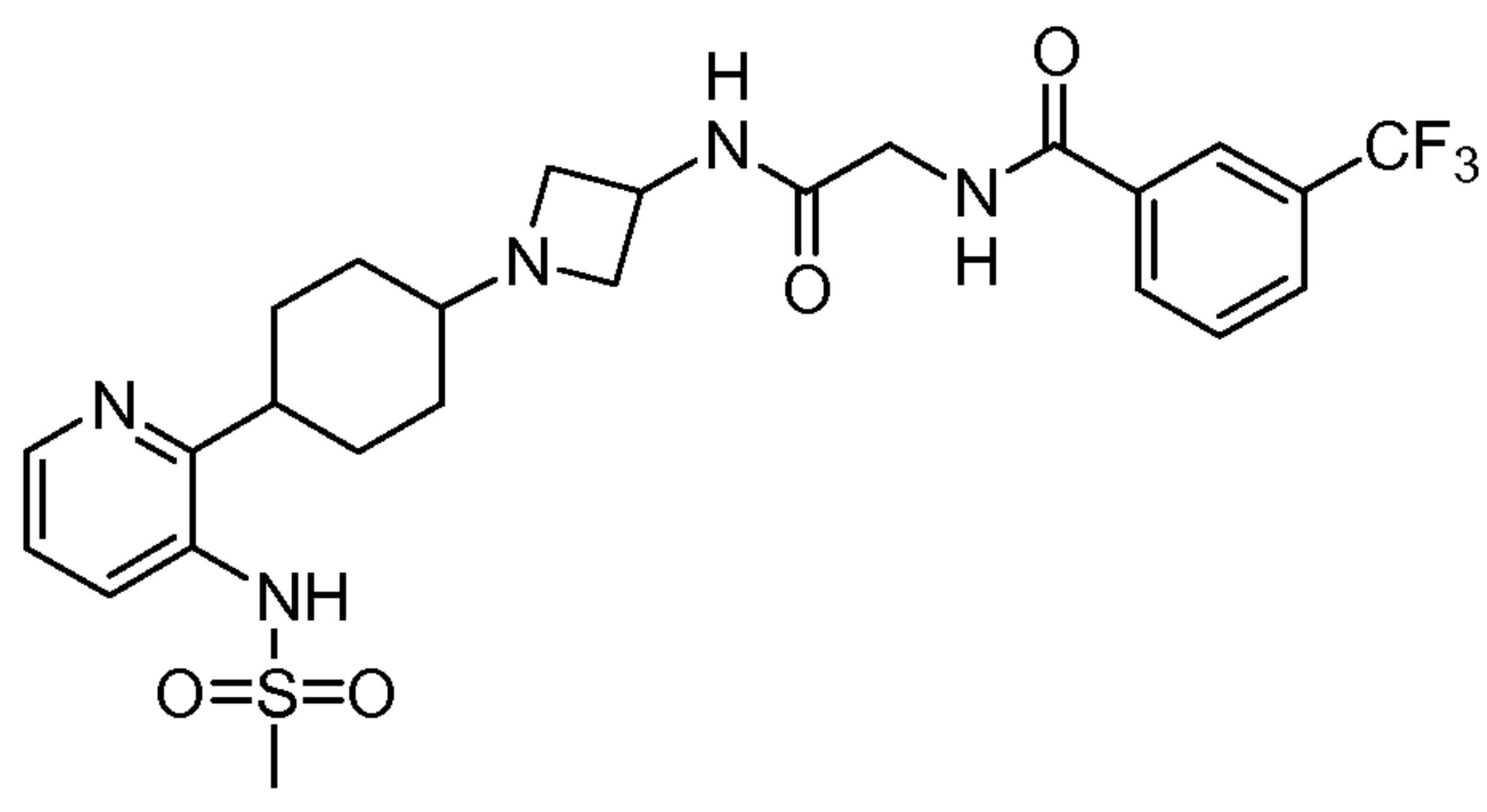
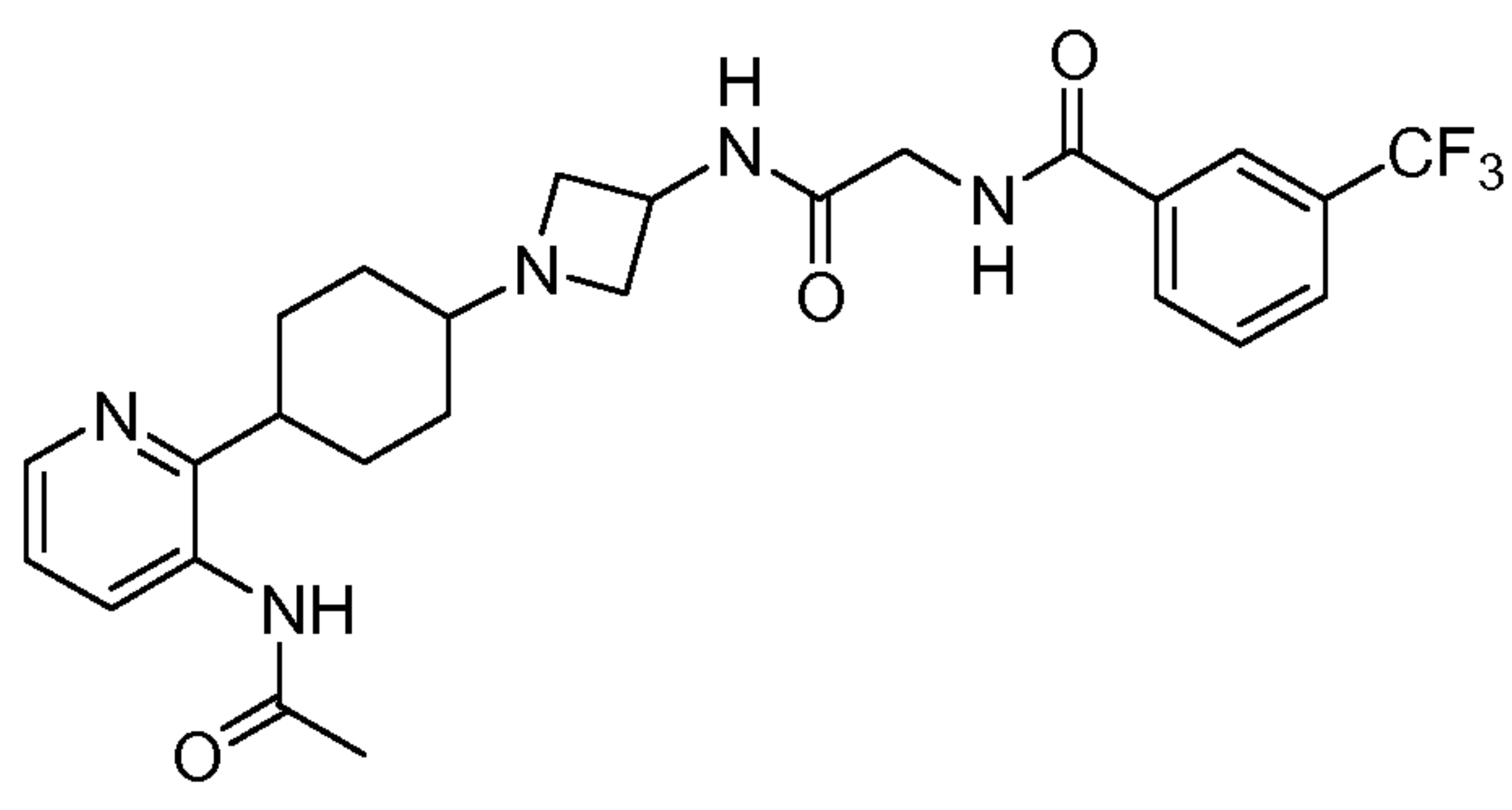
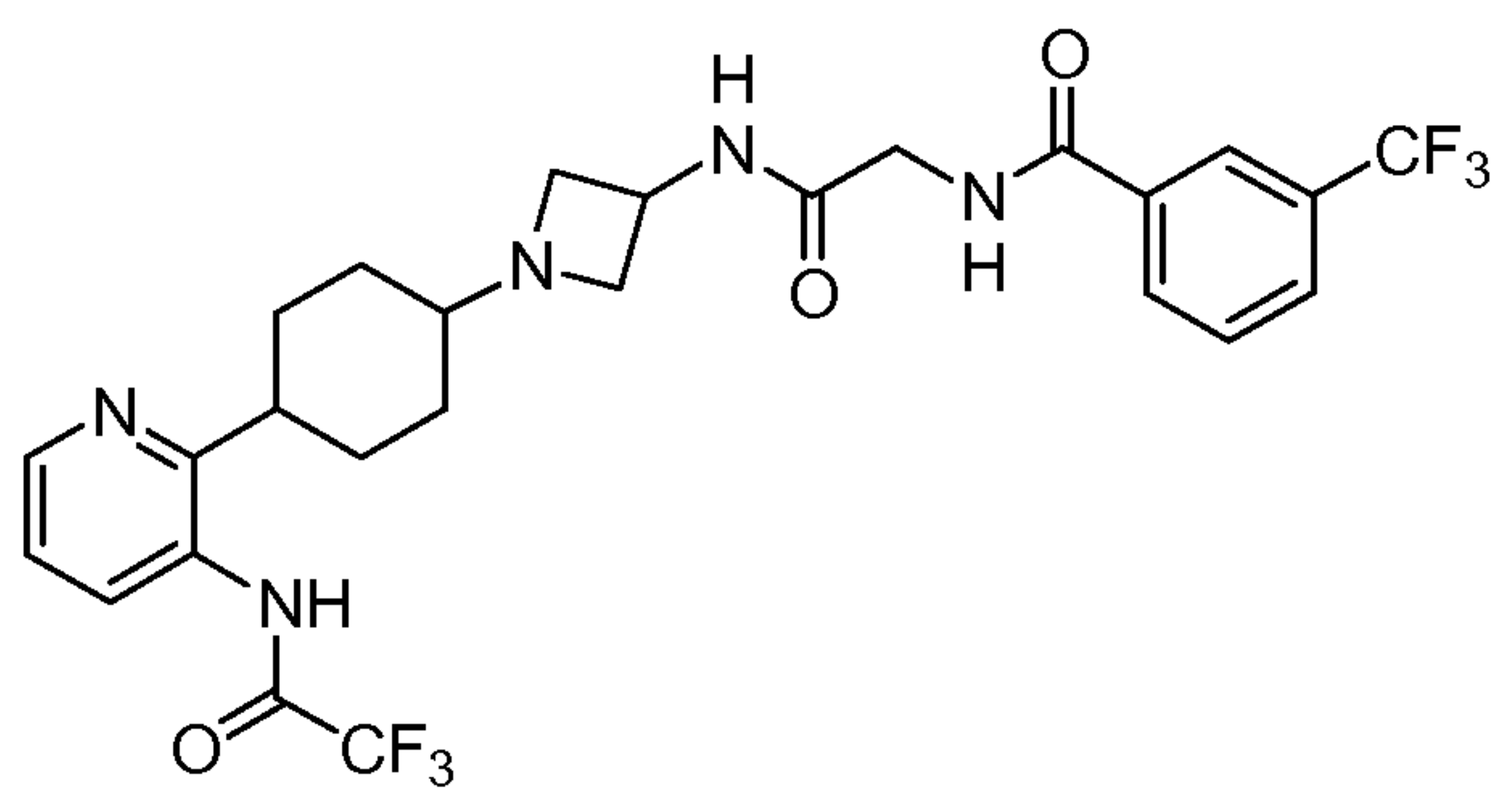
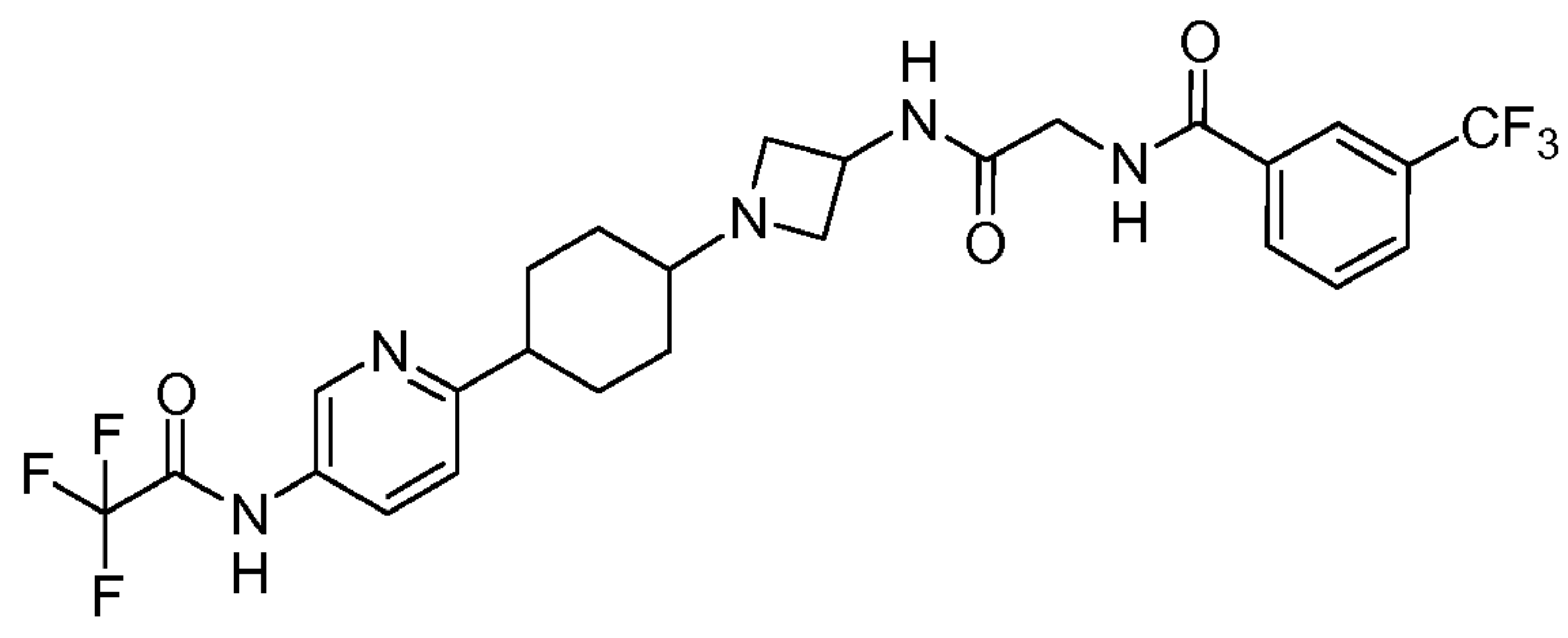
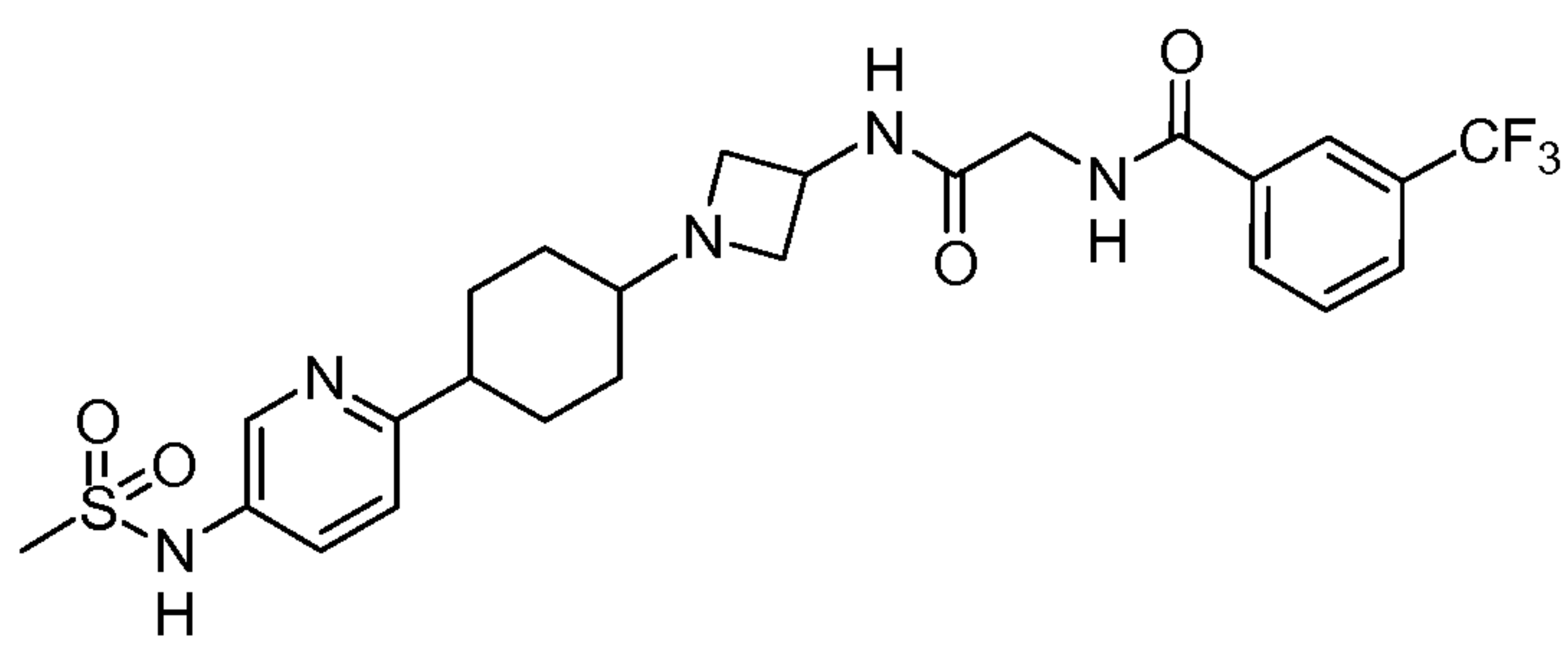


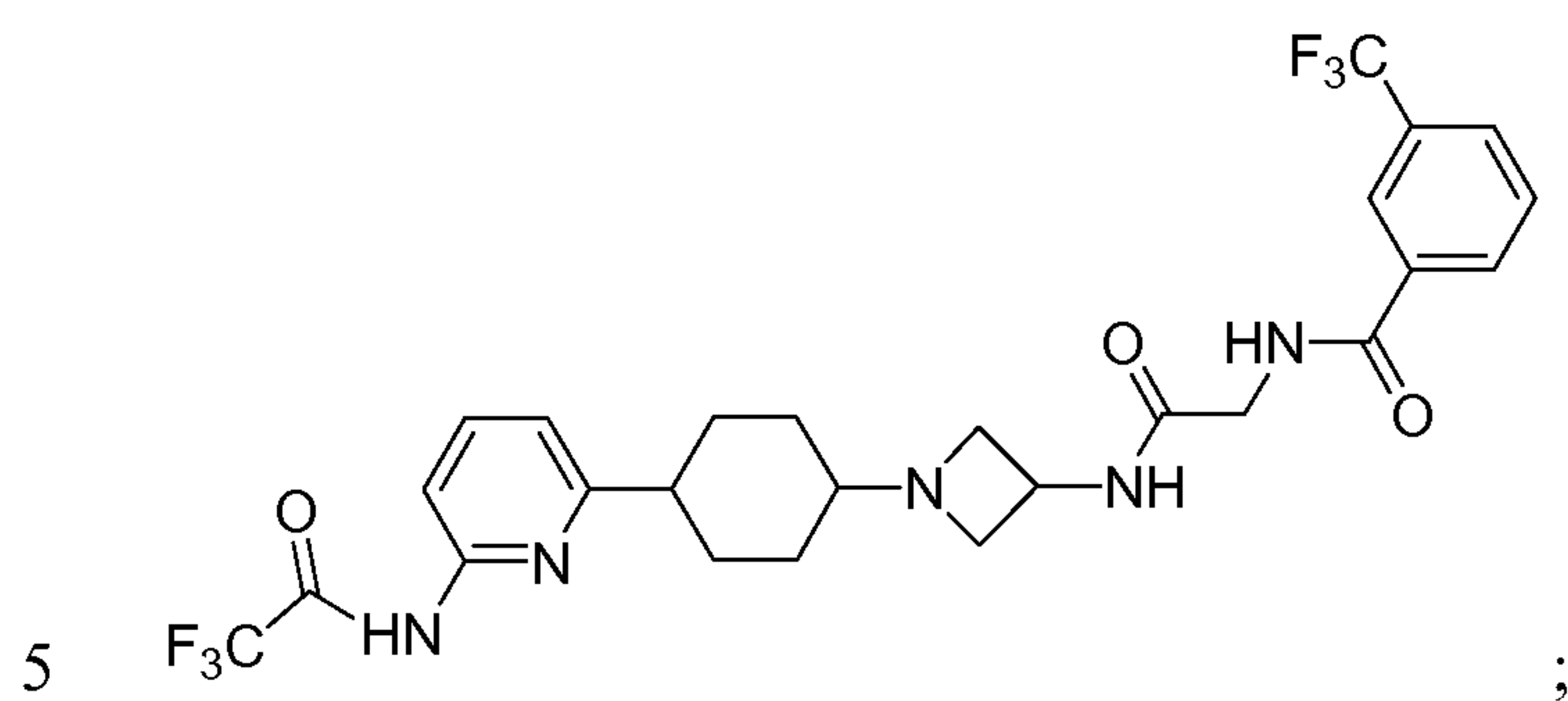
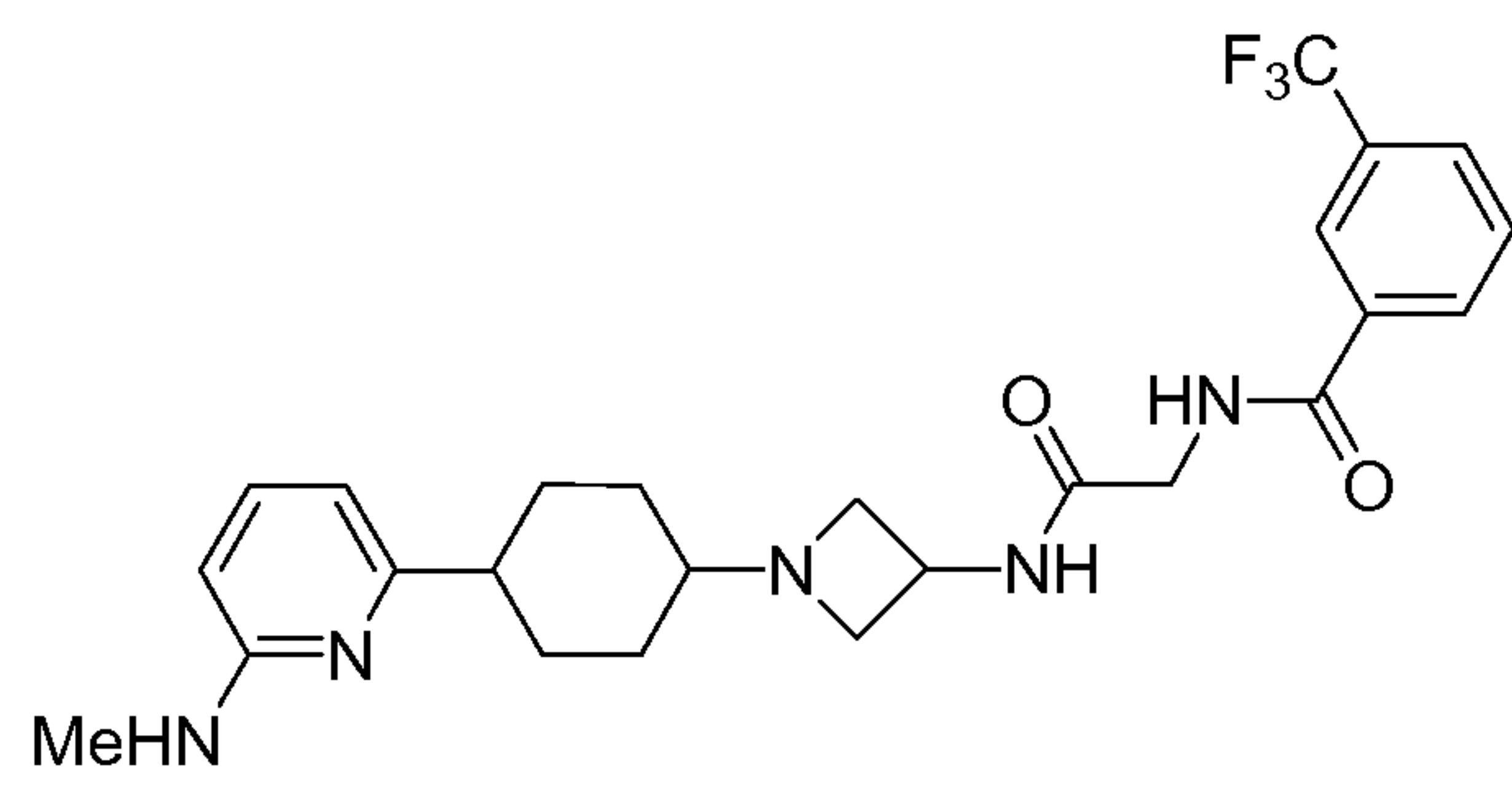
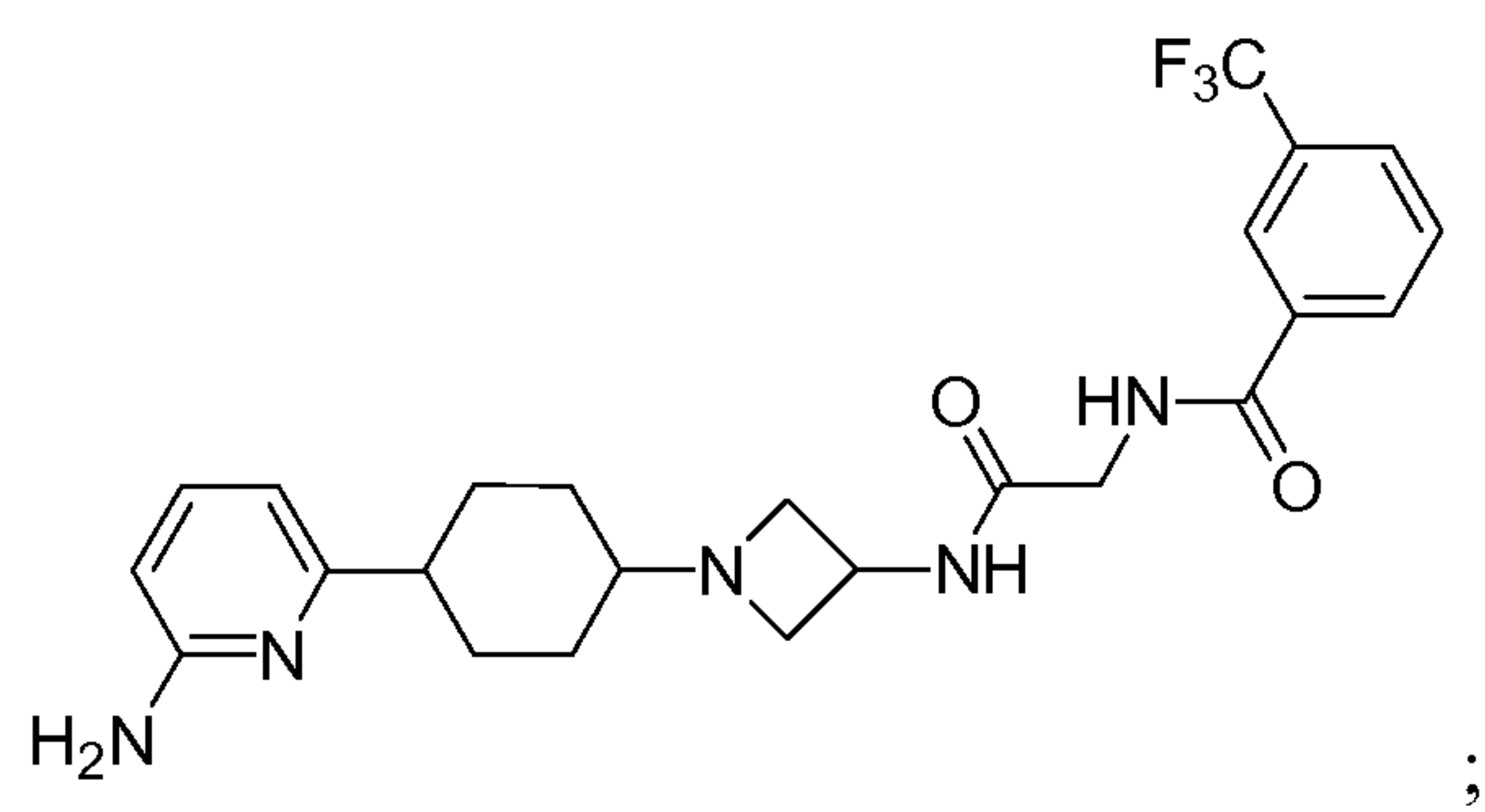
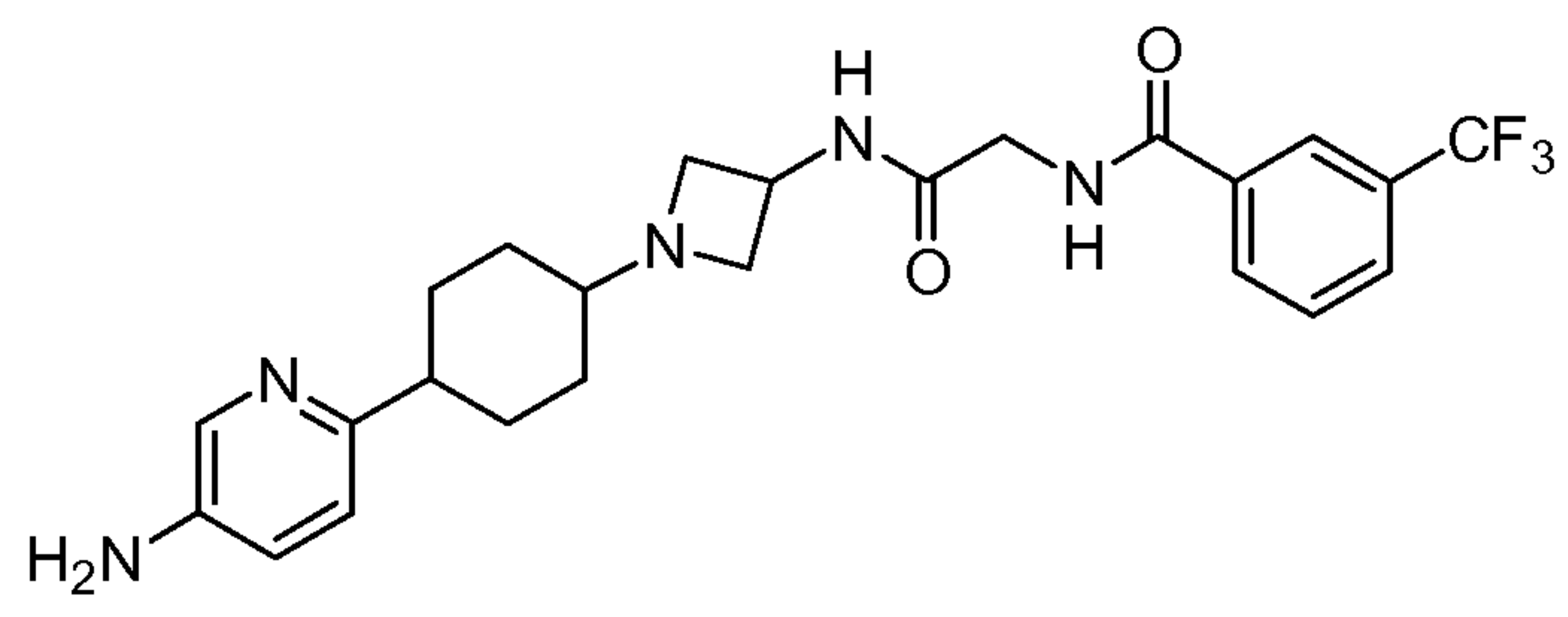
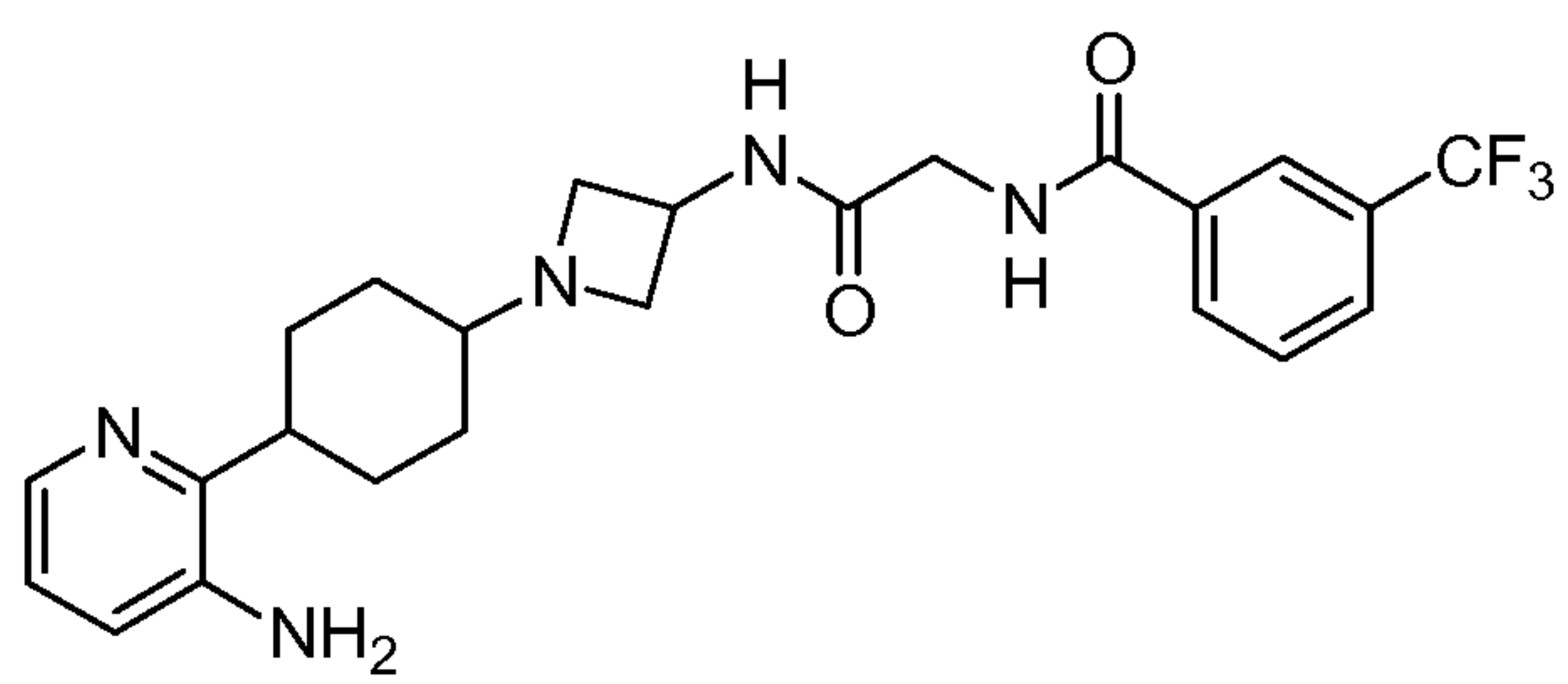
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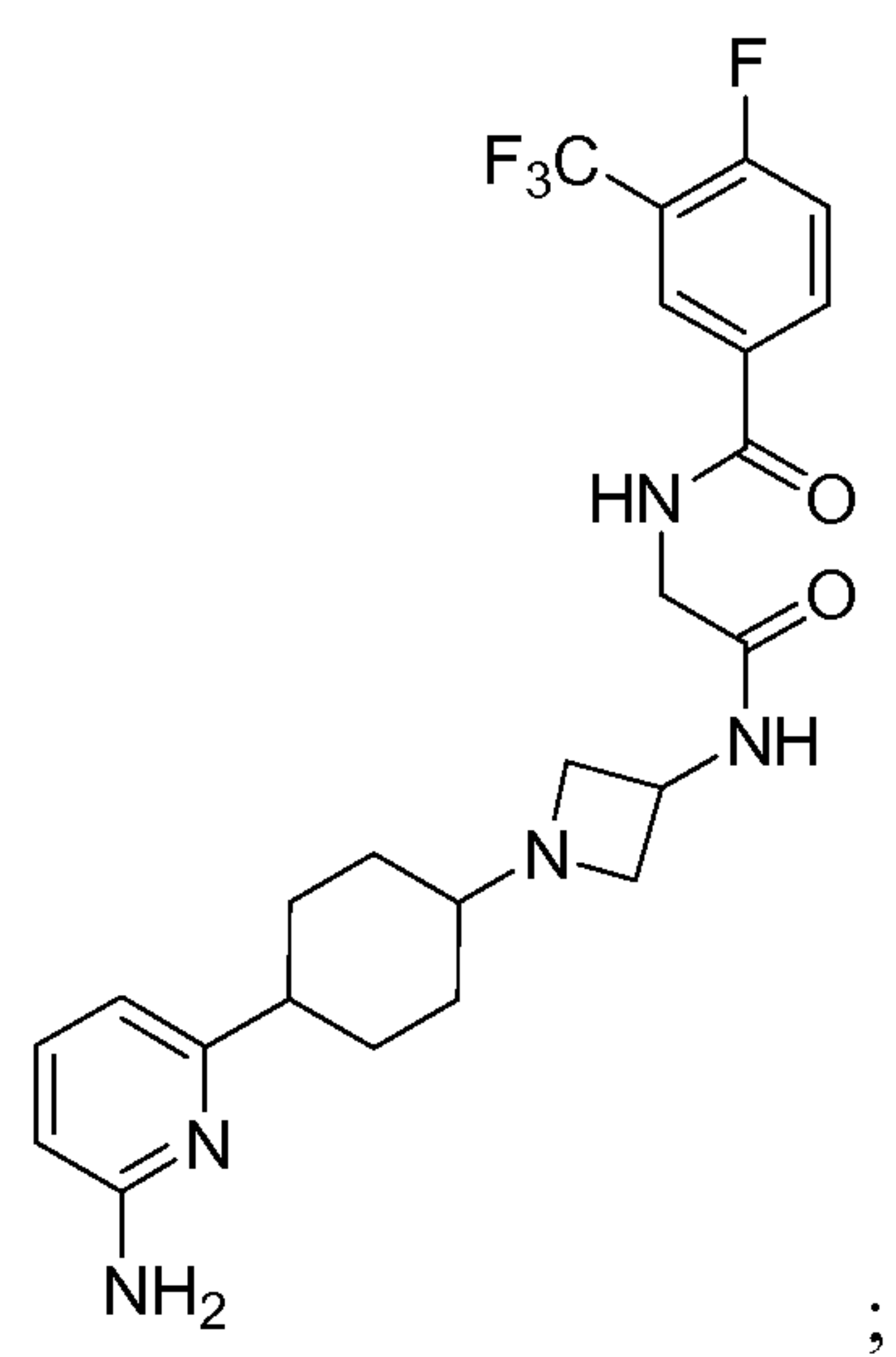
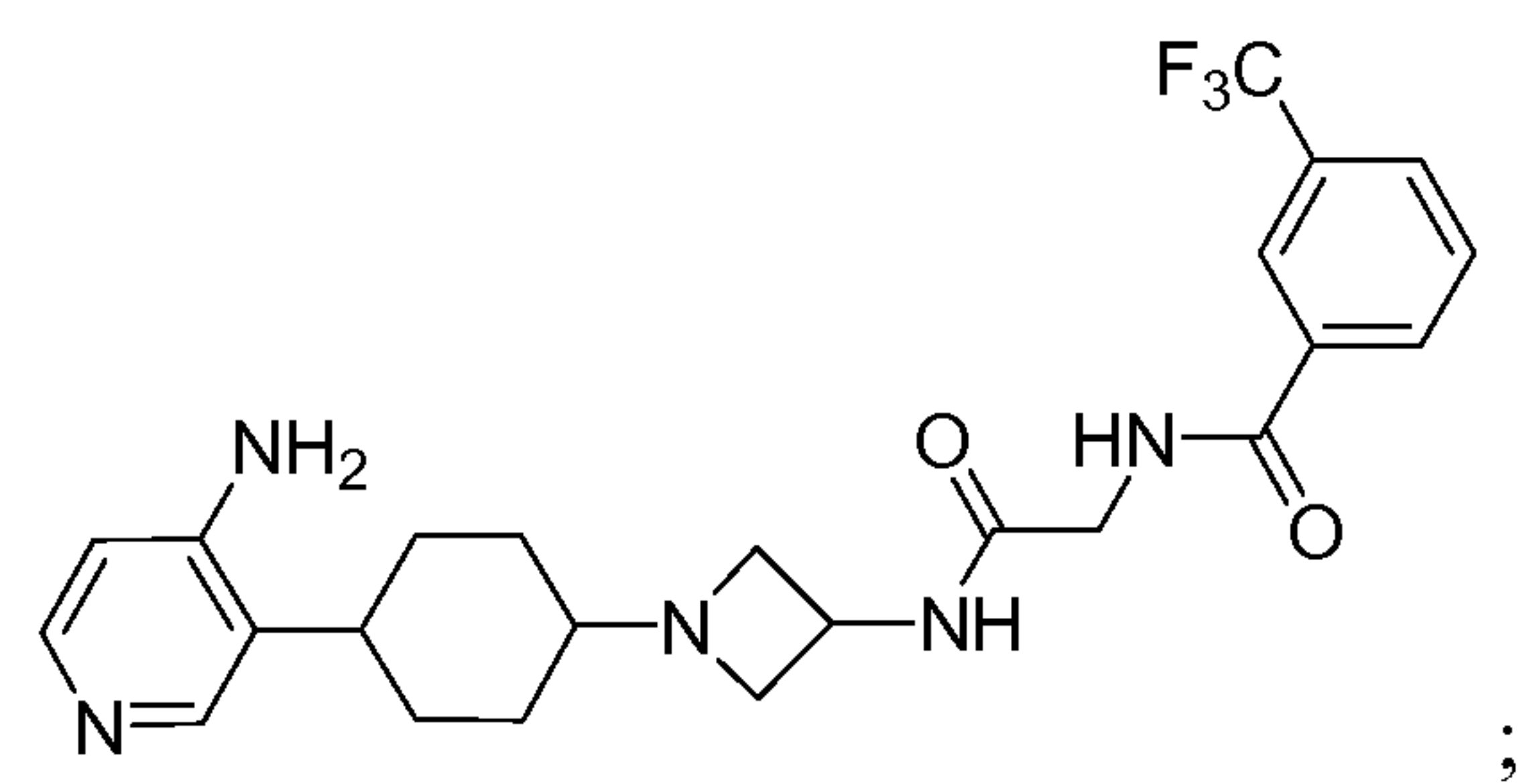
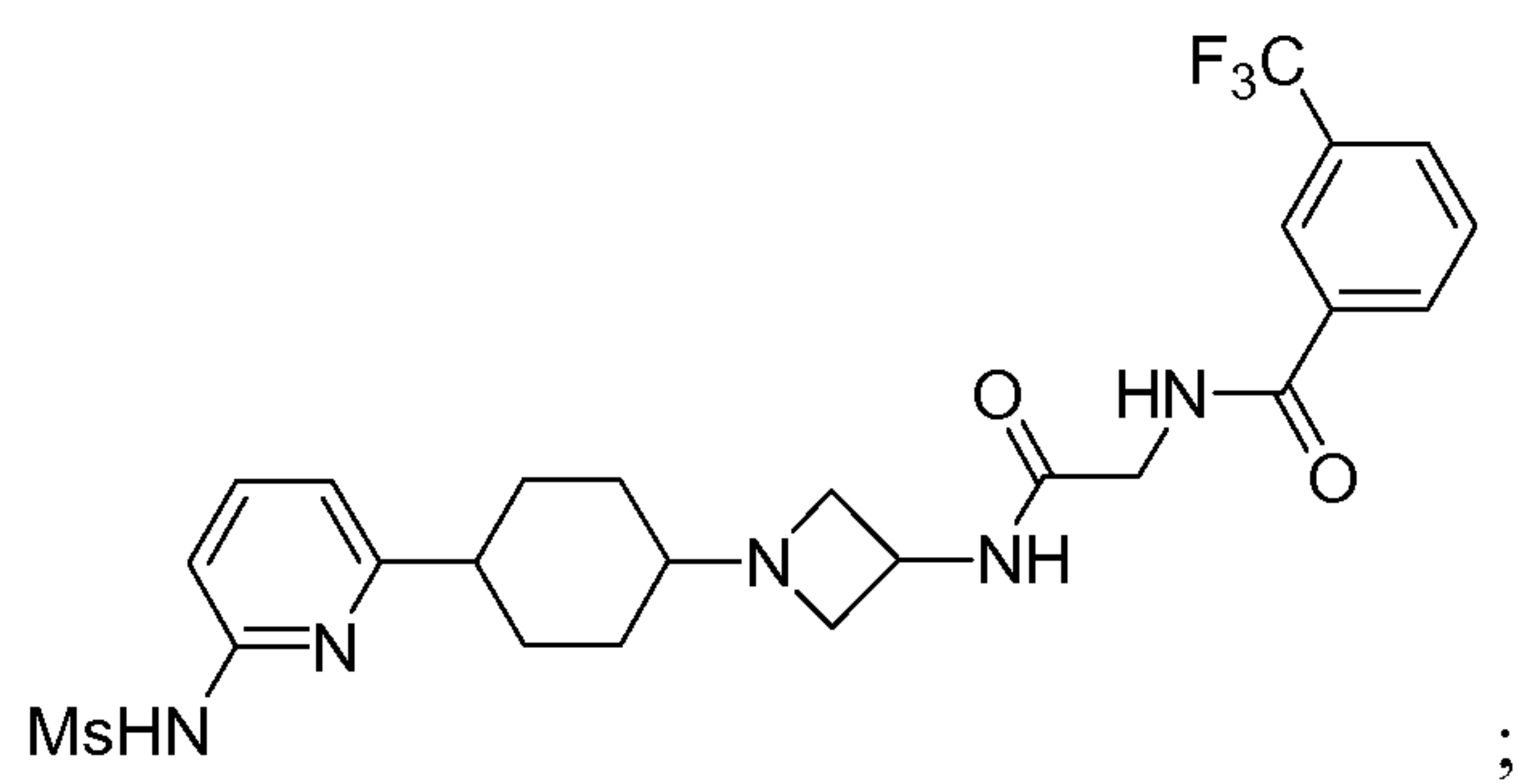
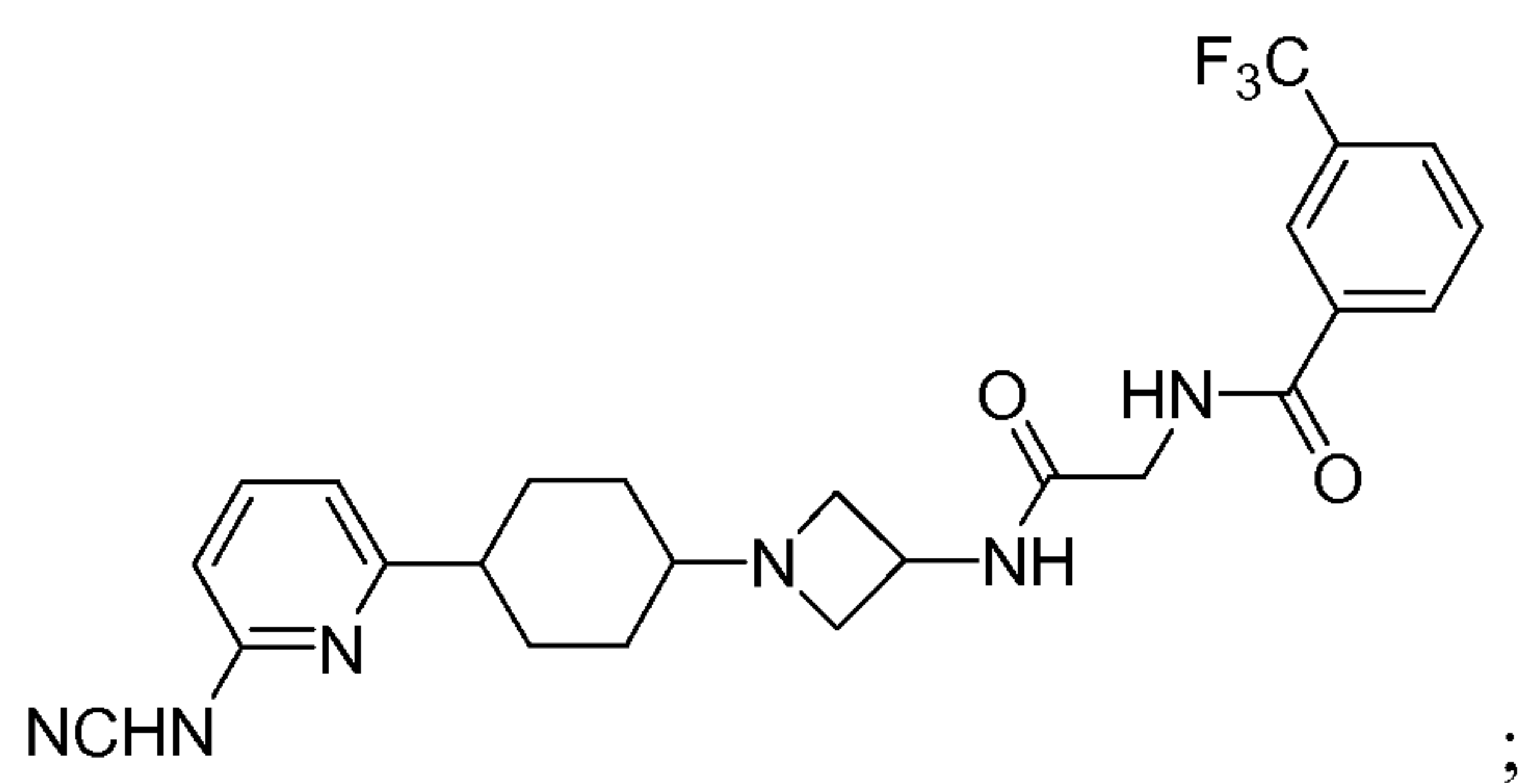
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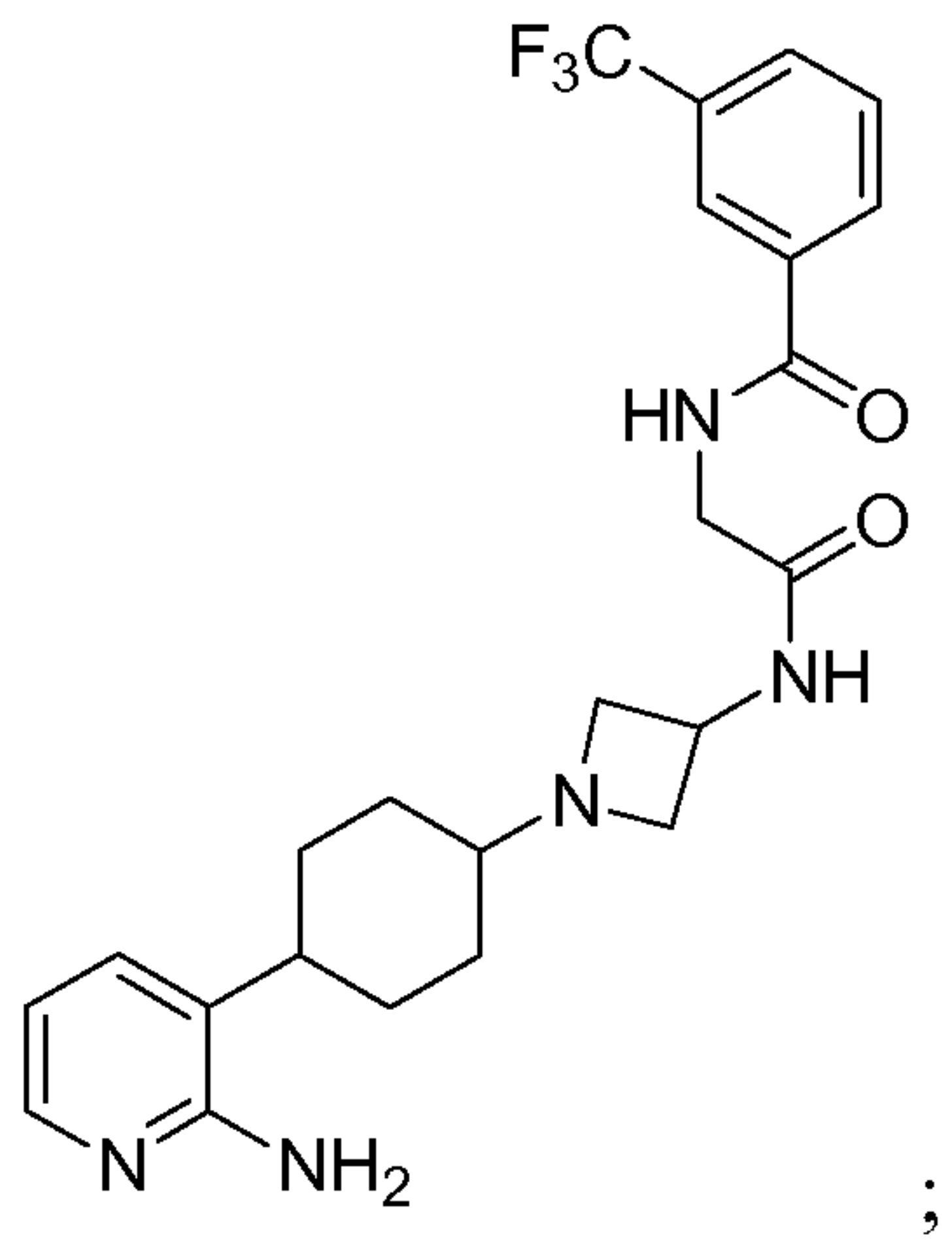
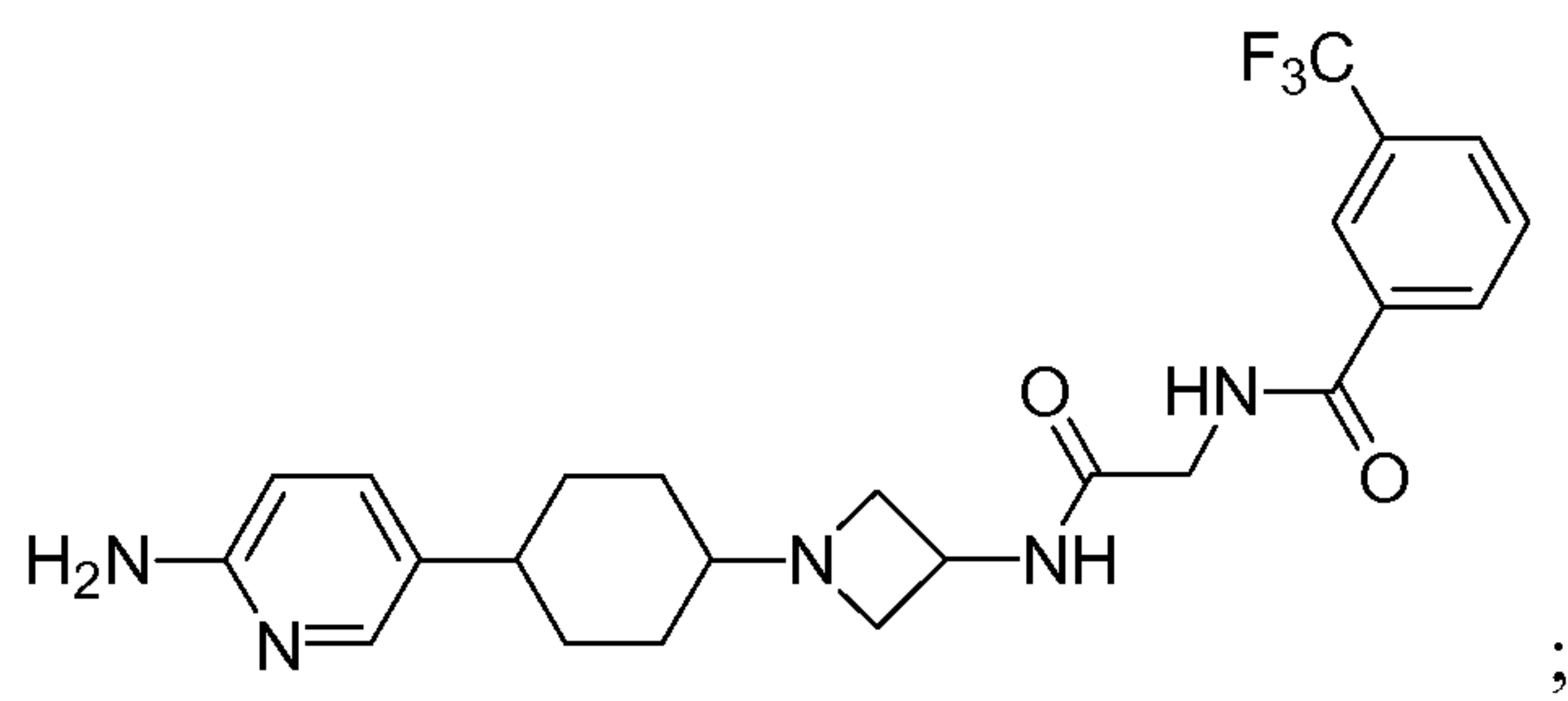
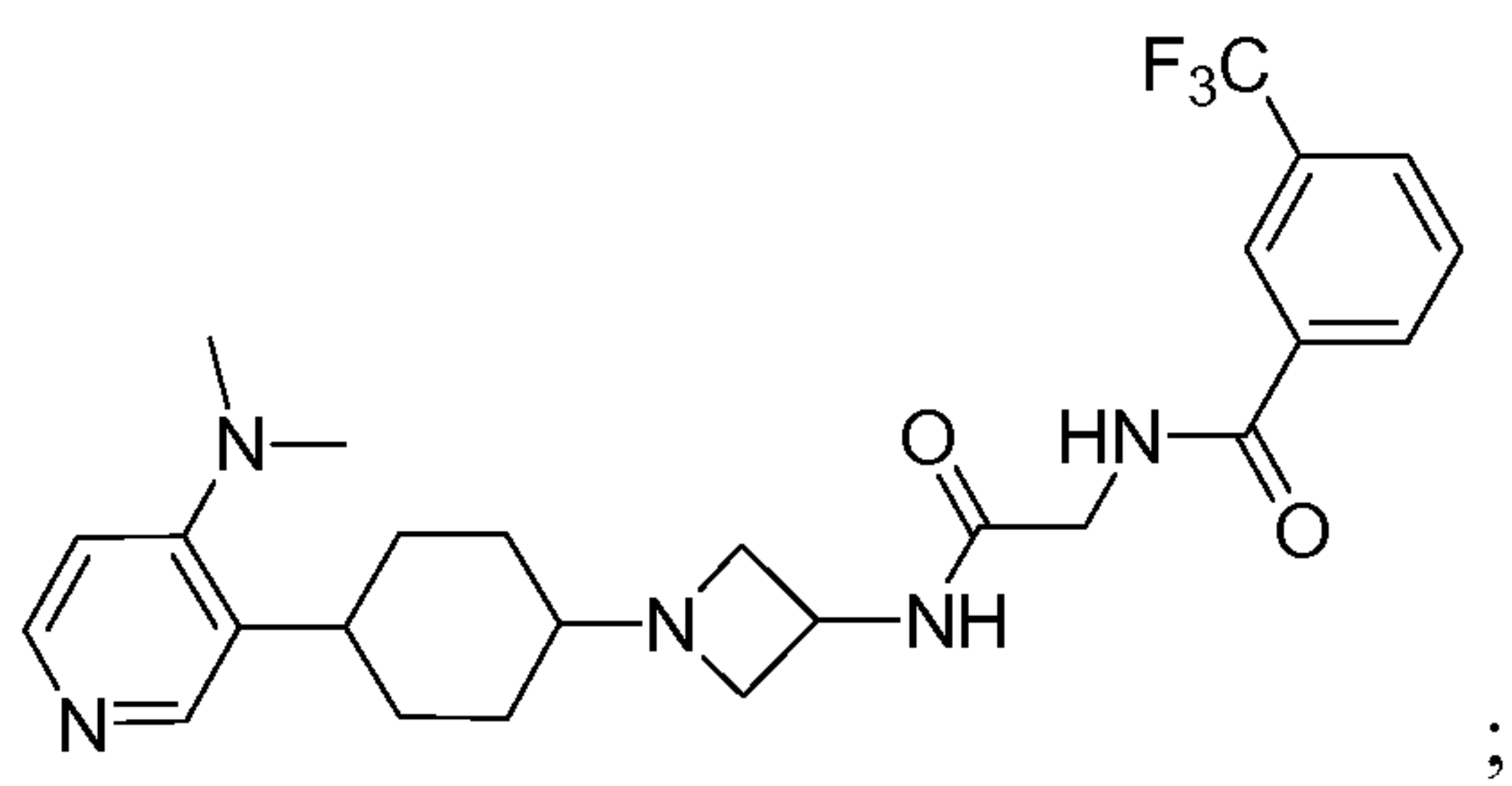
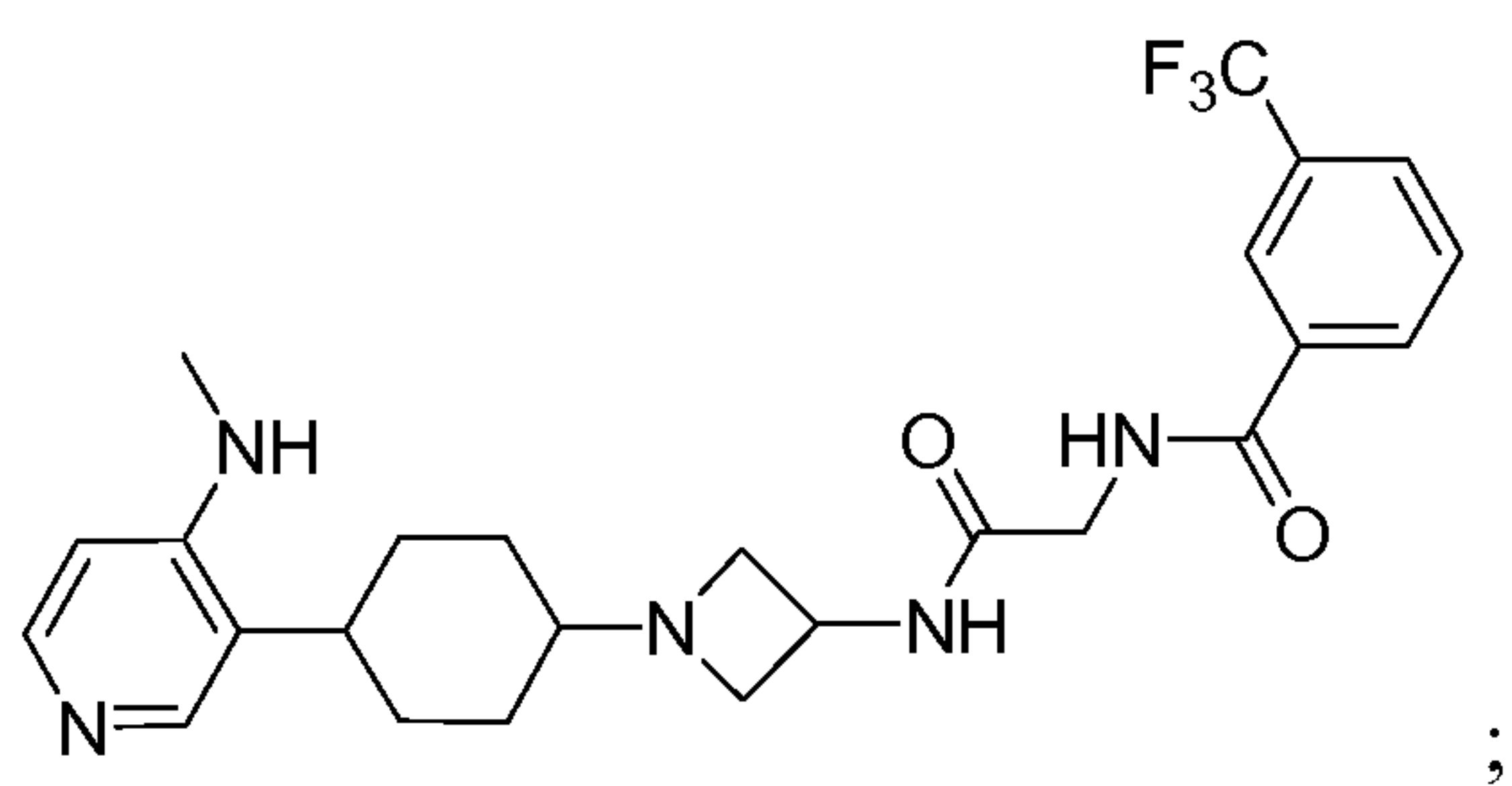


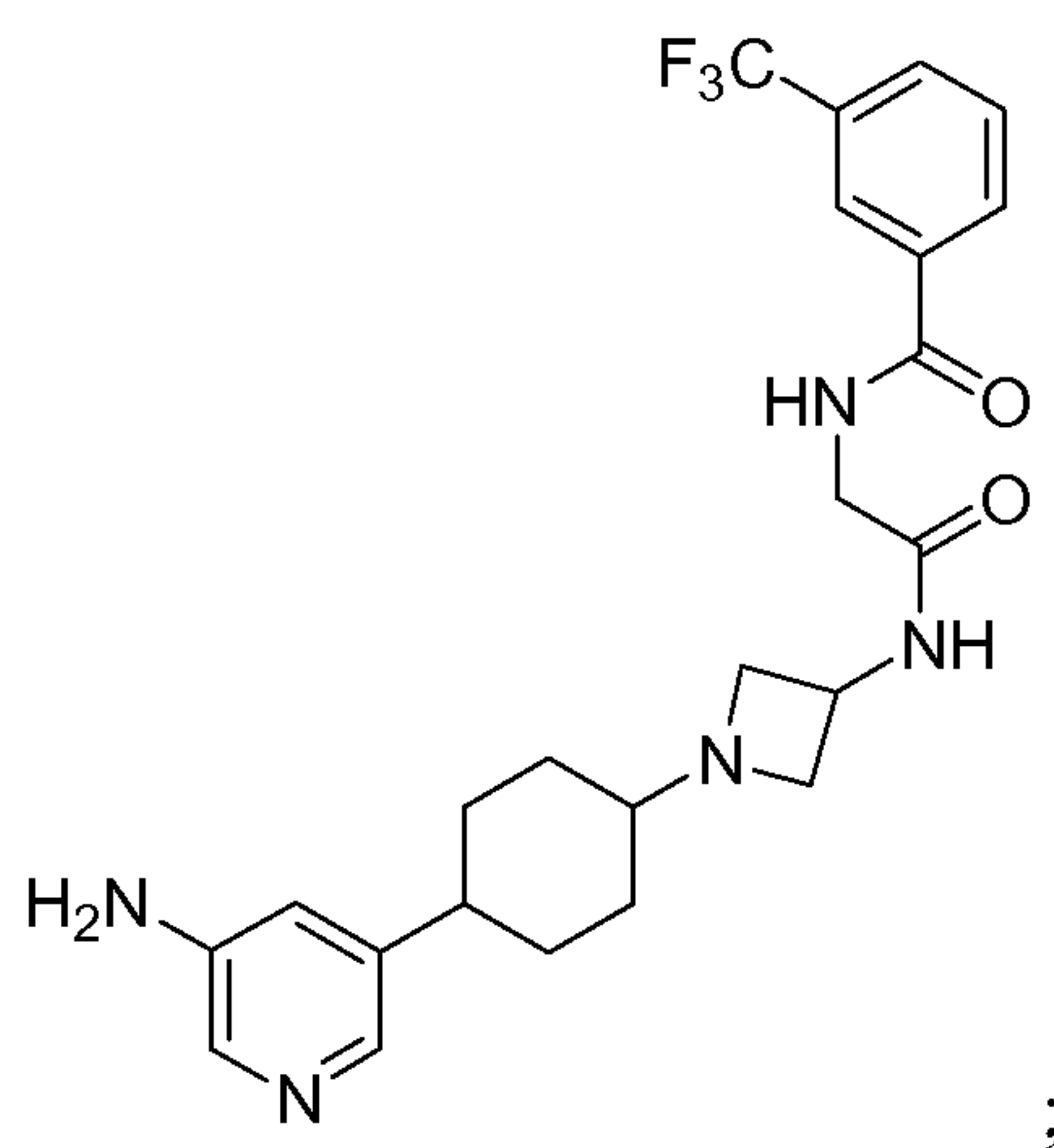




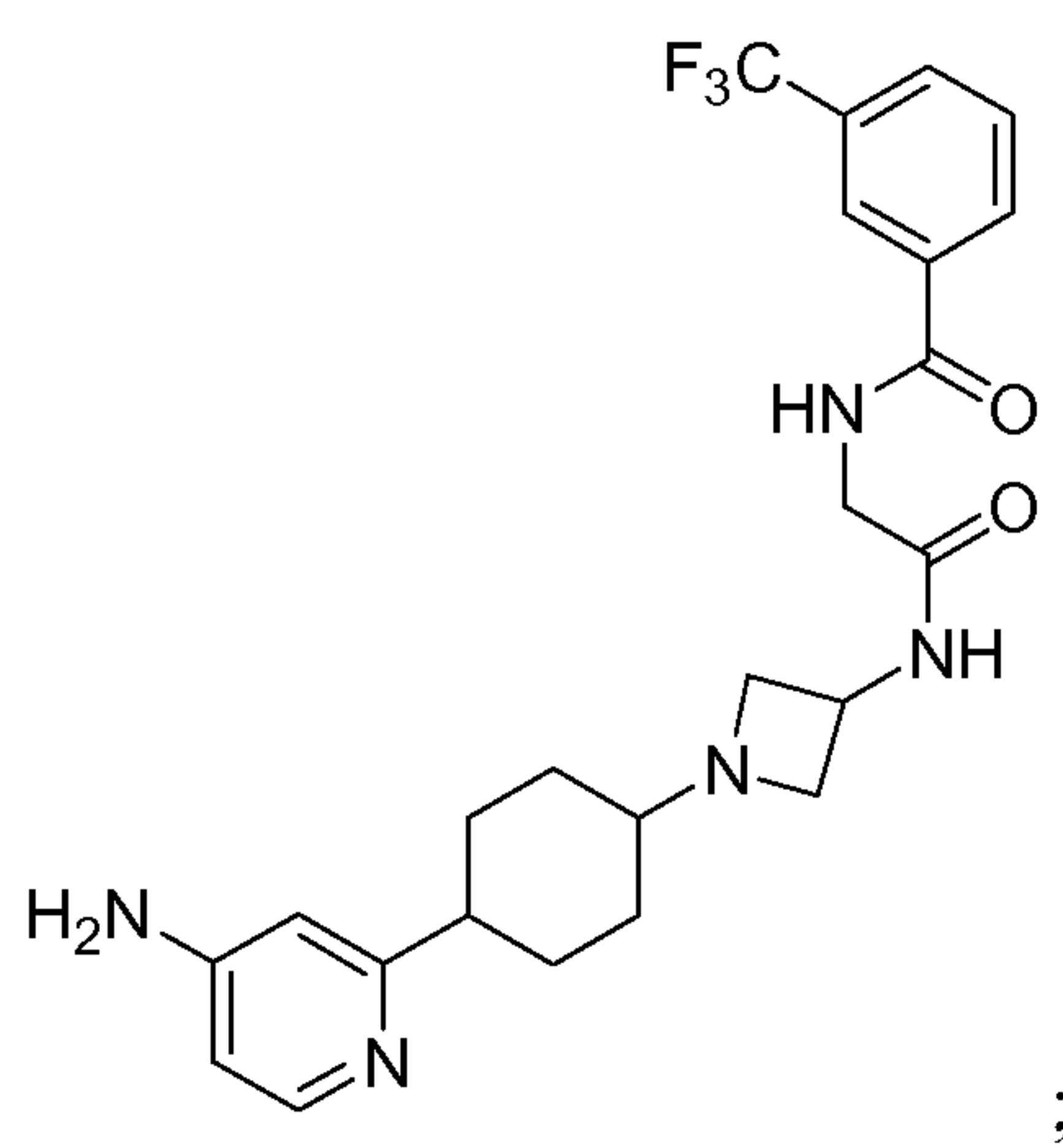




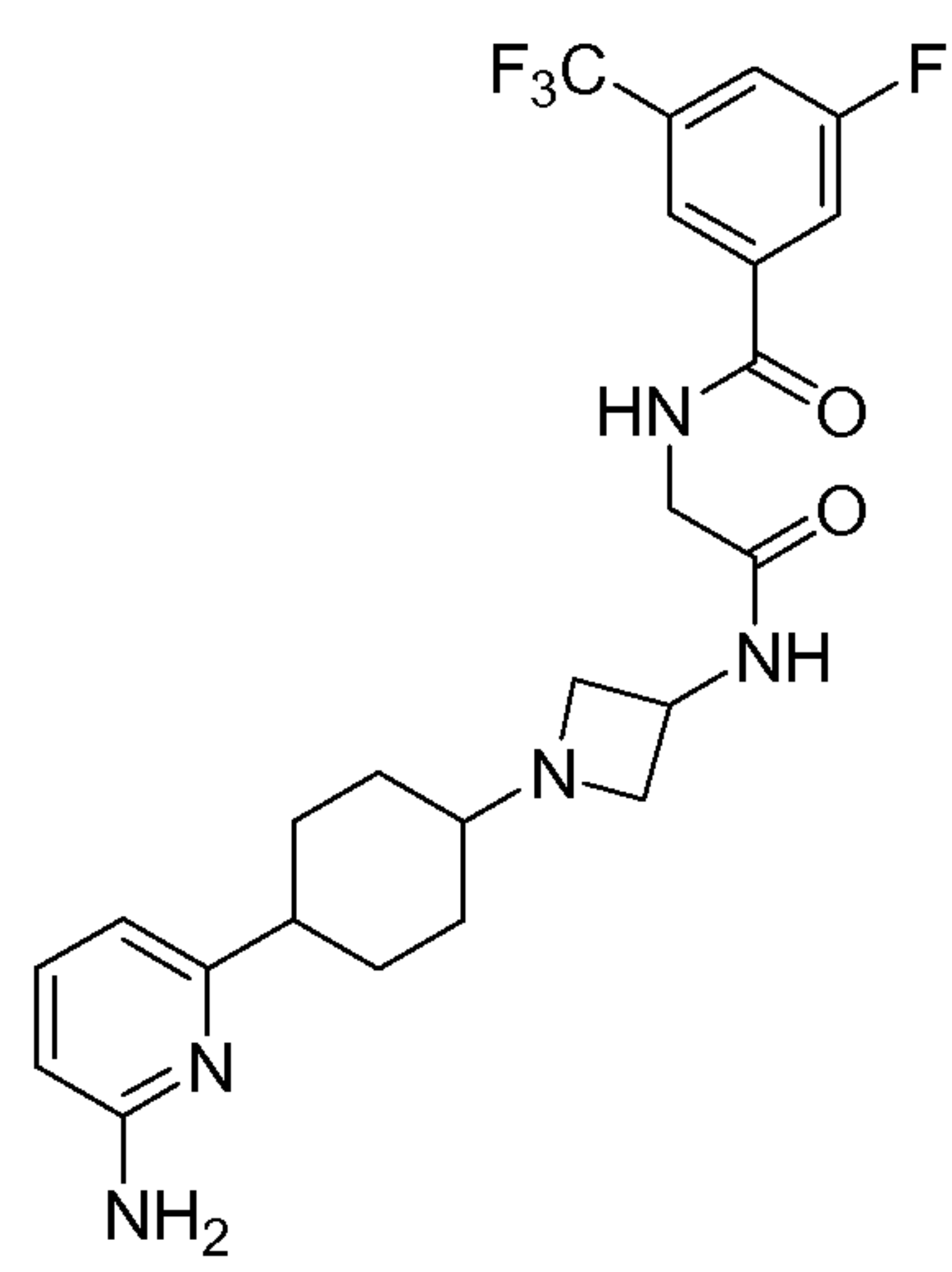




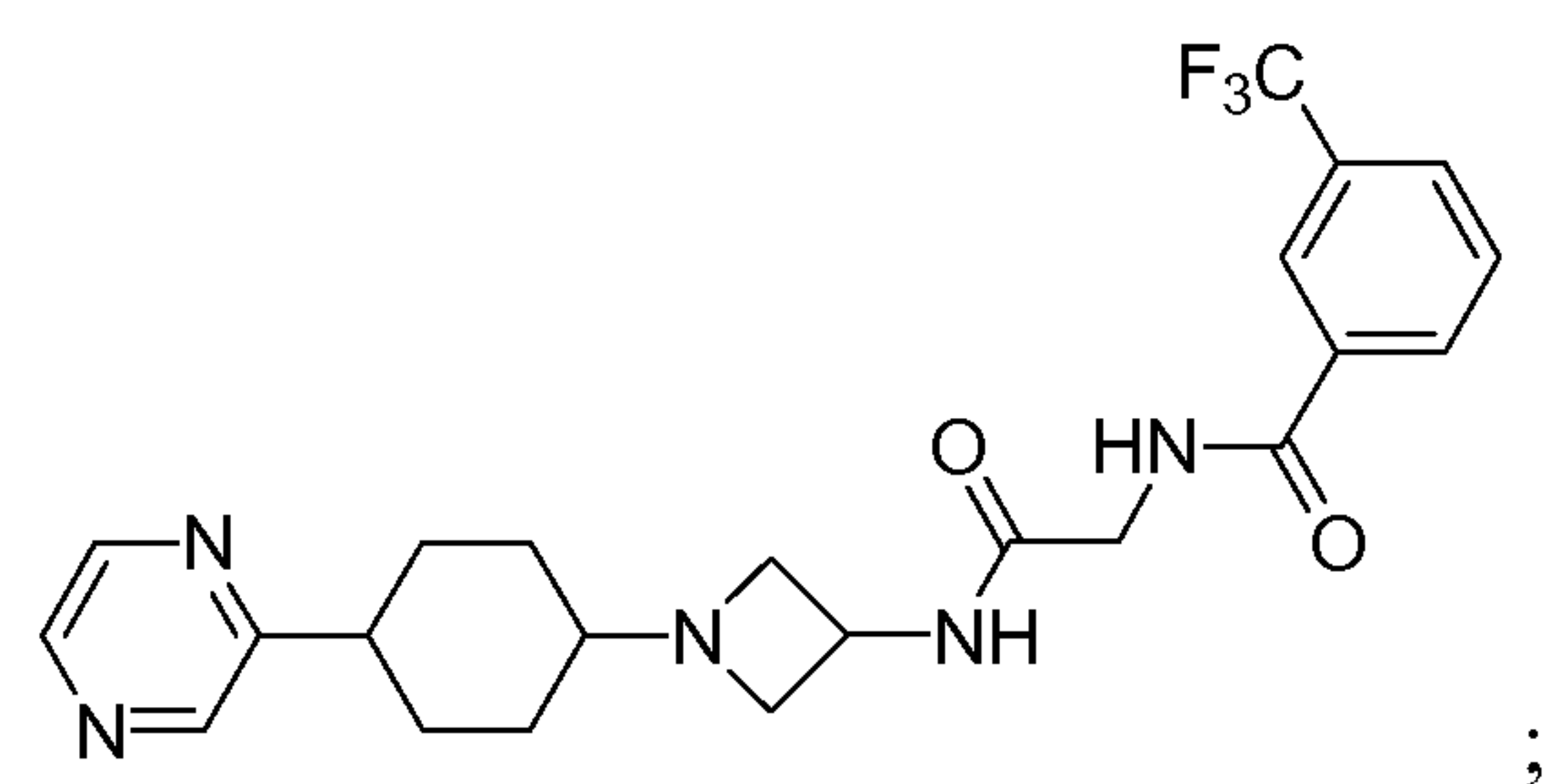
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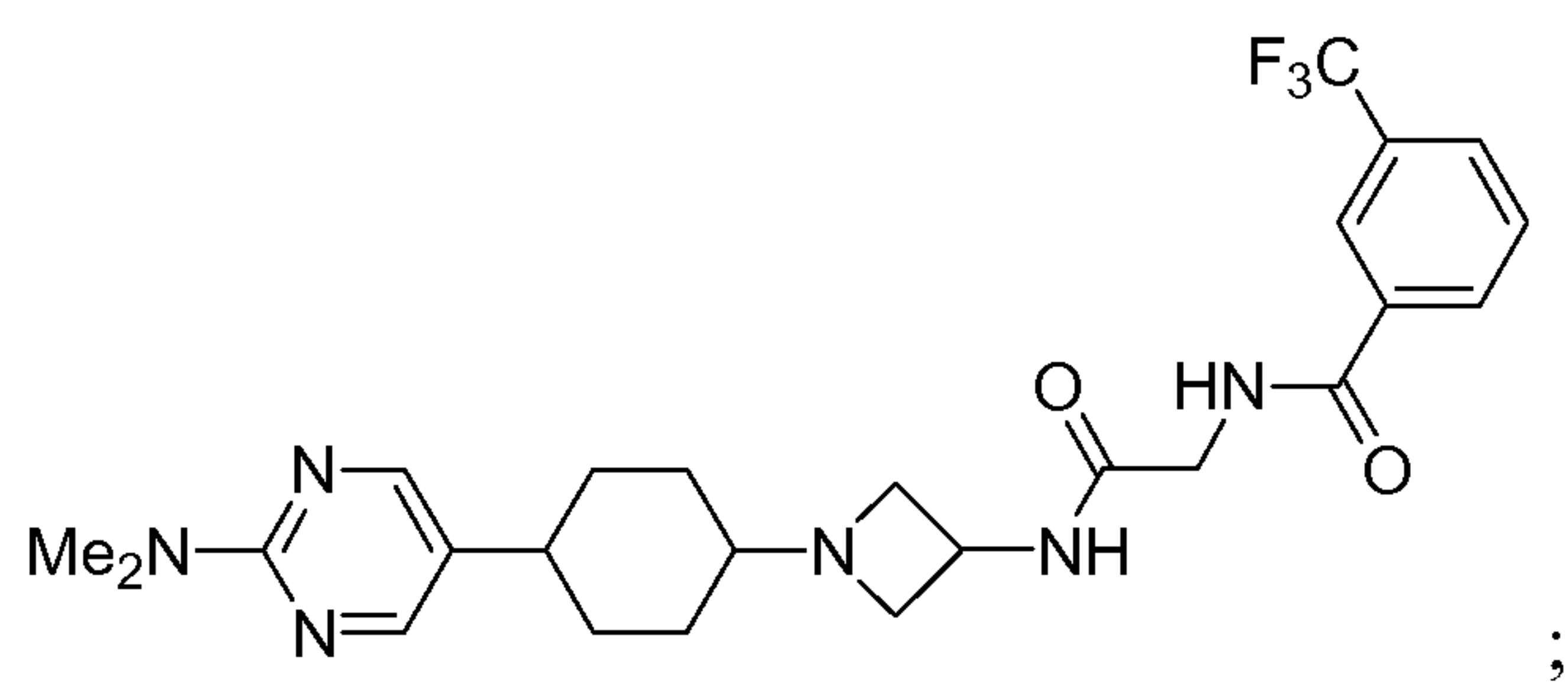
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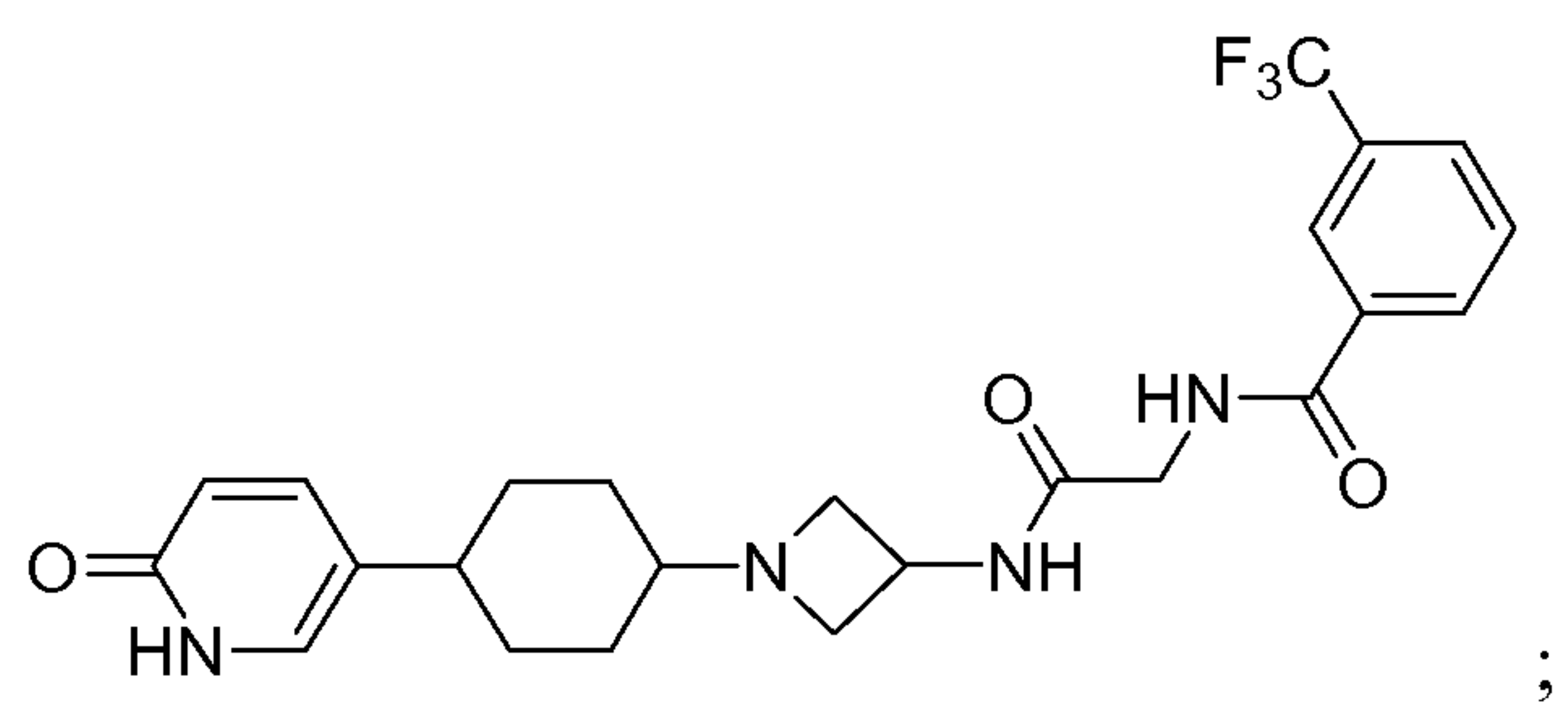
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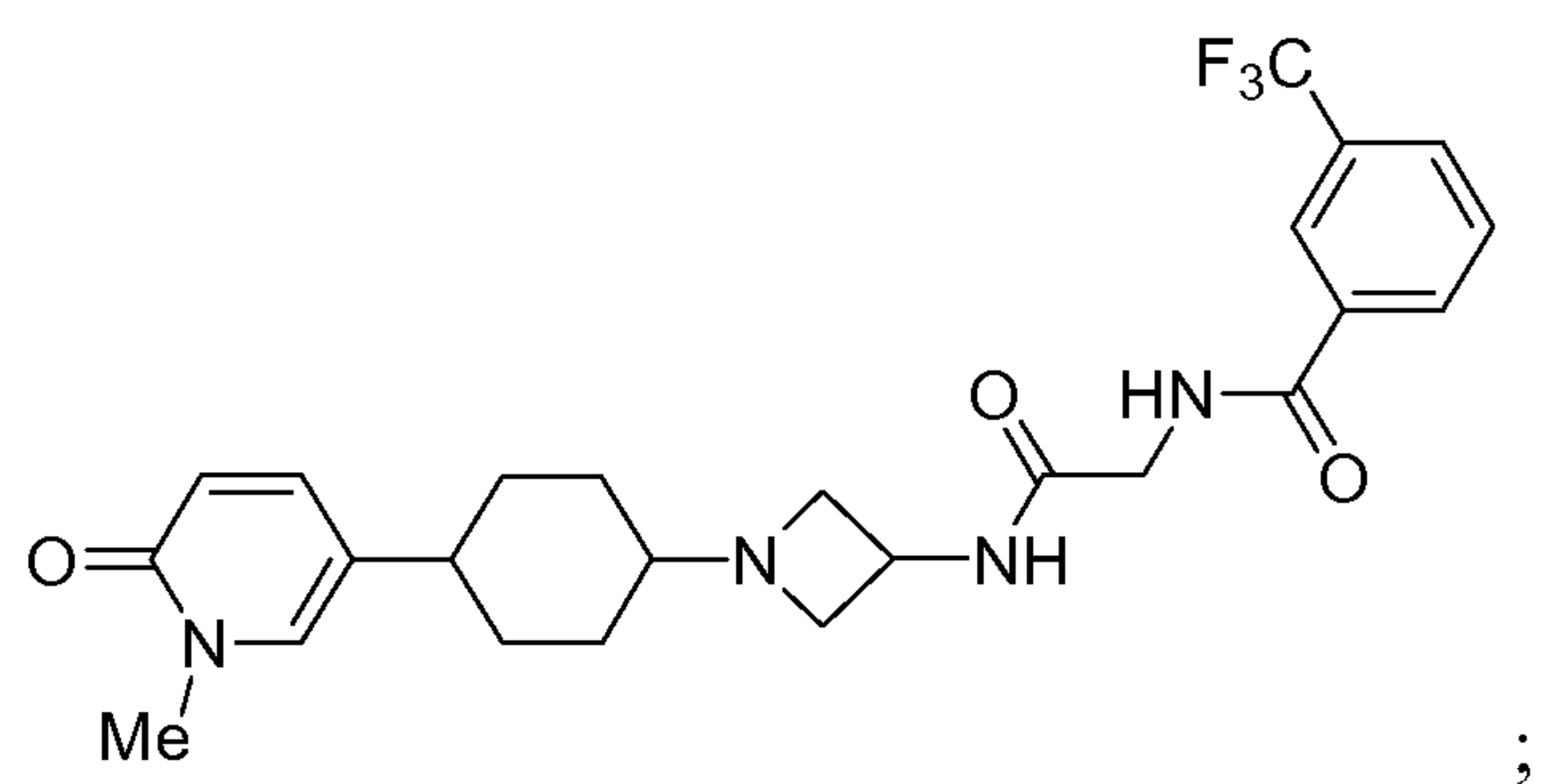
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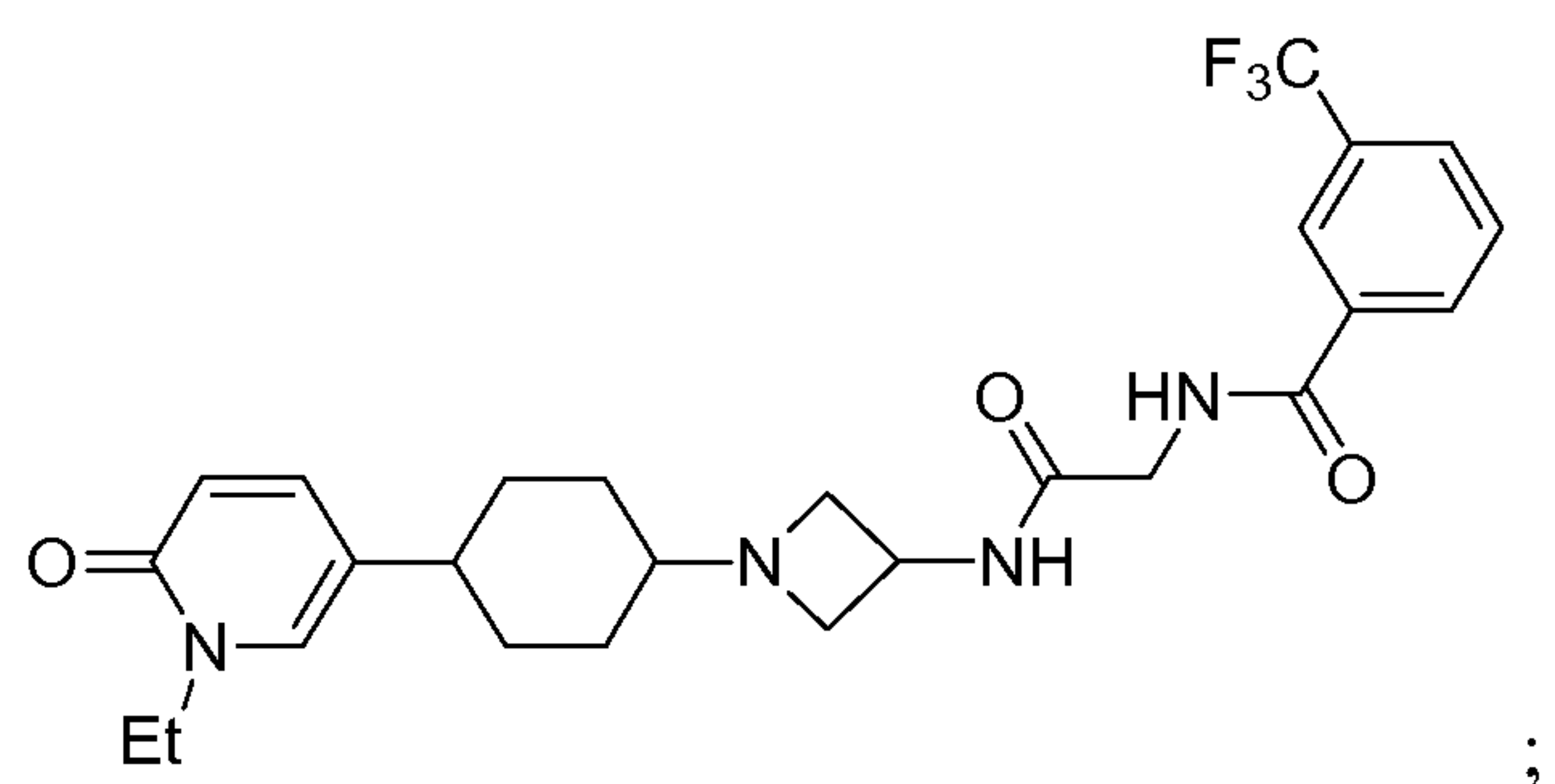
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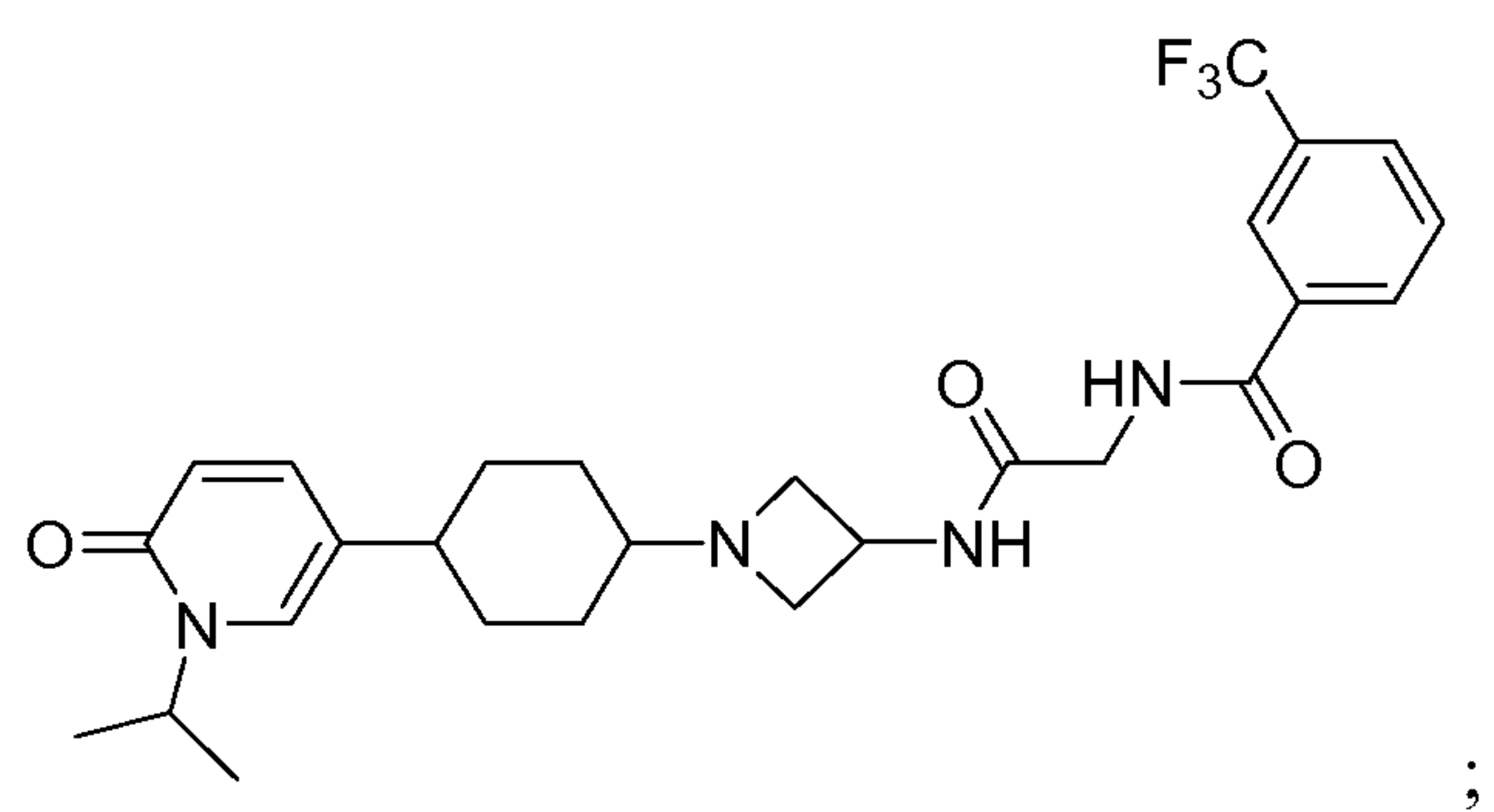
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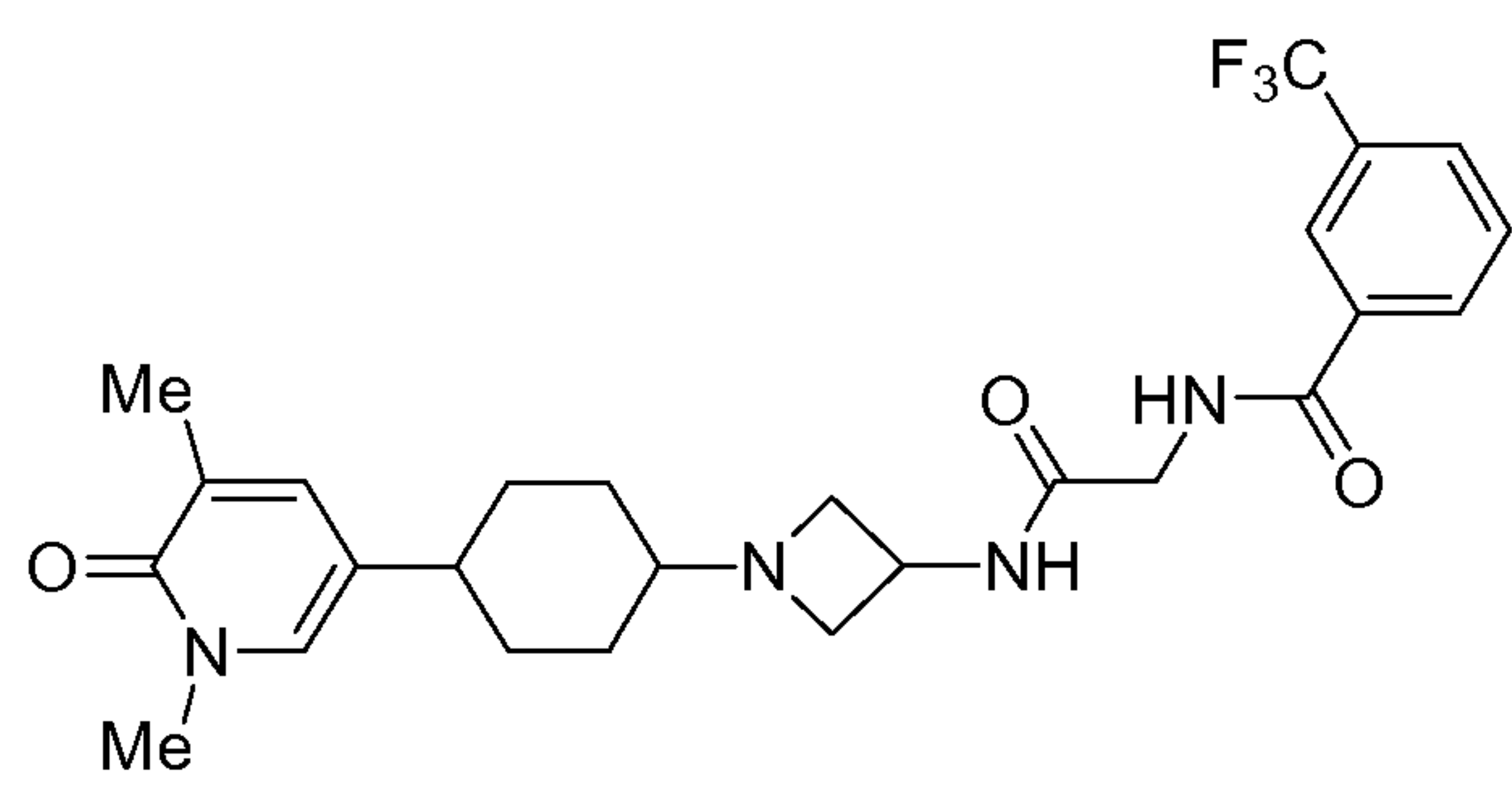
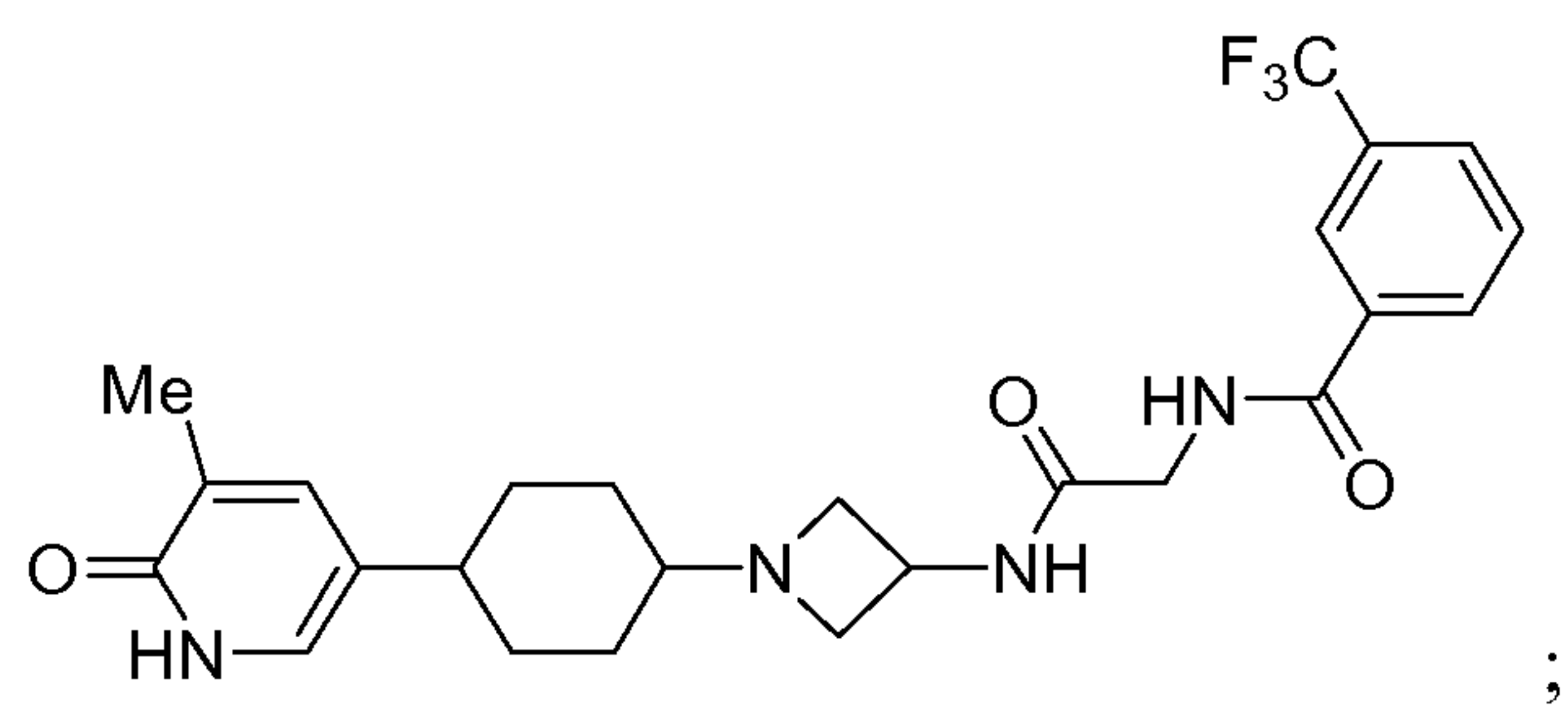
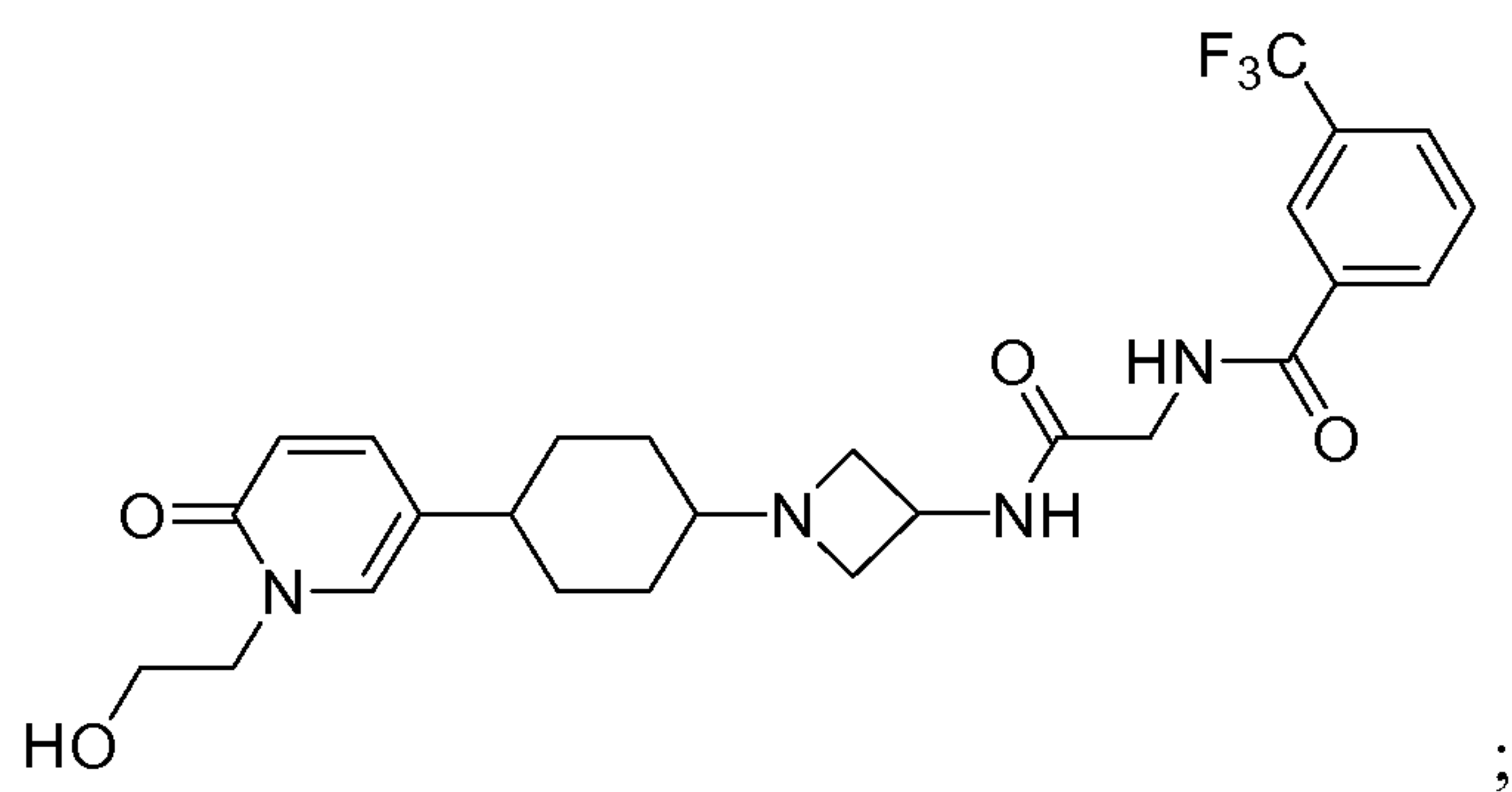
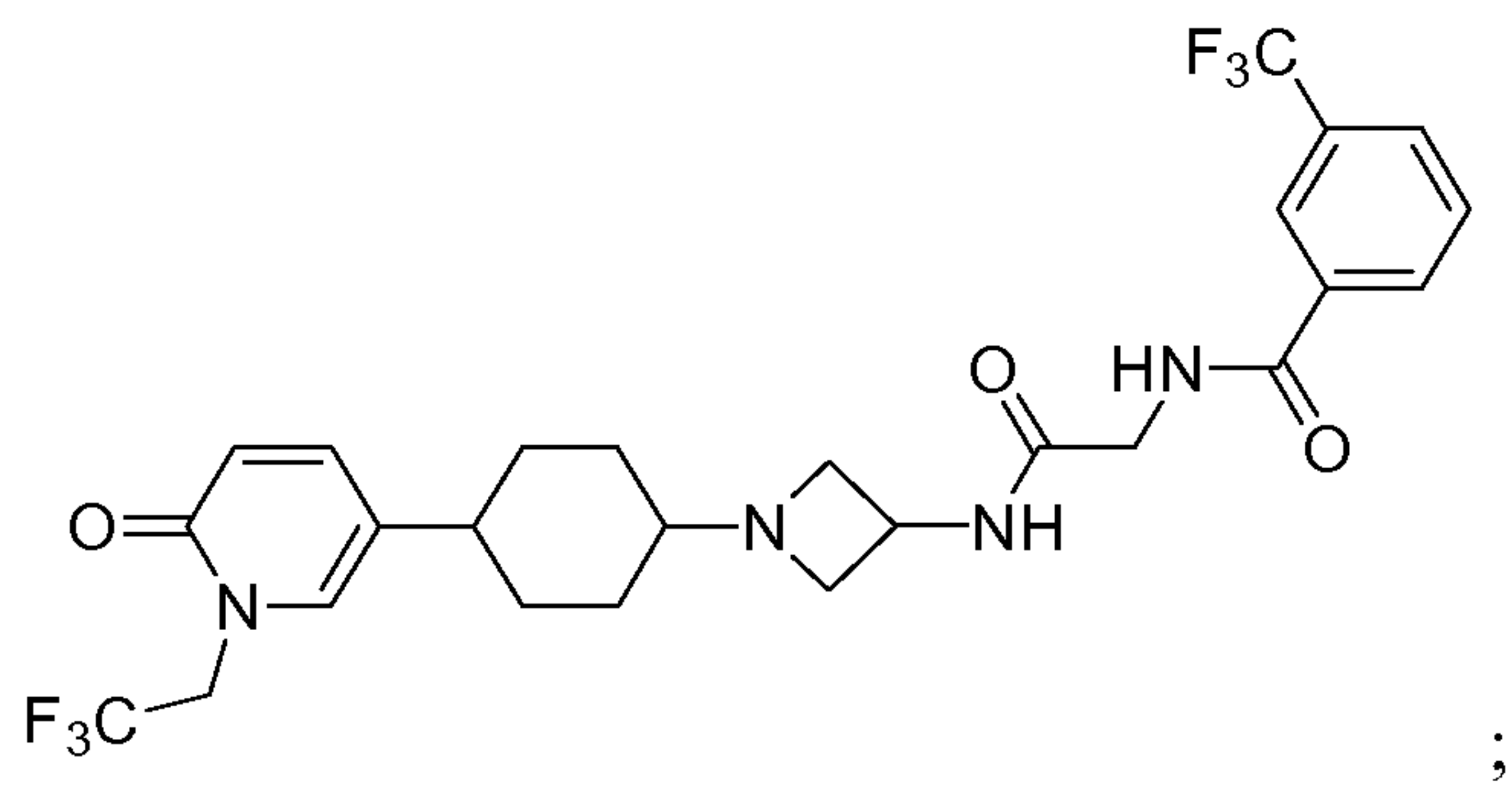
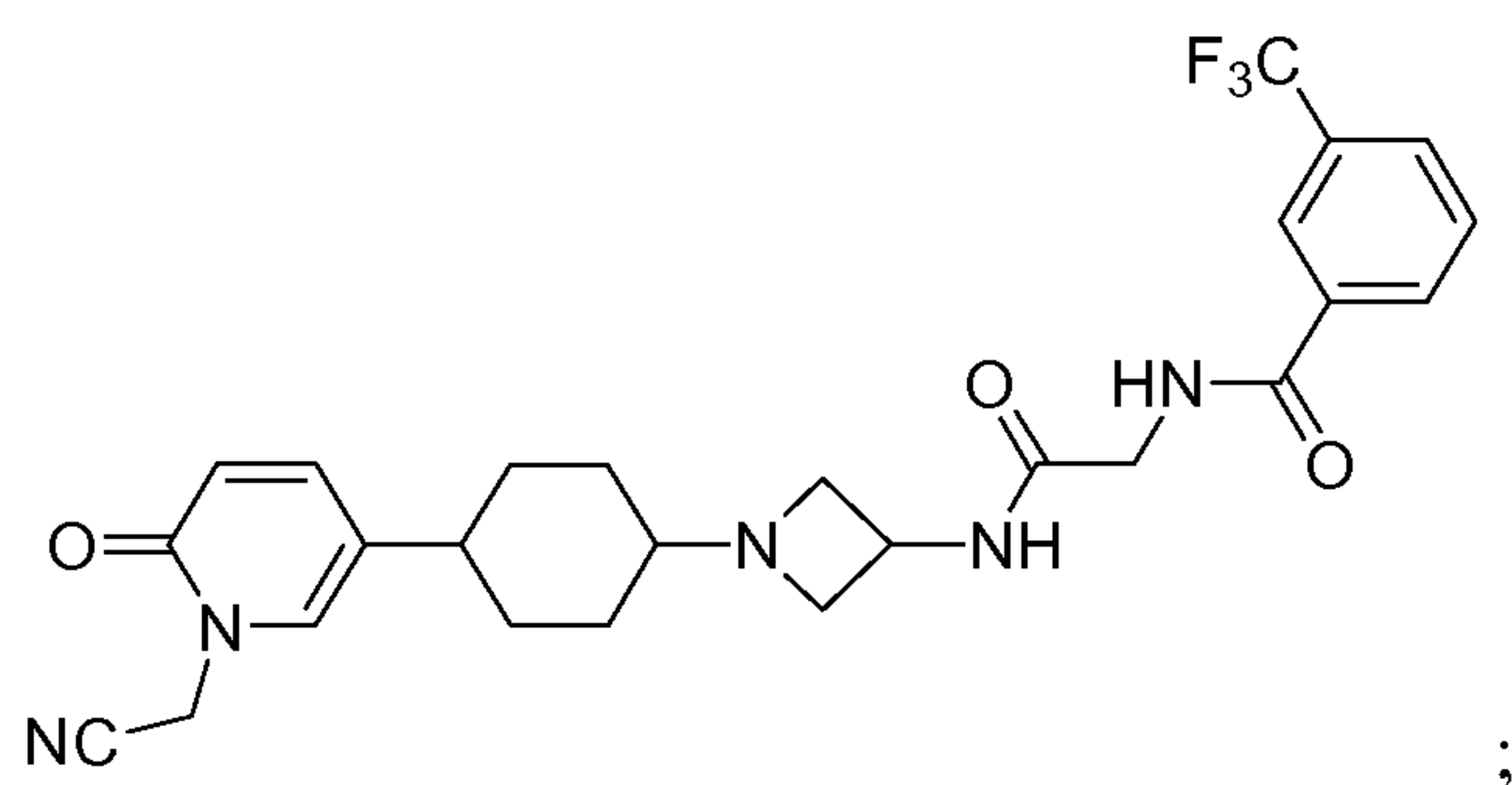


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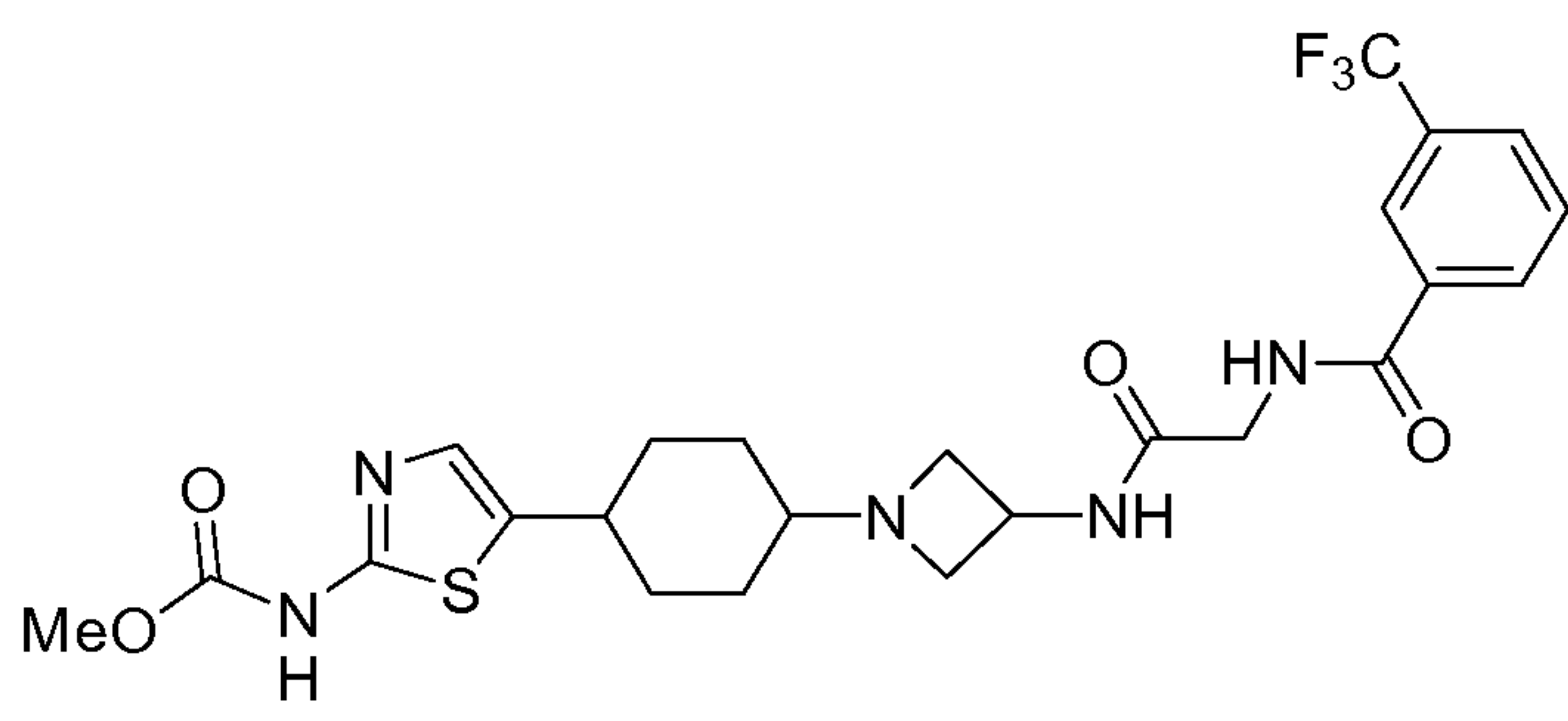
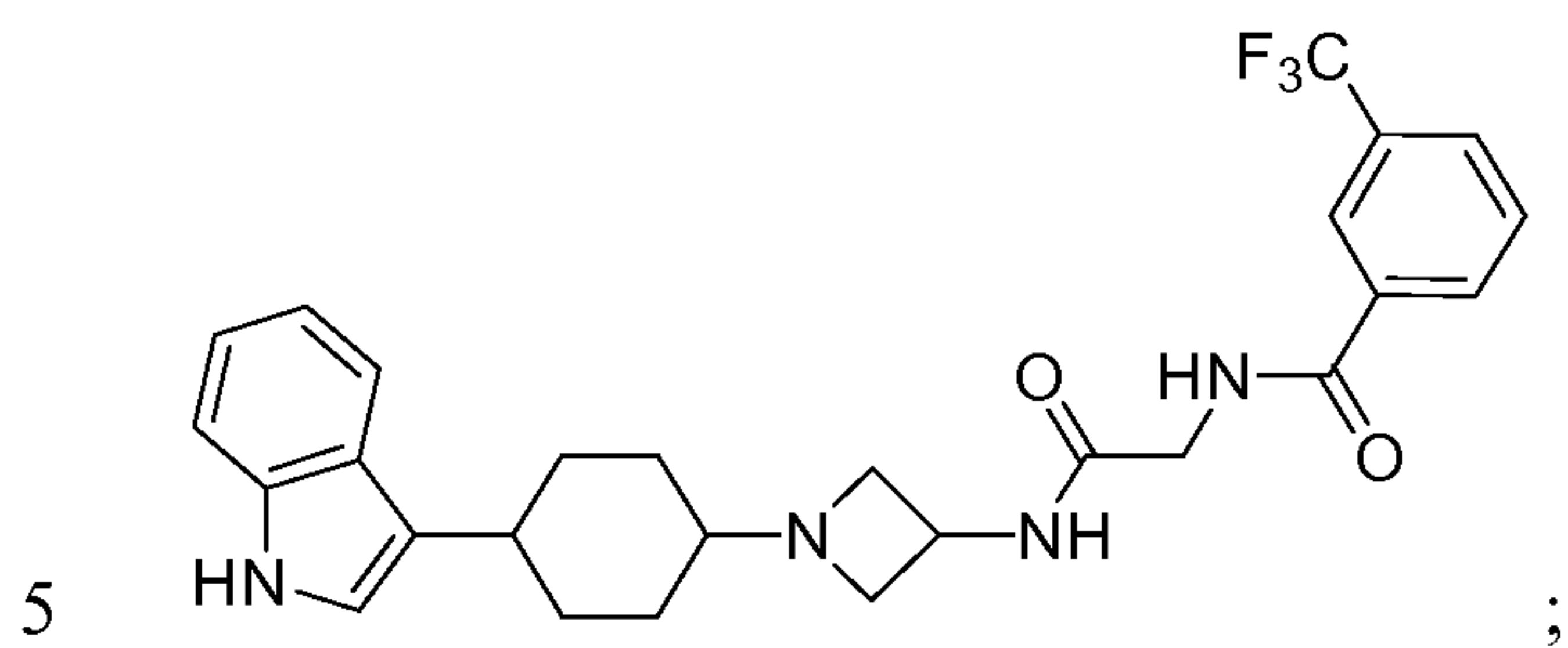
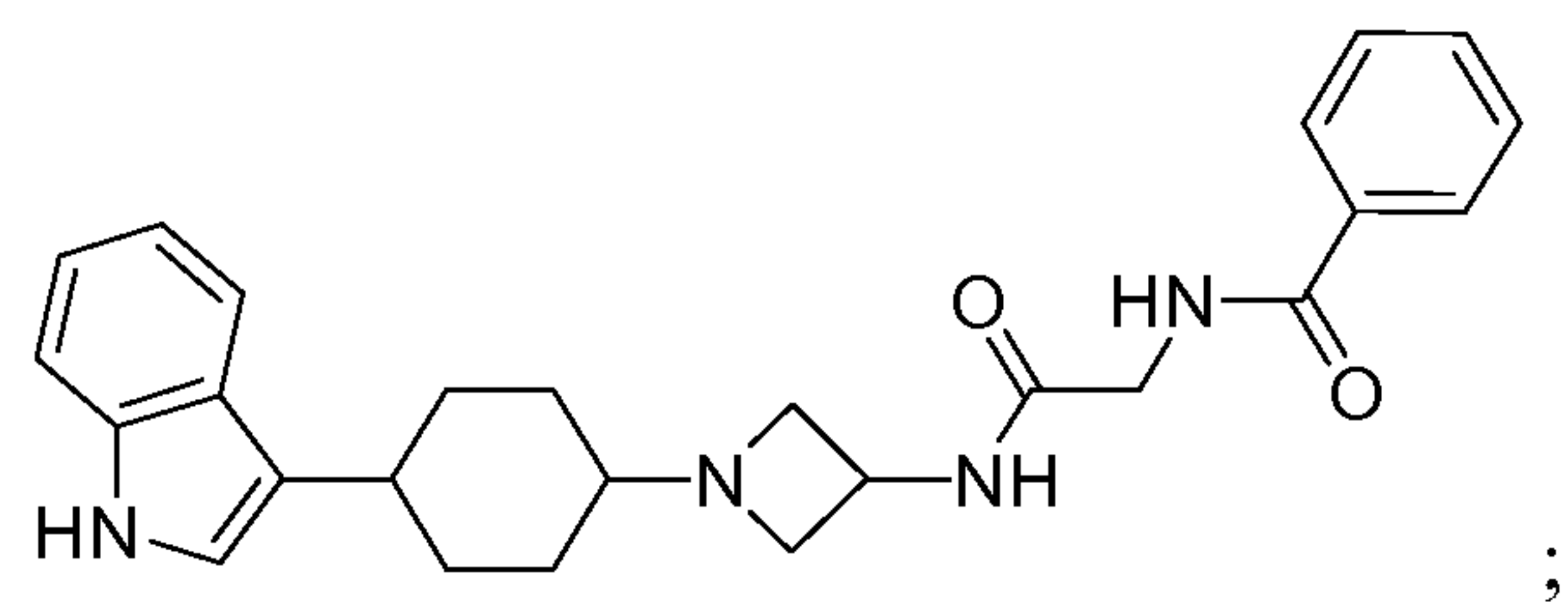
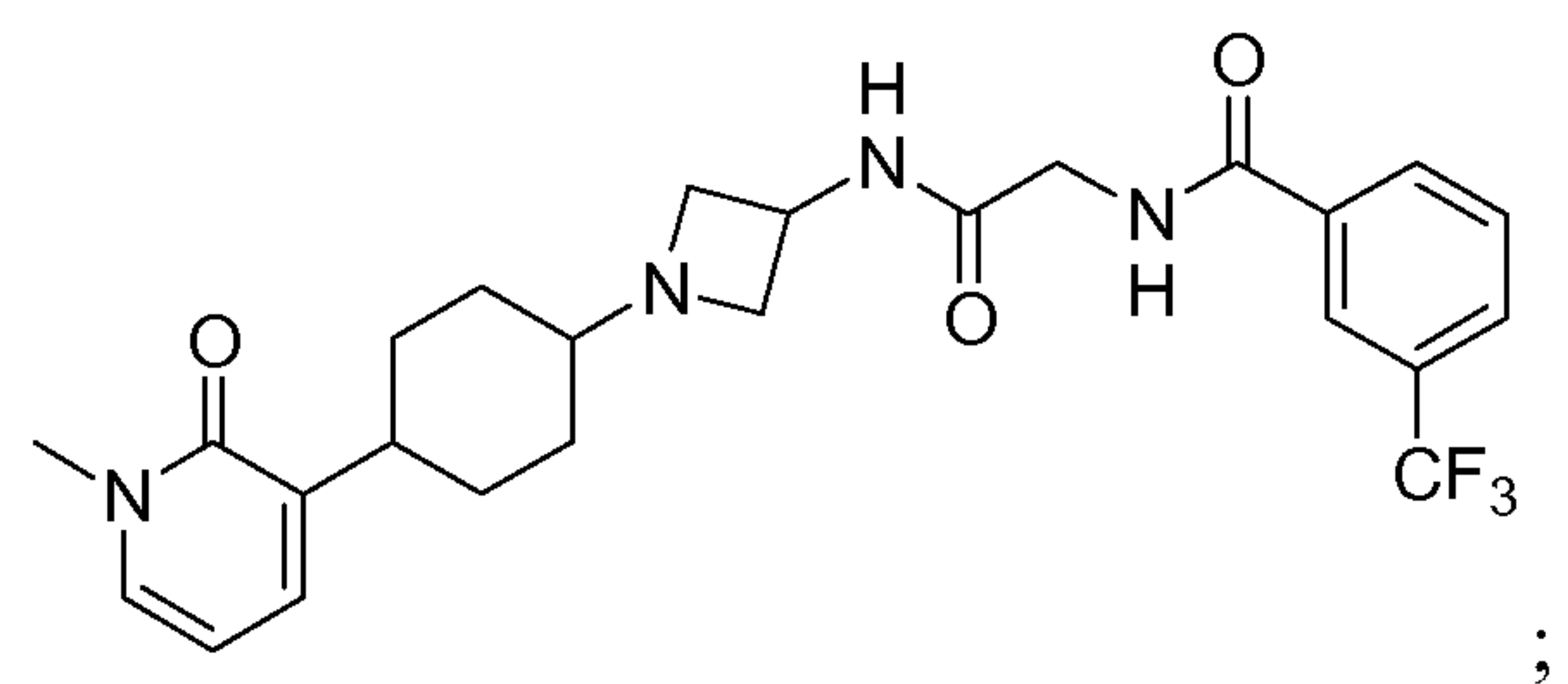
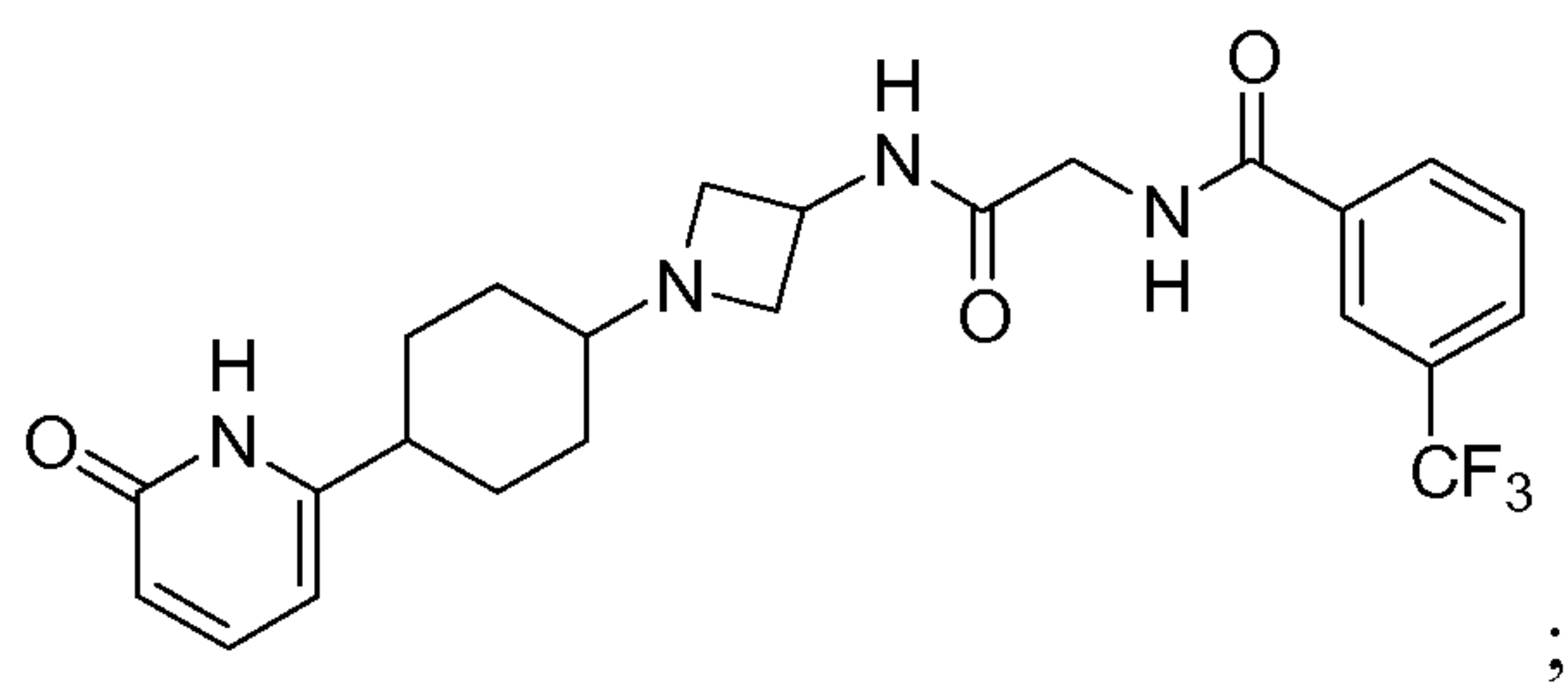
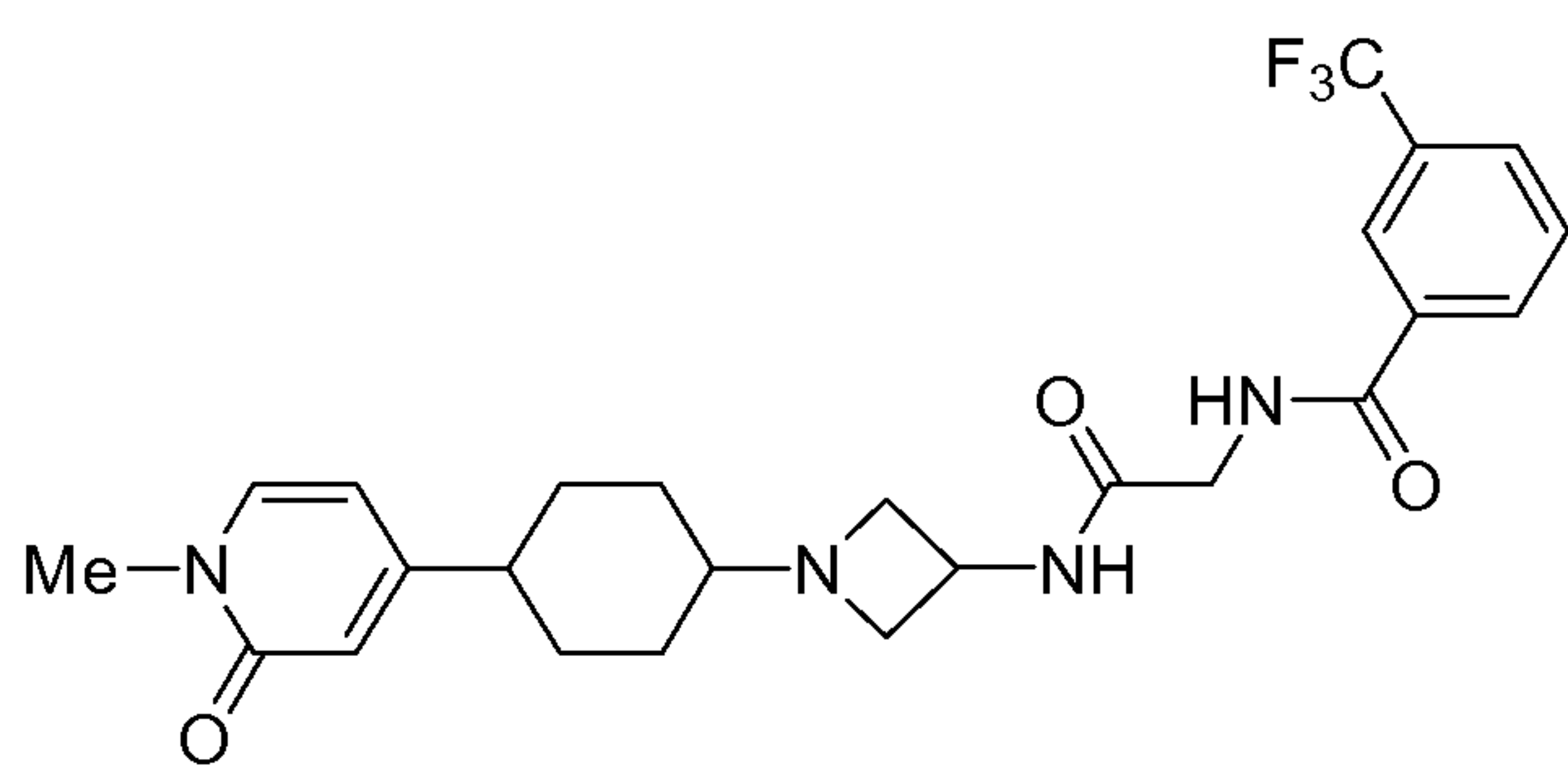


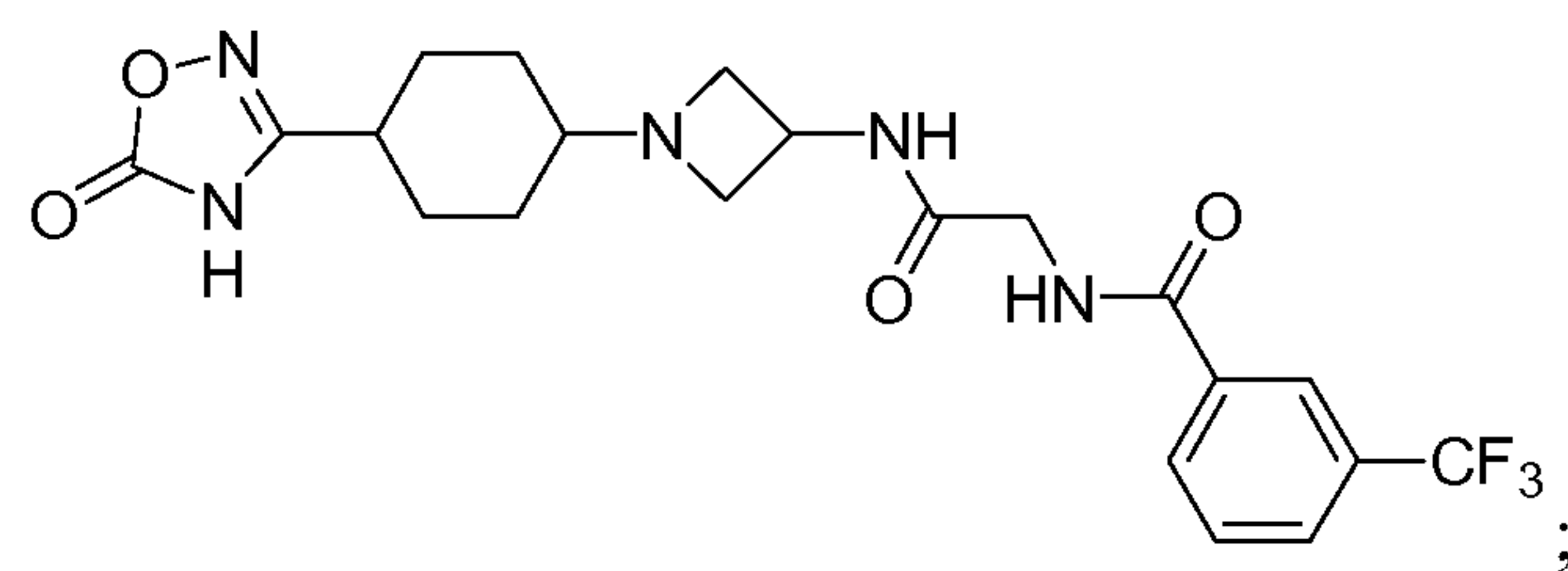
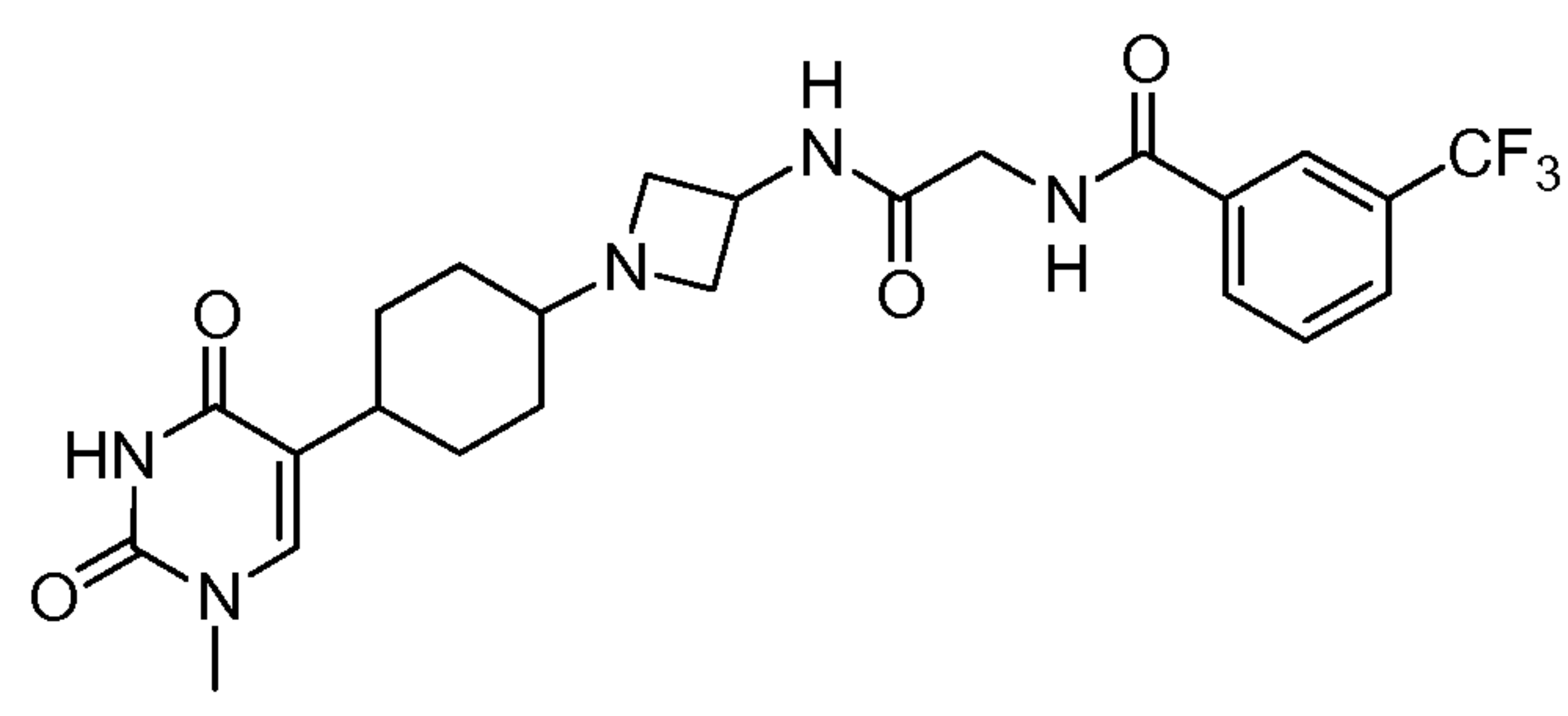
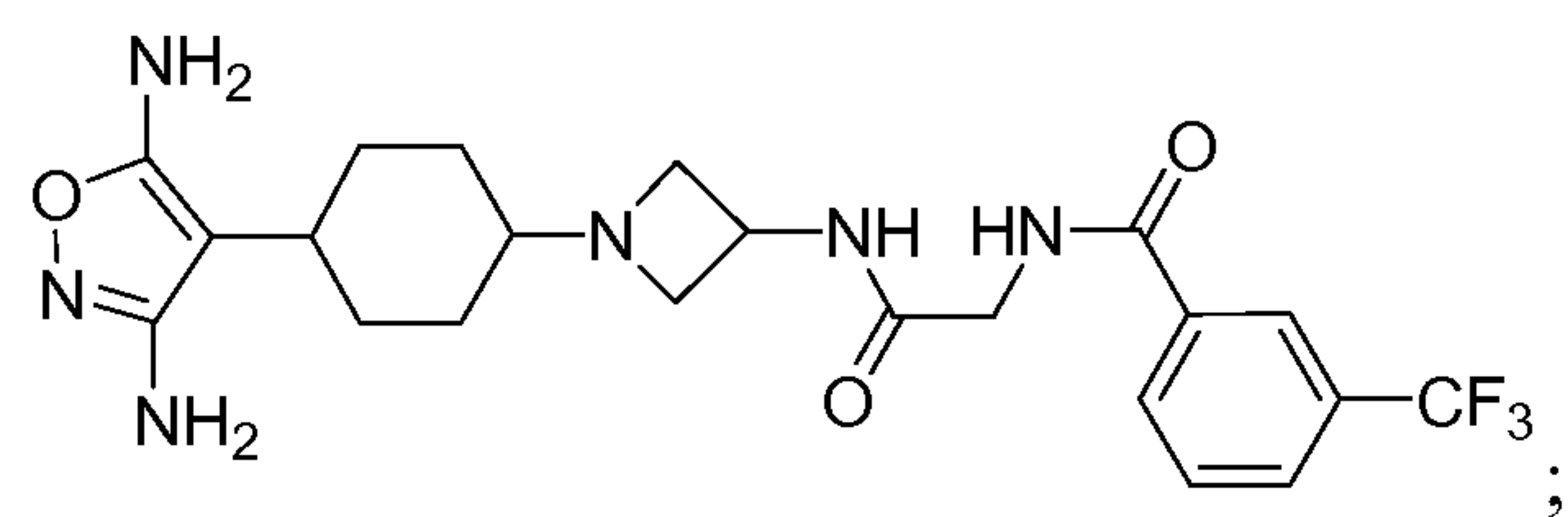
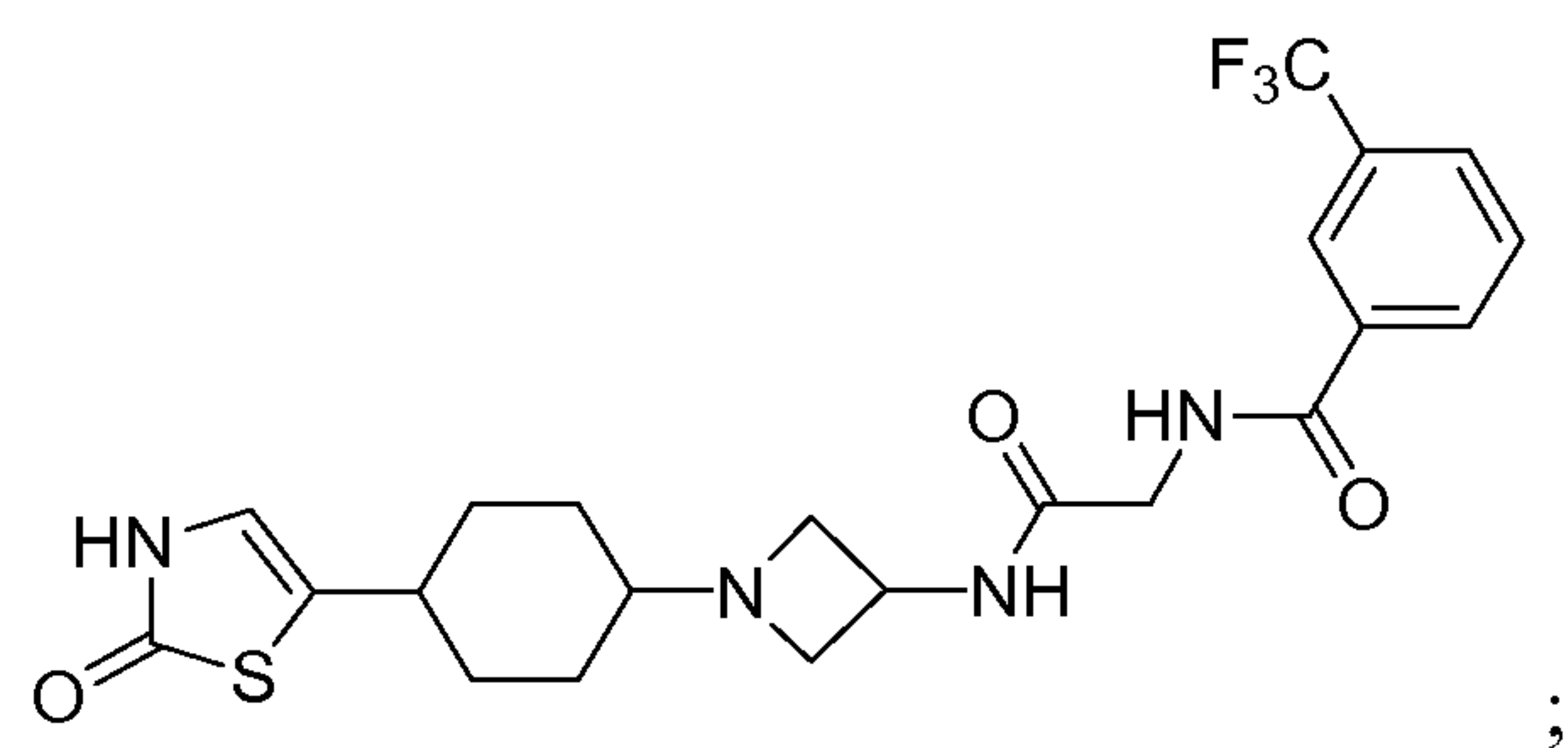
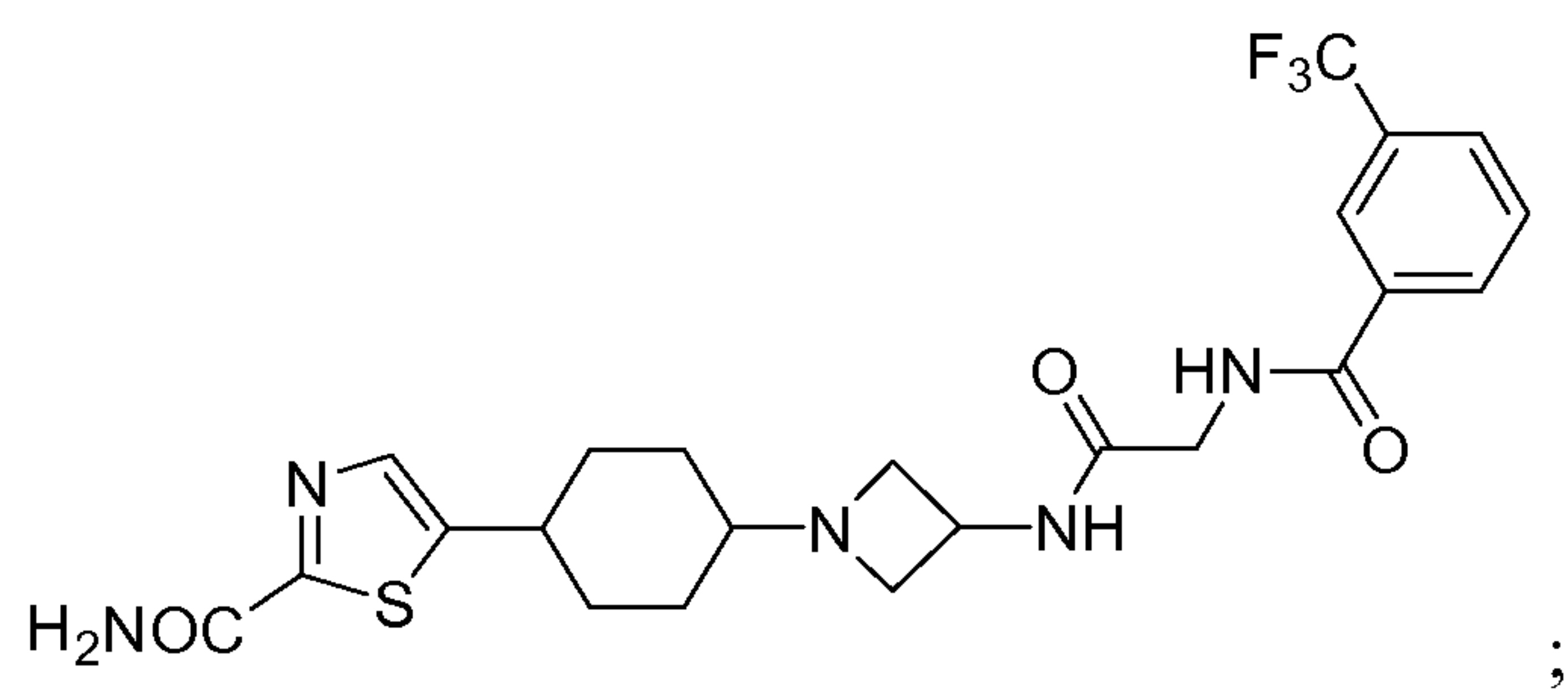
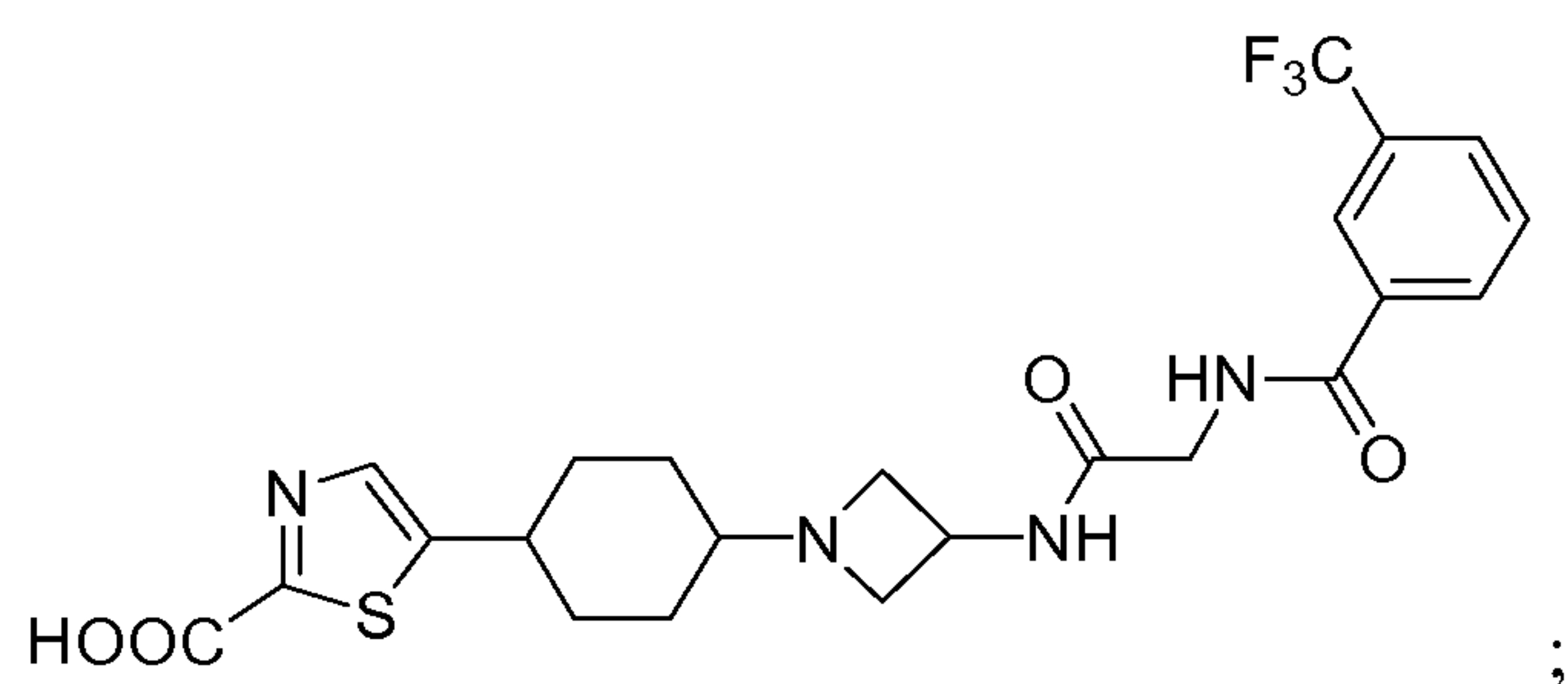
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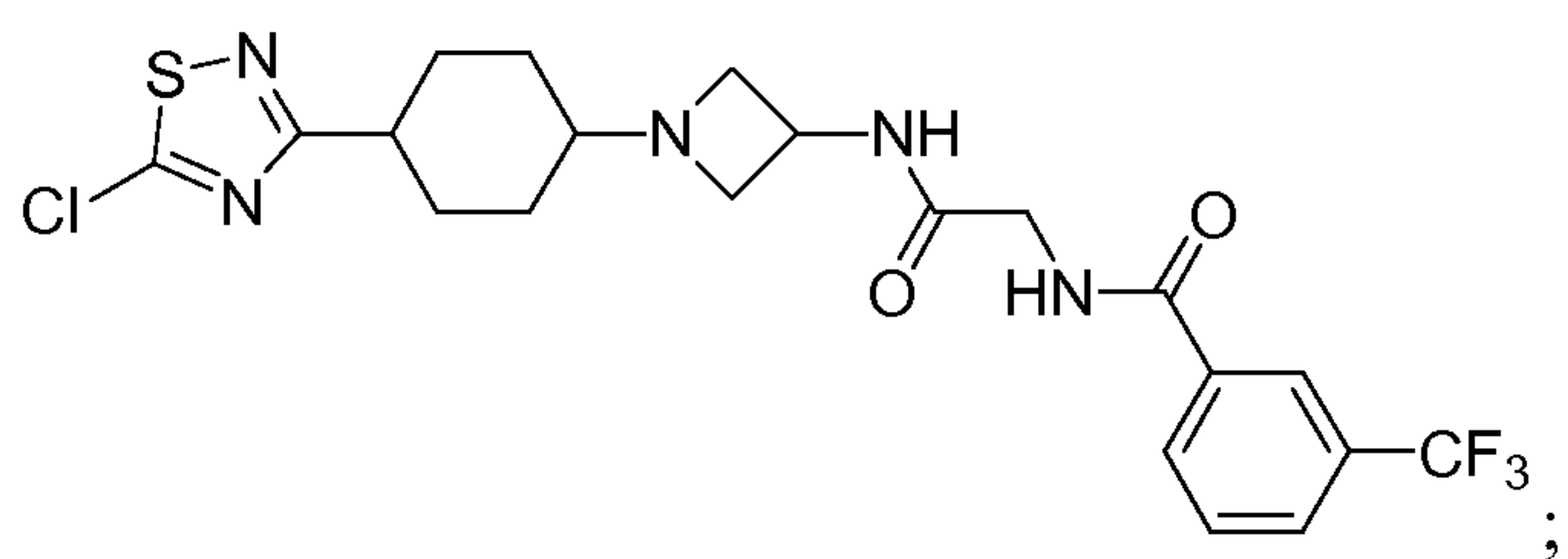
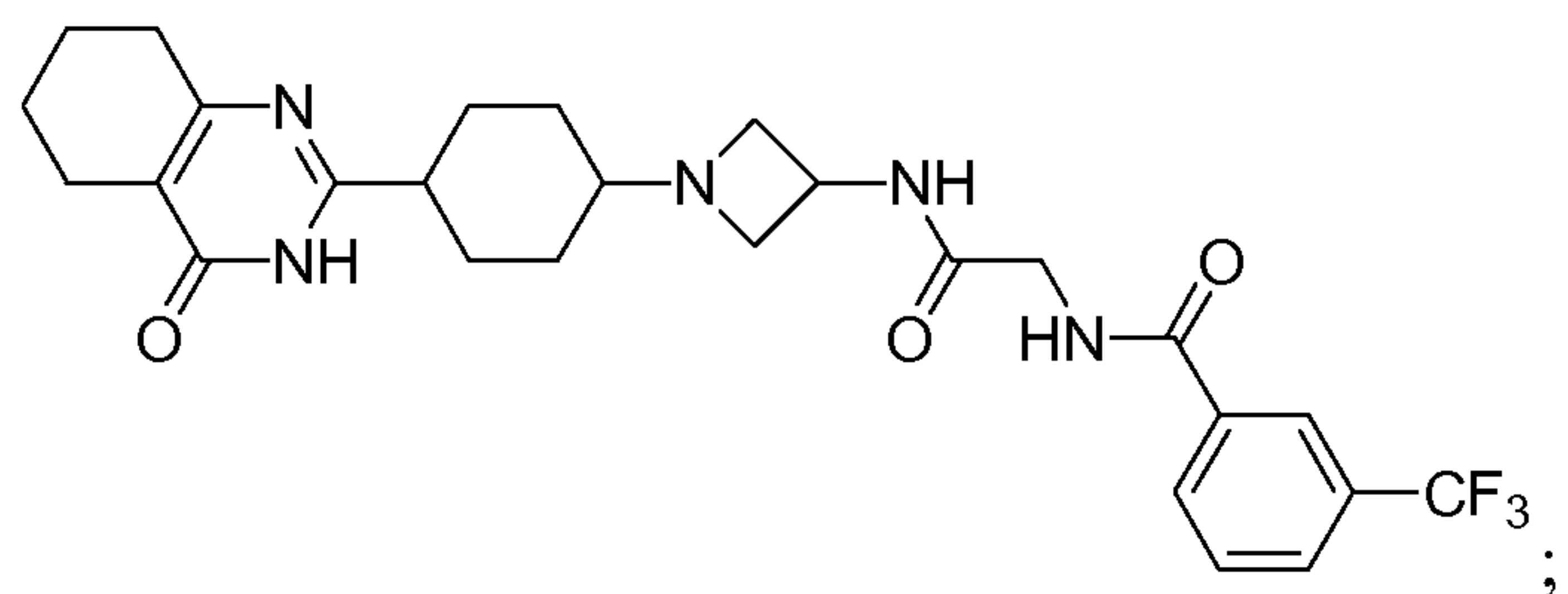
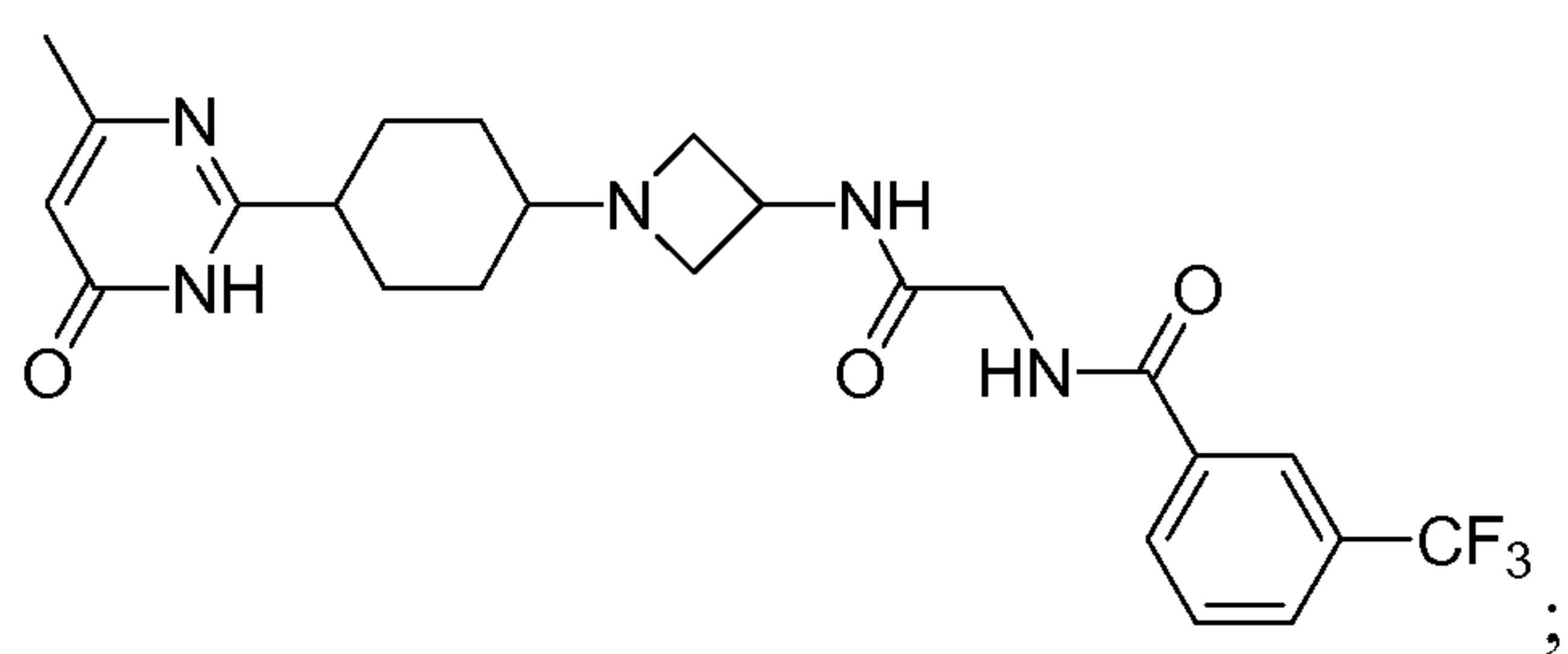
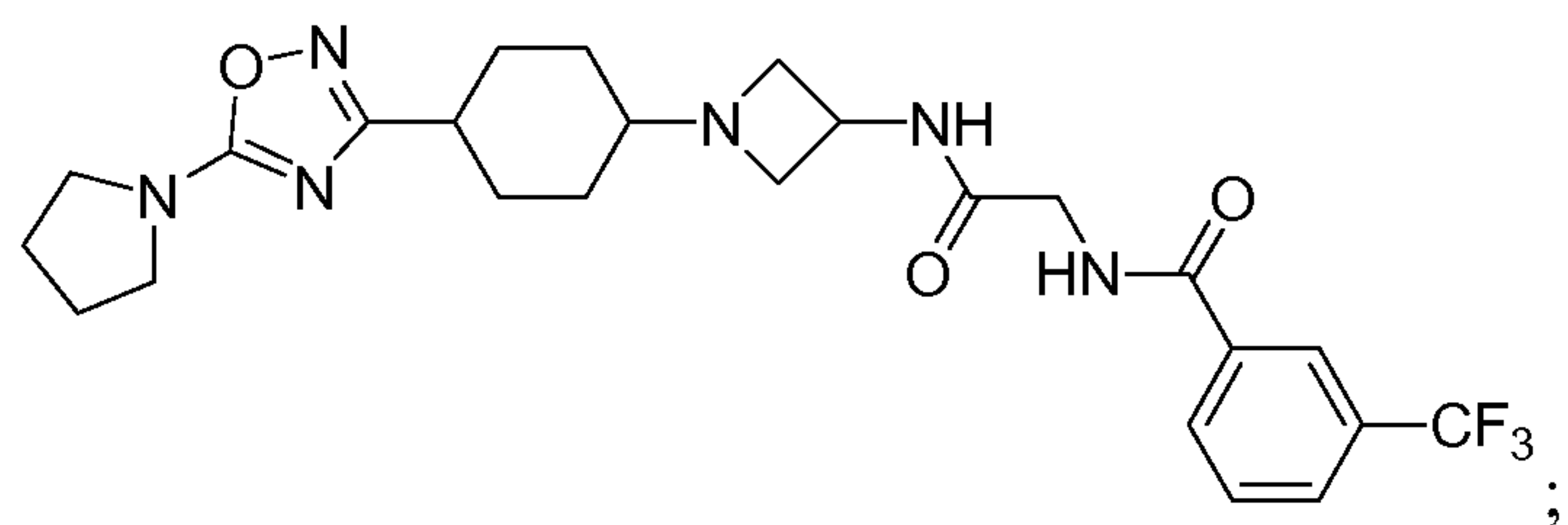
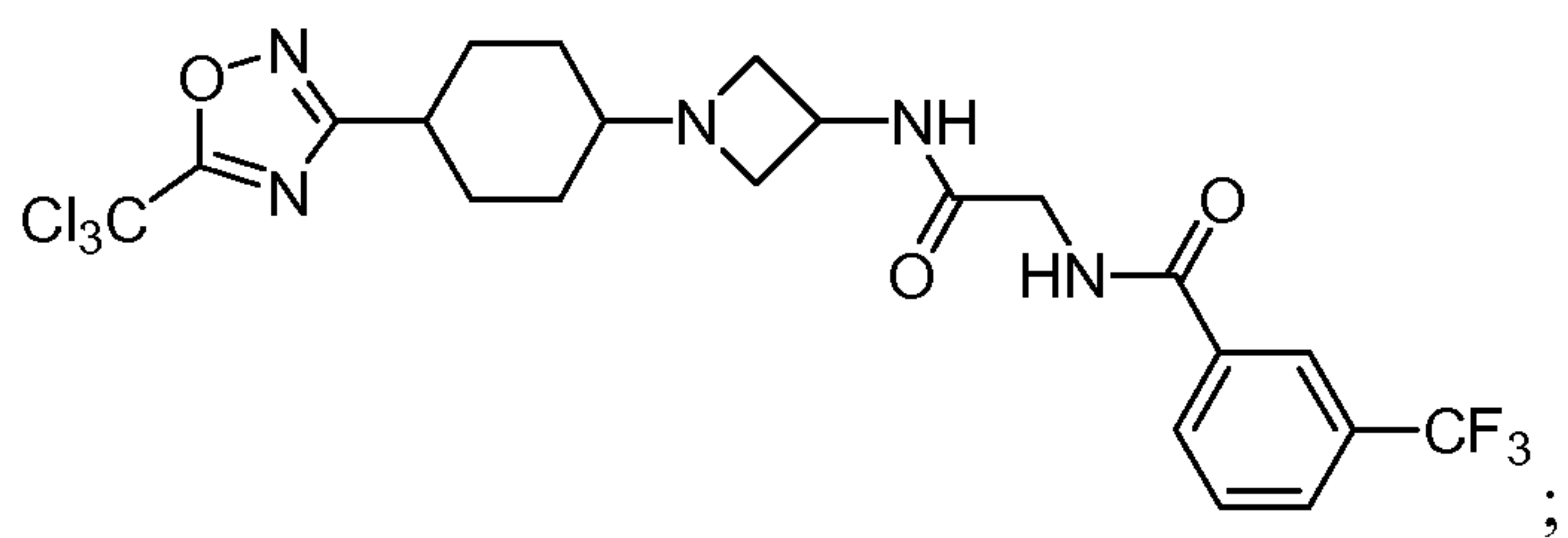
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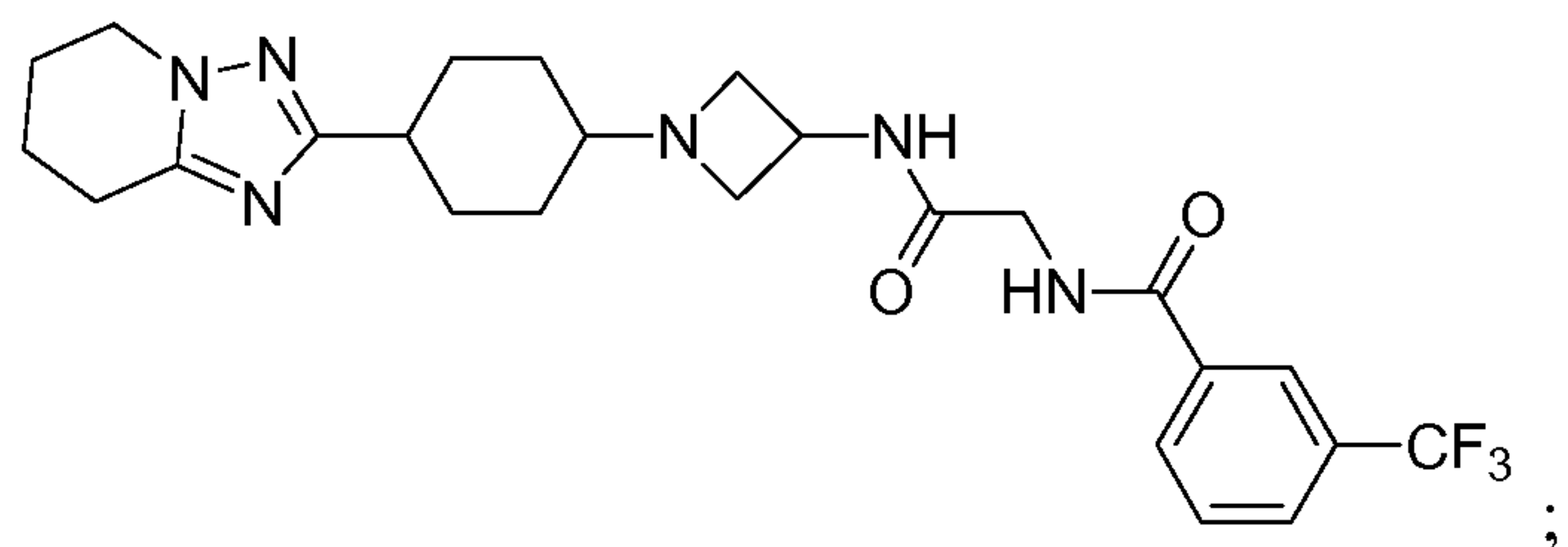
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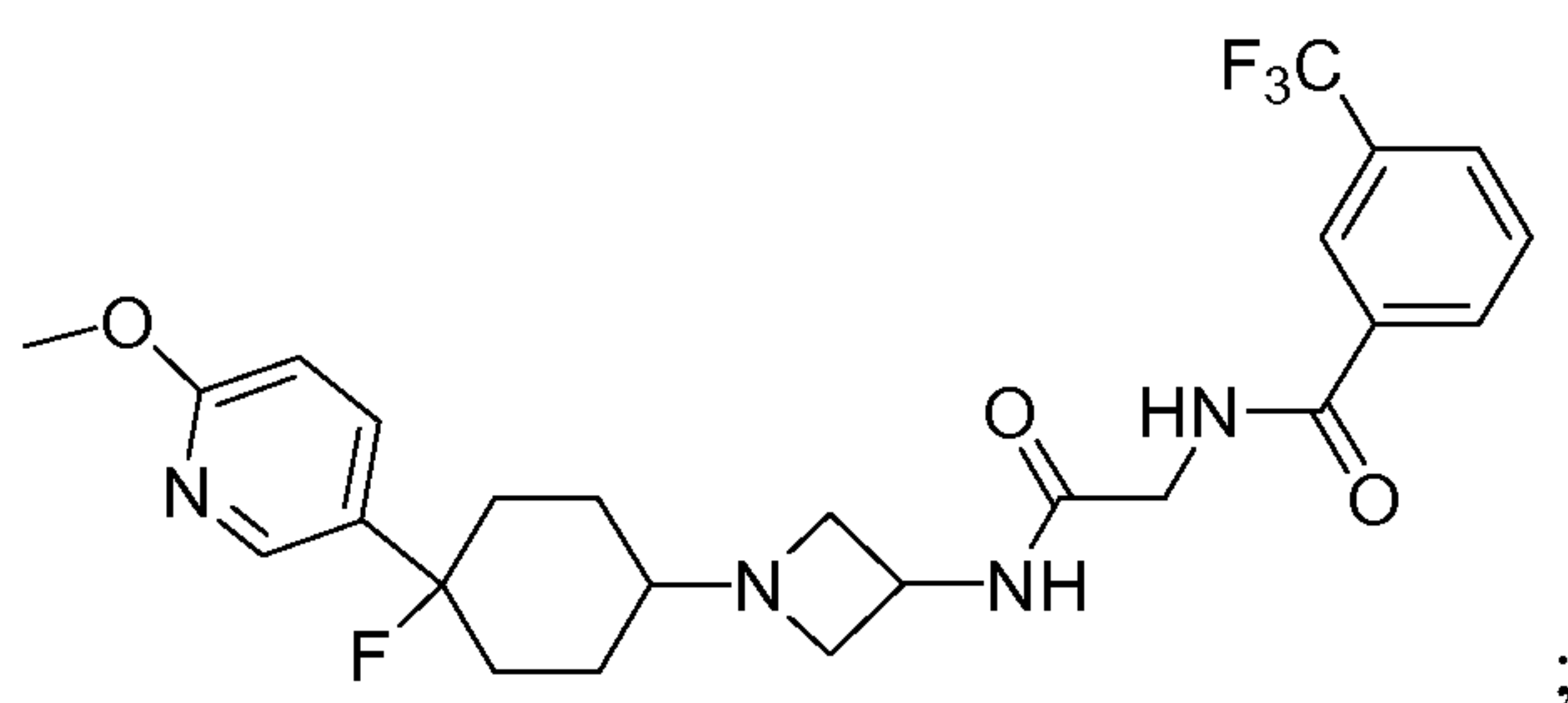






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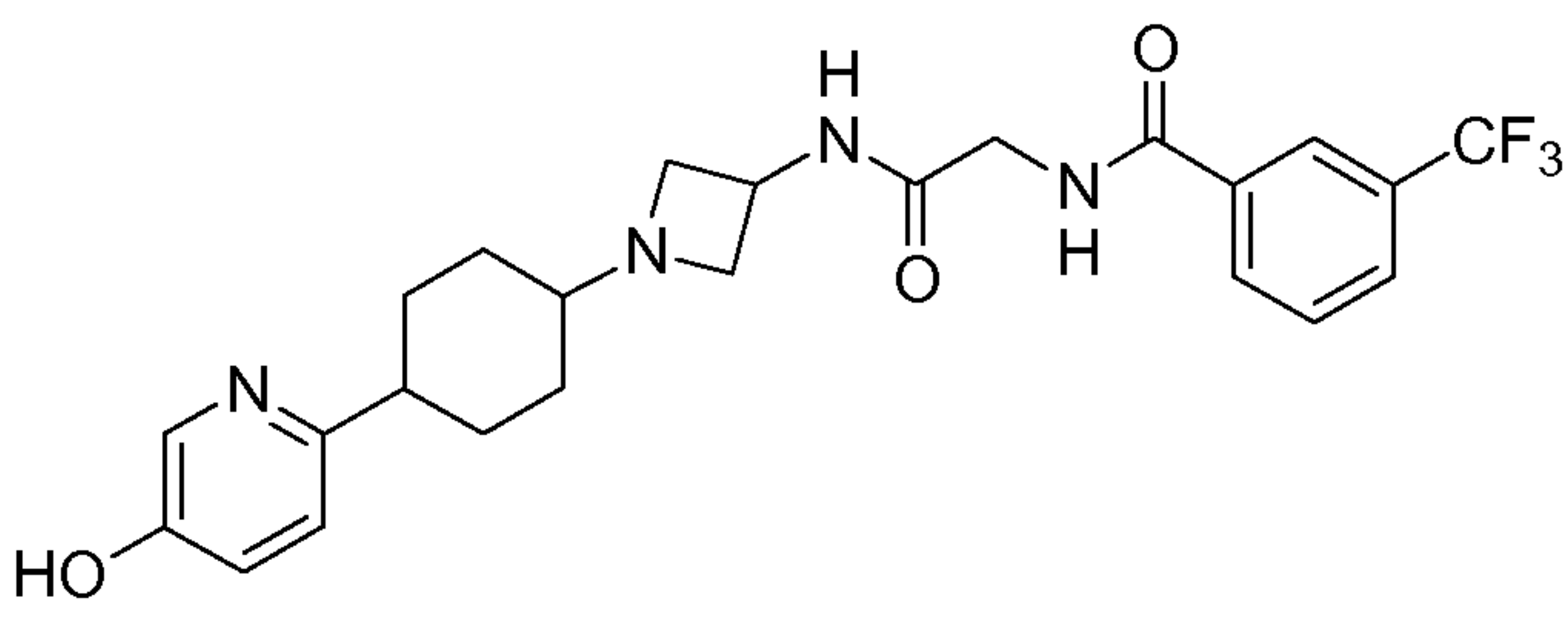
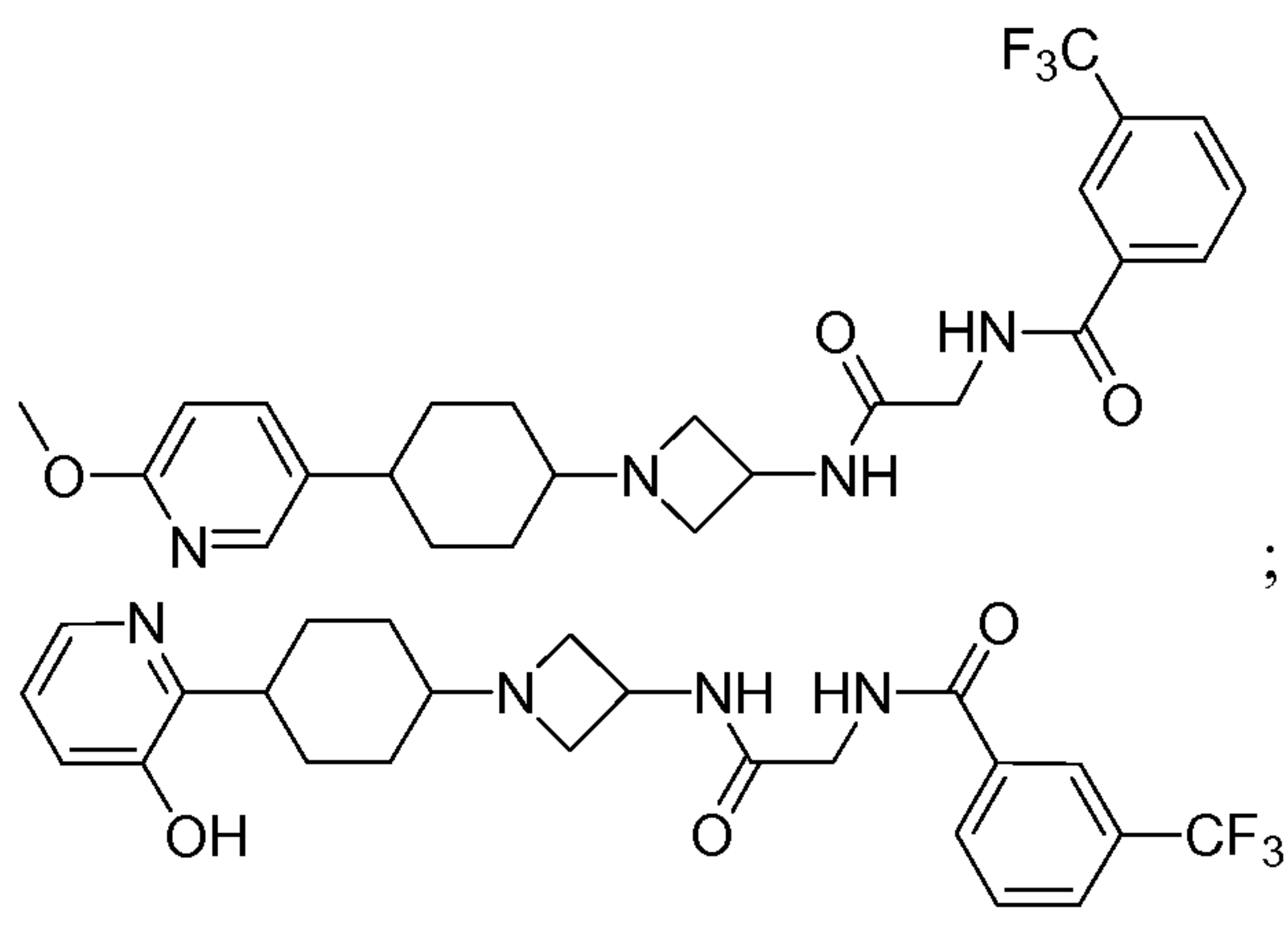




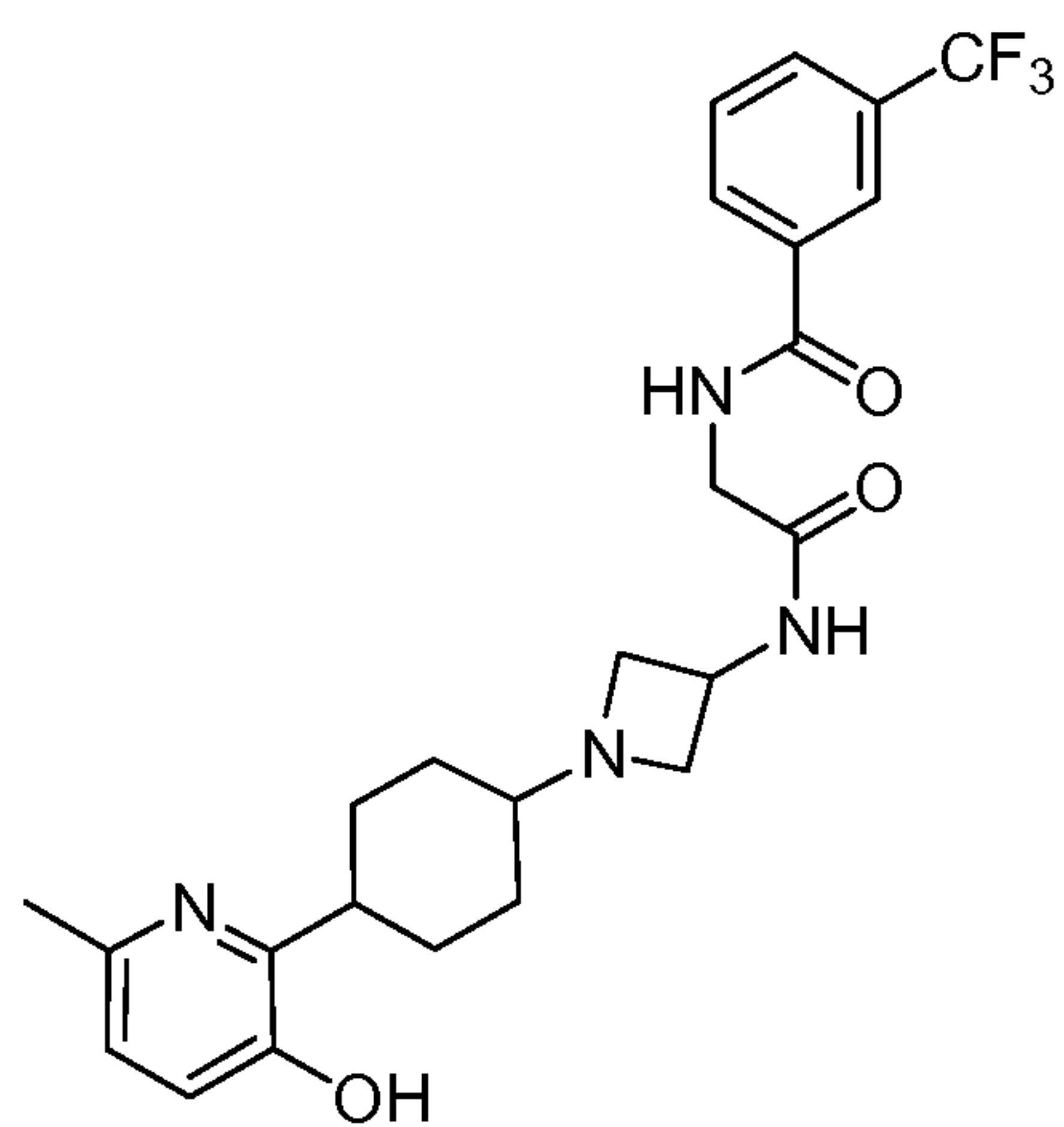
and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

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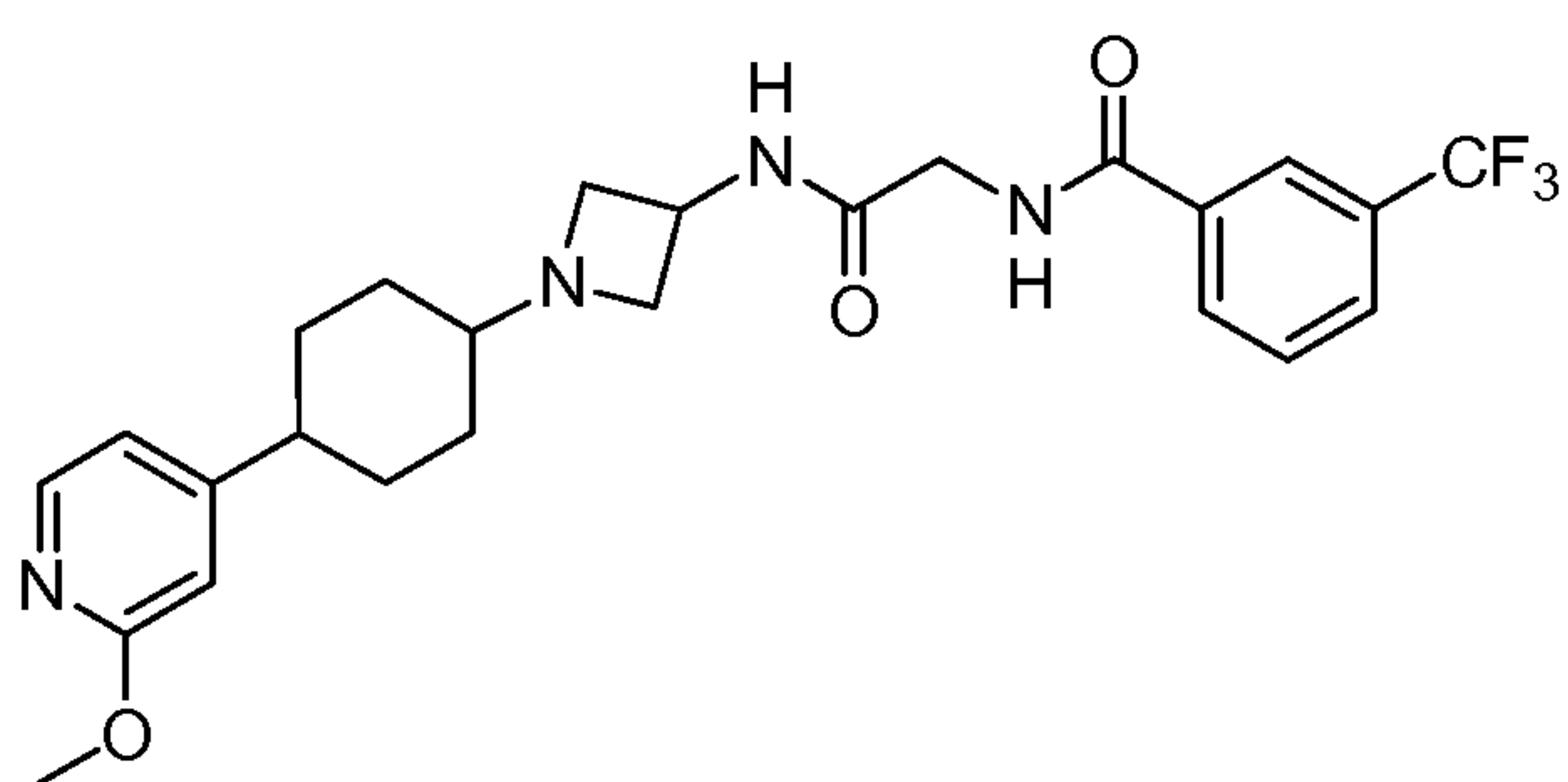
Another embodiment of the invention is a compound selected from the group consisting of:



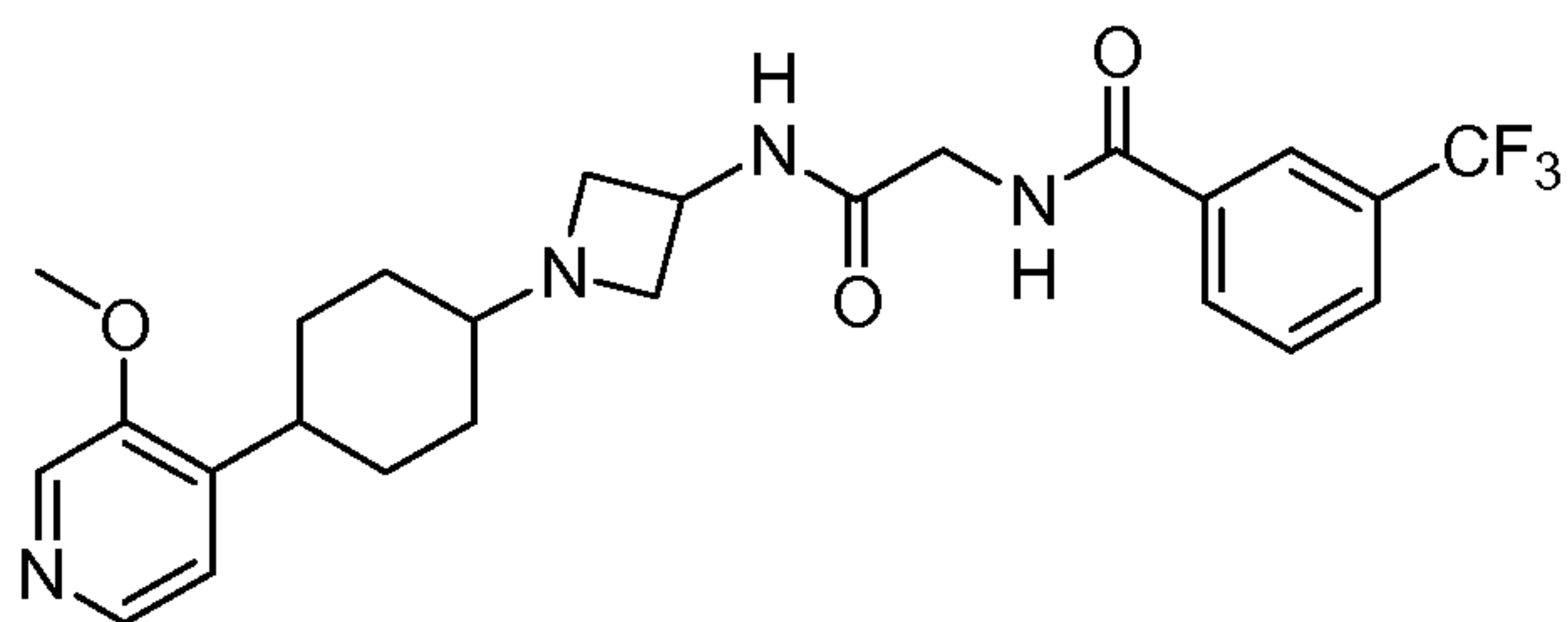
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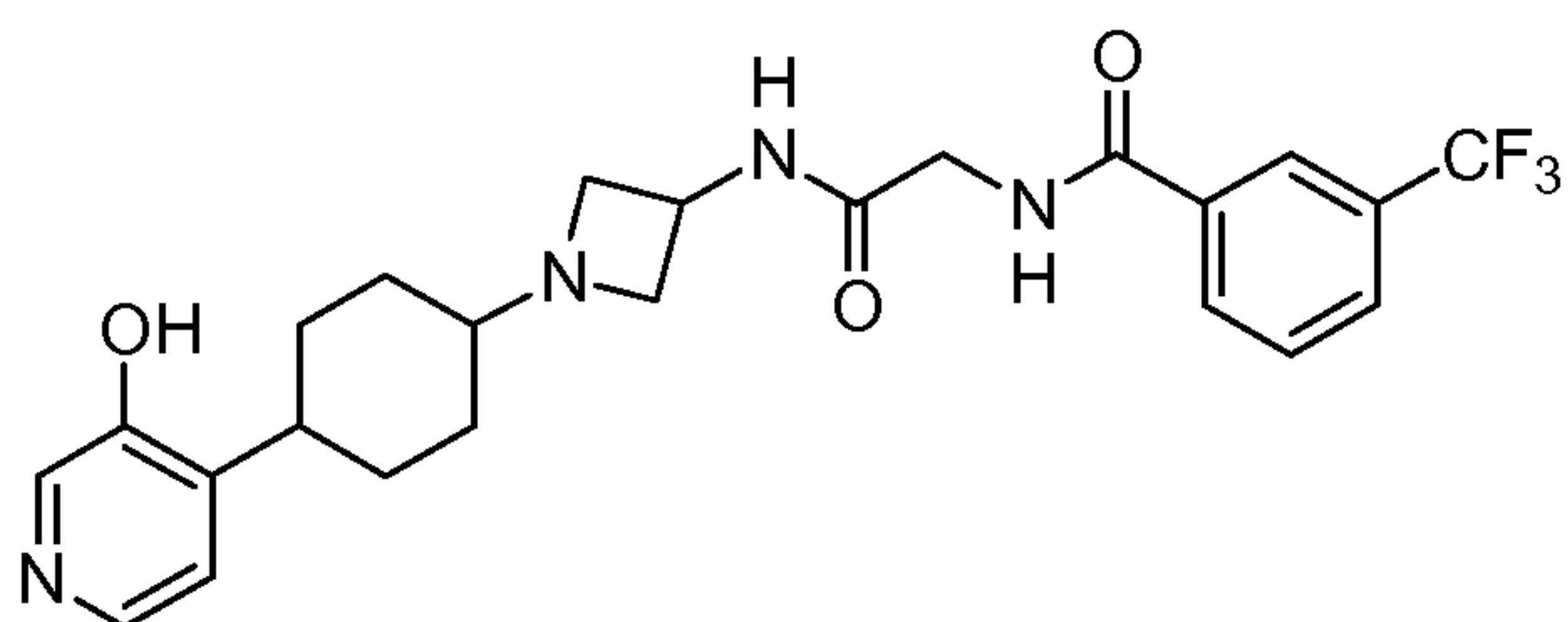
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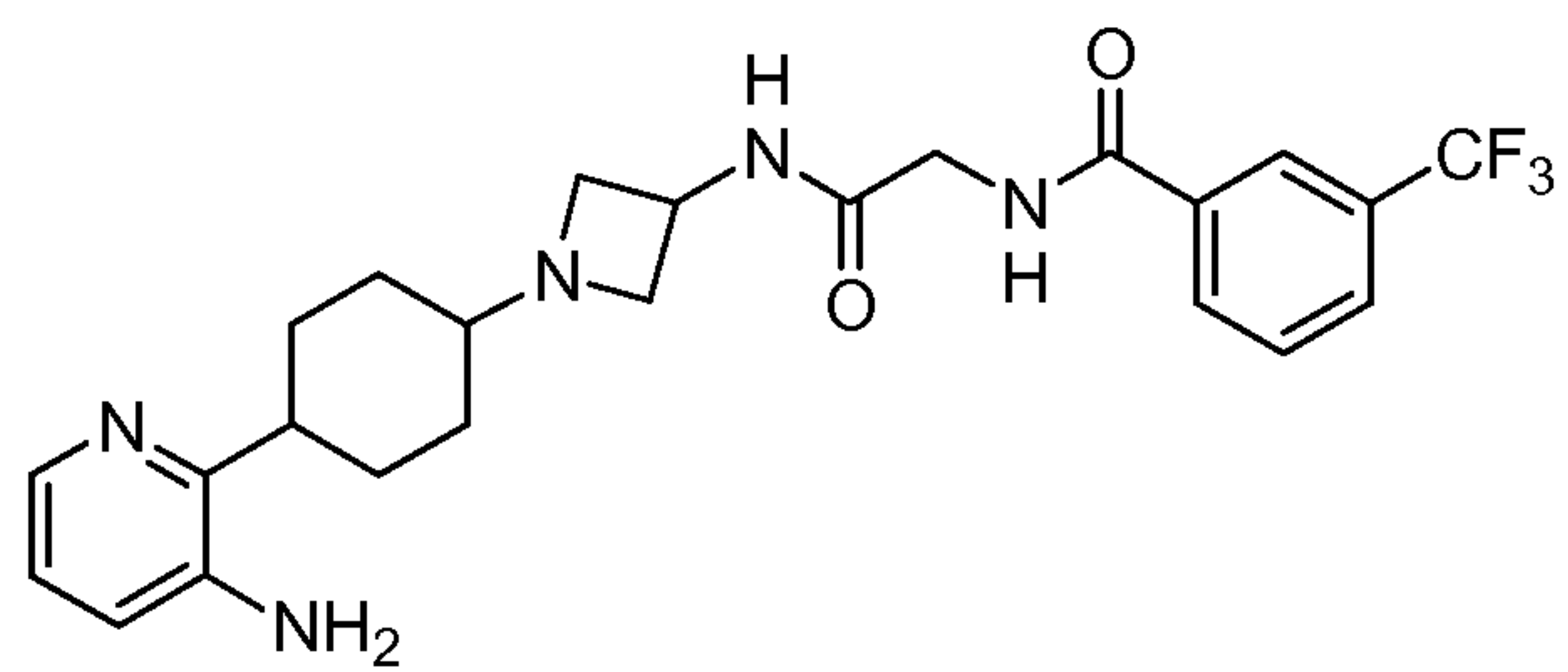
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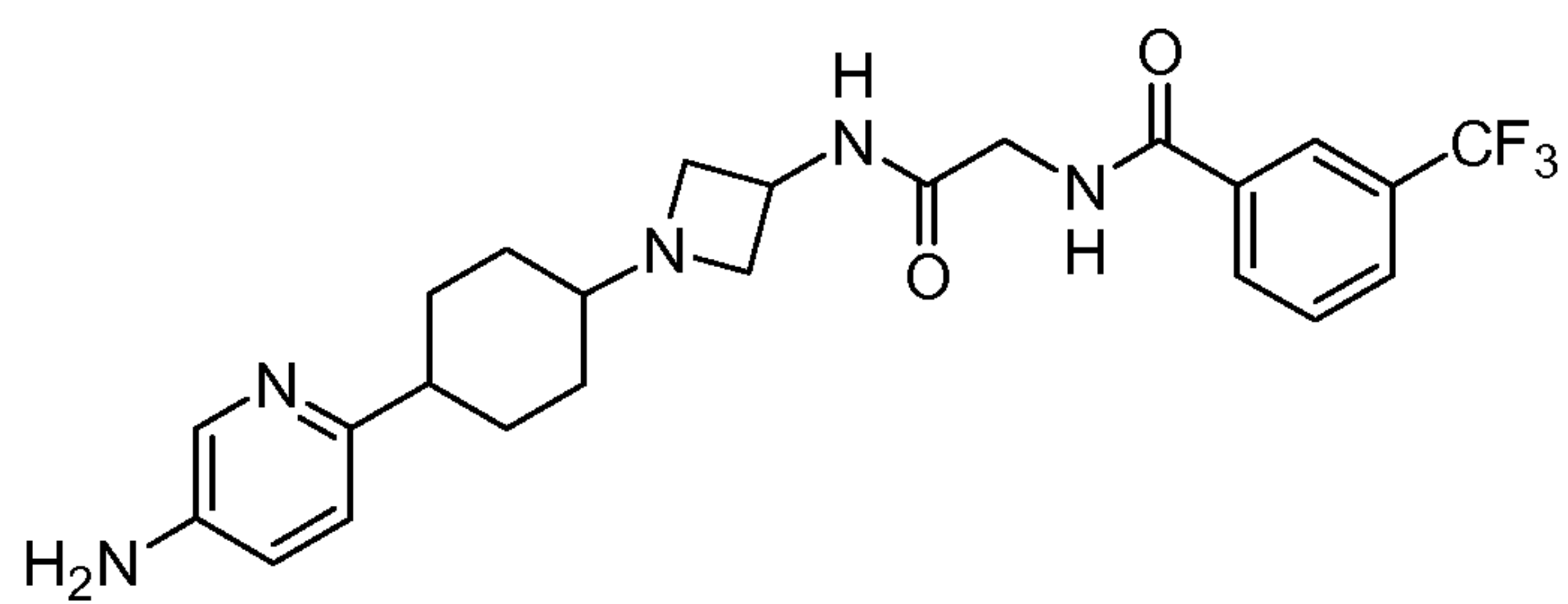
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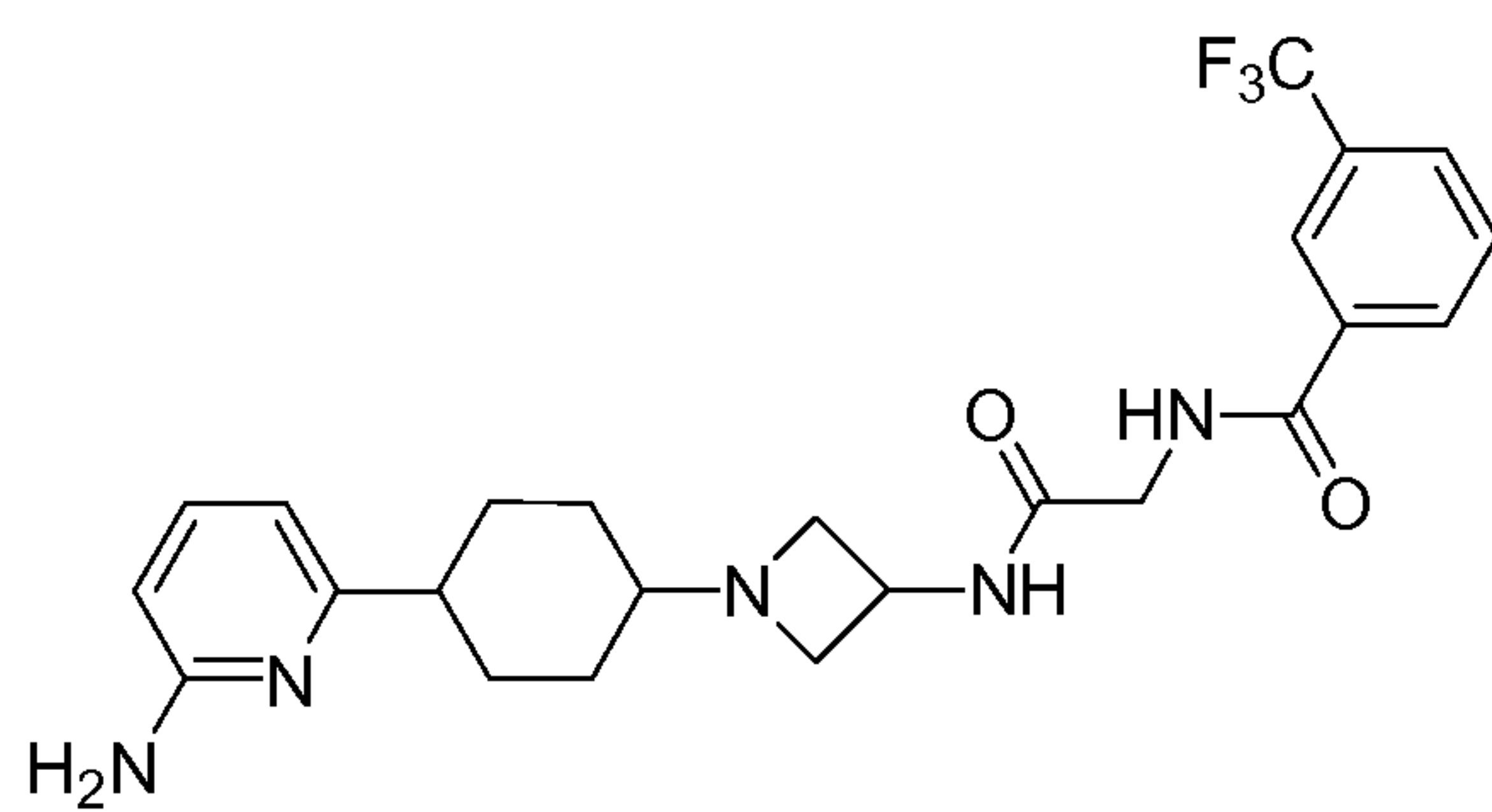
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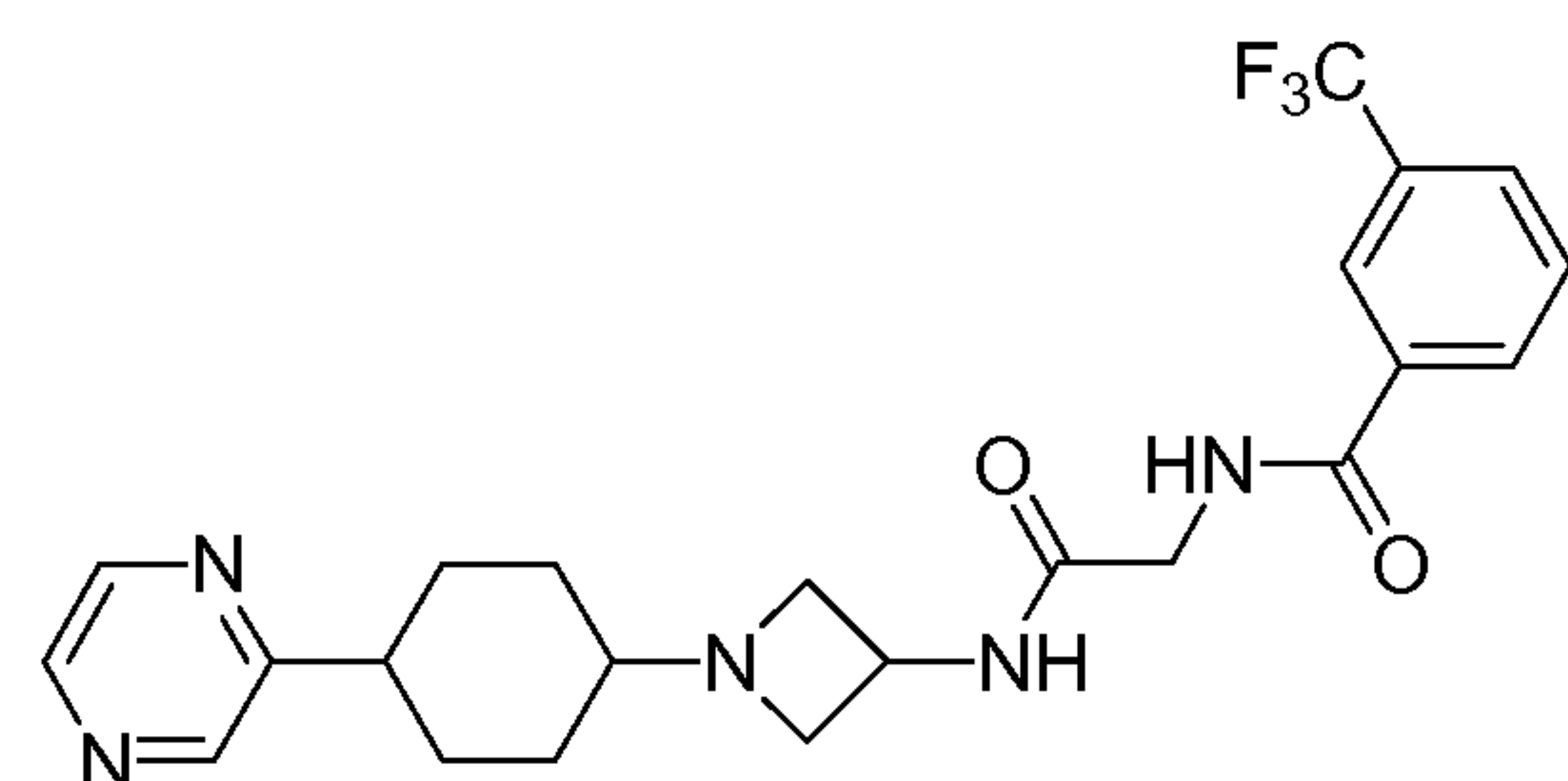
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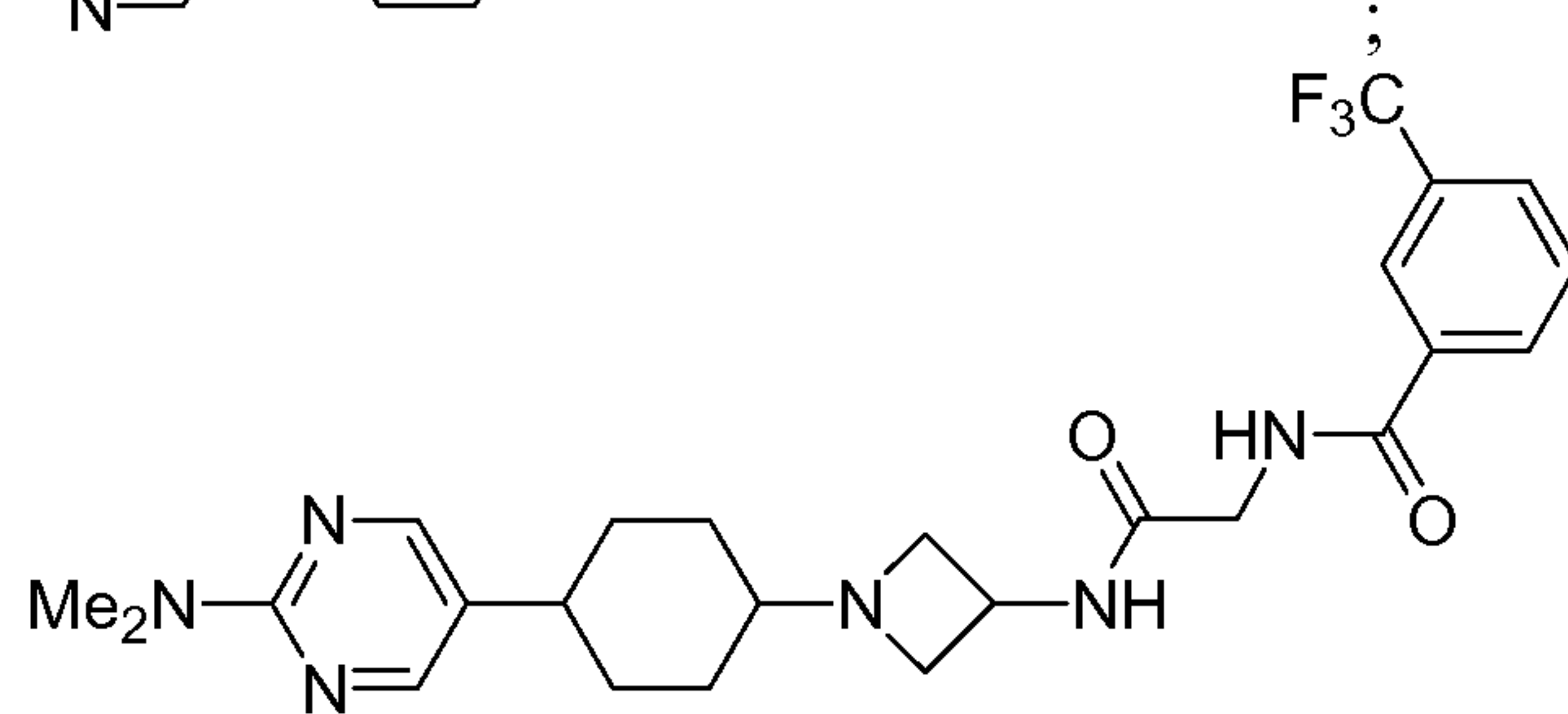
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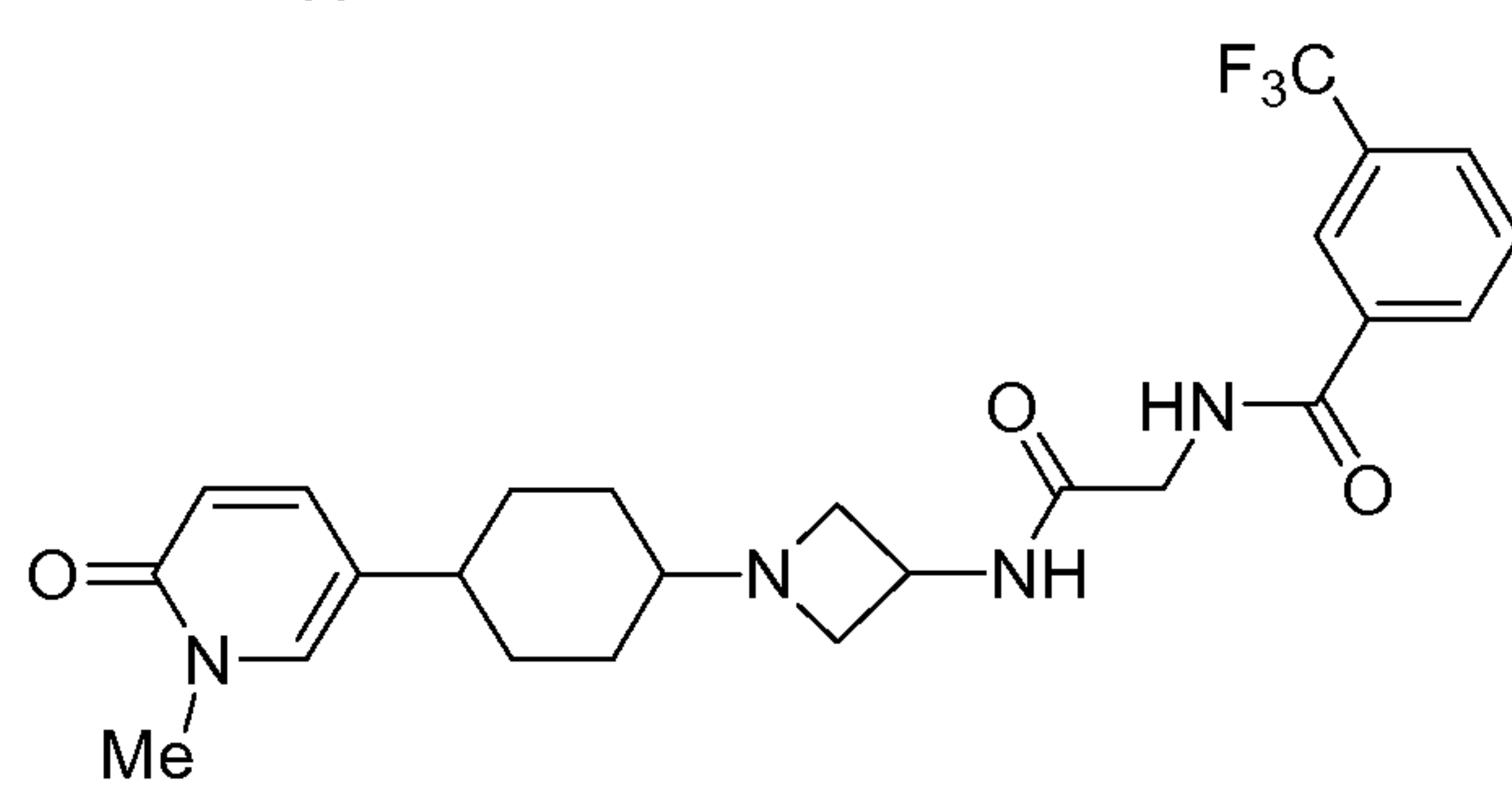
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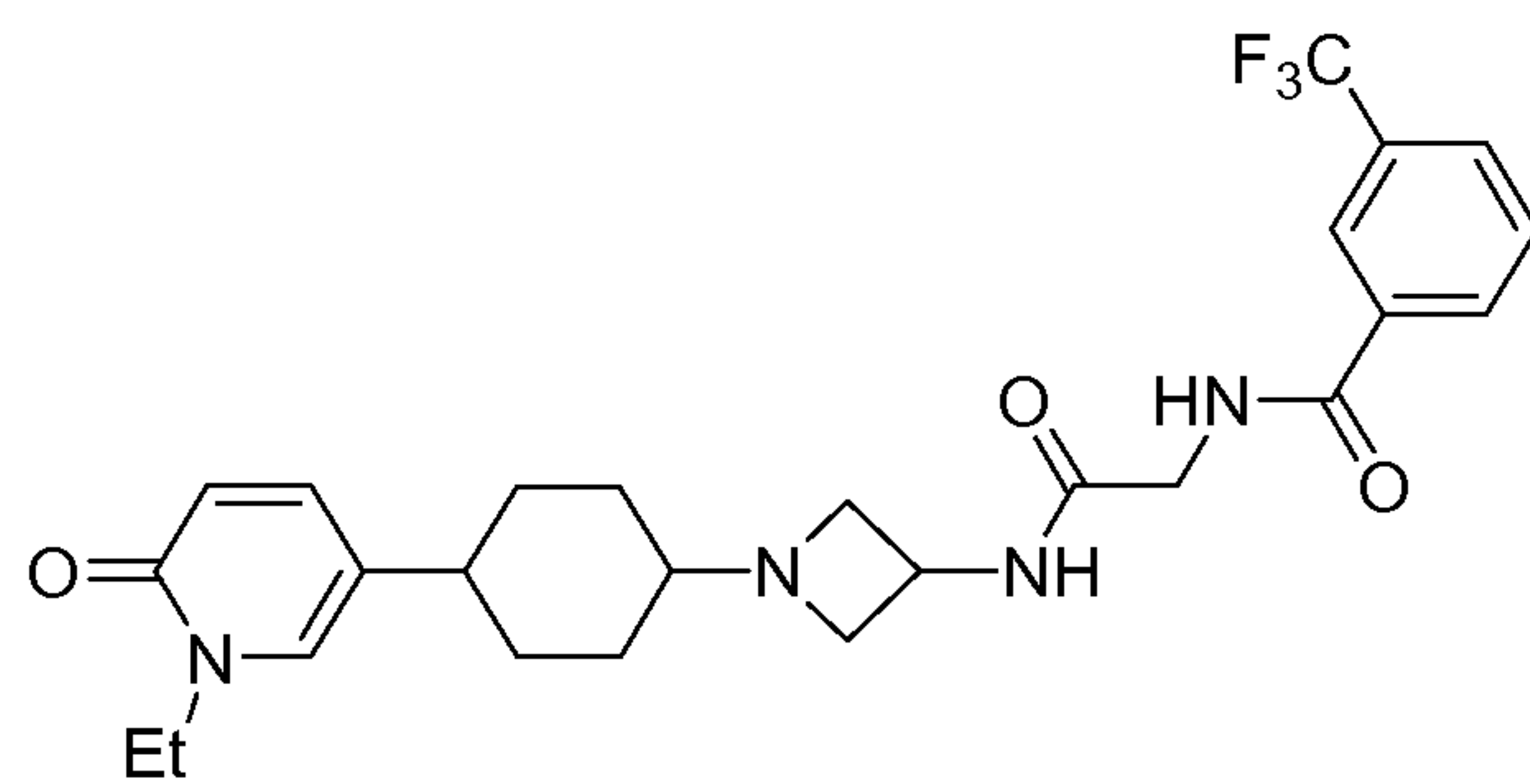


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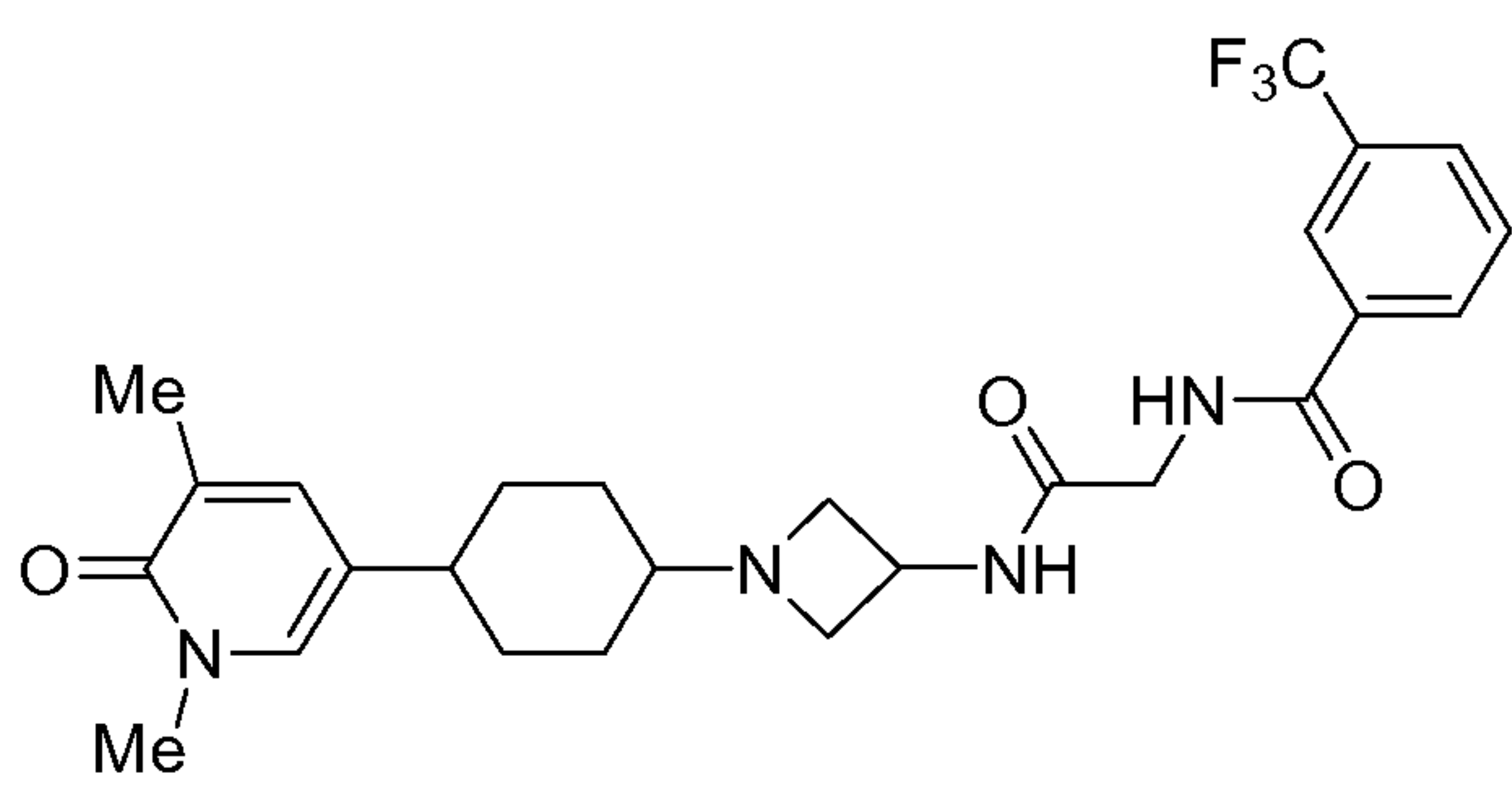


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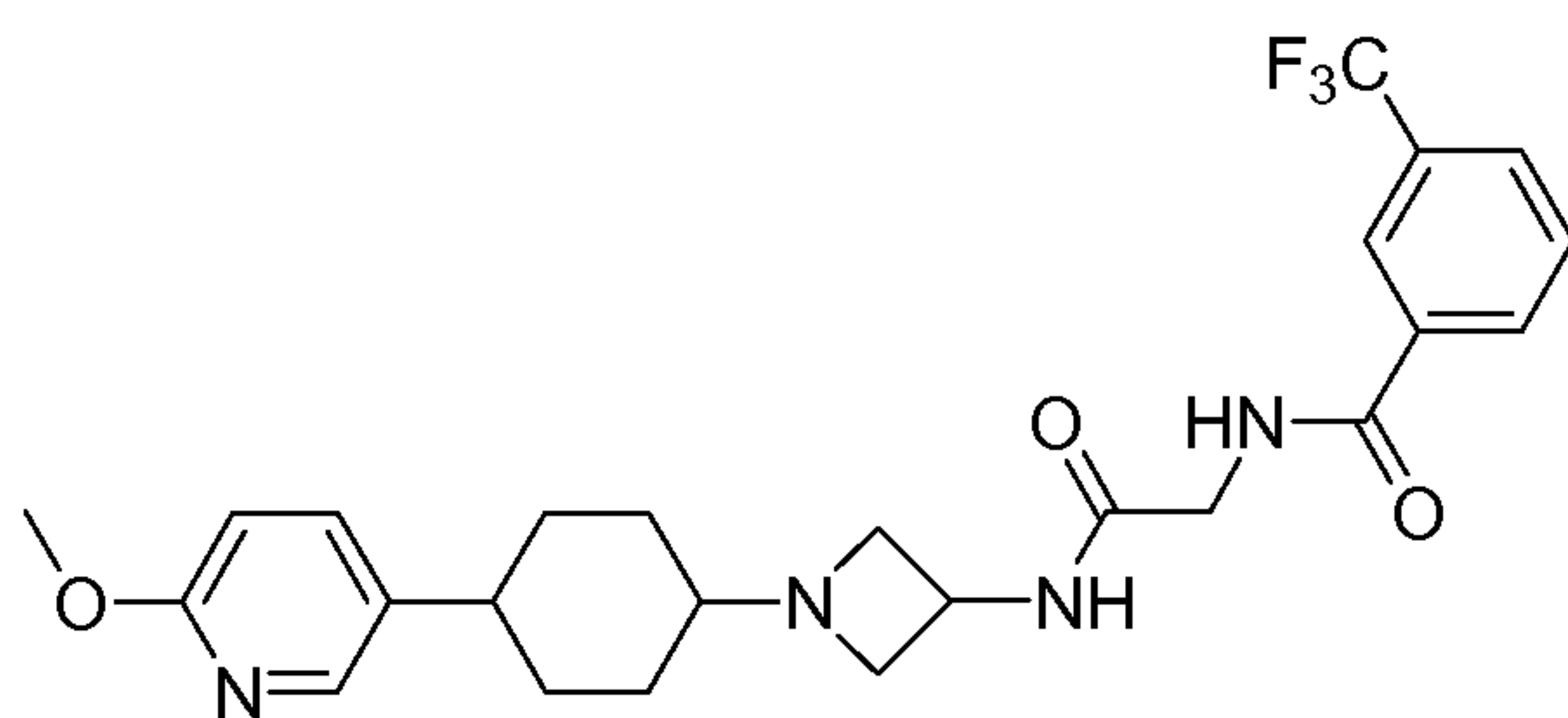


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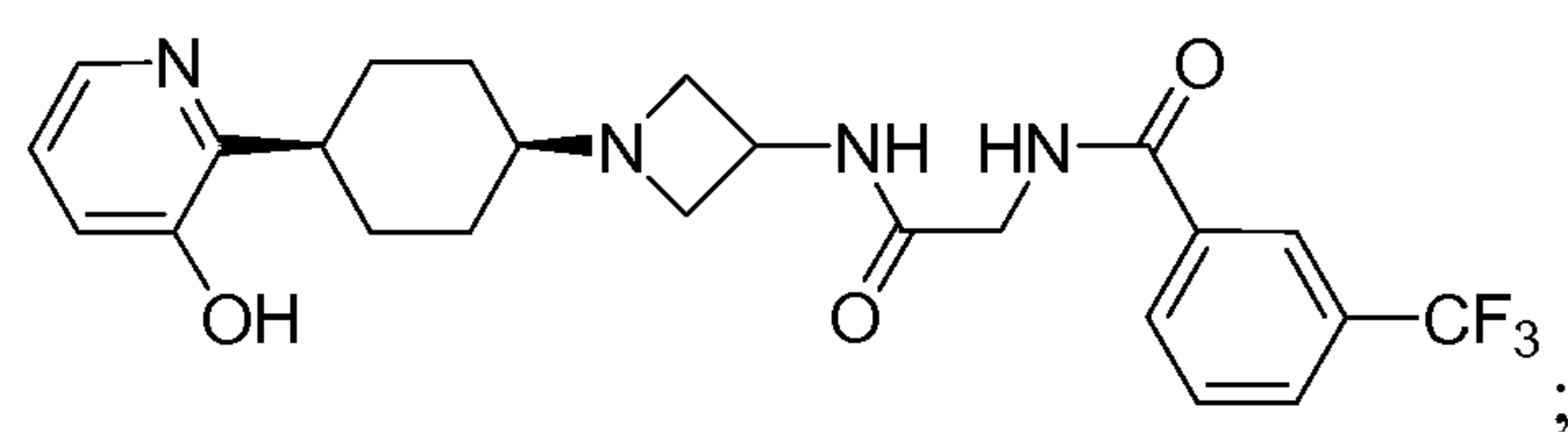
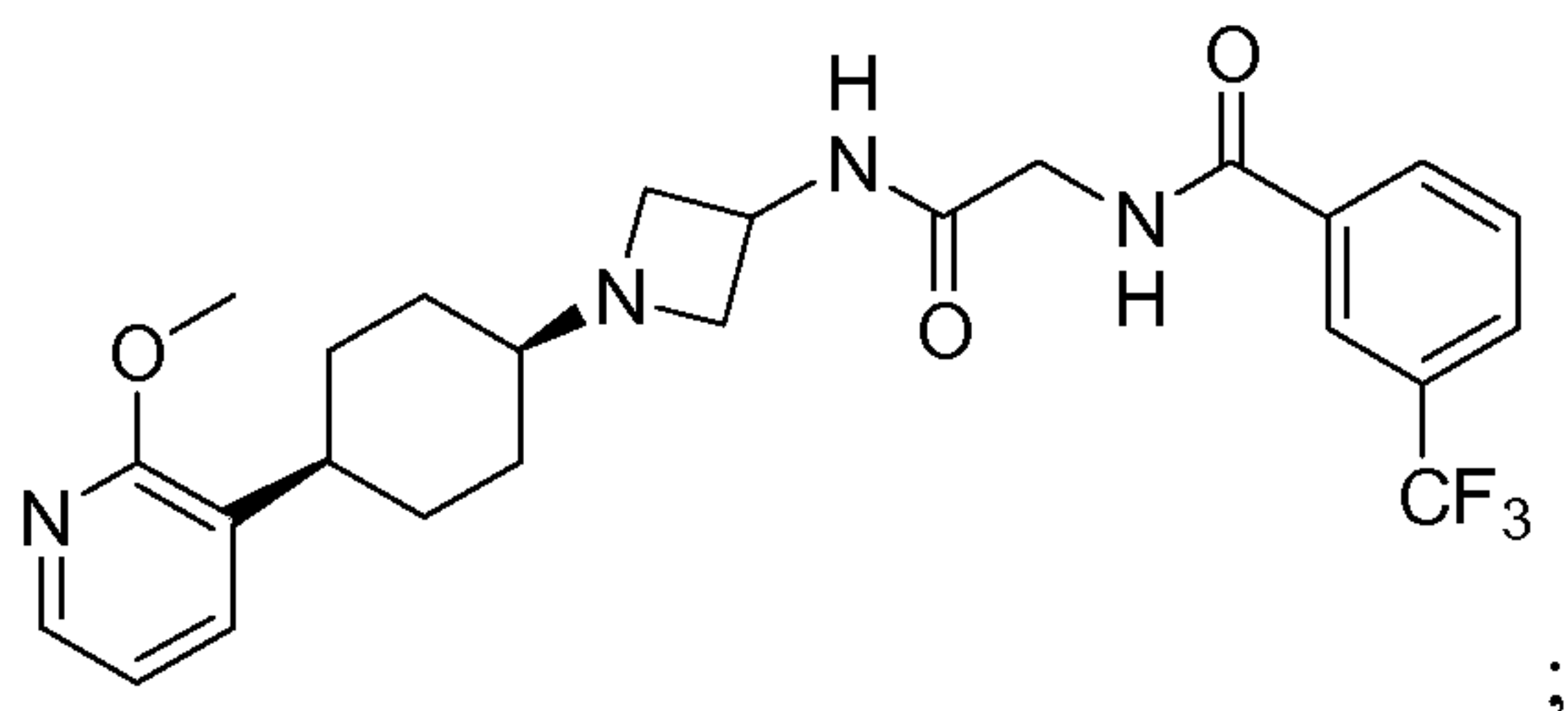
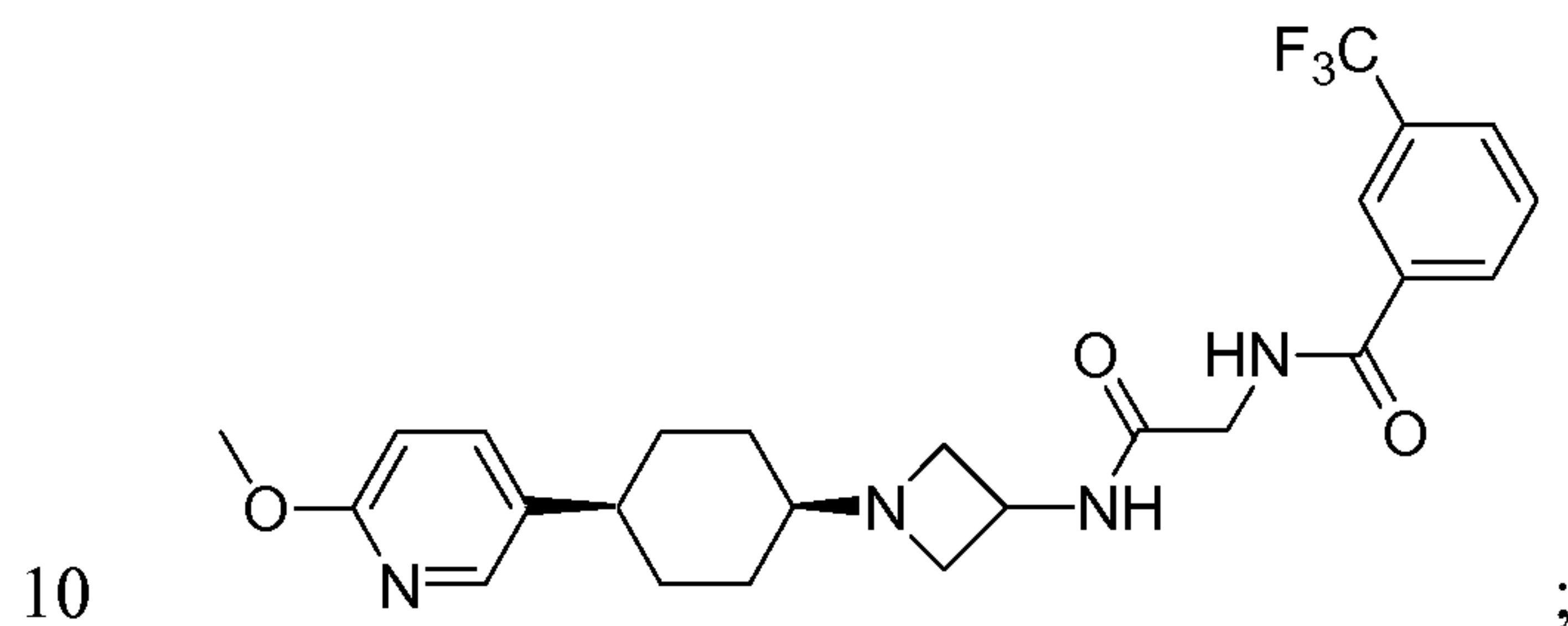
and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

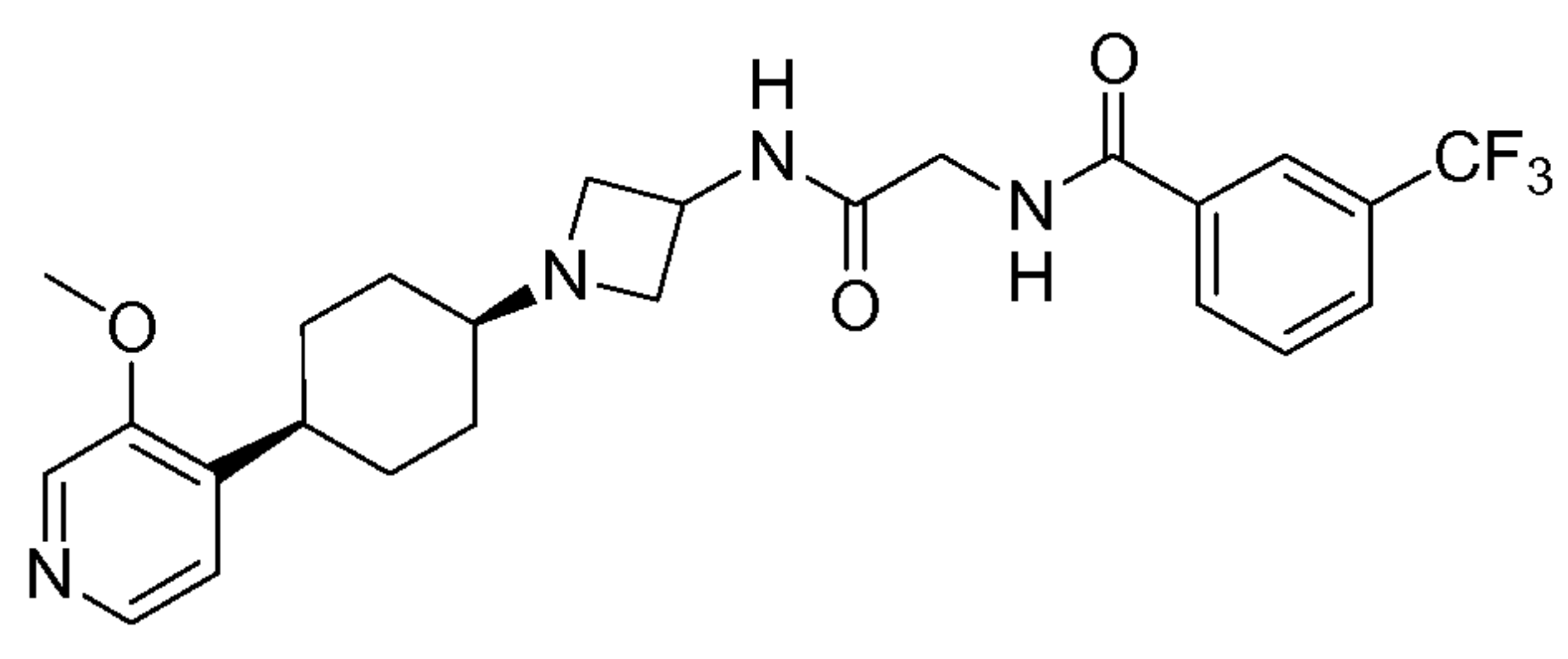
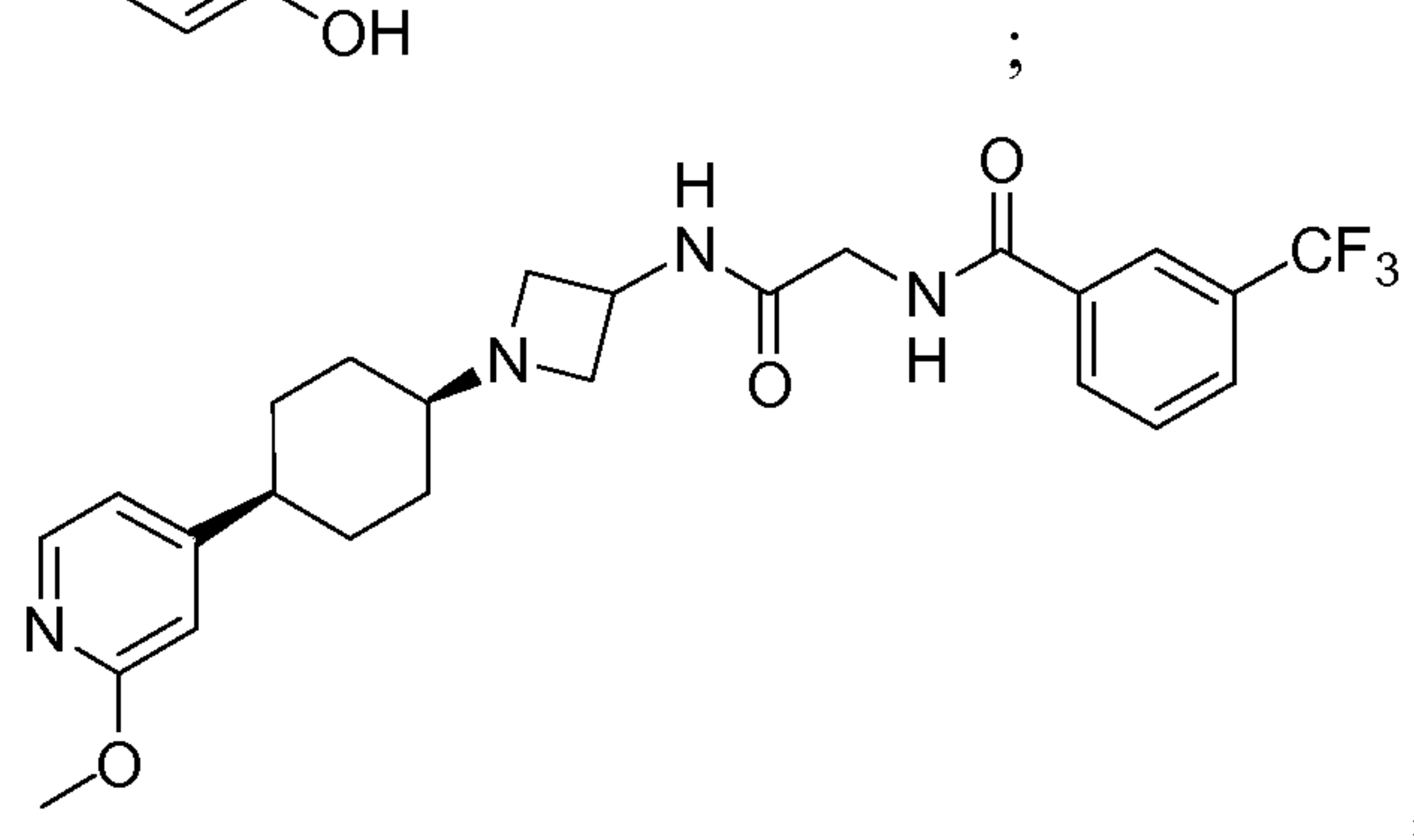
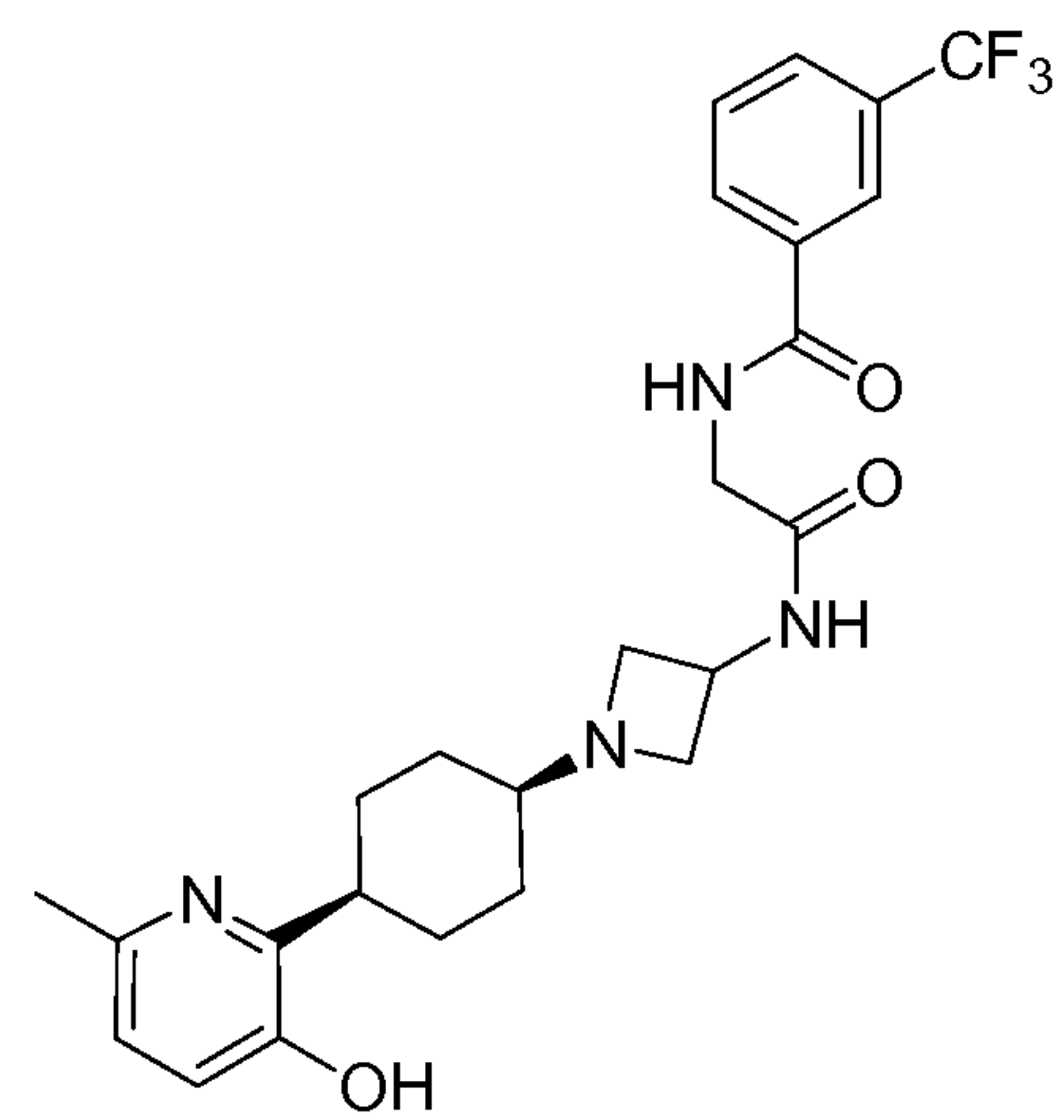
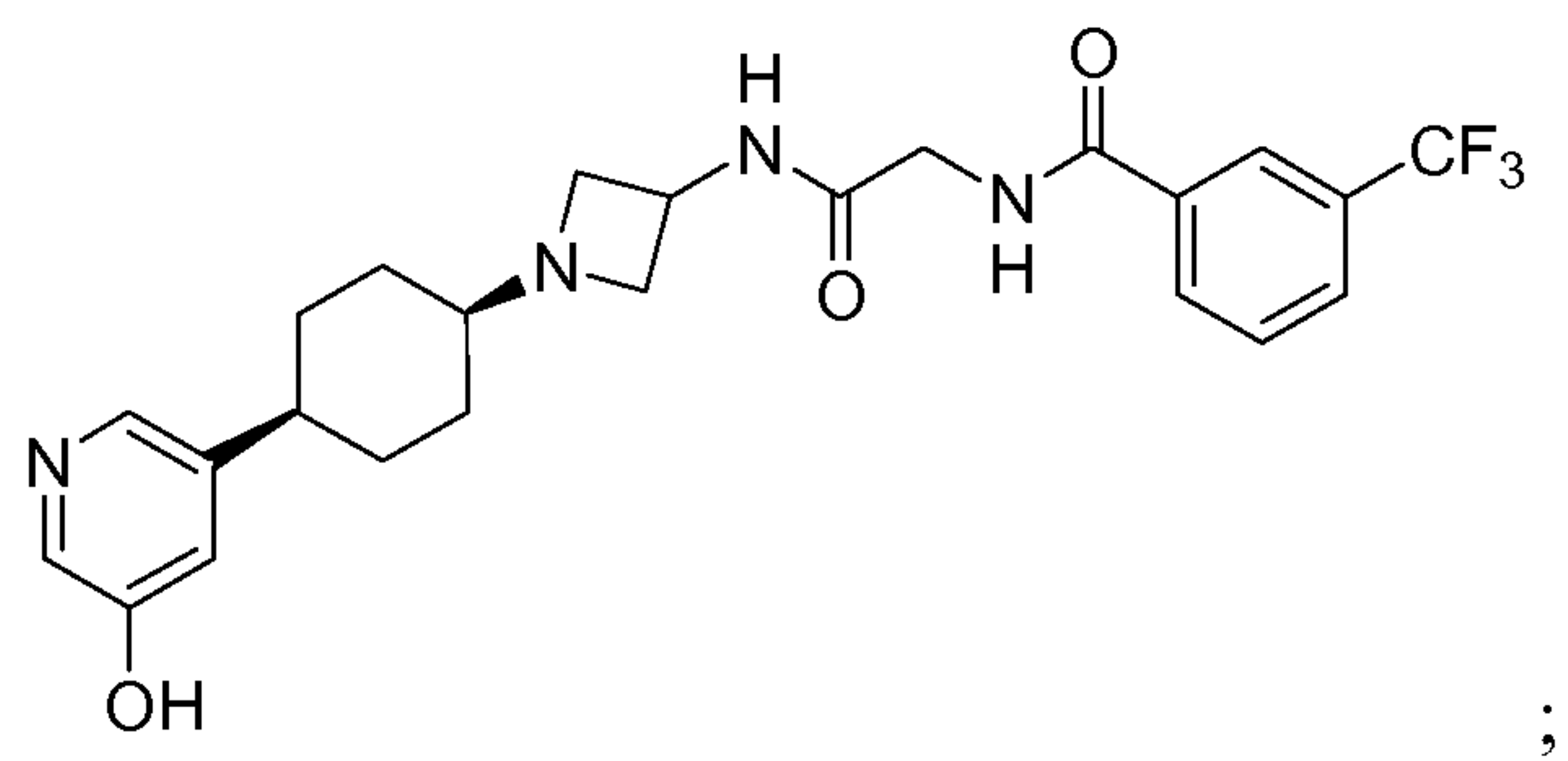
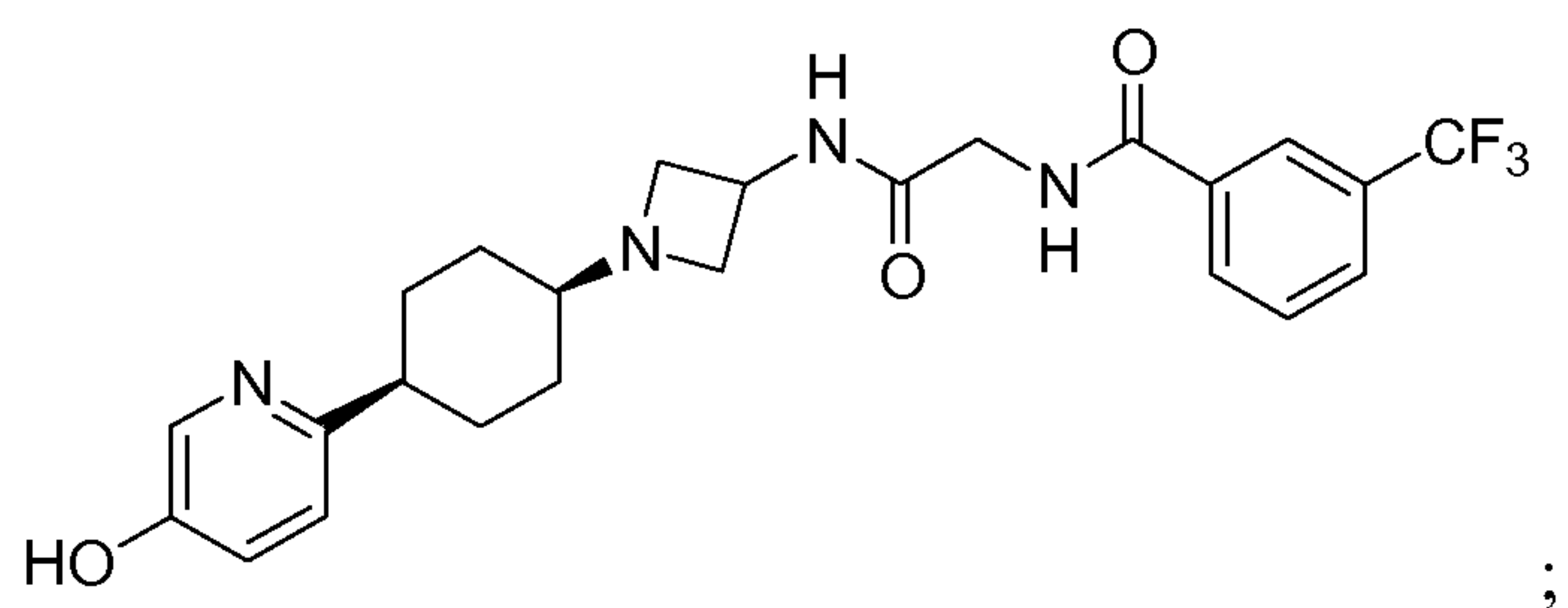
5 Another embodiment of the invention is a compound which is

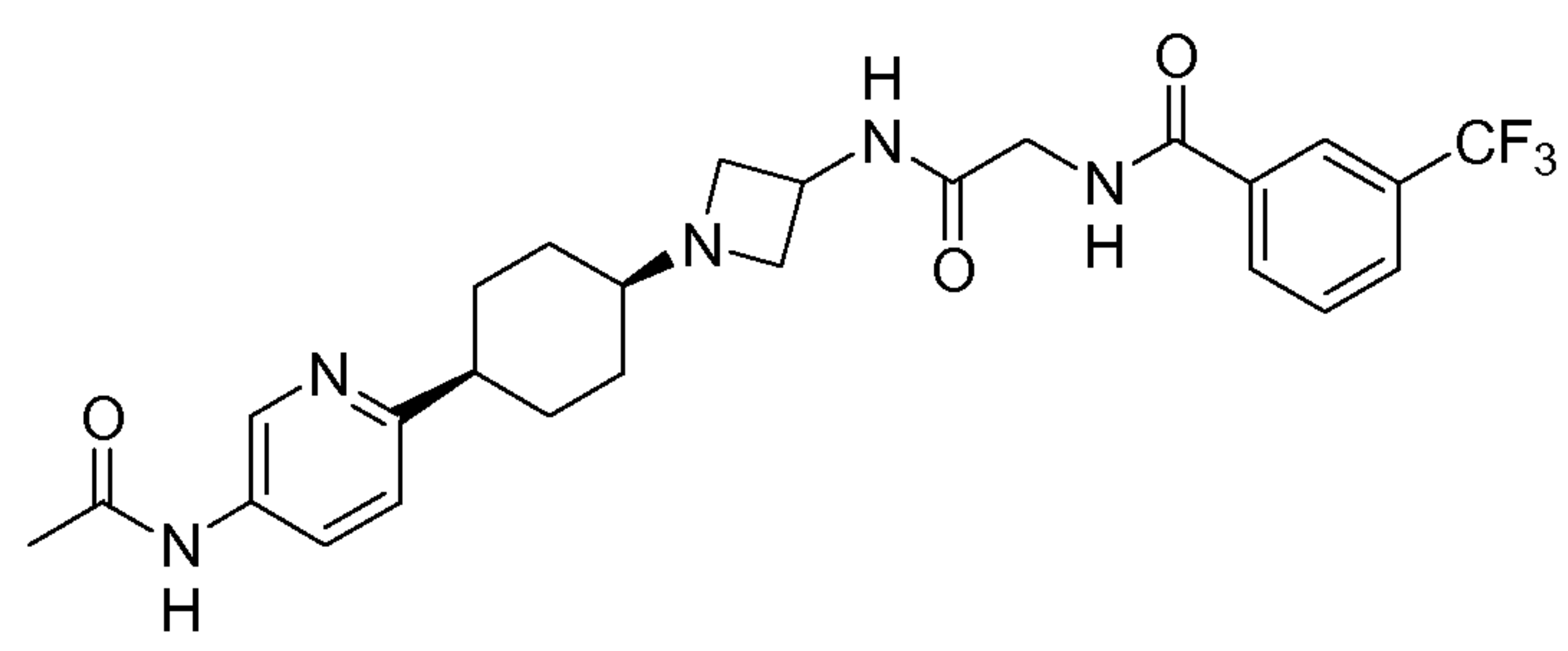
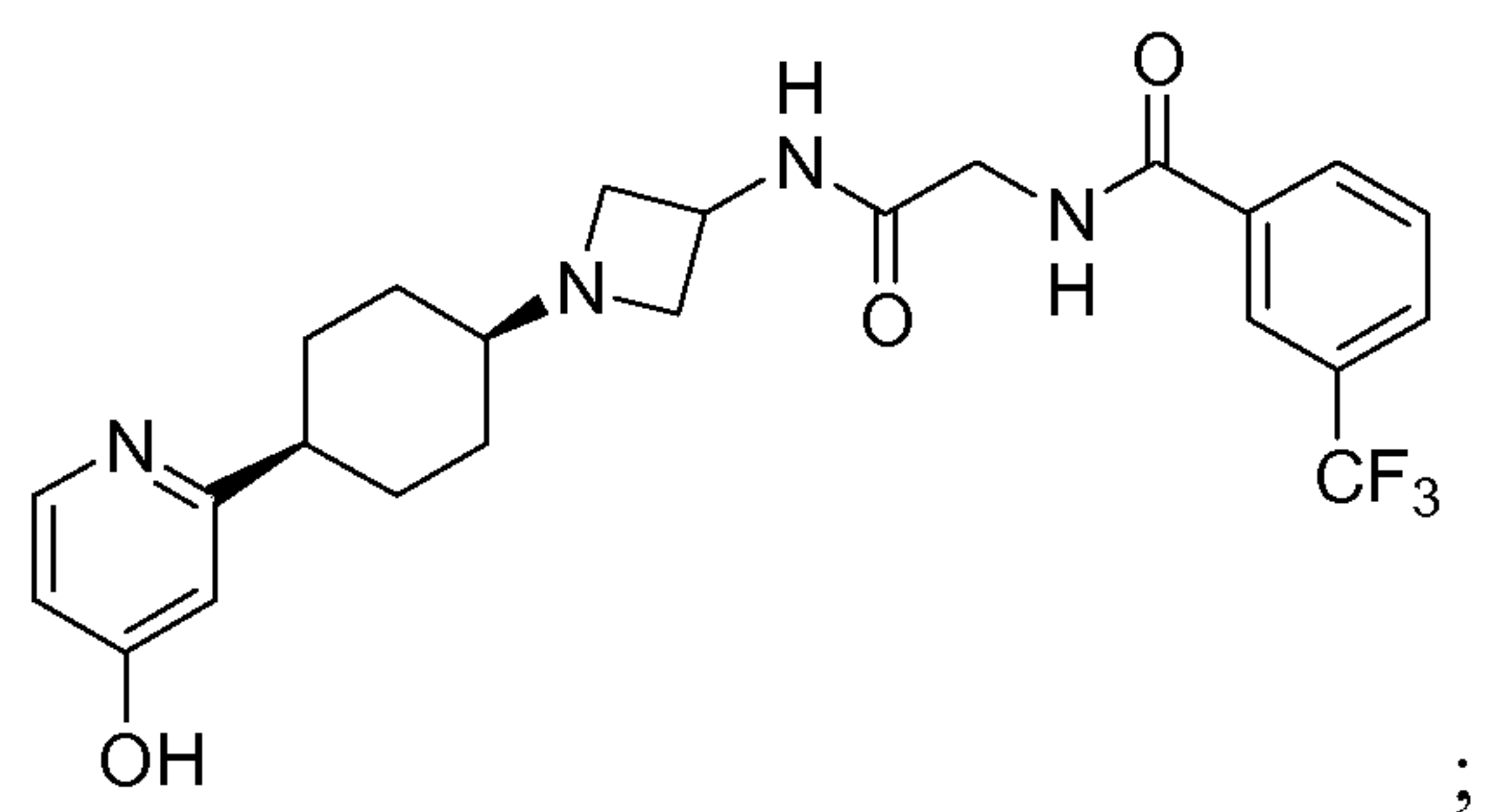
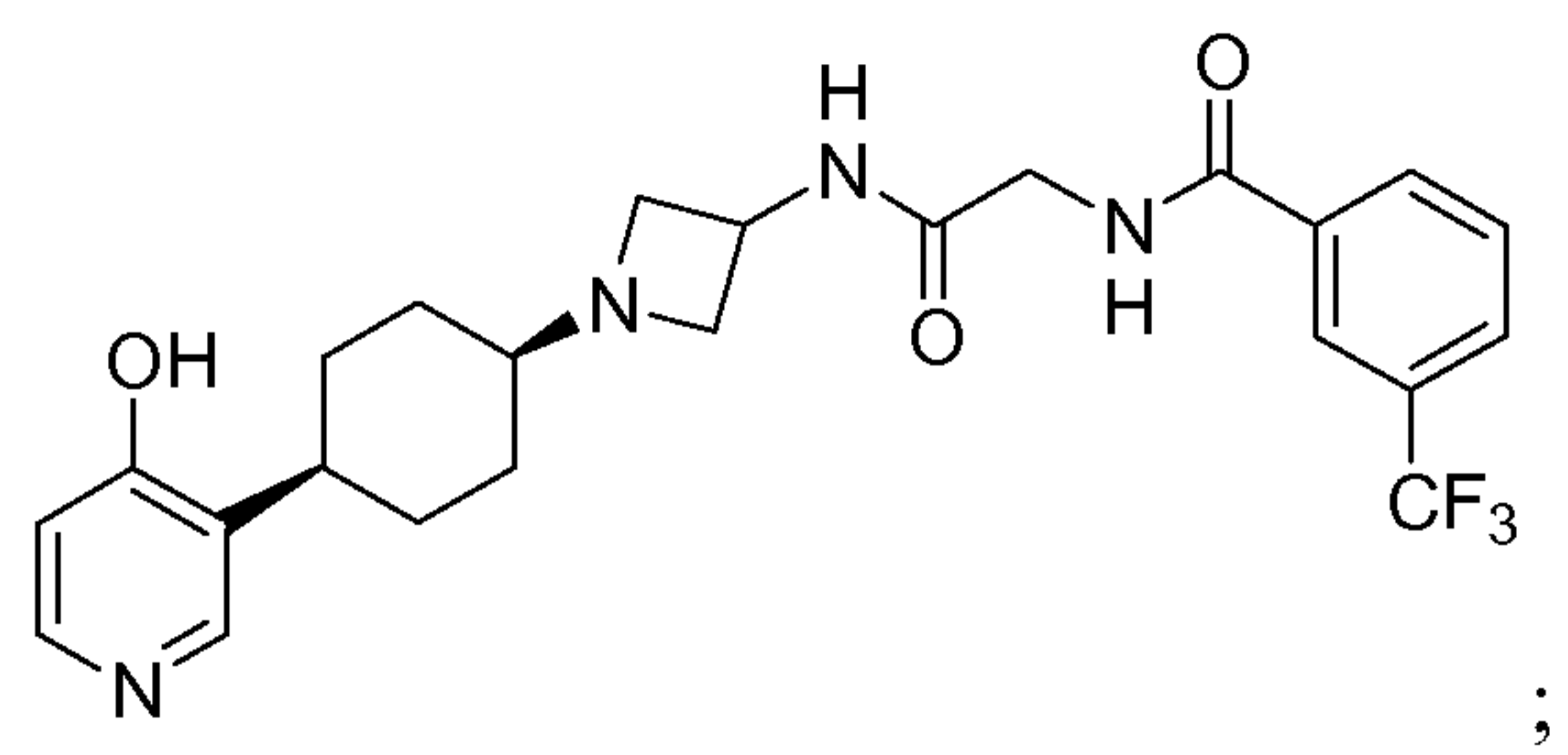
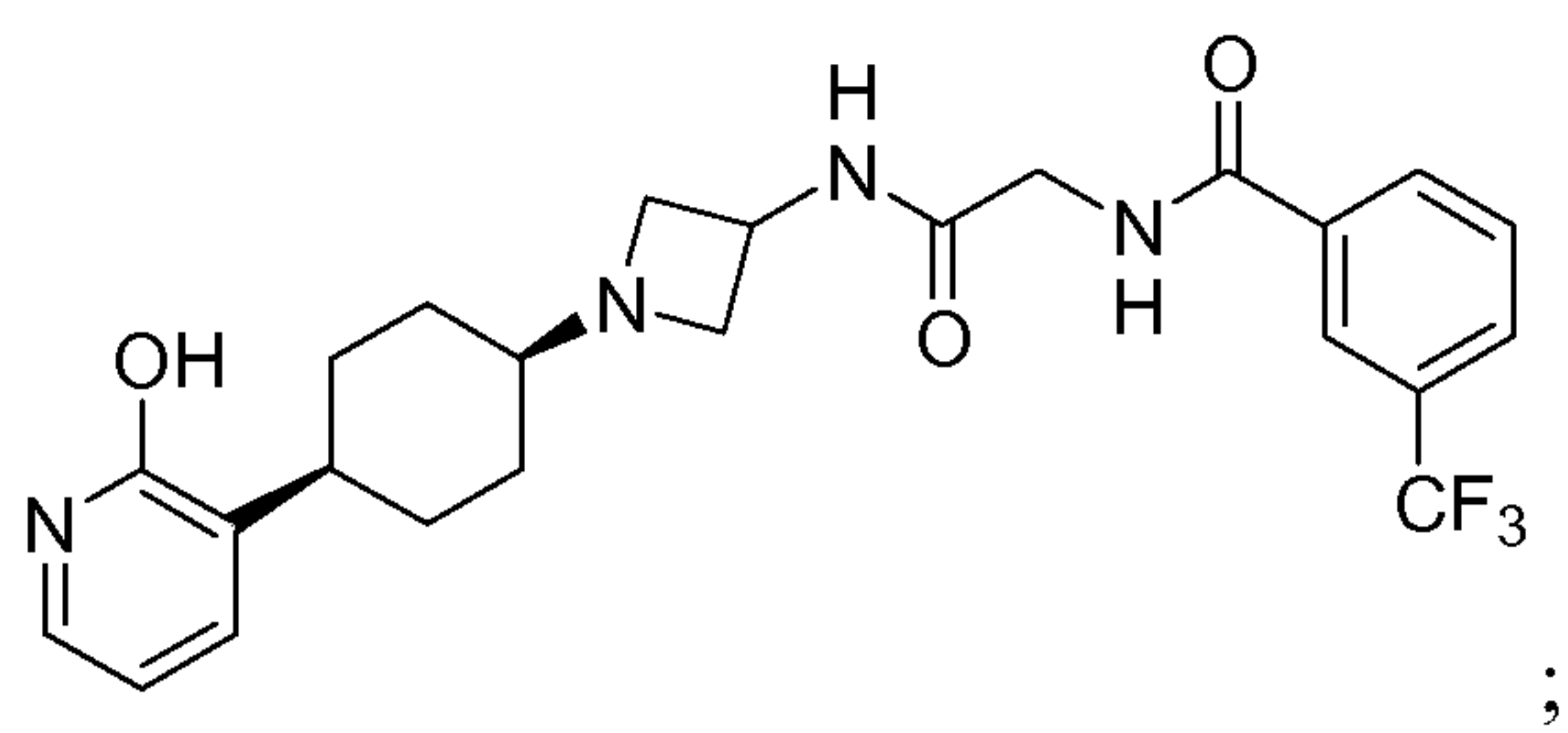
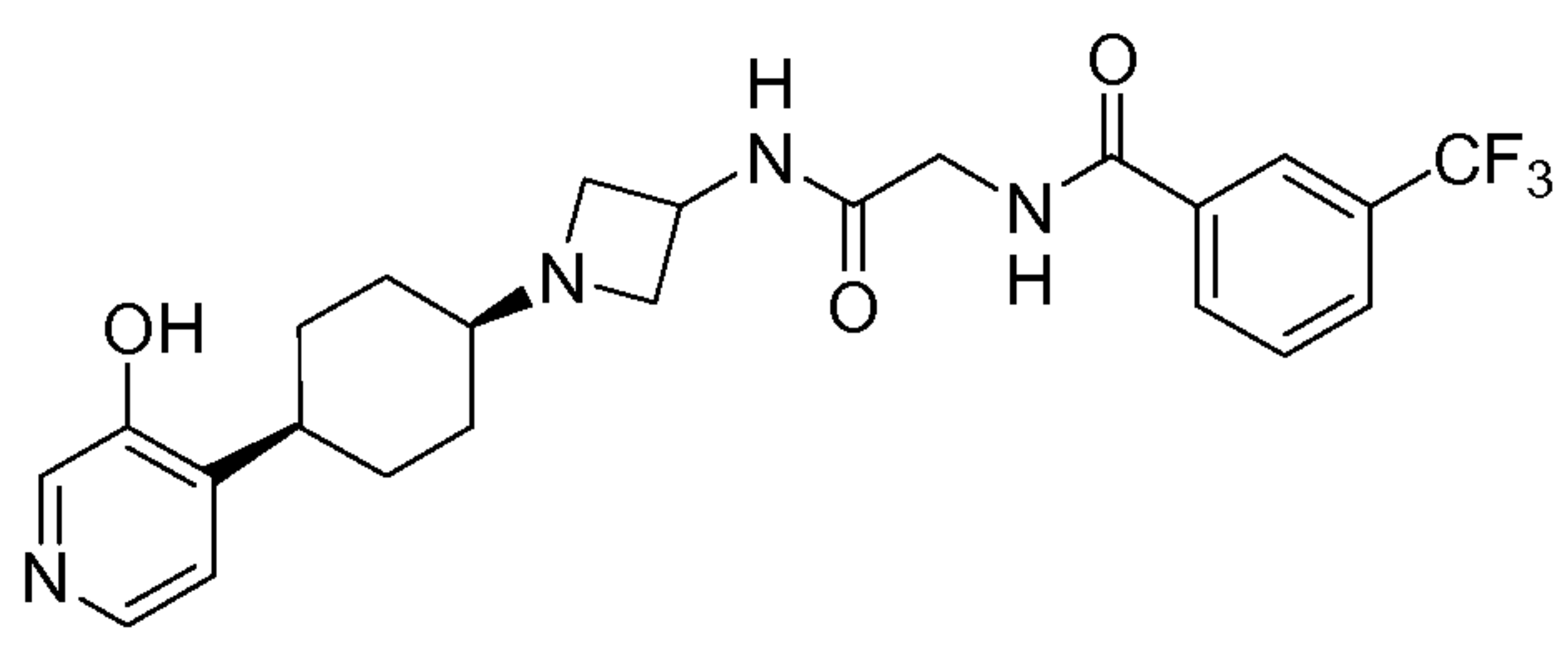


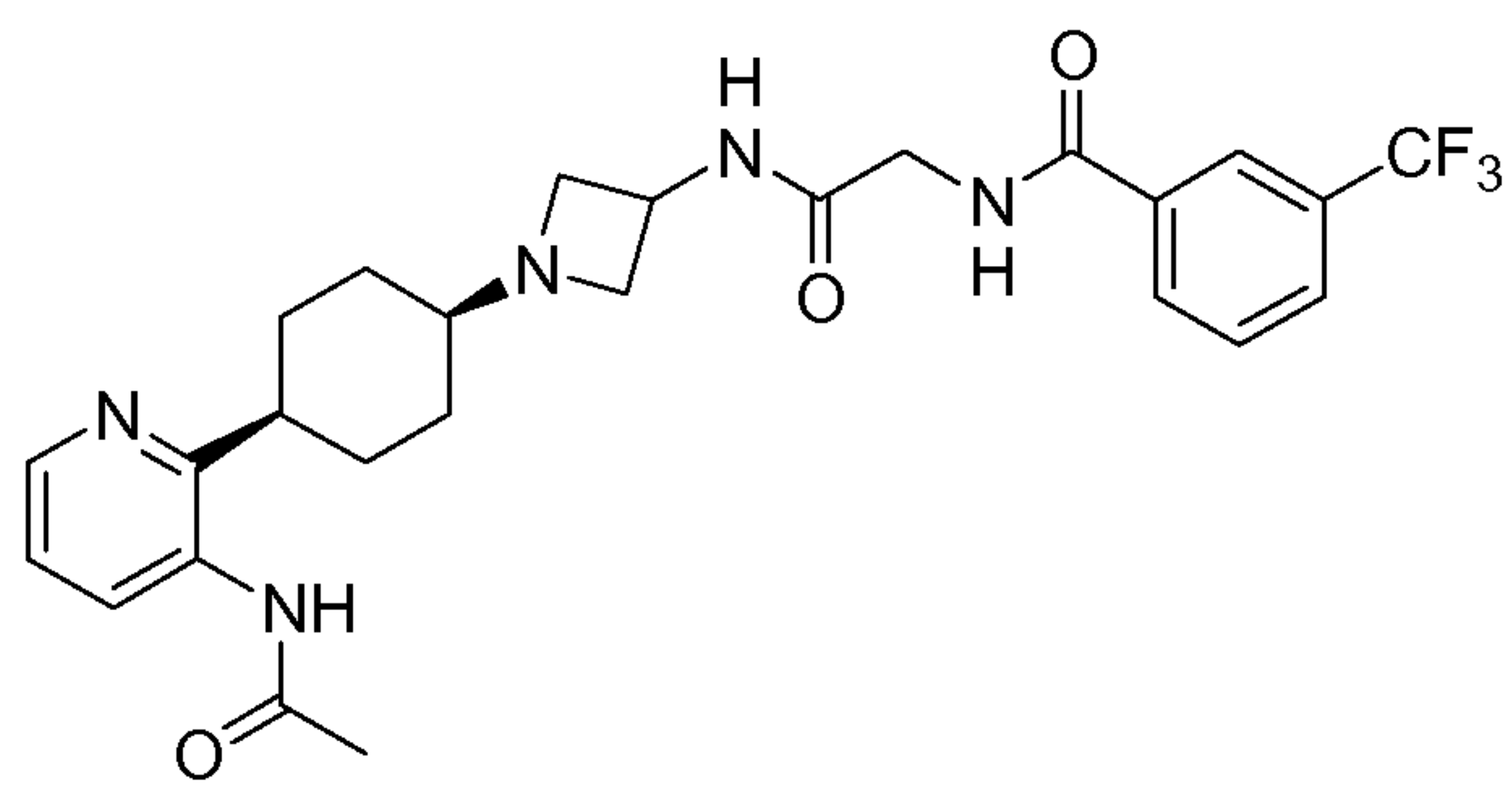
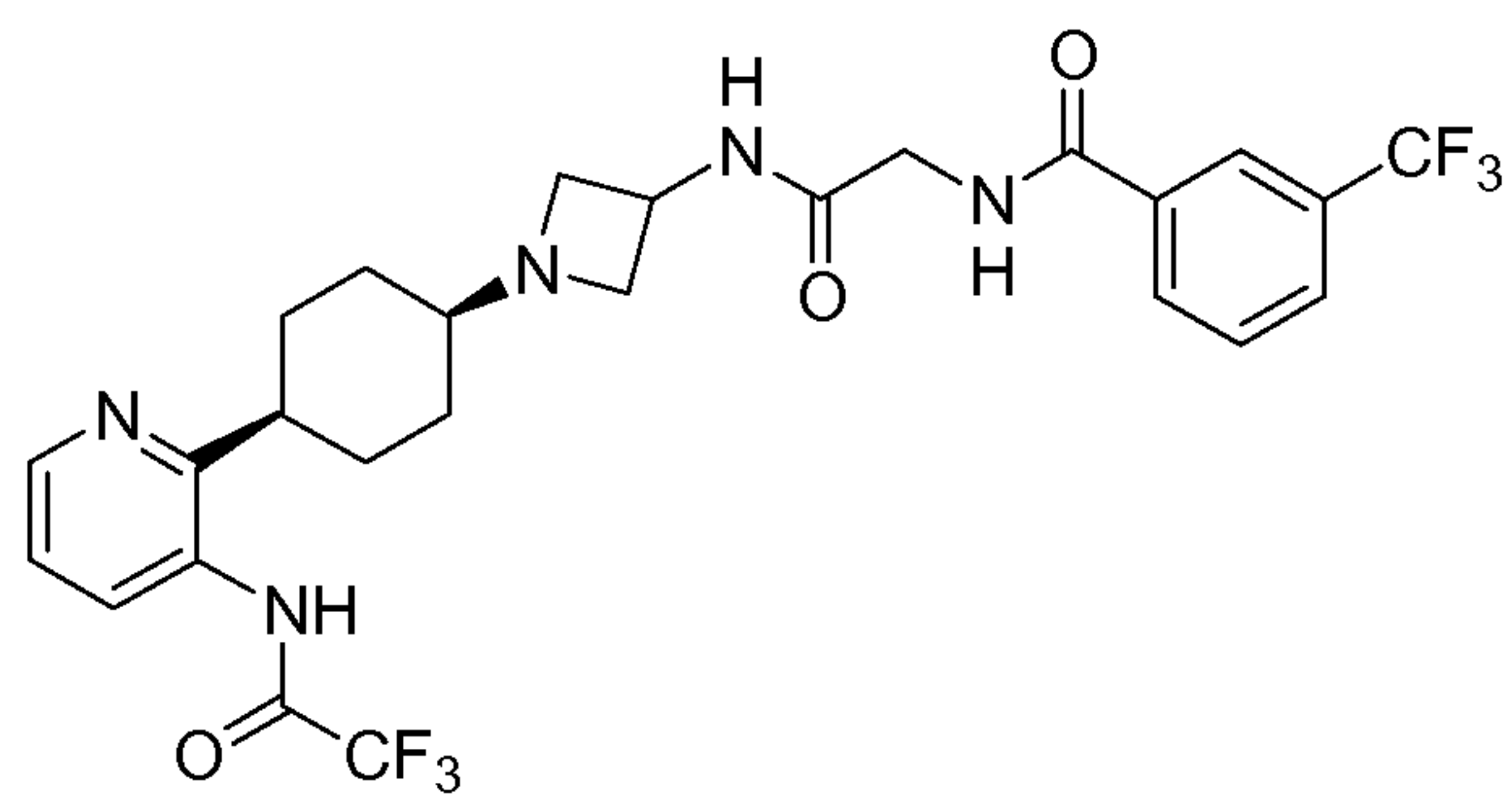
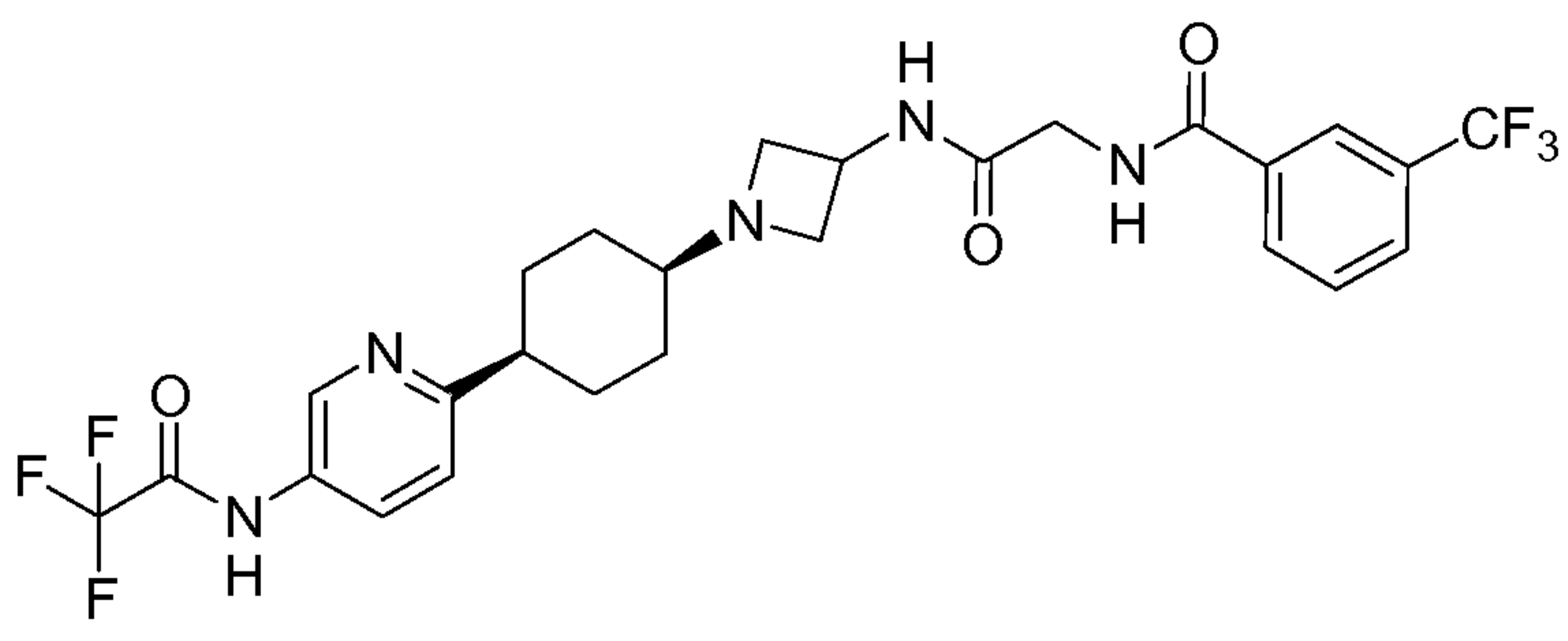
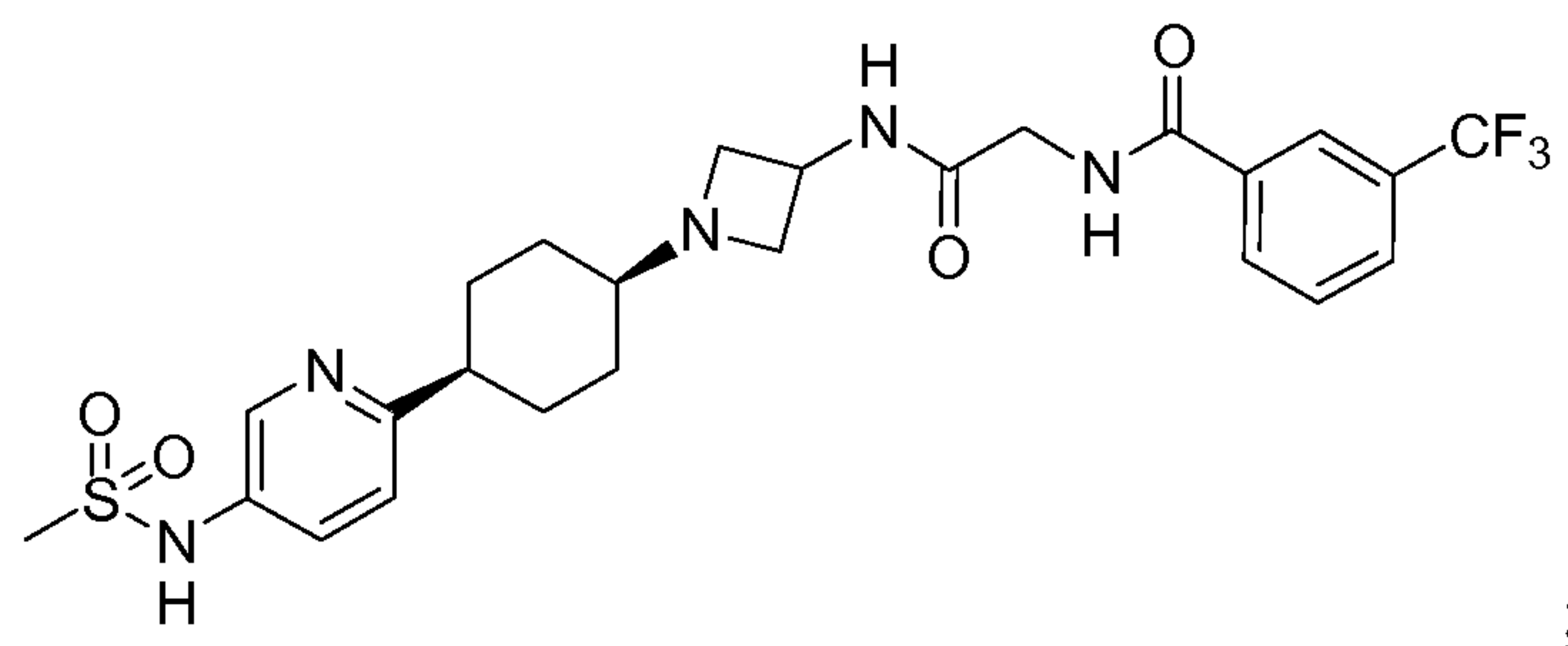
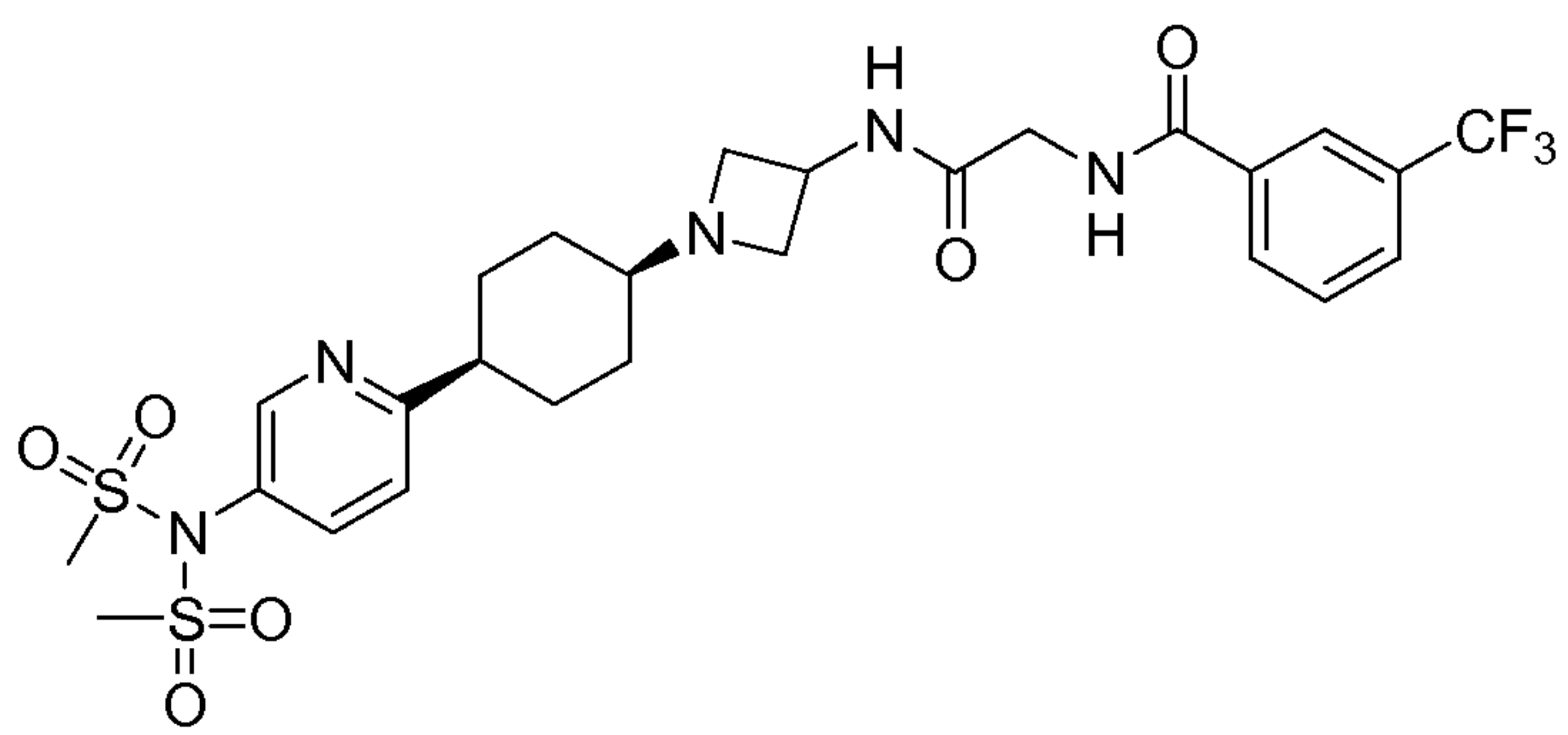
and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof.

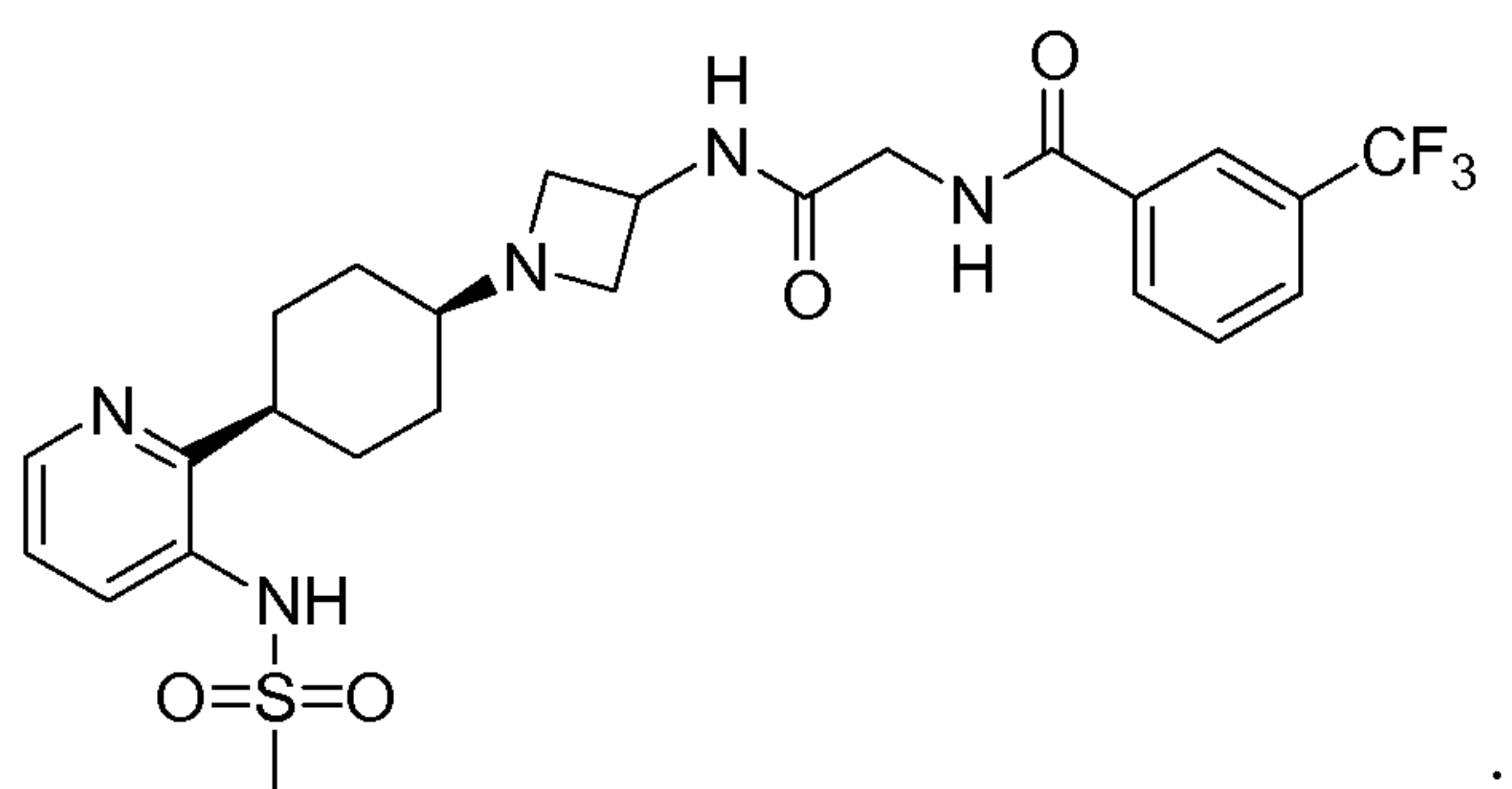
Another embodiment of the invention is a compound selected from the group consisting of:



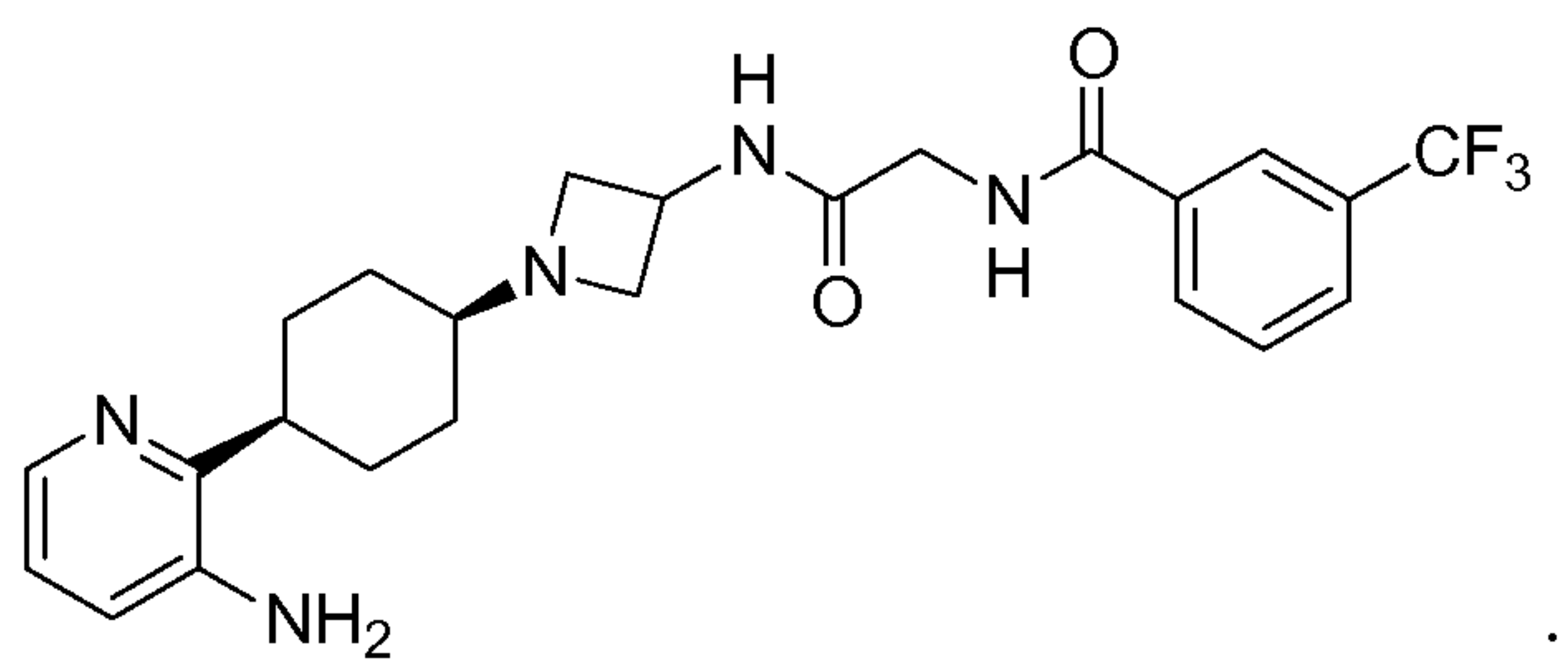




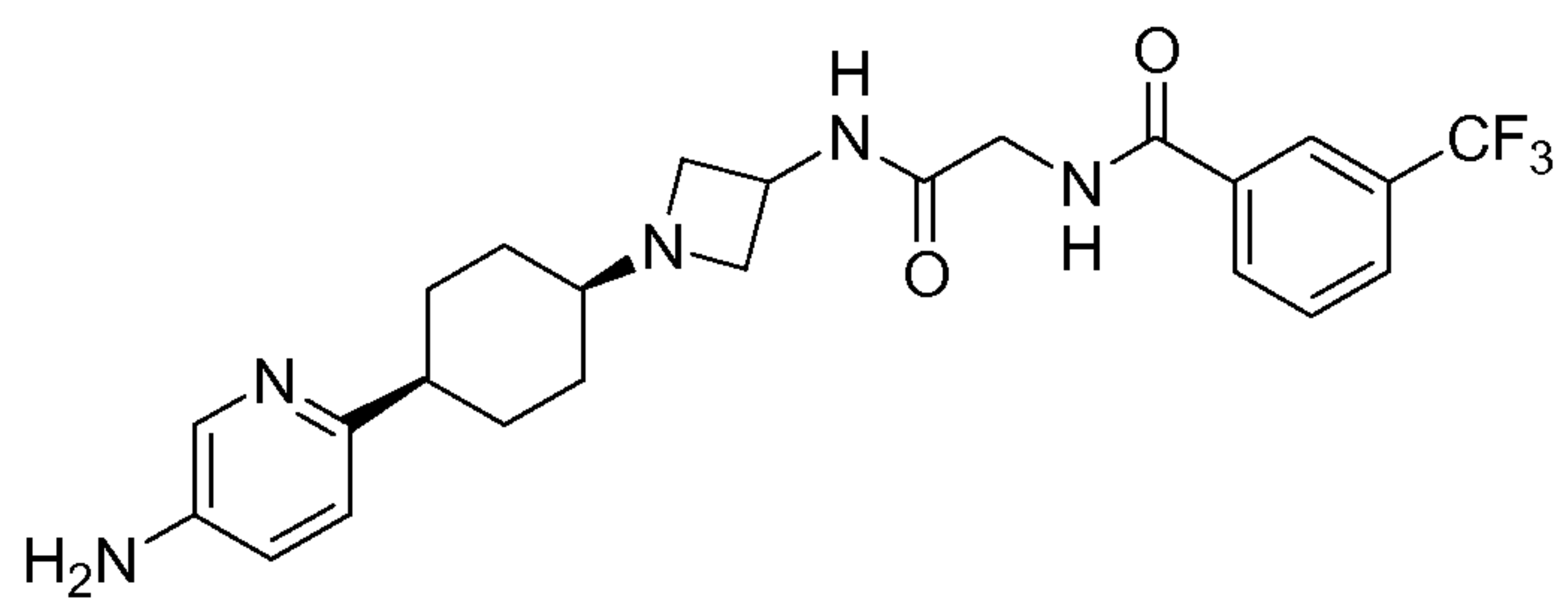




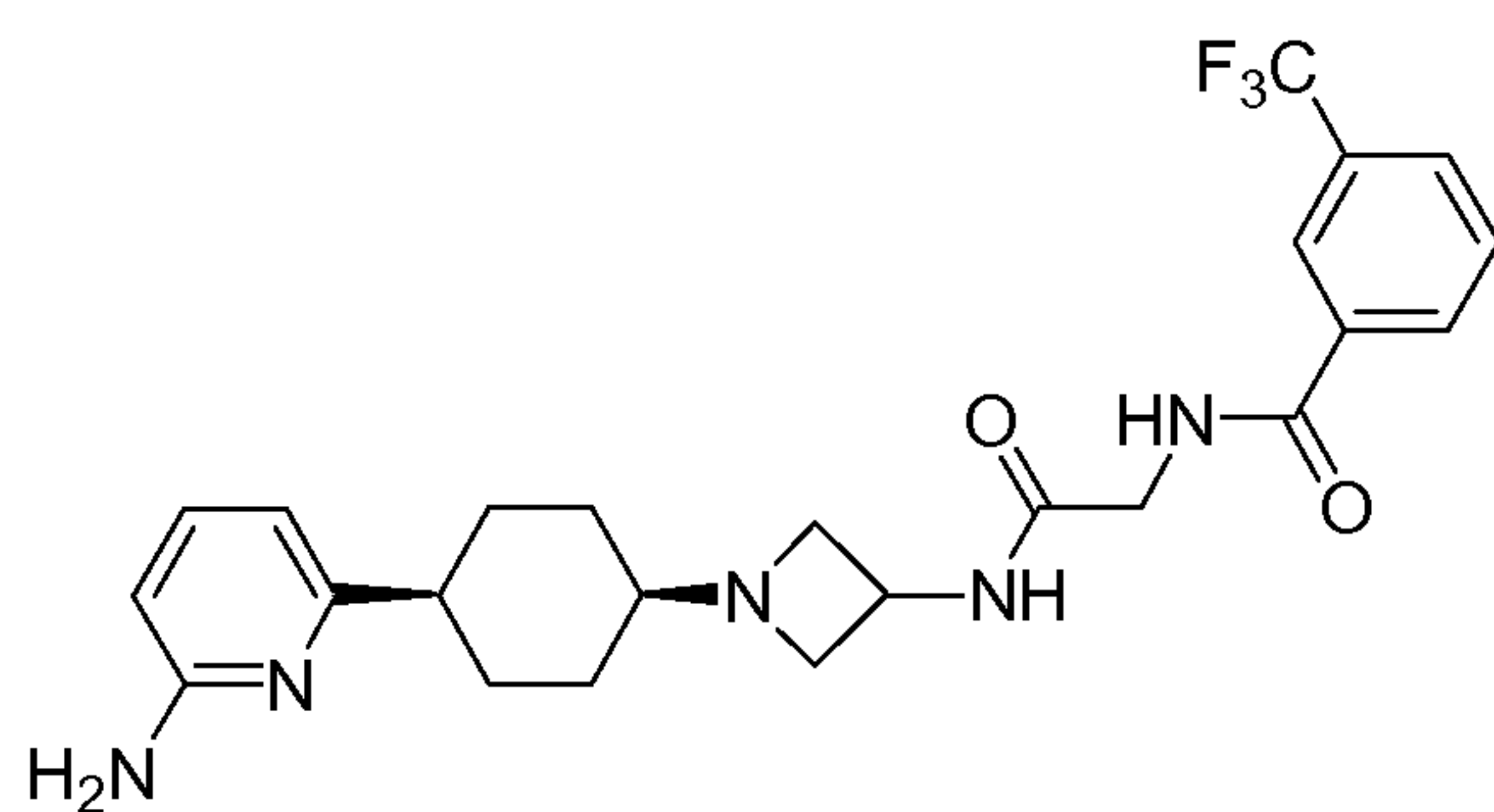
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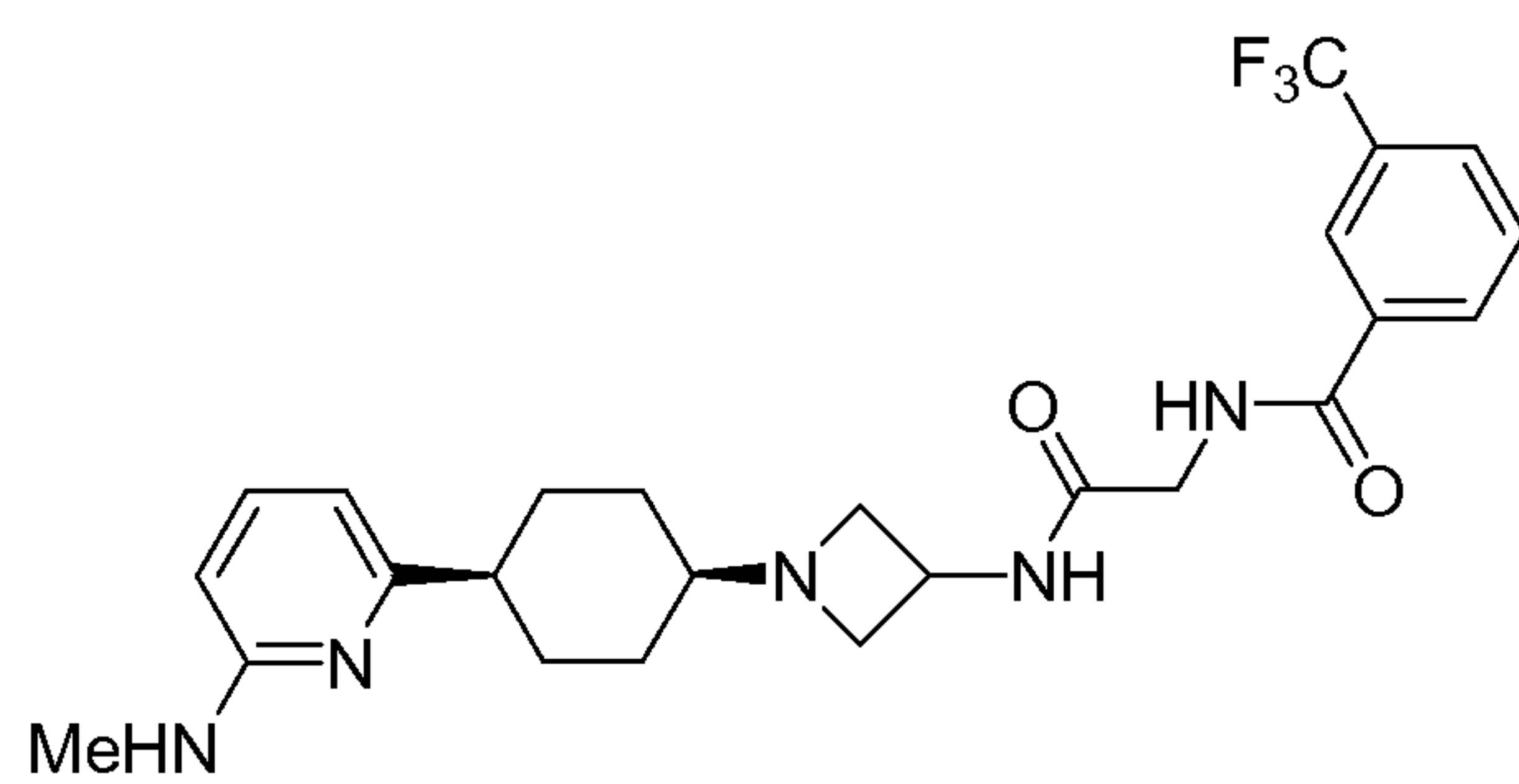
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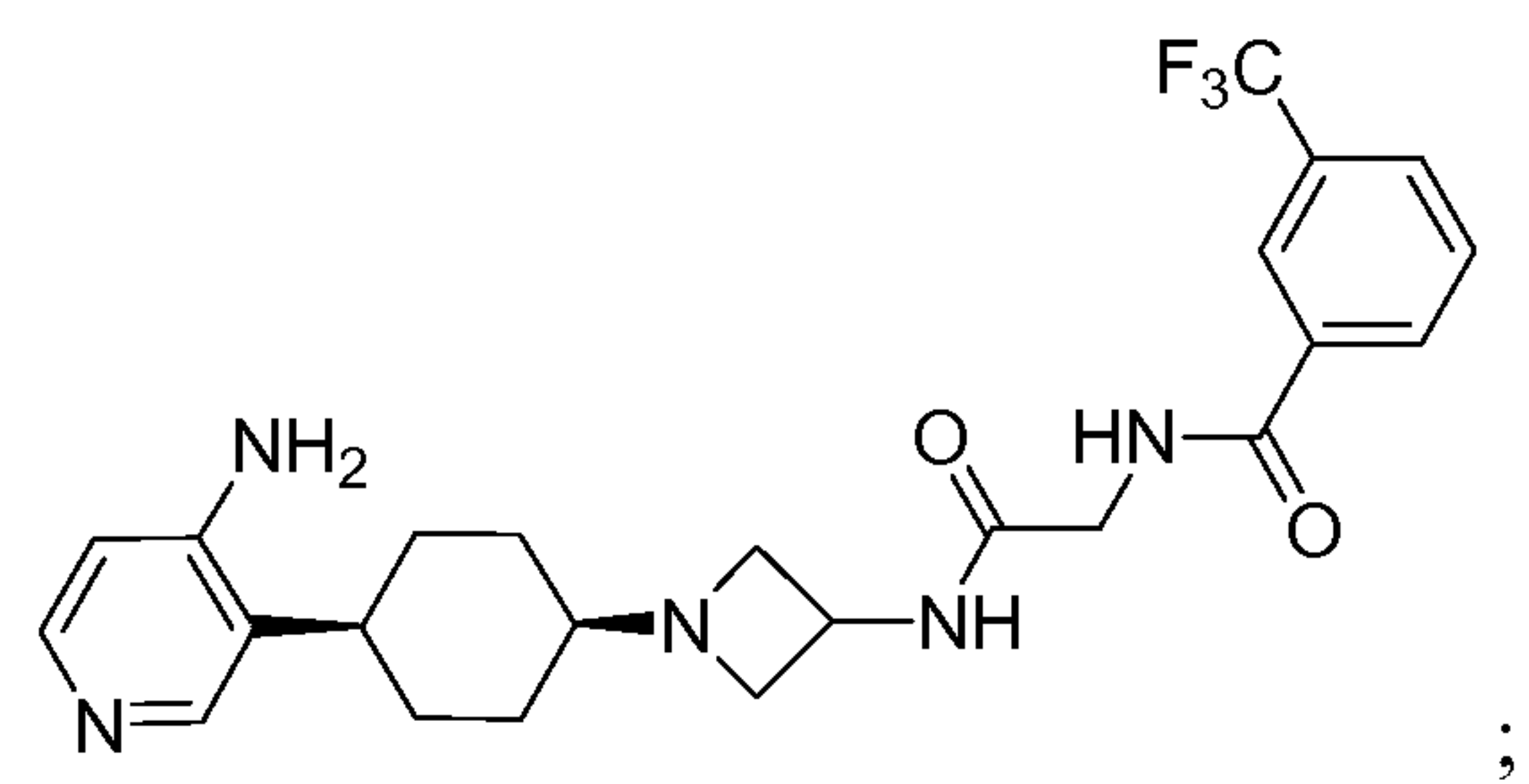
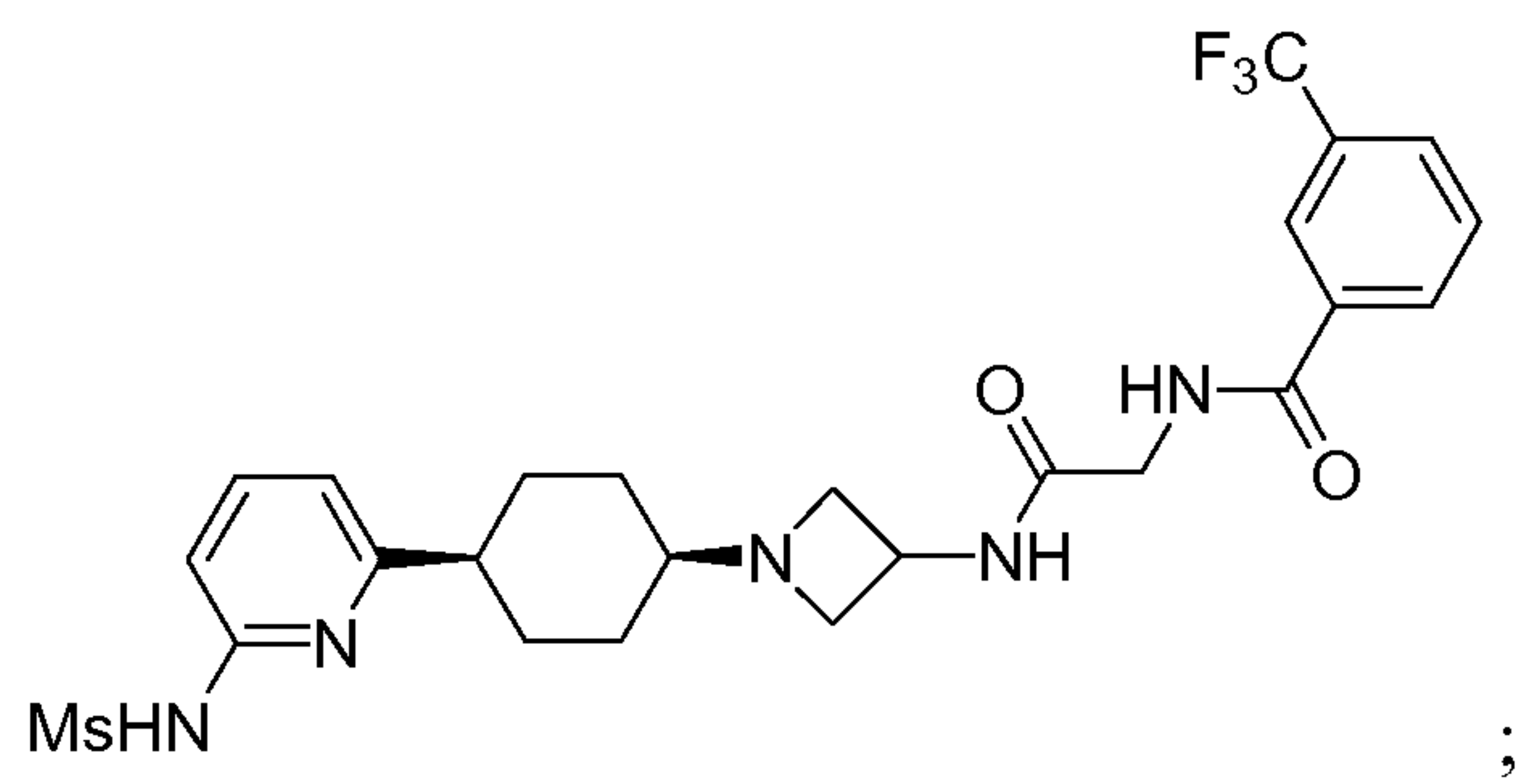
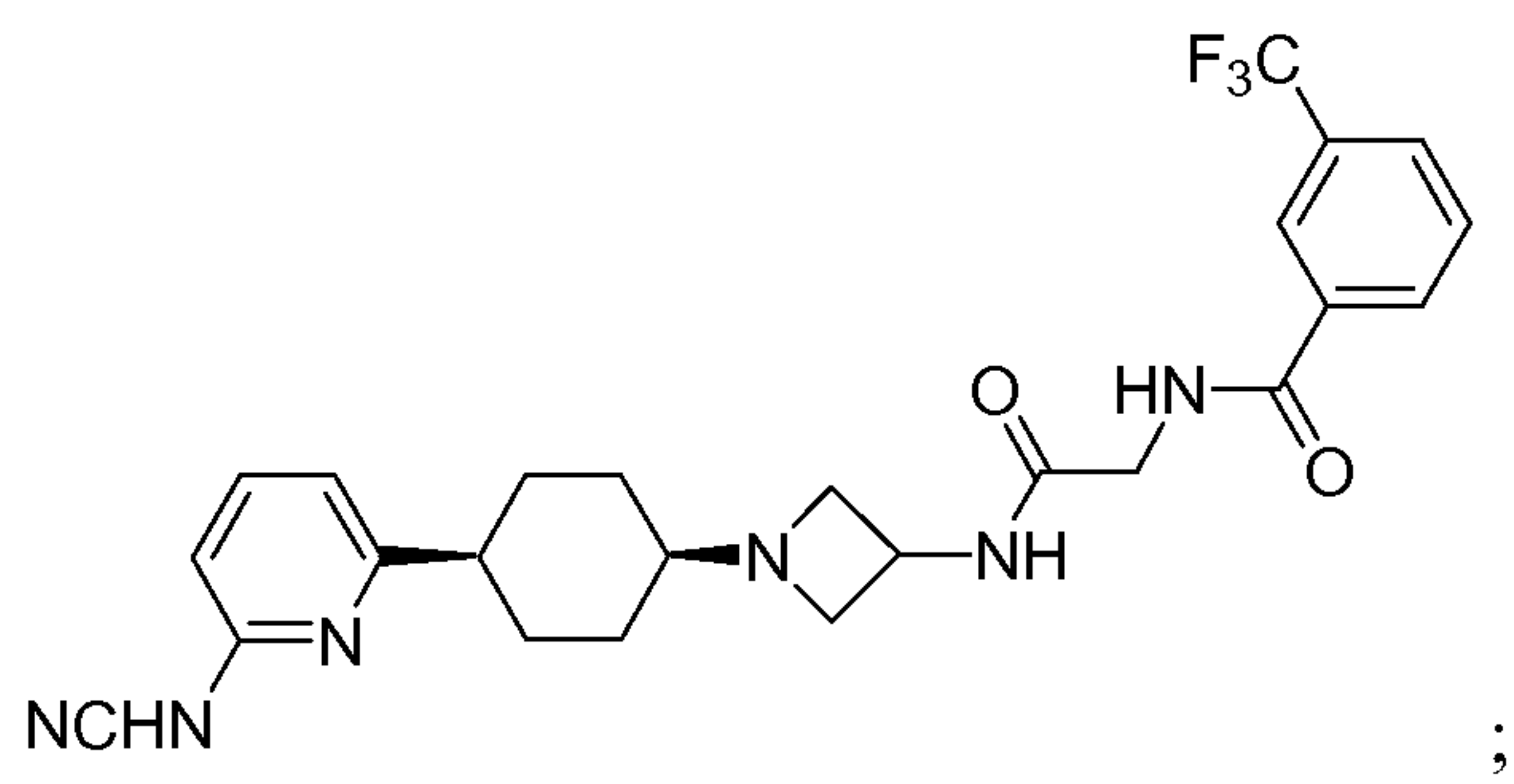
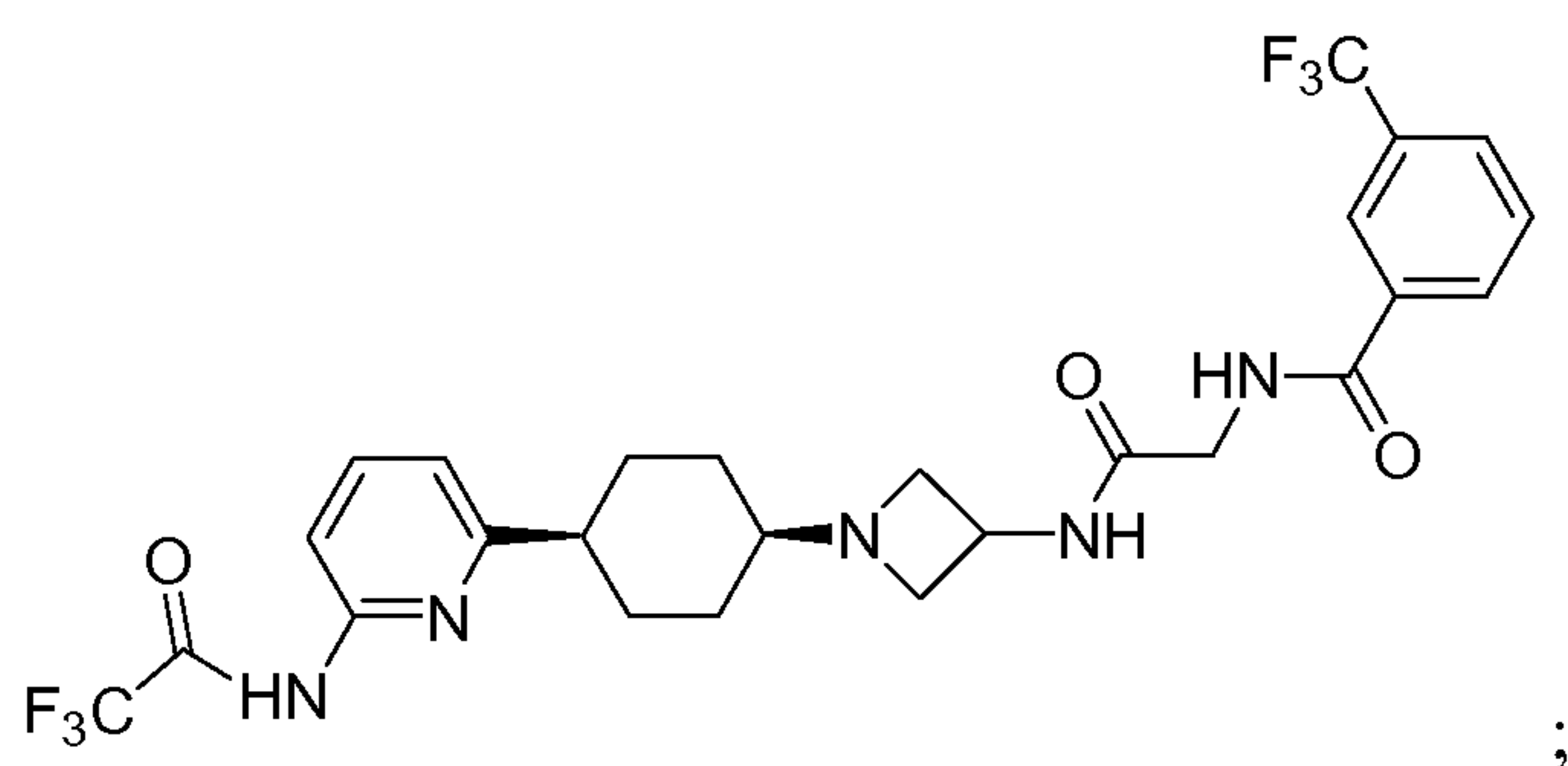


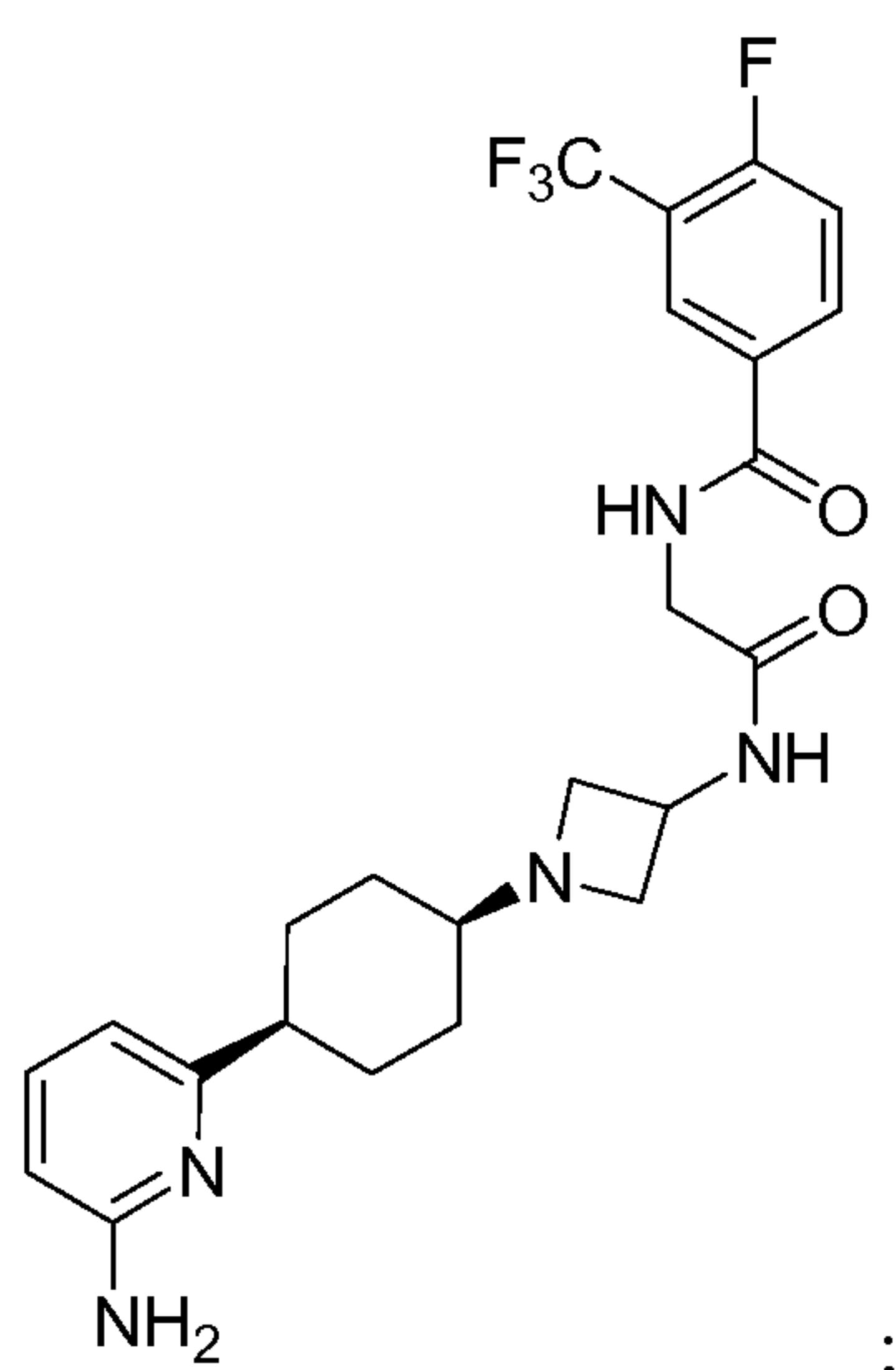
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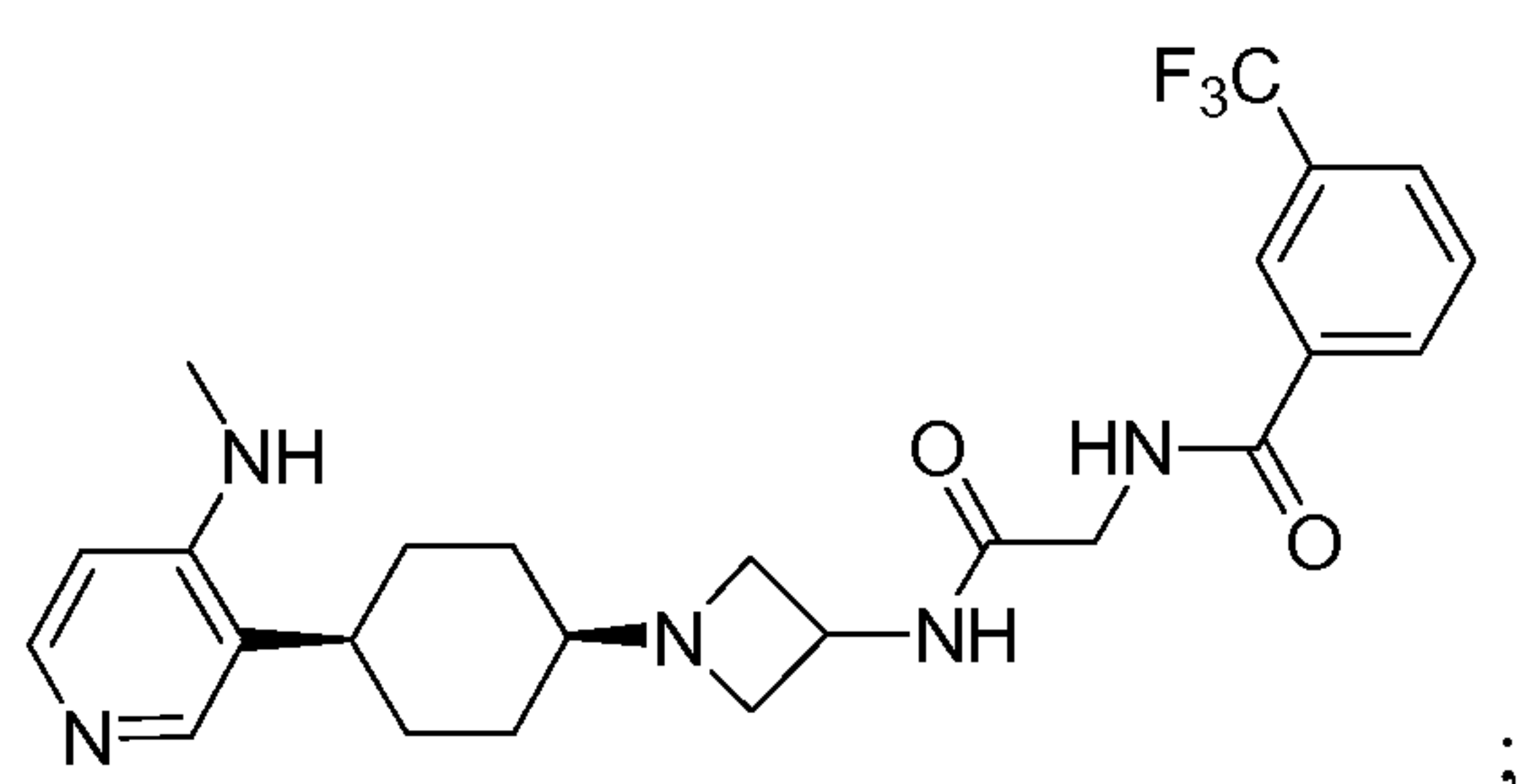
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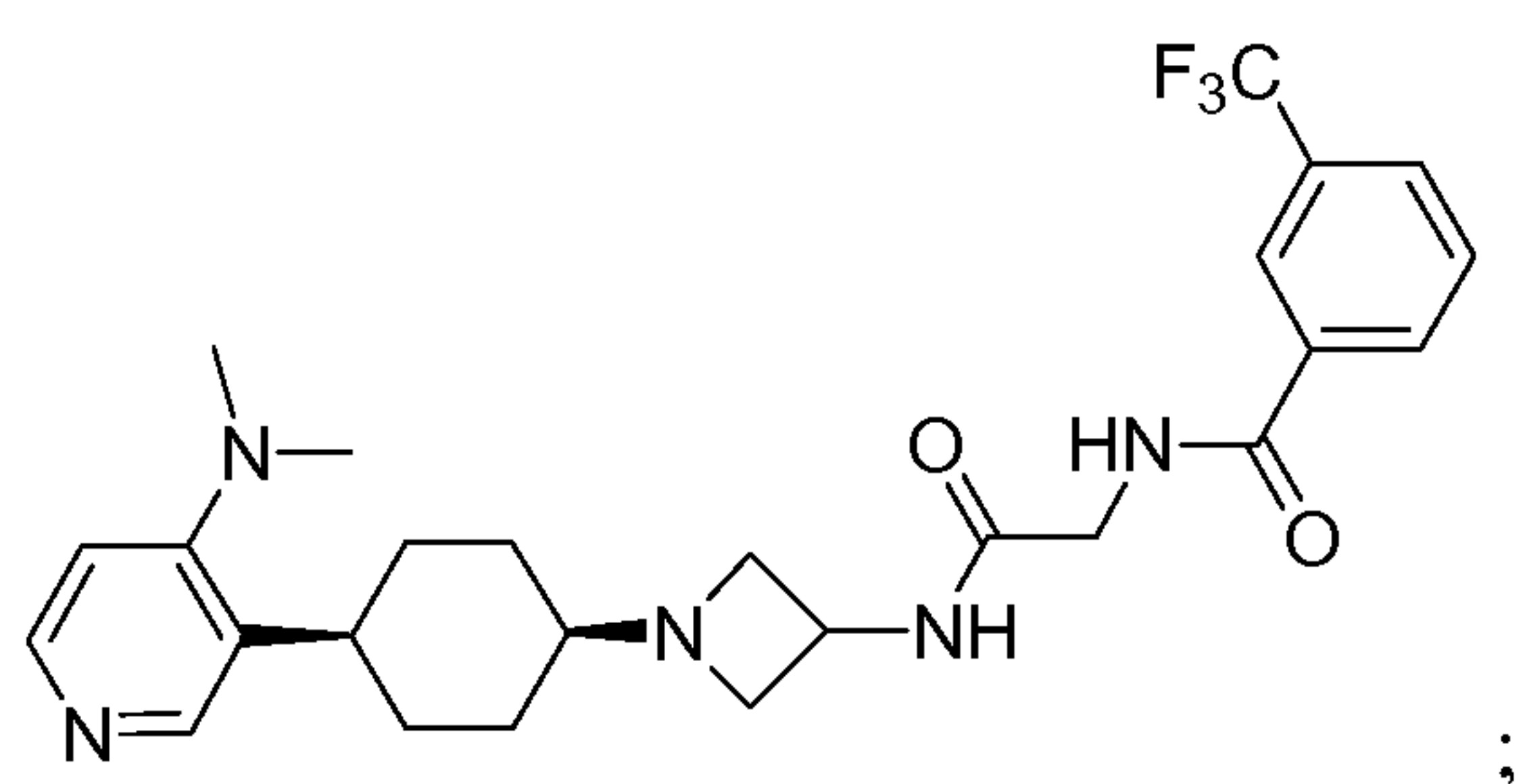




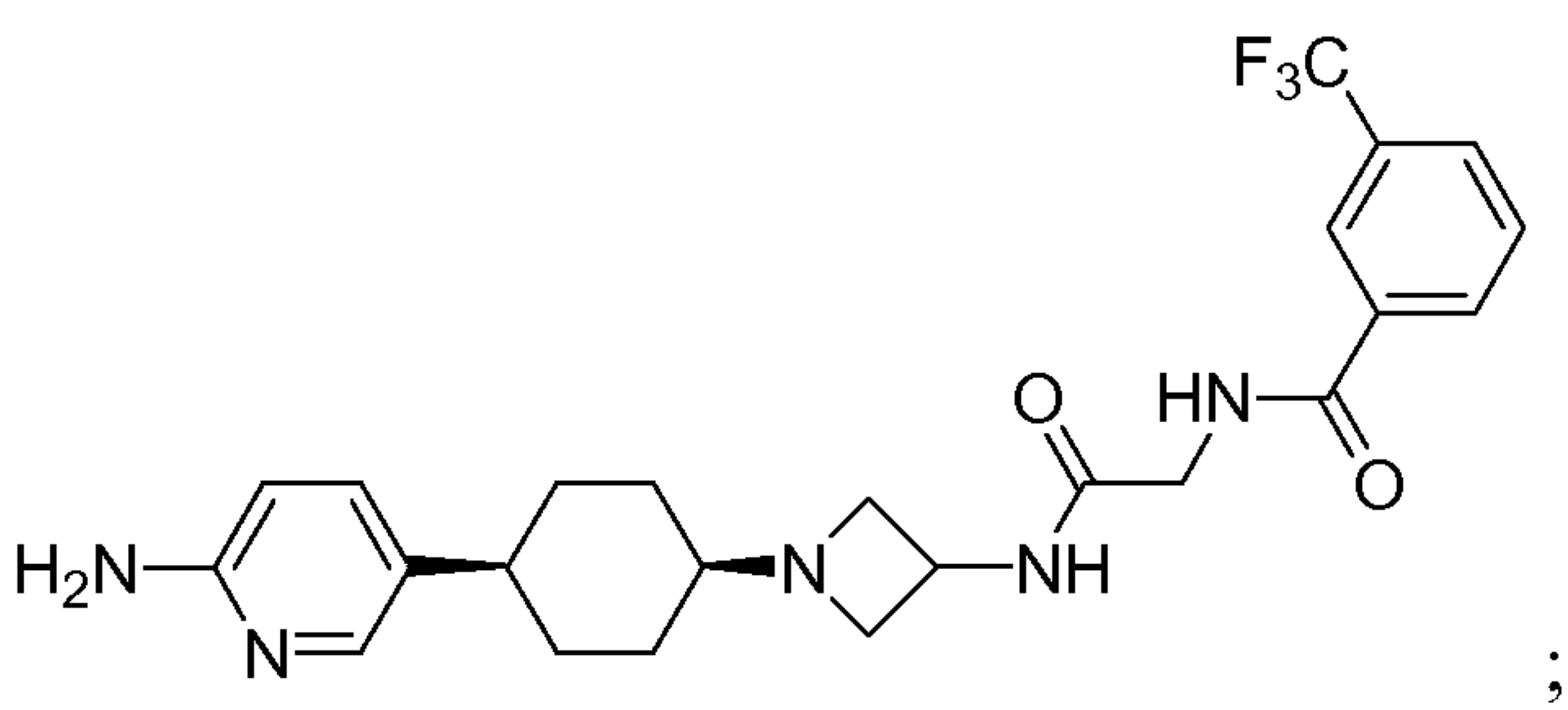
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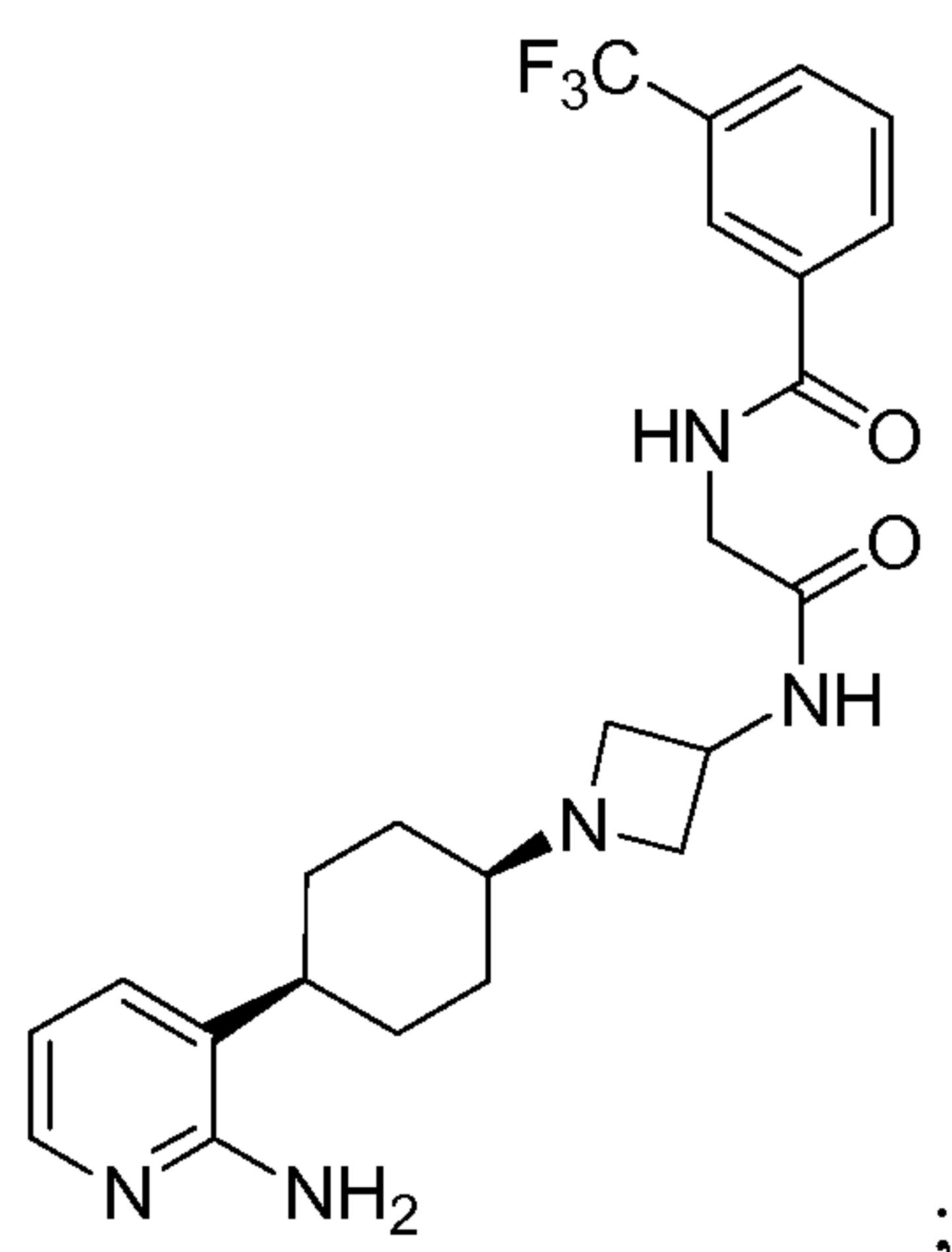
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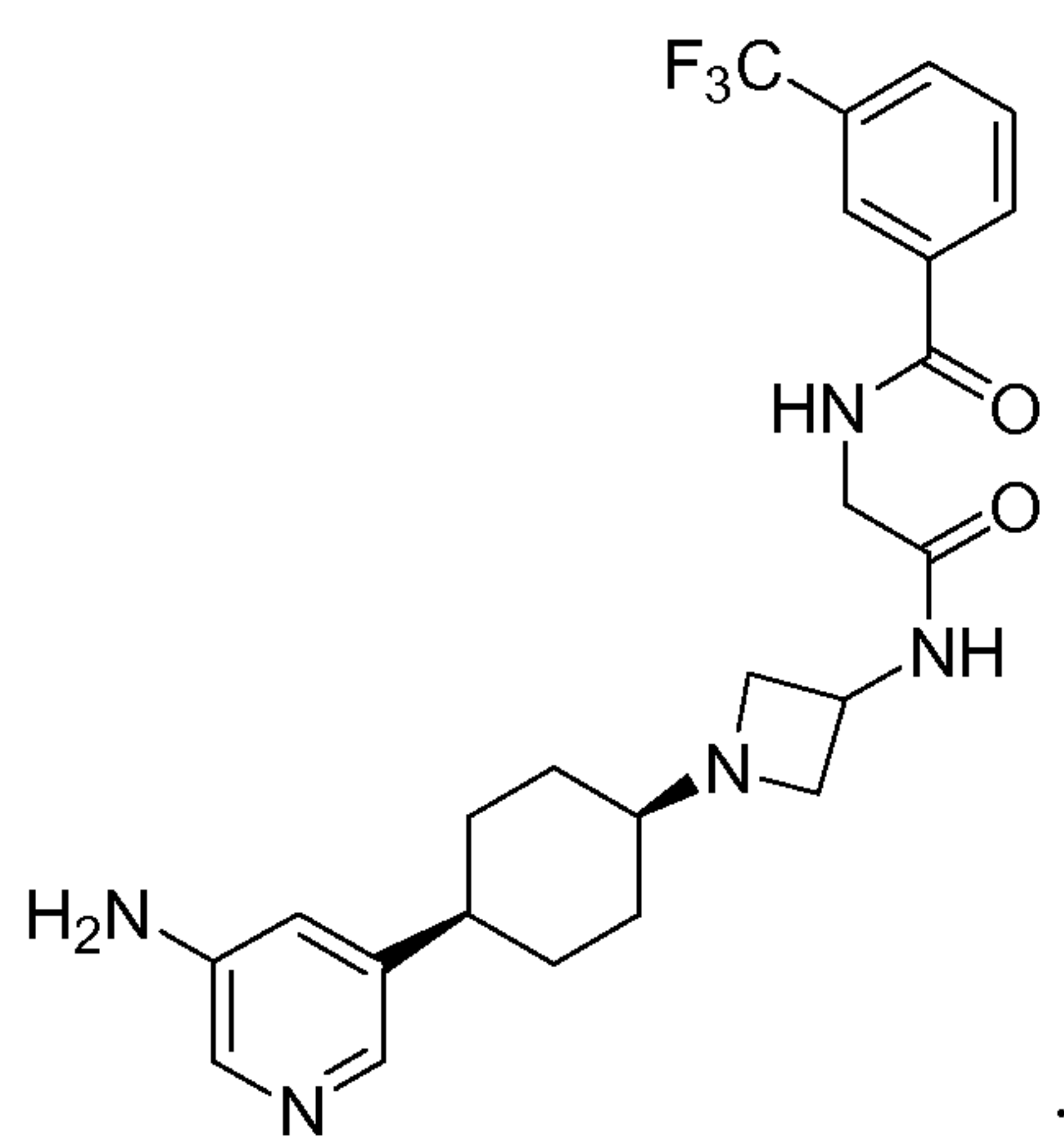
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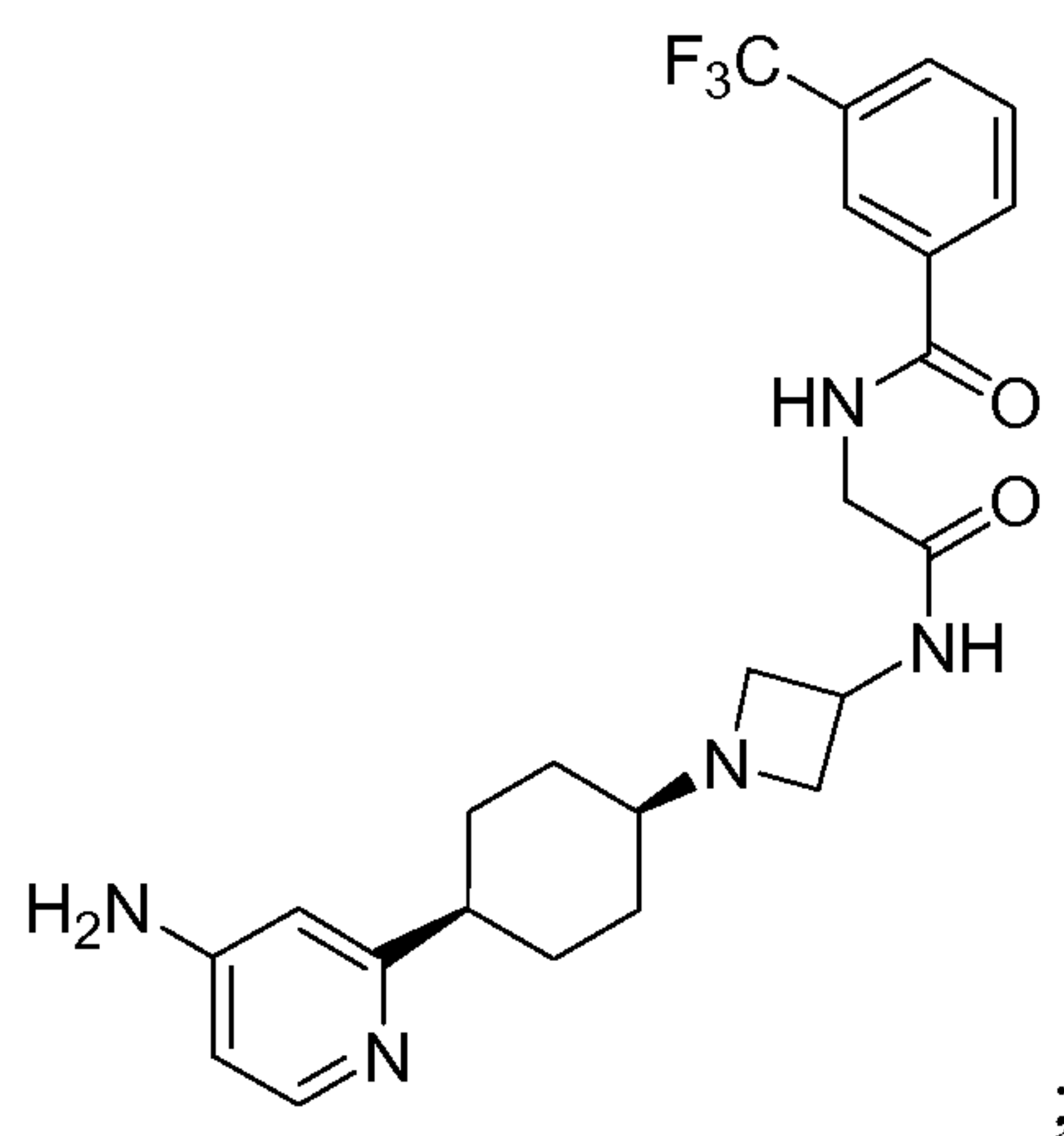
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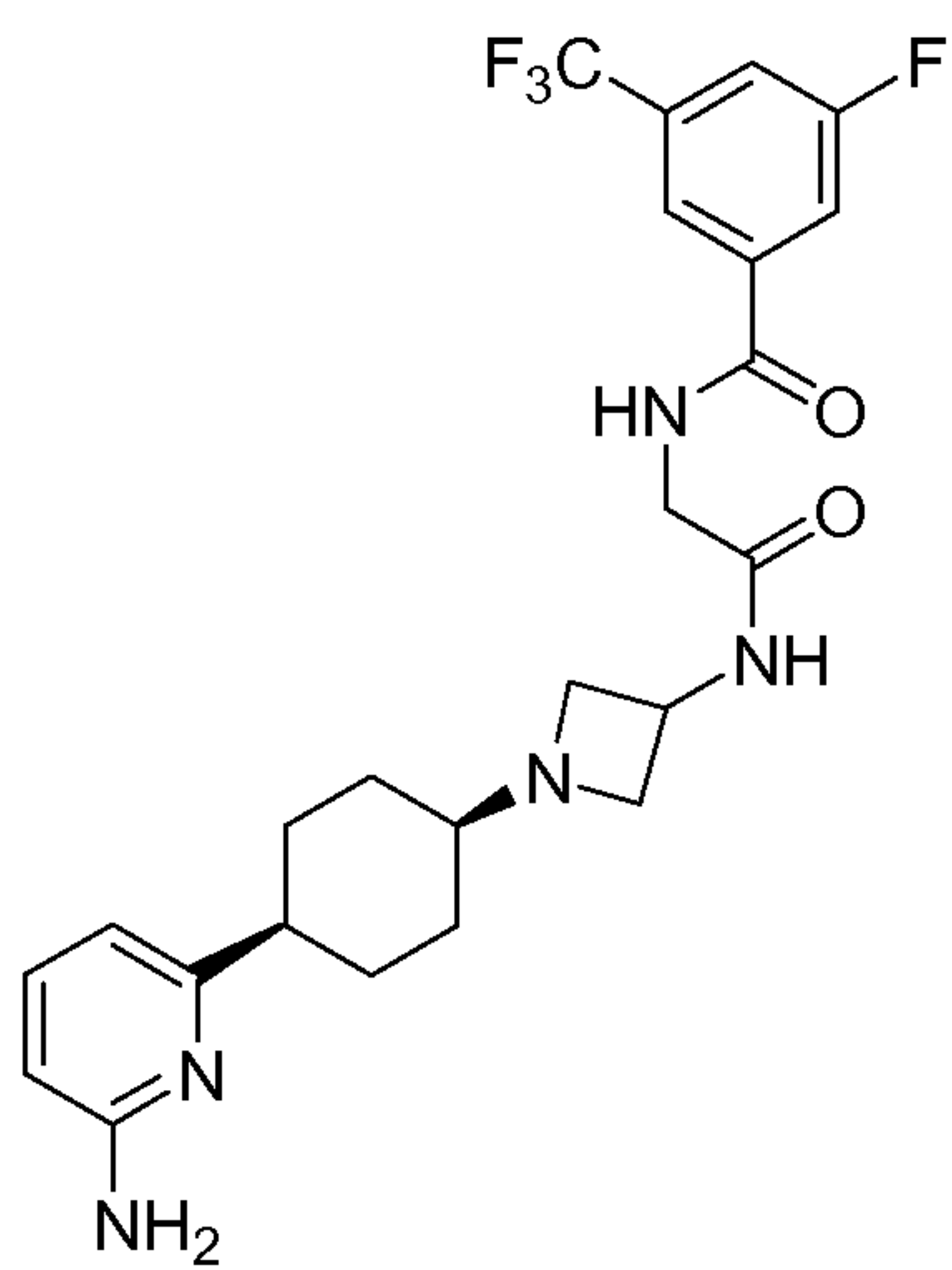
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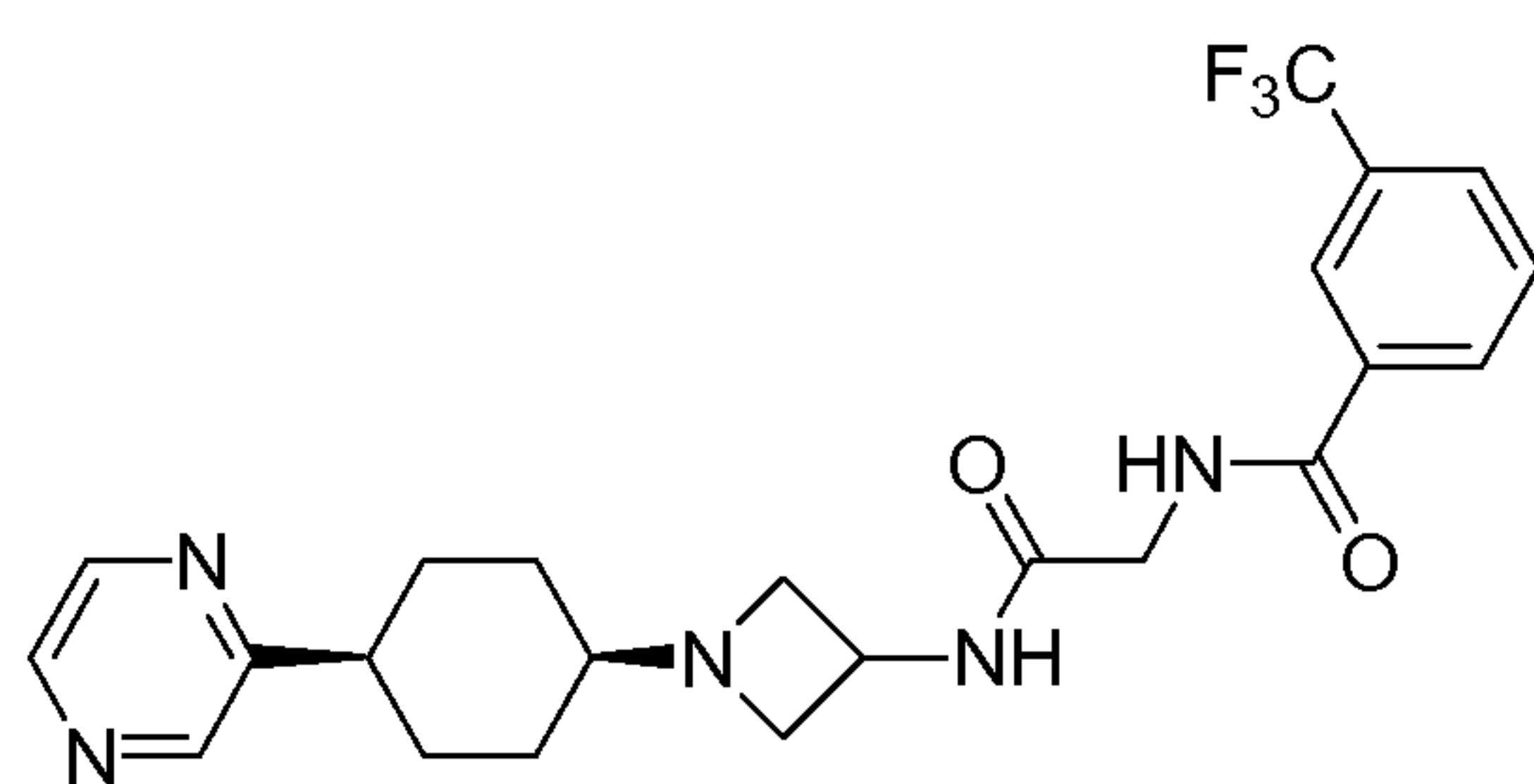
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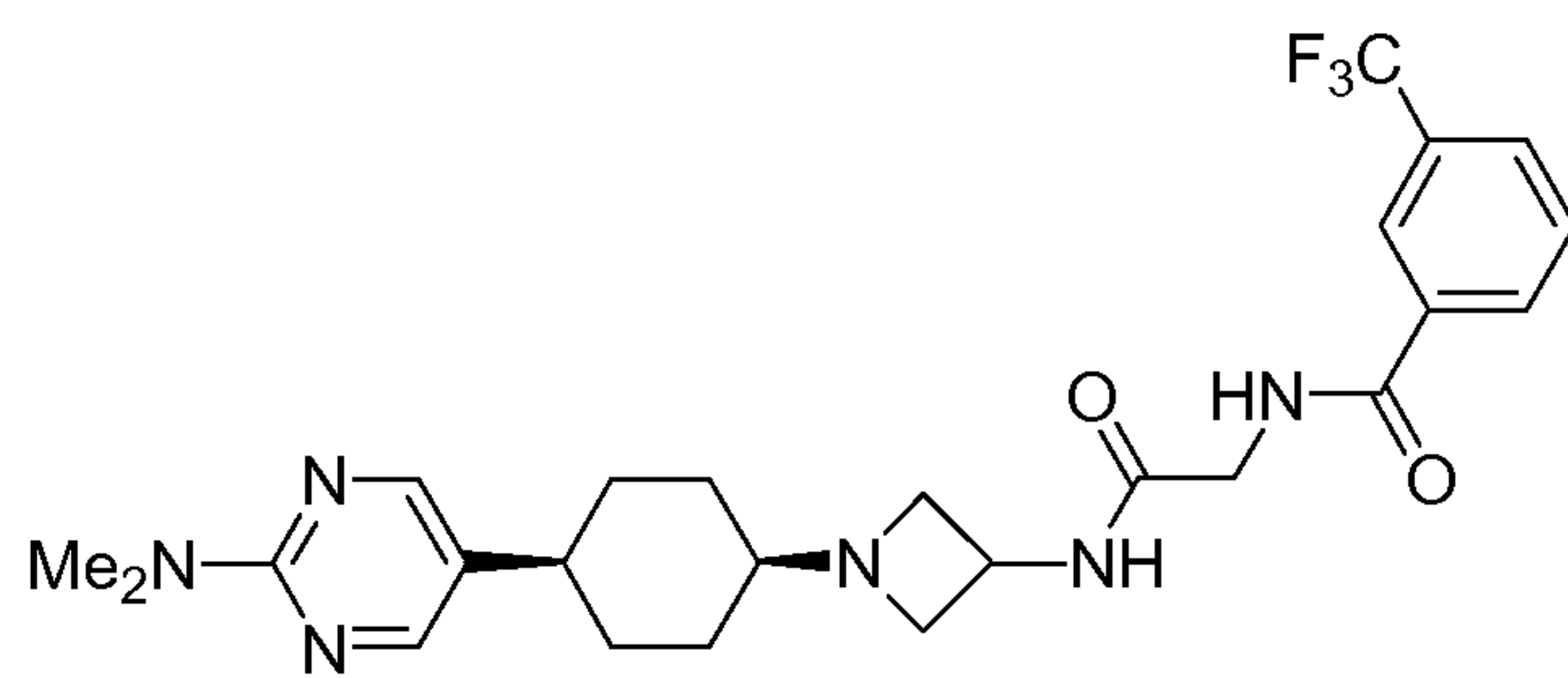
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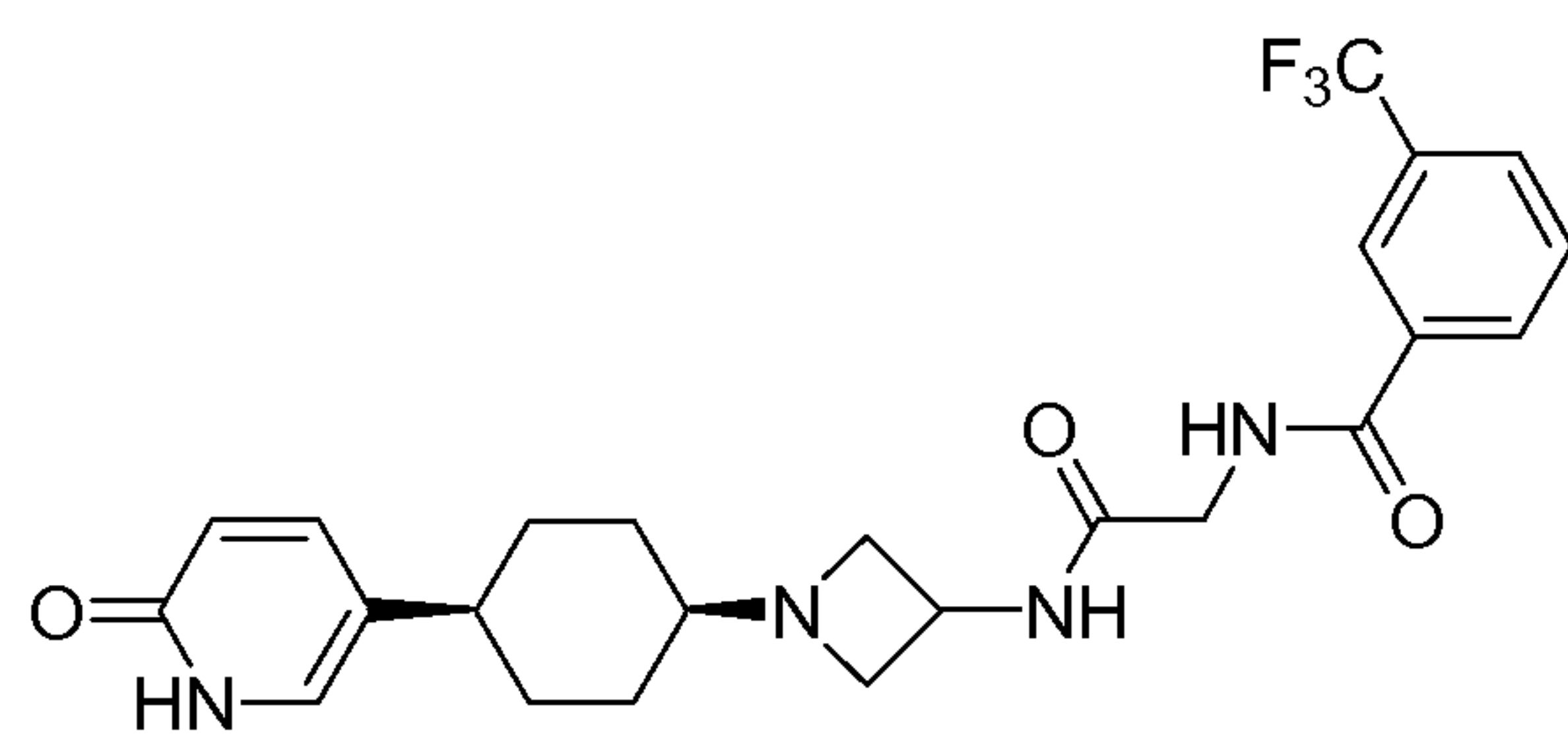
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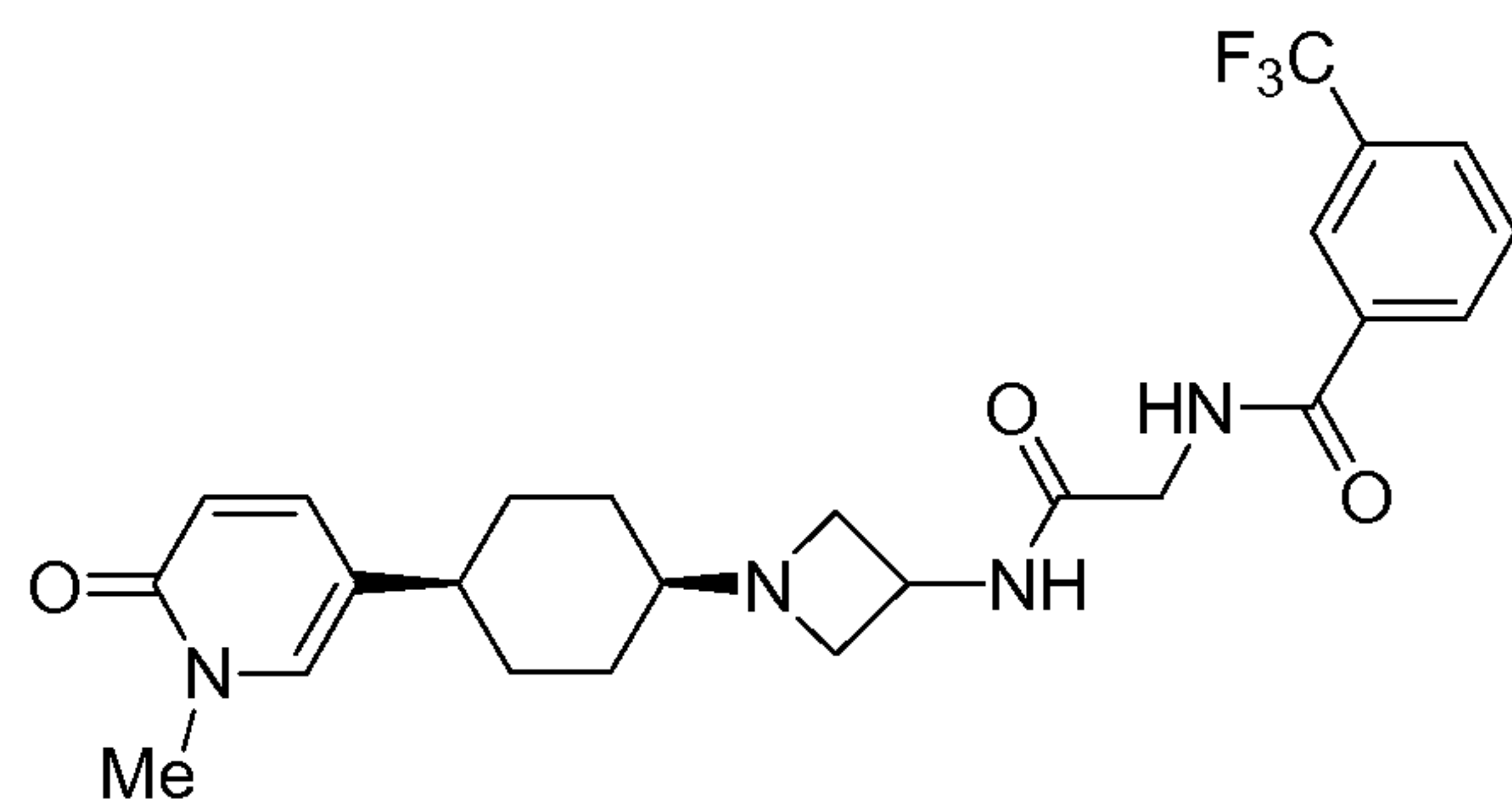
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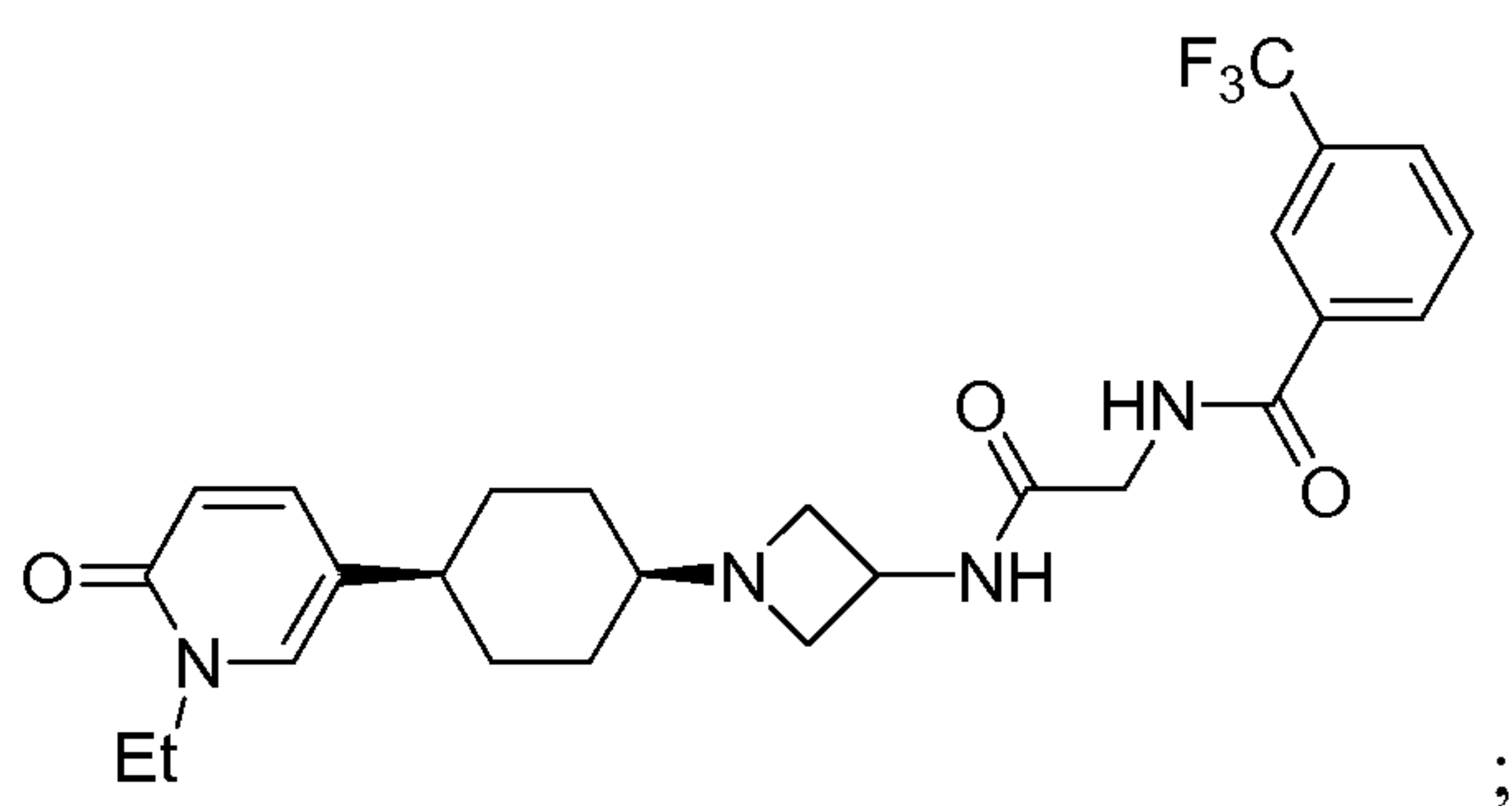


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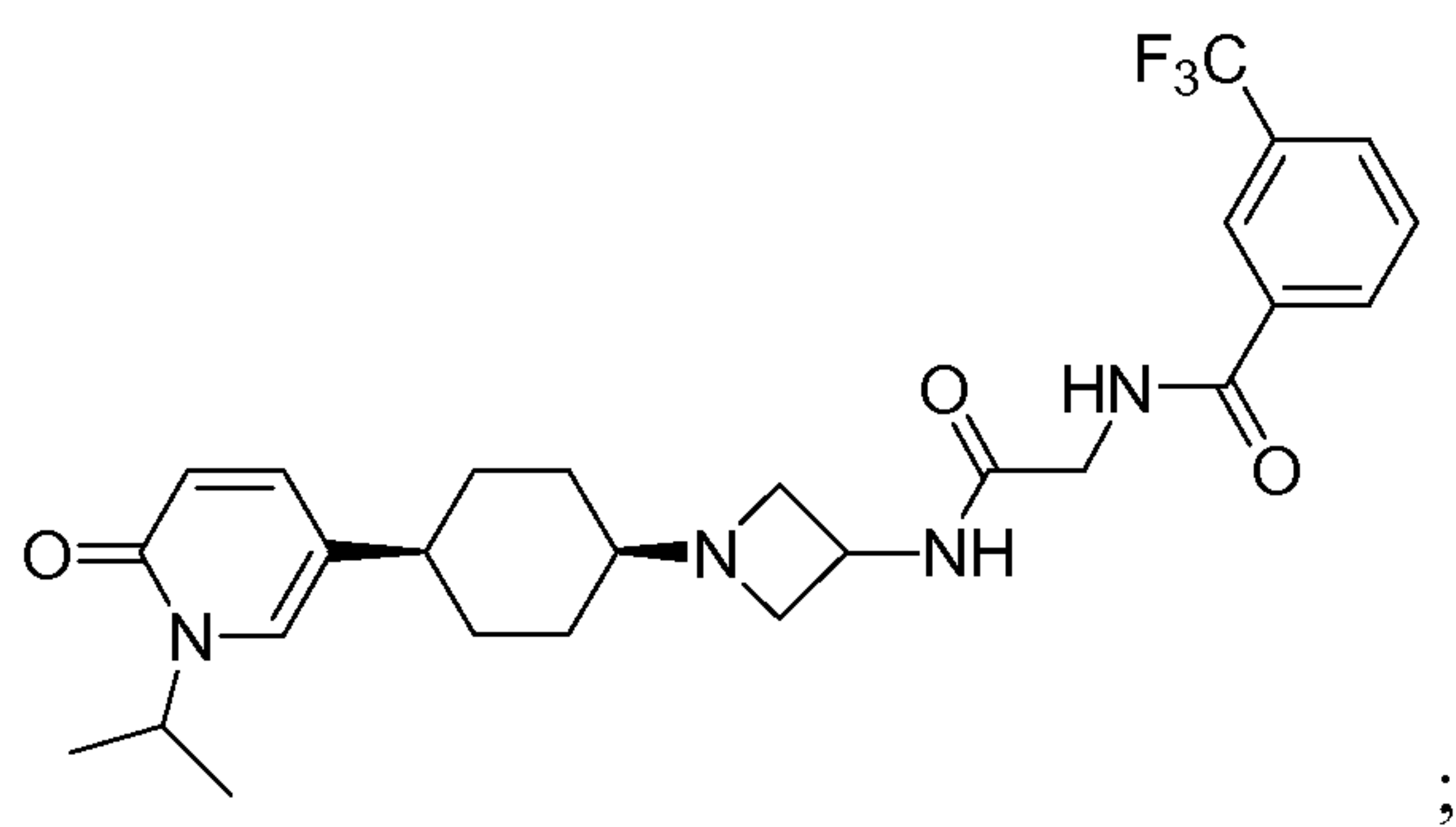


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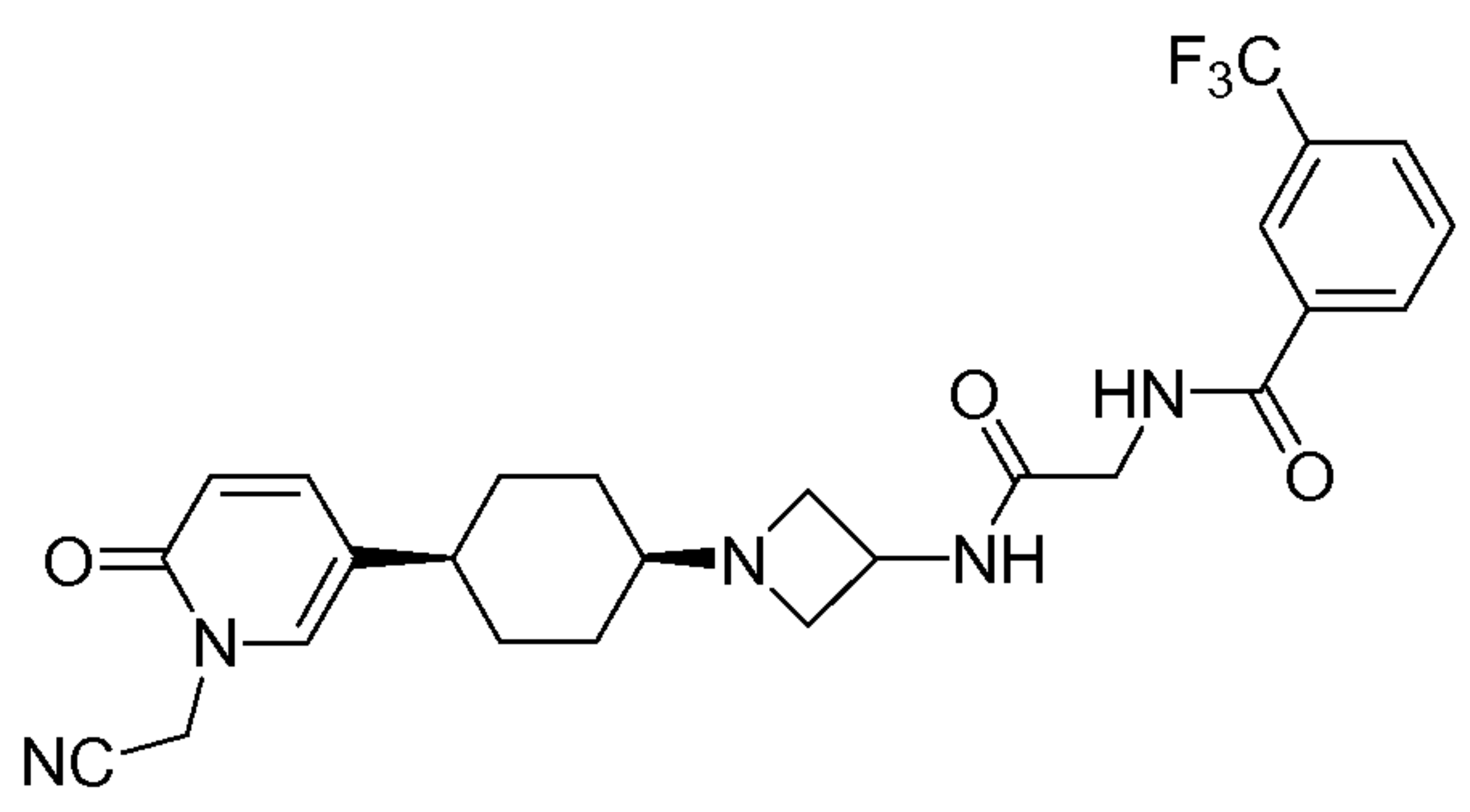
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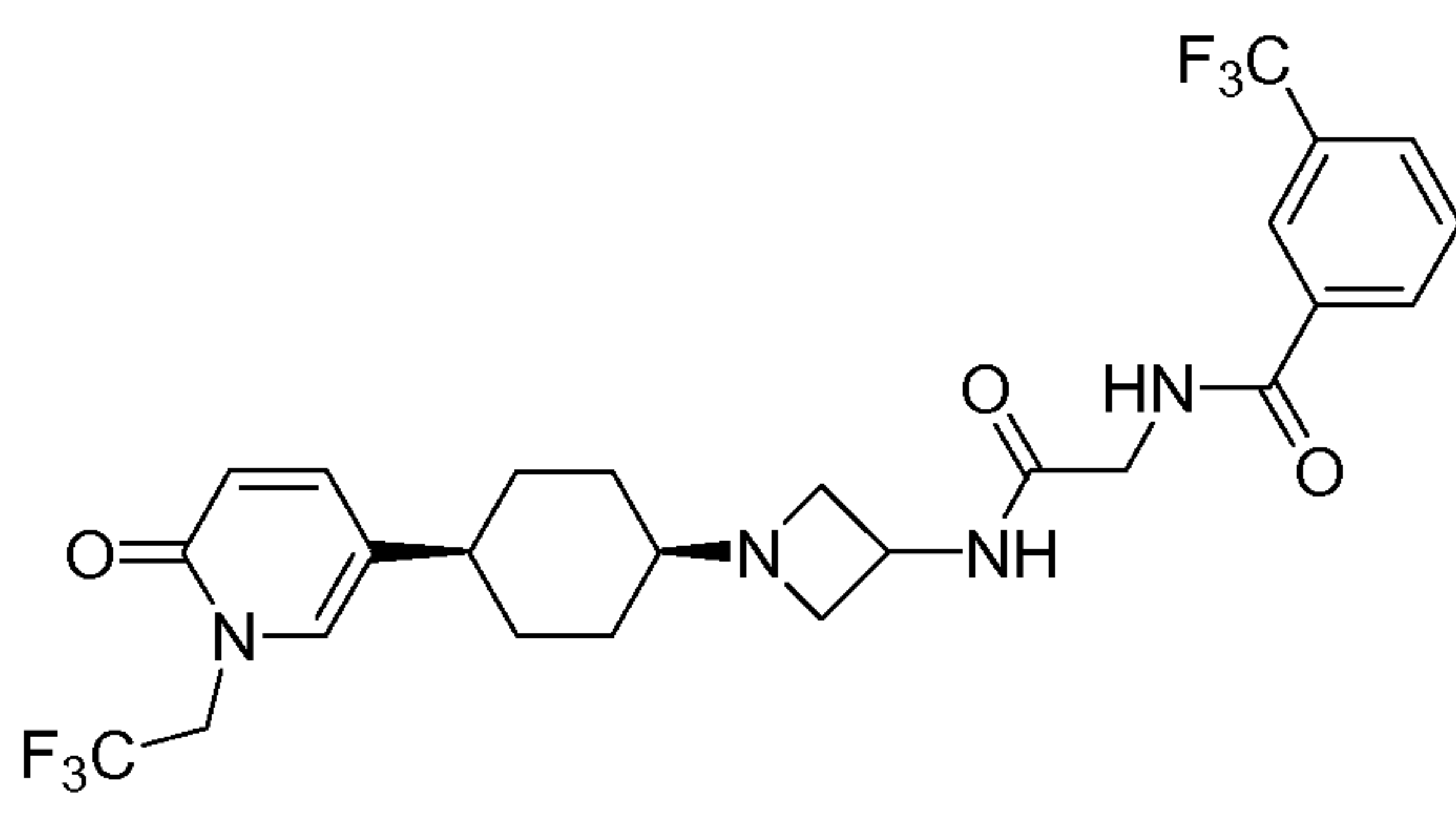
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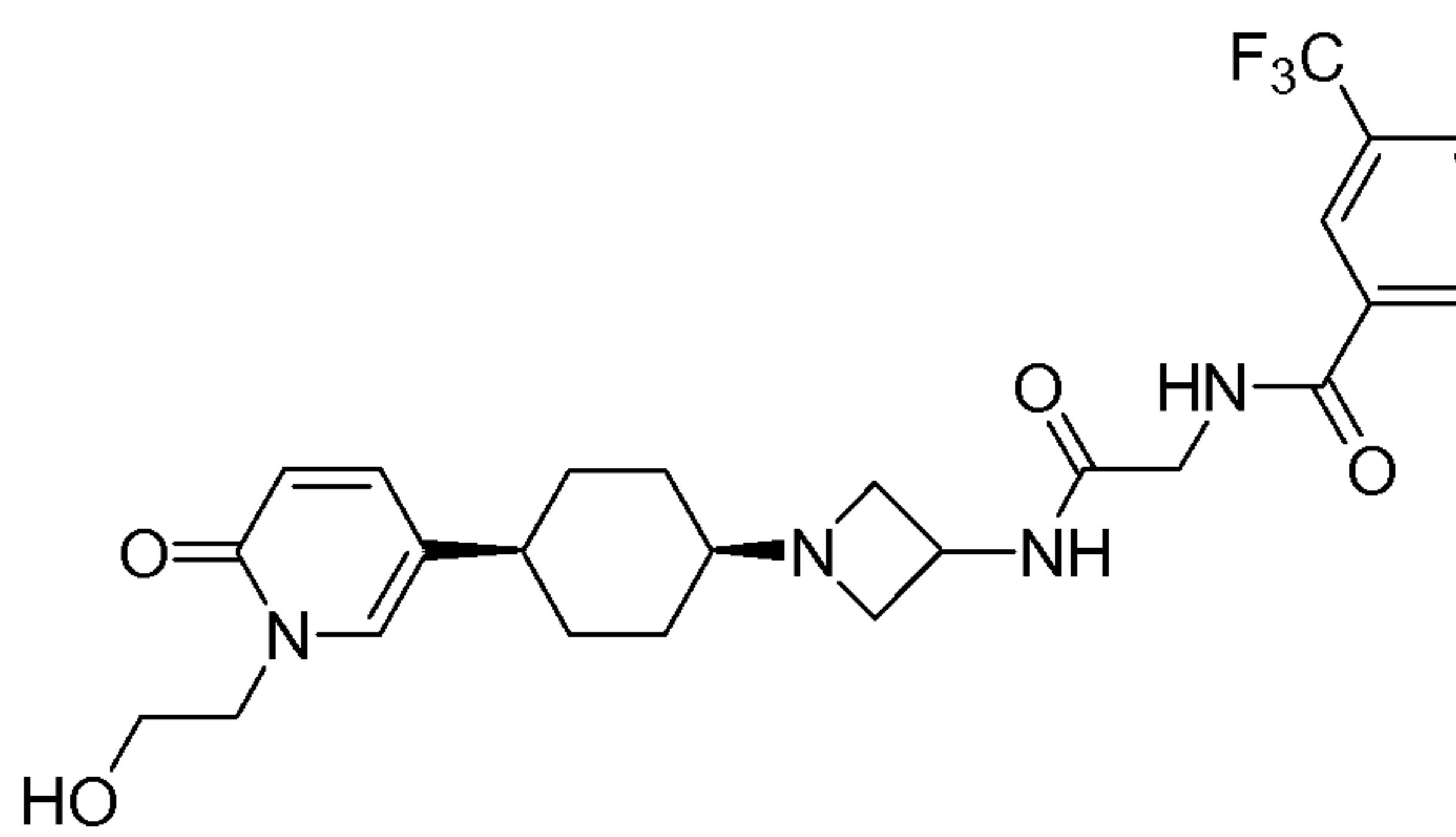
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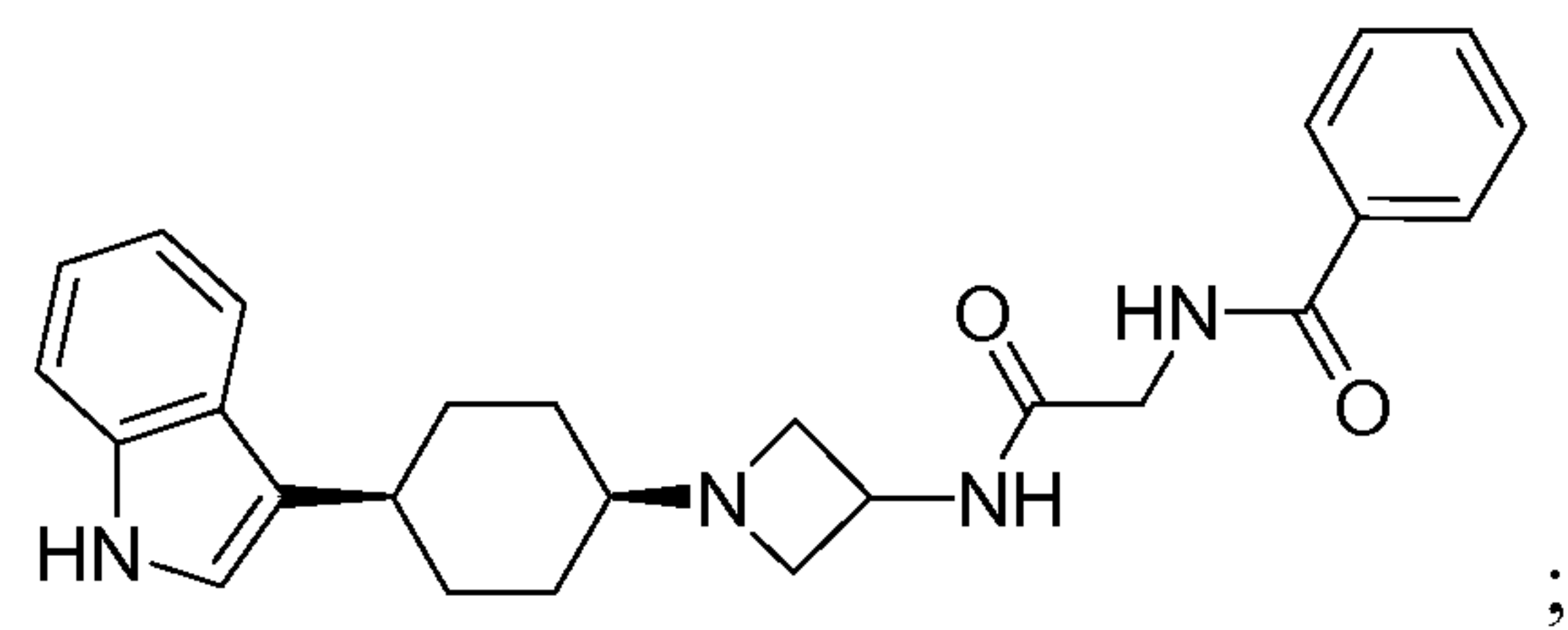
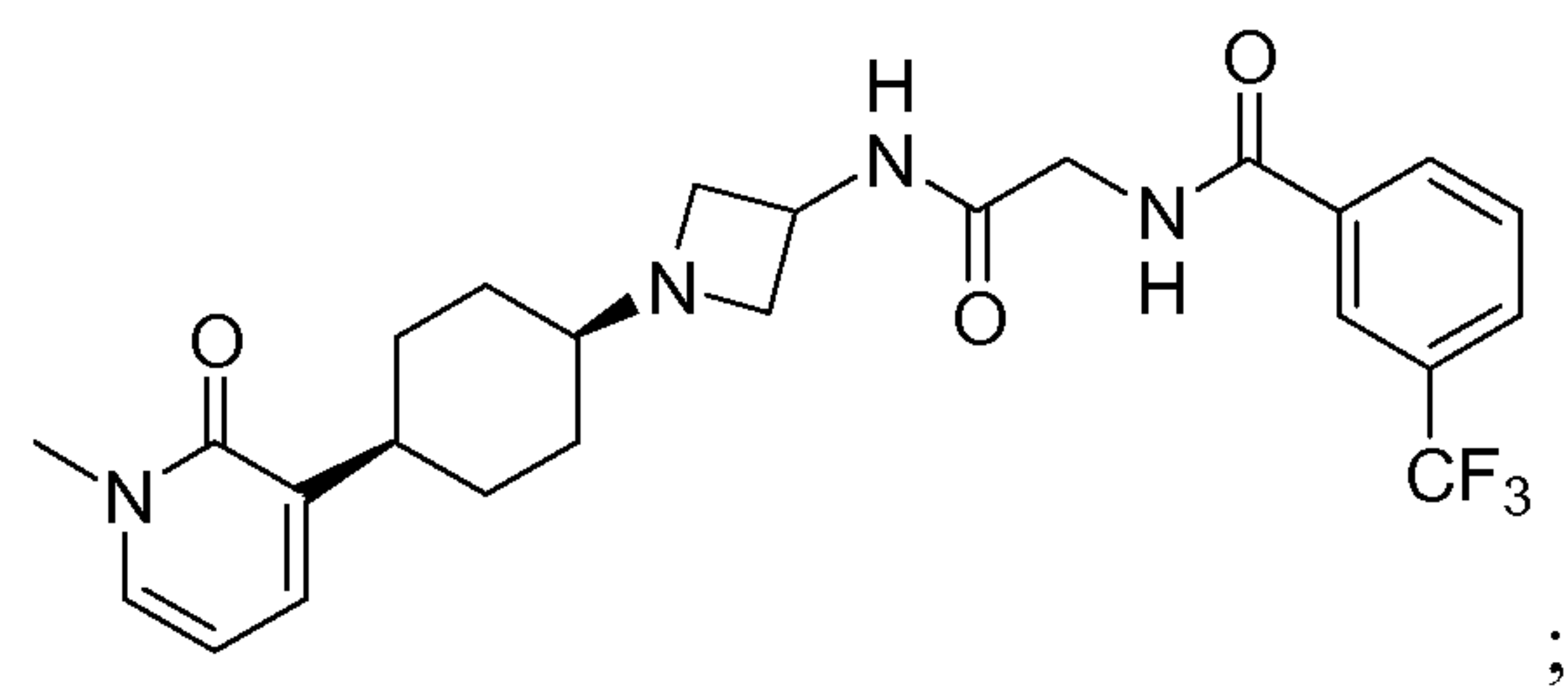
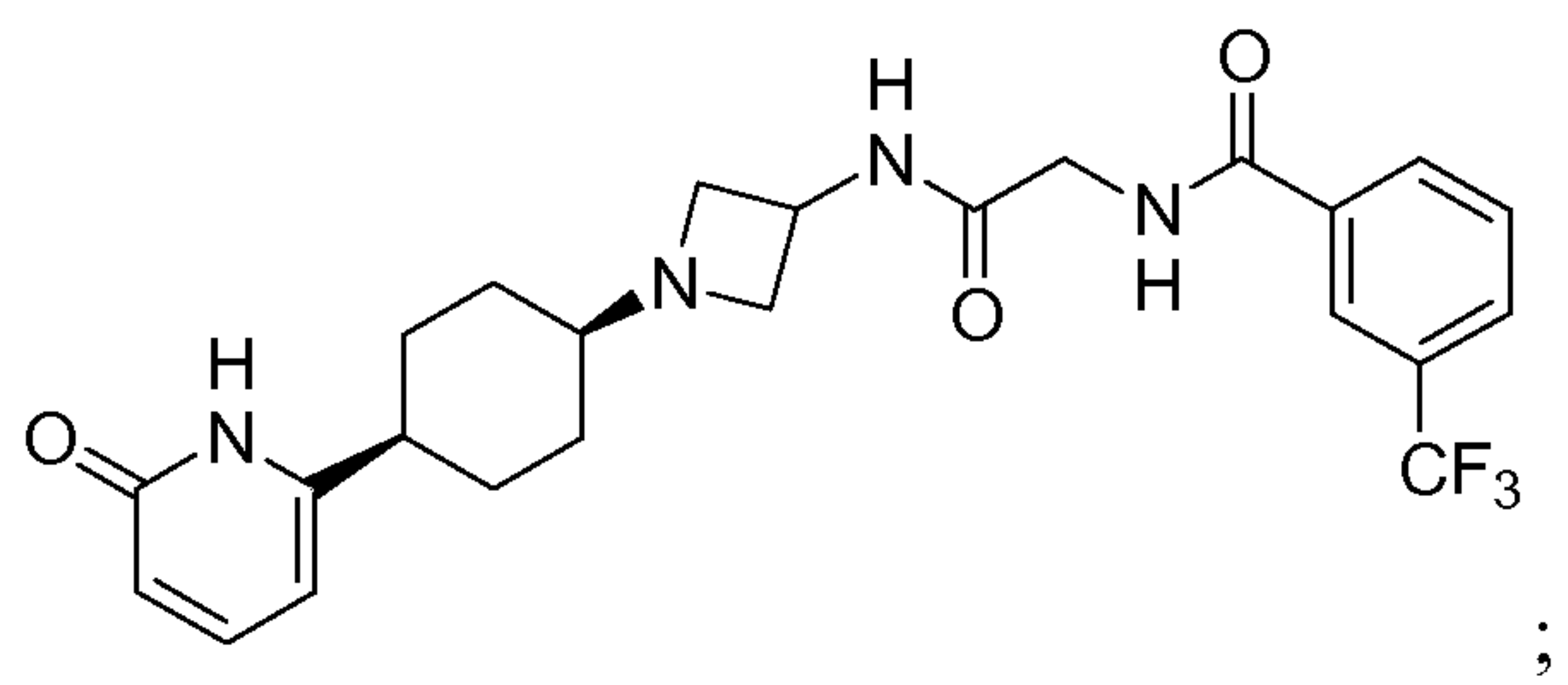
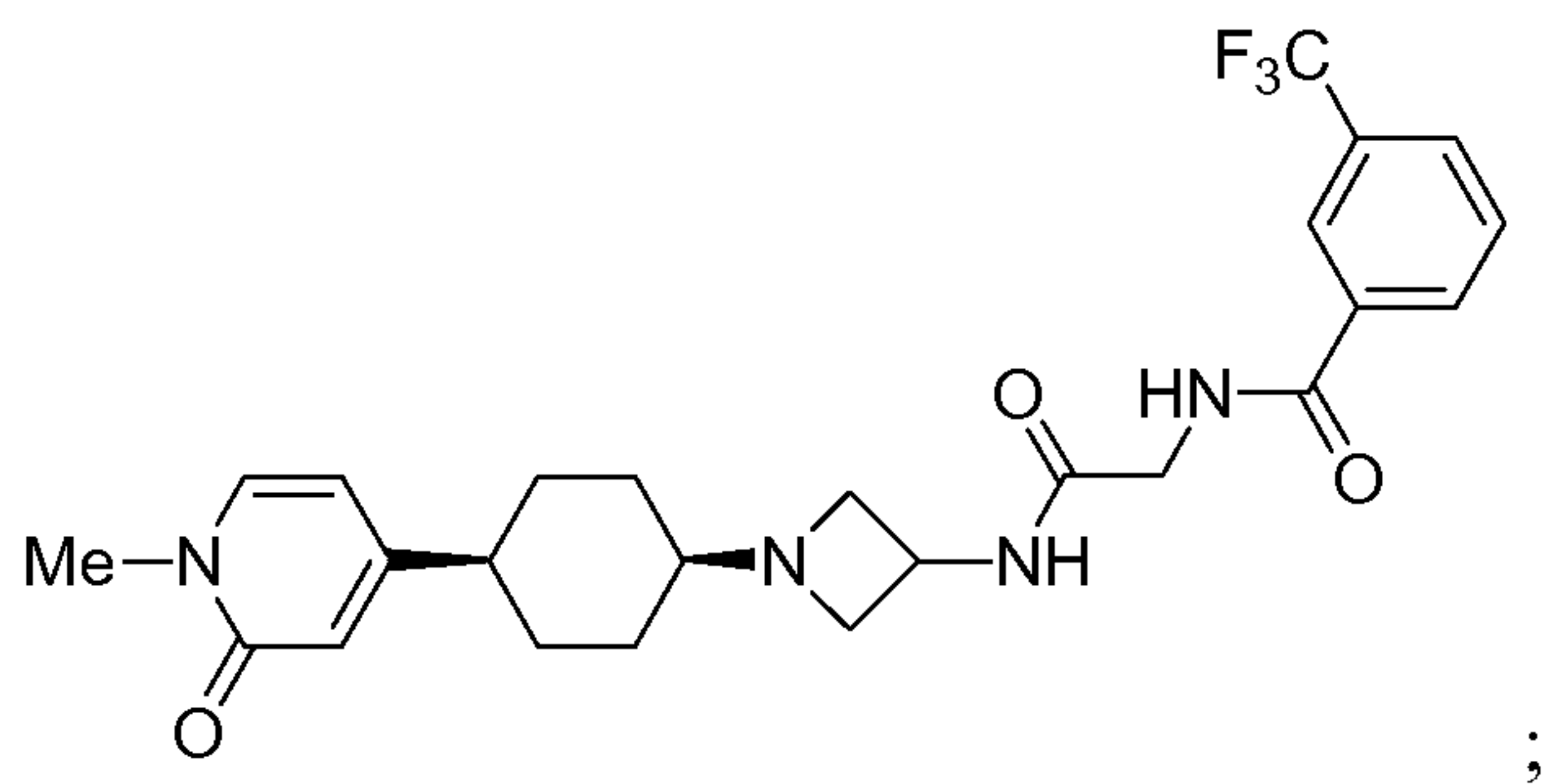
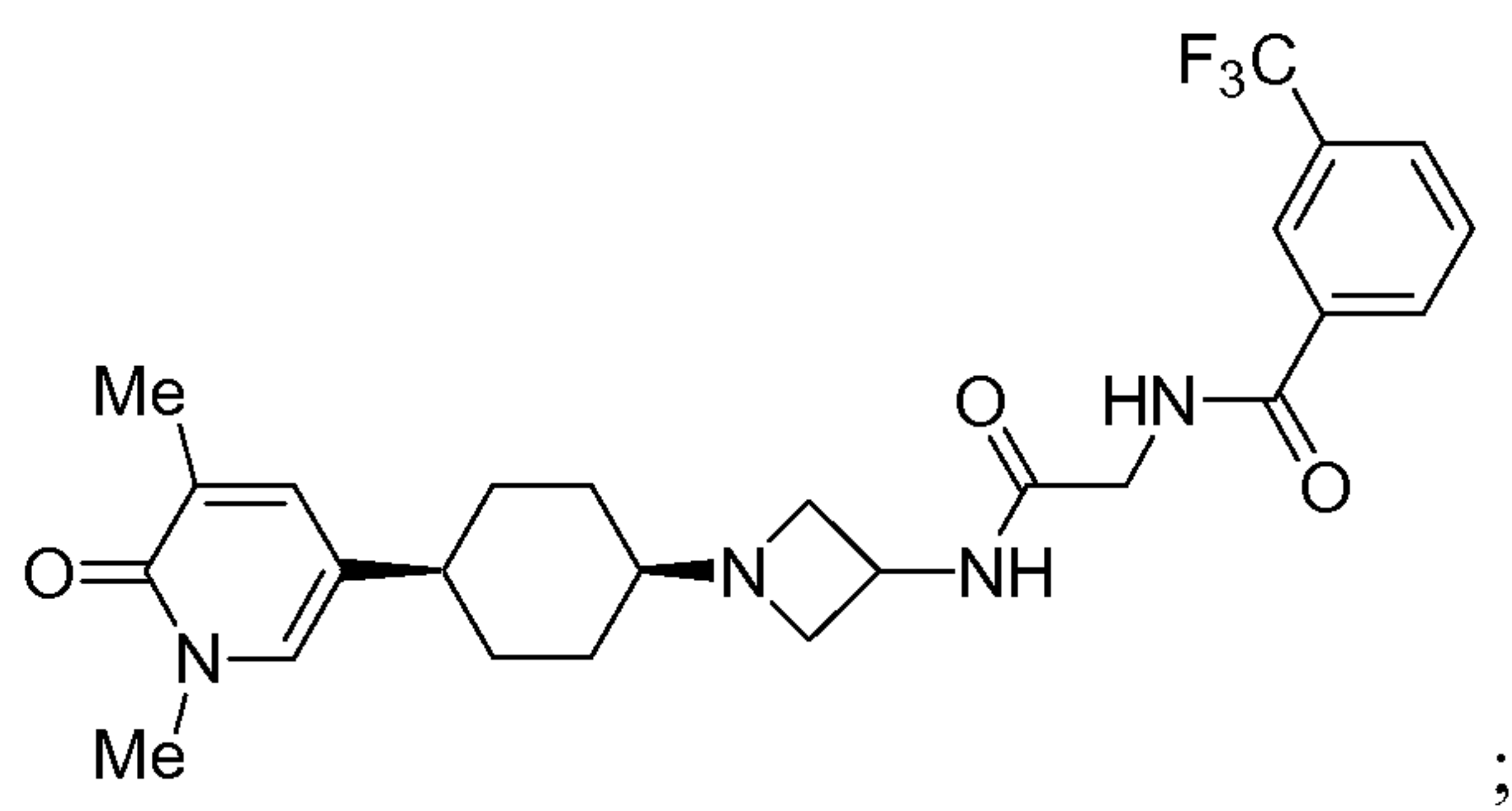
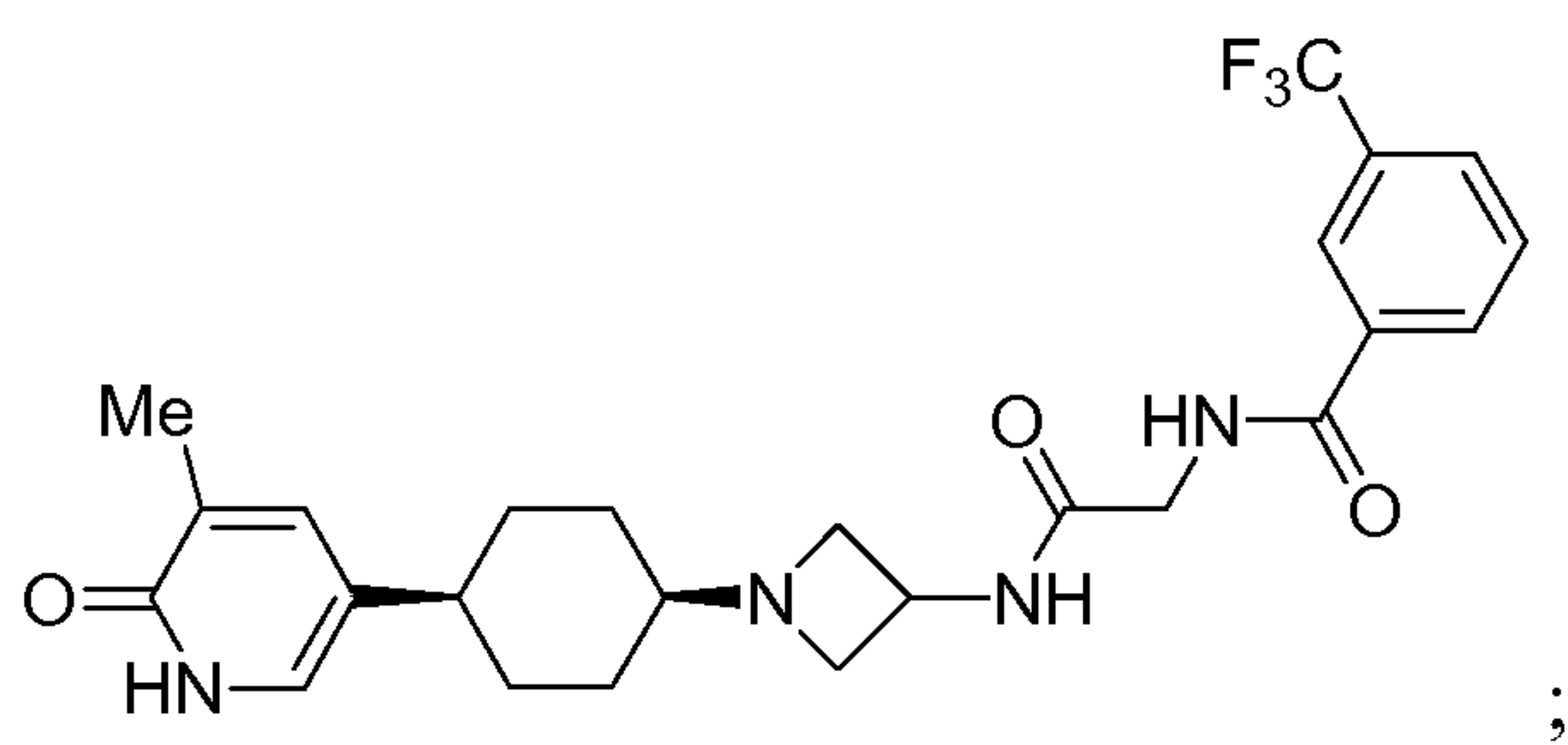


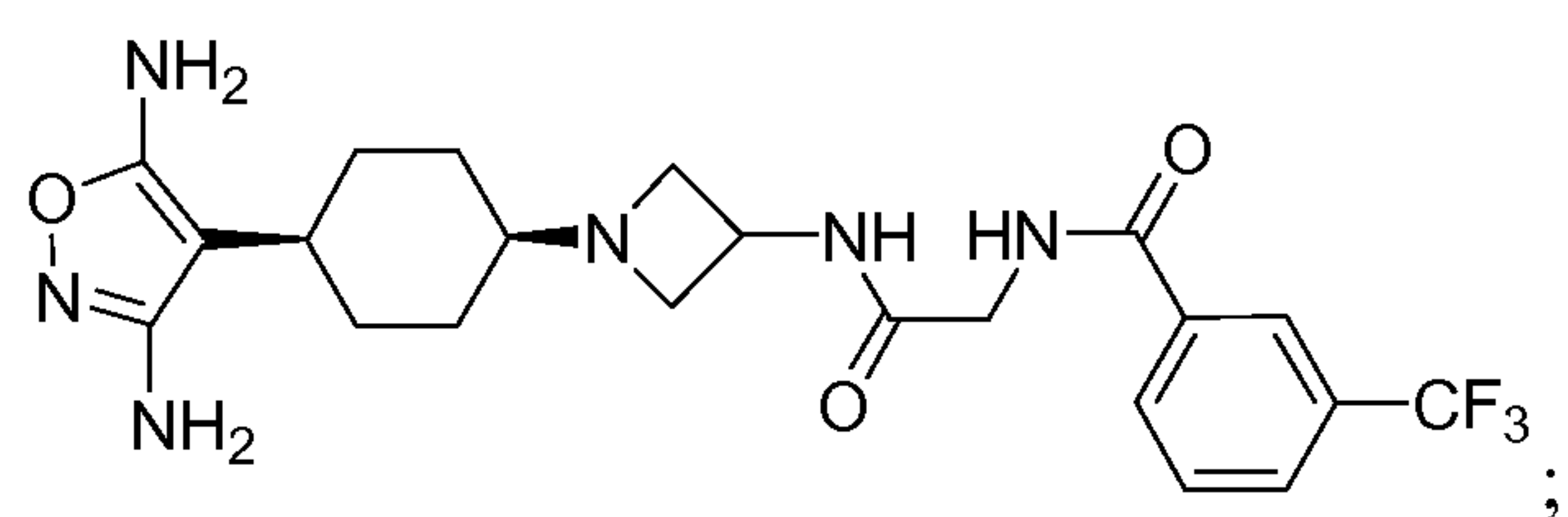
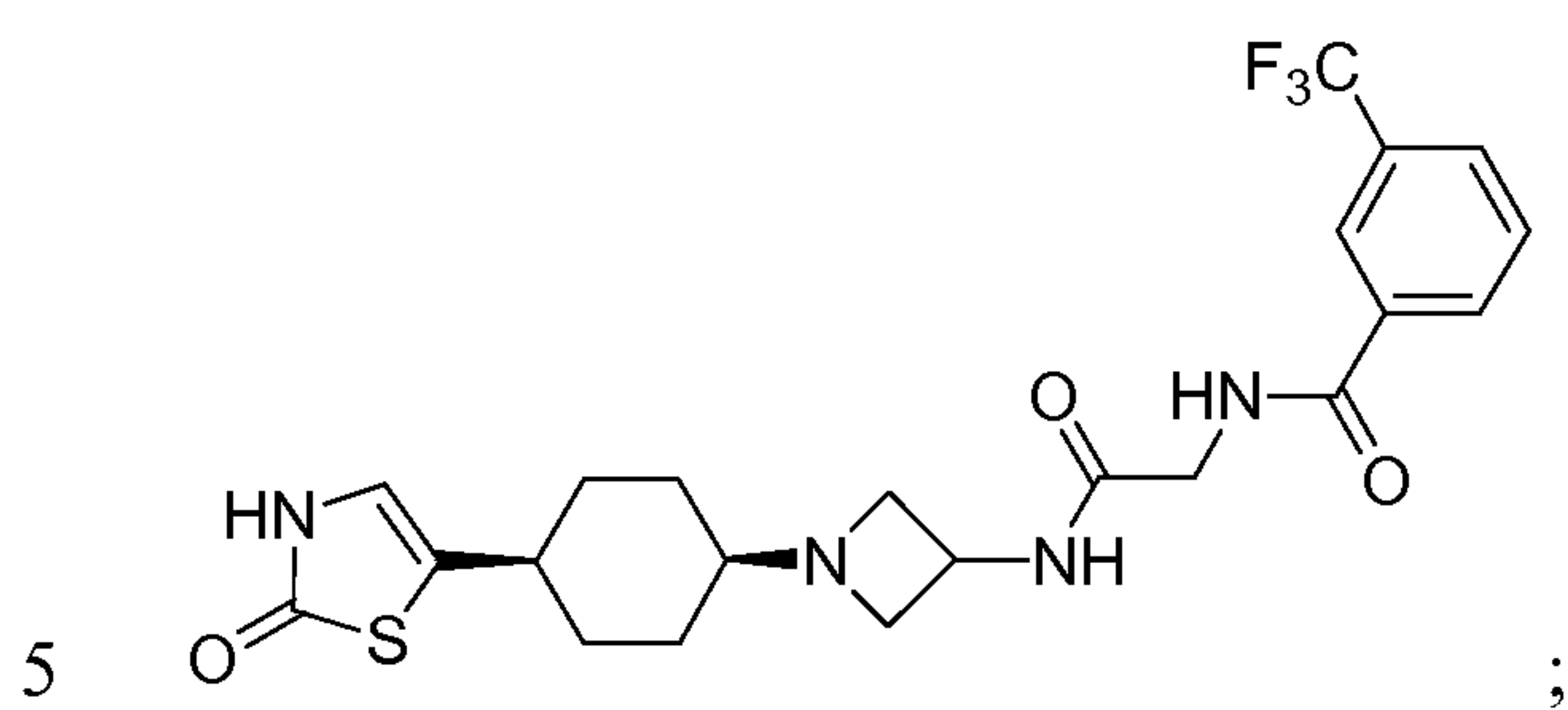
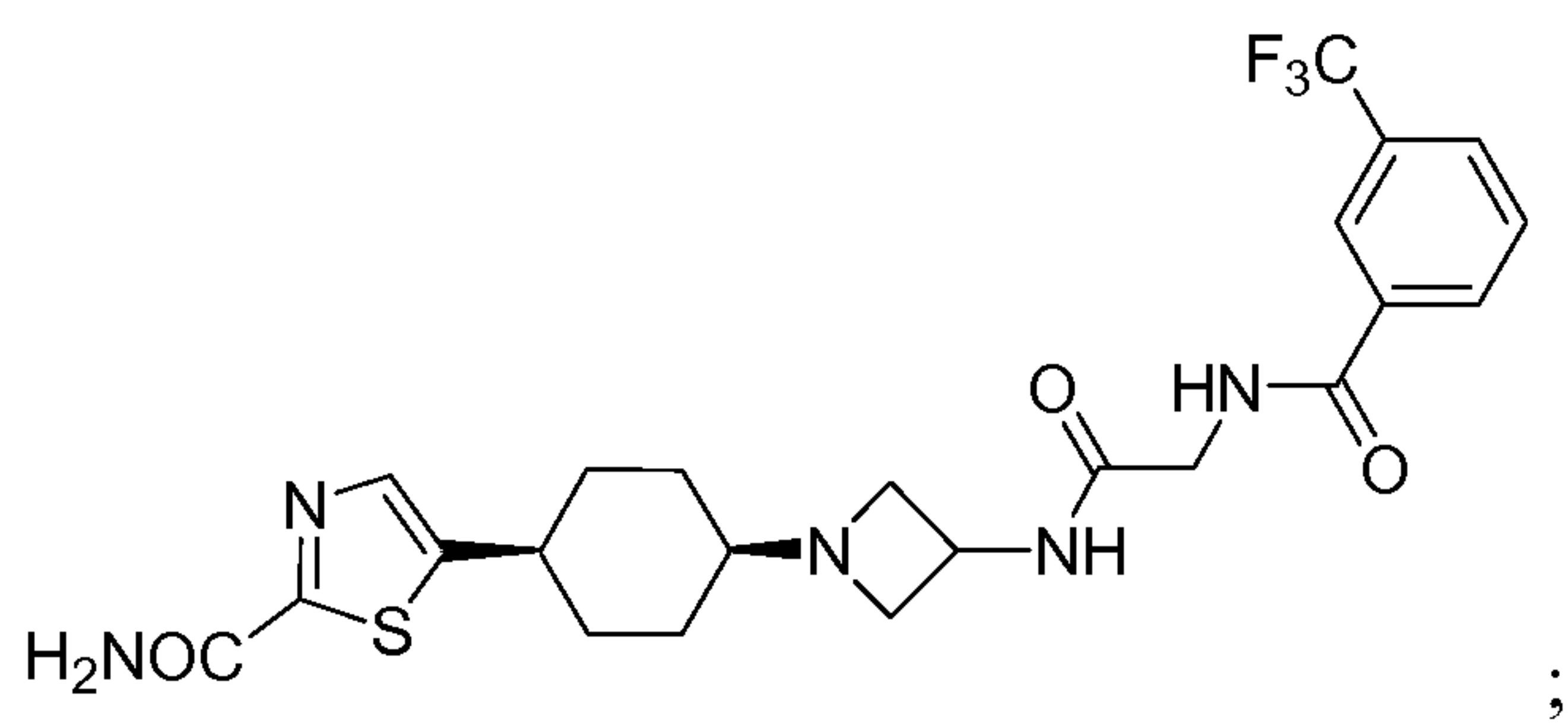
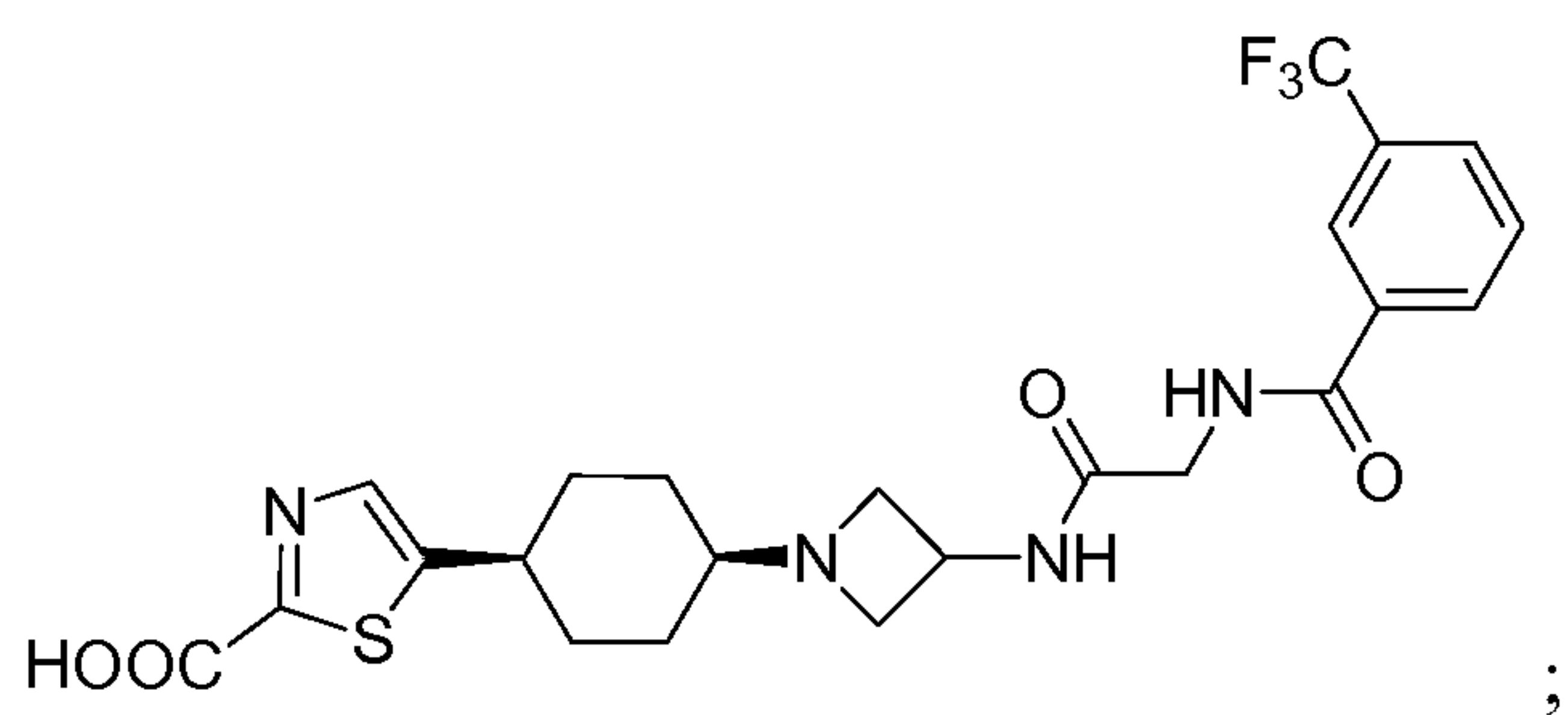
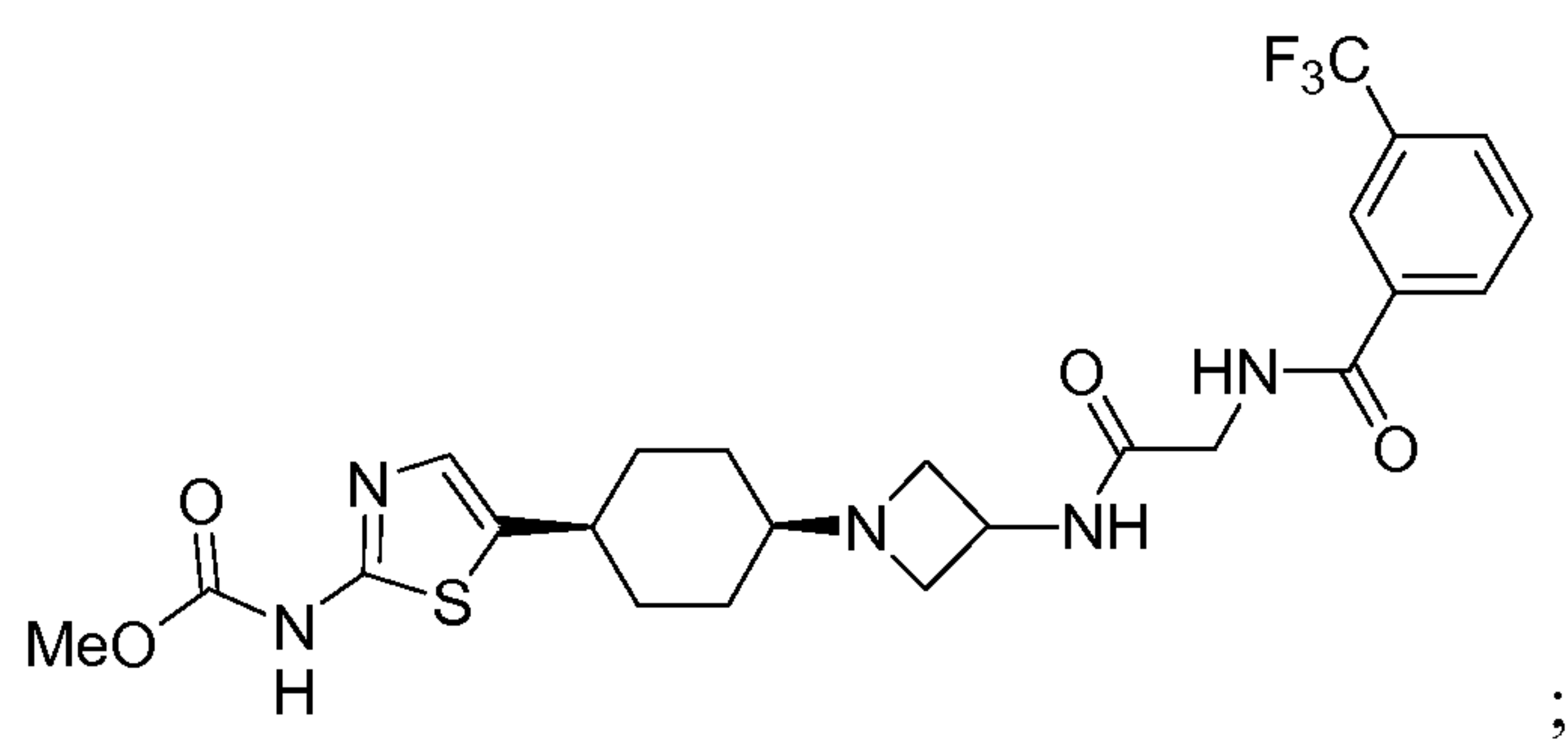
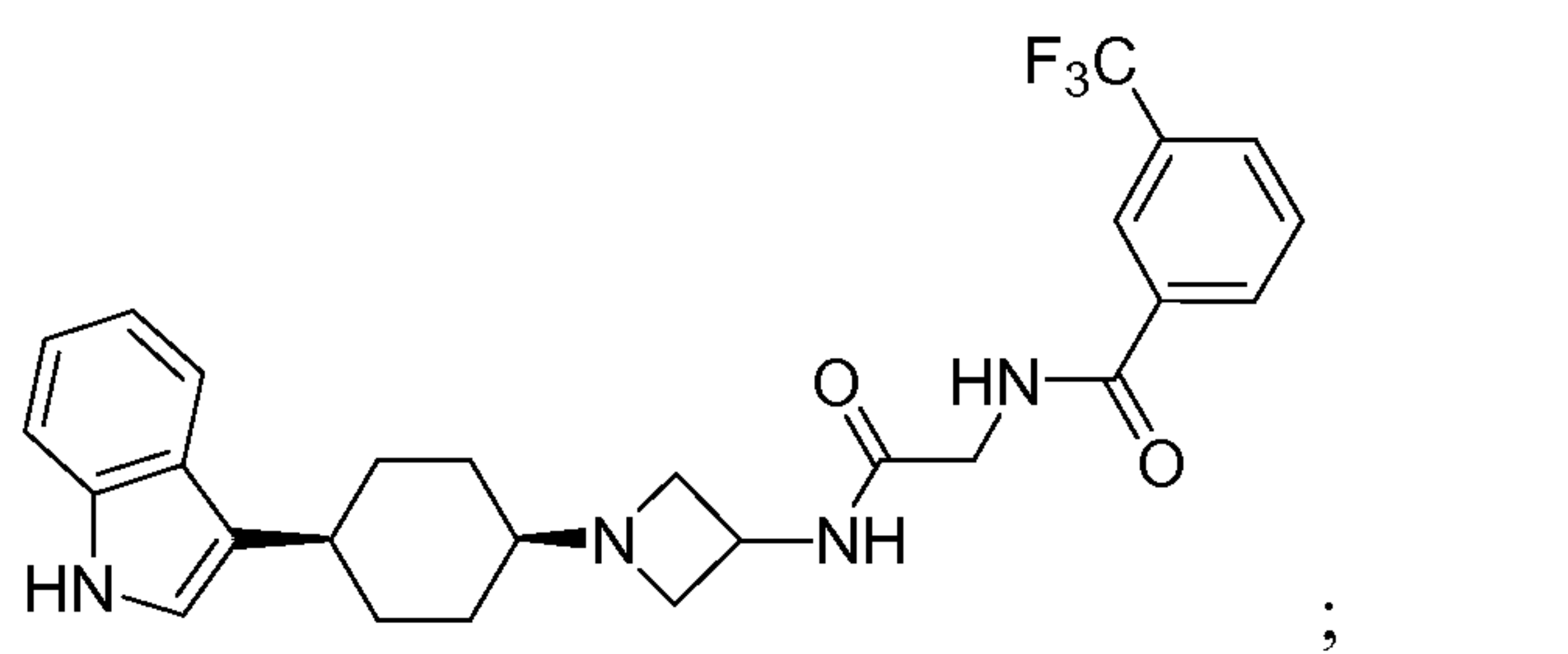
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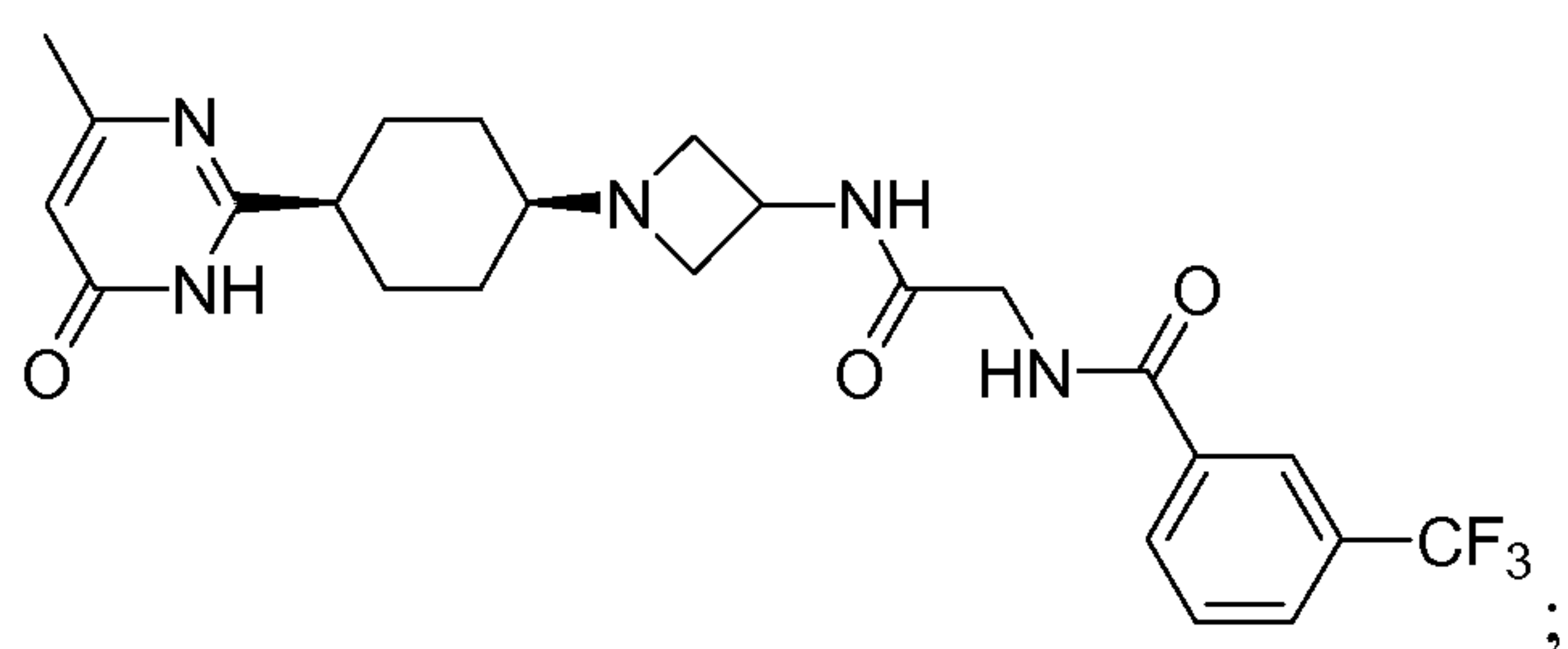
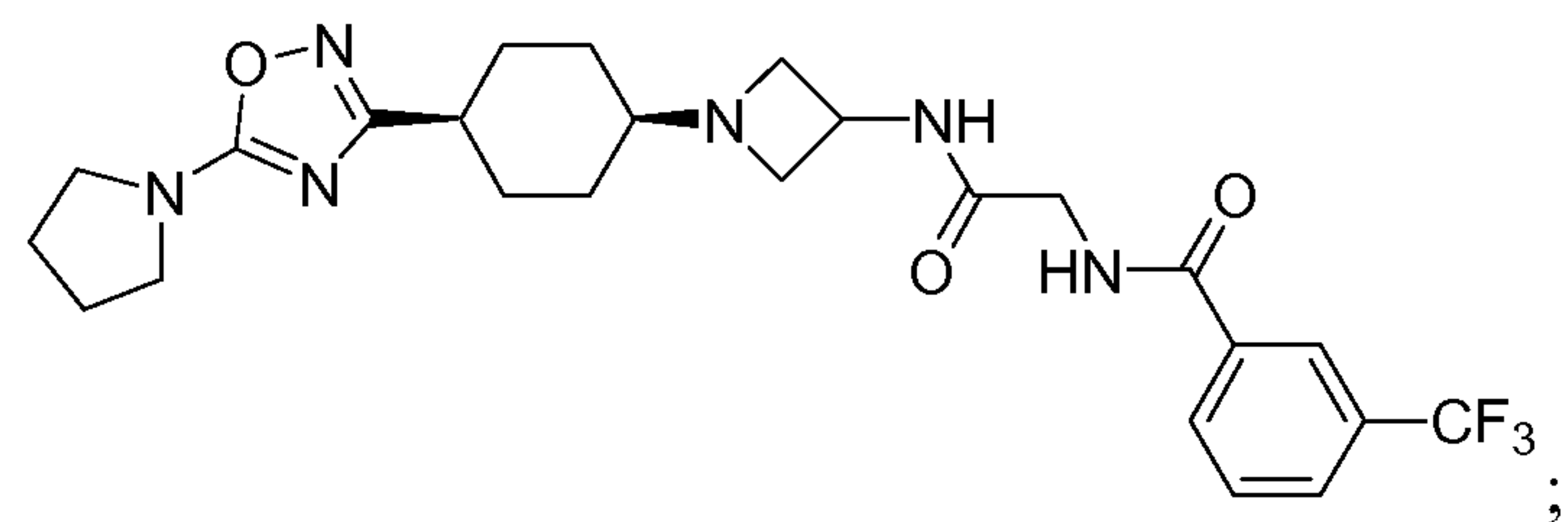
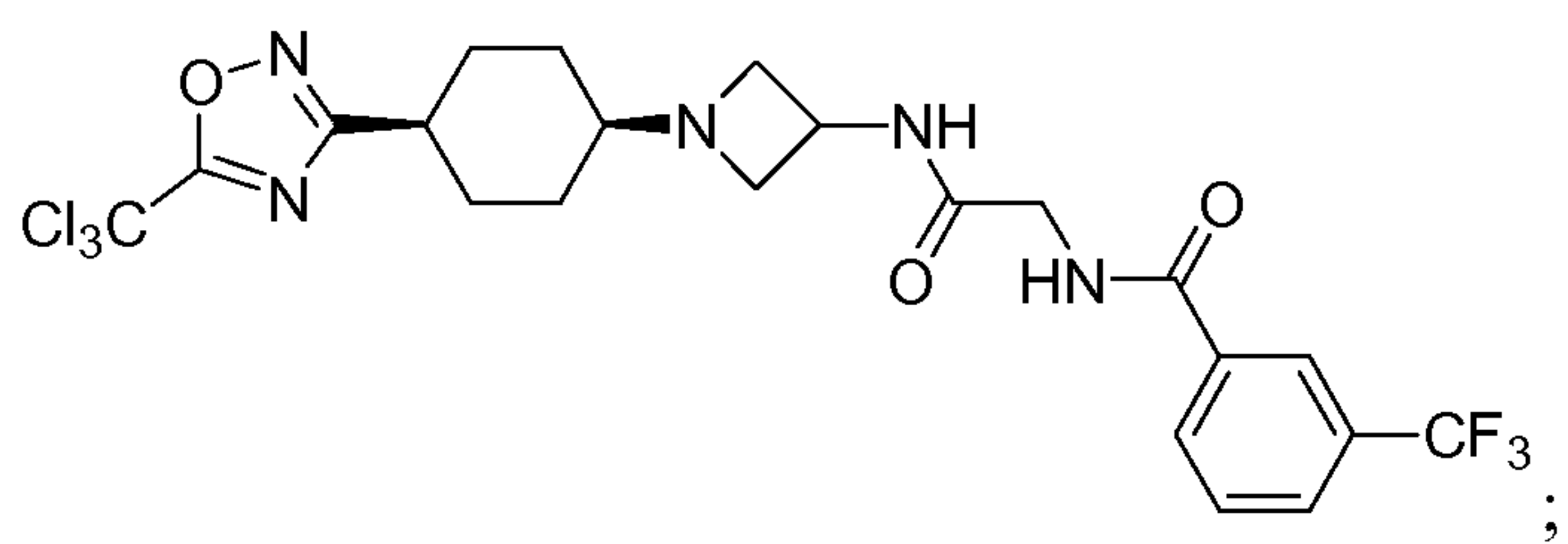
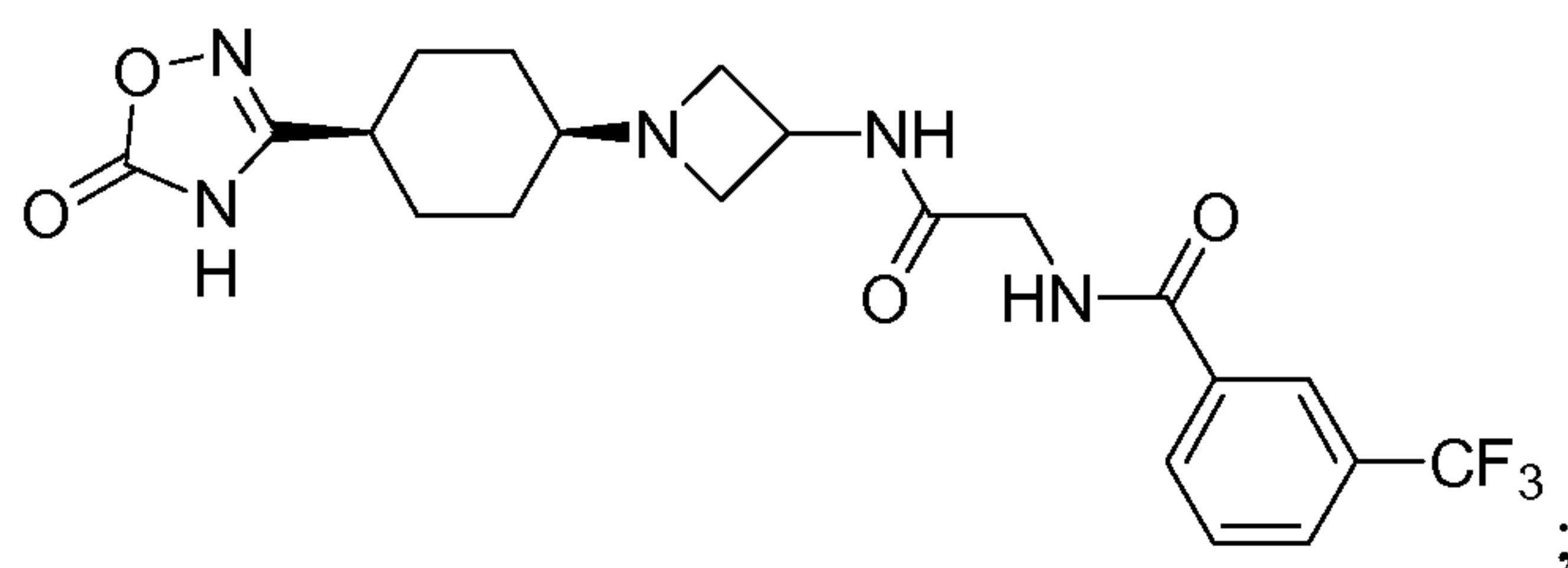
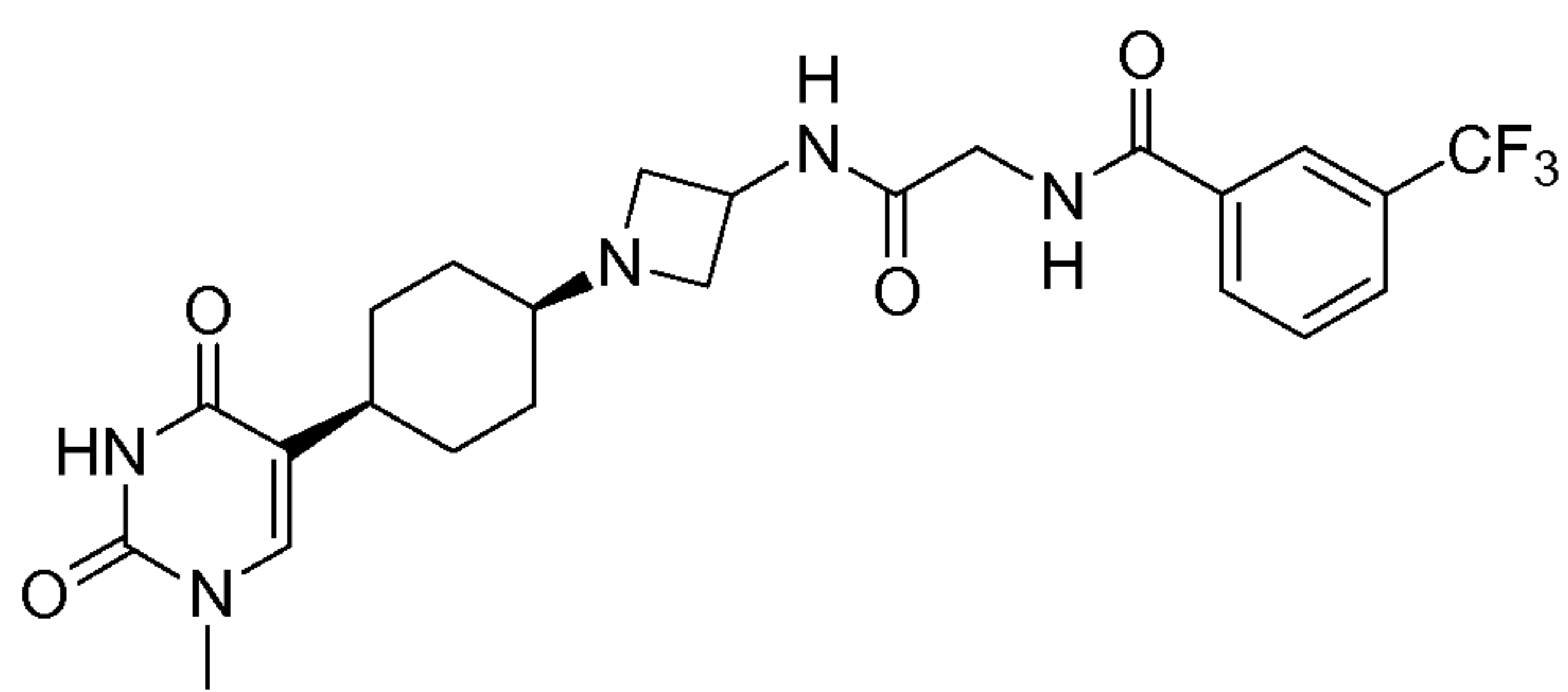


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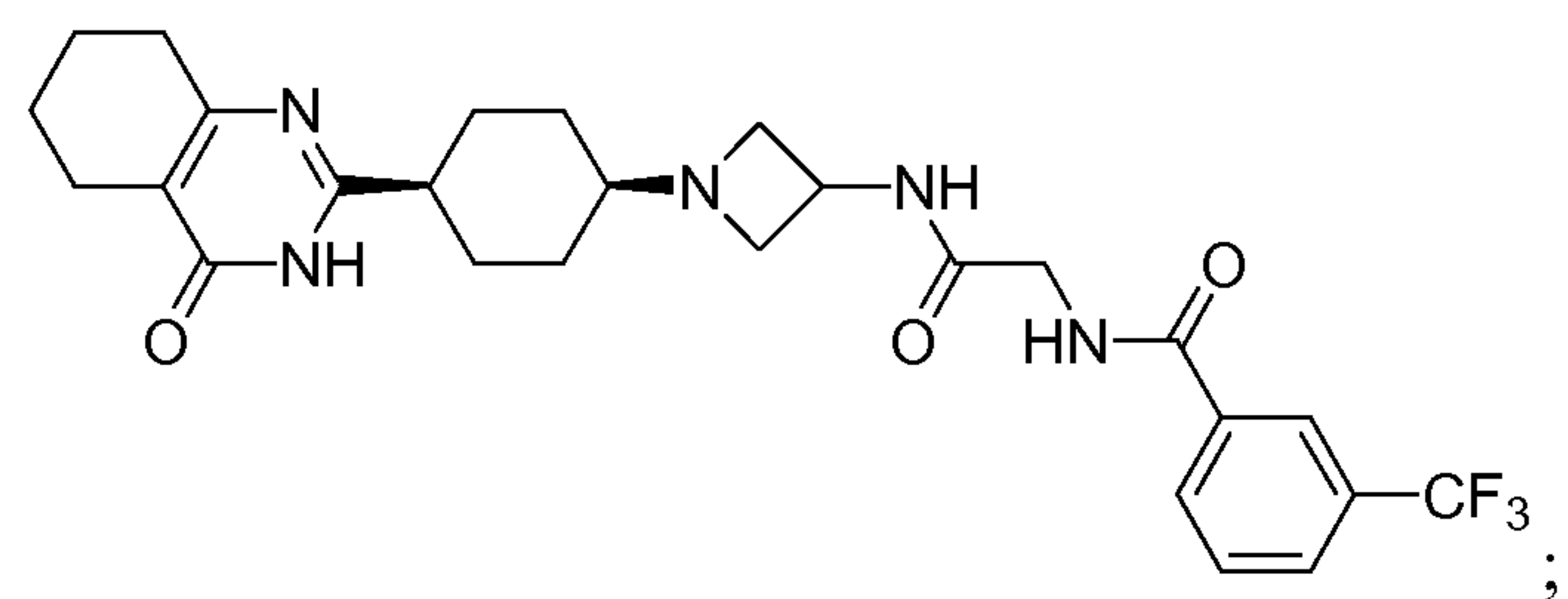
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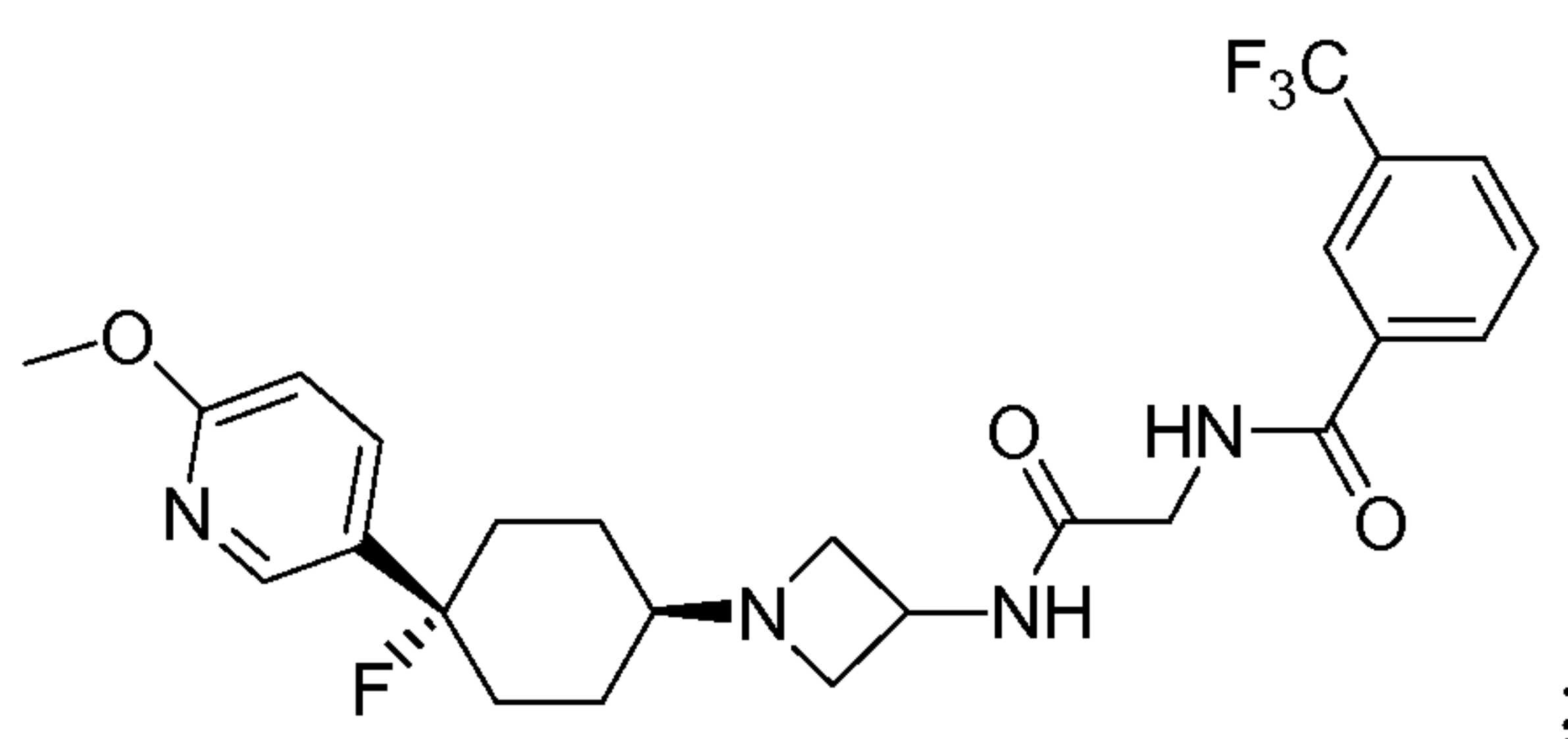
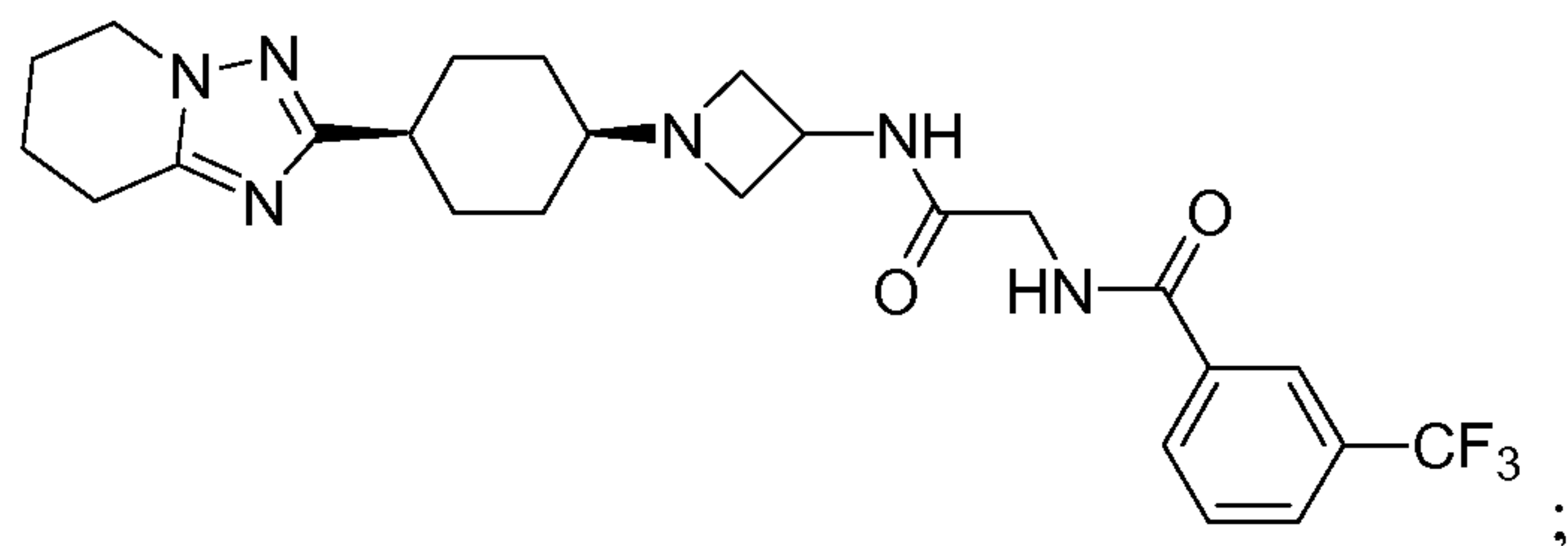
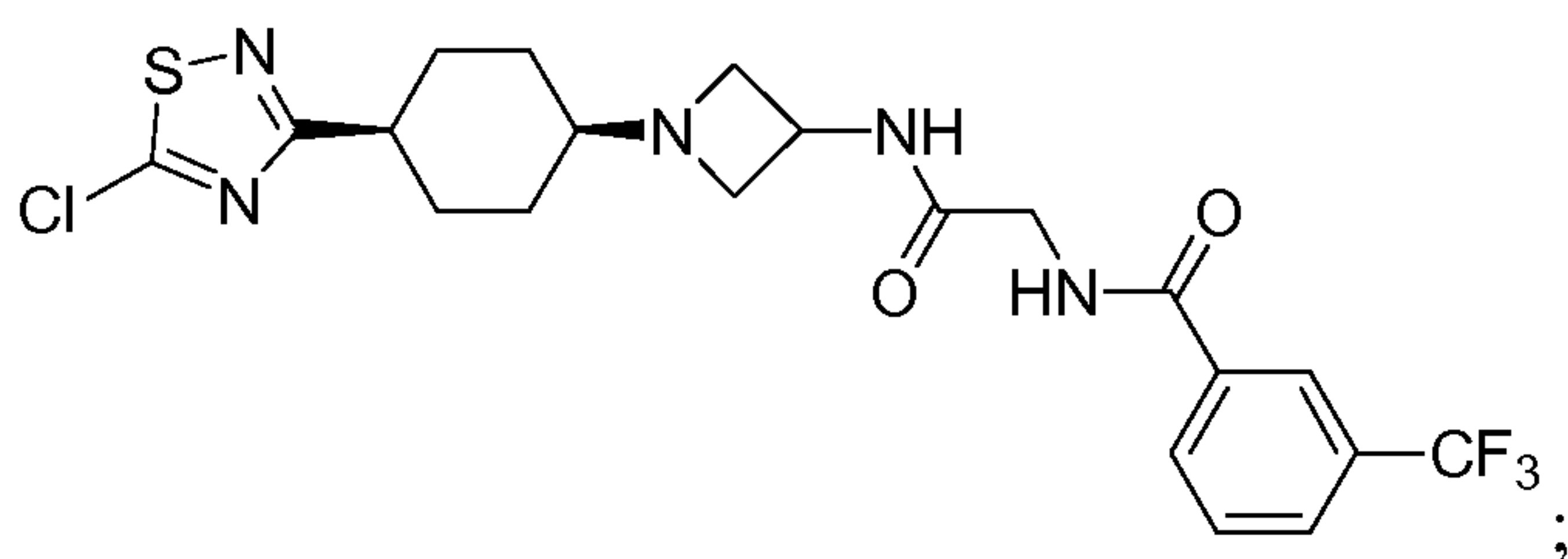






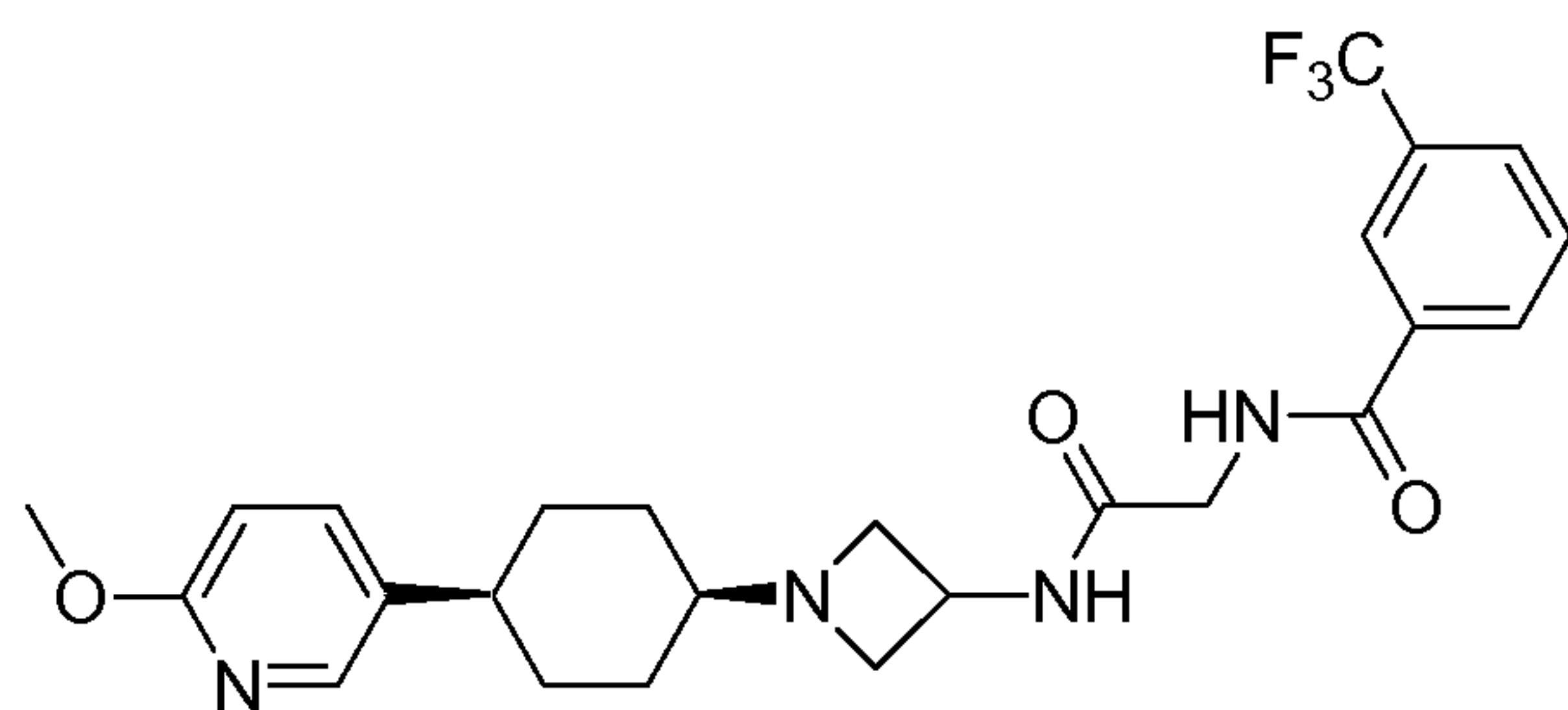
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and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

Another embodiment of the invention is the compound:



and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

Another embodiment of the invention is a pharmaceutical composition, comprising a compound of Formula (I) and/or (Ia) and a pharmaceutically acceptable carrier.

Another embodiment of the invention is a pharmaceutical composition, comprising a compound listed in the Examples section of this specification and a pharmaceutically acceptable carrier.

The present invention also provides a method for preventing, treating or ameliorating a CCR2 mediated syndrome, disorder or disease comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I) and/or (Ia) or a form, composition or medicament thereof. In one embodiment of the present invention, the CCR2 mediated syndrome, disorder or disease is an inflammatory syndrome, disorder or disease.

The present invention also provides a method for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease wherein the syndrome, disorder or disease is associated with elevated MCP-1 expression or MCP-1 overexpression, or is an inflammatory condition that accompanies syndromes, disorders or diseases associated with elevated MCP-1 expression or MCP-1 overexpression comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I) and/or (Ia) or a form, composition or medicament thereof.

The present invention also provides a method of preventing, treating or ameliorating a syndrome, disorder or disease, wherein said syndrome, disorder or disease is selected from the group consisting of: Chronic Obstructive Pulmonary Disease (COPD), ophthalmic disorders, uveitis, atherosclerosis, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, multiple sclerosis, Crohn's Disease, ulcerative colitis, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, type II diabetes and diabetic complications, diabetic nephropathy, obesity, weight disorders, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, tuberculosis, chronic obstructive pulmonary disease, sarcoidosis, invasive *staphylococci*, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, asthma, allergic asthma, periodontal diseases, periodontitis, gingivitis, gum disease, diastolic cardiomyopathies, cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, glomerulonephritis, solid tumors and cancers, chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, and carcinomas of the bladder, breast, cervix, colon, lung,

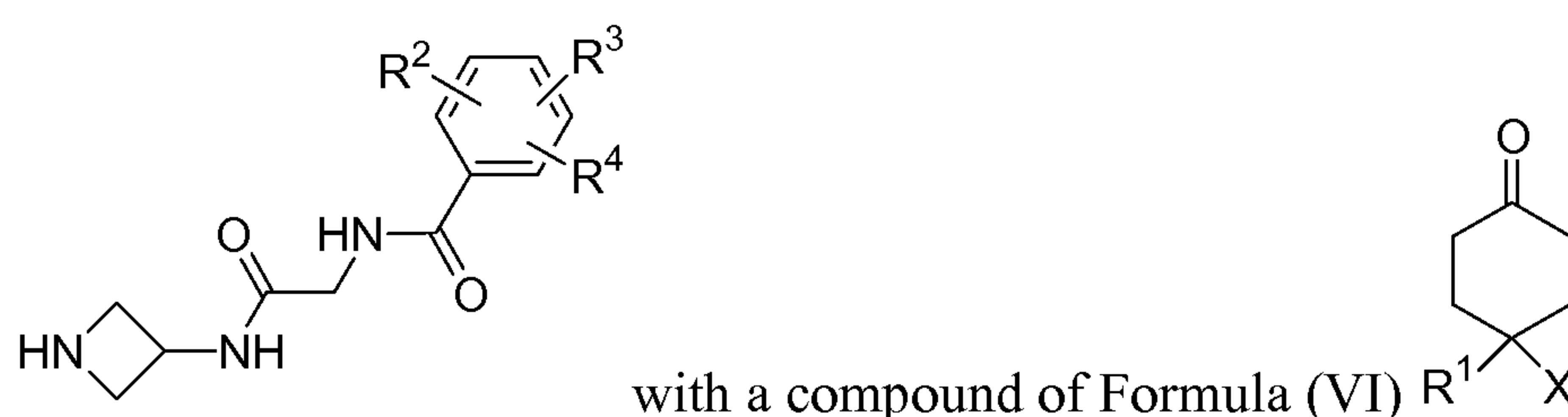
prostate, or stomach comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I) and/or (Ia) or a form, composition or medicament thereof. Preferably, the syndrome, disorder or disease is selected from the group consisting of: ophthalmic disorders, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, chronic obstructive pulmonary disease, allergic rhinitis, asthma, allergic asthma, and periodontal diseases.

The invention also relates to methods of inhibiting CCR2 activity in a mammal by administration of an effective amount of at least one compound of Formula (I) and/or (Ia).

In another embodiment, the invention relates to a product made by the process of any of Examples from Example 1 to Example 64.

In another embodiment, the invention relates to a compound which is the less polar isomer of any of Examples #1-64. Preferably, the compound is the less polar isomer of Example #1.

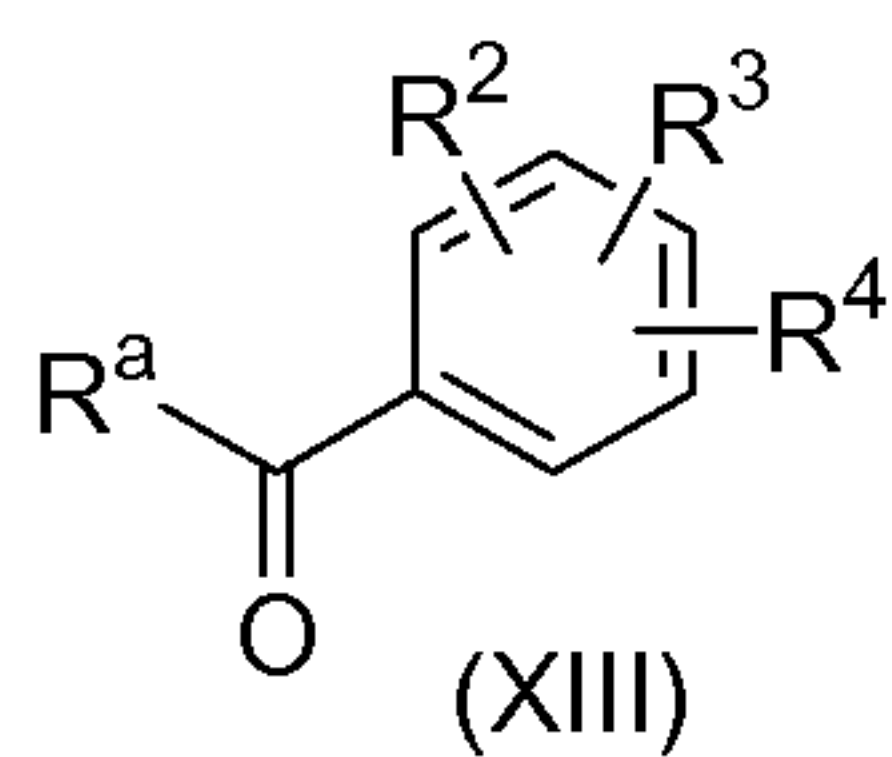
In another embodiment, the invention relates to a process for the preparation of a compound of Formula (I), comprising reacting a compound of Formula (V)



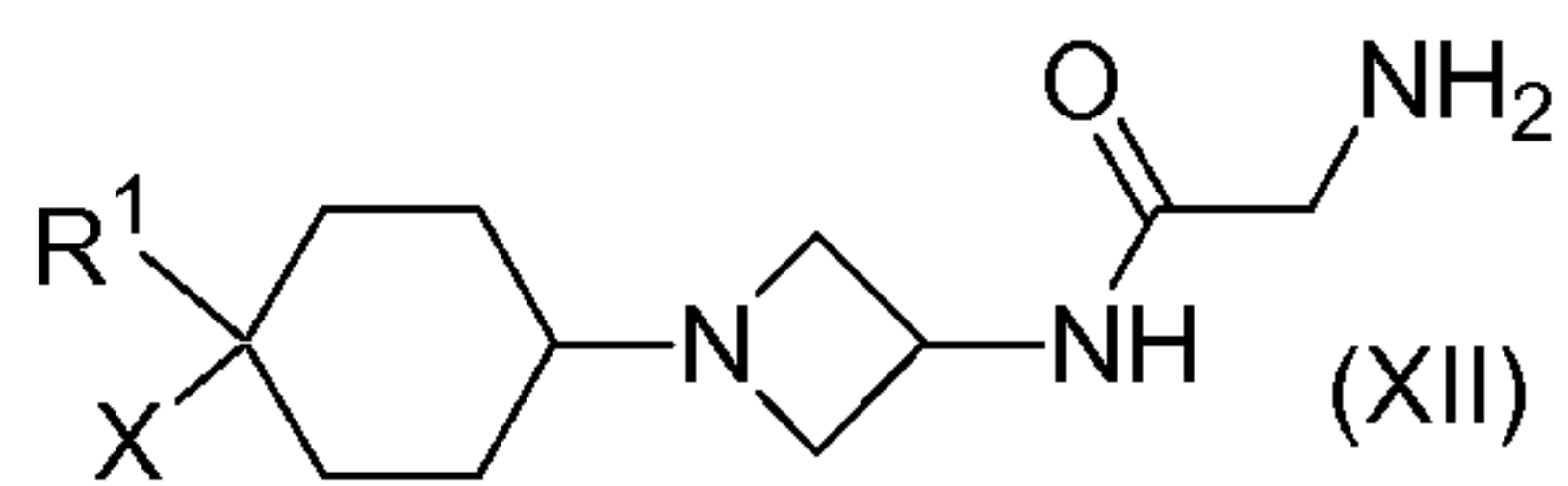
in the presence of a reducing agent to provide the compound of Formula (I).

In another embodiment, the invention relates to a product made by the above process.

In another embodiment, the invention relates to a process for the preparation of a compound of Formula (I), comprising reacting a compound of Formula (XIII)



, where R_a is OH or Cl, with a compound of Formula (XII)



in the presence of HOBt/EDCI or Et_3N to provide the compound of Formula (I).

5 In another embodiment, the invention relates to a product made by the above process.

In another embodiment, the invention relates to the use of hCCR2 knock-in mice to identify antagonists of CCR2 for use in the treatment a disorder selected from asthma or obesity.

10

In another embodiment, the invention relates to the use of hCCR2 knock-in mice to identify antagonists of CCR2 as described in any of Examples 69, 70 or 71.

Definitions

15 The term “alkyl” refers to both linear and branched chain radicals of up to 12 carbon atoms, preferably up to 6 carbon atoms, unless otherwise indicated, and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, isohexyl, heptyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl and dodecyl.

20

The term “ $C_{(a-b)}$ ” (where a and b are integers referring to a designated number of carbon atoms) refers to an alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl radical or to the alkyl portion of a radical in which alkyl appears as the prefix root containing from a to b carbon atoms inclusive. For example, $C_{(1-4)}$ denotes a radical containing 1, 2, 3 or 4

25 carbon atoms.

The term “cycloalkyl” refers to a saturated or partially unsaturated monocyclic or bicyclic hydrocarbon ring radical derived by the removal of one hydrogen atom from a single ring carbon atom. Typical cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl and cyclooctyl. Additional examples include C₍₃₋₈₎cycloalkyl, C₍₅₋₈₎cycloalkyl, C₍₃₋₁₂₎cycloalkyl, C₍₃₋₂₀₎cycloalkyl, decahydronaphthalenyl, and 2,3,4,5,6,7-hexahydro-1H-indenyl.

The term “oxo” refers to the functional group >C=O .

The term “heterocyclyl” refers to a saturated or partially unsaturated monocyclic cycloalkyl ring radical wherein from 1 to 3 ring carbon atoms have been replaced with heteroatoms selected from N, O, or S. Said heteroatoms may exist in any allowed oxidation state. The radical may be derived from the removal of a hydrogen atom from a carbon or a nitrogen atom. Typical heterocyclyl radicals include, but are not limited to, 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, 2-imidazoliny (also referred to as 4,5-dihydro-1H-imidazolyl), imidazolidinyl, 2-pyrazoliny, pyrazolidinyl, tetrazolyl, piperidinyl, 1,4-dioxanyl, morpholiny, 1,4-dithianyl, thiomorpholiny, piperazinyl, azepanyl, hexahydro-1,4-diazepiny and the like.

The term “heteroaromatic” or “heteroaryl” refers to 5- to 7-membered mono- or 8- to 10-membered bicyclic aromatic ring systems, containing from one to four heteroatoms selected from N, O, or S where the nitrogen and sulfur atoms can exist in any allowed oxidation state. Examples include, but are not limited to, benzimidazolyl, benzothiazolyl, benzothienyl, benzoxazolyl, furyl, imidazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinoliny, thiazolyl and thienyl.

The term “heteroatom” refers to a nitrogen atom, an oxygen atom or a sulfur atom wherein the nitrogen and sulfur atoms can exist in any allowed oxidation states.

For use in medicines, the salts of the compounds of this invention refer to non-toxic “pharmaceutically acceptable salts.” FDA approved pharmaceutically acceptable salt forms (*Ref. International J. Pharm.* 1986, 33, 201-217; *J. Pharm. Sci.*, **1977**, Jan, 66(1), p1) include pharmaceutically acceptable acidic/anionic or basic/cationic salts.

5

Throughout this specification, compounds are described as being separated, usually by silica gel column, although preparatory thin layer chromatography, or high or low pressure liquid chromatography may also be used. It is generally accepted that when eluting compounds through a silica gel-type separation medium, that the least polar compounds elute before the more polar compounds. Therefore, the term “less polar isomer”, refers to the isomer that will elute first from a silica gel type separation medium.

10

Abbreviations

Herein and throughout this application, the following abbreviations may be used.

15	BOC or Boc	tert-butyloxycarbonyl
	Bu	butyl
	DAST	diethylaminosulfur trifluoride
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCC	dicyclohexylcarbodiimide
20	DCM	dichloromethane
	DMF	dimethylformamide
	EDCI	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
	Et	ethyl
	EtOAc	ethyl acetate
25	HOBt	hydroxybenzotriazole
	IPA	isopropyl alcohol
	Me	methyl
	Ms	mesylate
	OAc	acetate
30	PdCl ₂ (dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
	PPh ₃	triphenylphosphine
	iPr	isopropyl
	PyBrop	bromo-tris-pyrrolidinophosphonium hexafluorophosphate
	TEA	triethylamine
35	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	Ts	tosylate

Pharmaceutically acceptable acidic/anionic salts include, and are not limited to acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, 5 hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate and triethiodide. Organic or inorganic acids 10 also include, and are not limited to, hydriodic, perchloric, sulfuric, phosphoric, propionic, glycolic, methanesulfonic, hydroxyethanesulfonic, oxalic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, saccharinic or trifluoroacetic acid.

Pharmaceutically acceptable basic/cationic salts include, and are not limited to aluminum, 15 2-amino-2-hydroxymethyl-propane-1,3-diol (also known as tris(hydroxymethyl)aminomethane, tromethane or "TRIS"), ammonia, benzathine, *t*-butylamine, calcium, calcium gluconate, calcium hydroxide, chloroprocaine, choline, choline bicarbonate, choline chloride, cyclohexylamine, diethanolamine, ethylenediamine, lithium, LiOMe, L-lysine, magnesium, meglumine, NH₃, NH₄OH, 20 N-methyl-D-glucamine, piperidine, potassium, potassium-*t*-butoxide, potassium hydroxide (aqueous), procaine, quinine, sodium, sodium carbonate, sodium-2-ethylhexanoate (SEH), sodium hydroxide, triethanolamine, or zinc.

Methods of Use

25 The present invention is directed to a method for preventing, treating or ameliorating a CCR2 mediated syndrome, disorder or disease comprising administering to a subject in need thereof an effective amount of a compound of Formula (I) or (Ia) or a form, composition or medicament thereof.

30 Examples of a CCR2 mediated syndrome, disorder or disease for which the compounds of Formula (I) or (Ia) are useful include chronic obstructive pulmonary disorder (COPD),

ophthalmic disorders, uveitis, atherosclerosis, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, multiple sclerosis, Crohn's Disease, ulcerative colitis, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, type-I diabetes, type II diabetes and diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, overweight, obesity, obesity-associated insulin resistance, tuberculosis, chronic obstructive pulmonary disease, sarcoidosis, invasive *staphylococci*, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, asthma, allergic asthma, periodontal diseases, periodontitis, gingivitis, gum disease, diastolic cardiomyopathies, cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, glomerulonephritis, solid tumors and cancers, chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, and carcinomas of the bladder, breast, cervix, colon, lung, prostate, or stomach.

The term "administering" with respect to the methods of the invention, means a method for therapeutically or prophylactically preventing, treating or ameliorating a syndrome, disorder or disease as described herein by using a compound of Formula (I) or (Ia) or a form, composition or medicament thereof. Such methods include administering an effective amount of said compound, compound form, composition or medicament at different times during the course of a therapy or concurrently in a combination form. The methods of the invention are to be understood as embracing all known therapeutic treatment regimens.

The term "subject" refers to a patient, which may be animal, typically a mammal, typically a human, which has been the object of treatment, observation or experiment. In one aspect of the invention, the subject is at risk of (or susceptible to) developing a syndrome, disorder or disease that is associated with elevated MCP-1 expression or MCP-1 overexpression, or a patient with an inflammatory condition that accompanies syndromes, disorders or diseases associated with elevated MCP-1 expression or MCP-1 overexpression.

The term "therapeutically effective amount" means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes preventing, treating or ameliorating the symptoms of a syndrome, disorder or disease being treated.

The term "uveitis" generically refers to any inflammatory disease involving the eye.

Uveitis can be divided into clinically distinct subtypes based on the part of the eye in which the inflammation is present (percentages correspond to patients known to fit these categories): anterior (51%), intermediate (13%), posterior (20%), or panuveitis (16%)

and, according to the course of the disease, as either acute (16%), recurring (26%), or chronic (58%). Those with anterior uveitis (19%) eventually develop irreparable vision damage despite aggressive treatment such as unilateral blindness (9%), bilateral blindness (2%), or unilateral or bilateral vision impairment (8%). Most cases of uveitis are idiopathic, but known causes include infection (e.g., toxoplasmosis, cytomegalovirus, and the like) or development as a component of a systemic inflammatory and/or autoimmune disorder (e.g., juvenile RA, HLA-B27 associated spondyloarthropathies, sarcoidosis, and the like). (HLA-B27: Human Leukocyte Antigen B*27- is a class I surface antigen encoded by the B locus in the major histocompatibility complex (MHC) on chromosome 6 and presents microbial antigens to T cells. HLA-B27 is strongly associated with a certain set of autoimmune diseases referred to as the seronegative spondyloarthropathies.)

When employed as CCR2 inhibitors, the compounds of the invention may be administered in a therapeutically effective amount within the dosage range of about 0.5 mg to about 10 g, preferably between about 0.5 mg to about 5 g, in single or divided daily doses. The dosage administered will be affected by factors such as the route of administration, the health, weight and age of the recipient, the frequency of the treatment and the presence of concurrent and unrelated treatments.

It is also apparent to one skilled in the art that the therapeutically effective dose for compounds of the present invention or a pharmaceutical composition thereof will vary

according to the desired effect. Therefore, optimal dosages to be administered may be readily determined by one skilled in the art and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease condition. In addition, factors associated with the particular subject being
5 treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level. The above dosages are thus exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

10 The compounds of Formula (I) and/or (Ia) may be formulated into pharmaceutical compositions comprising any known pharmaceutically acceptable carriers. Exemplary carriers include, but are not limited to, any suitable solvents, dispersion media, coatings, antibacterial and antifungal agents and isotonic agents. Exemplary excipients that may also be components of the formulation include fillers, binders, disintegrating agents and
15 lubricants.

The pharmaceutically-acceptable salts of the compounds of Formula (I) and/or (Ia) include the conventional non-toxic salts or the quaternary ammonium salts which are formed from inorganic or organic acids or bases. Examples of such acid addition salts
20 include acetate, adipate, benzoate, benzenesulfonate, citrate, camphorate, dodecylsulfate, hydrochloride, hydrobromide, lactate, maleate, methanesulfonate, nitrate, oxalate, pivalate, propionate, succinate, sulfate and tartrate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamino salts
25 and salts with amino acids such as arginine. Also, the basic nitrogen-containing groups may be quaternized with, for example, alkyl halides.

The pharmaceutical compositions of the invention may be administered by any means that accomplish their intended purpose. Examples include administration by parenteral,
30 subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal or ocular routes. Alternatively or concurrently, administration may be by the oral route. Suitable

formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts, acidic solutions, alkaline solutions, dextrose-water solutions, isotonic carbohydrate solutions and cyclodextrin inclusion complexes.

5

The present invention also encompasses a method of making a pharmaceutical composition comprising mixing a pharmaceutically acceptable carrier with any of the compounds of the present invention. Additionally, the present invention includes pharmaceutical compositions made by mixing a pharmaceutically acceptable carrier with
10 any of the compounds of the present invention. As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

15 ***Polymorphs and Solvates***

Furthermore, the compounds of the present invention may have one or more polymorph or amorphous crystalline forms and as such are intended to be included in the scope of the invention. In addition, the compounds may form solvates, for example with water (i.e., hydrates) or common organic solvents. As used herein, the term "solvate" means a
20 physical association of the compounds of the present invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The term "solvate" is intended to encompass both solution-
25 phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like.

It is intended that the present invention include within its scope polymorphs and solvates of the compounds of the present invention. Thus, in the methods of treatment of the
30 present invention, the term “administering” shall encompass the means for treating, ameliorating or preventing a syndrome, disorder or disease described herein with the

compounds of the present invention or a polymorph or solvate thereof, which would obviously be included within the scope of the invention albeit not specifically disclosed.

5 In another embodiment, the invention relates to a compound as described in the Examples or Formula (I) or Formula (Ia) for use as a medicament, in particular, for use as a medicament for treating a CCR2 mediated syndrome disorder or disease.

10 In another embodiment, the invention relates to the use of a compound as described in the Examples of Formula (I) or Formula (Ia) for the preparation of a medicament for the treatment of a disease associated with an elevated or inappropriate CCR2 activity.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which are readily convertible *in vivo* into the required compound. Thus, in the methods
15 of treatment of the present invention, the term “administering” shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for
20 example, in “Design of Prodrugs”, Ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such
25 isomers and mixtures thereof are encompassed within the scope of the present invention.

Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in
30 racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric

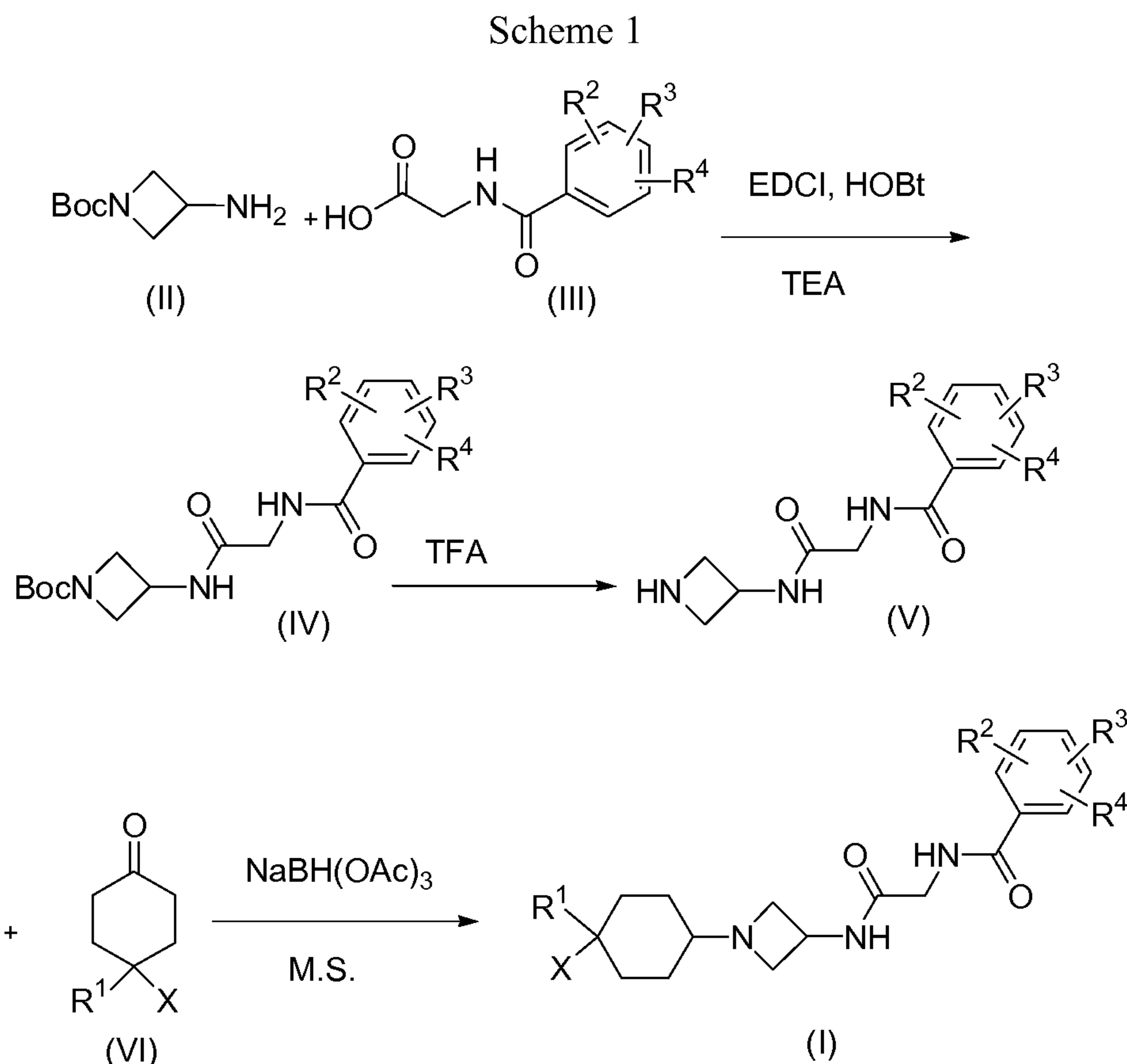
pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-D-tartaric acid and/or (+)-di-p-toluoyl-L-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

GENERAL REACTION SCHEME

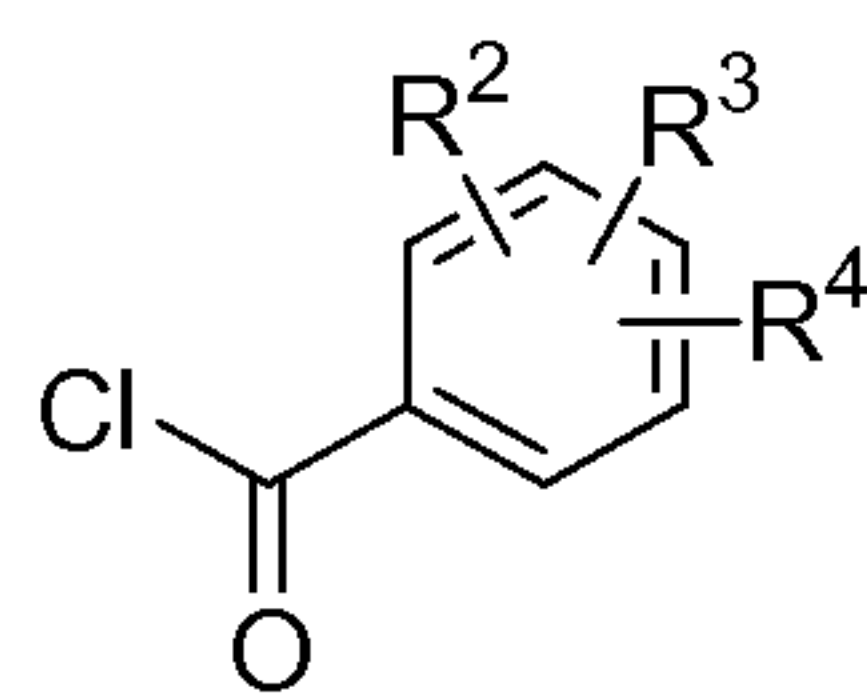
Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below. Compounds of Formula (I) can be prepared by methods known to those who are skilled in the art. The following reaction schemes are only meant to represent examples of the invention and are in no way meant to be a limit of the invention.

Compounds of Formula (I) may be prepared according to the processes outlined in Scheme 1.



Scheme 1 illustrates a synthetic route leading to compounds of Formula (I).

- 5 Commercially available azetidine (II) is reacted with acid (III), wherein (III) is prepared according to the procedure described by Ingersoll, A. W. *et. al.*, Organic Syntheses **1932**,



XII, 40-2 substituting commercially available for benzoyl chloride, in the presence of a coupling reagent such as EDCI/HOBt, PyBrop, or DCC, in an organic solvent such as THF, dichloromethane or 1,2-dichloroethane, at a temperature in the range of about 0 °C to about 25 °C, to yield the corresponding amide (IV).

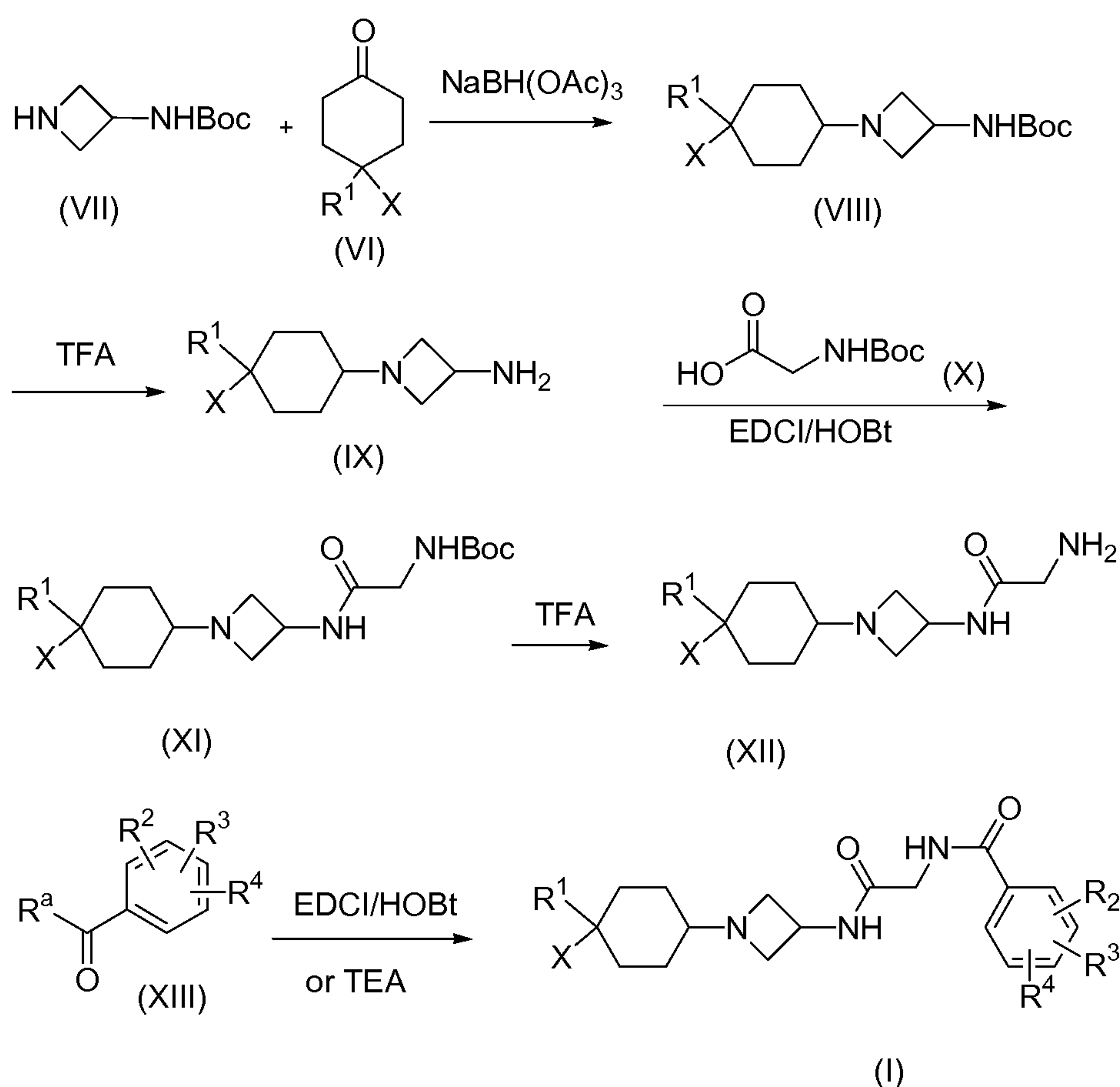
Amide (IV) is treated with an acid such as 1N HCl, 1N H₂SO₄ or trifluoroacetic acid in an organic solvent such as diethyl ether, THF, dichloromethane or dioxane, at a temperature in the range of about 0 °C to about 25 °C to yield amine (V).

- 15 Amine (V) is reacted with a suitably substituted ketone (VI), in the presence of a reducing reagent such as NaBH₄, NaBH(CN)₃ or NaBH(OAc)₃, in an organic base such

as triethylamine, diethylpropylamine or N-methylmorpholine with or without molecule sieves, in an organic solvent such as dichloromethane, 1,2-dichloroethane or THF, at a temperature in the range of 0 °C to about 25 °C, to yield the corresponding azetidine (I).

- 5 Alternatively, compounds of Formula (I) may be prepared according to the processes outlined in Scheme 2.

Scheme 2



wherein R^a is OH, or Cl

- 10 Commercially available azetidine (VII) is reacted with a suitably substituted ketone (VI), in the presence of a reducing reagent such as NaBH_4 , NaBH(CN)_3 or NaBH(OAc)_3 , in an organic base such as triethylamine, diethylpropylamine or N-methylmorpholine, with or without molecule sieves, in an organic solvent such as dichloromethane, 1,2-dichloroethane or THF at a temperature in the range of 0 °C to about 25 °C, to yield the corresponding azetidine (VIII).

Azetidine (VIII) is treated with 1N HCl, 1N H₂SO₄ or trifluoroacetic acid in an organic solvent such as diethyl ether, THF, dioxane or dichloromethane, at a temperature in the range of about 0 °C to about 25 °C, to yield the corresponding amine (IX).

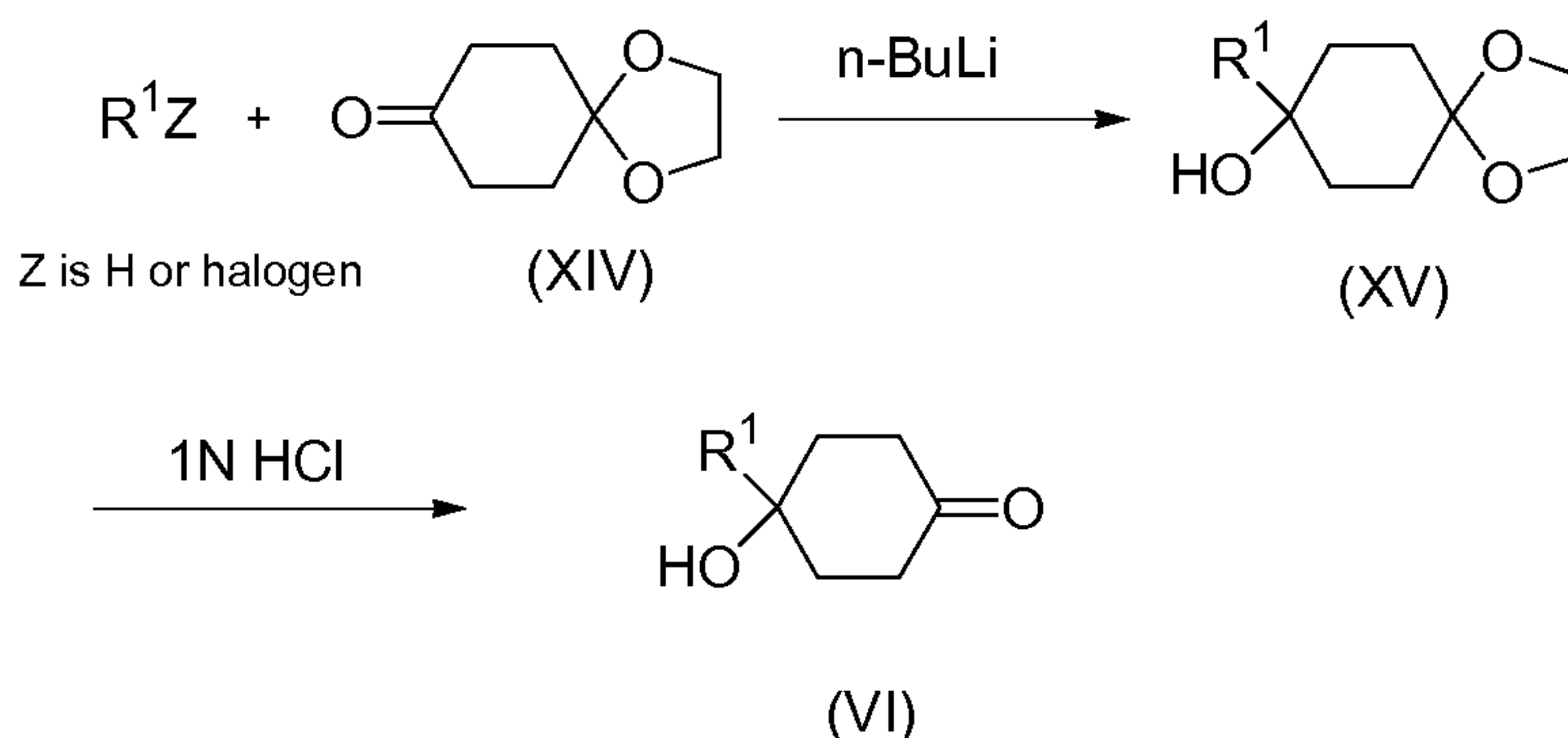
Amine (IX) is reacted with acid (X), in the presence of a coupling reagent such as EDCI/HOBt, PyBrop or DCC, in an organic solvent such as THF, dichloromethane or 1,2-dichloroethane, at a temperature in the range of about 0 °C to about 25 °C, to yield the corresponding azetidine (XI).

Azetidine (XI) is treated with 1N HCl or H₂SO₄ or trifluoroacetic acid, in an organic solvent such as diethyl ether, THF or dioxane, at a temperature in the range of about 0 °C to about 25 °C, to yield the corresponding amine (XII).

Amine (XII) is reacted with acid (XIII). When R^a is OH, the reaction is performed in the presence of a coupling reagent such as EDCI/HOBt, PyBrop or DCC, in an organic solvent such as THF, dichloromethane or 1,2-dichloroethane, at a temperature in the range of about 0 °C to about 25 °C. When R^a is Cl, the reaction is performed in the presence of an organic base such triethylamine, diethylpropylamine or N-methylmorpholine, in an organic solvent such as THF, dichloromethane or 1,2-dichloroethane, at a temperature in the range of about 0 °C to about 25 °C, to yield the corresponding azetidine (I).

Compounds of Formula (I) may be derived from ketone (VI). Preparation of (VI) is outlined in Scheme 3.

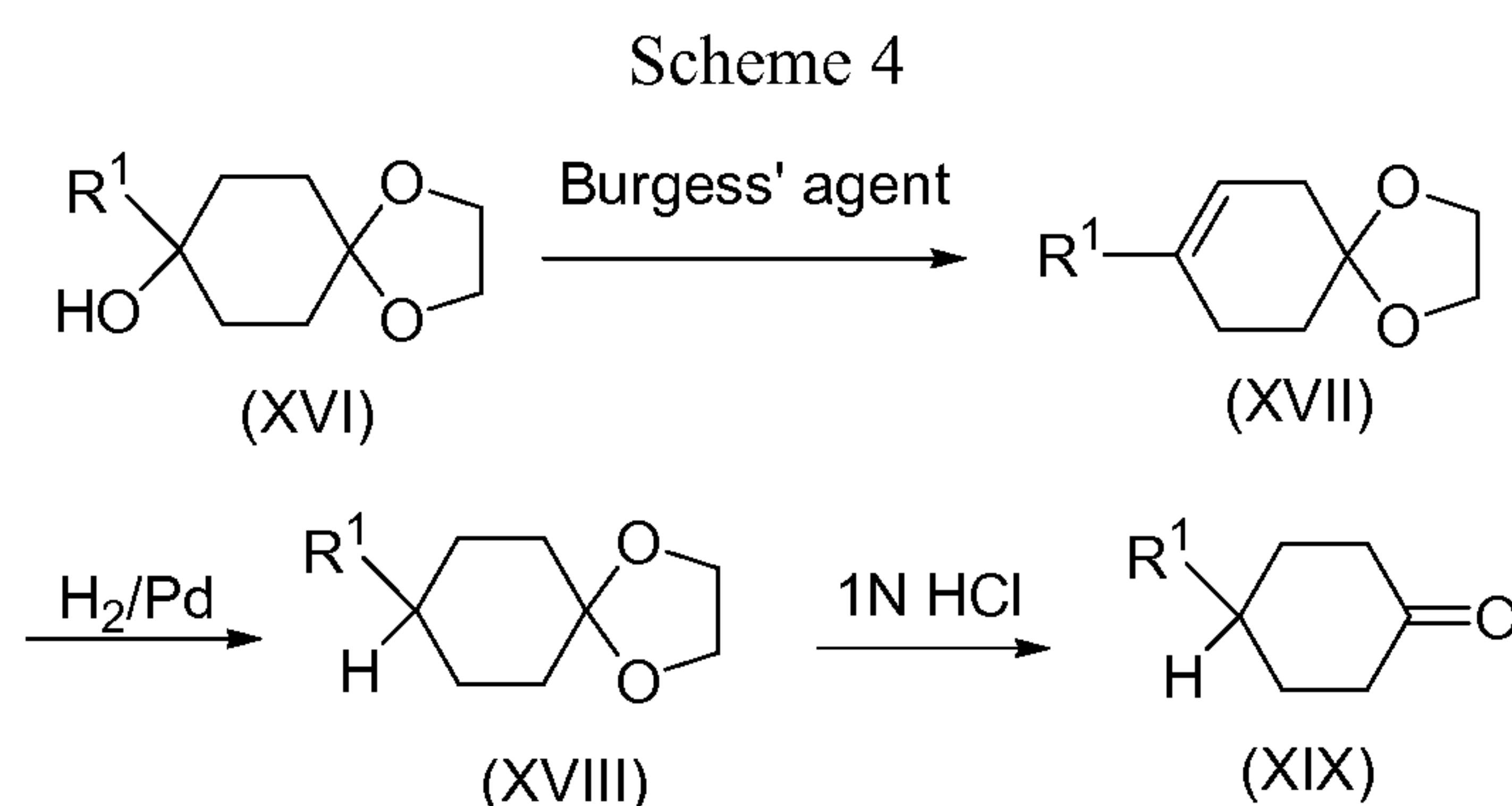
Scheme 3



Commercially available aryl halide or aryl alkane R^1Z (where R^1 is as defined in Formula (I)) is reacted with commercially available ketone (XIV) in the presence of organometallic agent such as n-BuLi, i-PrMgBr or i-PrMgCl, in an organic solvent such as ether, THF or dioxane, at a temperature in the range of about $-78\text{ }^{\circ}\text{C}$ to about $0\text{ }^{\circ}\text{C}$, to yield the
 5 corresponding ketal (XV).

Ketal (XV) is treated with an acid such as 1N HCl or 1N H_2SO_4 in an organic solvent such as acetone, acetonitrile or THF, at a temperature in the range of about $0\text{ }^{\circ}\text{C}$ to about $25\text{ }^{\circ}\text{C}$, to yield the corresponding ketone (VI).

- 10 Compounds of Formula (I) may be derived from ketone (XIX). Preparation of (XIX) is outlined in Scheme 4.



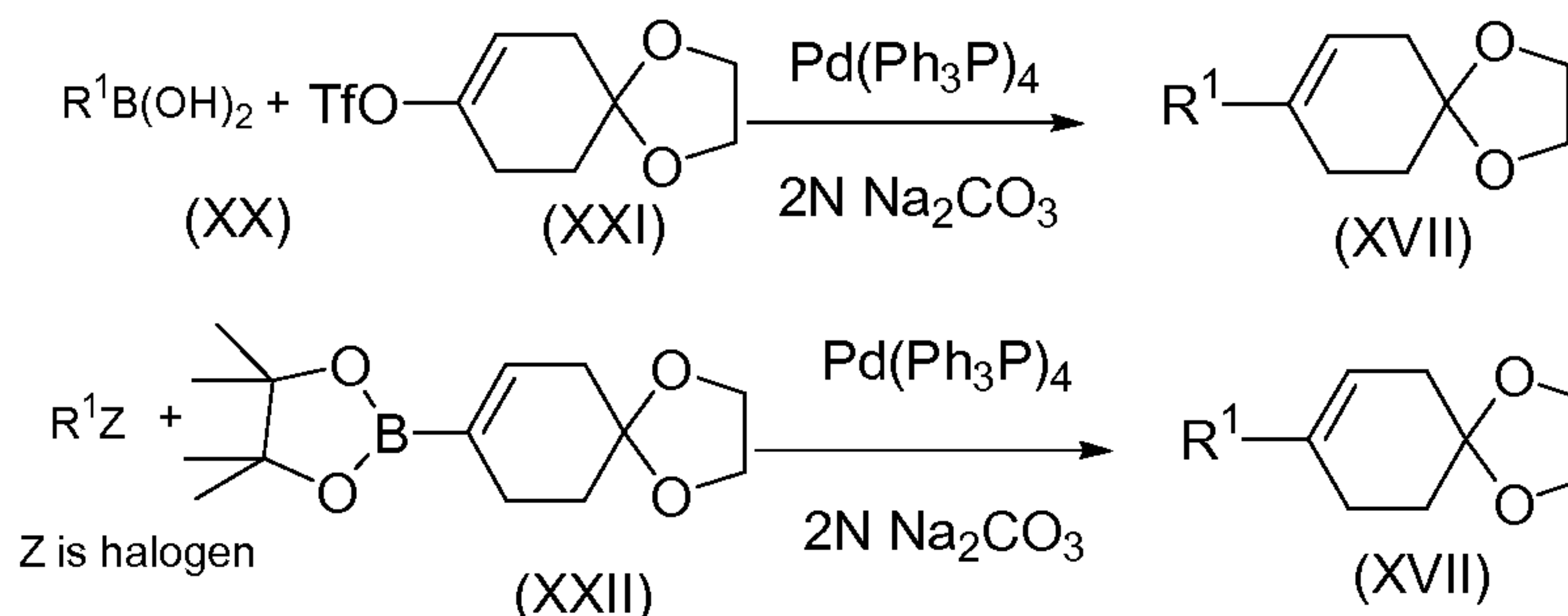
- 15 Ketal (XVI) is treated with a dehydrating agent such as Burgess' reagent, in an organic solvent such as ether, THF or dioxane, at a temperature in the range of about $0\text{ }^{\circ}\text{C}$ to about $25\text{ }^{\circ}\text{C}$, to yield the corresponding alkene (XVII).

Alkene (XVII) is treated with hydrogen gas under pressure from 5 to 50 psi catalyzed by 5-10% Pd/C, in an organic solvent such as methanol, at a temperature in the range of about $25\text{ }^{\circ}\text{C}$ to about $50\text{ }^{\circ}\text{C}$, to yield the corresponding alkane (XVIII).

- 20 Alkane (XVIII) is treated with 1N HCl or 1N H_2SO_4 , in an organic solvent such as acetone, acetonitrile or THF, at a temperature in the range of about $0\text{ }^{\circ}\text{C}$ to about $25\text{ }^{\circ}\text{C}$, to yield the corresponding ketone (XIX).

- 25 Alternatively compound (XVII) may be prepared according to the processes outlined in Scheme 5.

Scheme 5

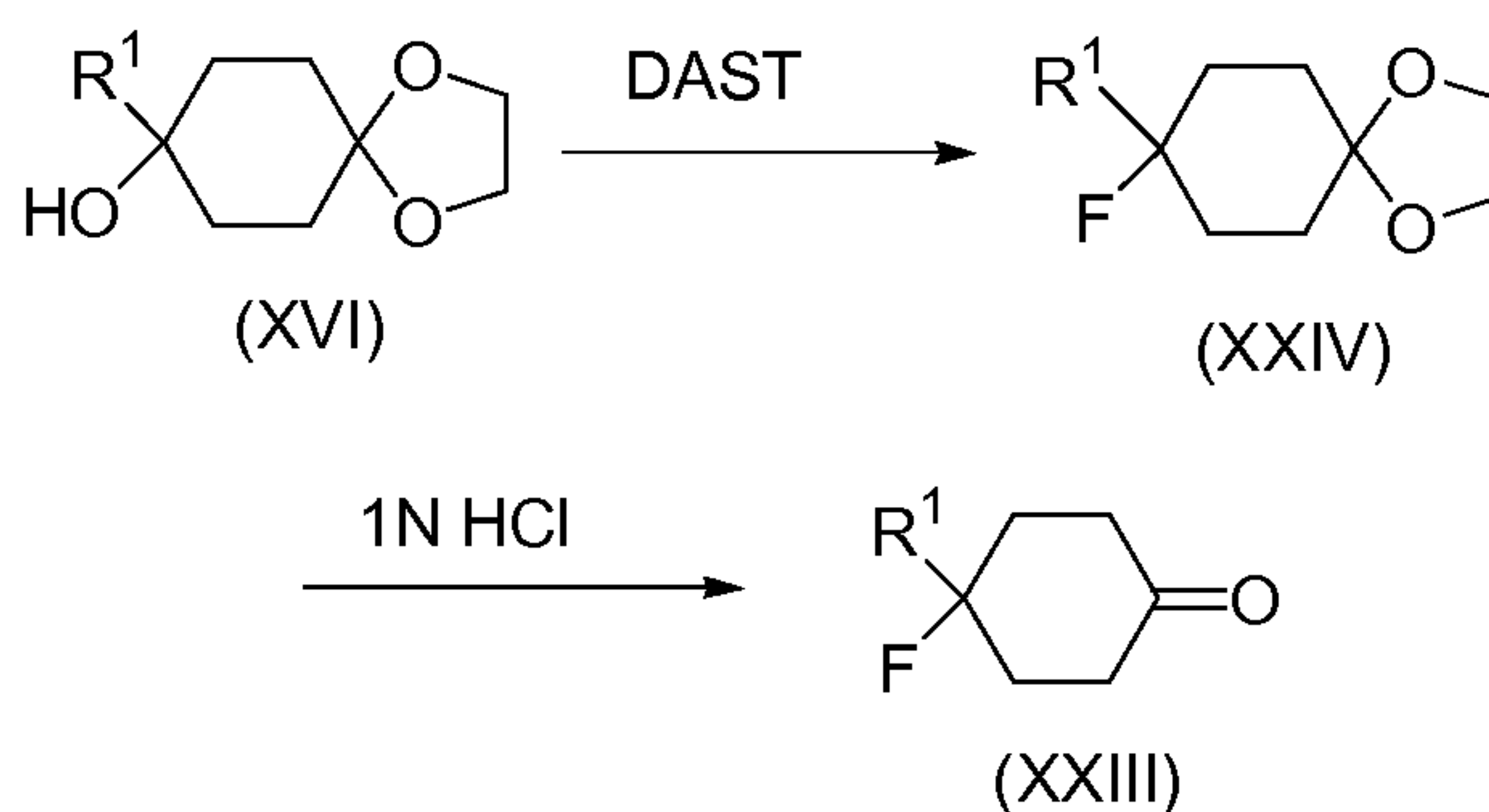


Commercially available aryl boronic acid (XX), (wherein R^1 is as defined in Formula (I)) is reacted with vinyl triflate (XXI) prepared according to the procedure of Pearson, W. *et. al.*, *J. Org. Chem.* **2004**, 69, 9109-9122, in the presence of a catalyst such as $Pd(Ph_3P)_4$, $PdCl_2(Ph_3P)_2$ or $PdCl_2(dppf)$ and a base such as 2N Na_2CO_3 or K_2CO_3 , in an organic solvent such as toluene, dioxane or THF, at a temperature in the range of about 80 °C to about 120 °C, to yield the corresponding alkene (XVII).

Alternatively, commercially available aryl or heteroaryl halide R^1Z is reacted with vinyl boronic ester (XXII) prepared according to Birch, A.M. *et. al.*, PCT Int. Appl. 2006, WO 2006064189, in the presence of a catalyst such as $Pd(Ph_3P)_4$, $PdCl_2(Ph_3P)_2$ or $PdCl_2(dppf)$ and a base such as 2N Na_2CO_3 or K_2CO_3 , in an organic solvent such as toluene, dioxane or THF, at a temperature in the range of about 80 °C to about 120 °C, to yield the corresponding alkene (XVII).

Compounds of Formula (I) may be derived from ketone (XXIII). Ketone (XXIII) may be prepared according to the processes outlined in Scheme 6.

Scheme 6

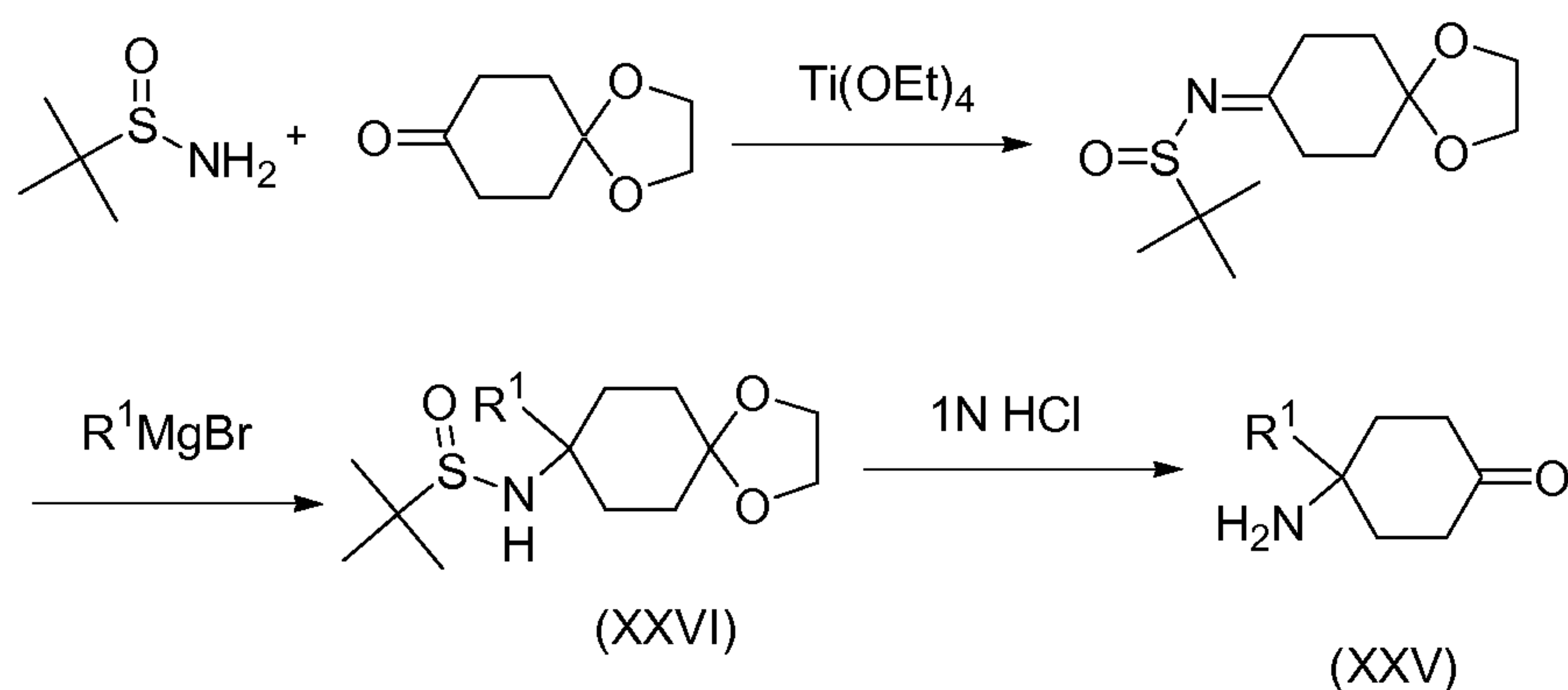


Ketal (XVI) is treated with a fluorinating agent such as DAST or trifluorosulfonyl fluoride, in an organic solvent such as dichloromethane, THF or dioxane, at a temperature in the range of about $-78\text{ }^{\circ}\text{C}$ to about $0\text{ }^{\circ}\text{C}$, to yield the corresponding fluoride (XXIV).

Fluoride (XXIV) is treated with an acid such as 1N HCl or 1N H_2SO_4 , in an organic solvent such as acetone, acetonitrile or THF, at a temperature in the range of about $0\text{ }^{\circ}\text{C}$ to about $25\text{ }^{\circ}\text{C}$, to yield the corresponding ketone (XXIII).

Compounds of Formula (I) may be derived from ketone (XXV). Ketone (XXV) may be prepared according to the processes outlined in Scheme 7.

10 Scheme 7



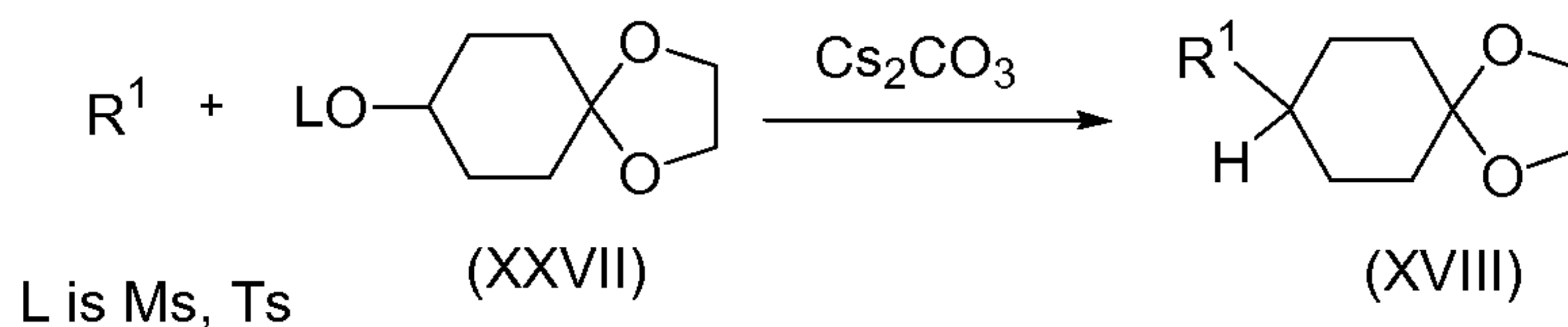
Commercially available 2-methyl-propane-2-sulfinic acid amide is reacted with commercially available 1,4-dioxaspiro[4.5]decan-8-one in the presence of a coupling agent such as $\text{Ti}(\text{OEt})_4$ or CuSO_4 , in an organic solvent such as dichloromethane, THF or dioxane, at a temperature in the range of about $25\text{ }^{\circ}\text{C}$ to about $80\text{ }^{\circ}\text{C}$, to yield 2-methyl-propane-2-sulfinic acid (1,4-dioxaspiro[4.5]dec-8-ylidene)-amide.

2-Methyl-propane-2-sulfinic acid (1,4-dioxaspiro[4.5]dec-8-ylidene)-amide is treated with an organometallic agent such as R^1MgBr or R^1Li , in an organic solvent such as ether, THF or dioxane, at a temperature in the range of about $-78\text{ }^{\circ}\text{C}$ to about $25\text{ }^{\circ}\text{C}$, to yield the corresponding sulfonamide (XXVI).

Sulfonamide (XXVI) is treated with an acid such as 1N HCl or 1N H_2SO_4 in an organic solvent such as acetone, acetonitrile or THF, at a temperature in the range of about $0\text{ }^{\circ}\text{C}$ to about $25\text{ }^{\circ}\text{C}$, to yield the corresponding ketone (XXV).

Compounds of Formula (I) where R¹ is linked with the cyclohexyl ring through N or O may be prepared according to the process outlined in Scheme 8.

Scheme 8



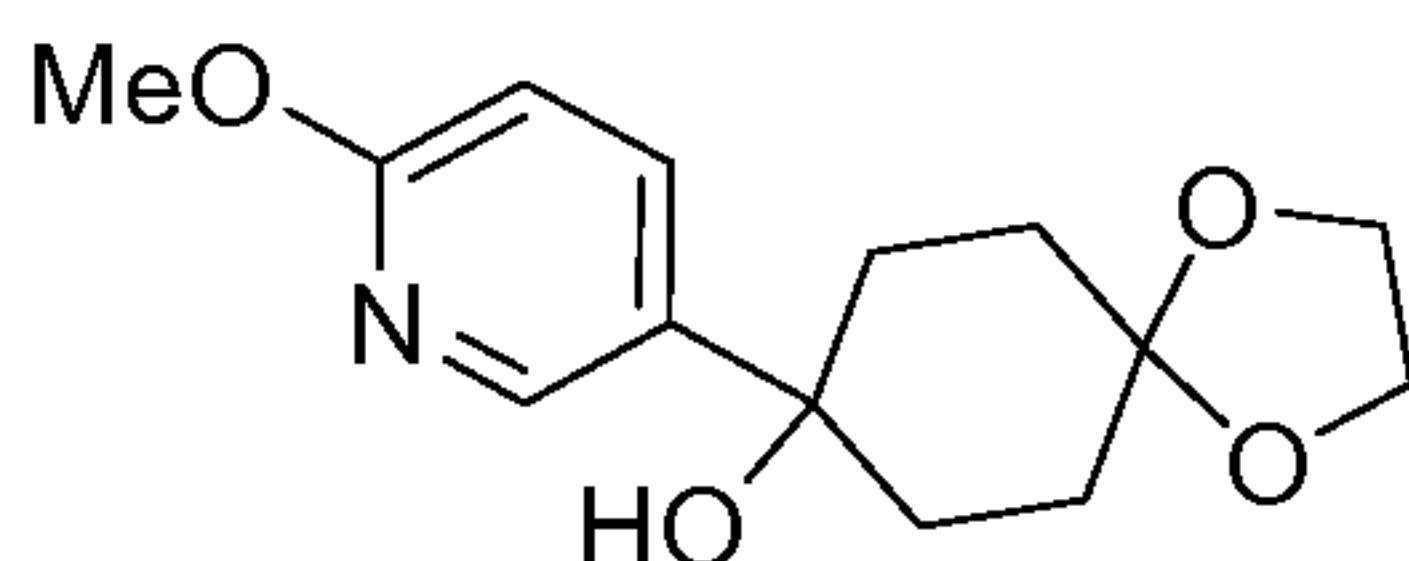
- 5 Commercially available OH or NH substituted R¹ is reacted with alkyl tosylate or alkyl mesylate (XXVII) in the presence of inorganic base such as K₂CO₃, Cs₂CO₃ or NaH, in an organic solvent such as DMF or THF, at a temperature in the range of about 25 °C to about 80 °C, to yield the corresponding ketal (XVIII).

10 EXAMPLES

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below. Compounds of Formula (I) can be prepared by methods known to those who are skilled in the art. The following examples are only meant to represent examples of the invention and are in no way meant to be a
15 limit of the invention.

Example 1: N-({1-[4-(6-Methoxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

Step A: 8-(6-Methoxy-pyridin-3-yl)-1,4-dioxaspiro[4.5]decan-8-ol



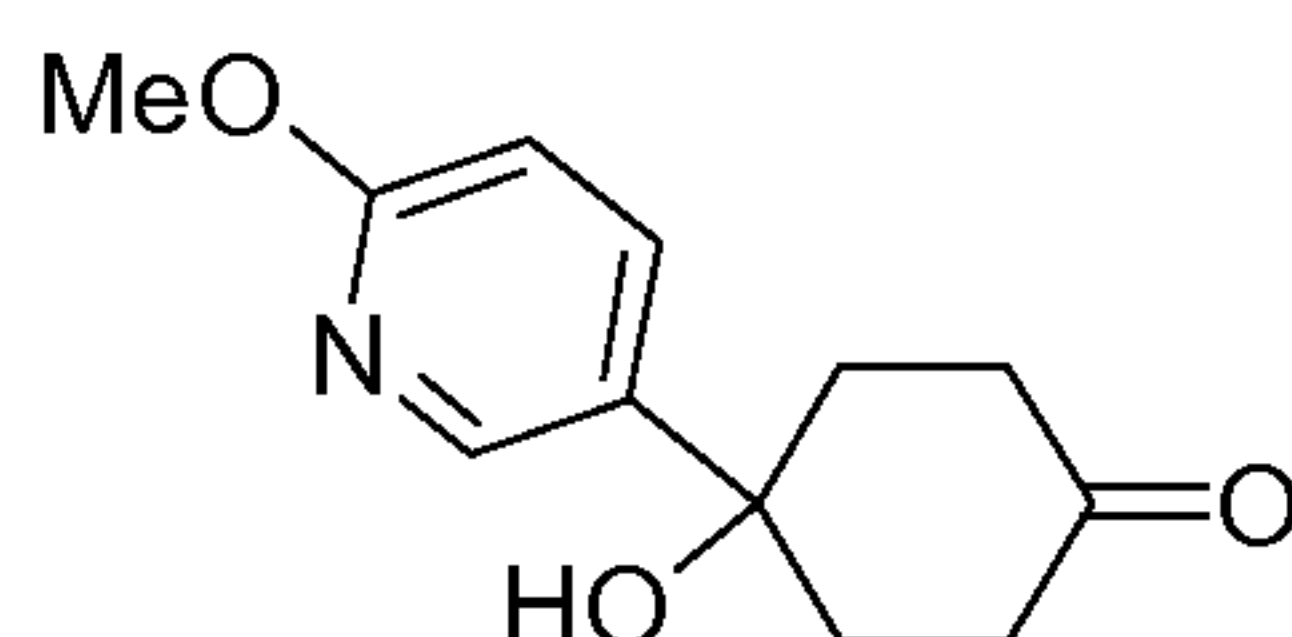
20

A solution of 5-bromo-2-methoxy-pyridine (Aldrich, 5.0 g, 26.6 mmol) in THF or ether (30 mL) at -78 °C was treated with *n*-BuLi (2.5 M in hexanes, 12 mL, 30 mmol) dropped slowly over 10 min. The reaction was stirred for an additional 20 min. at -78 °C. A solution of 1,4-dioxaspiro[4.5]decan-8-one (Aldrich, 4.37 g, 28 mmol) in THF (10 mL)
25 was slowly dropped into the reaction. After addition, the reaction was stirred for an additional 2 hours at -78 °C. The reaction was then quenched with water and warmed to room temperature. The solvent was removed *in vacuo* and the residue was partitioned

between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give a yellow solid, which was then purified by silica gel column on a CombiFlash® system (Teledyne Isco, Inc, Lincoln, NE) using hexanes and ethyl acetate (from 10% ethyl acetate to 100% ethyl acetate) to afford the title compound as a yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 8.28 (s, 1H), 7.75 (d, $J = 7.5$ Hz, 1H), 6.72 (d, $J = 7.5$ Hz, 1H), 3.95 (m, 4H), 2.35 (s, br, 1H), 2.10 (m, 1H), 1.85 (m, 2H), 1.65 (m, 2H).

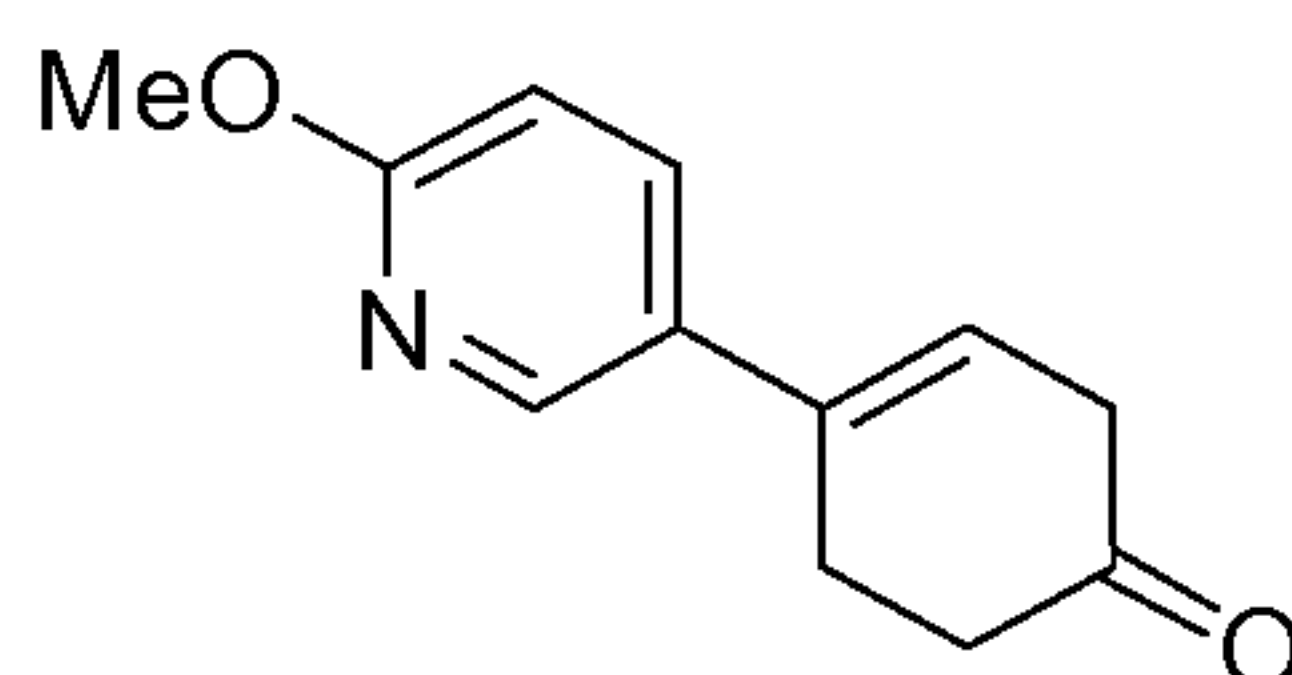
Step B: 4-Hydroxy-4-(6-methoxy-pyridin-3-yl)-cyclohexanone



8-(6-Methoxy-pyridin-3-yl)-1,4-dioxo-spiro[4.5]decan-8-ol (4.00 g, 15.7 mmol) as prepared in the previous step was treated with 1N HCl (~16 mL) in acetone (20 mL) at room temperature for 4 hours. The reaction was neutralized with saturated NaHCO_3 solution and the solvent was removed. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give a yellow solid, which was purified by silica gel column on a CombiFlash® system using hexanes and ethyl acetate (from 10% ethyl acetate to 100% ethyl acetate) to afford the title compound as a pale yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 8.30 (s, 1H), 7.75 (d, $J = 7.0$ Hz, 1H), 6.75 (d, $J = 6.5$ Hz, 1H), 3.90 (s, 4H), 2.91 (m, 2H), 2.35 (d, $J = 6.8$ Hz, 2H), 2.22 (m, 4H).

Step C: 4-(6-Methoxy-pyridin-3-yl)-cyclohex-3-enone

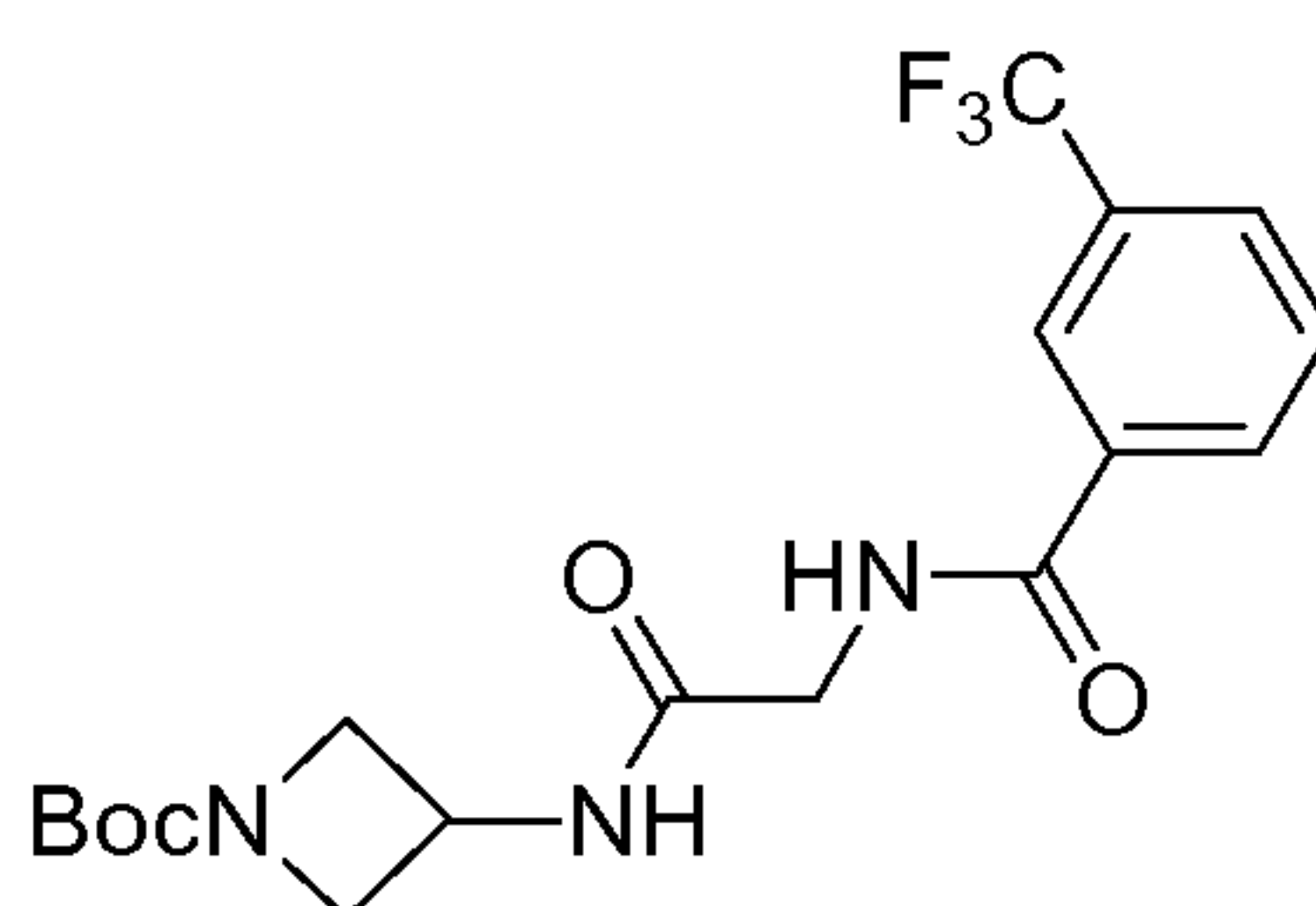


4-Hydroxy-4-(6-methoxy-pyridin-3-yl)-cyclohexanone (as prepared in the previous step, 750 mg, 3.40 mmol) in THF (5 mL) was treated with Burgess' reagent (Aldrich, 1.19 g, 5.0 mmol) at room temperature. The reaction was stirred for 10 hours. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The

organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give yellow oil, which was then purified by silica gel column on a CombiFlash® system using hexanes and ethyl acetate (from 10% ethyl acetate to 100% ethyl acetate) to afford the title compound as white solid.

- 5 ^1H NMR (400 MHz, CDCl_3) δ 8.25 (s, 1H), 7.61 (d, $J = 7.2$ Hz, 1H), 6.72 (d, $J = 7.0$ Hz, 1H), 6.02 (t, $J = 4.3$ Hz, 1H), 3.90 (s, 3H), 3.08 (d, $J = 2.5$ Hz, 2H), 2.81 (t, $J = 6.5$ Hz, 2H), 2.62 (t, $J = 6.8$ Hz, 2H).

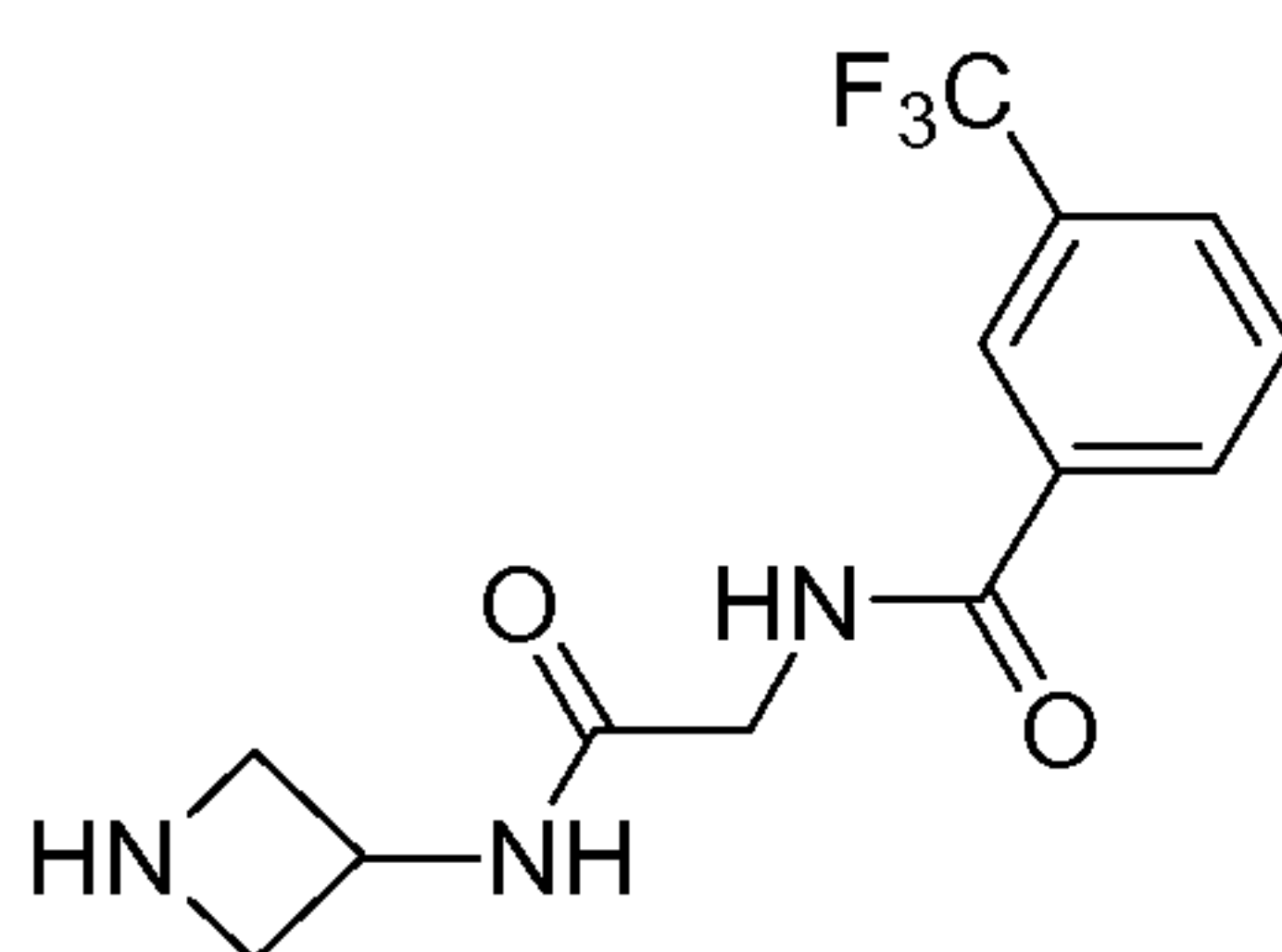
10 *Step D: 3-[2-(3-Trifluoromethyl-benzoylamino)-acetylamino]-azetidine-1-carboxylic acid tert-butyl ester*



- 15 3-Amino-azetidine-1-carboxylic acid tert-butyl ester (AstaTech, 1.2 g, 6.97 mmol) and (3-trifluoromethyl-benzoylamino)-acetic acid (Bionet Building Blocks, 1.57 g, 6.36 mmol) were treated with EDCI (Aldrich, 1.57 g, 6.36 mmol), HOBT (Aldrich, 1.22 g, 6.36 mmol) in DCM (10 mL) at room temperature for 4 hours. The reaction solution was partitioned between DCM and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give a yellow oil, and purified by silica gel column on a CombiFlash® system using hexanes and ethyl acetate (from 10% ethyl acetate to 100% ethyl acetate) to afford the title compound as a white solid.

- 20 ^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, 1H), 8.02 (d, $J = 6.6$ Hz, 1H), 7.80 (d, $J = 6.8$ Hz, 1H), 7.56 (t, $J = 6.5$ Hz, 1H), 4.61 (m, 1H), 4.25 (t, $J = 7.2$ Hz, 2H), 4.18 (d, $J = 5.5$ Hz, 2H), 3.82 (t, $J = 7.5$ Hz, 2H), 1.41 (s, 9H).

- 25 *Step E: N-(Azetidin-3-ylcarbamoylemethyl)-3-trifluoromethyl-benzamide free base, HCl and TFA salt*



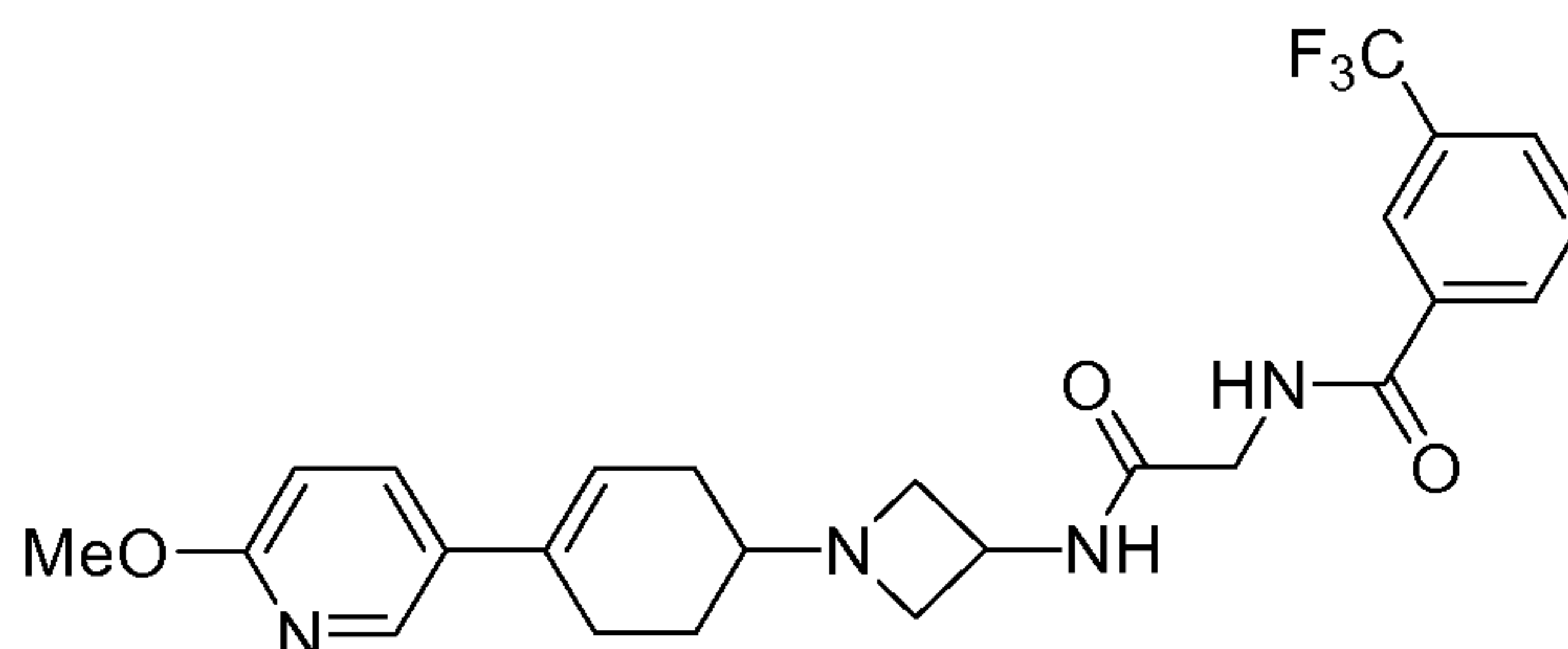
3-[2-(3-Trifluoromethyl-benzoylamino)-acetylamino]-azetidine-1-carboxylic acid tert-butyl ester (7.5 g, 18.7 mmol), as prepared in the previous step, was dissolved in 4N HCl in dioxane (5 mL) and MeOH (20 mL) at room temperature. The reaction was stirred for another 4 hours. The solvent was removed and the residue was dried to give the title compound as a HCl salt (yellow foam).

3-[2-(3-Trifluoromethyl-benzoylamino)-acetylamino]-azetidine-1-carboxylic acid tert-butyl ester (2.10 g, 5.24 mmol) was dissolved in 1:1 TFA and DCM mixed solution (10 mL) at room temperature. The reaction was stirred for another 2 hours. The solvent was removed and the residue was dried to give the title compound as a TFA salt containing extra TFA (colorless oil).

The free base was obtained by treating the salt in MeOH with solid Na_2CO_3 overnight. The solid was filtered and residue was dried to give the title compound for analytical characterization. The HCl or TFA salt was general used for the further reactions.

^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, 1H), 8.05 (d, $J = 6.0$ Hz, 1H), 7.78 (d, $J = 6.2$ Hz, 1H), 7.55 (m, 2H), 4.78 (m, 1H), 4.15 (d, $J = 3.2$ Hz, 2H), 3.95 (t, $J = 7.0$ Hz, 2H), 3.52 (t, $J = 7.0$ Hz, 2H).

Step F: N-(1-[4-(6-Methoxy-pyridin-3-yl)-cyclohex-3-enyl]-azetidin-3-ylcarbamoyl)-3-trifluoromethyl-benzamide



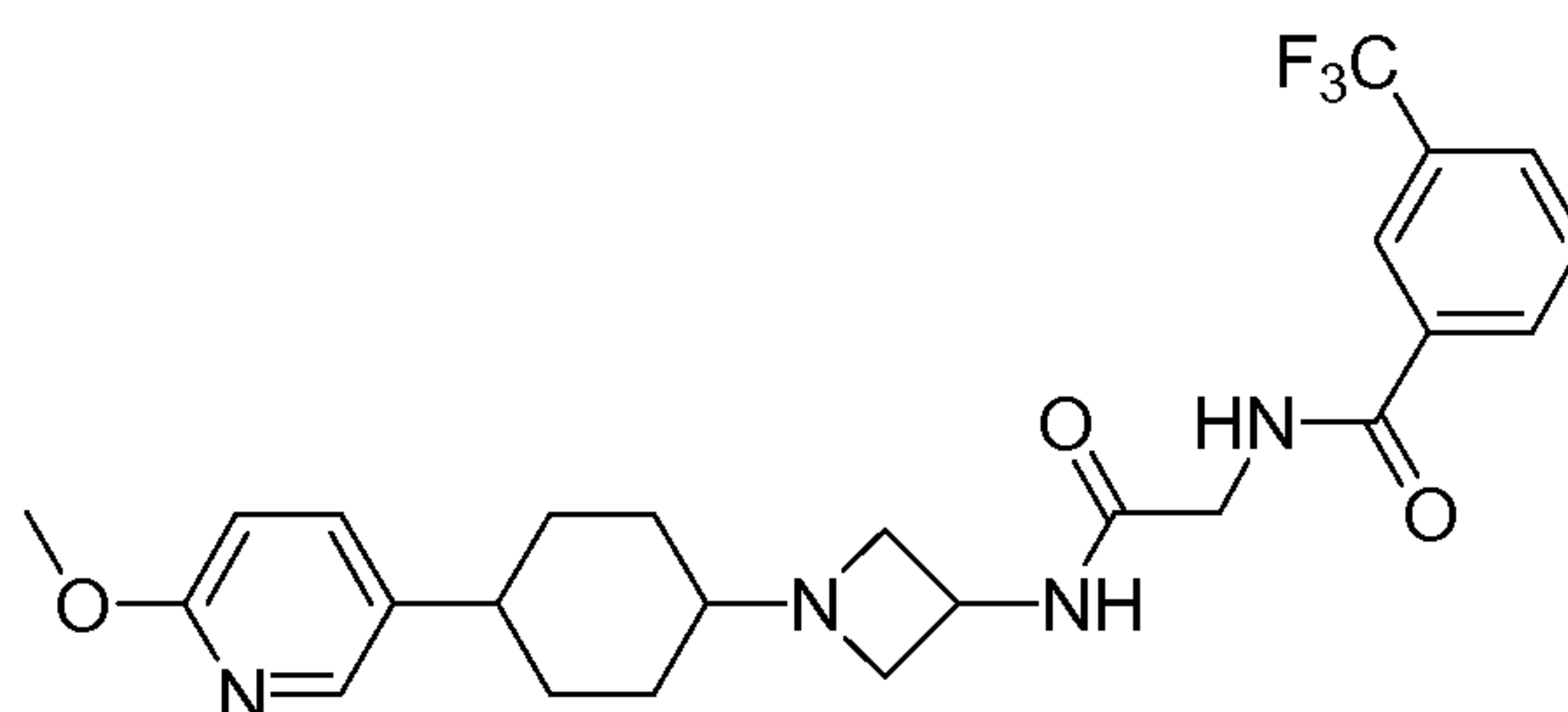
4-(6-Methoxy-pyridin-3-yl)-cyclohex-3-enone (as prepared in Step C, 1.02 g, 5.02 mmol) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide HCl salt (as

prepared in the previous step, 2.54 g, 7.53 mmol) in DCM (15 mL) was treated with TEA (2.80 mL, 20 mmol) for 10 min followed by NaBH(OAc)₃ (Aldrich, 3.20 g, 15 mmol) for another 4 hours at room temperature. The reaction was quenched with saturated sodium bicarbonate. The organic layer was separated and the aqueous layer was
 5 extracted 3 times with chloroform/IPA "cocktail" (~ 3:1, v/v). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude product, which was then purified by a CombiFlash® system using ethyl acetate and 7N NH₃ in MeOH as eluent (from pure ethyl acetate to 5% 7N NH₃ in MeOH in ethyl acetate) to afford the title compound as white solids.

10 ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 8.10 (s, 1H), 8.05 (d, J = 6.5 Hz, 1H), 7.75 (d, J = 6.5 Hz, 1H), 7.60 (d, J = 6.6 Hz, 1H), 7.55 (t, J = 6.5 Hz, 1H), 7.40 (m, 1H), 7.02 (d, J = 6.3 Hz, 1H), 6.70 (d, J = 6.5 Hz, 1H), 5.92 (m, 1H), 4.58 (m, 1H), 4.20 (d, J = 4.5 Hz, 2H), 3.90 (s, 3H), 3.65 (t, J = 6.8 Hz, 2H), 3.05 (t, J = 6.8 Hz, 2H), 2.45 (m, 1H), 2.30 (m, 2H), 1.92 (m, 2H), 1.45 (m, 1H), 1.28 (m, 1H).

15

Step G: N-({1-[4-(6-Methoxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



N-({1-[4-(6-Methoxy-pyridin-3-yl)-cyclohex-3-enyl]-azetidin-3-ylcarbamoyl}-methyl)-
 20 3-trifluoromethyl-benzamide (as prepared in the previous step, 500 mg, 1.02 mmol) from step B in MeOH (40 mL) was driven through an H-Cube® Continuous-flow Hydrogenation reactor (ThalesNano, Budapest, Hungary) under full hydrogen mode at room temperature using a 5% Pd/C cartridge. The resulting solution was concentrated and purified by silica gel column on a CombiFlash® system using ethyl acetate and 7N
 25 NH₃ in MeOH as eluent (from pure ethyl acetate to 5% 7N NH₃ in MeOH in ethyl acetate) to afford the two title compounds as white solids.

1a: less polar isomer from silica gel column

¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 8.05 (d, J = 7.0 Hz, 2H), 7.85 (s, 1H), 7.80 (d, J = 6.2 Hz, 1H), 7.60 (d, J = 6.0 Hz, 1H), 7.50 (d, J = 6.1 Hz, 1H), 7.36 (d, J = 5.5 Hz, 1H), 6.76 (d, J = 6.5 Hz, 1H), 4.55 (m, 1H), 4.25 (s, br, 2H), 4.01 (s, 3H), 3.65 (t, J = 5.8 Hz, 2H), 2.90 (t, J = 5.5 Hz, 2H), 2.48 (m, 1H), 1.85 (m, 2H), 1.70 (m, 2H), 1.45 (m, 4H).

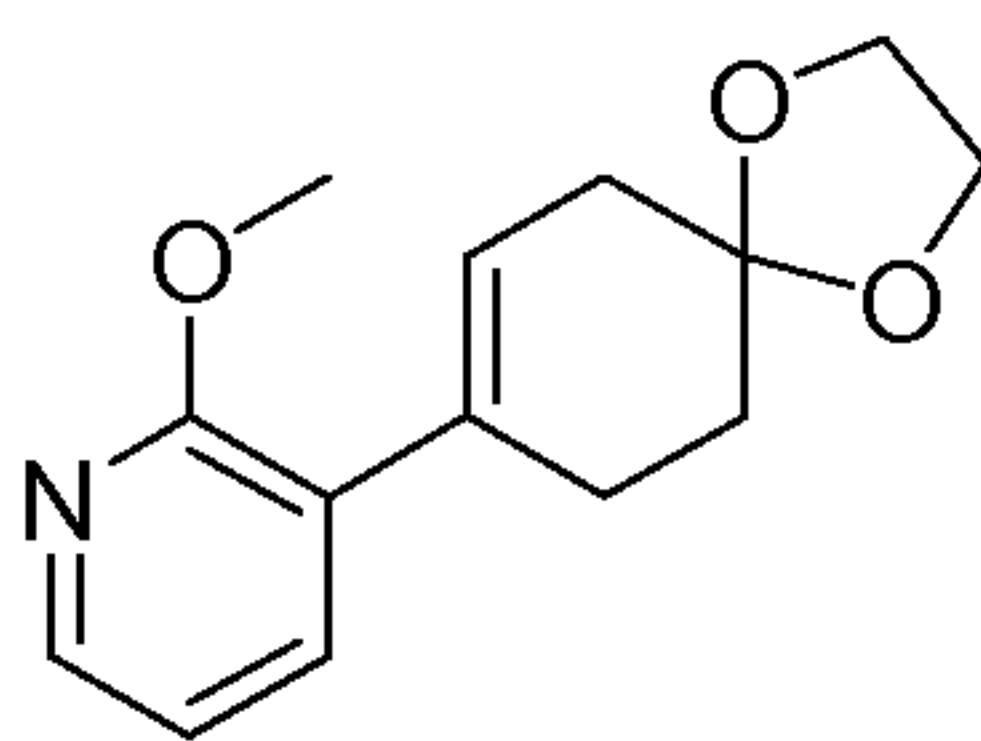
5 **1b**: more polar isomer from silica gel column

¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 8.02 (d, J = 6.0 Hz, 1H), 8.00 (s, 1H), 7.78 (d, J = 5.5 Hz, 1H), 7.60 (t, J = 6.5 Hz, 1H), 6.80 (m, 1H), 6.67 (d, J = 7.0 Hz, 1H), 4.55 (m, 1H), 4.19 (d, J = 4.5 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 3.02 (t, J = 6.6 Hz, 2H), 2.38 (m, 1H), 1.90 (m, 4H), 1.36 (m, 2H), 1.15 (m, 2H).

10

Example 2: N-({1-[4-(2-Methoxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide

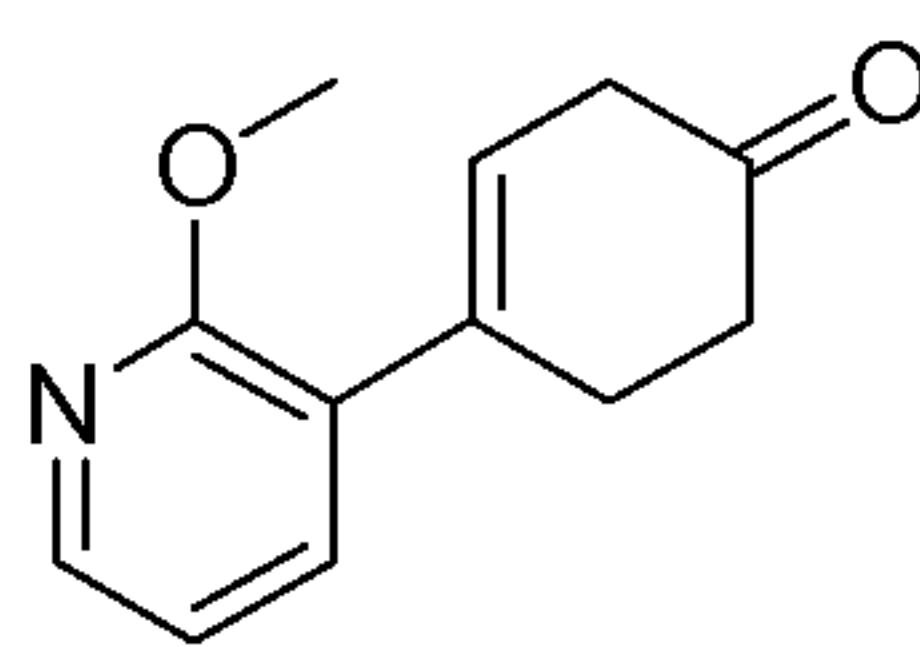
Step A: 3-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-2-methoxy-pyridine



15 To a mixture of trifluoro-methanesulfonic acid 1,4-dioxo-spiro[4.5]dec-7-en-8-yl ester (prepared according to JOC, 69, 3943, 2004, 1.27 g, 3.47 mmol) and 2-methoxypyridine-3-boronic acid (Aldrich, 637 mg, 4.17 mmol) was added tetrakis(triphenylphosphine) palladium (120 mg, 0.10 mmol), dioxane (10 mL) and aqueous sodium carbonate (4.00 mL, 8.00 mmol, 2N). The reaction mixture was heated to 100 °C under argon for 16
20 hours and then cooled to room temperature and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, 0-10% MeOH/CH₂Cl₂) to afford 3-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-2-methoxy-pyridine as a colorless oil.

¹H NMR (CHLOROFORM-d) δ: 8.04 (dd, J = 4.9, 1.9 Hz, 1H), 7.44 (dd, J = 7.3, 2.0 Hz, 1H), 6.83 (dd, J = 7.2, 4.9 Hz, 1H), 5.80 (s, 1H), 3.99 - 4.07 (m, 4H), 3.70 (s, 3H), 2.62 (d, J = 1.8 Hz, 2H), 2.46 (d, J = 3.5 Hz, 2H), 1.89 (t, J = 6.6 Hz, 2H).

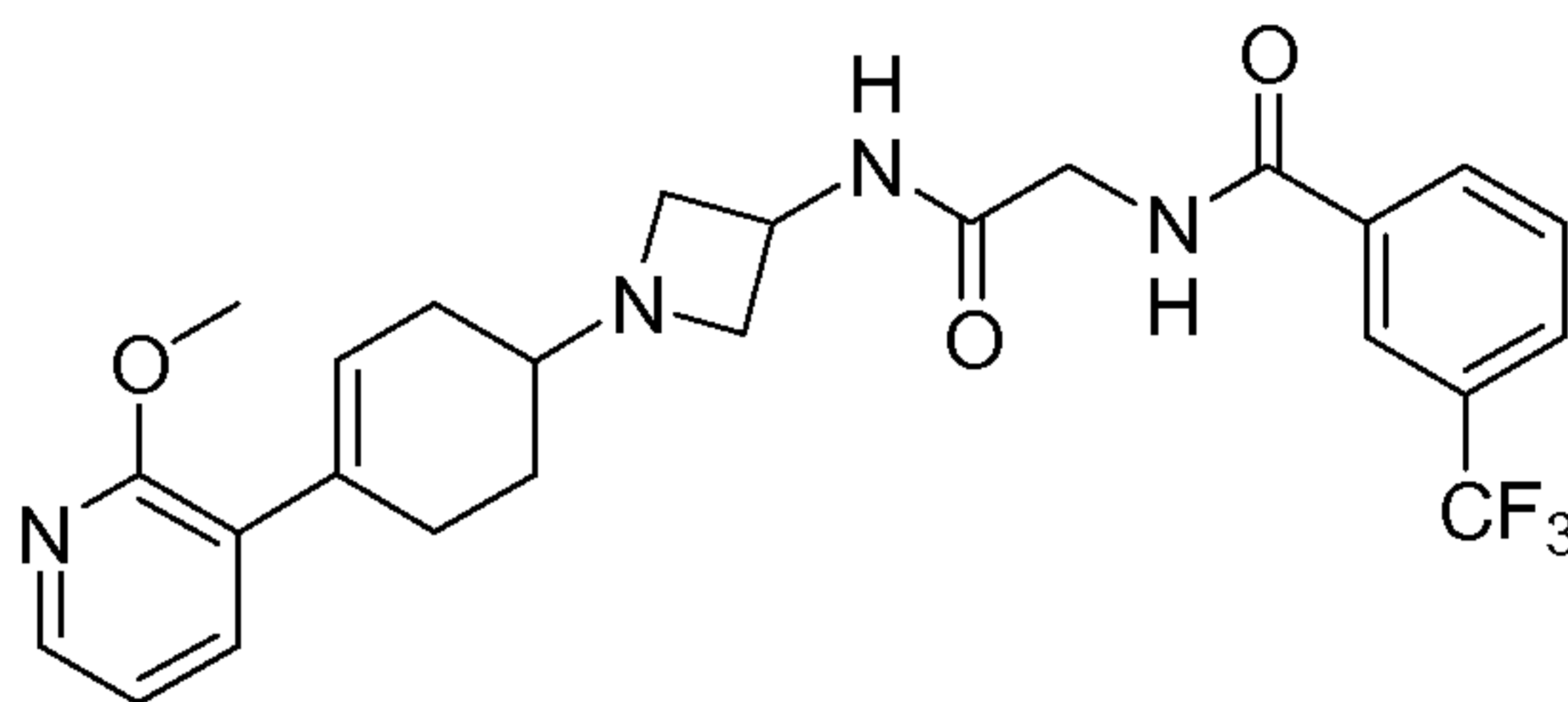
Step B: 4-(2-Methoxy-pyridin-3-yl)-cyclohex-3-enone



To a mixture of 3-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-2-methoxy-pyridine (as prepared in the previous step, 211 mg, 0.854 mmol) in acetonitrile was added aqueous HCl (5 mL, 5 mmol, 1M). The mixture was stirred at room temperature until HPLC indicated consumption of starting material. The reaction mixture was poured onto saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, 0-10% MeOH/CH₂Cl₂) to afford 4-(2-methoxy-pyridin-3-yl)-cyclohex-3-enone.

LCMS (ESI, M/Z): 204 (MH⁺).

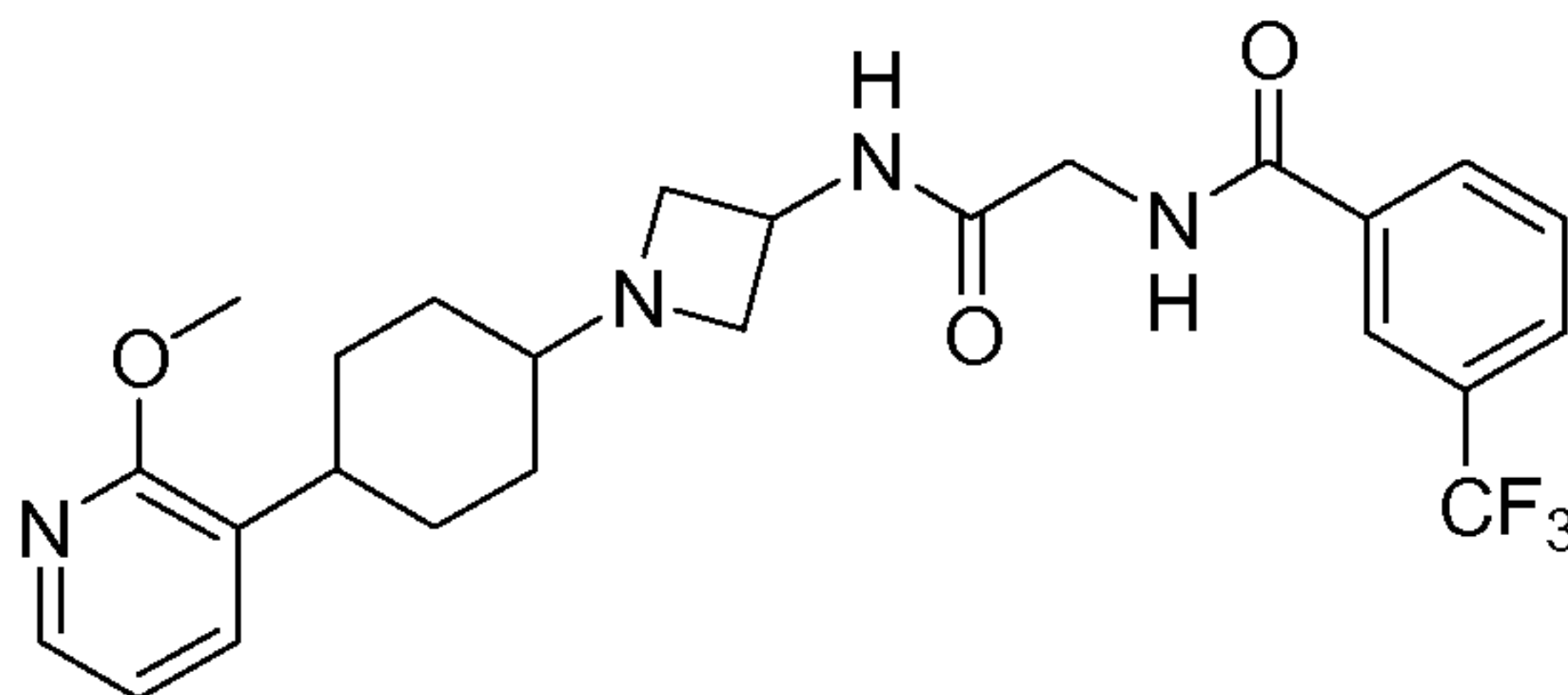
Step C: N-({1-[4-(2-Methoxy-pyridin-3-yl)-cyclohex-3-enyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



The title compound was prepared as a white solid from reductive amination of 4-(2-methoxy-pyridin-3-yl)-cyclohex-3-enone (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

¹H NMR (CHLOROFORM-d) δ: 8.12 (s, 1H), 7.98 - 8.07 (m, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.52 - 7.63 (m, 2H), 7.39 (dd, J = 7.3, 1.8 Hz, 1H), 7.19 - 7.26 (m, 1H), 6.83 (dd, J = 7.2, 4.9 Hz, 1H), 5.76 - 5.82 (m, 1H), 4.52 - 4.64 (m, 1H), 4.19 (d, J = 4.8 Hz, 2H), 3.86 - 3.98 (m, 4H), 3.69 (d, J = 8.1 Hz, 2H), 3.03 (s, 2H), 2.40 (d, J = 3.0 Hz, 4H), 1.76 - 1.98 (m, 2H), 1.41 (none, 1H); LCMS (ESI, M/Z): 489 (MH⁺).

Step D: *N*-({1-[4-(2-Methoxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

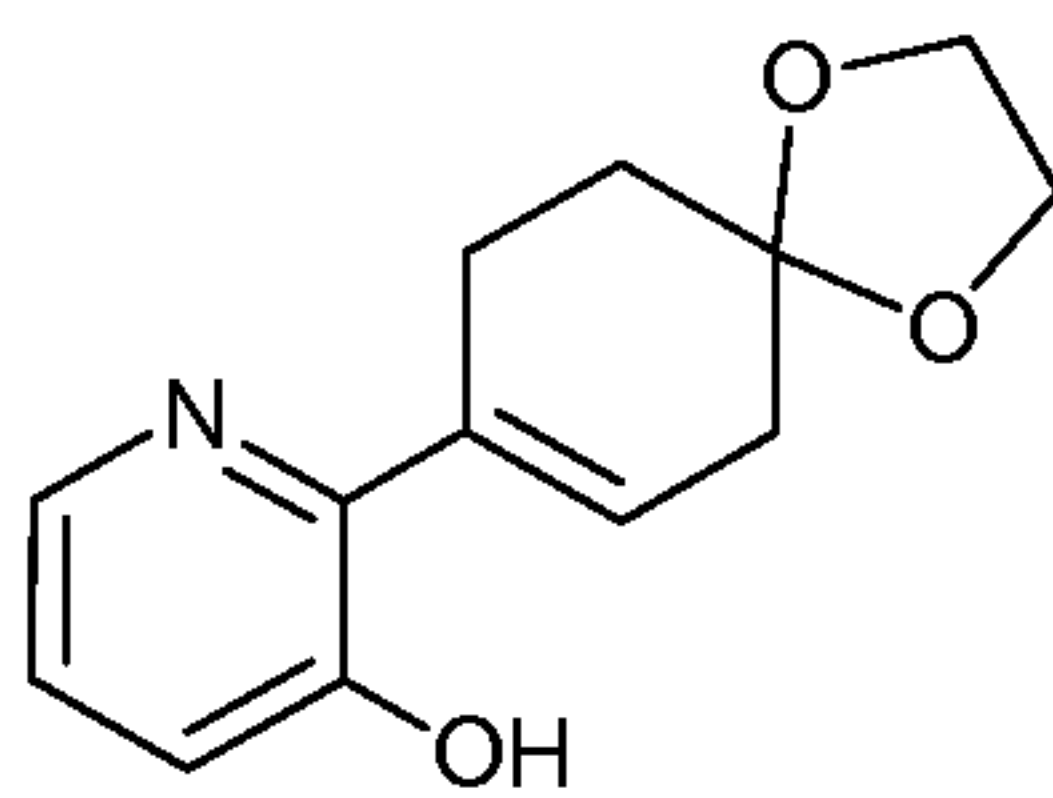


The title compound was prepared as a white solid from the hydrogenation of *N*-({1-[4-(2-methoxy-pyridin-3-yl)-cyclohex-3-enyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide (as prepared in the previous step) using the procedure described in Step G of Example 1.

¹H NMR (CHLOROFORM-*d*) δ: 8.13 (s, 1H), 7.95 - 8.06 (m, 2H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.49 (br. s., 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.10 - 7.22 (m, 1H), 6.76 - 6.88 (m, 1H), 5.78 (br. s., 1H), 4.47 - 4.66 (m, 1H), 4.19 (dd, *J* = 4.8, 1.8 Hz, 2H), 3.94 (s, 3H), 3.55 - 3.75 (m, 2H), 2.96 - 3.10 (m, 2H), 1.06 - 2.53 (series of m, 9H); LCMS (ESI, *M/Z*): 491 (MH⁺).

Example 3: *N*-({1-[4-(3-Hydroxy-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

Step A: 2-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-3-ol



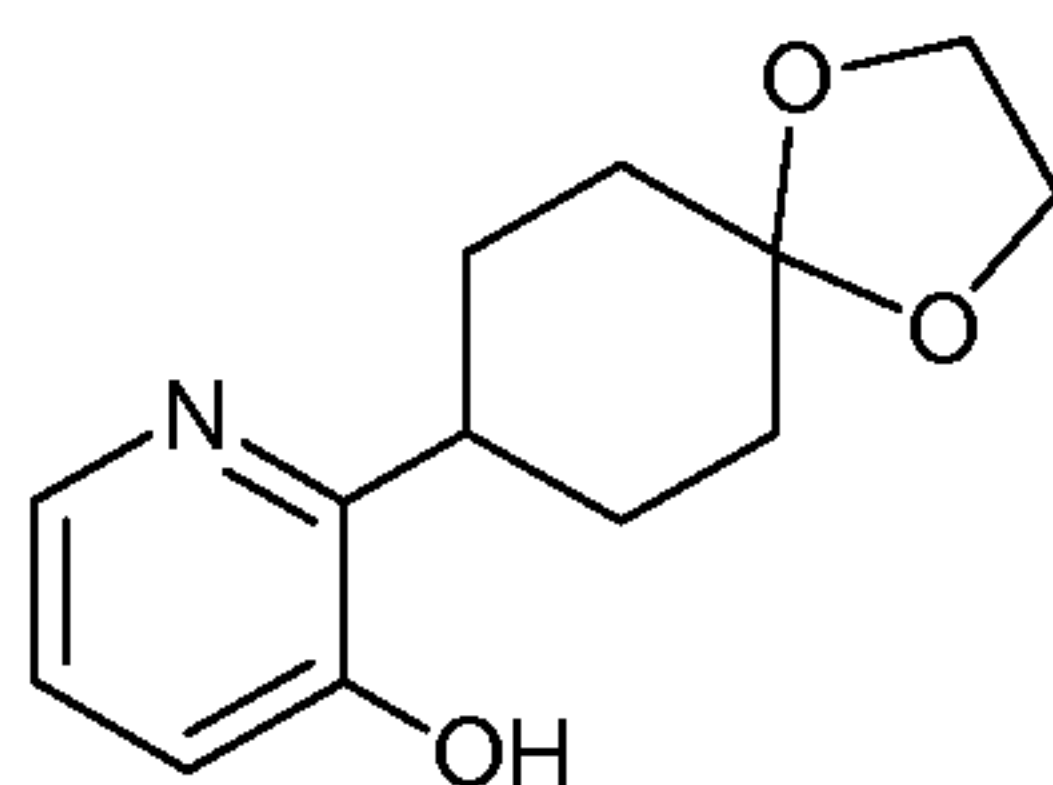
8-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,4-dioxo-spiro[4.5]dec-7-ene

(prepared as described in PCT Int. Appl. WO2006064189, 0.292 g, 1.10 mmol), 2-iodo-3-hydroxypyridine (Aldrich, 0.177 g, 0.801 mmol), and tetrakis(triphenylphosphino)palladium(0) (Aldrich, 0.048 g, 0.042 mmol) were dissolved in 1,4-dioxane (9 mL), treated with 2M aqueous Na₂CO₃ (2.0 mL, 4.0 mmol), bubbled with argon for a few minutes, and heated to 100 °C under reflux condenser for 24 h. After cooling to ambient temperature, the reaction was diluted with water (30 mL), extracted thrice with dichloromethane, aqueous layer acidified to ca. pH 7, extracted twice more

with dichloromethane, and the combined organic layers washed with brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give an orange oil. This was purified by thin layer chromatography on silica gel (EtOAc) to give the title compound as a yellow solid.

- 5 ^1H NMR (400 MHz, *CHLOROFORM-d*) δ 8.16 (dd, $J=4.5$, 1.3 Hz, 1 H), 7.22 (dd, $J=8.1$, 1.3 Hz, 0 H), 7.07 (dd, $J=8.2$, 4.7 Hz, 1 H), 5.95 - 6.09 (m, 2 H), 4.03 (s, 4 H), 2.73 (dddd, $J=6.4$, 4.4, 2.2, 2.0 Hz, 2 H), 2.49 (d, $J=2.8$ Hz, 2 H), 1.96 (t, $J=6.6$ Hz, 2 H). ESI-MS (m/z): Calcd. For $\text{C}_{13}\text{H}_{15}\text{NO}_3$: 233; found: 234 ($\text{M}+\text{H}$).

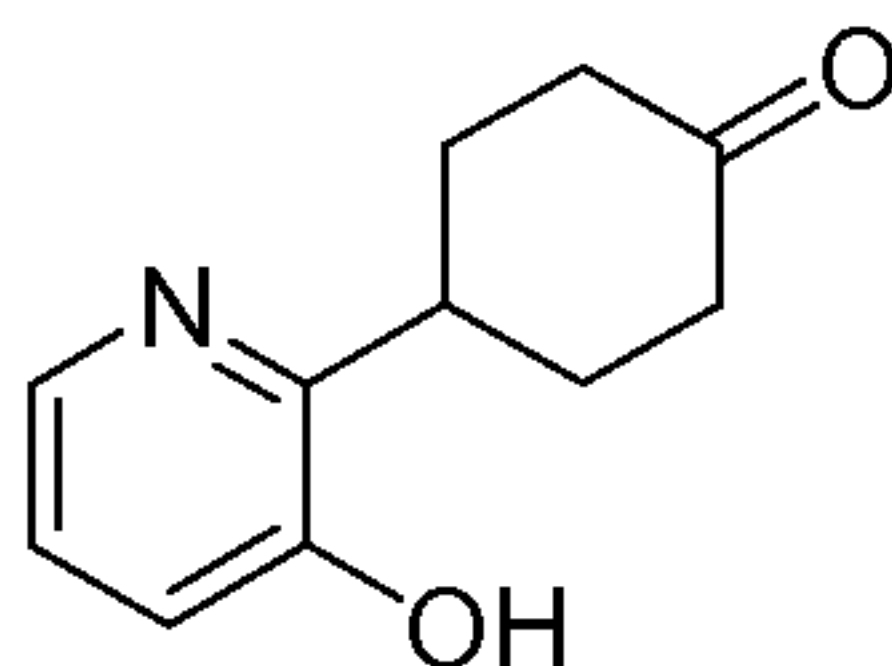
10 *Step B: 2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-ol*



The title compound was prepared as a white solid from the hydrogenation of 2-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-3-ol (as prepared in the previous step) using the procedure described in Step G of Example 1.

- 15 ^1H NMR (400 MHz, *ACETONITRILE-d*₃) δ 8.05 (dd, $J=4.7$, 1.4 Hz, 1 H), 7.19 (dd, $J=8.1$, 1.5 Hz, 1 H), 7.06 (dd, $J=8.1$, 4.5 Hz, 1 H), 3.86 - 3.99 (m, 4 H), 3.12 (tt, $J=11.7$, 3.7 Hz, 1 H), 1.72 - 1.94 (m, 6 H), 1.60 - 1.72 (m, 2 H). ESI-MS (m/z): Calcd. For $\text{C}_{13}\text{H}_{17}\text{NO}_3$: 235; found: 236 ($\text{M}+\text{H}$).

20 *Step C: 4-(3-Hydroxy-pyridin-2-yl)-cyclohexanone*

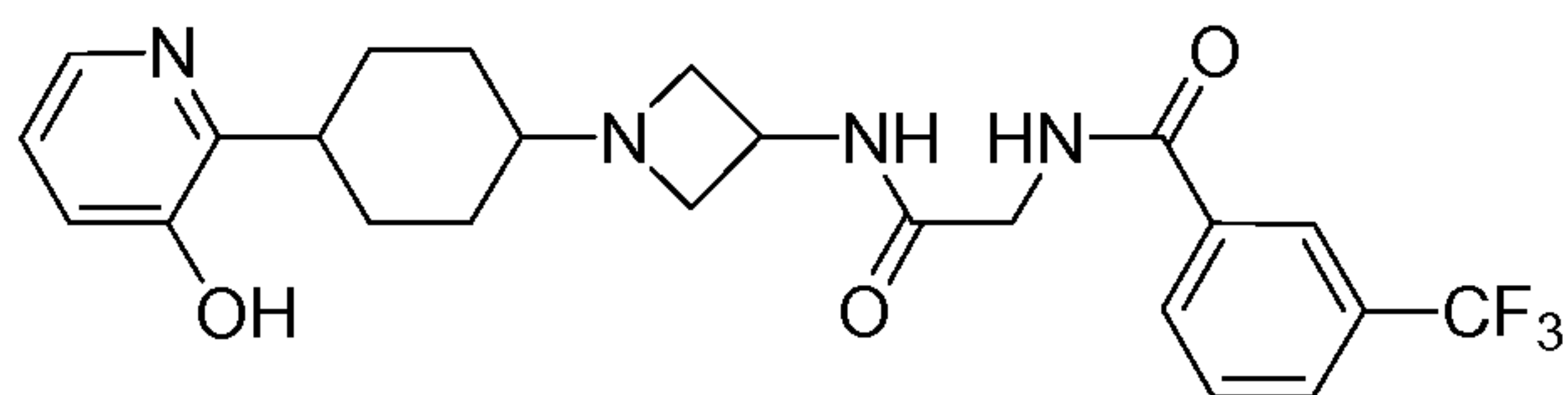


The title compound was prepared as a white solid from the deprotection of 2-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyridin-3-ol (as prepared in the previous step) using the procedure described in Step B of Example 2.

- 25 ^1H NMR (400 MHz, *ACETONITRILE-d*₃) δ 7.94 (dd, $J=4.7$, 1.4 Hz, 1 H), 7.28 (br. s., 1 H), 7.07 (dd, $J=8.1$, 1.5 Hz, 1 H), 6.96 (dd, $J=8.1$, 4.5 Hz, 1 H), 3.46 (tt, $J=11.2$, 3.7 Hz, 1

H), 2.34 - 2.52 (m, 2 H), 2.22 - 2.34 (m, 2 H), 1.99 - 2.07 (m, 2 H), 1.88 - 1.99 (m, 2 H).
ESI-MS (m/z): Calcd. For C₁₁H₁₃NO₂: 191; found: 192 (M+H).

Step D: *N-({1-[4-(3-Hydroxy-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-
3-trifluoromethyl-benzamide*



The title compounds were prepared as white solids from the reductive amination of 4-(3-hydroxy-pyridin-2-yl)-cyclohexanone (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in
Step F of Example 1.

¹H NMR (400 MHz, ACETONITRILE-*d*₃) δ 7.95 (s, 1 H), 7.89 (d, *J*=7.8 Hz, 1 H), 7.82 (dd, *J*=4.7, 1.4 Hz, 1 H), 7.66 (d, *J*=7.8 Hz, 1 H), 7.42 - 7.52 (m, 1 H), 7.33 (br. s., 1 H), 6.89 (dd, *J*=8.1, 1.3 Hz, 1 H), 6.83 (br. s., 1 H), 6.78 (dd, *J*=8.0, 4.7 Hz, 1 H), 4.18 (m, *J*=6.9, 6.9, 6.9, 6.9, 6.8 Hz, 1 H), 3.75 (d, *J*=5.8 Hz, 2 H), 3.42 (t, *J*=6.8 Hz, 2 H), 2.82 - 2.89 (m, 1 H), 2.61 - 2.74 (m, 2 H), 2.18 (br. s., 1 H), 1.51 (br. s., 2 H), 1.15 - 1.38 (m, 4 H). ESI-MS (m/z): Calcd. For C₂₄H₂₇N₄O₃F₃: 476; found: 477 (M+H).

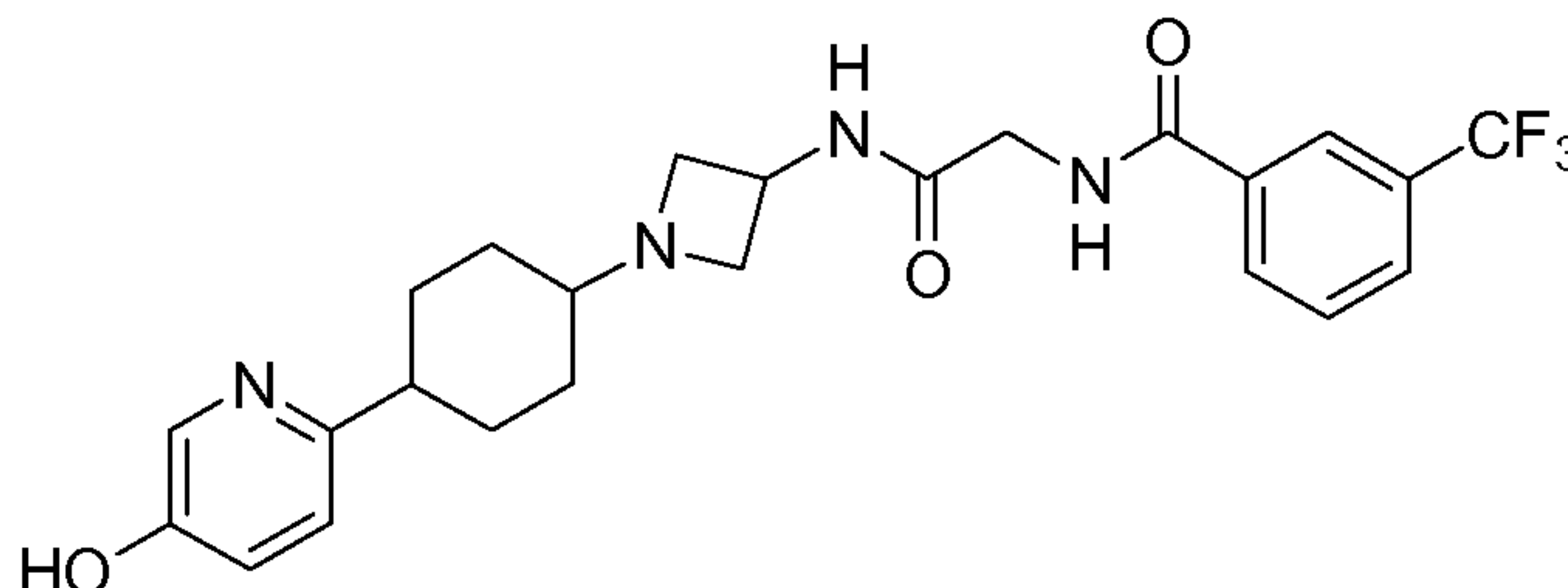
Step E: *N-({1-[4-(3-Hydroxy-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-
3-trifluoromethyl-benzamide hemisuccinate salt*

The product of the preceding step (0.556 g, 1.17 mmol) and succinic acid (0.069 g, 0.585 mmol) were dissolved in 2-propanol, concentrated to dryness in vacuo, dissolved in acetonitrile/water (100 mL), cooled to -78 °C (dry ice/acetone) until thoroughly frozen, and freeze-dried on a lyophilizer for 18 h giving the title compound as a fluffy, white, amorphous powder (672 mg).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.63 (br. s., 1 H), 9.02 (t, *J*=5.8 Hz, 1 H), 8.41 (d, *J*=7.1 Hz, 1 H), 8.23 (s, 1 H), 8.19 (d, *J*=7.8 Hz, 1 H), 7.88 - 7.97 (m, 2 H), 7.75 (t, *J*=7.8 Hz, 1 H), 7.08 (dd, *J*=8.1, 1.5 Hz, 1 H), 6.99 (dd, *J*=8.0, 4.7 Hz, 1 H), 4.29 (m, 1 H), 3.88 (d, *J*=6.1 Hz, 2 H), 3.77 (spt, *J*=6.1 Hz, 0.5 H [2-PrOH]), 3.55 (t, *J*=6.8 Hz, 2 H), 3.02

(m, 1 H), 2.86 (br. s., 2 H), 2.31 - 2.42 (m, 3 H), 1.79 - 1.96 (m, 2 H), 1.67 (m, 2 H), 1.29 - 1.51 (m, 4 H), 1.04 (d, $J=6.1$ Hz, 3 H [2-PrOH]). ESI-MS (m/z): Calcd. For $C_{24}H_{27}N_4O_3F_3$: 476; found: 477 ($M+H$).

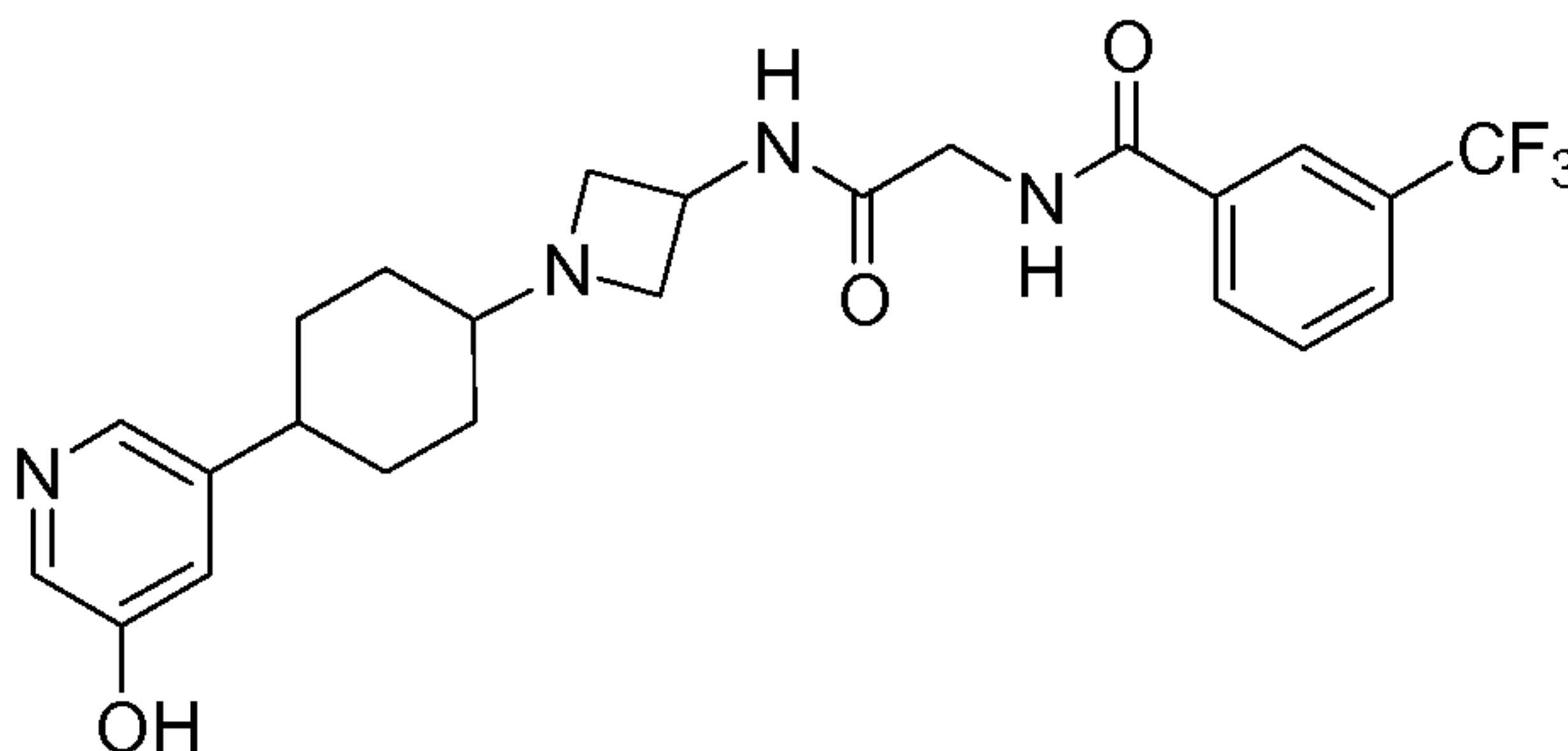
5 **Example 4: N-({1-[4-(5-Hydroxy-pyridin-2-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide hemisuccinate salt**



The title compound was prepared as described in Example 3: Steps A-E from 2-bromo-5-hydroxypyridine (Aldrich) as a white solid.

10 ^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 9.54 (br. s., 1 H), 9.00 (t, $J=5.8$ Hz, 1 H), 8.37 (d, $J=7.3$ Hz, 1 H), 8.23 (s, 1 H), 8.18 (d, $J=7.8$ Hz, 1 H), 8.02 (dd, $J=2.7, 0.6$ Hz, 1 H), 7.93 (d, $J=7.8$ Hz, 1 H), 7.74 (t, $J=7.8$ Hz, 1 H), 6.98 - 7.08 (m, 2 H), 4.28 (sxt, $J=7.0$ Hz, 1 H), 3.88 (d, $J=5.8$ Hz, 2 H), 3.53 (t, $J=6.7$ Hz, 2 H), 2.76 - 2.91 (m, 2 H), 2.54 - 2.61 (m, 1 H), 2.39 (s, 2 H), 2.31 - 2.37 (m, 1 H), 1.72 - 1.90 (m, 2 H), 1.53 - 1.67 (m, 2 H), 1.33 -
15 1.50 (m, 4 H). ESI-MS (m/z): Calcd. For $C_{24}H_{27}N_4O_3F_3$: 476; found: 477 ($M+H$).

Example 5: N-({1-[4-(5-Hydroxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide

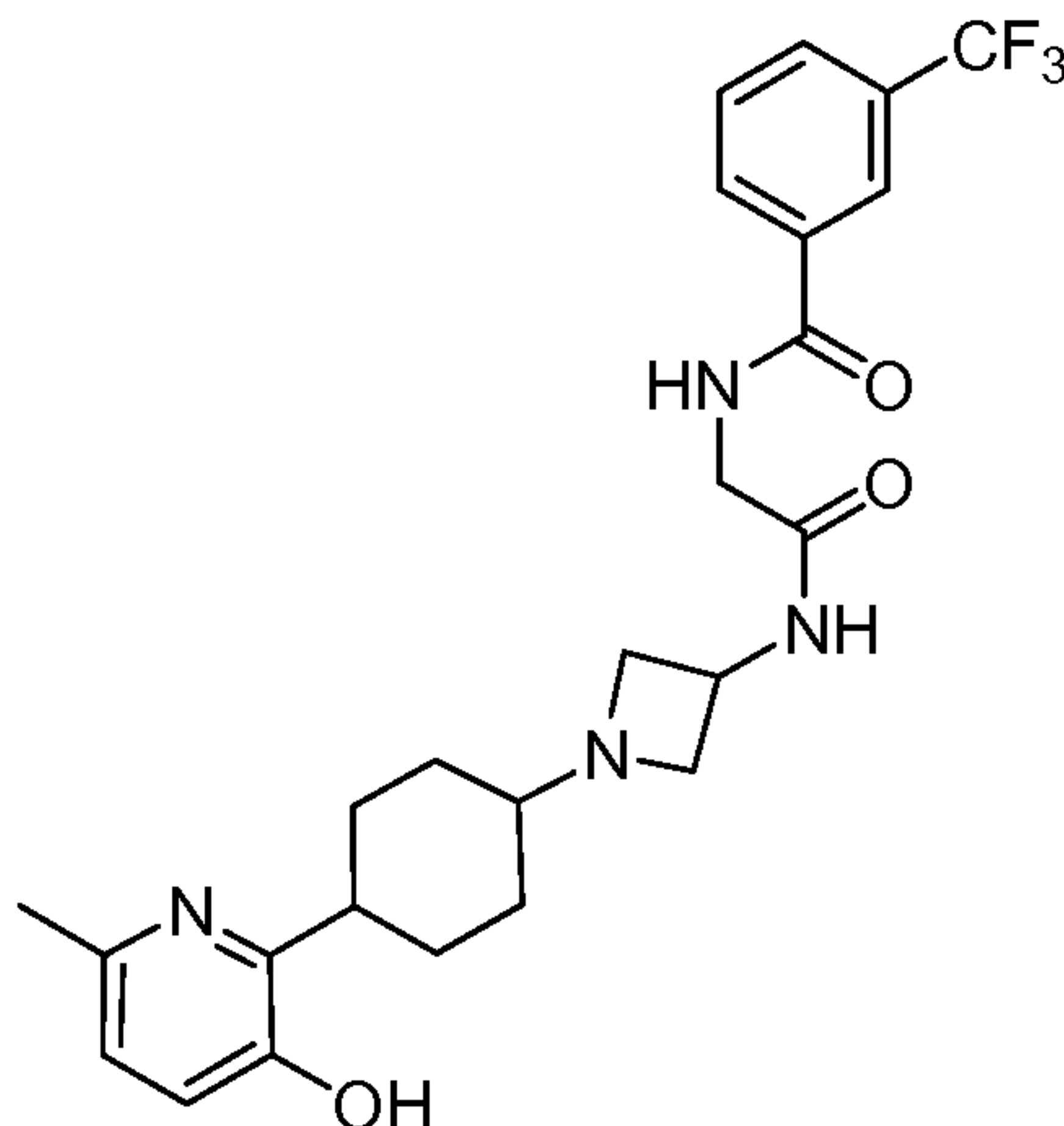


20 The title compound was prepared as described in Example 3: Steps A-D from 5-bromo-3-hydroxypyridine (Aldrich) as a white solid.

^1H NMR (400 MHz, $METHANOL-d_4$) δ ppm 8.22 (s, 1 H), 8.15 (d, $J=7.8$ Hz, 1 H), 7.93 (d, $J=1.5$ Hz, 1 H), 7.87 (d, $J=8.1$ Hz, 1 H), 7.70 (t, $J=7.8$ Hz, 1 H), 7.17 (t, $J=2.3$ Hz, 1

H), 7.10 (t, $J=2.1$ Hz, 1 H), 4.52 (quin, $J=7.2$ Hz, 1 H), 4.04 (s, 2 H), 3.55 - 3.67 (m, 1 H), 2.47 - 2.57 (m, 1 H), 2.00 - 2.11 (m, 2 H), 1.71 - 1.93 (m, 4 H), 1.48 - 1.65 (m, 4 H), 1.33 - 1.48 (m, 2 H). ESI-MS (m/z): Calcd. For $C_{24}H_{27}N_4O_3F_3$: 476; found: 477 ($M+H$).

5 **Example 6: N-({1-[4-(3-Hydroxy-6-methyl-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide**

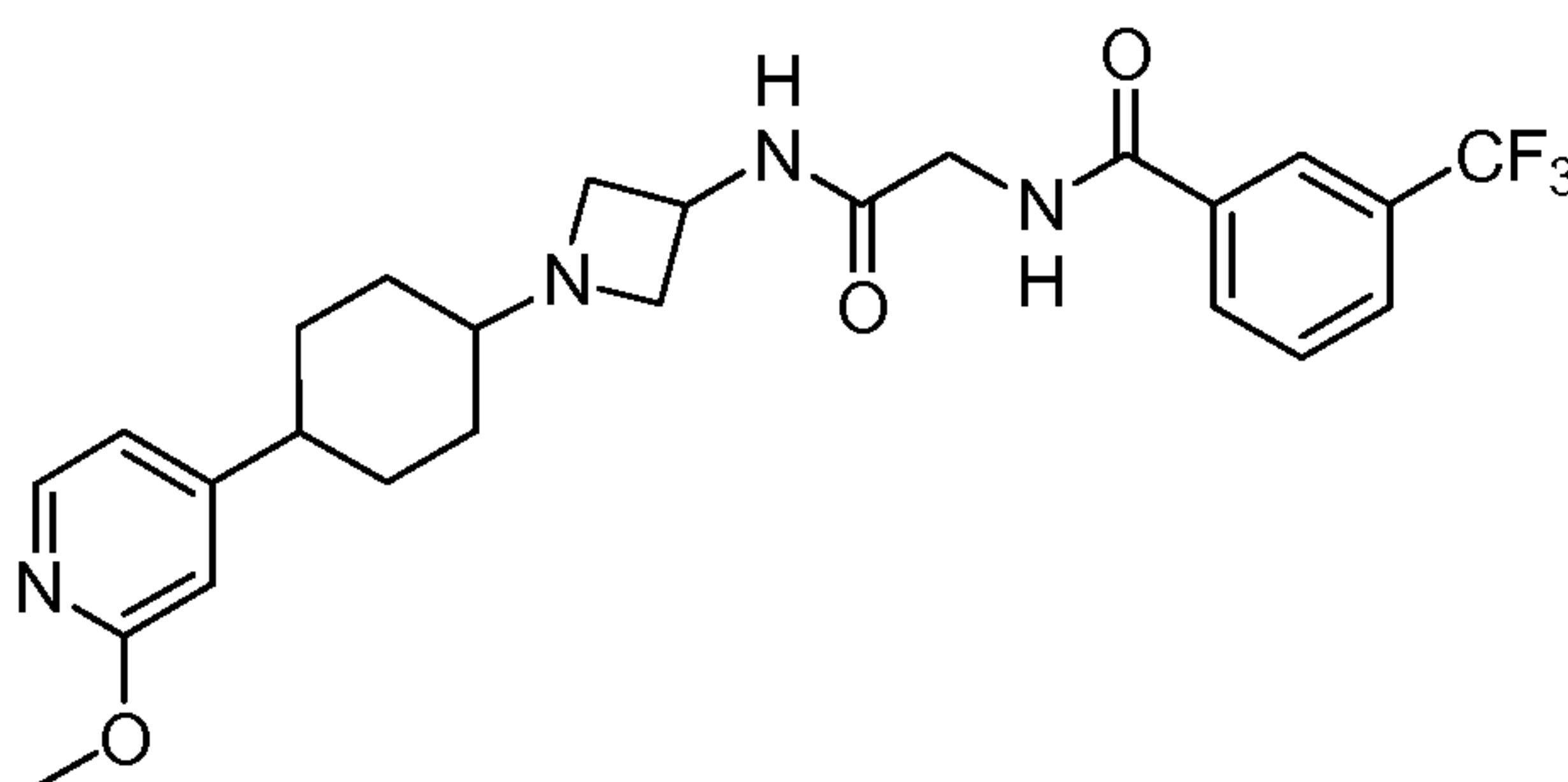


The title compound was prepared as described in Example 2: Steps A-D from 5-bromo-3-hydroxypyridine (Ryan Scientific) as a gold solid.

10 ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.19 (s, 1 H), 8.11 (d, $J=7.6$ Hz, 1 H), 7.78 (d, $J=8.1$ Hz, 1 H), 7.59 (t, $J=7.8$ Hz, 1 H), 7.39 (br. s., 1 H), 7.05 (d, $J=8.6$ Hz, 1 H), 6.89 (d, $J=8.3$ Hz, 1 H), 4.73 (s, 3 H), 4.25 (d, $J=5.1$ Hz, 2 H), 3.71 (m, 4 H), 2.39 - 2.45 (m, 2 H), 1.96 - 2.08 (m, 2 H), 1.81 (m, 2 H), 1.51 - 1.76 (m, 5 H). ESI-MS (m/z): Calcd. For $C_{25}H_{29}N_4O_3F_3$: 490; found: 491 ($M+H$).

15

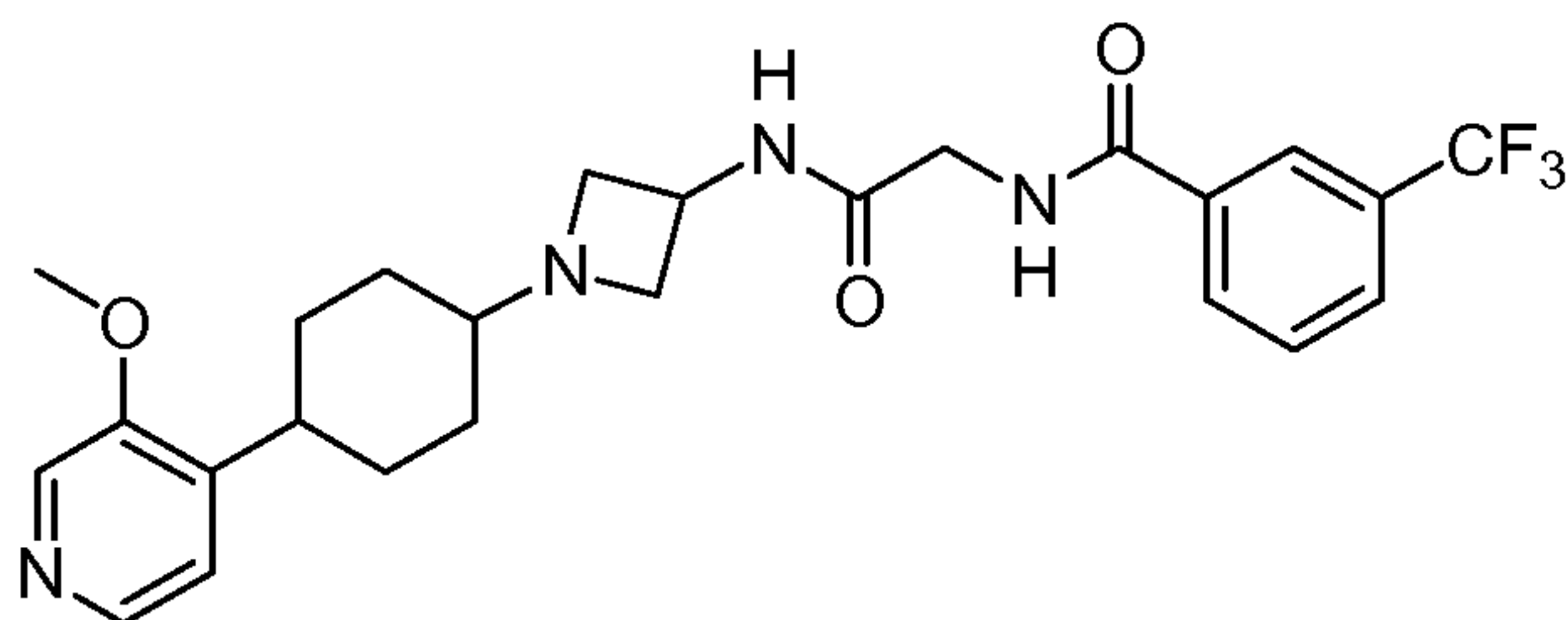
Example 7: N-({1-[4-(2-Methoxy-pyridin-4-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



The title compound was prepared as described in Example 3: Steps A-D from 4-iodo-2-methoxypyridine (Aldrich) as a white solid.

¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.15 (s, 1 H), 8.00 - 8.08 (m, 2 H), 7.77 (d, *J*=7.8 Hz, 1 H), 7.58 (t, *J*=7.8 Hz, 1 H), 7.44 (br. s., 1 H), 6.82 (d, *J*=5.1 Hz, 1 H), 6.64 (s, 1 H), 4.50 - 4.66 (m, 1 H), 4.19 (d, *J*=5.1 Hz, 2 H), 3.87 - 3.96 (m, 4 H), 3.63 - 3.82 (m, 2 H), 2.41 - 2.51 (m, 1 H), 1.79 - 1.97 (m, 3 H), 1.70 (m, 2 H), 1.36 - 1.63 (m, 5 H). ESI-MS (*m/z*): Calcd. For C₂₅H₂₉N₄O₃F₃: 490; found: 491 (M+H).

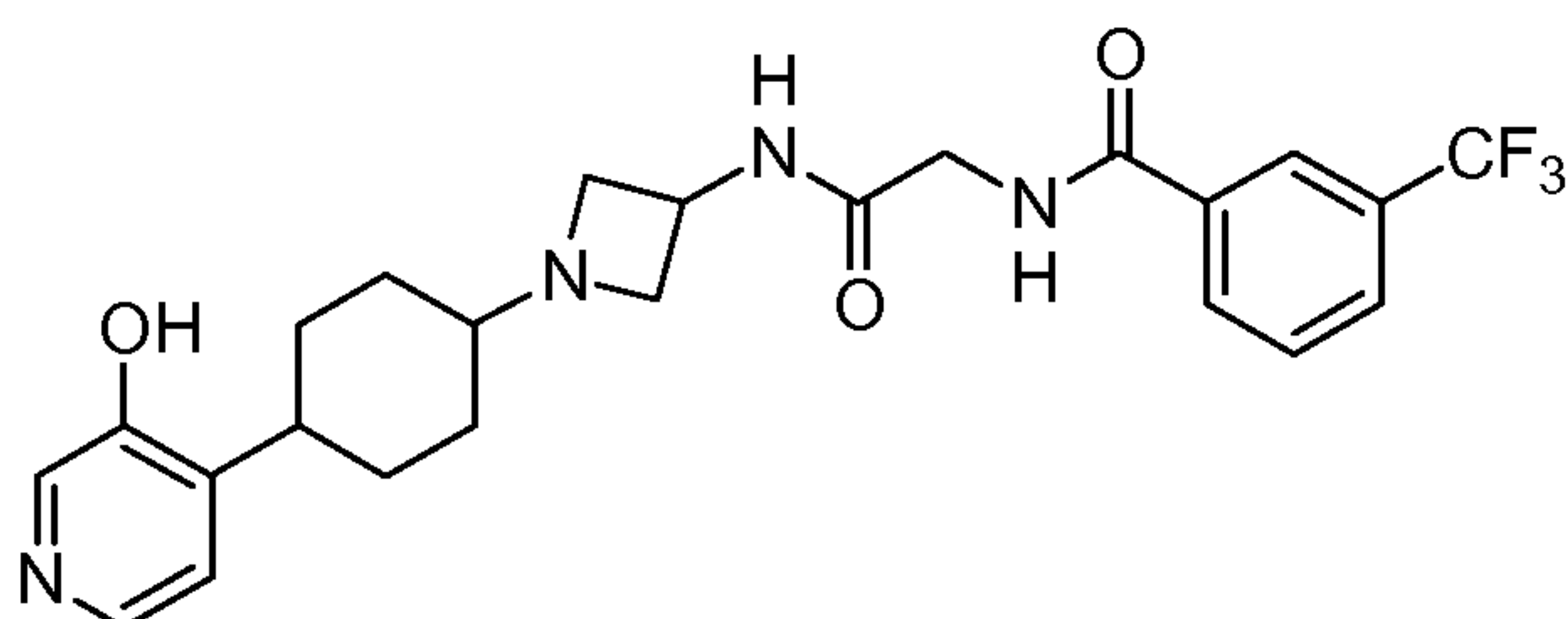
Example 8: N-({1-[4-(3-Methoxy-pyridin-4-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



The title compound was prepared as described in Example 3: Steps A-D from 4-bromo-3-methoxypyridine (Aldrich) as a white solid.

¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.22 (d, *J*=4.8 Hz, 1 H), 8.19 (s, 1 H), 8.13 (s, 1 H), 8.02 (d, *J*=7.8 Hz, 1 H), 7.78 (d, *J*=7.8 Hz, 1 H), 7.58 (t, *J*=7.8 Hz, 1 H), 7.42 (t, *J*=4.5 Hz, 1 H), 7.14 - 7.22 (m, 2 H), 4.56 (sxt, *J*=6.6 Hz, 1 H), 4.14 - 4.21 (m, 2 H), 3.91 (s, 3 H), 3.60 (t, *J*=7.5 Hz, 2 H), 2.84 - 3.04 (m, 3 H), 2.30 - 2.37 (m, 1 H), 1.88 (m, 3 H), 1.64 - 1.77 (m, 3 H), 1.47 - 1.54 (m, 2 H). ESI-MS (*m/z*): Calcd. For C₂₅H₂₉N₄O₃F₃: 490; found: 491 (M+H).

Example 9: N-({1-[4-(3-Hydroxy-pyridin-4-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

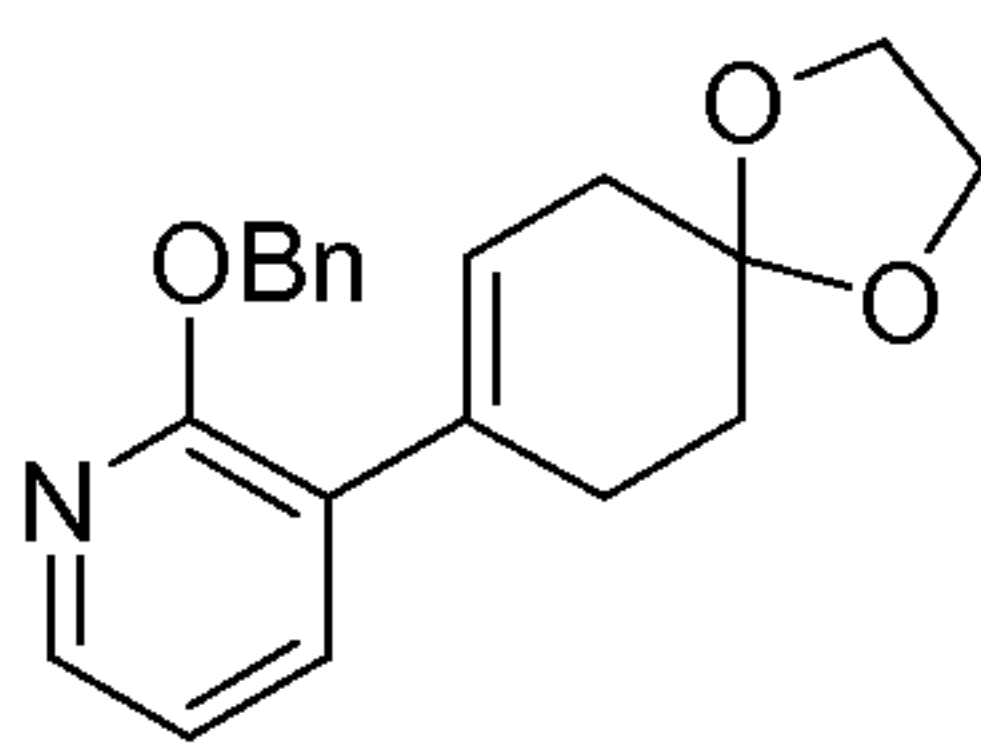


N-({1-[4-(3-Methoxy-pyridin-4-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide (0.101 g, 0.206 mmol, as prepared in Example 8) was dissolved in anhydrous dichloromethane (10 mL) under Ar, treated with 0.83 N boron tribromide in dichloromethane (Aldrich, 2.00 mL, 1.66 mmol), and stirred at ambient temperature for 24 h. After quenching with saturated aqueous NaHCO₃, the reaction was stirred at ambient temperature for 30 mins and extracted thrice with 3:1 EtOAc/2-propanol. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* giving a gold gum that was purified by preparative thin layer chromatography on silica gel (15% MeOH in CH₂Cl₂, 0.6N in ammonia), giving the title compound as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.65 (s, 1 H), 9.01 (t, *J*=5.9 Hz, 1 H), 8.39 (d, *J*=7.3 Hz, 1 H), 8.23 (s, 1 H), 8.18 (d, *J*=7.8 Hz, 1 H), 8.05 (s, 1 H), 7.89 - 7.99 (m, 2 H), 7.74 (t, *J*=7.8 Hz, 1 H), 7.07 (d, *J*=5.1 Hz, 1 H), 4.28 (sxt, *J*=7.0 Hz, 1 H), 3.88 (d, *J*=5.8 Hz, 2 H), 3.51 (t, *J*=6.6 Hz, 2 H), 2.70 - 2.89 (m, 3 H), 2.26 - 2.38 (m, 1 H), 1.58 - 1.76 (m, 4 H), 1.31 - 1.50 (m, 4 H). ESI-MS (*m/z*): Calcd. For C₂₄H₂₇N₄O₃F₃: 476; found: 477 (M+H).

Example 10: N-({1-[4-(2-Hydroxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide

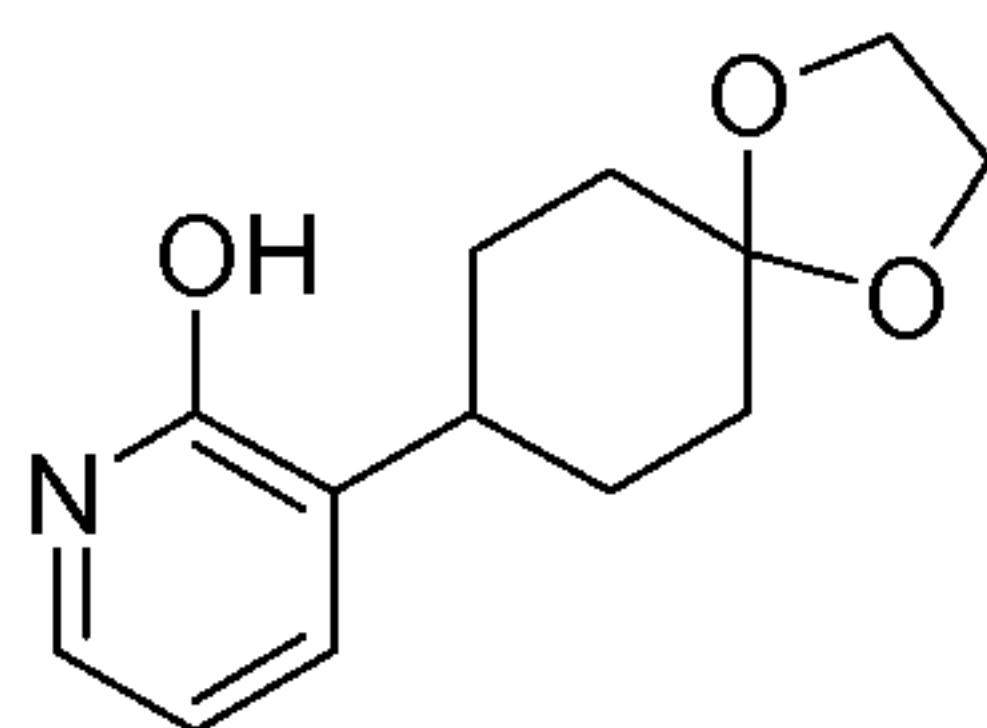
Step A: 2-Benzyloxy-3-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyridine



The title compound was prepared as described in Step A of Example 3 from 2-benzyloxy-3-bromo-pyridine (Alfa Aesar) as a white solid.

LCMS (ESI, M/Z): 324 (MH⁺).

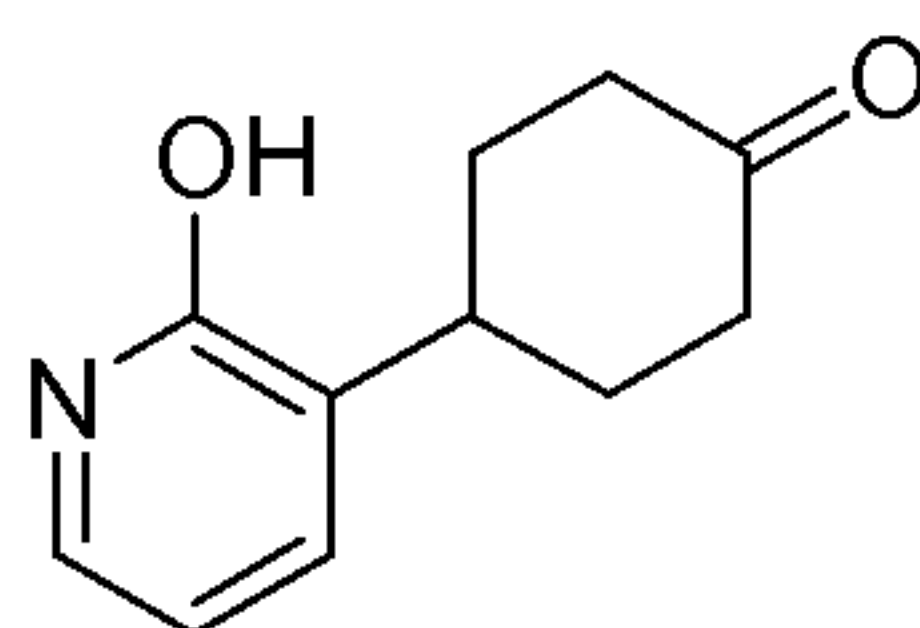
Step B: 3-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-2-ol



The title compound was prepared as a white solid from the hydrogenation of 2-benzyloxy-3-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-pyridine (as prepared in the previous step) using the procedure described in Step G of Example 1.

5 LCMS (ESI, M/Z): 236 (MH⁺).

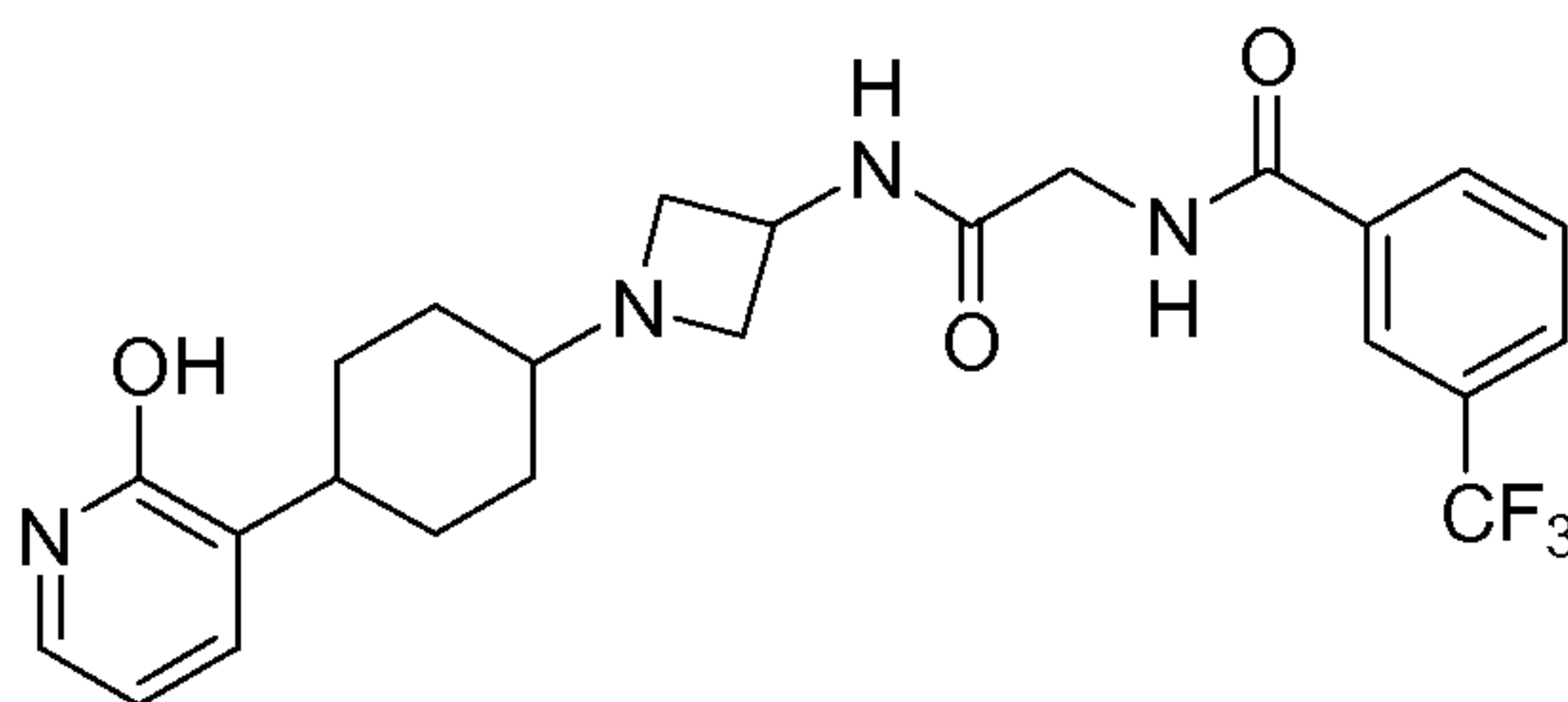
Step C: 4-(2-Hydroxy-pyridin-3-yl)-cyclohexanone



10 The title compound was prepared as a white solid from the deprotection of 3-(1,4-dioxaspiro[4.5]dec-8-yl)-pyridin-2-ol (as prepared in the previous step) using the procedure described in Step B of Example 2.

LCMS (ESI, M/Z): 192 (MH⁺).

Step D: N-({1-[4-(2-Hydroxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide

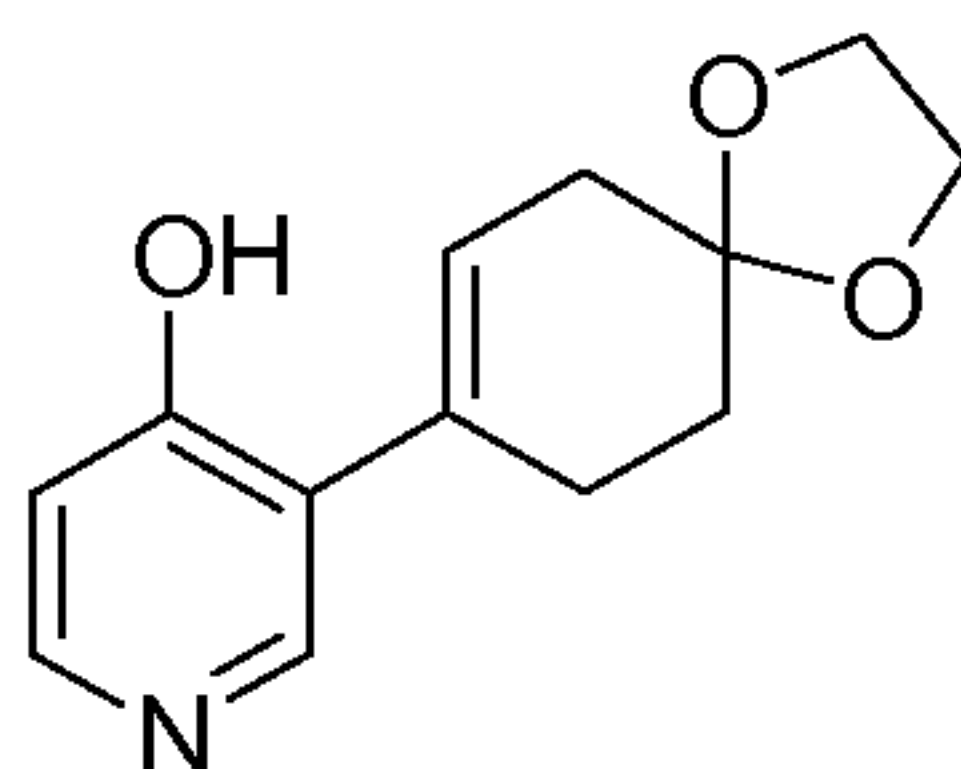


20 The title compounds were prepared as white solids from the reductive amination of 4-(2-hydroxy-pyridin-3-yl)-cyclohexanone (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

LCMS (ESI, M/Z): 477 (MH⁺).

Example 11: N-({1-[4-(4-Hydroxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

Step A: 3-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-4-ol

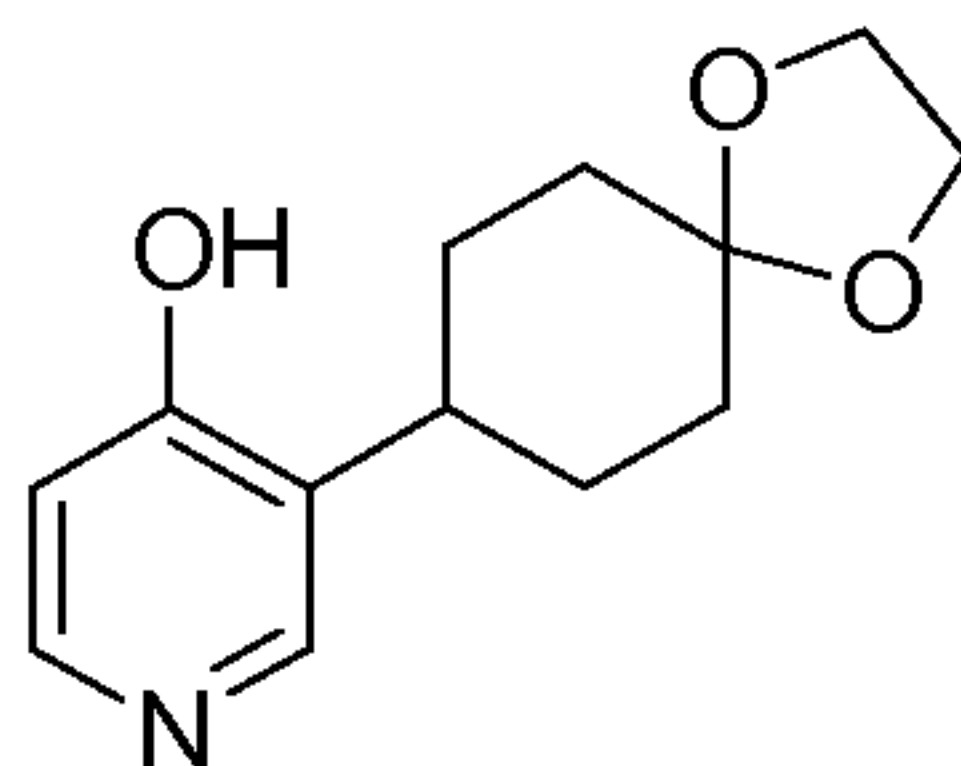


5 The title compound was prepared as described in Step A of Example 3 from 4-hydroxy-3-bromo-pyridine (SynChem) as a white solid.

¹H NMR (CHLOROFORM-d) δ: 7.89 (s, 1H), 7.79 (m, 1H), 6.76 - 6.90 (m, 1H), 5.89 - 6.04 (m, 1H), 3.99 (s, 4H), 2.55 - 2.72 (m, 2H), 2.42 (br. s., 2H), 1.87 (s, 2H). LCMS (ESI, M/Z): 234 (MH⁺).

10

Step B: 3-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-4-ol

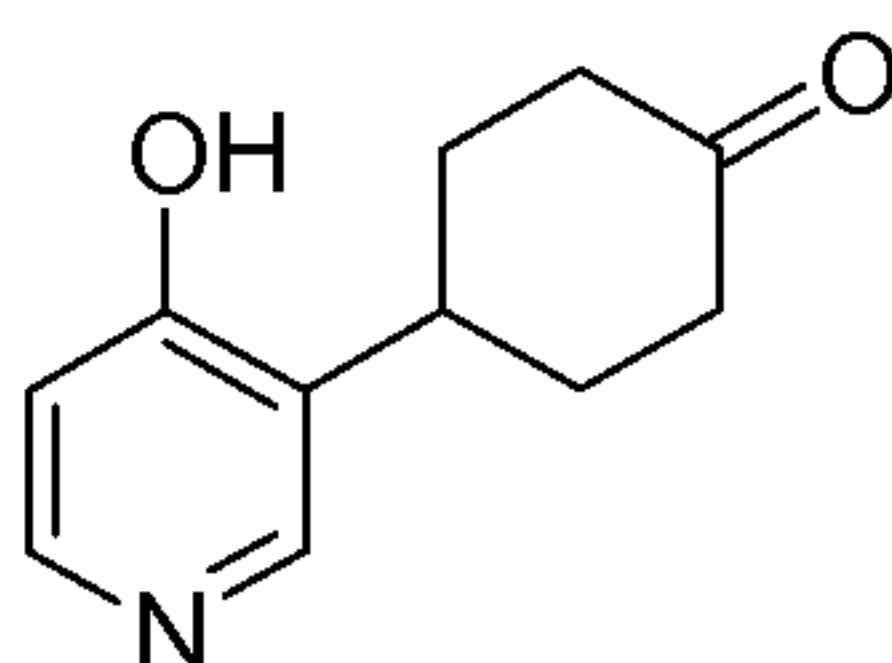


15 The title compound was prepared as a white solid from the hydrogenation of 3-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-4-ol (as prepared in the previous step) using the procedure described in Step G of Example 1.

¹H NMR (CHLOROFORM-d) δ: 7.81 - 7.94 (m, 2H), 6.98 (d, J = 6.3 Hz, 1H), 3.88 - 4.04 (m, 4H), 2.92 - 3.10 (m, 1H), 1.80 - 2.02 (m, 4H), 1.52 - 1.80 (m, 4H). LCMS (ESI, M/Z): 236 (MH⁺).

20

Step C: 4-(4-Hydroxy-pyridin-3-yl)-cyclohexanone

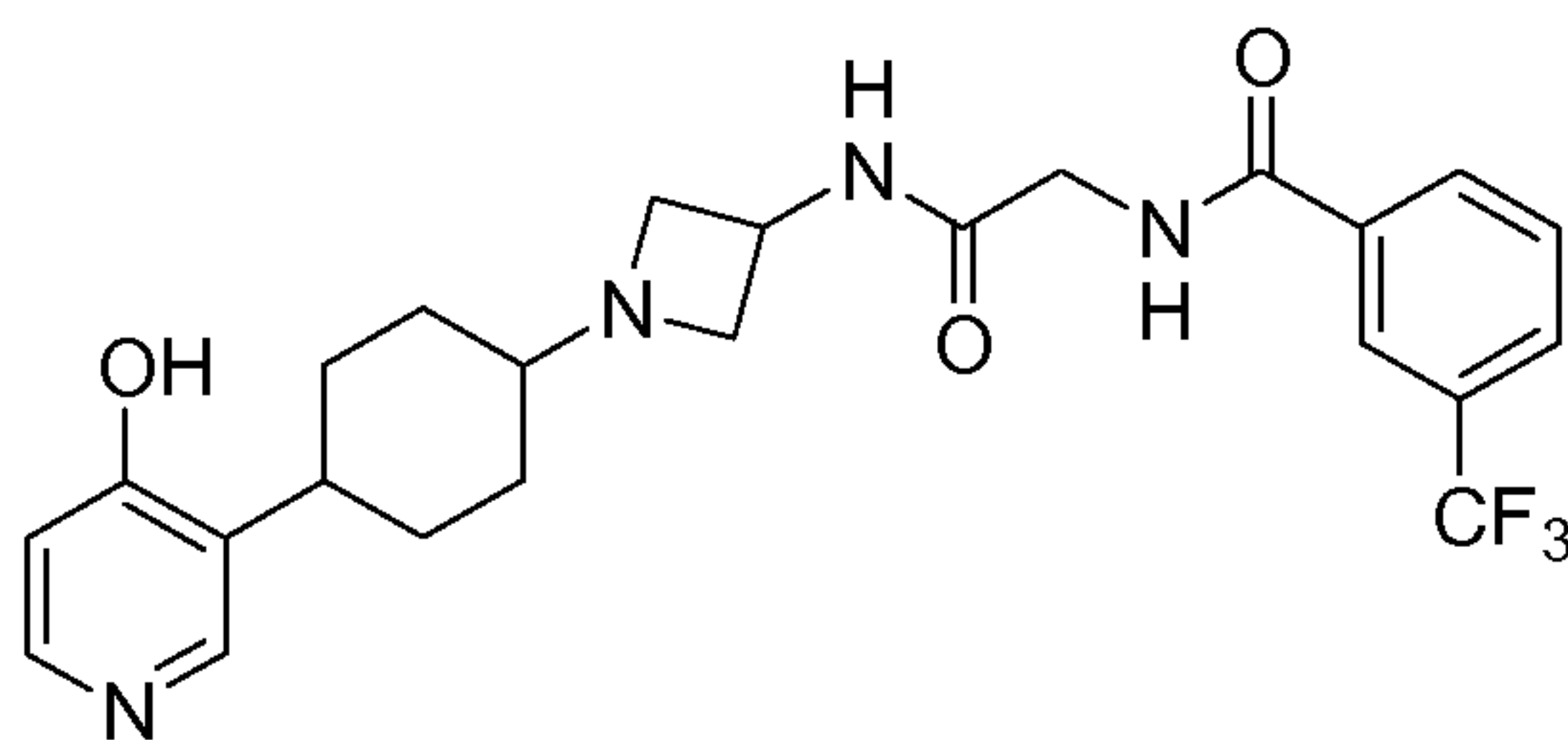


The title compound was prepared as a white solid from the deprotection of 3-(1,4-dioxaspiro[4.5]dec-8-yl)-pyridin-4-ol (as prepared in the previous step) using the procedure described in Step B of Example 2.

LCMS (ESI, M/Z): 192 (MH⁺).

5

Step D: N-({1-[4-(4-Hydroxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide



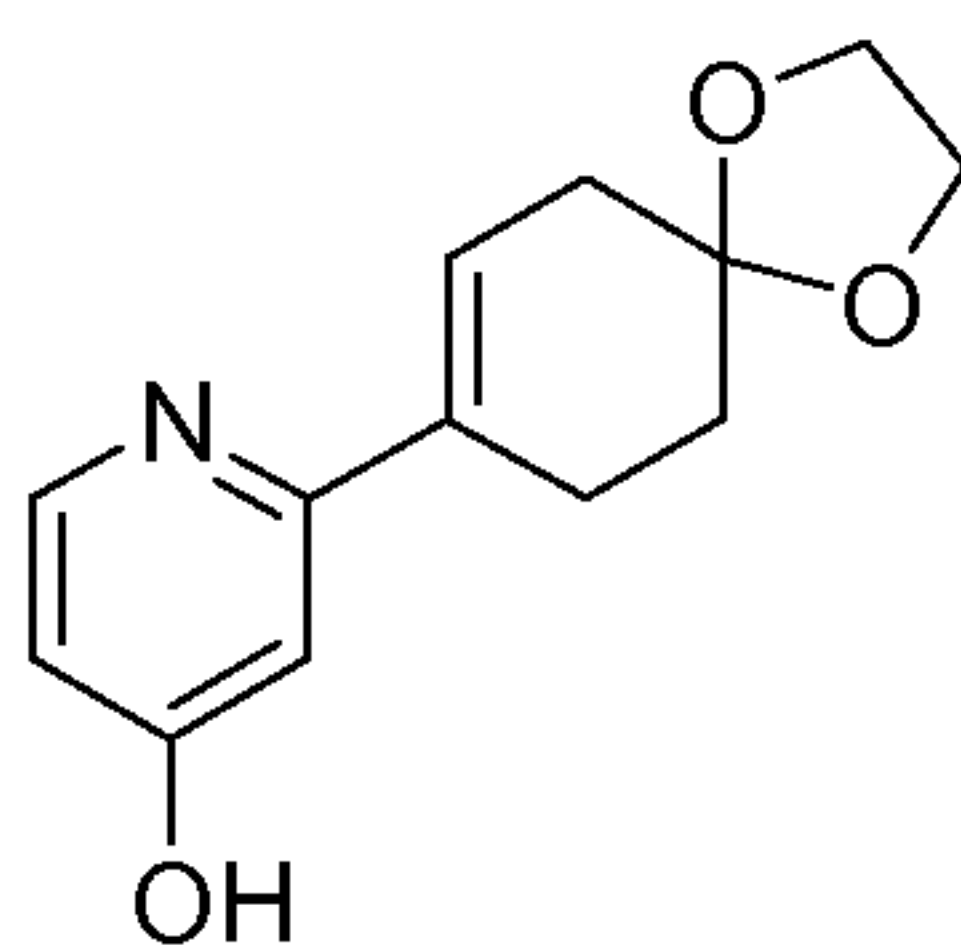
The title compound was prepared as a white solid from the reductive amination of 4-(4-hydroxy-pyridin-3-yl)-cyclohexanone (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

LCMS (ESI, M/Z): 477 (MH⁺).

15

Example 12: N-({1-[4-(4-Hydroxy-pyridin-2-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide

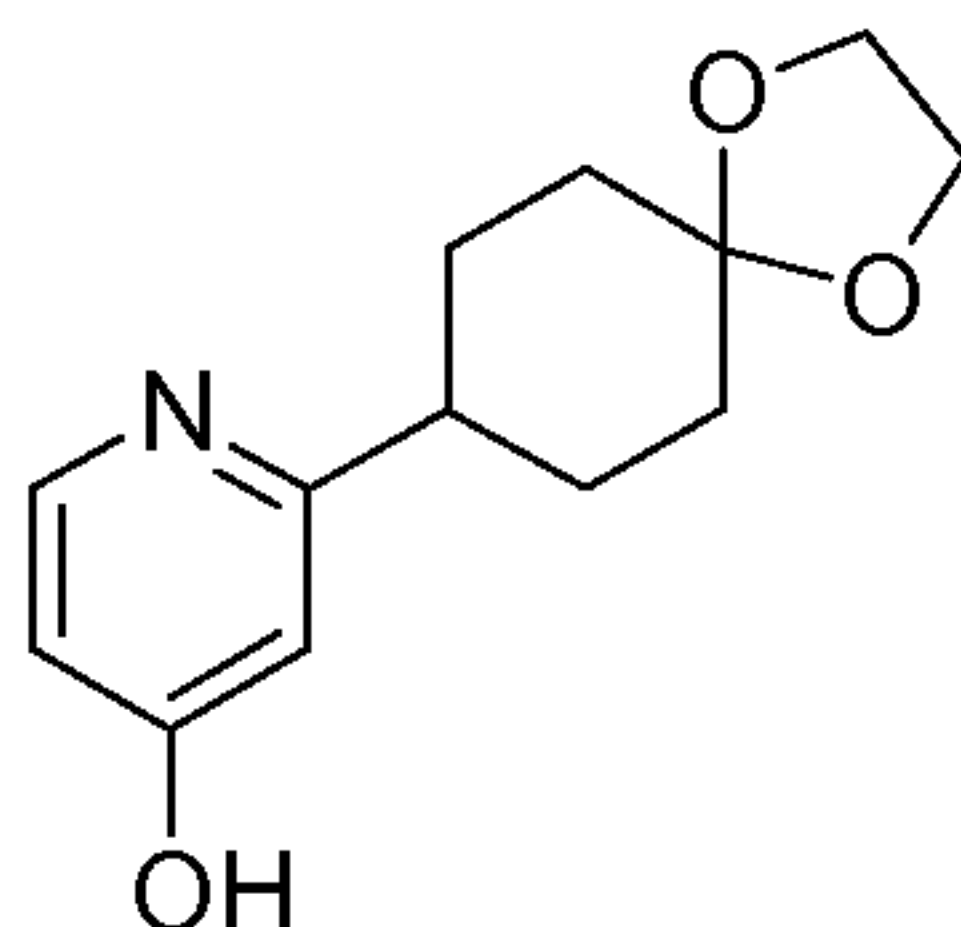
Step A: 2-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)-pyridin-4-ol



The title compound was prepared as described in Step A of Example 3 from 2-bromopyridin-4-ol (SynChem) as a white solid.

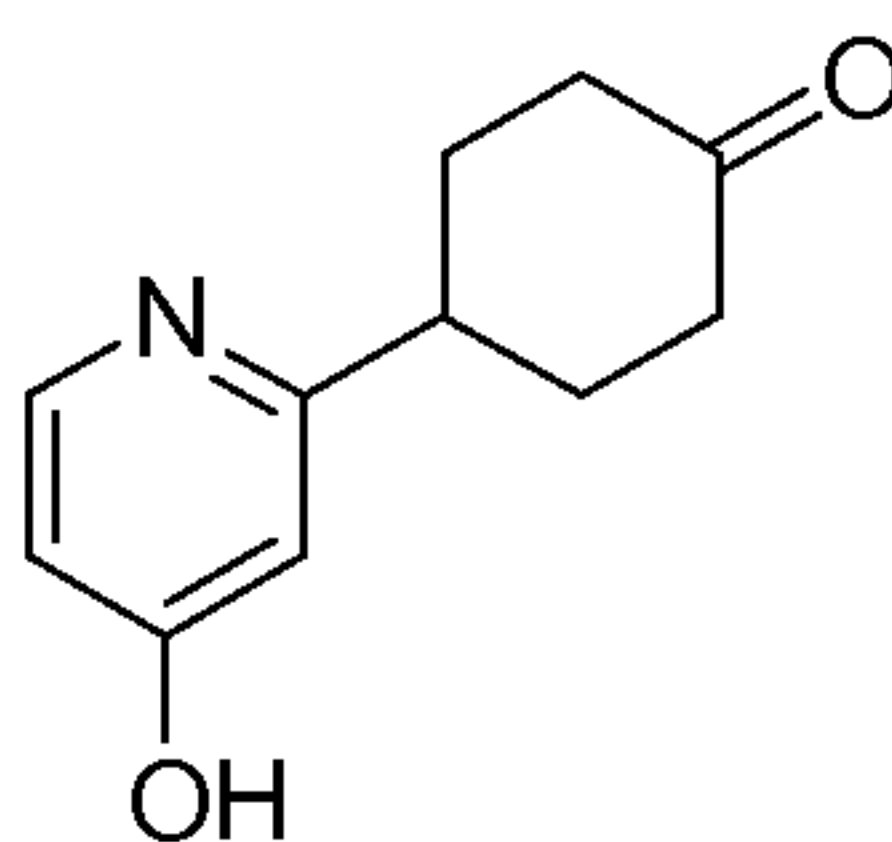
20

¹H NMR (CHLOROFORM-d) δ: 8.05 - 8.14 (m, 1H), 7.11 (s, 1H), 6.97 - 7.06 (m, 1H), 6.54 - 6.69 (m, 1H), 3.99 (s, 4H), 2.83 - 2.95 (m, 1H), 2.58 - 2.69 (m, 2H), 2.52 (d, J = 1.8 Hz, 2H), 1.90 (s, 2H). LCMS (ESI, M/Z): 234 (MH⁺).

Step B: 2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-4-ol

The title compound was prepared as a white solid from the hydrogenation of 2-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-4-ol (as prepared in the previous step) using the procedure described in Step G of Example 1.

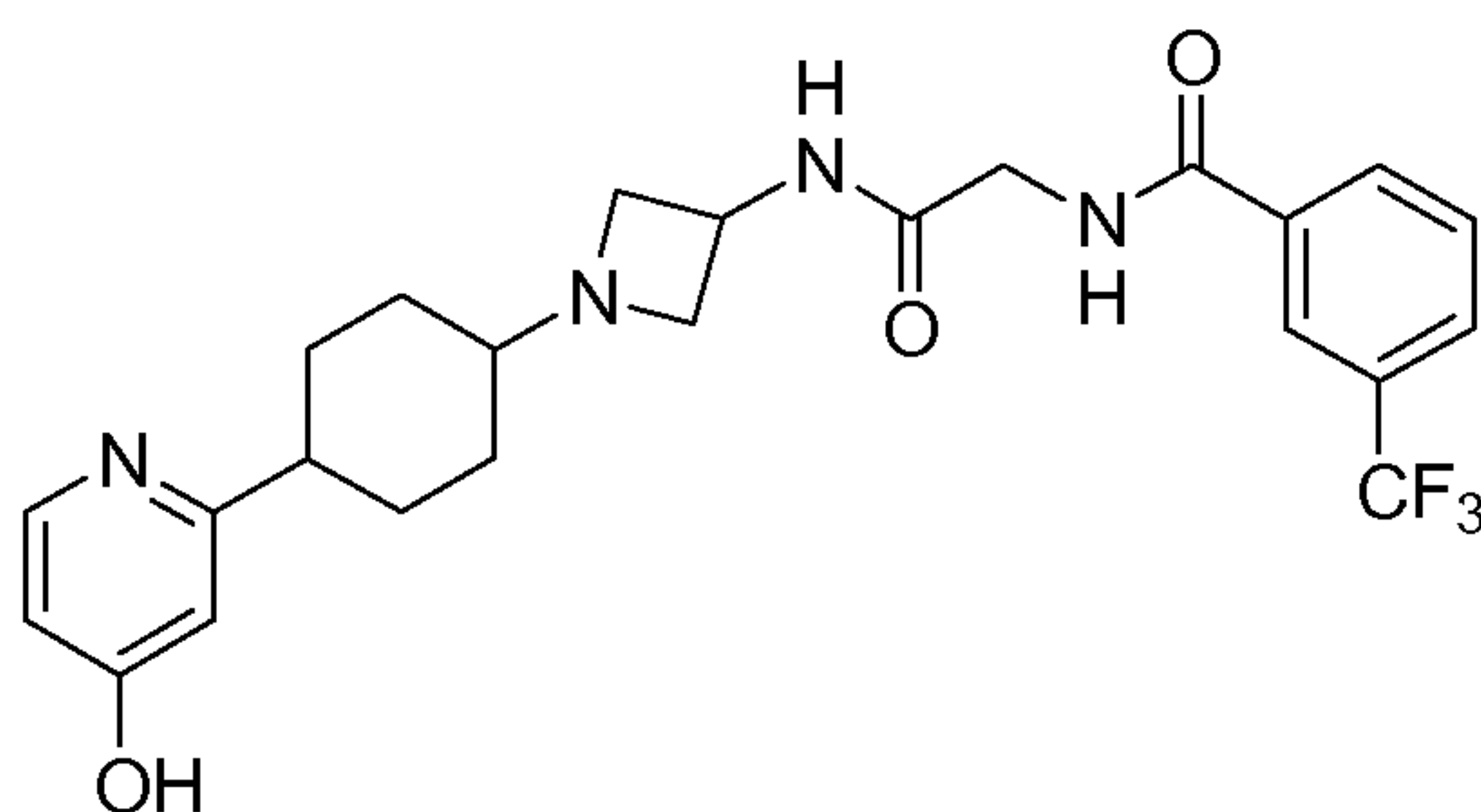
¹H NMR (CHLOROFORM-d) δ: 8.07 - 8.16 (m, 1H), 7.07 (none, 2H), 3.50 (s, 4H), 2.82 - 3.01 (m, 0H), 1.94 - 2.04 (m, 2H), 1.84 (s, 4H), 1.57 - 1.76 (m, 2H). LCMS (ESI, M/Z): 236 (MH⁺).

Step C: 4-(4-Hydroxy-pyridin-2-yl)-cyclohexanone

The title compound was prepared as a white solid from the deprotection of 2-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyridin-4-ol (as prepared in the previous step) using the procedure described in Step B of Example 2.

¹H NMR (CHLOROFORM-d) δ: 8.34 (d, J = 5.8 Hz, 1H), 6.71 (d, J = 2.3 Hz, 1H), 6.65 (dd, J = 5.8, 2.3 Hz, 1H), 2.66 - 2.81 (m, 1H), 1.60 - 2.04 (series of m, 8H). LCMS (ESI, M/Z): 192 (MH⁺).

Step D: N-({1-[4-(4-Hydroxy-pyridin-2-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide

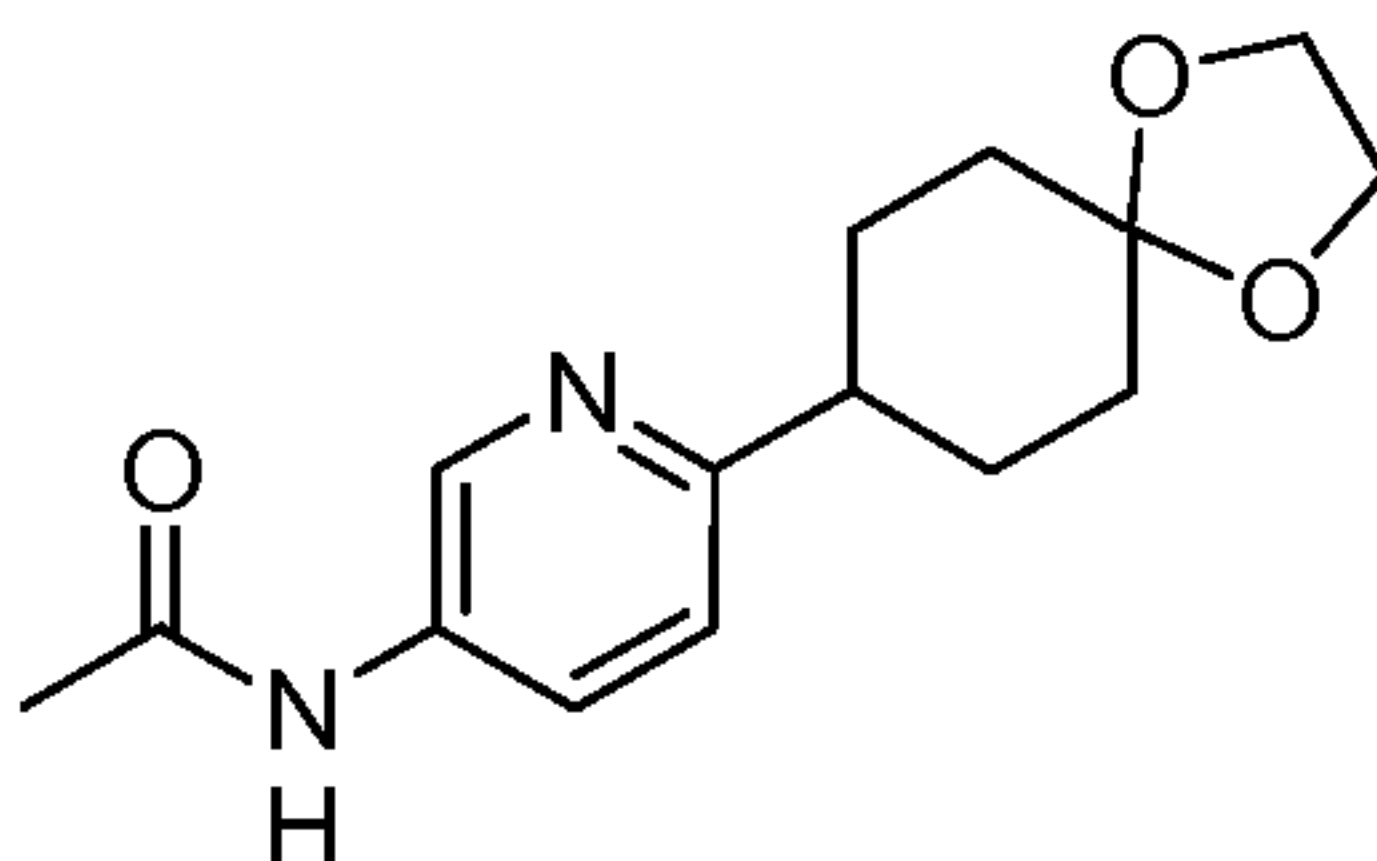


The title compound was prepared as a white solid from reductive amination of 4-(4-hydroxy-pyridin-2-yl)-cyclohexanone (as prepared in the previous step) and N-(azetidin-3-ylcarbonylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

LCMS (ESI, M/Z): 477 (MH⁺).

Example 13 : N-({1-[4-(5-Acetylamino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbonyl}-methyl)-3-trifluoromethyl-benzamide

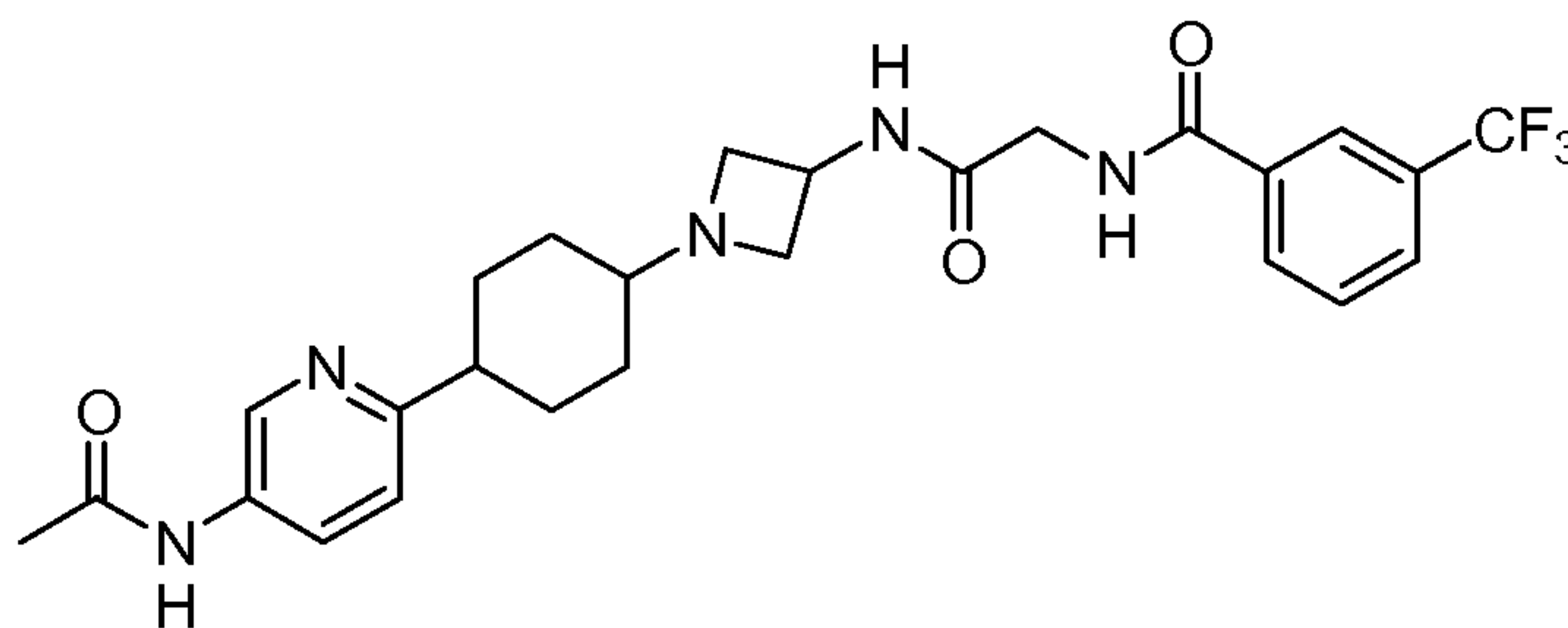
Step A: N-[6-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-acetamide



6-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-ylamine (0.158 g, 0.675 mmol, prepared as described in Example 3: Steps A-B from 5-amino-2-bromopyridine, Aldrich) was dissolved in anhydrous dichloromethane (10 mL), treated with acetic anhydride (Aldrich, 0.080 mL, 0.846 mmol), and stirred at ambient temperature under Ar for 18 h. The reaction was quenched with saturated aqueous NaHCO₃, extracted thrice with dichloromethane, and the combined organic layers washed with brine, dried over Na₂SO₄, filtered, and the filtrate concentrated *in vacuo* giving the title compound as a pale solid.

¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.41 (d, *J*=2.5 Hz, 1 H), 8.07 (dd, *J*=8.6, 2.5 Hz, 1 H), 7.42 (br. s., 1 H), 7.17 (d, *J*=8.6 Hz, 1 H), 3.98 (s, 4 H), 2.74 (m, 1 H), 2.19 (s, 3 H), 1.91 - 2.00 (m, 2 H), 1.77 - 1.91 (m, 4 H), 1.63 - 1.77 (m, 2 H). ESI-MS (*m/z*): Calcd. For C₁₅H₂₀N₂O₃: 276; found: 277 (M+H).

Step B: *N*-($\{1$ -[4-(5-Acetylamino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

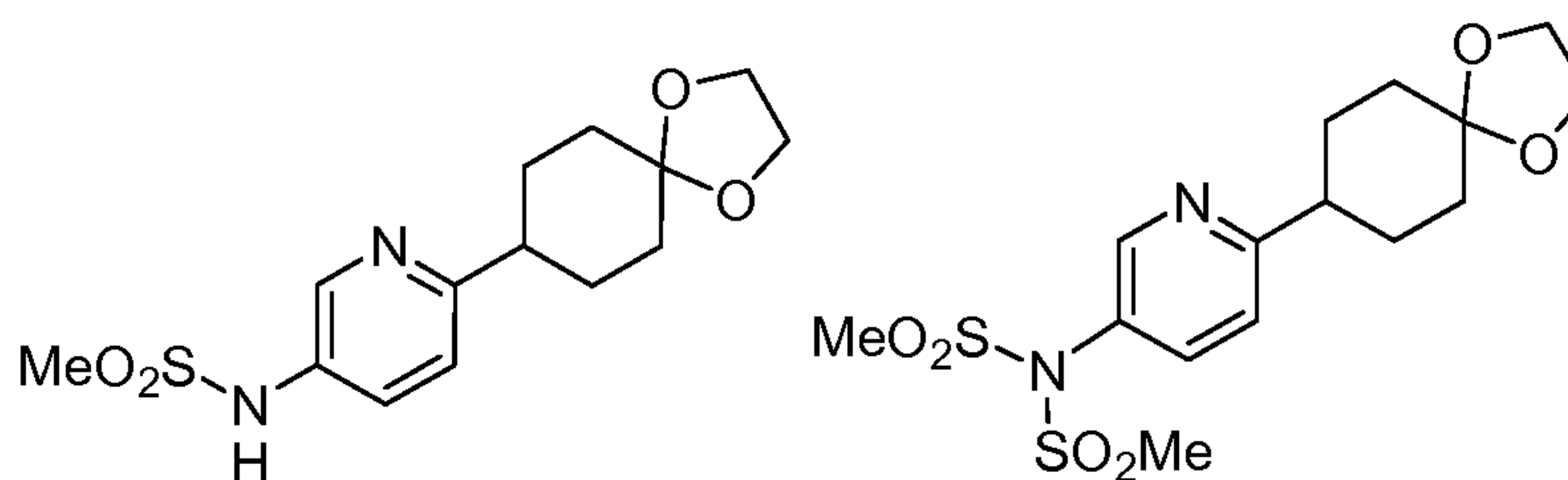


5 The title compound was prepared as described in Example 3: Steps C-D from *N*-[6-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-acetamide (as prepared in the previous step) to give a pale yellow solid.

¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 10.07 (s, 1 H), 9.03 (t, *J*=5.9 Hz, 1 H), 8.57 (d, *J*=2.5 Hz, 1 H), 8.41 (d, *J*=7.3 Hz, 1 H), 8.23 (s, 1 H), 8.19 (d, *J*=7.8 Hz, 1 H), 7.86 - 7.98 (m, 2 H), 7.75 (t, *J*=7.7 Hz, 1 H), 7.17 (d, *J*=8.6 Hz, 1 H), 4.21 - 4.34 (m, 1 H), 3.88 (d, *J*=5.8 Hz, 2 H), 3.49 - 3.62 (m, 2 H), 2.83 (br. s., 1 H), 2.56 - 2.69 (m, 1 H), 2.05 (s, 3 H), 1.77 - 1.93 (m, 2 H), 1.62 (m, 2 H), 1.35 - 1.56 (m, 4 H). ESI-MS (*m/z*): Calcd. For C₂₆H₃₀N₅O₃F₃: 517; found: 518 (M+H).

15 **Example 14: *N*-($\{1$ -[4-(5-bis-{Methanesulfonyl}-amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide**

Step A: *N*-[6-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-methanesulfonamide and *N*-[6-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-bis-(methanesulfonyl)-amide



20 6-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-ylamine (0.158 g, 0.675 mmol, prepared as described in Example 2: Steps A-B from 5-amino-2-bromopyridine) was dissolved in anhydrous dichloromethane (10 mL), treated with triethylamine (0.20 mL, 1.43 mmol) and methanesulfonyl chloride (Aldrich, 0.065 mL, 0.837 mmol), and stirred at ambient

temperature under Ar for 2 d. The reaction was concentrated to dryness *in vacuo* and purified by preparative thin layer chromatography on silica gel (1:1 EtOAc:CH₂Cl₂) giving the slow-running mono-sulfonamide as white needles and the fast-running bis-sulfonamide as a white amorphous powder.

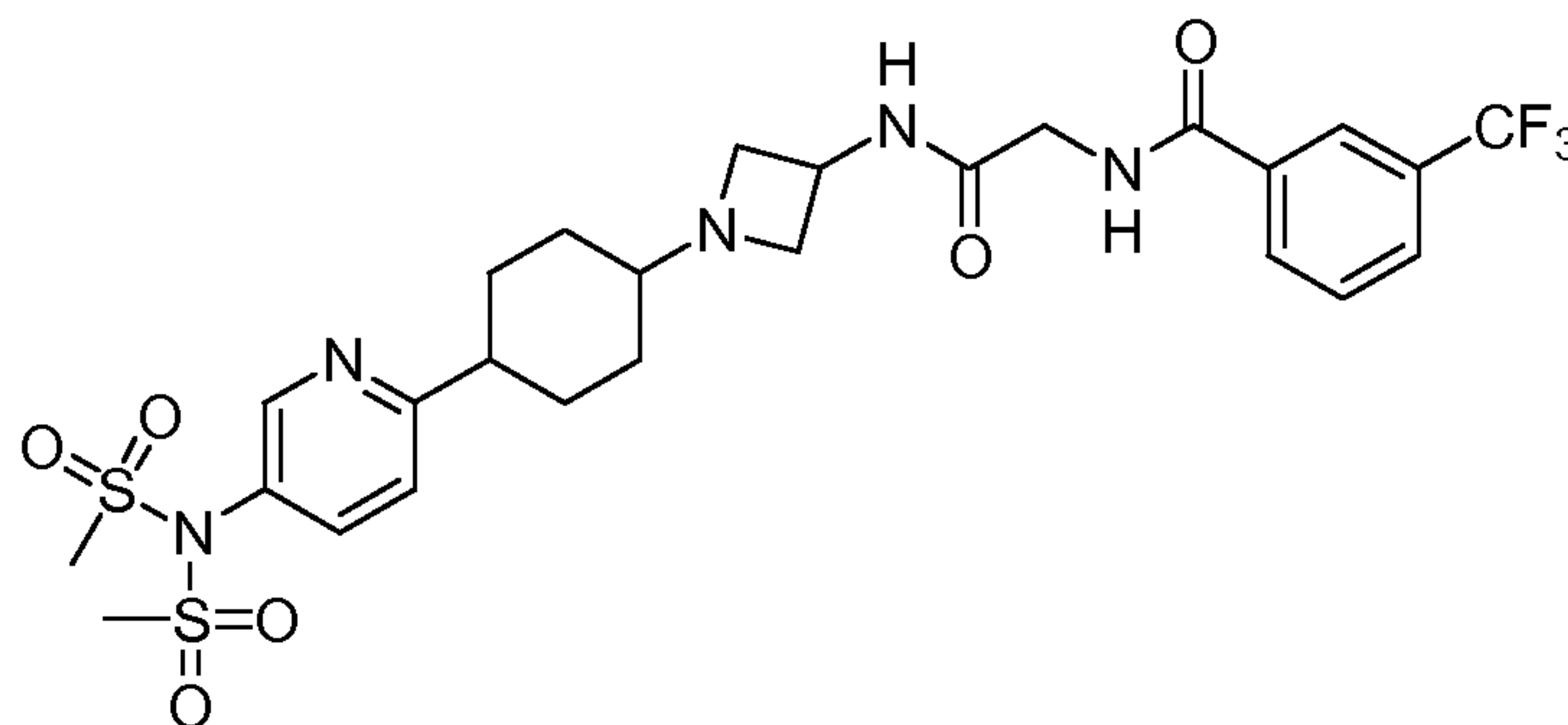
5 N-[6-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-methanesulfonamide

ESI-MS (m/z): Calcd. For C₁₄H₂₀N₂O₄S: 312; found: 313 (M+H).

N-[6-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-bis-(methanesulfonyl)-amide

ESI-MS (m/z): Calcd. For C₁₅H₂₂N₂O₆S₂: 390; found: 391 (M+H).

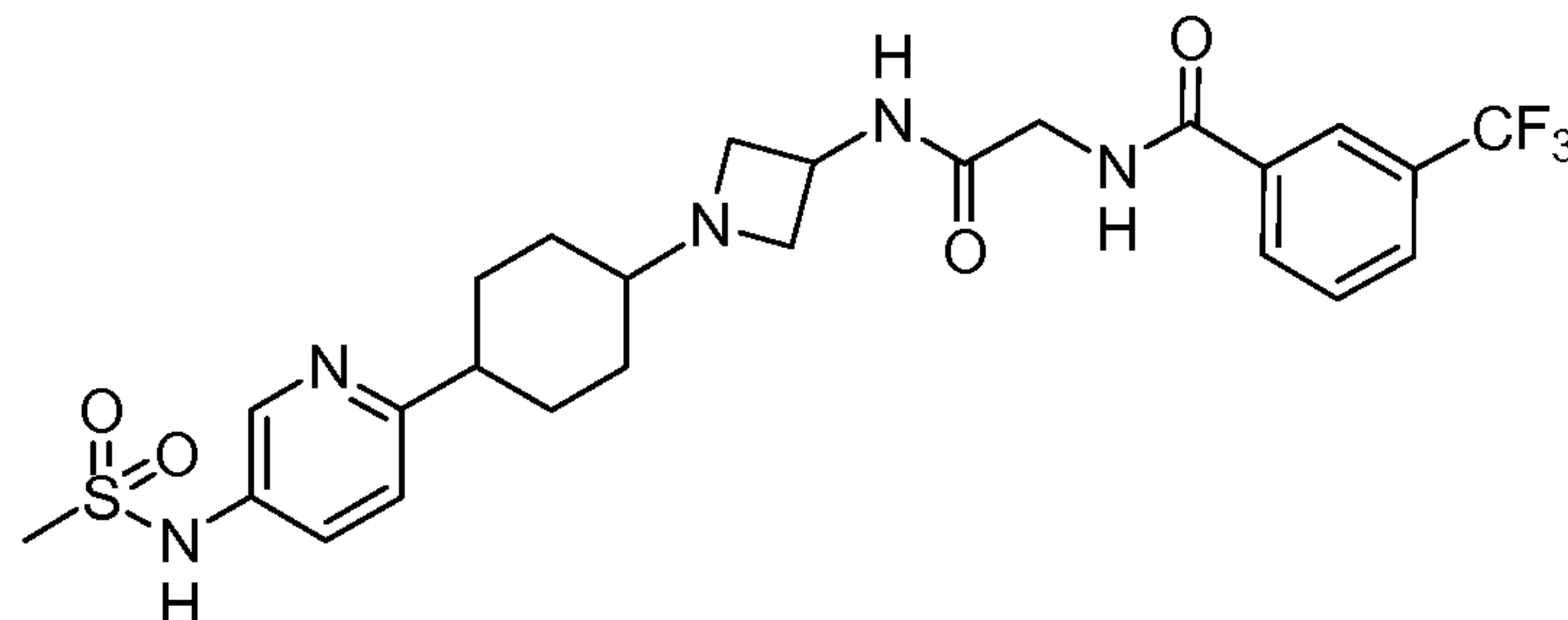
10 *Step B: N-({1-[4-(5-bis-{Methanesulfonyl}-amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide*



The title compound was prepared as described in Example 3: Steps C-D from N-[6-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-bis-(methanesulfonyl)-amide (as prepared in the previous step) and purified by preparative thin layer chromatography on silica gel (15% MeOH in CH₂Cl₂) giving a yellow-orange solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.01 (t, *J*=5.9 Hz, 1 H), 8.59 (d, *J*=2.3 Hz, 1 H), 8.39 (d, *J*=7.3 Hz, 1 H), 8.23 (s, 1 H), 8.18 (d, *J*=7.8 Hz, 1 H), 7.93 (d, *J*=7.8 Hz, 1 H), 7.89 (dd, *J*=8.3, 2.5 Hz, 1 H), 7.74 (t, *J*=7.8 Hz, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 4.27 (m, 1 H), 3.88 (d, *J*=6.1 Hz, 2 H), 3.56 (s, 6 H), 3.49 (t, *J*=7.1 Hz, 2 H), 2.77 (m, 3 H), 2.31 (br. s., 1 H), 1.83 - 1.97 (m, 2 H), 1.58 - 1.69 (m, 2 H), 1.39 - 1.58 (m, 4 H). ESI-MS (m/z): Calcd. For C₂₆H₃₂N₅O₆F₃S₂: 631; found: 632 (M+H).

Example 15: N-({1-[4-(5-Methanesulfonyl-amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

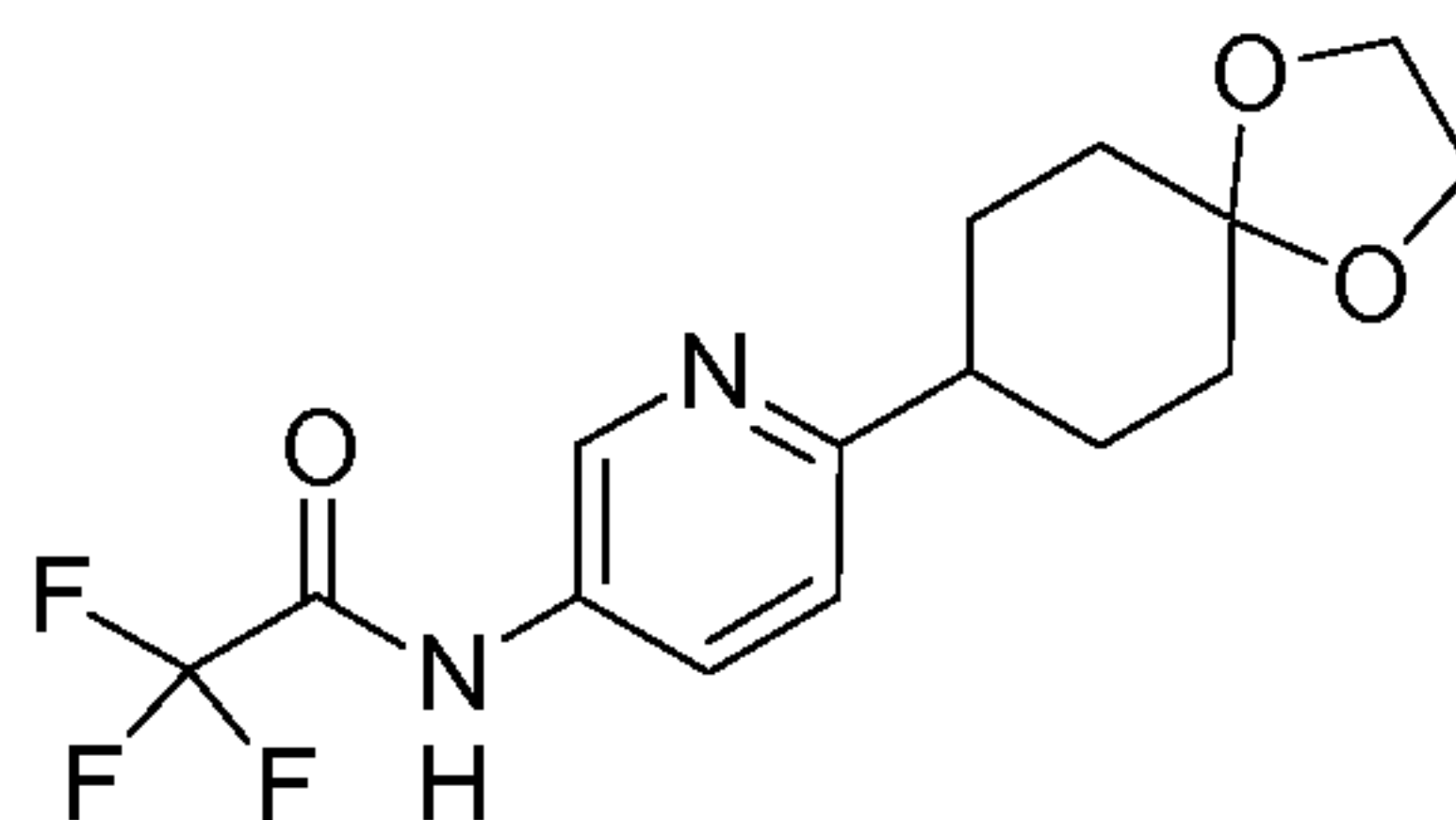


The title compound was prepared as described in Example 3: Steps C-D from N-[6-(1,4-dioxa-spiro[4.5]dec-8-yl)-pyridin-3-yl]-methanesulfonamide (as described in Example 14, Step A) and purified by preparative thin layer chromatography on silica gel (15% MeOH in CH₂Cl₂) giving a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.81 (br. s., 1 H), 9.02 (t, *J*=5.8 Hz, 1 H), 8.39 (d, *J*=7.3 Hz, 1 H), 8.32 (d, *J*=2.5 Hz, 1 H), 8.23 (s, 1 H), 8.18 (d, *J*=8.1 Hz, 1 H), 7.93 (d, *J*=7.8 Hz, 1 H), 7.74 (t, *J*=7.8 Hz, 1 H), 7.53 (dd, *J*=8.5, 2.7 Hz, 1 H), 7.22 (d, *J*=8.3 Hz, 1 H), 4.27 (sxt, *J*=7.1 Hz, 1 H), 3.88 (d, *J*=5.8 Hz, 2 H), 3.50 (t, *J*=6.7 Hz, 2 H), 3.01 (s, 3 H), 2.78 (t, *J*=6.4 Hz, 2 H), 2.56 - 2.70 (m, 1 H), 2.30 (br. s., 1 H), 1.75 - 1.93 (m, 2 H), 1.55 - 1.68 (m, 2 H), 1.35 - 1.55 (m, 4 H). ESI-MS (*m/z*): Calcd. For C₂₅H₃₀N₅O₄F₃S: 553; found: 554 (M+H).

Example 16: N-[(1-{4-[5-(2,2,2-Trifluoro-acetyl-amino)-pyridin-2-yl]-cyclohexyl}-azetidin-3-ylcarbamoyl)-methyl]-3-trifluoromethyl-benzamide

Step A: N-[6-(1,4-Dioxa-spiro[4.5]dec-8-yl)-pyridin-3-yl]-2,2,2-trifluoro-acetamide

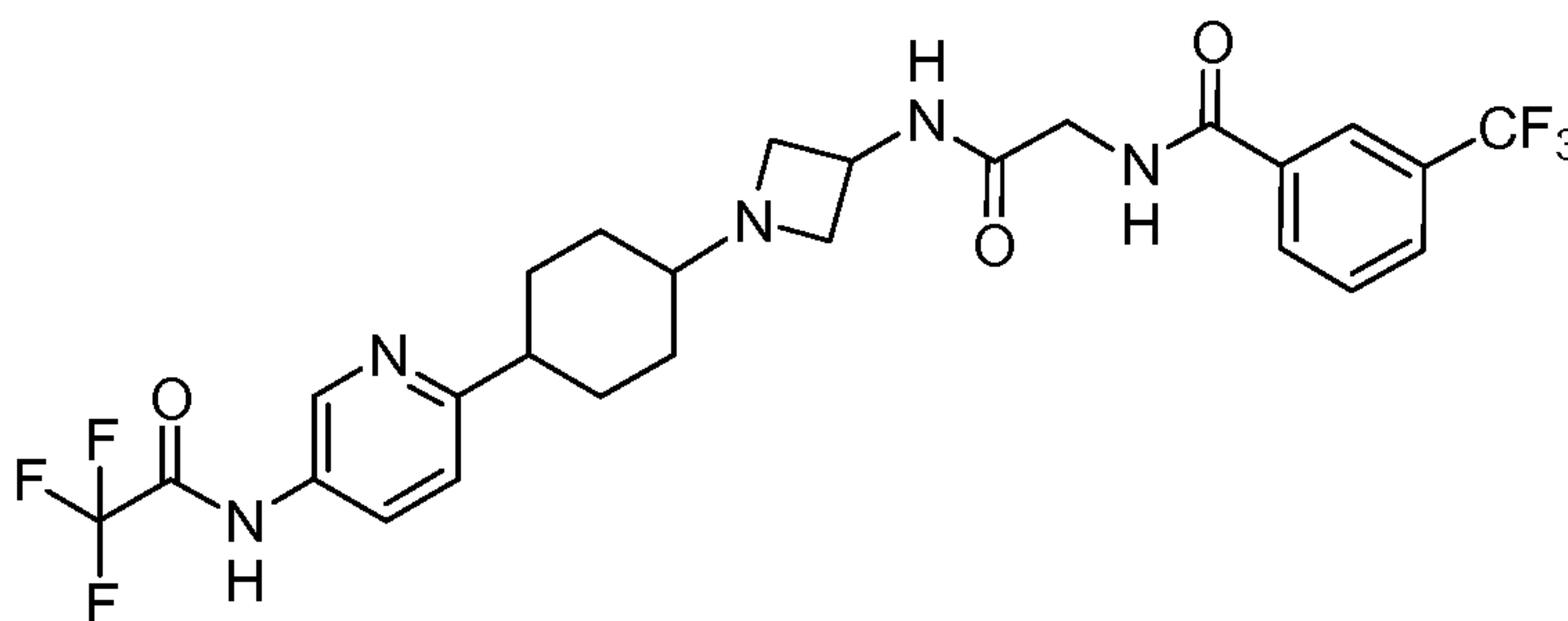


6-(1,4-Dioxa-spiro[4.5]dec-8-yl)-pyridin-3-ylamine (0.148 g, 0.632 mmol, prepared as described in Example 3: Steps A-B from 5-amino-2-bromopyridine) was dissolved in anhydrous dichloromethane (10 mL) under Ar, treated with trifluoroacetic anhydride (Aldrich, 0.100 mL, 0.720 mmol), and stirred at 50 °C under a reflux condenser for 3 d.

The reaction was cooled to ambient temperature, diluted with dichloromethane, washed with saturated aqueous NaHCO_3 , the aqueous layer extracted twice with dichloromethane, and the combined organic layers washed with brine, dried over Na_2SO_4 , filtered, and the filtrate concentrated *in vacuo* giving the title compound as a pale yellow solid.

ESI-MS (m/z): Calcd. For $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_3\text{F}_3$: 330; found: 331 ($\text{M}+\text{H}$)

Step B: *N*-[(1-{4-[5-(2,2,2-Trifluoro-acetylamino)-pyridin-2-yl]-cyclohexyl}-azetidin-3-ylcarbamoyl)-methyl]-3-trifluoromethyl-benzamide

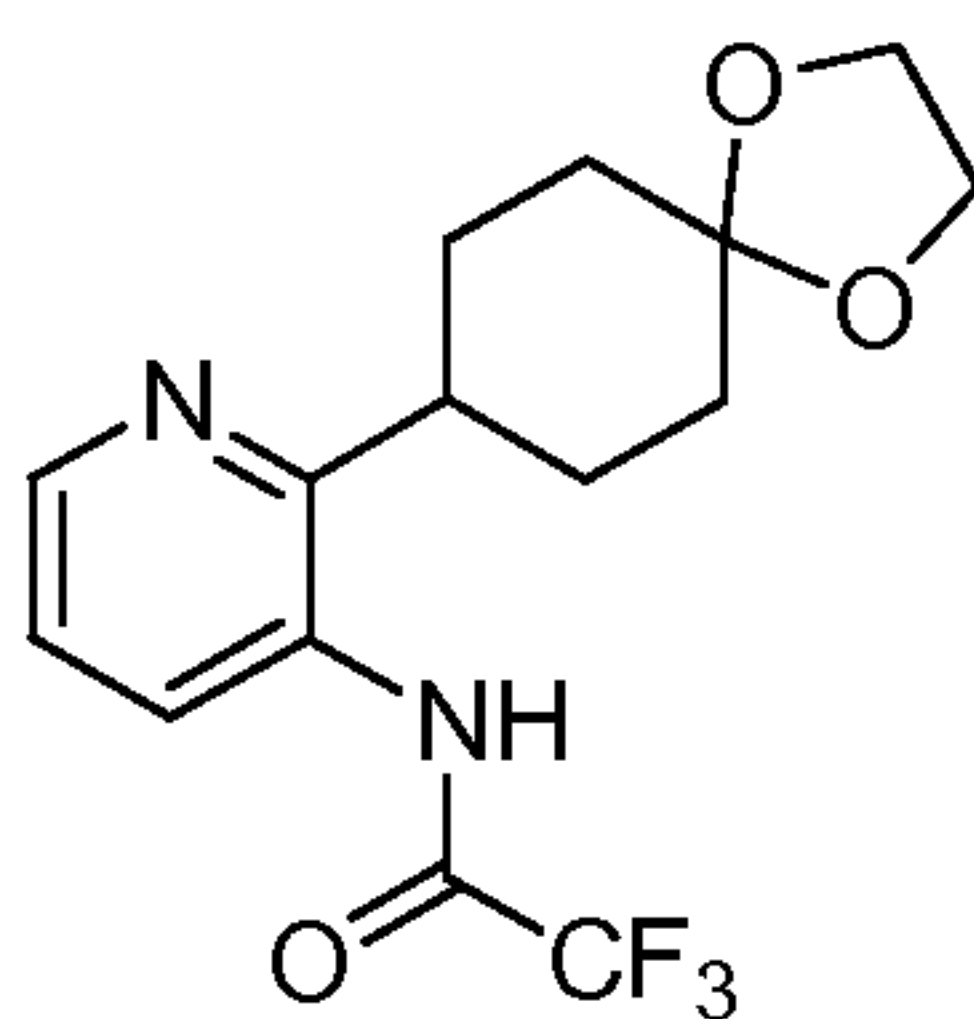


The title compound was prepared as described in Example 3: Steps C-D from *N*-[6-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-2,2,2-trifluoro-acetamide (as prepared in the previous step) and purified by preparative thin layer chromatography on silica gel (3:2:1 $\text{MeCN}:\text{CH}_2\text{Cl}_2:\text{MeOH}$) giving a pale yellow solid.

^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 11.45 (br. s., 1 H), 9.07 (m, 1 H), 8.72 (d, $J=2.5$ Hz, 1 H), 8.45 (m, 1 H), 8.24 (s, 1 H), 8.20 (d, $J=7.6$ Hz, 1 H), 7.98 (dt, $J=8.5$, 2.9 Hz, 1 H), 7.94 (d, $J=7.8$ Hz, 1 H), 7.75 (t, $J=7.6$ Hz, 1 H), 7.33 (d, $J=8.6$ Hz, 1 H), 4.37 (m, 1 H), 3.83 - 3.94 (m, 3 H), 2.58 - 2.79 (m, 1 H), 1.82 - 2.01 (m, 3 H), 1.39 - 1.74 (m, 5 H). ESI-MS (m/z): Calcd. For $\text{C}_{26}\text{H}_{27}\text{N}_5\text{O}_3\text{F}_6$: 571; found: 572 ($\text{M}+\text{H}$).

Example 17: *N*-[(1-{4-[3-(2,2,2-Trifluoro-acetylamino)-pyridin-2-yl]-cyclohexyl}-azetidin-3-ylcarbamoyl)-methyl]-3-trifluoromethyl-benzamide

Step A: *N*-[2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-2,2,2-trifluoro-acetamide

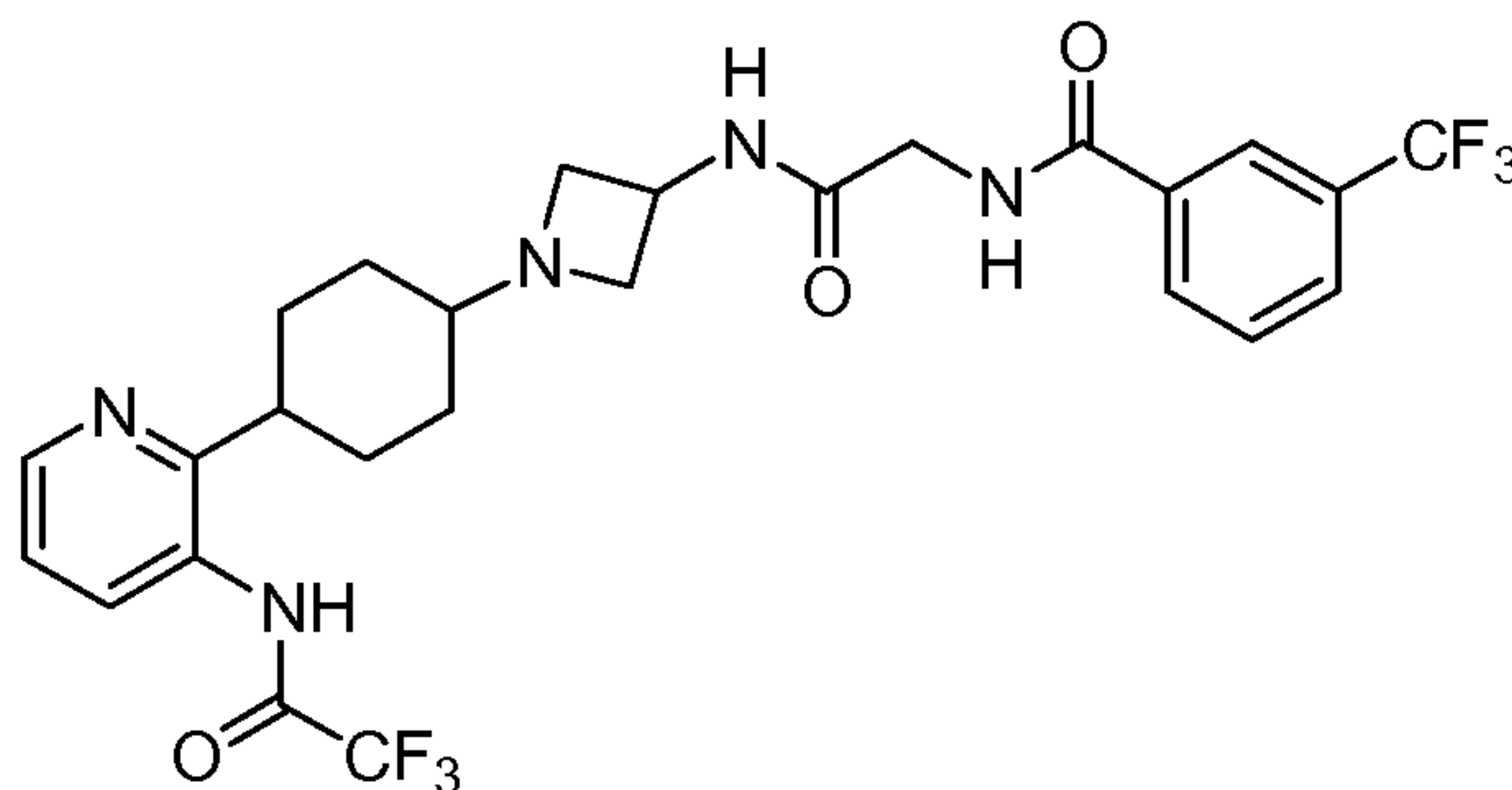


The title compound was prepared as described in Example 3: Steps A-B, and Example 16: Step A, from 3-amino-2-bromopyridine (Aldrich) as a white solid.

ESI-MS (m/z): Calcd. For C₁₅H₁₇N₂O₃F₃: 330; found: 331 (M+H)

5

Step B: *N-[(1-{4-[3-(2,2,2-Trifluoro-acetylaminomethyl)-pyridin-2-yl]-cyclohexyl}-azetidin-3-yl)carbonyl]-methyl]-3-trifluoromethyl-benzamide*

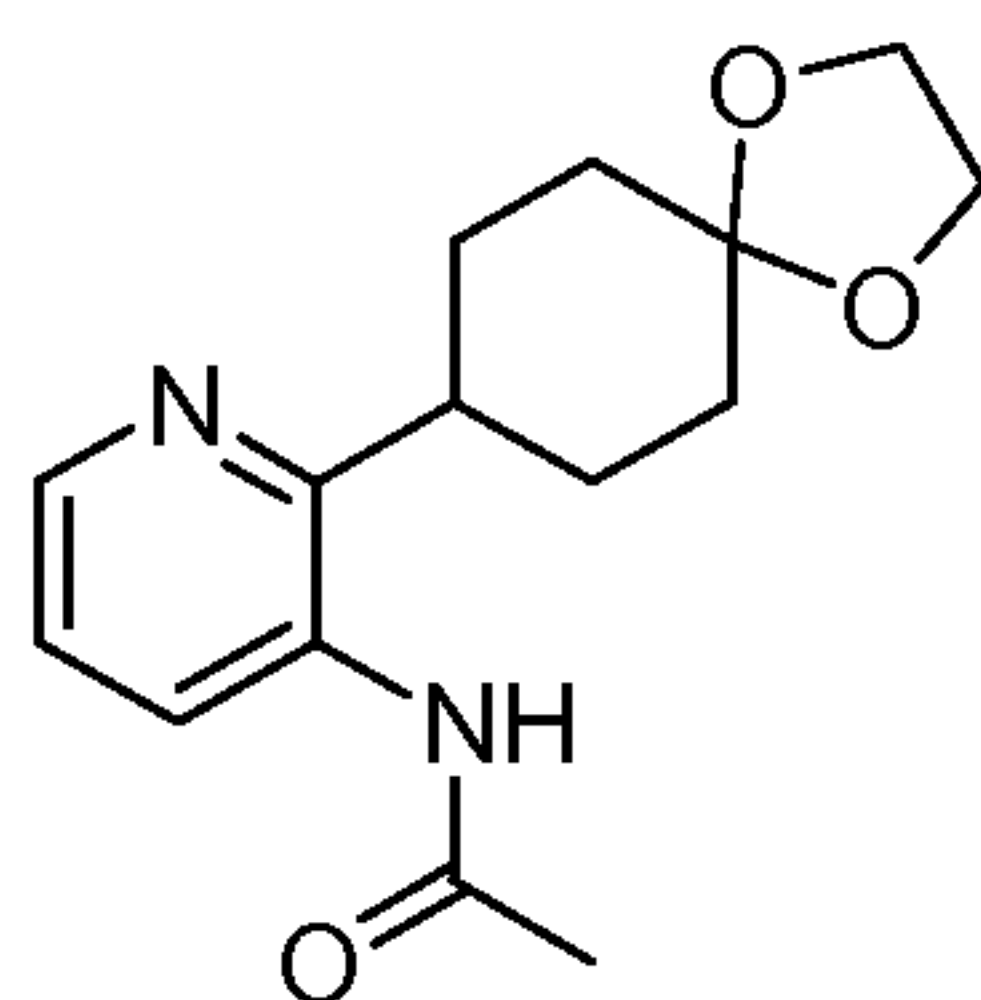


The title compound was prepared as described in Example 3: Steps C-D from N-[2-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-2,2,2-trifluoro-acetamide (as prepared in the previous step) and purified by preparative thin layer chromatography on silica gel (3:2:1 MeCN:CH₂Cl₂:MeOH) giving a light peach solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.21 (br. s., 1 H), 9.08 (br. s., 1 H), 8.50 - 8.55 (m, 1 H), 8.39 - 8.50 (m, 1 H), 8.24 (s, 1 H), 8.20 (d, *J*=7.8 Hz, 1 H), 7.94 (d, *J*=7.6 Hz, 1 H), 7.75 (t, *J*=7.8 Hz, 1 H), 7.68 (d, *J*=8.1 Hz, 1 H), 7.32 (dd, *J*=6.9, 5.2 Hz, 1 H), 4.20 - 4.55 (m, 1 H), 3.89 (d, *J*=5.6 Hz, 2 H), 2.83 (m, 1 H), 1.65 - 1.98 (m, 4 H), 1.16 - 1.64 (m, 4 H). ESI-MS (m/z): Calcd. For C₂₆H₂₇N₅O₃F₆: 571; found: 572 (M+H).

Example 18: N-({1-[4-(3-Acetylaminomethyl)-pyridin-2-yl]-cyclohexyl}-azetidin-3-yl)carbonyl]-methyl)-3-trifluoromethyl-benzamide

Step A: N-[2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-acetamide

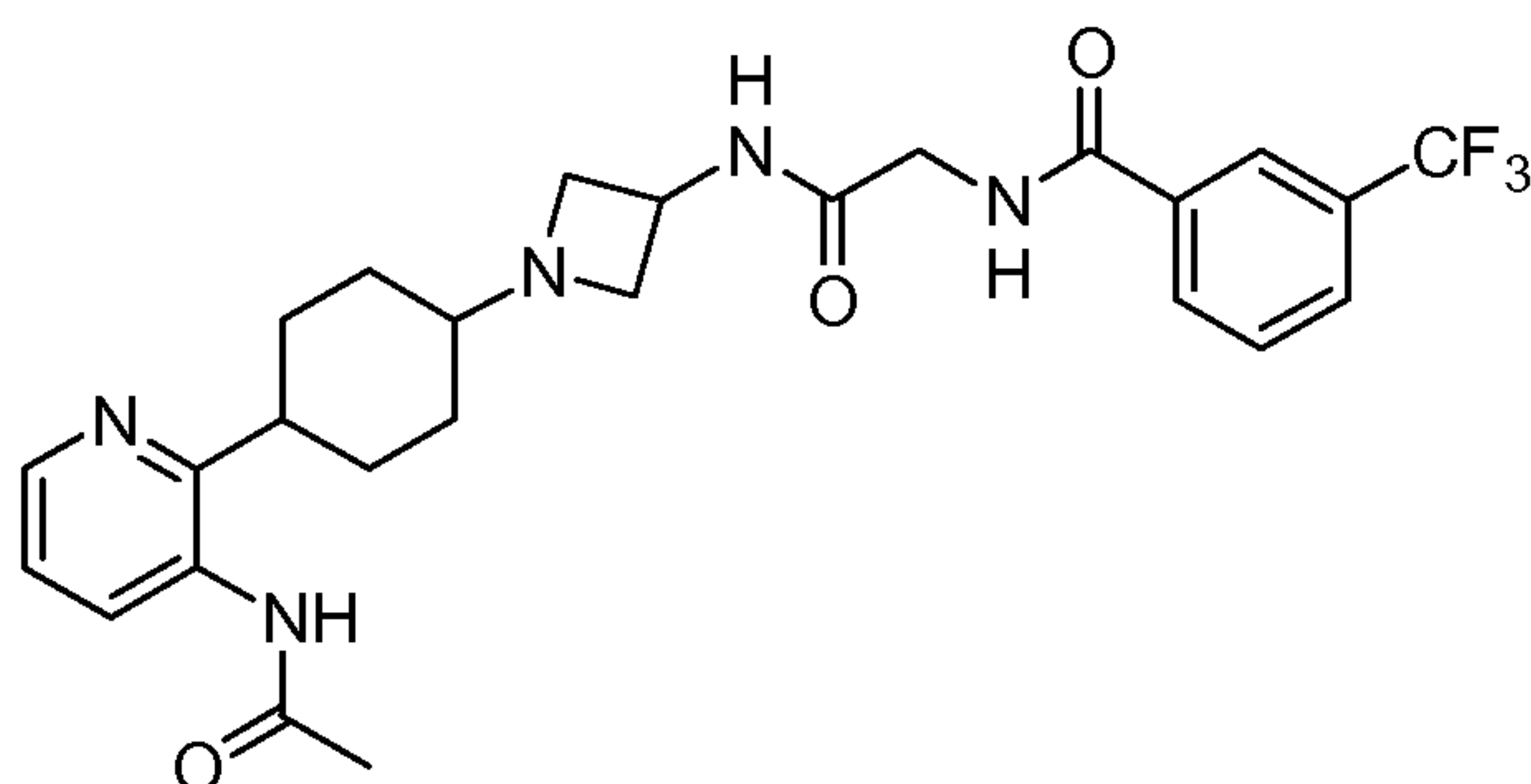


The title compound was prepared as described in Example 2: Steps A-B, and Example 13: Step A, from 3-amino-2-bromopyridine (Aldrich) as a white solid.

ESI-MS (m/z): Calcd. For C₁₅H₂₀N₂O₃: 276; found: 277 (M+H)

5

Step B: N-(1-[4-(3-Acetylaminopyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl)-methyl)-3-trifluoromethyl-benzamide



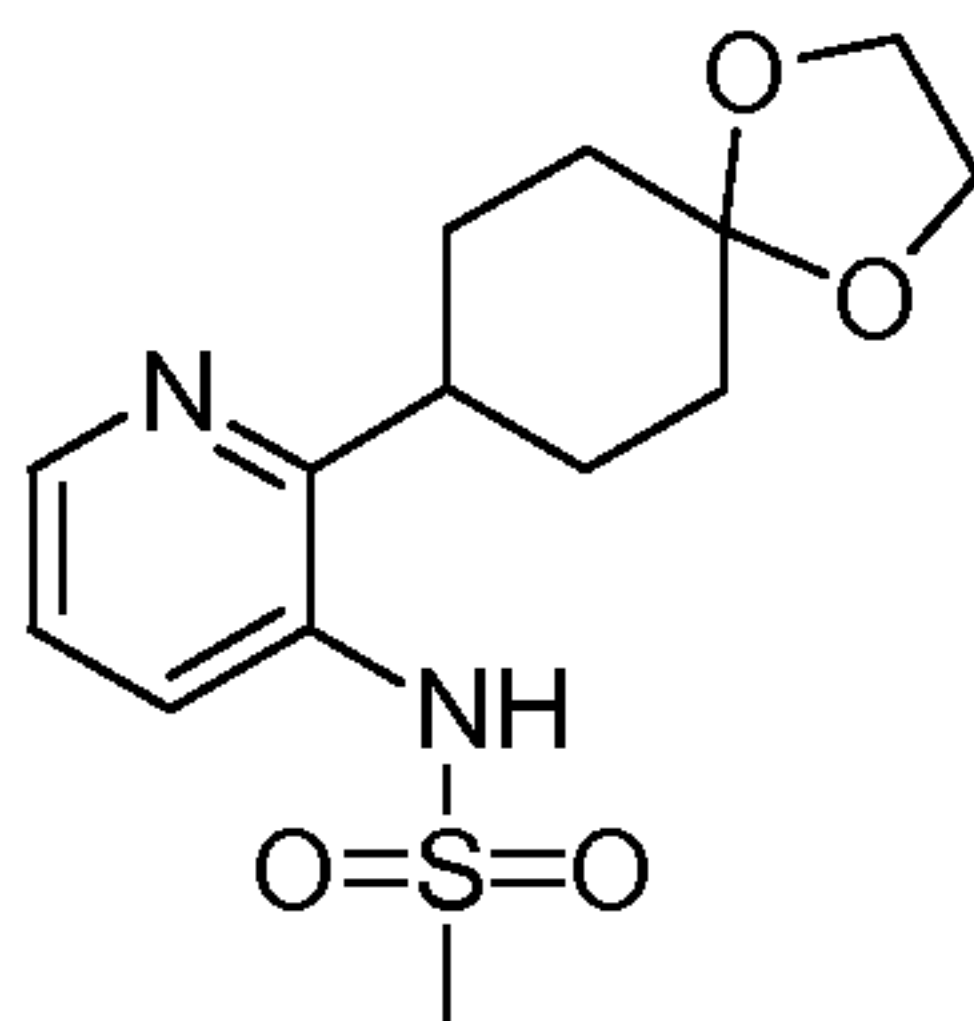
The title compound was prepared as described in Example 3: Steps C-D from N-[2-(1,4-dioxaspiro[4.5]dec-8-yl)-pyridin-3-yl]-acetamide (as prepared in the previous step) and purified by preparative thin layer chromatography on silica gel (15% MeOH in CH₂Cl₂) giving a pale solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.49 (s, 1 H), 9.03 (t, *J*=5.6 Hz, 1 H), 8.41 (d, *J*=6.8 Hz, 1 H), 8.33 (dd, *J*=4.5, 1.3 Hz, 1 H), 8.23 (s, 1 H), 8.19 (d, *J*=7.8 Hz, 1 H), 7.93 (d, *J*=7.6 Hz, 1 H), 7.75 (t, *J*=7.8 Hz, 1 H), 7.68 (dd, *J*=8.0, 1.1 Hz, 1 H), 7.17 (dd, *J*=8.0, 4.7 Hz, 1 H), 4.18 - 4.38 (m, 1 H), 3.89 (d, *J*=5.8 Hz, 2 H), 3.42 - 3.59 (m, 2 H), 2.94 (t, *J*=11.5 Hz, 1 H), 2.66 - 2.88 (m, 2 H), 2.22 - 2.41 (m, 1 H), 2.07 (s, 3 H), 1.90 (m, 2 H), 1.57 - 1.75 (m, 2 H), 1.33 (m, 4 H). ESI-MS (m/z): Calcd. For C₂₆H₃₀N₅O₃F₃: 517; found: 518 (M+H).

20

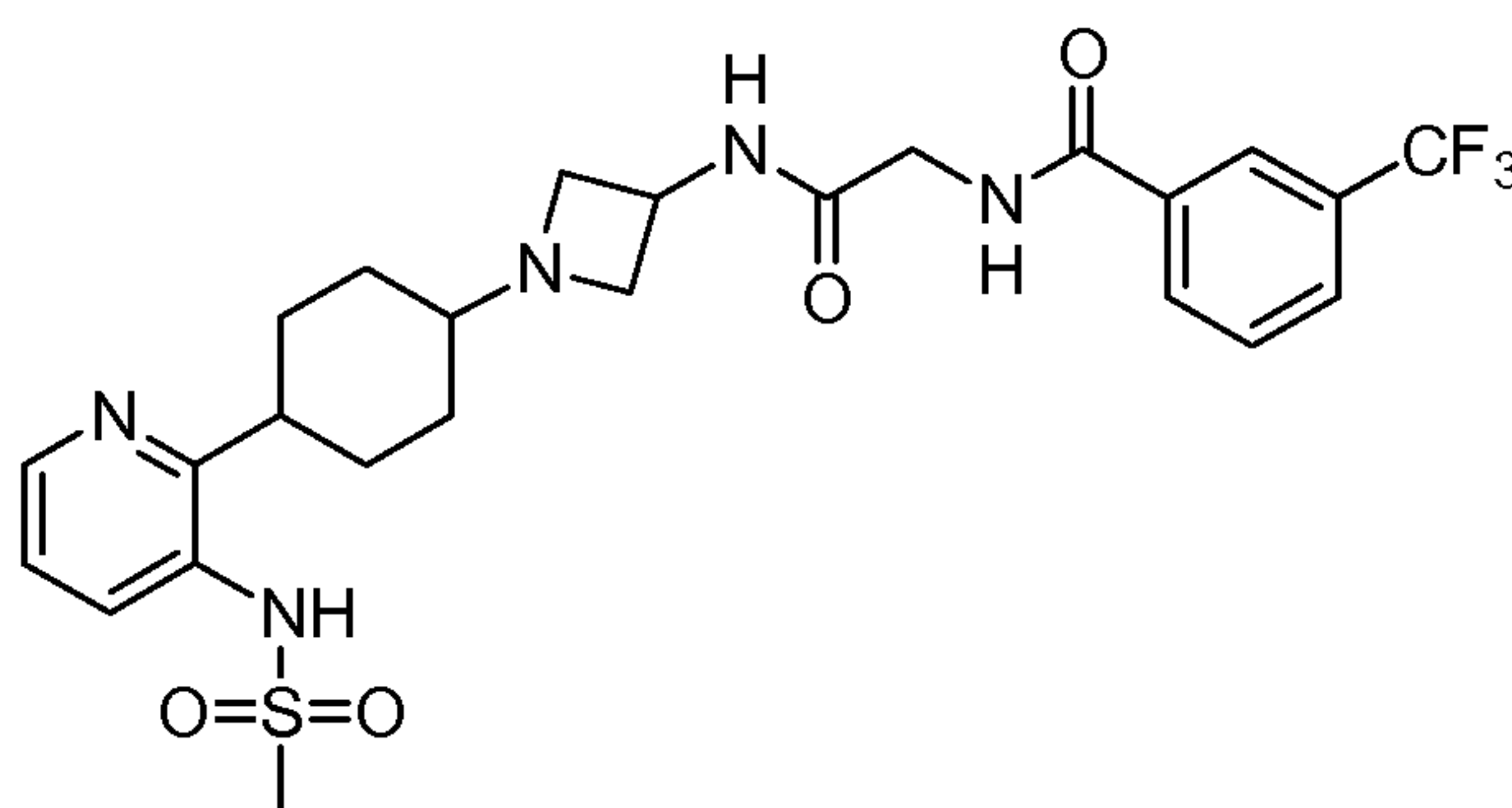
Example 19: N-({1-[4-(3-Methanesulfonylamino-pyridin-2-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide

Step A: N-[2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-methanesulfonamide



5 2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-3-ylamine (0.141 g, 0.603 mmol, prepared as described in Example 3: Steps A-B from 3-amino-2-bromopyridine) was dissolved in anhydrous dichloromethane (10 mL) under Ar, treated with methanesulfonyl chloride (0.155 mL, 1.48 mmol), a few drops of anhydrous pyridine, and stirred at ambient temperature for 24 h. The reaction was quenched with saturated aqueous NaHCO₃, the
10 aqueous layer extracted thrice with dichloromethane, and the combined organic layers washed with brine, dried over Na₂SO₄, filtered, and the filtrate concentrated *in vacuo* giving the title compound as a very hygroscopic yellow solid. ESI-MS (m/z): Calcd. For C₁₄H₂₀N₂O₄S: 312; found: 313 (M+H)

15 *Step B: N-({1-[4-(3-Methanesulfonylamino-pyridin-2-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide*



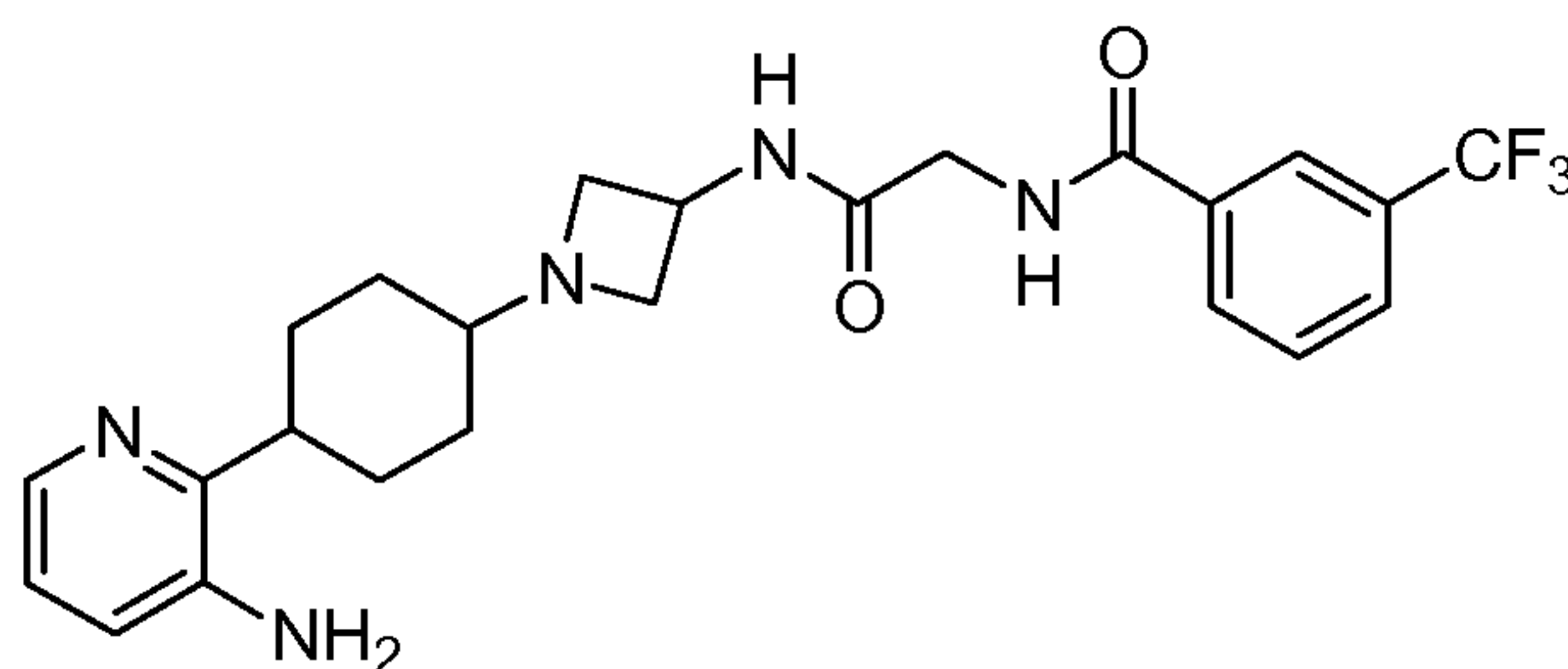
The title compound was prepared as described in Example 3: Steps C-D from N-[2-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyridin-3-yl]-methanesulfonamide (as prepared in the previous
20 step) as a pale solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.03 (t, *J*=5.8 Hz, 1 H), 8.41 (dd, *J*=4.7, 1.6 Hz, 2 H), 8.23 (s, 1 H), 8.19 (d, *J*=7.8 Hz, 1 H), 7.93 (d, *J*=7.8 Hz, 1 H), 7.75 (t, *J*=7.7 Hz, 1

H), 7.63 (dd, $J=8.0$, 1.6 Hz, 1 H), 7.21 (dd, $J=8.0$, 4.7 Hz, 1 H), 4.29 (sxt, $J=6.8$ Hz, 1 H), 3.89 (d, $J=5.8$ Hz, 2 H), 3.52 (m, 2 H), 3.16 (m, 1 H), 3.00 (s, 3 H), 2.82 (m, 2 H), 2.26 - 2.41 (m, 1 H), 1.83 - 2.00 (m, 2 H), 1.59 - 1.73 (m, 2 H), 1.37 - 1.51 (m, 2 H), 1.33 (m, 2 H). ESI-MS (m/z): Calcd. For $C_{25}H_{30}N_5O_4F_3S$: 553; found: 554 (M+H).

5

Example 20: N-({1-[4-(3-Amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

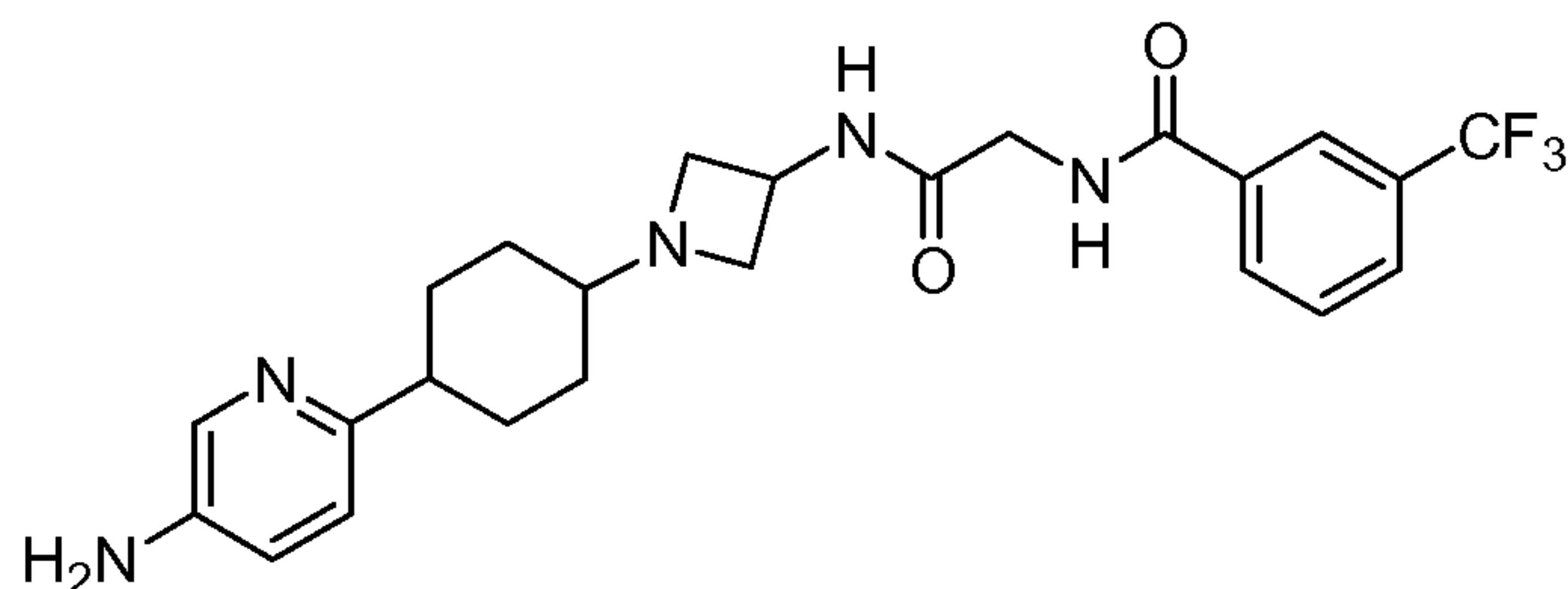


10 N-[(1-{4-[3-(2,2,2-Trifluoro-acetyl-amino)-pyridin-2-yl]-cyclohexyl}-azetidin-3-ylcarbamoyl)-methyl]-3-trifluoromethyl-benzamide (0.042 g, 0.073 mmol, as prepared in Example 17: Step B) was dissolved in methanol (3 mL), treated with a solution of powdered potassium carbonate (1.103, 0.730 mmol) in water (3 mL), and stirred at ambient temperature for 5 d, then heated to 70 °C under reflux condenser for 18 h. After
15 removing the methanol *in vacuo*, the reaction was diluted with water and extracted thrice with 3:1 EtOAc/2-PrOH. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and the filtrate concentrated *in vacuo* giving the title compound as a beige solid.

^1H NMR (400 MHz, $MeOH-d_4$) δ ppm 8.22 (s, 1 H), 8.15 (d, $J=8.1$ Hz, 1 H), 7.86 (d, $J=7.8$ Hz, 1 H), 7.77 (dd, $J=4.5$, 1.5 Hz, 1 H), 7.69 (t, $J=7.8$ Hz, 1 H), 7.04 (dd, $J=8.1$, 1.5 Hz, 1 H), 6.94 (dd, $J=8.0$, 4.7 Hz, 1 H), 4.44 (quin, $J=6.7$ Hz, 1 H), 4.05 (s, 2 H), 3.64 (t, $J=7.2$ Hz, 2 H), 2.92 - 3.04 (m, 2 H), 2.84 (tt, $J=10.8$, 3.6 Hz, 1 H), 2.37 - 2.51 (m, 1 H), 1.92 - 2.08 (m, 2 H), 1.78 (m, 2 H), 1.47 - 1.65 (m, 4 H). ESI-MS (m/z): Calcd. For $C_{24}H_{28}N_5O_2F_3$: 475; found: 476 (M+H).

25

Example 21: N-({1-[4-(5-Amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

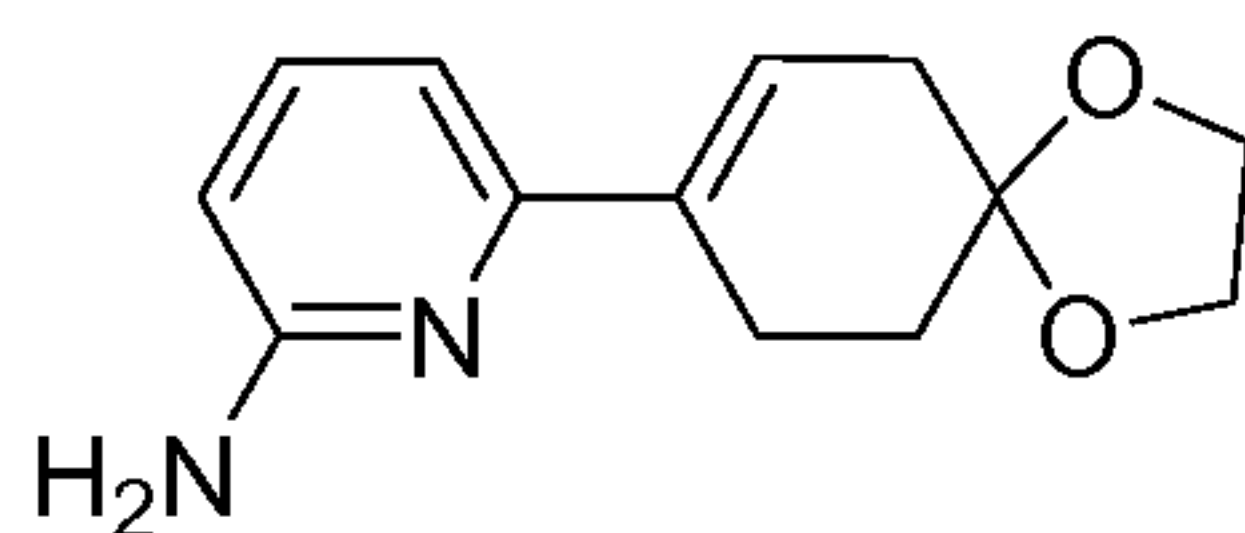


The title compound was prepared as described in Example 3: Steps A-D from 5-amino-2-bromopyridine (Aldrich) as a yellow solid.

¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 9.11 (br. s., 1 H), 8.47 - 8.75 (m, 1 H), 8.25 (s, 1 H), 8.21 (d, *J*=7.8 Hz, 1 H), 7.93 (d, *J*=7.8 Hz, 1 H), 7.83 (d, *J*=2.8 Hz, 1 H), 7.75 (t, *J*=7.8 Hz, 1 H), 7.00 (br. s., 1 H), 6.87 (dd, *J*=8.2, 2.7 Hz, 1 H), 5.04 (br. s., 2 H), 4.31 - 4.56 (m, 1 H), 3.97 - 4.23 (m, 1 H), 3.90 (d, *J*=5.8 Hz, 2 H), 2.54 - 2.62 (m, 1 H), 1.89 (m, 2 H), 1.35 - 1.75 (m, 6 H). ESI-MS (*m/z*): Calcd. For C₂₄H₂₈N₅O₂F₃: 475; found: 476 (M+H).

Example 22: N-({1-[4-(6-Amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

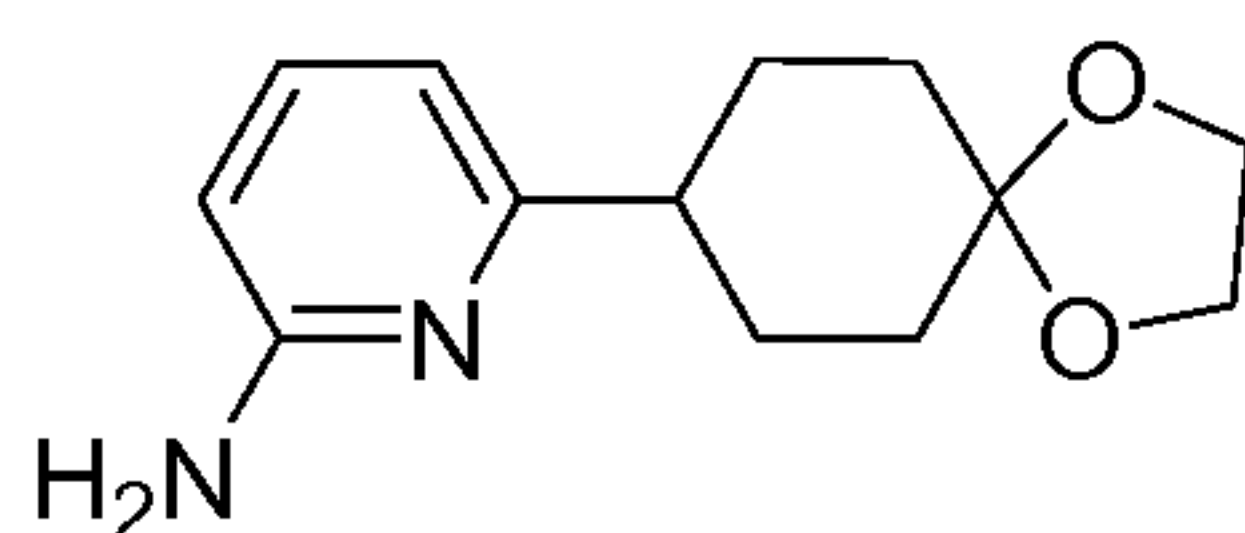
Step A: 6-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-2-ylamine



The title compound was prepared as described in Step A of Example 3 from 6-bromopyridin-2-ylamine (Aldrich) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.35 (t, *J* = 6.5 Hz, 1H), 6.72 9d, *J* = 6.2 Hz, 1H), 6.51 (m, 1H), 6.31 (d, *J* = 6.2 Hz, 1H), 4.32 (s, br, 1H), 4.02 9s, 4H), 2.70 (m, 2H), 2.41 (s, 2H), 1.95 (t, *J* = 5.8 Hz, 2H).

Step B: 6-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-2-ylamine

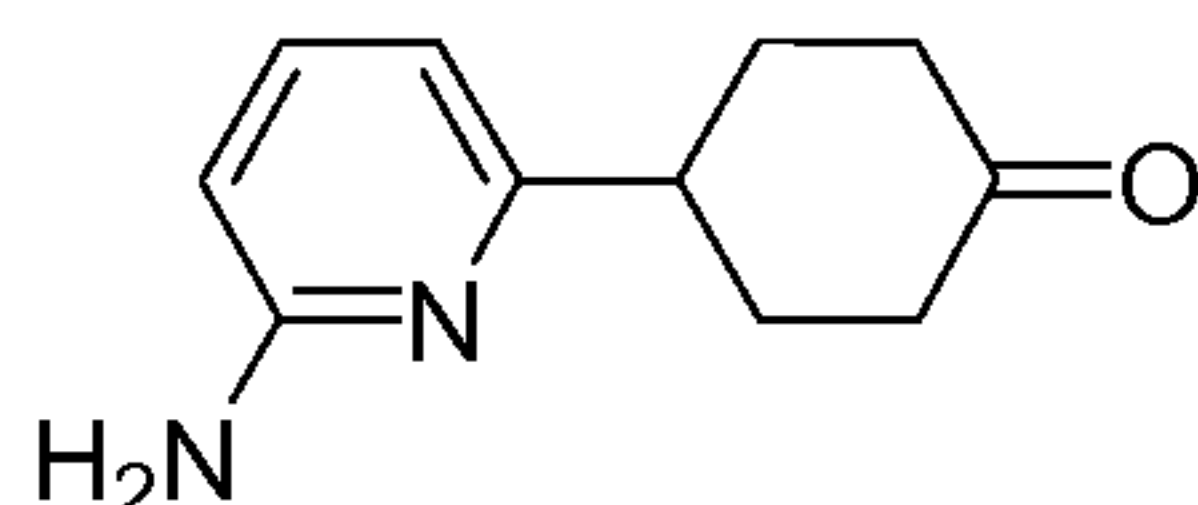


The title compound was prepared as a white solid from the hydrogenation of 6-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-2-ylamine (as prepared in the previous step) using the procedure described in Step G of Example 1.

ESI-MS (m/z): Calcd. For C₁₃H₁₈N₂O₂, 234; found: 235(M+H).

5

Step C: 4-(6-Amino-pyridin-2-yl)-cyclohexanone

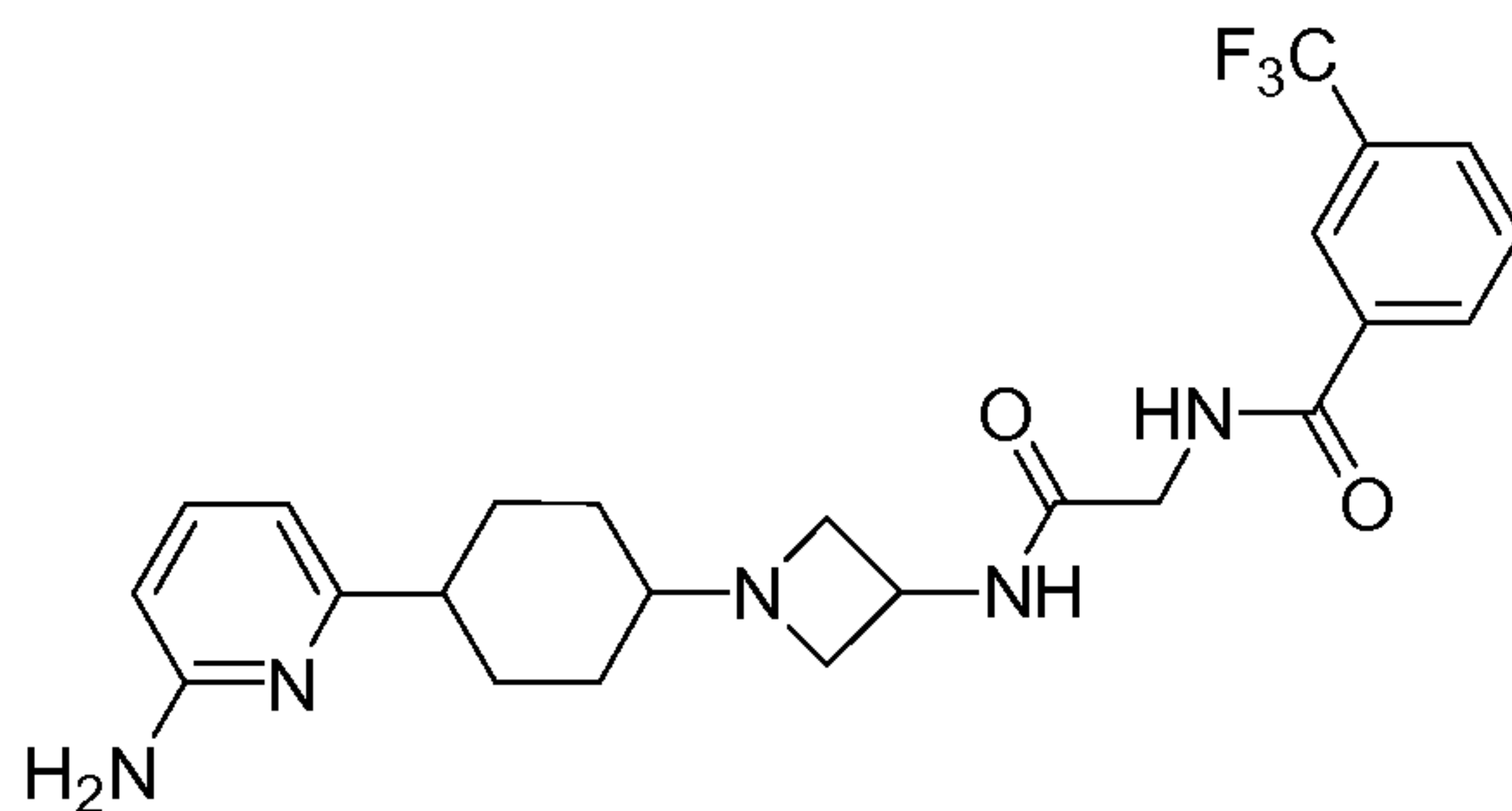


The title compound was prepared as a white solid from the deprotection of 6-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyridin-2-ylamine (as prepared in the previous step) using the procedure described in Step B of Example 2.

10

ESI-MS (m/z): Calcd. For C₁₁H₁₄N₂O, 190; found: 191 (M+H).

Step D: N-(1-[4-(6-Amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl)-methyl)-3-trifluoromethyl-benzamide



15

The title compounds were prepared as white solids from the reductive amination of 4-(6-amino-pyridin-2-yl)-cyclohexanone (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

20 **22a**: less polar isomer from silica gel column

¹H NMR (MeOH) δ: 8.24 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 6.8 Hz, 1H), 7.66 - 7.74 (m, 1H), 7.48 (dd, J = 7.5, 1.6 Hz, 1H), 6.65 (dd, J = 7.5, 5.2 Hz, 1H), 4.51 (t, J = 6.9 Hz, 1H), 4.06 (s, 2H), 3.70 (t, J = 7.6 Hz, 2H), 2.96 (t, J = 7.7 Hz, 2H), 2.51 - 2.68 (m, 1H), 2.45 (br. s., 1H), 1.70 - 1.86 (m, 4H), 1.52 - 1.69 (m, 4H).

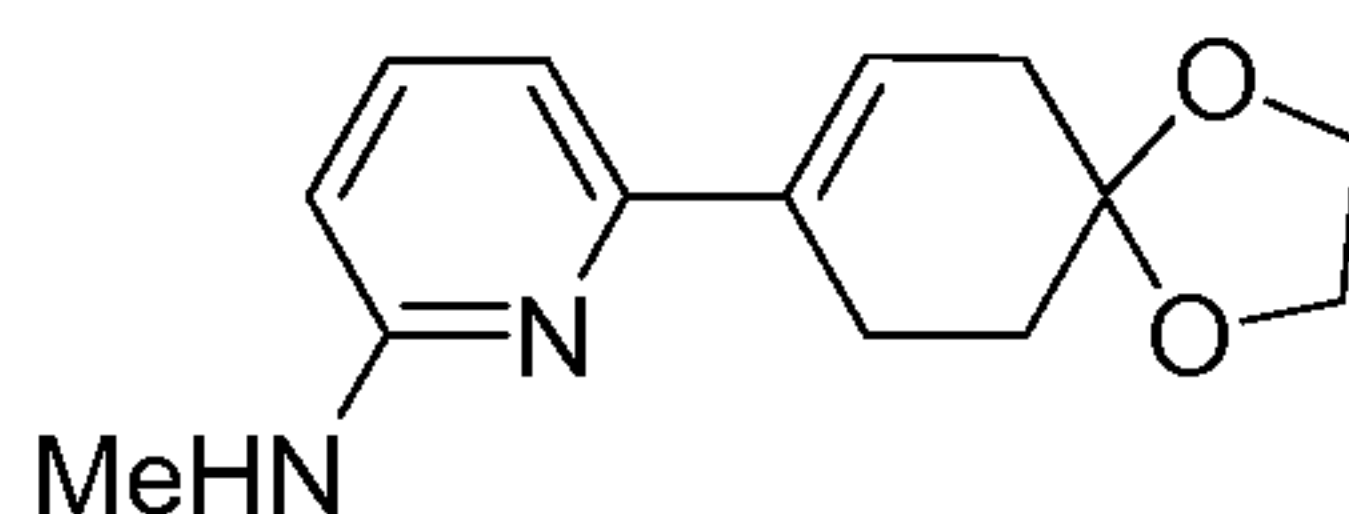
25 **22b**: more polar isomer from silica gel column

¹H NMR (MeOH) δ : 8.24 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.75 - 7.80 (m, 1H), 7.67 - 7.75 (m, 1H), 7.49 (t, J = 7.8 Hz, 1H), 6.61 - 6.74 (m, 1H), 4.52 (quin, J = 7.3 Hz, 1H), 4.06 (s, 2H), 3.65 - 3.76 (m, 2H), 2.95 - 3.00 (m, 1H), 2.83 (t, J = 6.8 Hz, 2H), 2.50 - 2.62 (m, 1H), 1.71 - 1.87 (m, 4H), 1.54 - 1.68 (m, 4H)

5

Example 23: N-({1-[4-(6-Methylamino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

Step A: [6-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-2-yl]-methyl-amine

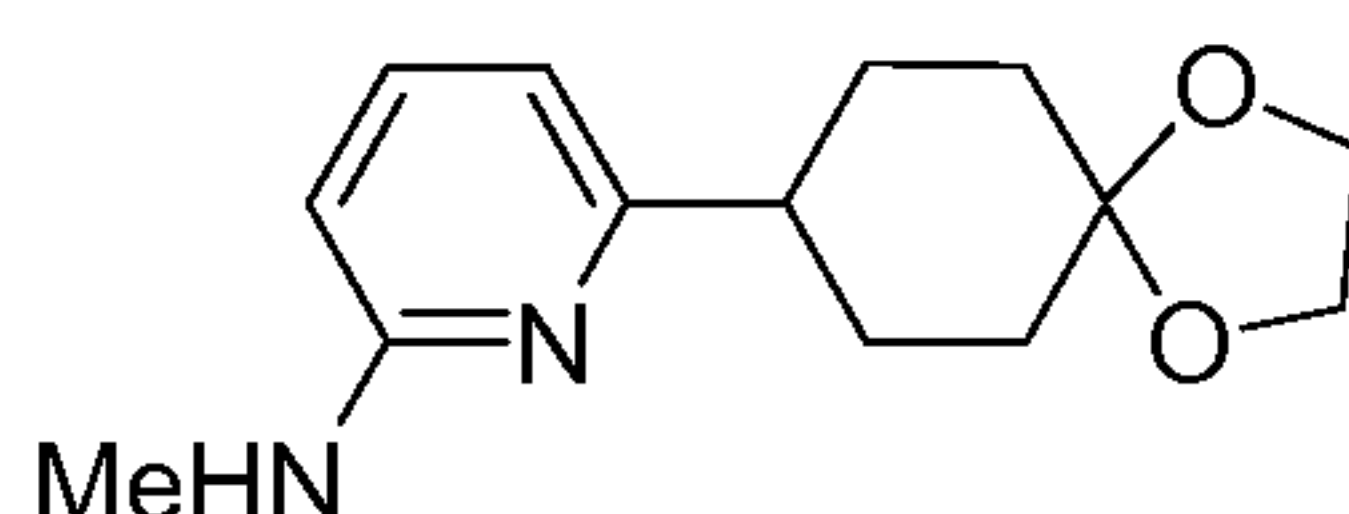


10 6-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-2-ylamine (as prepared in Example 22, Step A, 2.5 g, 10.8 mmol) in DMF (10 mL) was treated with NaH (Aldrich, 95%, 550 mg, 21.6 mmol) at 0 °C. The reaction was stirred for 20 min. and MeI (Aldrich, 810 μ L, 12 mmol) was slowly added. The reaction was warmed to room temperature over 2 hours. MeOH (~1 mL) was added to quench the extra NaH. The reaction solution was
15 partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a yellow oil, which was then purified by silica gel column on a CombiFlash® system using hexanes and ethyl acetate (from 10% ethyl acetate to 100% ethyl acetate) to afford the title compound as white solid.

20 ¹H NMR (400 MHz, CDCl₃) δ 7.35 (t, J = 6.5 Hz, 1H), 6.68 (d, J = 6.6 Hz, 1H), 6.55 (m, 1H), 6.22 (d, J = 6.5 Hz, 1H), 4.42 (s, br, 1H), 4.02 (s, 4H), 2.98 (d, J = 4.5 Hz, 3H), 2.72 (t, J = 4.6 Hz, 2H), 2.50 (s, 2H), 1.92 (t, J = 6.2 Hz, 2H).

Step B: [6-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-2-yl]-methyl-amine

25

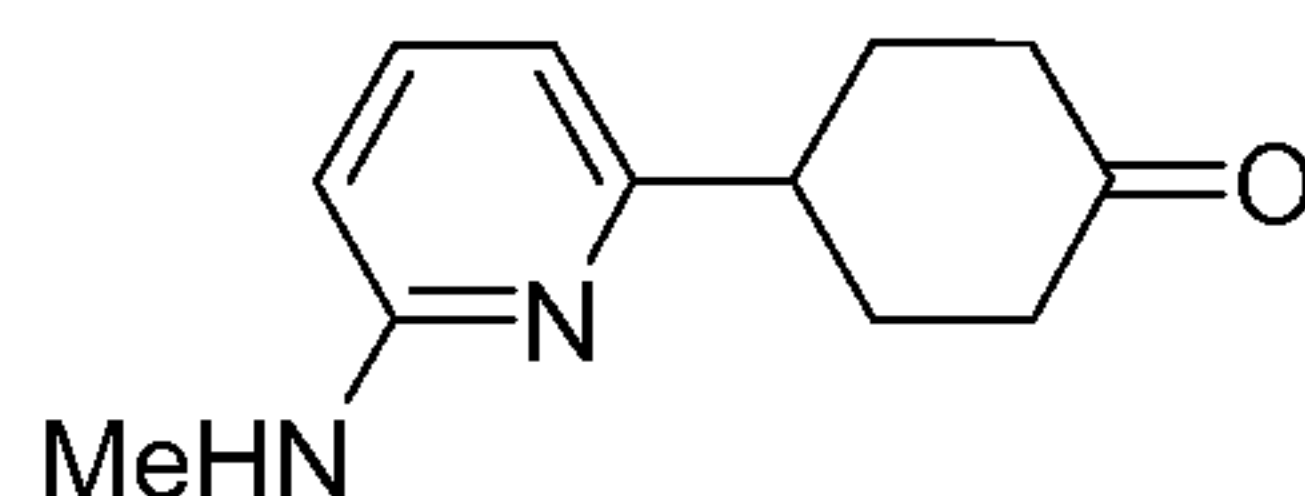


The title compound was prepared as a white solid from the hydrogenation of [6-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-2-yl]-methyl-amine (as prepared in the previous step) using the procedure described in Step G of Example 1.

ESI-MS (m/z): Calcd. For C₁₄H₂₀N₂O₂, 248; found: 249 (M+H).

5

Step C: 4-(6-Methylamino-pyridin-2-yl)-cyclohexanone

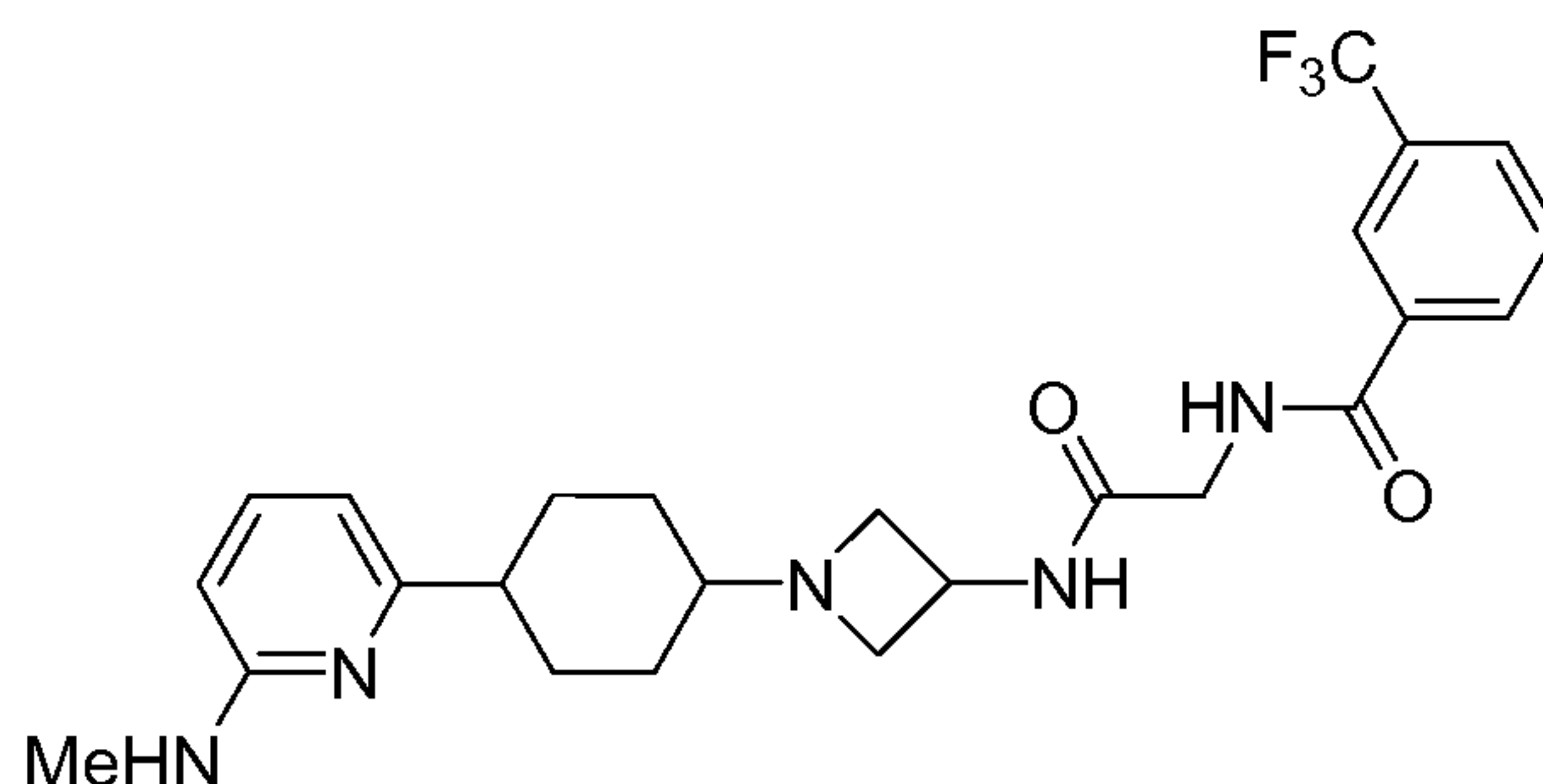


The title compound was prepared as a white solid from the deprotection of [6-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyridin-2-yl]-methyl-amine (as prepared in the previous step) using the procedure described in Step B of Example 2.

10

ESI-MS (m/z): Calcd. For C₁₂H₁₆N₂O, 204; found: 205(M+H).

Step D: N-({1-[4-(6-Methylamino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



15

The title compounds were prepared as white solids from the reductive amination of 4-(6-methylamino-pyridin-2-yl)-cyclohexanone (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

20 **23a**: less polar isomer from silica gel column,

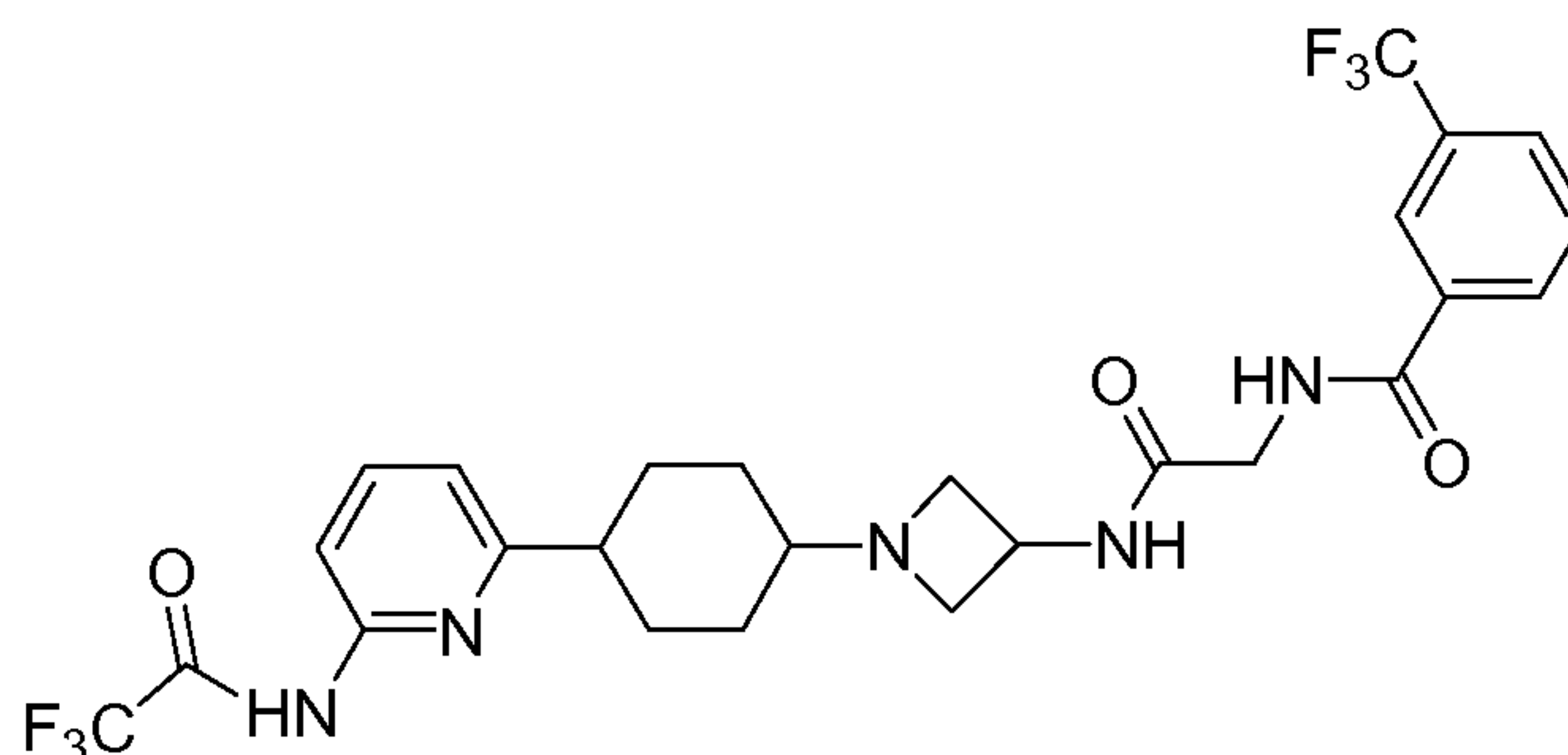
¹H NMR (400 MHz, CDCl₃) δ 8.25 (s, br, 2H), 8.20 (s, 1H), 8.05 (d, J = 6.5 Hz, 1H), 7.75 (d, J = 6.6 Hz, 1H), 7.55 (t, J = 6.6 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 6.45 (d, J = 6.8 Hz, 1H), 6.25 (d, J = 6.8 Hz, 1H), 4.58 (m, 1H), 4.21 (d, J = 4.0 Hz, 2H), 3.75 (t, J = 6.0 Hz, 2H), 3.40 (t, J = 6.0 Hz, 2H), 2.95 (d, J = 3.5 Hz, 3H), 2.70 (s, 1H), 2.58 (m, 1H), 1.98 (m, 2H), 1.80 (m, 2H), 1.55 (4H).

25

23b: more polar isomer from silica gel column

¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 8.10 (m, 1H), 7.85 (d, J = 6.5 Hz, 2H), 7.75 (t, J = 6.6 Hz, 1H), 7.70 (d, J = 6.0 Hz, 1H), 7.55 (t, J = 6.6 Hz, 1H), 4.58 (m, 1H), 4.21 (d, J = 4.0 Hz, 2H), 3.80 (t, J = 6.0 Hz, 2H), 3.40 (t, J = 6.0 Hz, 2H), 2.85 (d, J = 3.0 Hz, 3H), 2.60 (s, 1H), 2.48 (m, 1H), 1.98 (m, 2H), 1.50 (m, 2H), 1.35 (4H).

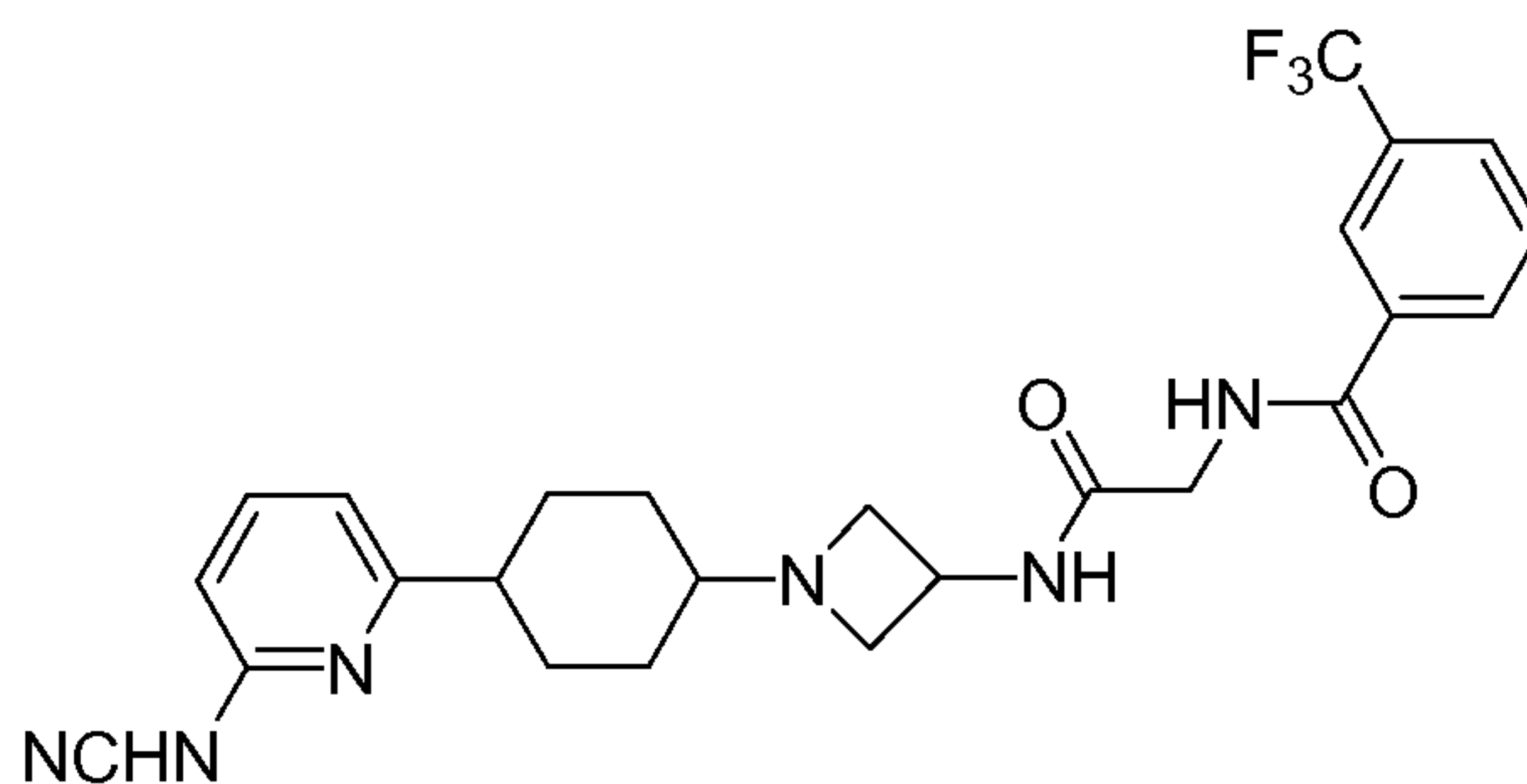
Example 24: N-[(1-{4-[6-(2,2,2-Trifluoro-acetyl-amino)-pyridin-2-yl]-cyclohexyl}-azetidin-3-ylcarbamoyl)-methyl]-3-trifluoromethyl-benzamide



10 The title compound was prepared as a white solid from trifluoroacetylation of N-({1-[4-(6-amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide using the procedure described in Step A of Example 16.

¹H NMR (400 MHz, *d*₄-MeOH) δ 8.11 (s, 1H), 8.00 (d, J = 6.6 Hz, 1H), 7.70 (d, J = 6.5 Hz, 1H), 7.62 (t, J = 6.0 Hz, 1H), 7.60 (d, J = 6.1 Hz, 1H), 6.95 (d, J = 6.0 Hz, 1H), 6.26 (d, J = 6.0 Hz, 1H), 4.35 (m, 1H), 3.98 (s, 2H), 3.60 (t, J = 7.0 Hz, 2H), 3.06 (t, J = 6.1 Hz, 2H), 3.00 (m, 1H), 2.35 (m, 1H), 1.95 (m, 2H), 1.88 (m, 2H), 1.65 (m, 4H).

Example 25: N-({1-[4-(6-Cyanoamino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

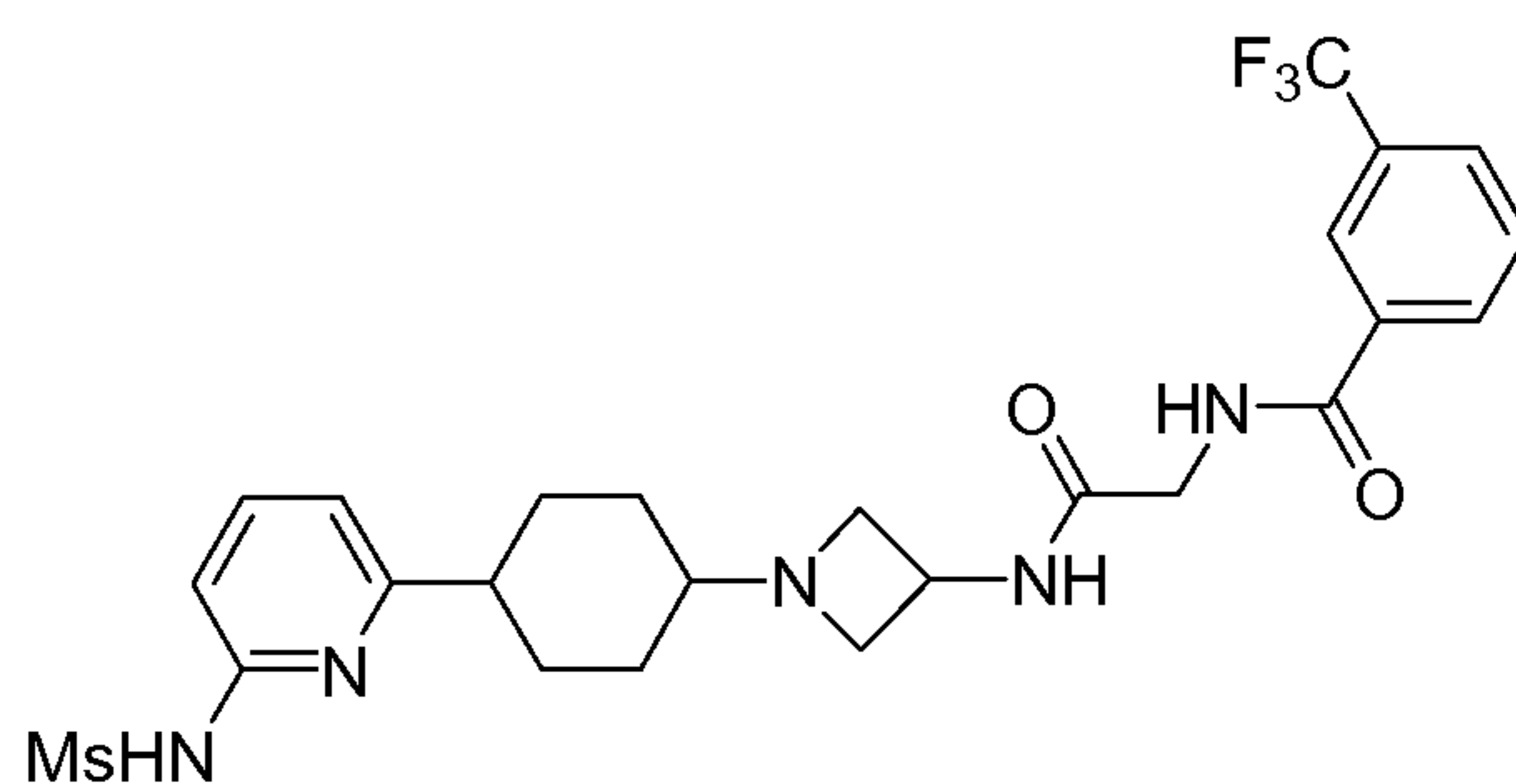


20

A solution of N-({1-[4-(6-amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide (120 mg, 0.25 mmol) in DMF (2 mL) was treated with NaH (95%, 10 mg, 0.40 mmol) at 0 °C. The reaction was stirred for 20 min. and BrCN (Aldrich, 32 mg, 0.30 mmol) was slowly added. The reaction was warmed to room temperature over 2 hours. MeOH (~0.2 mL) was added to quenched extra NaH. The reaction solution was partitioned between DCM and water. The aqueous layer was extracted with a chloroform/IPA "cocktail" (3:1 v/v). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a yellow oil, which was purified by silica gel column on a CombiFlash® system using ethyl acetate and 7N NH₃ in MeOH as eluent (from pure ethyl acetate to 5% 7N NH₃ in MeOH in ethyl acetate) to afford the title compound as white solid.

¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, br, 1H), 8.15 (s, 1H), 8.02 (d, J = 6.5 Hz, 1H), 7.80 (m, 1H), 7.72 (d, J = 6.6 Hz, 1H), 7.63 (m, 2H), 7.00 (d, J = 6.0 Hz, 1H), 6.32 (d, J = 6.2 Hz, 1H), 4.65 (m, 1H), 4.25 (m, 2H), 3.70 (t, J = 6.5 Hz, 2H), 3.25 (m, 1H), 2.91 (t, J = 6.1 Hz, 2H), 2.60 (m, 1H), 1.90 (m, 4H), 1.70 (m, 4H).

Example 26: N-({1-[4-(6-Methanesulfonylamino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

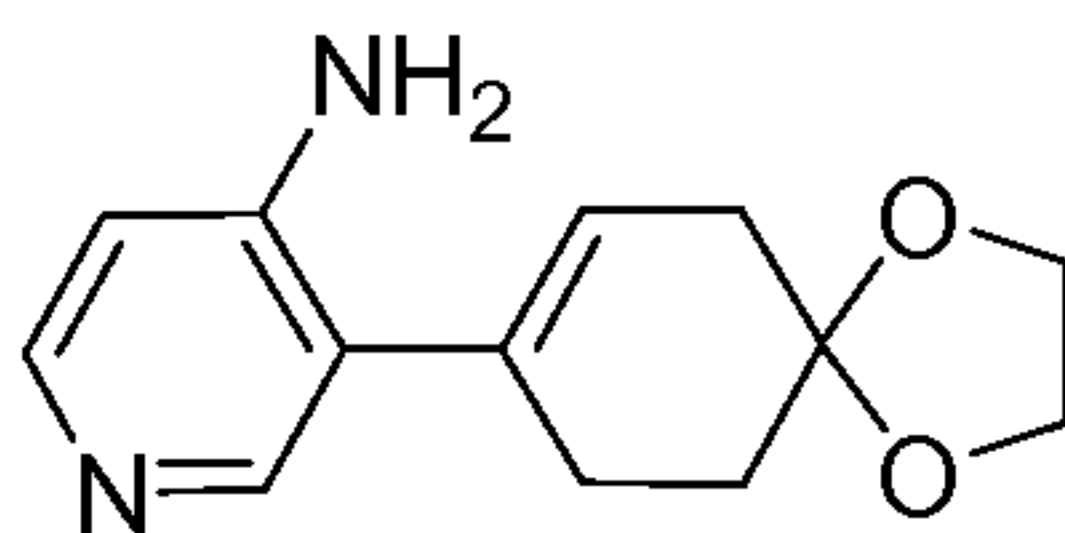


The title compound was prepared as a white solid from the mesylation of N-({1-[4-(6-amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide using the procedure described in Step A of Example 19.

¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 8.05 (m, 2H), 7.79 (d, J = 6.2 Hz, 1H), 7.62 (d, J = 3.6 Hz, 1H), 7.53 (t, J = 6.6 Hz, 1H), 7.30 (s, 1H), 4.65 (m, 1H), 4.20 (m, 2H), 3.85 (m, 2H), 3.20 (s, 3H), 3.10 (m, 2H), 2.55 (m, 1H), 1.90 (m, 4H), 1.65 (m, 4H).

Example 27: N-({1-[4-(4-Amino-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

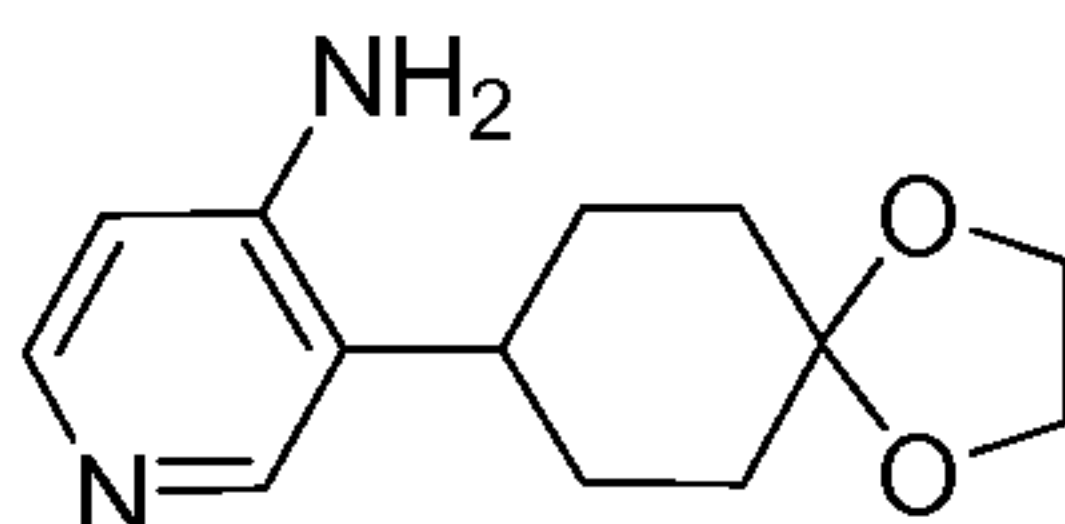
Step A: 3-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-4-ylamine



The title compound was prepared as described in Step A of Example 3 from 3-bromo-pyridin-4-ylamine (Aldrich) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, J = 5.6 Hz, 2H), 6.51 (s, 1H), 5.68 (m, 1H), 4.25 (s, br, 1H), 4.02 (s, 4H), 2.45 (m, 4H), 1.90 (t, J = 7.0 Hz, 2H). .

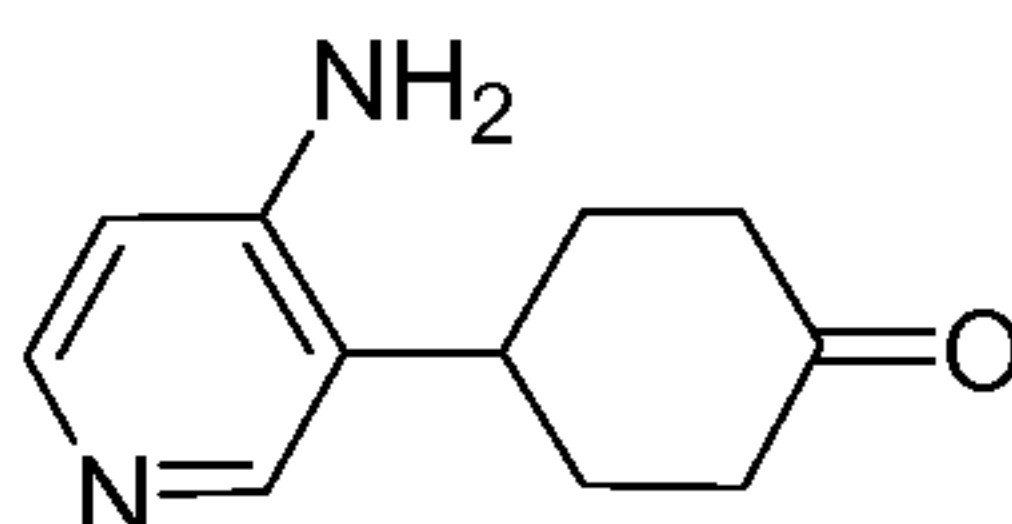
Step B: 3-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-4-ylamine



The title compound was prepared as a white solid from the hydrogenation of 3-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-4-ylamine (as prepared in the previous step) using the procedure described in Step G of Example 1.

ESI-MS (m/z): Calcd. For C₁₃H₁₈N₂O₂, 234; found: 235(M+H).

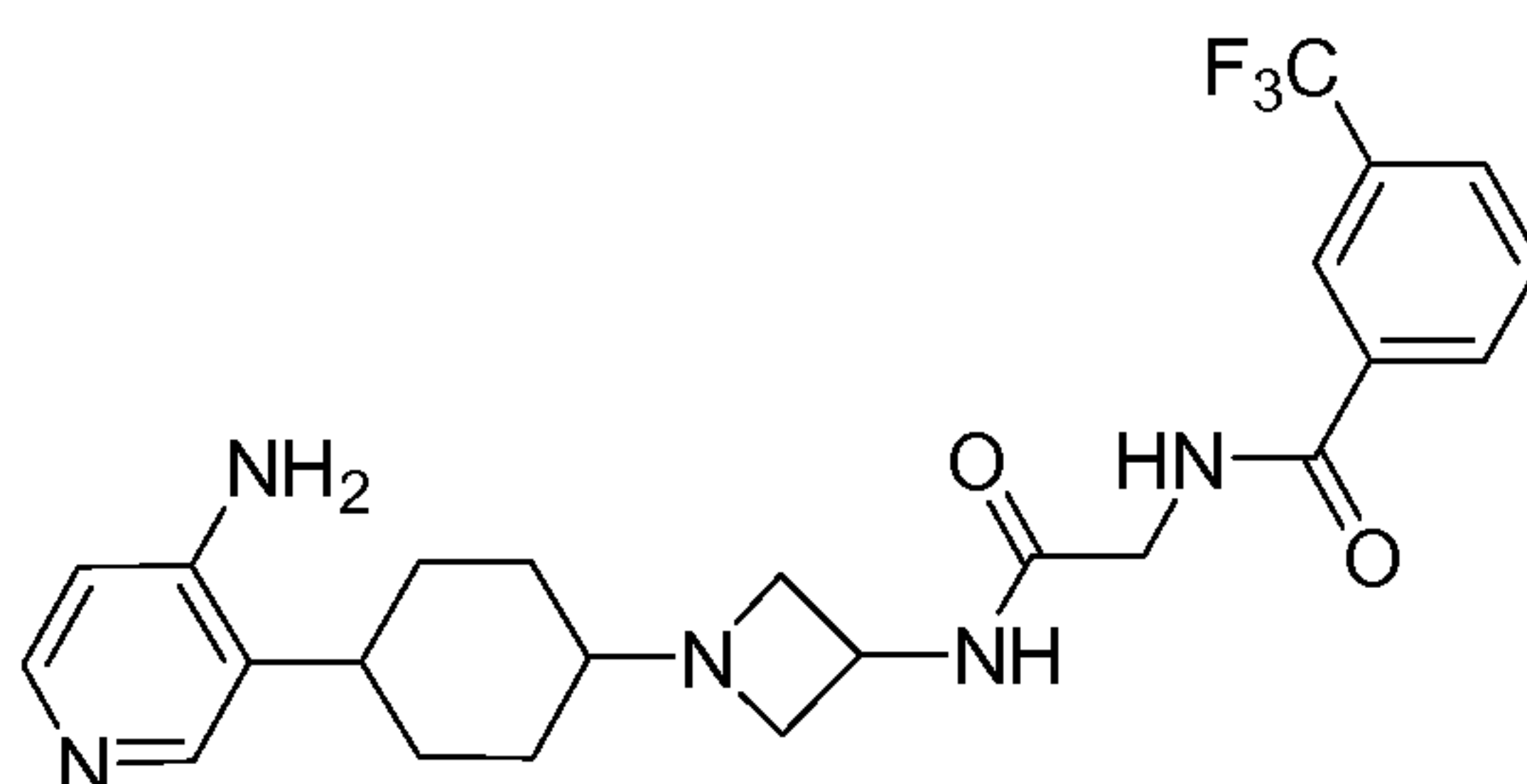
Step C: 4-(4-Amino-pyridin-3-yl)-cyclohexanone



The title compound was prepared as a white solid from the deprotection of 3-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyridin-4-ylamine (as prepared in the previous step) using the procedure described in Step B of Example 2.

ESI-MS (m/z): Calcd. For C₁₁H₁₄N₂O, 190; found: 191, (M+H).

Step D: N-({1-[4-(4-Amino-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



The title compounds were prepared as white solids from the reductive amination of 4-(4-amino-pyridin-3-yl)-cyclohexanone (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step

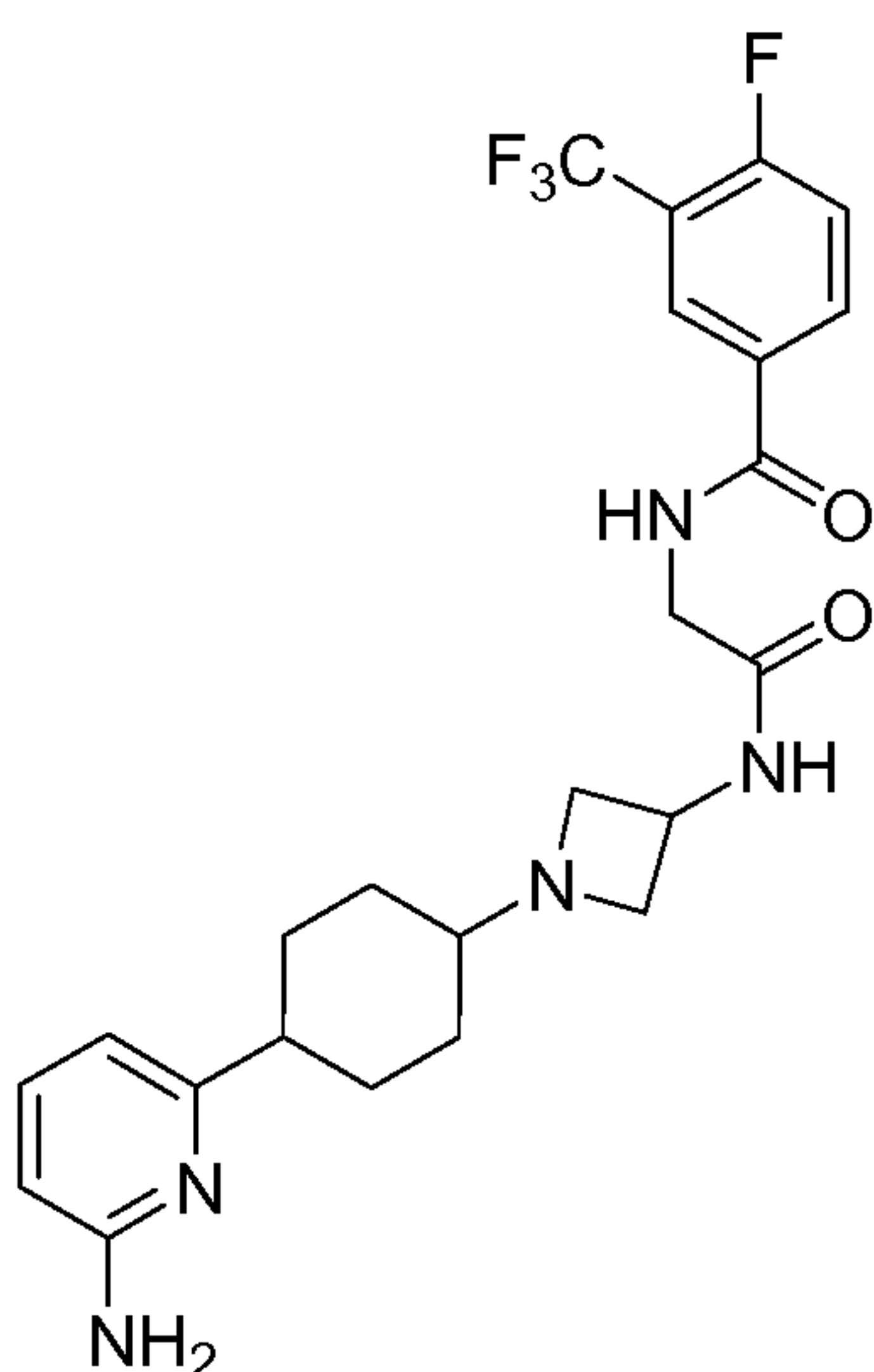
27a: less polar isomer from silica gel column,

¹H NMR (400 MHz, *d*₄-MeOH) δ 8.12 (s, 1H), 8.06 (d, *J* = 6.5 Hz, 1H), 8.02 (s, 1H), 7.95 (d, *J* = 5.2 Hz, 1H), 7.78 (d, *J* = 6.6 Hz, 1H), 7.60 (t, *J* = 6.6 Hz, 1H), 7.32 (m, 1H), 6.60 (d, *J* = 6.8 Hz, 1H), 4.45 (m, 1H), 4.05 (s, 2H), 3.65 (t, *J* = 7.0 Hz, 2H), 2.95 (t, *J* = 7.0

27b: more polar isomer from silica gel column

¹H NMR (400 MHz, *d*₄-MeOH) δ 8.21 (s, 1H), 8.18 (d, *J* = 6.1 Hz, 1H), 7.95 (s, 1H), 7.90 (d, *J* = 6.5 Hz, 2H), 7.70 (t, *J* = 6.6 Hz, 1H), 6.65 (d, *J* = 6.8 Hz, 1H), 4.50 (m, 1H), 4.08 (s, 2H), 3.75 (t, *J* = 7.0 Hz, 2H), 3.10 (t, *J* = 7.0 Hz, 2H), 2.55 (m, 1H), 2.25 (m, 1H), 2.02 (m, 4H), 1.55 (m, 2H), 1.24 (m, 2H).

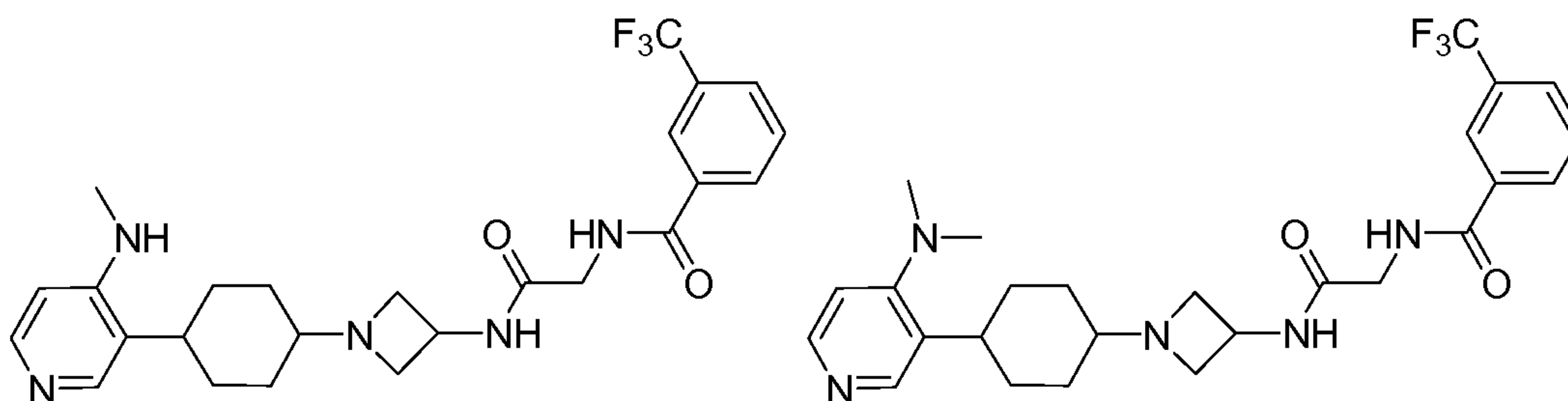
Example 28: N-({1-[4-(6-Amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-4-fluoro-3-trifluoromethyl-benzamide



The title compounds were prepared as white solids from the reductive amination of 4-(6-amino-pyridin-2-yl)-cyclohexanone (as prepared in the Example 22, Step C) and N-(azetidin-3-ylcarbonylmethyl)-4-fluoro-3-trifluoromethyl-benzamide (analog synthesis
5 by following the procedure described in Organic Synthesis XII, 40-2, 1932) using the procedure described in Step F of Example 1.

¹H NMR (MeOH) δ: 8.17 (d, J = 6.6 Hz, 1H), 8.10 (dd, J = 8.7, 2.4 Hz, 1H), 7.37 (t, J = 9.5 Hz, 1H), 7.28 (t, J = 7.7 Hz, 1H), 6.45 (d, J = 7.3 Hz, 1H), 6.27 (d, J = 8.3 Hz, 1H), 4.37 (t, J = 7.1 Hz, 1H), 3.93 (s, 2H), 3.55 (t, J = 7.6 Hz, 2H), 2.83 (t, J = 7.6 Hz, 2H),
10 2.35 - 2.46 (m, 1H), 2.20 - 2.34 (m, 1H), 1.70 - 1.85 (m, 2H), 1.61 (d, J = 15.2 Hz, 2H), 1.46 - 1.55 (m, 2H), 1.34 - 1.46 (m, 2H).

Example 29: N-({1-[4-(4-Methylamino-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbonyl}-methyl)-3-trifluoromethyl-benzamide and N-({1-[4-(4-Dimethylamino-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbonyl}-methyl)-3-trifluoromethyl-benzamide



The title compounds were prepared as white solids from the NaH induced methylation of N-({1-[4-(4-amino-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide (as prepared in Example 27) using the procedure described in Step A of Example 23.

5 **29a**: more polar fraction from silica gel column,

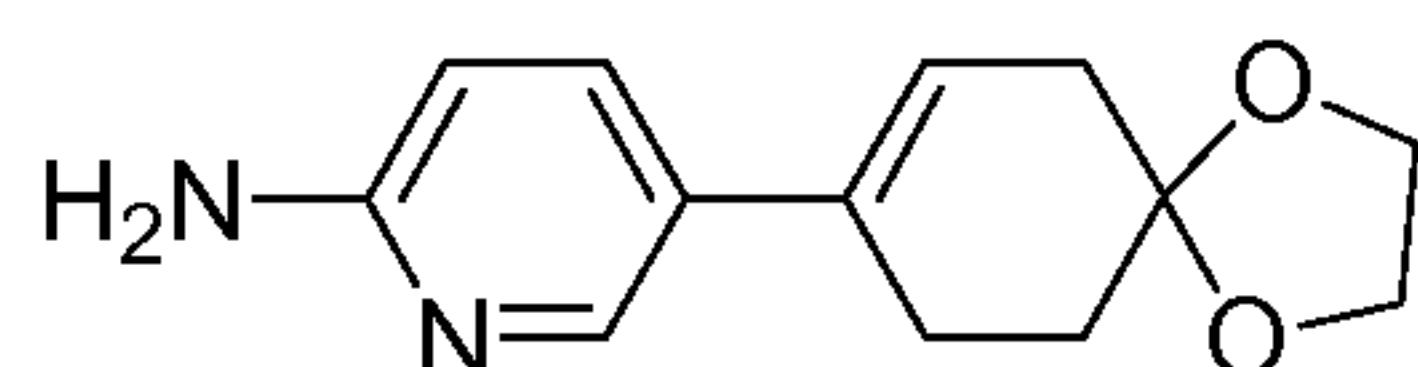
¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 8.12 (s, 1H), 8.06 (d, J = 6.5 Hz, 2H), 8.02 (s, 1H), 7.75 (d, J = 5.2 Hz, 1H), 7.59 (m, J = 6.6 Hz, 2H), 6.50 (d, J = 5.8 Hz, 1H), 4.65 (s, br, 1H), 4.48 (m, 1H), 4.20 (s, 2H), 3.55 (t, J = 7.0 Hz, 2H), 2.95 (t, J = 7.0 Hz, 2H), 2.55 (m, 1H), 2.30 (s, 1H), 2.28 (s, 3H), 1.95 (m, 2H), 1.80 (m, 2H), 1.55 (m, 4H).

10 **29b**: less polar fraction from silica gel column,

ESI-MS (m/z): Calcd. For C₂₆H₃₂F₃N₅O₂, 503; found: 504 (M+H).

Example 30: N-({1-[4-(6-Amino-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

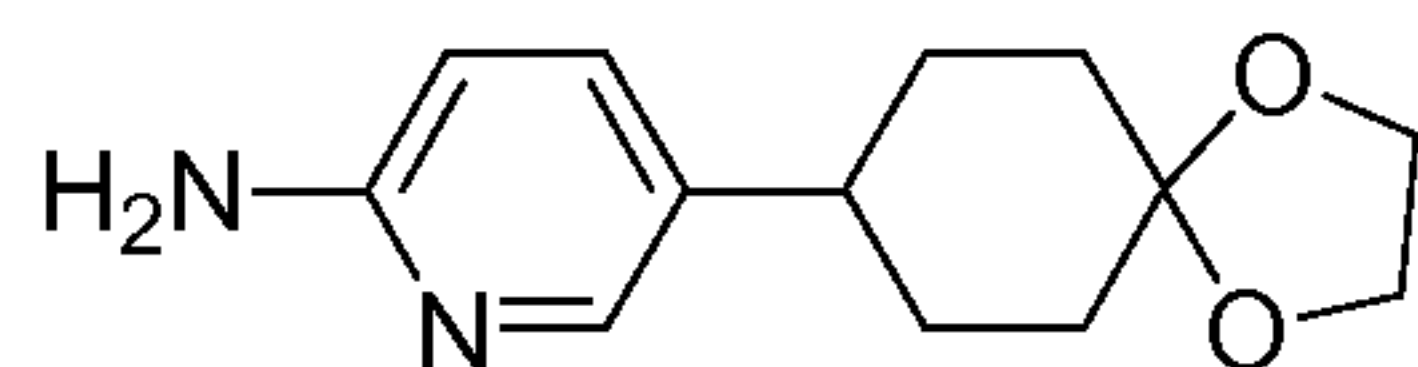
15 *Step A: 5-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-2-ylamine*



The title compound was prepared as described in Step A of Example 3 from 5-bromo-pyridin-2-ylamine (Aldrich) as a white solid.

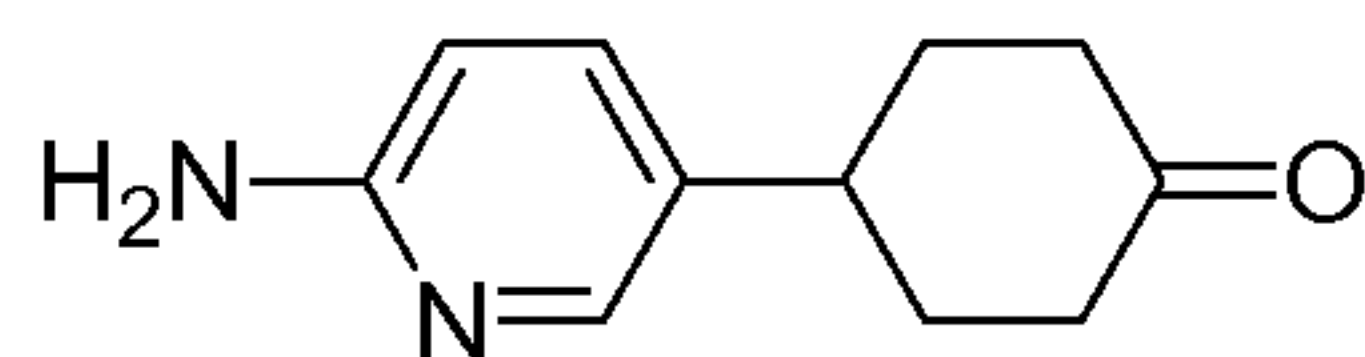
20 ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.42 (d, J = 6.2 Hz, 1H), 6.45 (d, J = 6.5 Hz, 1H), 5.86 (m, 1H), 4.55 (s, br, 2H), 4.02 (s, 4H), 2.59 (t, J = 3.5 Hz, 2H), 2.42 (s, 2H), 1.90 (t, J = 6.0 Hz, 2H).

Step B: 5-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyridin-2-ylamine



25 The title compound was prepared as a white solid from the hydrogenation of 5-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyridin-2-ylamine (as prepared in the previous step) using the procedure described in Step G of Example 1.

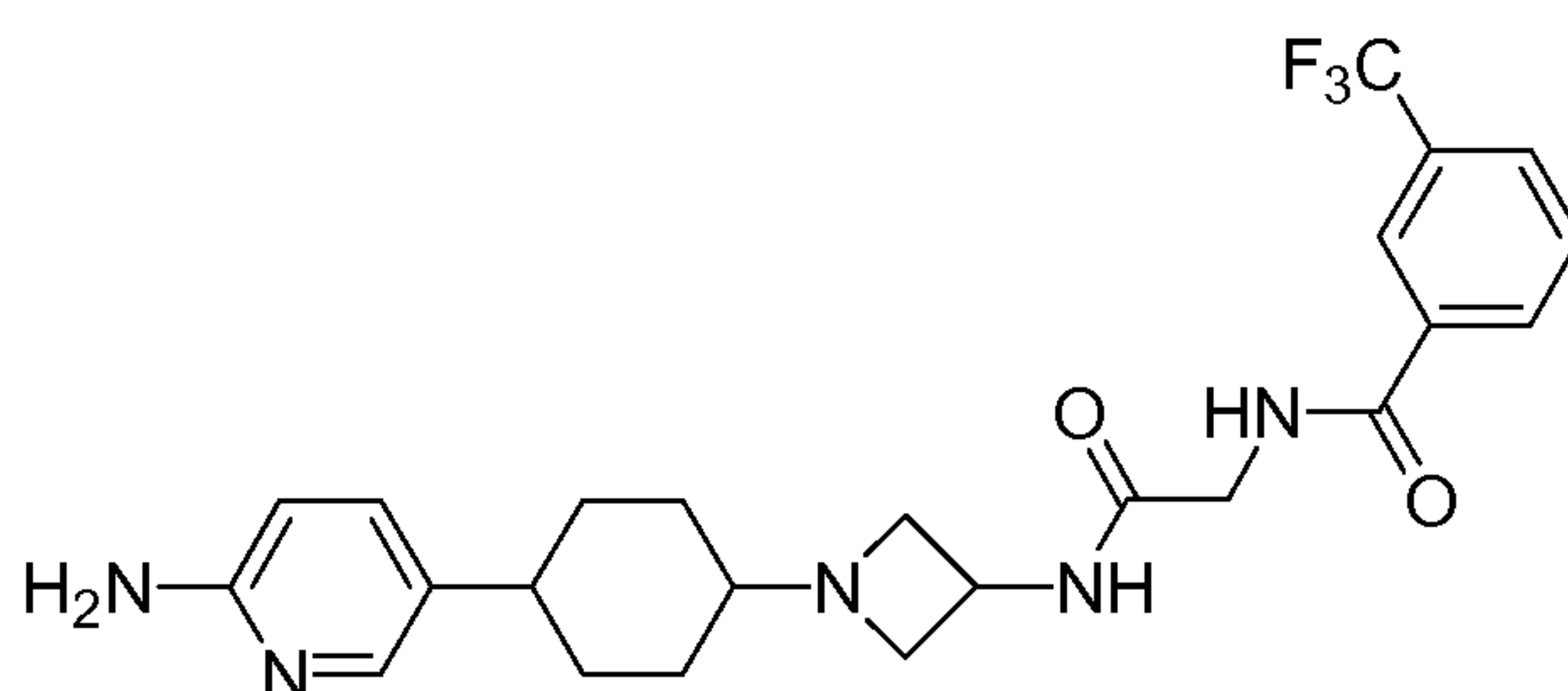
ESI-MS (m/z): Calcd. For C₁₃H₁₈N₂O₂, 234; found: 235 (M+H).

Step C: 4-(6-Amino-pyridin-3-yl)-cyclohexanone

The title compound was prepared as a white solid from the deprotection of 5-(1,4-dioxaspiro[4.5]dec-8-yl)-pyridin-2-ylamine (as prepared in the previous step) using the procedure described in Step B of Example 2.

ESI-MS (m/z): Calcd. For C₁₃H₁₈N₂O₂, 234; found: 235 (M+H).

Step D: N-(1-[4-(6-Amino-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl)-methyl)-3-trifluoromethyl-benzamide



The title compounds were prepared as white solids from the reductive amination of 4-(6-amino-pyridin-3-yl)-cyclohexanone (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

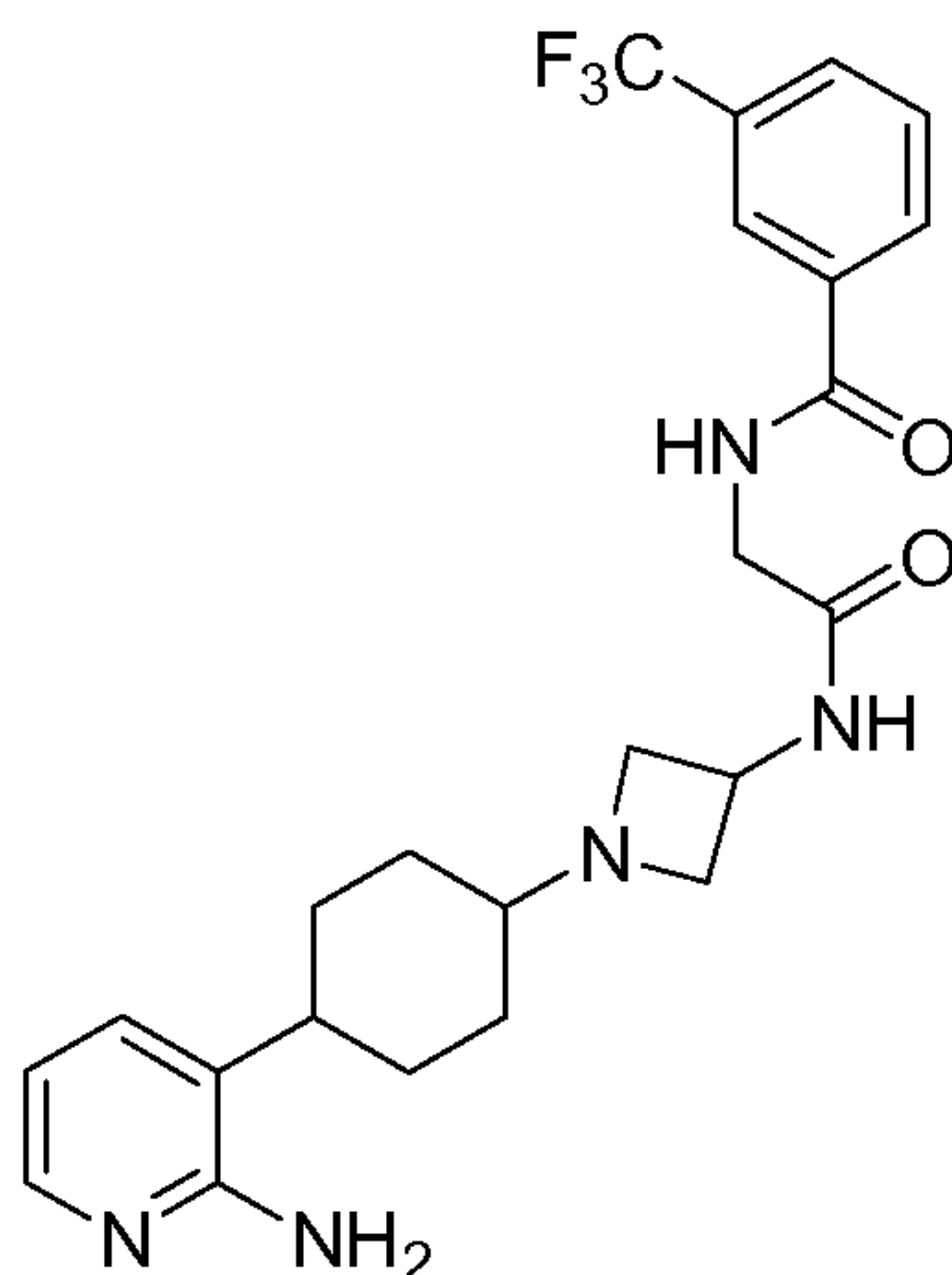
30a: less polar isomer from silica gel column,

¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 8.05 (d, J = 6.8 Hz, 1H), 7.85 (s, 1H), 7.78 (d, J = 6.5 Hz, 1H), 7.65 (t, J = 6.5 Hz, 1H), 7.34 (d, J = 6.5 Hz, 1H), 6.45 (d, J = 5.5 Hz, 1H), 4.48 (m, 1H), 4.05 (d, J = 4.5 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H), 2.95 (t, J = 6.5 Hz, 2H), 2.56 (m, 2H), 2.35 (m, 1H), 1.73 (m, 4H), 1.35 (m, 4H).

30b: more polar isomer from silica gel column

¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 8.05 (d, J = 6.5 Hz, 1H), 7.90 (m, 1H), 7.78 (d, J = 6.6 Hz, 1H), 7.63 (t, J = 6.6 Hz, 1H), 7.35 (d, J = 6.0 Hz, 1H), 4.65 (m, 1H), 4.15 (d, J = 3.5 Hz, 2H), 3.60 (m, J = 6.5 Hz, 2H), 3.20 (m, J = 6.1 Hz, 2H), 2.35 (m, 2H), 2.10 (m, 1H), 2.00 (m, 2H), 1.90 (m, 4H), 1.64 (m, 2H).

Example 31: N-({1-[4-(2-Amino-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



The title compound was prepared according to the procedure described in Example 3:

5 Steps A-D from 3-bromo-pyridin-2-ylamine (Lancaster) as a yellow solid.

31a: less polar isomer,

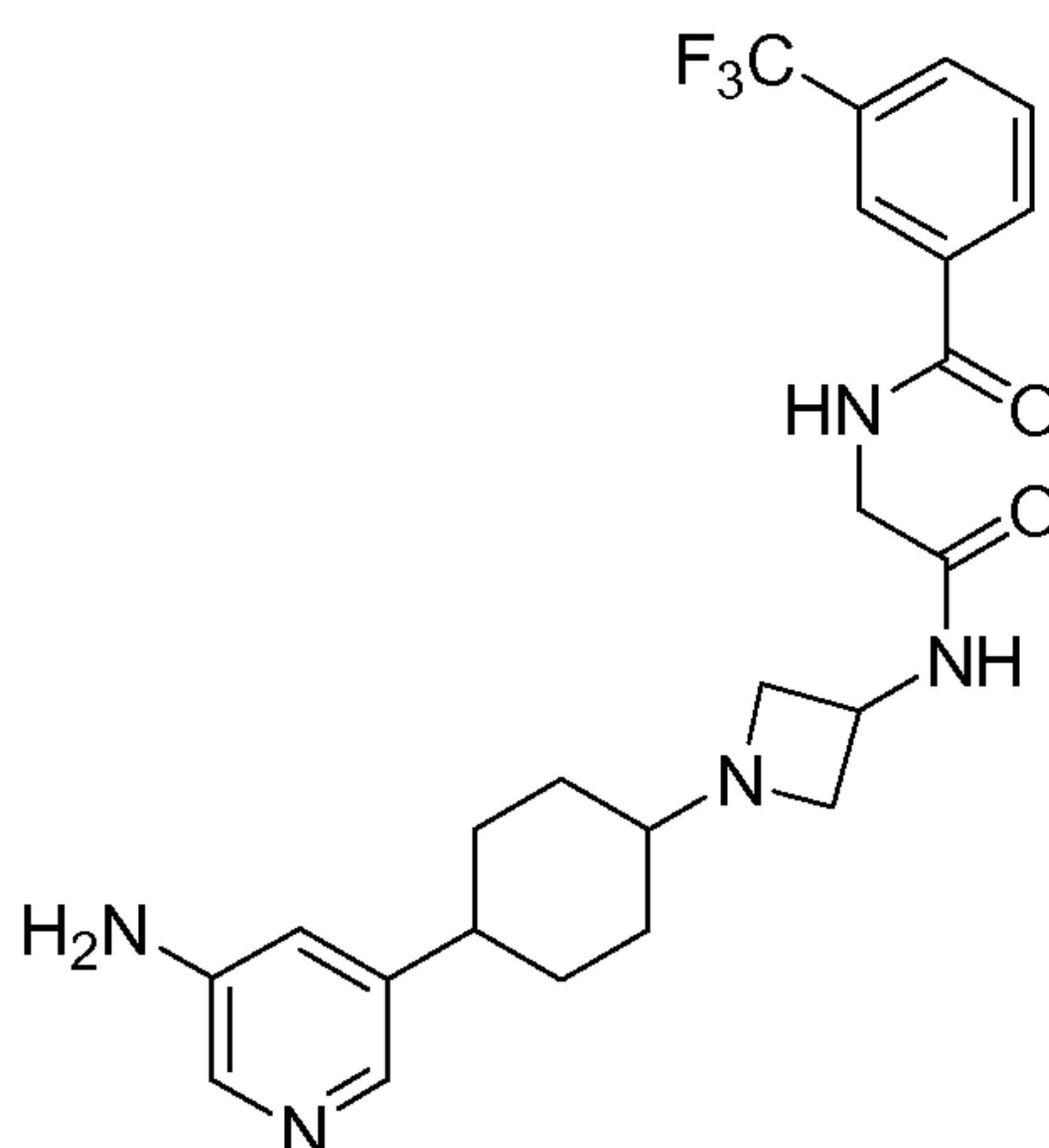
¹H NMR (MeOH) δ: 8.24 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 6.39 (d, J = 8.1 Hz, 1H), 4.50 (quin, J = 7.1 Hz, 1H), 4.06 (s, 2H), 3.68 (t, J = 7.7 Hz, 2H), 2.96 (t, J = 7.6 Hz, 10 2H), 2.46 - 2.62 (m, 1H), 2.42 (t, J = 3.5 Hz, 1H), 1.84 - 1.98 (m, 2H), 1.68 - 1.81 (m, 2H), 1.49 - 1.68 (m, 4H).

31b: more polar isomer

¹H NMR (MeOH) δ: 8.24 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 6.57 (d, J = 7.3 Hz, 1H), 6.39 (d, J = 8.1 Hz, 15 1H), 4.49 (t, J = 7.1 Hz, 1H), 4.06 (s, 2H), 3.68 (t, J = 7.5 Hz, 2H), 2.96 (t, J = 7.5 Hz, 2H), 2.52 - 2.60 (m, 1H), 2.42 (t, J = 3.3 Hz, 1H), 1.83 - 1.99 (m, 2H), 1.72 (d, J = 13.6 Hz, 2H), 1.63 (br. s., 2H), 1.44 - 1.60 (m, 2H)

Example 32: N-({1-[4-(5-Amino-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

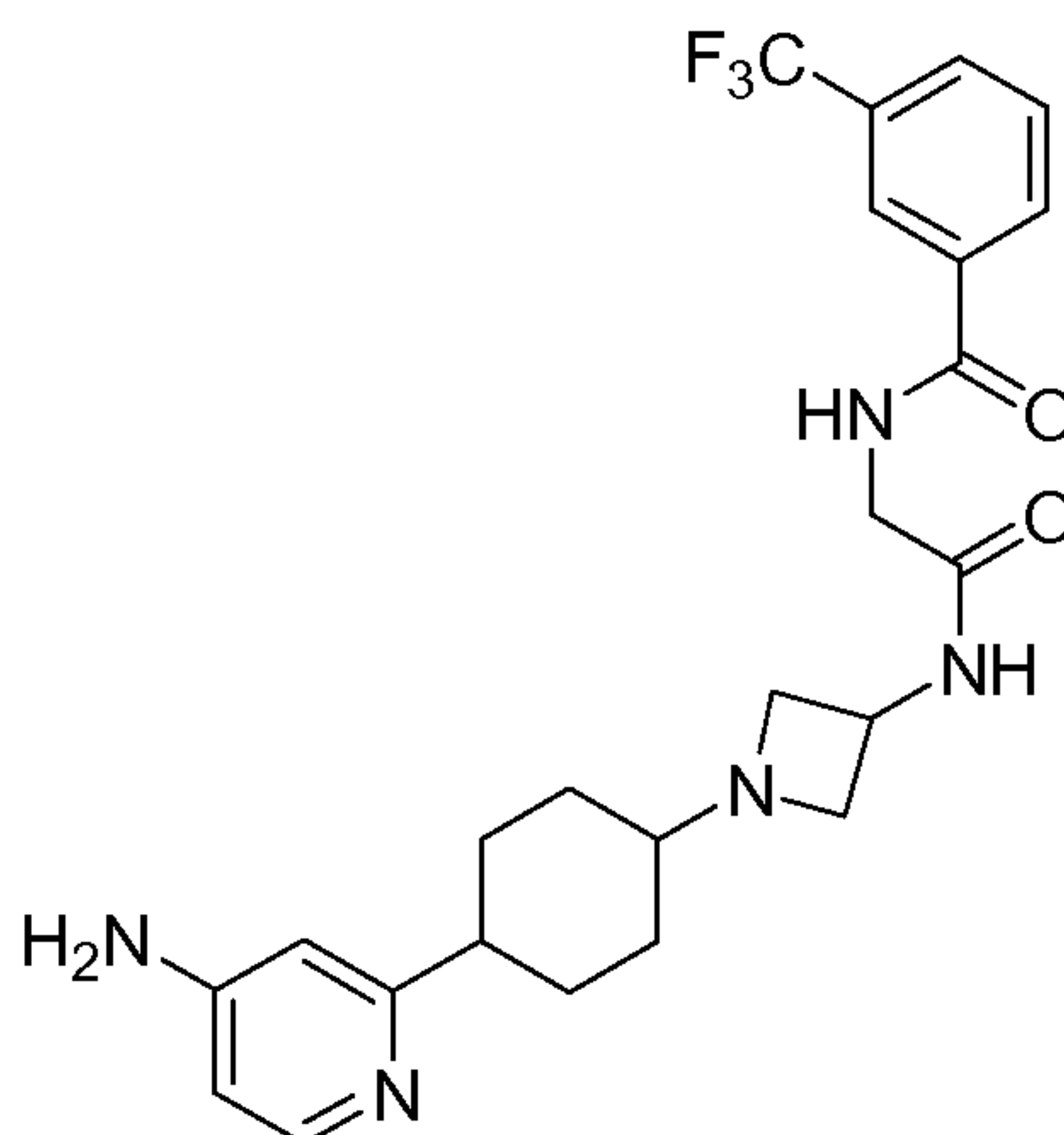
20



The title compound was prepared according to the procedure described in Example 3: Steps A-D from 5-bromo-pyridin-3-ylamine (Aldrich) as a yellow solid.

¹H NMR (MeOH) δ: 8.24 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.80 (s, 1H), 7.65 - 7.77 (m, 2H), 7.05 (s, 1H), 4.38 - 4.57 (m, 1H), 4.05 (s, 2H), 3.62 - 3.76 (m, 2H), 3.03 (br s, 2H), 2.95 (t, J = 7.7 Hz, 2H), 2.38 - 2.47 (m, 2H), 1.79 - 1.92 (m, 2H), 1.74 (br. s., 2H), 1.50 - 1.67 (m, 4H).

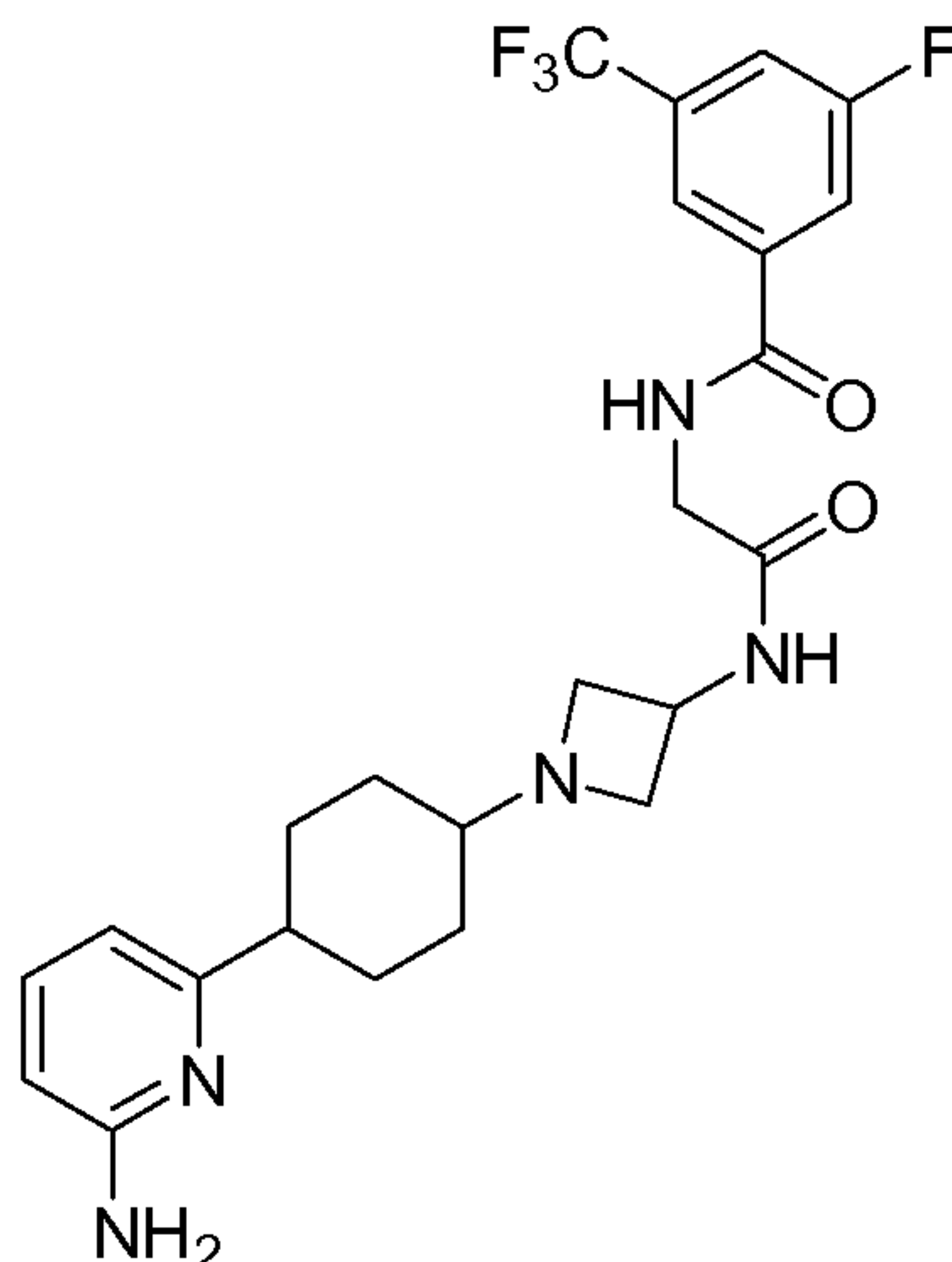
Example 33: N-({1-[4-(4-Amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-yl}carbonyl)-3-(trifluoromethyl)benzamide



The title compound was prepared according to the procedure described in Example 3: Steps A-D from 2-bromo-pyridin-4-ylamine (Aldrich) as a yellow solid.

¹H NMR (MeOH) δ: 8.24 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 2.8 Hz, 1H), 7.66 - 7.77 (m, 2H), 7.05 (t, J = 2.0 Hz, 1H), 4.43 - 4.59 (m, 1H), 4.06 (s, 2H), 3.92 (br. s., 2H), 3.74 (t, J = 7.8 Hz, 2H), 2.96 - 3.08 (m, 1H), 2.46 - 2.59 (m, 1H), 1.85 (d, J = 12.1 Hz, 2H), 1.76 (d, J = 12.6 Hz, 2H), 1.46 - 1.67 (m, 4H).

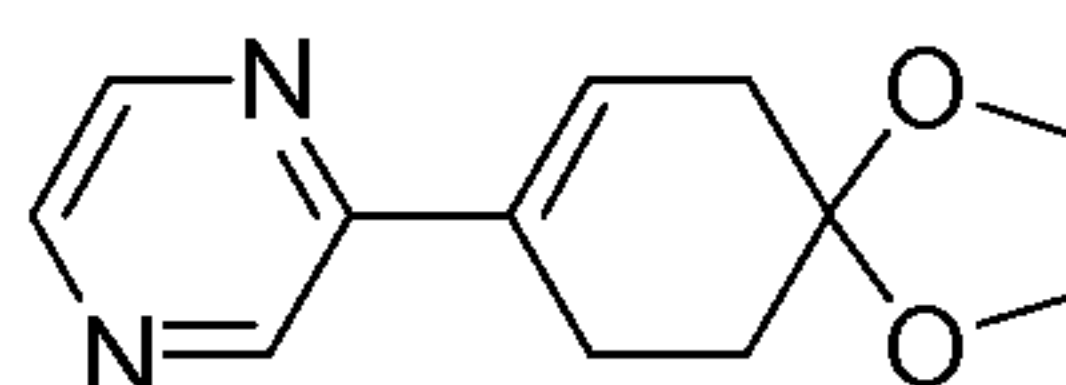
Example 34: N-({1-[4-(6-Amino-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-fluoro-5-trifluoromethyl-benzamide



- 5 The title compounds were prepared as white solids from the reductive amination of 4-(6-amino-pyridin-2-yl)-cyclohexanone (as prepared in Example 22, Step C) and N-(azetidin-3-ylcarbamoylmethyl)-5-fluoro-3-trifluoromethyl-benzamide (analog synthesis by following the procedure described in Organic Synthesis XII, 40-2, 1932) using the procedure described in Step F of Example 1.
- 10 ¹H NMR (MeOH) δ : 7.97 (br. s., 1H), 7.82 (d, J = 9.3 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.15 - 7.34 (m, 1H), 6.37 (d, J = 6.8 Hz, 1H), 6.29 (d, J = 8.1 Hz, 1H), 4.23 - 4.46 (m, 1H), 3.93 (s, 2H), 3.54 - 3.69 (m, 2H), 2.74 - 2.89 (m, 2H), 2.50 (d, J = 7.3 Hz, 1H), 2.18 (s, 1H), 2.12 (br. s., 2H), 1.87 (br. s., 2H), 1.82 (br. s., 4H).

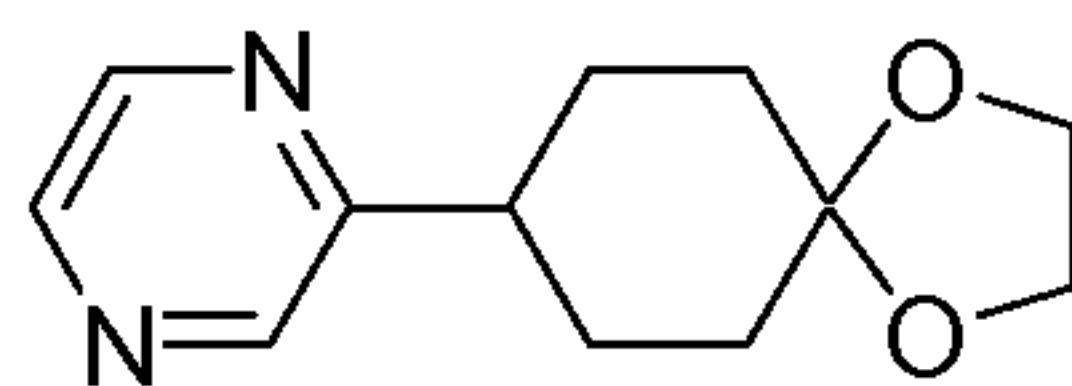
15 **Example 35: N-{{1-[4-Pyrazin-2-yl]-cyclohexyl}-azetidin-3-ylcarbamoyl}-methyl}-3-trifluoromethyl-benzamide**

Step A: 2-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyrazine



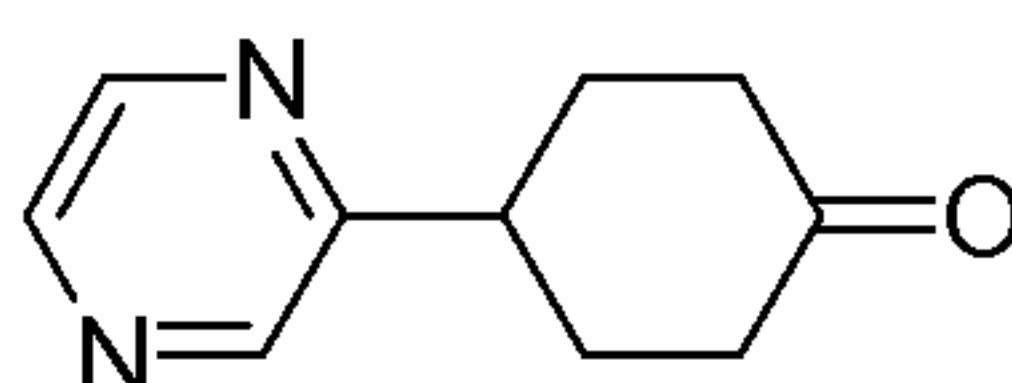
The title compound was prepared as described in Step A of Example 3 from 2-iodo-pyrazine (Aldrich) as a white solid.

ESI-MS (m/z): Calcd. For C₁₂H₁₄N₂O₂, 218; found: 219 (M+H).

Step B: 2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyrazine

The title compound was prepared as a white solid from the hydrogenation of 2-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyrazine (as prepared in the previous step) using the procedure described in Step G of Example 1.

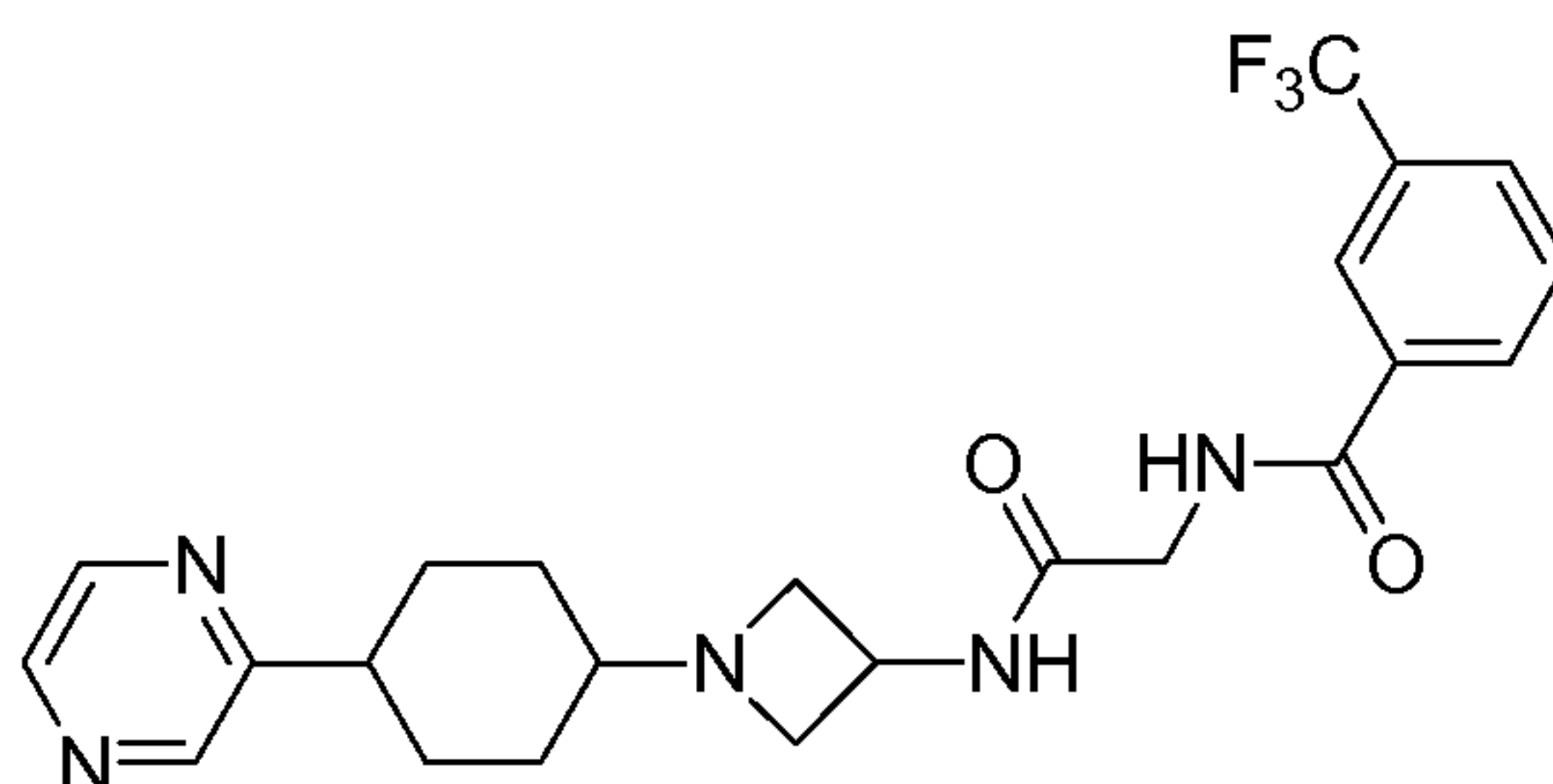
ESI-MS (m/z): Calcd. For $C_{12}H_{16}N_2O_2$, 220; found: 221 ($M+H$).

Step C: 4-Pyrazin-2-yl-cyclohexanone

The title compound was prepared as a white solid from the de-protection of 2-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyrazine (as prepared in the previous step) using the procedure described in Step B of Example 2.

^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, $J = 6.0$ Hz, 2H), 8.47 (s, 1H), 3.25 (m, 1H), 2.51 (m, 4H), 2.30 (m, 2H), 2.15 (m, 2H).

Step D: N-{[1-(4-Pyrazin-2-yl-cyclohexyl)-azetidin-3-ylcarbamoyl]-methyl}-3-trifluoromethyl-benzamide



The title compounds were prepared as white solids from the reductive amination of 4-pyrazin-2-yl-cyclohexanone (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

35a: less polar isomer

^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (m, 2H), 8.40 (s, 1H), 8.15 (s, 1H), 8.05 (d, $J = 6.5$ Hz, 1H), 7.75 (d, $J = 6.6$ Hz, 1H), 7.55 (t, $J = 6.6$ Hz, 1H), 4.50 (m, 1H), 4.20 (d, $J = 4.0$

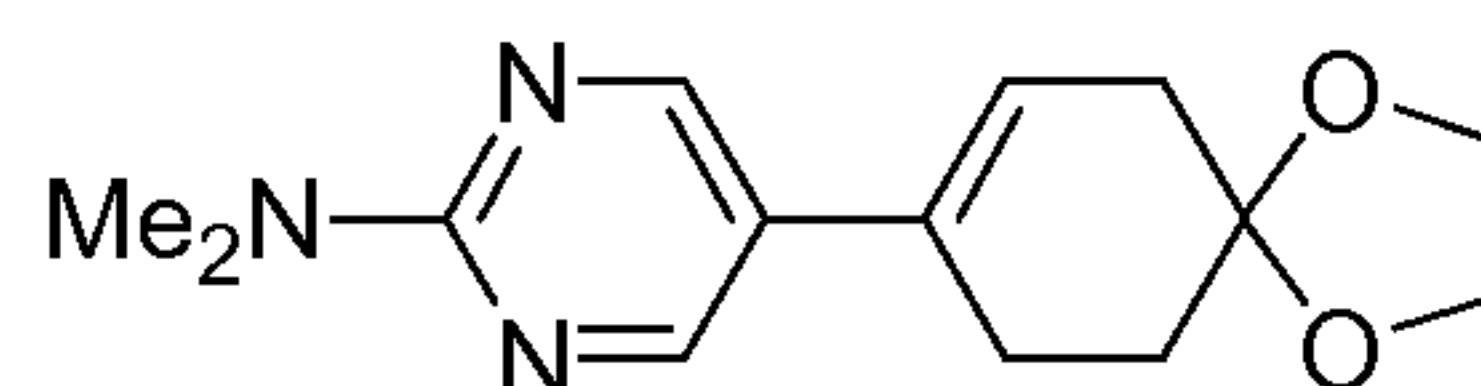
Hz, 2H), 3.60 (t, J = 7.0 Hz, 2H), 3.05 (t, J = 7.0 Hz, 2H), 2.80 (m, 1H), 2.40 (s, 1H), 2.02 (m, 4H), 1.70 (m, 2H), 1.45 (m, 2H).

35b: more polar isomer

¹H NMR (400 MHz, CDCl₃) δ 8.40 (m, 2H), 8.38 (s, 1H), 8.30 (s, 1H), 8.25 (d, J = 6.5 Hz, 1H), 8.10 (s, 1H), 8.01 (d, J = 6.5 Hz, 1H), 7.90 (d, J = 6.6 Hz, 1H), 7.75 (t, J = 6.6 Hz, 1H), 7.58 (t, J = 6.6 Hz, 1H), 4.52 (m, 1H), 4.21 (d, J = 4.0 Hz, 2H), 3.60 (t, J = 7.0 Hz, 2H), 2.95 (t, J = 7.0 Hz, 2H), 2.80 (m, 1H), 2.30 (s, br, 1H), 2.05 (m, 2H), 1.75 (m, 2H), 1.50 (m, 2H), 1.31 (m, 2H).

Example 36: N-({1-[4-(2-Dimethylamino-pyrimidin-5-yl)-cyclohexyl]-azetidin-3-ylcarbonyl}-methyl)-3-trifluoromethyl-benzamide

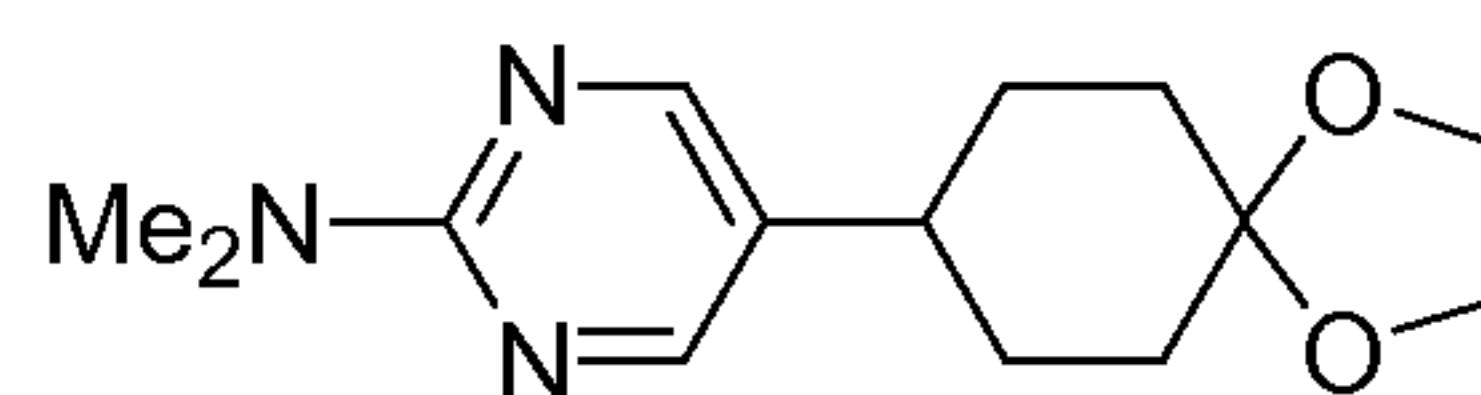
Step A: [5-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyrimidin-2-yl]-dimethyl-amine



The title compound was prepared as described in Step A of Example 3 from (5-bromopyrimidin-2-yl)-dimethyl-amine (Aldrich) as a white solid.

ESI-MS (m/z): Calcd. For C₁₄H₁₉N₃O₂, 261; found: 262 (M+H).

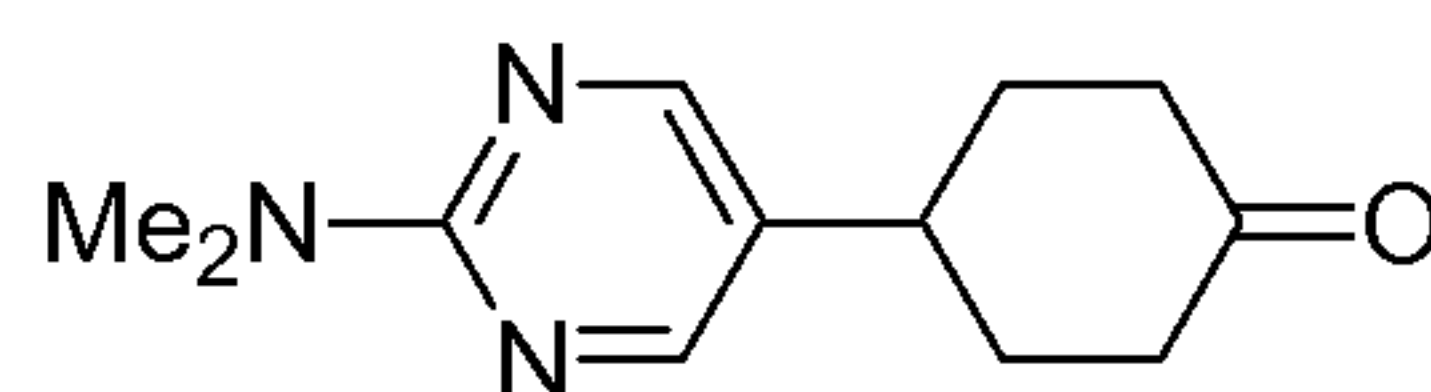
Step B: [5-(1,4-Dioxo-spiro[4.5]dec-8-yl)-pyrimidin-2-yl]-dimethyl-amine



The title compound was prepared as a white solid from the hydrogenation of [5-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyrimidin-2-yl]-dimethyl-amine (as prepared in the previous step) using the procedure described in Step G of Example 1.

¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 3.98 (s, 4H), 3.17 (s, 6H), 2.42 (m, 1H), 1.85 (m, 4H), 1.70 (m, 4H).

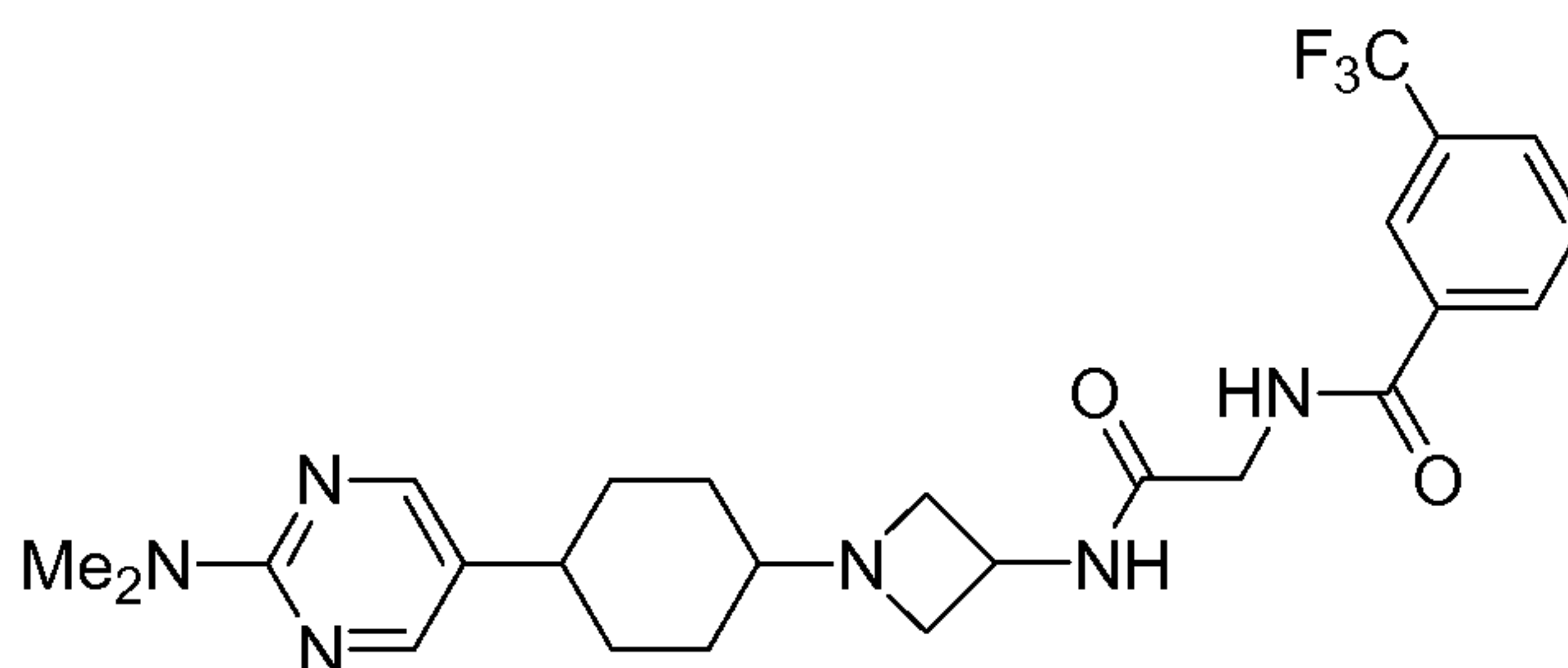
Step C: 4-(2-Dimethylamino-pyrimidin-5-yl)-cyclohexanone



The title compound was prepared as a white solid from the de-protection of [5-(1,4-dioxo-spiro[4.5]dec-8-yl)-pyrimidin-2-yl]-dimethyl-amine (as prepared in the previous step) using the procedure described in Step B of Example 2.

¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 3.20 (s, 6H), 2.90 (m, 1H), 2.50 (m, 4H),
5 2.18 (m, 2H), 1.92 (m, 2H).

Step D: N-({1-[4-(2-Dimethylamino-pyrimidin-5-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



10 The title compounds were prepared as white solids from the reductive amination of 4-(2-dimethylamino-pyrimidin-5-yl)-cyclohexanone (as prepared in the previous step) and N-(azetidin-3-ylcarbamoymethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

36a: less polar isomer,

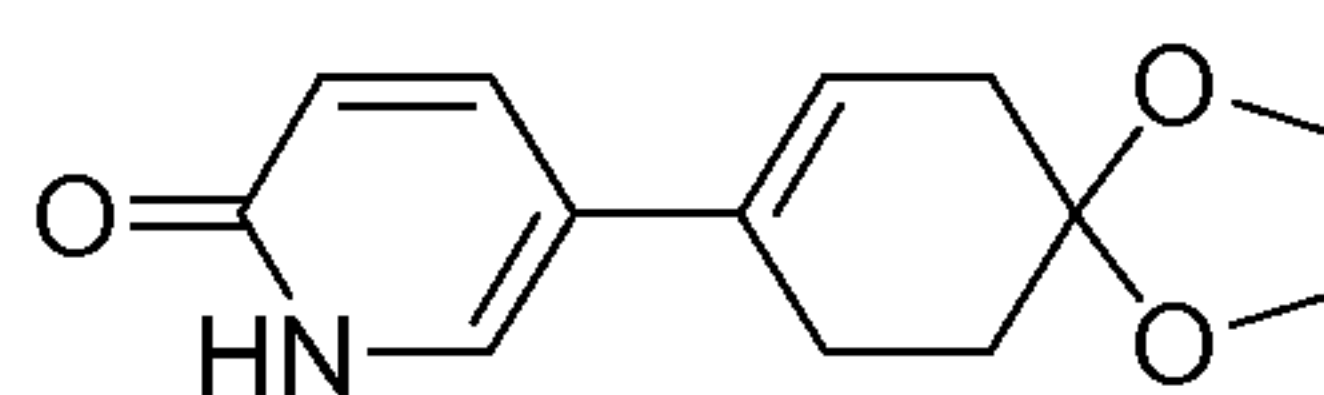
15 ¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 2H), 8.10 (s, 1H), 8.00 (d, J = 6.5 Hz, 1H), 7.80 (d, J = 6.6 Hz, 1H), 7.52 (m, 2H), 7.20 (m, 1H), 7.15 (d, J = 5.1 Hz, 1H), 4.55 (m, 1H), 4.20 (d, J = 4.0 Hz, 2H), 3.65 (t, J = 7.0 Hz, 2H), 3.20 (s, 6H), 2.85 (t, J = 7.0 Hz, 2H), 2.35 (m, 1H), 2.30 (s, 1H), 1.80 (m, 2H), 1.65 (m, 2H), 1.48 (m, 4H).

36b: more polar isomer

20 ¹H NMR (400 MHz, CDCl₃) δ 8.25 (s, 1H), 8.18 (s, 1H), 8.08 (d, J = 6.5 Hz, 1H), 7.78 (d, J = 6.6 Hz, 1H), 7.55 (m, 2H), 7.45 (m, 1H), 4.52 (m, 1H), 4.20 (d, J = 4.0 Hz, 2H), 3.65 (t, J = 7.0 Hz, 2H), 3.20 (s, 6H), 3.10 (t, J = 7.0 Hz, 2H), 2.60 (m, 1H), 2.30 (s, 1H), 2.02 (m, 2H), 1.70 (m, 2H), 1.55 (m, 2H), 1.26 (m, 2H).

25 **Example 37: N-({1-[4-(6-Oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoymethyl}-methyl)-3-trifluoromethyl-benzamide**

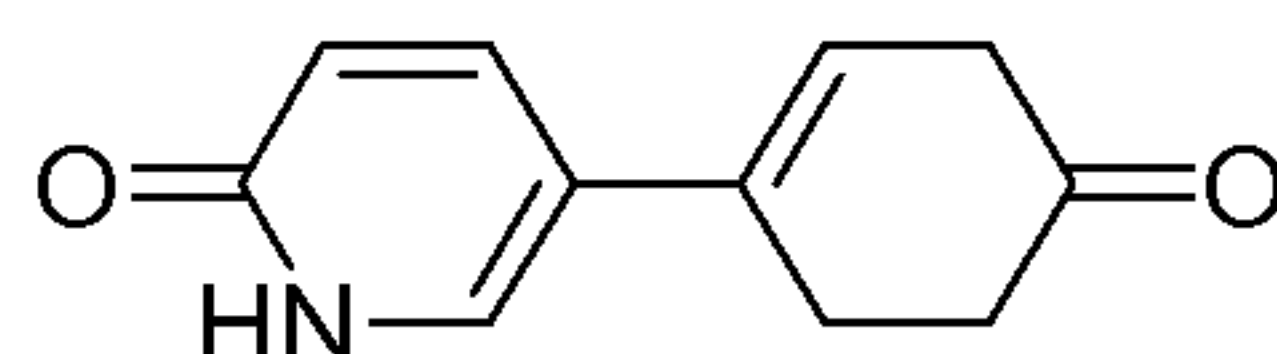
Step A: 5-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-1H-pyridin-2-one



The title compound was prepared as described in Step A of Example 3 from 5-iodo-1H-pyridin-2-one (Aldrich) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, J = 6.5 Hz, 1H), 7.52 (d, J = 6.2 Hz, 1H), 7.48 (d, J = 5.0 Hz, 1H), 7.42 (t, J = 6.2 Hz, 1H), 6.45 (t, J = 4.5 Hz, 1H), 4.02 (s, 4H), 2.35 (m, 2H), 2.27 (m, 2H), 1.75 (m, 2H).

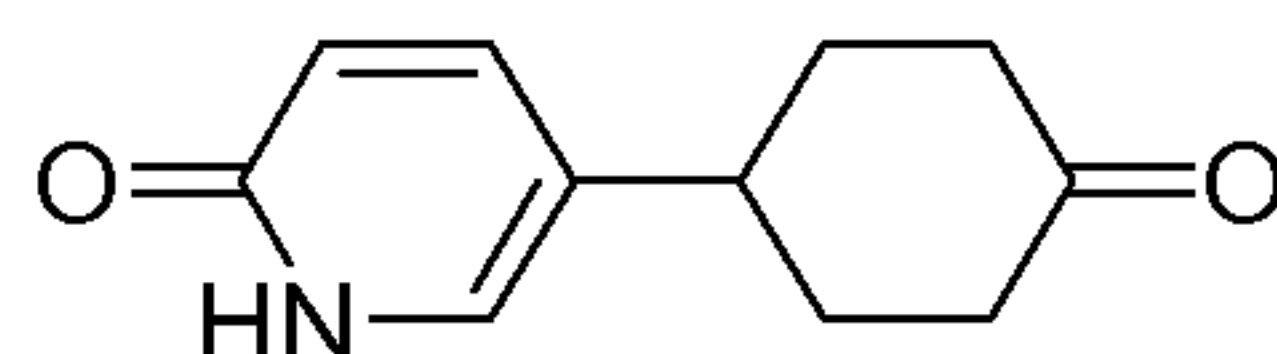
Step B: 5-(4-Oxo-cyclohex-1-enyl)-1H-pyridin-2-one



The title compound was prepared as a white solid from the de-protection of 5-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step B of Example 2.

¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, J = 6.8 Hz, 1H), 7.40 (s, 1H), 6.61 (s, J = 7.0 Hz, 1H), 5.98 (m, 1H), 3.05 (s, 2H), 2.75 (t, J = 5.8 Hz, 2H), 2.66 (t, J = 6.3 Hz, 2H).

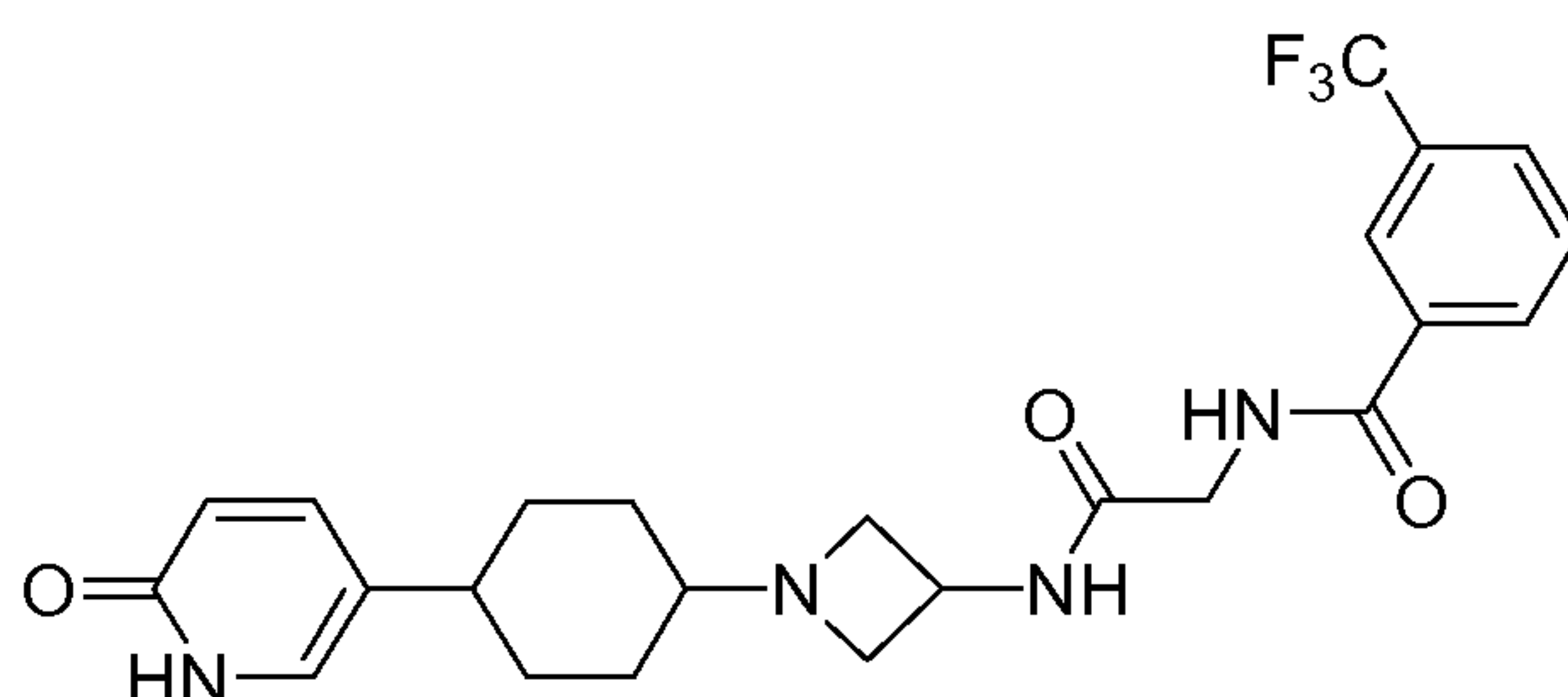
Step C: 5-(4-Oxo-cyclohexyl)-1H-pyridin-2-one



The title compound was prepared as a white solid from the hydrogenation of 5-(4-oxo-cyclohex-1-enyl)-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step G of Example 1.

¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.52 (d, J = 6.6 Hz, 1H), 7.23 (d, J = 6.5 Hz, 1H), 2.55 (m, 4H), 2.25 (m, 1H), 1.67 (m, 4H).

Step D: N-({1-[4-(6-Oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-yl}carbonyl)-3-methyl-3-trifluoromethyl-benzamide



The title compounds were prepared as white solids from the reductive amination of 5-(4-oxo-cyclohexyl)-1H-pyridin-2-one (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

37a: less polar isomer,

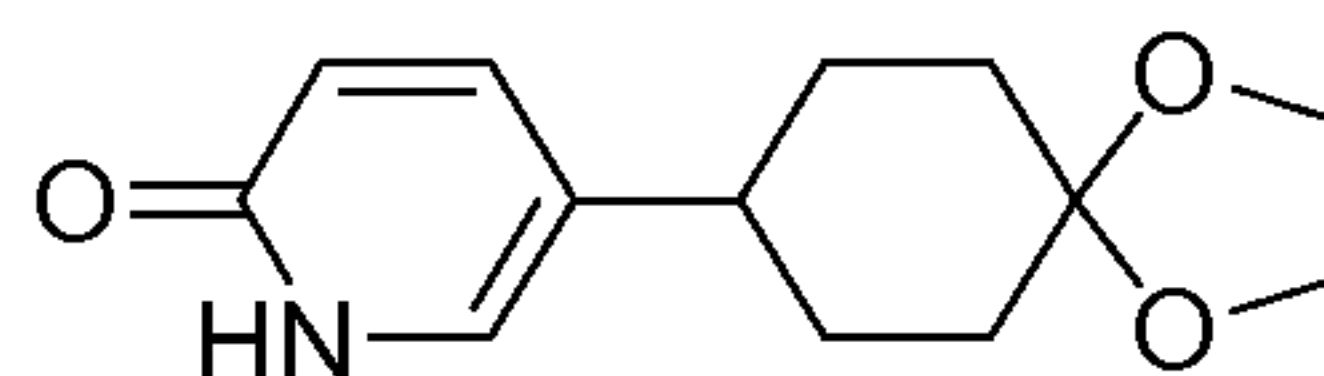
¹H NMR (400 MHz, CDCl₃) δ 8.25 (s, br, 1H), 8.20 (s, 1H), 8.09 (d, J = 6.0 Hz, 1H), 7.78 (d, J = 6.2 Hz, 1H), 7.61 (t, J = 6.2 Hz, 1H), 7.45 (m, 1H), 7.40 (d, J = 6.2 Hz, 1H), 7.18 (s, 1H), 6.52 (d, J = 6.4 Hz, 1H), 4.55 (m, 1H), 4.21 (d, J = 4.3 Hz, 2H), 3.58 (t, J = 5.2 Hz, 2H), 2.99 (t, J = 4.2 Hz, 2H), 2.35 (m, 2H), 1.80 (m, 2H), 1.65 (m, 2H), 1.48 (m, 4H).

37b: more polar isomer

¹H NMR (400 MHz, CDCl₃) δ 9.35 (s, br, 1H), 8.15 (s, 1H), 8.05 (d, J = 6.2 Hz, 1H), 7.80 (d, J = 6.2 Hz, 1H), 7.60 (t, J = 6.5 Hz, 1H), 7.40 (d, J = 6.5 Hz, 1H), 7.10 (s, 1H), 6.55 (d, J = 6.4 Hz, 1H), 4.58 (m, 1H), 4.15 (d, J = 4.5 Hz, 2H), 3.68 (t, J = 6.5 Hz, 2H), 3.25 (t, J = 6.0 Hz, 2H), 2.36 (m, 1H), 2.32 (m, 1H), 1.80 (4, 2H), 1.56 (m, 2H), 1.32 (m, 2H).

Example 38: N-({1-[4-(1-Methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

Step A: 5-(1,4-Dioxo-spiro[4.5]dec-8-yl)-1H-pyridin-2-one



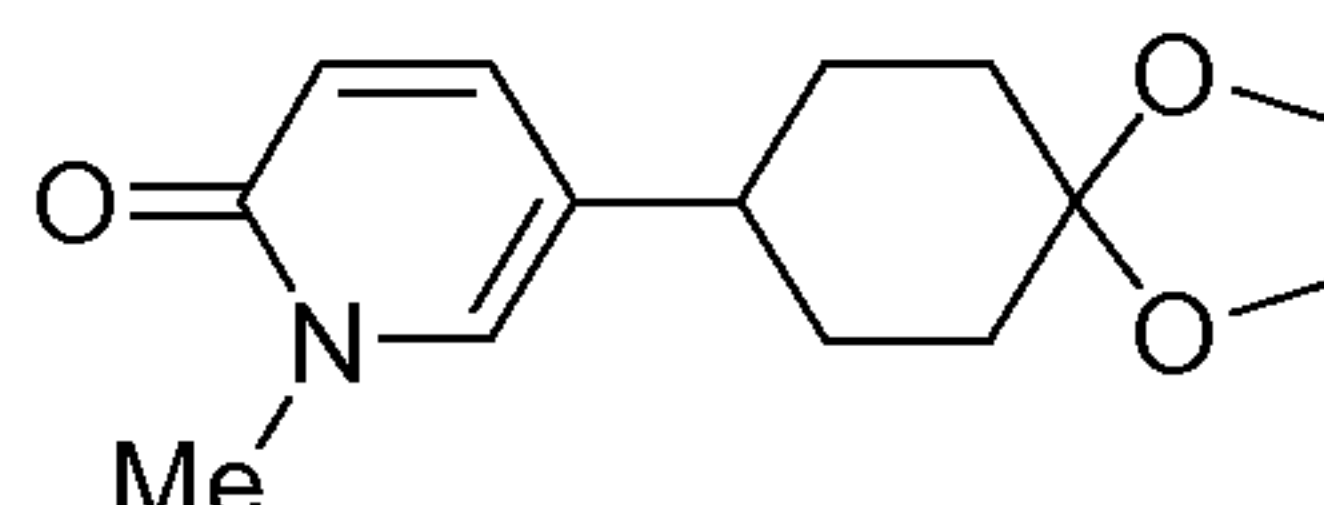
5-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-1H-pyridin-2-one from Step A of Example 37 (5.2 g, 22.1 mmol) in ethyl acetate (30 mL) was treated with 5% Pd/C (Aldrich, 2.6 g) at room temperature. The reaction mixture was then charged with a hydrogen balloon and stirred for 2 hours. The catalyst was removed by filtering the reaction through a pad of

Celite. The filtrate was concentrated to give the crude product, which was then purified with a CombiFlash® system using silica gel column and 40% ethyl acetate in hexanes as eluent to give the title compound as a white solid.

ESI-MS (m/z): Calcd. For C₁₃H₁₇NO₃, 235; found: 236 (M+H), 258 (M+Na).

5

Step B: 5-(1,4-Dioxo-spiro[4.5]dec-8-yl)-1-methyl-1H-pyridin-2-one



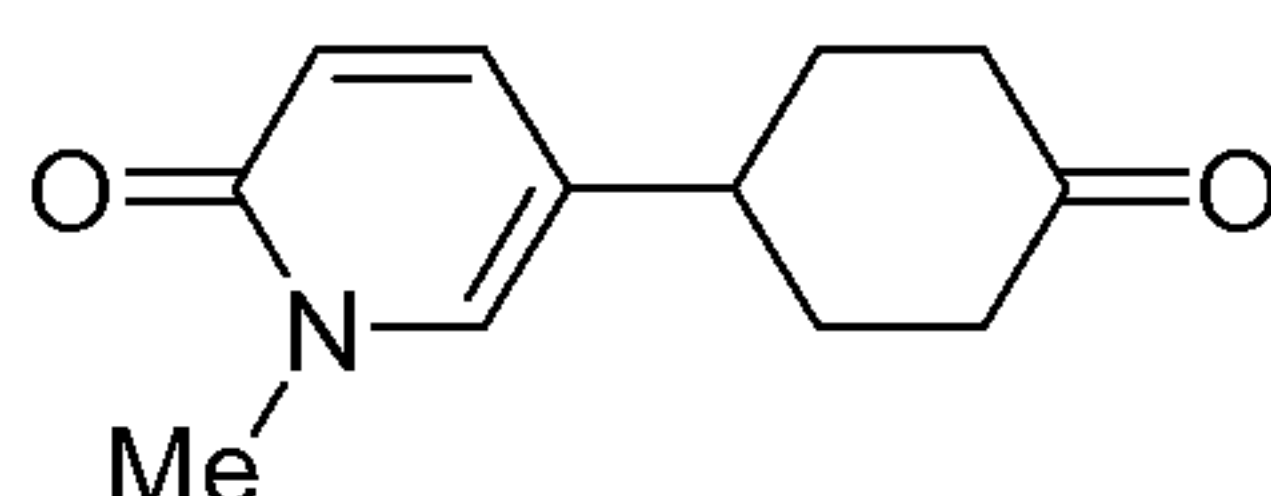
A solution of 5-(1,4-dioxo-spiro[4.5]dec-8-yl)-1H-pyridin-2-one (as prepared in the previous step, 750 mg, 3.19 mmol) in DMF (5mL) was treated with Cs₂CO₃ (Aldrich, 1.56 g, 4.80 mmol) at room temperature for 10 min. MeI (Aldrich, 330 µL, 4.80 mmol) was added into the reaction solution and heated at 70 °C for 6 hours. The reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give yellow oil, which was then purified by silica gel column on a CombiFlash® system using hexanes and ethyl acetate (from 10% ethyl acetate to 100% ethyl acetate) to afford the title compound as a white solid along with O-allylated product, 5-(1,4-dioxo-spiro[4.5]dec-8-yl)-2-methoxy-pyridine.

15

ESI-MS (m/z): Calcd. For C₁₄H₁₉NO₃, 249; found: 250 (M+H).

20

Step C: 1-Methyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one

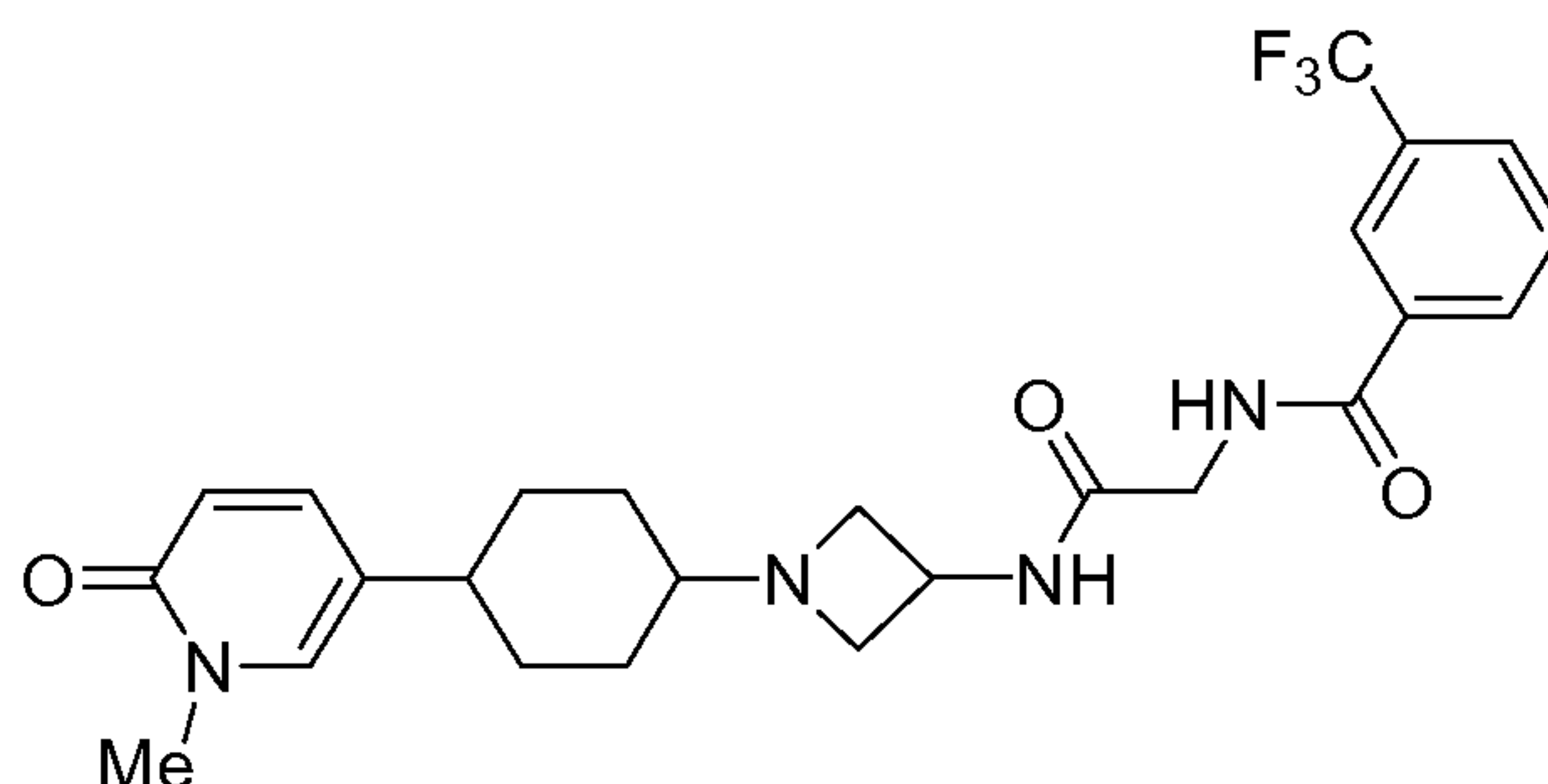


The title compound was prepared as a white solid from the de-protection of 5-(1,4-dioxo-spiro[4.5]dec-8-yl)-1-methyl-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step B of Example 2.

25

¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, J = 6.5 Hz, 1H), 7.18 (s, 1H), 6.57 (d, J = 6.5 Hz, 1H), 3.52 (s, 3H), 2.80 (m, 1H), 2.44 (d, J = 6.0 Hz, 4H), 2.21 (m, 2H), 1.80 (m, 2H).

Step D: *N*-(*{1-[4-(1-Methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}*-methyl)-3-trifluoromethyl-benzamide



The title compounds were prepared as white solids from the reductive amination of 1-methyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

38a: Less polar isomer

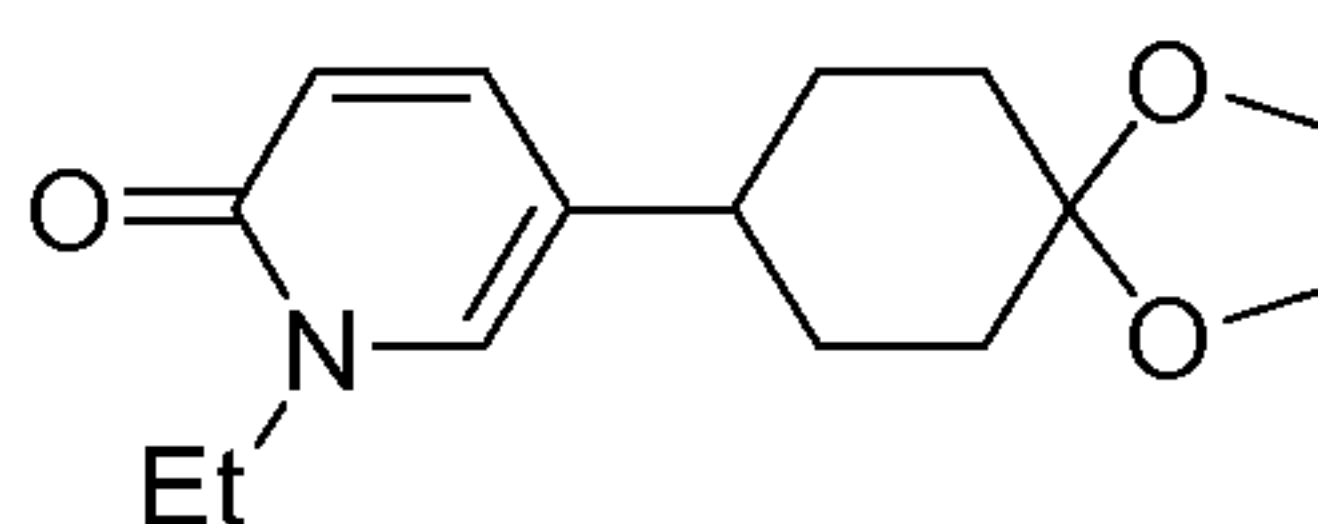
¹H NMR (400 MHz, CDCl₃) δ 8.12 (s, 1H), 8.02 (d, J = 6.2 Hz, 1H), 7.78 (d, J = 6.5 Hz, 1H), 7.66 (s, 1H), 7.57 (t, J = 6.5 Hz, 1H), 7.30 (d, J = 6.6 Hz, 1H), 7.20 9s, br, 1H), 7.08 (s, 1H), 7.48 (d, J = 6.7 Hz, 1H), 4.52 (m, 1H), 4.18 (d, J = 4.5 Hz, 2H), 3.58 (t, J = 6.0 Hz, 2H), 3.48 (s, 3H), 2.80 (t, J = 6.0 Hz, 2H), 2.25 (m, 1H), 1.69 (m, 4H), 1.45 (m, 4H).

38b: more polar isomer

¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 8.04 (d, J = 6.2 Hz, 1H), 7.70 (d, J = 6.5 Hz, 1H), 6.65 (s, 1H), 6.56 (t, J = 7.0 Hz, 1H), 7.33 (s, br, 1H), 7.18 (d, J = 6.8 Hz, 1H), 6.98 (s, 1H), 6.48 (d, J = 6.6 Hz, 1H), 4.50 (m, 1H), 4.12 (d, J = 4.5 Hz, 2H), 3.60 (d, J = 7.1 Hz, 2H), 3.42 (s, 3H), 3.05 (t, J = 7.0 Hz, 2H), 2.20 (m, 1H), 1.85 (m, 4H), 1.25 (m, 2H), 1.10 (m, 2H).

Example 39: *N*-(*{1-[4-(1-Ethyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}*-methyl)-3-trifluoromethyl-benzamide

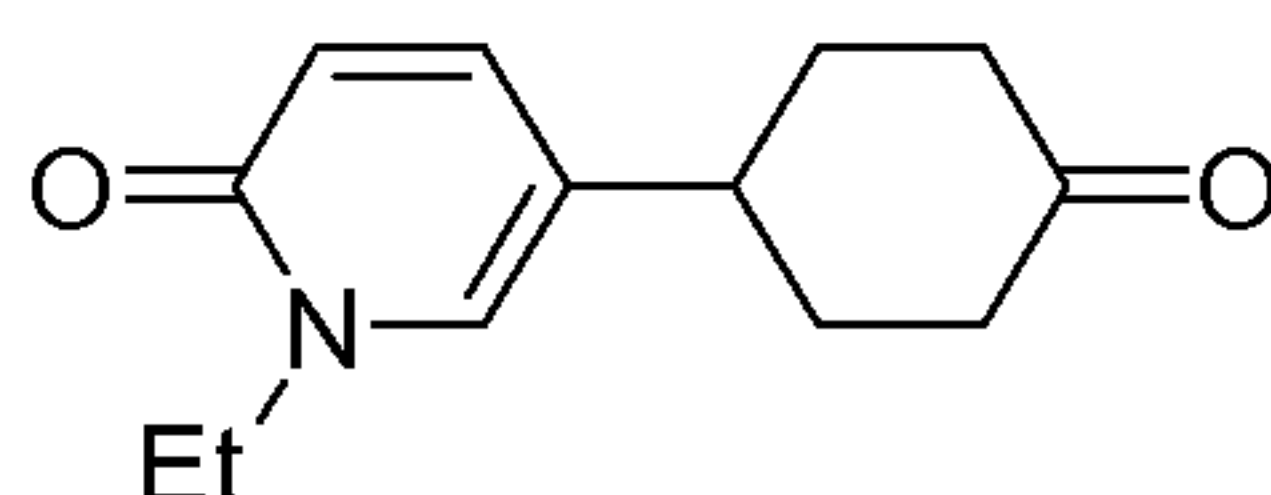
Step A: 5-(1,4-Dioxo-spiro[4.5]dec-8-yl)-1-ethyl-1H-pyridin-2-one



The title compound was prepared as a white solid from the ethylation of 5-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1H-pyridin-2-one with EtI (Aldrich) using the procedure described in Step B of Example 38.

¹H NMR (400 MHz, CDCl₃) δ 7.90 (s, 1H), 7.75 (d, J = 6.0 Hz, 1H), 6.60 (d, J = 6.2 Hz, 1H), 4.00 (q, J = 6.5 Hz, 2H), 3.98 (m, 4H), 2.75 (m, 1H), 2.10 (m, 2H), 1.75 (m, 4H), 1.64 (m, 2H), 1.45 (t, J = 6.5 Hz, 3H).

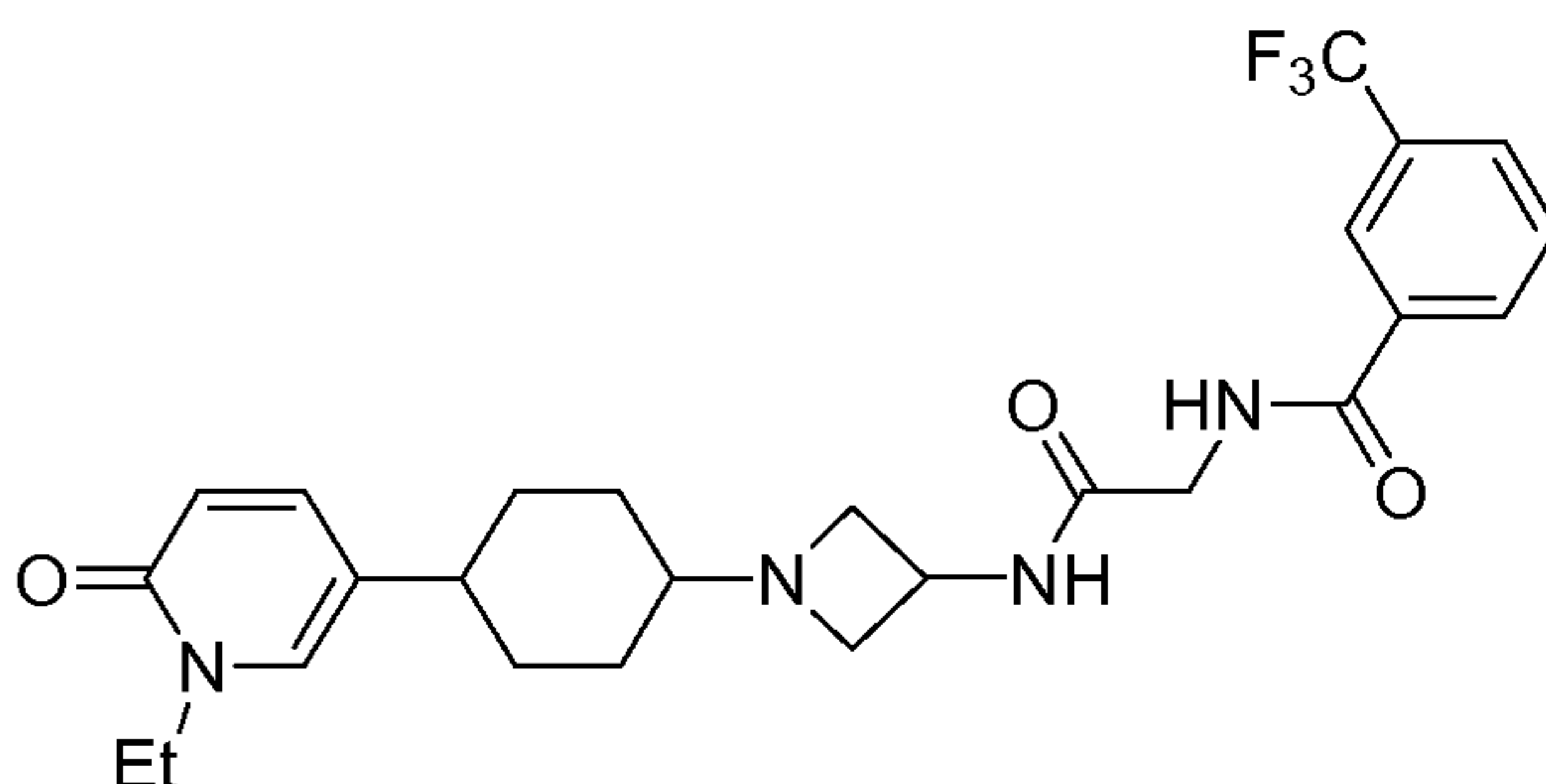
Step B: 1-Ethyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one



The title compound was prepared as a white solid from the deprotection of 5-(1,4-dioxaspiro[4.5]dec-8-yl)-1-ethyl-1H-pyridin-2-one using the procedure described in Step B of Example 2.

¹H NMR (400 MHz, CDCl₃) δ 7.95 (s, 1H), 7.80 (d, J = 6.5 Hz, 1H), 6.60 (d, J = 6.8 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 2.80 (m, 1H), 2.65 (m, 2H), 2.34 (m, 2H), 2.05 (m, 4H), 1.42 (t, J = 7.0 Hz, 3H).

Step C: N-({1-[4-(1-Ethyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-yl}carbonyl)-methyl)-3-trifluoromethyl-benzamide



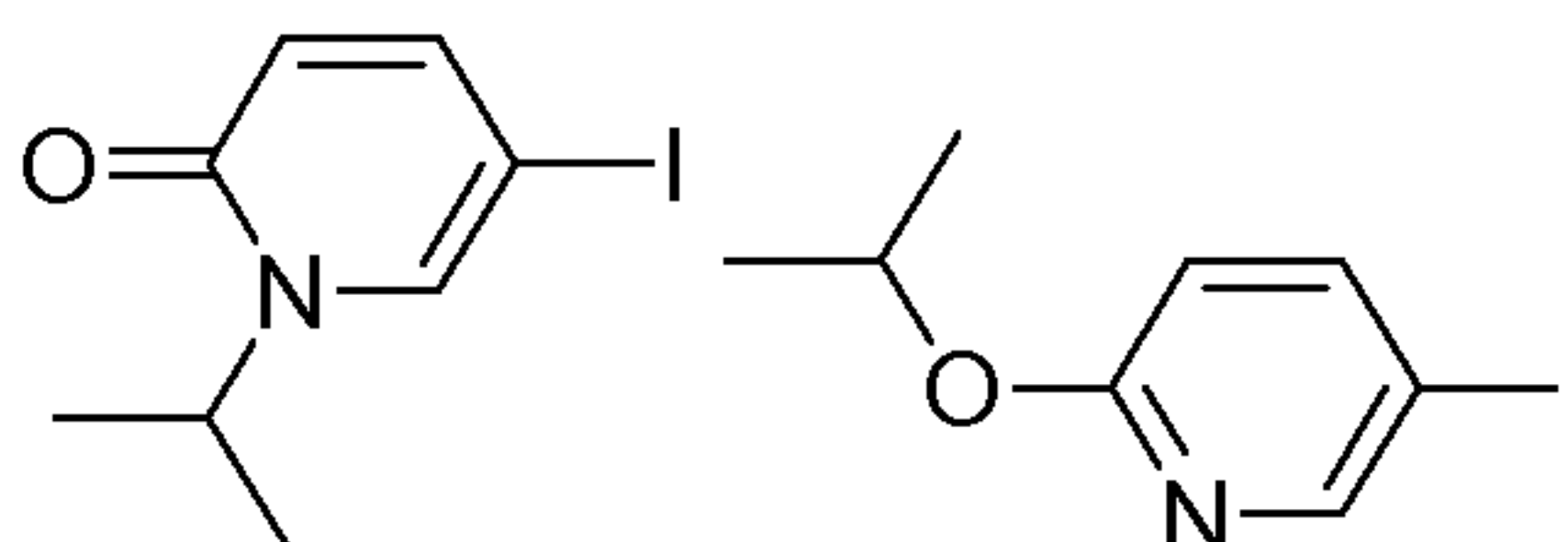
The title compounds were prepared as white solids from the reductive amination of 1-ethyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one (as prepared in the previous step) and N-(azetidin-3-ylcarbonylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

¹H NMR (400 MHz, *d*₄-MeOH) δ 8.18 (s, 1H), 8.08 (d, J = 6.5 Hz, 1H), 7.78 (d, J = 6.4 Hz, 1H), 7.60 (t, J = 6.5 Hz, 1H), 7.15 (d, J = 7.0 Hz, 2H), 7.02 (d, J = 3.0 Hz, 2H), 6.05

(d, J = 7.0 Hz, 1H), 4.51 (m, 1H), 4.25 (s, 2H), 4.10 (s, 2H), 3.98 (q, J = 7.5 Hz, 2H), 3.60 (t, J = 6.5 Hz, 2H), 3.05 (t, J = 6.0 Hz, 2H), 2.48 (m, 1H), 2.45 (m, 1H), 1.75 (m, 4H), 1.55 (m, 4H), 1.32 (t, J = 7.5 Hz, 3H).

5 **Example 40: N-({1-[4-(1-Isopropyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide**

Step A: 5-Iodo-1-isopropyl-1H-pyridin-2-one and 5-Iodo-2-isopropoxy-pyridine



The title compounds were prepared as white solids from the iso-propylation of 5-iodo-1H-pyridin-2-one with i-PrI (Aldrich) using the procedure described in Step A of Example 38.

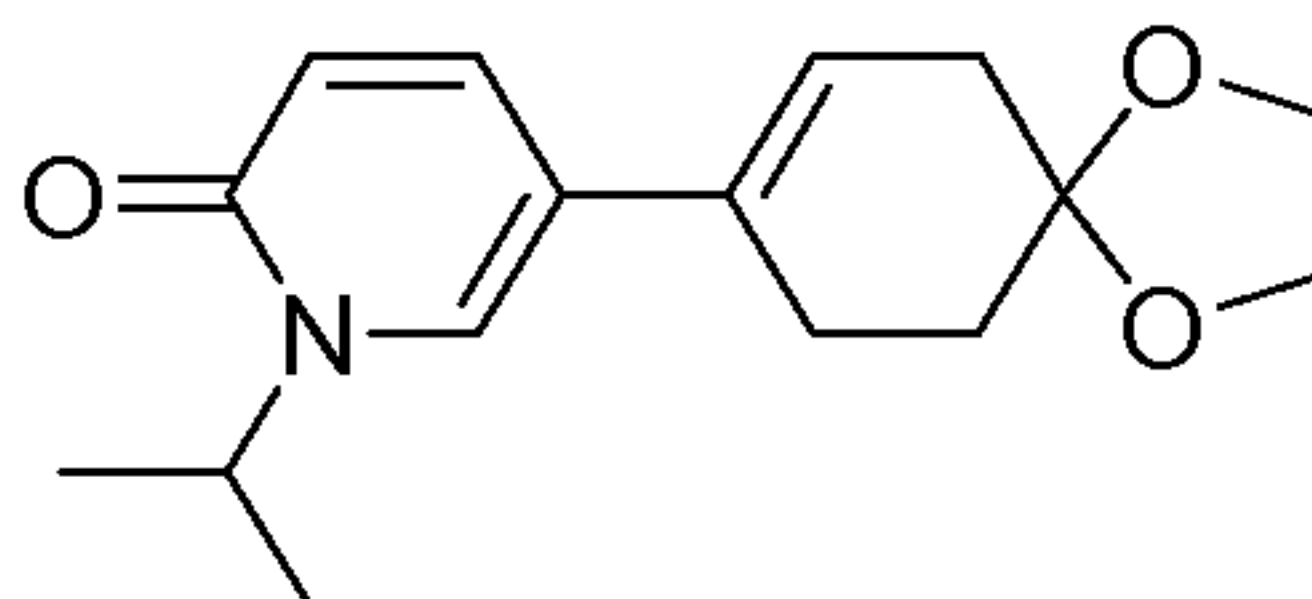
5-Iodo-1-isopropyl-1H-pyridin-2-one

¹H NMR (400 MHz, CDCl₃) δ 7.60 (s, 1H), 7.48 (d, J = 6.5 Hz, 1H), 6.38 (d, J = 6.6 Hz, 1H), 5.02 (m, 1H), 1.42 (d, J = 8.5 Hz, 6H).

15 5-Iodo-2-isopropoxy-pyridine

¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.75 (d, J = 6.8 Hz, 1H), 6.48 (d, J = 6.5 Hz, 1H), 5.22 (m, 1H), 1.36 (d, J = 6.5 Hz, 6H).

Step B: 5-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-1-isopropyl-1H-pyridin-2-one



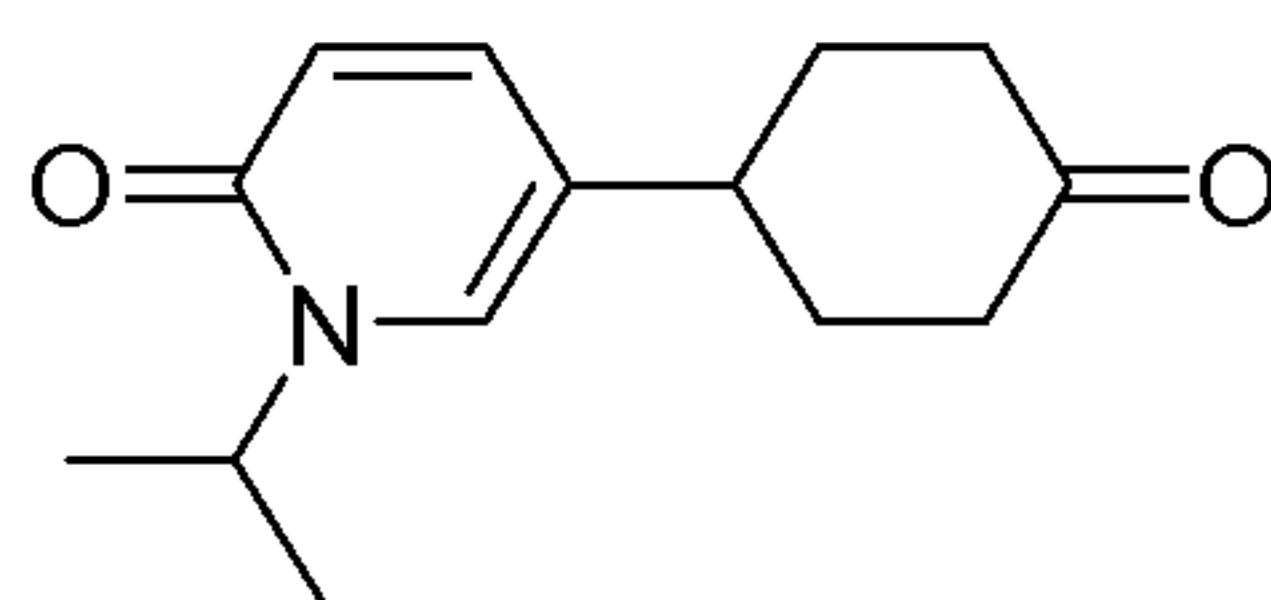
20

The title compound was prepared as a white solid as described in Step A of Example 3 from 5-iodo-1-isopropyl-1H-pyridin-2-one as prepared in the previous step.

¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, J = 6.4 Hz, 1H), 7.20 (s, 1H), 6.50 (d, J = 7.0 Hz, 1H), 5.85 (m, 1H), 5.25 (m, 1H), 4.05 (s, 4H), 3.33 (m, 1H), 2.48 (m, 2H), 2.42 (s, 2H), 1.95 (t, J = 5.5 Hz, 2H), 1.35 (d, J = 7.2 Hz, 6H).

25

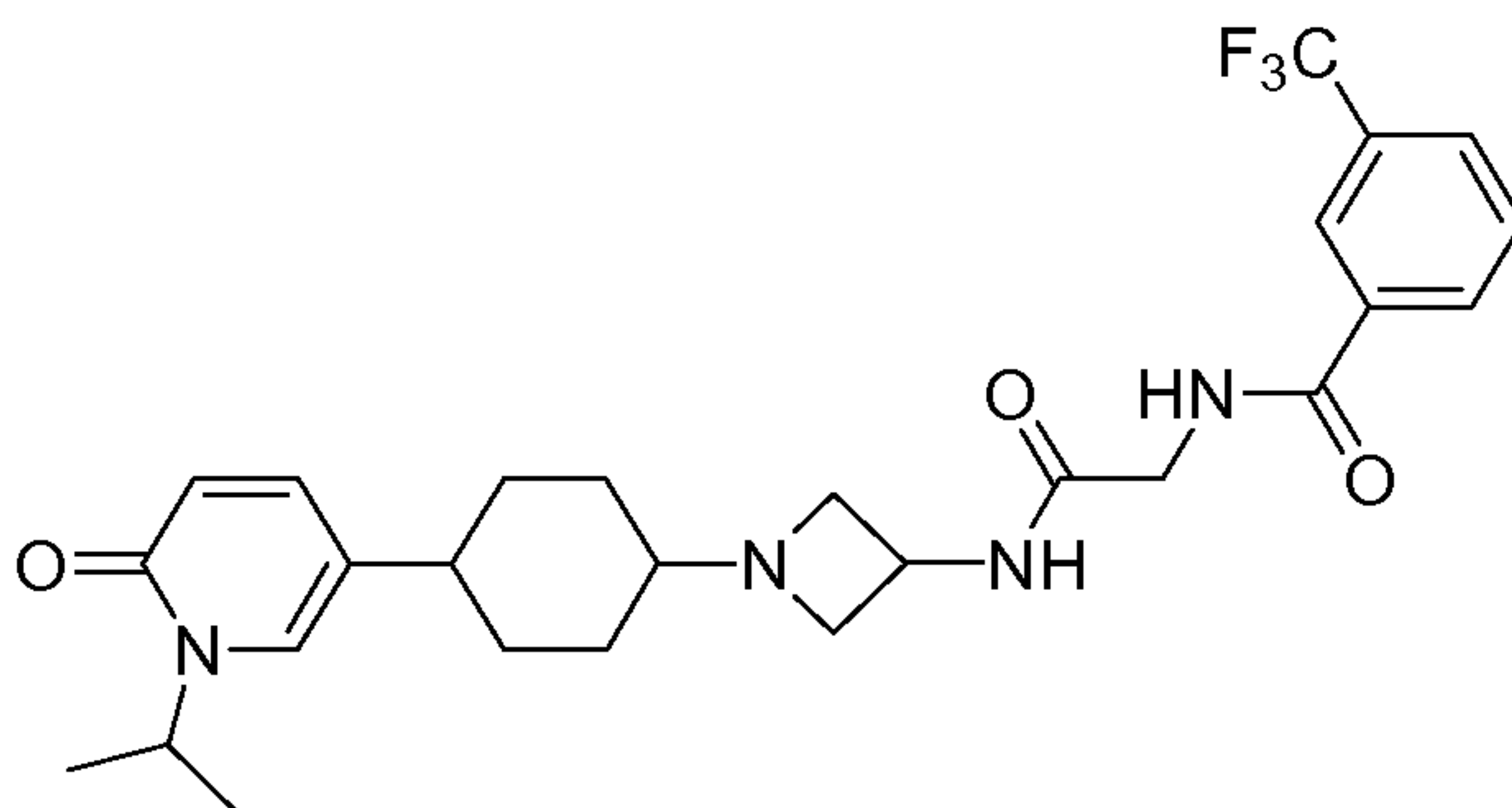
Step C: 1-Isopropyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one



The title compound was prepared as a white solid from the hydrogenation of 5-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-1-isopropyl-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step G of Example 1 followed by de-protection of the corresponding ketal using the procedure described in Step B of Example 2.

ESI-MS (m/z): Calcd. For C₁₄H₁₉NO₂, 233; found: 234 (M+H).

Step D: N-({1-[4-(1-Isopropyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



The title compounds were prepared as white solids from the reductive amination of 1-isopropyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

40a: less polar isomer

¹H NMR (400 MHz, d₄-MeOH) δ 8.25 (s, 1H), 8.18 (d, J = 6.5 Hz, 1H), 7.90 (d, J = 6.4 Hz, 1H), 7.72 (t, J = 6.5 Hz, 1H), 7.51 (s, 1H), 7.48 (d, J = 7.0 Hz, 1H), 6.51 (d, J = 7.0 Hz, 1H), 5.25 (m, 1H), 4.55 (m, 1H), 4.15 (s, 2H), 3.75 (t, J = 6.5 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H), 2.48 (m, 1H), 1.75 (m, 4H), 1.55 (m, 4H), 1.38 (d, J = 7.5 Hz, 6H).

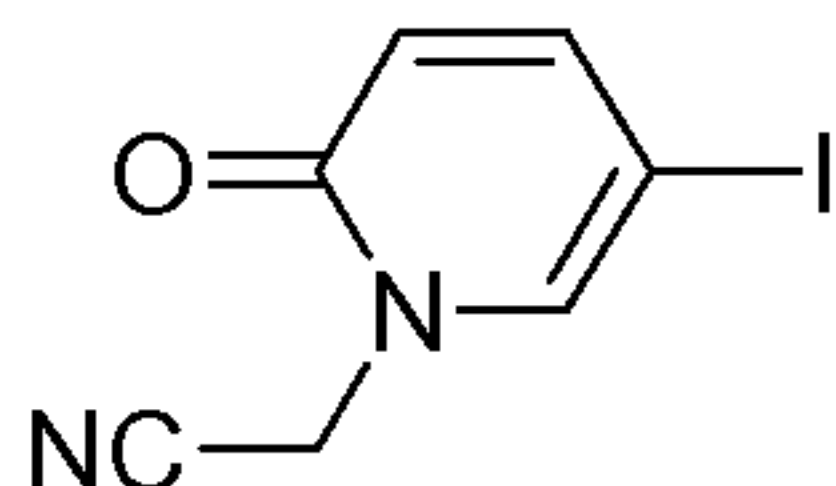
40b: more polar isomer

¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1H), 8.05 (d, J = 6.5 Hz, 1H), 7.80 (d, J = 6.1 Hz, 1H), 7.61 (d, J = 6.6 Hz, 1H), 7.55 (t, J = 6.6 Hz, 1H), 7.21 (d, J = 6.0 Hz, 1H), 7.05 (s, 1H), 6.52 (d, J = 6.5 Hz, 1H), 5.27 (m, 1H), 4.65 (m, 1H), 4.20 (d, J = 3.5 Hz, 2H), 3.67

(t, J = 6.5 Hz, 2H), 3.00 (m, J = 6.1 Hz, 2H), 2.40 (m, 1H), 2.25 (m, 1H), 2.10 (m, 2H), 1.90 (m, 2H), 1.40 (m, 2H), 1.35 (d, J = 7.0 Hz, 6H), 1.25 (m, 2H).

Example 41: N-({1-[4-(1-Cyanomethyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

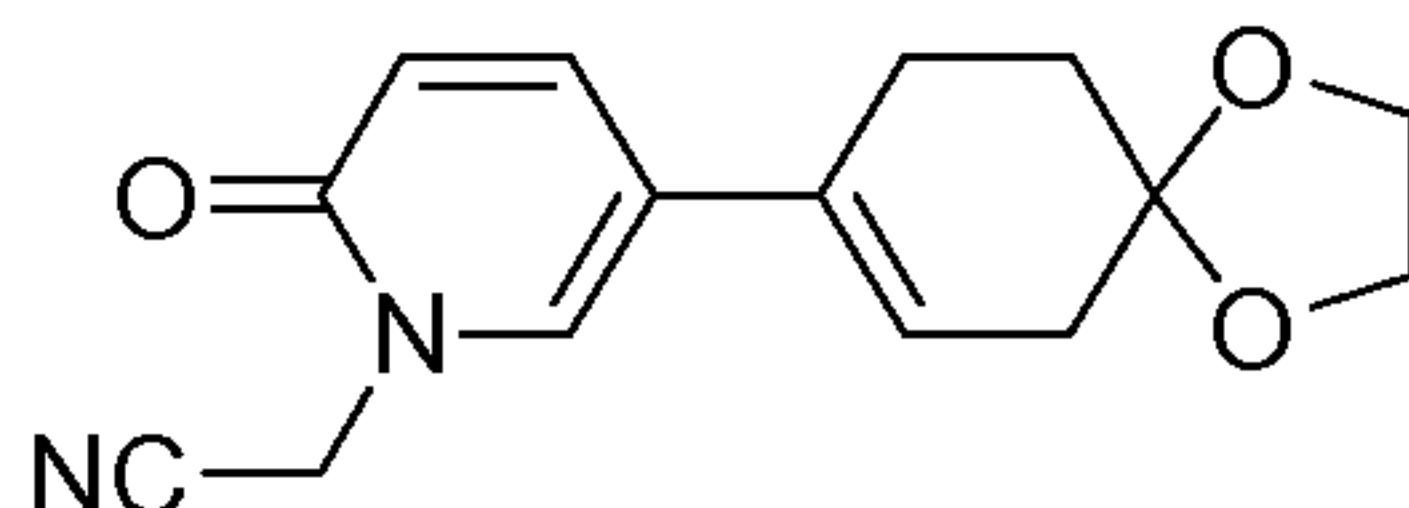
Step A: (5-Iodo-2-oxo-2H-pyridin-1-yl)-acetonitrile



The title compound was prepared as a white solid from the alkylation of 5-iodo-1H-pyridin-2-one with CNCH₂I using the procedure described in Step A of Example 38.

¹H NMR (400 MHz, CDCl₃) δ 7.61 (s, 1H), 7.45 (d, J = 6.6 Hz, 1H), 6.45 (d, J = 6.6 Hz, 1H), 4.79 (s, 2H).

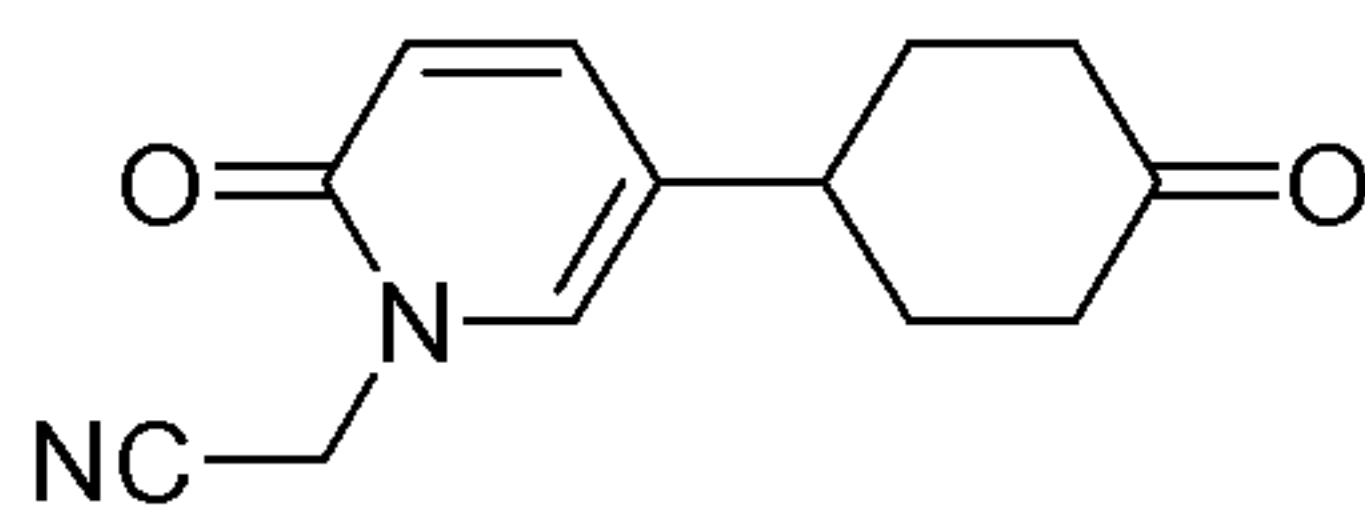
Step B: [5-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-2-oxo-2H-pyridin-1-yl]-acetonitrile



The title compound was prepared using the procedure described in Step A of Example 3 from (5-iodo-2-oxo-2H-pyridin-1-yl)-acetonitrile (Aldrich) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, J = 6.5 Hz, 1H), 7.30 (s, 1H), 6.58 (d, J = 6.5 Hz, 1H), 5.89 (m, 1H), 4.85 (s, 2H), 4.01 (s, 4H), 2.50 (t, J = 3.5 Hz, 2H), 2.45 (s, 2H), 1.92 (t, J = 6.5 Hz, 2H).

Step C: [2-Oxo-5-(4-oxo-cyclohexyl)-2H-pyridin-1-yl]-acetonitrile

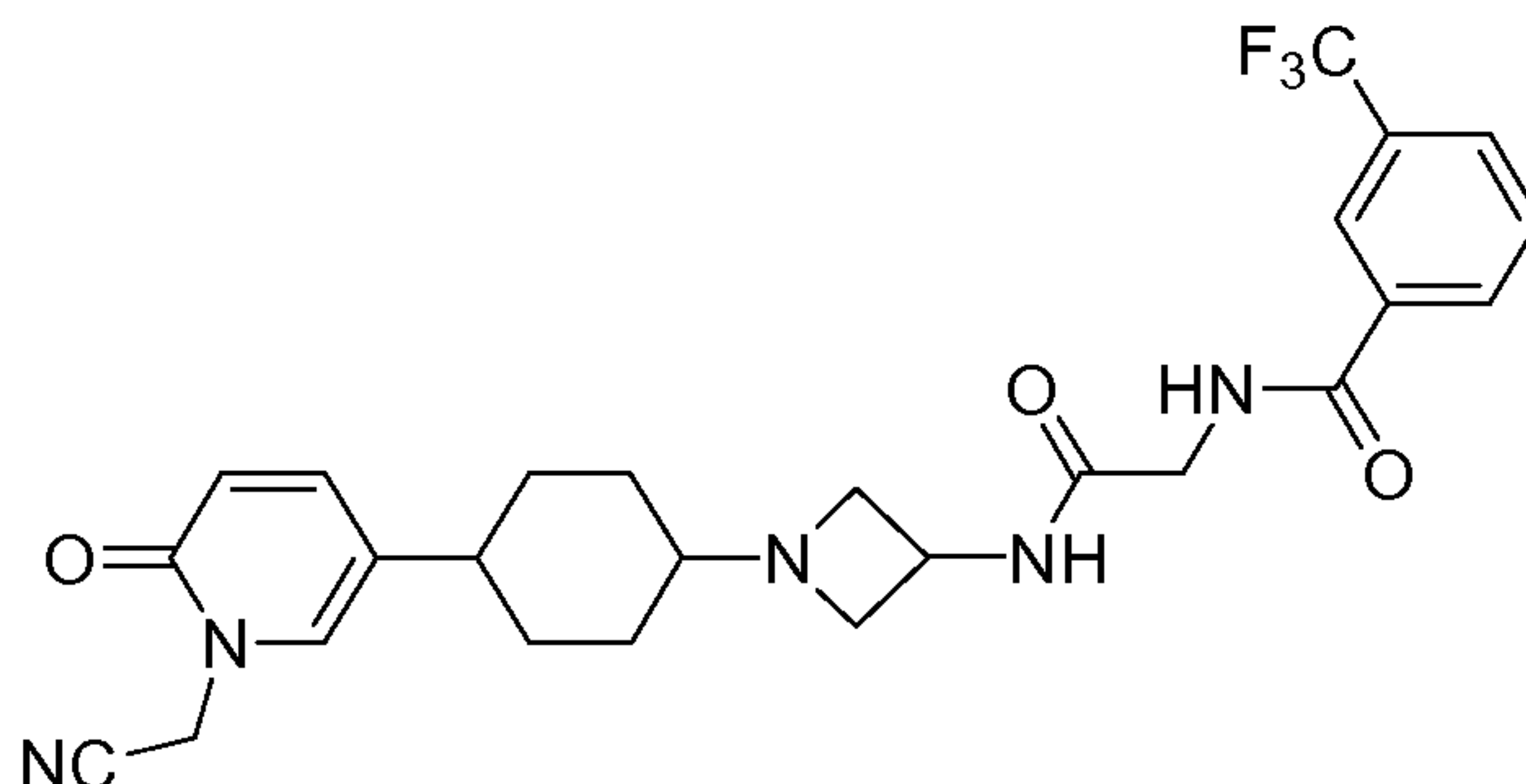


The title compound was prepared as a white solid from the hydrogenation of [5-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-2-oxo-2H-pyridin-1-yl]-acetonitrile (as prepared in the previous step) using the procedure described in Step G of Example 1 followed by de-

protection of the corresponding ketal using the procedure described in Step B of Example 2.

ESI-MS (m/z): Calcd. For C₁₃H₁₄N₂O₂, 230; found: 231 (M+H).

- 5 *Step D: N-({1-[4-(1-Cyanomethyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide*

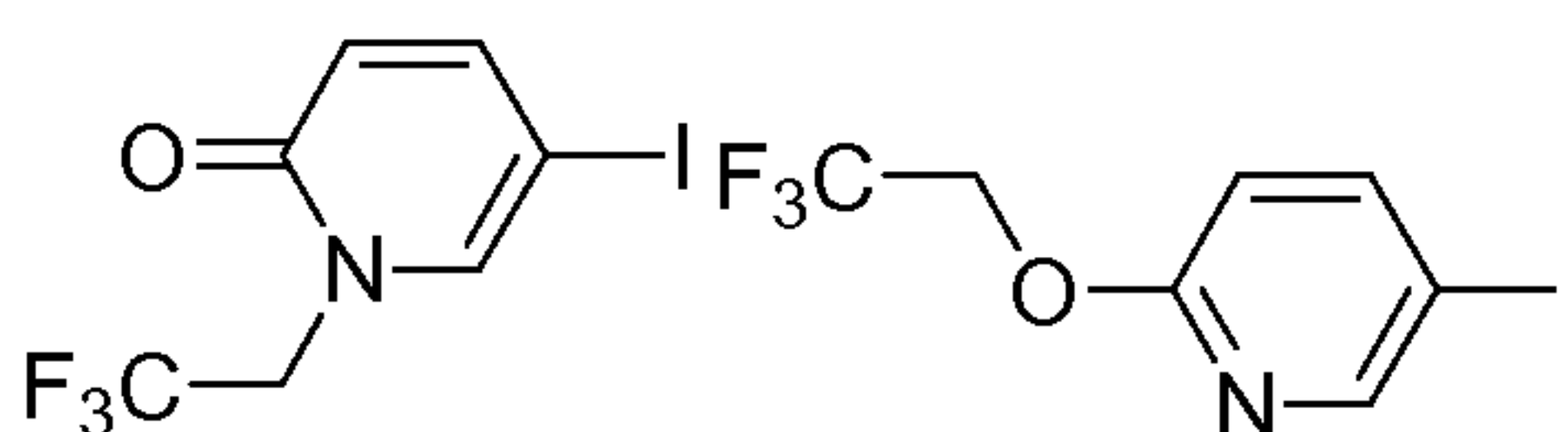


The title compounds were prepared as white solids from the reductive amination of [2-oxo-5-(4-oxo-cyclohexyl)-2H-pyridin-1-yl]-acetonitrile (as prepared in the previous step) and N-(azetidin-3-ylcarbamoymethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

¹H NMR (400 MHz, d₄-MeOH) δ 8.18 (s, 1H), 8.11 (d, J = 6.5 Hz, 1H), 7.88 (d, J = 6.4 Hz, 1H), 7.70 (t, J = 6.5 Hz, 1H), 7.45 (s, 1H), 7.37 (d, J = 7.0 Hz, 1H), 6.41 (d, J = 7.0 Hz, 1H), 4.80 (s, 2H), 4.45 (m, 1H), 4.03 (s, 2H), 3.65 (t, J = 6.5 Hz, 2H), 2.98 (t, J = 6.0 Hz, 2H), 2.38 (m, 1H), 1.80 (m, 4H), 1.50 (m, 4H).

Example 42: N-[(1-{4-[6-Oxo-1-(2,2,2-trifluoro-ethyl)-1,6-dihydro-pyridin-3-yl]-cyclohexyl}-azetidin-3-ylcarbamoyl)-methyl]-3-trifluoromethyl-benzamide

Step A: 5-Iodo-1-(2,2,2-trifluoro-ethyl)-1H-pyridin-2-one and 5-Iodo-2-(2,2,2-trifluoro-ethoxy)-pyridine



The title compounds were prepared as white solids from the alkylation of 5-iodo-1H-pyridin-2-one with CF₃CH₂I (Aldrich) using the procedure described in Step A of Example 38.

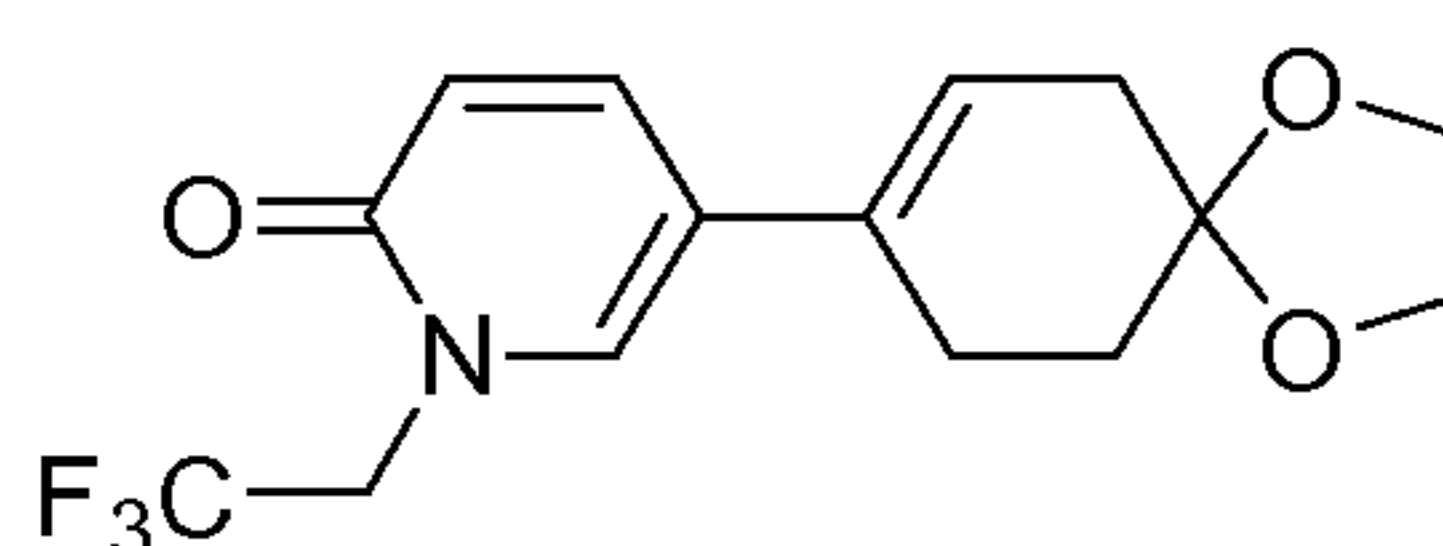
5-Iodo-1-(2,2,2-trifluoro-ethyl)-1H-pyridin-2-one

¹H NMR (400 MHz, CDCl₃) δ 7.51 (s, 1H), 7.45 (d, J = 6.8 Hz, 1H), 6.42 (d, J = 6.8 Hz, 1H), 4.55 (q, J = 6.5 Hz, 2H).

5-Iodo-2-(2,2,2-trifluoro-ethoxy)-pyridine

5 ¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 7.85 (d, J = 6.5 Hz, 1H), 6.68 (d, J = 6.6 Hz, 1H), 4.71 (q, J = 6.8 Hz, 2H).

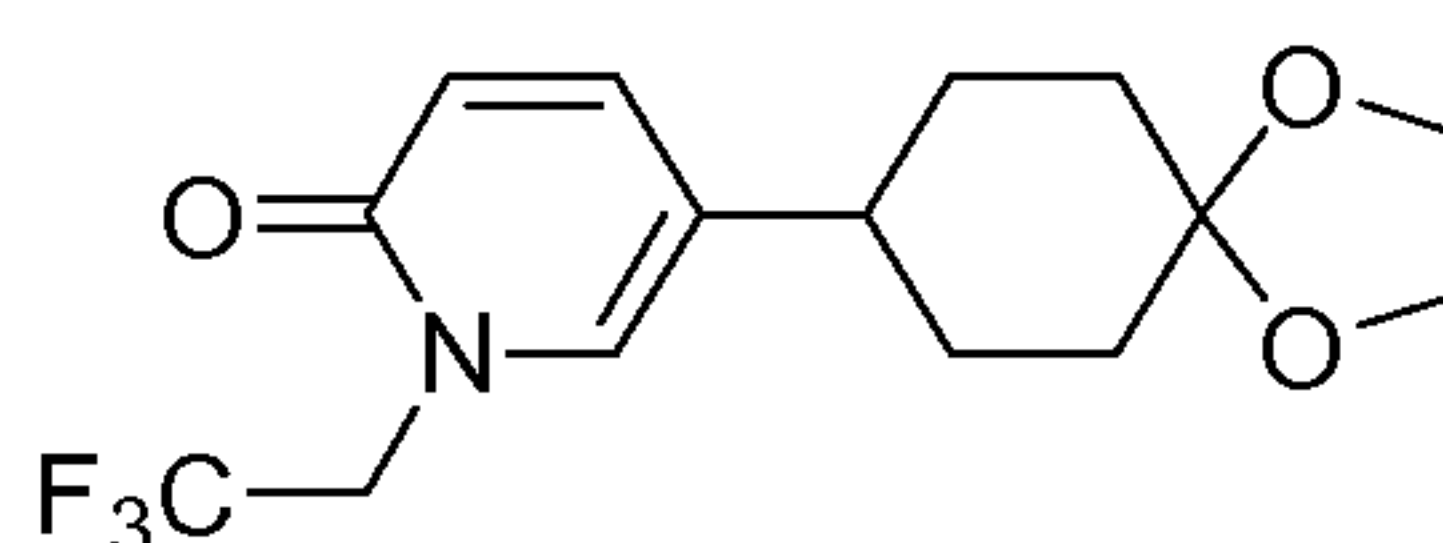
Step B: 5-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-1-(2,2,2-trifluoro-ethyl)-1H-pyridin-2-one



10 The title compound was prepared as described in Step A of Example 3 from 5-iodo-1-(2,2,2-trifluoro-ethyl)-1H-pyridin-2-one (as prepared in the previous step) as a white solid.

ESI-MS (m/z): Calcd. For C₁₅H₁₆F₃NO₃, 315; found: 316 (M+H).

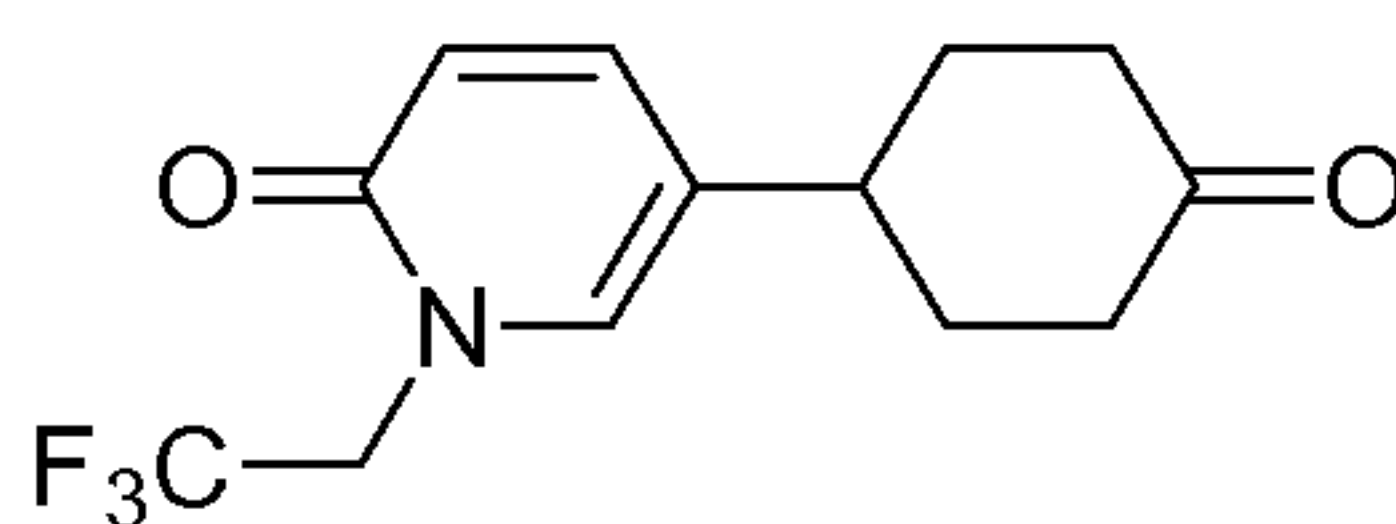
15 *Step C: 5-(1,4-Dioxo-spiro[4.5]dec-8-yl)-1-(2,2,2-trifluoro-ethyl)-1H-pyridin-2-one*



The title compound was prepared as a white solid from the hydrogenation of 5-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-1-(2,2,2-trifluoro-ethyl)-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step G of Example 1.

20 ¹H NMR (400 MHz, CDCl₃) δ 7.48 (s, 1H), 7.40 (d, J = 6.5 Hz, 1H), 6.36 (d, J = 6.5 Hz, 1H), 4.42 (q, J = 7.5 Hz, 2H), 3.95 (m, 4H), 2.70 (m, 1H), 2.105 (m, 2H), 1.70 (m, 4H), 1.55 (m, 2H).

Step D: 5-(4-Oxo-cyclohexyl)-1-(2,2,2-trifluoro-ethyl)-1H-pyridin-2-one



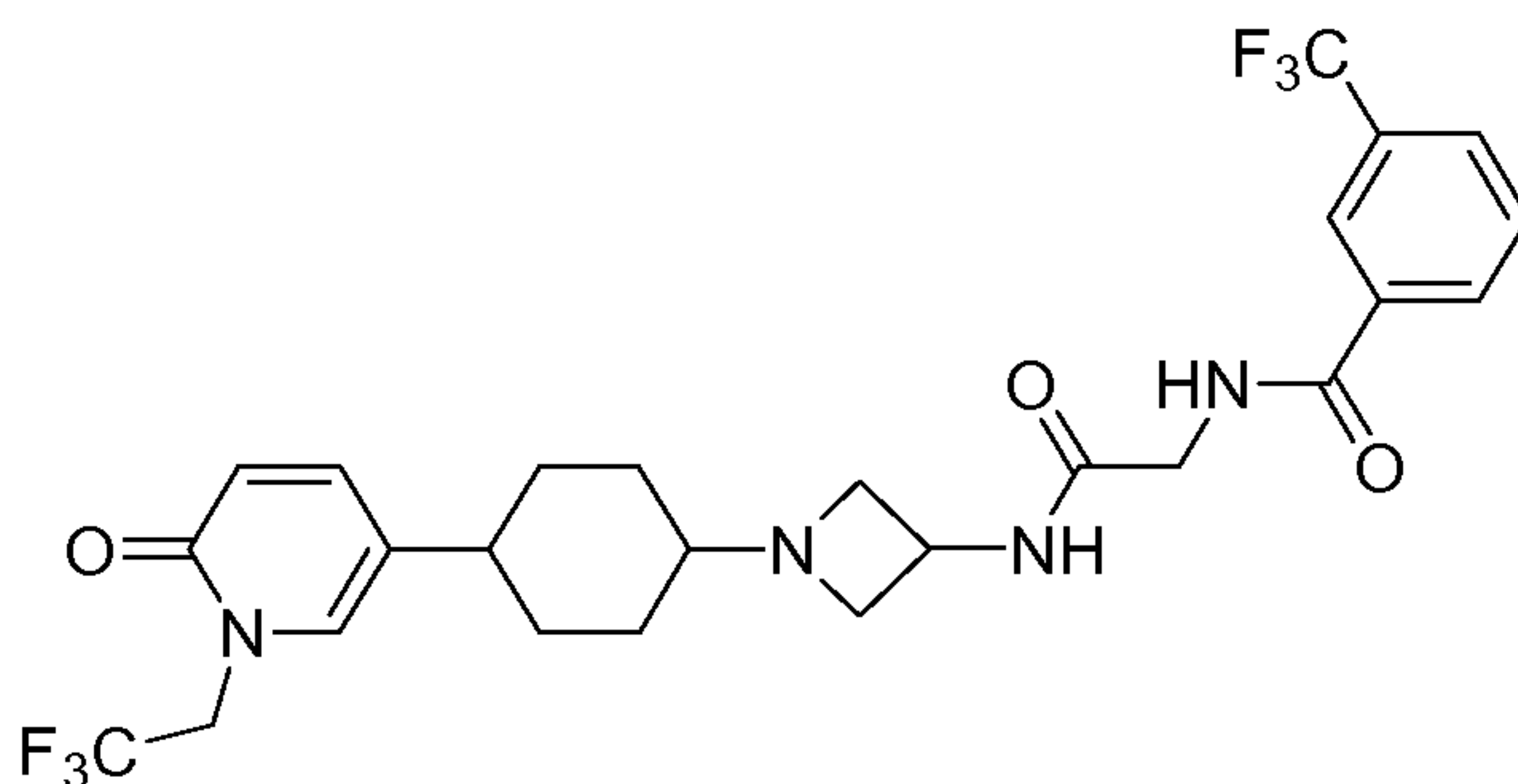
25

The title compound was prepared as a white solid from the de-protection of 5-(1,4-dioxaspiro[4.5]dec-8-yl)-1-(2,2,2-trifluoro-ethyl)-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step B of Example 2.

ESI-MS (m/z): Calcd. For C₁₃H₁₄F₃NO₂, 273; found: 274 (M+H).

5

Step E: N-[(1-{4-[6-Oxo-1-(2,2,2-trifluoro-ethyl)-1,6-dihydro-pyridin-3-yl]-cyclohexyl}-azetidin-3-ylcarbamoyl)-methyl]-3-trifluoromethyl-benzamide



The title compounds were prepared as white solids from the reductive amination of 5-(4-oxo-cyclohexyl)-1-(2,2,2-trifluoro-ethyl)-1H-pyridin-2-one (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

42a: less polar isomer,

¹H NMR (400 MHz, d₄-MeOH) δ 8.25 (s, 1H), 8.14 (d, J = 6.2 Hz, 1H), 7.87 (d, J = 6.0 Hz, 1H), 7.73 (t, J = 6.2 Hz, 1H), 7.65 (d, J = 6.4 Hz, 1H), 7.42 (s, 1H), 6.55 (d, J = 6.5 Hz, 1H), 4.80 (q, J = 9.5 Hz, 2H), 4.45 (m, 1H), 4.08 (s, 2H), 3.70 (t, J = 7.5 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H), 2.45 (m, 2H), 1.75 (m, 4H), 1.58 (m, 4H).

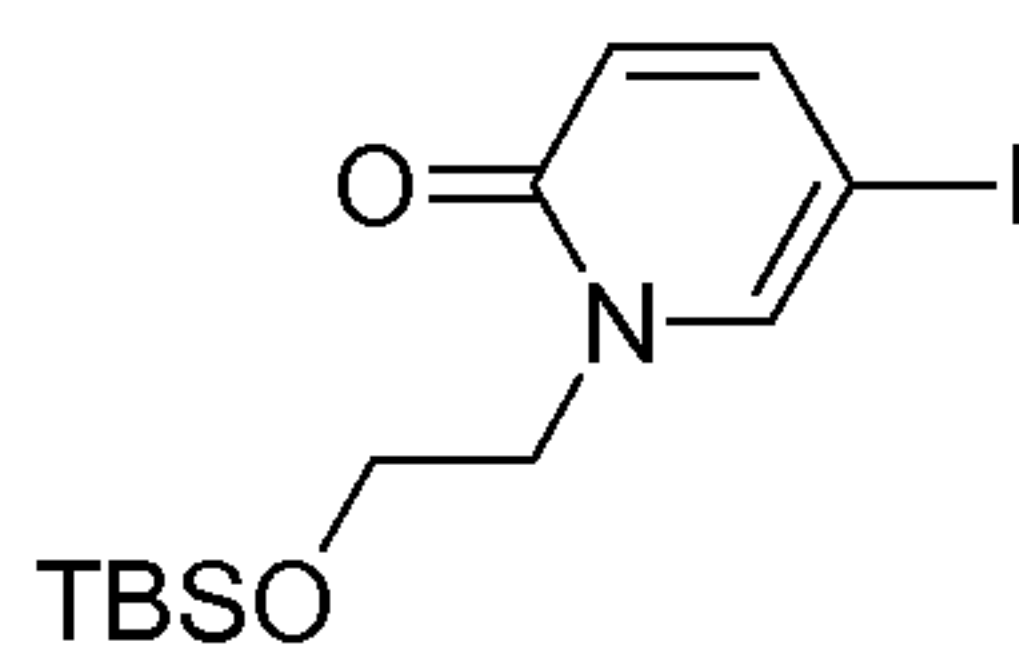
42b: more polar isomer

¹H NMR (400 MHz, d₄-MeOH) δ 8.15 (s, 1H), 8.02 (d, J = 6.5 Hz, 1H), 7.82 (d, J = 5.0 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.60 (m, 1H), 7.32 (d, J = 6.1 Hz, 1H), 6.55 (d, J = 6.1 Hz, 1H), 4.63 (q, J = 8.5 Hz, 2H), 4.52 (m, 1H), 4.18 (s, 2H), 3.65 (t, J = 7.5 Hz, 2H), 3.10 (t, J = 7.2 Hz, 2H), 2.85 (m, 1H), 2.30 (m, 3H), 2.21 (m, 2H), 1.65 (m, 2H), 1.42 (m, 2H).

Example 43: N-[(1-{4-[1-(2-Hydroxy-ethyl)-6-oxo-1,6-dihydro-pyridin-3-yl]-cyclohexyl}-azetidin-3-ylcarbamoyl)-methyl]-3-trifluoromethyl-benzamide

25

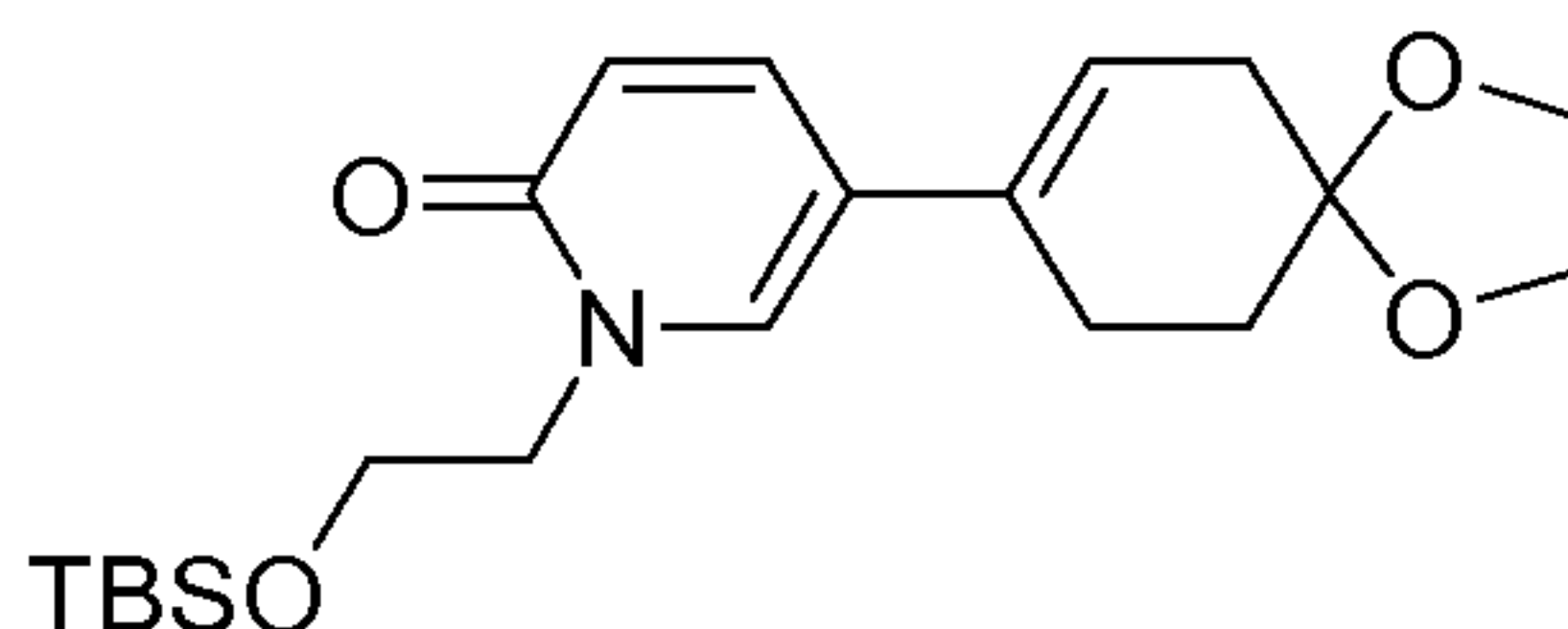
Step A: 1-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-5-iodo-1H-pyridin-2-one



The title compounds were prepared as white solids from the alkylation of 5-iodo-1H-pyridin-2-one with BrCH₂CH₂OTBS (Aldrich) using the procedure described in Step A of Example 38.

5 ESI-MS (m/z): Calcd. For C₁₃H₂₂INO₂Si, 379; found: 380 (M+H).

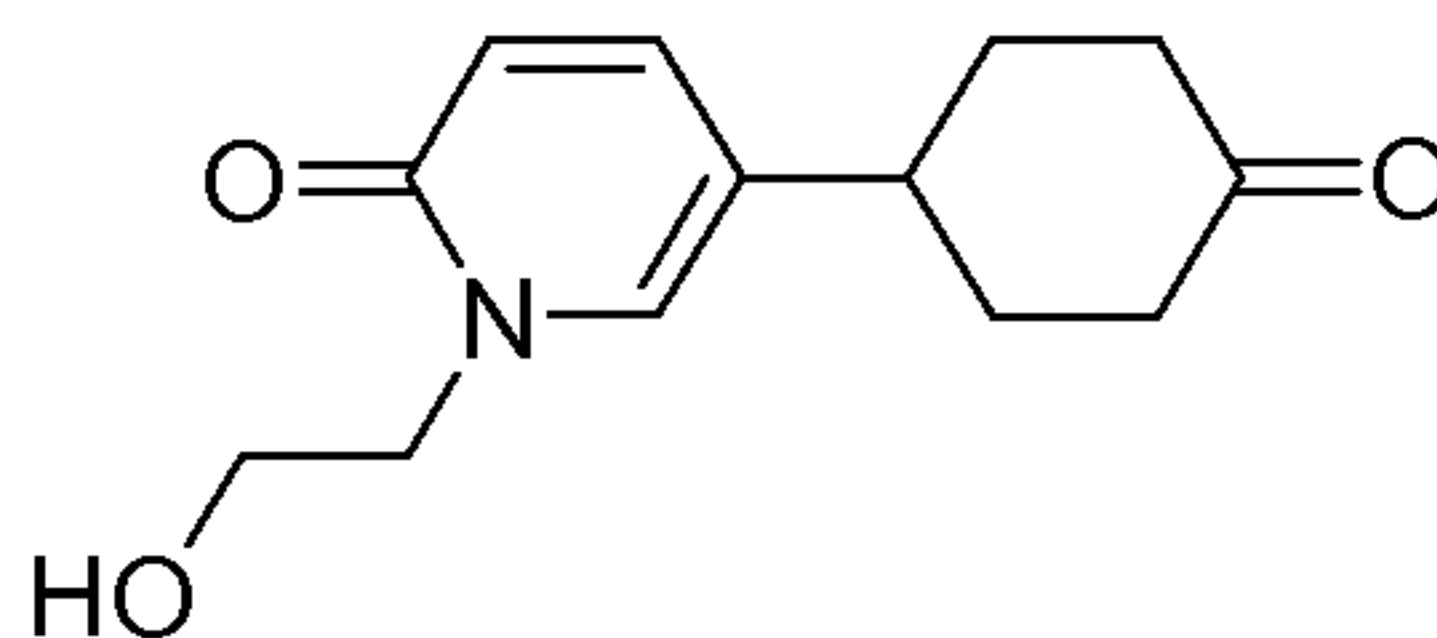
Step B: 1-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-5-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-1H-pyridin-2-one



10 The title compound was prepared as described in Step A of Example 3 from 1-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-5-iodo-1H-pyridin-2-one (as prepared in the previous step) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, J = 5.5 Hz, 1H), 7.33 (s, 1H), 6.58 (d, J = 6.8 Hz, 1H), 5.90 (m, 1H), 4.15 (t, J = 4.5 Hz, 2H), 4.10 (s, 4H), 4.02 (t, J = 4.6 Hz, 2H), 2.58 (t, J = 3.5 Hz, 2H), 2.45 (s, 2H), 1.98 (t, J = 6.1 Hz, 2H), 0.92 (s, 9H).

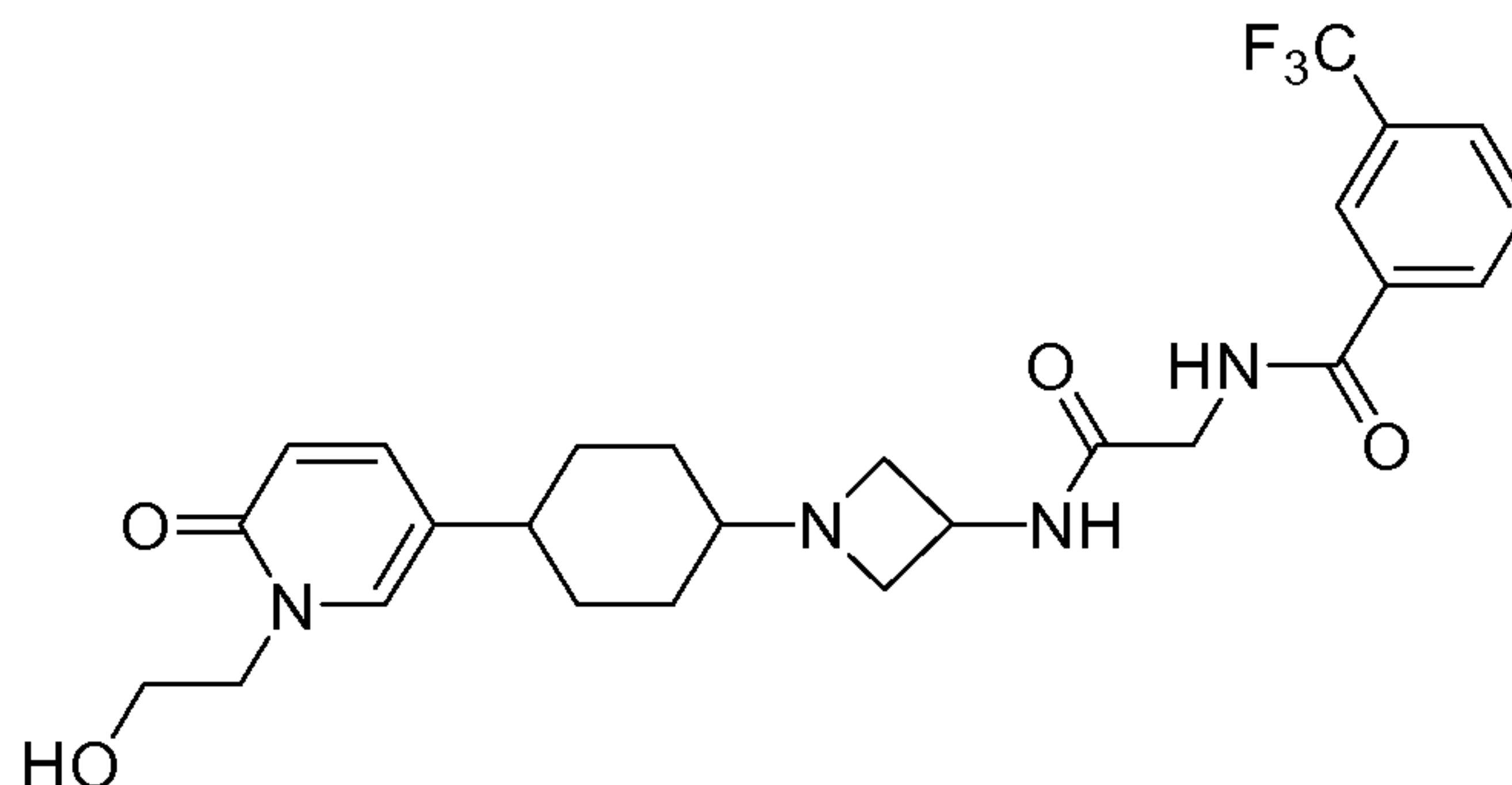
Step C: 1-(2-Hydroxy-ethyl)-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one



20 The title compound was prepared as a white solid from the hydrogenation of 1-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-5-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step G of Example 1 followed by de-protection of the corresponding ketal using the procedure described in Step B of Example 2.

ESI-MS (m/z): Calcd. For C₁₃H₁₇NO₃, 235; found: 236 (M+H).

Step D: *N*-[(1-{4-[1-(2-Hydroxy-ethyl)-6-oxo-1,6-dihydro-pyridin-3-yl]-cyclohexyl}-azetidin-3-ylcarbamoyl)-methyl]-3-trifluoromethyl-benzamide

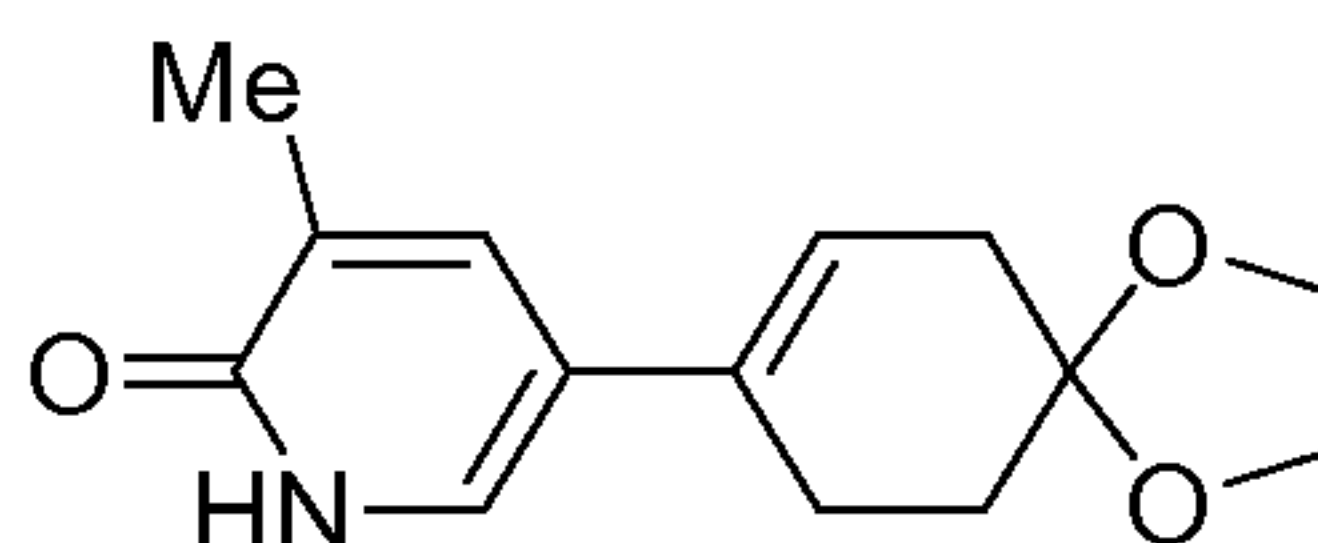


5 The title compounds were prepared as white solids from the reductive amination of 1-(2-hydroxy-ethyl)-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one (as prepared in the previous step) and *N*-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

¹H NMR (400 MHz, *d*₄-MeOH) δ 8.25 (s, 1H), 8.14 (d, *J* = 6.2 Hz, 1H), 7.87 (d, *J* = 6.0 Hz, 1H), 7.73 (t, *J* = 6.2 Hz, 1H), 7.62 (d, *J* = 6.4 Hz, 1H), 7.42 (s, 1H), 6.50 (d, *J* = 6.5 Hz, 1H), 4.45 (m, 1H), 4.12 (t, *J* = 6.3 Hz, 2H), 4.08 (s, 2H), 3.80 (t, *J* = 5.5 Hz, 2H), 3.61 (m, 2H), 3.43 (m, 1H), 2.98 (t, *J* = 5.2 Hz, 2H), 2.35 (m, 2H), 1.80 (m, 4H), 1.45 (m, 4H).

Example 44: *N*-(1-[4-(5-Methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl)-methyl)-3-trifluoromethyl-benzamide

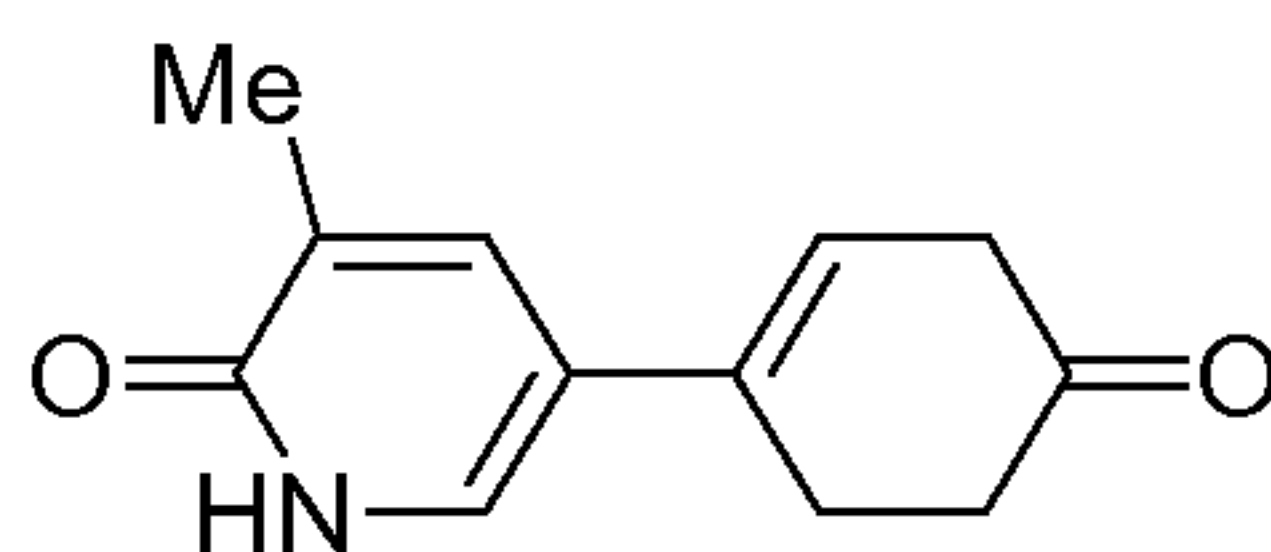
Step A: *5-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-3-methyl-1H-pyridin-2-one*



The title compound was prepared as described in Step A of Example 3 from 5-bromo-3-methyl-1H-pyridin-2-one (Aldrich) as a white solid.

ESI-MS (*m/z*): Calcd. For C₁₄H₁₇NO₃, 247; found: 248 (*M*+*H*).

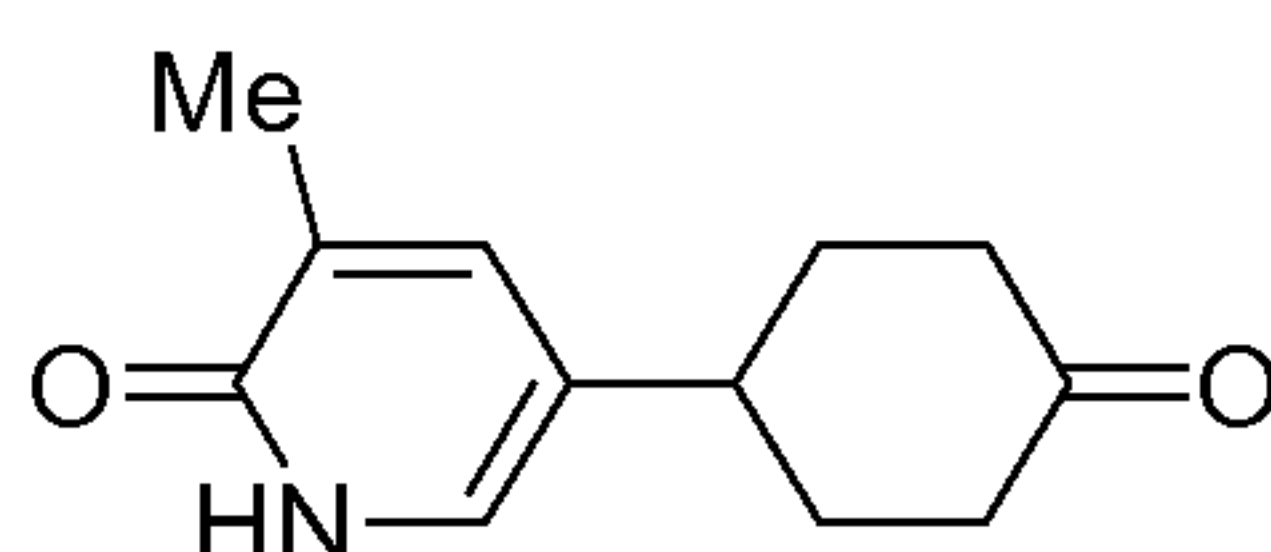
Step B: *3-Methyl-5-(4-oxo-cyclohex-1-enyl)-1H-pyridin-2-one*



The title compound was prepared as a white solid from the de-protection of 5-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-3-methyl-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step B of Example 2.

- 5 ^1H NMR (400 MHz, d_4 -MeOH) δ 7.67 (s, 1H), 7.25 (s, 1H), 3.00 (m, 2H), 2.67 (t, J = 6.0 Hz, 2H), 2.66 (t, J = 6.4 Hz, 2H).

Step C: 3-Methyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one

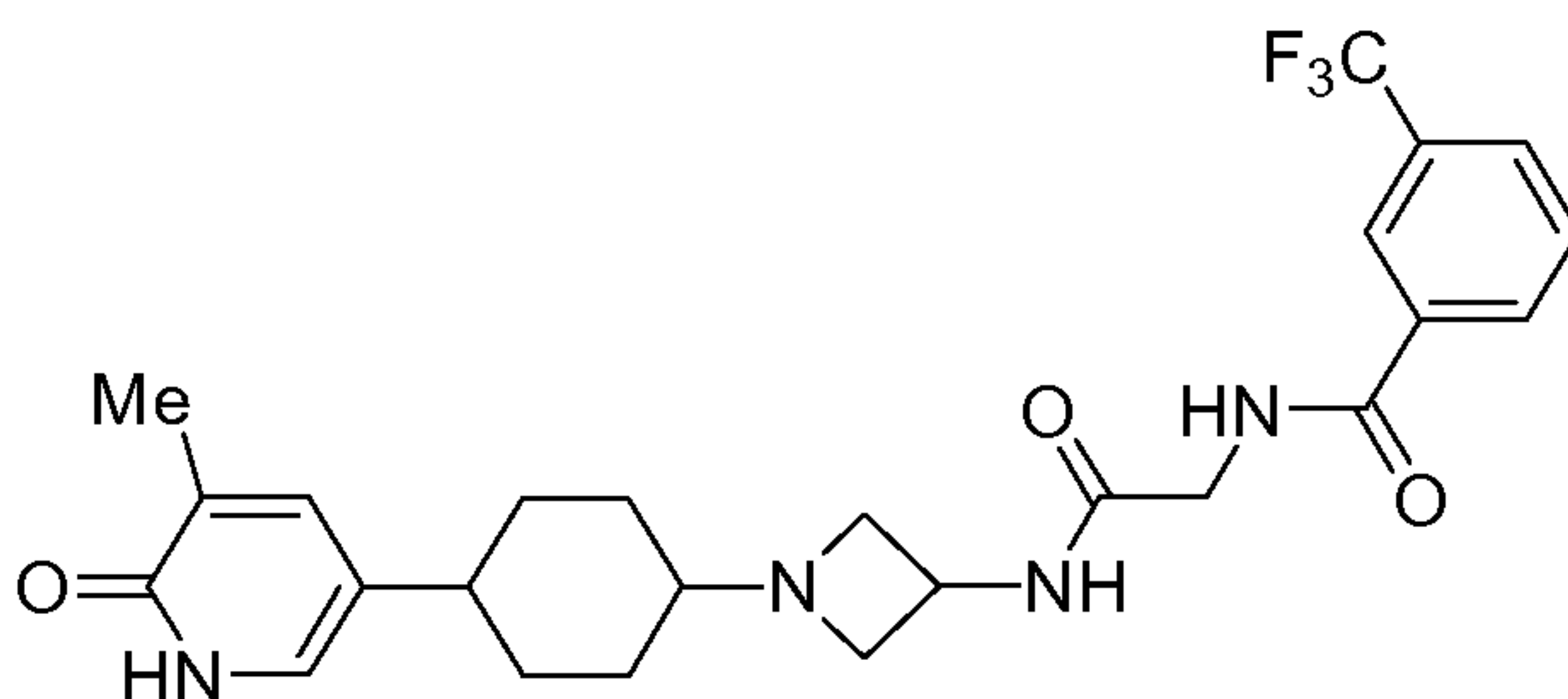


- 10 The title compound was prepared as a white solid from the hydrogenation of 3-methyl-5-(4-oxo-cyclohex-1-en-1-yl)-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step G of Example 1.

^1H NMR (400 MHz, d_4 -MeOH) δ 7.40 (s, 1H), 7.07 (s, 1H), 2.65 (m, 1H), 2.45 (m, 2H), 2.28 (m, 2H), 2.02 (m, 2H), 1.78 (m, 2H).

15

Step D: N-({1-[4-(5-Methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide



- 20 The title compounds were prepared as white solids from the reductive amination of 3-methyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

44a: less polar isomer,

¹H NMR (400 MHz, *d*₄-MeOH) δ 8.25 (s, 1H), 8.14 (d, *J* = 6.6 Hz, 1H), 7.90 (d, *J* = 6.5 Hz, 1H), 7.73 (t, *J* = 6.5 Hz, 1H), 7.52 (s, 1H), 7.12 (s, 1H), 4.48 (m, 1H), 4.02 (s, 2H), 3.68 (t, *J* = 7.1 Hz, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.41 (m, 2H), 2.15 (s, 3H), 1.75 (m, 4H), 1.54 (m, 4H).

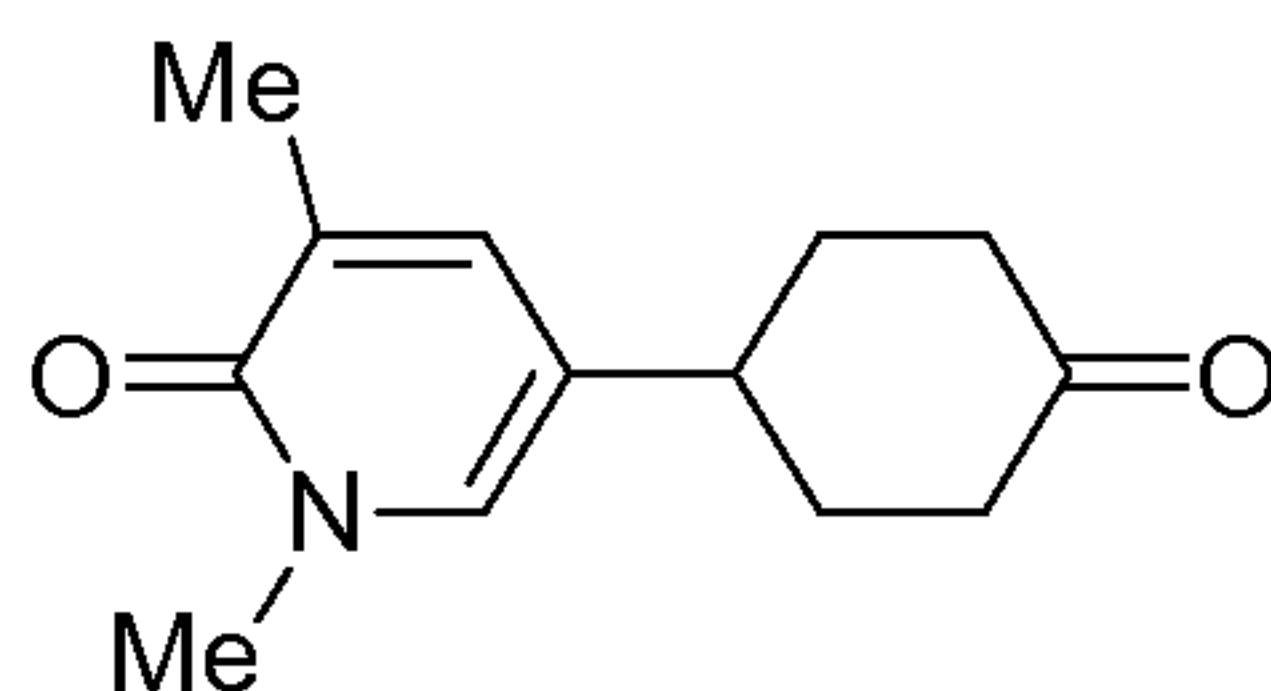
5 **44b**: more polar isomer

¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 8.18 (d, *J* = 6.5 Hz, 1H), 7.90 (d, *J* = 6.6 Hz, 1H), 7.73 (t, *J* = 6.6 Hz, 1H), 7.45 (s, 1H), 7.10 (s, 1H), 4.45 (m, 1H), 4.05 (s, 2H), 3.70 (m, *J* = 6.5 Hz, 2H), 3.10 (m, *J* = 6.1 Hz, 2H), 2.45 (m, 2H), 2.10 (s, 3H), 2.01 (m, 4H), 1.90 (m, 2H), 1.44 (m, 2H), 1.20 (m, 2H).

10

Example 45: N-(1-[4-(1,5-Dimethyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

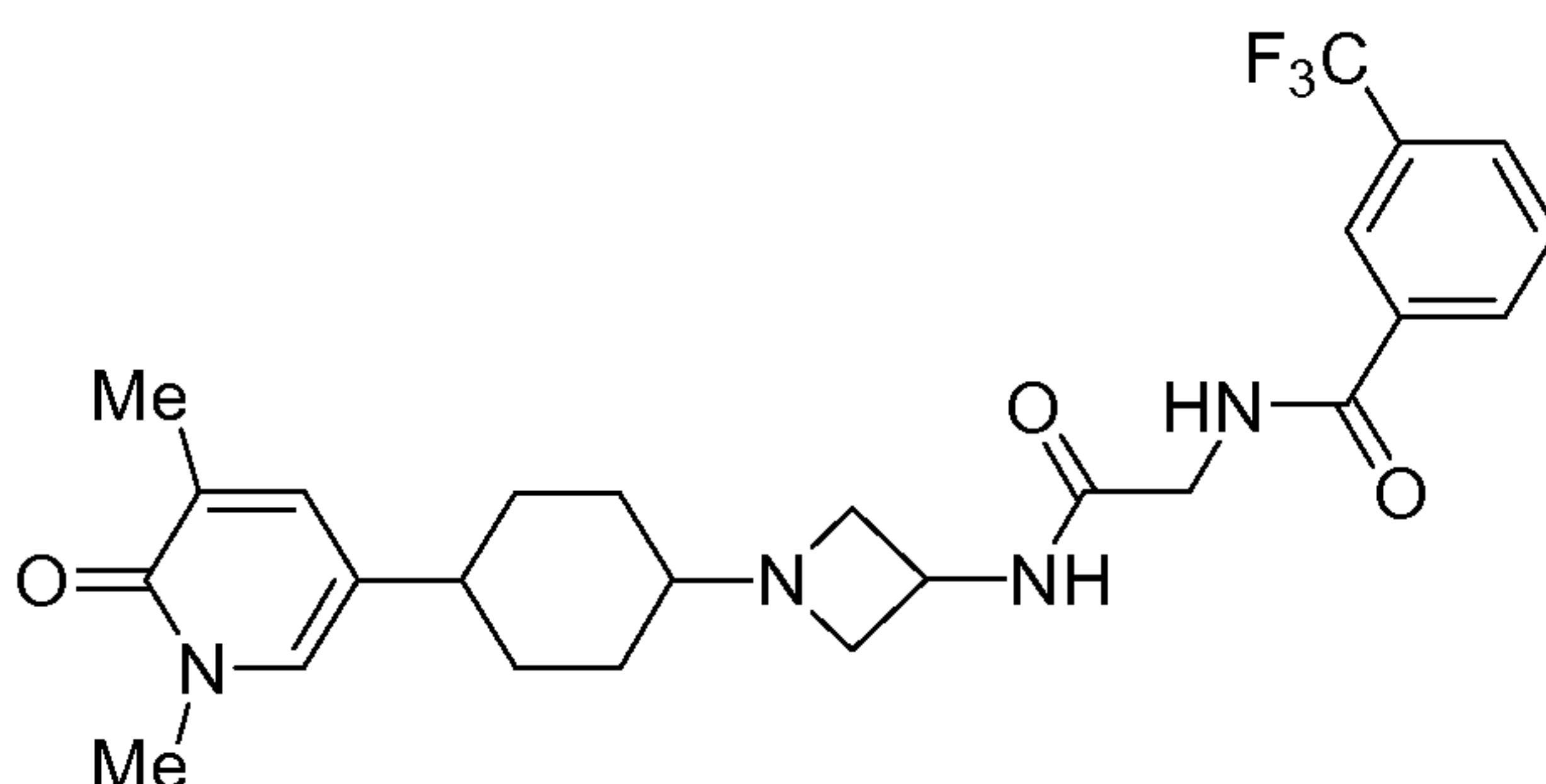
Step A: 1,3-Dimethyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one



15 The title compound was prepared as a white solid from the methylation of 3-methyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one (as prepared in Example 44, Step C) with MeI using the procedure described in Step B of Example 38.

ESI-MS (*m/z*): Calcd. For C₁₃H₁₇NO₂, 219; found: 220 (M+H).

20 *Step B: N-(1-[4-(1,5-Dimethyl-6-oxo-1,6-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide*



The title compounds were prepared as white solids from the reductive amination of 1,3-dimethyl-5-(4-oxo-cyclohexyl)-1H-pyridin-2-one (as prepared in the previous step) and

N-(azetidin-3-ylcarbamoymethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

45a: less polar isomer,

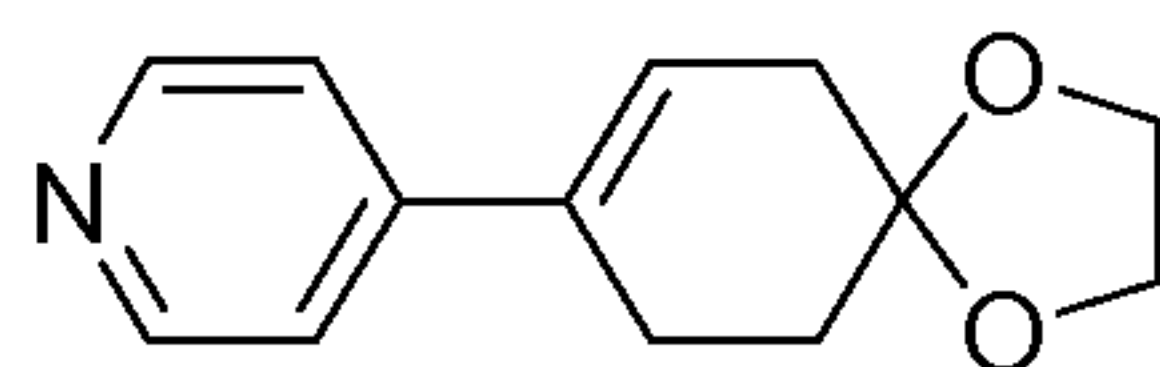
¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 8.11 (d, J = 6.5 Hz, 1H), 7.99 (m, 1H), 7.72 (d, J = 6.6 Hz, 1H), 7.63 (t, J = 6.6 Hz, 1H), 7.20 (s, 1H), 4.75 (m, 1H), 4.15 (m, 2H), 4.06 (m, J = 6.5 Hz, 2H), 3.55 (s, 3H), 3.21 (s, 1H), 3.10 (m, J = 6.1 Hz, 2H), 2.25 (m, 1H), 2.10 (s, 3H), 1.90 (m, 4H), 1.60 (m, 4H).

45b: more polar isomer

¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 8.10 (d, J = 5.8 Hz, 1H), 7.90 (m, 1H), 7.79 (d, J = 6.0 Hz, 1H), 7.75 (d, J = 5.5 Hz, 1H), 7.63 (t, J = 6.6 Hz, 1H), 7.15 (s, 1H), 4.70 (m, 1H), 4.15 (t, J = 4.5 Hz, 2H), 3.80 (t, J = 6.5 Hz, 2H), 3.62 (m, 1H), 3.48 (s, 3H), 3.15 (m, 2H), 2.75 (m, 1H), 2.25 (m, 2H), 2.14 (s, 3H), 1.90 (m, 2H), 1.75 (m, 2H), 1.33 (m, 2H).

Example 46: N-({1-[4-(1-Methyl-2-oxo-1,2-dihydro-pyridin-4-yl)-cyclohexyl]-azetidin-3-ylcarbamoymethyl}-methyl)-3-trifluoromethyl-benzamide

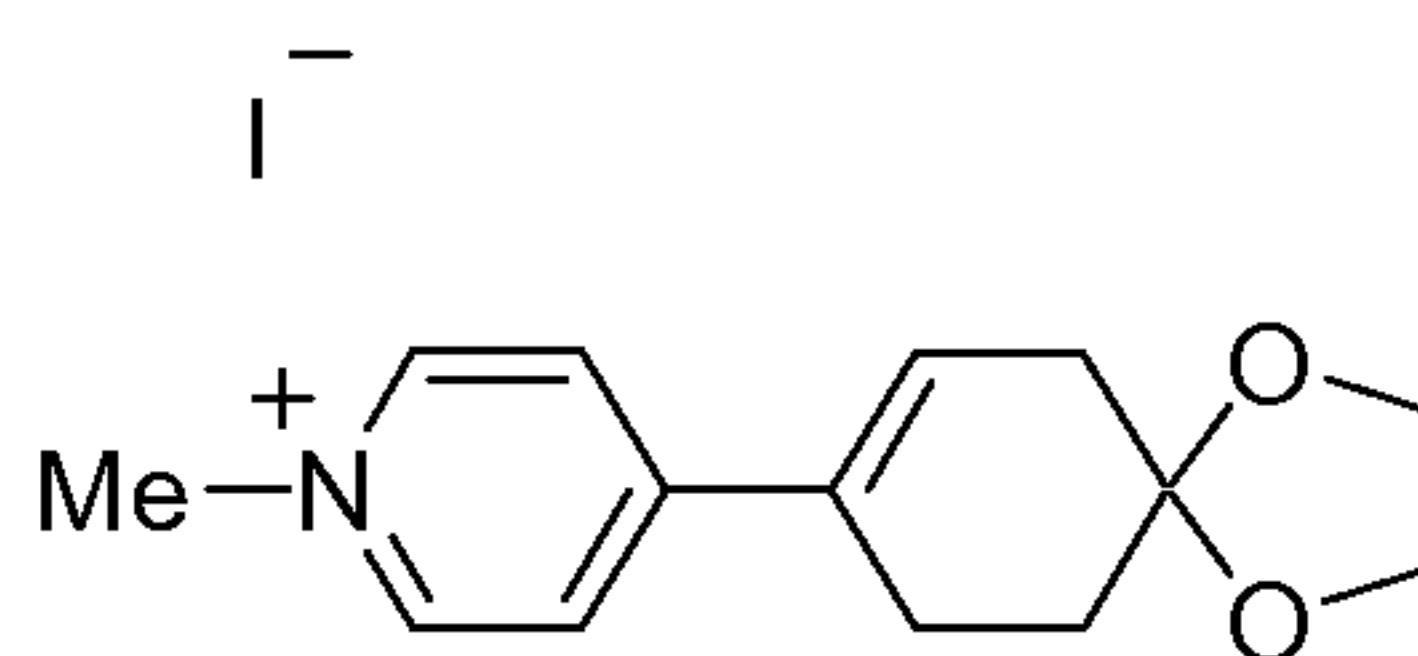
Step A: 4-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyridine



The title compound was prepared as described in Step A of Example 3 from 4-bromopyridine as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 8.52 (d, J = 6.8 Hz, 2H), 7.28 (d, J = 6.8 Hz, 2H), 6.26 (t, J = 3.5 Hz, 1H), 4.10 (s, 4H), 2.80 (m, 2H), 2.58 (m, 2H), 2.05 (t, J = 6.0 Hz, 2H).

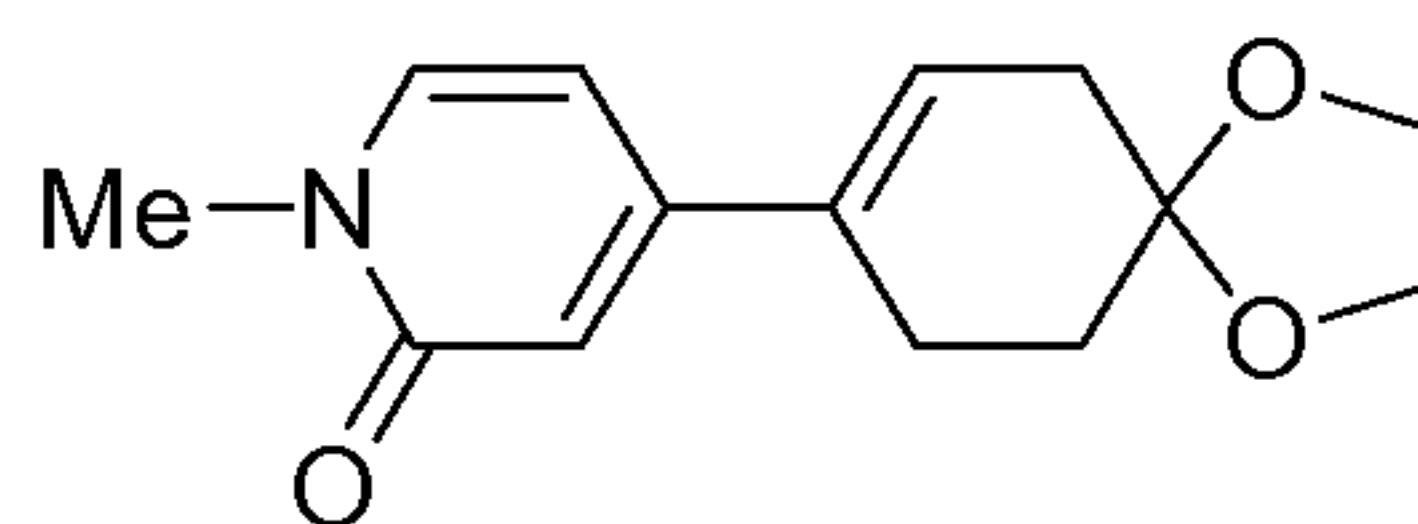
Step B: 4-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-1-methyl-pyridinium iodide



4-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-pyridine (as prepared in the previous step, 1.5 g, 6.91 mmol) in MeI (~10 mL) was heated to reflux until the precipitate was completely

dissolved. The reaction was cooled and filtered to collect the brown solid as the title compound.

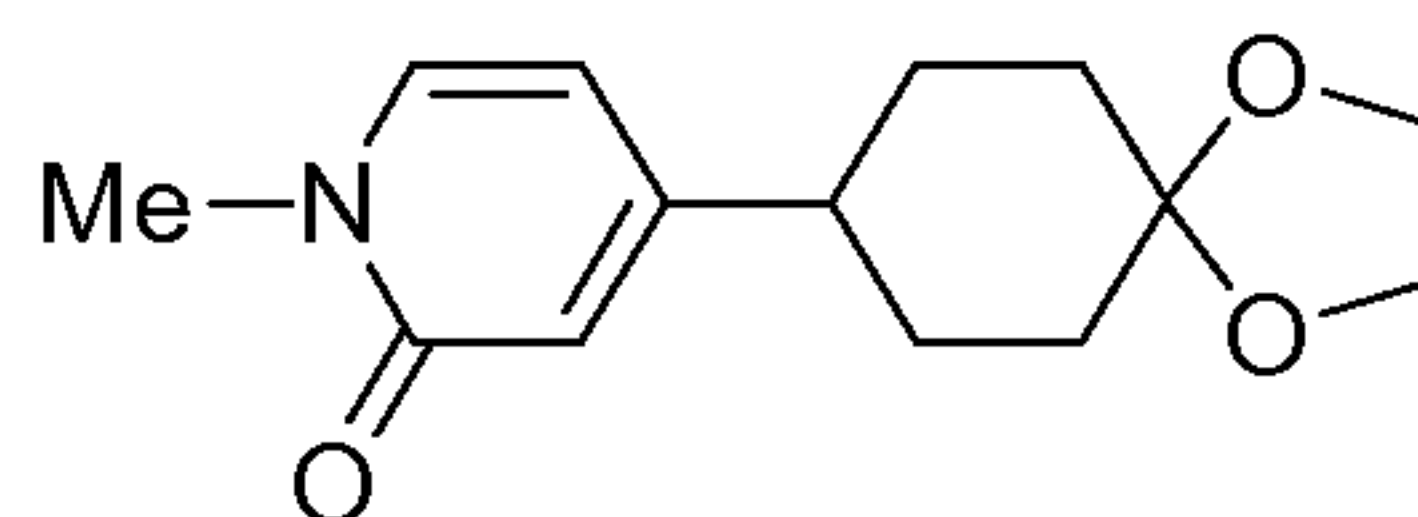
Step C: 4-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-1-methyl-1H-pyridin-2-one



4-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-1-methyl-pyridinium iodide (as prepared in the previous step, 864 mg, 2.40 mmol) in THF (5 mL) and 1N NaOH (5 mL) was treated with $K_3Fe(CN)_6$ (Aldrich, 1.58 g, 4.80 mmol) at room temperature for 4 hours. The reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give a yellow oil, which was then purified by silica gel column on a CombiFlash® system using hexanes and ethyl acetate (from 10% ethyl acetate to 100% ethyl acetate) to afford the title compound as a white solid.

^1H NMR (400 MHz, d_4 -MeOH) δ 7.82 (d, J = 7.0 Hz, 1H), 7.45 (d, J = 6.0 Hz, 1H), 7.36 (s, 1H), 5.95 (m, 1H), 4.02 (s, 4H), 2.55 (m, 2H), 2.47 (s, br, 2H), 1.90 (t, J = 6.5 Hz, 2H).

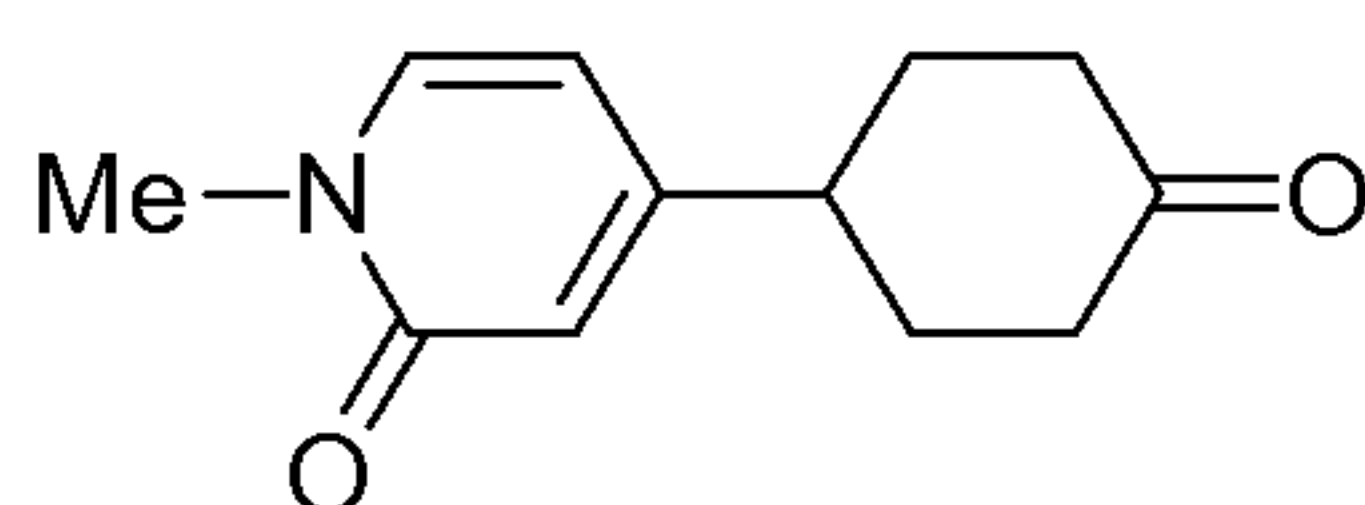
Step D: 4-(1,4-Dioxo-spiro[4.5]dec-8-yl)-1-methyl-1H-pyridin-2-one



The title compound was prepared as a white solid from the hydrogenation of 4-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-1-methyl-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step G of Example 1.

^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 6.0 Hz, 1H), 6.40 (s, 1H), 6.08 (d, J = 6.5 Hz, 1H), 3.98 (m, 4H), 3.50 (s, 3H), 2.35 (m, 1H), 1.80 (m, 4H), 1.65 (m, 4H).

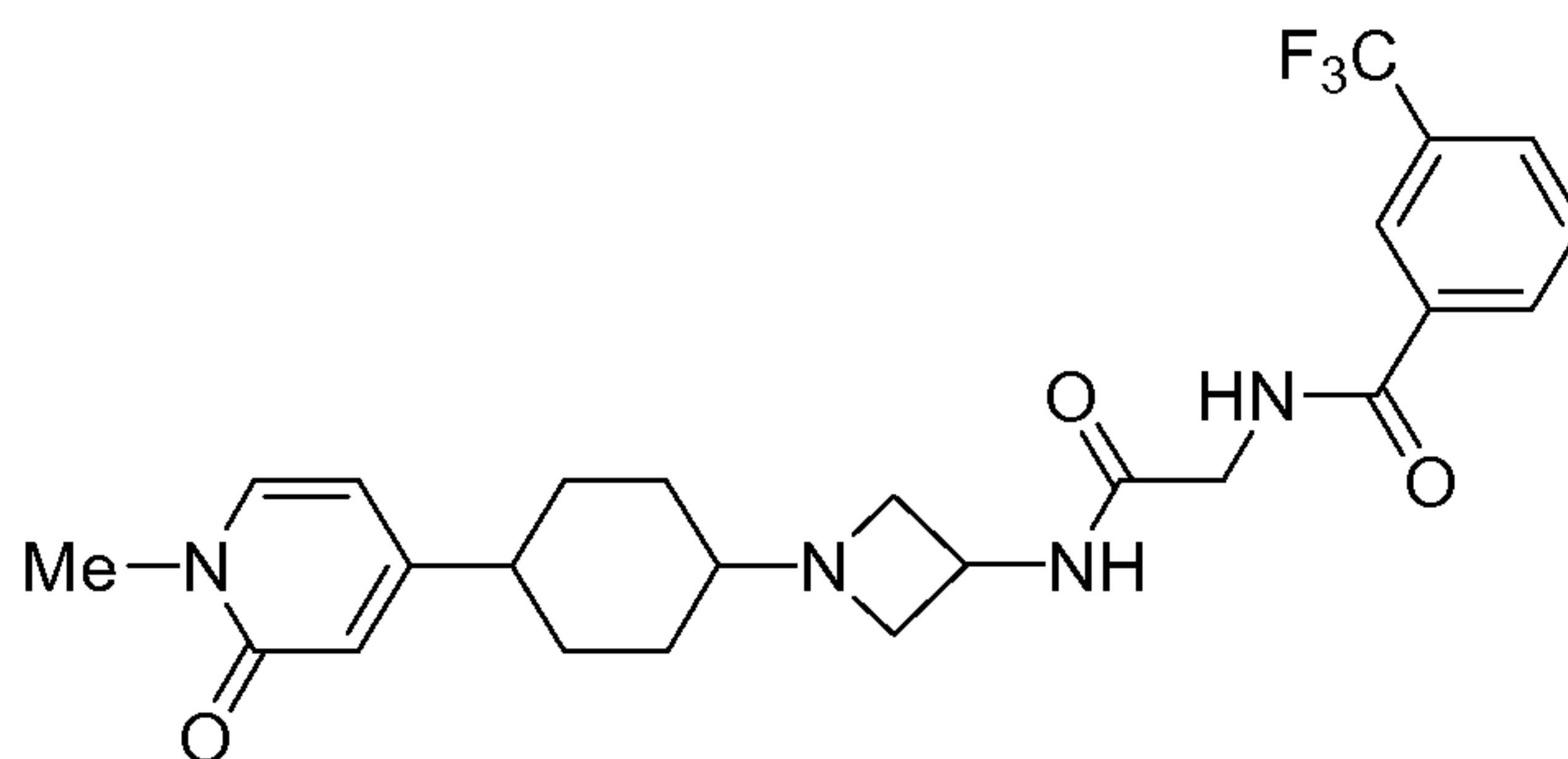
Step E: 1-Methyl-4-(4-oxo-cyclohexyl)-1H-pyridin-2-one



The title compound was prepared as a white solid from the deprotection of 4-(1,4-dioxaspiro[4.5]dec-8-yl)-1-methyl-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step B of Example 2.

- 5 ^1H NMR (400 MHz, CDCl_3) δ 7.25 (d, $J = 6.5$ Hz, 1H), 6.42 (s, 1H), 6.05 (d, $J = 6.3$ Hz, 1H), 3.48 (s, 3H), 2.45 (m, 4H), 2.20 (m, 2H), 1.82 (m, 2H).

Step F: N-(\{1-[4-(1-Methyl-2-oxo-1,2-dihydro-pyridin-4-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl\}-methyl)-3-trifluoromethyl-benzamide



10

The title compounds were prepared as white solids from the reductive amination of 1-methyl-4-(4-oxo-cyclohexyl)-1H-pyridin-2-one (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

- 15 **46a**: less polar isomer,

^1H NMR (400 MHz, d_4 -MeOH) δ 8.25 (s, 1H), 8.11 (d, $J = 6.5$ Hz, 1H), 7.82 (d, $J = 6.0$ Hz, 1H), 7.65 (t, $J = 7.2$ Hz, 1H), 7.21 (d, $J = 6.2$ Hz, 1H), 6.25 (s, 1H), 6.22 (d, $J = 6.5$ Hz, 1H), 4.50 (m, 1H), 3.98 (s, 2H), 3.76 (s, 3H), 3.65 (t, $J = 7.5$ Hz, 2H), 2.95 (t, $J = 7.2$ Hz, 2H), 2.30 (m, 2H), 1.65 (m, 4H), 1.42 (m, 4H).

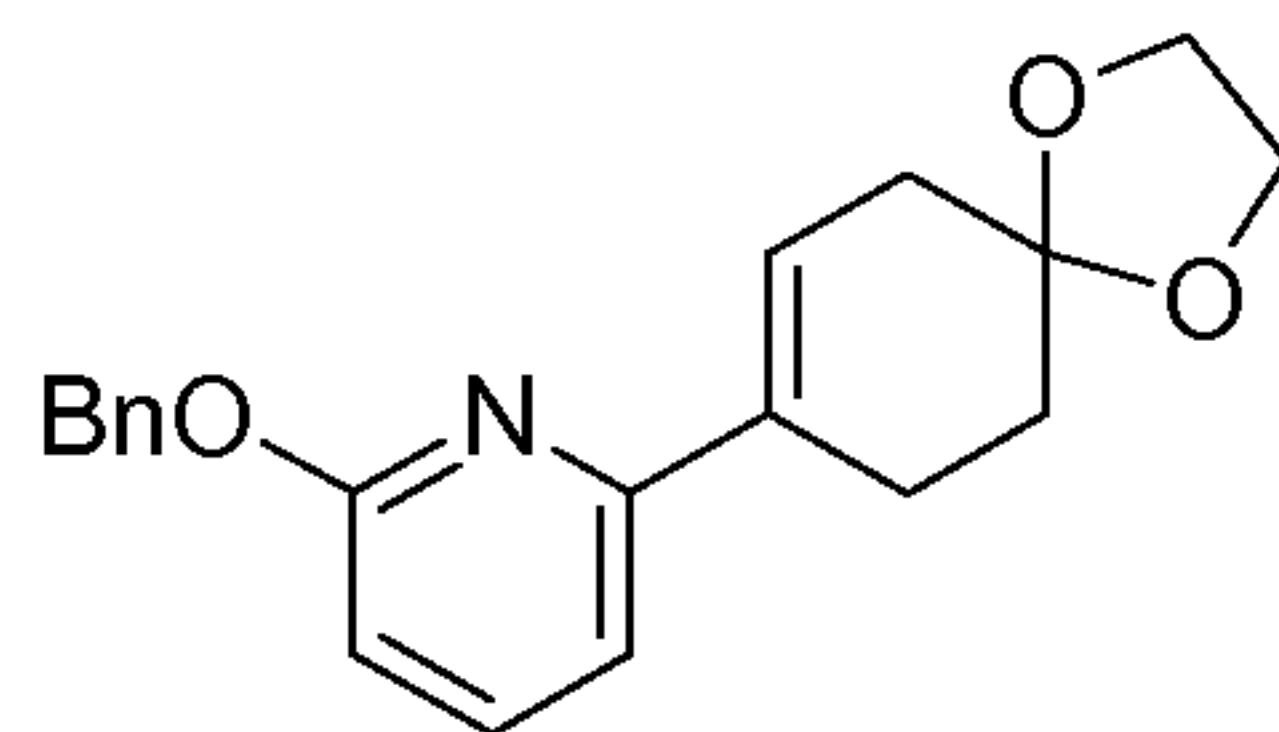
- 20 **46b**: more polar isomer

^1H NMR (400 MHz, d_4 -MeOH) δ 8.21 (s, 1H), 8.18 (d, $J = 6.5$ Hz, 1H), 7.92 (d, $J = 6.5$ Hz, 1H), 7.73 (t, $J = 7.0$ Hz, 1H), 7.50 (d, $J = 5.2$ Hz, 1H), 6.38 (s, 1H), 6.35 (d, $J = 6.0$ Hz, 1H), 4.72 (m, 1H), 4.52 (m, 2H), 4.20 (m, 2H), 4.01 (s, 2H), 3.65 (s, 3H), 3.02 (m, 1H), 2.20 (m, 2H), 2.01 (m, 2H), 1.85 (m, 2H), 1.62 (m, 2H).

25

Example 47: N-({1-[4-(6-Oxo-1,6-dihydro-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

Step A: 2-Benzyloxy-6-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyridine

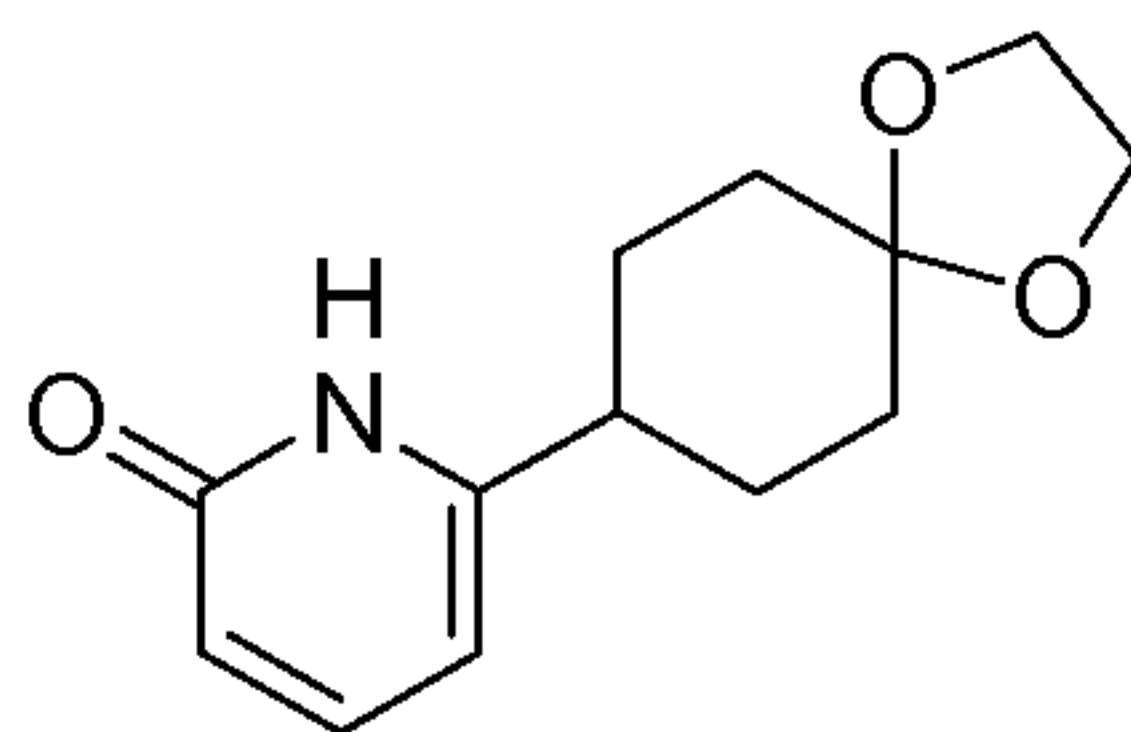


5 The title compound was prepared as described in Step A of Example 3 from 2-benzyloxy-6-bromo-pyridine (TCI) as a white solid.

¹H NMR (CHLOROFORM-d) δ: 7.43 - 7.55 (m, 3H), 7.28 - 7.41 (m, 3H), 6.96 (d, J = 7.6 Hz, 1H), 6.71 (s, 1H), 6.64 (d, J = 8.1 Hz, 1H), 5.41 (s, 2H), 4.03 (s, 4H), 2.75 (d, J = 1.8 Hz, 2H), 2.52 (d, J = 1.3 Hz, 2H), 1.94 (t, J = 6.4 Hz, 2H); LCMS (ESI, M/Z): 324

10 (MH+).

Step B: 6-(1,4-Dioxo-spiro[4.5]dec-8-yl)-1H-pyridin-2-one

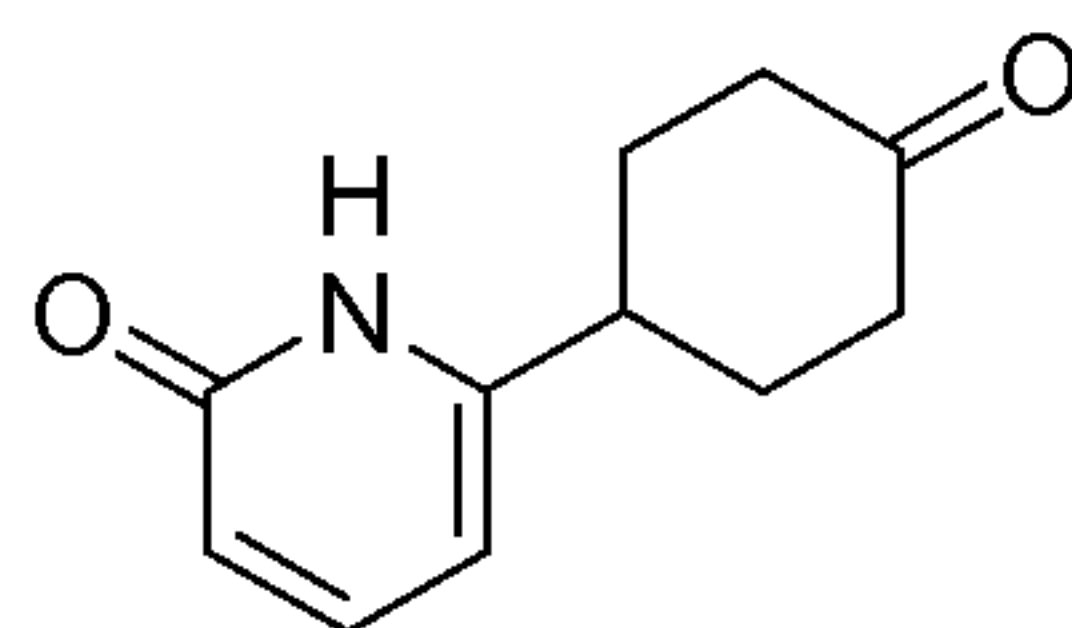


15 The title compound was prepared as a white solid from the hydrogenation of 2-benzyloxy-6-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-pyridine (as prepared in the previous step) using the procedure described in Step G of Example 1.

¹H NMR (DMSO-d₆) δ: 11.26 - 11.60 (m, 1H), 7.33 (dd, J = 9.1, 6.8 Hz, 1H), 6.13 (d, J = 9.1 Hz, 1H), 5.97 (d, J = 6.6 Hz, 1H), 3.87 (s, 4H), 2.38 - 2.50 (m, 2H), 1.44 - 1.90 (m, 8H); LCMS (ESI, M/Z): 236 (MH+).

20

Step C: 6-(4-Oxo-cyclohexyl)-1H-pyridin-2-one

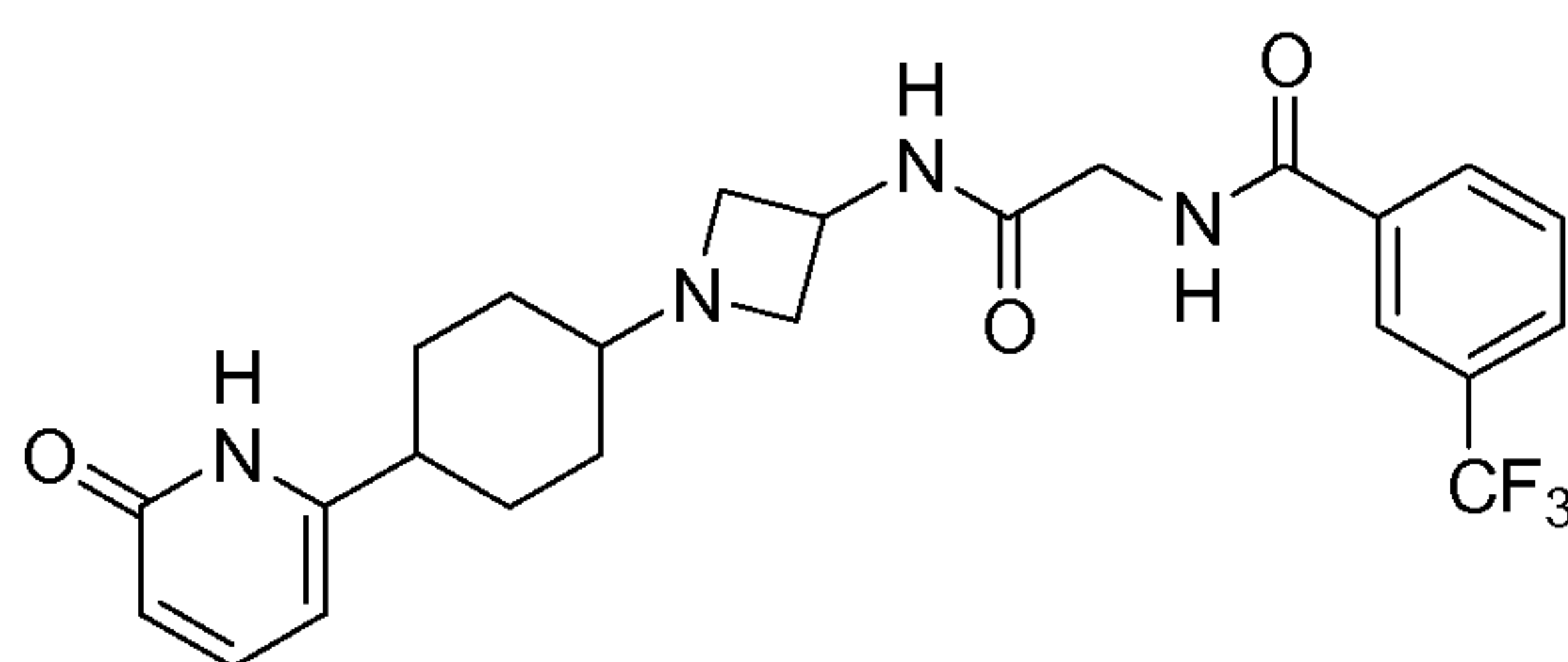


The title compound was prepared as a white solid from the deprotection of 6-(1,4-dioxaspiro[4.5]dec-8-yl)-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step B of Example 2.

LCMS (ESI, M/Z): 192 (MH⁺).

5

Step D: N-({1-[4-(6-Oxo-1,6-dihydro-pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



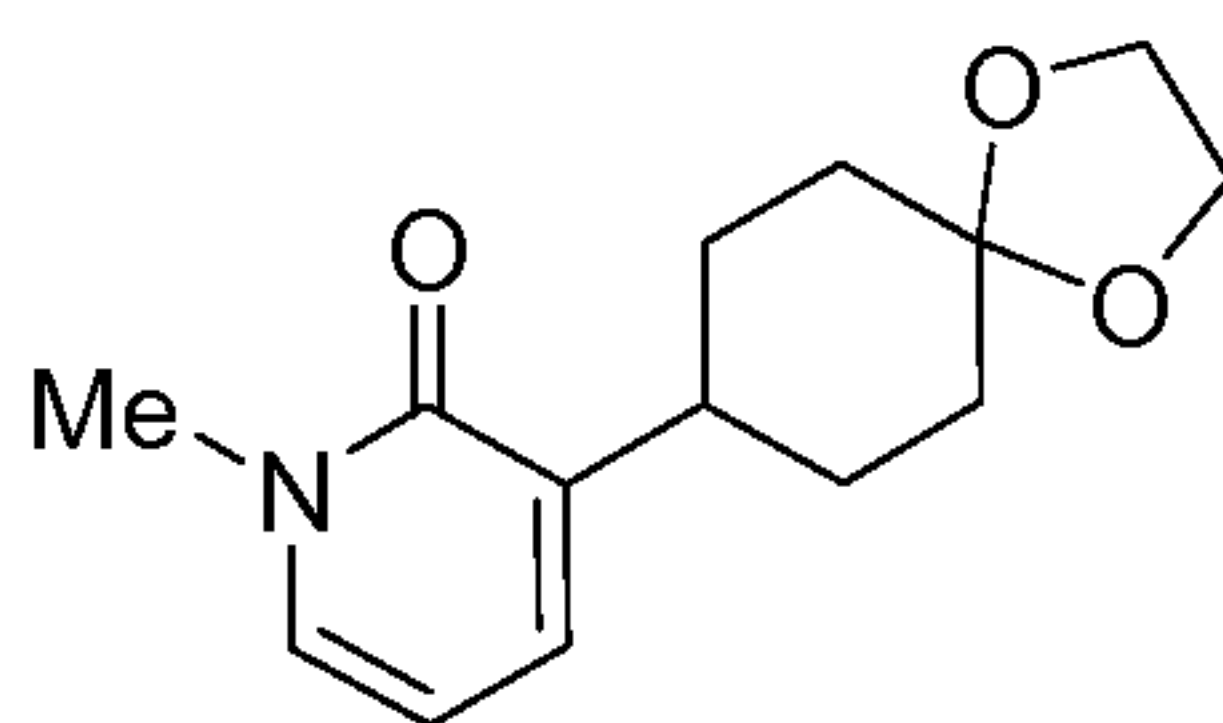
The title compounds were prepared as white solids from the reductive amination of 6-(4-oxo-cyclohexyl)-1H-pyridin-2-one (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

¹H NMR (DMSO-d₆) δ: 9.53 - 9.72 (m, 1H), 9.06 - 9.24 (m, 1H), 8.52 - 8.66 (m, 1H), 8.11 - 8.28 (m, 2H), 7.87 - 8.01 (m, 1H), 7.70 - 7.83 (m, 1H), 7.28 - 7.47 (m, 1H), 6.13 - 6.21 (m, 1H), 5.98 - 6.10 (m, 1H), 4.52 - 4.68 (m, 1H), 4.37 - 4.51 (m, 2H), 3.99 - 4.21 (m, 3H), 3.81 - 3.98 (m, 3H), 1.69 (none, 8H); LCMS (ESI, M/Z): 477 (MH⁺).

Example 48: N-({1-[4-(1-Methyl-2-oxo-1,2-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

20

Step A: 3-(1,4-Dioxaspiro[4.5]dec-8-yl)-1-methyl-1H-pyridin-2-one



To a mixture of 3-(1,4-Dioxaspiro[4.5]dec-8-yl)-pyridin-2-ol (as prepared in example 10, Step B, 182 mg, 0.774 mmol) in dry DMF (5 mL) was added cesium carbonate (367 mg, 1.13 mmol) and methyl iodide (80 μL, 1.28 mmol). The reaction mixture was stirred at room temperature for 16 hours, poured onto saturated sodium bicarbonate solution and

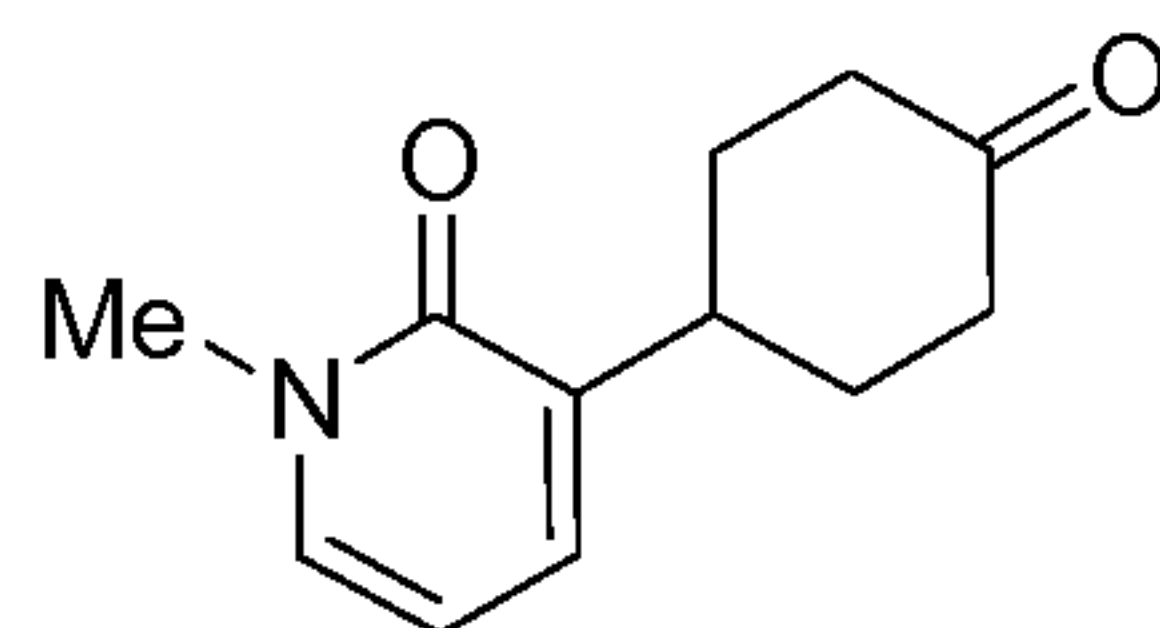
25

extracted with ethyl acetate. Purification by flash chromatography (SiO₂, 0-10% MeOH/CH₂Cl₂) afforded 2-(1,4-dioxaspiro[4.5]dec-8-yl)-1-methyl-1H-pyridin-4-one as the more polar material along with the O-Methyl isomer as the less polar isomer.

LCMS (ESI, M/Z): 250 (MH⁺).

5

Step B: 1-Methyl-3-(4-oxo-cyclohexyl)-1H-pyridin-2-one

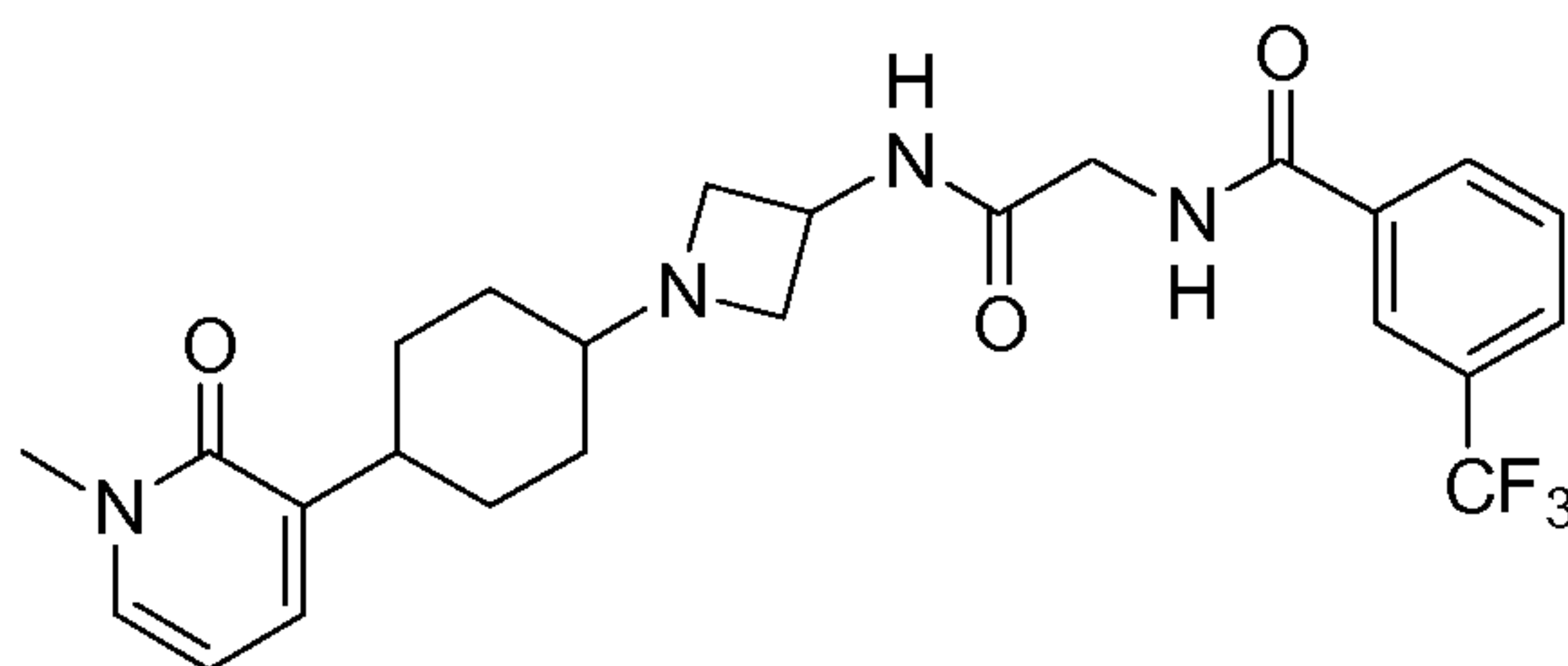


The title compound was prepared as a white solid from the deprotection of 3-(1,4-dioxaspiro[4.5]dec-8-yl)-1-methyl-1H-pyridin-2-one (as prepared in the previous step) using the procedure described in Step B of Example 2.

10

LCMS (ESI, M/Z): 206 (MH⁺).

Step C: N-({1-[4-(1-Methyl-2-oxo-1,2-dihydro-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



15

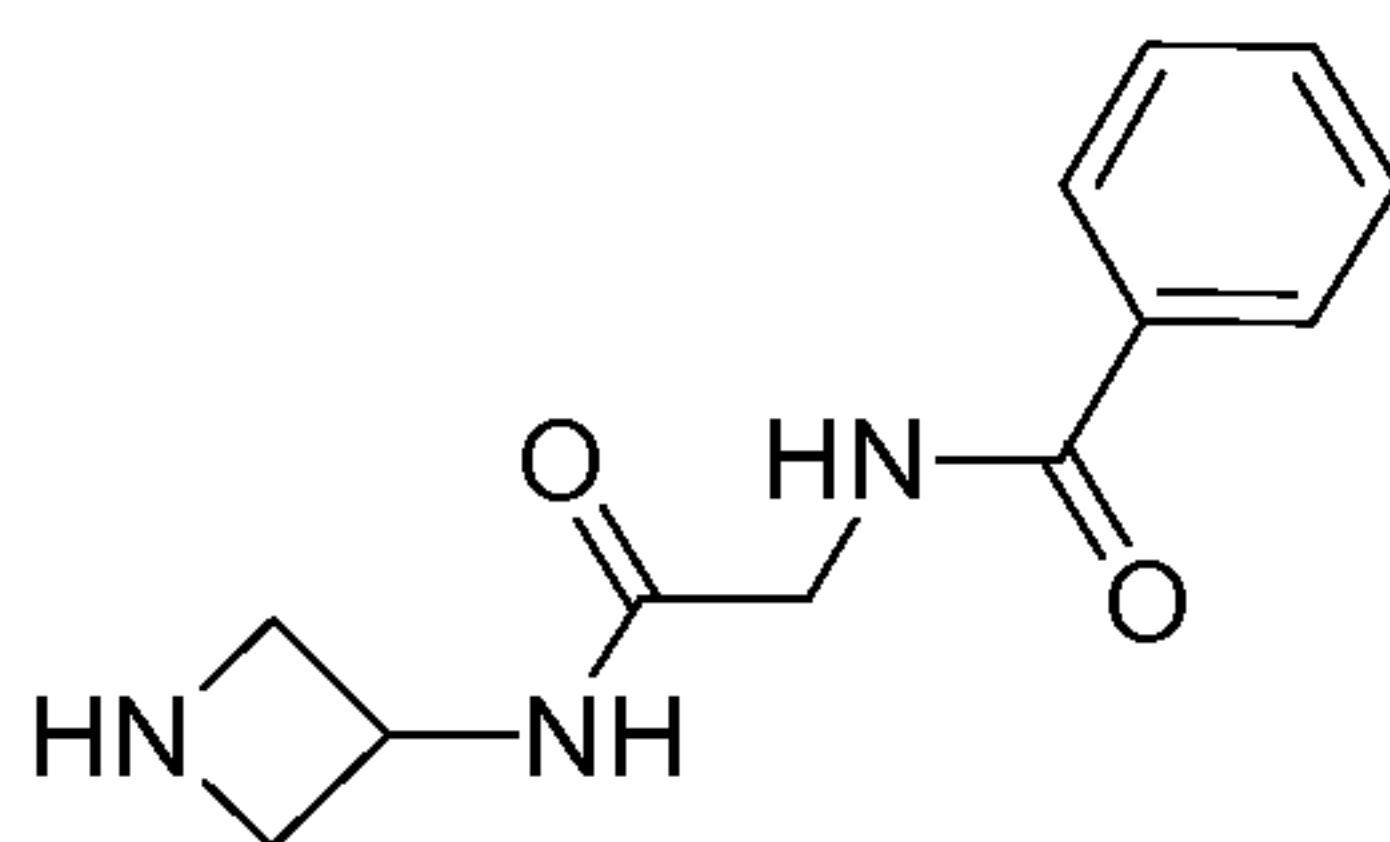
The title compound was prepared as a white solid from the reductive amination of 1-methyl-3-(4-oxo-cyclohexyl)-1H-pyridin-2-one (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

20

LCMS (ESI, M/Z): 477 (MH⁺).

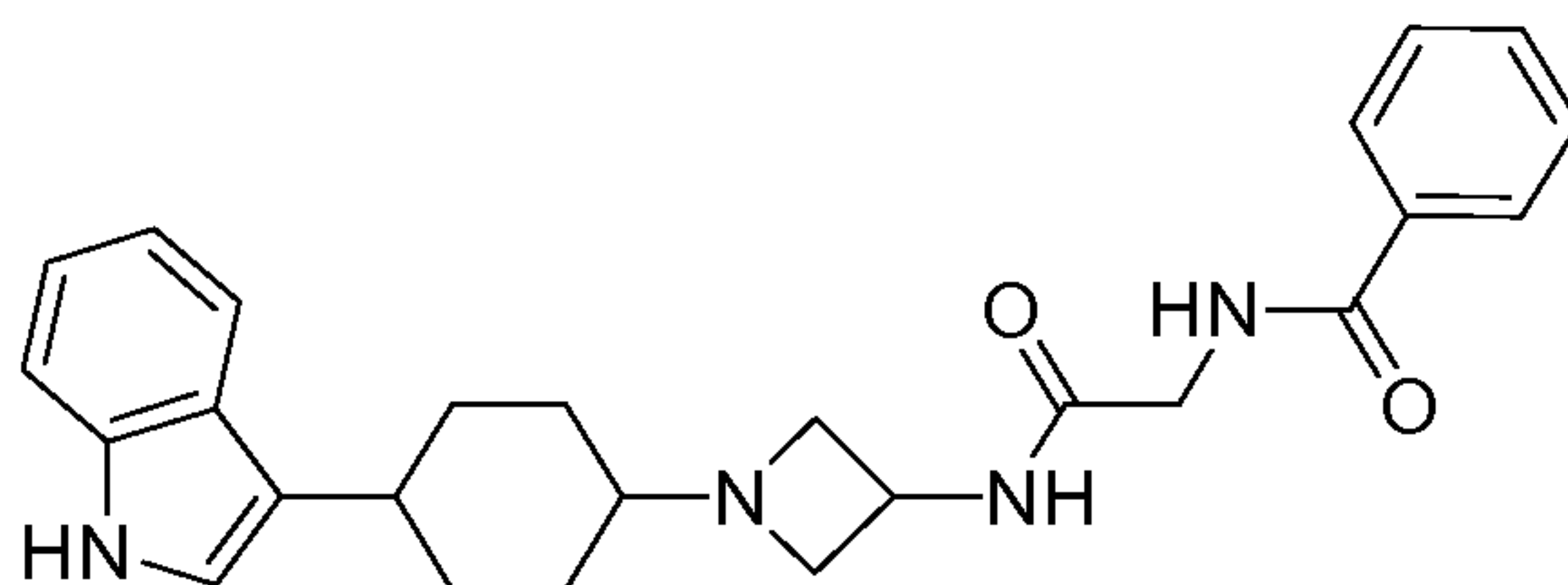
Example 49: N-({1-[4-(1H-Indol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-benzamide

Step A: N-(Azetidin-3-ylcarbamoylmethyl)-benzamide TFA salt



The title compound was prepared as a TFA salt from the EDCI coupling of hippuric acid (Fluka) and 3-amino-azetidine-1-carboxylic acid tert-butyl ester (BetaPharm) followed by the de-protection of N-Boc by TFA using the procedures described in Example 1, steps D and E.

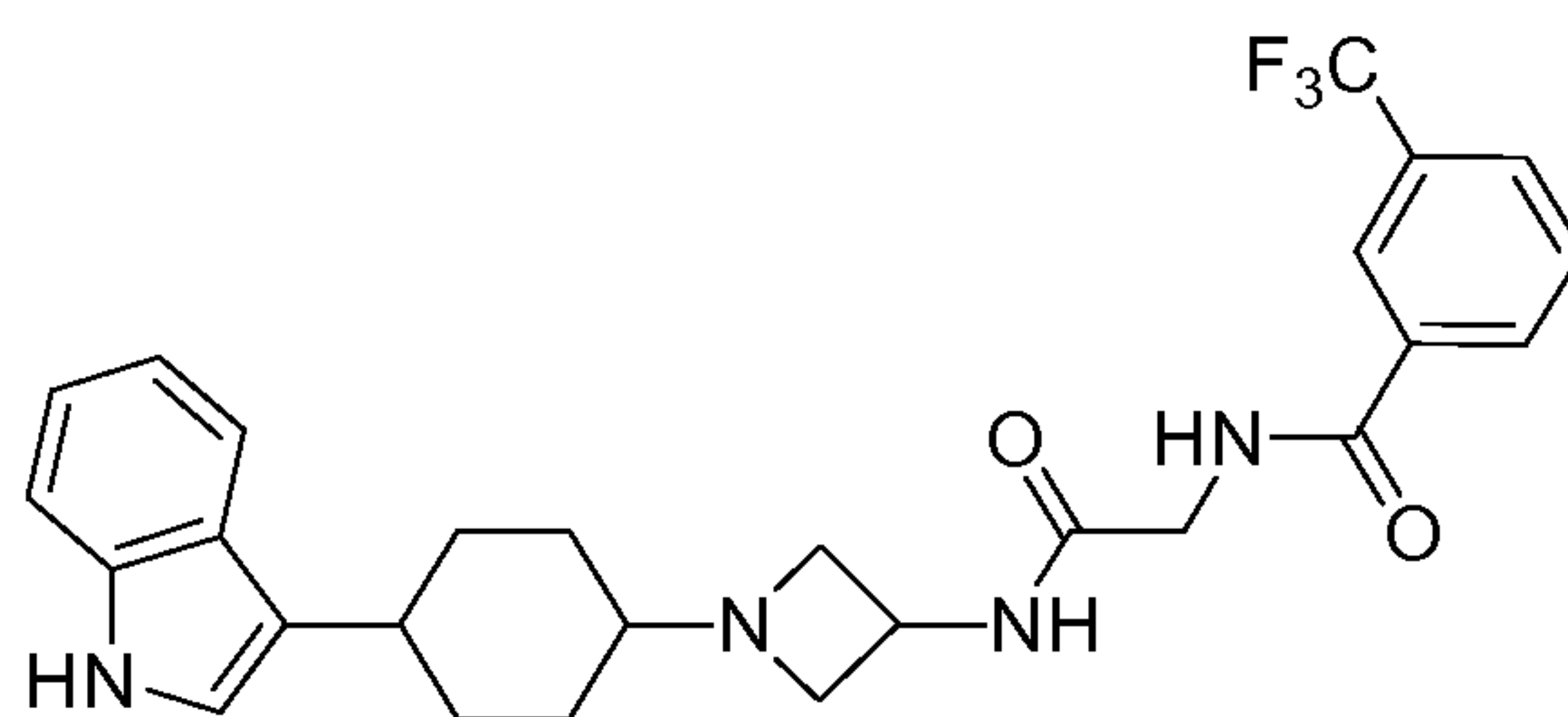
Step B: N-({1-[4-(1H-Indol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-benzamide



The title compounds were prepared as white solids from the reductive amination of 4-(1H-indol-3-yl)-cyclohexanone (prepared following the procedure described in EP 345808 A119891213) and N-(azetidin-3-ylcarbamoylmethyl)-benzamide TFA salt using the procedure described in Step F of Example 1.

¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 7.85 (d, J = 6.5 Hz, 1H), 6.62 (d, J = 6.6 Hz, 1H), 6.55 (d, J = 6.4 Hz, 1H), 6.48 (t, J = 6.8 Hz, 1H), 7.36 (d, J = 6.5 Hz, 1H), 7.22 (t, J = 6.4 Hz, 1H), 7.10 (t, J = 6.6 Hz, 1H), 7.01 (s, 1H), 5.45 (s, br, 1H), 4.52 (m, 1H), 4.15 (d, J = 3.0 Hz, 2H), 3.55 (t, J = 7.0 Hz, 2H), 2.90 (m, 1H), 2.88 (t, J = 7.0 Hz, 2H), 1.98~1.55 (m, 8H).

Example 50: N-({1-[4-(1H-Indol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

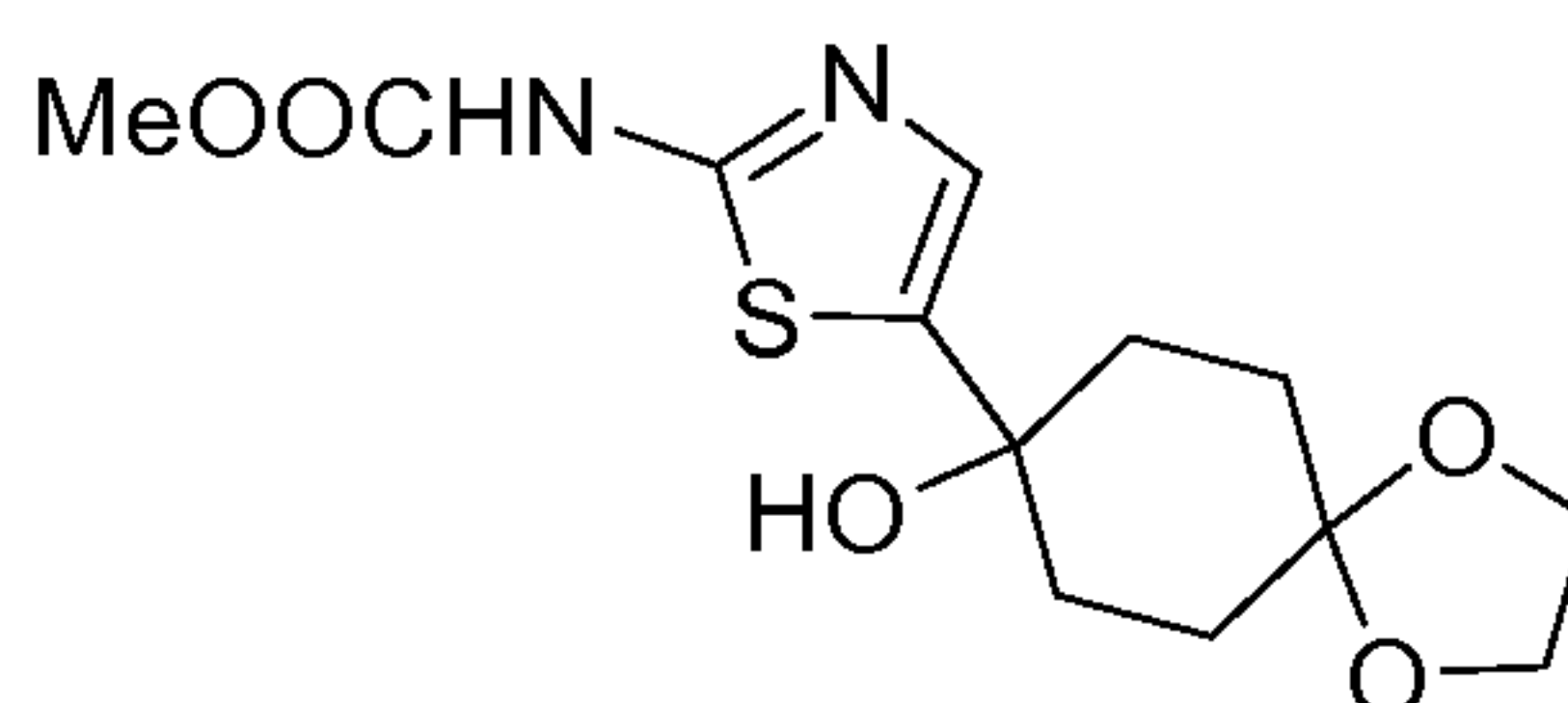


The title compounds were prepared as white solids from the reductive amination of 4-(1H-indol-3-yl)-cyclohexanone (prepared following the procedure described in EP 345808 A119891213) and N-(azetidin-3-ylcarbamoymethyl)-3-trifluoromethyl-
 5 benzamide using the procedure described in Step F of Example 1.

¹H NMR (400 MHz, *d*₄-MeOH) δ 8.25 (s, 1H), 8.20 (d, *J* = 7.0 Hz, 1H), 7.88 (d, *J* = 6.5 Hz, 1H), 7.72 (t, *J* = 6.8 Hz, 1H), 7.55 (d, *J* = 6.4 Hz, 1H), 7.42 (d, *J* = 5.8 Hz, 1H), 7.18 (s, 1H), 7.15 (t, *J* = 6.0 Hz, 1H), 7.02 (t, *J* = 6.8 Hz, 1H), 4.68 (m, 1H), 4.32 (t, *J* = 7.4 Hz, 2H), 4.26 (t, *J* = 7.5 Hz, 2H), 4.10 (d, *J* = 3.2 Hz, 2H), 3.50 (m, 1H), 3.20 (m, 1H),
 10 2.05~1.81 (m, 8H).

Example 51: [5-(4-{3-[2-(3-Trifluoromethyl-benzoylamino)-acetylamino]-azetidin-1-yl}-cyclohexyl)-thiazol-2-yl]-carbamic acid methyl ester

Step A: [5-(8-Hydroxy-1,4-dioxo-spiro[4.5]dec-8-yl)-thiazol-2-yl]-carbamic acid methyl ester
 15

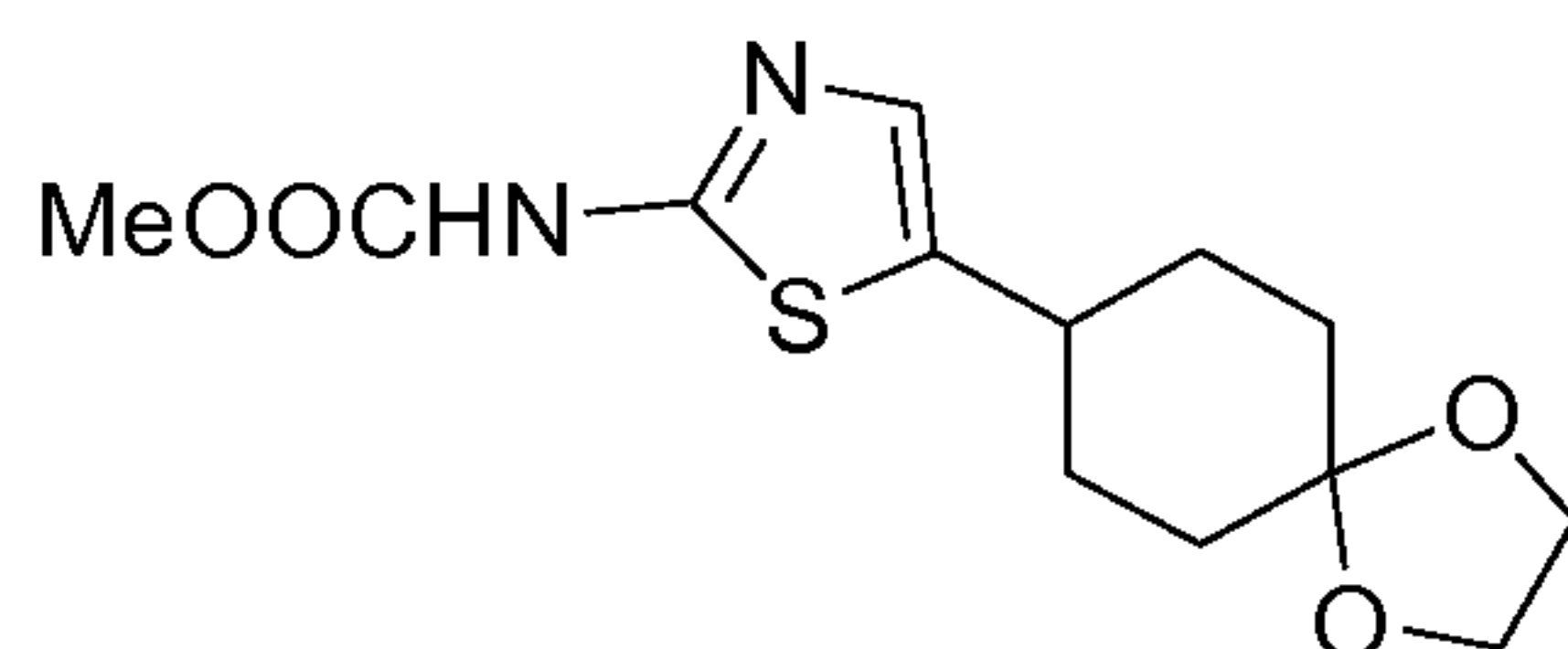


A solution of n-BuLi (2.5 M in hexanes, 28 mL, 70 mmol) was dropped slowly into a solution of thiazol-2-yl-carbamic acid methyl ester (Aldrich, 5.0 g, 31.6 mmol) in THF (100 mL) at -78 °C, over 10 min. The reaction was stirred for additional 20 min. at -78
 20 °C. A solution of 1,4-dioxo-spiro[4.5]decan-8-one (Aldrich, 7.0 g, 45 mmol) in THF (20 mL) was slowly dropped into the reaction. After addition, the reaction was stirred for an additional 2 hours at -78 °C. The reaction was then quenched with diluted NH₄Cl solution and warmed to room temperature. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was washed

with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give a yellow solid, which was then purified by silica gel column on a CombiFlash® system using hexanes and ethyl acetate (from 10% ethyl acetate to 100% ethyl acetate) to afford the title compound as a white solid.

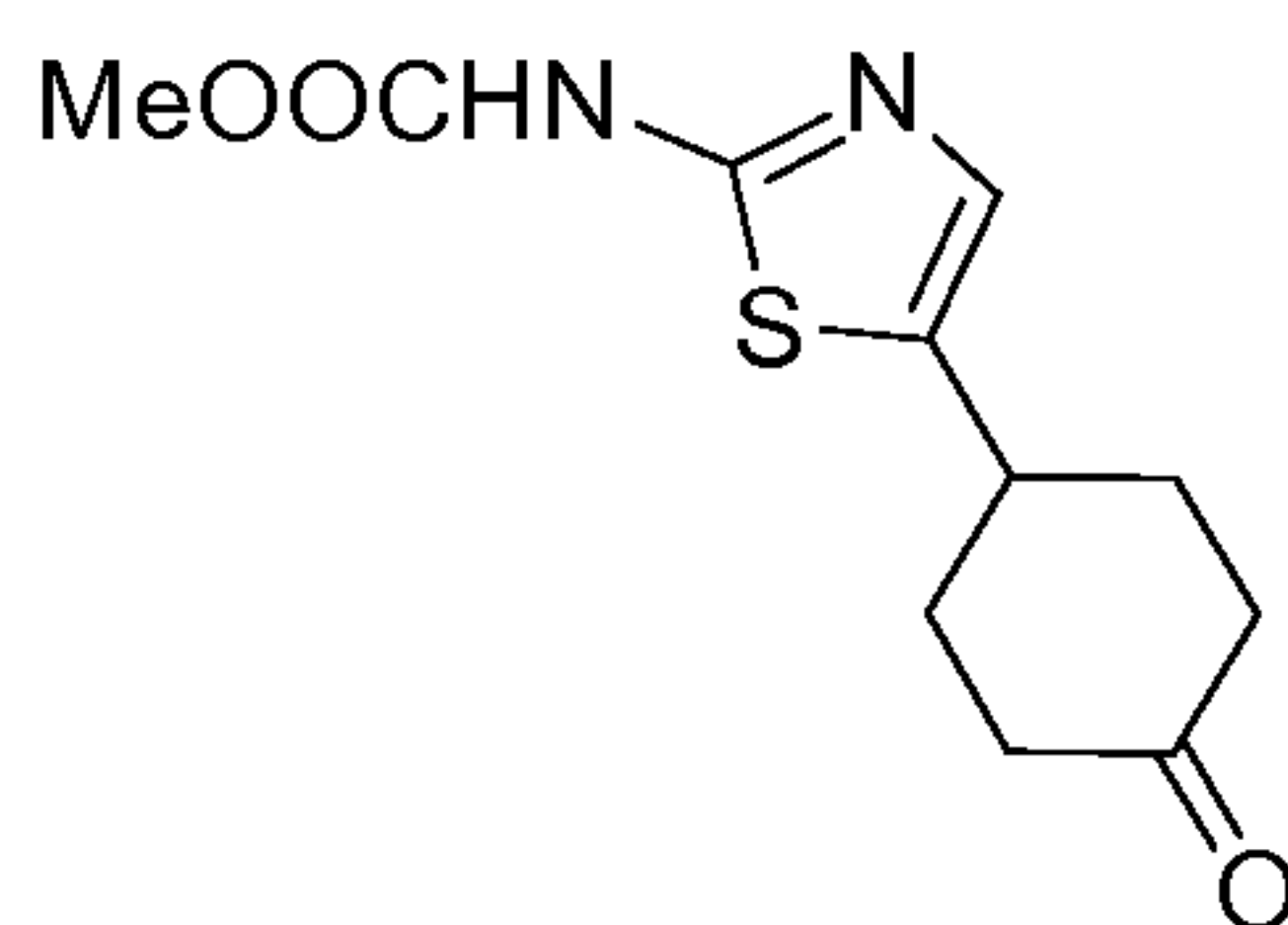
- 5 ^1H NMR (400 MHz, CDCl_3) δ 7.21 (s, 1H), 4.02 (m, 4H), 3.87 (s, 3H), 2.10 (m, 2H), 2.05 (m, 4H), 1.72 (m, 2H).

Step B: [5-(1,4-Dioxo-spiro[4.5]dec-8-yl)-thiazol-2-yl]-carbamic acid methyl ester



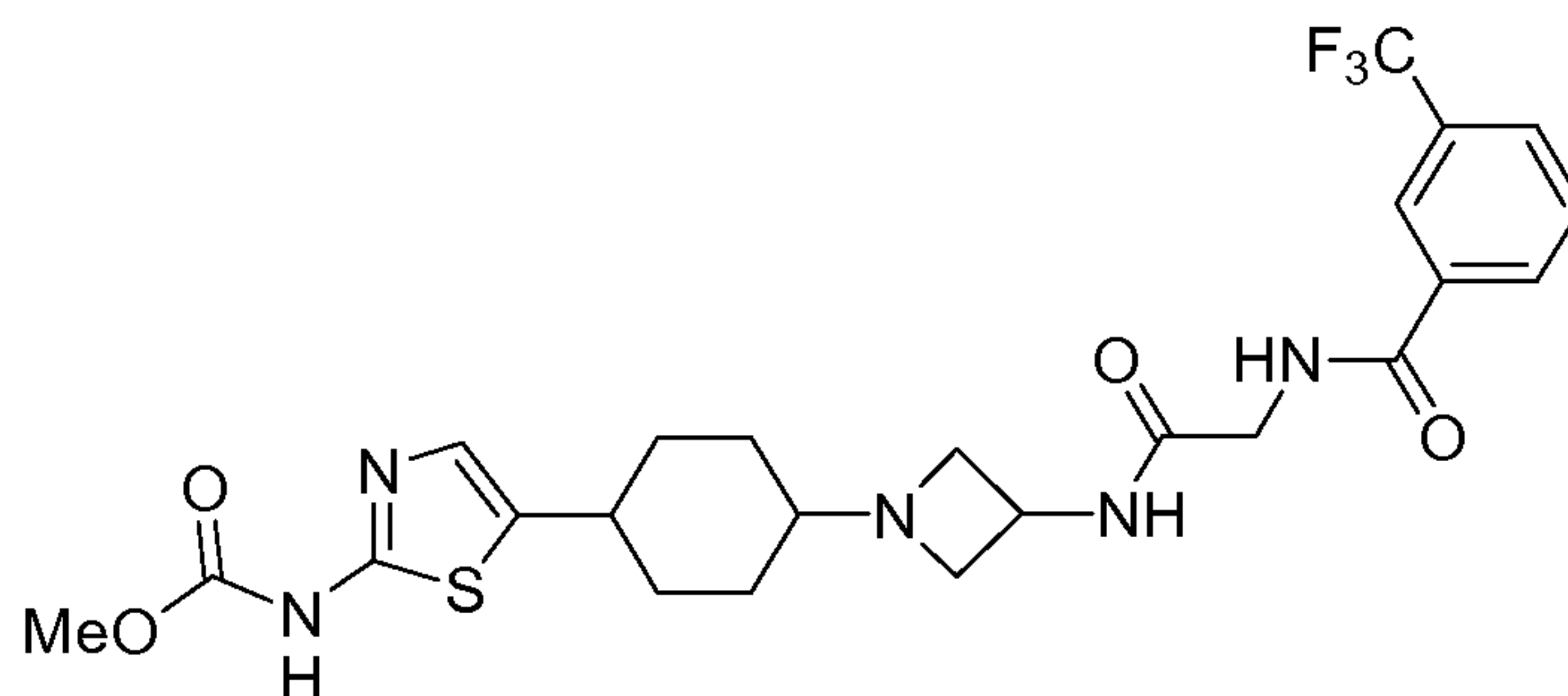
- 10 The title compounds were prepared as white solids from Burgess's reagent catalyzed dehydration of [5-(8-Hydroxy-1,4-dioxo-spiro[4.5]dec-8-yl)-thiazol-2-yl]-carbamic acid methyl ester (as prepared in the previous step) using the procedure described in Step C of Example 1 followed by hydrogenation of the corresponding alkene following the procedure described in Step G of Example 1.
- 15 ^1H NMR (400 MHz, CDCl_3) δ 7.05 (s, 1H), 3.98 (s, 4H), 3.85 (s, 3H), 2.78 (m, 1H), 2.02 (m, 2H), 1.85 (m, 4H), 1.70 (m, 2H).

Step C: [5-(4-Oxo-cyclohexyl)-thiazol-2-yl]-carbamic acid methyl ester



- 20 The title compound was prepared as a white solid from the deprotection of [5-(1,4-dioxo-spiro[4.5]dec-8-yl)-thiazol-2-yl]-carbamic acid methyl ester (as prepared in the previous step) using the procedure described in Step B of Example 2.
- ^1H NMR (400 MHz, CDCl_3) δ 7.15 (s, 1H), 3.90 (s, 3H), 3.31 (m, 1H), 2.52 (m, 4H), 2.40 (m, 2H), 2.02 (m, 2H).

Step D: [5-(4-{3-[2-(3-Trifluoromethyl-benzoylamino)-acetylamino]-azetidin-1-yl}-cyclohexyl)-thiazol-2-yl]-carbamic acid methyl ester



The title compounds were prepared as white solids from the reductive amination of [5-(4-oxo-cyclohexyl)-thiazol-2-yl]-carbamic acid methyl ester (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

51a: less polar isomer,

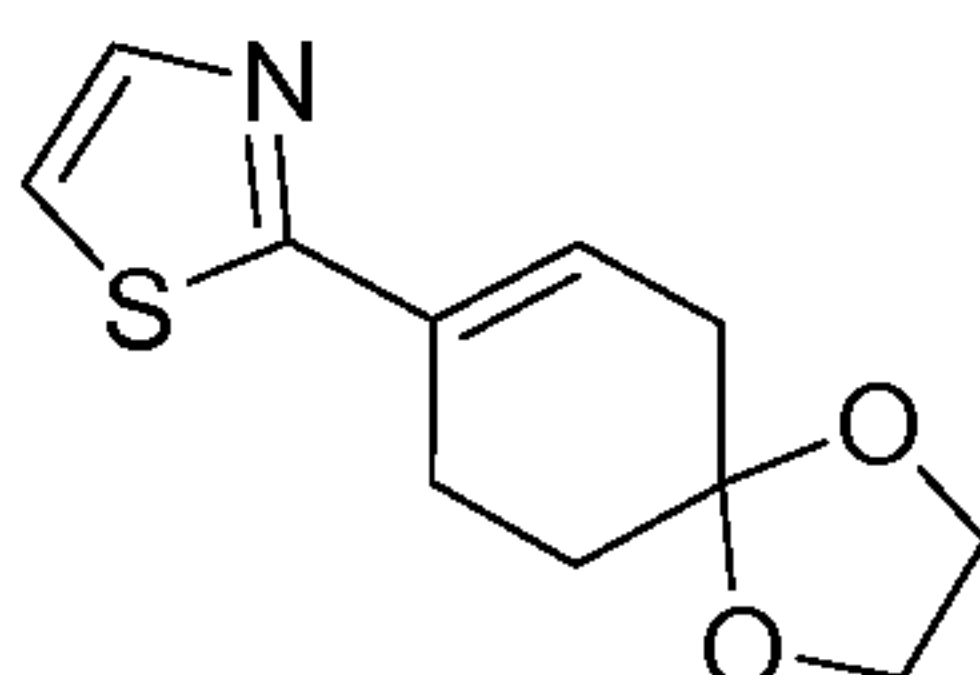
¹H NMR (400 MHz, *d*₄-MeOH) δ 8.25 (s, 1H), 8.20 (d, *J* = 6.0 Hz, 1H), 7.88 (d, *J* = 6.0 Hz, 1H), 7.69 (t, *J* = 6.0 Hz, 1H), 7.10 (s, 1H), 4.45 (m, 1H), 4.10 (s, 2H), 3.88 (s, 3H), 3.75 (t, *J* = 4.0 Hz, 2H), 3.12 (s, br, 2H), 2.85 (s, br, 1H), 2.35 (m, 1H), 1.90 (m, 2H), 1.82 (m, 2H), 1.62 (m, 4H).

51b: more polar isomer

¹H NMR (400 MHz, *d*₄-MeOH) δ 8.23 (s, 1H), 8.16 (d, *J* = 6.1 Hz, 1H), 7.87 (d, *J* = 5.5 Hz, 1H), 7.72 (t, *J* = 5.5 Hz, 1H), 7.02 (s, 1H), 4.42 (m, 1H), 4.08 (s, 2H), 3.86 (s, 3H), 3.68 (t, *J* = 5.0 Hz, 2H), 3.10 (t, *J* = 5.2 Hz, 2H), 2.52 (m, 1H), 2.10 (m, 2H), 1.95 (m, 2H), 1.54 (m, 2H), 1.21 (m, 2H).

Example 52: 5-(4-{3-[2-(3-Trifluoromethyl-benzoylamino)-acetylamino]-azetidin-1-yl}-cyclohexyl)-thiazole-2-carboxylic acid

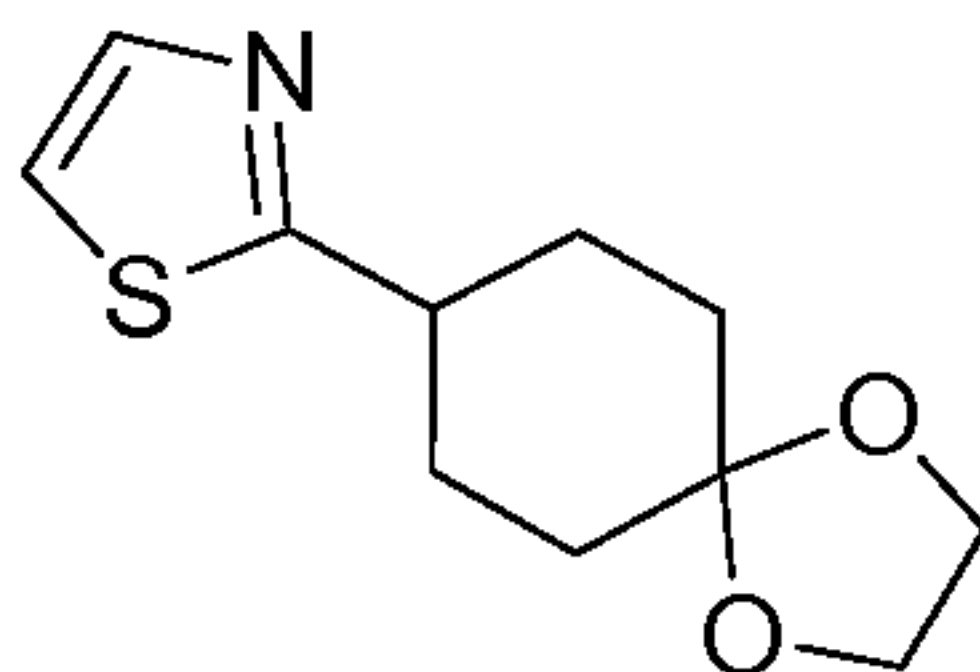
Step A: 2-(1,4-Dioxo-spiro[4.5]dec-7-en-8-yl)-thiazole



The title compound was prepared as described in Step A of Example 3 from 2-bromothiazole (Aldrich) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.72 (s, 1H), 7.18 (s, 1H), 6.52 (t, $J = 3.5$ Hz, 1H), 4.01 (s, 4H), 2.82 (t, $J = 4.1$ Hz, 2H), 2.50 (m, 2H), 1.92 (t, $J = 4.0$ Hz, 2H).

Step B: 2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-thiazole



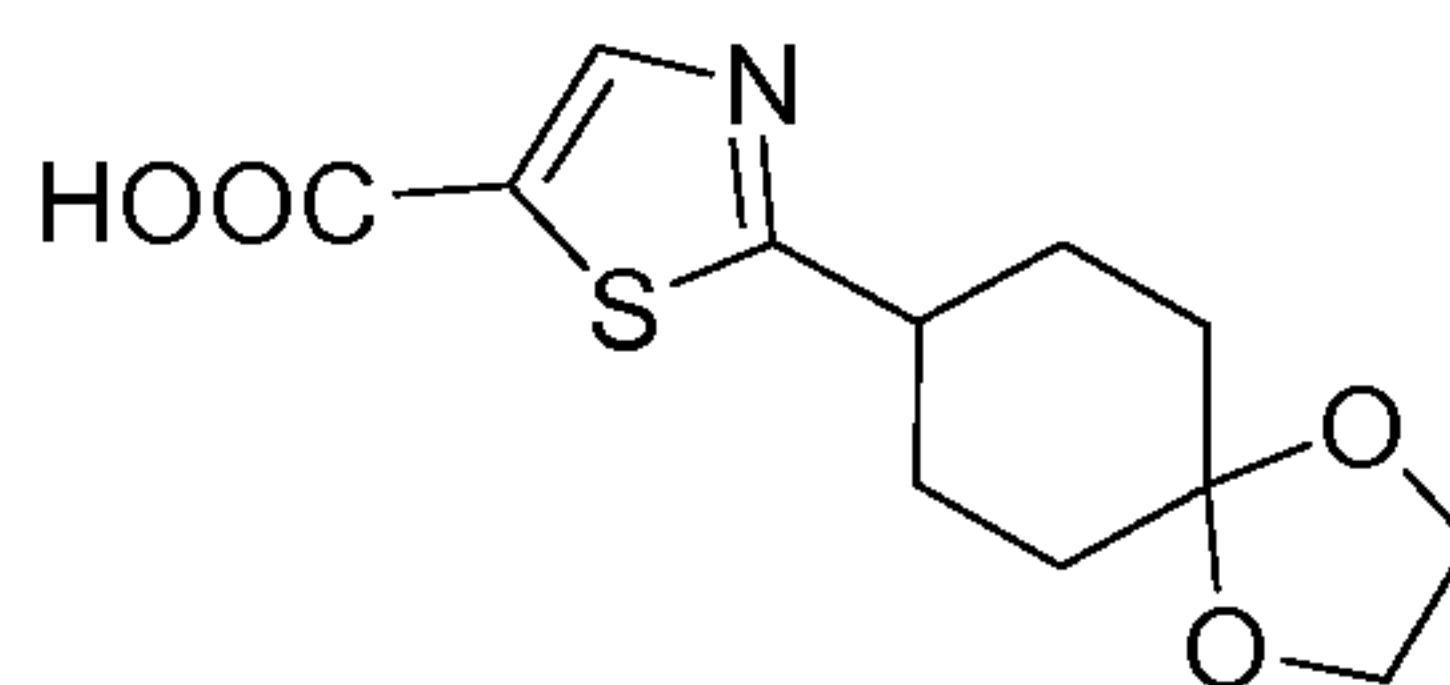
5

The title compound was prepared as a white solid from the hydrogenation of 2-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-thiazole (as prepared in the previous step) using the procedure described in Step G of Example 1.

ESI-MS (m/z): Calcd. For $\text{C}_{11}\text{H}_{15}\text{NO}_2\text{S}$, 225; Found: 226 ($\text{M}+\text{H}$).

10

Step C: 2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-thiazole-5-carboxylic acid



15

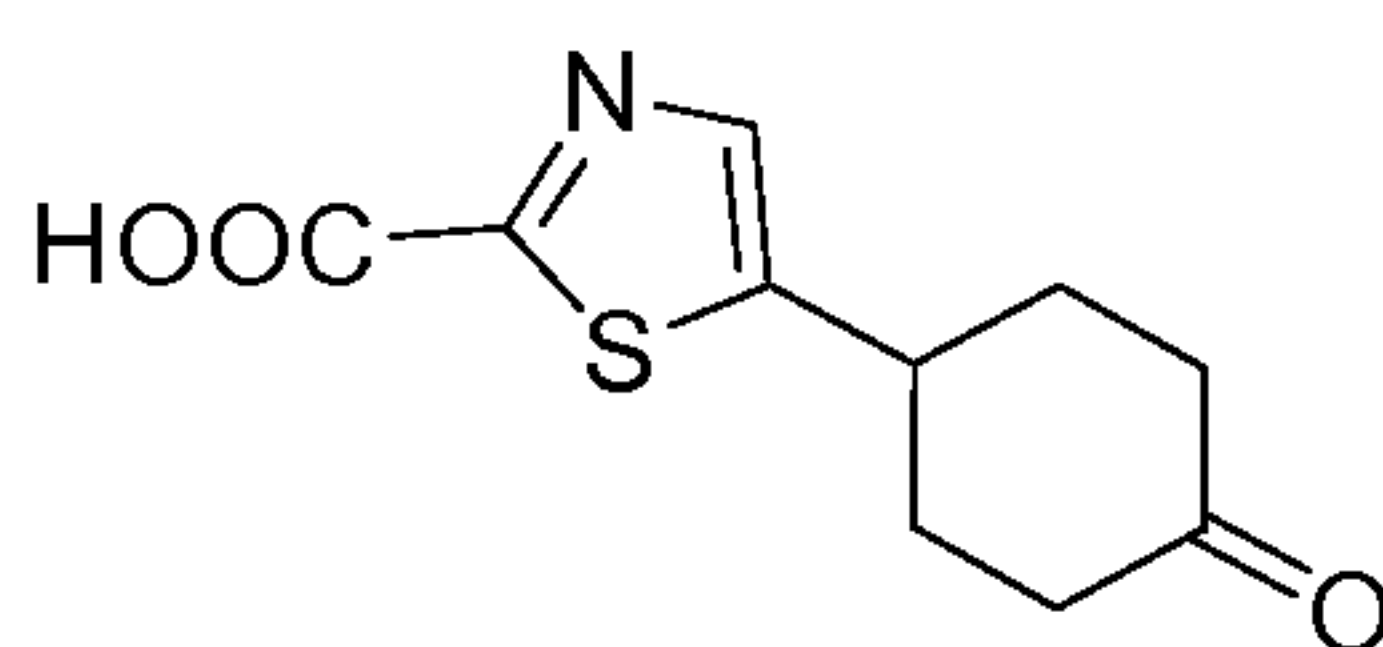
A solution of $n\text{-BuLi}$ (2.5 M in hexanes, 5 mL, 12 mmol) was added dropwise into 2-(1,4-dioxo-spiro[4.5]dec-8-yl)-thiazole (2.50 g, 11 mmol) in THF (10 mL) at -78°C . The reaction was kept at -78°C for 30 min. The solution was added to solid dry ice (~ 5 g) dropwise. After addition, the reaction was warmed to room temperature slowly over 1 hour and quenched with 1 N NaOH (~ 10 mL) solution. The solvent was removed and the residue was partitioned between ether and water. The aqueous layer was adjusted to $\text{pH} = 6$ with 5% HCl and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give the title compound as white solid.

20

^1H NMR (400 MHz, CDCl_3) δ 10.9 (s, br, 1H), 8.38 (s, 1H), 4.01 (s, 4H), 3.15 (m, 1H), 2.21 (m, 2H), 1.95 (m, 4H), .76 (m, 2H).

25

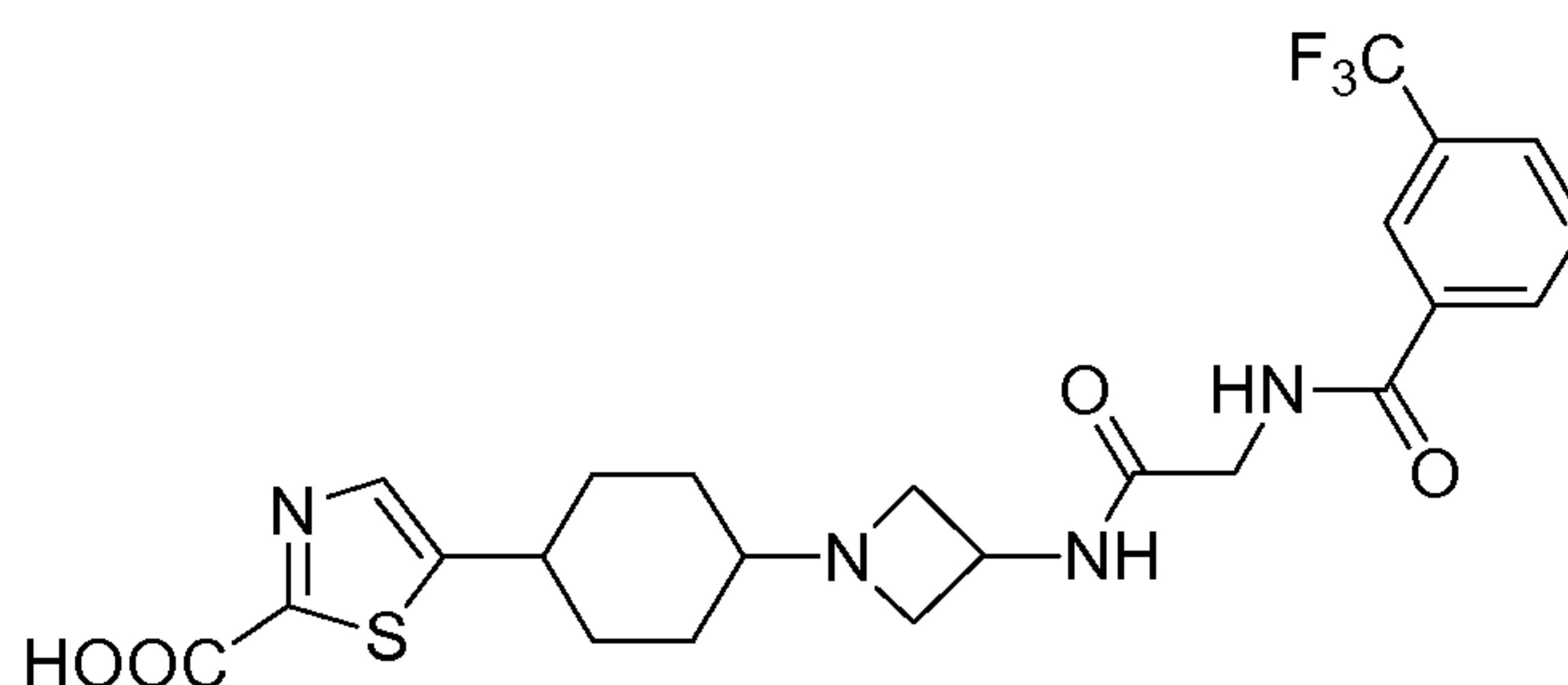
Step D: 5-(4-Oxo-cyclohexyl)-thiazole-2-carboxylic acid



The title compound was prepared as a white solid from the deprotection of 2-(1,4-dioxaspiro[4.5]dec-8-yl)-thiazole-5-carboxylic acid (as prepared in the previous step) using the procedure described in Step B of Example 2.

- 5 ESI-MS (m/z): Calcd. For C₁₀H₁₁NO₃S, 225; found: 226 (M+H).

Step E: 5-(4-{3-[2-(3-Trifluoromethyl-benzoylamino)-acetylamino]-azetidin-1-yl}-cyclohexyl)-thiazole-2-carboxylic acid



- 10 The title compounds were prepared as white solids from the reductive amination of 5-(4-oxo-cyclohexyl)-thiazole-2-carboxylic acid (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylemethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

52a: less polar isomer,

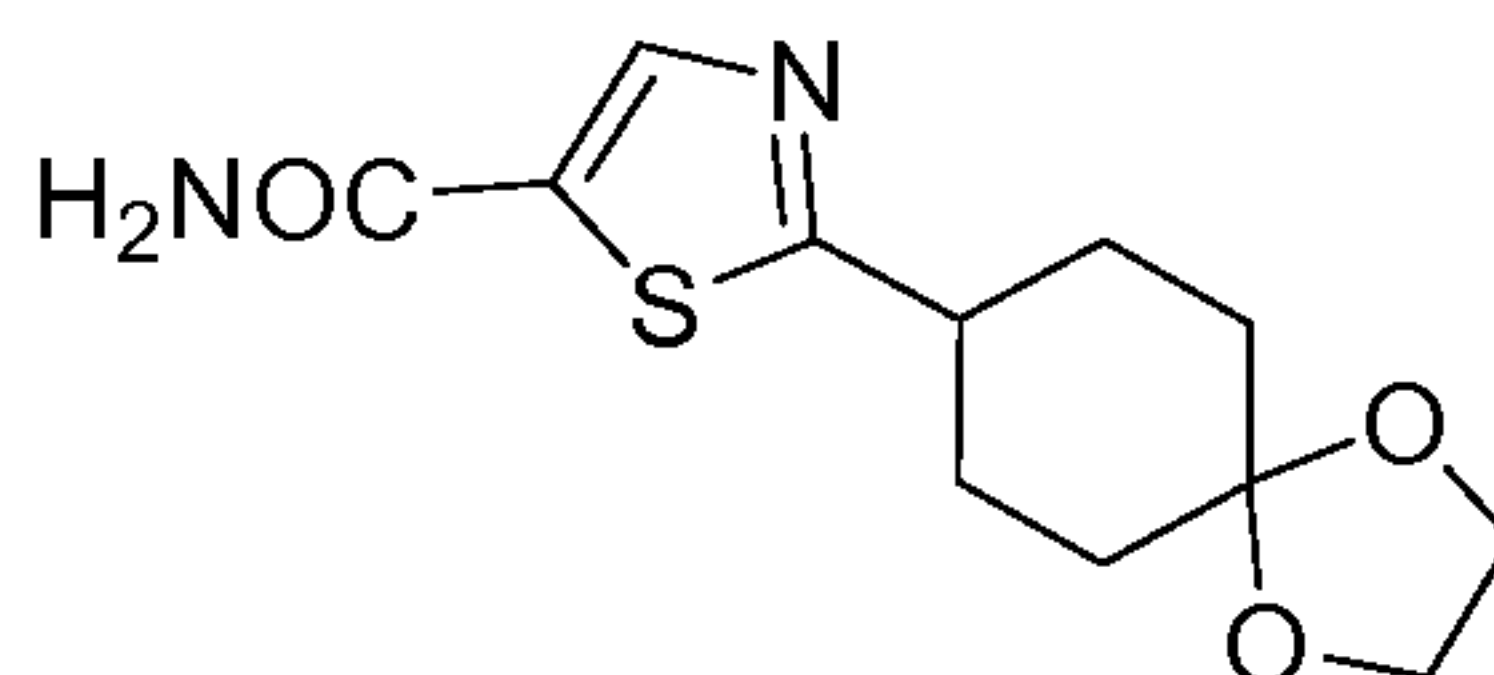
- 15 ¹H NMR (400 MHz, d₄-MeOH) δ 8.25 (s, 1H), 8.20 (d, J = 6.0 Hz, 1H), 7.92 (s, 1H), 7.88 (d, J = 6.0 Hz, 1H), 7.70 (t, J = 6.0 Hz, 1H), 4.62 (m, 1H), 4.20 (t, J = 6.0 Hz, 2H), 4.08 (s, 2H), 3.78 (t, J = 6.5 Hz, 2H), 3.02 (m, 1H), 2.35 (s, br, 1H), 2.25 (m, 4H), 1.82 (m, 4H).

52b: more polar isomer

- 20 ¹H NMR (400 MHz, d₄-MeOH) δ 8.20 (s, 1H), 8.16 (d, J = 6.5 Hz, 1H), 7.90 (d, J = 6.0 Hz, 1H), 7.88 (s, 1H), 7.68 (t, J = 6.1 Hz, 1H), 4.70 (m, 1H), 4.23 (t, J = 6.8 Hz, 2H), 4.10 (s, 2H), 3.86 (t, J = 6.0 Hz, 2H), 3.18 (m, 1H), 2.97 (m, 1H), 2.21 (m, 2H), 1.85 (m, 4H), 1.64 (m, 1H), 1.35 (m, 1H).

Example 53: 5-(4-{3-[2-(3-Trifluoromethyl-benzoylamino)-acetylamino]-azetidin-1-yl}-cyclohexyl)-thiazole-2-carboxylic acid amide

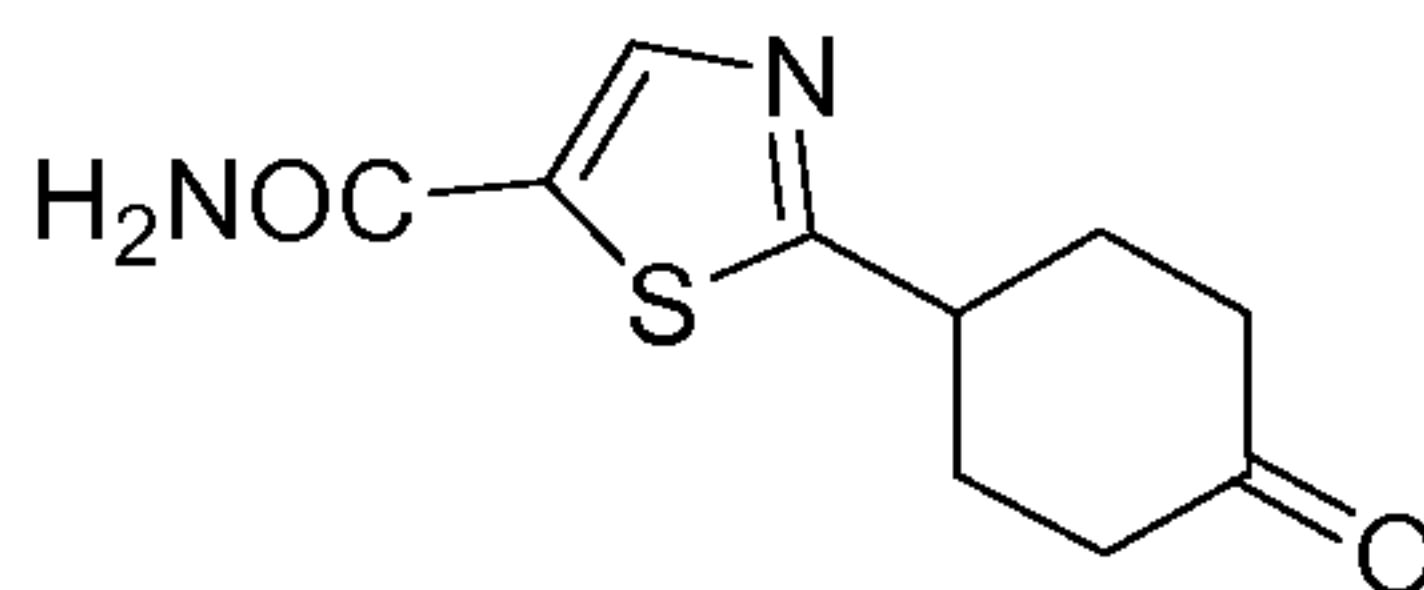
Step A: 2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-thiazole-5-carboxylic acid amide



5 A solution of 2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-thiazole-5-carboxylic acid (as prepared in Example 52, Step C, 700 mg, 2.60 mmol), EDCI (600 mg, 3.12 mmol), HOBt (420 mg, 3.12 mmol) and TEA (490 μ L, 3.50 mmol) in DCM (10 mL) were treated with 2N NH_3 in dioxane (2 mL) at room temperature overnight. The solvent was removed in vacuo and the residue was purified by a CombiFlash[®] system using hexanes and ethyl acetate to
10 afford the title compound as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 5.85 (s, br, 2H), 3.98 (s, 4H), 3.03 (m, 2H), 2.20 (m, 2H), 1.92 (m, 4H), 2.75 (m, 2H).

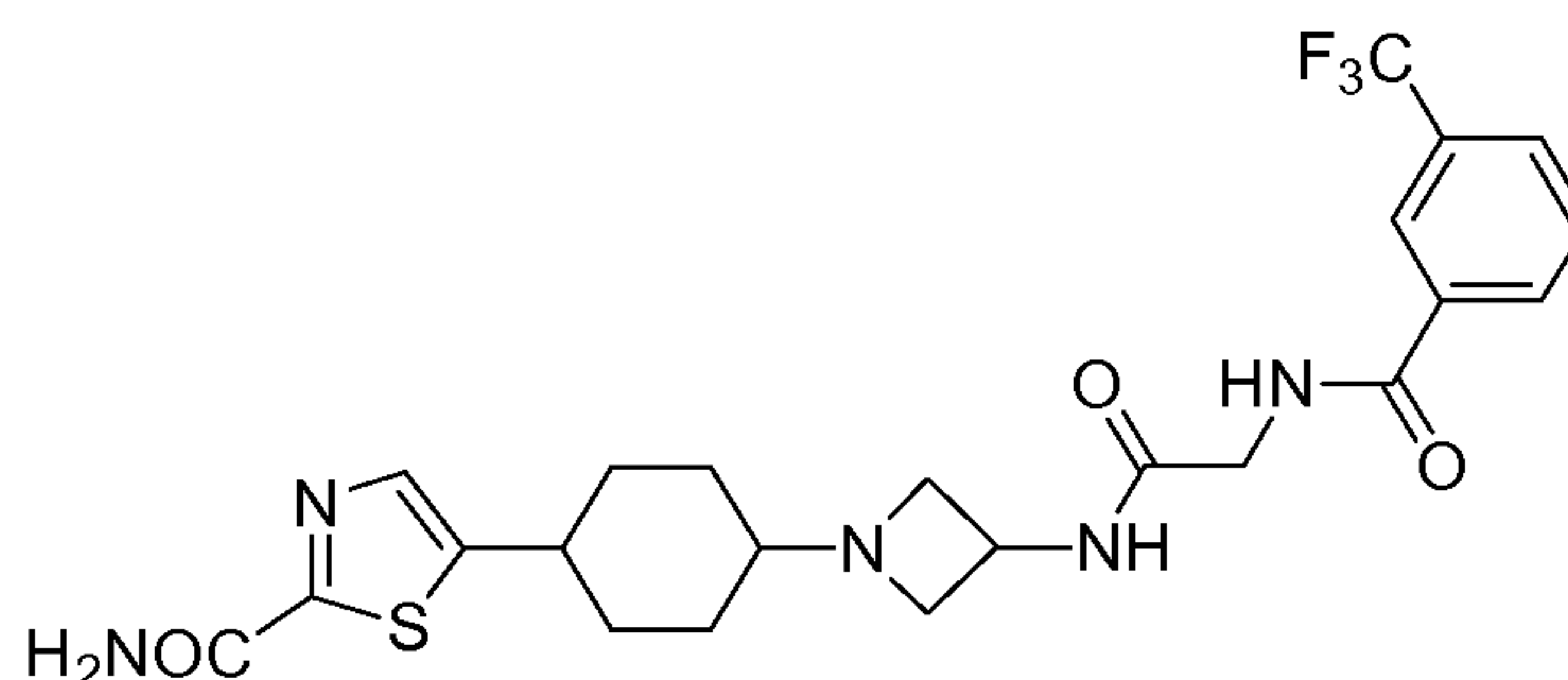
Step B: 2-(4-Oxo-cyclohexyl)-thiazole-5-carboxylic acid amide



15 The title compound was prepared as a white solid from the deprotection of 2-(1,4-dioxo-spiro[4.5]dec-8-yl)-thiazole-5-carboxylic acid amide (as prepared in the previous step) using the procedure described in Step B of Example 2.

^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, 1H), 5.95 (s, br, 2H), 3.38 (m, 1H), 2.51 (m, 4H),
20 2.15 (m, 2H), 2.00 (m, 2H).

Step C: 5-(4-{3-[2-(3-Trifluoromethyl-benzoylamino)-acetylamino]-azetidin-1-yl}-cyclohexyl)-thiazole-2-carboxylic acid amide

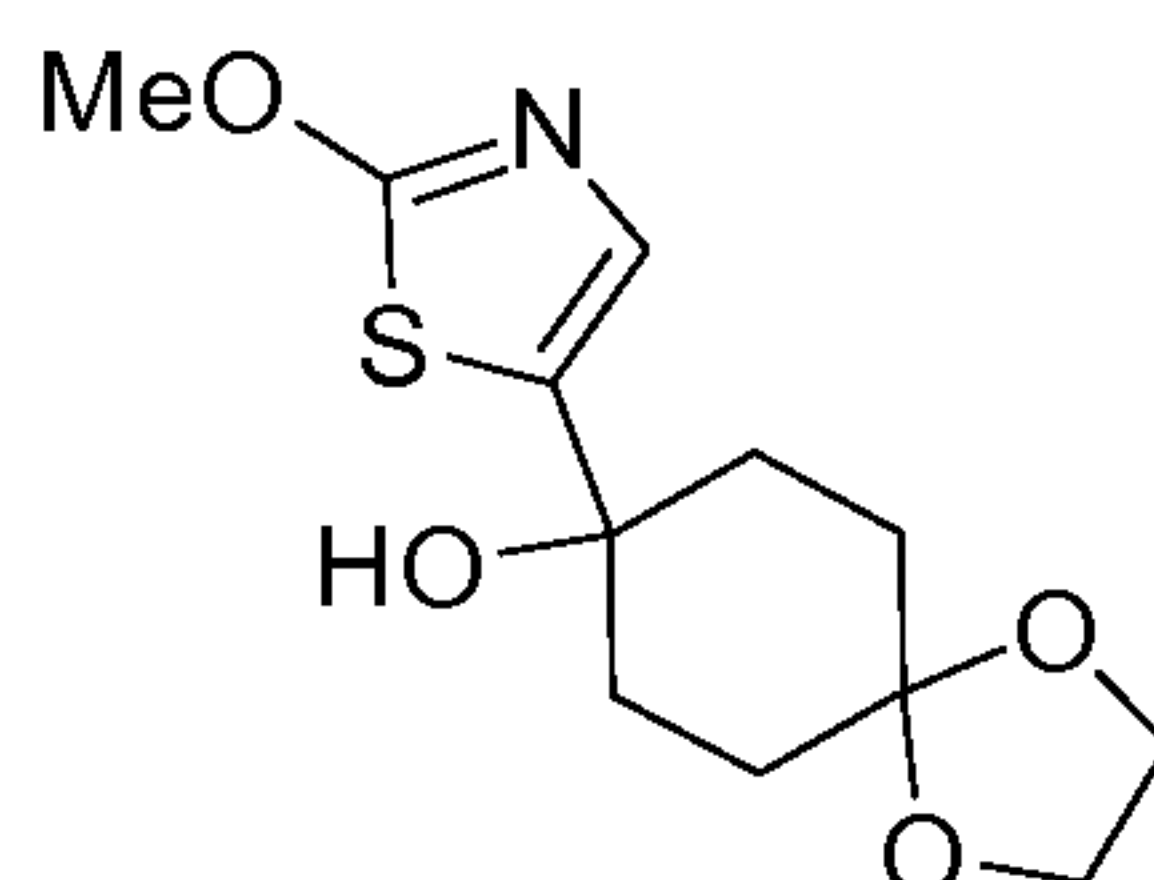


The title compound was prepared as a white solid from the reductive amination of 2-(4-oxo-cyclohexyl)-thiazole-5-carboxylic acid amide (as prepared in the previous step) and N-(azetidin-3-ylcarbonylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

¹H NMR (400 MHz, *d*₄-MeOH) δ 8.18 (s, 1H), 8.15 (s, 1H), 8.05 (d, *J* = 6.3 Hz, 1H), 7.78 (d, *J* = 6.5 Hz, 1H), 7.59 (t, *J* = 6.0 Hz, 1H), 4.37 (m, 1H), 3.99 (s, 2H), 3.58 (t, *J* = 7.0 Hz, 2H), 3.08 (m, 1H), 2.98 (t, *J* = 7.0 Hz, 2H), 2.25 (s, br, 1H), 2.05 (m, 2H), 1.82 (m, 2H), 1.45 (m, 4H).

Example 54: N-({1-[4-(2-Oxo-2,3-dihydro-thiazol-5-yl)-cyclohexyl]-azetidin-3-yl}carbonylmethyl)-3-(trifluoromethyl)-benzamide

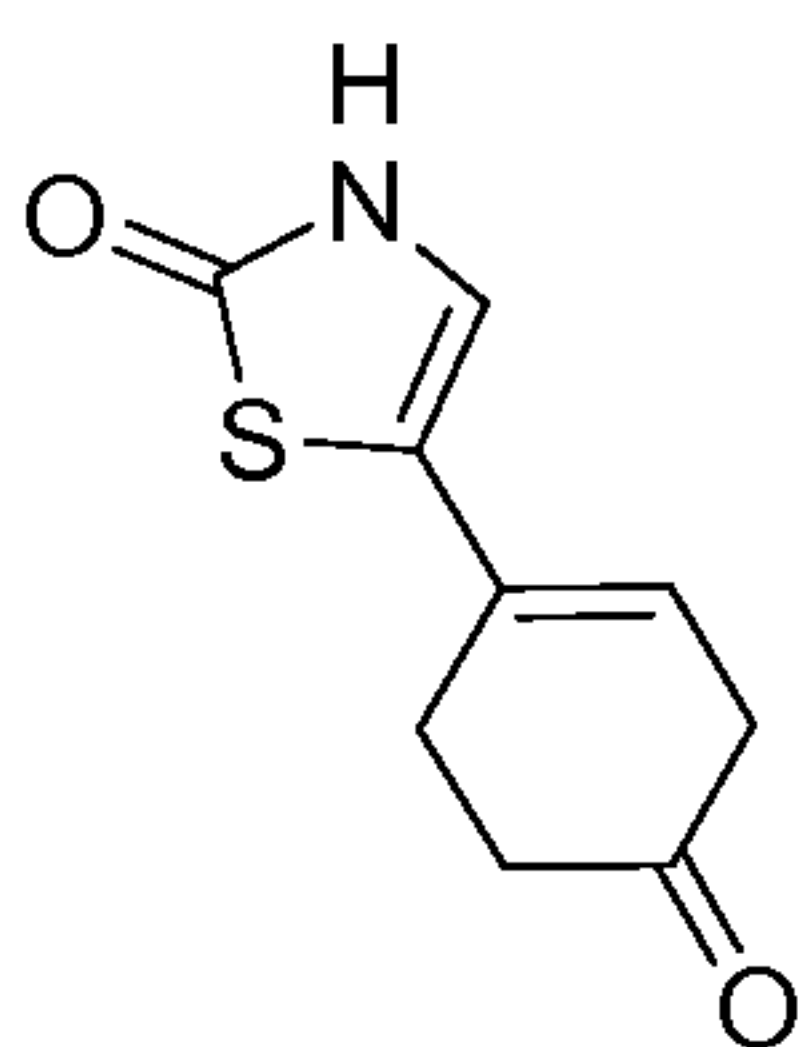
Step A: 8-(2-Methoxy-thiazol-5-yl)-1,4-dioxo-spiro[4.5]decan-8-ol



The title compound was prepared as a white solid from 2-methoxy-thiazole (Aldrich) using the procedure described in Step A of Example 51.

¹H NMR (400 MHz, CDCl₃) δ 6.95 (s, 1H), 4.05 (s, 3H), 3.95 (m, 4H), 2.10 (m, 2H), 2.00 (m, 4H), 1.69 (m, 2H).

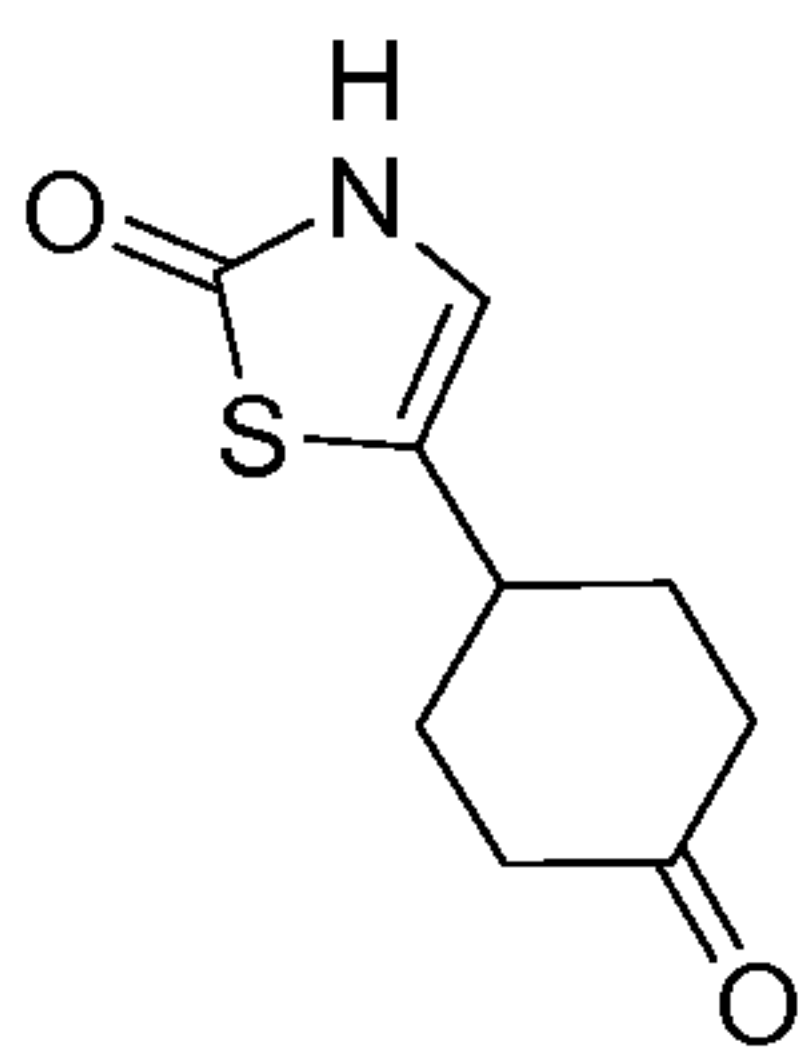
Step B: 5-(4-Oxo-cyclohex-1-enyl)-3H-thiazol-2-one



8-(2-Methoxy-thiazol-5-yl)-1,4-dioxaspiro[4.5]decan-8-ol (as prepared in the previous step, 1.05 g, 3.87 mmol) was treated with 6N HCl (~ 2 mL) in THF (5 mL) at room temperature for 4 hours. The reaction was neutralized with saturated NaHCO₃ solution and the solvent was removed. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a yellow solid, which was then purified by silica gel column on a CombiFlash® system using hexanes and ethyl acetate (from 10% ethyl acetate to 100% ethyl acetate) to afford the title compound as white solid.

¹H NMR (400 MHz, CDCl₃) δ 9.78 (s, br, 1H), 6.55 (s, 1H), 5.78 (m, 1H), 2.98 (s, br, 1H), 2.65 (, 2H), 2.58 (m, 2H)

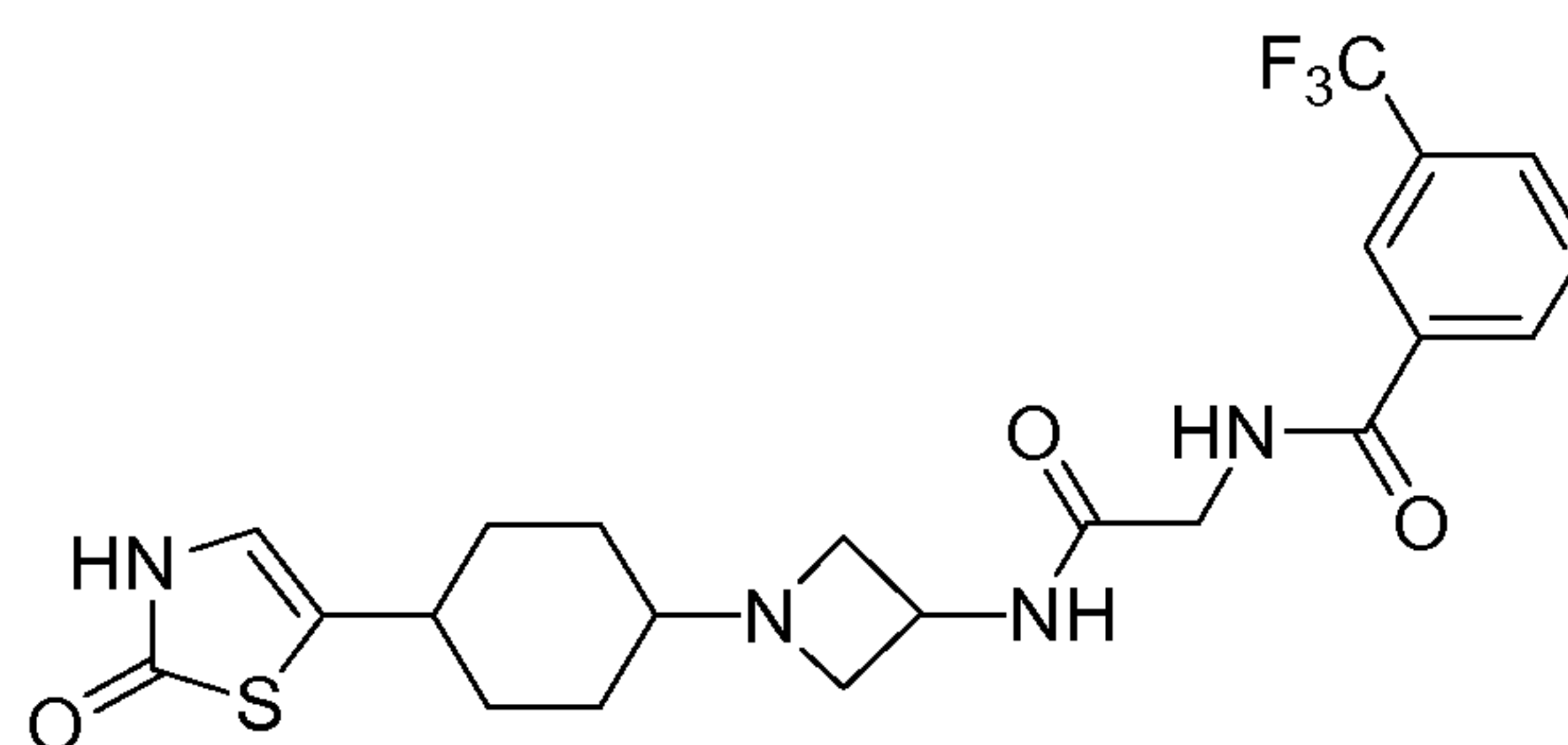
Step C: 5-(4-Oxo-cyclohexyl)-3H-thiazol-2-one



The title compound was prepared as a white solid from the hydrogenation of 5-(4-oxo-cyclohex-1-enyl)-3H-thiazol-2-one (as prepared in the previous step) using the procedure described in Step G of Example 1.

¹H NMR (400 MHz, CDCl₃) δ 9.65 (s, br, 1H), 6.38 (s, 1H), 2.45 (m, 5H), 2.31 (m, 2H), 1.87 (m, 2H).

Step D: N-({1-[4-(2-Oxo-2,3-dihydro-thiazol-5-yl)-cyclohexyl]-azetidin-3-yl}carbonyl)-methyl)-3-trifluoromethyl-benzamide

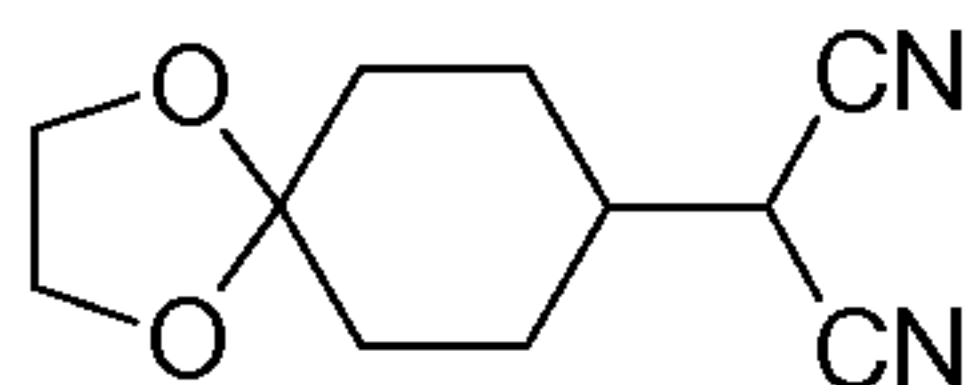


The title compounds were prepared as white solids from the reductive amination of 5-(4-oxo-cyclohexyl)-3H-thiazol-2-one (as prepared in the previous step) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide using the procedure described in Step F of Example 1.

¹H NMR (400 MHz, CDCl₃) δ 9.80 (s, br, 1H), 8.10 (s, 1H), 6.25 (s, 1H), 4.50 (m, 1H), 4.18 (d, J = 4.0 Hz, 2H), 3.60 (t, J = 7.0 Hz, 2H), 3.05 (d, J = 6.5 Hz, 2H), 2.35 (m, 1H), 2.30 (m, 1H), 2.10 (m, 2H), 1.85 (m, 2H), 1.60 (m, 2H), 158 (m, 2H).

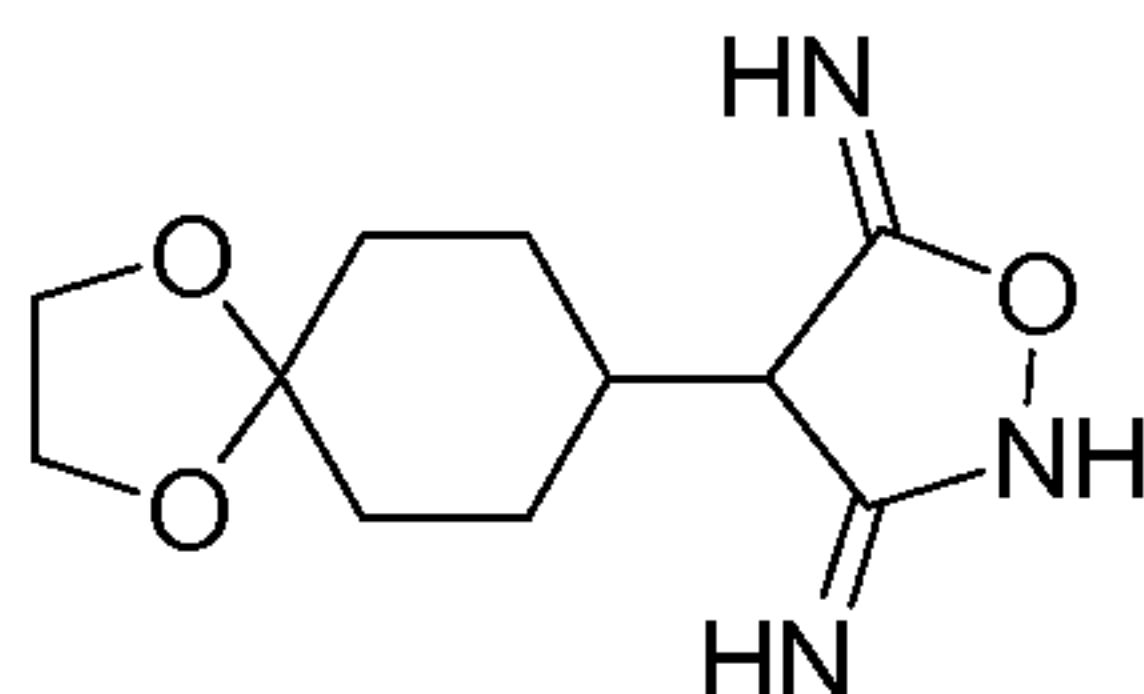
Example 55: N-({1-[4-(3,5-Diimino-isoxazolidin-4-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

Step A: 2-(1,4-Dioxo-spiro[4.5]dec-8-yl)-malononitrile



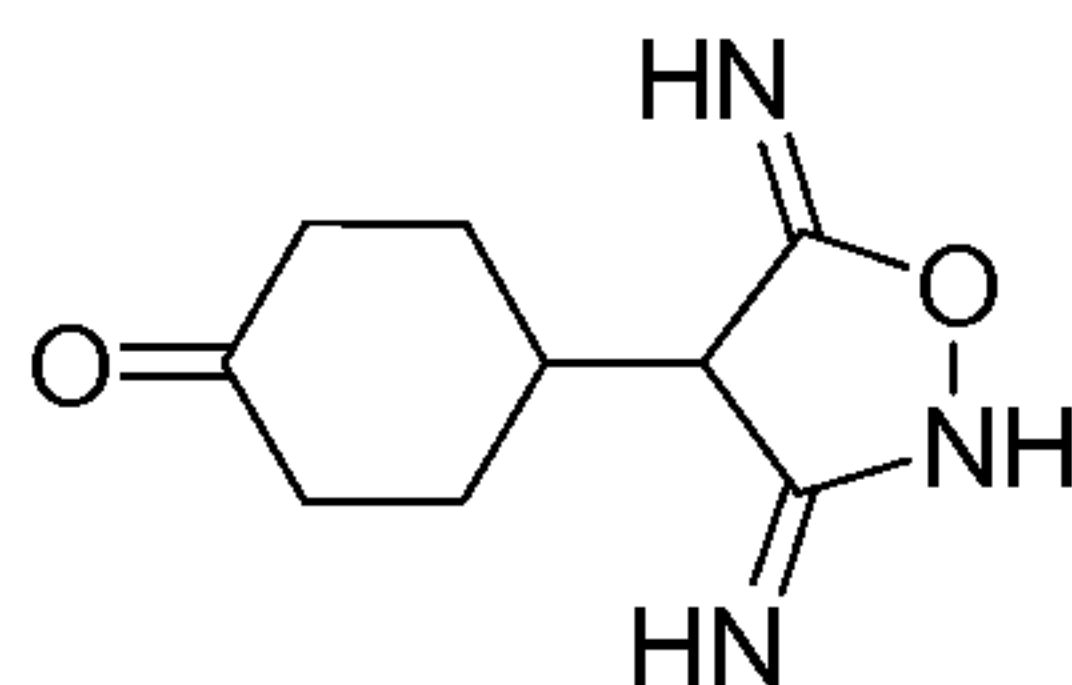
The title compound was prepared by the method of Dunham et al. (Synthesis 2006 (4), 680). 1,4-Cyclohexanedione monoethylene ketal (3.15 g, 20.0 mmol) was dissolved in anhydrous 2-propanol (20 mL), treated with warm malononitrile (Aldrich, 0.70 mL, 11.1 mmol) via syringe, and the reaction was cooled in ice and treated with powdered sodium borohydride (Aldrich, 0.42 g, 11.1 mmol). After stirring for 2 h in ice, the reaction was quenched with water and acidified to pH 6 with 1N aqueous HCl, and the resulting suspension was extracted thrice with dichloromethane. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a pale yellow oil, which was purified by flash column chromatography on silica gel (gradient elution, 30 to 80% EtOAc in hexanes) giving the title compound as a pale yellow crystalline solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 3.96 (t, J=3.7 Hz, 4 H), 3.59 (d, J=6.8 Hz, 1 H), 2.00 (m, 3H), 1.80 – 1.91 (m, 2H), 1.57 – 1.73 (m, 4H).

Step B: 4-(1,4-Dioxo-spiro[4.5]dec-8-yl)-isoxazolidine-3,5-diylidenediamine

A solution of 2-(1,4-dioxo-spiro[4.5]dec-8-yl)-malononitrile (as prepared in the previous
 5 step, 0.207 g, 1.00 mmol) and hydroxylamine hydrochloride (Aldrich, 0.107 g, 1.54 mmol) in anhydrous pyridine (5 mL) were heated to 100 °C under a reflux condenser for 18 h. After cooling to ambient temperature and evaporation of the solvent in vacuo, the crude product was purified by thin layer chromatography on silica gel (10% methanol in dichloromethane) giving the title compound as an orange solid.

10 ¹H NMR (400 MHz, *DMSO-d*₆) δ 7.68 (br. s., 1 H), 7.47 (br. s., 1 H), 5.70 (s, 1 H), 3.84 (s, 4 H), 3.58 (d, *J*=7.1 Hz, 1 H), 1.83 - 2.03 (m, 1 H), 1.55 - 1.83 (m, 4 H), 1.25 - 1.55 (m, 4 H). ESI-MS (*m/z*): Calcd. For C₁₁H₁₇N₃O₃: 239; found: 240 (M+H).

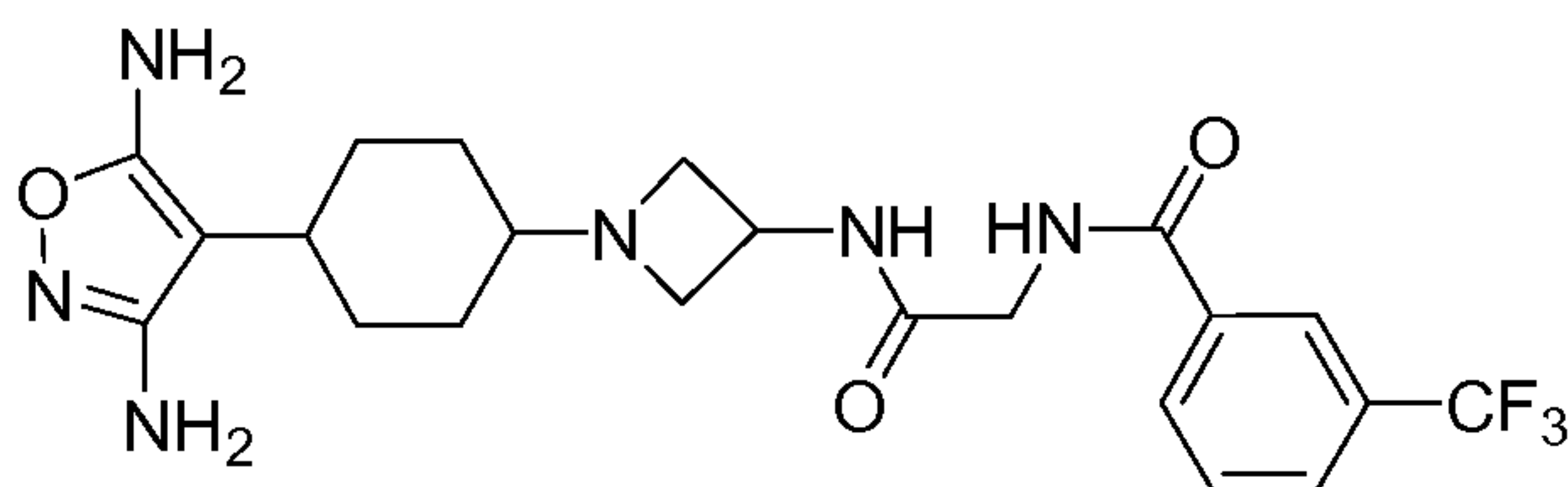
Step C: 4-(3,5-Diimino-isoxazolidin-4-yl)-cyclohexanone

15

A solution of 4-(1,4-dioxo-spiro[4.5]dec-8-yl)-isoxazolidine-3,5-diylidenediamine (as prepared in the previous step, 0.078 g, 0.326 mmol) in acetonitrile (10 mL) was treated with 1N aqueous HCl (3.2 mL, 3.2 mmol), and stirred at ambient temperature for 6 h. After removing the MeCN in vacuo, the reaction was treated with saturated aqueous
 20 NaHCO₃ (ca. 7 mL), stirred at ambient temperature overnight, and extracted thrice with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the title compound as an orange gum.

¹H NMR (400 MHz, *ACETONITRILE-d*₃) δ 6.47 (br. s., 1 H), 6.06 (br. s., 1 H), 4.70 (br. s., 0 H), 3.52 (d, *J*=6.6 Hz, 1 H), 2.34 - 2.55 (m, 3 H), 2.18 - 2.34 (m, 2 H), 1.97 - 2.12
 25 (m, 2 H), 1.61 (m, 2 H). ESI-MS (*m/z*): Calcd. For C₉H₁₃N₃O₂: 195; found: 196 (M+H).

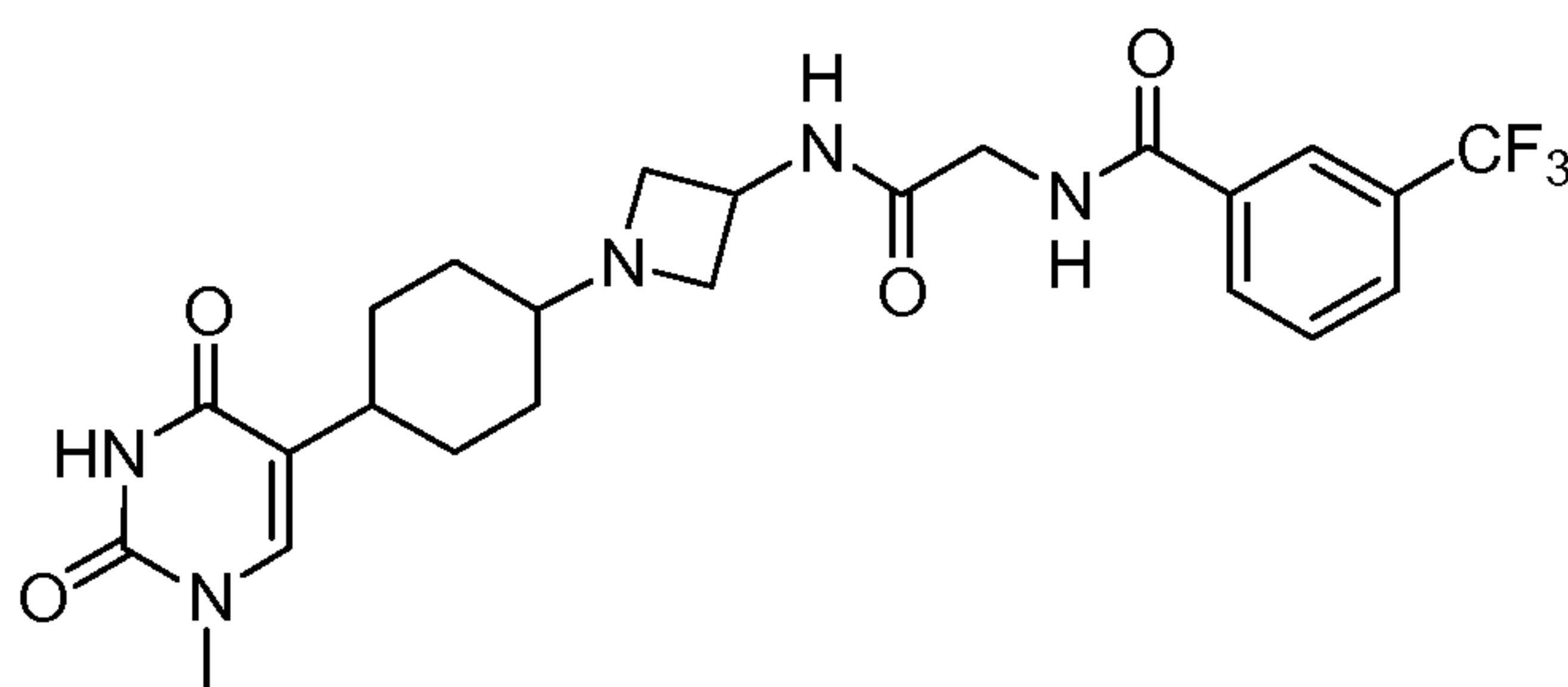
Step D: *N*-({1-[4-(3,5-Diimino-isoxazolidin-4-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide



The title compound was prepared as described in Step F of Example 1 from 4-(3,5-diimino-isoxazolidin-4-yl)-cyclohexanone (as prepared in the previous step) as a pale yellow solid.

¹H NMR (400 MHz, *ACETONITRILE-d*₃) δ 8.06 (s, 1 H), 8.01 (d, *J*=7.8 Hz, 1 H), 7.78 (d, *J*=7.8 Hz, 1 H), 7.60 (t, *J*=7.8 Hz, 1 H), 7.48 (br. s., 1 H), 6.93 (d, *J*=5.8 Hz, 1 H), 6.40 (br. s., 1 H), 5.97 (br. s., 1 H), 4.26 (sxt, *J*=7.0 Hz, 1 H), 3.86 (d, *J*=5.8 Hz, 2 H), 3.48 (t, *J*=7.3 Hz, 2 H), 3.32 (d, *J*=7.3 Hz, 1 H), 2.72 (t, *J*=7.1 Hz, 2 H), 2.16 - 2.23 (m, 1 H), 1.37 - 1.60 (m, 5 H), 1.22 - 1.37 (m, 3 H). ESI-MS (*m/z*): Calcd. For C₂₂H₂₇N₆O₃F₃: 480; found: 481 (M+H).

Example 56: *N*-({1-[4-(1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

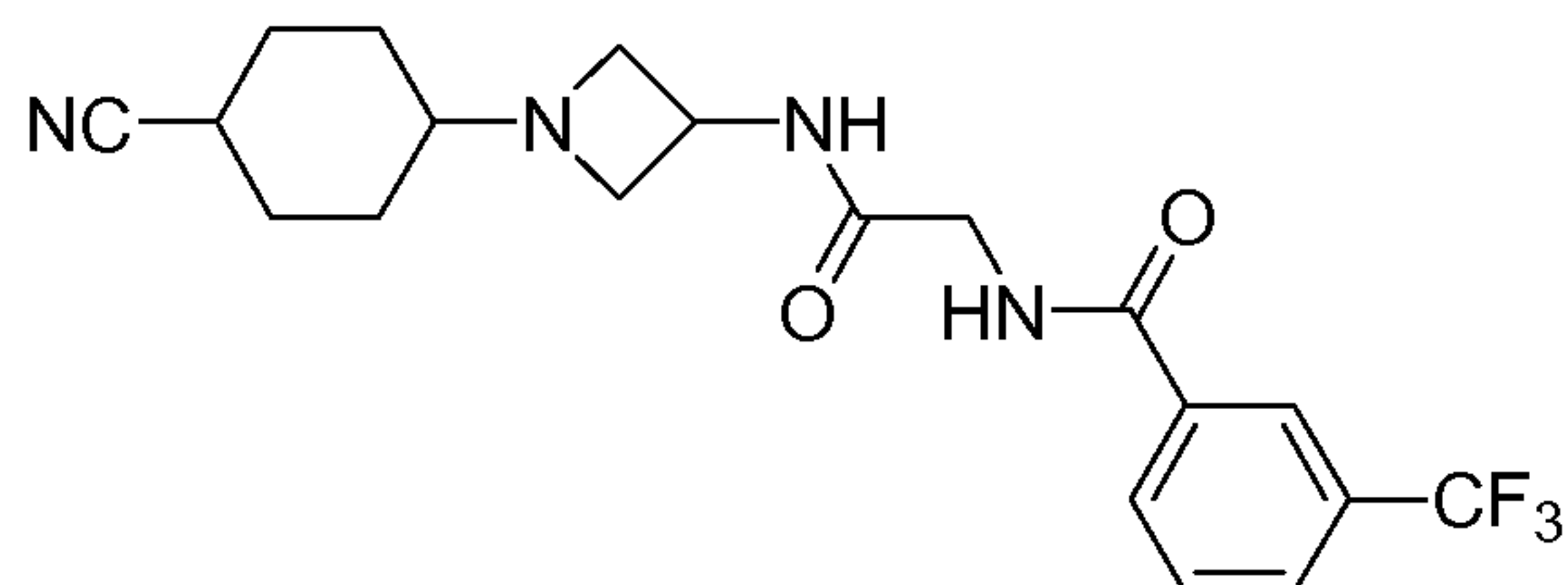


The title compound was prepared as described in Example 3: Steps A-D from 5-bromo-1-methyl-1H-pyrimidine-2,4-dione (Aldrich) as a white solid.

¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 11.15 (br. s., 1 H), 9.00 (br. s., 1 H), 8.35 (d, *J*=7.3 Hz, 1 H), 8.22 (s, 1 H), 8.18 (d, *J*=7.8 Hz, 1 H), 7.93 (d, *J*=7.8 Hz, 1 H), 7.74 (t, *J*=7.8 Hz, 1 H), 7.33 (s, 1 H), 4.24 (br. s., 1 H), 3.87 (d, *J*=5.6 Hz, 2 H), 3.49 (br. s., 2 H), 3.23 (s, 3 H), 2.74 (br. s., 2 H), 2.20 - 2.43 (m, 2 H), 1.57 - 1.71 (m, 2 H), 1.27 - 1.57 (m, 5 H). ESI-MS (*m/z*): Calcd. For C₂₅H₂₉N₄O₃F₃: 490; found: 491 (M+H).

Example 57: N-({1-[4-(5-Oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

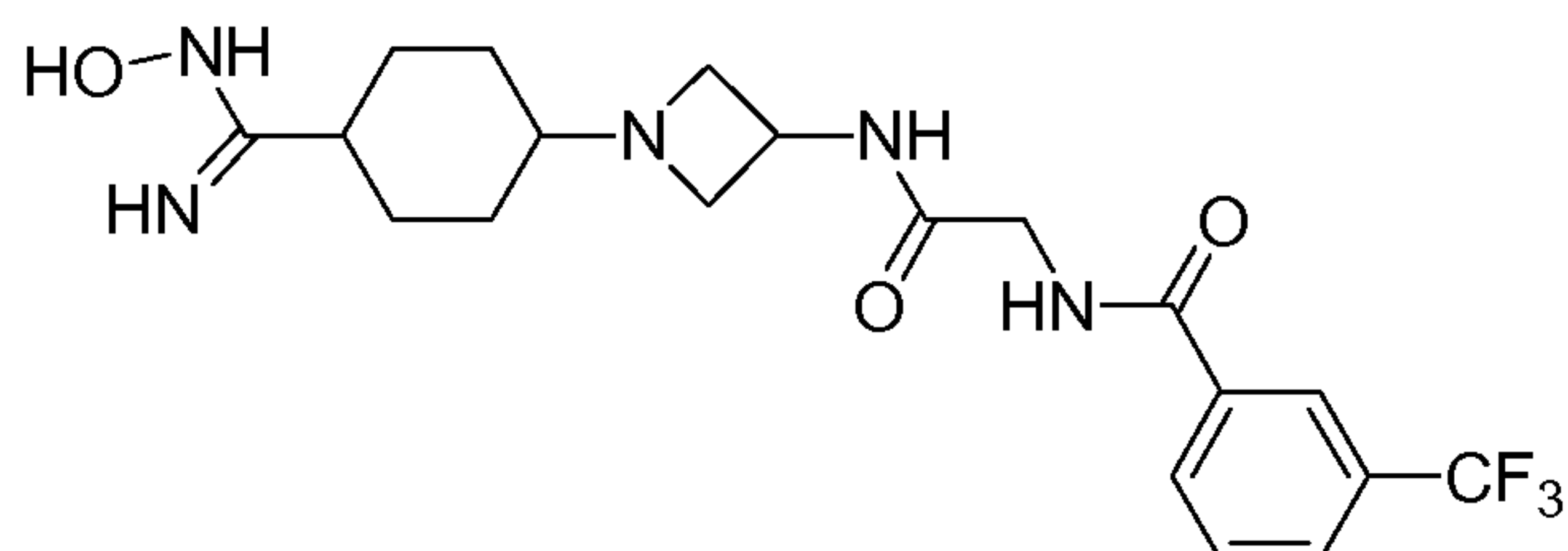
5 *Step A: N-([1-(4-Cyano-cyclohexyl)-azetidin-3-ylcarbamoyl]-methyl)-3-trifluoromethyl-benzamide*



The title compound was prepared from 4-oxo-cyclohexanecarbonitrile (prepared according to the procedure from Tremblay, Maxime, PCT Int. Appl. (2007), WO 10 2007013848) according to the general reductive amination procedure in Step F of Example 1.

A mixture of cis/trans isomers. LC/MS: 409.0 [M+H].

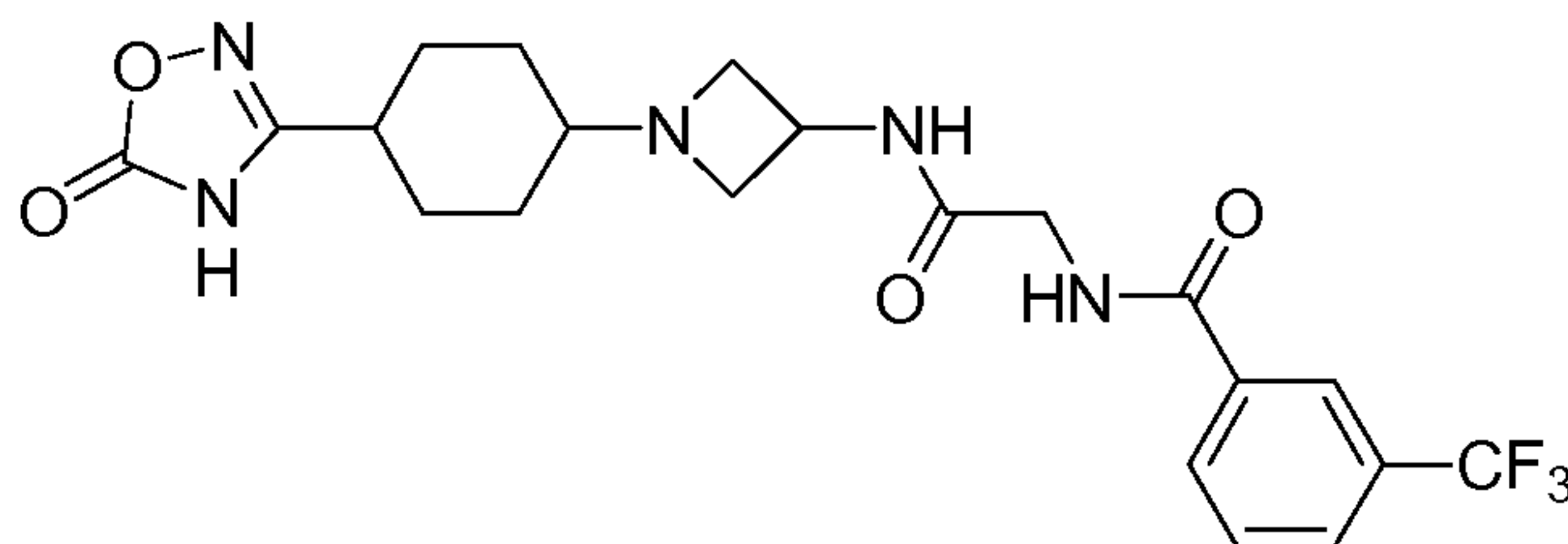
15 *Step B: N-({1-[4-(N-Hydroxycarbamimidoyl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide*



A mixture of the above intermediate from Step A (1 g, 2.4 mmol), hydroxylamine hydrochloride (Aldrich, 0.51 g, 7.32 mmol) and K₂CO₃ (0.67 g, 4.88 mmol) in ethanol (10 mL) in a sealed tube was heated to 86 °C for 18 h. After removal of organic solvent 20 by evaporation, the residue was dissolved in water, extracted with EtOAc and dried over Na₂SO₄. Filtration and evaporation to dryness gave the product as a mixture of cis/trans isomers.

LC/MS: 442.2 [M+H].

Step C: *N*-(*{1-[4-(5-Oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl*)-3-trifluoromethyl-benzamide

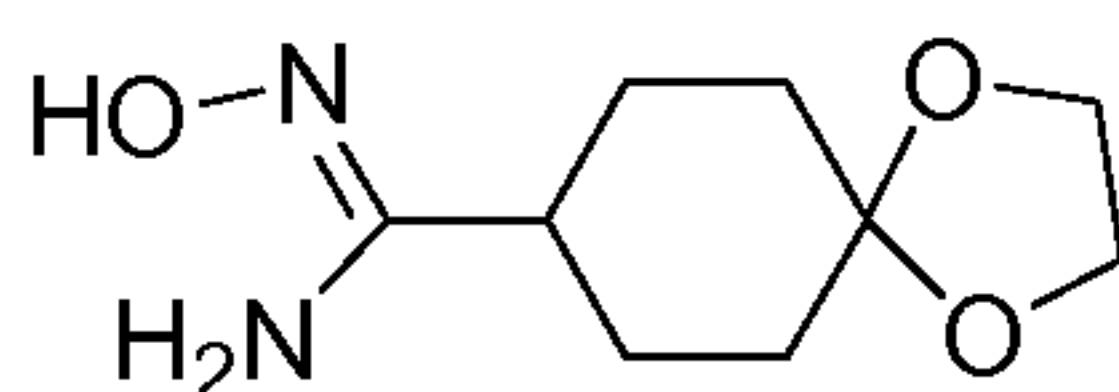


A mixture of the above intermediate from Step B (0.044 g, 0.1 mmol), 1,1'-carbonyldiimidazole (Aldrich, 0.0178 g, 0.11 mmol), DBU (Acros, 0.06 mL, 0.4 mmol) in CH₃CN (1 mL) was stirred at rt overnight. The crude product was purified by HPLC to give a TFA salt as a yellowish solid.

LC/MS: 468.2 [M+H].

Example 58: *N*-(*{1-[4-(5-Trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl*)-3-trifluoromethyl-benzamide

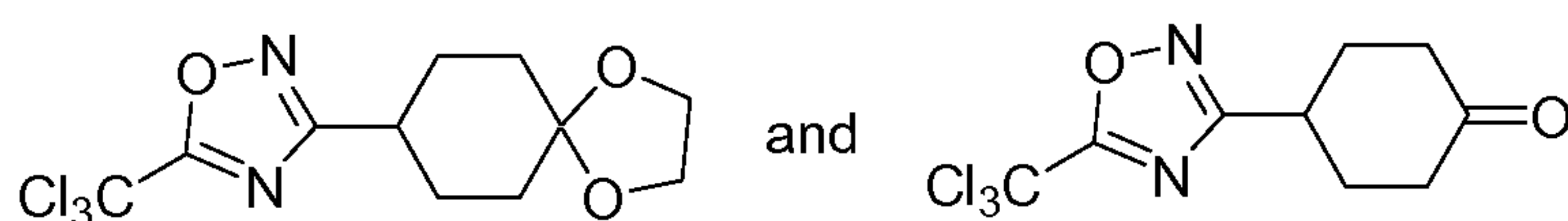
Step A: N-Hydroxy-1,4-dioxa-spiro[4.5]decane-8-carboxamidine



A mixture of 1,4-dioxa-spiro[4.5]decane-8-carbonitrile (0.40 g, 2.4 mmol, prepared according to the procedure from Tremblay, Maxime, PCT Int. Appl. (2007), WO 2007013848) and hydroxylamine (Aldrich, 50% in H₂O, 0.7 mL, 9.6 mmol) in ethanol (1.5 mL) in a sealed tube was heated to 80 °C for 6 h. After removal of organic solvent by evaporation, the residue was dissolved in water, extracted with EtOAc and dried over Na₂SO₄. Filtration and evaporation to dryness gave the product as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 4.5 (2H, br s), 3.92-3.97 (4H, m), 2.13-2.20 (1H, m), 1.57-1.90 (8H, m).

Step B: 3-(1,4-Dioxa-spiro[4.5]dec-8-yl)-5-trichloromethyl-[1,2,4]oxadiazole and 4-(5-Trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclohexanone



To a mixture of the above intermediate from Step A (0.34 g, 1.7 mmol) in toluene (11 mL) was added trichloroacetic anhydride (Fluka, 0.36 mL, 1.97 mmol) dropwise under Ar. The resulting mixture was then heated to reflux at 80 °C for 2 h. After the reaction was cooled to room temperature, it was then poured into an ice- diluted NaHCO₃ solution and separated. The aqueous phase was extracted with EtOAc, the combined organic layers were dried over Na₂SO₄. Purification by column chromatography (eluent: 10% to 30% EtOAc in hexanes) gave the ketal, as well as the deprotected ketone as the title compound.

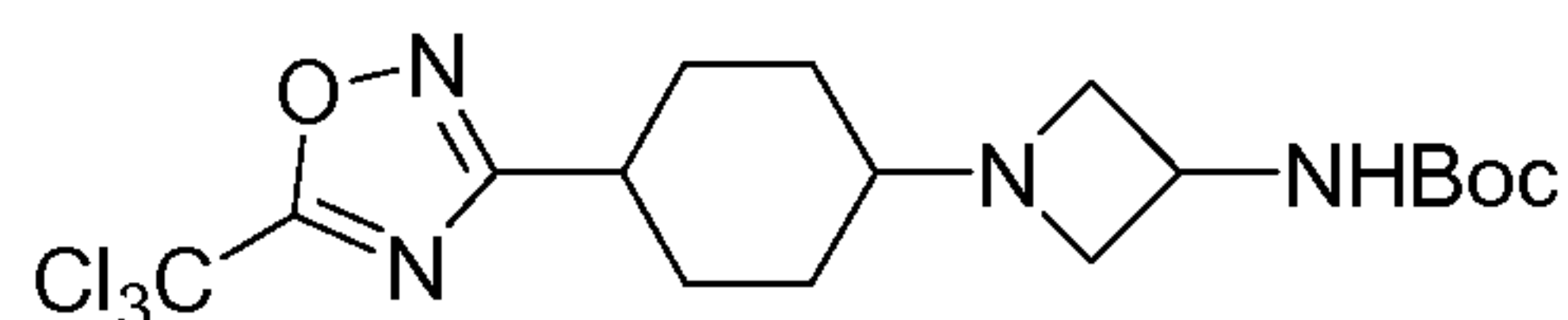
The ketal

¹H NMR (400 MHz, CDCl₃): δ 3.96-3.99 (4H, m), 2.88-2.96 (1H, m), 2.10-2.14 (2H, m), 1.86-2.03 (4H, m), 1.64-1.72 (2H, m).

4-(5-Trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclohexanone

¹H NMR (400 MHz, CDCl₃): δ 3.33-3.40 (1H, m), 2.37-2.63 (6H, m), 2.15-2.26 (2H, m).

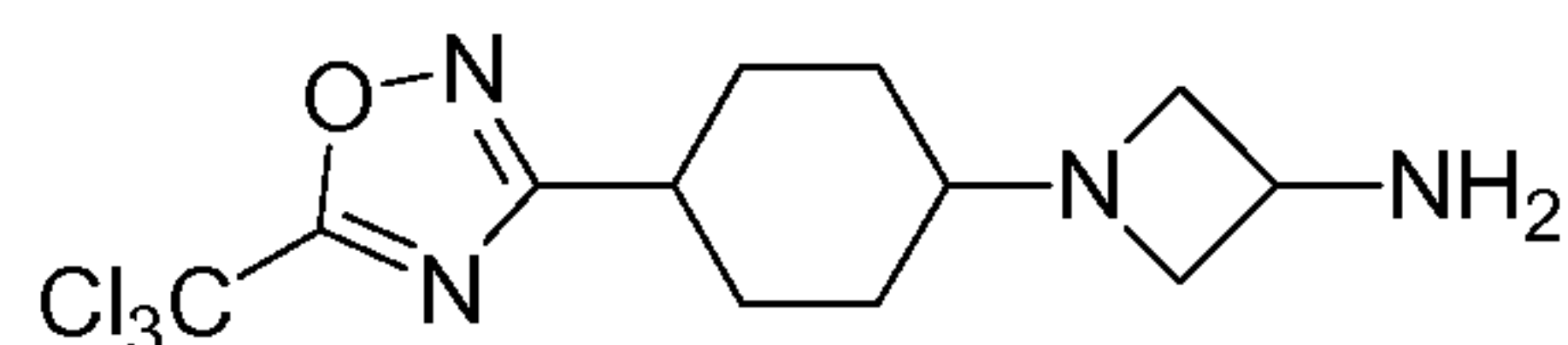
Step C: {1-[4-(5-Trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclohexyl]-azetidin-3-yl}-carbamic acid tert-butyl ester



The title compound was prepared from 4-(5-trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclohexanone (as prepared in the previous step) and azetidine-3-yl-carbonic acid tert-butyl ester (Beta Pharma) according to the general reductive amination procedure described in Step F of Example 1.

A mixture of cis/trans isomers: LC/MS: 439.2 [M+H].

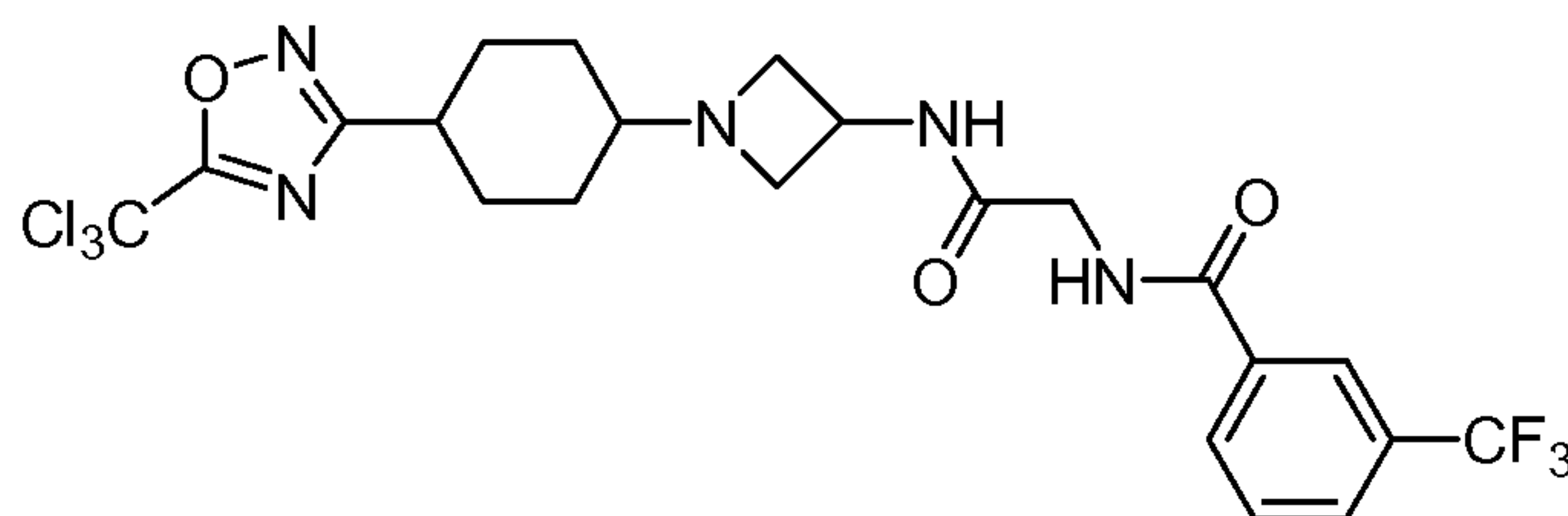
Step D: 1-[4-(5-Trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclohexyl]-azetidin-3-ylamine



{1-[4-(5-Trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclohexyl]-azetidin-3-yl}-carbamic acid tert-butyl ester (as prepared in the previous step) was treated with 1:1 ratio of DCM and TFA at room temperature. After 2 hours, the solvent was removed in vacuo and the residue was dried overnight to give the title compound as TFA salt (colorless oil).

A mixture of cis/trans isomers: LC/MS: 339.0 [M+H].

Step E: N-({1-[4-(5-Trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

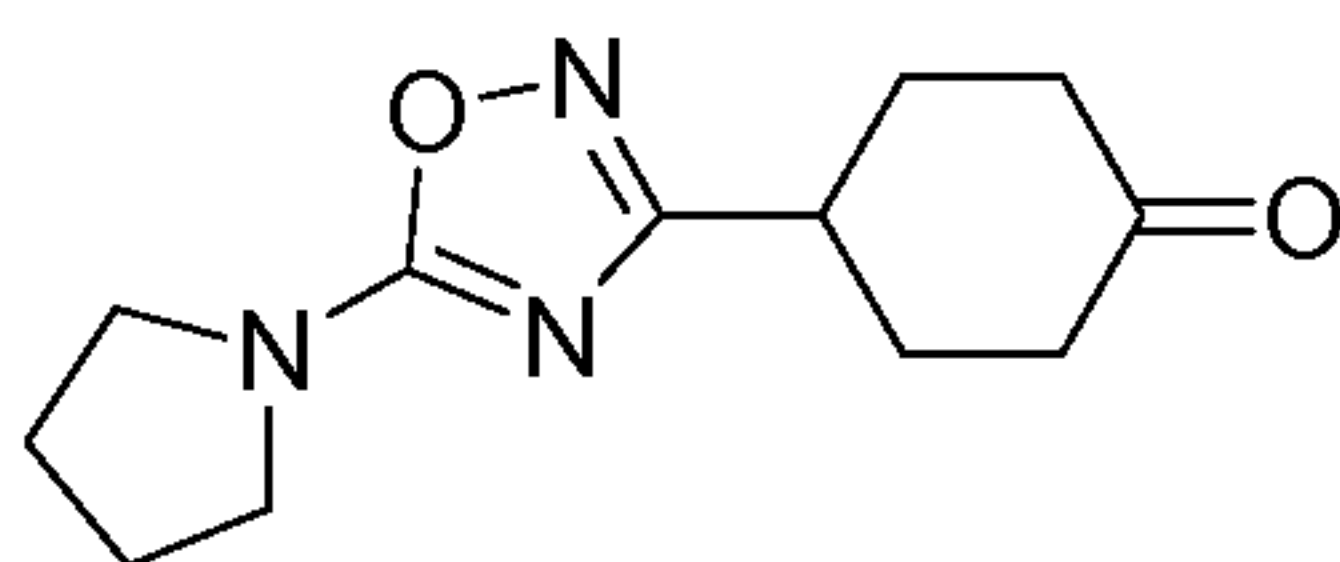


The title compound was prepared by the EDCI coupling of 1-[4-(5-trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclohexyl]-azetidin-3-ylamine (as prepared in the previous step) and (3-trifluoromethyl-benzoylamino)-acetic acid (Bionet Building Blocks). Purification by HPLC gave cis and trans isomers.

LC/MS: 568.0 [M+H].

Example 59: N-({1-[4-(5-Pyrrolidin-1-yl-[1,2,4]oxadiazol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

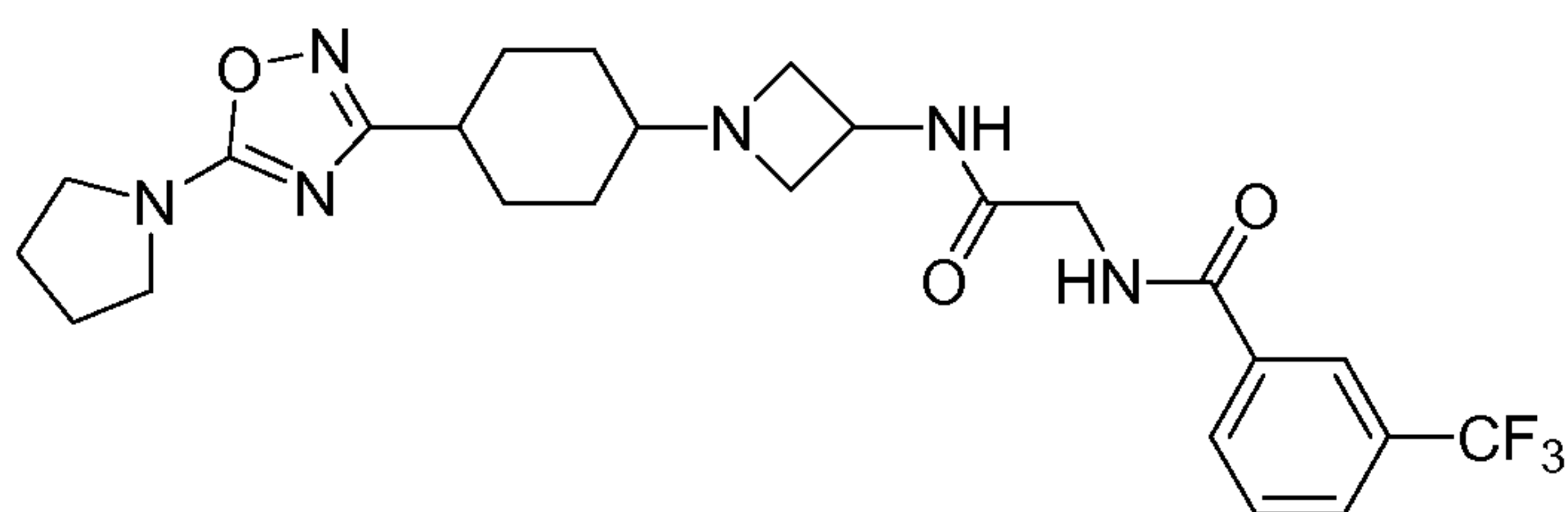
Step A: 4-(5-Pyrrolidin-1-yl-[1,2,4]oxadiazol-3-yl)-cyclohexanone



A solution of the intermediate 3-(1,4-dioxo-spiro[4.5]dec-8-yl)-5-trichloromethyl-[1,2,4]oxadiazole from Example 58, Step B (0.2 g, 0.6 mmol) and pyrrolidine (Aldrich, 0.45 mL, 5.4 mmol) in methanol (30 mL) was stirred at rt for 2 days. After evaporation of solvents, the residue was purified by column chromatography (eluent: EtOAc to 10% MeOH in DCM) and gave 0.08 g of the ketal, which was dissolved in CH₃CN (5 mL) and 2N HCl (5 mL), stirred at rt overnight. Removal of volatiles by evaporation gave the product as a HCl salt.

LC/MS: 236.0 [M+H].

Step B: N-({1-[4-(5-Pyrrolidin-1-yl-[1,2,4]oxadiazol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

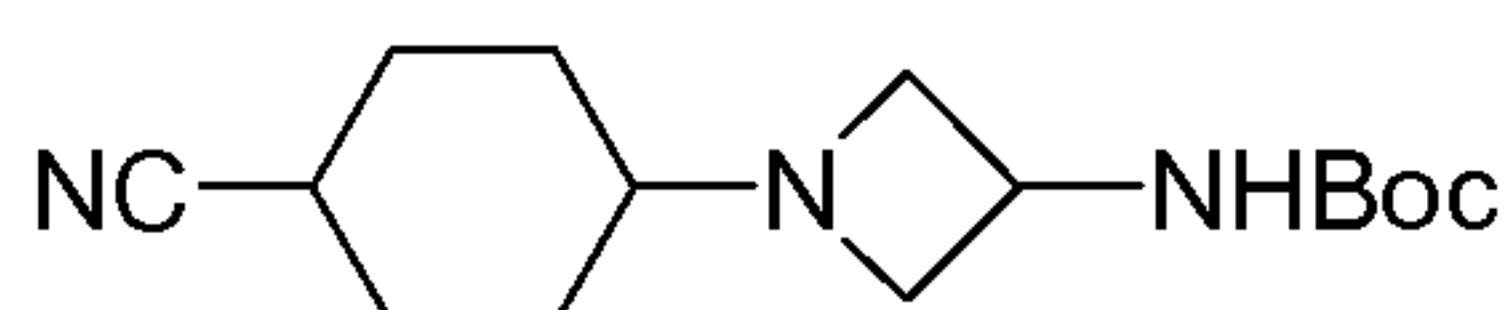


The title compound was prepared from 4-(5-pyrrolidin-1-yl-[1,2,4]oxadiazol-3-yl)-cyclohexanone (as prepared in the previous step) according to the general reductive amination procedure in Step F of Example 1.

5 A mixture of cis/trans (1:1) isomers. LC/MS: 521.3 [M+H].

Example 60: N-({1-[4-(4-Methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

Step A: [1-(4-Cyano-cyclohexyl)-azetidin-3-yl]-carbamic acid tert-butyl ester

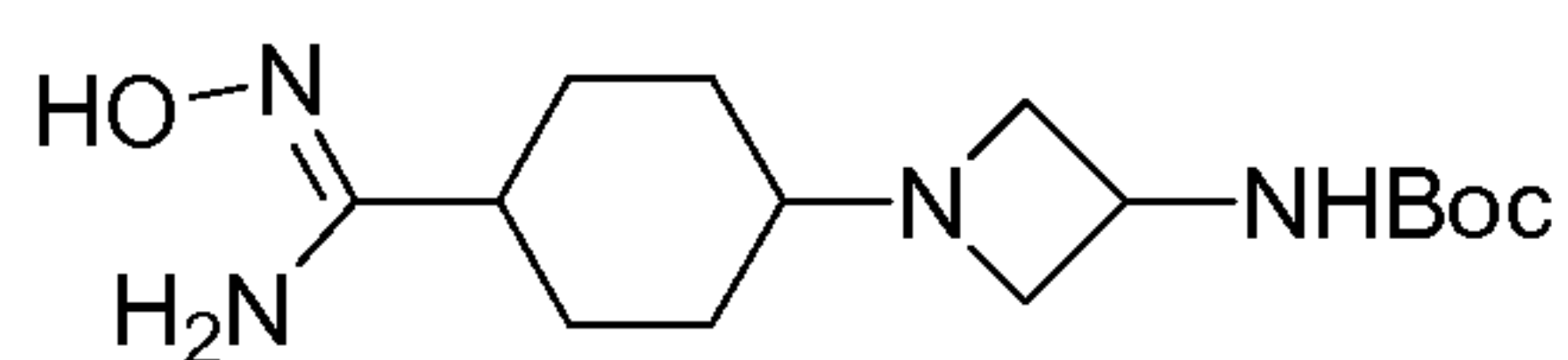


10

To a solution of 4-oxo-cyclohexanecarbonitrile (2.66 g, 21.5 mmol, prepared according to the procedure from Tremblay, Maxime, PCT Int. Appl. (2007), WO 2007013848) and azetidine-3-yl-carbonic acid tert-butyl ester (Beta Pharma, 3.70 g, 21.5 mmol) in DCM (20 mL) was added NaBH(OAc)₃ (Aldrich, 6.84 g, 32.25 mmol). The resulting mixture
15 was stirred at rt for 6 h and quenched with saturated NaHCO₃. Workup and purification by column chromatograph (eluent: 80% EtOAc in hexanes to EtOAc only) gave the product as a mixture of cis/trans isomers. LC/MS: 280.2 [M+H].

Step B: {1-[4-(N-Hydroxycarbamimidoyl)-cyclohexyl]-azetidin-3-yl}-carbamic acid tert-butyl ester

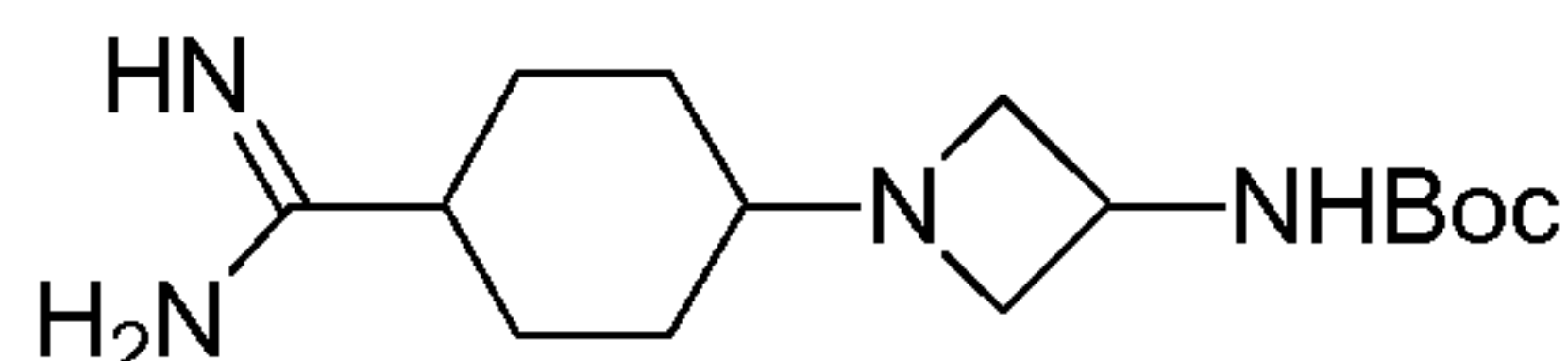
20



A mixture of the above intermediate (1.68 g, 6 mmol) and hydroxylamine (Aldrich, 50% in H₂O, 1.75 mL, 24 mmol) in ethanol (4 mL) in a sealed tube was heated at 86 °C for 6 h. After removal of organic solvent by evaporation, the residue was dissolved in water,
25 extracted with EtOAc and dried over Na₂SO₄. Filtration and evaporation to dryness gave the mixture of *cis/trans* isomers as a white solid.

LC/MS: 313.3 [M+H].

Step C: [1-(4-Carbamimidoyl-cyclohexyl)-azetidin-3-yl]-carbamic acid tert-butyl ester

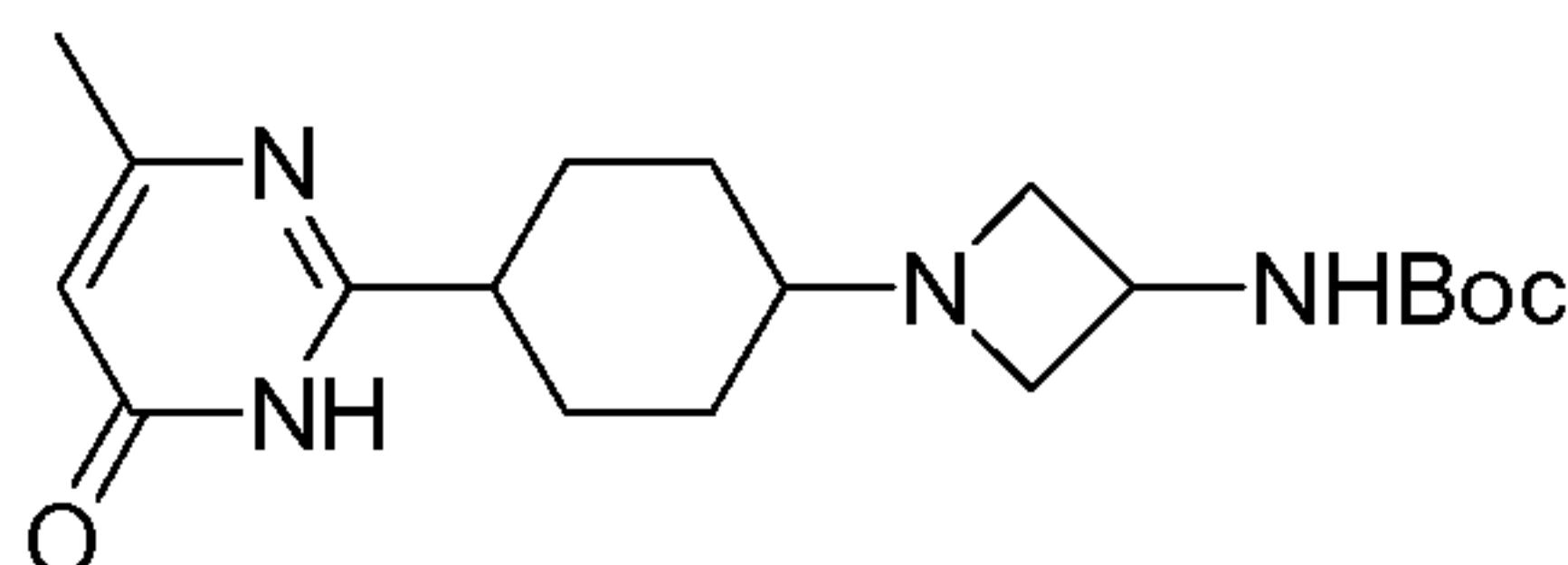


- 5 A mixture of the above intermediate (1.30 g, 4.16 mmol) and 10% Pd-C (0.1 g) in HOAc (14 mL) and acetic anhydride (0.6 mL) was hydrogenated on Parr shaker at 55 psi at rt overnight. Filtration and evaporation to dryness gave the mixture of *cis/trans* isomers as an HOAc salt.

LC/MS: 270.2 [M+H].

10

Step D: {1-[4-(4-Methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-cyclohexyl]-azetidin-3-yl}-carbamic acid tert-butyl ester

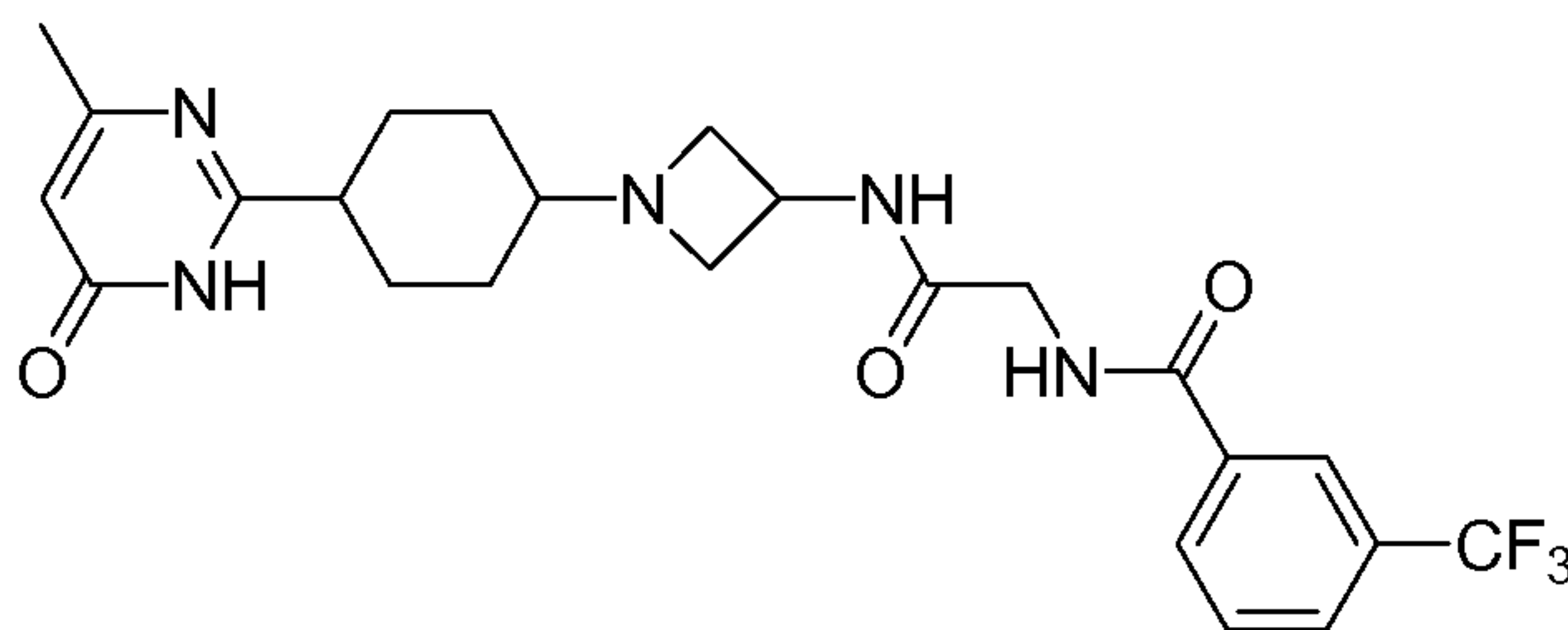


- 15 A mixture of the above intermediate (0.2 mmol), ethyl acetoacetate (Fluka, 0.025 mL, 0.2 mmol) and NaOH (0.018 g, 0.44 mmol) in ethanol (6 mL) in a sealed tube was heated at 80 °C for 8 h. After removal of organic solvent by evaporation, the residue was dissolved in water, extracted with EtOAc and dried over Na₂SO₄. Filtration and evaporation to dryness gave the product as a mixture of *cis/trans* isomers.

LC/MS: 363.3 [M+H].

20

Step E: N-({1-[4-(4-Methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl)-3-trifluoromethyl-benzamide

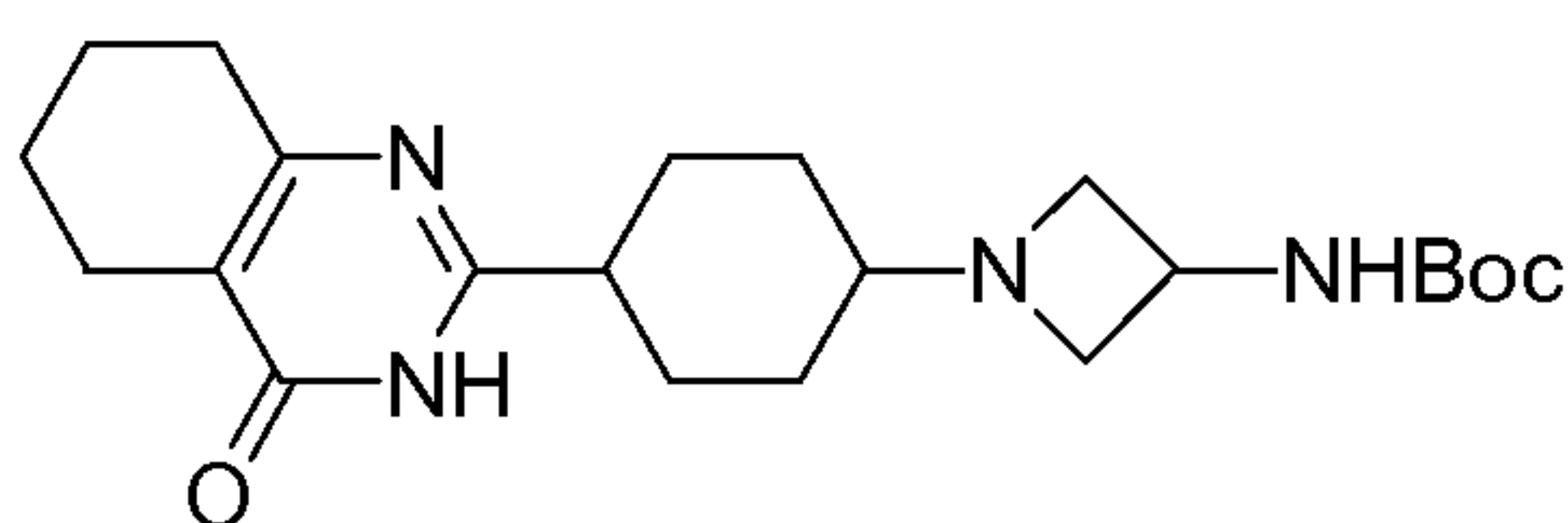


The title compound was prepared from {1-[4-(4-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-cyclohexyl]-azetidin-3-yl}-carbamic acid tert-butyl ester (as prepared in the previous step) according to the de-protection and coupling procedure described in Steps D and E of Example 58.

- 5 The TFA salt, a mixture of *cis/trans* (1:1) isomers: LC/MS: 492.3 [M+H].

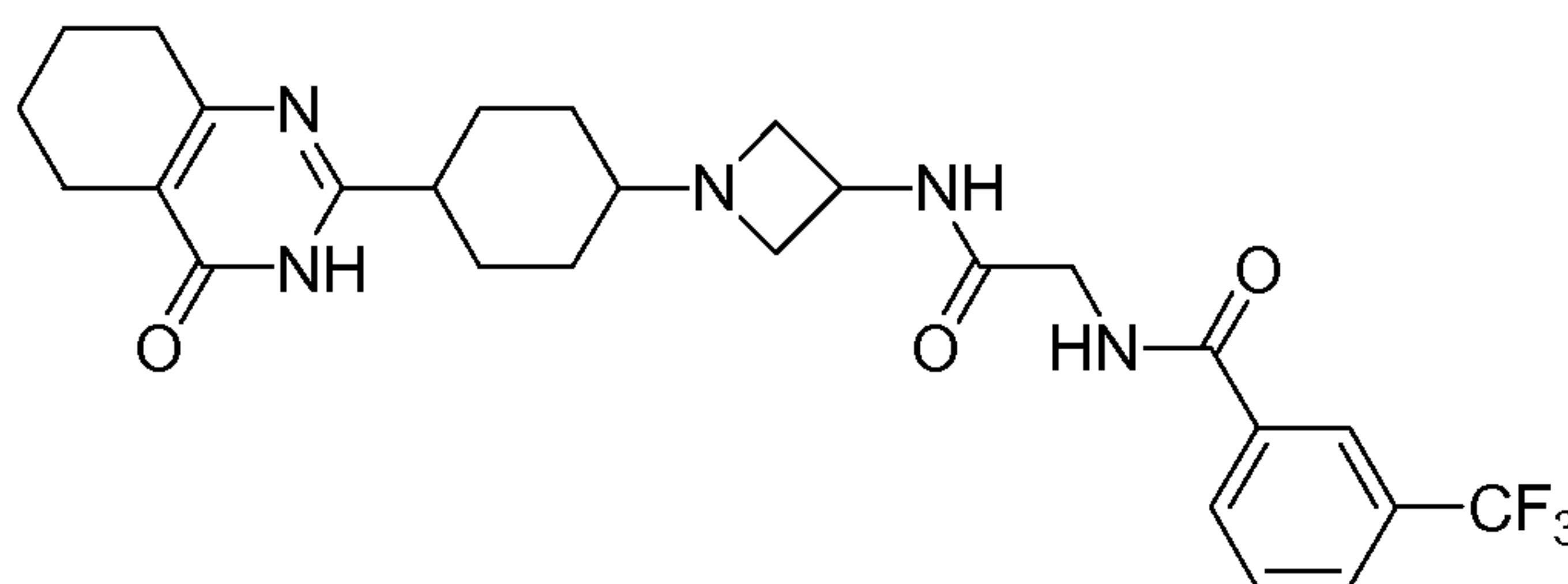
Example 61: N-(1-[4-(4-Oxo-3,4,5,6,7,8-hexahydro-quinazolin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

10 *Step A: {1-[4-(4-Oxo-3,4,5,6,7,8-hexahydro-quinazolin-2-yl)-cyclohexyl]-azetidin-3-yl}-carbamic acid tert-butyl ester*



15 The title compound was prepared according to the procedure described in Example 60, Step D by using ethyl 2-cyclohexanone carboxylate (Aldrich, 0.1 mL, 0.6 mmol), the intermediate [1-(4-Carbamimidoyl-cyclohexyl)-azetidin-3-yl]-carbamic acid tert-butyl ester (prepared as described in Example 60, Step C, 0.6 mmol), NaOH (0.53 g, 1.32 mmol) in ethanol (16 mL).
LC/MS: 403.3 [M+H].

20 *Step B: N-(1-[4-(4-Oxo-3,4,5,6,7,8-hexahydro-quinazolin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide*

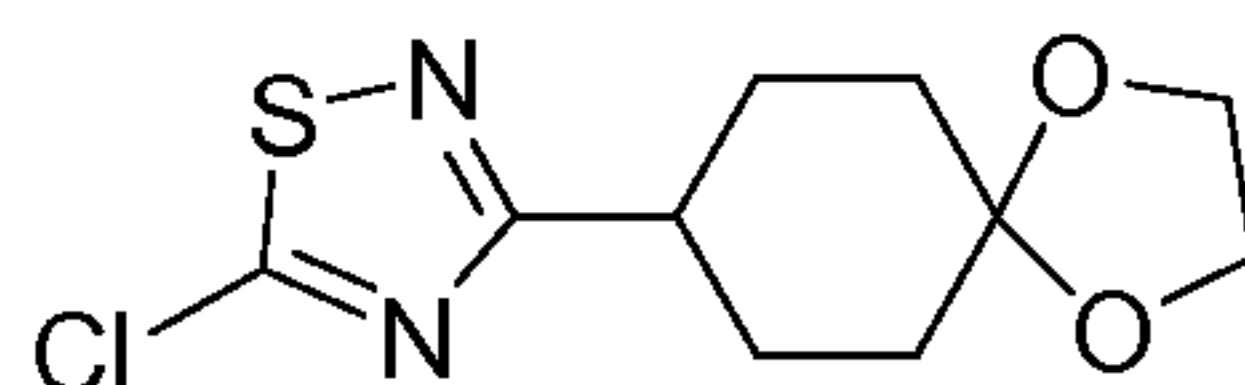


25 The title compound was prepared from {1-[4-(4-oxo-3,4,5,6,7,8-hexahydro-quinazolin-2-yl)-cyclohexyl]-azetidin-3-yl}-carbamic acid tert-butyl ester (as prepared in the previous step) according to the general de-protection and coupling procedure in Step D and E of Example 58.

The TFA salt, a mixture of *cis/trans* (1:1) isomers: LC/MS: 532.3 [M+H].

Example 62: N-({1-[4-(5-Chloro-[1,2,4]thiadiazol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

5 *Step A: 5-Chloro-3-(1,4-dioxo-spiro[4.5]dec-8-yl)-[1,2,4]thiadiazole*

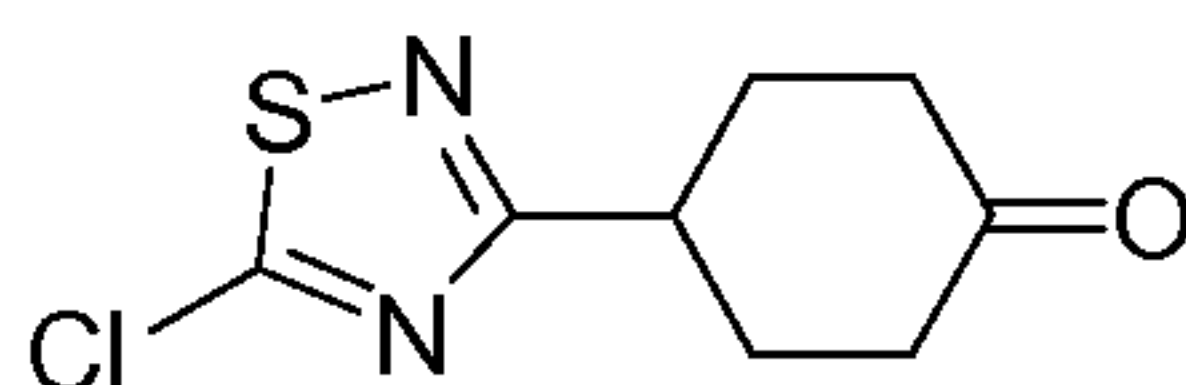


To a stirred suspension of NH_4Cl (0.29 g, 5.4 mmol) in dry toluene (2 mL) at 5 °C was slowly added a solution of trimethylaluminium in toluene (Aldrich, 2M, 2.5 mL, 5 mmol) under Ar. After the addition, the mixture was warmed to rt and stirred for 2 h until gas evolution had ceased. Then a solution of the intermediate 1,4-dioxo-spiro[4.5]decane-8-carbonitrile (0.50 g, 3 mmol, prepared according to the procedure from Tremblay, Maxime, PCT Int. Appl. (2007)) in toluene (1 mL) was added and the mixture was heated to 80 °C for 18 h. The reaction mixture was slowly poured into a slurry of silica gel (1.5 g) in CHCl_3 (5 mL) and stirred for 5 min. The silica gel was filtered and washed with methanol. The filtrate was condensed to 1/3 volume and filtered again. The filtrate was evaporated to dryness to give the crude intermediate as an HCl salt, which was dissolved in a NaOH solution (5N, 3.48 mL, 17.4 mmol) and cooled to 0 °C, followed by addition of a solution of perchloromethyl mercaptan (Aldrich, 0.39 mL, 3.6 mmol). The mixture was vigorously stirred at rt overnight. Aqueous workup and purification by column chromatography (eluent: EtOAc/hexanes, 1:6) gave the product.

10
15
20

^1H NMR (400 MHz, CDCl_3): δ 3.95-3.97 (4H, m), 2.98-3.03 (1H, m), 2.08-2.14 (2H, m), 1.98-2.04 (2H, m), 1.83-1.88 (2H, m), 1.53-1.70 (2H, m).

Step B: 4-(5-Chloro-[1,2,4]thiadiazol-3-yl)-cyclohexanone

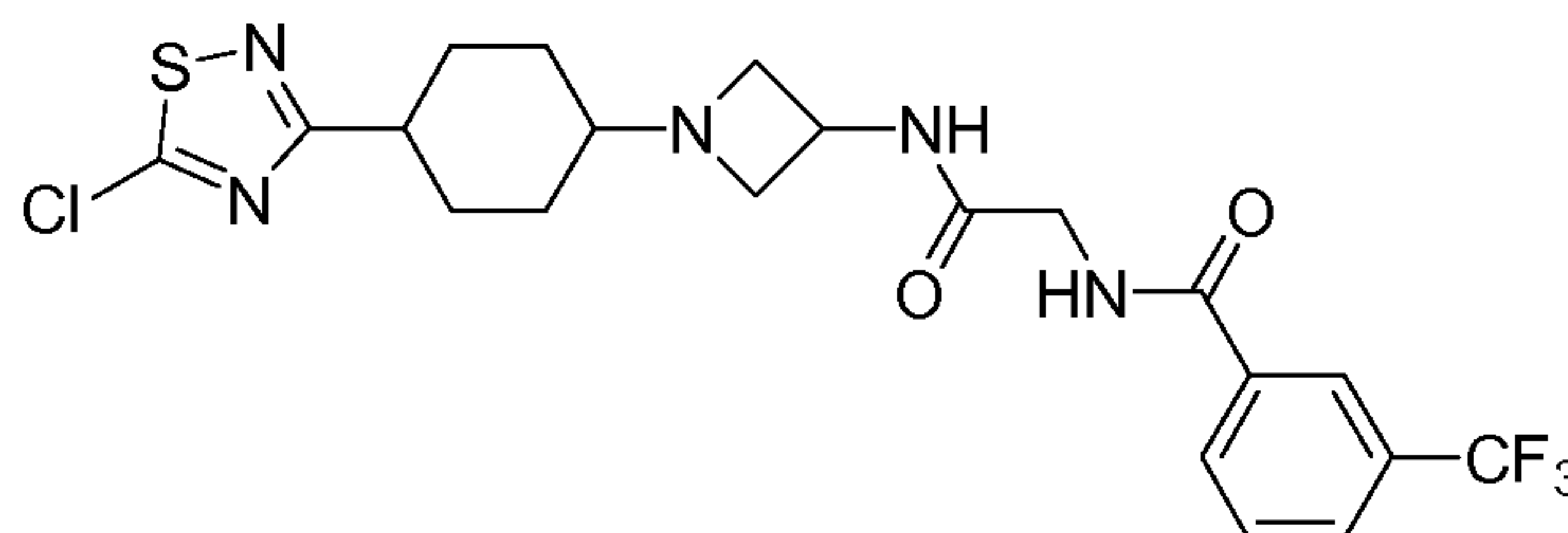


25 The above intermediate ketal (0.08 g, 0.3 mmol) was dissolved in CH_3CN (6 mL) and added to an 8N HCl solution (6 mL). The resulting solution was stirred at rt for 3 h and carefully neutralized with NaOH to pH ~7, and condensed. The aqueous phase was

extracted with EtOAc and dried over Na₂SO₄. Filtration and evaporation to dryness gave the title compound as a HCl salt.

LC/MS: 217.0 [M+H].

- 5 *Step C: N-({1-[4-(5-Chloro-[1,2,4]thiadiazol-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide*

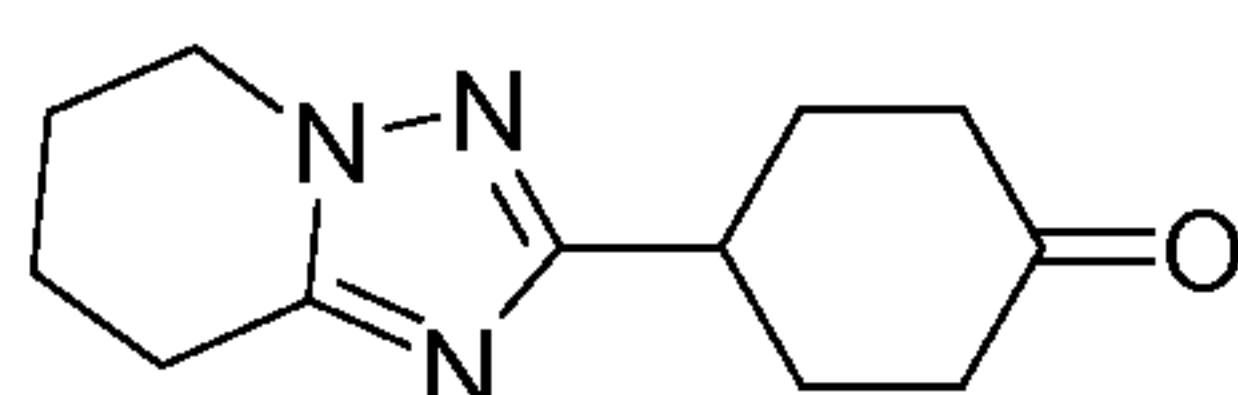


The title compound was prepared from 4-(5-chloro-[1,2,4]thiadiazol-3-yl)-cyclohexanone (as prepared in the previous step) according to the general reductive amination procedure
10 described in Step F of Example 1.

A mixture of cis/trans isomers. LC/MS: 502.0 [M+H].

Exempl 63: N-({1-[4-(5,6,7,8-Tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

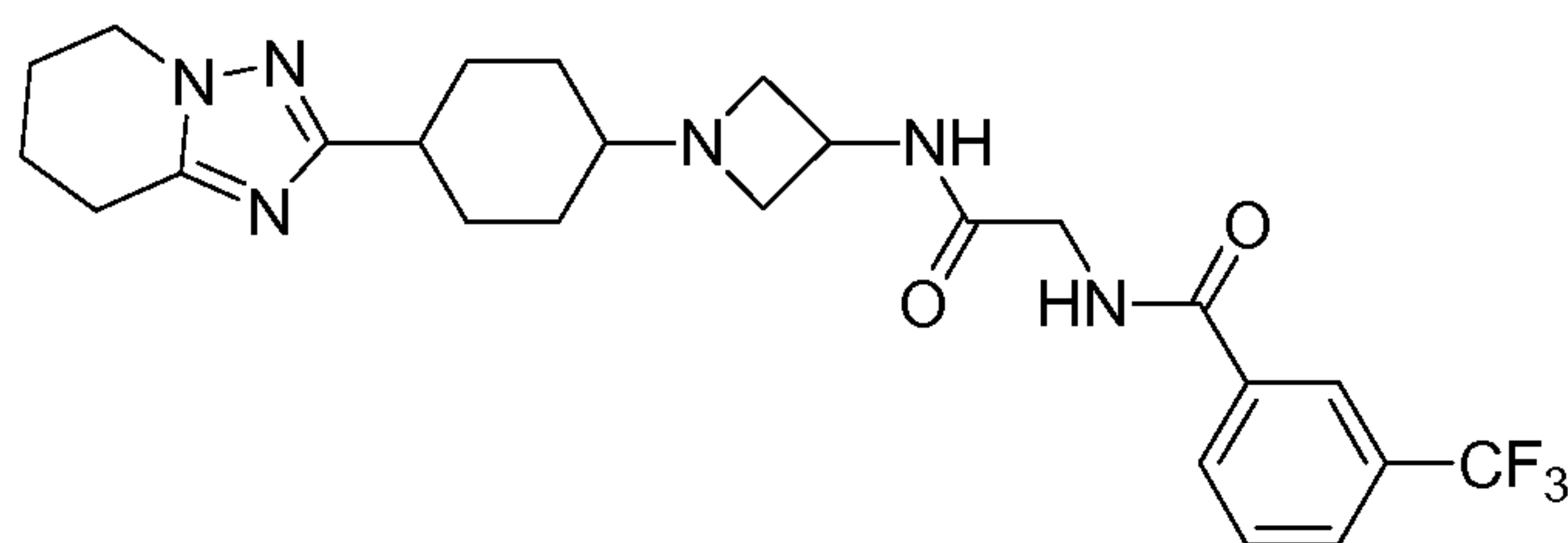
- 15 *Step A: 4-(5,6,7,8-Tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-cyclohexanone*



A solution of 2-(1,4-dioxa-spiro[4.5]dec-8-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine (1.05 g, 4 mmol, prepared according to the literature procedure: Quanrui Wang, Atef Amer, Susanne Mohr, Eveline Ertel, Johannes C. Jochims, Tetrahedron,
20 1993, 49(44), 9973-9986) in CH₃CN (20 mL) and 2N HCl (30 mL) was stirred at rt for 2 h. Evaporation to dryness gave the intermediate as a HCl salt.

LC/MS: 220.0 [M+H].

- 25 *Step B: N-({1-[4-(5,6,7,8-Tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide*



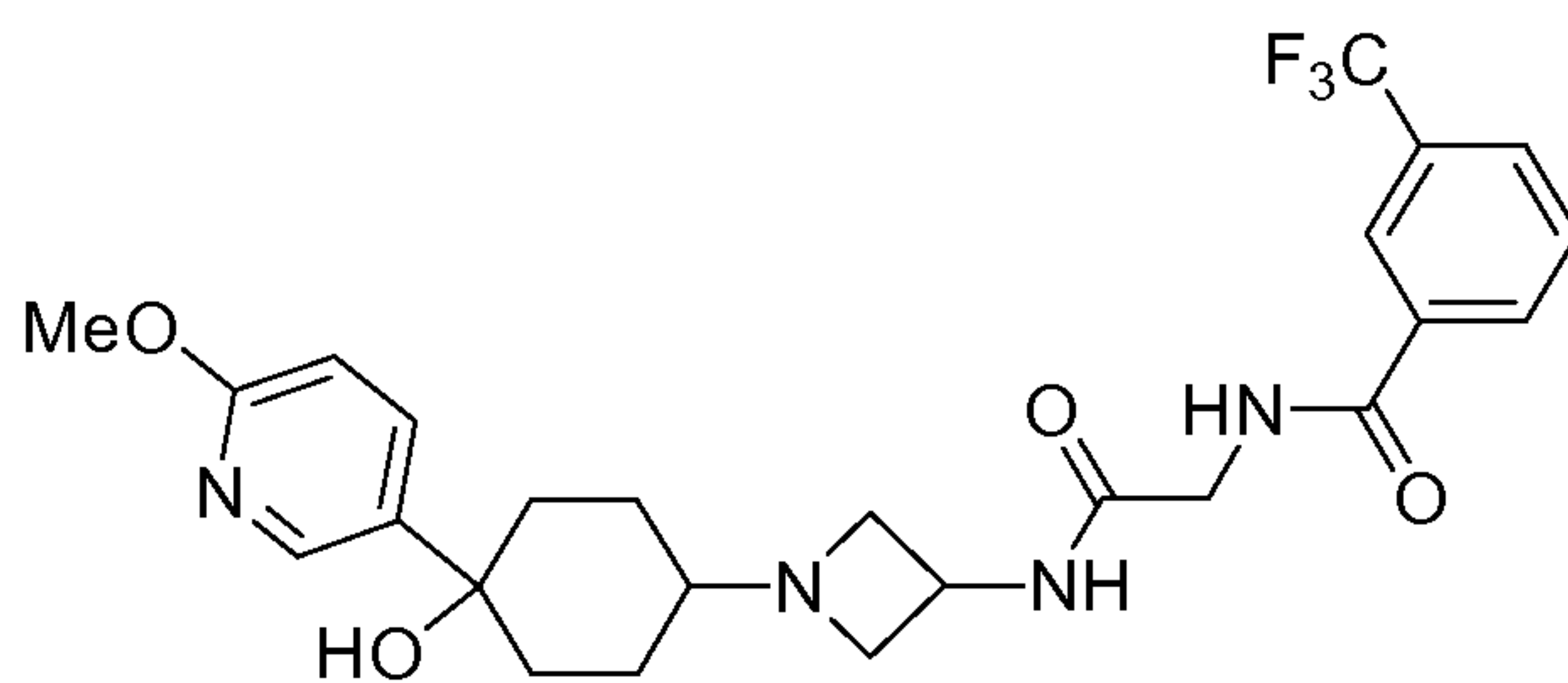
The title compound was prepared from 4-(5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-cyclohexanone (as prepared in the previous step) according to the general reductive amination procedure described in Step F of Example 1.

5 A mixture of cis/trans (1:3) isomers. LC/MS: 505.3 [M+H].

Example 64: N-({1-[4-Fluoro-4-(6-methoxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

Step A: N-({1-[4-Hydroxy-4-(6-methoxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-ylcarbamoyl}-methyl)-3-trifluoromethyl-benzamide

10



A solution of 4-hydroxy-4-(6-methoxy-pyridin-3-yl)-cyclohexanone (300 mg, 1.36 mmol) and N-(azetidin-3-ylcarbamoylmethyl)-3-trifluoromethyl-benzamide HCl salt (460 mg, 1.36 mmol) in DCM (5 mL) was treated with TEA (1 mL, 7.12 mmol) for 10 min followed by NaBH(OAc)₃ (860 mg, 4.07 mmol) for another 4 hours at room temperature. The reaction was quenched with saturated sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted 3 times with a chloroform/IPA “cocktail” (~ 3:1, v/v). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude product, and purified by a CombiFlash® system using ethyl acetate and 7N NH₃ in MeOH as eluent (from pure ethyl acetate to 5% 7N NH₃ in MeOH in ethyl acetate) to afford the two title compounds as white solids:

20

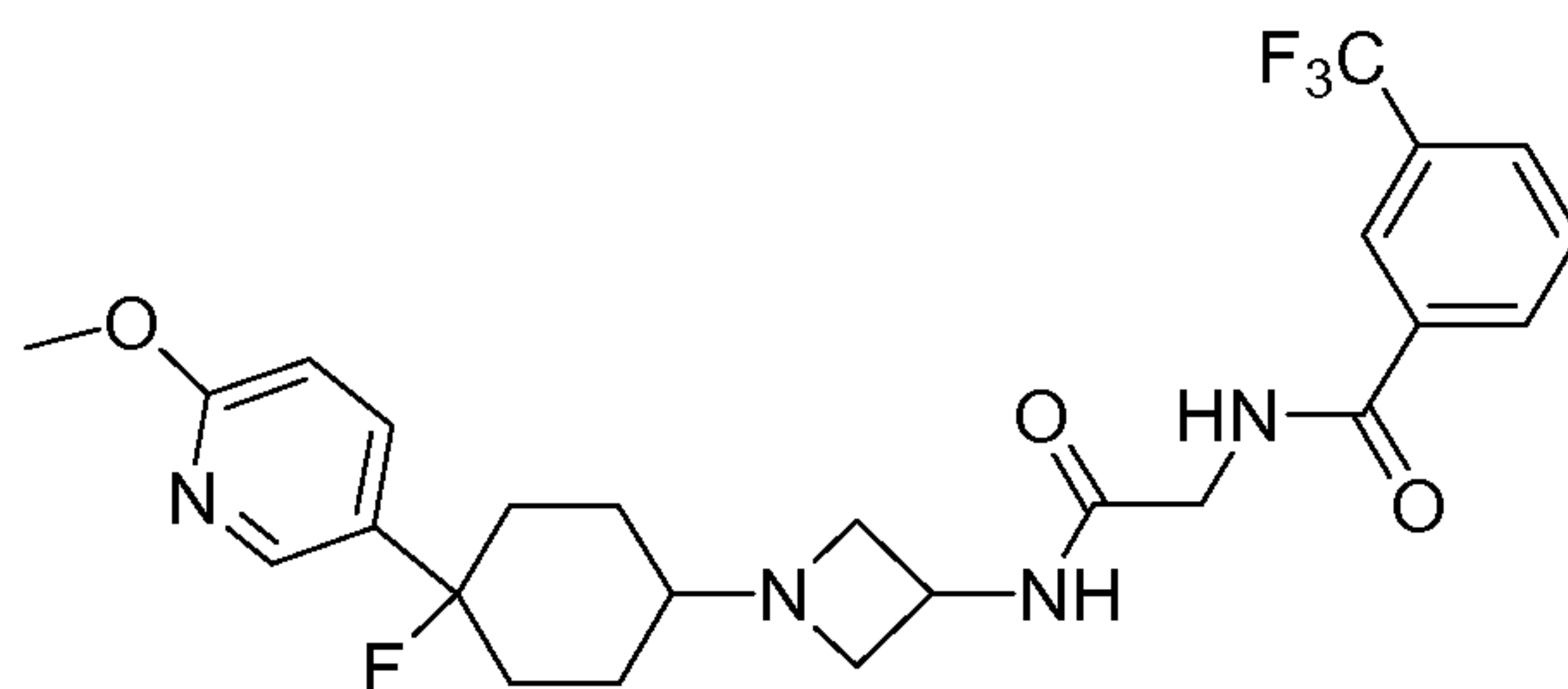
less polar isomer from silica gel column,

¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 8.11 (s, 1H), 8.05 (d, J = 5.8 Hz, 1H), 7.78 (d, J = 6.5 Hz, 1H), 7.70 (d, J = 6.5 Hz, 1H), 7.57 (t, J = 6.8 Hz, 1H), 6.70 (d, J = 6.5 Hz,

1H), 4.51 (m, 1H), 4.20 (d, J = 3.2 Hz, 2H), 3.88 (s, 3H), 3.65 (t, J = 6.0 Hz, 2H), 2.92 (t, J = 5.8 Hz, 2H), 2.20 (m, 2H), 1.85 (m, 2H), 1.56 (m, 2H), 1.45 (m, 2H).

more polar isomer from silica gel column

¹H NMR (400 MHz, CDCl₃) δ 8.25 (s, 1H), 8.10 (s, 1H), 8.05 (d, J = 6.5 Hz, 1H), 7.80 (d, J = 6.4 Hz, 1H), 7.71 (d, J = 6.5 Hz, 1H), 7.62 (d, J = 6.5 Hz, 1H), 7.60 (t, J = 6.8 Hz, 1H), 7.37 (d, J = 6.2 Hz, 1H), 6.70 (d, J = 6.8 Hz, 1H), 4.55 (m, 1H), 4.20 (d, J = 3.5 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H), 3.08 (t, J = 6.5 Hz, 2H), 1.85~1.50 (m, 8H).



10 A solution of N-({1-[4-hydroxy-4-(6-methoxy-pyridin-3-yl)-cyclohexyl]-azetidin-3-yl}carbamoyl)-methyl-3-trifluoromethyl-benzamide (300 mg, 0.60 mmol) in DCM (5 mL) was treated with DAST (Aldrich, 292 μL, 3.0 mmol) dropwise at -78 °C for 4 hours. The reaction was quenched with MeOH, warmed to room temperature and partitioned between DCM and water. The organic layer was washed with brine, dried over anhydrous
15 Na₂SO₄, filtered, concentrated and the residue was purified by a CombiFlash® system using ethyl acetate and 7N NH₃ in MeOH as eluent (from pure ethyl acetate to 5% 7N NH₃ in MeOH in ethyl acetate) to afford the two title compounds as white solids.

64a: less polar fraction from silica gel column,

¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 8.15 (s, 1H), 8.05 (d, J = 6.4 Hz, 1H), 7.80 (d, J = 6.6 Hz, 1H), 7.68 (m, 1H), 7.65 (d, J = 6.4 Hz, 1H), 7.55 (t, J = 7.1 Hz, 1H), 7.28 (d, J = 6.5 Hz, 1H), 6.72 (d, J = 6.8 Hz, 1H), 4.51 (m, 1H), 4.20 (d, J = 3.0 Hz, 2H), 3.90 (s, 3H), 3.62 (t, J = 6.8 Hz, 2H), 2.90 (t, J = 6.6 Hz, 2H), 2.20~2.01 (m, 2H), 1.80 (m, 4H), 1.55 (d, J = 6.0 Hz, 2H).

64b: more polar fraction from silica gel column

25 ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 2H), 8.05 (d, J = 6.0 Hz, 1H), 7.80 (d, J = 6.2 Hz, 1H), 7.65 (m, 2H), 7.24 (d, J = 6.5 Hz, 1H), 6.72 (d, J = 6.6 Hz, 1H), 4.55 (m, 1H), 4.21

(d, J = 3.0 Hz, 2H), 3.95 (s, 3H), 3.70 (t, J = 6.9 Hz, 2H), 3.02 (t, J = 6.8 Hz, 2H), 2.10 (m, 3H), 1.75 (m, 3H), 1.55 (m, 2H).

Example 65: IN VITRO BIOLOGICAL DATA

5 Compounds of the invention were subjected to various representative biological tests. The results of these tests are intended to illustrate the invention in a non-limiting fashion.

MCP-1 Receptor Binding Assay in THP-1 Cells

Human monocytic cell line THP-1 cells were obtained from American Type Culture Collection (Manassas, Va., USA). The THP-1 cells were grown in RPMI-1640 (RPMI:
10 Roswell Park Memorial Institute Medium-cell culture growth media) supplemented with 10% fetal bovine serum in a humidified 5% CO₂ atmosphere at 37 °C. The cell density was maintained between 0.5×10⁶ cells/mL.

THP-1 (cells were incubated with 0.5 nM ¹²⁵I labeled MCP-1 (Perkin-Elmer Life Sciences, Inc. Boston, Mass.) in the presence of varying concentrations of either
15 unlabeled MCP-1 (R & D Systems, Minneapolis, Minn.) or test compound for 2 hours at 30° C. in a 96 well plate. Cells were then harvested onto a filter plate, dried, and 20 µL of Microscint 20 was added to each well. Plates were counted in a TopCount NXT, Microplate Scintillation & Luminescence Counter (Perkin-Elmer Life Sciences, Inc. Boston, Mass.). Blank values (buffer only) were subtracted from all values and drug
20 treated values were compared to vehicle treated values. 1 µM cold MCP-1 was used for nonspecific binding.

Table 1 lists IC₅₀ values for inhibition of MCP-1 binding to CCR2 obtained for test compounds of the invention. Where an IC₅₀ value was not obtained for a particular compound, the percent inhibition is provided at a test concentration of 25 µM.

25

Table 1: Inhibition of MCP-1 Binding IC₅₀

Example	CCR2 Binding (nM)
1a	7.0
2	210

3	24
4	13
5	260
6	50
7	32
8	25
9	52
10	970
11	460
12	> 25,000
13	90
14	280
15	230
16	95
17	920
18	380
19	1,900
20	43
21	85
22a	25
23a	72
24	60
25	210
26	840
27a	2,700
28	89
29a	1,200
29b	10,000
30a	189
31a	150
32	320
33	250
34	120
35a	44
36a	31
37a	170
38a	46
39a	37
40a	330
41	130
42a	150
43	330
44a	250
45a	61
46a	550

47	180
48	630
49	> 25,000
50	920
51a	340
52a	2,800
53	1,000
54	340
55	125
56	5,800
57	1,100
58	510
59	400
60	3,900
61	4,000
62	390
63	1,500
64a	110

Example 66: Animals.

Mouse CCR2 knock-out / human CCR2 knock-in mice were generated using targeted 129Sv/Evbrd embryonic stem cell clones injected into C57BL/6 mice. Expression of the *hCCR2* transcript was confirmed by quantitative reverse transcription-polymerase chain reaction performed on spleen and blood total RNA from homozygous *hCCR2* knock-in mice. Backcrossing into C57BL/6 genetic background continued to the eighth generation. Transgenic mice were housed in a specific-pathogen-free, temperature-controlled facility that maintained a 12-hour light/12-hour dark cycle. Mice had free access to water and food. Experimental procedures were carried out in accordance with institutional standards for animal care and were approved by the institute's animal care and use committee.

Example 67: Murine In vivo Cell Migration Assay.

Animals are orally dosed with vehicle or CCR2 antagonists at 3, 10 and 30 mg/kg bid. Animals undergo anesthesia and laparotomy. A distal loop of small bowel (5 cm in length) is gently everted onto moist sterile gauze. Synthetic human MCP-1 (1 mg/100 ml sterile PBS) or PBS alone is administered drop-wise onto the serosa of the everted loop. A suture knot is placed into the mesentery to mark the terminus of the treated area. Twenty-four hours later, the animal is sacrificed and the segment of bowel plus the

adjacent region is removed. The tissue is opened along the mesenteric border, pinned flat and the mucosa removed. The remaining muscle layer is fixed briefly in 100% EtOH and then stained using Hanker-Yates reagent to detect myeloperoxidase-containing immune cells. At 10 mpk, P.O. bid, a compound is deemed efficacious if the inhibition of cell migration reaches 30% compared with vehicle-treated animals.

Example 68: Thiolycollate-Induced Peritonitis in Mice.

Animals are orally dosed with vehicle or CCR2 antagonists at 3, 10, 30 and 100 mg/kg bid). One hour later, the animals are intraperitoneally injected with sterile thioglycollate (25 mL/kg, ip, Sigma) for induction of peritonitis. Animals are orally treated twice daily with vehicle or CCR2 antagonists. At the 72-hour time point, peritoneal cavities are lavaged with 10 mL of sterile saline. Total cell counts in the peritoneal lavage fluid are performed using a microscope and cell differentiation is performed using cytopsin analysis after Giemsa staining (Hema Tek 2000). Percent inhibition of the thioglycollate-induced peritonitis is calculated by comparing the change in number of leukocytes of CCR2 antagonist treated mice to the vehicle-treated mice.

Example 69: MCP-1-Induced Monocyte Recruitment to Airway of Mice.

Animals are orally treated with vehicle or CCR2 antagonists at 3, 10, and 30 mg/kg po bid). One hour later, the animals are intranasally dosed with 4 µg of MCP-1 in sterile saline. The animals are orally treated twice daily with vehicle or CCR2 antagonists. After 48 h, mice are euthanized by intraperitoneal injection of anesthesia solution (Sleepaway-Sodium pentobarbital). Whole bronchoalveolar lavage (BAL) is performed using 1.4 ml of ice-cold PBS containing 3 mM EDTA. Total cell counts in the BAL lavage fluid are performed using a microscope and cell differentiation is performed using cytopsin analysis after Giemsa staining (Hema Tek 2000). Percent inhibition is calculated by comparing the change in number of total leukocyte counts (including monocytes/macrophages and lymphocytes) of compound-treated mice to the vehicle-treated mice. Compounds are deemed efficacious if percent inhibition reaches 30%.

Example 70: High-fat Diet Induced Obesity and Insulin Resistance in Mice.

Obesity is induced by a high-fat diet that derived approximately 60% calories from lipids (D-12492; Research Diets Inc.) in animals for 10- 24 weeks at age of 7 weeks. Prior to age 7 weeks, animals are fed a standard pellet diet, in which 5% of calories were provided as fat. Obese animals were randomized by body weight and fat mass. The obese animals are orally treated with vehicle or CCR2 antagonists at 3, 10 and 30 mg/kg, po bid. Body weight and food intake and were fasting blood glucose levels monitored. Body mass was determined by a NMR analyzer (Burker MiniSpec). Insulin tolerance test is carried out in animals that were fasted for 3 hours. After an intraperitoneal bolus injection of recombinant human insulin (1.5 U/kg), blood glucose concentrations are measured using a Glucometer before and 15, 30, 45, 60, 90 and 120 minutes after injection. Glucose tolerance tests are performed after an overnight (17-hour) fast. Blood glucose concentrations are measured before and after 15, 30, 60, 90, 120 minutes after an oral dose of glucose dissolved in water (1g/kg). Energy expenditure analysis was monitored by a complete laboratory animal monitor system. After 40 days treatment with vehicle or CCR2 antagonists, the animals are sacrificed by CO₂ asphyxiation. Percent of weight loss is calculated by comparing the body weight changes of the compound-treated mice with the vehicle-treated mice.

Example 71: Mouse Model of Allergic Asthma.

Animals are sensitized by intraperitoneal injection of 10 µg chicken egg albumin (OVA) absorbed to 1 mg Imject[®] in 100 µL phosphate-buffered saline (PBS) on days 0 and 5. Control animals received PBS ip. OVA-immunized animals were challenged by inhalation of 0.5% OVA aerosol for 10 minutes by an ultrasonic nebulizer on days 12, 16 and 20. Control animals were challenged with PBS in similar fashion. The OVA-sensitized animals receive vehicle (0.5% Methocel) or CCR2 antagonists orally at 3, 10, 30 mg/kg twice daily from days 9-20 and once daily on Day 21, 2 hours before sacrifice. Dexamethason (5 mg/kg) and Montelukast (1 mg/kg) are given orally once a day. On day 21, 2 hours post the last dose of CCR2 compounds, bronchial reactivity to aerosolized methacholine is measured using a Buxco whole body plethysmograph. On day 21, the animals are sacrificed. Bronchoalveolar lavage fluid is collected (1 mL) and total cells counted. The numbers of eosinophils, lymphocytes, monocytes and neutrophils are

determined using cytospin analysis after Giemsa staining (Hema Tek 2000). Percent inhibition of total BAL leukocyte count (and eosinophil count) is calculated by comparing the compound-treated mice with vehicle-treated mice. Compounds are deemed efficacious if the inhibition reaches 30%.

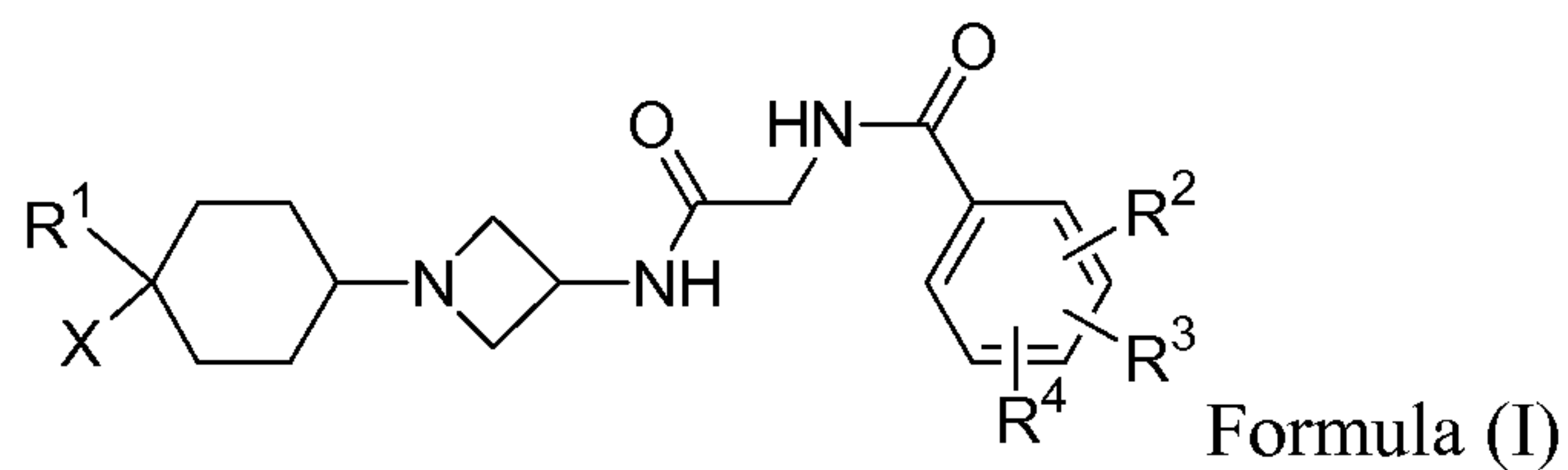
5

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

10

We Claim:

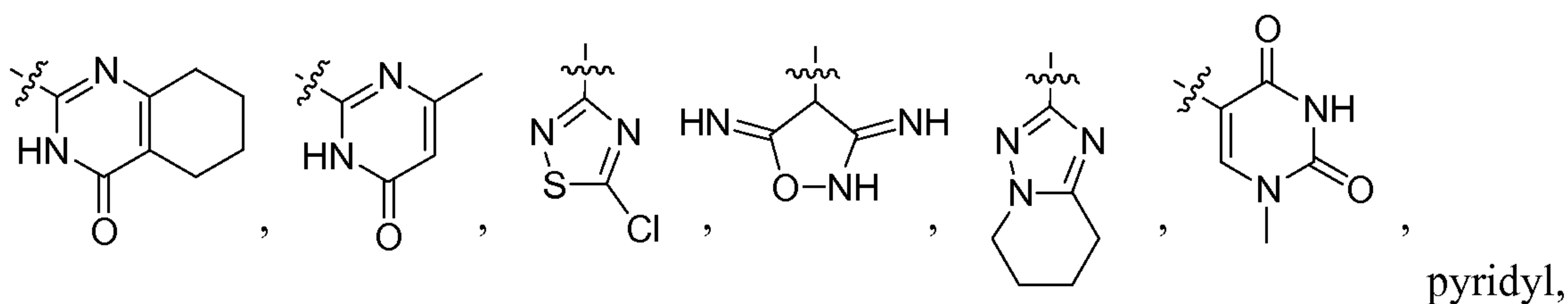
1. A compound of Formula (I)



wherein:

5 X is F, NH₂, or H;

R¹ is



pyridyl-*N*-oxide, pyridin-2-onyl, indolyl, pyrazinyl, 3-*H*-thiazol-2-onyl, pyrimidyl, benzooxazolyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, thiophenyl, furyl, [1,2,4]oxadiazolyl or [1,3,4]thiadiazolyl; wherein said pyridyl, pyridyl-*N*-oxide, pyrimidyl, pyrazolyl, imidazolyl, thiophenyl, or thiazolyl is optionally substituted with one substituent selected from the group consisting of OC₍₁₋₄₎alkyl, OC₍₃₋₆₎cycloalkyl, OCH₂CF₃, OCH₂Ph, F, CN, Cl, OCF₃, CF₃, CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, N(C₍₁₋₄₎alkyl)₂, C₍₁₋₄₎alkylOH, Si(CH₃)₃, —C≡CH, SCH₃, S(O)CH₃, SO₂CH₃, pyrrolidinyl, OH, NH₂, NHCN, CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl, N(SO₂CH₃)₂, NHSO₂CH₃, NHC(O)CF₃, NHC₍₁₋₄₎alkyl, NHCO₂H, NHCO₂C₍₁₋₄₎alkyl, NHCOC₍₁₋₄₎alkyl, NHCONH₂, NHCONHC₍₁₋₄₎alkyl, and Br; or said pyridyl may be substituted with one OCH₃ group and one CH₃; wherein said pyrimidyl is optionally substituted on any carbon atom with one N(C₍₁₋₄₎alkyl)₂ group; or said pyrimidinyl is substituted on any two carbon atoms with two substituents independently selected from the group consisting of OH, OCH₃, and CH₃; wherein said thiazolyl is substituted with CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl, or OH; or said thiazolyl is optionally substituted on two adjacent carbon atoms to form a fused bicyclic system benzothiazol-2-yl, wherein said benzothiazol-2-yl is optionally substituted with Br or OCH₃; wherein said pyridin-2-onyl is optionally substituted with one substituent selected from the group consisting of CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, and

CH₂CH₂OH, or said pyridin-2-onyl is substituted with 2 methyl groups; wherein said [1,2,4]oxadiazolyl is optionally substituted on any carbon atom with OH, CCl₃, or pyrrolidinyl;

R² is C₍₁₋₄₎alkyl, NH₂, NO₂, NHCH₂CH₂OH, N(C₍₁₋₄₎alkyl)₂, N(SO₂CH₃)₂, CN, F, Cl, Br,

5 CF₃, C₍₃₋₆₎cycloalkyl, heterocyclyl, OCF₃, OCF₂H, CF₂H, or OC₍₁₋₄₎alkyl;

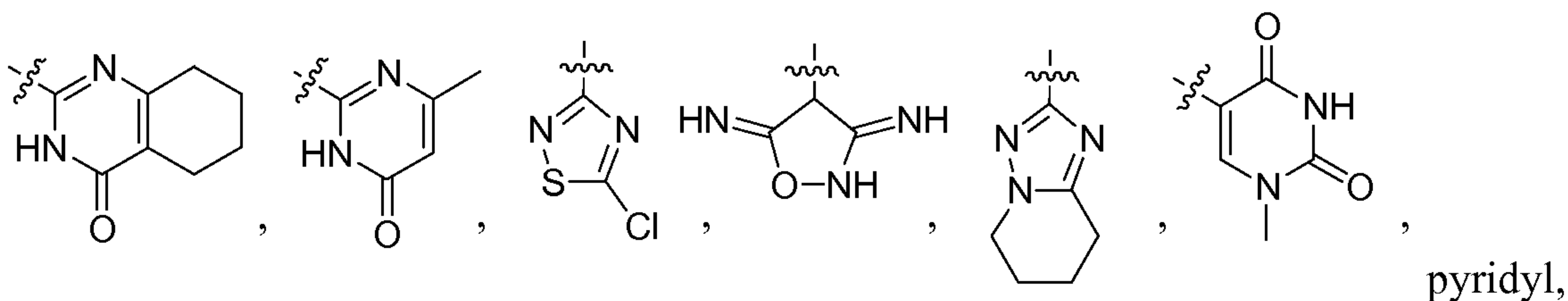
R³ is H, F, Cl, CF₃, or OC₍₁₋₄₎alkyl; alternatively, R² and R³ may be taken together with their attached phenyl to form a benzo[1,3]dioxolyl, 2,3-dihydro-benzofuranyl, or 2,3-dihydro-benzo[1,4]dioxinyl group;

R⁴ is H, OC₍₁₋₄₎alkyl, or F;

10 and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

2. A compound of claim 1 wherein:

R¹ is



pyridyl-*N*-oxide, pyridin-2-onyl, indolyl, pyrazinyl, 3-*H*-thiazol-2-onyl, pyrimidyl, methyl substituted imidazolyl, methyl substituted pyrazolyl optionally substituted with Br, thiophenyl optionally substituted with Br, benzooxazolyl, oxazolyl, thiazolyl, isothiazolyl, [1,2,4]oxadiazolyl or [1,3,4]thiadiazolyl; wherein said pyridyl, pyridyl-*N*-

20 oxide, or thiazolyl is optionally substituted with one substituent selected from the group consisting of OC₍₁₋₄₎alkyl, OC₍₃₋₆₎cycloalkyl, OCH₂CF₃, OCH₂Ph, F, CN, CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, N(C₍₁₋₄₎alkyl)₂, C₍₁₋₄₎alkylOH, Si(CH₃)₃, —C≡CH, SCH₃, S(O)CH₃, SO₂CH₃, pyrrolidinyl, OH, NH₂, NHCN, CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl,

N(SO₂CH₃)₂, NHSO₂CH₃, NHC(O)CH₃, NHC(O)CF₃, NHC₍₁₋₄₎alkyl, and Br; or said

25 pyridyl may be substituted with one OCH₃ group and one CH₃; wherein said pyrimidyl is optionally substituted on any carbon atom with one N(C₍₁₋₄₎alkyl)₂ group; or said pyrimidinyl is substituted on any two carbon atoms with one OH group and one CH₃; wherein said thiazolyl is substituted with CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl, or OH; or

said thiazolyl is optionally substituted on two adjacent carbon atoms to form a fused bicyclic system benzothiazol-2-yl, wherein said benzothiazol-2-yl is optionally substituted with Br or OCH₃; wherein said pyridin-2-onyl is optionally substituted with one substituent selected from the group consisting of CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, and CH₂CH₂OH, or said pyridin-2-onyl is substituted with 2 methyl groups; wherein said [1,2,4]oxadiazolyl is optionally substituted on any carbon atom with OH, CCl₃, or pyrrolidinyl;

R² is C₍₁₋₄₎alkyl, NH₂, NO₂, NHCH₂CH₂OH, N(C₍₁₋₄₎alkyl)₂, N(SO₂CH₃)₂, CN, F, Cl, Br, CF₃, pyrrolidinyl, OCF₃, OCF₂H, CF₂H, or OC₍₁₋₄₎alkyl;

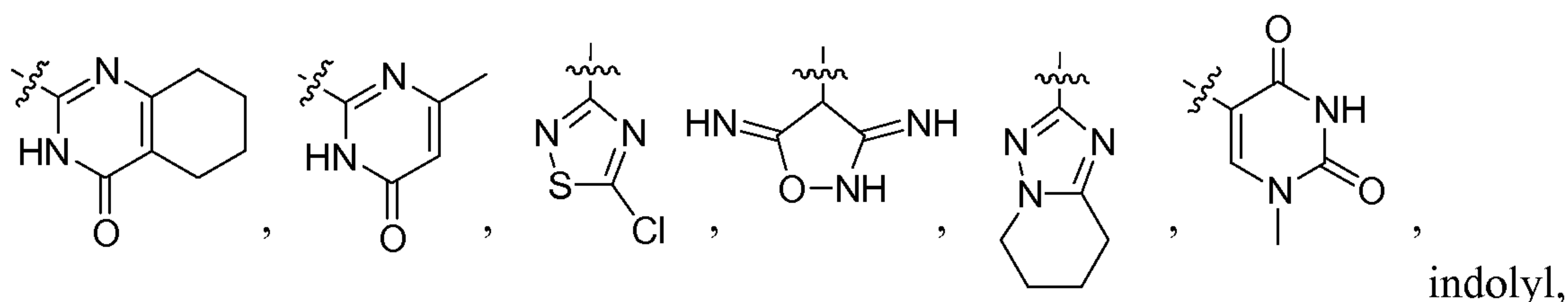
R³ is H, F, Cl, CF₃, or OC₍₁₋₄₎alkyl; alternatively, R² and R³ may be taken together with their attached phenyl to form a benzo[1,3]dioxolyl group;

R⁴ is H, OCH₃, or F;

and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

3. A compound of claim 2 wherein:

R¹ is



pyridyl, pyridyl-*N*-oxide, pyridin-2-onyl, pyrimidyl, pyrazinyl, methyl substituted imidazolyl, methyl substituted pyrazolyl optionally substituted with Br, thiophenyl optionally substituted with Br, benzooxazolyl, oxazolyl, thiazolyl, [1,2,4]oxadiazolyl, isothiazolyl, or [1,3,4]thiadiazolyl; wherein said pyridyl, pyridyl-*N*-oxide, or thiazolyl is optionally substituted with one substituent selected from the group consisting of OH, OC₍₁₋₄₎alkyl, NHC(O)CH₃, N(SO₂CH₃)₂, NHSO₂CH₃, NHC(O)CF₃, NHC₍₁₋₄₎alkyl, OC₍₃₋₆₎cycloalkyl, OCH₂CF₃, OCH₂Ph, F, CN, C₍₁₋₄₎alkyl, N(C₍₁₋₄₎alkyl)₂, C₍₁₋₄₎alkylOH, Si(CH₃)₃, —C≡CH, SCH₃, S(O)CH₃, SO₂CH₃, pyrrolidinyl, NH₂, NHCN, and Br; or said pyridyl may be substituted with one OCH₃ group and one CH₃; wherein said pyrimidyl is optionally substituted on any carbon atom with one N(C₍₁₋₄₎alkyl)₂ group; or

said pyrimidinyl is substituted on any two carbon atoms with one OH group and one CH₃; wherein said pyridin-2-onyl is optionally substituted with one substituent selected from the group consisting of CH₂CN, C₍₁₋₄₎alkyl, CH₂CF₃, and CH₂CH₂OH, or said pyridin-2-onyl is substituted with 2 methyl groups; wherein said thiazolyl is substituted with CO₂H, CONH₂, NHCO₂C₍₁₋₄₎alkyl, or OH; or said thiazolyl is optionally substituted on two adjacent carbon atoms to form a fused bicyclic system benzothiazol-2-yl, wherein said benzothiazol-2-yl is optionally substituted with Br or OCH₃; wherein said [1,2,4]oxadiazolyl is optionally substituted on any carbon atom with OH, CCl₃, or pyrrolidinyl;

10 R² is NH₂, NO₂, NHCH₂CH₂OH, N(CH₃)₂, N(SO₂CH₃)₂, CN, F, Cl, Br, CF₃, pyrrolidinyl, or OCH₃;

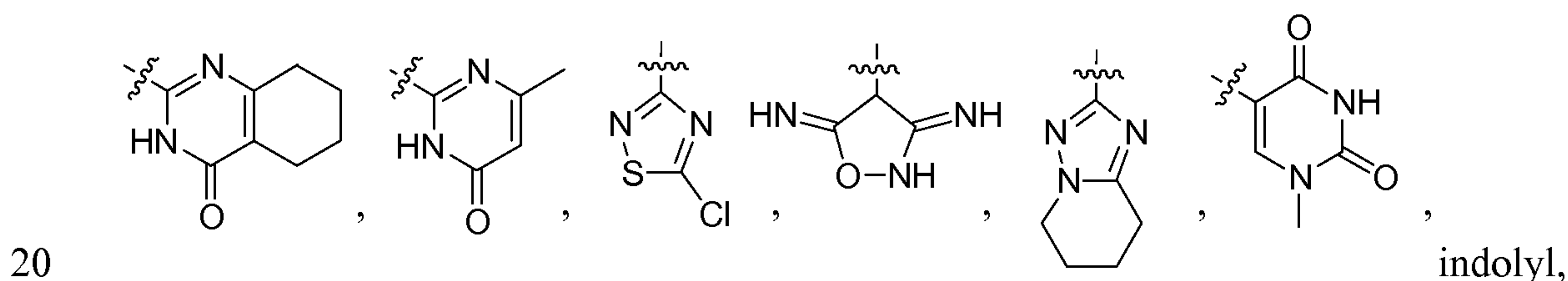
R³ is H, F, Cl, CF₃, or OCH₃; alternatively, R² and R³ may be taken together with their attached phenyl to form a benzo[1,3]dioxolyl group;

R⁴ is H, or F;

15 and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

4. A compound of Claim 3 wherein:

R¹ is



pyrimidyl, pyridin-2-onyl, pyrazinyl, thiazolyl, [1,2,4] oxadiazolyl, or pyridyl, wherein said pyridyl is optionally substituted on any carbon atom with one substituent selected from the group consisting of OH, OC₍₁₋₄₎alkyl, NHC(O)CH₃, N(SO₂CH₃)₂, NHSO₂CH₃, NHC(O)CF₃, NH₂, NHC₍₁₋₄₎alkyl, N(CH₃)₂, NHCN, SO₂CH₃; or said pyridyl is optionally substituted on any two carbon atoms with one OH group and one CH₃; wherein said pyrimidinyl is optionally substituted on any carbon atom with one N(CH₃)₂ group; or said pyrimidinyl is substituted on any two carbon atoms with one OH group and one CH₃; wherein said pyridin-2-onyl is optionally substituted with one substituent selected from

the group consisting of CH_2CN , $\text{C}_{(1-4)}\text{alkyl}$, CH_2CF_3 , and $\text{CH}_2\text{CH}_2\text{OH}$, or said pyridin-2-onyl is substituted with 2 methyl groups; wherein said thiazolyl is substituted with CO_2H , CONH_2 , $\text{NHCO}_2\text{C}_{(1-4)}\text{alkyl}$, or OH ; wherein said [1,2,4]oxadiazolyl is optionally substituted on any carbon atom with OH , CCl_3 , or pyrrolidinyl;

5 R^2 is CF_3 , CN , F , or Cl ;

R^3 is H , Cl , CF_3 , or F ;

R^4 is H , or F ;

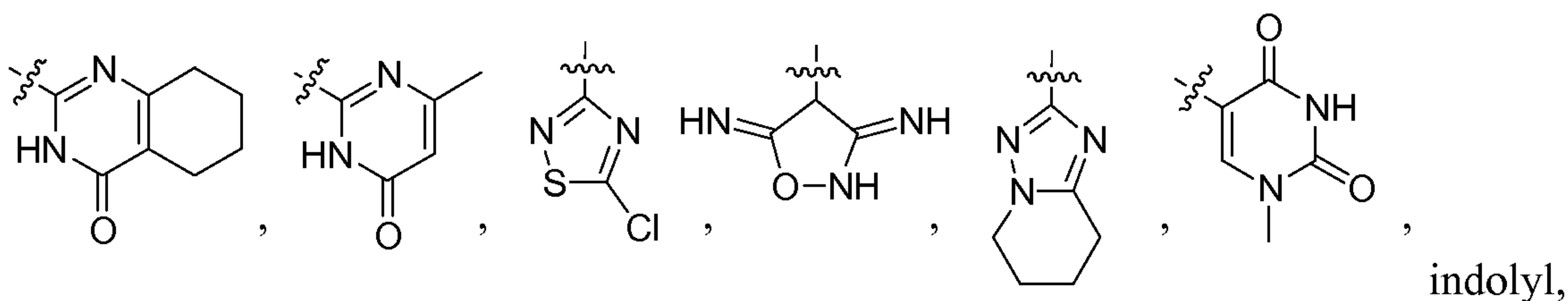
and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

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5. A compound of Claim 4 wherein:

X is F , or H ;

R^1 is



15 pyrimidyl, pyridin-2-onyl, methyl pyridin-2-onyl, pyrazinyl, thiazolyl, [1,2,4]oxadiazolyl, or pyridyl, wherein said pyridyl is optionally substituted on any carbon atom with one substituent selected from the group consisting of OH , OCH_3 , $\text{NHC}(\text{O})\text{CH}_3$, $\text{N}(\text{SO}_2\text{CH}_3)_2$, $\text{NH}\text{SO}_2\text{CH}_3$, $\text{NHC}(\text{O})\text{CF}_3$, NH_2 , NHCH_3 , $\text{N}(\text{CH}_3)_2$, NHCN , SO_2CH_3 ; or
 20 said pyridyl is optionally substituted on any two carbon atoms with one OH group and one CH_3 ; wherein said pyrimidinyl is substituted on any carbon atom with one $\text{N}(\text{CH}_3)_2$ group; wherein said pyridin-2-onyl is *N* substituted with one substituent selected from the group consisting of CH_2CN , $\text{C}_{(1-4)}\text{alkyl}$, CH_2CF_3 , and $\text{CH}_2\text{CH}_2\text{OH}$, or said pyridin-2-onyl is substituted with 2 methyl groups; wherein said thiazolyl is substituted with CO_2H , CONH_2 , NHCO_2CH_3 , or OH ; wherein said [1,2,4]oxadiazolyl is optionally substituted on
 25 any carbon atom with OH , CCl_3 , or pyrrolidinyl;

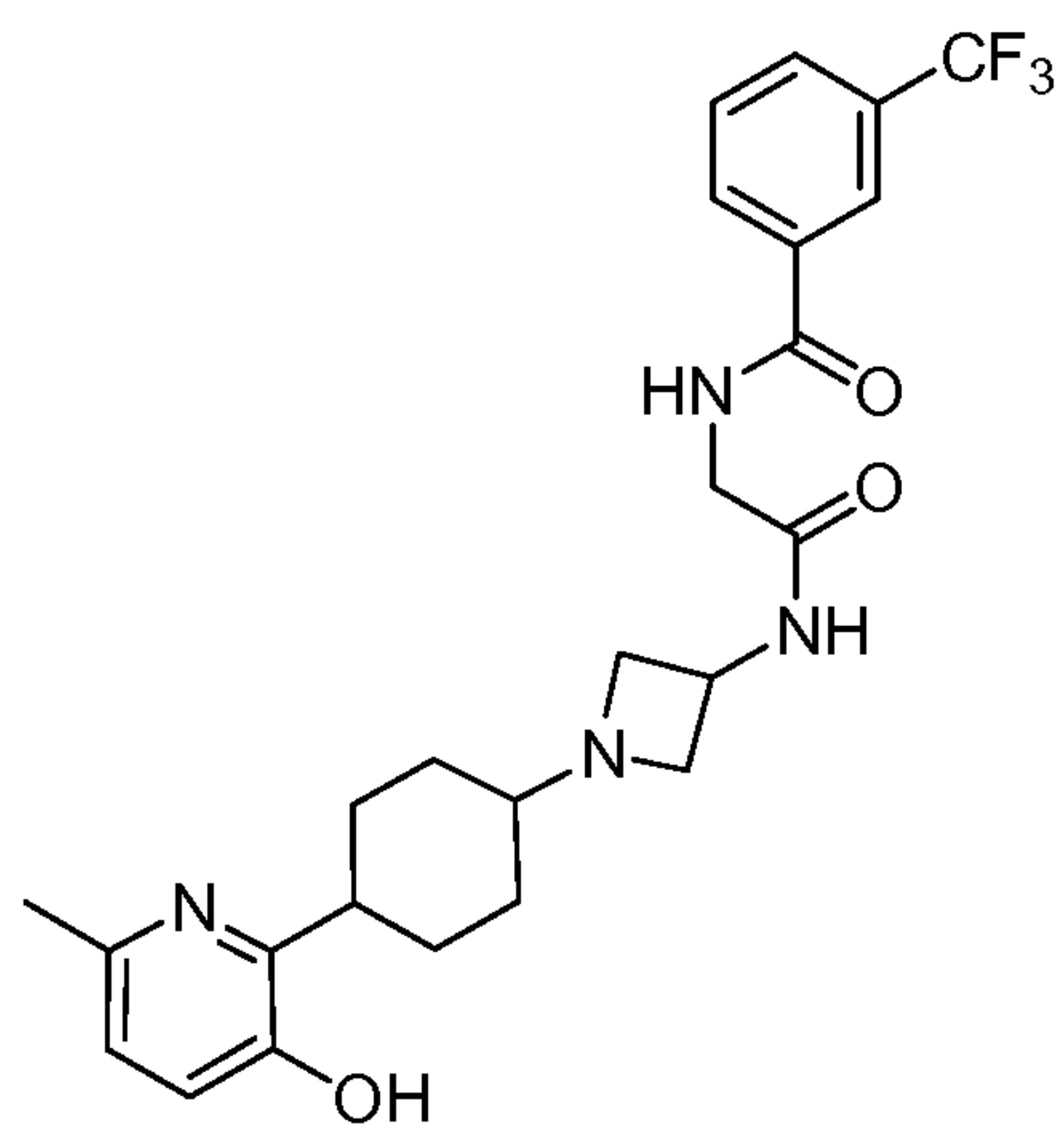
R^2 is CF_3 ;

R^3 is H , or F ;

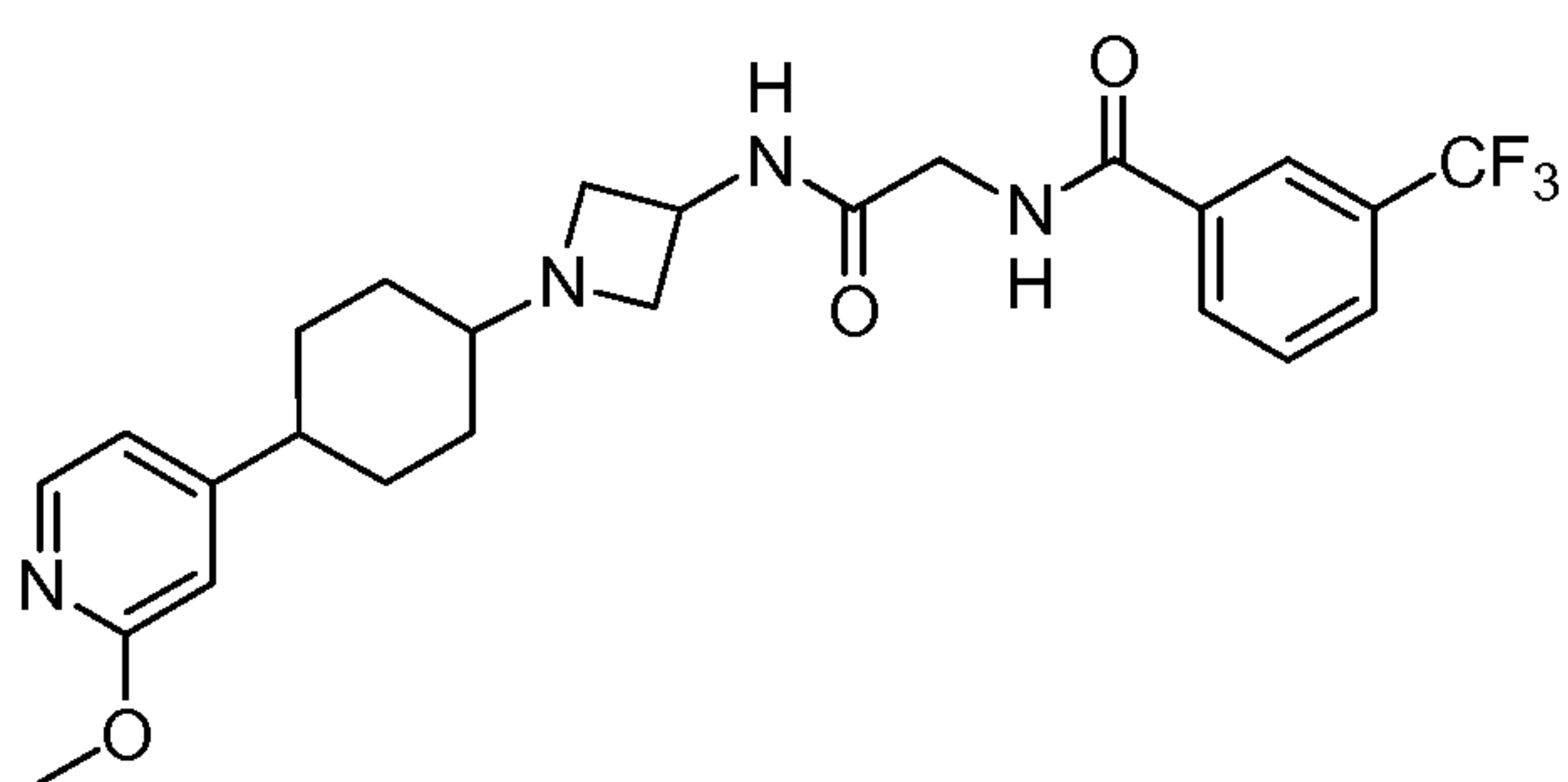
R^4 is H ;

6. A compound selected from the group consisting of:

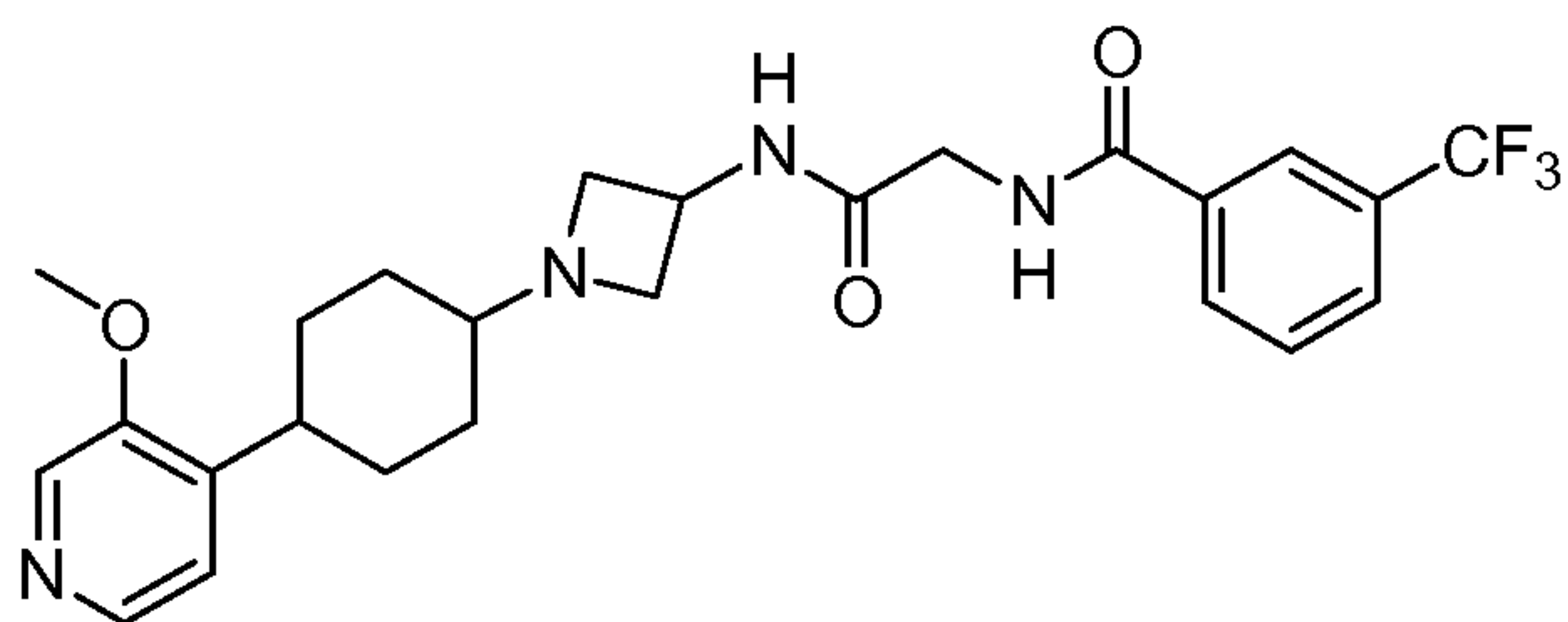




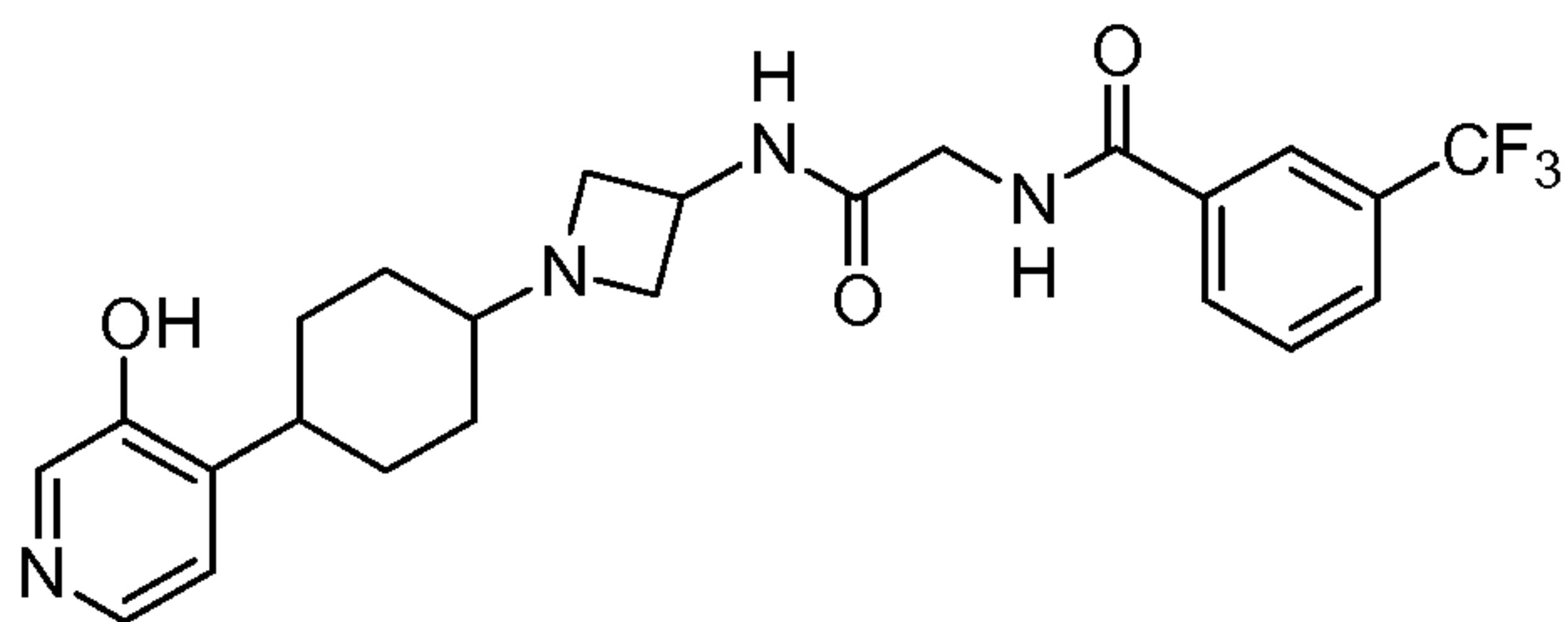
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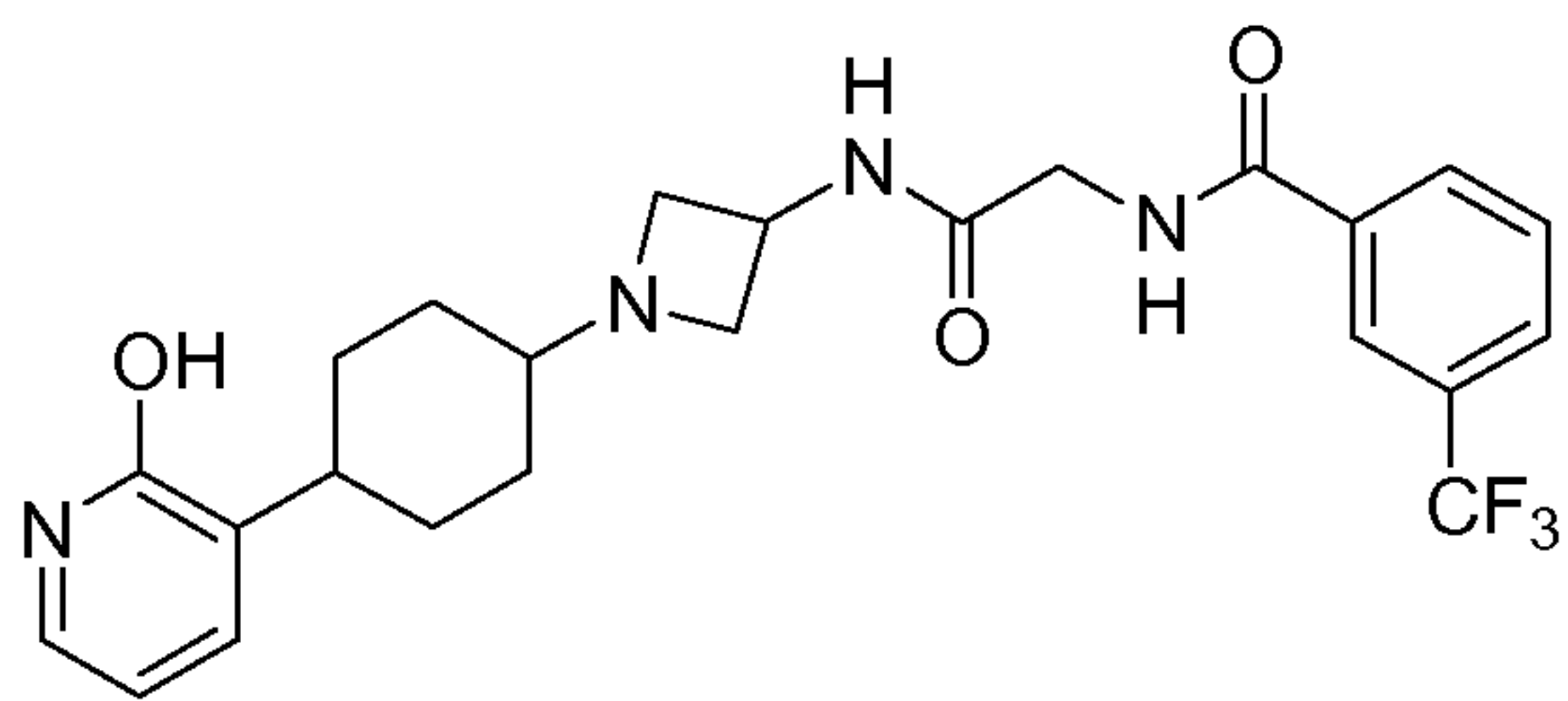
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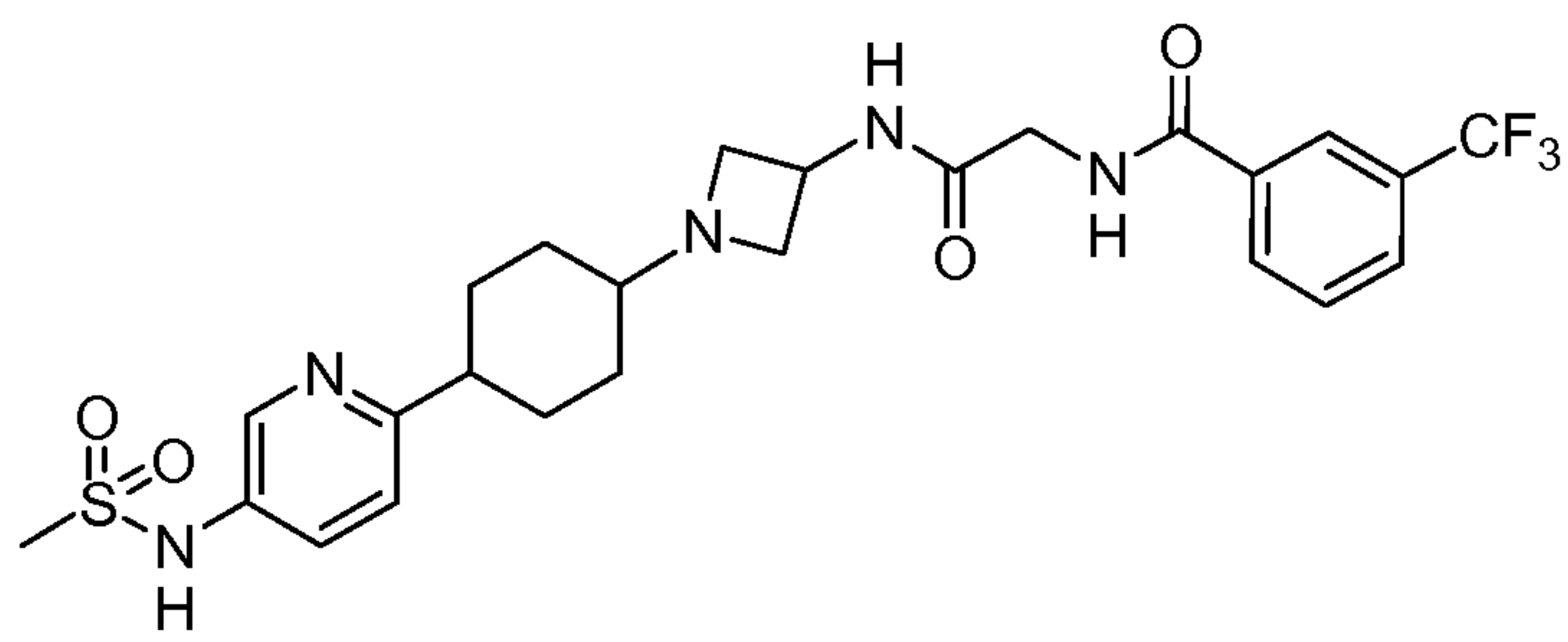
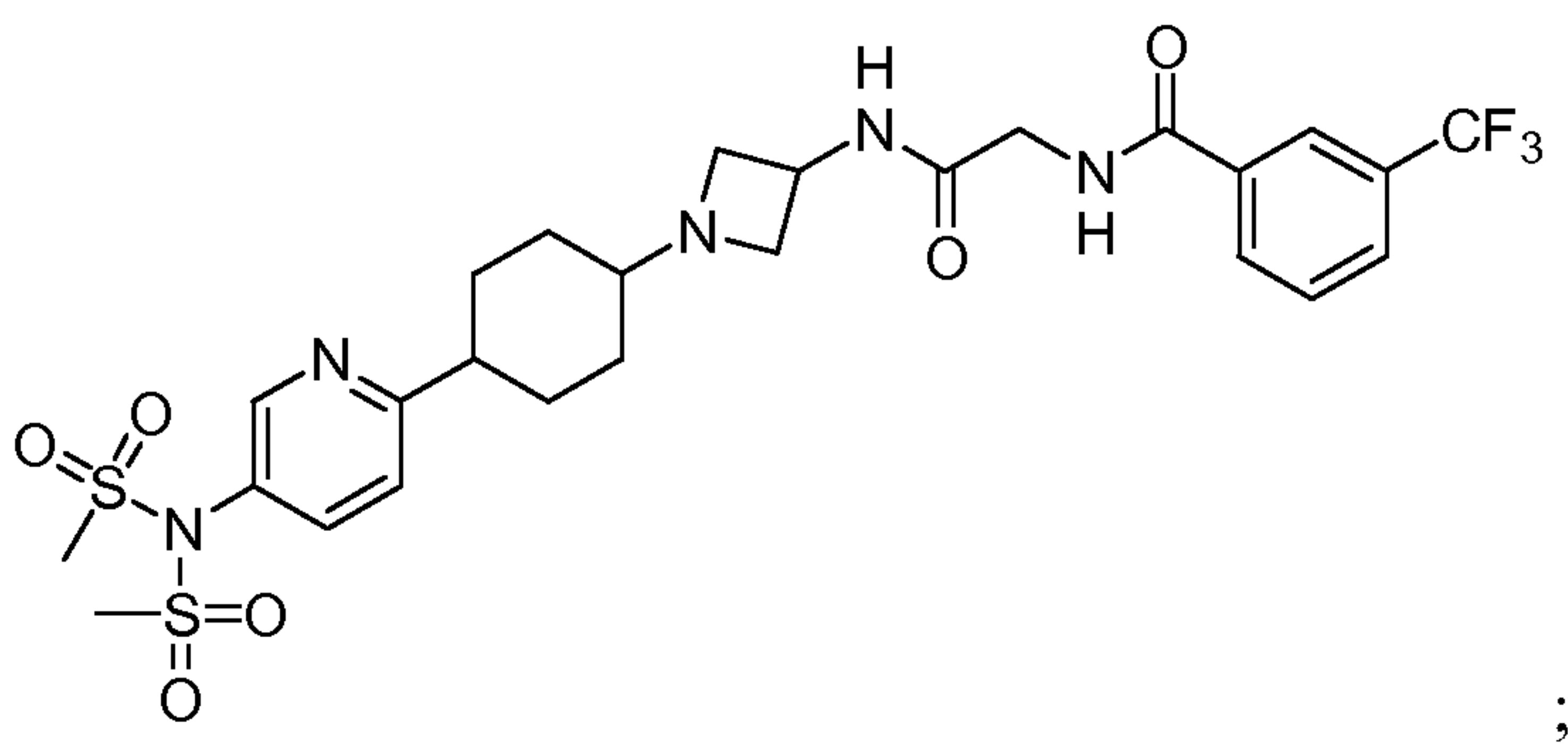
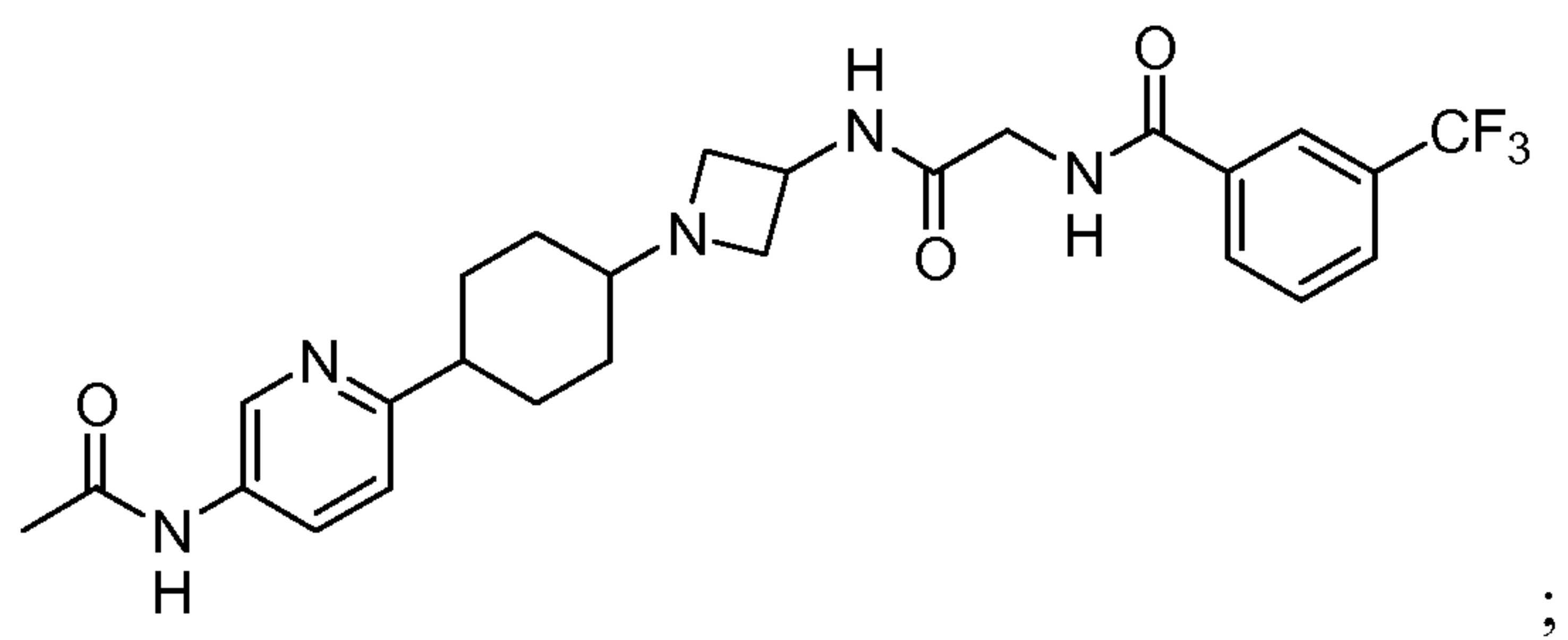
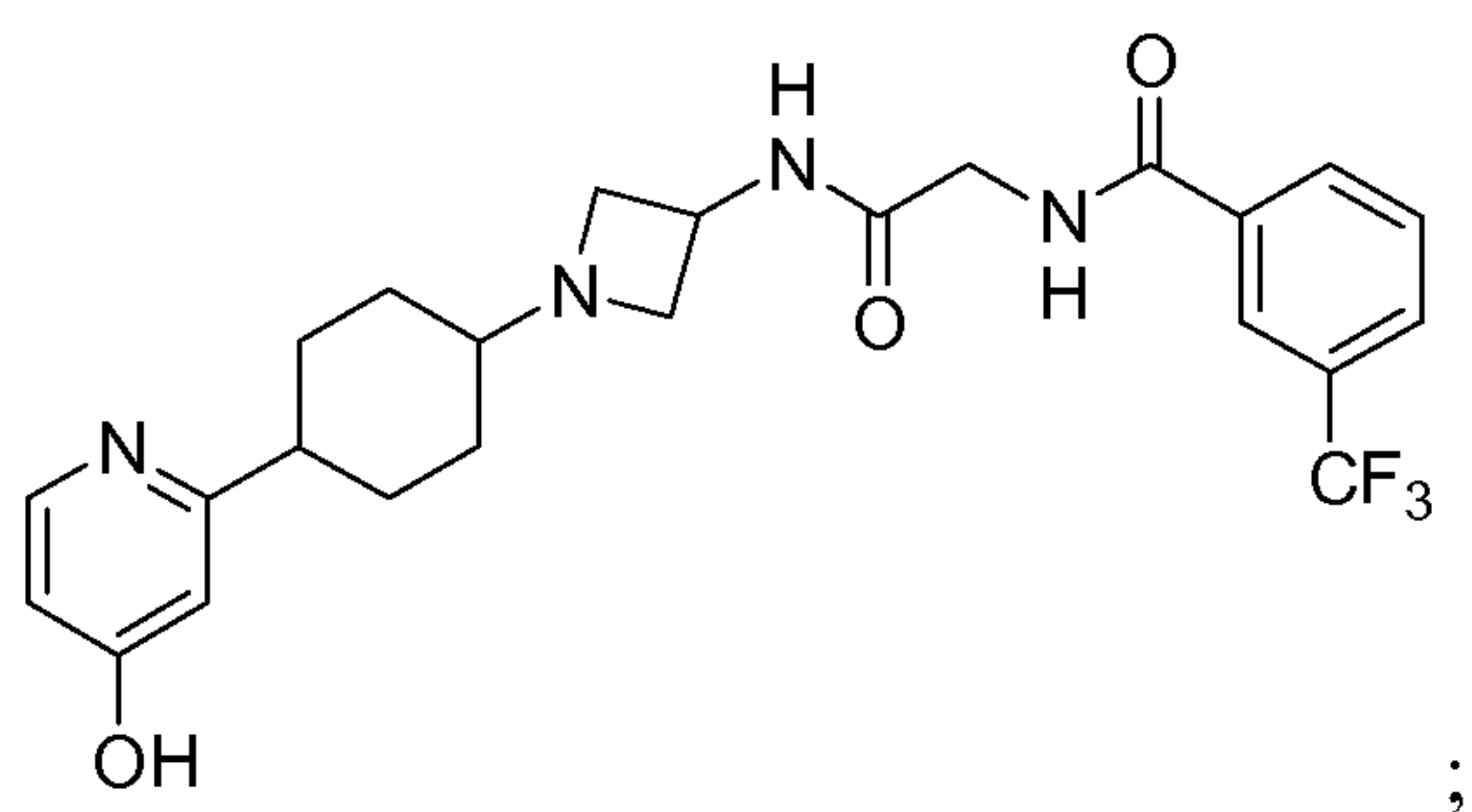
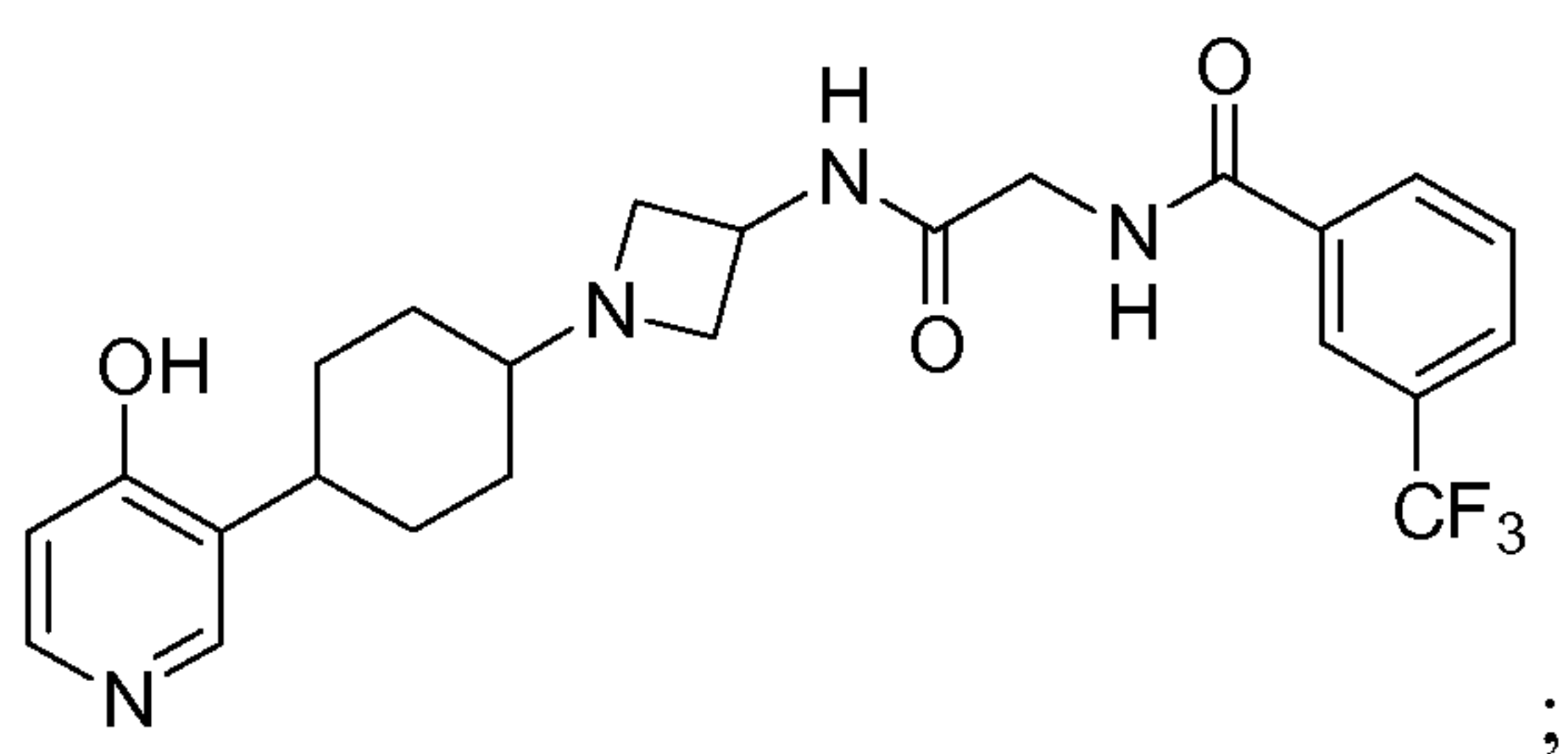
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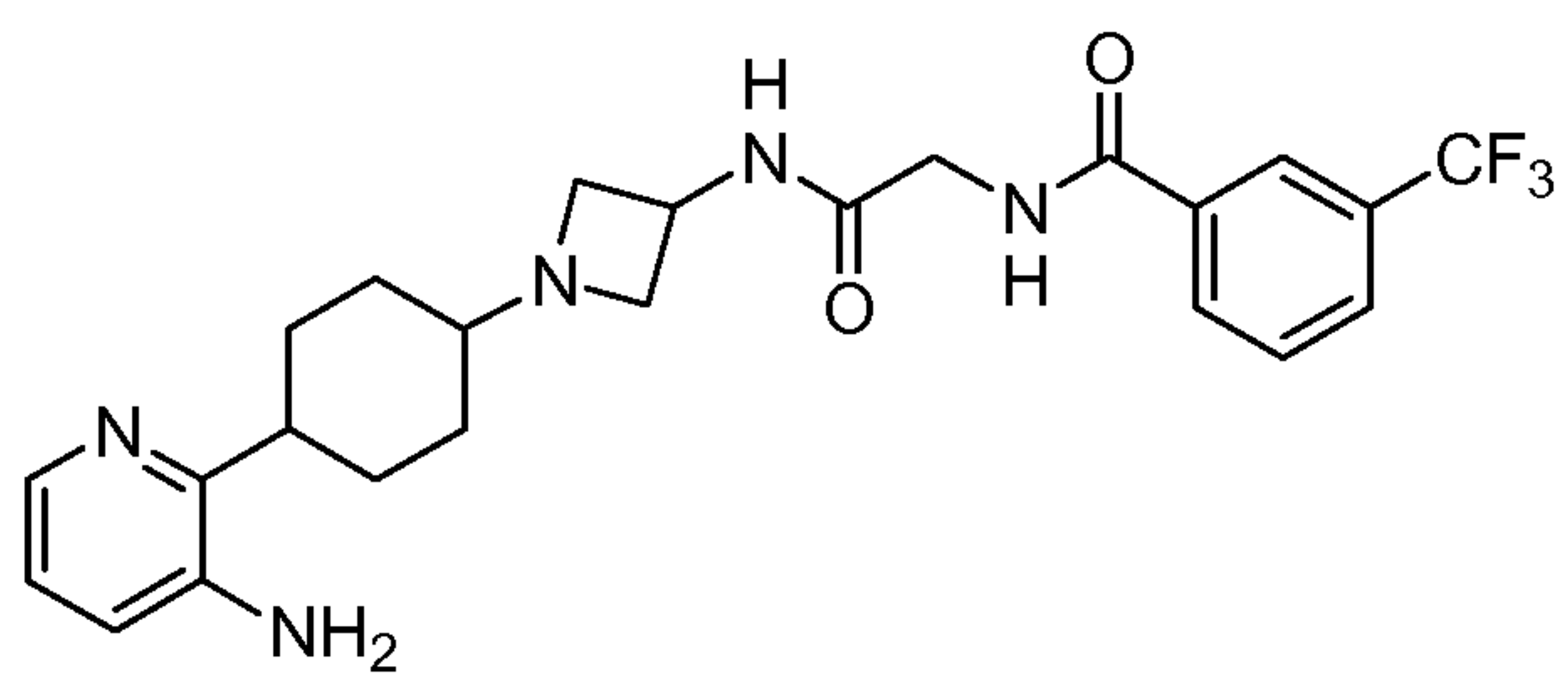
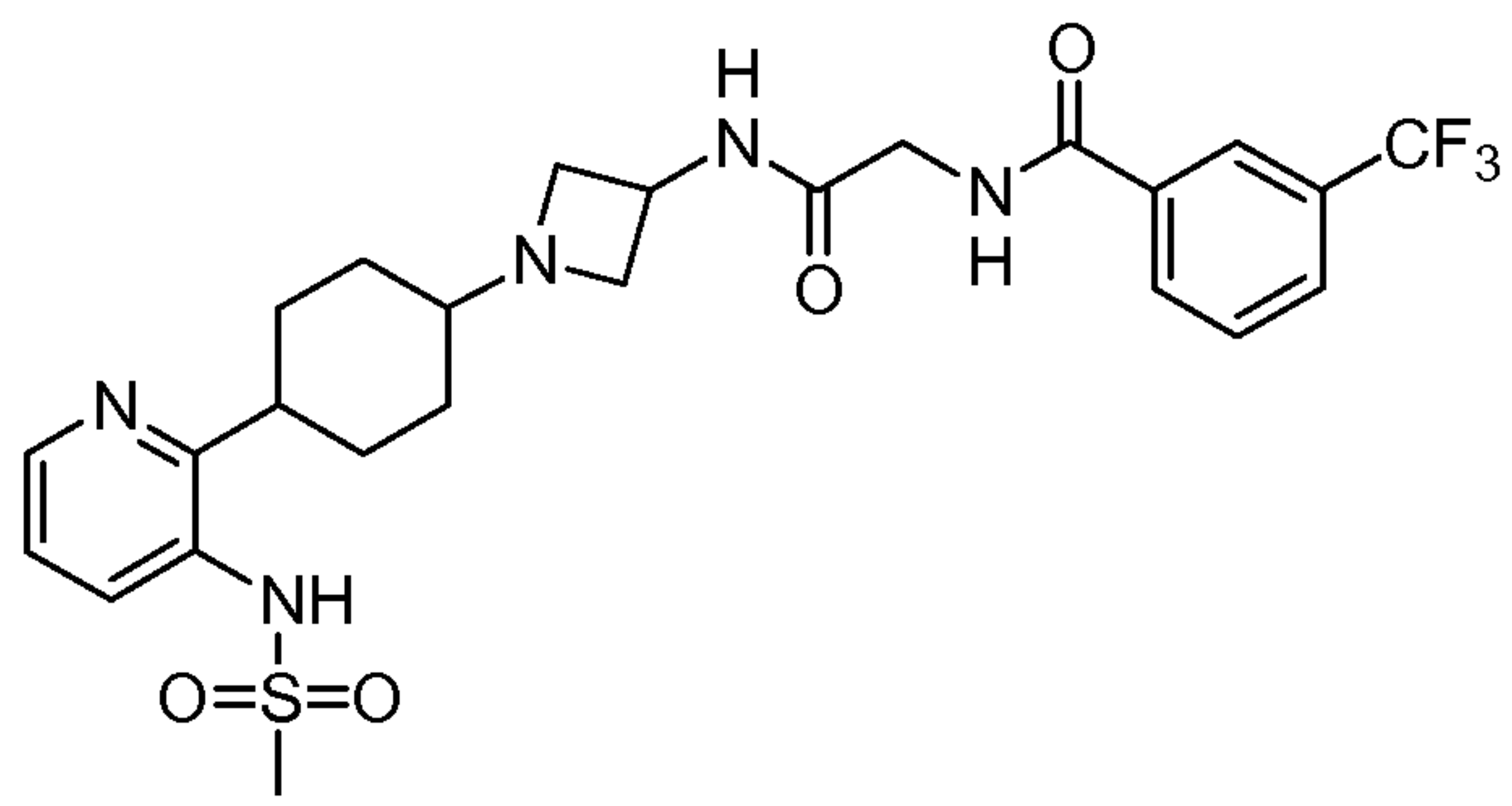
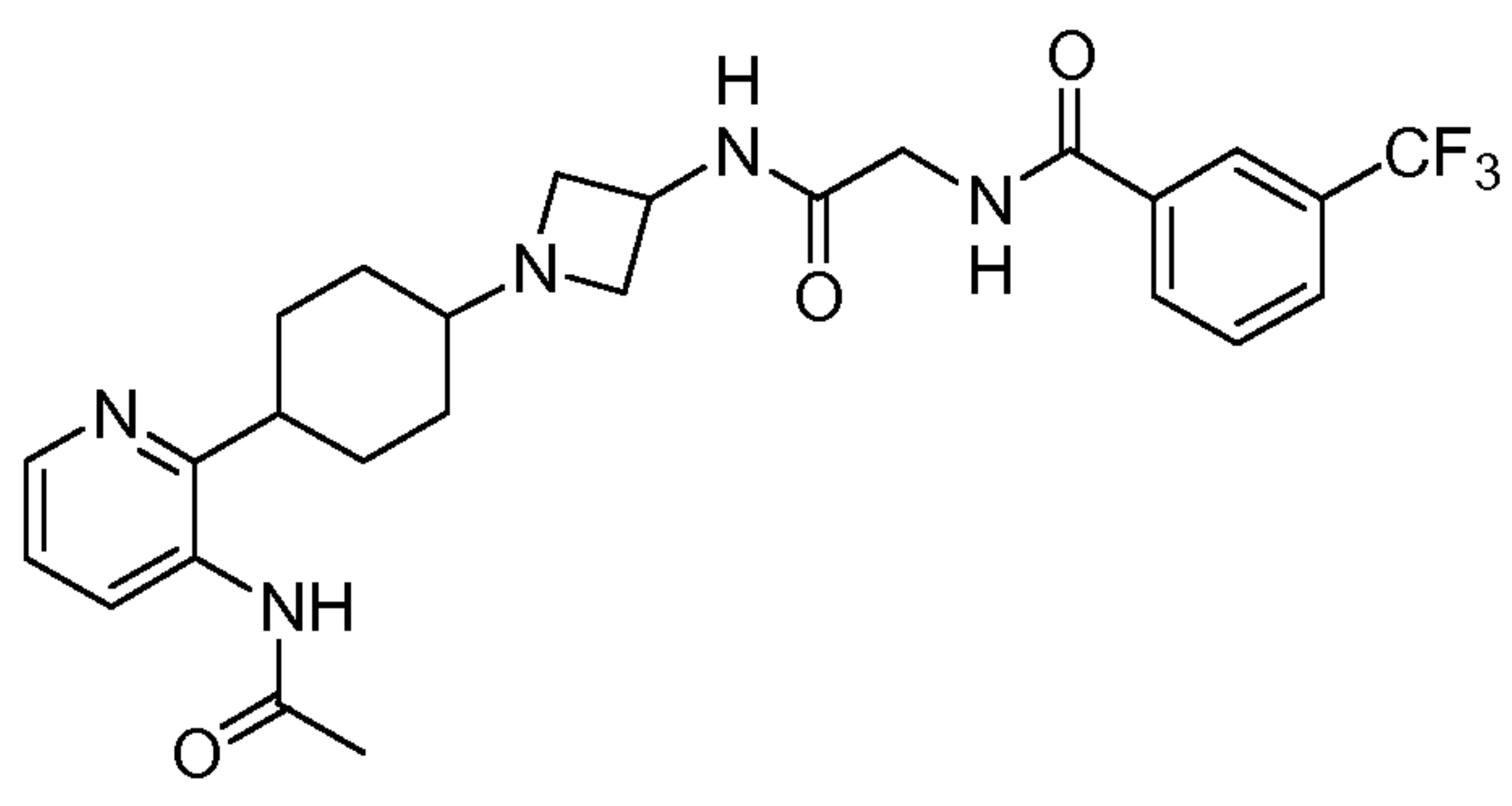
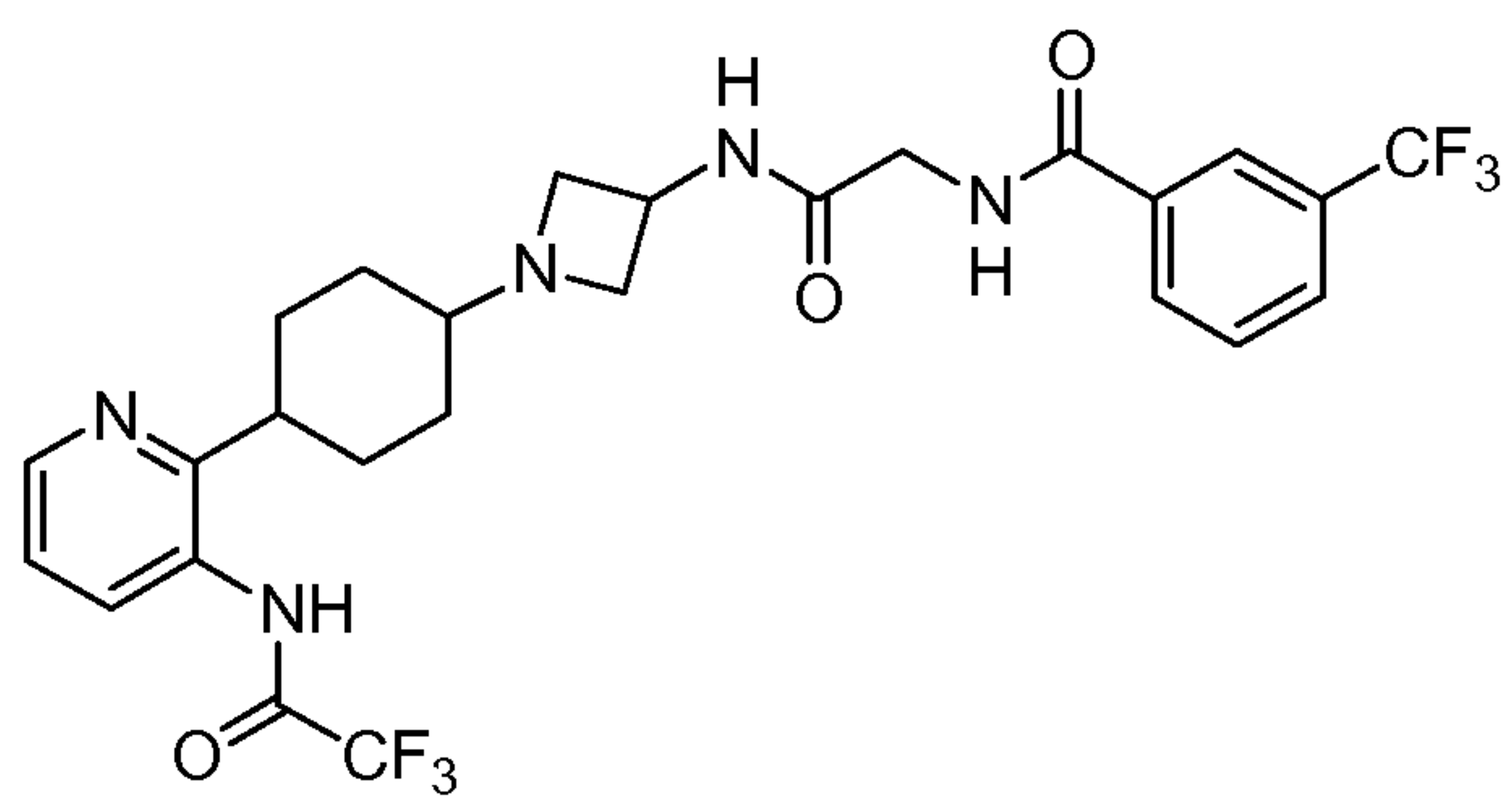
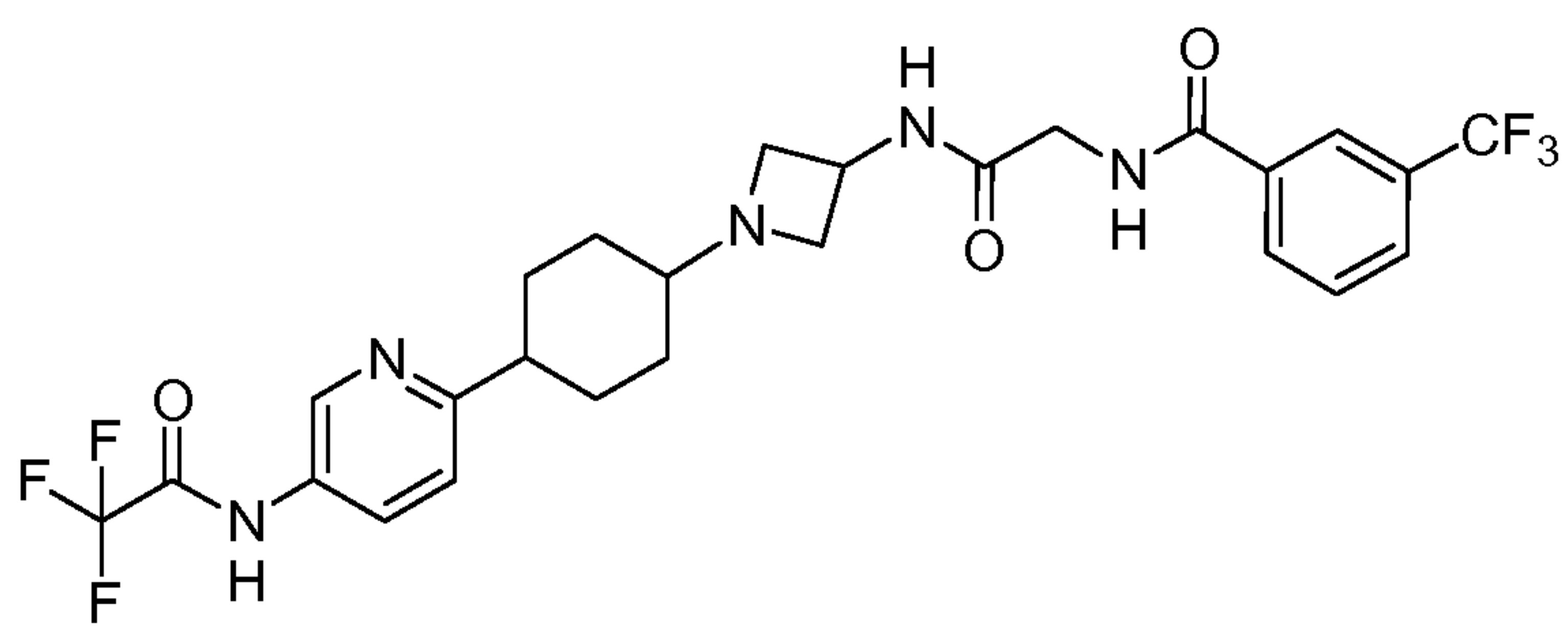
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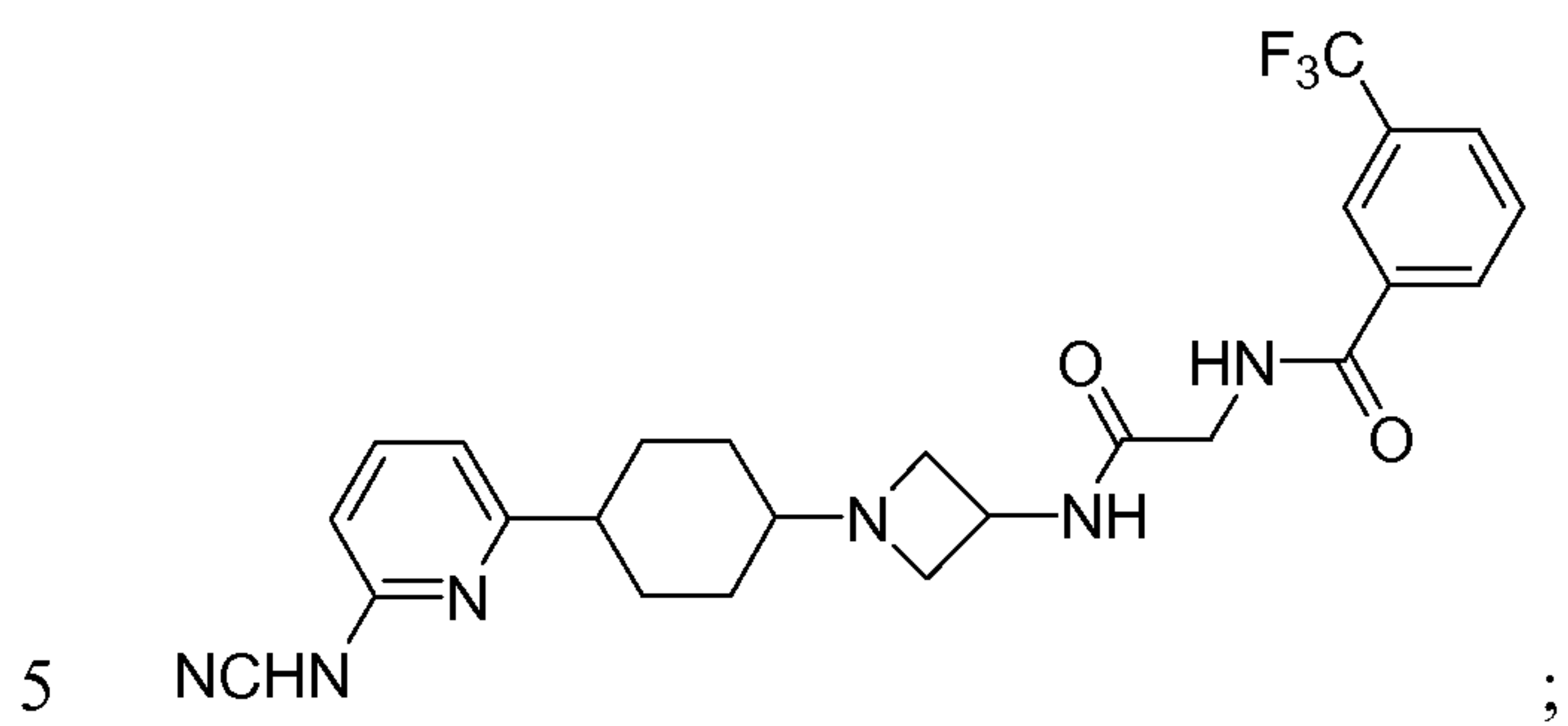
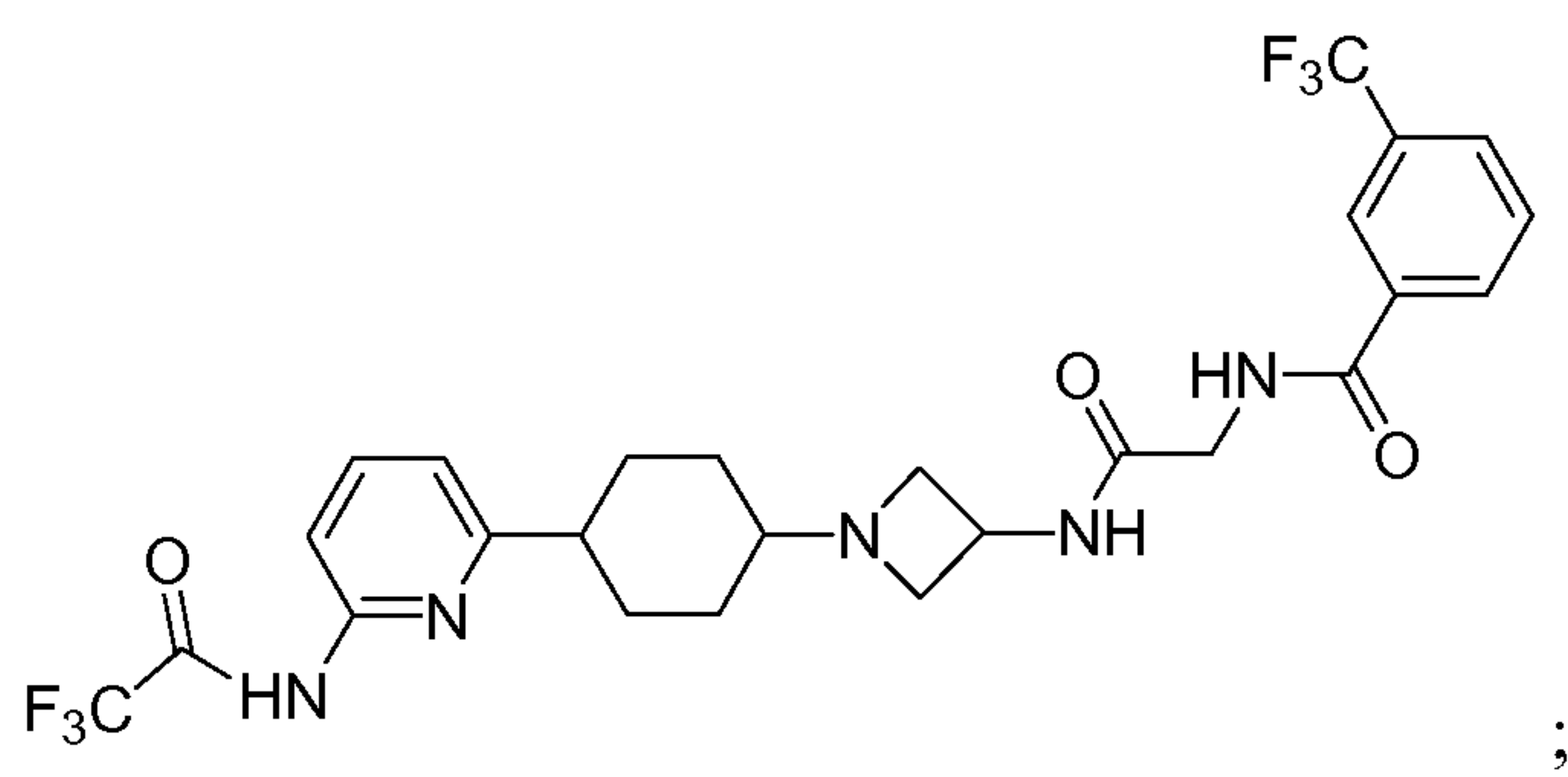
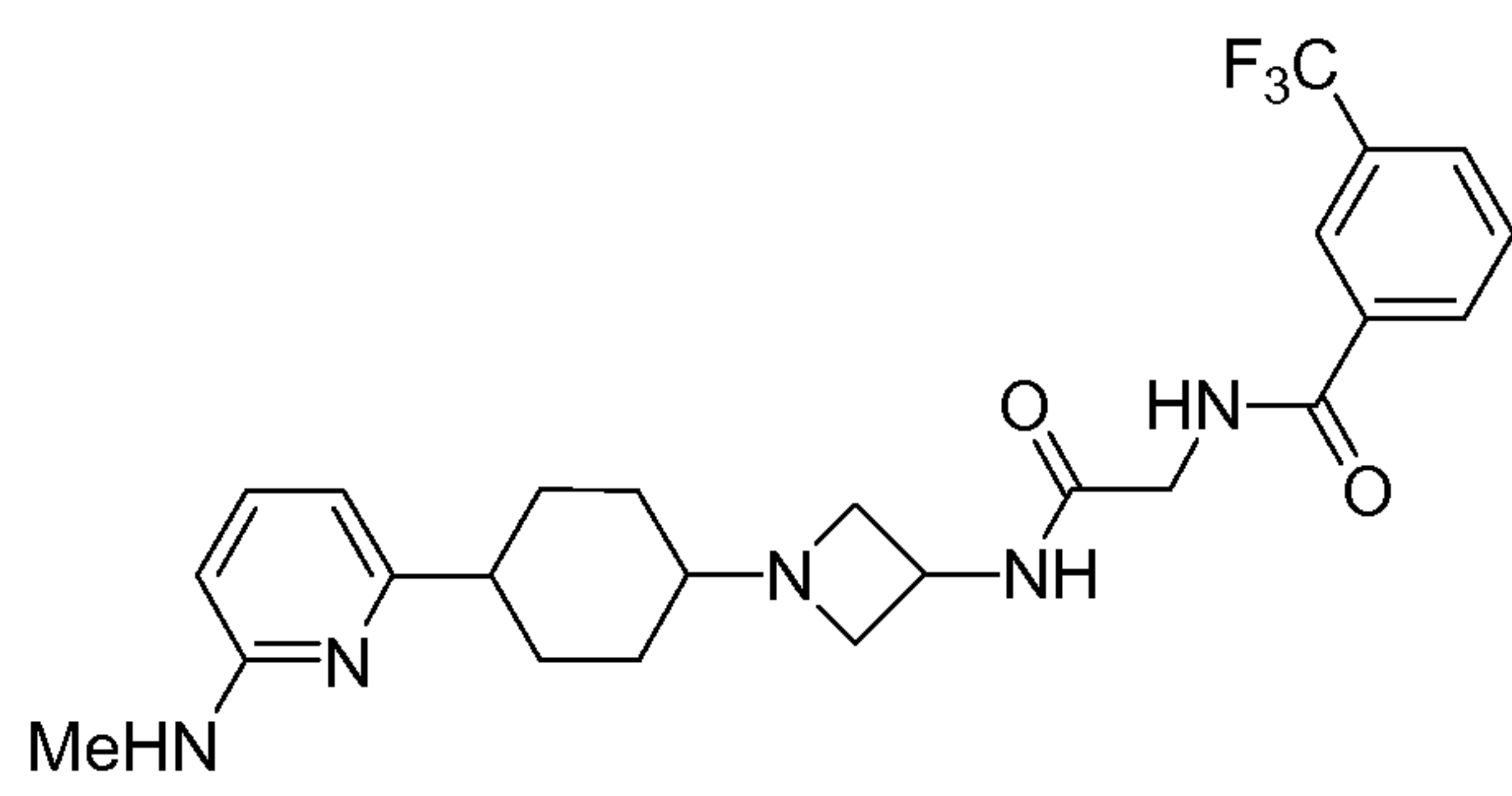
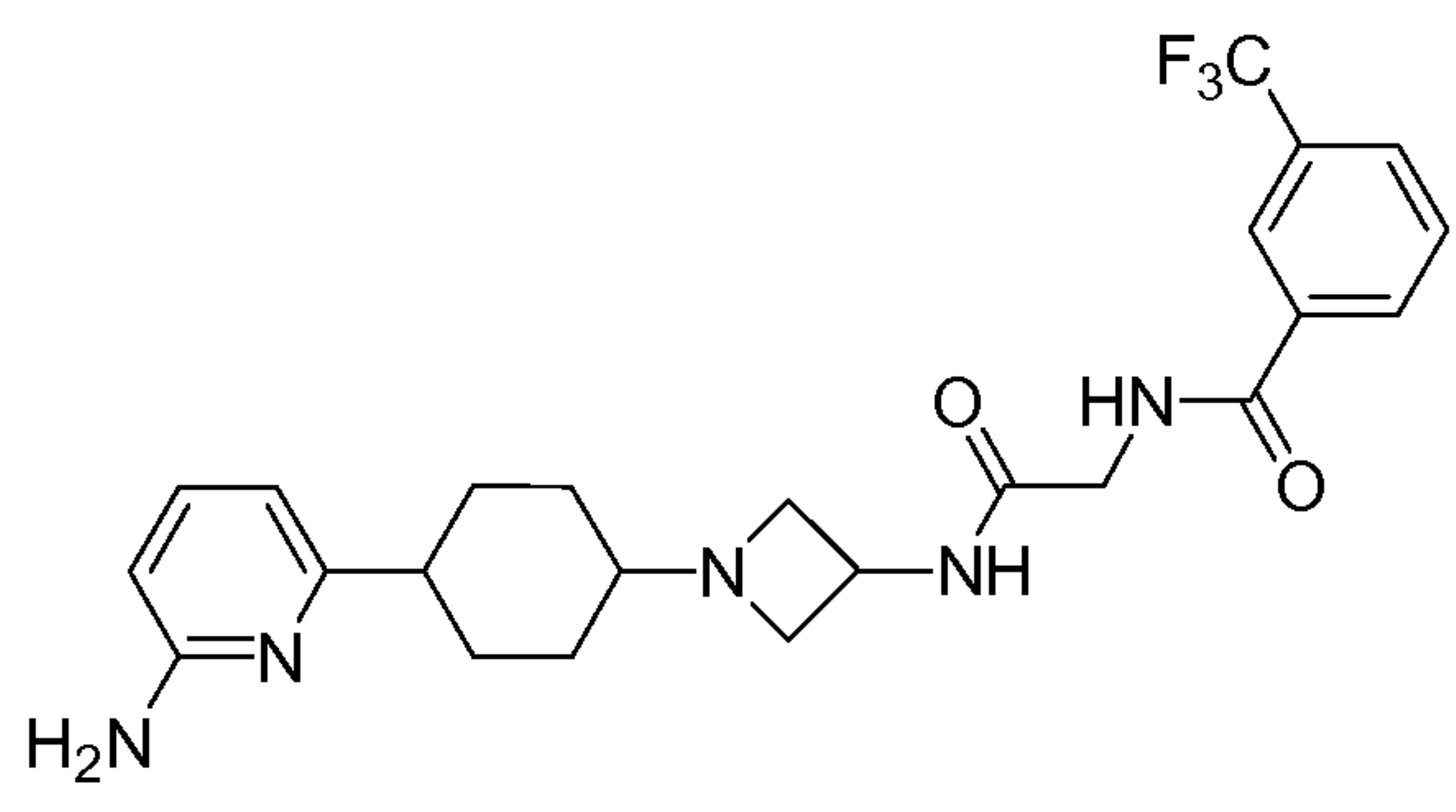
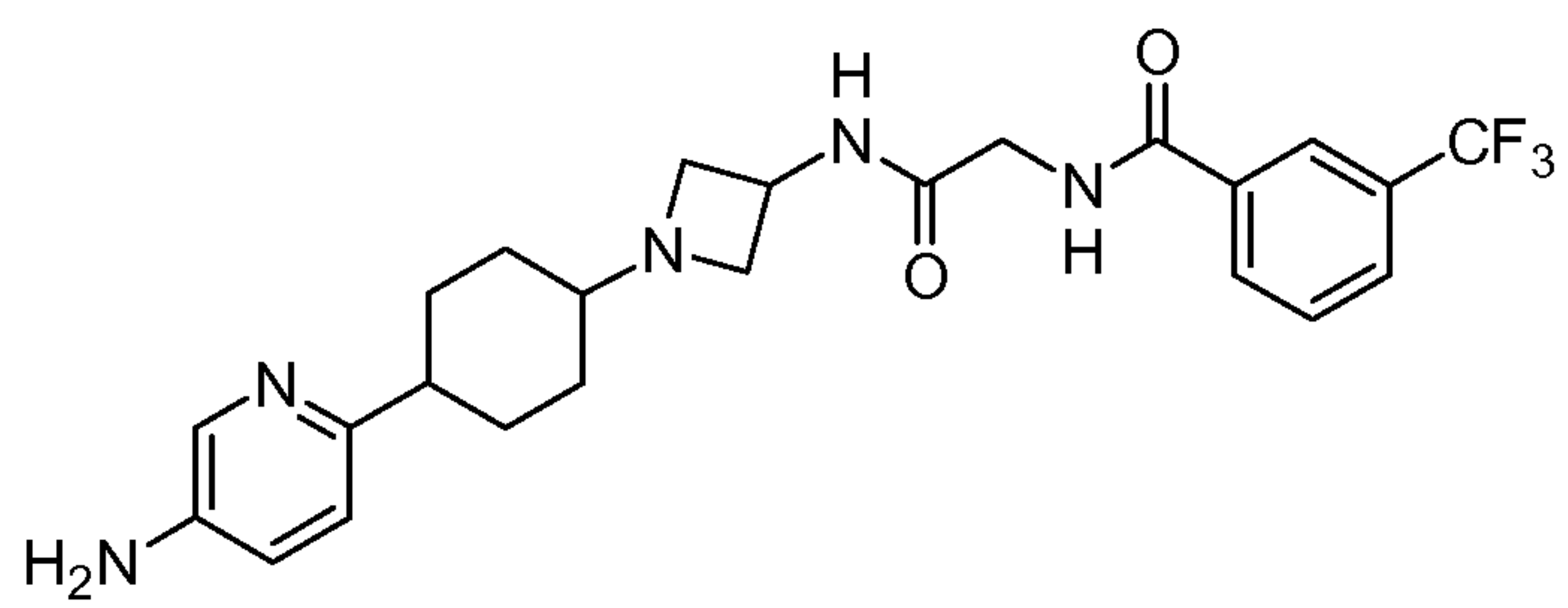


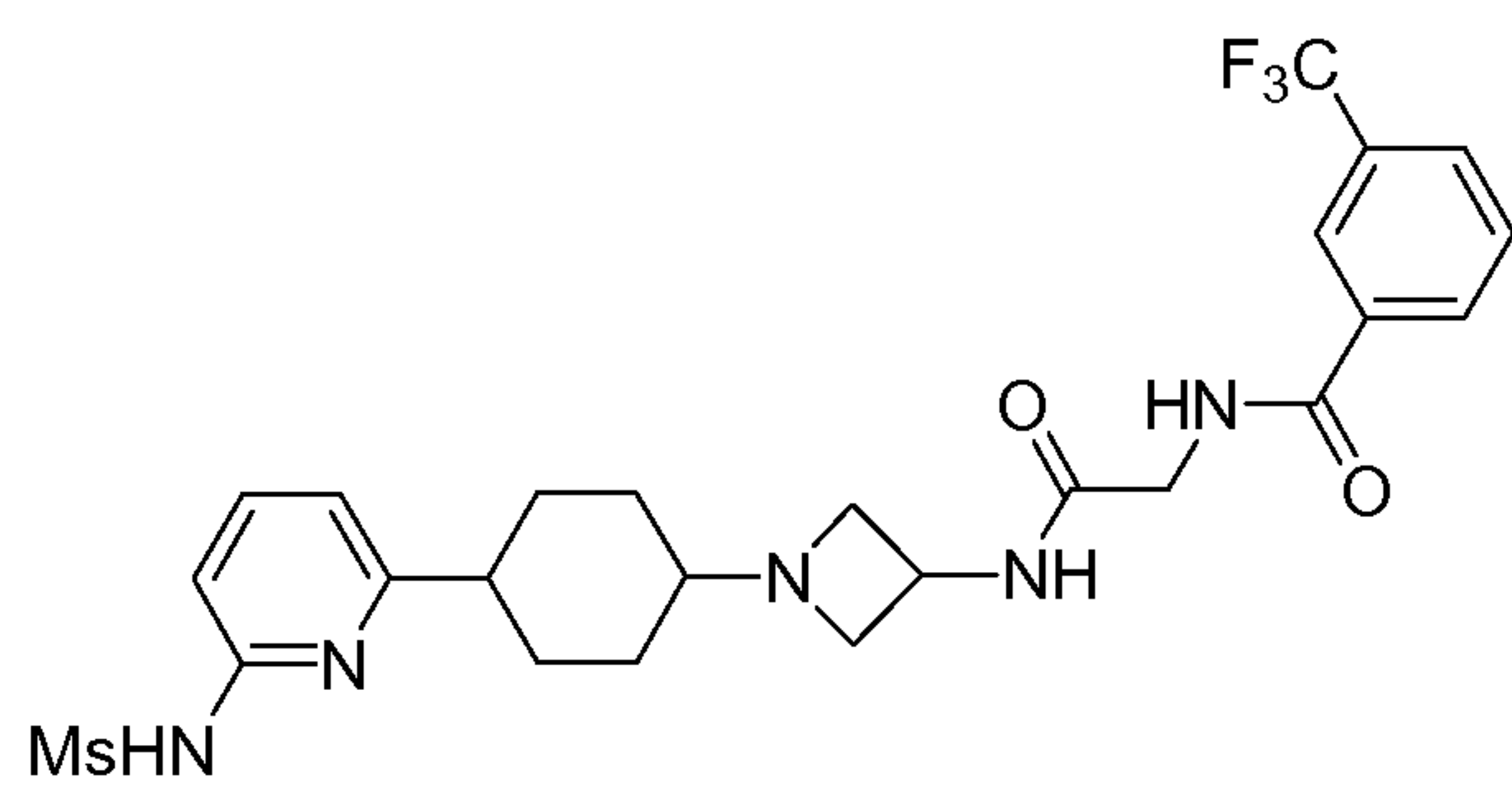
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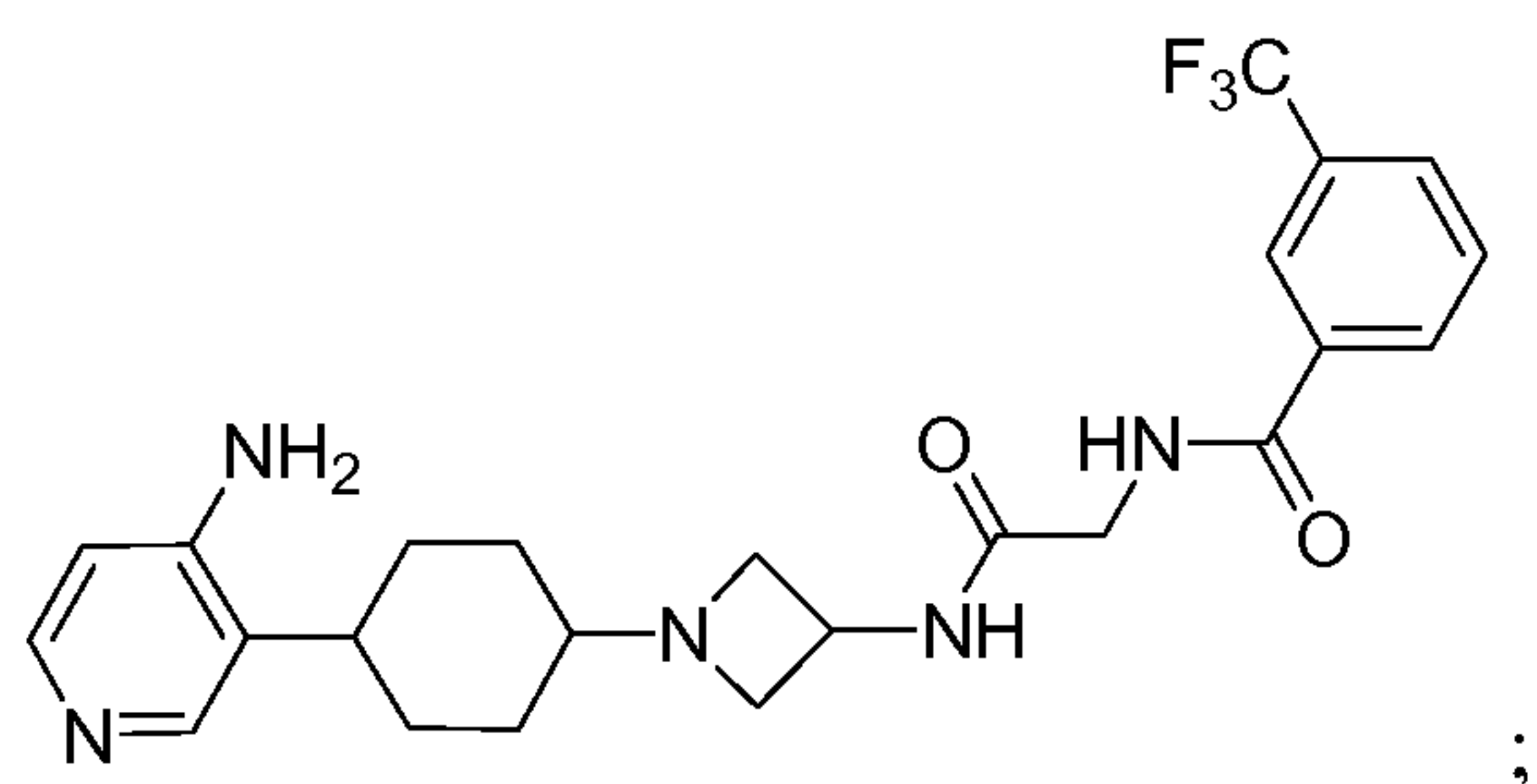
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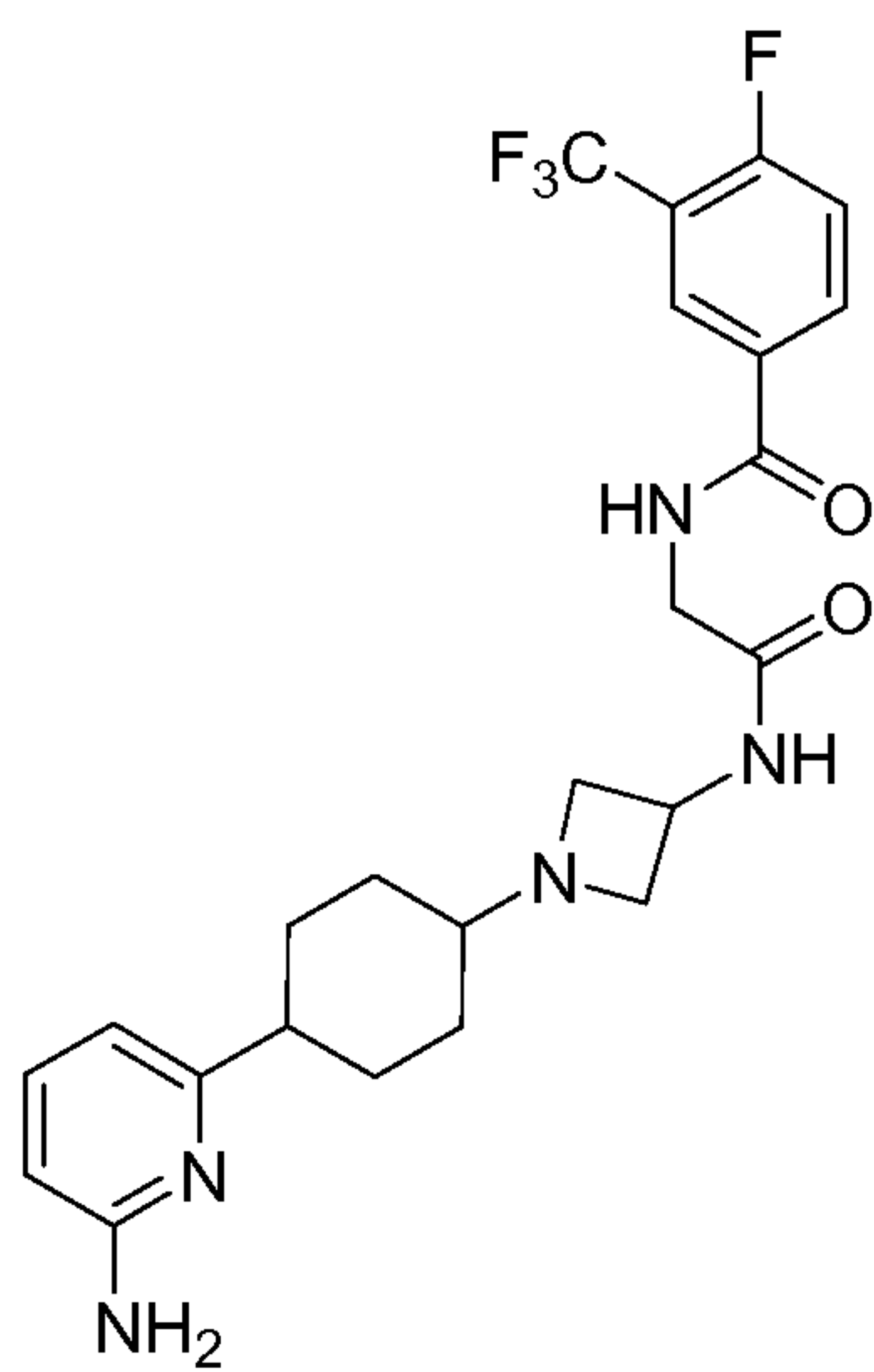




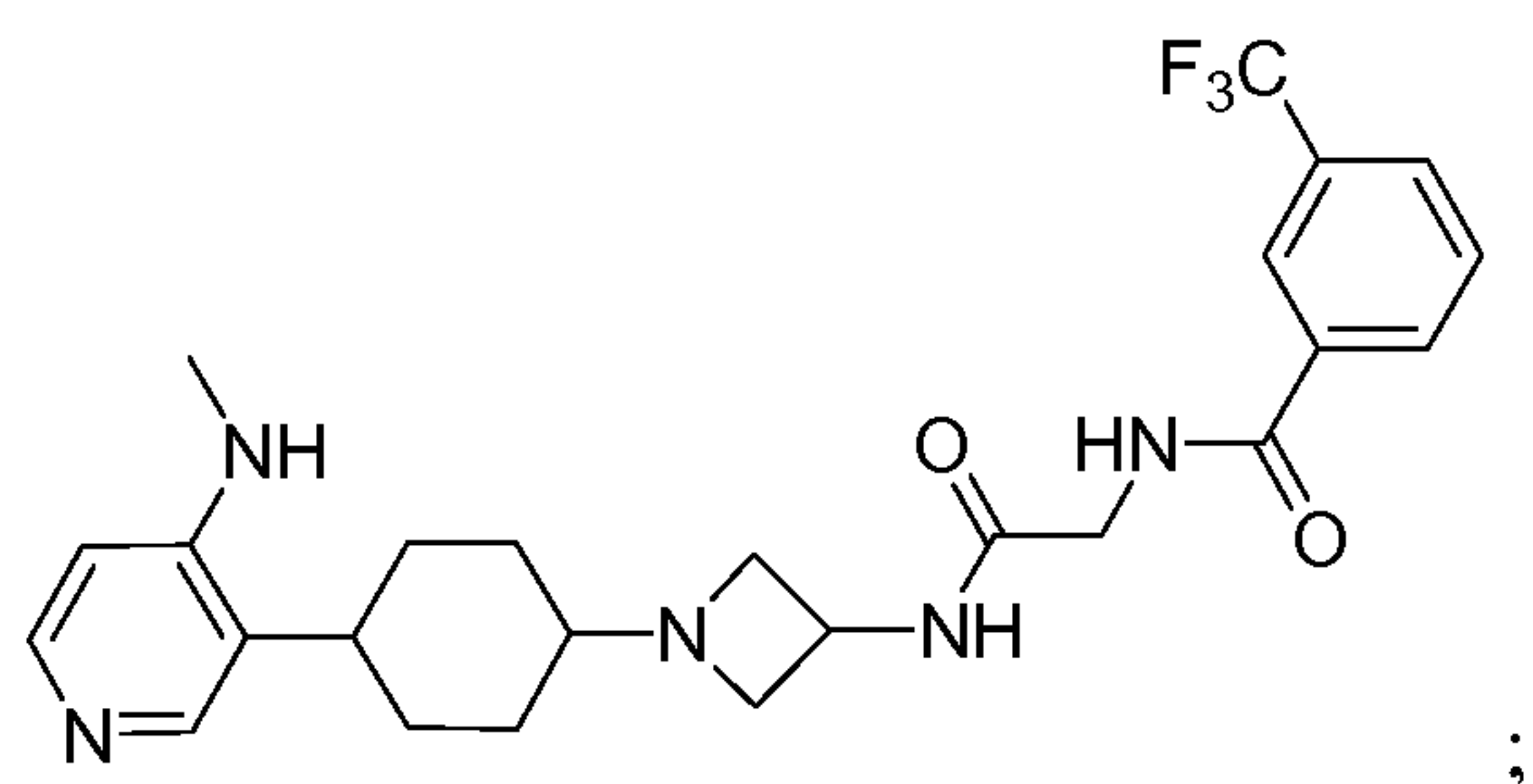
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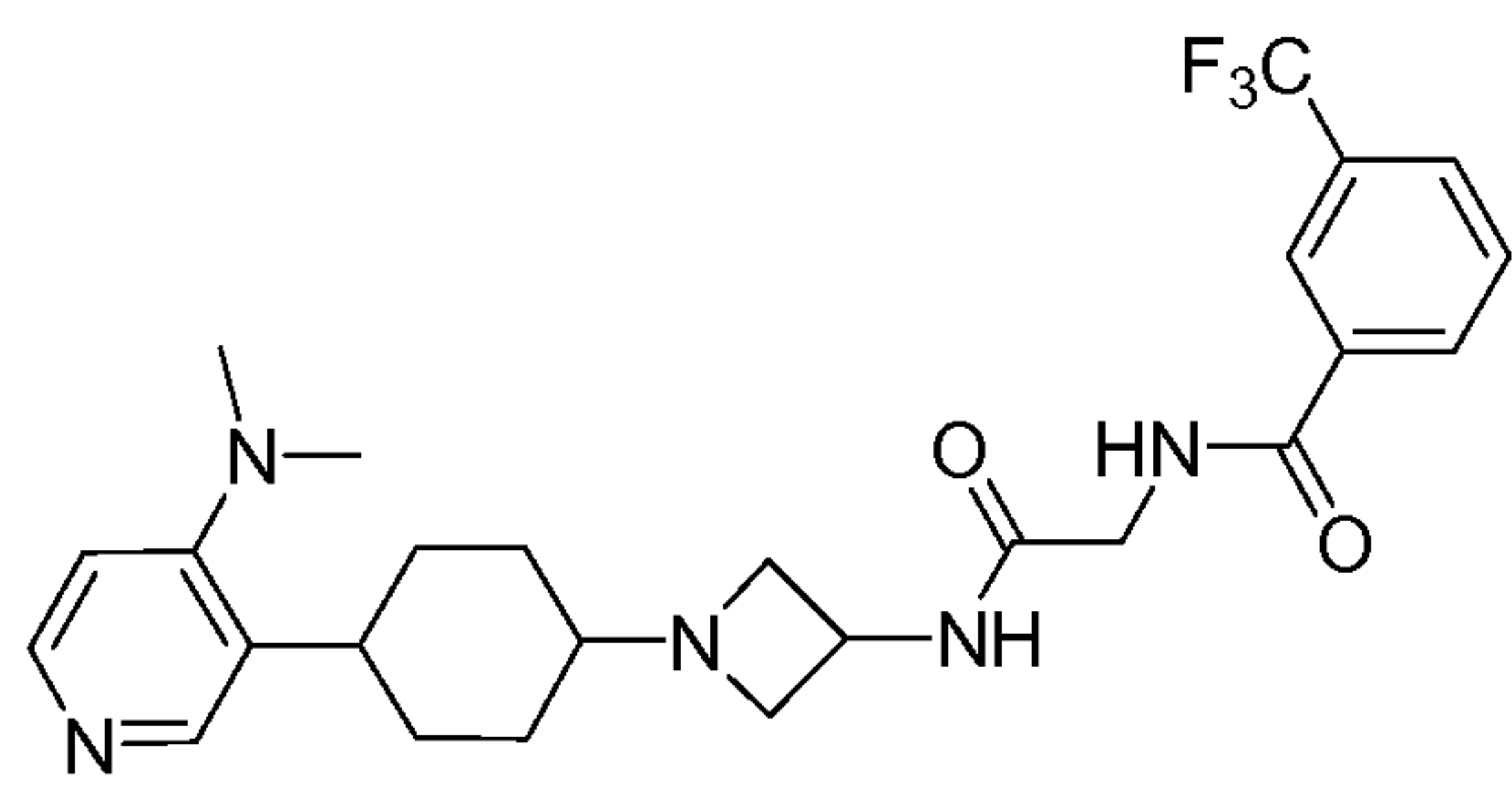
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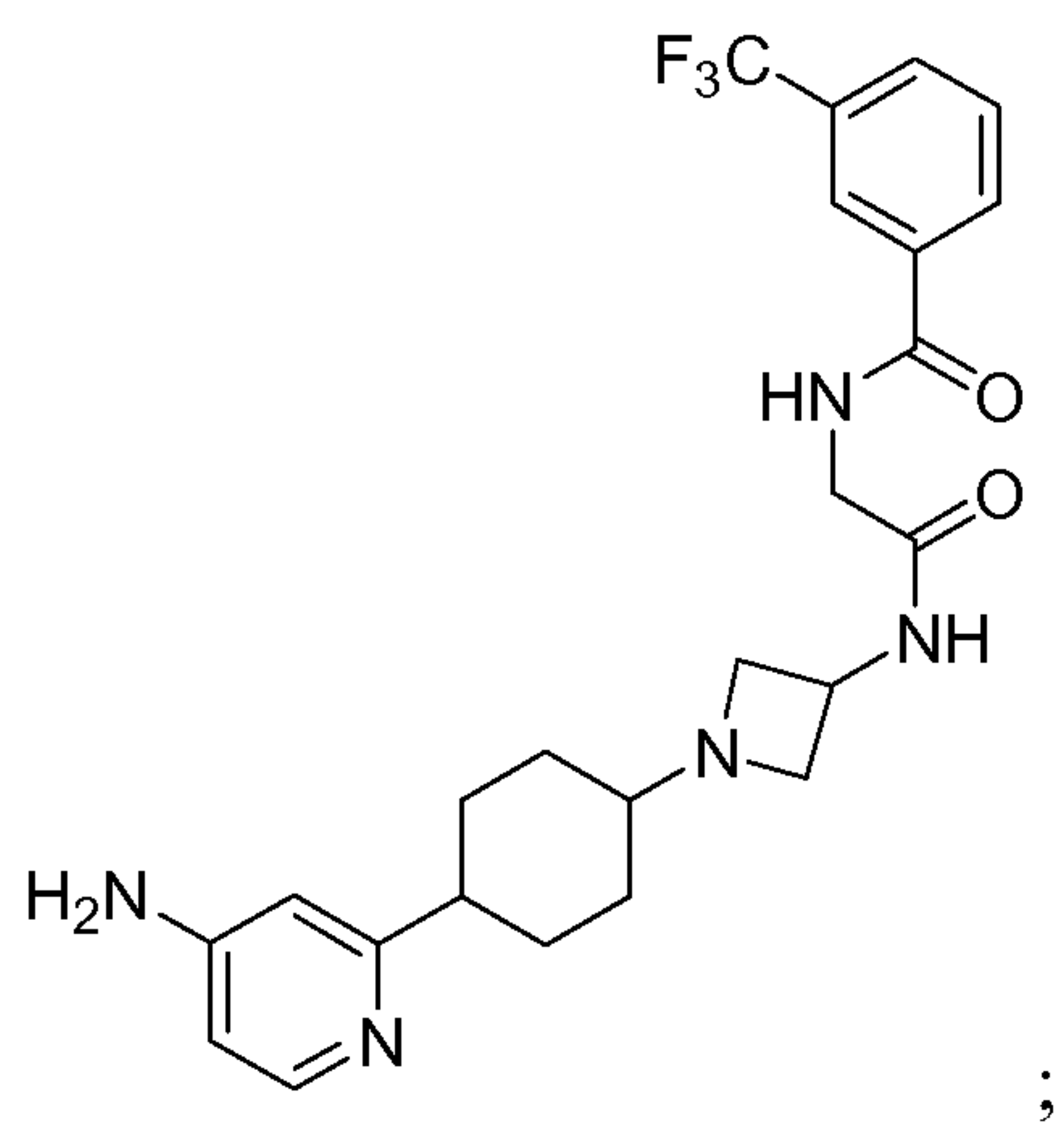
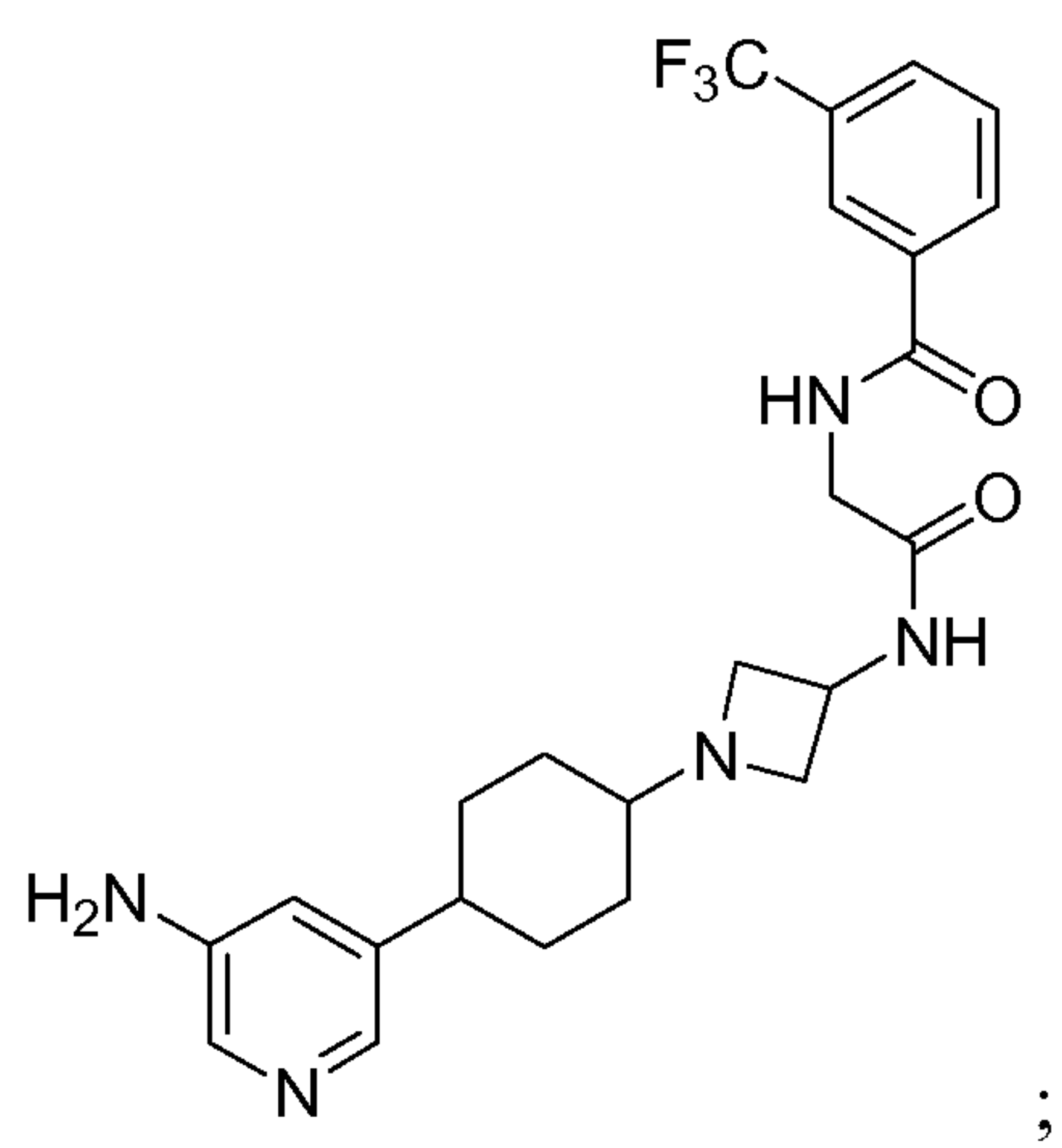
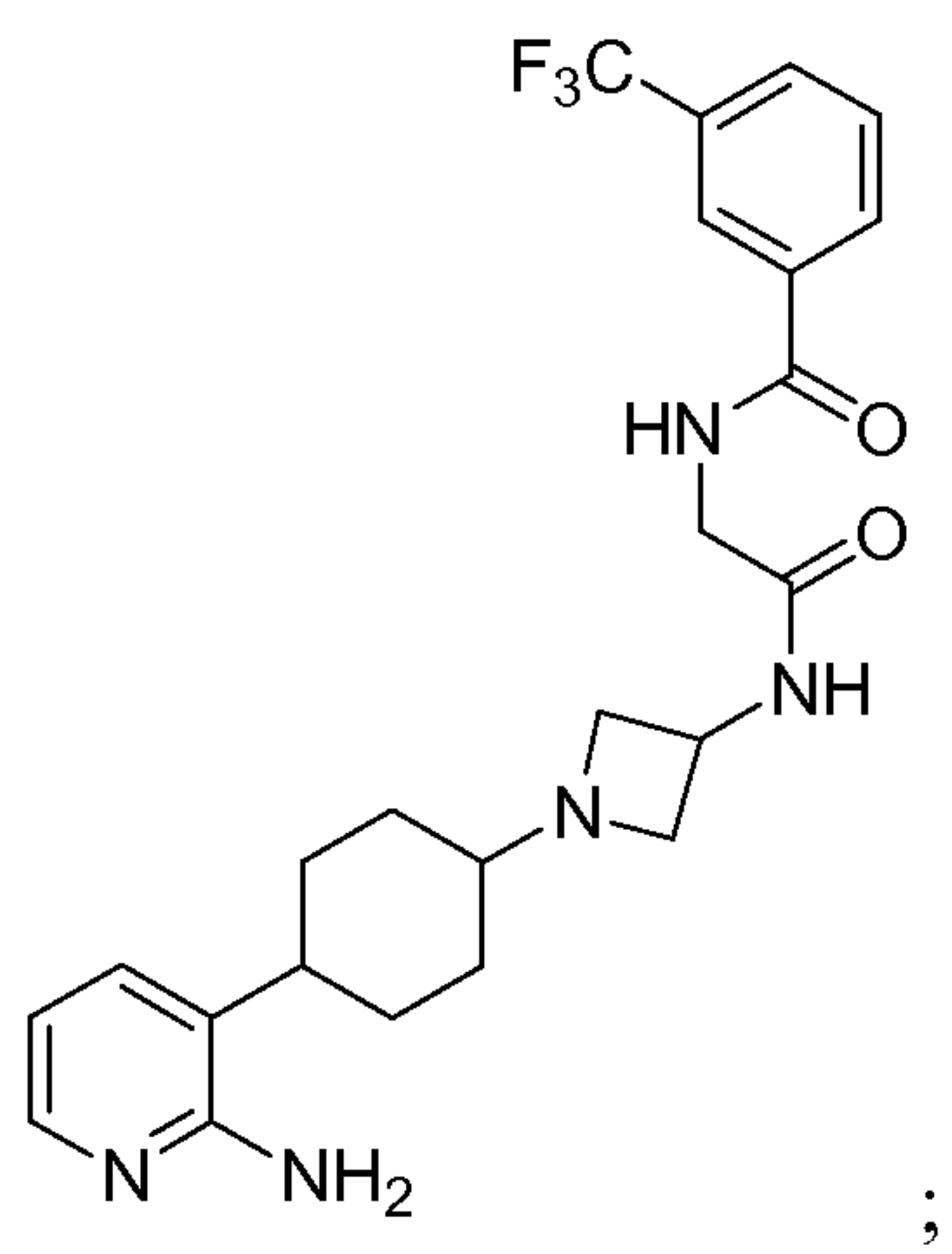
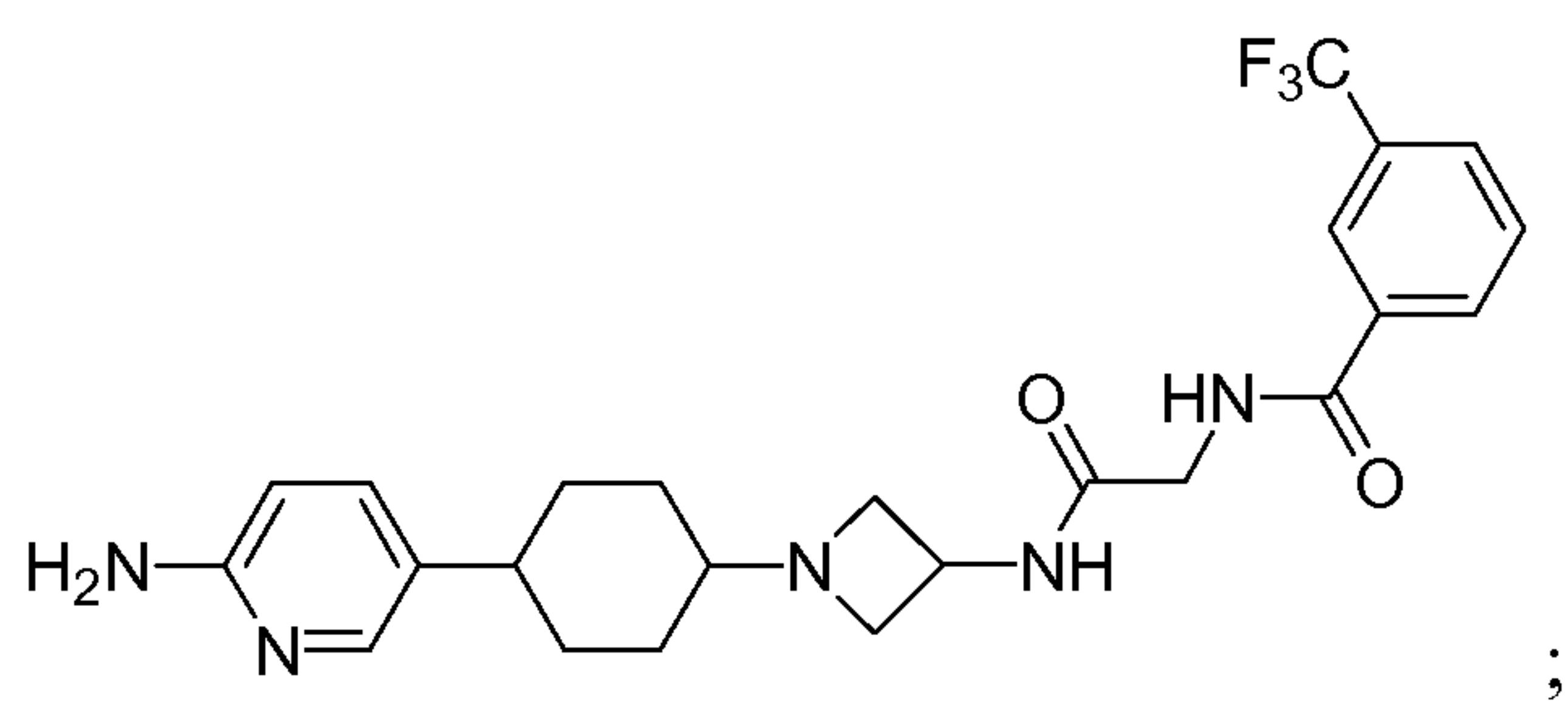


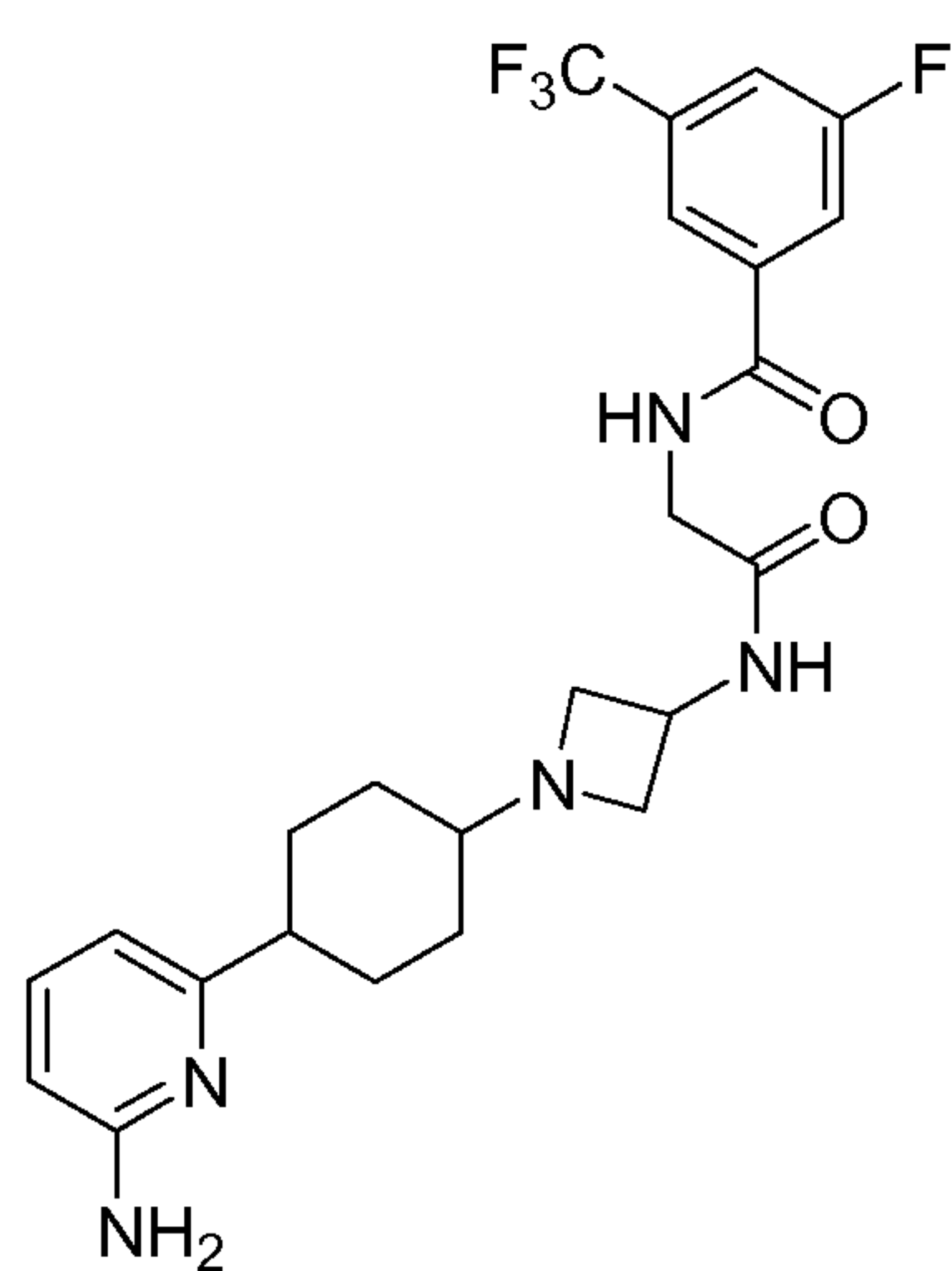
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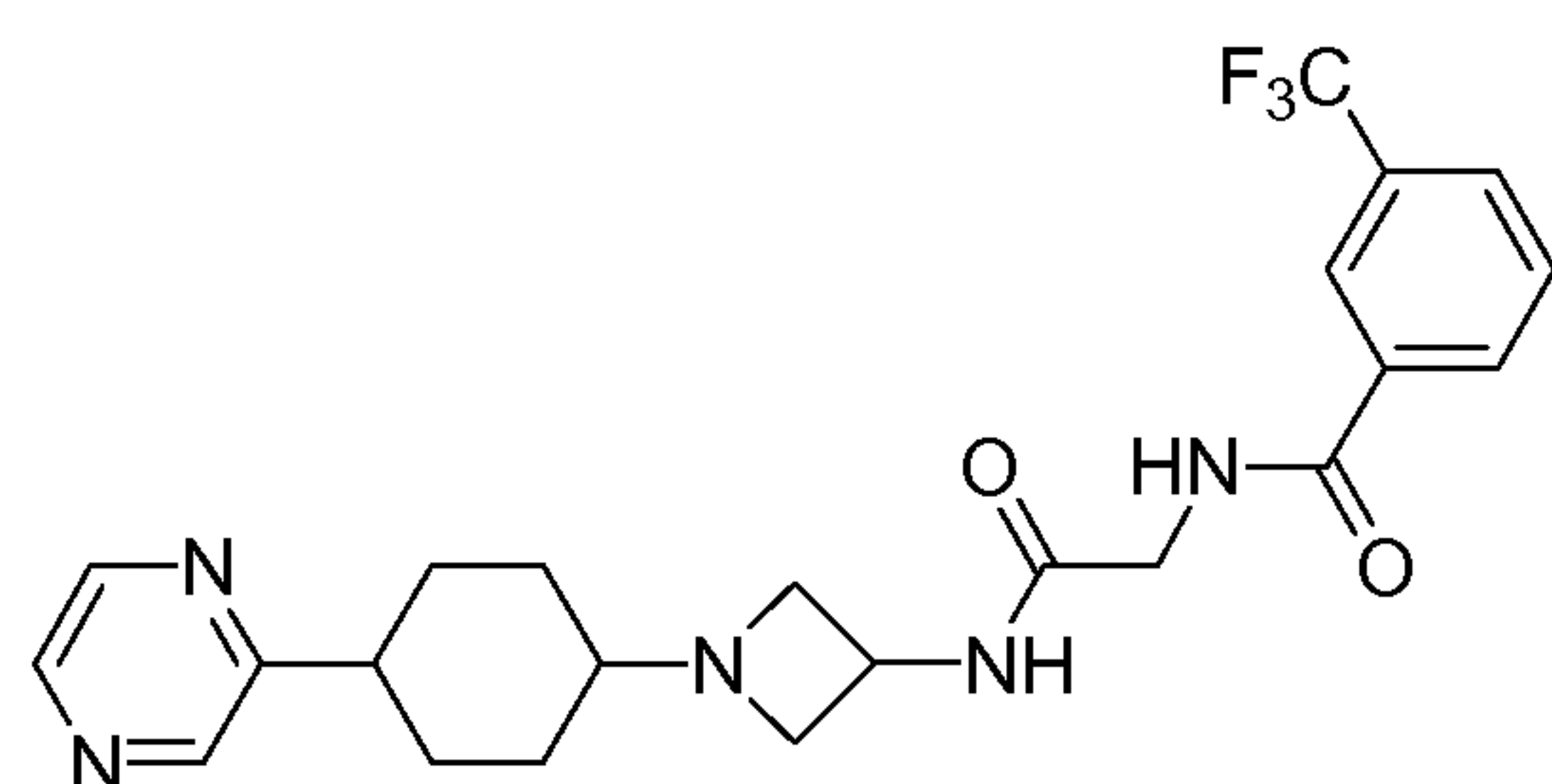
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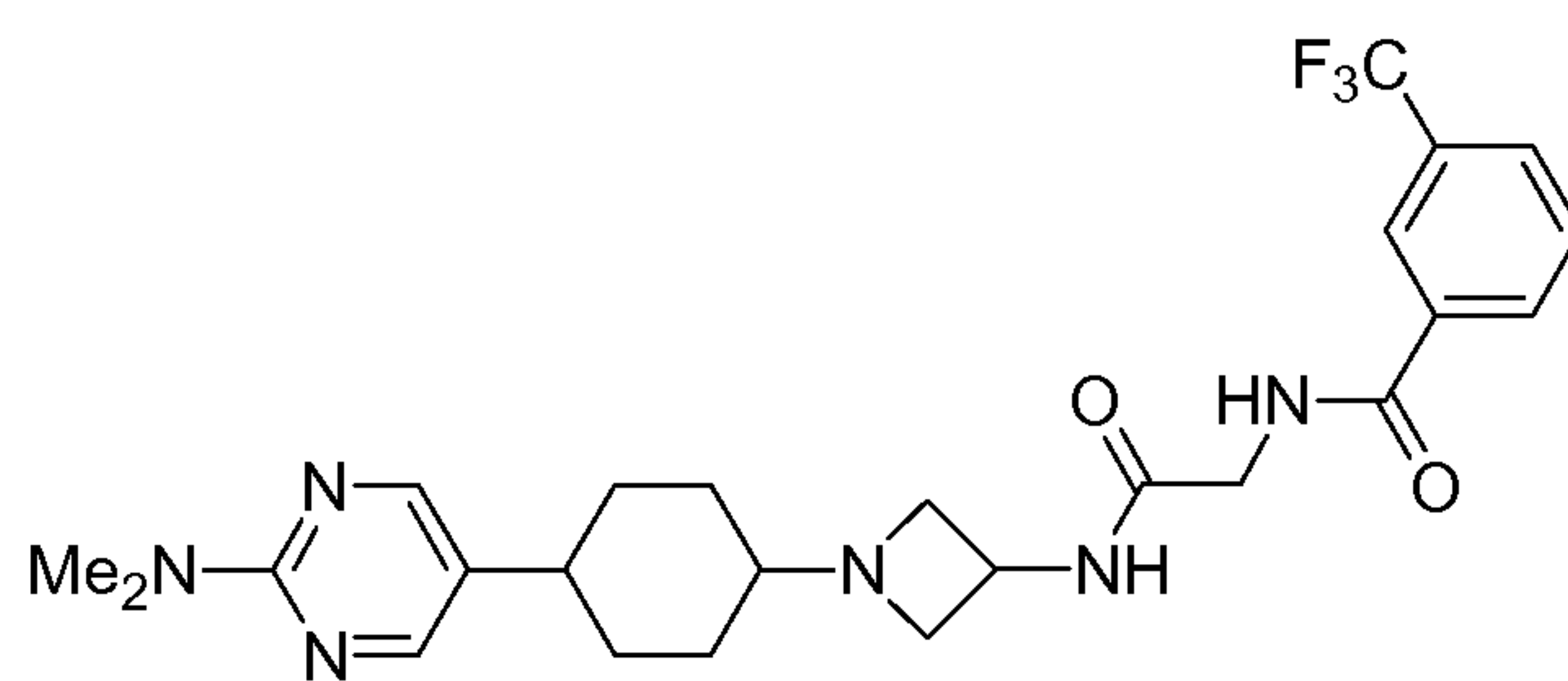




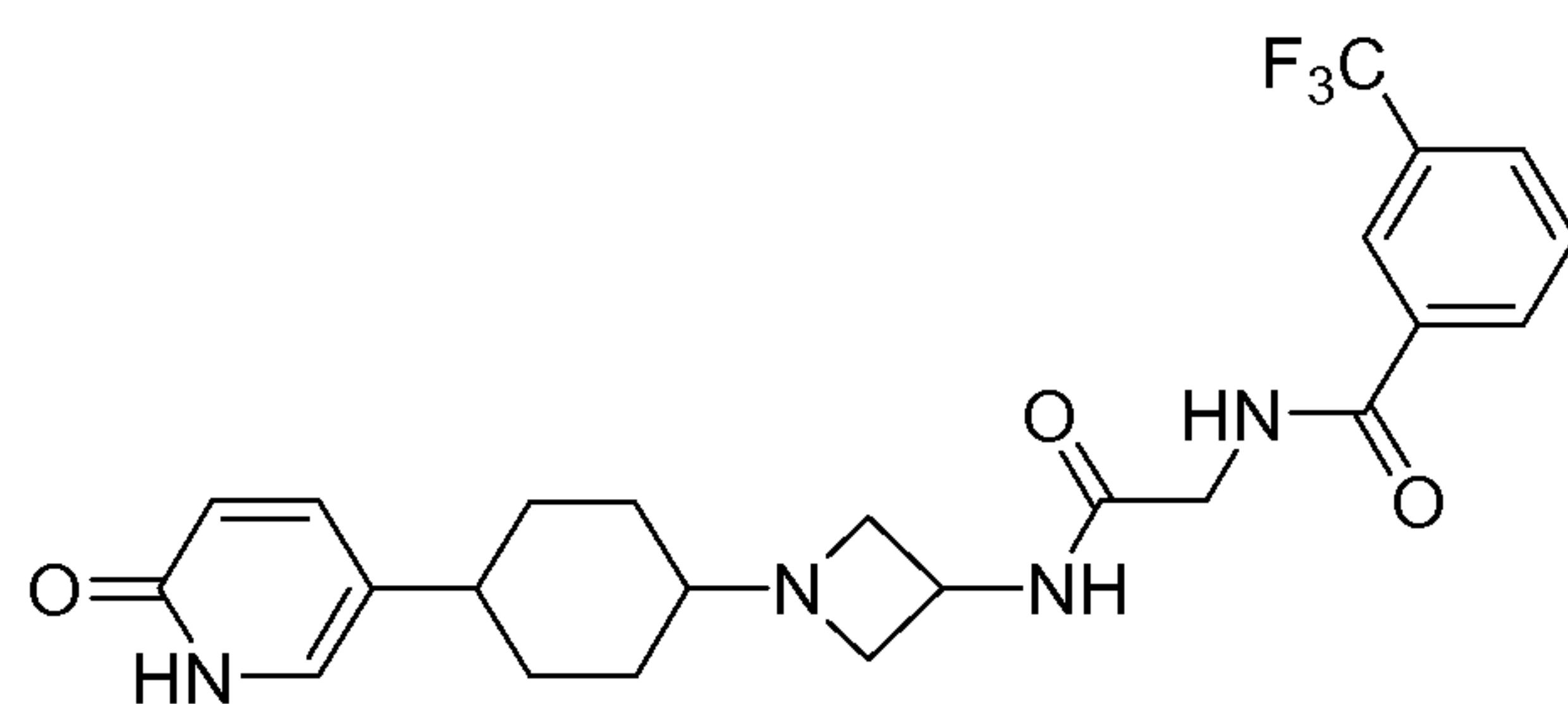
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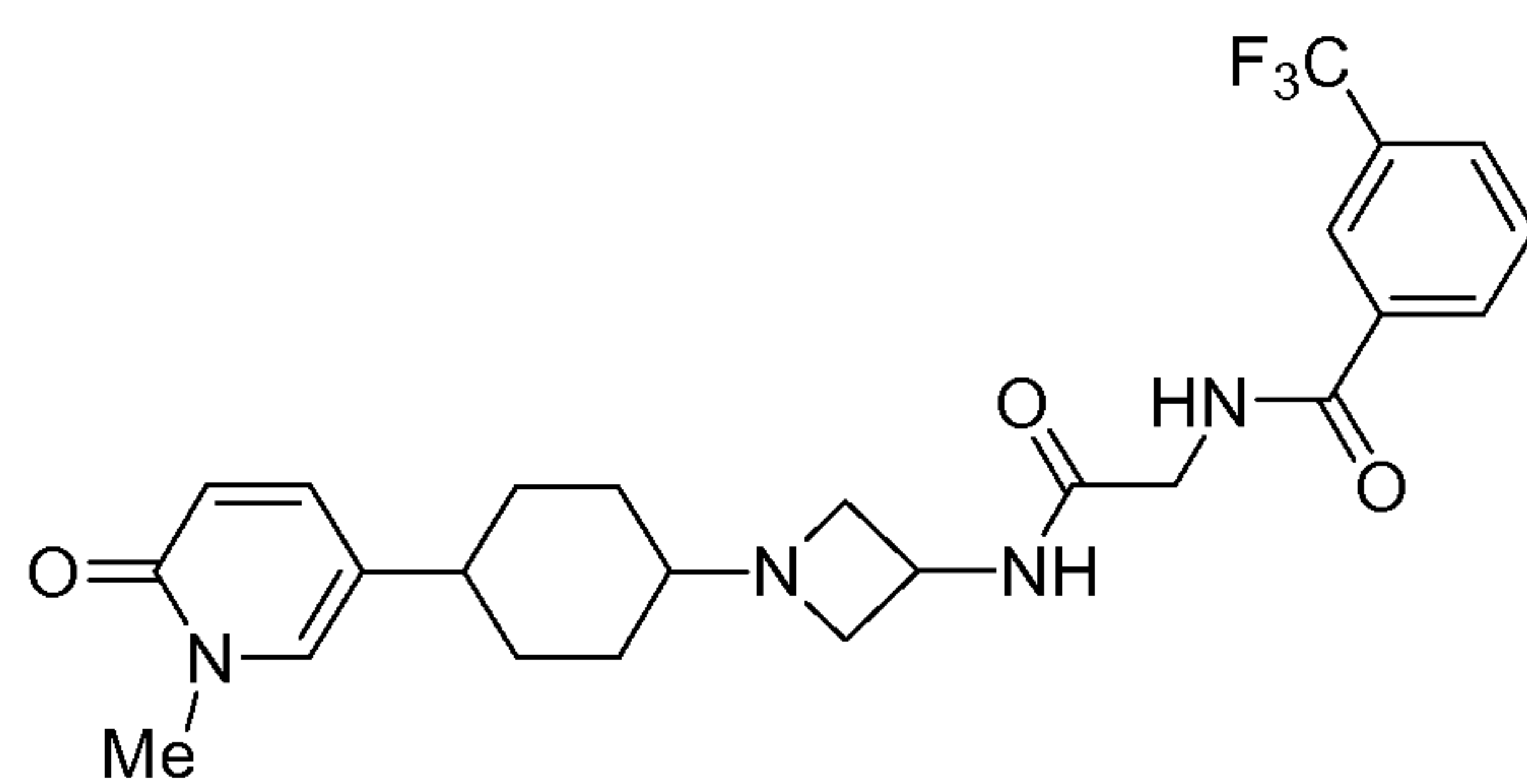
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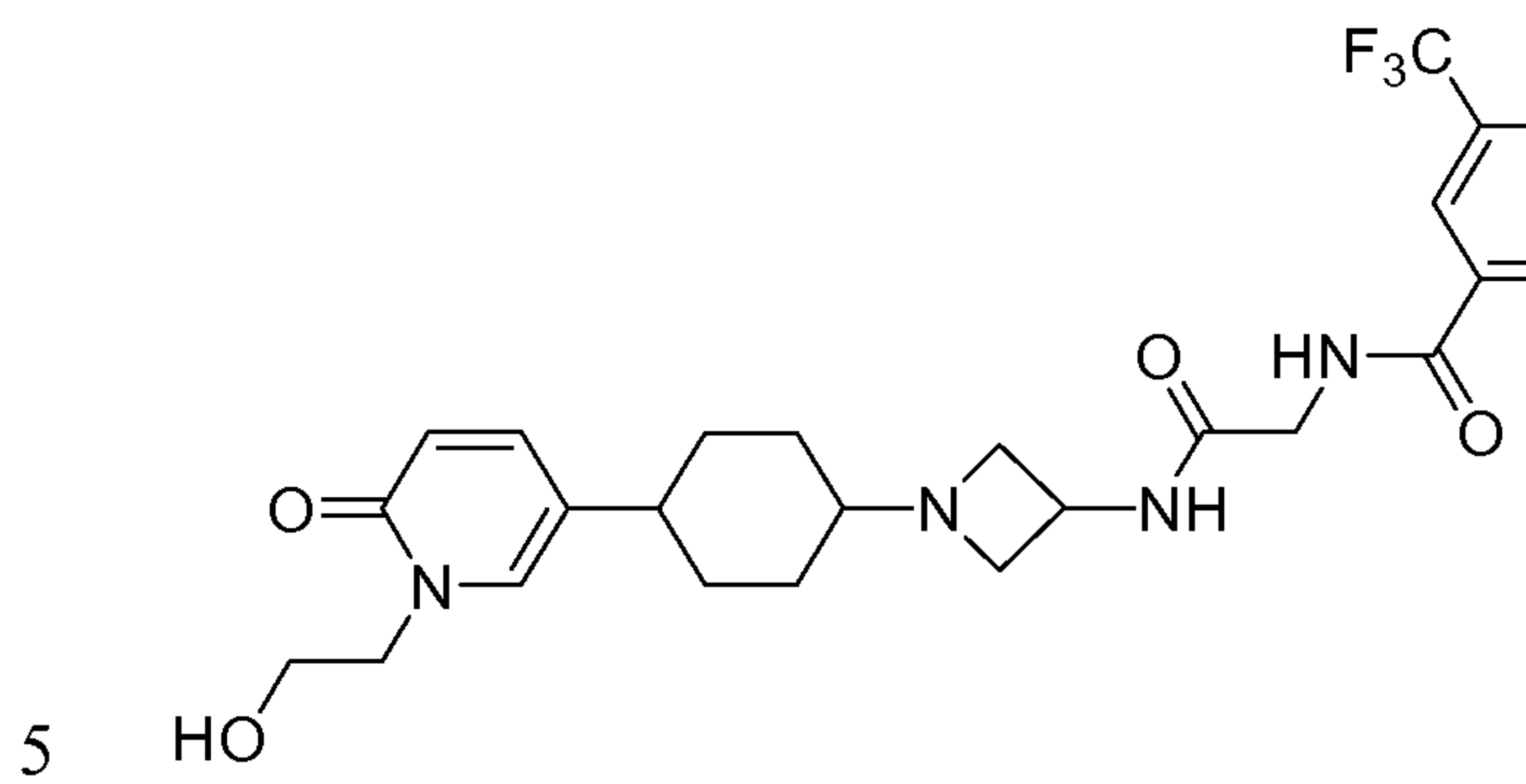
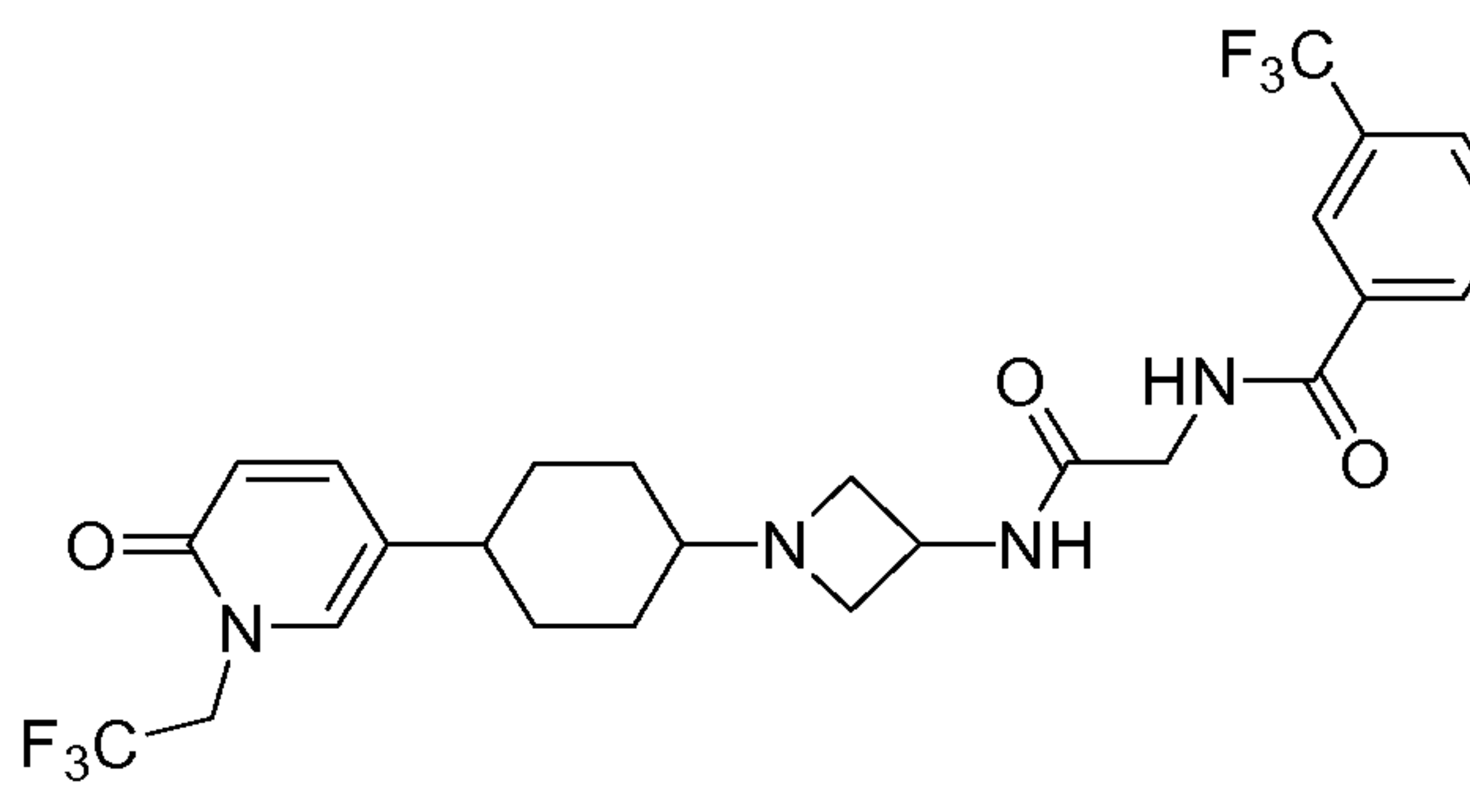
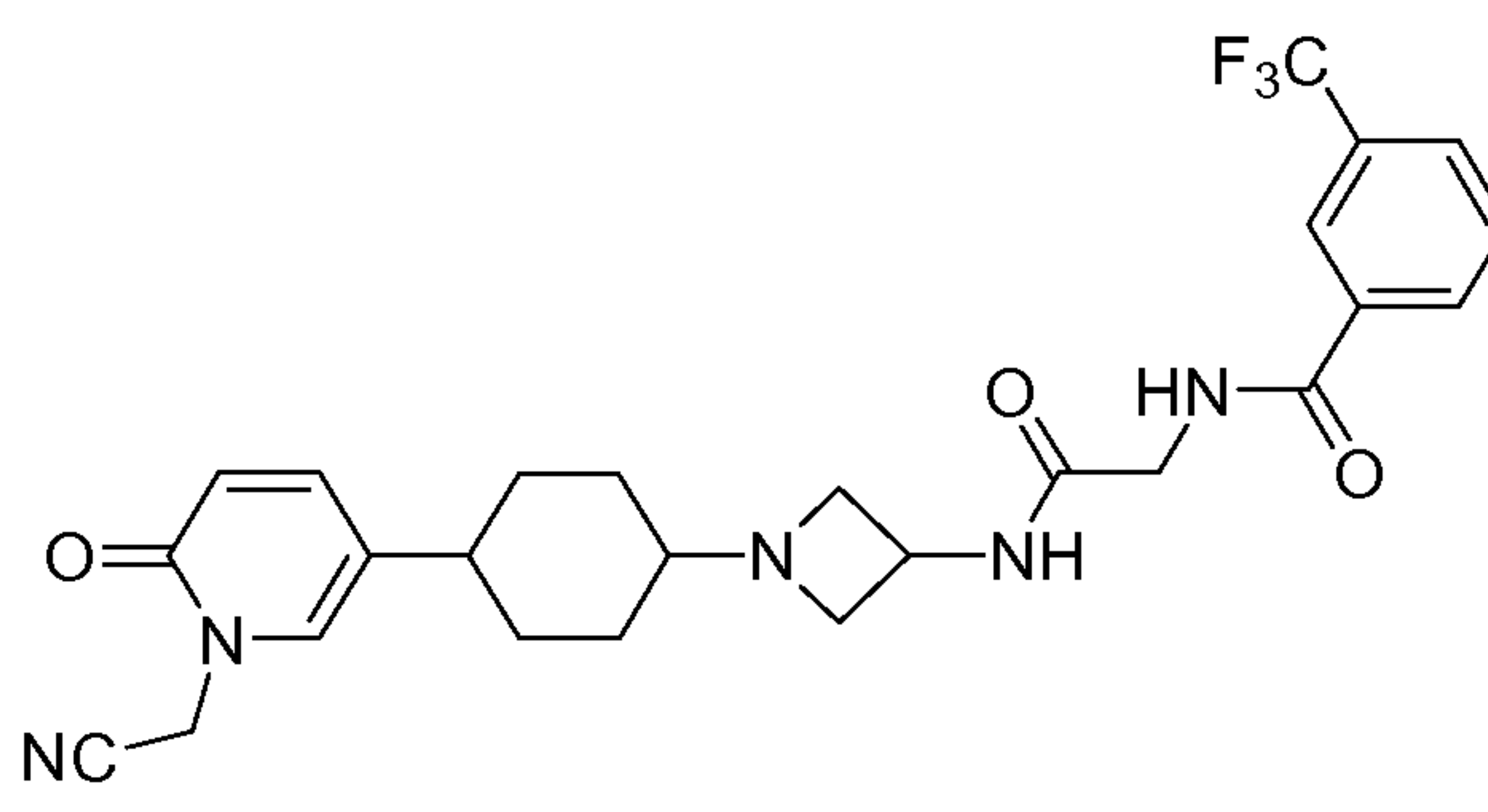
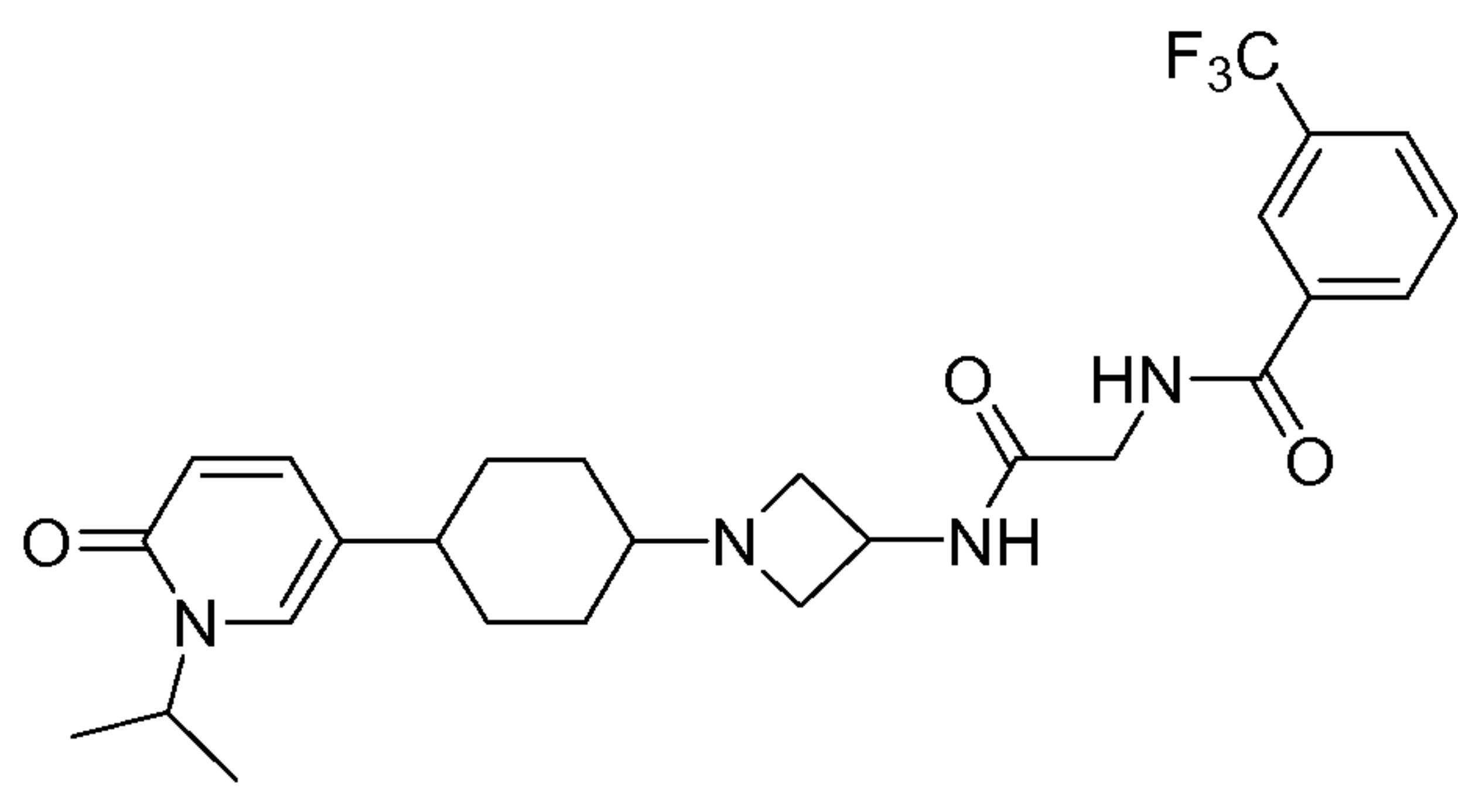
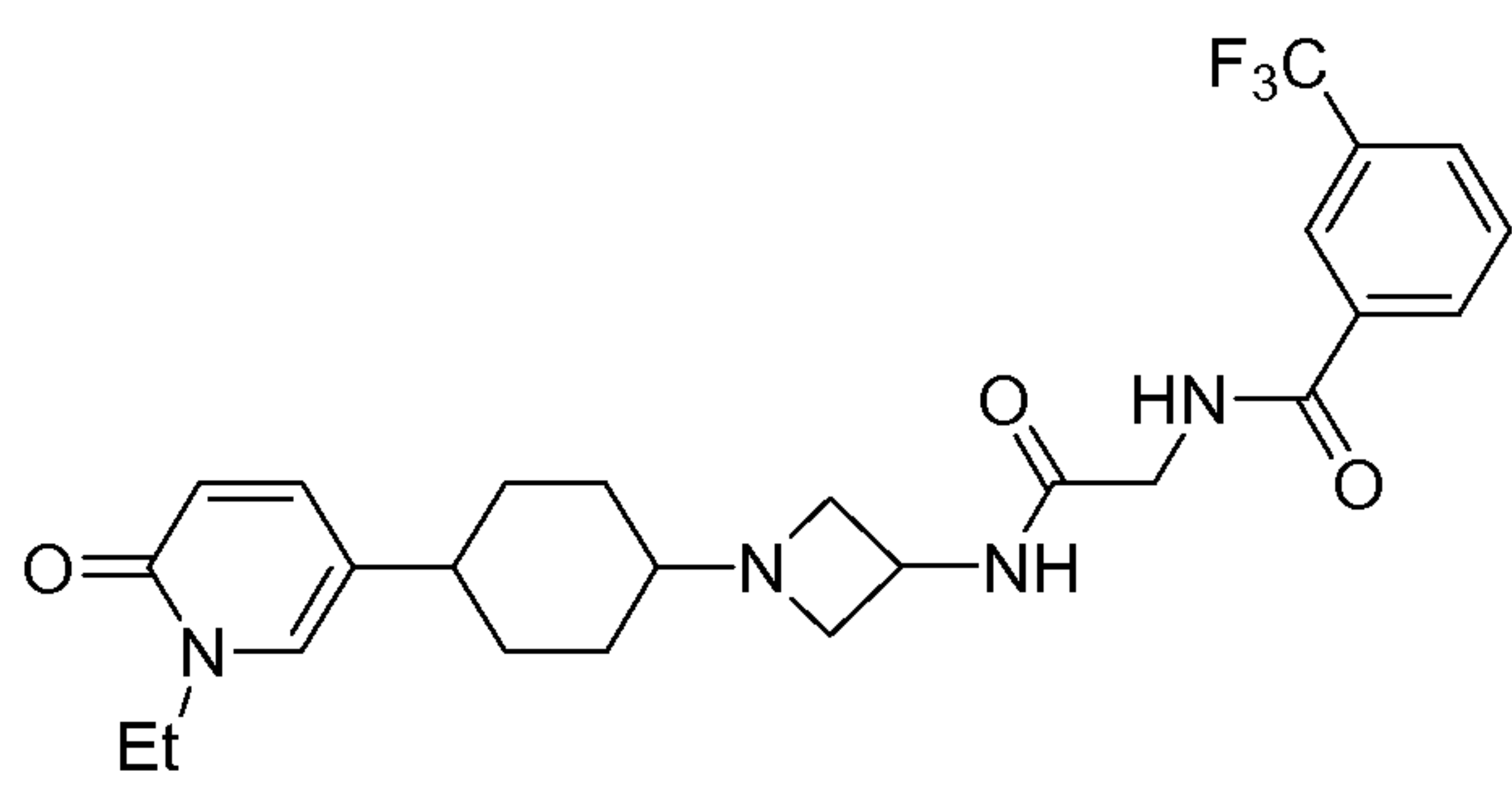


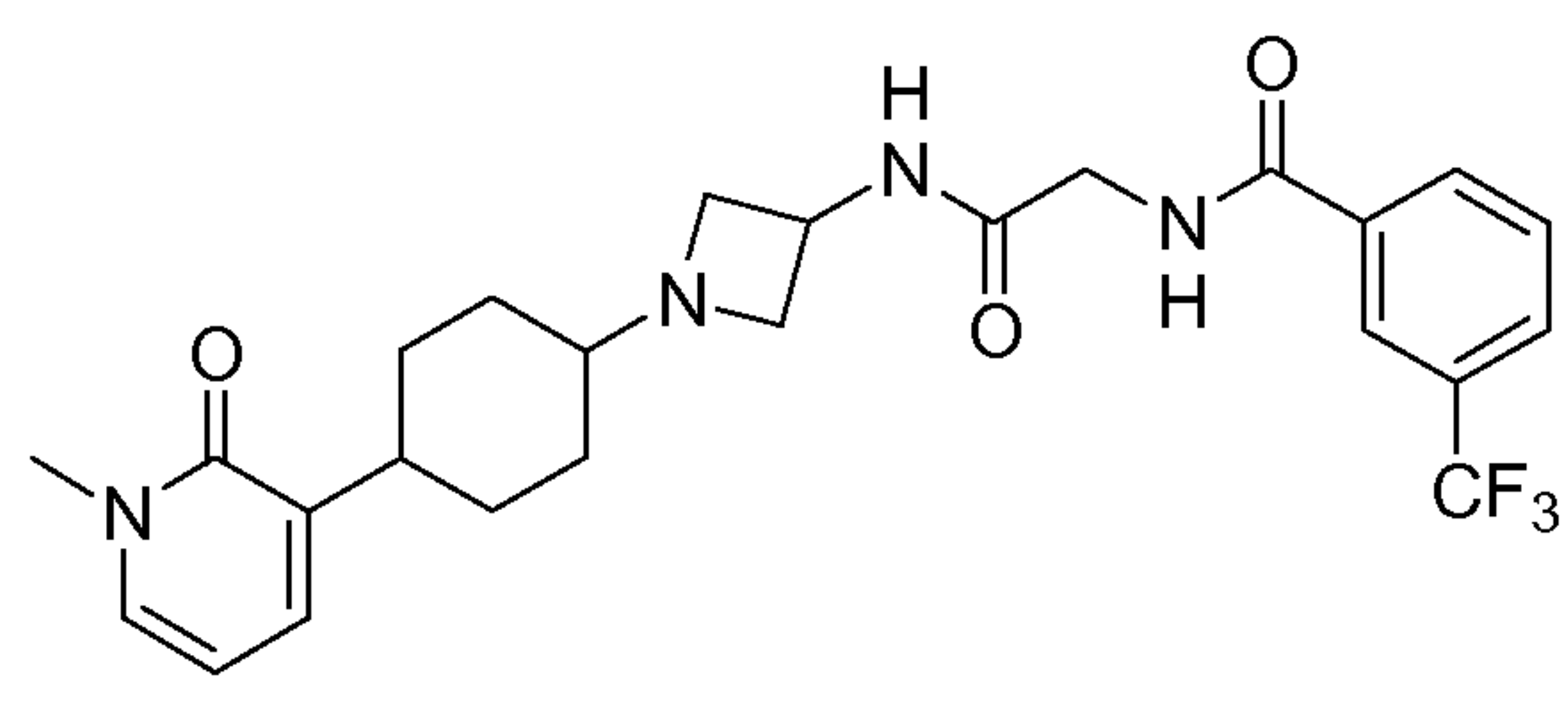
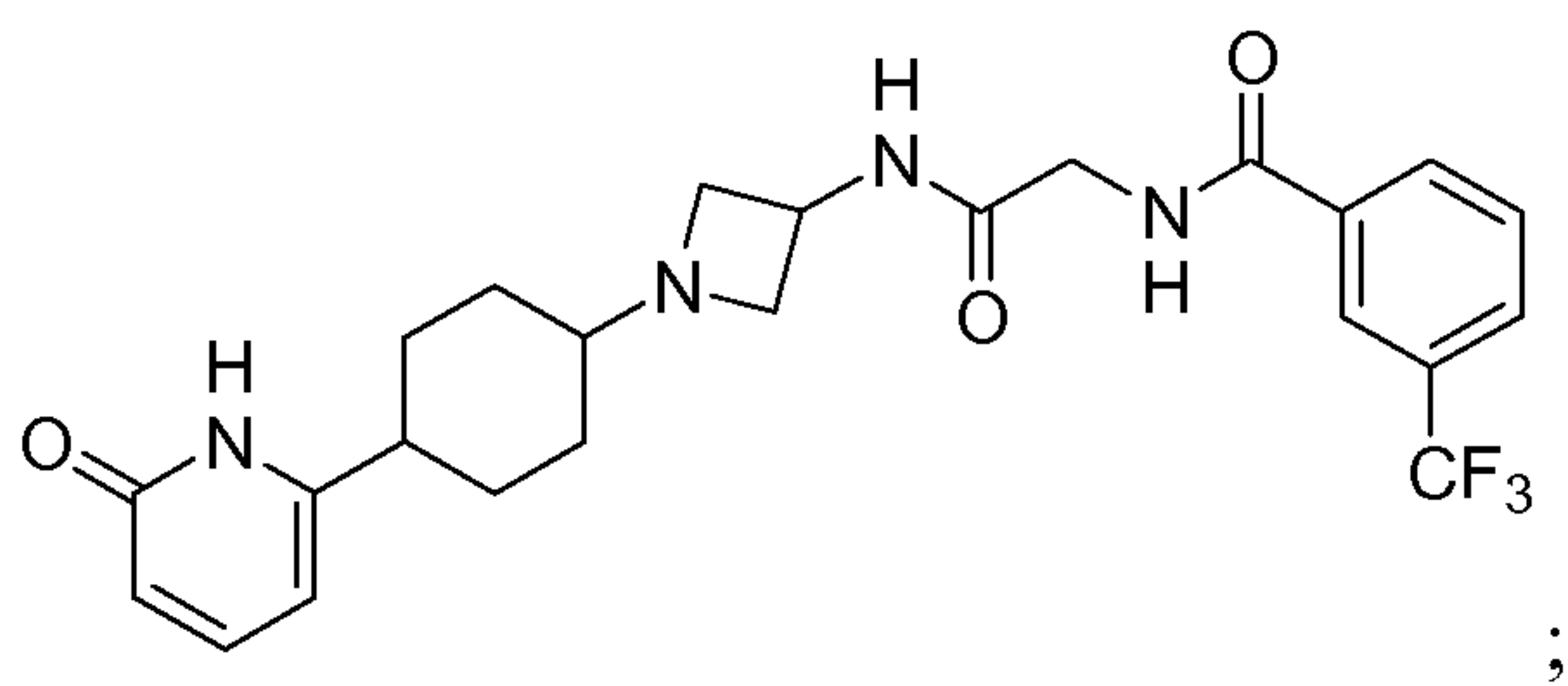
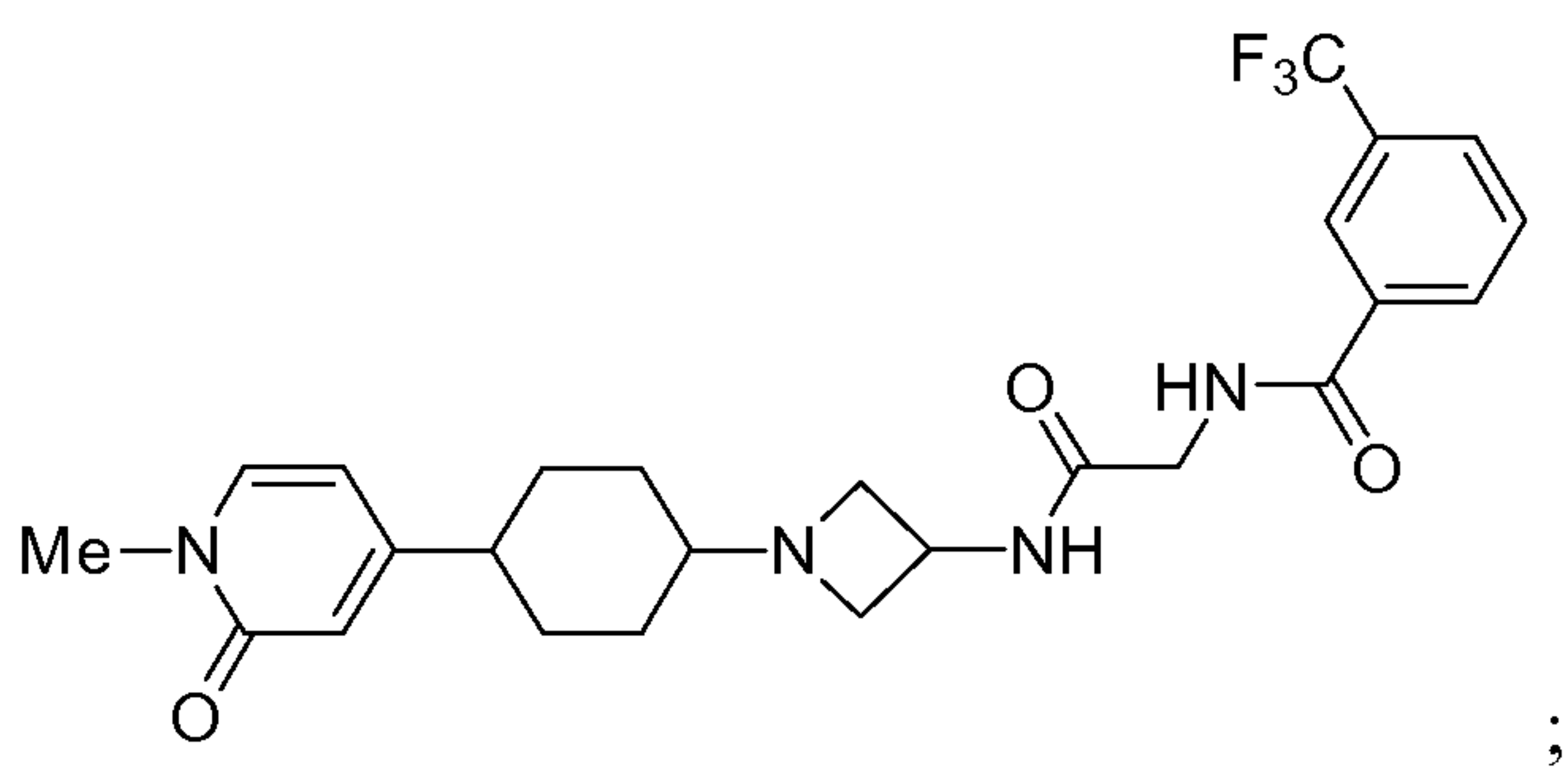
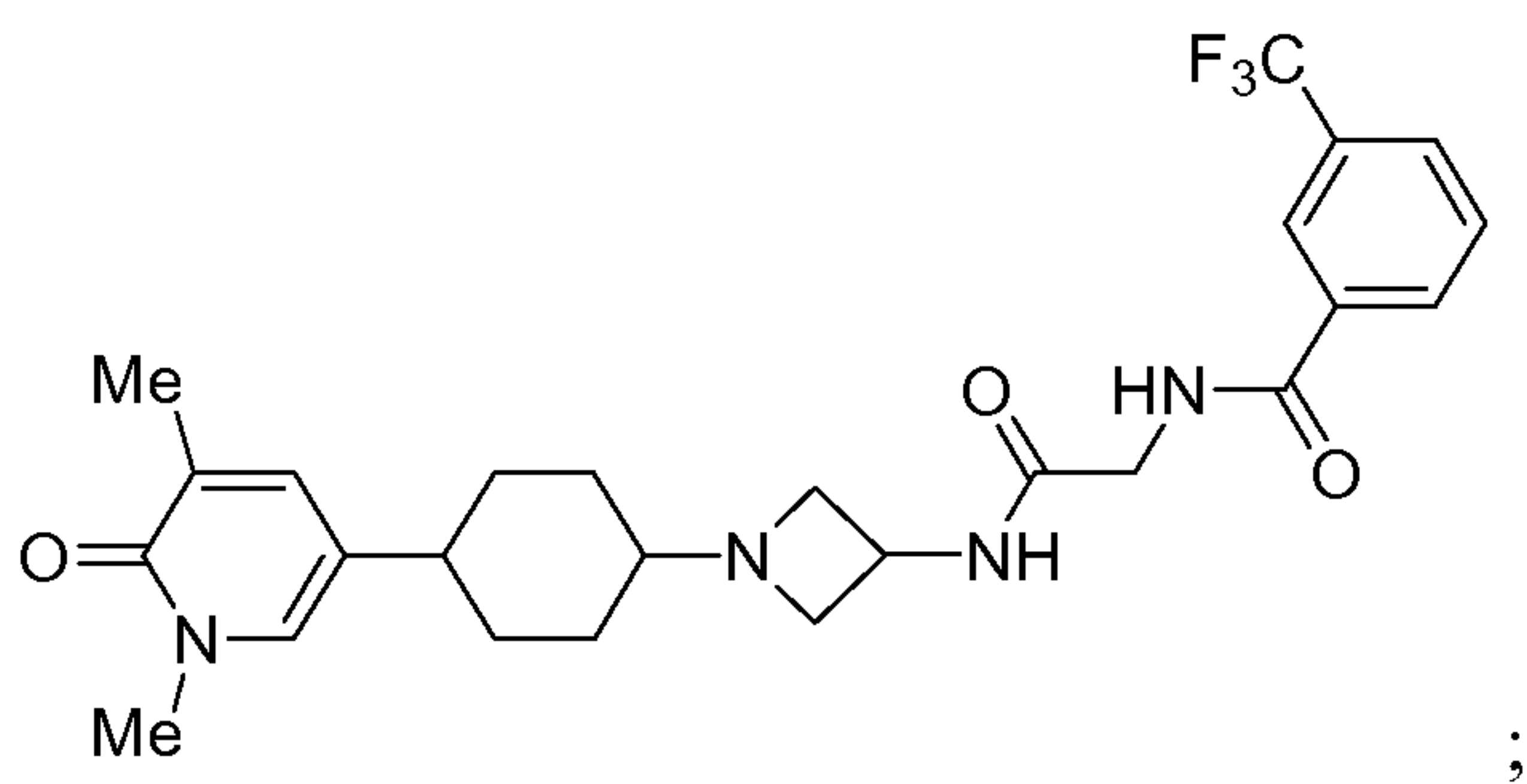
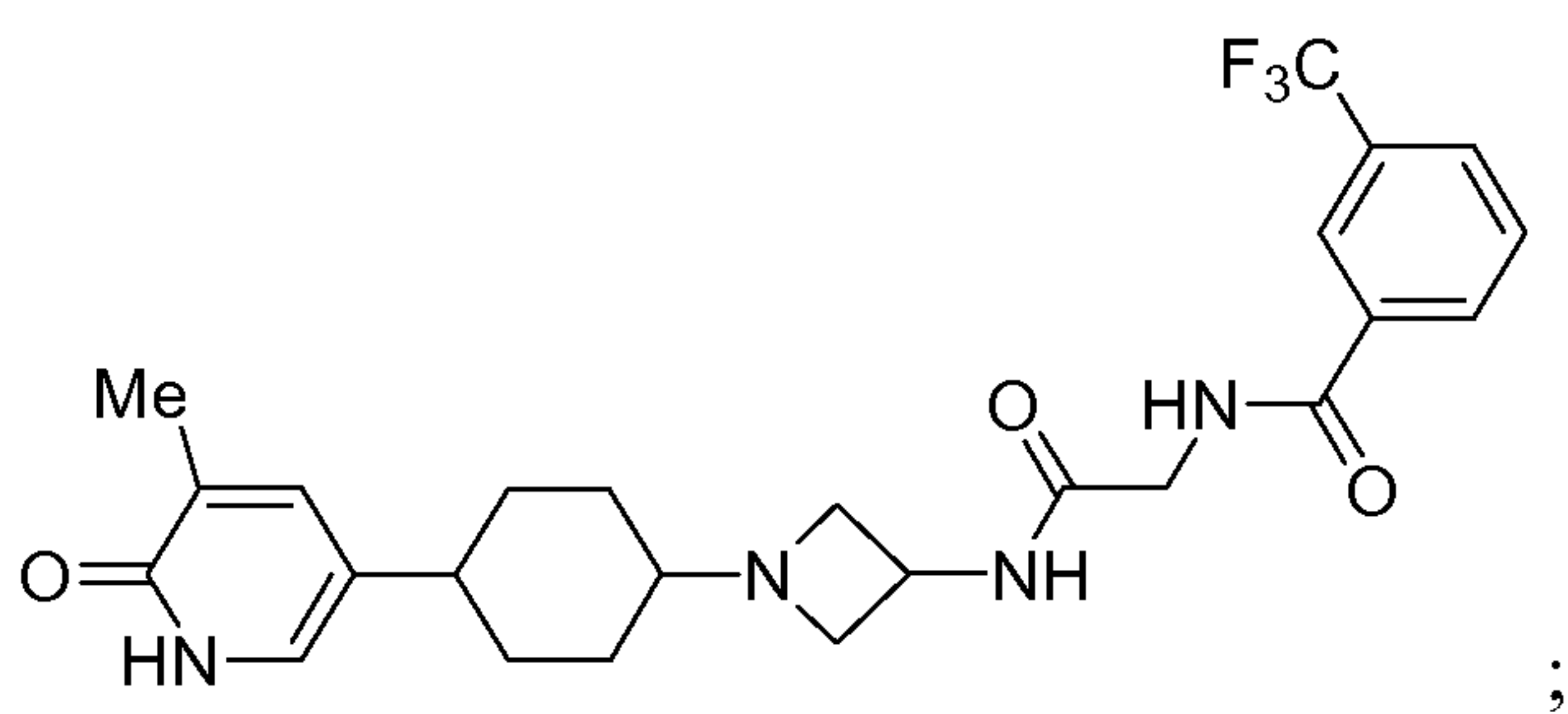
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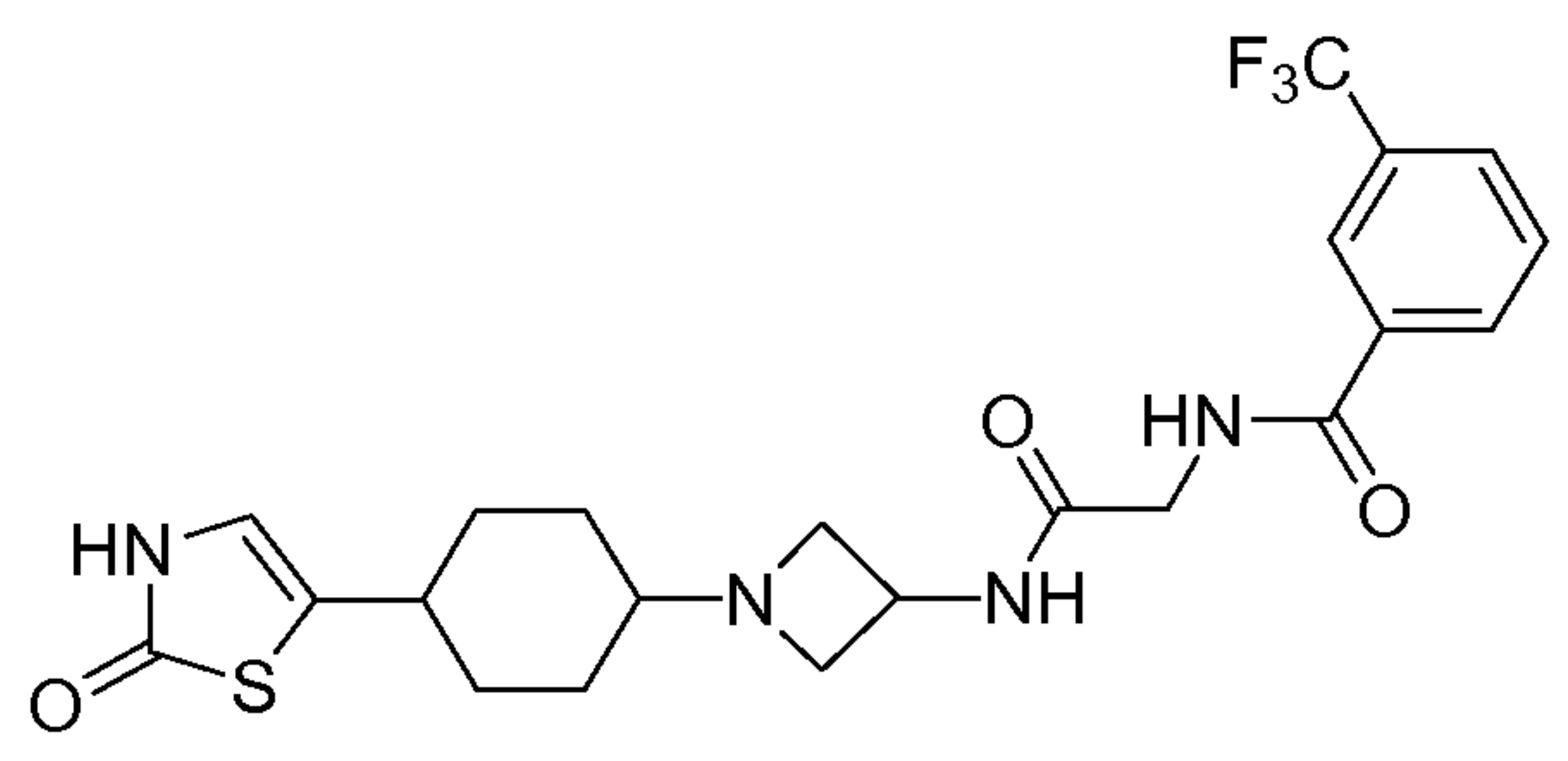
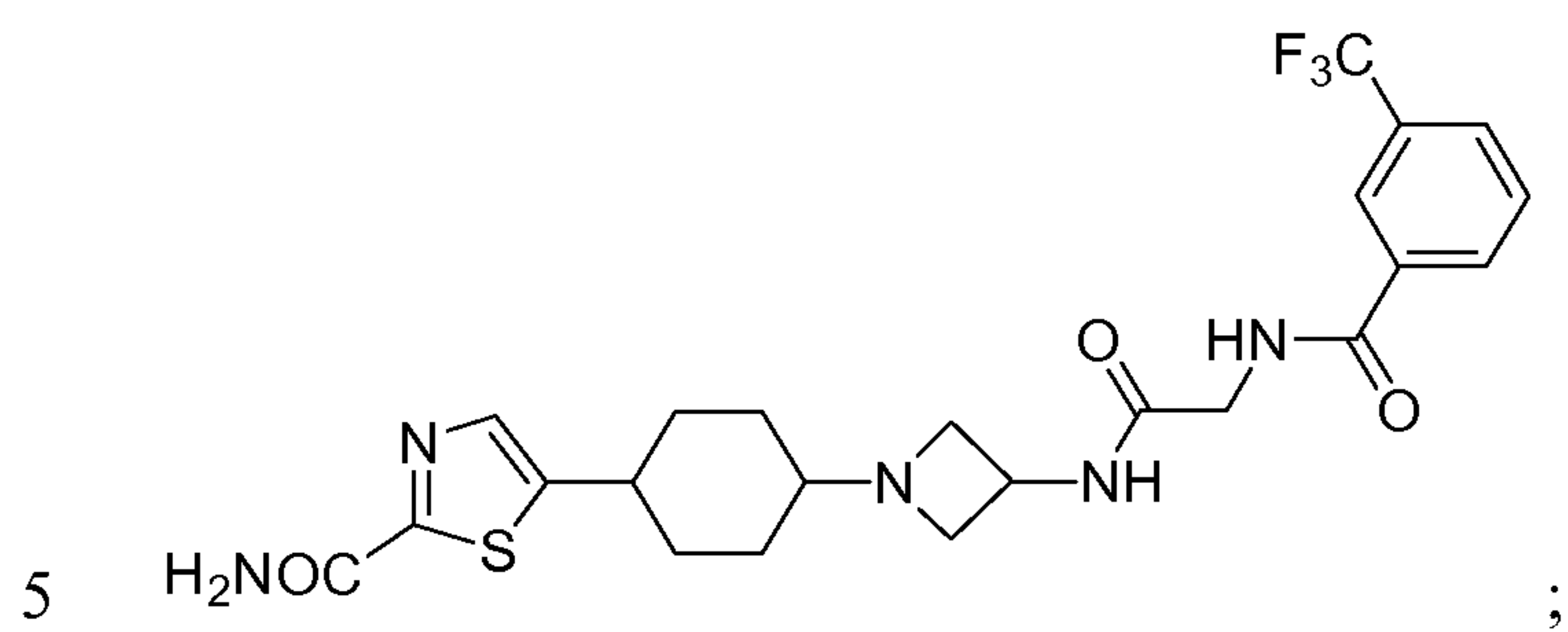
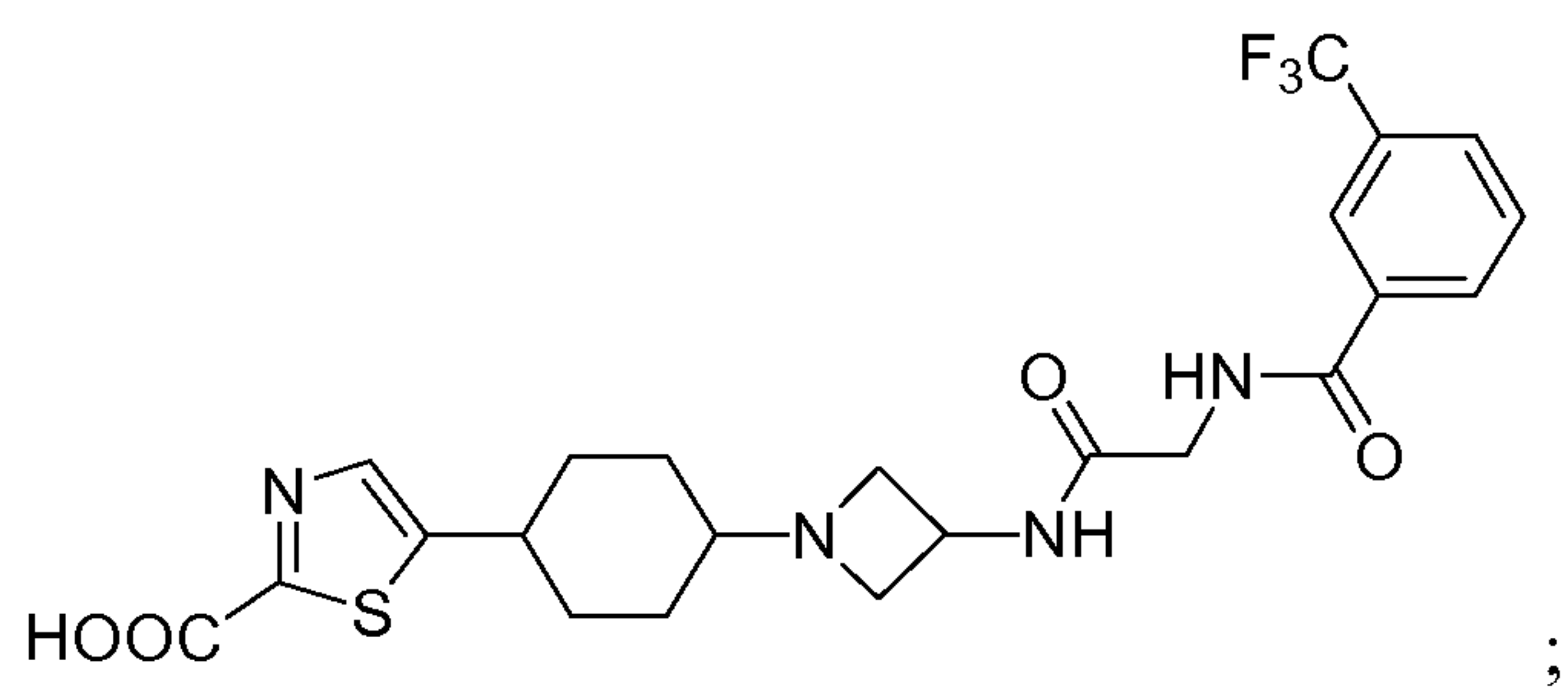
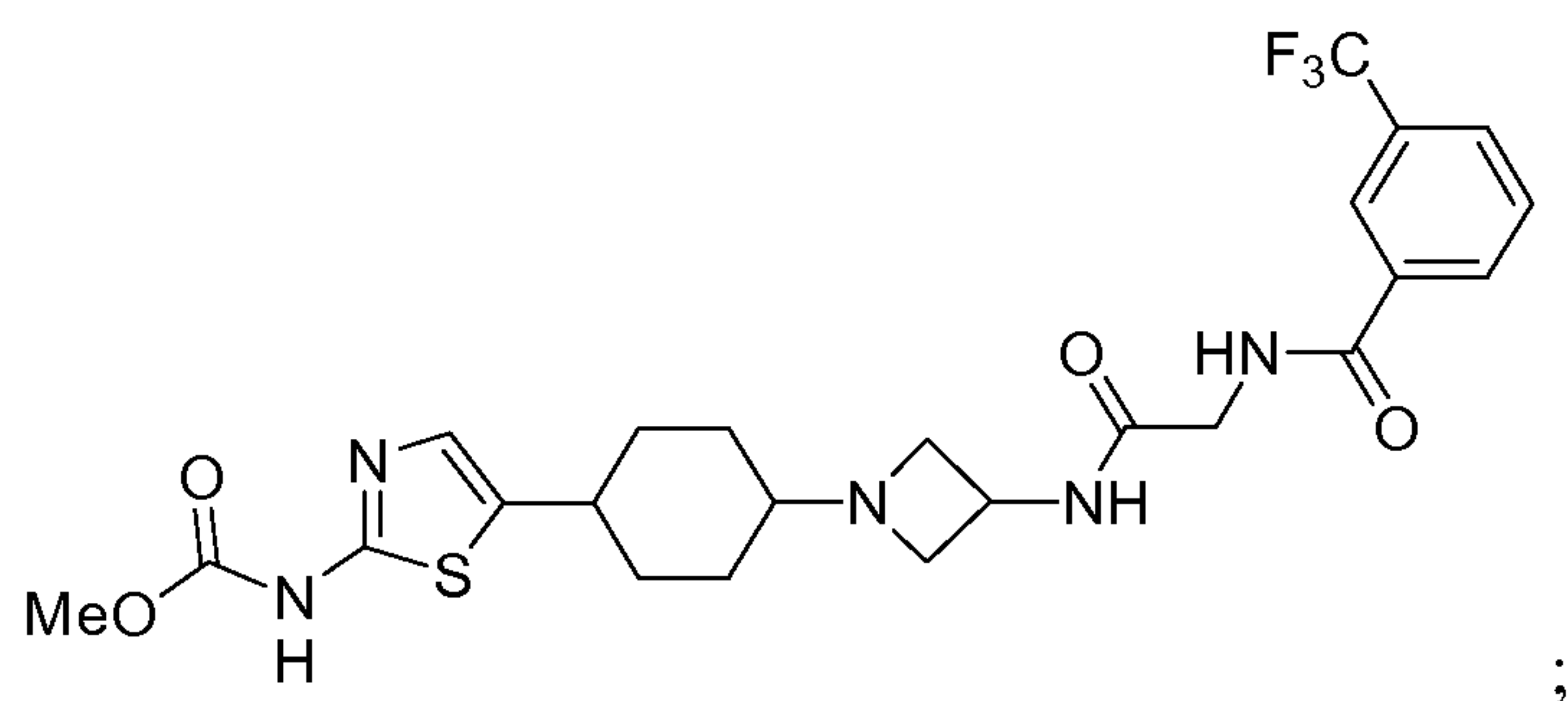
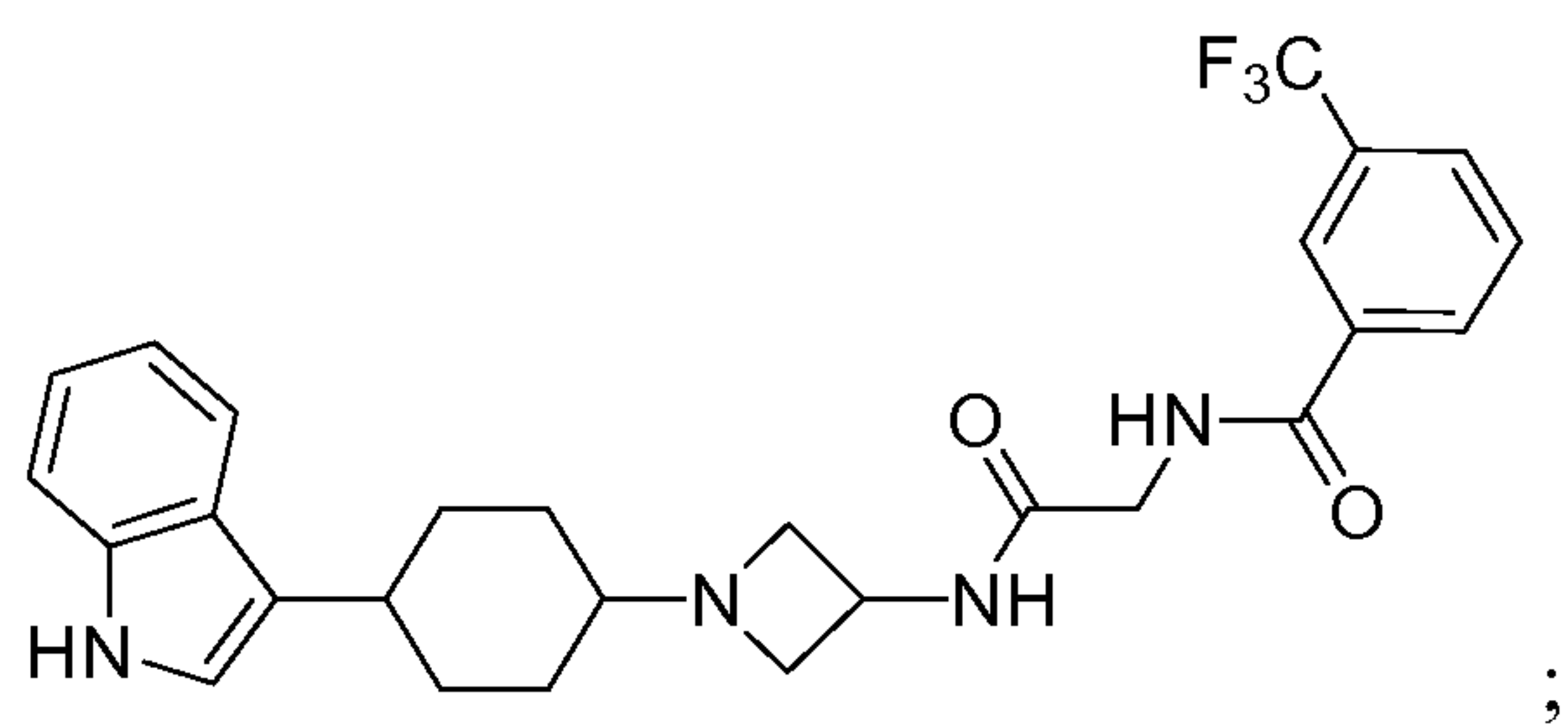
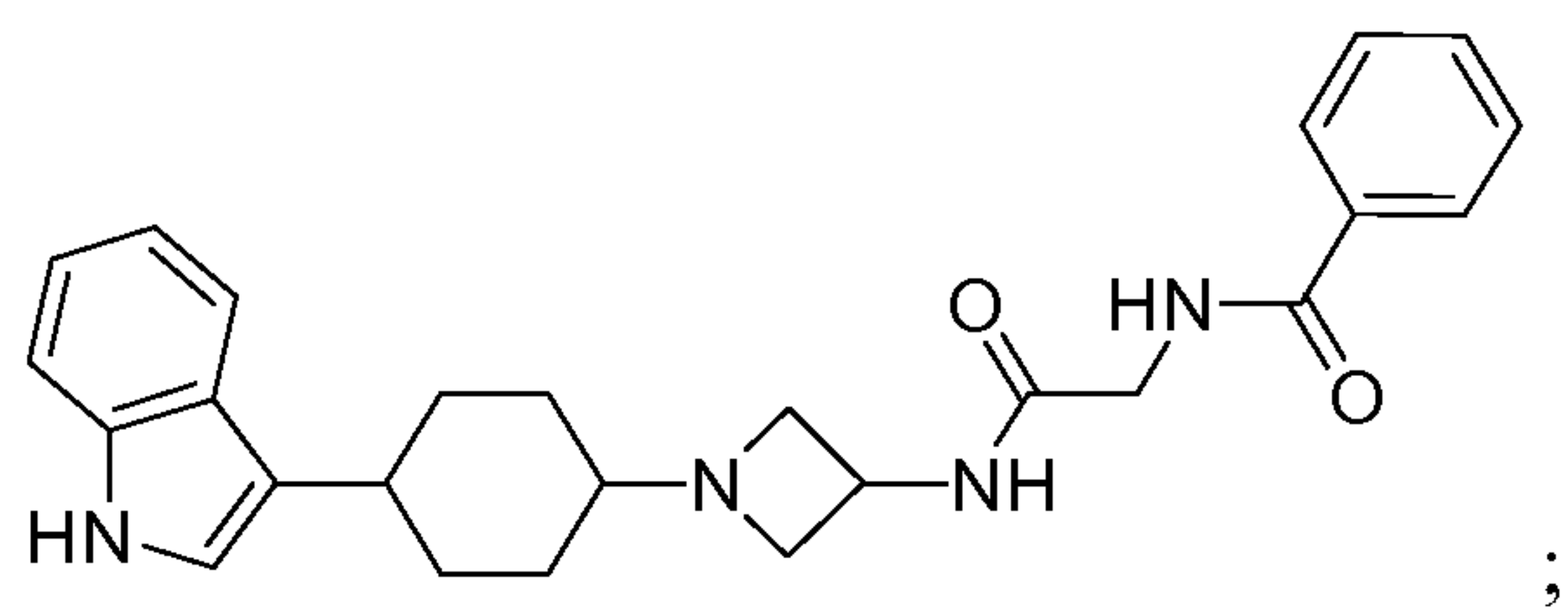


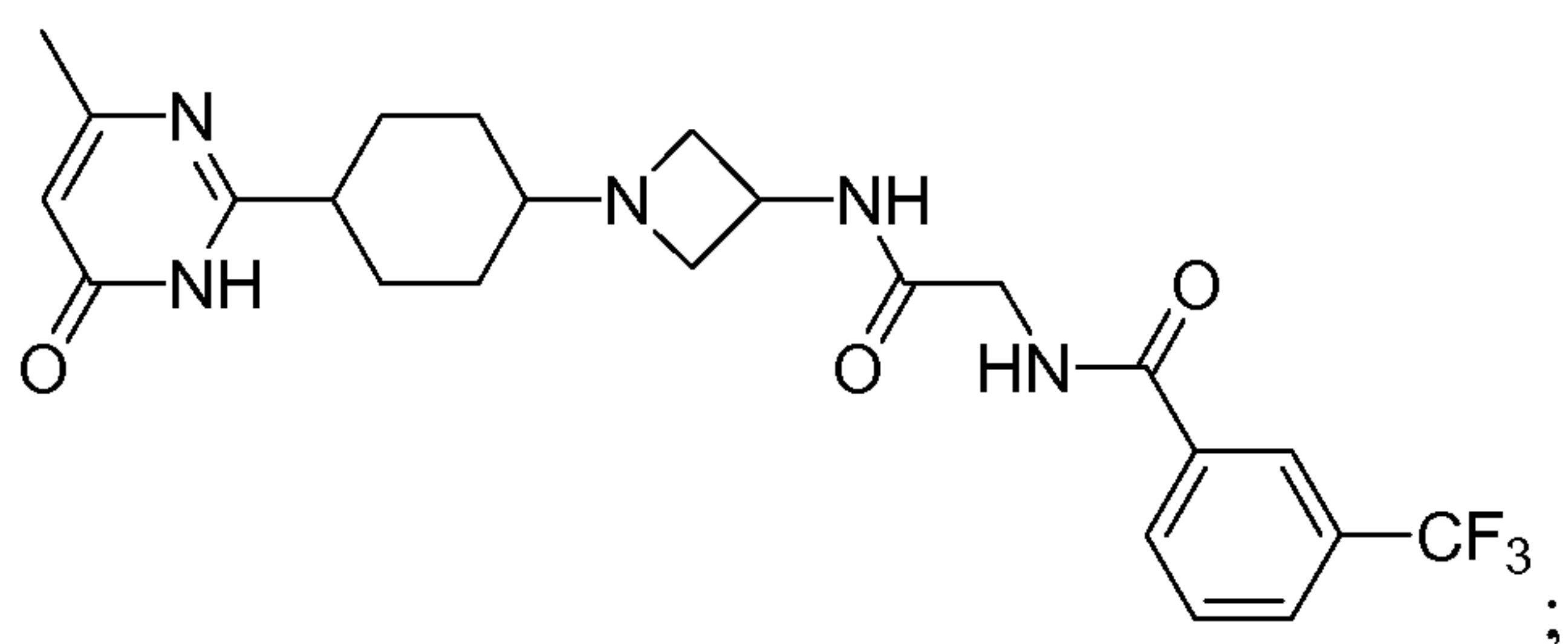
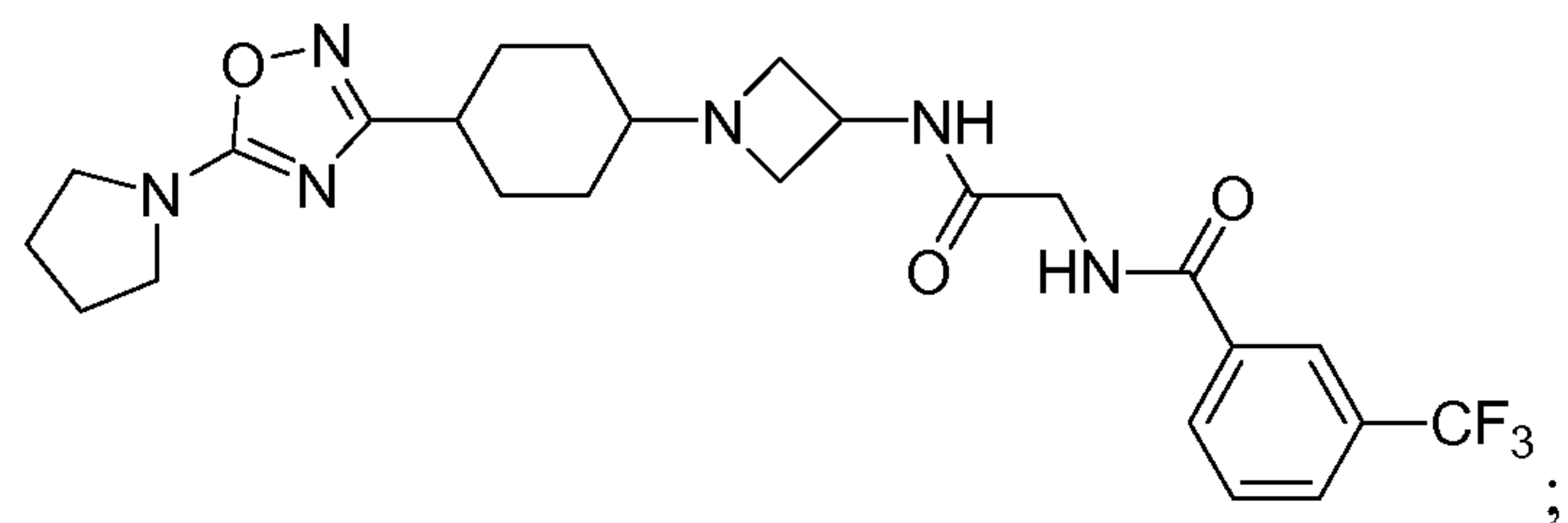
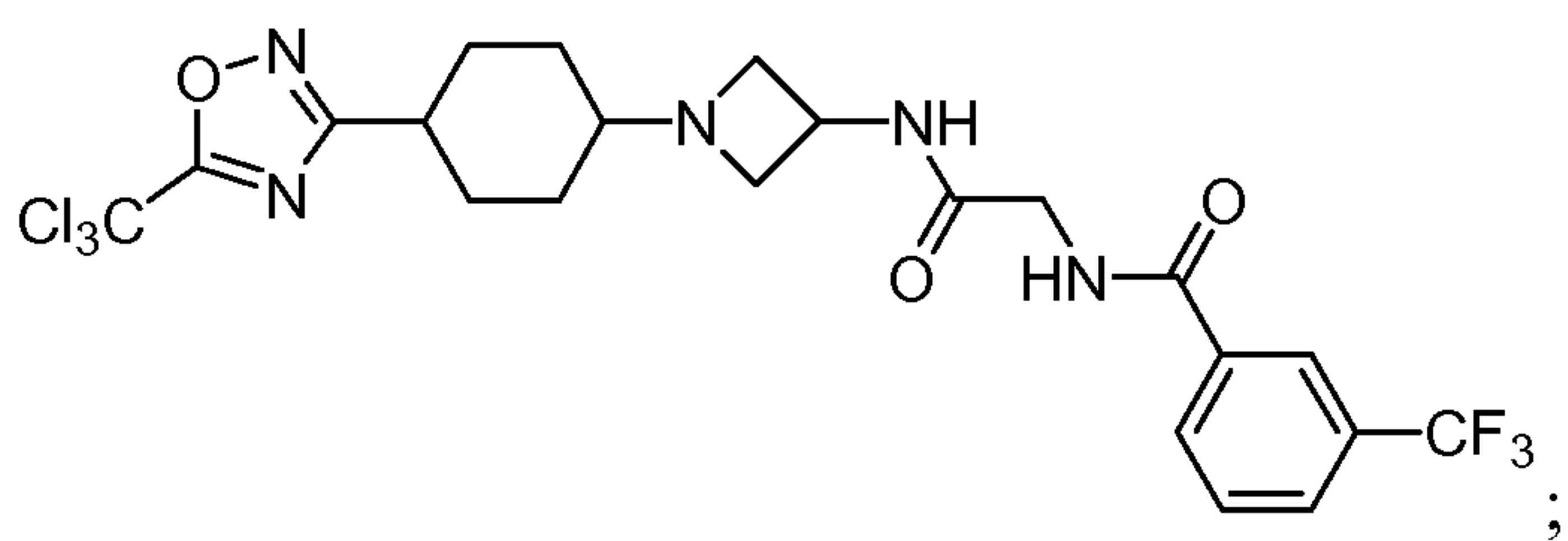
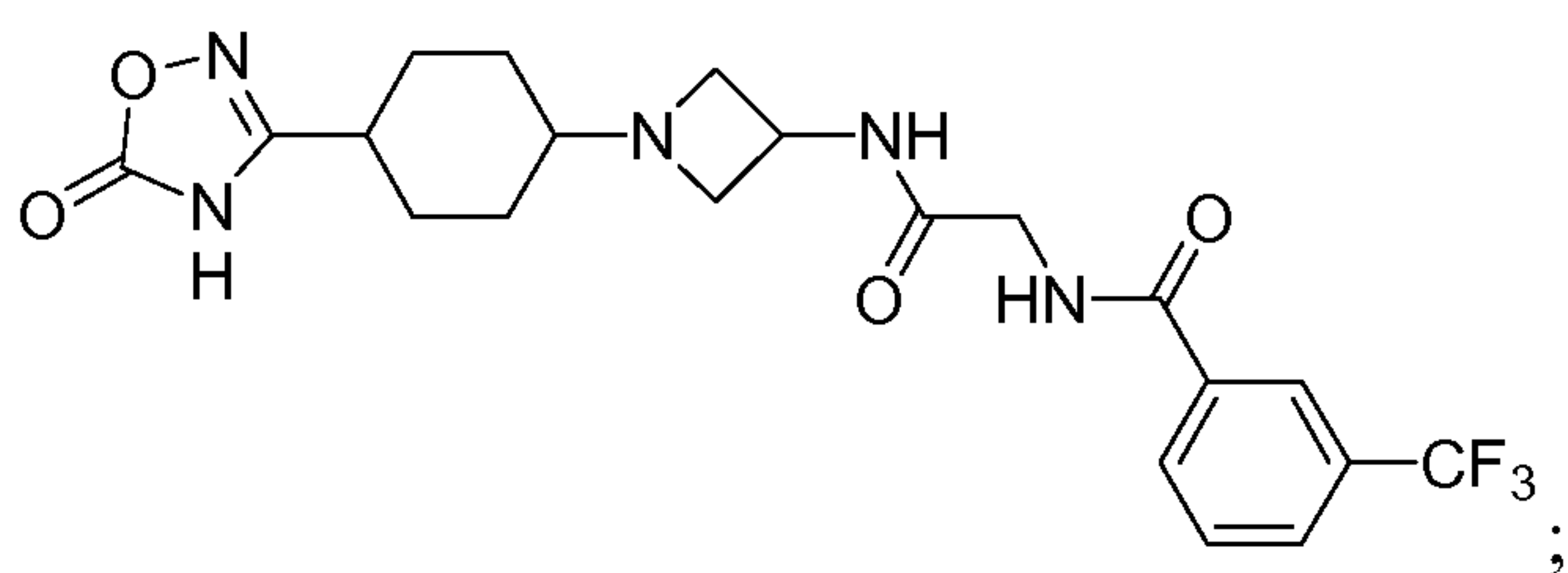
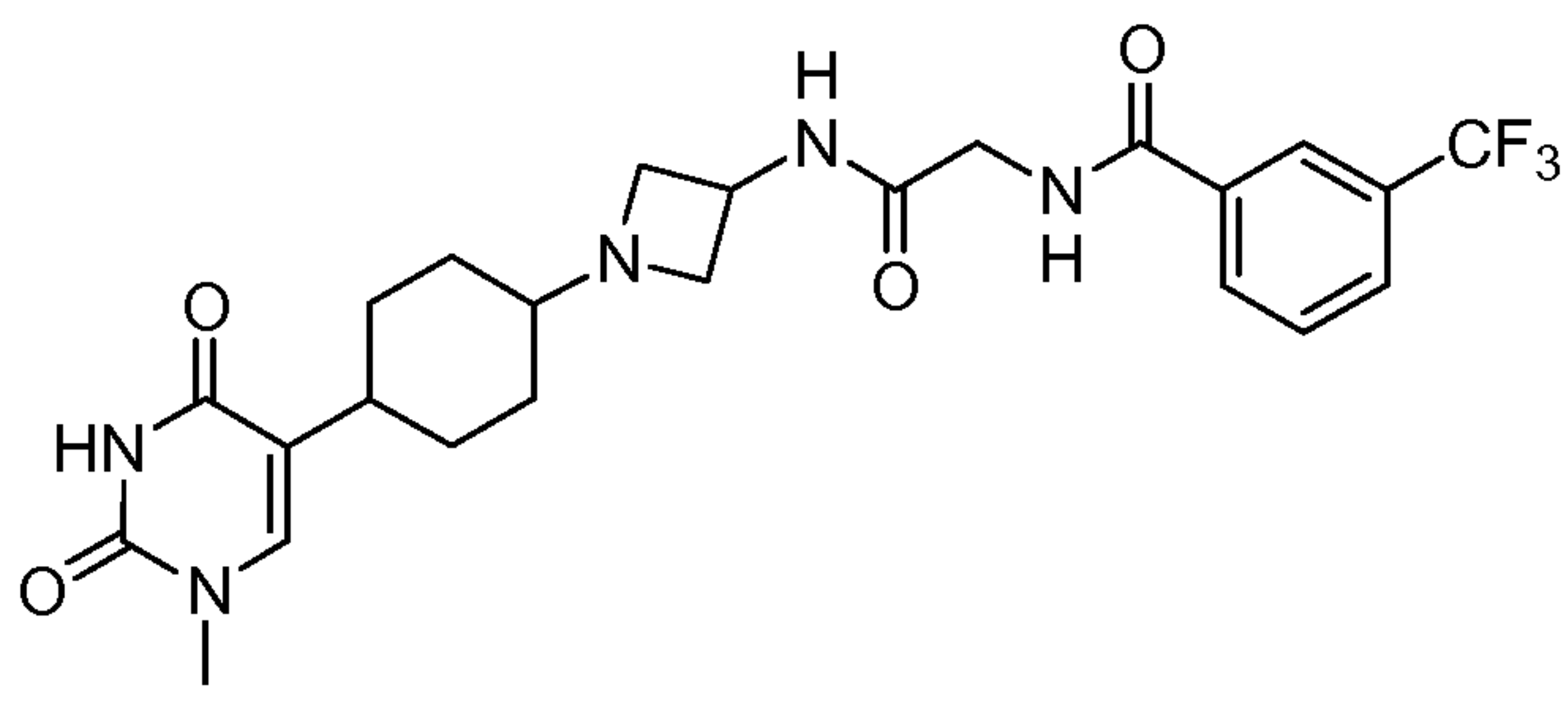
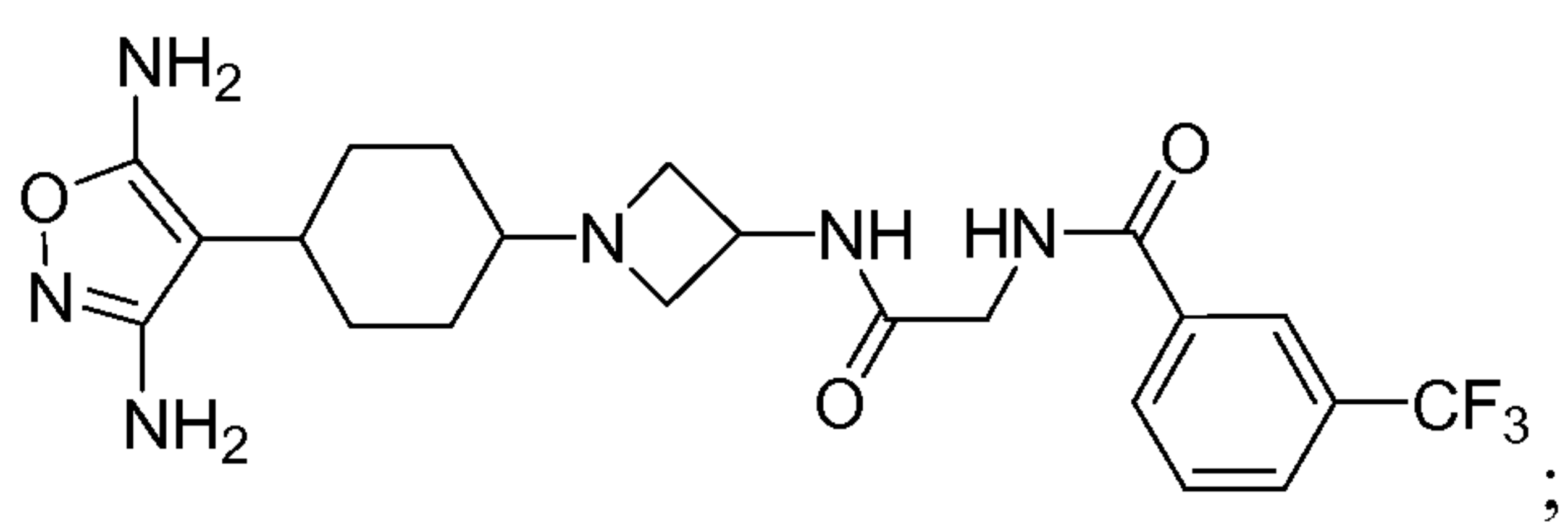
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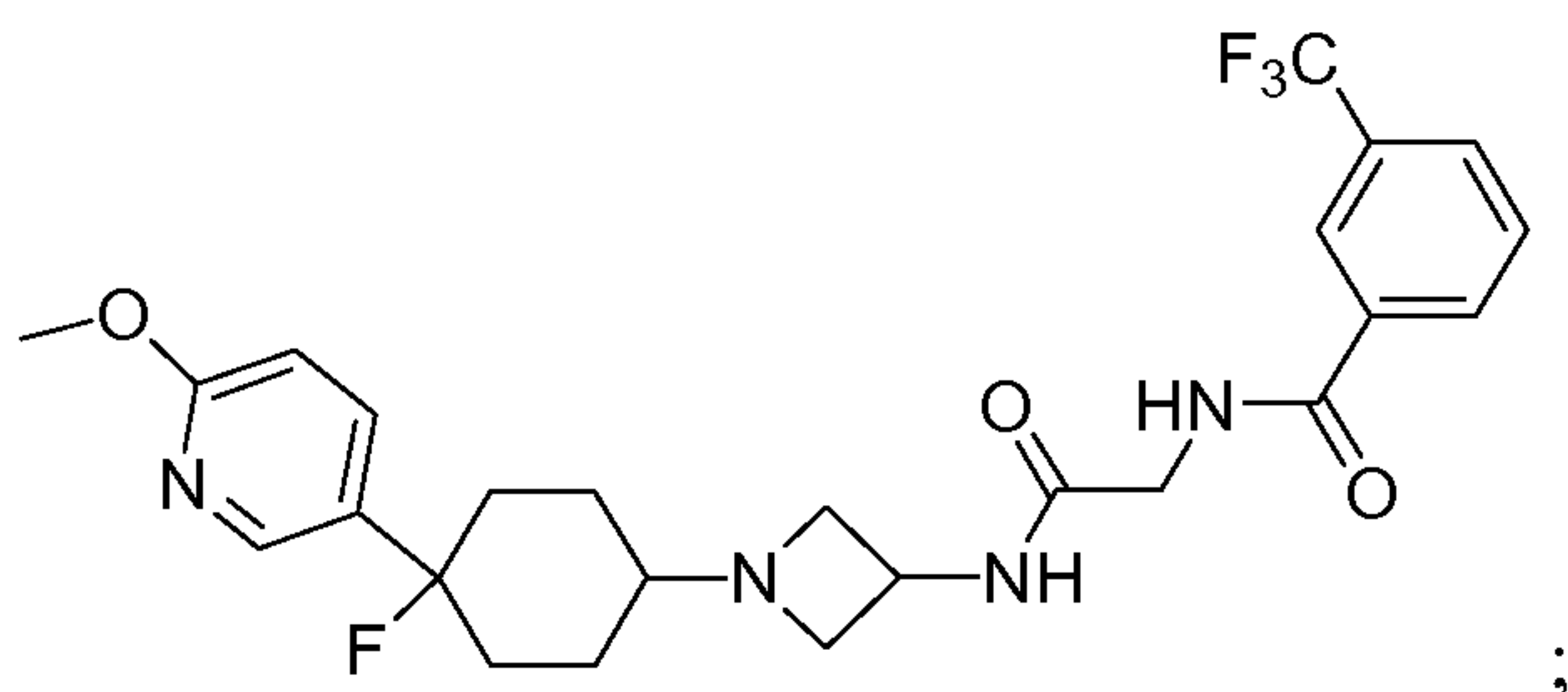
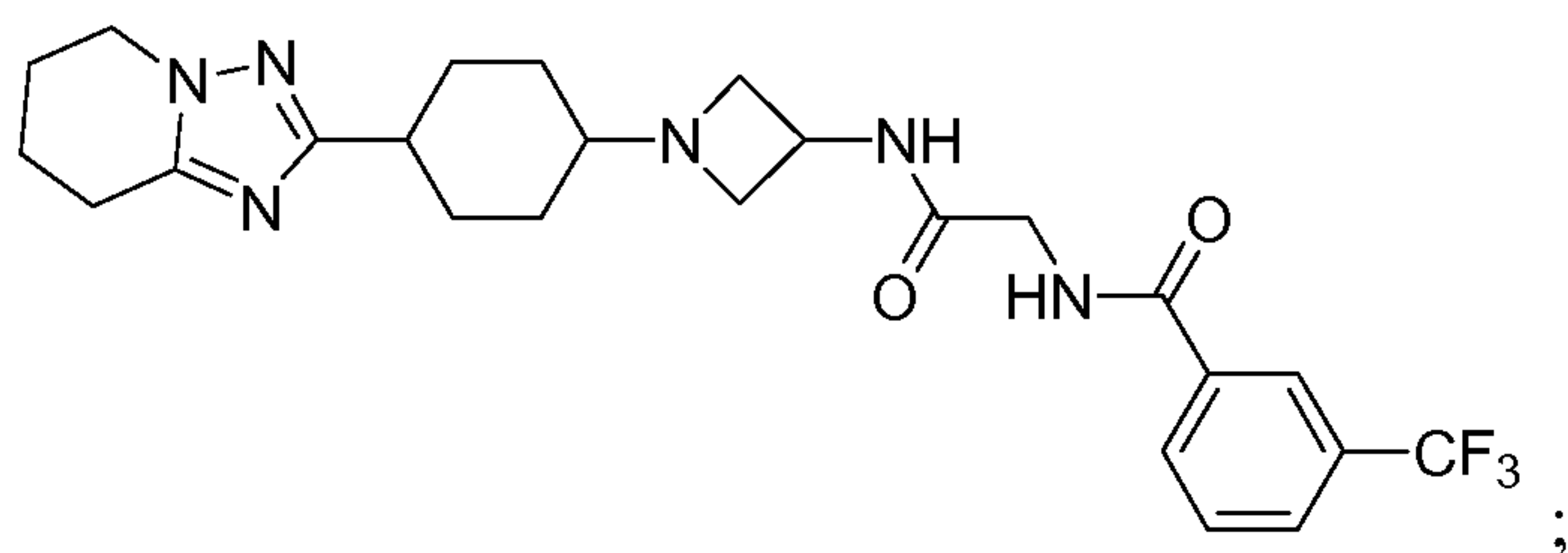
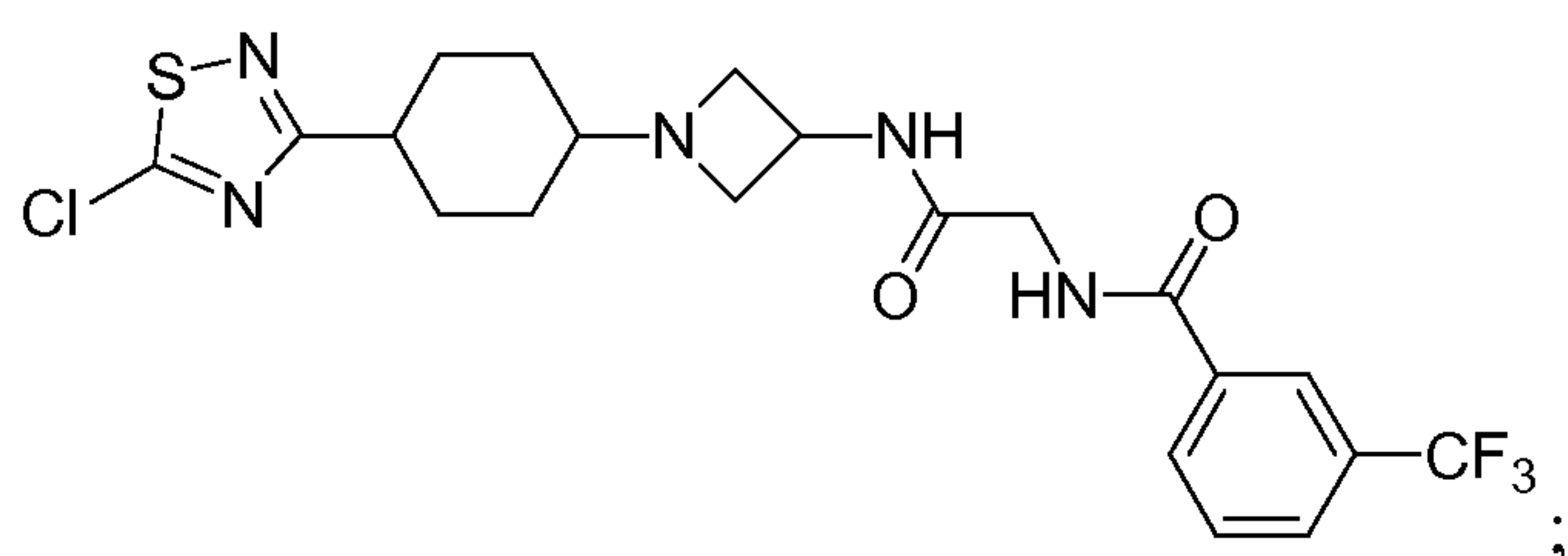
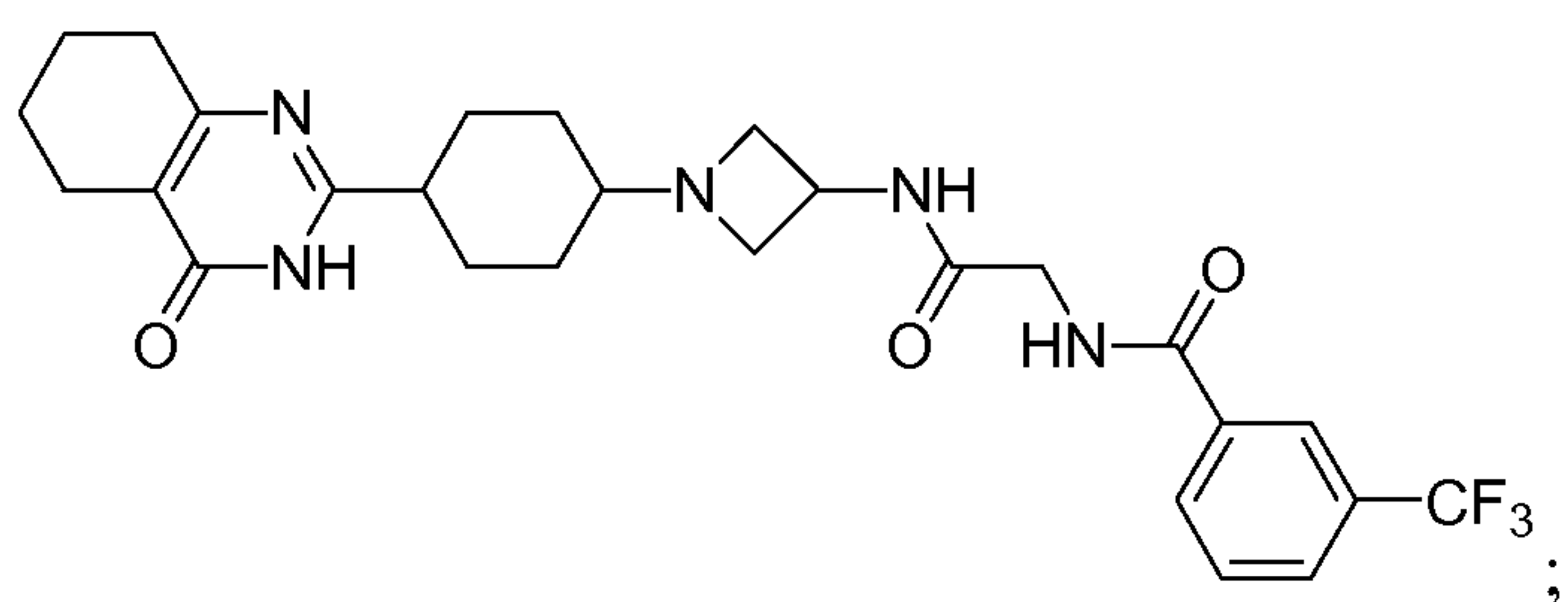
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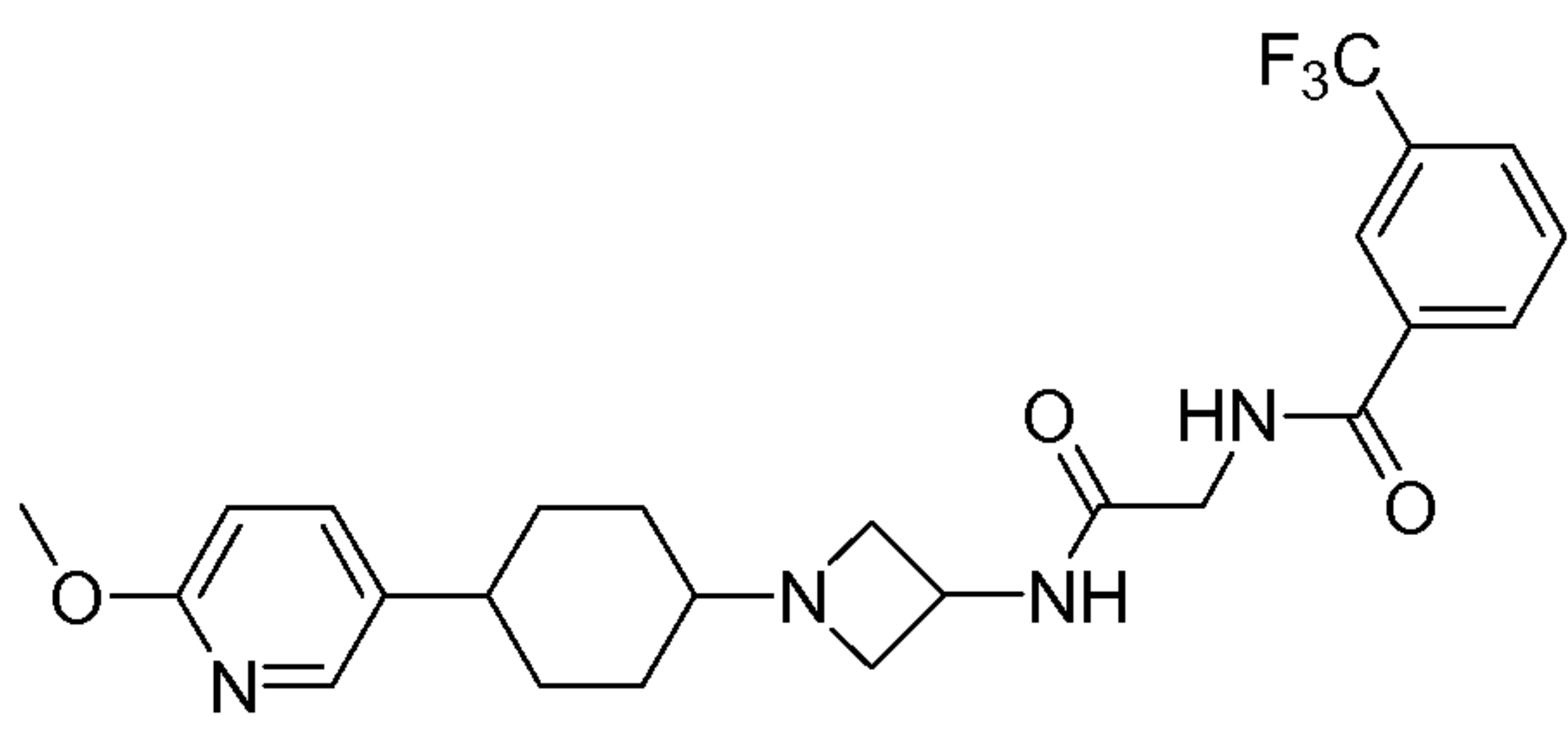


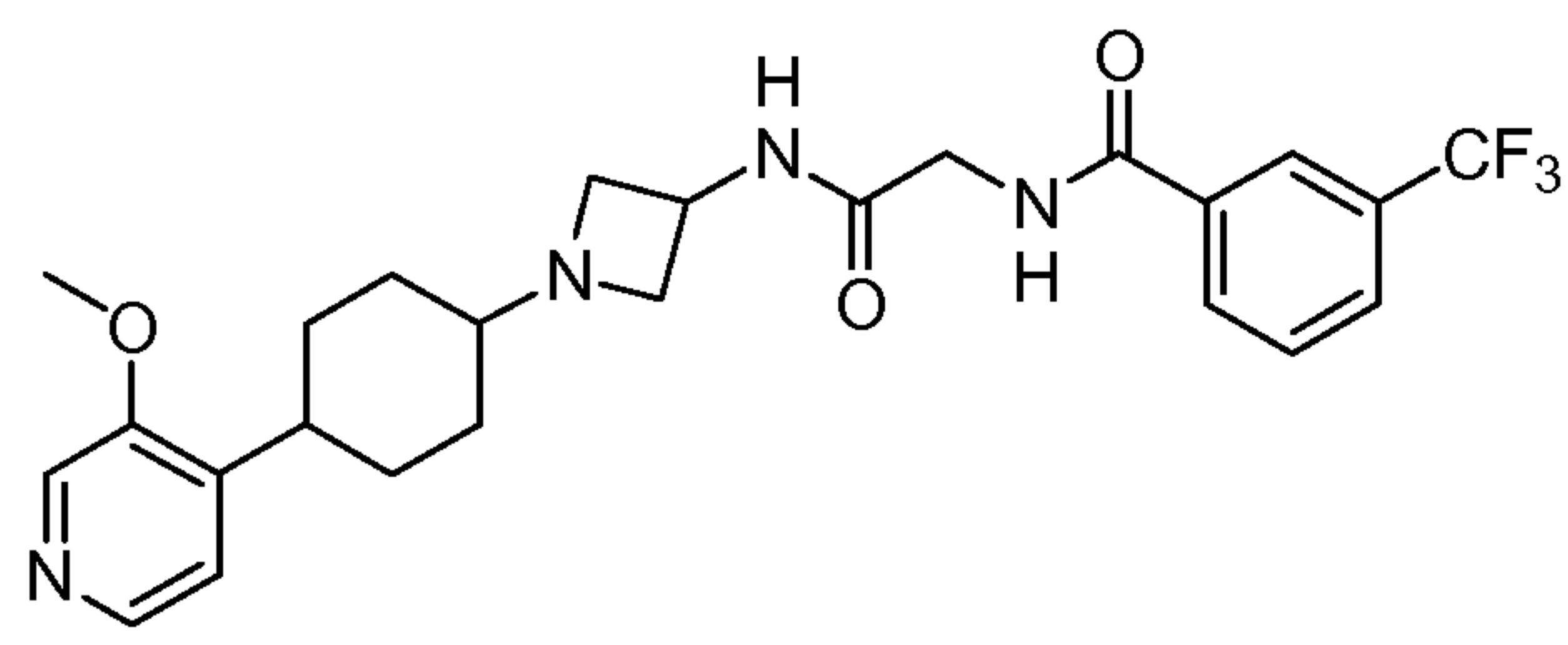
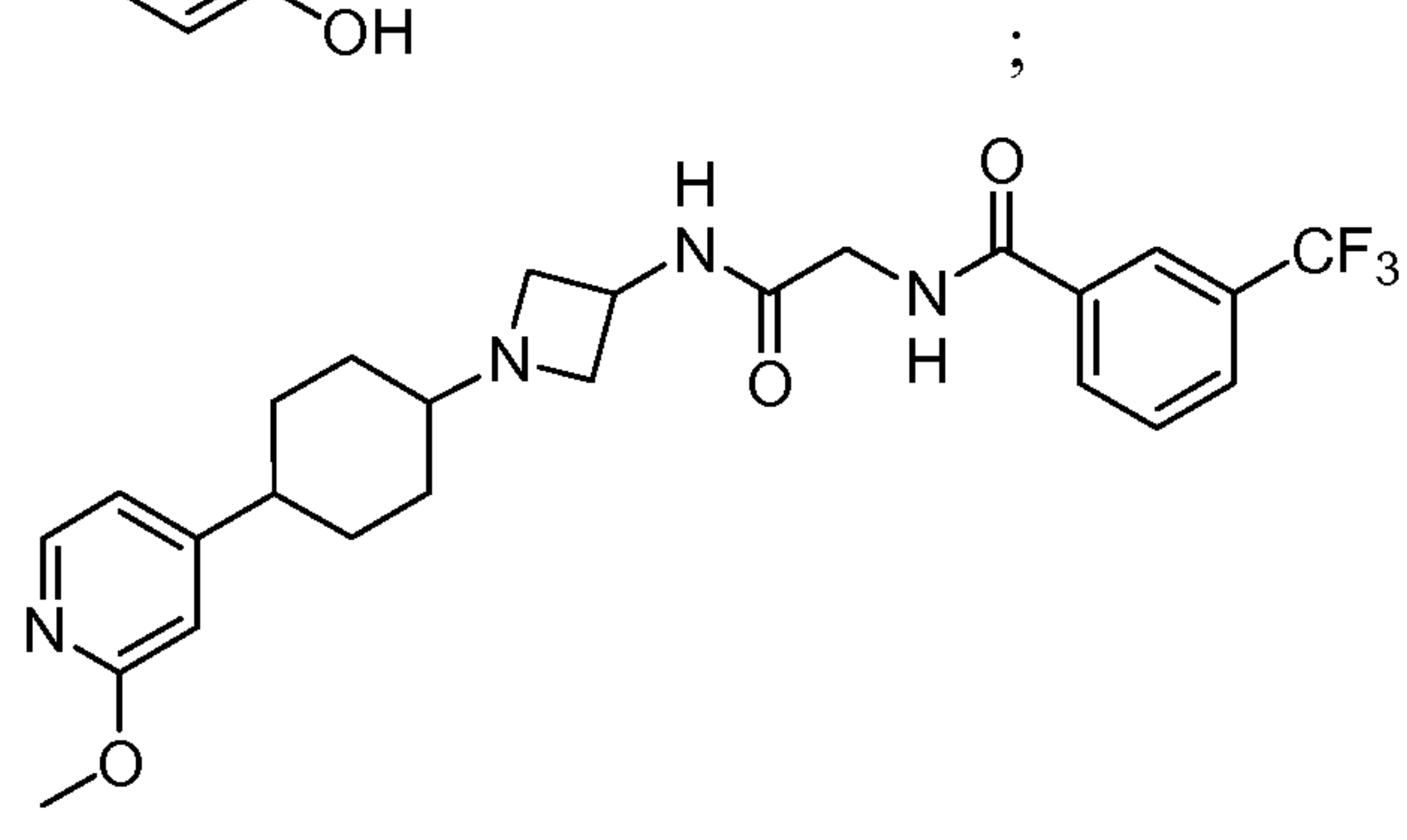
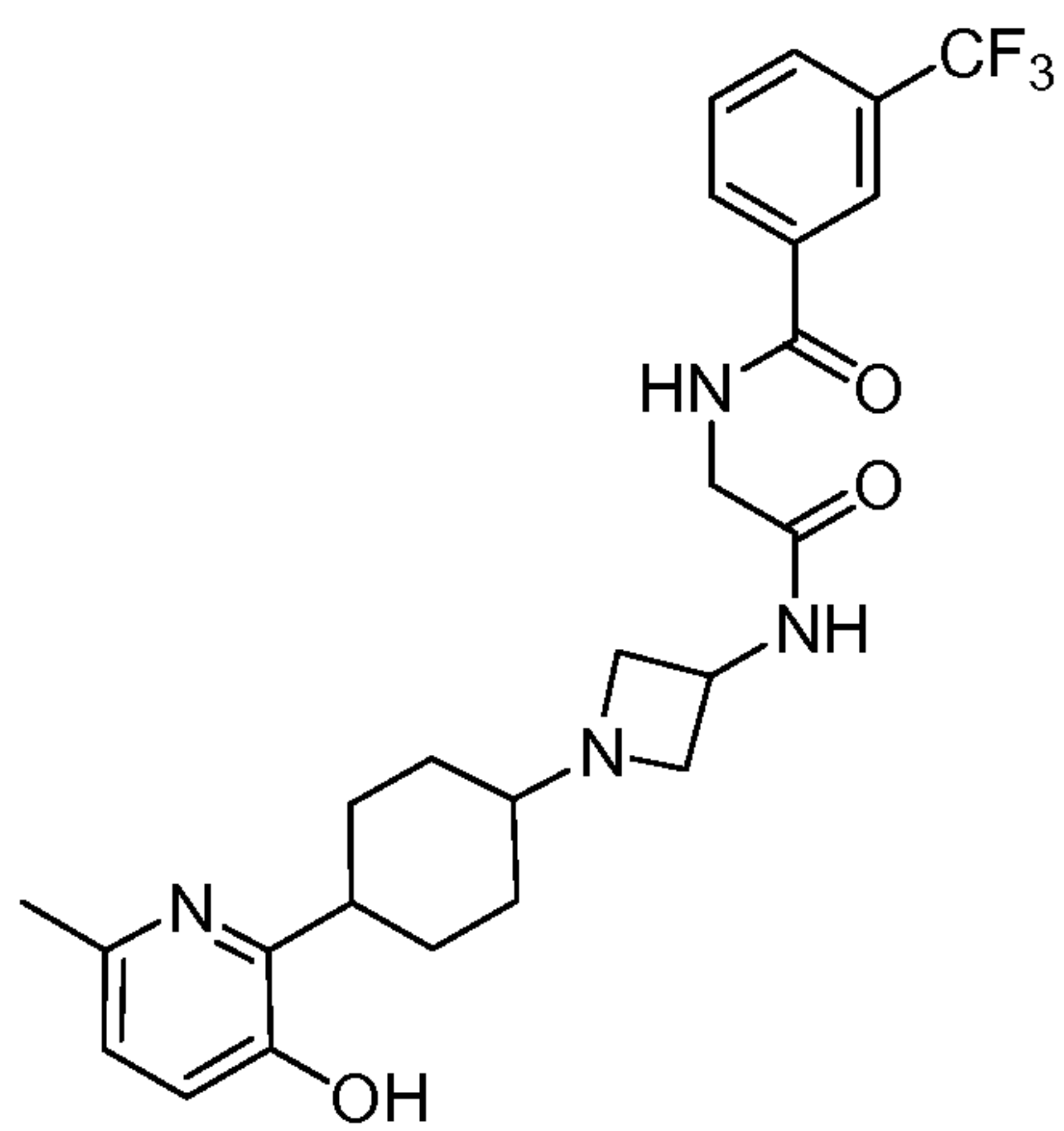
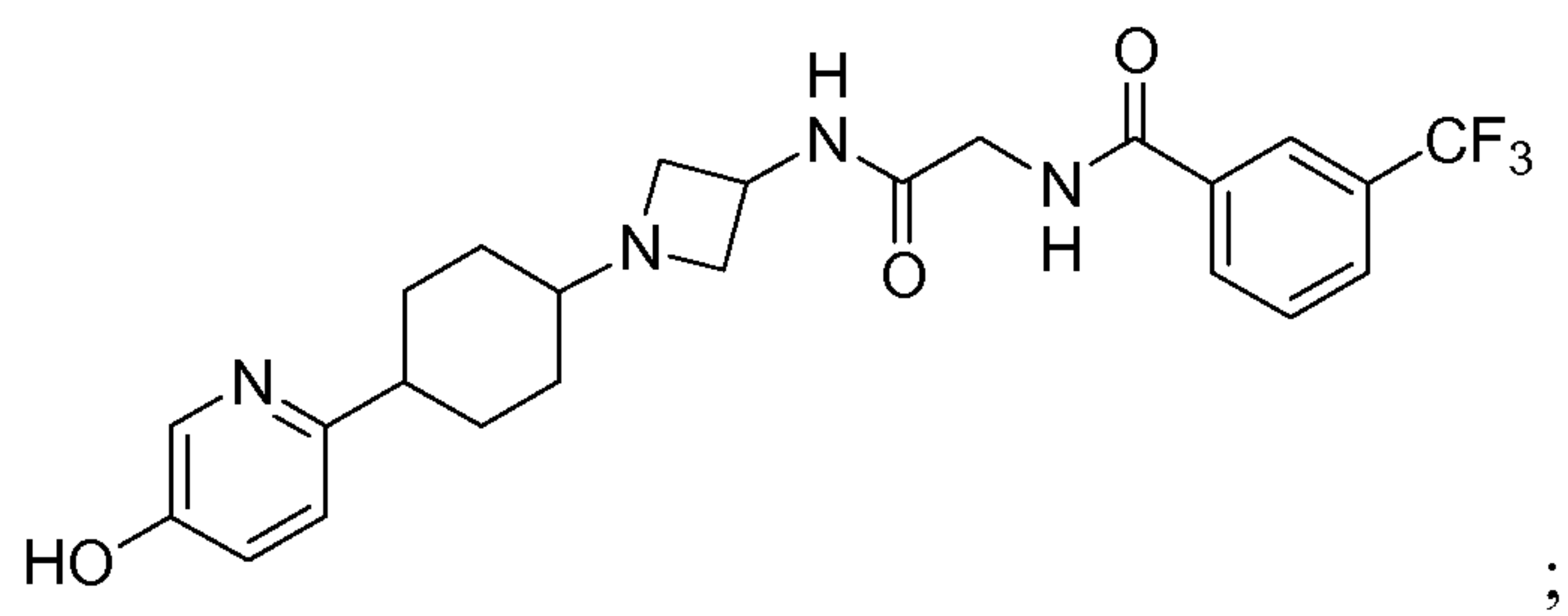
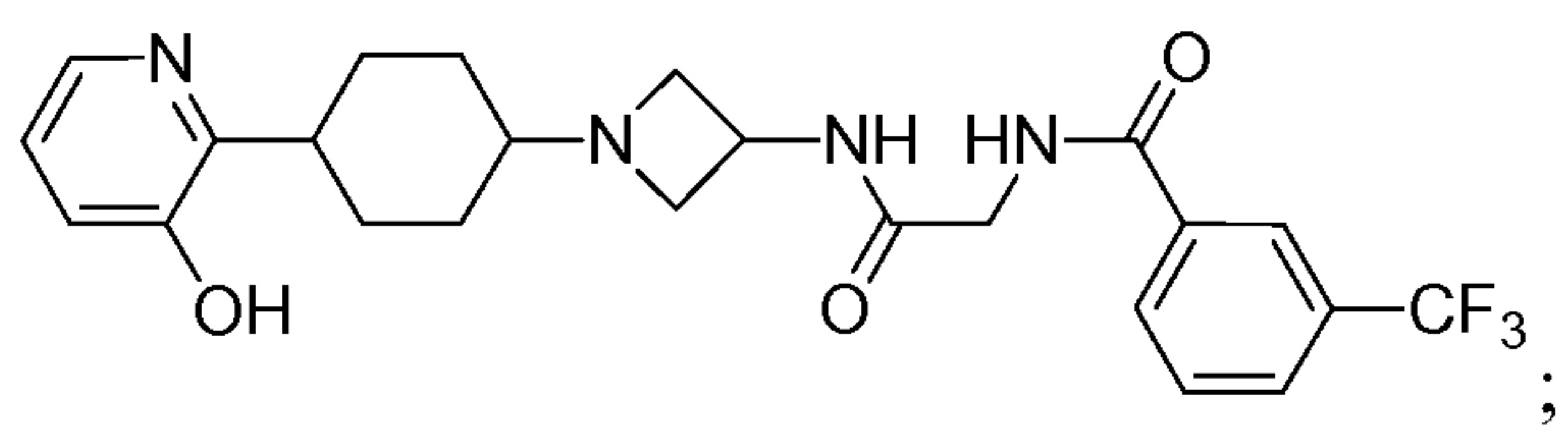
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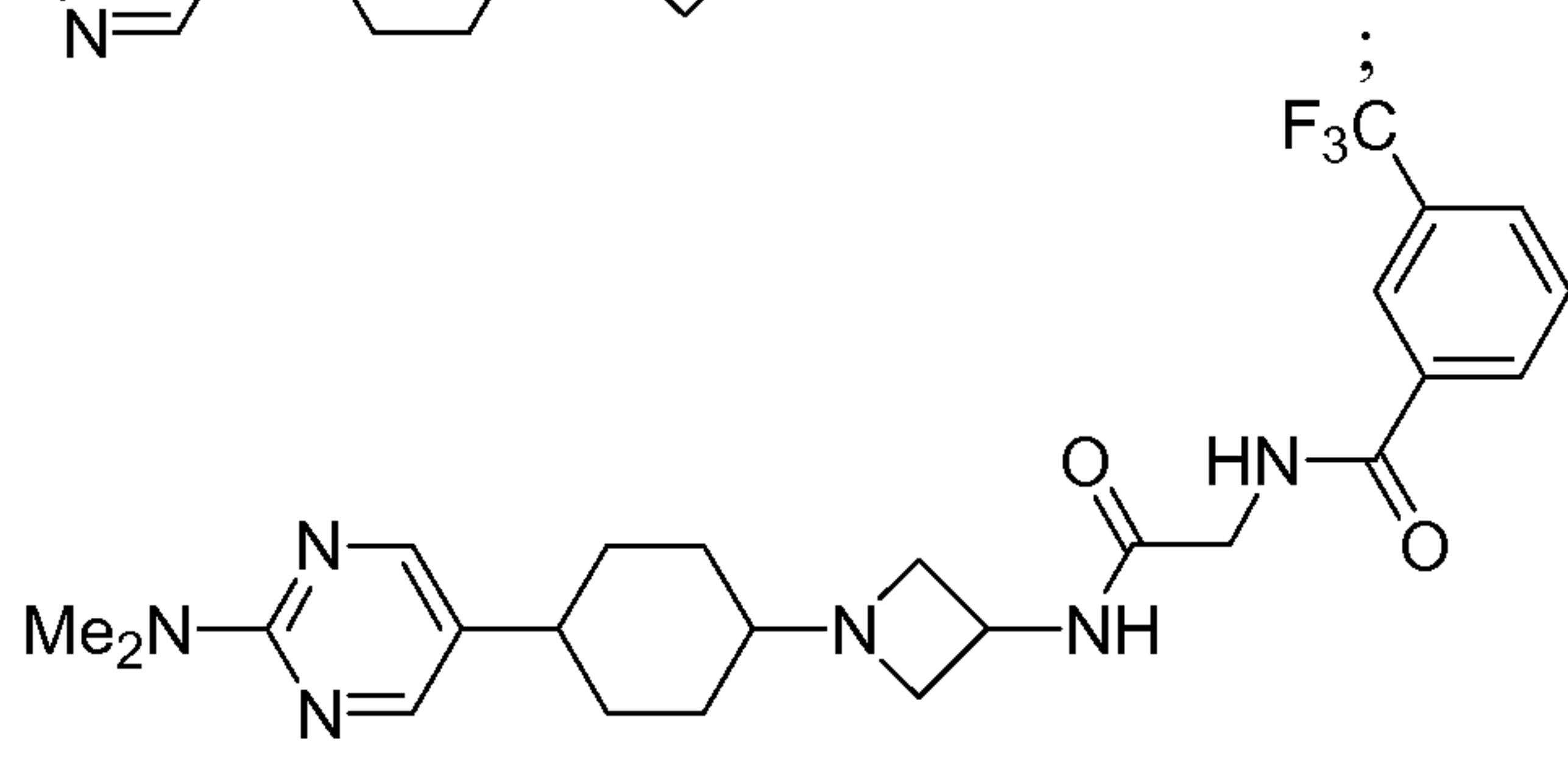
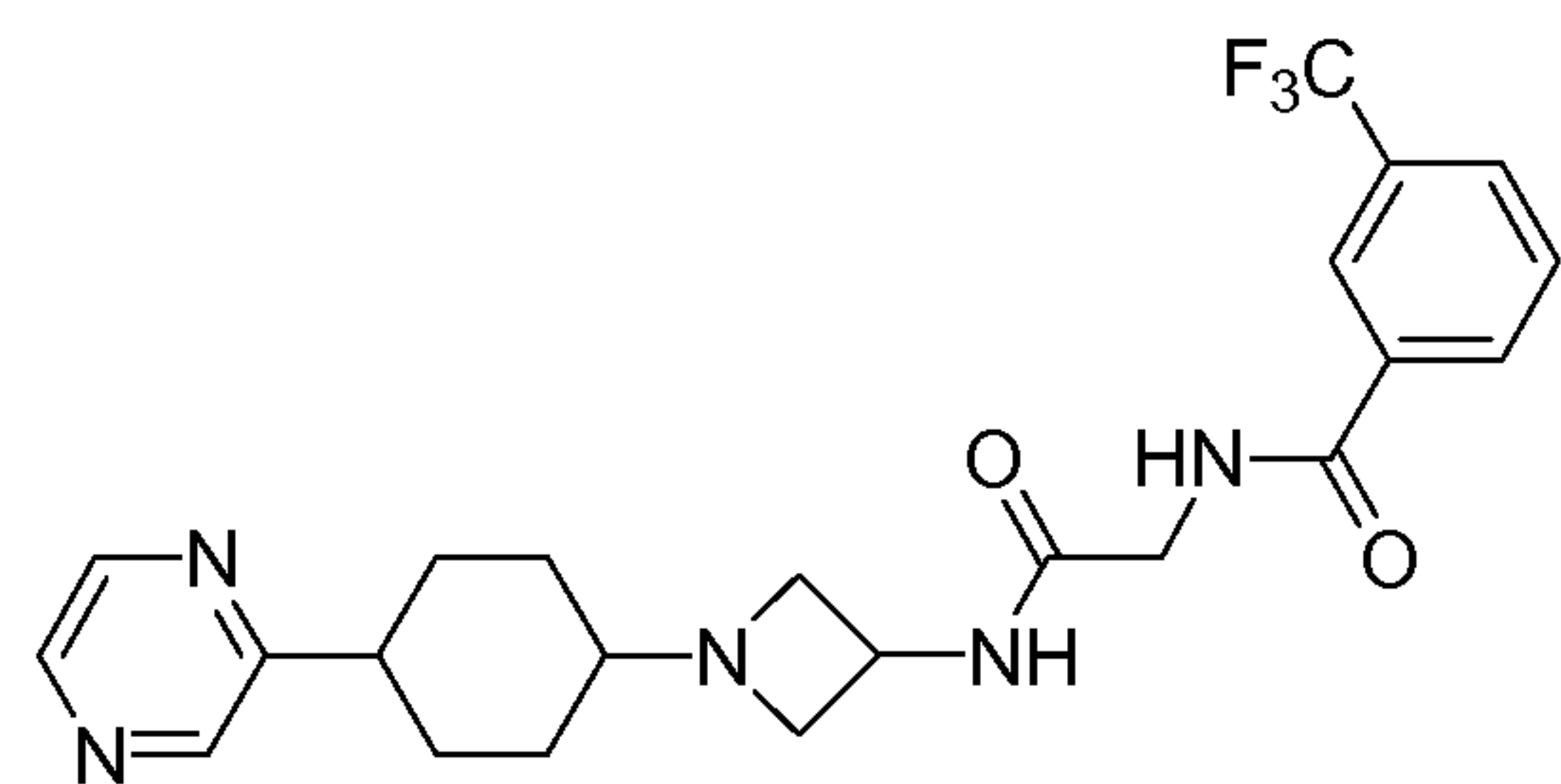
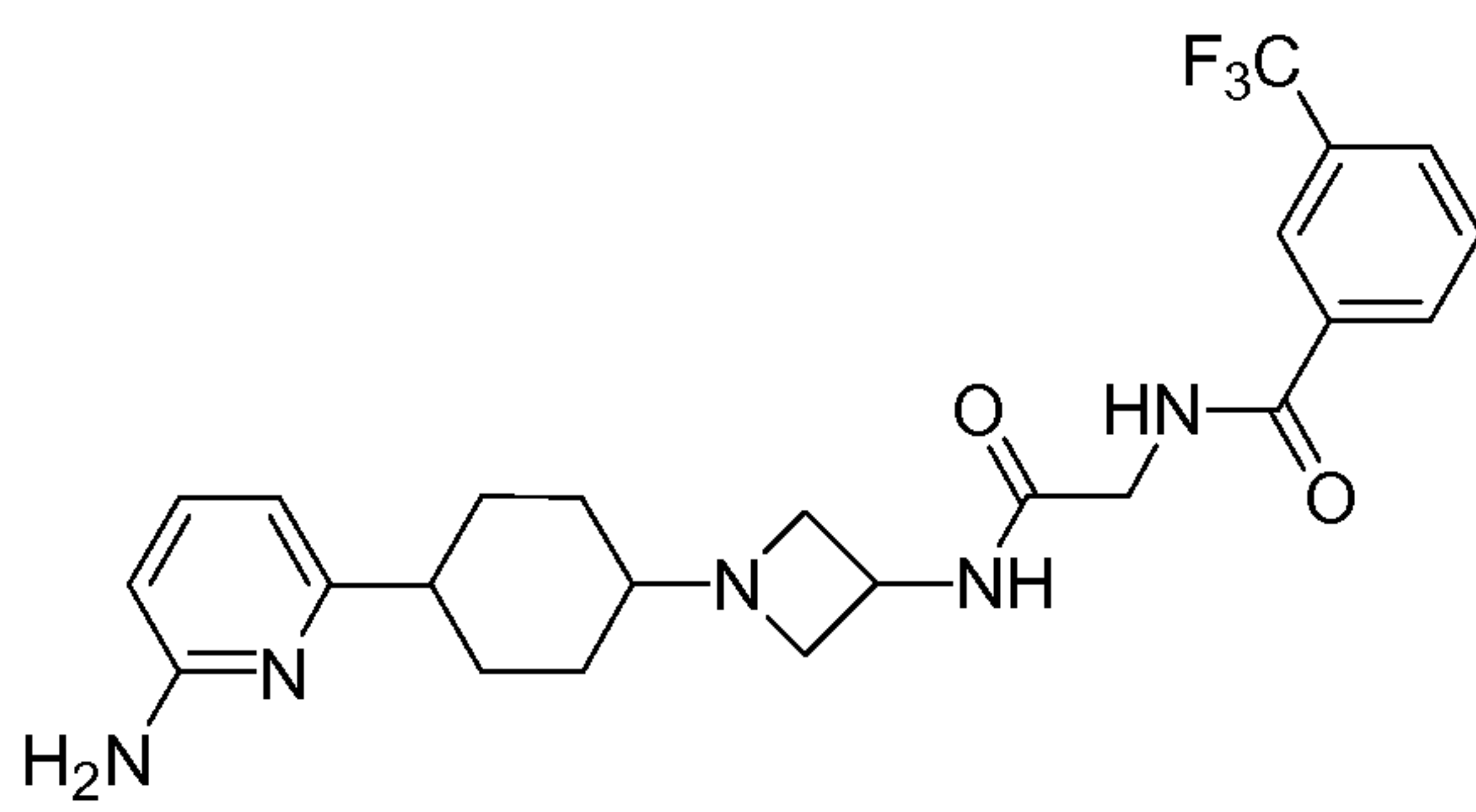
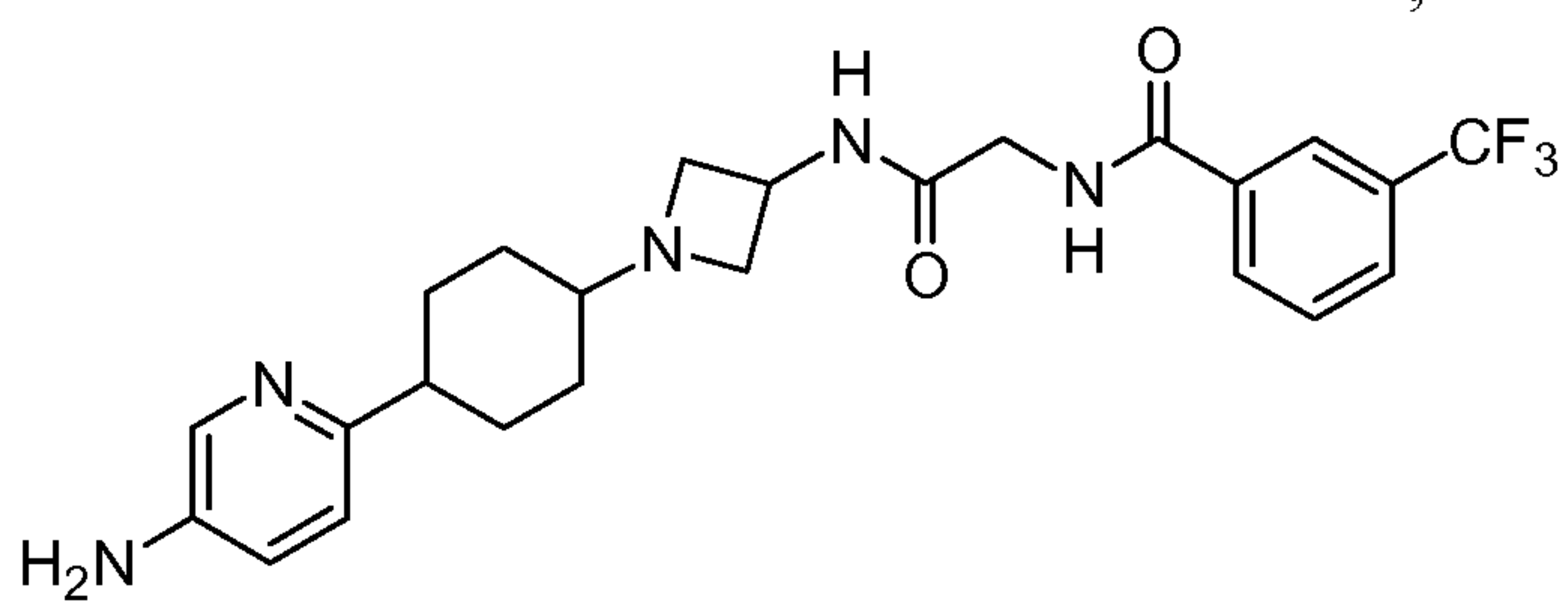
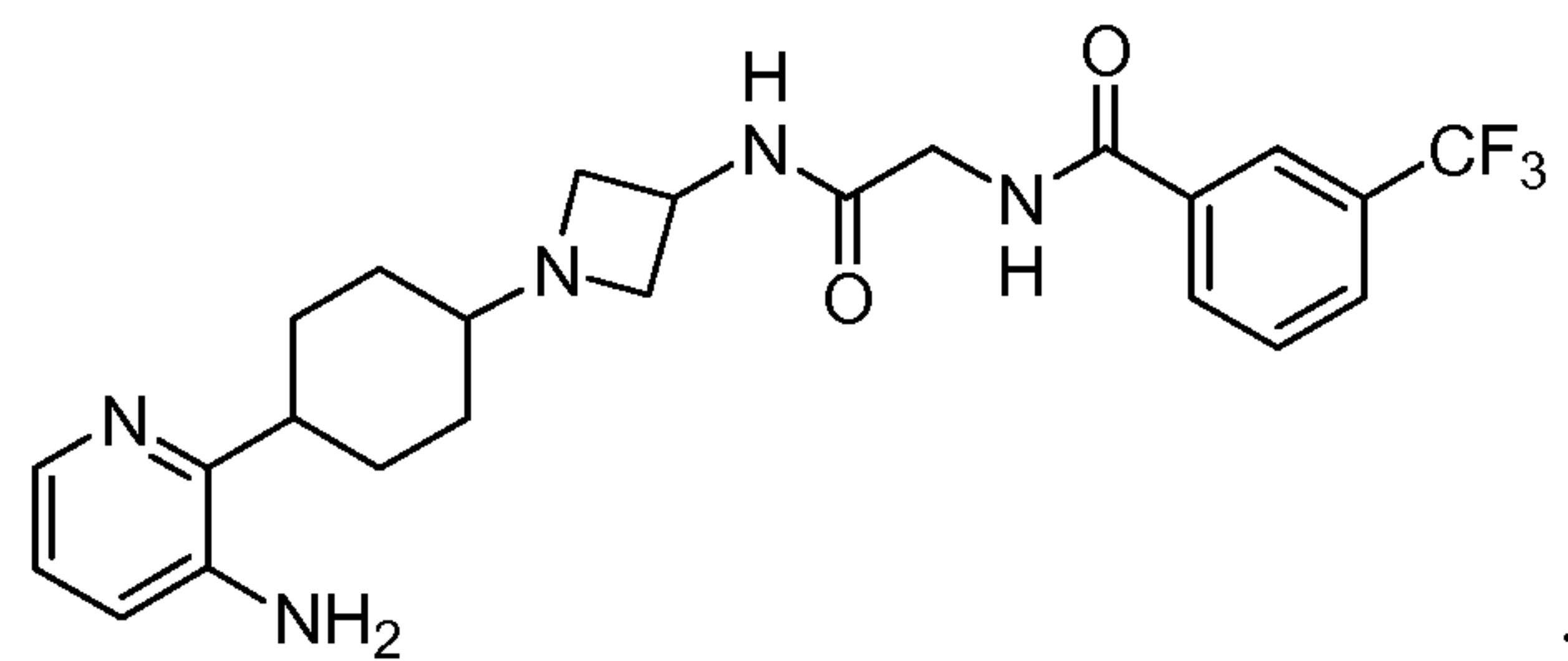
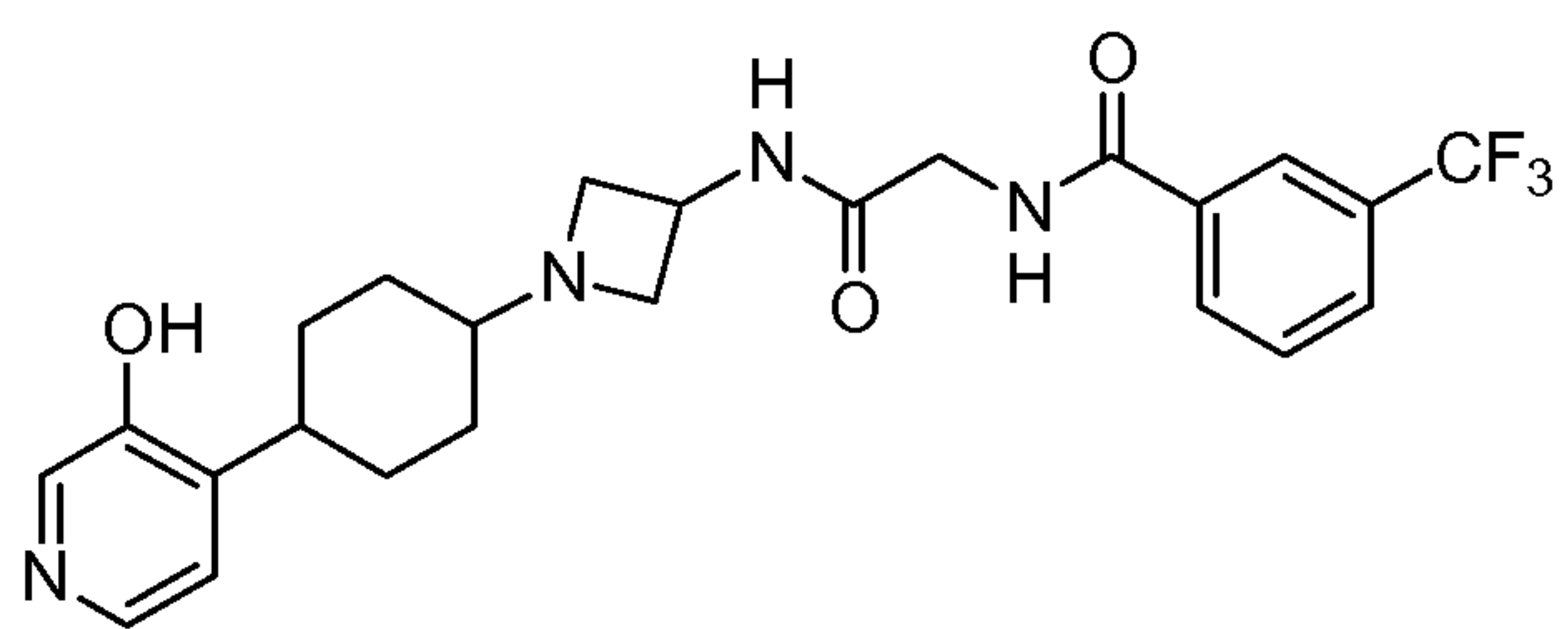
and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

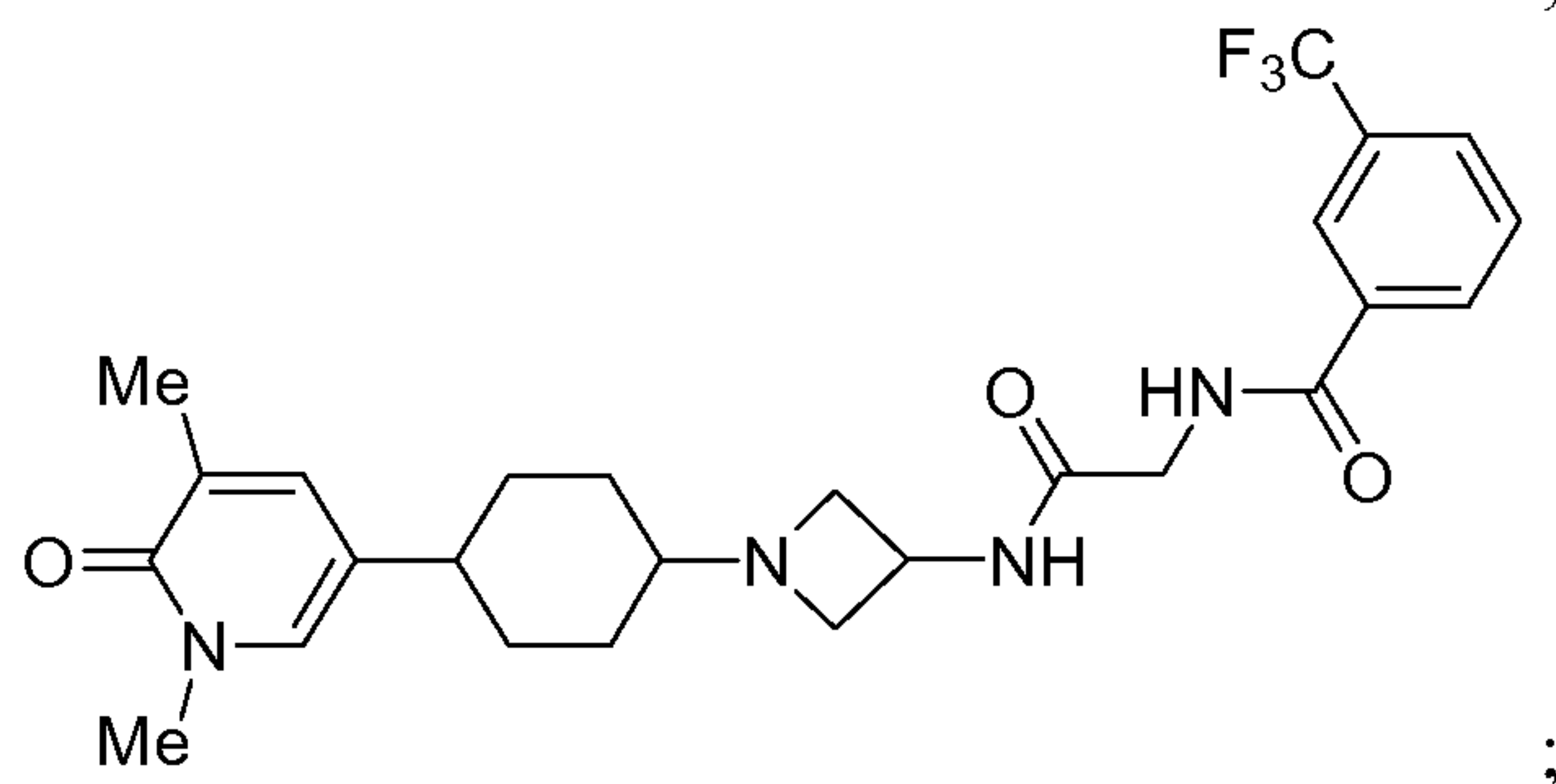
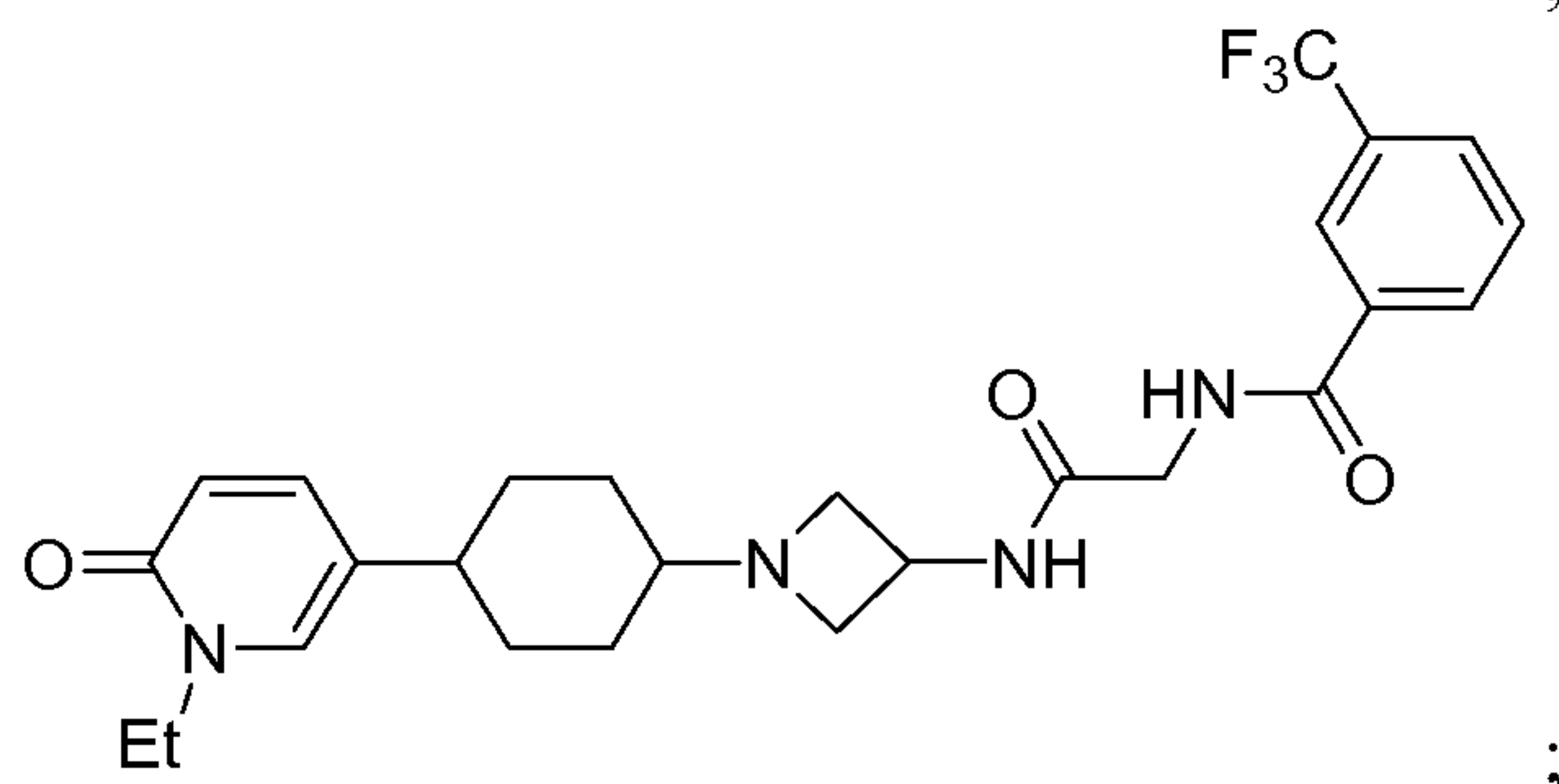
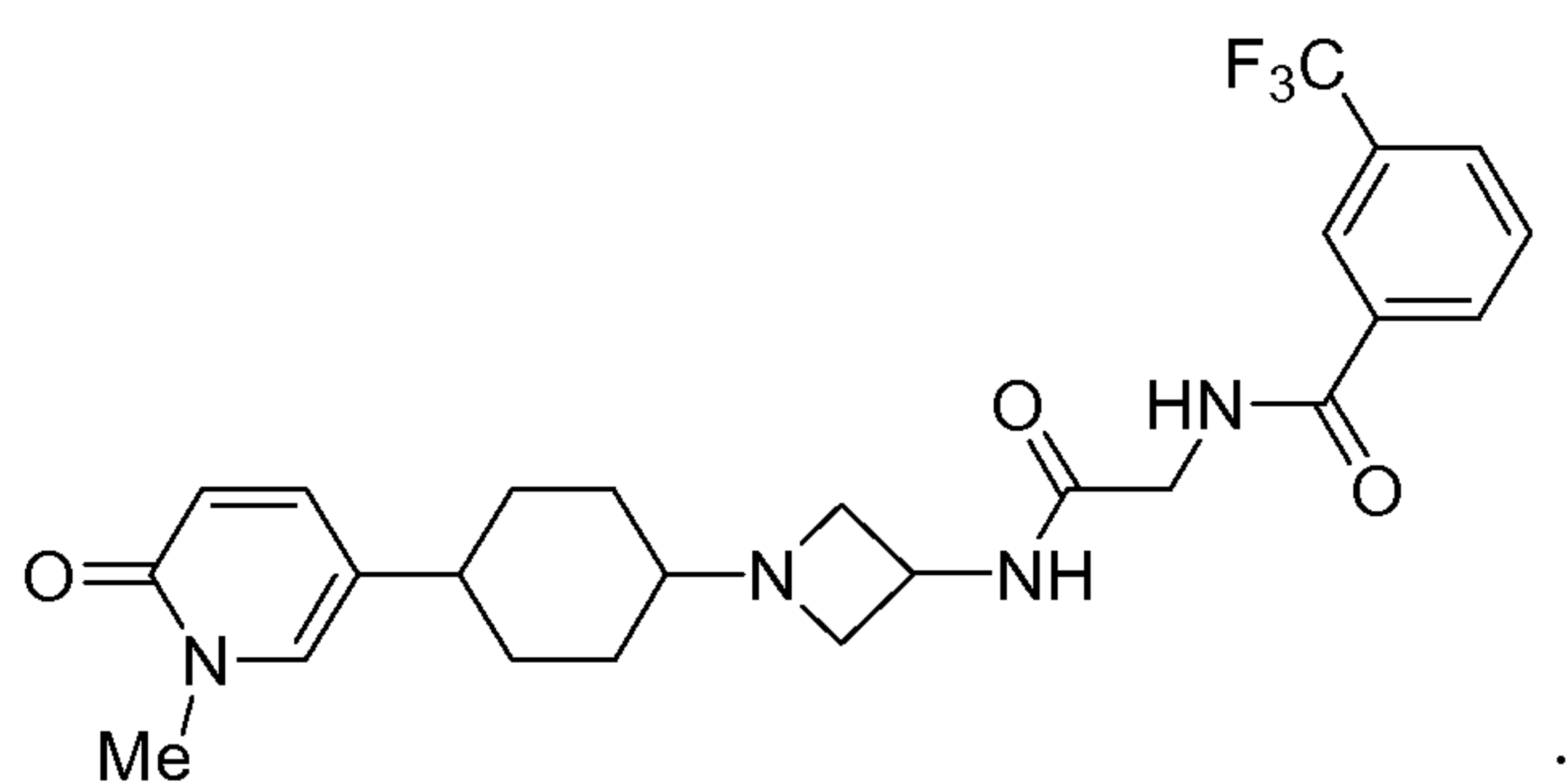
7. A compound of claim 6 selected from the group consisting of:

10



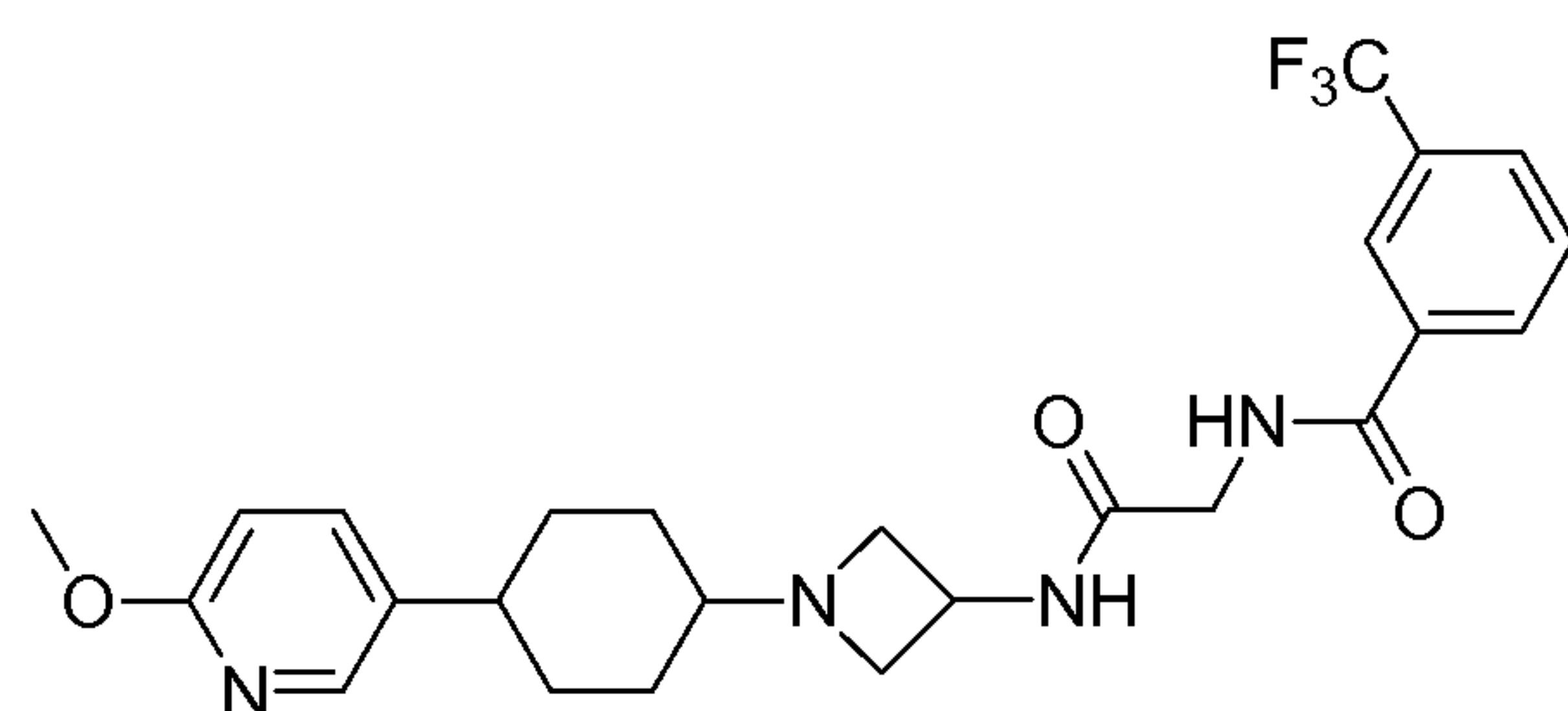






and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

8. A compound of claim 7, which is



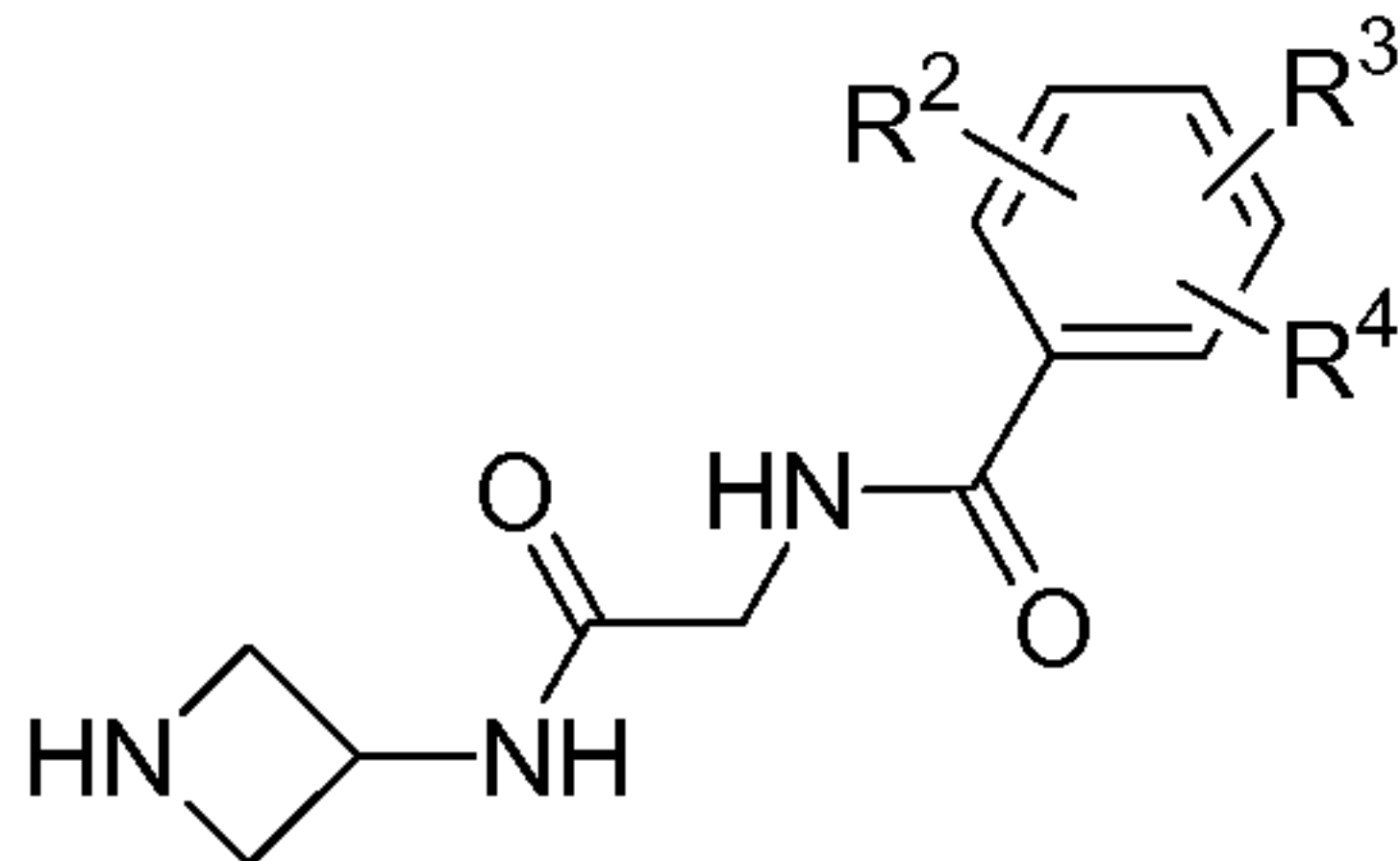
and solvates, hydrates, tautomers, prodrugs, and pharmaceutically acceptable salts thereof.

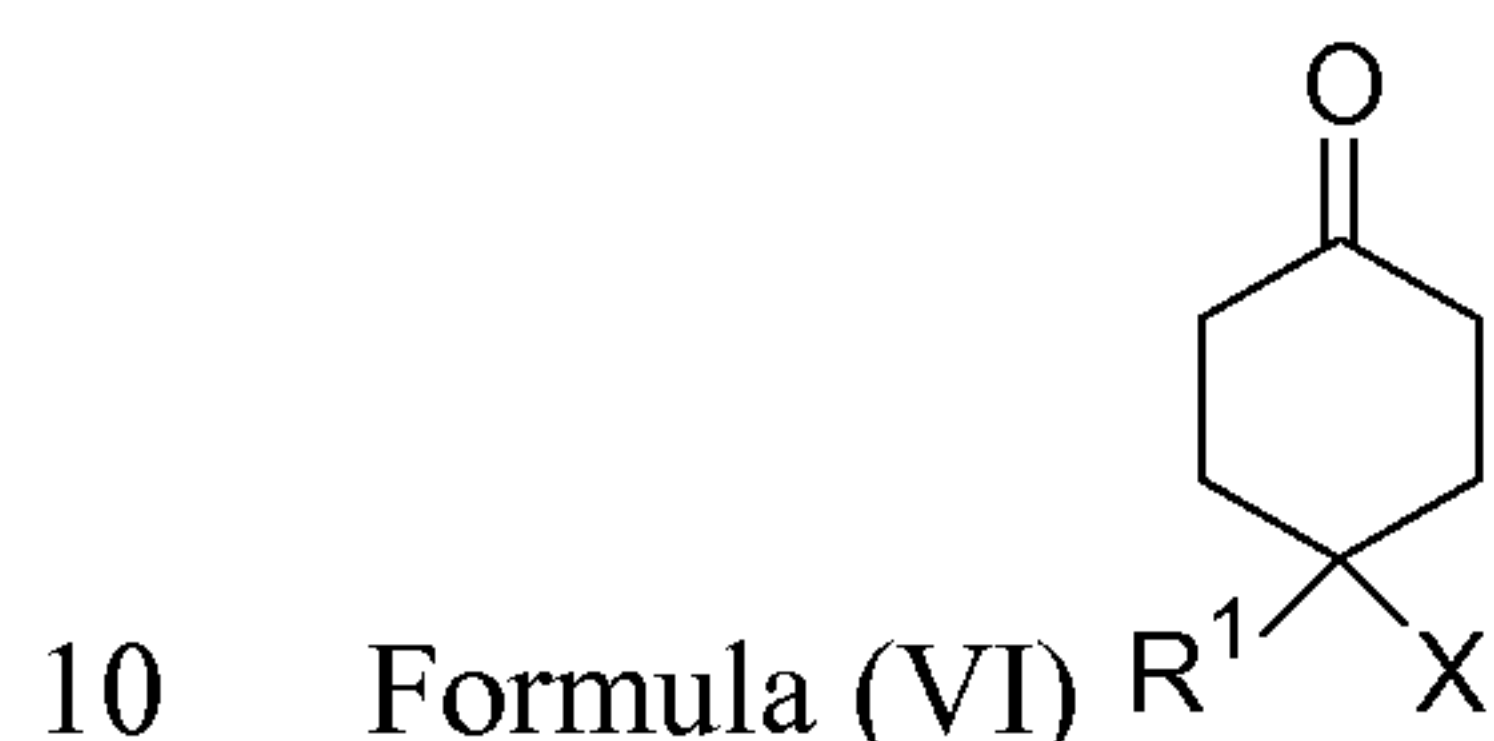
9. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition made by mixing a compound of claim 1 and a pharmaceutically acceptable carrier.

5 11. A process for making a pharmaceutical composition comprising mixing a compound of claim 1 and a pharmaceutically acceptable carrier.

12. A process for the preparation of a compound of Formula (I) of claim 1, comprising

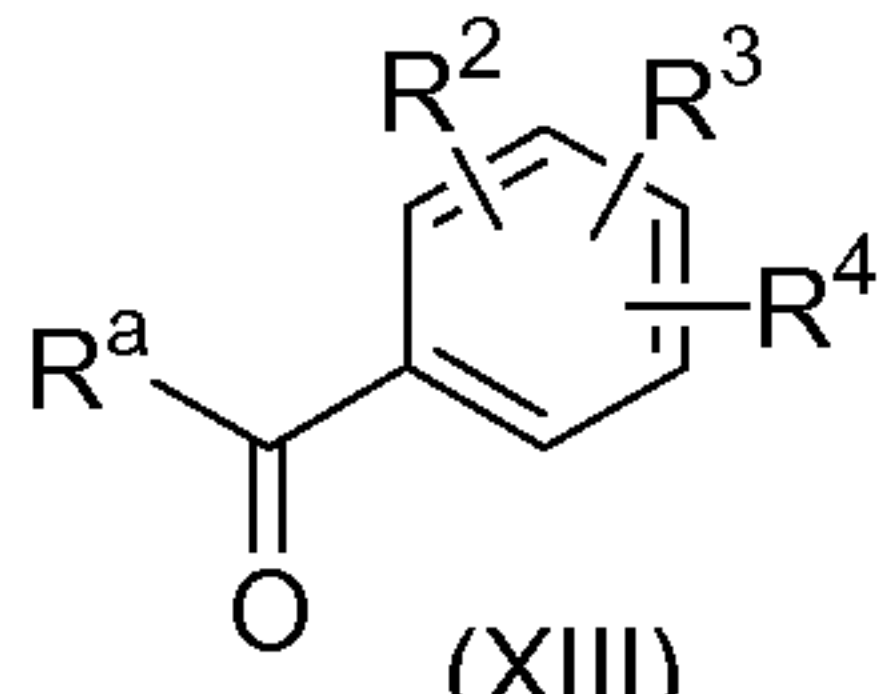
reacting a compound of Formula (V)  with a compound of

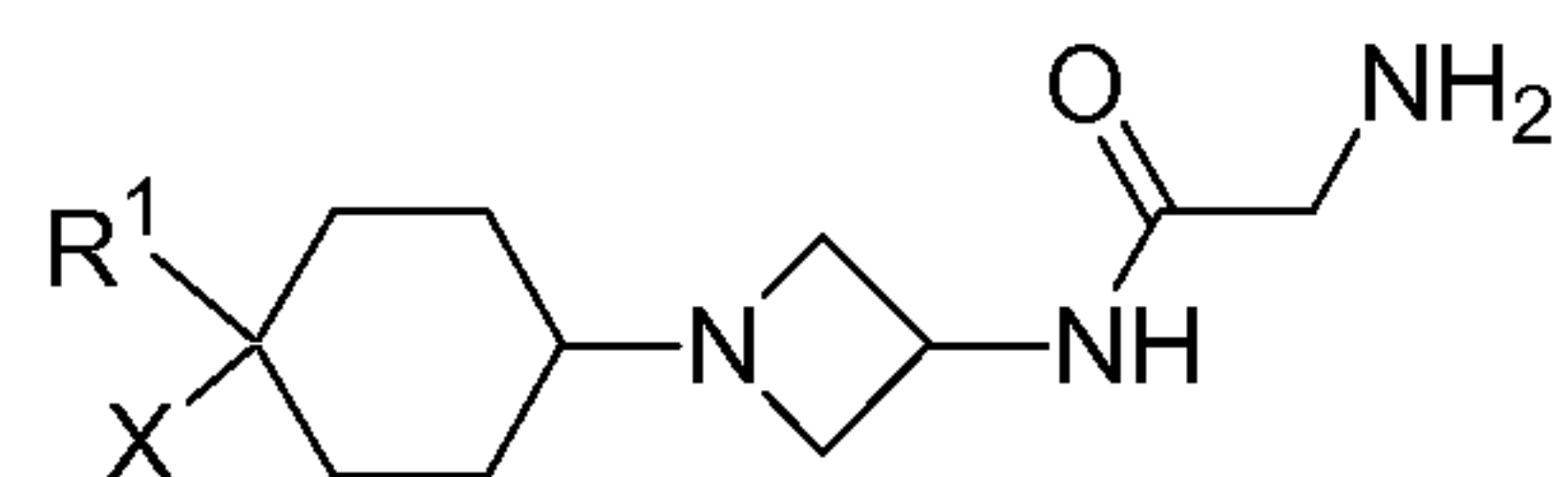


in the presence of a reducing agent to provide the compound of Formula (I).

13. A product made by the process of claim 12.

15 14. A process for the preparation of a compound of Formula (I) of claim 1, comprising

reacting a compound of Formula (XIII)  (XIII), where R_a is OH or Cl, with



in the presence of HOBt/EDCI or Et_3N to provide the compound of Formula (I).

20 15. A product made by the process of claim 14.

16. A method for preventing, treating or ameliorating a CCR2 mediated syndrome, disorder or disease comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

5 17. A method for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease wherein the syndrome, disorder or disease is associated with elevated MCP-1 expression or MCP-1 overexpression, or is an inflammatory condition that accompanies syndromes, disorders or diseases associated with elevated MCP-1 expression or MCP-1 overexpression comprising administering to a subject in
10 need thereof a therapeutically effective amount of a compound of claim 1.

18. A method of preventing, treating or ameliorating a syndrome, disorder or disease, wherein said syndrome, disorder or disease is selected from the group consisting of: Chronic Obstructive Pulmonary Disease (COPD), ophthalmic disorders, uveitis,
15 atherosclerosis, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, multiple sclerosis, Crohn's Disease, ulcerative colitis, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, type-I diabetes, type II diabetes and diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, overweight, obesity, obesity-associated insulin resistance, tuberculosis,
20 chronic obstructive pulmonary disease, sarcoidosis, invasive *staphylococci*, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, asthma, allergic asthma, periodontal diseases, periodontitis, gingivitis, gum disease, diastolic cardiomyopathies, cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, glomerulonephritis, solid tumors and
25 cancers, chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, and carcinomas of the bladder, breast, cervix, colon, lung, prostate, or stomach comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

30 19. A method of preventing, treating or ameliorating a syndrome, disorder or disease, wherein said syndrome, disorder or disease is selected from the group consisting of: type

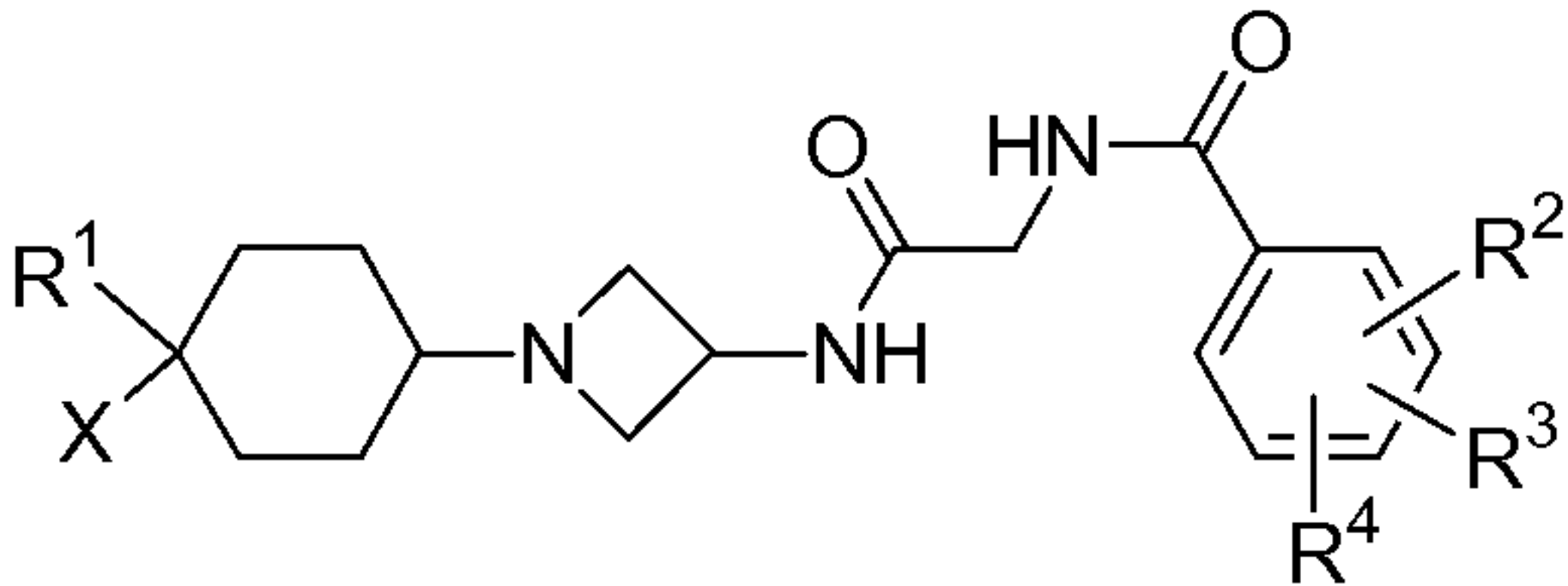
II diabetes and diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, obesity, asthma, and allergic asthma, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

5

20. A method of treating a disorder selected from the group consisting of type II diabetes, obesity and asthma comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

10 21. A compound of claim 1, which is the less polar isomer of any of Examples #1-64.

22. A compound of claim 1, which is the less polar isomer of Example #1.



(I)