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(54) Title: OXADIAZOLE COMPOUNDS WHICH INHIBIT BETA-SECRETASE ACTIVITY AND METHODS OF USE THEREOF

(57) Abstract: The invention provides novel beta-secretase inhibitors and methods for their including methods of treating Alzheimer's disease.



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## OXADIAZOLE COMPOUNDS WHICH INHIBIT BETA-SECRETASE ACTIVITY AND METHODS OF USE THEREOF

### CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of United States Provisional Application No. 61/394,680, filed on October 19, 2010, the content of which is incorporated by reference in its entirety.

### BACKGROUND OF THE INVENTION

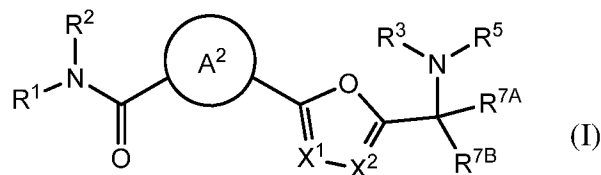
[0002] Alzheimer's disease is a progressive mental deterioration in a human resulting, *inter alia*, in loss of memory, confusion and disorientation. Alzheimer's disease accounts for the majority of senile dementias and is a leading cause of death in adults (Anderson, R. N., *Natl. Vital Stat. Rep.* 49:1-87 (2001), the teachings of which are incorporated herein in their entirety). Histologically, the brain of persons afflicted with Alzheimer's disease is characterized by a distortion of the intracellular neurofibrils and the presence of senile plaques composed of granular or filamentous argentophilic masses with an amyloid protein core, largely due to the accumulation of  $\beta$ -amyloid protein ( $A\beta$ ) in the brain.  $A\beta$  accumulation plays a role in the pathogenesis and progression of the disease (Selkoe, D.J., *Nature* 399: 23-31 (1999)) and is a proteolytic fragment of amyloid precursor protein (APP). APP is cleaved initially by  $\beta$ -secretase followed by  $\gamma$ -secretase to generate  $A\beta$  (Lin, X., *et al.*, *Proc. Natl. Acad. Sci. USA* 97:1456-1460 (2000); De Stropper, B., *et al.*, *Nature* 391:387-390 (1998)). Inhibitors of  $\beta$ -secretase are described in US 7,214,715; US 7,504,420; US 2007/0032470; WO 2002/02520; WO 2002/02505; WO 2002/02512; WO 2002/02518; WO 2003/040096; WO 2003/050073; WO 2003/072535; WO 2004/043916; WO 2004/050619; WO 2004/080376; WO 2005/030709; WO 2005/103020; WO 2006/034296; WO 2006/110668; WO 2009/015369; WO 2009/042694; Stachel, S.J., *J. Med. Chem.* 47, 6447-6450 (2004); Stachel, S.J., *Bioorg. Med. Chem. Lett.* 16, 641-644 (2006); and Varghese, J., *Curr. Top. Med. Chem.* 6: 569-578 (2006).

[0003] There is a need to develop effective compounds and methods for the treatment of Alzheimer's disease. The present invention fulfills these and other needs.

### BRIEF SUMMARY OF THE INVENTION

[0004] Disclosed are novel beta-secretase inhibitors and methods for their use, including methods of treating Alzheimer's disease.

[0005] In one aspect, the invent provides a compound of the formula (I):



wherein

- $R^1$  is  $A^1-L^1$ - or taken together with  $R^2$  and the nitrogen to which they are attached form a 5- or 6-membered heterocycloalkyl ring substituted with  $A^1-L^1$ -,  $R^{6A}$  and  $R^{6B}$ ;
- $R^2$  is hydrogen,  $-N(R^8)R^9$ ,  $-S(O)_2R^{11}$ ,  $-C(O)R^{12}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or taken together with  $R^1$  and the nitrogen to which they are attached form a 5- or 6-membered heterocycloalkyl ring substituted with  $A^1-L^1$ -,  $R^{6A}$  and  $R^{6B}$ ;
- $A^1$  is an optionally substituted heteroaryl;
- $L^1$  is a bond,  $-N(R^{17})$ -,  $-S$ -,  $-S(O)$ -,  $-S(O)_2$ -, or an optionally substituted alkylene;
- $R^{6A}$  and  $R^{6B}$  are independently hydrogen, halogen,  $-OH$ ,  $-NO_2$ ,  $-N(R^8)R^9$ ,  $-OR^{10}$ ,  $-SH$ ,  $-SR^{11}$ ,  $-S(O)R^{11}$ ,  $-S(O)_2R^{11}$ ,  $-C(O)R^{12}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl,  $-alkyl-OR^{10}$ ,  $-alkyl-N(R^8)R^9$ , heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl;
- $A^2$  is an optionally substituted moiety selected from cycloalkylene, heterocycloalkylene, arylene and heteroarylene;
- $X^1$  and  $X^2$  are independently N or CH;
- $R^3$  is hydrogen,  $-N(R^8)R^9$ ,  $-S(O)_2R^{11}$ ,  $-C(O)R^{12}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;
- $R^5$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl;

- $R^{7A}$  is an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, -alkyl-OR<sup>10</sup>, -alkyl-N(R<sup>8</sup>)R<sup>9</sup>, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl, or taken together with R<sup>7B</sup> and the carbon to which they are attached form a cycloalkyl ring substituted with R<sup>4</sup>-L<sup>4</sup>;
- R<sup>7B</sup> is R<sup>4</sup>-L<sup>4</sup>- or taken together with R<sup>7A</sup> and the carbon to which they are attached form a cycloalkyl ring substituted with R<sup>4</sup>-L<sup>4</sup>;
- R<sup>4</sup> is hydrogen, halogen, -OH, -NO<sub>2</sub>, -N(R<sup>8</sup>)R<sup>9</sup>, -OR<sup>10</sup>, -SH, -SR<sup>11</sup>, -S(O)R<sup>11</sup>, -S(O)<sub>2</sub>R<sup>11</sup>, -C(O)R<sup>12</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, -alkyl-OR<sup>10</sup>, -alkyl-N(R<sup>8</sup>)R<sup>9</sup>, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl;
- L<sup>4</sup> is a bond or an optionally substituted alkylene;
- R<sup>8</sup> is independently hydrogen, -C(O)R<sup>13</sup>, -S(O)<sub>2</sub>R<sup>14</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;
- R<sup>9</sup> is independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;
- R<sup>10</sup> is independently -C(O)R<sup>13</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;
- R<sup>11</sup> is independently an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, wherein if attached to S(O)<sub>2</sub>, R<sup>11</sup> can also be -NR<sup>15</sup>R<sup>16</sup>;
- R<sup>12</sup> and R<sup>13</sup> are each independently hydrogen, -N(R<sup>18</sup>)R<sup>19</sup>, -OR<sup>19</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;



$R^{14}$  is independently hydrogen,  $-N(R^{18})R^{19}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; and  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ , and  $R^{19}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

provided that when  $R^3$  and  $R^5$  are both hydrogen, one of  $R^{7A}$  and  $R^{7B}$  is methyl and the other is benzyl, each  $X^1$  and  $X^2$  is N,  $A^2$  is 5-substituted-1,3-phenylene and  $R^1$  is taken together with  $R^2$  and the nitrogen to which they are attached to form a 5-membered heterocycloalkyl ring, the 5-membered heterocycloalkyl ring formed by taking  $R^1$  together with  $R^2$  and the nitrogen to which they are attached is a moiety other than a 2-substituted-pyrrolidinyl substituted with 5-chlorofuran-2-yl, 5-methylfuran-2-yl, 3-pyridyl or 5-bromo-3-pyridyl;

or a pharmaceutically acceptable salt or solvate thereof.

**[0006]** In one embodiment, the  $\beta$ -secretase inhibitor compound includes any one, any combination, or all of the compounds of Example 2 and/or Table 1; or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound has a memapsin 2  $K_i$  of less than about 300 nM. In some embodiments, the compound has an apparent memapsin 2  $K_i$  of less than about 300 nM as measured by inhibition of memapsin 2 catalytic activity toward the fluorogenic substrate FS-2 (MCA-SEVNLDAEFK-DNP; SEQ ID NO.: 2). In some embodiments, the compound is capable of inhibiting cellular  $A\beta$  production with an  $IC_{50}$  of less than about 1.5  $\mu$ M, or less than about 500 nM. In some embodiments, the compound has a memapsin 1  $K_i$  and/or cathepsin D  $K_i$  of greater than about 300 nM. In some embodiments, the compound has an apparent memapsin 1  $K_i$  and/or apparent cathepsin D  $K_i$  of greater than about 300 nM, as measured by the substrate peptide MCA-GKPILFFRLK(DNP)-dR (SEQ ID NO.: 1). In some embodiments, the compound has a CYP 3A  $K_i$  of greater than about 1  $\mu$ M, or greater than 5  $\mu$ M, or greater than 10  $\mu$ M, as determined by the metabolism of midazolam. In some embodiments, the compound is capable of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 catalytic activity. In some embodiments, the compound is capable of selectively reducing memapsin 2 catalytic activity relative to cathepsin D catalytic activity. In some embodiments, the compound is

capable of selectively reducing memapsin 2 catalytic activity relative to CYP3A catalytic activity. In some of these embodiments, the relative reduction is greater than about 5-fold. In other embodiments, the reduction is greater than about 10-fold. In another embodiment, the  $\beta$ -secretase inhibitor compound (a) has a memapsin 2  $K_i$  of less than about 750 nM (or less than about any one of 500 nM, 300 nM, 250 nM, 100 nM, 50 nM, or 10 nM); (b) is capable of inhibiting cellular A $\beta$  production with an  $IC_{50}$  of less than about 1.5  $\mu$ M (or less than about any one of 1  $\mu$ M, 500 nM, 250 nM, 100 nM, 40 nM, or 10 nM); (c) is capable of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 or cathepsin D catalytic activity by greater than about 5-fold (or greater than about 10-fold, or about 100-fold), and/or (d) is capable of selectively reducing memapsin 2 catalytic activity relative to CYP3A catalytic activity by greater than about 5-fold (or greater than about 10-fold, or about 100-fold). In some embodiments, the compound has a hepatic intrinsic clearance in liver microsomes of less than about 700 mL/min/kg, or less than about 400 mL/min/kg, as measured by LC/MS/MS. In some embodiments, the compound has an AUC more than 50 hr·ng/ml, or more than 500 hr·ng/ml, as measured in rats after an oral dose of 10 mg/kg of the drug is administered.

[0007] In another aspect, is provided any one of the  $\beta$ -secretase inhibitor compounds is present in substantially pure form.

[0008] In another aspect, provided are formulations comprising any one of the  $\beta$ -secretase inhibitor compounds described herein and a carrier (*e.g.*, a pharmaceutically acceptable carrier). In some embodiments, the formulation is suitable for administration to an individual.

[0009] In another aspect, provided are formulations comprising an effective amount of any one of the  $\beta$ -secretase inhibitor compounds described herein and a carrier (*e.g.*, a pharmaceutically acceptable carrier).

[0010] In another aspect, provided are pharmaceutical formulations comprising a  $\beta$ -secretase inhibitor compound or a  $\beta$ -secretase inhibitor compound in combination with a pharmaceutically acceptable carrier.

[0011] In another aspect, provided are methods of treating Alzheimer's disease in an individual in need thereof, comprising administering to the individual an effective amount of any one of the  $\beta$ -secretase inhibitor compounds described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the

individual has one or more symptoms of Alzheimer's disease. In some embodiments, the individual has been diagnosed with Alzheimer's disease.

**[0012]** In another aspect is provided methods of treating of a condition mediated by memapsin 2 catalytic activity, comprising administering to the individual an effective amount of any one of the  $\beta$ -secretase inhibitor compounds described herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the individual has one or more symptoms of the condition mediated by memapsin 2 catalytic activity. In some embodiments, the individual has been diagnosed with condition mediated by memapsin 2 catalytic activity.

**[0013]** In another aspect is provided methods of reducing memapsin 2 catalytic activity, comprising contacting memapsin 2 with an effective amount of any one of the  $\beta$ -secretase inhibitor compounds described herein. In some variations, the memapsin 2 beta-secretase is contacted in a cell. In some embodiments, the cell is contacted *in vivo*. In some embodiments, the cell is contacted *in vitro*.

**[0014]** In another aspect is provided methods of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 catalytic activity, comprising contacting memapsin 2 with an effective amount of any one of the  $\beta$ -secretase inhibitor compounds described herein in the presence of memapsin 1.

**[0015]** In another aspect is provided methods of selectively reducing memapsin 2 catalytic activity relative to cathepsin D catalytic activity, comprising contacting memapsin 2 with an effective amount of any one of the  $\beta$ -secretase inhibitor compounds described herein in the presence of cathepsin D.

**[0016]** In another aspect is provided methods of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 catalytic activity and cathepsin D catalytic activity, comprising contacting memapsin 2 with an effective amount of any one of the  $\beta$ -secretase inhibitor compounds described herein in the presence of memapsin 1 and cathepsin D.

**[0017]** In another aspect is provided methods of selectively reducing memapsin 2 catalytic activity relative to CYP3A4 catalytic activity, comprising contacting memapsin 2 with an effective amount of any one of the  $\beta$ -secretase inhibitor compounds described herein in the presence of CYP3A4.

**[0018]** In another aspect is provided methods of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 catalytic activity, cathepsin D catalytic activity, and CYP3A4 catalytic activity, comprising contacting memapsin 2 with an effective amount of any one of

the  $\beta$ -secretase inhibitor compounds described herein in the presence of memapsin 1, cathepsin D, and CYP3A4.

**[0019]** In another aspect is provided methods of treating Glaucoma in an individual in need thereof, comprising administering to the individual an effective amount of any one of the  $\beta$ -secretase inhibitor compounds described herein. In some embodiments, the individual has one or more symptoms of glaucoma. In some embodiments, the individual has been diagnosed with Glaucoma.

**[0020]** In another aspect is provided any one of the  $\beta$ -secretase inhibitor compounds described herein or a pharmaceutically acceptable salt or solvate thereof for use as a medicament. Also provided is any one of the  $\beta$ -secretase inhibitor compounds described herein or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of Glaucoma in an individual in need thereof.

**[0021]** Another aspect is provided the use of any one of the  $\beta$ -secretase inhibitor compounds described herein or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment or prevention of a condition mediated by memapsin 2 catalytic activity. In another aspect is provided the use of one or more of the  $\beta$ -secretase inhibitor compounds described herein or a pharmaceutically acceptable salt or solvate thereof for the treatment or prevention of a condition mediated by memapsin 2 catalytic activity. In some variations, the condition is Alzheimer's disease.

**[0022]** In another aspect is provided kits for the treatment or prevention in an individual with Alzheimer's disease, comprising any one of the  $\beta$ -secretase inhibitor compounds described herein or a pharmaceutically acceptable salt or solvate thereof; and packaging. In some embodiments, the kit comprises a formulation of any one of the compounds described herein or a pharmaceutically acceptable salt or solvate thereof; and packaging.

**[0023]** In another aspect is provided kits for the treatment or prevention in an individual of a condition mediated by memapsin 2 catalytic activity, comprising any one of the  $\beta$ -secretase inhibitor compounds described herein or a pharmaceutically acceptable salt or solvate thereof; and packaging. In some embodiments, the kit comprises a formulation of any one of the compounds described herein or a pharmaceutically acceptable salt or solvate thereof; and packaging.

**[0024]** In another aspect, the  $\beta$ -secretase inhibitor compounds can be employed in methods to mediate memapsin 2 activity, *e.g.*, decrease memapsin 2 activity, decrease hydrolysis of a  $\beta$ -secretase site of a memapsin 2 substrate, and/or decrease the accumulation of  $\beta$ -amyloid

protein relative to the amount of memapsin 2 activity, hydrolysis of a  $\beta$ -secretase site, and accumulation of  $\beta$ -amyloid protein, respectively, in the absence of the  $\beta$ -secretase inhibitor.

[0025] In another aspect, the  $\beta$ -secretase inhibitor compounds can be employed in the treatment of diseases or conditions associated with  $\beta$ -secretase activity, hydrolysis of a  $\beta$ -secretase site of a  $\beta$ -amyloid precursor protein, and/or  $\beta$ -amyloid protein accumulation. Typically, a mammal is treated for the disease or condition. In an exemplary embodiment, the disease is Alzheimer's disease.

## DETAILED DESCRIPTION OF THE INVENTION

[0026] The invention provides, *inter alia*, compositions of beta-secretase inhibitors and methods for their use, e.g. methods of treating Alzheimer's disease.

[0027] Abbreviations and Definitions

[0028] The abbreviations used herein have their conventional meaning within the chemical and biological arts, unless otherwise specified.

[0029] Nomenclature of some compounds described herein (e.g., some compounds described in Example 2 and Table 1) may be identified using IUPAC or other naming conventions including ChemDraw Ultra Version 12.0, available from CambridgeSoft®.

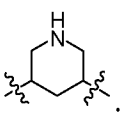
[0030] Where substituent groups are specified by their conventional chemical formula, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*,  $-\text{CH}_2\text{O}-$  is equivalent to  $-\text{OCH}_2-$ .

[0031] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (*i.e.* unbranched) or branched hydrocarbon chain, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.*  $\text{C}_1\text{-C}_{10}$  means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker ( $-\text{O}-$ ).

**[0032]** The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkyl, as exemplified, but not limited, by  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ . Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms. In some embodiments, an alkyl group will have from 1 to 6 carbon atoms. In some embodiments, the alkylene groups are methylene and methylenemethylene.

**[0033]** The term "cycloalkyl" by itself or in combination with other terms, represents, unless otherwise stated, cyclic versions of "alkyl." Additionally, cycloalkyl may contain multiple rings, but excludes aryl and heteroaryl groups. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, norbornyl, and the like. The term "cycloalkylene" by itself or as part of another substituent means a divalent radical derived from a cycloalkyl, as exemplified, but not limited, by  $-\text{cyclohexyl}-$ .

**[0034]** The term "heterocycloalkyl," by itself or in combination with other terms, represents a stable saturated or unsaturated cyclic hydrocarbon radical containing of at least one carbon atom and at least one annular heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S and Si may be placed at any interior position of the heterocycloalkyl group or at the position at which the heterocycloalkyl group is attached to the remainder of the molecule. Additionally, heterocycloalkyl may contain multiple rings, but excludes aryl and heteroaryl groups. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. The term "heterocycloalkylene" by itself or as part of another substituent means a divalent radical derived from a heterocycloalkyl, as exemplified, but not

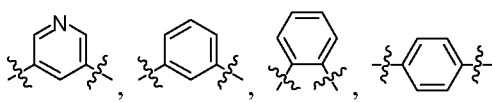
limited, by .

**[0035]** The term "cycloalkyl-alkyl" and "heterocycloalkyl-alkyl" designates an alkyl-substituted cycloalkyl group and alkyl-substituted heterocycloalkyl, respectively, where the alkyl portion is attached to the parent structure. Non-limiting examples include cyclopropyl-ethyl, cyclobutyl-propyl, cyclopentyl-hexyl, cyclohexyl-isopropyl, 1-cyclohexenyl-propyl, 3-cyclohexenyl-t-butyl, cycloheptyl-heptyl, norbornyl-methyl, 1-piperidinyl-ethyl, 4-morpholinyl-propyl, 3-morpholinyl-t-butyl, tetrahydrofuran-2-yl-hexyl, tetrahydrofuran-3-yl-

isopropyl, and the like. Cycloalkyl-alkyl and heterocycloalkyl-alkyl also include substituents in which a carbon atom of the alkyl group (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, cyclopropoxymethyl, 2-piperidinyloxy-*t*-butyl, and the like).

**[0036]** The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent. Aryl may contain additional fused rings (*e.g.*, from 1 to 3 rings), including additionally fused aryl, heteroaryl, cycloalkyl, and/or heterocycloalkyl rings. Examples of aryl groups include, but are not limited to, phenyl, 1-naphthyl, 2-naphthyl, and 4-biphenyl. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four annular heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule at an annular carbon or annular heteroatom. Heteroaryl may contain additional fused rings (*e.g.*, from 1 to 3 rings), including additionally fused aryl, heteroaryl, cycloalkyl, and/or heterocycloalkyl rings. Non-limiting examples of heteroaryl groups are 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for substituted aryl and heteroaryl ring systems are described below.

**[0037]** The term "arylene" and "heteroarylene" means a divalent radical derived from an aryl and heteroaryl, respectively. Each of the two valencies of arylene and heteroarylene may

be located at any portion of the ring (*e.g.*, , and



). Non-limiting examples of arylene include phenylene, biphenylene, naphthylene, and the like. Examples of heteroarylene groups include, but are not limited to, pyridinylene, oxazolylene, thioazolylene, pyrazolylene, pyranylene, imidazolylene, and furanylene.

**[0038]** The term "aralkyl" designates an alkyl-substituted aryl group, where the alkyl portion is attached to the parent structure. Examples are benzyl, phenethyl, phenylvinyl, phenylallyl, pyridylmethyl, and the like. "Heteroaralkyl" designates a heteroaryl moiety attached to the parent structure via an alkyl residue. Examples include furanylmethyl, pyridinylmethyl, pyrimidinylethyl, and the like. Aralkyl and heteroaralkyl also include

substituents in which a carbon atom of the alkyl group (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

**[0039]** The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C<sub>1</sub>-C<sub>4</sub>)alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

**[0040]** The term "substituted" refers to the replacement of one or more hydrogen atoms of a moiety with a monovalent or divalent radical. "Optionally substituted" indicates that the moiety may be substituted or unsubstituted. A moiety lacking the terms "optionally substituted" and "substituted" is intended an unsubstituted moiety (*e.g.*, "phenyl" is intended an unsubstituted phenyl unless indicated as a substituted phenyl or an optionally substituted phenyl).

**[0041]** The terms, "pharmaceutically effective amount," "therapeutically effective amount," "effective amount," and cognates of these terms, as used herein refer to an amount that results in a desired pharmacological and/or physiological effect for a specified condition (*e.g.*, disease, disorder, etc.) or one or more of its symptoms and/or to completely or partially prevent the occurrence of the condition or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for the condition and/or adverse effect attributable to the condition. In reference to conditions mediated by memapsin 2 beta-secretase, a pharmaceutically or therapeutically effective amount comprises an amount sufficient to, among other things, cause antagonism of memapsin 2 beta-secretase. In reference to glaucoma, a pharmaceutically or therapeutically effective amount comprises an amount sufficient to, among other things, decrease intraocular pressure; and/or halt, reverse, and/or diminish the loss of retinal ganglion cells (RGCs). In certain embodiments, the pharmaceutically effective amount is sufficient to prevent the condition, as in being administered to an individual prophylactically.

**[0042]** The "pharmaceutically effective amount" or "therapeutically effective amount" will vary depending on the composition being administered, the condition being treated/prevented, the severity of the condition being treated or prevented, the age and relative health of the individual, the route and form of administration, the judgment of the



attending medical or veterinary practitioner, and other factors appreciated by the skilled artisan in view of the teaching provided herein.

**[0043]** A "pharmaceutically suitable carrier" or "pharmaceutically acceptable carrier," as used herein refers to pharmaceutical excipients, for example, pharmaceutically, physiologically, acceptable organic, or inorganic carrier substances suitable for enteral or parenteral application which do not deleteriously react with the extract.

**[0044]** When used with respect to methods of treatment/prevention and the use of the compounds and compositions thereof described herein, an individual "in need thereof" may be an individual who has been diagnosed with or previously treated for the condition to be treated. With respect to prevention, the individual in need thereof may also be an individual who is at risk for a condition (*e.g.*, a family history of the condition, life-style factors indicative of risk for the condition, etc.).

**[0045]** In some variations, the individual has been identified as having one or more of the conditions described herein. Identification of the conditions as described herein by a skilled physician is routine in the art and may also be suspected by the individual or others, for example, due to loss of memory in the case of Alzheimer's, exhibiting the symptoms of schizophrenia, etc., and due to a decrease and/or loss of contrast sensitivity or vision in the case of Glaucoma.

**[0046]** In some embodiments, the individual has been identified as susceptible to one or more of the conditions as described herein. The susceptibility of an individual may be based on any one or more of a number of risk factors and/or diagnostic approaches appreciated by the skilled artisan, including, but not limited to, genetic profiling, family history, medical history (*e.g.*, appearance of related conditions), lifestyle or habits.

**[0047]** In some embodiments, the individual is a mammal, including, but not limited to, bovine, horse, feline, rabbit, canine, rodent, or primate. In some embodiments, the mammal is a primate. In some embodiments, the primate is a human. In some embodiments, the individual is human, including adults, children and premature infants. In some embodiments, the individual is a non-mammal. In some variations, the primate is a non-human primate such as chimpanzees and other apes and monkey species. In some embodiments, the mammal is a farm animal such as cattle, horses, sheep, goats, and swine; pets such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs; and the like. Examples of non-mammals include, but are not limited to, birds, and the like. The term "individual" does not denote a particular age or sex.

**[0048]** “Pharmaceutically acceptable salts” are those salts which retain the biological activity and which can be administered as drugs or pharmaceuticals to and individual (*e.g.*, a human).

**[0049]** As used herein, “isomer” includes all stereoisomers of the compounds referred to in the formulas herein, including enantiomers, diastereomers, as well as all conformers, rotomers, and tautomers.

**[0050]** “Amyloid precursor protein,” or “APP,” as used herein, refers to a  $\beta$ -amyloid precursor comprising a  $\beta$ -secretase site.

**[0051]** “Memapsin-2,” as used herein, refers to proteins identified by National Center for Biotechnology Information (“NCBI”) accession number NP\_036236 (sometimes referred to as “ $\beta$ -site APP-cleaving enzyme 1” or “BACE-1” or generically as “ $\beta$ -secretase” or “beta-secretase”), including homologs, isoforms and subdomains thereof that retain proteolytic activity. Sequence identities of active memapsin 2 proteins and protein fragments (and nucleic acid coding sequences thereof) have been previously disclosed and discussed in detail in U.S. Application No. 20040121947, and International Application No. PCT/USO2/34324 (Publication No. WO 03/039454), which are herein incorporated by reference for all purposes in their entirety.

**[0052]** “Memapsin-1,” as used herein, refers to proteins identified by National Center for Biotechnology Information (“NCBI”) accession number NP\_036237 (sometimes referred to as “ $\beta$ -site APP-cleaving enzyme 2” or “BACE-2”) and/or those previously disclosed and discussed in detail in see U.S. Patent Application Publication No. 20040121947, and International Application No. PCT/USO2/34324 (Publication No. WO 03/039454), incorporated by reference herein in their entirety for all purposes, including homologs, isoforms and subdomains thereof that retain proteolytic activity.

**[0053]** “Cathepsin D,” as used herein, refers to proteins identified by National Center for Biotechnology Information (“NCBI”), for example accession number NP\_599161, and/or proteins identified by Enzyme Commission number EC3.4.23.5, including that from any species, homologs, isoforms, and subdomains thereof that retain proteolytic activity.

**[0054]** A “ $\beta$ -secretase site” is an amino acid sequence that is cleaved by an active memapsin 2 or active fragment thereof. Specific  $\beta$ -secretase sites have also been previously set forth and discussed in detail in U.S. Application No. 20040121947, and International Application No. PCT/USO2/34324 (Publication No. WO 03/039454), which are herein incorporated by reference for all purposes in their entirety, and include the Swedish mutation

sequence, and the native  $\beta$ -amyloid precursor protein cleavage sequence. Thus,  $\beta$ -secretase inhibitors may be tested for their ability to decrease the hydrolysis of the  $\beta$ -secretase site of a substrate, such as the  $\beta$ -amyloid precursor protein, compounds of  $\beta$ -amyloid precursor protein, or fragments of  $\beta$ -amyloid precursor protein.

**[0055]** A "beta-secretase inhibitor" (i.e.  $\beta$ -secretase inhibitor) refers to a compound capable of reducing the proteolytic activity of memapsin-2 relative to the activity in the absence of inhibitor.

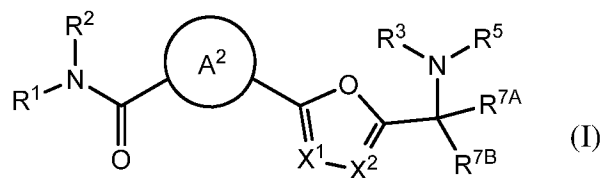
**[0056]** "Cytochrome P450 3A4" or "CYP3A4," as used herein refers to proteins identified by Genbank Sequence Accession Number: AF280107; HGNC:2637; Enzyme ID: 1.1.1.161, e.g., which can be found in the product *InVitroCYP™M-class™* Human Liver Microsomes from Celsis.

**[0057]** Reference to "about" a value or parameter herein includes (and describes) variations that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

**[0058]** The terms "a" or "an," as used in herein means one or more.

### *I. $\beta$ -Secretase Inhibitors*

**[0059]** In one aspect, is provided compounds that mediate (e.g., inhibit) the catalytic activity of the  $\beta$ -secretase enzyme (memapsin 2). These compounds may be referred to herein as " $\beta$ -secretase inhibitor compounds," or "memapsin 2  $\beta$ -secretase inhibitors." In this aspect, the compounds have the formula (I):



wherein

$R^1$  is  $A^1-L^1$ - or taken together with  $R^2$  and the nitrogen to which they are attached form a 5- or 6-membered heterocycloalkyl ring substituted with  $A^1-L^1$ -,  $R^{6A}$  and  $R^{6B}$ ;

$R^2$  is hydrogen,  $-N(R^8)R^9$ ,  $-S(O)_2R^{11}$ ,  $-C(O)R^{12}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or taken

together with R<sup>1</sup> and the nitrogen to which they are attached form a 5- or 6-membered heterocycloalkyl ring substituted with A<sup>1</sup>-L<sup>1</sup>-, R<sup>6A</sup> and R<sup>6B</sup>;

A<sup>1</sup> is an optionally substituted heteroaryl;

L<sup>1</sup> is a bond, -N(R<sup>17</sup>)-, -S-, -S(O)-, -S(O)<sub>2</sub>-, or an optionally substituted alkylene;

R<sup>6A</sup> and R<sup>6B</sup> are independently hydrogen, halogen, -OH, -NO<sub>2</sub>, -N(R<sup>8</sup>)R<sup>9</sup>, -OR<sup>10</sup>, -SH, -SR<sup>11</sup>, -S(O)R<sup>11</sup>, -S(O)<sub>2</sub>R<sup>11</sup>, -C(O)R<sup>12</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, -alkyl-OR<sup>10</sup>, -alkyl-N(R<sup>8</sup>)R<sup>9</sup>, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl;

A<sup>2</sup> is an optionally substituted moiety selected from cycloalkylene, heterocycloalkylene, arylene and heteroarylene;

X<sup>1</sup> and X<sup>2</sup> are independently N or CH;

R<sup>3</sup> is hydrogen, -N(R<sup>8</sup>)R<sup>9</sup>, -S(O)<sub>2</sub>R<sup>11</sup>, -C(O)R<sup>12</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

R<sup>5</sup> is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl;

R<sup>7A</sup> is an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, -alkyl-OR<sup>10</sup>, -alkyl-N(R<sup>8</sup>)R<sup>9</sup>, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl, or taken together with R<sup>7B</sup> and the carbon to which they are attached form a cycloalkyl ring substituted with R<sup>4</sup>-L<sup>4</sup>-;

R<sup>7B</sup> is R<sup>4</sup>-L<sup>4</sup>- or taken together with R<sup>7A</sup> and the carbon to which they are attached form a cycloalkyl ring substituted with R<sup>4</sup>-L<sup>4</sup>-;

R<sup>4</sup> is hydrogen, halogen, -OH, -NO<sub>2</sub>, -N(R<sup>8</sup>)R<sup>9</sup>, -OR<sup>10</sup>, -SH, -SR<sup>11</sup>, -S(O)R<sup>11</sup>, -S(O)<sub>2</sub>R<sup>11</sup>, -C(O)R<sup>12</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, -alkyl-OR<sup>10</sup>, -alkyl-N(R<sup>8</sup>)R<sup>9</sup>, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl;

L<sup>4</sup> is a bond or an optionally substituted alkylene;

$R^8$  is independently hydrogen,  $-C(O)R^{13}$ ,  $-S(O)_2R^{14}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^9$  is independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^{10}$  is independently  $-C(O)R^{13}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^{11}$  is independently an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, wherein if attached to  $S(O)_2$ ,  $R^{11}$  can also be  $-NR^{15}R^{16}$ ;

$R^{12}$  and  $R^{13}$  are each independently hydrogen,  $-N(R^{18})R^{19}$ ,  $-OR^{19}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^{14}$  is independently hydrogen,  $-N(R^{18})R^{19}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; and

$R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ , and  $R^{19}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

provided that when  $R^3$  and  $R^5$  are both hydrogen, one of  $R^{7A}$  and  $R^{7B}$  is methyl and the other is benzyl, each  $X^1$  and  $X^2$  is N,  $A^2$  is 5-substituted-1,3-phenylene and  $R^1$  is taken together with  $R^2$  and the nitrogen to which they are attached to form a 5-membered heterocycloalkyl ring, the 5-membered heterocycloalkyl ring formed by taking  $R^1$  together with  $R^2$  and the nitrogen to which they are attached is a moiety other than a 2-substituted-pyrrolidinyl substituted with 5-chlorofuran-2-yl, 5-methylfuran-2-yl, 3-pyridyl or 5-bromo-3-pyridyl;

or a pharmaceutically acceptable salt or solvate thereof.

**[0060]** The substituents on an optionally substituted moiety of formula (I) (*e.g.*, substituents on any optionally substituted alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and/or heteroaralkyl) may be one, two, three, or more groups selected from, but not limited to, hydroxyl, nitro, amino (*e.g.*, -NH<sub>2</sub> or dialkyl amino), imino, cyano, halo (such as F, Cl, Br, I), haloalkyl (such as -CCl<sub>3</sub> or -CF<sub>3</sub>), thio, sulfonyl, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, alkoxy, alkoxy-alkyl, alkylcarbonyl, alkylcarbonyloxy (-OCOR), aminocarbonyl, arylcarbonyl, aralkylcarbonyl, carbonylamino, heteroarylcarbonyl, heteroaralkyl-carbonyl, alkylthio, aminoalkyl, cyanoalkyl, carbamoyl (-NHCOOR- or -OCONHR-), urea (-NHCONHR-), aryl and the like, where R is any suitable group, *e.g.*, alkyl or alkylene. In some embodiments, the optionally substituted moiety is optionally substituted only with select radicals, as described herein. In some embodiments, the above groups (*e.g.*, alkyl groups) are optionally substituted with, for example, alkyl (*e.g.*, methyl or ethyl), haloalkyl (*e.g.*, -CCl<sub>3</sub>, -CH<sub>2</sub>CHCl<sub>2</sub> or -CF<sub>3</sub>), cycloalkyl (*e.g.*, -C<sub>3</sub>H<sub>5</sub>, -C<sub>4</sub>H<sub>7</sub>, -C<sub>5</sub>H<sub>9</sub>), amino (*e.g.*, -NH<sub>2</sub> or dialkyl amino), alkoxy (*e.g.*, methoxy), heterocycloalkyl (*e.g.*, as morpholine, piperazine, piperidine, azetidine), hydroxyl, and/or heteroaryl (*e.g.*, oxazolyl). In some embodiments, a substituent group is itself optionally substituted. In some embodiments, a substituent group is not itself substituted. The group substituted onto the substitution group can be, for example, carboxyl, halo, nitro, amino, cyano, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, aminocarbonyl, -SR, thioamido, -SO<sub>3</sub>H, -SO<sub>2</sub>R or cycloalkyl, where R is any suitable group, *e.g.*, a hydrogen or alkyl.

**[0061]** In some of these embodiments, A<sup>1</sup> is an optionally substituted 5 to 7 membered heteroaryl (*e.g.*, wherein the heteroaryl is attached to L<sub>1</sub> at the 1, 2, 3, 4, or 5 position and/or wherein the heteroaryl is substituted at the 1, 2, 3, 4, and/or 5 position(s)). In other embodiments, A<sup>1</sup> is an optionally substituted 5-membered heteroaryl (*e.g.*, wherein the heteroaryl is attached to L<sub>1</sub> at the 1, 2, 3, 4, or 5 position and/or wherein the heteroaryl is substituted at the 1, 2, 3, 4, and/or 5 position(s)).

**[0062]** In some of these embodiments, A<sup>1</sup> is an optionally substituted moiety selected from the group consisting of pyrazolyl, furanyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, pyridyl, pyrimidyl, pyridazinyl, thiazolyl, triazolyl, thienyl, dihydrothienopyrazolyl, thianaphthenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl,

quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, isoindolyl, acridinyl, benzisoxazolyl, pyrazinyl, pyrrolinyl, indolyl, and benzodiazepinyl.

**[0063]** In some of these embodiments, A<sup>1</sup> is an optionally substituted moiety selected from the group consisting of pyrazolyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, pyrimidyl, pyridazinyl, thiazolyl, triazolyl, thienyl, dihydrothieno-pyrazolyl, thianaphthenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, isoindolyl, acridinyl, benzisoxazolyl, pyrazinyl, pyrrolinyl, indolyl, and benzodiazepinyl.

**[0064]** In some of these embodiments, A<sup>1</sup> is an optionally substituted moiety selected from the group consisting of pyrazolyl, furanyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, thiophenyl, pyridyl, pyrimidyl, pyridazinyl, thiazolyl, triazolyl, thienyl, dihydrothieno-pyrazolyl, thianaphthenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, isoindolyl, acridinyl, benzisoxazolyl, pyrazinyl, pyrrolinyl, indolyl, and benzodiazepinyl.

**[0065]** In some of these embodiments, A<sup>1</sup> is an optionally substituted moiety selected from the group consisting of pyrazolyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, thiophenyl, pyrimidyl, pyridazinyl, thiazolyl, triazolyl, thienyl, dihydrothieno-pyrazolyl, thianaphthenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, isoindolyl, acridinyl, benzisoxazolyl, pyrazinyl, pyrrolinyl, indolyl, and benzodiazepinyl.

**[0066]** In some of these embodiments, A<sup>1</sup> is an optionally substituted moiety selected from the group consisting of thiazolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, thiophenyl, pyridyl, pyrimidyl, oxadiazolyl, and pyranyl.

**[0067]** In some of these embodiments, A<sup>1</sup> is an optionally substituted moiety selected from the group consisting of thiazolyl (*e.g.*, an optionally substituted 2-thiazolyl or a an optionally substituted 4-thiazolyl, such as a 2-(4-substituted)thiazolyl or a 4-(2-substituted)thiazolyl), oxazolyl (*e.g.*, an optionally substituted 2-oxazolyl or an optionally substituted 4-oxazolyl, such as a 2-(4-substituted)oxazolyl or a 4-(2-substituted)oxazolyl), imidazolyl, pyrazolyl, isoxazolyl, pyrimidyl, oxadiazolyl and pyranyl. In some embodiments, A<sup>1</sup> is an optionally substituted moiety selected from the group consisting of thiazolyl (*e.g.*, an optionally substituted 2-thiazolyl or a an optionally substituted 4-thiazolyl, such as a 2-(4-substituted)thiazolyl or a 4-(2-substituted)thiazolyl), oxadiazolyl, and oxazolyl (*e.g.*, an

optionally substituted 2-oxazolyl or an optionally substituted 4-oxazolyl, such as a 2-(4-substituted)oxazolyl or a 4-(2-substituted)oxazolyl). In some embodiments, A<sup>1</sup> is an optionally substituted thiazolyl (e.g., an optionally substituted 2-thiazolyl or an optionally substituted 4-thiazolyl, such as a 2-(4-substituted)thiazolyl or a 4-(2-substituted)thiazolyl). In some embodiments, A<sup>1</sup> is an optionally substituted oxazolyl (e.g., an optionally substituted 2-oxazolyl or an optionally substituted 4-oxazolyl, such as a 2-(4-substituted)oxazolyl or a 4-(2-substituted)oxazolyl). In some embodiments, A<sup>1</sup> is an optionally substituted oxadiazolyl. In some embodiments, A<sup>1</sup> is an optionally substituted imidazolyl. In some embodiments, A<sup>1</sup> is an optionally substituted pyrazolyl. In some embodiments, A<sup>1</sup> is an optionally substituted isoxazolyl. In some embodiments, A<sup>1</sup> is an optionally substituted pyrimidyl. In some embodiments, A<sup>1</sup> is an optionally substituted 2-thiazolyl. In some embodiments, A<sup>1</sup> is an optionally substituted 2-oxazolyl.

**[0068]** In some of these embodiments, A<sup>1</sup> is an optionally substituted thiophenyl (e.g., an optionally substituted 2-thiophenyl). In some of these embodiments, A<sup>1</sup> is an optionally substituted pyridyl (e.g., an optionally substituted 2-pyridyl, an optionally substituted 3-pyridyl or an optionally substituted 4-pyridyl, such as 6-methylpyridin-3-yl, 6-methylpyridin-2-yl and 4-pyridyl). In some of these embodiments, A<sup>1</sup> is an optionally substituted pyrazinyl (e.g., an optionally substituted 2-pyrazinyl). In some of these embodiments, A<sup>1</sup> is an optionally substituted oxadiazolyl (e.g., an optionally substituted 1,2,4-oxadiazolyl or an optionally substituted 1,2,3-oxadiazolyl, such as 3-methyl-1,2,4-oxadiazol-5-yl). In some of these embodiments, A<sup>1</sup> is an optionally substituted pyrazolyl (e.g., an optionally substituted 3-pyrazolyl, an optionally substituted 4-pyrazolyl or an optionally substituted 5-pyrazolyl, such as 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 1,3-dimethylpyrazol-5-yl, 1-methylpyrazol-5-yl, and 1,5-dimethylpyrazol-4-yl). In some of these embodiments, A<sup>1</sup> is an optionally substituted oxazolyl (e.g., an optionally substituted 2-oxazolyl or an optionally substituted 4-oxazolyl, such as 2-methyloxazol-4-yl and 2,5-dimethyloxazol-4-yl). In some of these embodiments, A<sup>1</sup> is an optionally substituted thiazolyl (e.g., an optionally substituted 2-thiazolyl or an optionally substituted 4-thiazolyl, such as thiazol-2-yl, 4-methylthiazol-2-yl, 4-ethylthiazol-2-yl, 4-bromothiazol-2-yl, 4-cyclopropylthiazol-2-yl, 4-(methoxymethyl)thiazol-2-yl, 4,5-dimethylthiazol-2-yl, and 2-methylthiazol-4-yl).

**[0069]** In some embodiments, R<sup>1</sup> is taken together with R<sup>2</sup> and the nitrogen to which they are attached to form a 5-membered heterocycloalkyl ring and A<sup>1</sup> is an optionally substituted 5 to 7 membered heteroaryl other than an optionally substituted furanyl and an optionally



substituted pyridyl. In some of these embodiments, A<sup>1</sup> is an optionally substituted 5-membered heteroaryl other than a substituted or unsubstituted furanyl. In some of these embodiments, A<sup>1</sup> is an optionally substituted 5-membered heteroaryl other than a substituted furanyl. In some of these embodiments, A<sup>1</sup> is an optionally substituted 5-membered heteroaryl other than a 5-substituted furan-2-yl. In some of these embodiments, A<sup>1</sup> is an optionally substituted 5-membered heteroaryl other than 5-chlorofuran-2-yl and 5-methylfuran-2-yl. In some of these embodiments, A<sup>1</sup> is an optionally substituted 6-membered heteroaryl other than a substituted or unsubstituted pyridyl. In some of these embodiments, A<sup>1</sup> is an optionally substituted 6-membered heteroaryl other than an unsubstituted pyridyl. In some of these embodiments, A<sup>1</sup> is an optionally substituted 6-membered heteroaryl other than a substituted pyridyl. In some of these embodiments, A<sup>1</sup> is an optionally substituted 6-membered heteroaryl other than a substituted 3-pyridyl. In some of these embodiments, A<sup>1</sup> is an optionally substituted 6-membered heteroaryl other than 3-pyridyl and 5-bromo-3-pyridyl.

**[0070]** The substituents on an optionally substituted A<sup>1</sup> of formula (I) may be one, two, three, or more groups selected from, but not limited to, hydroxyl, nitro, amino, imino, cyano, halo, haloalkyl, thiol, thioalkyl, sulfonyl, thioamido, amidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, cycloalkyl, alkoxy, alkoxy-alkyl, alkylcarbonyl, alkylcarbonyloxy, aminocarbonyl, aryl, heteroaryl, arylcarbonyl, aralkylcarbonyl, carbonylamino, heteroarylcarbonyl, heteroaralkyl-carbonyl, alkylthio, aminoalkyl, cyanoalkyl, carbamoyl, and urea.

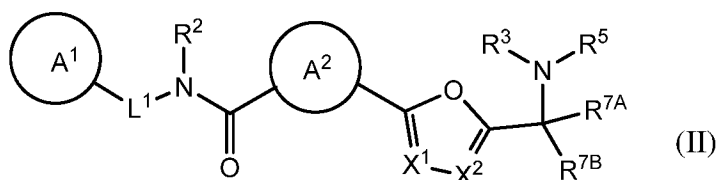
**[0071]** In some embodiments, substituents on an optionally substituted A<sup>1</sup> may be one, two, three, or more groups selected from, but not limited to, hydroxyl, halo (such as F, Cl, Br, I), C<sub>1</sub>-C<sub>6</sub> alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl) or C<sub>1</sub>-C<sub>6</sub> alkoxy (methoxy, ethoxy, propoxy, isopropoxy, wherein each C<sub>1</sub>-C<sub>6</sub> alkyl and C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with 1-3 halogens (*e.g.*, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -OCH<sub>2</sub>F, OCHF<sub>2</sub>)). In some embodiments, A<sup>1</sup> (*e.g.*, thiazolyl) is substituted with alkyl, such as methyl (*e.g.*, at the 1, 2, 3, or 4 position of A<sup>1</sup>). In some of these embodiments, the alkyl (*e.g.*, methyl) is optionally substituted with 1-3 halogens (*e.g.*, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F).

**[0072]** In some of these embodiments, L<sup>1</sup> is a bond or an optionally substituted alkylene. In other embodiments, L<sup>1</sup> is -N(R<sup>17</sup>)-, -S-, -S(O)-, -S(O)<sub>2</sub>-, or an optionally substituted alkylene. In other embodiments, L<sup>1</sup> is -N(R<sup>17</sup>)-, -S-, -S(O)- or -S(O)<sub>2</sub>-. In other embodiments, L<sup>1</sup> is -N(R<sup>17</sup>)-. In other embodiments, L<sup>1</sup> is -S-, -S(O)- or -S(O)<sub>2</sub>-. In other

embodiments,  $L^1$  is a bond. In other embodiments,  $L^1$  is an optionally substituted alkylene. In other embodiments,  $L^1$  is an optionally substituted  $C_1$ - $C_6$  alkylene. In other embodiments,  $L^1$  is an optionally substituted methylene. In other embodiments,  $L^1$  is a  $C_1$ - $C_6$  alkylene (*e.g.*, methylene or methylenemethylene). In other embodiments,  $L^1$  is a branched  $C_1$ - $C_6$  alkylene (*e.g.*, methylenemethylene). In other embodiments,  $L^1$  is methylene. In other embodiments,  $L^1$  is methylenemethylene.

**[0073]** In some embodiments, substituents on an optionally substituted  $L^1$  may be one, two, three, or more groups selected from, but not limited to, hydroxyl, halo (such as F, Cl, Br, I),  $C_1$ - $C_6$  alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl) or  $C_1$ - $C_6$  alkoxy (methoxy, ethoxy, propoxy, isopropoxy, wherein each  $C_1$ - $C_6$  alkyl and  $C_1$ - $C_6$  alkoxy is optionally substituted with 1-3 halogens (*e.g.*,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCH_2F$ ,  $OCHF_2$ )).

**[0074]** In some of these embodiments, the compound has the formula (II):



or a pharmaceutically acceptable salt or solvate thereof; wherein  $A^1$ ,  $A^2$ ,  $L^1$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^{7A}$ , and  $R^{7B}$  are as defined for Formula (I) and any variations thereof.

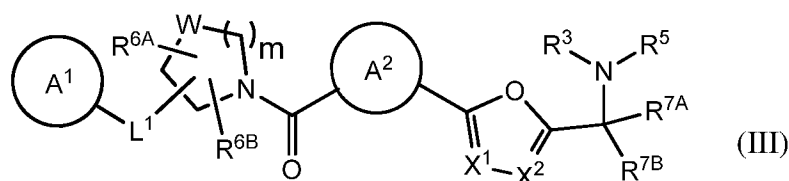
**[0075]** In some of these embodiments,  $R^2$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl. In some embodiments,  $R^2$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, and cycloalkyl-alkyl. In some embodiments,  $R^2$  is hydrogen or an optionally substituted alkyl. In some embodiments,  $R^2$  is hydrogen or an optionally substituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^2$  is hydrogen. In some embodiments,  $R^2$  is an optionally substituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^2$  is an optionally substituted  $C_1$ - $C_3$  alkyl. In some embodiments,  $R^2$  is an optionally substituted  $C_3$ - $C_6$  cycloalkyl. In some embodiments,  $R^2$  is cyclopropyl. In some embodiments,  $R^2$  is methyl.

**[0076]** In some of these embodiments,  $R^2$  is hydrogen, an optionally substituted  $C_1$ - $C_6$  alkyl, or an optionally substituted  $C_3$ - $C_6$  cycloalkyl. In some embodiments,  $R^2$  is an optionally substituted  $C_1$ - $C_6$  alkyl, such as methyl, ethyl, 2-fluoroethyl, propyl (*e.g.*, *n*-propyl or isopropyl), butyl (*e.g.*, *n*-butyl, isobutyl, *sec*-butyl or *tert*-butyl). In some embodiments,  $R^2$

is an optionally substituted C<sub>3</sub>-C<sub>6</sub> cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

**[0077]** In some embodiments, substituents on an optionally substituted R<sup>2</sup> may be one, two, three, or more groups selected from, but not limited to, hydroxyl, halo (such as F, Cl, Br, I), C<sub>1</sub>-C<sub>6</sub> alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl) or C<sub>1</sub>-C<sub>6</sub> alkoxy (methoxy, ethoxy, propoxy, isopropoxy, wherein each C<sub>1</sub>-C<sub>6</sub> alkyl and C<sub>1</sub>-C<sub>6</sub> alkoxy is optionally substituted with 1-3 halogens (*e.g.*, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -OCH<sub>2</sub>F, -OCHF<sub>2</sub>). In some embodiments, substituents on an optionally substituted R<sup>2</sup> are selected from methyl and cyclopropyl.

**[0078]** In some embodiments, the compound has the formula (III):



or a pharmaceutically acceptable salt or solvate thereof,

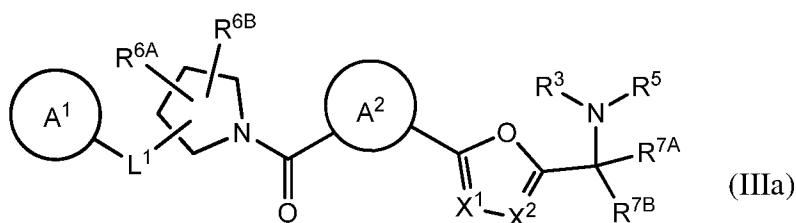
wherein:

W is -CH<sub>2</sub>-, -O-, -N(R<sup>17</sup>)-, -S-, -S(O)-, or -S(O)<sub>2</sub>-, or where W is -CH- or -N-, and is substituted with R<sup>6A</sup> or R<sup>6B</sup>, or where W is -C-, and is substituted with R<sup>6A</sup> and R<sup>6B</sup>; m is 1 or 2; and

A<sup>1</sup>, A<sup>2</sup>, L<sup>1</sup>, X<sup>1</sup>, X<sup>2</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6A</sup>, R<sup>6B</sup>, R<sup>7A</sup>, R<sup>7B</sup>, and R<sup>17</sup> are as defined above in the discussion of Formula (I).

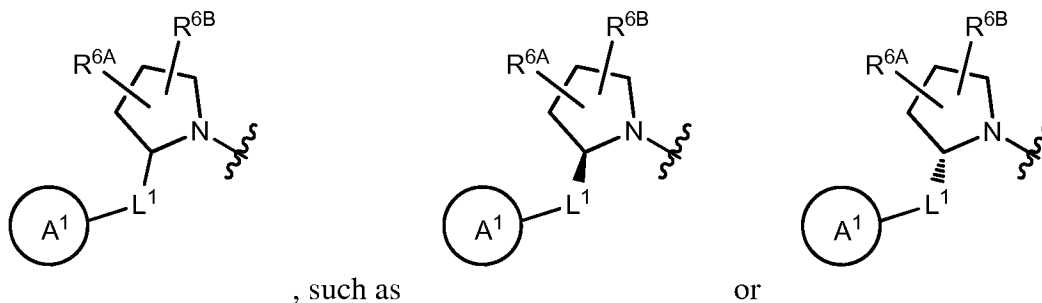
**[0079]** In some variations of the formula (III), W is -O-. In some variations, W is -S-, -S(O)-, or -S(O)<sub>2</sub>-. In some variations, W is -S-. In some variations, W is -N(R<sup>17</sup>)-. In some variations, W is -N(R<sup>6A</sup>)- or -N(R<sup>6B</sup>)-. In some variations, W is -CH<sub>2</sub>-. In some variations, W is -CH(R<sup>6A</sup>)- or -CH(R<sup>6B</sup>)-. In some variations, W is -C(R<sup>6A</sup>)(R<sup>6B</sup>)-. In some variations, m is 1. In some variations, m is 2. In some variations, W is -O- and m is 1. In some variations, W is -S- and m is 1.

**[0080]** In some embodiments, the compound has the formula (IIIa):

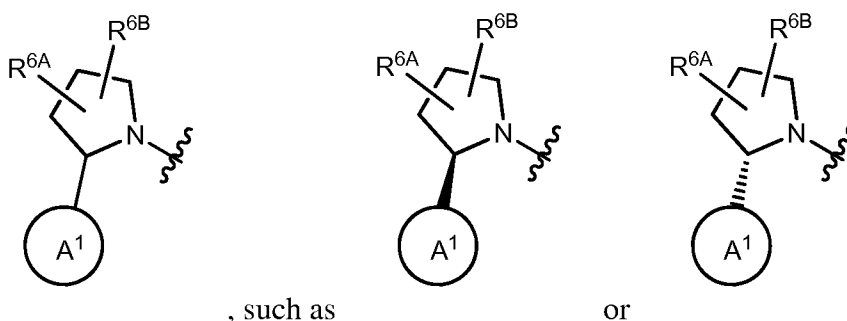


or a pharmaceutically acceptable salt or solvate thereof; wherein  $A^1$ ,  $A^2$ ,  $L^1$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^{6A}$ ,  $R^{6B}$ ,  $R^{7A}$ , and  $R^{7B}$  are as defined above in the discussion of Formula (I).

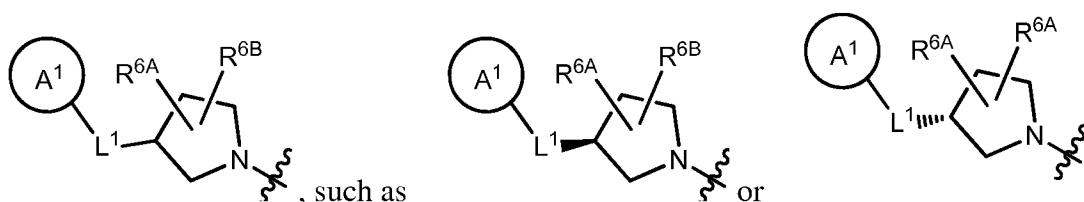
**[0081]** In some embodiments, the A<sup>1</sup>-L<sup>1</sup>- moiety is substituted on the pyrrolidine heterocycloalkyl ring according to the formula:



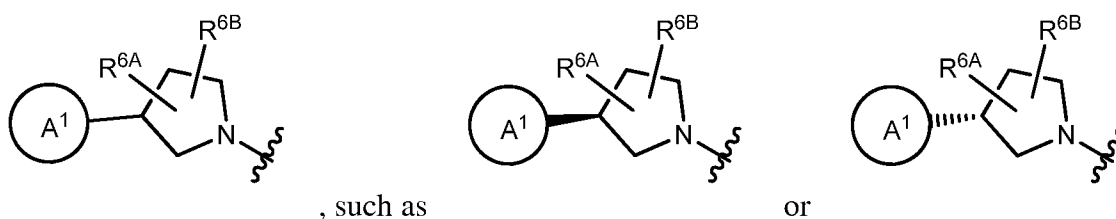
**[0082]** In some of these embodiments, L<sup>1</sup> is a bond, and A<sup>1</sup> is substituted on the pyrrolidine heterocycloalkyl ring according to the formula:



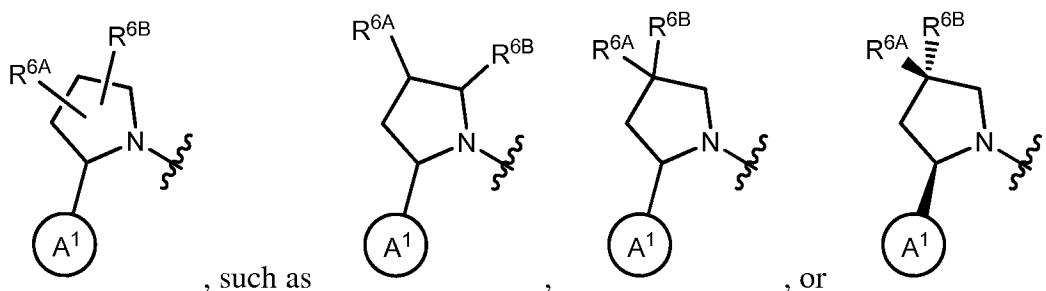
**[0083]** In some embodiments, the A<sup>1</sup>-L<sup>1</sup>- moiety is substituted on the pyrrolidine heterocycloalkyl ring according to the formula:



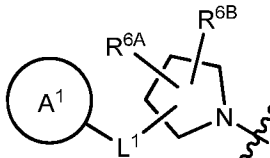
**[0084]** In some embodiments, L<sup>1</sup> is a bond, and A<sup>1</sup> is substituted on the pyrrolidine heterocycloalkyl ring according to the formula:

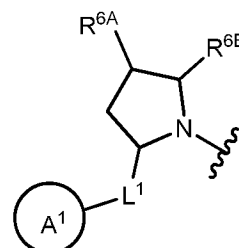


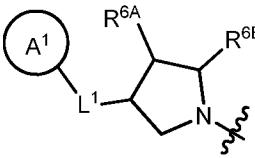
[0085] In some embodiments,  $L^1$  is a bond, and  $A^1$ ,  $R^{6A}$  and  $R^{6B}$  are substituted on the pyrrolidine heterocycloalkyl ring according to the formula:

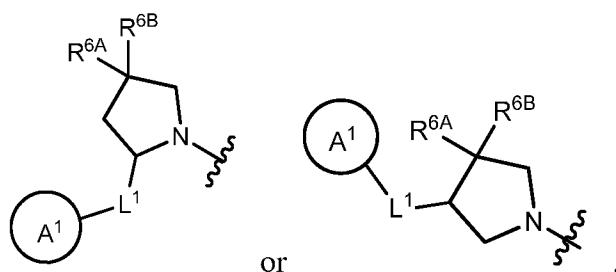


[0086] In some embodiments, the  $A^1-L^1$ - moiety,  $R^{6A}$  and  $R^{6B}$  are substituted on the

pyrrolidine heterocycloalkyl ring according to the formula , wherein

$R^{6A}$  and  $R^{6B}$  may be substituted on different carbon atoms, e.g.  or

, or  $R^{6A}$  and  $R^{6B}$  may be substituted on the same carbon atom, e.g.

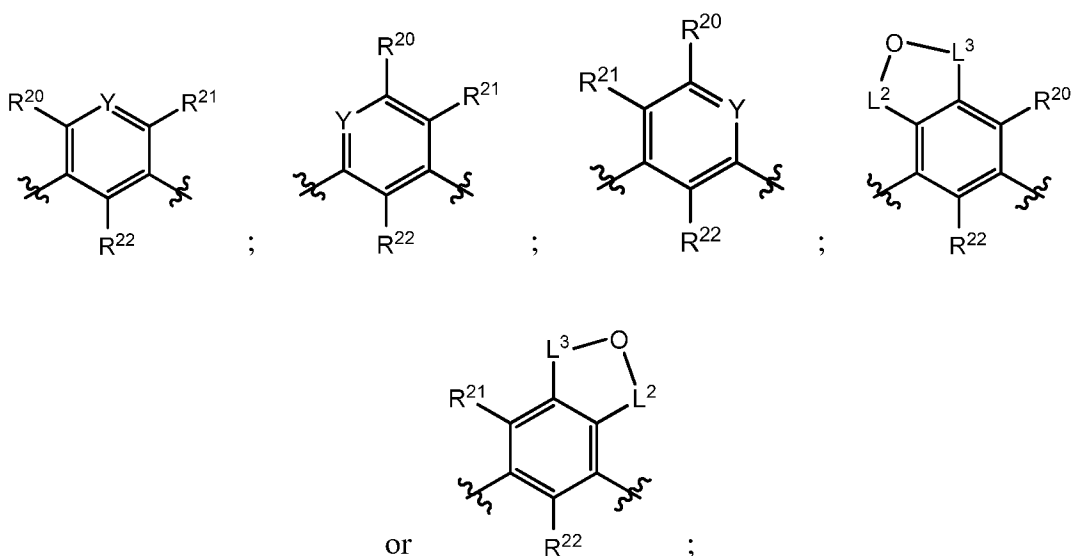


[0087] In some embodiments,  $R^{6A}$  and  $R^{6B}$  are independently hydrogen, halogen,  $-OH$ ,  $-N(R^8)R^9$ ,  $-OR^{10}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl. In some embodiments,  $R^{6A}$  is hydrogen, or an optionally substituted moiety selected from aryl, aralkyl, heteroaryl, and heteroaralkyl. In some embodiments,  $R^{6A}$  is hydrogen, halogen (e.g., F or Cl), an optionally substituted alkyl (e.g.,

haloalkyl), or an optionally substituted  $-OR^{10}$  (e.g., an optionally substituted -O-alkyl, such as methoxy, ethoxy, propoxy, isopropoxy, or halogenated variants thereof). In some embodiments,  $R^{6A}$  is hydrogen, F, an optionally substituted  $(C_1-C_4)$ alkyl (e.g., methyl, ethyl, propyl, butyl,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ), an optionally substituted -O- $(C_1-C_4)$ alkyl (e.g., -O- $(C_1-C_4)$ alkyl, such as methoxy, ethoxy, propoxy, or isopropoxy, substituted with 1, 2, or 3 fluoro groups, such as  $-OCH_2F$ ,  $-OCHF_2$ ). In some embodiments,  $R^{6A}$  is hydrogen or halogen. In some embodiments,  $R^{6A}$  is halogen, e.g. fluoro. In some embodiments,  $R^{6A}$  is hydrogen. In some variations of these embodiments,  $R^{6B}$  is hydrogen. In some variations of these embodiments,  $R^{6B}$  is an optionally substituted alkyl. In some variations of these embodiments,  $R^{6B}$  is a halogen (e.g. fluoro). In some particular variations,  $R^{6A}$  and  $R^{6B}$  are independently halogen. In some particular variations, each  $R^{6A}$  and  $R^{6B}$  is fluoro.

**[0088]** In some embodiments, the compound is of the formula I, II, III, IV, V, VI or any variations thereof, where  $A^2$  is an optionally substituted arylene or an optionally substituted heteroarylene. In some embodiments,  $A^2$  is an optionally substituted moiety selected from the group consisting of phenylene, pyridinylene, oxazolylene, thiazolylene, pyrazolylene, pyranylene, imidazolylene, and furanylene. In some variations,  $A^2$  is an arylene bearing at least two substituents and the two substituents may be taken together to form another heterocycle that is fused to the arylene, e.g. chromanylene or dihydrobenzofuranylene. In some variations,  $A^2$  is an optionally substituted pyridonylene.

**[0089]** In some of these embodiments,  $A^2$  has the formula:



wherein

$L^2$  and  $L^3$  are independently a bond or an optionally substituted  $C_1$ - $C_5$  alkylene;  
 $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are independently hydrogen, halogen,  $-N(R^{24})R^{25}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; and  
 $Y$  is  $-N=$  or  $-C(R^{23})=$ , wherein  $R^{23}$  is hydrogen, halogen,  $-NO_2$ ,  $-N(R^{24})R^{25}$ ,  $-OR^{26}$ ,  $-SR^{27}$ ,  $-S(O)R^{27}$ ,  $-S(O)_2R^{27}$ , or  $-C(O)R^{28}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;  
 wherein

$R^{24}$  and  $R^{25}$  are independently hydrogen,  $-C(O)R^{29}$ , or  $-S(O)_2R^{30}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

$R^{29}$  is independently hydrogen,  $-N(R^{31})R^{32}$ , or  $-OR^{33}$ , an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

$R^{31}$ ,  $R^{32}$ , and  $R^{33}$  are independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; and

$R^{30}$  is an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^{26}$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^{27}$  is  $-N(R^{34})R^{35}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

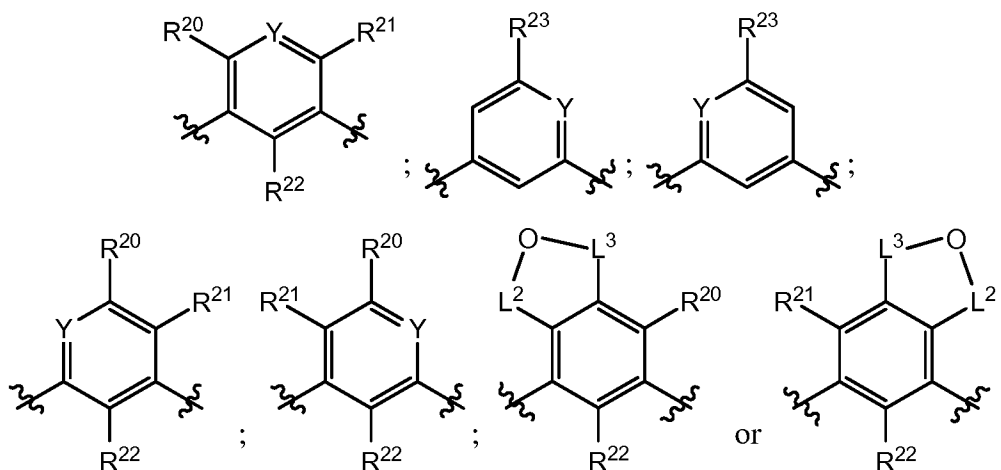
$R^{34}$  and  $R^{35}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; and

$R^{28}$  is  $-OR^{36}$ ,  $-N(R^{37})R^{38}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

$R^{36}$ ,  $R^{37}$ , and  $R^{38}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl.

[0090] In some of these embodiments,  $A^2$  has the formula:



wherein

$L^2$  and  $L^3$  are independently a bond or an optionally substituted  $C_1-C_5$  alkylene;

$R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are independently hydrogen, halogen,  $-N(R^{24})R^{25}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

each  $R^{23}$  is independently hydrogen, halogen, cyano,  $-NO_2$ ,  $-N(R^{24})R^{25}$ ,  $-OR^{26}$ ,  $-SR^{27}$ ,  $-S(O)R^{27}$ ,  $-S(O)_2R^{27}$ , or  $-C(O)R^{28}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl,



heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; and

Y is  $-N=$  or  $-C(R^{23})=$ ;

wherein

$R^{24}$  and  $R^{25}$  are each independently hydrogen,  $-C(O)R^{29}$ , or  $-S(O)_2R^{30}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

$R^{29}$  is independently hydrogen,  $-N(R^{31})R^{32}$ , or  $-OR^{33}$ , an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

$R^{31}$ ,  $R^{32}$ , and  $R^{33}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; and

$R^{30}$  is independently an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^{26}$  is independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^{27}$  is independently  $-N(R^{34})R^{35}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

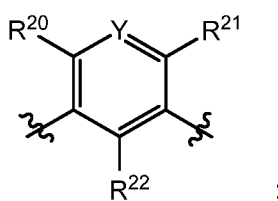
$R^{34}$  and  $R^{35}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; and

$R^{28}$  is independently  $-OR^{36}$ ,  $-N(R^{37})R^{38}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

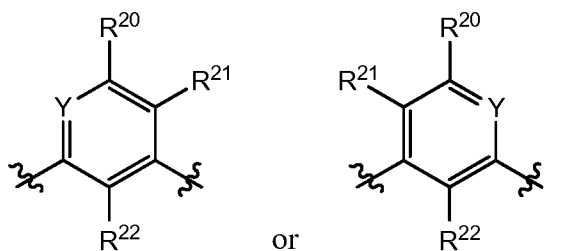
$R^{36}$ ,  $R^{37}$ , and  $R^{38}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl.

**[0091]** In other of these embodiments,  $A^2$  has the formula:



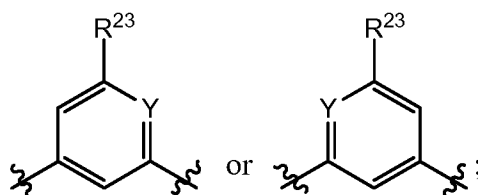
wherein  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are defined herein.

**[0092]** In other of these embodiments,  $A^2$  has the formula:



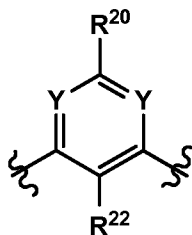
wherein  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are as defined herein.

**[0093]** In some of these embodiments,  $A^2$  has the formula:



wherein  $R^{23}$  is as defined herein.

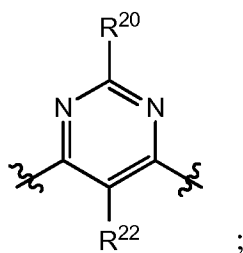
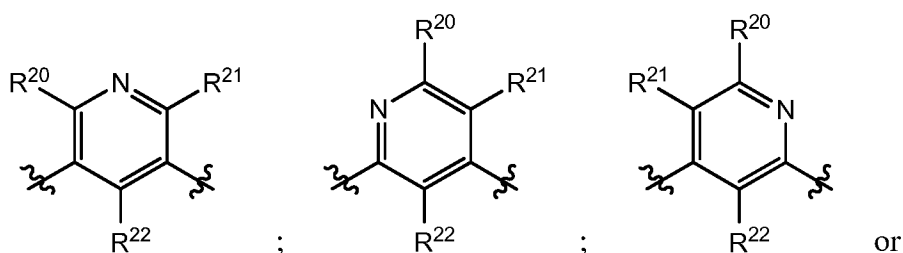
[0094] In other of these embodiments,  $A^2$  has the formula:



wherein  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are as defined herein.

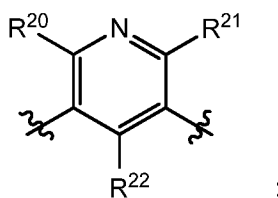
[0095] In some of these embodiments, Y is  $-C(R^{23})=$ . In other embodiments, Y is  $-N=$ .

[0096] In some of these embodiments,  $A^2$  has the formula.



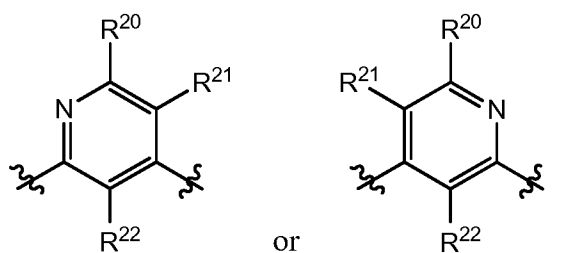
wherein  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are as defined herein.

[0097] In other of these embodiments,  $A^2$  has the formula:



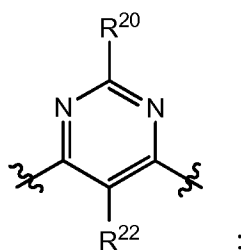
wherein  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are as defined herein.

[0098] In other of these embodiments,  $A^2$  has the formula:



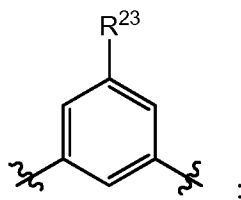
wherein  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are as defined herein.

[0099] In other of these embodiments,  $A^2$  has the formula:



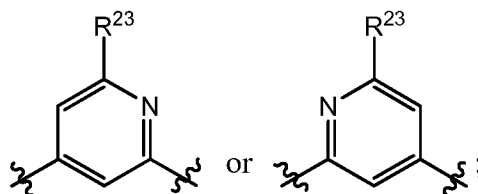
wherein  $R^{20}$  and  $R^{22}$  are as defined herein.

[0100] In some of these embodiments,  $A^2$  has the formula:



wherein  $R^{23}$  is as defined herein.

[0101] In some of these embodiments,  $A^2$  has the formula:



wherein  $R^{23}$  is as defined herein.

[0102] In some embodiments,  $R^{23}$  is hydrogen, halogen, cyano,  $-\text{NO}_2$ ,  $-\text{N}(\text{R}^{24})\text{R}^{25}$ ,  $-\text{OR}^{26}$ ,  $-\text{SR}^{27}$ ,  $-\text{S}(\text{O})\text{R}^{27}$ ,  $-\text{S}(\text{O})_2\text{R}^{27}$ , or  $-\text{C}(\text{O})\text{R}^{28}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl. In some embodiments,  $R^{23}$  is halogen, cyano, or  $-\text{NO}_2$ .

In some embodiments,  $R^{23}$  is halogen (e.g., F, Cl, Br or I). In some embodiments,  $R^{23}$  is cyano. In some embodiments,  $R^{23}$  is  $-\text{NO}_2$ .

**[0103]** In some embodiments,  $R^{23}$  is  $-\text{N}(\text{R}^{24})\text{R}^{25}$  where each  $\text{R}^{24}$  and  $\text{R}^{25}$  is independently hydrogen, an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl (e.g., methyl, ethyl and 2-methoxyethyl), or  $-\text{C}(\text{O})\text{R}^{29}$  where  $\text{R}^{29}$  is hydrogen, an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl (e.g., methyl). In some embodiments,  $R^{23}$  is  $-\text{NH}_2$ . In some embodiments,  $R^{23}$  is  $-\text{NH}(\text{CH}_2\text{CH}_3)$ . In some embodiments,  $R^{23}$  is  $-\text{NH}(\text{CH}_2\text{CH}_2\text{OCH}_3)$ . In some embodiments,  $R^{23}$  is  $-\text{N}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{OCH}_3)$ . In some embodiments,  $R^{23}$  is  $-\text{N}(\text{CH}_3)\text{C}(\text{O})\text{CH}_3$ .

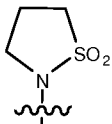
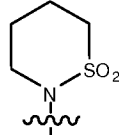
**[0104]** In some embodiments,  $R^{23}$  is  $-\text{OR}^{26}$ . In some embodiments,  $\text{R}^{26}$  is hydrogen or an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl. In some embodiments,  $\text{R}^{26}$  is unsubstituted  $\text{C}_1\text{-C}_6$  alkyl (e.g., methyl) or substituted  $\text{C}_1\text{-C}_6$  alkyl (e.g.,  $\text{C}_1\text{-C}_6$  alkyl substituted with one or more halogen atoms, such as fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl). In some embodiments,  $R^{23}$  is  $-\text{OH}$ . In some embodiments,  $R^{23}$  is  $-\text{OCH}_3$ . In some embodiments,  $R^{23}$  is  $-\text{OCH}_2\text{CH}_3$ . In some embodiments,  $R^{23}$  is  $-\text{OCHF}_2$ . In some embodiments,  $R^{23}$  is  $-\text{OCF}_3$ .

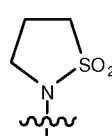
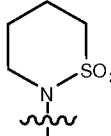
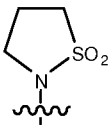
**[0105]** In some embodiments,  $R^{23}$  is  $-\text{C}(\text{O})\text{R}^{28}$ . In some embodiments,  $\text{R}^{28}$  is an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl (e.g., methyl) or an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl. In some embodiments,  $\text{R}^{28}$  is  $-\text{OR}^{36}$  where  $\text{R}^{36}$  is hydrogen or an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl (e.g., methyl or ethyl). In some embodiments,  $\text{R}^{28}$  is  $-\text{N}(\text{R}^{37})\text{R}^{38}$  where each  $\text{R}^{37}$  and  $\text{R}^{38}$  is independently hydrogen or an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl (e.g., methyl and ethyl). In some embodiments,  $R^{23}$  is  $-\text{C}(\text{O})\text{OH}$ . In some embodiments,  $R^{23}$  is  $-\text{C}(\text{O})\text{OCH}_2\text{CH}_3$ . In some embodiments,  $R^{23}$  is  $-\text{C}(\text{O})\text{NH}_2$ . In some embodiments,  $R^{23}$  is  $-\text{C}(\text{O})\text{NHCH}_3$ . In some embodiments,  $R^{23}$  is  $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$ .

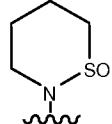
**[0106]** In some embodiments,  $R^{23}$  is hydrogen, an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl or an optionally substituted  $\text{C}_3\text{-C}_6$  cycloalkyl. In some embodiments,  $R^{23}$  is unsubstituted  $\text{C}_1\text{-C}_6$  alkyl (e.g., methyl) or substituted  $\text{C}_1\text{-C}_6$  alkyl (e.g.,  $\text{C}_1\text{-C}_6$  alkyl substituted with one or more halogen atoms, such as fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 1,1-difluoroethyl and 2,2,2-trifluoroethyl). In some embodiments,  $R^{23}$  is an optionally substituted  $\text{C}_3\text{-C}_6$  cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl).

**[0107]** In some of these embodiments,  $R^{23}$  is hydrogen, halogen,  $-\text{N}(\text{R}^{24})\text{R}^{25}$ ,  $-\text{OR}^{26}$ ,  $-\text{SR}^{27}$ ,  $-\text{S}(\text{O})\text{R}^{27}$ ,  $-\text{S}(\text{O})_2\text{R}^{27}$ ,  $-\text{C}(\text{O})\text{R}^{28}$ , or an optionally substituted heterocycloalkyl. In other embodiments,  $R^{23}$  is hydrogen,  $-\text{N}(\text{R}^{24})\text{R}^{25}$  (e.g.,  $-\text{N}(\text{alkyl})\text{alkylsulfonamido}$ , such as N-

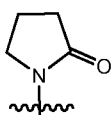
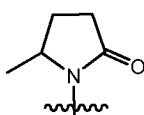
methyl-methanesulfonamido), or an optionally substituted heterocycloalkyl (*e.g.*, an optionally substituted cyclic sulfonamido). In other embodiments,  $R^{23}$  is hydrogen or  $-N(R^{24})R^{25}$  (*e.g.*,  $-N(\text{alkyl})\text{alkylsulfonamido}$ , such as  $N\text{-methyl-methanesulfonamido}$ ). In other embodiments,  $R^{23}$  is hydrogen. In other embodiments,  $R^{23}$  is  $-N(R^{24})R^{25}$  (*e.g.*,  $-N(\text{alkyl})\text{alkylsulfonamido}$ , such as  $N\text{-methyl-methanesulfonamido}$ ) or an optionally substituted heterocycloalkyl (*e.g.*, a cyclic sulfonamido). In other embodiments,  $R^{23}$  is  $-N(R^{24})R^{25}$  (*e.g.*,  $-N(\text{alkyl})\text{alkylsulfonamido}$ , such as  $N\text{-methyl-methanesulfonamido}$ ). In other embodiments  $R^{23}$  is an optionally substituted heterocycloalkyl (*e.g.*, an optionally

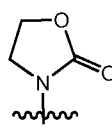
substituted cyclic sulfonamido, such as an optionally substituted  or  ). In

some embodiments,  $R^{23}$  is  or  . In some embodiments,  $R^{23}$  is  . In

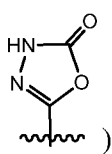
some embodiments,  $R^{23}$  is  . In other embodiments,  $R^{23}$  is  $-OR^{26}$ . In other embodiments,  $R^{23}$  is  $-SR^{27}$ ,  $-S(O)R^{27}$ , or  $-S(O)_2R^{27}$ . In other embodiments,  $R^{23}$  is  $-C(O)R^{28}$ . In some embodiments,  $R^{23}$  is hydrogen, an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl. In some embodiments,  $R^{23}$  is an optionally substituted moiety selected from alkyl, cycloalkyl, and heterocycloalkyl. In some embodiments,  $R^{23}$  is an optionally substituted alkyl. In some embodiments,  $R^{23}$  is an optionally substituted  $C_1\text{-}C_6$  alkyl. In some embodiments,  $R^{23}$  is methyl. In some embodiments,  $R^{23}$  is an optionally substituted cycloalkyl. In some embodiments,  $R^{23}$  is an optionally substituted heterocycloalkyl. In some embodiments,  $R^{23}$  is an optionally substituted moiety selected from cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl. In some embodiments,  $R^{23}$  is an optionally substituted moiety selected from aryl, aralkyl, heteroaryl, and heteroaralkyl. In some embodiments,  $R^{23}$  is an optionally substituted moiety selected from aryl and heteroaryl. In some embodiments,  $R^{23}$  is an optionally substituted aryl. In some embodiments,  $R^{23}$  is an optionally substituted heteroaryl.

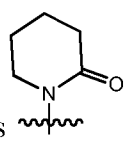
[0108] In some embodiments,  $R^{23}$  is an optionally substituted heterocycloalkyl. In some embodiments,  $R^{23}$  is an optionally substituted pyrrolidinyl (e.g., 1-pyrrolidinyl or an oxo-

substituted pyrrolidinyl such as  and ). In some embodiments,  $R^{23}$  is an

optionally substituted oxazolidinyl (e.g., an oxo-substituted oxazolidinyl such as ).

In some embodiments,  $R^{23}$  is an optionally substituted oxadiazolinyl (e.g., an oxo-substituted

oxadiazolinyl such as ). In some embodiments,  $R^{23}$  is an optionally substituted

piperidinyl (e.g., 1-piperidinyl or an oxo-substituted piperidinyl such as ).

[0109] In some embodiments,  $R^{23}$  is an optionally substituted moiety selected from pyridyl, phenyl, thiazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, isoxazolyl, pyrimidyl, pyranyl, pyrazinyl, pyrrolyl and furanyl. In some embodiments,  $R^{23}$  is an optionally substituted moiety selected from thiazolyl, oxadiazolyl, oxazolyl, imidazolyl, pyrrolyl and pyrazinyl. In some embodiments,  $R^{23}$  is an optionally substituted phenyl. In some embodiments,  $R^{23}$  is an optionally substituted pyridyl. In some embodiments,  $R^{23}$  is an optionally substituted thiazolyl. In some embodiments,  $R^{23}$  is an optionally substituted oxazolyl. In some embodiments,  $R^{23}$  is an optionally substituted oxadiazolyl. In some embodiments,  $R^{23}$  is an optionally substituted imidazolyl. In some embodiments,  $R^{23}$  is an optionally substituted pyrazolyl. In some embodiments,  $R^{23}$  is an optionally substituted isoxazolyl. In some embodiments,  $R^{23}$  is an optionally substituted pyrimidyl. In some embodiments,  $R^{23}$  is an optionally substituted pyrazinyl. In some embodiments,  $R^{23}$  is an optionally substituted pyranyl. In some embodiments,  $R^{23}$  is an optionally substituted furanyl. In some embodiments,  $R^{23}$  is an optionally substituted 2-thiazolyl. In some embodiments,  $R^{23}$  is an optionally substituted 2-oxazolyl. In some embodiments,  $R^{23}$  is an optionally substituted 5-oxazolyl.

[0110] In some embodiments,  $R^{23}$  is an optionally substituted aryl or an optionally substituted heteroaryl. In some embodiments,  $R^{23}$  is an optionally substituted phenyl (e.g., phenyl, 2-methoxyphenyl, 3-methoxyphenyl or 2-cyanophenyl). In some embodiments,  $R^{23}$

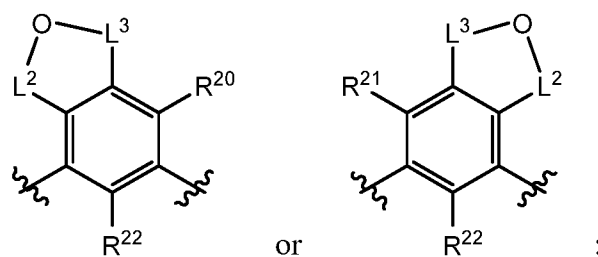
is an optionally substituted furanyl (e.g., 2-furanyl or 3-furanyl). In some embodiments,  $R^{23}$  is an optionally substituted thiophenyl (e.g., 2-thiophenyl or 3-thiophenyl). In some embodiments,  $R^{23}$  is an optionally substituted pyrrolyl (e.g., 1-pyrrolyl or 1-methylpyrrol-2-yl). In some embodiments,  $R^{23}$  is an optionally substituted oxazolyl (e.g., 2-oxazolyl or 5-oxazolyl). In some embodiments,  $R^{23}$  is an optionally substituted isoxazolyl (e.g., 3-isoxazolyl or 5-isoxazolyl). In some embodiments,  $R^{23}$  is an optionally substituted thiazolyl (e.g., 2-thiazolyl, 2-methylthiazol-4-yl or 4,5-dimethylthiazol-2-yl). In some embodiments,  $R^{23}$  is an optionally substituted pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl or 1-methylpyrazol-5-yl). In some embodiments,  $R^{23}$  is an optionally substituted imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl or 1-methylimidazol-2-yl). In some embodiments,  $R^{23}$  is an optionally substituted oxadiazolyl (e.g., 1,3,4-oxadiazol-2-yl or 5-methyl-1,3,4-oxadiazol-2-yl). In some embodiments,  $R^{23}$  is an optionally substituted triazolyl (e.g., 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl or 1,2,5-triazol-1-yl). In some embodiments,  $R^{23}$  is an optionally substituted pyridyl (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some embodiments,  $R^{23}$  is an optionally substituted pyrimidyl (e.g., 5-pyrimidyl). In some embodiments,  $R^{23}$  is an optionally substituted pyrazinyl (e.g., 2-pyrazinyl).

**[0111]** The substituents on an optionally substituted  $R^{23}$  may be one, two, three, or more groups selected from, but not limited to, hydroxyl, nitro, amino, imino, cyano, halo, haloalkyl, thiol, thioalkyl, sulfonyl, thioamido, amidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, cycloalkyl, alkoxy, alkoxy-alkyl, alkylcarbonyl, alkylcarbonyloxy, aminocarbonyl, aryl, heteroaryl, arylcarbonyl, aralkylcarbonyl, carbonylamino, heteroarylcarbonyl, heteroaralkyl-carbonyl, alkylthio, aminoalkyl, cyanoalkyl, carbamoyl, and urea.

**[0112]** In some embodiments, substituents on an optionally substituted  $R^{23}$  may be one, two, three, or more groups selected from, but not limited to, hydroxyl, halo (such as F, Cl, Br, I),  $C_1$ - $C_6$  alkyl (e.g., methyl, ethyl, propyl, isopropyl) or  $C_1$ - $C_6$  alkoxy (methoxy, ethoxy, propoxy, isopropoxy, wherein each  $C_1$ - $C_6$  alkyl and  $C_1$ - $C_6$  alkoxy is optionally substituted with 1-3 halogens (e.g.,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCH_2F$ ,  $OCHF_2$ )).

**[0113]** In some embodiments,  $A^2$  has the formula:





where  $L^2$ ,  $L^3$ ,  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are as defined herein.

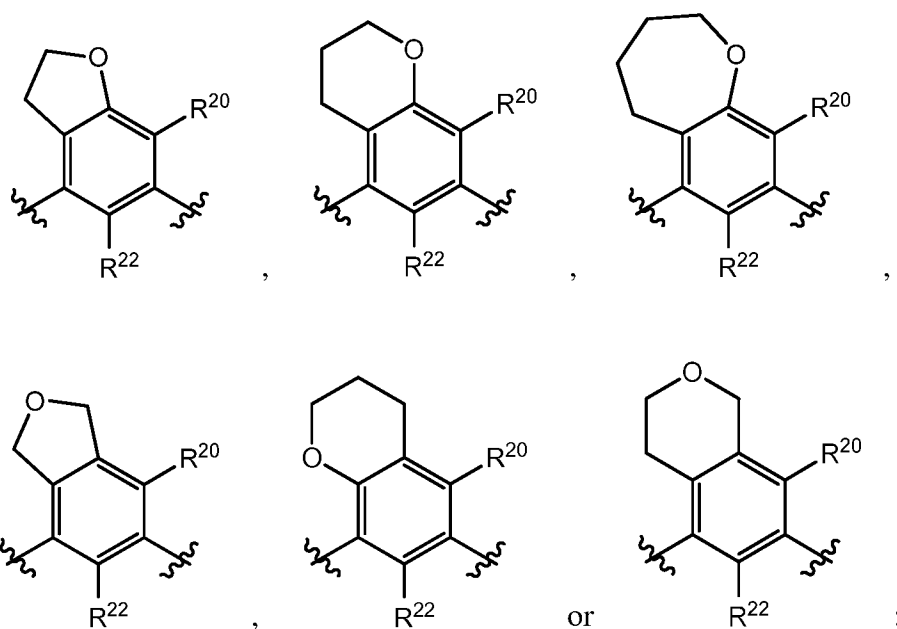
**[0114]** In some embodiments,  $L^2$  is an optionally substituted  $C_2$ - $C_5$  alkylene and  $L^3$  is a bond. In one variation,  $L^2$  is an optionally substituted  $C_2$ - $C_4$  alkylene and  $L^3$  is a bond. In another variation,  $L^2$  is an optionally substituted ethylene and  $L^3$  is a bond. In another variation,  $L^2$  is an optionally substituted propylene and  $L^3$  is a bond. In another variation,  $L^2$  is an optionally substituted butylene and  $L^3$  is a bond. In one variation,  $L^2$  is a  $C_2$ - $C_4$  alkylene and  $L^3$  is a bond. In another variation,  $L^2$  is ethylene, propylene or butylene and  $L^3$  is a bond. In another variation,  $L^2$  is propylene and  $L^3$  is a bond. In another variation,  $L^2$  is butylene and  $L^3$  is a bond.

**[0115]** In some embodiments,  $L^2$  is an optionally substituted  $C_1$ - $C_4$  alkylene and  $L^3$  is an optionally substituted methylene. In one variation,  $L^2$  is an optionally substituted  $C_2$ - $C_4$  alkylene and  $L^3$  is an optionally substituted methylene. In another variation,  $L^2$  is an optionally substituted ethylene and  $L^3$  is an optionally substituted methylene. In another variation,  $L^2$  is an optionally substituted propylene and  $L^3$  is an optionally substituted methylene. In one variation,  $L^2$  is a  $C_1$ - $C_3$  alkylene and  $L^3$  is methylene. In another variation,  $L^2$  is methylene or ethylene and  $L^3$  is methylene. In a specific variation, each  $L^2$  and  $L^3$  is methylene.

**[0116]** In some embodiments,  $L^2$  is an optionally substituted  $C_1$ - $C_3$  alkylene and  $L^3$  is an optionally substituted ethylene. In some variations,  $L^2$  is an optionally substituted methylene or ethylene and  $L^3$  is an optionally substituted propylene. In some variations,  $L^2$  is an optionally substituted methylene and  $L^3$  is an optionally substituted butylene.

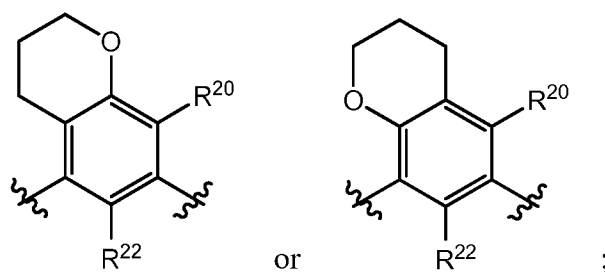
**[0117]** In some embodiments,  $L^2$  is a bond and  $L^3$  is an optionally substituted  $C_2$ - $C_5$  alkylene. In one variation,  $L^2$  is a bond and  $L^3$  is an optionally substituted  $C_2$ - $C_4$  alkylene. In another variation,  $L^2$  is a bond and  $L^3$  is an optionally substituted ethylene. In another variation,  $L^2$  is a bond and  $L^3$  is an optionally substituted propylene. In another variation,  $L^2$  is a bond and  $L^3$  is an optionally substituted butylene.

**[0118]** In some embodiments,  $A^2$  has the formula:



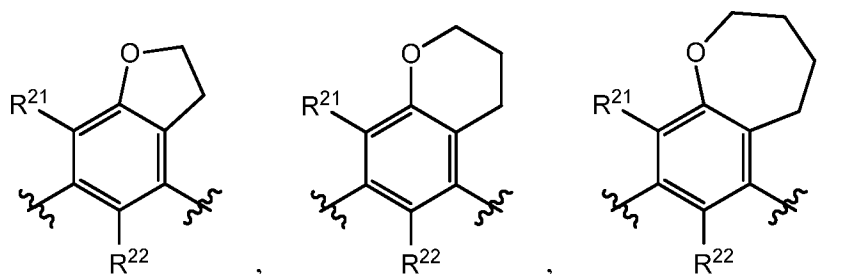
where  $R^{20}$  and  $R^{22}$  are as defined herein.

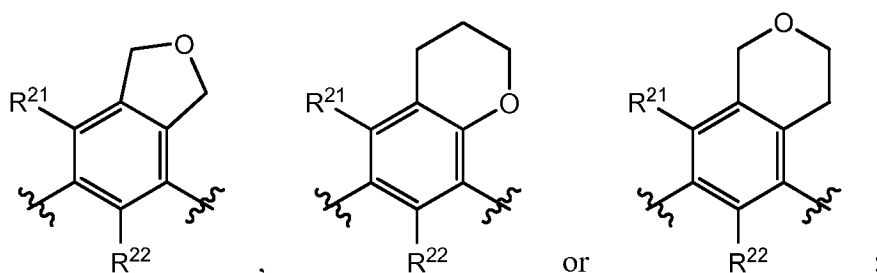
**[0119]** In some embodiments,  $A^2$  has the formula:



where  $R^{20}$  and  $R^{22}$  are as defined herein. In one variation, each  $R^{20}$  and  $R^{22}$  is hydrogen.

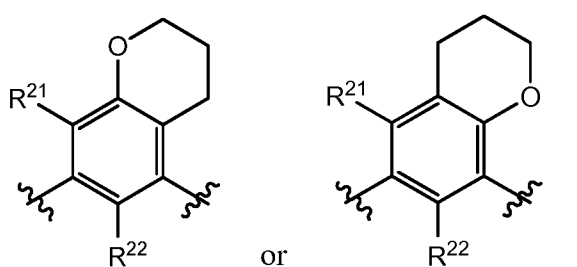
**[0120]** In some embodiments,  $A^2$  has the formula:





where  $R^{21}$  and  $R^{22}$  are as defined herein.

**[0121]** In some embodiments,  $A^2$  has the formula:



where  $R^{21}$  and  $R^{22}$  are as defined herein. In one variation, each  $R^{21}$  and  $R^{22}$  is hydrogen.

**[0122]** In some of these embodiments,  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are independently hydrogen, or an optionally substituted  $C_1$ - $C_{10}$  alkyl. In some embodiments,  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are independently hydrogen, or an optionally substituted  $C_1$ - $C_6$  alkyl. In some embodiments, at least one of  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  is hydrogen. In some embodiments,  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are hydrogen.

**[0123]** In some of these embodiments,  $R^{22}$  is hydrogen. In some embodiments,  $R^{22}$  is hydrogen; and  $R^{20}$  or  $R^{21}$ , where applicable, is hydrogen or an optionally substituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^{22}$  is hydrogen; and  $R^{20}$  and  $R^{21}$ , where applicable, is hydrogen or methyl. In some embodiments,  $R^{22}$  is hydrogen and  $R^{20}$  or  $R^{21}$ , where applicable, is methyl. In some embodiments, at least one of  $R^{20}$ ,  $R^{21}$ , or  $R^{22}$  is  $-N(R^{24})R^{25}$ . In some embodiments,  $R^{20}$  or  $R^{21}$ , where applicable, is  $-N(R^{24})R^{25}$ . In some embodiments,  $R^{22}$  is  $-N(R^{24})R^{25}$ .

**[0124]** In some of these embodiments,  $R^{24}$  and  $R^{25}$  are independently hydrogen, or an optionally substituted moiety selected from alkyl and heteroalkyl. In some embodiments,  $R^{24}$  and  $R^{25}$  are independently hydrogen, or an optionally substituted alkyl. In some embodiments, at least one of  $R^{24}$  and  $R^{25}$  is hydrogen. In some embodiments, wherein  $R^{24}$  and  $R^{25}$  are hydrogen. In some embodiments, at least one of  $R^{24}$  and  $R^{25}$  is an optionally substituted alkyl. In some embodiments,  $R^{24}$  and  $R^{25}$  are independently an optionally

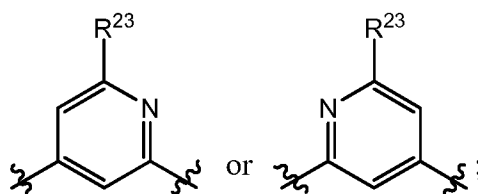
substituted alkyl. In some embodiments, at least one of  $R^{24}$  and  $R^{25}$  is methyl. In some embodiments,  $R^{24}$  and  $R^{25}$  are independently hydrogen, an optionally substituted alkyl,  $-C(O)R^{29}$ , or  $-S(O)_2R^{30}$ . In some embodiments, one of  $R^{24}$  and  $R^{25}$  is  $-C(O)R^{29}$  or  $-S(O)_2R^{30}$ . In some embodiments, one of  $R^{24}$  and  $R^{25}$  is  $-C(O)R^{29}$ . In some embodiments, one of  $R^{24}$  and  $R^{25}$  is  $-S(O)_2R^{30}$ .

**[0125]** In some of these embodiments,  $R^{29}$  is independently hydrogen, an optionally substituted alkyl,  $-N(R^{31})R^{32}$ , or  $-OR^{33}$ . In some embodiments,  $R^{29}$  is independently hydrogen, or an optionally substituted alkyl. In some embodiments,  $R^{29}$  is hydrogen. In some embodiments,  $R^{29}$  is an optionally substituted alkyl. In some embodiments,  $R^{29}$  is methyl. In some embodiments,  $R^{29}$  is independently  $-N(R^{31})R^{32}$ , or  $-OR^{33}$ . In some embodiments,  $R^{29}$  is  $-N(R^{31})R^{32}$ . In some embodiments,  $R^{29}$  is  $-OR^{33}$ .

**[0126]** In some of these embodiments,  $R^{31}$ ,  $R^{32}$ , and  $R^{33}$  are independently hydrogen, or an optionally substituted alkyl.

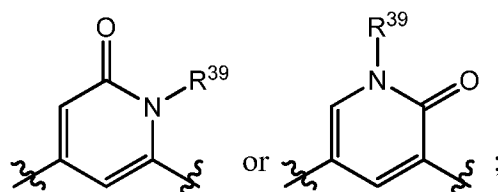
**[0127]** In some embodiments,  $R^{30}$  is an optionally substituted alkyl. In some embodiments,  $R^{30}$  is methyl.

**[0128]** In some of these embodiments,  $A^2$  has the formula:



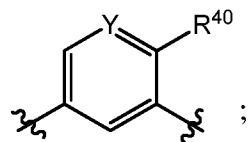
where  $R^{23}$  is halogen (e.g., F, Cl, Br or I) or an optionally substituted alkoxy (e.g., methoxy or trifluoromethoxy).

**[0129]** In some embodiments,  $A^2$  has the formula:



where each  $R^{39}$  is independently hydrogen or an optionally substituted alkyl. In some embodiments,  $R^{39}$  is hydrogen. In some embodiments,  $R^{39}$  is an optionally substituted alkyl. In some embodiments,  $R^{39}$  is an optionally substituted  $C_1$ - $C_6$  alkyl (e.g., methyl or ethyl).

**[0130]** In some embodiments,  $A^2$  has the formula:



where each  $R^{40}$  is independently halogen or an optionally substituted alkyl. In some embodiments,  $R^{40}$  is halogen (e.g., F, Cl, Br or I). In some embodiments,  $R^{40}$  is or an optionally substituted alkoxy (e.g., methoxy or trifluoromethoxy).

**[0131]** In some embodiments, the compound is of the formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, where  $X^1$  and  $X^2$  are independently N or CH. In some embodiments,  $X^1$  is N. In some embodiments,  $X^2$  is N. In some embodiments, each  $X^1$  and  $X^2$  is N. In some embodiments,  $X^1$  is CH. In some embodiments,  $X^2$  is CH. In some embodiments, each  $X^1$  and  $X^2$  is CH. In some embodiments,  $X^1$  is N and  $X^2$  is CH. In some embodiments,  $X^1$  is CH and  $X^2$  is N.

**[0132]** In some embodiments, the compound is of the formula I, II, III, IV or any variations thereof, where  $R^3$  is hydrogen,  $-N(R^8)R^9$ ,  $-S(O)_2R^{11}$ ,  $-C(O)R^{12}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl. In some embodiments,  $R^3$  is hydrogen. In some embodiments,  $R^3$  is  $-N(R^8)R^9$ ,  $-S(O)_2R^{11}$ ,  $-C(O)R^{12}$ . In some embodiments,  $R^3$  is an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl.

**[0133]** In some of these embodiments,  $R^3$  is hydrogen,  $-C(O)^tBu$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl. In some embodiments,  $R^3$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, and cycloalkyl-alkyl. In some embodiments,  $R^3$  is hydrogen or an optionally substituted alkyl. In some embodiments,  $R^3$  is hydrogen or an optionally substituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^3$  is hydrogen. In some embodiments,  $R^3$  is an optionally substituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^3$  is methyl. In some embodiments,  $R^3$  is  $-C(O)^tBu$ .

**[0134]** In some embodiments, substituents on an optionally substituted  $R^3$  may be one, two, three, or more groups selected from, but not limited to, hydroxyl, halo (such as F, Cl, Br, I),  $C_1$ - $C_6$  alkyl (e.g., methyl, ethyl, propyl, isopropyl) or  $C_1$ - $C_6$  alkoxy (methoxy, ethoxy, propoxy, isopropoxy, wherein each  $C_1$ - $C_6$  alkyl and  $C_1$ - $C_6$  alkoxy is optionally substituted with 1-3 halogens (e.g.,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCH_2F$ ,  $OCHF_2$ )).

**[0135]** In some embodiments, the compound is of the formula I, II, III, IV or any variations thereof, where  $R^5$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl. In some embodiments,  $R^5$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl. In some embodiments,  $R^5$  is hydrogen, or an optionally substituted alkyl. In some embodiments,  $R^5$  is hydrogen, or an optionally substituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^5$  is hydrogen. In some embodiments,  $R^5$  is an optionally substituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^5$  is a  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^5$  is an optionally substituted  $C_1$ - $C_3$  alkyl. In some embodiments,  $R^5$  is a  $C_1$ - $C_3$  alkyl. In some embodiments,  $R^5$  is methyl.

**[0136]** In some embodiments, substituents on an optionally substituted  $R^5$  may be one, two, three, or more groups selected from, but not limited to, hydroxyl, halo (such as F, Cl, Br, I),  $C_1$ - $C_6$  alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl) or  $C_1$ - $C_6$  alkoxy (methoxy, ethoxy, propoxy, isopropoxy, wherein each  $C_1$ - $C_6$  alkyl and  $C_1$ - $C_6$  alkoxy is optionally substituted with 1-3 halogens (*e.g.*,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{OCH}_2\text{F}$ ,  $-\text{OCHF}_2$ ).

**[0137]** In some embodiments, the compound is of the formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, where  $R^{7A}$  is an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl,  $-\text{alkyl-OR}^{10}$ ,  $-\text{alkyl-N(R}^8\text{)R}^9$ , heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl. In some embodiments,  $R^{7A}$  is an optionally substituted moiety selected from alkyl, cycloalkyl and cycloalkyl-alkyl. In some embodiments,  $R^{7A}$  is an optionally substituted alkyl. In some embodiments,  $R^{7A}$  is an optionally substituted  $C_1$ - $C_6$  alkyl. In some embodiments,  $R^{7A}$  is methyl.

**[0138]** In some embodiments,  $R^{7A}$  is an optionally substituted moiety selected from  $-\text{alkyl-OR}^{10}$  and  $-\text{alkyl-N(R}^8\text{)R}^9$ . In some embodiments,  $R^{7A}$  is an optionally substituted  $-\text{alkyl-OR}^{10}$ . In some embodiments,  $R^{7A}$  is  $-\text{CH}_2\text{OCH}_3$ .

**[0139]** In some embodiments,  $R^{7A}$  is an optionally substituted moiety selected from heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl. In some embodiments,  $R^{7A}$  is an optionally substituted aralkyl. In some embodiments,  $R^{7A}$  is optionally substituted  $-\text{alkylene-phenyl}$  (*e.g.* benzyl or 3-phenylpropyl).

**[0140]** In some embodiments,  $R^{7A}$  is an optionally substituted moiety selected from phenyl, pyrazolyl, furanyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, pyridyl, pyrimidyl, pyridazinyl, thiazolyl, triazolyl, thienyl, dihydrothieno-pyrazolyl, thianaphthenyl, carbazolyl,

benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, isoindolyl, acridinyl, benzoisazolyl, dimethylhydantoin, pyrazinyl, tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, morpholinyl, indolyl, diazepinyl, azepinyl, thiepinyl, piperidinyl, and oxepinyl. In some embodiments,  $R^{7A}$  is an optionally substituted moiety selected from pyridyl, phenyl, thiazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, isoxazolyl, pyrimidyl, pyrazinyl and furanyl. In some embodiments,  $R^{7A}$  is an optionally substituted moiety selected from pyridyl and imidazolyl (e.g. 1-methylimidazol-2-yl).

**[0141]** In some embodiments, substituents on an optionally substituted  $R^{7A}$  may be one, two, three, or more groups selected from, but not limited to, hydroxyl, halo (such as F, Cl, Br, I),  $C_1$ - $C_6$  alkyl (e.g., methyl, ethyl, propyl, isopropyl) or  $C_1$ - $C_6$  alkoxy (methoxy, ethoxy, propoxy, isopropoxy, wherein each  $C_1$ - $C_6$  alkyl and  $C_1$ - $C_6$  alkoxy is optionally substituted with 1-3 halogens (e.g.,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCH_2F$ ,  $-OCHF_2$ )).

**[0142]** In some embodiments, the compound is of the formula I, II, III, IV or any variations thereof, where  $R^{7A}$  is taken together with  $R^5$  to form an optionally substituted propylene. In some embodiments,  $R^{7A}$  is taken together with  $R^5$  to form an unsubstituted propylene. In some embodiments,  $R^{7A}$  is taken together with  $R^5$  to form an propylene optionally substituted with one, two, three, or more groups selected from, but not limited to, hydroxyl, halo (such as F, Cl, Br, I),  $C_1$ - $C_6$  alkyl (e.g., methyl, ethyl, propyl, isopropyl) or  $C_1$ - $C_6$  alkoxy (methoxy, ethoxy, propoxy, isopropoxy, wherein each  $C_1$ - $C_6$  alkyl and  $C_1$ - $C_6$  alkoxy is optionally substituted with 1-3 halogens (e.g.,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCH_2F$ ,  $-OCHF_2$ )).

**[0143]** In some embodiments, the compound is of the formula I, II, III or any variations thereof, where  $R^{7B}$  is  $R^4$ - $L^4$ - or taken together with  $R^{7A}$  and the carbon to which they are attached form a cycloalkyl ring substituted with  $R^4$ - $L^4$ -.

**[0144]** In some of these embodiments,  $R^4$  is hydrogen. In some embodiments,  $R^4$  is an optionally substituted moiety selected from alkyl and heteroalkyl. In some embodiments,  $R^4$  is an optionally substituted moiety selected from cycloalkyl, heterocycloalkyl, aryl, and heteroaryl. In some embodiments,  $R^4$  is an optionally substituted moiety selected from cycloalkyl and heterocycloalkyl. In some embodiments,  $R^4$  is an optionally substituted moiety selected from aryl and heteroaryl. In some embodiments,  $R^4$  is an optionally substituted aryl (e.g., phenyl, 4-fluorophenyl, 3,5-difluorophenyl or 3-fluorophenyl). In some embodiments,  $R^4$  is an optionally substituted heteroaryl. In some embodiments,  $R^4$  is phenyl, optionally substituted with one or more halogens. In some embodiments,  $R^4$  is phenyl, 4-

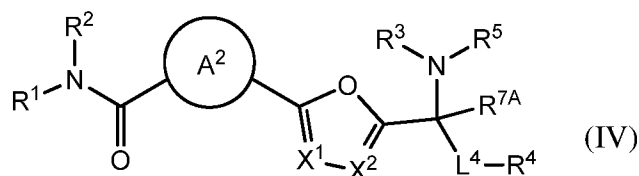
fluorophenyl, 3,5-difluorophenyl, or 3-fluorophenyl. In some embodiments,  $R^4$  is phenyl or 4-fluorophenyl. In some embodiments,  $R^4$  is phenyl. In some embodiments,  $R^4$  is 3,5-difluorophenyl. In some embodiments,  $R^4$  is 4-fluorophenyl. In some embodiments,  $R^4$  is 3-fluorophenyl.

**[0145]** In some embodiments, substituents on an optionally substituted  $R^4$  may be one, two, three, or more groups selected from, but not limited to, hydroxyl, halo (such as F, Cl, Br, I),  $C_1$ - $C_6$  alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl) or  $C_1$ - $C_6$  alkoxy (methoxy, ethoxy, propoxy, isopropoxy, wherein each  $C_1$ - $C_6$  alkyl and  $C_1$ - $C_6$  alkoxy is optionally substituted with 1-3 halogens (*e.g.*,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCH_2F$ ,  $-OCHF_2$ ).

**[0146]** In some of these embodiments,  $L^4$  is a bond, or an optionally substituted alkylene. In some embodiments,  $L^4$  is a bond. In some embodiments,  $L^4$  is an optionally substituted alkylene. In some embodiments,  $L^4$  is an optionally substituted  $C_1$ - $C_6$  alkylene. In some embodiments,  $L^4$  is a  $C_1$ - $C_6$  alkylene. In some embodiments,  $L^4$  is methylene (*e.g.*, when  $L^4$ - $R^4$  is (*e.g.*,  $-CH_2$ -phenyl or  $-CH_2$ -difluorophenyl).

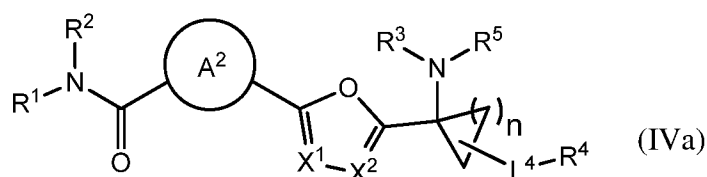
**[0147]** In some embodiments, substituents on an optionally substituted  $L^4$  may be one, two, three, or more groups selected from, but not limited to, hydroxyl, halo (such as F, Cl, Br, I),  $C_1$ - $C_6$  alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl) or  $C_1$ - $C_6$  alkoxy (methoxy, ethoxy, propoxy, isopropoxy, wherein each  $C_1$ - $C_6$  alkyl and  $C_1$ - $C_6$  alkoxy is optionally substituted with 1-3 halogens (*e.g.*,  $-CF_3$ ,  $-CHF_2$ ,  $-CH_2F$ ,  $-OCH_2F$ ,  $-OCHF_2$ ).

**[0148]** In some of these embodiments, the compound has the formula (IV):



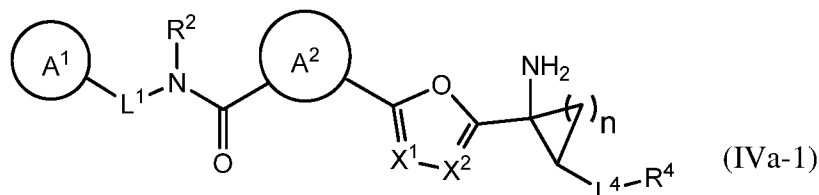
or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^2$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , and  $R^{7A}$  are as defined for Formula (I) and any variations thereof.

**[0149]** In some of these embodiments, the compound has the formula (IVa):

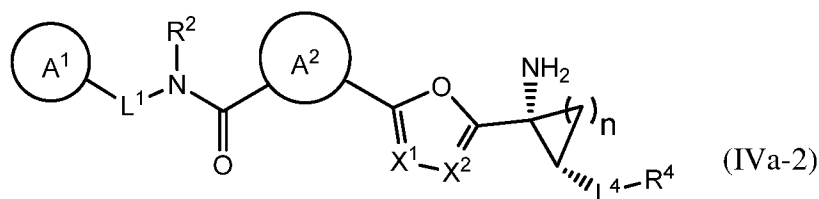




or a pharmaceutically acceptable salt or solvate thereof, wherein  $n$  is 1, 2, 3 or 4, and  $A^2$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^{7A}$  and  $R^{7B}$  are as defined for Formula (I) and any variations thereof. In some of these embodiments, the compound has the formula (IVa-1):

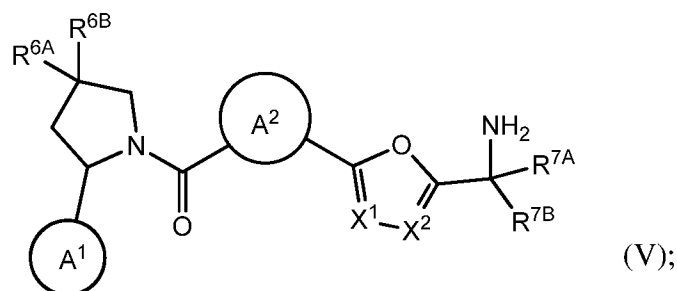


In some of these embodiments, the compound has the formula (IVa-2):



In some embodiments,  $n$  is 1. In some embodiments,  $n$  is 2. In some embodiments,  $n$  is 3. In some embodiments,  $n$  is 4.

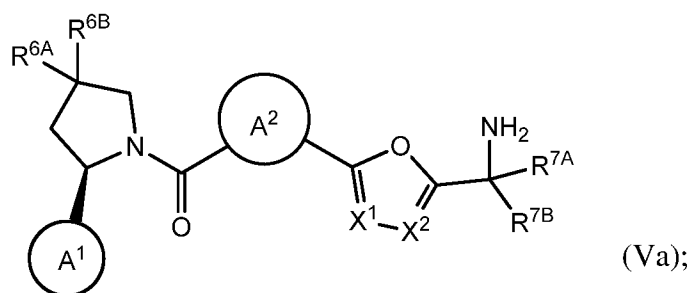
**[0150]** In some embodiments, the compound has the formula (V)



or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $A^2$ ,  $X^1$ ,  $X^2$ ,  $R^{6A}$ ,  $R^{6B}$ ,  $R^{7A}$  and  $R^{7B}$  are as defined for Formula (I) and any variations thereof. In some embodiments,  $R^{6A}$  is hydrogen. In some embodiments,  $R^{6A}$  is halogen (e.g. fluoro). In some embodiments,  $R^{6B}$  is hydrogen. In some embodiments,  $R^{6B}$  is halogen (e.g. fluoro). In some embodiments, both  $R^{6A}$  and  $R^{6B}$  are hydrogen. In some embodiments, both  $R^{6A}$  and  $R^{6B}$  are fluoro. In some embodiments,  $A^1$  is optionally substituted thiazolyl (e.g. 4-methylthiazol-2-yl or 4-(fluoromethyl)thiazol-2-yl). In some embodiments,  $A^1$  is optionally substituted oxazolyl (e.g. 4-methyloxazol-2-yl). In some embodiments,  $X^1$  is N. In some embodiments,  $X^2$  is N. In some embodiments, both  $X^1$  and  $X^2$  are N. In some embodiments,  $X^1$  is N and  $X^2$  is CH. In

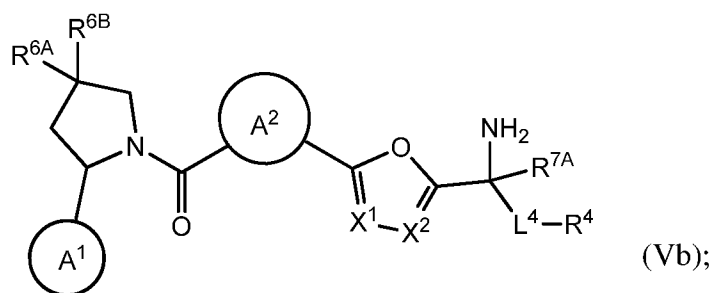
some embodiments,  $X^1$  is CH and  $X^2$  is N. In some embodiments, both  $X^1$  and  $X^2$  are CH. In some embodiments,  $R^{7A}$  is substituted or unsubstituted alkyl or substituted or unsubstituted heteroaryl. In some embodiments,  $R^{7A}$  is methyl. In some embodiments,  $R^{7B}$  is optionally substituted -alkylene-phenyl (e.g. benzyl or 4-fluorobenzyl).

**[0151]** In some embodiments, the compound has the formula (Va):



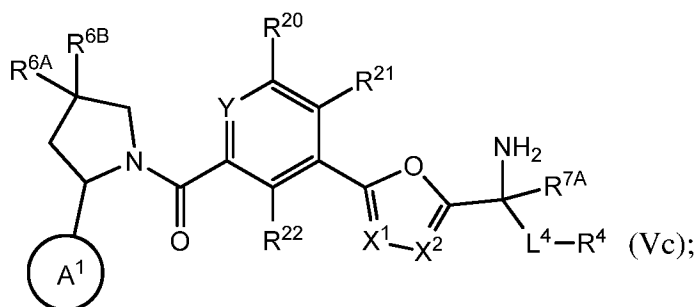
or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $A^2$ ,  $X^1$ ,  $X^2$ ,  $R^{6A}$ ,  $R^{6B}$ ,  $R^{7A}$  and  $R^{7B}$  are as defined for Formula (V).

**[0152]** In some embodiments, the compound has the formula (Vb):



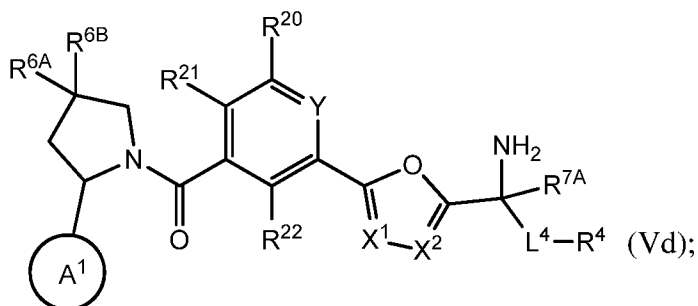
or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $A^2$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^4$ ,  $R^{6A}$ ,  $R^{6B}$  and  $R^{7A}$  are as defined for Formula (I) and any variations thereof. In some embodiments,  $A^1$ ,  $A^2$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^{6A}$ ,  $R^{6B}$  and  $R^{7A}$  are as defined for Formula (V). In some embodiments,  $L^4$  is methylene. In some embodiments,  $R^4$  is substituted or unsubstituted aryl (e.g. phenyl or 4-fluorophenyl). In some embodiments,  $A^1$  is optionally substituted thiazolyl and  $R^4$  is optionally substituted phenyl. In some embodiments,  $A^1$  is 4-methylthiazol-2-yl, 4-(fluoromethyl)thiazol-2-yl or 4-methyloxazol-2-yl and  $R^4$  is phenyl or 4-fluorophenyl.

**[0153]** In some embodiments, the compound has the formula (Vc):



or a pharmaceutically acceptable salt or solvate thereof, wherein A<sup>1</sup>, A<sup>2</sup>, L<sup>4</sup>, X<sup>1</sup>, X<sup>2</sup>, Y, R<sup>4</sup>, R<sup>6A</sup>, R<sup>6B</sup>, R<sup>7A</sup>, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> are as defined for Formula (I). In some embodiments, A<sup>1</sup>, A<sup>2</sup>, L<sup>4</sup>, X<sup>1</sup>, X<sup>2</sup>, Y, R<sup>4</sup>, R<sup>6A</sup>, R<sup>6B</sup>, R<sup>7A</sup>, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> are as described for any applicable variations of formula (I) detailed herein as if each and every variation is individually described. In some embodiments, A<sup>1</sup>, L<sup>4</sup>, X<sup>1</sup>, X<sup>2</sup>, R<sup>4</sup>, R<sup>6A</sup>, R<sup>6B</sup> and R<sup>7A</sup> are as defined for Formula (V). In some embodiments, each X<sup>1</sup> and X<sup>2</sup> is N. In some embodiments, one of X<sup>1</sup> and X<sup>2</sup> is N and the other is CH. In some embodiments, R<sup>7A</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl (e.g., methyl). In some embodiments, R<sup>6A</sup> and R<sup>6B</sup> are independently hydrogen or fluoro. In some embodiments, one of R<sup>6A</sup> and R<sup>6B</sup> is hydrogen and the other is fluoro. In some embodiments, each R<sup>6A</sup> and R<sup>6B</sup> is hydrogen. In some embodiments, each R<sup>6A</sup> and R<sup>6B</sup> is fluoro. In some embodiments, L<sup>4</sup> is methylene. In some embodiments, R<sup>4</sup> is substituted or unsubstituted aryl (e.g. phenyl or 4-fluorophenyl). In some embodiments, A<sup>1</sup> is optionally substituted thiazolyl and R<sup>4</sup> is optionally substituted phenyl. In some embodiments, A<sup>1</sup> is 2-methylthiazol-4-yl, 4-methylthiazol-2-yl, 4-ethylthiazol-2-yl, 4-cyclopropylthiazol-2-yl, 4-(fluoromethyl)thiazol-2-yl, 4-(methoxymethyl)thiazol-2-yl, 4,5-dimethylthiazol-2-yl or 4-methyloxazol-2-yl and R<sup>4</sup> is phenyl or 4-fluorophenyl. In some embodiments, R<sup>23</sup> is as described for any applicable variations of formula (I) detailed herein as if each and every variation is individually described.

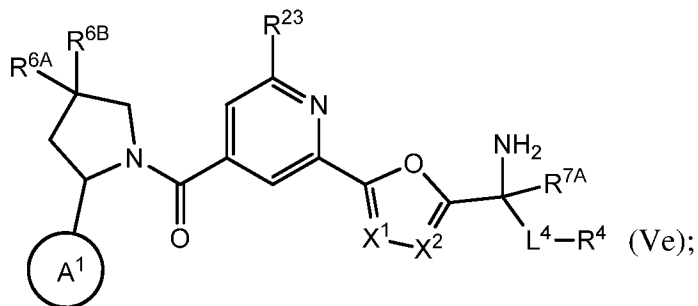
**[0154]** In some embodiments, the compound has the formula (Vd):



or a pharmaceutically acceptable salt or solvate thereof, wherein A<sup>1</sup>, A<sup>2</sup>, L<sup>4</sup>, X<sup>1</sup>, X<sup>2</sup>, Y, R<sup>4</sup>, R<sup>6A</sup>, R<sup>6B</sup>, R<sup>7A</sup>, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> are as defined for Formula (I). In some embodiments, A<sup>1</sup>, A<sup>2</sup>,

$L^4$ ,  $X^1$ ,  $X^2$ ,  $Y$ ,  $R^4$ ,  $R^{6A}$ ,  $R^{6B}$ ,  $R^{7A}$ ,  $R^{20}$ ,  $R^{21}$  and  $R^{22}$  are as described for any applicable variations of formula (I) detailed herein as if each and every variation is individually described. In some embodiments,  $A^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^4$ ,  $R^{6A}$ ,  $R^{6B}$  and  $R^{7A}$  are as defined for Formula (V). In some embodiments, each  $X^1$  and  $X^2$  is N. In some embodiments, one of  $X^1$  and  $X^2$  is N and the other is CH. In some embodiments,  $R^{7A}$  is  $C_1$ - $C_6$  alkyl (e.g., methyl). In some embodiments,  $R^{6A}$  and  $R^{6B}$  are independently hydrogen or fluoro. In some embodiments, one of  $R^{6A}$  and  $R^{6B}$  is hydrogen and the other is fluoro. In some embodiments, each  $R^{6A}$  and  $R^{6B}$  is hydrogen. In some embodiments, each  $R^{6A}$  and  $R^{6B}$  is fluoro. In some embodiments,  $L^4$  is methylene. In some embodiments,  $R^4$  is substituted or unsubstituted aryl (e.g. phenyl or 4-fluorophenyl). In some embodiments,  $A^1$  is optionally substituted thiazolyl and  $R^4$  is optionally substituted phenyl. In some embodiments,  $A^1$  is 2-methylthiazol-4-yl, 4-methylthiazol-2-yl, 4-ethylthiazol-2-yl, 4-cyclopropylthiazol-2-yl, 4-(fluoromethyl)thiazol-2-yl, 4-(methoxymethyl)thiazol-2-yl, 4,5-dimethylthiazol-2-yl or 4-methyloxazol-2-yl and  $R^4$  is phenyl or 4-fluorophenyl. In some embodiments,  $R^{23}$  is as described for any applicable variations of formula (I) detailed herein as if each and every variation is individually described.

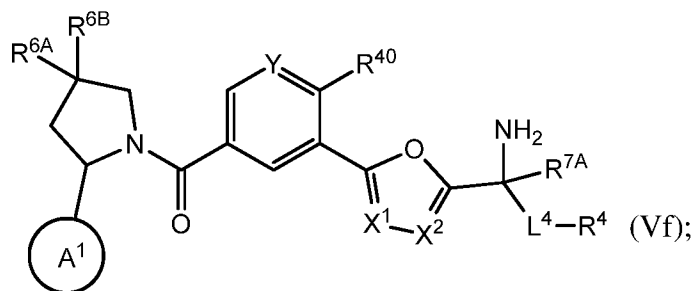
**[0155]** In some embodiments, the compound has the formula (Ve):



or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^4$ ,  $R^{6A}$ ,  $R^{6B}$ ,  $R^{7A}$  and  $R^{23}$  are as defined for Formula (I). In some embodiments,  $A^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^4$ ,  $R^{6A}$ ,  $R^{6B}$ ,  $R^{7A}$  and  $R^{23}$  are as described for any applicable variations of formula (I) detailed herein as if each and every variation is individually described. In some embodiments,  $A^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^4$ ,  $R^{6A}$ ,  $R^{6B}$  and  $R^{7A}$  are as defined for Formula (V). In some embodiments, each  $X^1$  and  $X^2$  is N. In some embodiments, one of  $X^1$  and  $X^2$  is N and the other is CH. In some embodiments,  $R^{7A}$  is  $C_1$ - $C_6$  alkyl (e.g., methyl). In some embodiments,  $R^{6A}$  and  $R^{6B}$  are independently hydrogen or fluoro. In some embodiments, one of  $R^{6A}$  and  $R^{6B}$  is hydrogen and the other is fluoro. In some embodiments, each  $R^{6A}$  and  $R^{6B}$  is hydrogen. In some embodiments, each  $R^{6A}$  and  $R^{6B}$  is fluoro. In some embodiments,  $L^4$  is methylene. In some

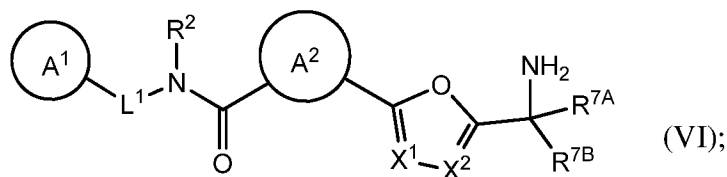
embodiments,  $R^4$  is substituted or unsubstituted aryl (e.g. phenyl or 4-fluorophenyl). In some embodiments,  $A^1$  is optionally substituted thiazolyl and  $R^4$  is optionally substituted phenyl. In some embodiments,  $A^1$  is 2-methylthiazol-4-yl, 4-methylthiazol-2-yl, 4-ethylthiazol-2-yl, 4-cyclopropylthiazol-2-yl, 4-(fluoromethyl)thiazol-2-yl 4-(methoxymethyl)thiazol-2-yl, 4,5-dimethylthiazol-2-yl or 4-methyloxazol-2-yl and  $R^4$  is phenyl or 4-fluorophenyl. In some embodiments,  $R^{23}$  is as described for any applicable variations of formula (I) detailed herein as if each and every variation is individually described.

**[0156]** In some embodiments, the compound has the formula (Vf):



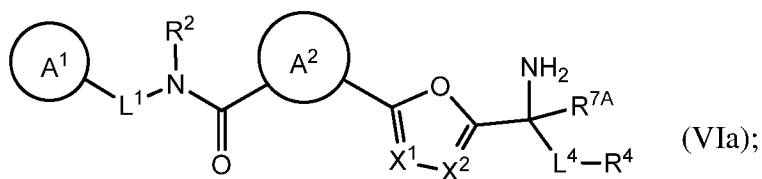
or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^4$ ,  $R^{6A}$ ,  $R^{6B}$  and  $R^{7A}$  are as defined for Formula (I),  $Y$  is N or CH,  $R^{40}$  is halogen or optionally substituted alkoxy. In some embodiments,  $Y$  is CH. In some embodiments,  $Y$  is N. In some embodiments,  $R^{40}$  is optionally substituted  $C_1$ - $C_6$  alkoxy (e.g., methoxy). In some embodiments,  $R^{40}$  is halogen (e.g., F, Cl, Br or I). In some embodiments,  $R^{40}$  is fluoro. In some embodiments,  $R^{40}$  is chloro. In some embodiments,  $A^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^4$ ,  $R^{6A}$ ,  $R^{6B}$  and  $R^{7A}$  are as described for any applicable variations of formula (I) detailed herein as if each and every variation is individually described. In some embodiments,  $A^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^4$ ,  $R^{6A}$ ,  $R^{6B}$  and  $R^{7A}$  are as defined for Formula (V). In some embodiments, each  $X^1$  and  $X^2$  is N. In some embodiments, one of  $X^1$  and  $X^2$  is N and the other is CH. In some embodiments,  $R^{7A}$  is  $C_1$ - $C_6$  alkyl (e.g., methyl). In some embodiments,  $R^{6A}$  and  $R^{6B}$  are independently hydrogen or fluoro. In some embodiments, one of  $R^{6A}$  and  $R^{6B}$  is hydrogen and the other is fluoro. In some embodiments, each  $R^{6A}$  and  $R^{6B}$  is hydrogen. In some embodiments, each  $R^{6A}$  and  $R^{6B}$  is fluoro. In some embodiments,  $L^4$  is methylene. In some embodiments,  $R^4$  is substituted or unsubstituted aryl (e.g. phenyl or 4-fluorophenyl). In some embodiments,  $A^1$  is optionally substituted thiazolyl and  $R^4$  is optionally substituted phenyl. In some embodiments,  $A^1$  is 2-methylthiazol-4-yl, 4-methylthiazol-2-yl, 4-ethylthiazol-2-yl, 4-cyclopropylthiazol-2-yl, 4-(fluoromethyl)thiazol-2-yl 4-(methoxymethyl)thiazol-2-yl, 4,5-dimethylthiazol-2-yl or 4-methyloxazol-2-yl and  $R^4$  is phenyl or 4-fluorophenyl.

[0157] In some embodiments, the compound has the formula (VI):



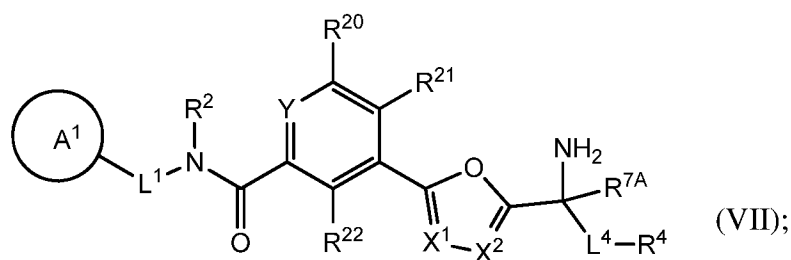
or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $A^2$ ,  $L^1$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^{7A}$  and  $R^{7B}$  are as defined for Formula (I) and any variations thereof. In some embodiments,  $A^1$  is optionally substituted thiazolyl (e.g. 4-methylthiazol-2-yl or 4-(fluoromethyl)thiazol-2-yl). In some embodiments,  $A^1$  is optionally substituted oxazolyl (e.g. 4-methyloxazol-2-yl). In some embodiments,  $L^1$  is methylene. In some embodiments,  $R^2$  is H or optionally substituted alkyl. In some embodiments,  $R^2$  is H. In some embodiments,  $R^2$  is optionally substituted alkyl (e.g. methyl). In some embodiments,  $R^2$  is optionally substituted cycloalkyl (e.g. cyclopropyl or cyclopentyl). In some embodiments,  $X^1$  is N. In some embodiments,  $X^2$  is N. In some embodiments, both  $X^1$  and  $X^2$  are N. In some embodiments,  $X^1$  is N and  $X^2$  is CH. In some embodiments,  $X^1$  is CH and  $X^2$  is N. In some embodiments, both  $X^1$  and  $X^2$  are CH. In some embodiments,  $R^{7A}$  is substituted or unsubstituted alkyl or substituted or unsubstituted heteroaryl. In some embodiments,  $R^{7A}$  is methyl. In some embodiments,  $R^{7B}$  is optionally substituted -alkylene-phenyl (e.g. benzyl or 4-fluorobenzyl).

[0158] In some embodiments, the compound has the formula (VIa):



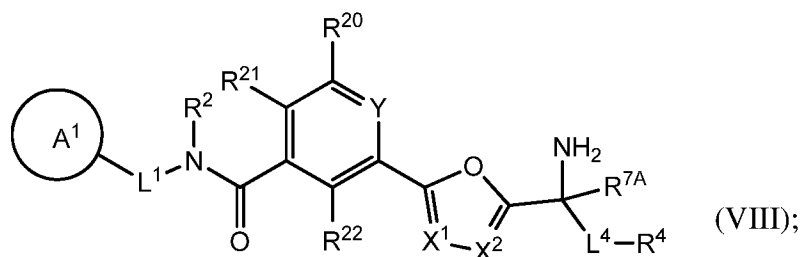
or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $A^2$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^4$  and  $R^{7A}$  are as defined for Formula (I) and any variations thereof. In some embodiments,  $A^1$ ,  $A^2$ ,  $L^1$ ,  $X^1$ ,  $X^2$ ,  $R^2$  and  $R^{7A}$  are as defined for Formula (VI). In some embodiments,  $L^4$  is methylene. In some embodiments,  $R^4$  is substituted or unsubstituted aryl (e.g. phenyl or 4-fluorophenyl). In some embodiments,  $A^1$  is optionally substituted thiazolyl and  $R^4$  is optionally substituted phenyl. In some embodiments,  $A^1$  is 4-methylthiazol-2-yl, 4-(fluoromethyl)thiazol-2-yl or 4-methyloxazol-2-yl and  $R^4$  is phenyl or 4-fluorophenyl.

[0159] In some embodiments, the compound has the formula (VII):



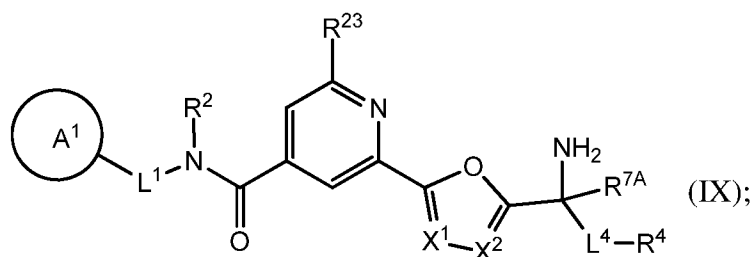
or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $Y$ ,  $R^2$ ,  $R^4$ ,  $R^{7A}$ ,  $R^{20}$ ,  $R^{21}$  and  $R^{22}$  are as defined for Formula (I) and any variations thereof. In some embodiments,  $A^1$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^4$  and  $R^{7A}$  are as defined for Formula (VI) or (VIa). In some embodiments,  $Y$  is CH. In some embodiments,  $Y$  is N. In some embodiments,  $R^{20}$  is hydrogen. In some embodiments,  $R^{22}$  is hydrogen. In some embodiments,  $R^{20}$  and  $R^{22}$  are both hydrogen. In some embodiments,  $R^{21}$  is hydrogen.

**[0160]** In some embodiments, the compound has the formula (VIII):



or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $Y$ ,  $R^2$ ,  $R^4$ ,  $R^{7A}$ ,  $R^{20}$ ,  $R^{21}$  and  $R^{22}$  are as defined for Formula (I) and any variations thereof. In some embodiments,  $A^1$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^4$  and  $R^{7A}$  are as defined for Formula (VI) or (VIa). In some embodiments,  $Y$  is CH. In some embodiments,  $Y$  is N. In some embodiments,  $R^{20}$  is hydrogen. In some embodiments,  $R^{22}$  is hydrogen. In some embodiments,  $R^{20}$  and  $R^{22}$  are both hydrogen. In some embodiments,  $R^{21}$  is hydrogen.

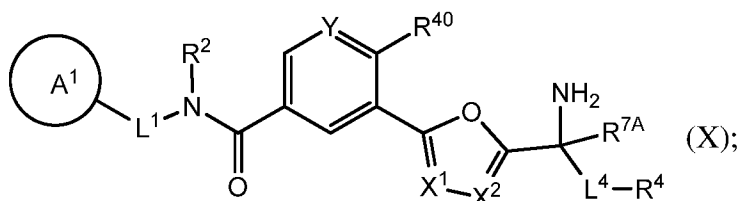
**[0161]** In some embodiments, the compound has the formula (IX):



or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^4$ ,  $R^{7A}$  and  $R^{23}$  are as defined for Formula (I). In some embodiments,  $A^1$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^4$ ,

$R^{7A}$  and  $R^{23}$  are as described for any applicable variations of formula (I) detailed herein as if each and every variation is individually described. In some embodiments,  $A^1$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^4$  and  $R^{7A}$  are as defined for Formula (VI) or (VIa). In some embodiments, each  $X^1$  and  $X^2$  is N. In some embodiments, one of  $X^1$  and  $X^2$  is N and the other is CH. In some embodiments,  $R^{7A}$  is  $C_1$ - $C_6$  alkyl (e.g., methyl). In some embodiments,  $L^4$  is methylene. In some embodiments,  $R^4$  is substituted or unsubstituted aryl (e.g. phenyl or 4-fluorophenyl). In some embodiments,  $A^1$  is optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted pyrazolyl, optionally substituted thiophenyl, optionally substituted oxadiazolyl, optionally substituted pyridyl or optionally substituted pyrazinyl. In some embodiments,  $L^1$  is optionally substituted  $C_1$ - $C_6$  alkylene (e.g., methylene or methylmethylene). In some embodiments,  $A^1$  is 2-methyloxazol-4-yl and 2,5-dimethyloxazol-4-yl). In some embodiments,  $A^1$  is thiazol-2-yl, 4-methylthiazol-2-yl, 4-ethylthiazol-2-yl, 4-bromothiazol-2-yl, 4-cyclopropylthiazol-2-yl, 4-(methoxymethyl)thiazol-2-yl, 4,5-dimethylthiazol-2-yl, and 2-methylthiazol-4-yl). In some embodiments,  $A^1$  is 2-thiophenyl. In some embodiments,  $A^1$  is 3-methyl-1,2,4-oxadiazol-5-yl. In some embodiments,  $A^1$  is 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 1,3-dimethylpyrazol-5-yl, 1-methylpyrazol-5-yl, and 1,5-dimethylpyrazol-4-yl). In some embodiments,  $A^1$  is 6-methylpyridin-3-yl, 6-methylpyridin-2-yl or 4-pyridyl. In some embodiments,  $A^1$  is 2-pyrazinyl. In some embodiments,  $R^2$  is hydrogen, an optionally substituted  $C_1$ - $C_6$  alkyl, or an optionally substituted  $C_3$ - $C_6$  cycloalkyl. In some embodiments,  $R^2$  is hydrogen. In some embodiments,  $R^2$  is methyl, ethyl, 2-fluoroethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl or *tert*-butyl. In some embodiments,  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In some embodiments,  $R^{23}$  is as described for any applicable variations of formula (I) detailed herein as if each and every variation is individually described.

**[0162]** In some embodiments, the compound has the formula (X):



or a pharmaceutically acceptable salt or solvate thereof, wherein  $A^1$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^4$  and  $R^{7A}$  are as defined for Formula (I), Y is N or CH,  $R^{40}$  is halogen or optionally substituted alkoxy. In some embodiments, Y is CH. In some embodiments, Y is N. In some embodiments,  $R^{40}$  is optionally substituted  $C_1$ - $C_6$  alkoxy (e.g., methoxy). In some



embodiments,  $R^{40}$  is halogen (e.g., F, Cl, Br or I). In some embodiments,  $R^{40}$  is fluoro. In some embodiments,  $R^{40}$  is chloro. In some embodiments,  $A^1$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^4$  and  $R^{7A}$  are as described for any applicable variations of formula (I) detailed herein as if each and every variation is individually described. In some embodiments,  $A^1$ ,  $L^1$ ,  $L^4$ ,  $X^1$ ,  $X^2$ ,  $R^2$ ,  $R^4$  and  $R^{7A}$  are as defined for Formula (VI) or (VIa). In some embodiments, each  $X^1$  and  $X^2$  is N. In some embodiments, one of  $X^1$  and  $X^2$  is N and the other is CH. In some embodiments,  $R^{7A}$  is  $C_1$ - $C_6$  alkyl (e.g., methyl). In some embodiments,  $L^4$  is methylene. In some embodiments,  $R^4$  is substituted or unsubstituted aryl (e.g. phenyl or 4-fluorophenyl). In some embodiments,  $L^1$  is optionally substituted  $C_1$ - $C_6$  alkylene (e.g., methylene or methylenemethylene). In some embodiments,  $A^1$  is optionally substituted thiazolyl, optionally substituted oxazolyl, optionally substituted pyrazolyl, optionally substituted thiophenyl, optionally substituted oxadiazolyl, optionally substituted pyridyl or optionally substituted pyrazinyl. In some embodiments,  $A^1$  is 2-methyloxazol-4-yl and 2,5-dimethyloxazol-4-yl). In some embodiments,  $A^1$  is thiazol-2-yl, 4-methylthiazol-2-yl, 4-ethylthiazol-2-yl, 4-bromothiazol-2-yl, 4-cyclopropylthiazol-2-yl, 4-(methoxymethyl)thiazol-2-yl, 4,5-dimethylthiazol-2-yl, and 2-methylthiazol-4-yl). In some embodiments,  $A^1$  is 2-thiophenyl. In some embodiments,  $A^1$  is 3-methyl-1,2,4-oxadiazol-5-yl. In some embodiments,  $A^1$  is 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 1,3-dimethylpyrazol-5-yl, 1-methylpyrazol-5-yl, and 1,5-dimethylpyrazol-4-yl). In some embodiments,  $A^1$  is 6-methylpyridin-3-yl, 6-methylpyridin-2-yl or 4-pyridyl. In some embodiments,  $A^1$  is 2-pyrazinyl. In some embodiments,  $R^2$  is hydrogen, an optionally substituted  $C_1$ - $C_6$  alkyl, or an optionally substituted  $C_3$ - $C_6$  cycloalkyl. In some embodiments,  $R^2$  is hydrogen. In some embodiments,  $R^2$  is methyl, ethyl, 2-fluoroethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl or *tert*-butyl. In some embodiments,  $R^2$  is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

**[0163]** In some embodiments, provided are any one, any combination, or all of the compounds of Table 1. In some embodiments, provided are any one, any combination, or all of the compounds detailed in Example 2, such a compound of Examples 2.1 to 2.213, or a pharmaceutically acceptable salt thereof.

**[0164]** In some embodiments, the compounds described herein (e.g., any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) is in substantially pure form. Unless otherwise stated, "substantially pure" intends a preparation of the compound that contains no more than 15 % impurity, wherein the impurity

intends compounds other than the indicated inhibitor compound, but does not include other forms of the inhibitor compound (*e.g.*, different salt form or a different stereoisomer, conformer, rotamer, or tautomer of the compound depicted). In one variation, a preparation of substantially pure compound is provided wherein the preparation contains no more than 25 % impurity, or no more than 20 % impurity, or no more than 10 % impurity, or no more than 5 % impurity, or no more than 3 % impurity, or no more than 1 % impurity, or no more than 0.5 % impurity. In some embodiments, the compound is present with no more than 15% or no more than 10% or no more than 5% or no more than 3% or no more than 1% of the total amount of compound in a different stereochemical form (*e.g.*, when the an S,S compound no more than 15% or no more than 10% or no more than 5% or no more than 3% or no more than 1% of the total R,R; S,R; and R,S form is present).

**[0165]** The compounds described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) and methods of using the same, unless otherwise stated, include all solvate and/or hydrate forms. In some embodiments, the compounds described herein can exist in unsolvated forms as well as solvated forms (*i.e.*, solvates). The compounds may also include hydrated forms (*i.e.*, hydrates).

**[0166]** The compounds described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1), as well as methods of using the same, unless otherwise stated, include all salt forms of the compounds. The compounds also include all non-salt forms of any salt of a compound described herein, as well as other salts of any salt of a compound described herein. In some embodiments, the salts of the compounds are pharmaceutically acceptable salts. The desired salt of a basic functional group of a compound may be prepared by methods known to those of skill in the art by treating the compound with an acid. The desired salt of an acidic functional group of a compound can be prepared by methods known to those of skill in the art by treating the compound with a base. Examples of inorganic salts of acid compounds include, but are not limited to, alkali metal and alkaline earth salts, such as sodium salts, potassium salts, magnesium salts, bismuth salts, and calcium salts; ammonium salts; and aluminum salts. Examples of organic salts of acid compounds include, but are not limited to, procaine, dibenzylamine, *N*-ethylpiperidine, *N,N'*-dibenzylethylenediamine, trimethylamine, and

triethylamine salts. Examples of inorganic salts of base compounds include, but are not limited to, hydrochloride and hydrobromide salts. Examples of organic salts of base compounds include, but are not limited to, tartrate, citrate, maleate, fumarate, and succinate. In some embodiments, the compounds in the salt form of hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (*e.g.*, (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures), succinates, benzoates and salts with amino acids such as glutamic acid. In some embodiments, the compounds described herein exist as a citrate salt (*e.g.*, mono citrate, hydrogen citrate, or dihydrogen citrate) and/or a mesylate salt (*e.g.*, dimesylate). These salts may be prepared by methods known to those skilled in the art.

**[0167]** The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

**[0168]** In addition to salt forms, also provided are compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the desired compound (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1). Additionally, prodrugs can be converted to the compounds described herein by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds described herein when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

**[0169]** Metabolites of the compounds are also embraced. Metabolites may include primary metabolites and/or secondary metabolites. However, metabolites of substances which occur naturally in subjects are excluded from the claimed compounds.

**[0170]** Unless stereochemistry is explicitly indicated in a chemical structure or chemical name, the chemical structure or chemical name is intended to embrace all possible stereoisomers, conformers, rotomers, and tautomers of the compound depicted. For example, a compound containing a chiral carbon atom is intended to embrace both the (*R*) enantiomer and the (*S*) enantiomer. A compound containing multiple chiral carbon atoms is intended to embrace all enantiomers and diastereomers (including (*R,R*), (*S,S*), (*R,S*), and (*S,R*) isomers). When a compound is explicitly indicated in a particular stereochemical arrangement (*e.g.*,

2S,3R), the compound may, in other embodiments, be described in another specific stereochemical arrangement (*e.g.*, 2R,3S) and/or a mixture of stereochemical arrangements.

**[0171]** A composition may contain the compound as mixtures of such stereoisomers, where the mixture may be enantiomers (*e.g.*, S,S and R,R) or diastereomers (*e.g.*, S,S and R,S or S,R) in equal or unequal amounts. A composition may contain the compound as a mixture of 2 or 3 or 4 such stereoisomers in any ratio of stereoisomers.

**[0172]** The compounds herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium ( $^3\text{H}$ ), iodine-125 ( $^{125}\text{I}$ ) or carbon-14 ( $^{14}\text{C}$ ). All isotopic variations or isotopologues of the compounds herein, whether radioactive or not, are contemplated.

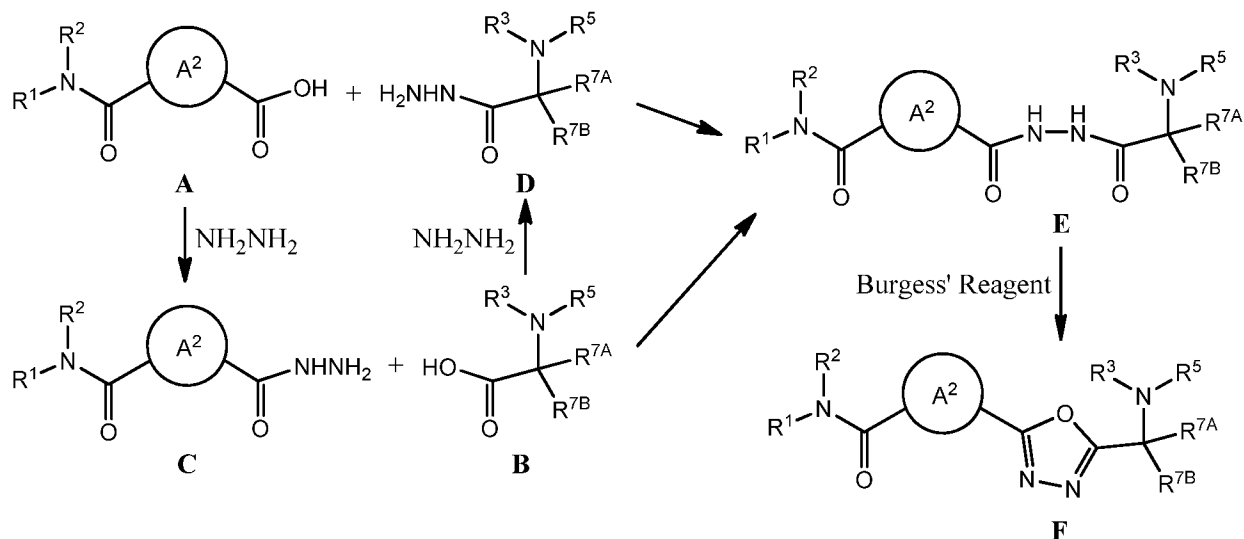
**[0173]** Included in all uses of the compounds disclosed herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1), is any or all of the stereochemical, enantiomeric, diastereomeric, conformational, rotameric, tautomeric, isotopic, solvate, hydrate, salt, and pharmaceutically acceptable salts of the compounds as described.

## II. General Synthetic Methods

**[0174]** The compounds herein are synthesized by an appropriate combination of generally well-known synthetic methods. Techniques useful in synthesizing the compounds herein are both readily apparent and accessible to those of skill in the relevant art in light of the teachings described herein. The discussion below is offered to illustrate certain of the diverse methods available for use in assembling the compounds herein. However, the discussion is not intended to define the scope of reactions or reaction sequences that are useful in preparing the compounds herein.

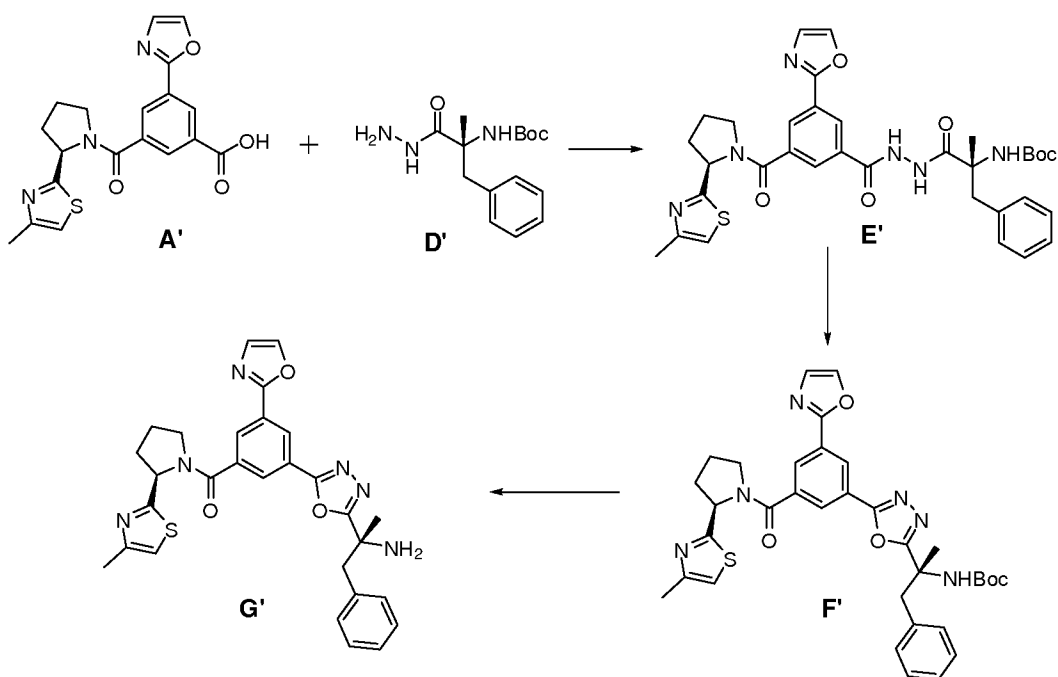
**[0175]** The oxadiazole compounds describe herein may be synthesized according to Scheme I. In one alternative, carboxylic acid **A** is converted to acyl hydrazide **C**, which is coupled with carboxylic acid **B** to form intermediate **E**. In another alternative, carboxylic acid **B** is converted to acyl hydrazide **D**, which is coupled with carboxylic acid **A** to form intermediate **E**. Intermediate **E** is treated with a dehydrating agent such as Burgess' Reagent to form the oxadiazole compound **F**. Appropriate protection groups are used when necessary in any of the reaction steps.

Scheme 1



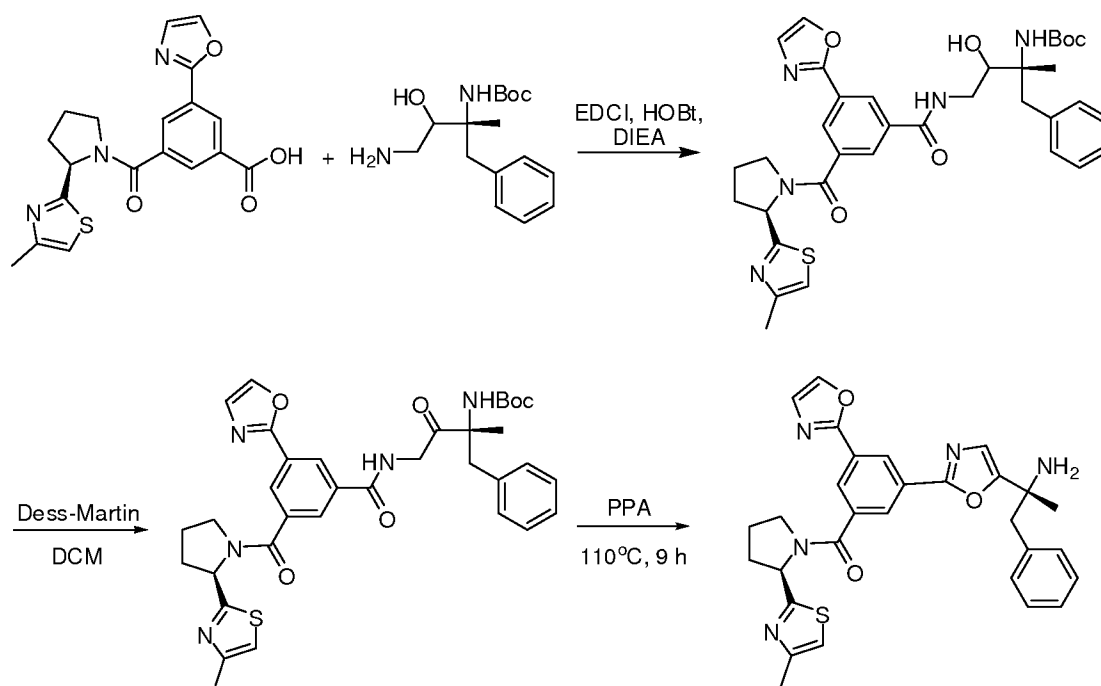
[0176] Scheme 2 shows an exemplary synthesis of an oxadiazole compound described herein according to Scheme 1. Coupling of acid A' with acyl hydrazide D' affords intermediate E', which undergoes cyclization to form oxadiazole F'. Deprotection of F' gives  $\beta$ -secretase inhibitor compound G'.

Scheme 2



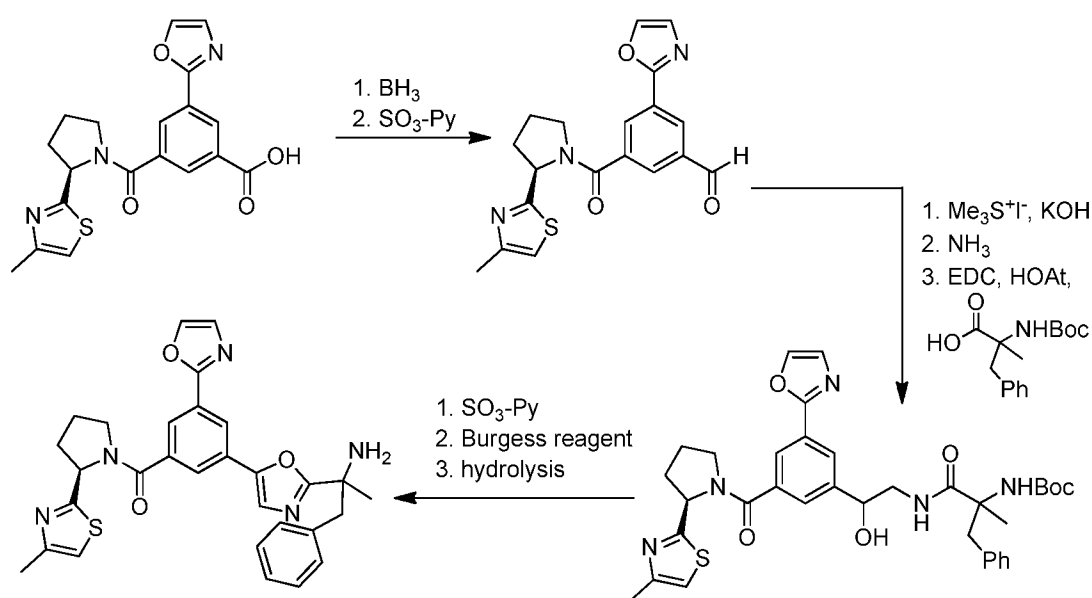
[0177] An exemplary synthesis of an oxazole compound is shown in Scheme 3.

Scheme 3



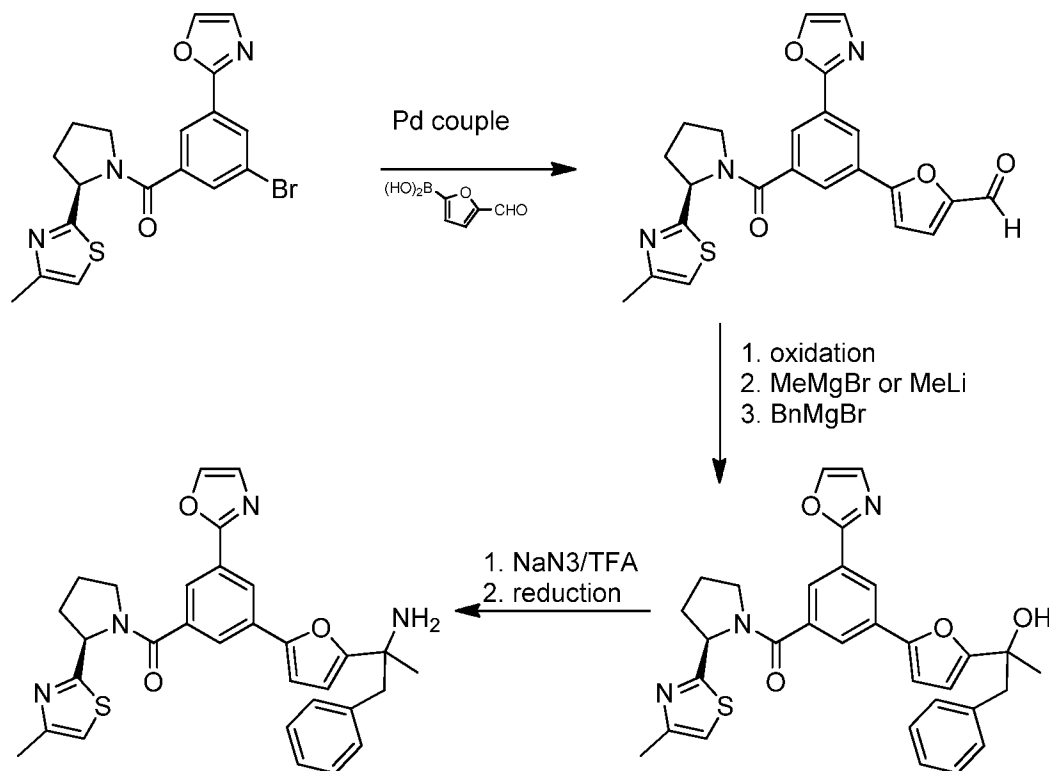
**[0178]** An oxazole compound of formula (I) where  $X_1$  is CH and  $X_2$  is N may be synthesized following the exemplary Scheme 4.

Scheme 4

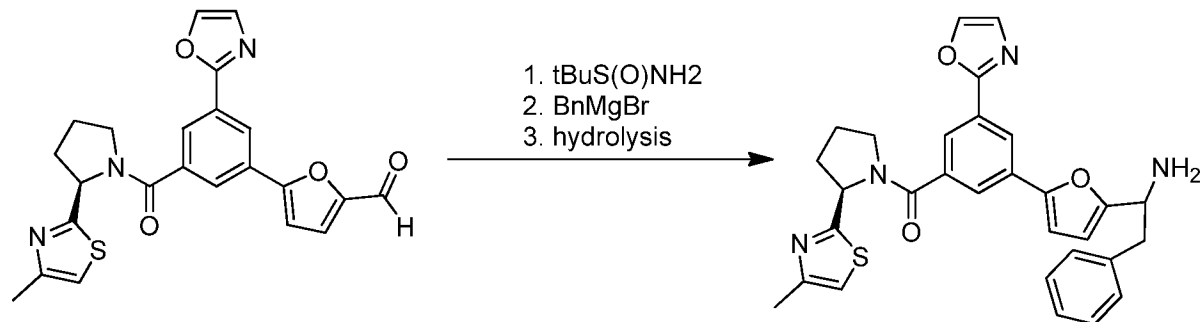


**[0179]** A furan compound of formula (I) where both  $X_1$  and  $X_2$  are CH may be synthesized following the exemplary Scheme 5a or 5b.

Scheme 5a



Scheme 5b



**[0180]** Compounds of formula (I) – (VIII) or any variations thereof may be synthesized following Scheme 1, 2 or 3 using appropriate starting materials, either available from commercial sources or synthesized following literature procedures or procedures described in Examples herein.

### III. Beta-Secretase Inhibitor Activity

**[0181]** To develop useful  $\beta$ -secretase inhibitors, candidate inhibitors capable of selectively mediating, *e.g.*, decreasing, memapsin 2 catalytic activity may be identified *in vitro* and subsequently tested for their ability to reduce the production of A $\beta$ . The activity of the inhibitor compounds can be assayed utilizing methods known in the art and/or those methods presented herein.

[0182] Compounds that decrease memapsin 2 catalytic activity may be identified and tested using biologically active memapsin 2, either recombinant or naturally occurring. Memapsin 2 can be found in native cells, isolated *in vitro*, or co-expressed or expressed in a cell. Measuring the reduction in the memapsin 2 catalytic activity in the presence of an inhibitor relative to the activity in the absence of the inhibitor may be performed using a variety of methods known in the art.

[0183] For example, the compounds may be tested for their ability to cause a detectable decrease in hydrolysis of a  $\beta$ -secretase site of a peptide in the presence of memapsin 2. These data can be expressed, for example, as  $K_i$ ,  $K_i$  apparent,  $V_i/V_o$ , or percentage inhibition.  $K_i$  is the inhibition equilibrium constant which indicates the ability of compounds to inhibit a given enzyme (such as memapsin 2, memapsin 1, and/or cathepsin D). Numerically lower  $K_i$  values indicate a higher affinity of the compounds herein for the enzyme. The  $K_i$  value is independent of the substrate concentration, and converted from  $K_i$  apparent.

[0184]  $K_i$  apparent is determined in the presence of substrate according to established techniques (see, for example, Bieth, J., *Bayer-Symposium V: Proteinase Inhibitors*, pp. 463-469, Springer-Verlag, Berlin (1994)). The standard error for the  $K_i$  apparent is the error from the nonlinear regression of the  $V_i/V_o$  data measured at different concentrations of the compounds herein (*e.g.*, between about 10 nM to about 1000 nM) employing well-known techniques (see, for example, Bieth, J., *Bayer-Symposium V: Proteinase Inhibitors*, pp. 463-469, Springer-Verlag, Berlin (1994), Ermolieff, J., *et al.*, *Biochemistry* 39:12450-12456 (2000), the teachings of which are incorporated herein by reference in their entirety).  $V_i/V_o$  depicts the ratio of initial conversion velocities of a substrate (Ermolieff, *et al.*, *Biochemistry* 40:12450-12456 (2000)) by an enzyme in the absence ( $V_o$ ) or presence ( $V_i$ ) of an inhibitor. A  $V_i/V_o$  value of 1.0 indicates that a compound does not inhibit the enzyme at the concentration tested. A  $V_i/V_o$  value less than 1.0 indicates that a compound herein inhibits enzyme activity.

[0185] In some embodiments, the compounds described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) are capable of reducing memapsin 2 beta-secretase activity. In some embodiments, the compounds have a memapsin 2 beta-secretase  $K_i$  and/or  $K_i$  apparent (*e.g.*, using any inhibitory assay described herein) of less than about any one of 10  $\mu$ M, 5  $\mu$ M, 1  $\mu$ M, or less than about any one of 750, 500, 400, 300, 200, 100, 50, 25, 10, 5, 2, or 1 nM; or from about 1



to 5, 1 to 10, 1 to 100, 1 to 300, 1 to 500, 1 to 1000, 100 to 500, 200 to 500, 300 to 500, 100 to 750, 200 to 750, 300 to 750, 400 to 750, 500 to 750, 100 to 1000, 250 to 1000, 500 to 1000, or 750 to 1000 nM. In some embodiments, the compounds have a memapsin 2 beta-secretase  $K_i$  and/or  $K_i$  apparent (*e.g.*, using any inhibitory assay described herein) of less than about 300, 301 to 500, or greater than 501 nM.

**[0186]** Once compounds are identified that are capable of mediating, *e.g.*, reducing, the hydrolysis of a  $\beta$ -secretase site of a peptide in the presence of memapsin 2, the compounds may be further tested for their ability to selectively inhibit memapsin 2 relative to other enzymes. Typically, the other enzyme is a peptide hydrolase, such as memapsin 1 or cathepsin D; or from another family of interest, such as Cytochrome P450 3A4 (CYP3A4). Compounds that decrease cathepsin D catalytic activity or memapsin 1 catalytic activity are tested using biologically active enzyme, either recombinant or naturally occurring. Cathepsin D or memapsin 1 catalytic activity can be found in native cells, isolated *in vitro*, or co-expressed or expressed in a cell. Inhibition by a compound described herein is measured using standard *in vitro* or *in vivo* assays such as those well known in the art or as otherwise described herein.

**[0187]** For example, selectivity of a compound may be measured by determining the extent to which memapsin 2 hydrolyzes a substrate peptide compared to the extent to which the same compound inhibits memapsin 1 and/or cathepsin D cleaving of a substrate peptide in the presence of the compound. Exemplary substrate peptides that are useful in determining the activity of memapsin 2 and or memapsin 1 include APP and derivatives thereof, such as FS-2 (MCA-SEVNLDAEFK-DNP; SEQ ID NO.: 2) (Bachem Americas, Torrance, CA).

Exemplary substrate peptides that are useful in determining the activity of cathepsin D include, for example, peptides which include the sequence MCA-GKPILFFRLK(DNP)-dR (SEQ ID NO.: 1). These substrate peptides can be synthesized using known peptide synthesis methods, *e.g.*, solid-phase peptide synthesis (*e.g.*, Fmoc amino acid coupling etc.). These data can be expressed, for example, as  $K_i$ ,  $K_i$  apparent,  $V_i/V_o$ , or percentage inhibition and depict the inhibition of a compound for memapsin 2 catalytic activity relative to memapsin 1 or cathepsin D catalytic activity. For example, if the  $K_i$  of a reaction between an inhibitor compound herein and memapsin 1 or cathepsin D is 1000 and the  $K_i$  of a reaction between an inhibitor compound herein and memapsin 2 is 100, the inhibitor compound inhibits the  $\beta$ -secretase activity of memapsin 2 with ten-fold selectivity over memapsin 1 or cathepsin D.

**[0188]** The compounds described herein may be capable of selectively inhibiting memapsin 2 over Cytochrome P450 3A4 (CYP3A4). CYP3A4 plays an important role in the metabolism of xenobiotics. Inhibition of CYP3A4 can lead to unwanted drug-drug interactions by modulating the metabolism of other therapeutics. Many patients, particularly those patients in advanced age seeking treatment for conditions such as Alzheimer's disease, are prescribed multiple therapeutics for various conditions, wherein drug-drug interactions caused by inhibition of CYP3A4 would be highly undesirable. Accordingly, the ability to selectively inhibit memapsin 2 over CYP3A4 (*e.g.*, not effect or minimally effect CYP3A4) may aid in decreasing unwanted drug-drug interactions leading to decreased toxicity and increased effectiveness of beta-secretase inhibitors. Some compounds described herein have been shown to exhibit strikingly selective inhibition of memapsin 2 in the presence of Cytochrome P450 3A4.

**[0189]** In some embodiments, the compounds described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) are capable of selectively reducing memapsin 2 relative to memapsin 1, cathepsin D and/or CYP3A4. In some embodiments, the compounds are capable of selectively reducing memapsin 2 relative to memapsin 1, cathepsin D, and/or CYP3A4 with greater than about 2-fold selectivity, or greater than about any one of 3, 5, 7, 10, 25, 50, 75, 100, 300, 200, 500, 750, 1000, 2000, 5000, or 10000-fold selectivity. In some embodiments, the compounds have a memapsin 2 beta-secretase  $K_i$  and/or  $K_i$  apparent (*e.g.*, using any inhibitory assay described herein) of less than about 10  $\mu$ M, 5  $\mu$ M, 1  $\mu$ M, or less than about any one of 750, 500, 400, 300, 250, 200, 100, 75, 50, 25, 10, 5, 2, or 1 nM, or from about any of 1 to 5, 1 to 10, 1 to 100, 1 to 250, 1 to 500, 1 to 1000, 100 to 500, 200 to 500, 300 to 500, 100 to 750, 200 to 750, 250 to 750, 300 to 750, 400 to 750, 500 to 750, 100 to 1000, 250 to 1000, 500 to 1000, or 750 to 1000 nM; and have a memapsin 1 and/or cathepsin D  $K_i$  and/or  $K_i$  apparent of more than about 10  $\mu$ M, 5  $\mu$ M, 1  $\mu$ M, or more than about any one of 750, 500, 400, 300, 200, 100, 50, 25, 10, 5, 2, or 1 nM, or from about any of 1 to 5, 1 to 10, 1 to 100, 1 to 300, 1 to 500, 1 to 1000, 100 to 500, 200 to 500, 300 to 500, 100 to 750, 200 to 750, 300 to 750, 400 to 750, 500 to 750, 100 to 1000, 250 to 1000, 500 to 1000, or 750 to 1000 nM. In some embodiments, the compounds have a memapsin 2 beta-secretase  $K_i$  and/or  $K_i$  apparent (*e.g.*, using any inhibitory assay described herein) of less than about 10  $\mu$ M, 5  $\mu$ M, 1  $\mu$ M, or less than about any one of 750, 500, 400, 300, 250, 200, 100, 50, 25, 10, 5, 2, or 1 nM, or from about any of

1 to 5, 1 to 10, 1 to 100, 1 to 250, 1 to 500, 1 to 1000, 100 to 500, 200 to 500, 300 to 500, 100 to 750, 200 to 750, 250 to 750, 400 to 750, 500 to 750, 100 to 1000, 250 to 1000, 500 to 1000, or 750 to 1000 nM; and have a CYP3A4  $K_i$  and/or  $K_i$  apparent of more than about 100  $\mu$ M, 50  $\mu$ M, 25  $\mu$ M, 10  $\mu$ M, 5  $\mu$ M, 1  $\mu$ M, or more than about any one of 750, 500, 400, 300, 200, 100, 50, 25, 10, 5, 2, or 1 nM, or from about any of 1 to 5, 1 to 10, 1 to 100, 1 to 300, 1 to 500, 1 to 1000, 100 to 500, 200 to 500, 300 to 500, 100 to 750, 200 to 750, 300 to 750, 400 to 750, 500 to 750, 100 to 1000, 250 to 1000, 500 to 1000, or 750 to 1000 nM.

**[0190]** Compounds demonstrating the ability to cause a detectable decrease in hydrolysis of a  $\beta$ -secretase site of a peptide in the presence of memapsin 2 (or, in addition, selectivity of action toward memapsin 2), may be tested in cell models or animal models for their ability to cause a detectable decrease in the amount or production of  $\beta$ -amyloid protein ( $A\beta$ ). For example, isosteric inhibitors of memapsin 2 have been tested for their ability to decrease  $A\beta$  production in cultured cells (see U.S. Patent Application Publication No. 20040121947, International Application No. PCT/US02/34324 (Publication No. WO 03/039454), and International Application No. PCT/US06/13342 (Publication No. WO 06/110668, the contents of which are hereby incorporated by reference)). Briefly, inhibitors may be added to a culture of cells (*e.g.*, human embryonic kidney (HEK293) cells, HeLa cells, Chinese hamster ovary cells, or neuroblastoma line SK-N-BE(2)) stably transfected if needed with a nucleic acid constructs that encode human APP and, if needed, a nucleic acid construct encoding human memapsin 2. Immunoprecipitation of  $A\beta$  followed by SDS-gel electrophoresis allows detection and quantitation of the amount of  $A\beta$  produced in the presence and absence of inhibitor.

**[0191]** In addition to cell cultures, animal models may be used to test inhibitors of memapsin 2 for their ability to decrease  $A\beta$  production. For example, an animal (*e.g.*, rat) may be administered an inhibitor orally or intravenously. The plasma may then be collected and  $A\beta$  levels determined by capture ELISA (BioSource International, Camarillo, CA).

**[0192]** In some embodiments, the compounds described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) are capable of reducing cellular  $A\beta$  production. In some embodiments, the compounds are capable of reducing cellular  $A\beta$  production with a  $IC_{50}$  (*e.g.*, using an  $A\beta$  inhibitory assay described herein) of less than about 10  $\mu$ M, 5  $\mu$ M, 1  $\mu$ M, or less than about 750, 500, 400, 300, 200, 100, 50, 25, 10, 5, 2, or 1 nM, or from about 1 to 5, 1 to 10, 1 to 100, 1 to 300, 1 to

500, 1 to 1000, 100 to 500, 200 to 500, 300 to 500, 100 to 750, 200 to 750, 300 to 750, 400 to 750, 500 to 750, 100 to 1000, 250 to 1000, 500 to 1000, or 750 to 1000 nM. In some embodiments, the compounds are capable of reducing cellular A $\beta$  production with a IC<sub>50</sub> (*e.g.*, using an A $\beta$  inhibitory assay described herein) of less than 1  $\mu$ M, between 1 and 5  $\mu$ M, or greater than 5  $\mu$ M.

**[0193]** The presence of inhibitors in organs of animal models or within cellular compartments may be ascertained using a fluorescent tag conjugated to the inhibitor and visualization via confocal microscopy (see U.S. Patent Application Publication No. 20040121947, and International Application No. PCT/USO2/34324 (Publication No. WO 03/039454), the contents of which are hereby incorporated by reference in their entireties).

**[0194]** The sample obtained from the mammal can be a fluid sample, such as a plasma or serum sample; or can be a tissue sample or extract, such as a brain biopsy. The amount of  $\beta$ -amyloid protein or a decrease in the production of  $\beta$ -amyloid protein can be measured using standard techniques (*e.g.*, western blotting and ELISA assays).

**[0195]** Further examples of assays for identifying memapsin 2- $\beta$ -secretase inhibitors are set forth in the Examples section below. Other methods for assaying the activity of memapsin 2, memapsin 1, cathepsin D, and CYP3A4 and the activity of agents that decrease the activity of these enzymes are known in the art. The selection of appropriate assay methods is well within the capabilities of those of skill in the art, particularly in view of the teaching provided herein.

#### *IV. Formulations*

**[0196]** In another aspect, provided are formulations (*e.g.*, pharmaceutical formulations) comprising a memapsin 2  $\beta$ -secretase inhibitor compound (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) with a carrier, such as a pharmaceutically acceptable carrier. The formulations may include optical isomers, diastereomers, or pharmaceutically acceptable salts of the inhibitors disclosed herein. The memapsin 2  $\beta$ -secretase inhibitor included in the formulation may be covalently attached to a carrier moiety. Alternatively, the memapsin 2  $\beta$ -secretase inhibitor included in the formulation is not covalently linked to a carrier moiety.

**[0197]** Suitable pharmaceutically acceptable carriers include water, salt solutions (such as Ringer's solution), alcohols, oils, gelatins and carbohydrates such as lactose, amylose or

starch, fatty acid esters, hydroxymethylcellulose, and polyvinyl pyrrolidine. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like which preferably do not deleteriously react with the intended compound of use.

**[0198]** The compounds described herein can be administered alone or can be coadministered to the individual. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances related to the treatment of a specified condition (*e.g.*, to reduce metabolic degradation).

**[0199]** The  $\beta$ -secretase inhibitors described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Thus, the compounds herein can be administered by injection (*e.g.*, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally). Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds herein can be administered transdermally. Compounds herein may also be administered locally (*e.g.*, ocular administration such as topical eye drops or ointment). It is also envisioned that multiple routes of administration (*e.g.*, intramuscular, oral, transdermal) can be used to administer the inhibitor compounds described herein. Accordingly, also provided are pharmaceutical formulations comprising a pharmaceutically acceptable carrier or excipient and one or more inhibitor compounds described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1).

**[0200]** For preparing pharmaceutical formulations from the compounds described herein, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substance, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

**[0201]** In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

**[0202]** The powders and tablets preferably contain from 5% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

**[0203]** For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

**[0204]** Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

**[0205]** When parenteral application is needed or desired, particularly suitable admixtures for the compounds herein are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-block polymers, and the like. Ampules are convenient unit dosages. The compounds herein can also be incorporated into liposomes or administered via transdermal pumps or patches. Pharmaceutical admixtures suitable for use herein are well-known to those of skill in the art and are described, for example, in *Pharmaceutical Sciences* (17th Ed., Mack Pub. Co., Easton, PA) and WO 96/05309, the teachings of both of which are hereby incorporated by reference.

[0206] Ocular administration preparations (*e.g.*, in use of glaucoma treatment) include, but are not limited to, formulations in saline, optionally with additional carriers, stabilizers, etc. known to those of skill in the art.

[0207] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0208] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0209] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0210] Also provided are unit dosage forms comprising the formulations described herein. These unit dosage forms can be stored in a suitable packaging in single or multiple unit dosages and may also be further sterilized and sealed. For example, the pharmaceutical formulation (*e.g.*, a dosage or unit dosage form of a pharmaceutical formulation) may include (i) an inhibitor (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) and (ii) a pharmaceutically acceptable carrier. In some embodiments, the formulation also includes one or more other compounds (or pharmaceutically acceptable salts thereof). In various variations, the amount of inhibitor compound in the formulation is included in any of the following ranges: about 5 to about 50 mg, about 20 to about 50 mg, about 50 to about 100 mg, about 100 to about 125 mg, about 125 to about 150 mg, about 150 to about 175 mg, about 175 to about 200 mg, about 200 to about 225 mg, about 225 to about 250 mg, about 250 to about 300 mg, about 300 to about

350 mg, about 350 to about 400 mg, about 400 to about 450 mg, or about 450 to about 500 mg. In some embodiments, the amount of compound in the formulation (*e.g.*, a dosage or unit dosage form containing any compound of formula I, II, III, or any variations thereof, Example 2 and/or Table 1) is in the range of about 5 mg to about 500 mg, such as about 30 mg to about 300 mg or about 50 mg to about 200 mg, of the compound.

**[0211]** Some compounds may have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60 and 80; Pluronic F-68, F-84 and P-103; cyclodextrin; polyoxyl 35 castor oil; or other agents known to those skilled in the art. Such co-solvents are typically employed at a level between about 0.01 % and about 2% by weight.

**[0212]** Viscosity greater than that of simple aqueous solutions may be desirable to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, combinations of the foregoing, and other agents known to those skilled in the art. Such agents are typically employed at a level between about 0.01% and about 2% by weight. Determination of acceptable amounts of any of the above adjuvants is readily ascertained by one skilled in the art.

**[0213]** The formulations described may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes.

#### **A. Effective Dosages**

**[0214]** Pharmaceutical formulations described include formulations wherein the active ingredient (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) is contained in an effective amount, *i.e.*, in an amount effective to achieve its intended purpose. The actual amount effective for a particular



application will depend, *inter alia*, on the condition being treated. For example, when administered in methods to treat Alzheimer's disease, such compositions will contain an amount of active ingredient effective to achieve the desired result (*e.g.*, decreasing  $\beta$ -secretase activity or  $\beta$ -amyloid production). Determination of an effective amount of a compound herein is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure herein.

**[0215]** The dosage and frequency (single or multiple doses) administered to a mammal can vary depending upon a variety of factors, including a disease that results in increased activity of memapsin 2 or increased accumulation of  $\beta$ -amyloid protein, whether the mammal suffers from another disease, and its route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated (*e.g.*, Alzheimer's disease), kind of concurrent treatment, complications from the disease being treated or other health-related problems. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds described herein. Adjustment and manipulation of established dosages (*e.g.*, frequency and duration) are well within the ability of those skilled in the art.

**[0216]** For any compound described herein, the effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of reducing the activity of memapsin 2 activity, as measured using the methods described herein or known in the art.

**[0217]** As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring memapsin 2 inhibition and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan, particularly in view of the teaching provided herein.

**[0218]** Dosages may be varied depending upon the requirements of the individual and the compound being employed. The dose administered to an individual, should be sufficient to affect a beneficial therapeutic response in the individual over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the

practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. In one embodiment, the dosage range is 0.001% to 10% w/v. In another embodiment, the dosage range is 0.1% to 5% w/v.

**[0219]** Additional examples of dosages which can be used are an effective amount within the dosage range of about 0.1 µg/kg to about 300 mg/kg, or within about 1.0 µg/kg to about 40 mg/kg body weight, or within about 1.0 µg/kg to about 20 mg/kg body weight, or within about 1.0 µg/kg to about 10 mg/kg body weight, or within about 10.0 µg/kg to about 10 mg/kg body weight, or within about 100 µg/kg to about 10 mg/kg body weight, or within about 1.0 mg/kg to about 10 mg/kg body weight, or within about 10 mg/kg to about 100 mg/kg body weight, or within about 50 mg/kg to about 150 mg/kg body weight, or within about 100 mg/kg to about 200 mg/kg body weight, or within about 150 mg/kg to about 250 mg/kg body weight, or within about 200 mg/kg to about 300 mg/kg body weight, or within about 250 mg/kg to about 300 mg/kg body weight. Other dosages which can be used are about 0.01 mg/kg body weight, about 0.1 mg/kg body weight, about 1 mg/kg body weight, about 10 mg/kg body weight, about 20 mg/kg body weight, about 30 mg/kg body weight, about 40 mg/kg body weight, about 50 mg/kg body weight, about 75 mg/kg body weight, about 100 mg/kg body weight, about 125 mg/kg body weight, about 150 mg/kg body weight, about 175 mg/kg body weight, about 200 mg/kg body weight, about 225 mg/kg body weight, about 250 mg/kg body weight, about 275 mg/kg body weight, or about 300 mg/kg body weight. Compounds herein may be administered in a single daily dose, or the total daily dosage may be administered in divided dosage of two, three or four times daily.

**[0220]** Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the clinical symptoms demonstrated by the particular individual. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, individual body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

## **B. Kits**

**[0221]** Also provided are kits for administration of the compounds described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb),

(Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1, formulations, and dosage forms thereof).

**[0222]** In certain embodiments the kits may include a dosage amount of at least one formulation as disclosed herein. Kits may further comprise suitable packaging and/or instructions for use of the formulation. Kits may also comprise a means for the delivery of the formulation thereof.

**[0223]** The kits may include other pharmaceutical agents for use in conjunction with the one or more compounds described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1). In some variations, the pharmaceutical agent(s) may be one or more anti-psychotic drugs. These agents may be provided in a separate form, or mixed with the compounds described herein, provided such mixing does not reduce the effectiveness of either the pharmaceutical agent or compound described herein and is compatible with the route of administration. Similarly the kits may include additional agents for adjunctive therapy or other agents known to the skilled artisan as effective in the treatment or prevention of the conditions described herein.

**[0224]** The kits may optionally include appropriate instructions for preparation and administration of the composition, side effects of the composition, and any other relevant information. The instructions may be in any suitable format, including, but not limited to, printed matter, videotape, computer readable disk, optical disc or directions to internet-based instructions.

**[0225]** In another aspect, provided are kits for treating an individual who suffers from or is susceptible to the conditions described herein, comprising a first container comprising a dosage amount of a formulation as disclosed herein, and instructions for use. The container may be any of those known in the art and appropriate for storage and delivery of intravenous formulation. In certain embodiments the kit further comprises a second container comprising a pharmaceutically acceptable carrier, diluent, adjuvant, etc. for preparation of the composition to be administered to the individual.

**[0226]** Kits may also be provided that contain sufficient dosages of the inhibitor (including formulation thereof) as disclosed herein to provide effective treatment for an individual for an extended period, such as 1-3 days, 1-5 days, a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months or more.

[0227] Kits may also include multiple doses of the compound and instructions for use and packaged in quantities sufficient for storage and use in pharmacies, for example, hospital pharmacies and compounding pharmacies.

[0228] The kits may include the compounds as described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) packaged in either a unit dosage form or in a multi-use form. The kits may also include multiple units of the unit dose form. In certain embodiments, provided are the compound described herein in a unit dose form. In other embodiments the compositions may be provided in a multi-dose form (*e.g.*, a blister pack, etc.).

### C. Toxicity

[0229] The ratio between toxicity and therapeutic effect for a particular compound is its therapeutic index and can be expressed as the ratio between LD<sub>50</sub> (the amount of compound lethal in 50% of the population) and ED<sub>50</sub> (the amount of compound effective in 50% of the population). Compounds that exhibit high therapeutic indices are preferred. Therapeutic index data obtained from cell culture assays and/or animal studies can be used in formulating a range of dosages for use in humans. The dosage of such compounds preferably lies within a range of plasma concentrations that include the ED<sub>50</sub> with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. See, *e.g.*, Fingl *et al.*, *In: THE PHARMACOLOGICAL BASIS OF THERAPEUTICS*, Ch.1, p.1, 1975. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the individual's condition and the particular method in which the compound is *used*.

### V. *Methods of Reducing the Activity of Memapsin 2 Beta-Secretase*

[0230] In another aspect, the  $\beta$ -secretase inhibitor compounds herein can be employed in methods to decrease memapsin 2 activity, decrease hydrolysis of a  $\beta$ -secretase site of a memapsin 2 substrate, and/or decrease the accumulation of  $\beta$ -amyloid protein relative to the amount of memapsin 2 activity, hydrolysis of a  $\beta$ -secretase site, and accumulation of  $\beta$ -amyloid protein, respectively, in the absence of the  $\beta$ -secretase inhibitor.

[0231] In an exemplary embodiment, a method of reducing memapsin 2 activity is provided. The method includes contacting a memapsin 2 with a  $\beta$ -secretase inhibitor

compound herein. The memapsin 2 may be contacted in any appropriate environment (*e.g.*, *in vitro*, *in vivo*). The memapsin 2 activity is decreased relative to the amount of activity in the absence of  $\beta$ -secretase inhibitor.

**[0232]** In another exemplary embodiment, a method is provided of selectively mediating (*e.g.*, reducing) memapsin 2 activity using an inhibitor described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1). Selective reduction of the activity of memapsin 2 means that memapsin 2 is not only reduced relative to its activity in the absence of inhibitor, but is reduced to a greater extent as compared to the reduction in activity due to inhibitor action against another enzyme, such as a peptide hydrolase (*e.g.*, cathepsin D, memapsin 1) and/or Cytochrome P450 3A4. For example, as described above, the reduction in activity of an enzyme may be expressed in terms of the inhibitory constant ( $K_i$ ). Where an inhibitor selectively reduces the activity of memapsin 2, the  $K_i$  of the reaction between an inhibitor compound described herein and memapsin 2 is less than the  $K_i$  of the reaction between an inhibitor compound herein and another peptide hydrolase and/or Cytochrome P450 3A4.

**[0233]** In some embodiments, the  $K_i$  of the reaction between an inhibitor compound (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) and memapsin 2 is less than the  $K_i$  of the reaction between an inhibitor compound and another peptide hydrolase (*e.g.*, cathepsin D, memapsin 1). In some related embodiments, the inhibitor selectively reduces the activity of memapsin 2 as compared to memapsin 1. In other related embodiments, the inhibitor selectively reduces the activity of memapsin 2 as compared to cathepsin D. In some embodiments, the  $K_i$  of the reaction between an inhibitor compound (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) and memapsin 2 is less than the  $K_i$  of the reaction between an inhibitor compound and Cytochrome P450 3A4. In an exemplary embodiment, the  $K_i$  of the reaction between an inhibitor compound herein and memapsin 2 is at least 2 times less than the  $K_i$  of the reaction between an inhibitor compound herein and another peptide hydrolase and/or Cytochrome P450 3A4. In another exemplary embodiment, the  $K_i$  of the reaction between an inhibitor compound herein and memapsin 2 is at least 3, 5, 7, 10, 25, 50, 75, 100, 300, 200, 500, 750, 1000, 2000, 5000, or 10000 times less

than the  $K_i$  of the reaction between an inhibitor compound herein and another peptide hydrolase and/or Cytochrome P450 3A4.

**[0234]** Thus, provided are methods of selectively reducing the activity of memapsin 2. The methods include contacting a memapsin 2 with a  $\beta$ -secretase inhibitor compound (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1). In a related embodiment, the method includes contacting the memapsin 2 with a  $\beta$ -secretase inhibitor in the presence of memapsin 1. In an alternative related embodiment, the method includes contacting the memapsin 2 with a  $\beta$ -secretase inhibitor in the presence of cathepsin D. In yet another related embodiment, the method includes contacting the memapsin 2 with a  $\beta$ -secretase inhibitor in the presence of cathepsin D and memapsin 1. In yet another embodiment, the method includes contacting the memapsin 2 with a  $\beta$ -secretase inhibitor in the presence of Cytochrome P450 3A4. In still another related embodiment, the method includes contacting the memapsin 2 with a  $\beta$ -secretase inhibitor in the presence of cathepsin D, memapsin 1, and Cytochrome P450 3A4.

**[0235]** In some embodiments, the activity of memapsin-2  $\beta$ -secretase may be determined by measuring the hydrolysis of a  $\beta$ -secretase site of a  $\beta$ -secretase substrate. Thus, described are methods of decreasing the hydrolysis of a  $\beta$ -secretase site of a  $\beta$ -secretase substrate by contacting a memapsin 2 with a  $\beta$ -secretase inhibitor compound (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1). In some embodiments, the hydrolysis of a  $\beta$ -secretase site is decreased relative the amount of hydrolysis in the absence of the inhibitor. In other embodiments, the hydrolysis is selectively reduced as compared to hydrolysis by memapsin 1 and/or cathepsin D. Thus, a method of selectively decreasing hydrolysis of a  $\beta$ -secretase site of a  $\beta$ -amyloid precursor protein relative to memapsin 1 and/or cathepsin D in a sample is provided. The method includes contacting a memapsin 2 with a  $\beta$ -secretase inhibitor compound.

**[0236]** In another embodiment, provided are methods of decreasing the amount of  $\beta$ -amyloid protein in a sample by contacting the memapsin 2 with an inhibitor compound (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1). The amount of  $\beta$ -amyloid protein in a sample is decreased relative the

amount of  $\beta$ -amyloid protein in the sample in the absence of the inhibitor. Thus, the accumulation of  $\beta$ -amyloid protein is thereby decreased.

**[0237]** Memapsin 2 may be contacted in any suitable environment or any suitable sample. For example, memapsin 2 may be contacted *in vitro*, within a cell, or within a mammal. Typically, *in vitro* solutions are selected such that the components do not substantially interfere with the enzymatic activity of memapsin 2 (*e.g.*, aqueous solutions). In some embodiments, the *in vitro* solution includes a biological sample, such as a mammalian sample. Exemplary mammalian samples include plasma or serum samples and tissue samples or extracts, such as a brain biopsy. Any appropriate cell or cellular sample may be selected in which to contact the memapsin 2 with the inhibitor. The cell may contain endogenous memapsin 2 or recombinant memapsin 2 as previously described (see U.S. Patent Application Publication No. 20040121947 (the contents of which are hereby incorporated by reference), and International Application No. PCT/USO2/34324 (Publication No. WO 03/039454)). Exemplary cells include human embryonic kidney (HEK293) cells, HeLa cells, Chinese hamster ovary cells, or neuroblastoma cell line SK-N-BE(2) (ATCC number CRL-2271), Hela cells, 293 cells. In an exemplary embodiment, the compounds herein are administered to a mammal to inhibit the hydrolysis of a  $\beta$ -secretase site of a  $\beta$ -amyloid precursor protein (*e.g.*, a mouse, rat or human).

#### VI. *Methods of Treating Alzheimer's Disease*

**[0238]** In another aspect, the  $\beta$ -secretase inhibitor compounds herein can be employed in the treatment of diseases or conditions associated with and/or mediated by  $\beta$ -secretase activity, hydrolysis of a  $\beta$ -secretase site of a  $\beta$ -amyloid precursor protein, and/or  $\beta$ -amyloid protein accumulation. Typically, a mammal is treated for the disease or condition. In an exemplary embodiment, the disease is Alzheimer's disease.

**[0239]** Thus, in some embodiments, provided are methods of treating Alzheimer's disease in a mammal comprising the step of administering to the mammal in need thereof an effective amount of a  $\beta$ -secretase inhibitor (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1). In some embodiments, the individual has one or more symptoms of Alzheimer's disease. In some embodiments, the individual has been diagnosed with Alzheimer's disease. The mammals treated with the inhibitors may be human primates, nonhuman primates or non-human mammals (*e.g.*,

rodents, canines). In one embodiment, the mammal is administered a compound herein that reduces  $\beta$ -secretase activity (inhibits memapsin 1 and memapsin 2 activity). In another embodiment, the mammal is administered a compound that selectively reduces memapsin 2 activity. In a related embodiment, the compound has minimal or no effect on reducing memapsin 1 activity. Therefore, also provided is a method of treating Alzheimer's disease in a subject in need thereof, the method comprising administering to the subject an effective amount of a  $\beta$ -secretase inhibitor compound. In an exemplary embodiment, the  $\beta$ -secretase inhibitor compound is part of a pharmaceutical formulation, as described above.

**[0240]** The inhibitor compounds herein can be employed in the treatment of diseases or conditions in an individual associated with  $\beta$ -secretase activity (*e.g.*, memapsin 2 activity), which can halt, reverse or diminish the progression of the disease or condition, in particular Alzheimer's disease. In some embodiments, the individual has one or more symptoms of the disease or condition associated with  $\beta$ -secretase activity. In some embodiments, the individual has been diagnosed with disease or condition associated with  $\beta$ -secretase activity. In addition to compounds that decrease memapsin 2 activity, compounds that selectively reduce memapsin 2 activity are useful to treat diseases or conditions or biological processes associated with memapsin 2 activity rather than diseases or conditions or biological processes associated with both memapsin 2 activity and another peptide hydrolase (such as cathepsin D or memapsin 1).

**[0241]** For example, both memapsin 1 and memapsin 2 cleave amyloid precursor protein (APP) at a  $\beta$ -secretase site to form  $\beta$ -amyloid protein (also referred to herein as A $\beta$  or  $\beta$ -amyloid protein). Thus, both memapsin 1 and memapsin 2 have  $\beta$ -secretase activity (Hussain, I., *et al.*, *J. Biol. Chem.* 276:23322-23328 (2001)). However, the  $\beta$ -secretase activity of memapsin 1 is significantly less than the  $\beta$ -secretase activity of memapsin 2 (Hussain, I., *et al.*, *J. Biol. Chem.* 276:23322-23328 (2001)). Memapsin 2 is localized in the brain, and pancreas, and other tissues (Lin, X., *et al.*, *Proc. Natl. Acad. Sci. USA* 97:1456-1460 (2000)) and memapsin 1 is localized preferentially in placentae (Lin, X., *et al.*, *Proc. Natl. Acad. Sci. USA* 97:1456-1460 (2000)). Alzheimer's disease is associated with the accumulation of A $\beta$  in the brain as a result of cleaving of APP by  $\beta$ -secretase (also referred to herein as memapsin 2, ASP2 and BACE). Thus, methods employing the compounds which selectively inhibit memapsin 2 activity relative to memapsin 1 activity may be important in the treatment of memapsin 2-related diseases, such as Alzheimer's disease. Selective



inhibition of memapsin 2 activity makes the compounds herein suitable drug candidates for use in the treatment of Alzheimer's disease.

#### VII. *Methods of Treating Glaucoma*

**[0242]** In another aspect, the  $\beta$ -secretase inhibitor compounds herein can be employed in the treatment of diseases associated with vision loss (*e.g.*, glaucoma). In some embodiments, provided are methods of treating glaucoma (*e.g.* closed-angle glaucoma and open-angle glaucoma) in an individual comprising the step of administering to the individual in need thereof an effective amount of the  $\beta$ -secretase inhibitors herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1). In an exemplary embodiment, the  $\beta$ -secretase inhibitor compound is part of a pharmaceutical formulation, as described above.

**[0243]** In some aspects, the inhibitor compounds herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) can be employed in the treatment of diseases or conditions associated with  $\beta$ -secretase activity, which can halt, reverse or diminish the progression of glaucoma (*e.g.* closed-angle glaucoma and open-angle glaucoma). In some embodiments, the inhibitor compounds herein can be used to halt, reverse or diminish the loss of retinal ganglion cells (RGCs). In other embodiments, compounds herein (*e.g.*, any compound of formula I, II, III, or any variations thereof, Example 2 and/or Table 1) are employed to improve or decrease intraocular pressure (IOP).

**[0244]** Compounds described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) may be used to treat glaucoma by one of several known routes of administration, including, but not limited to, orally (*e.g.*, in tablet or capsule form), parenterally (*e.g.*, injected into the anterior chamber, intravenous, intramuscular, or subcutaneous), or locally (*e.g.*, topical eye drops or ointment). Compounds herein may also be formulated for sustained release during glaucoma treatment.

**[0245]** Additional embodiments for treating glaucoma with compounds herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example

2 and/or Table 1) are described by adapting one or more of the methods in Guo, et. al. *Proc. Natl. Acad. Sci.*, 14, 13444-13449 (2007); Yamamoto, et. al., *Neuroscience Letters*, 370, 61-64 (2004); and/or Urcola et. al., *Exp. Eye Research*, 83, 429-437 (2006). The content of these applications are hereby incorporated by reference in its entirety.

#### **A. Methods of Administering Beta-Secretase Inhibitors to the CNS**

**[0246]** The inhibitor compounds of herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1) may be administered to the CNS through either invasive or non-invasive methods. Non-invasive methods of administration include those methods that do not require the use of a mechanical or physical means to breach the integrity of the blood-brain barrier. Typically, non-invasive methods include the use of immunoliposomes, blood-brain barrier disruption (BBBD), or the olfactory pathway.

**[0247]** Immunoliposomes are liposomes with antibodies or antibody fragments that bind to receptors or transporters expressed on brain capillary endothelial cells attached to the surface of the liposome. An exemplary immunoliposome combines polymer (*e.g.*, PEGylation) technology with that of chimeric peptide technology. For example, the  $\beta$ -secretase inhibitor may be packaged into a unilamellar lipid vesicle containing a PEG<sup>2000</sup> derivative that contains a reactive groups at one end, for attachment to a complementary reactive group of an antibody or fragment thereof. Complementary reactive groups are well known in the art and, include, for example, amine and activated carboxylic acids, thiols and maleimides, and the like (Ambikanandan et al., *J. Pharm Pharmaceut Sci* 6(2):252-273 (2003); Huwyler et al., *Proc. Natl. Acad. Sci. USA*, 93:14164-14169 (1996); and Huwyler et al., *J Pharmacol Exp Ther.* 282:1541-1546 (1997); and U.S. Pat. No. 6,372,250, all of which are herein incorporated by reference for all purposes in their entirety).

**[0248]** Blood-brain barrier disruption is a temporal loss of the integrity of the tight junctions between endothelial cells that comprise the blood brain barrier. Typically, the compound is administered via systemic or intercarotid injection in conjunction with transient blood-brain barrier disruption (BBBD). Exemplary agents useful for inducing BBBD include solvents such as dimethyl sulfoxide (DMSO); ethanol (EtOH); metals (*e.g.*, aluminum); X-irradiation; induction of pathological conditions (*e.g.*, hypertension, hypercapnia, hypoxia, or ischemia); anti-neoplastic agents (*e.g.*, VP-16, cisplatin, hydroxyurea, flurouracil and

etoposide); or concurrent systemic administration of the convulsant drug metrazol and the anti-convulsant drug pentobarbital (Ambikanandan et al., *J. Pharm Pharmaceut Sci* 6(2):252-273 (2003)); vasoactive leukotrienes (Black et al., *J Neurosurg*, 81(5):745-751 (1994)); intracarotid infusion of bradykinin, histamine, or the synthetic bradykinin compound RMP-7 (Miller et al., *Science* 297:1116-1118 (2002), Matsukado, et al., *Neurosurgery* 39:125-133 (1996), Abbott, et al., *Mol Med Today* 2:106-113 (1996), Emerich et al., *Clin Pharmacokinet* 40:105-123 (2001)); hyaluronidase (U.S. Patent Application Publication No. 20030215432, Kreil, et al. *Protein Sci.*, 4(9):1666-1669 (1995)); and intercarotid injection of inert hypertonic solutions such as mannitol, or arabinose (Neuwelt, E.A., et al., in Neuwelt EA (ed), *Implications of the Blood Brain Barrier and its Manipulation: Clinical Aspects*. Vol. 2, Plenum Press, New York, (1989), Neuwelt, et al., *J Nucl Med*, 35:1831-1841 (1994), Neuwelt et al., *Pediatr Neurosurg* 21:16-22 (1994), Kroll et al., *Neurosurg*, 42:1083-1099 (1998), Rapoport, *Cell Mol Neurobiol* 20:217-230 (2000), and Doran et al., *Neurosurg* 36:965-970, (1995)).

**[0249]** Olfactory pathway administration is the intranasal delivery of the compound to the olfactory nerves in the upper third of the nasal passages. After intranasal delivery, the compound is transported back along the sensory olfactory neurons to yield significant concentrations in the cerebral spinal fluid (CSF) and olfactory bulb (Thorne et al., *Brain Res*, 692(1-2):278-282 (1995); Thorne et al., *Clin Pharmacokinet* 40:907-946 (2001); Illum, *Drug Discov Today* 7:1184-1189 (2002); U.S. Pat. 6,180,603; U.S. Pat. 6,313,093; and U.S. Patent Application Publication No. 20030215398).

**[0250]** Invasive methods of administration are those methods that involve a physical breach of the blood-brain barrier typically through a mechanical or physical means to introduce the compound into the CSF, or directly into the parenchyma of the brain. Typically, invasive methods of administration may include injection or surgical implantation of the compound.

**[0251]** In injection methods, a needle is used to physically breach the BBB and deliver the compound directly into the CSF. Exemplary injection methods include intraventricular, intrathecal, or intralumbar routes of administration and may also involve infusion of the compound through a reservoir external to the body (Krewson et al., *Brain Res* 680:196-206 (1995); Harbaugh et al., *Neurosurg*. 23(6):693-698 (1988); Huang et al., *J Neurooncol* 45:9-17 (1999); Bobo et al. *Proc Natl Acad Sci USA* 91:2076-2082 (1994); Kroll et al., *Neurosurg*. 38(4): 746-752 (1996)).

**[0252]** In surgical implantation methods, the compound is placed directly into the parenchyma of the brain. Exemplary surgical implantation methods may include incorporation of the compound into a polyanhydride wafer placed directly into the interstitium of the brain (Bremet al., *Sci Med* 3(4):1-11 (1996); Brem et al., *J Control Release* 74:63-67 (2001)).

#### *VIII. Crystallized Complexes*

**[0253]** In another aspect, is provided a crystallized complex containing a memapsin 2 protein and a beta-secretase inhibitor herein. Memapsin 2 proteins useful in forming co-crystals with isostere compounds (*e.g.*, memapsin 2 protein fragments, transmembrane proteins, etc.) have been previously discussed in detail (see U.S. Patent Application Publication No. 20040121947, and International Application No. PCT/US02/34324 (Publication No. WO 03/039454)). These memapsin 2 proteins are equally useful in forming crystallized complexes with beta-secretase inhibitors described herein (*e.g.*, any compound of formula (I), (II), (III), (IIIa), (IV), (IVa), (IVa-1), (IVa-2), (V), (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (VI), (VIa), (VII), (VIII), (IX), (X) or any variations thereof, Example 2 and/or Table 1).

**[0254]** The crystallized complex may be formed employing techniques described in U.S. Patent Application Publication No. 20040121947, and International Application No. PCT/US02/34324 (Publication No. WO 03/039454). Briefly, a nucleic acid construct encoding the memapsin 2 protein is generated, and the protein is expressed in a host cell, such as a mammalian host cell (*e.g.*, Hela cell, 293 cell) or a bacterial host cell (*e.g.*, *E. coli*), the protein is then purified and crystallized with a compound or compounds herein. The diffraction resolution limit of the crystallized protein can be determined, for example, by x-ray diffraction or neutron diffraction techniques.

**[0255]** In an exemplary embodiment, the crystallized protein may have an x-ray diffraction resolution limit not greater than about 4.0 angstroms. The crystallized protein may also have an x-ray diffraction resolution limit not greater than about 4.0 angstroms, about 3.5 angstroms, about 3.0 angstroms, about 2.5 angstroms, about 2.0 angstroms, about 1.5 angstroms, about 1.0 angstroms, or about 0.5 angstroms. In some embodiments, the crystallized protein may also have an x-ray diffraction resolution limit not greater than about 2 angstroms. The diffraction resolution limit of the crystallized protein can be determined employing standard x-ray diffraction techniques.

[0256] The terms and expressions which have been employed herein are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding equivalents of the features shown and described, or portions thereof, it being recognized that various modifications are possible. Moreover, any one or more features of any embodiment described herein may be combined with any one or more other features of any other embodiment described herein, without departing from the envisioned scope. For example, the features of the  $\beta$ -secretase inhibitors described herein are equally applicable to the methods of treating disease states and/or the pharmaceutical formulations described herein. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

#### *IX. Examples*

##### ***Example 1: Preparation of Selected Beta-Secretase Inhibitors and Precursor Compounds***

[0257] The described synthesis of Beta-Secretase inhibitors and precursor compounds is related to WO 2006/110668, filed on 4/10/2006 and entitled "Compounds Which Inhibit Beta-Secretase Activity and Methods of Use Thereof," the content of which is incorporated herein by reference in its entirety, and particularly with respect to the synthetic methods described therein, *e.g.*, paragraphs 150-153 and paragraphs 215-285; and United States Provisional Patent Application No. 60/952,198, filed on 07/26/2007 and entitled "Compounds Which Inhibit Beta-Secretase Activity and Methods of Use Thereof," the content of which is incorporated herein by reference in its entirety, and particularly with respect to the synthetic methods described therein, *e.g.*, paragraphs 83-86 and paragraphs 161-354.

[0258] The precursor compounds synthesized below are useful in the methods of making compounds provided herein. Using the guidance provided, (for example, in the Exemplary Syntheses of Scheme 1) one skilled in the art will immediately recognize that the exemplified synthesis of the below precursor compounds may be modified using well known techniques and the teaching provided herein to arrive at a wide variety of inhibitor compounds (*e.g.*, compounds of Example 2). Certain starting materials described, and some precursor compounds not described, may be commercially available and purchased from, for example, Sigma-Aldrich, Alfa Aesar, or Ryan Scientific.

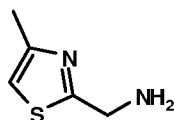
[0259] NMR spectra were collected on a commercially available NMR spectrometer such as a Varian Mercury model VX-300 NMR spectrometer or other commercially available NMR

spectrometers. NMR solvents were purchased from commercial sources such as Cambridge Isotope Laboratories and other commercial sources. Chemical shifts are reported in ppm and coupling constants (J) are reported in Hertz. In addition, characterization of some compounds was performed using standard LCMS instrumentation.

**[0260]** Solvents used in the synthesis of inhibitor compounds were purchased from commercial sources including, but not limited to, Aldrich, VWR, and EMD. Typically, solvents were ACS Reagent Grade or higher, and used without further purification.

**Example 1.1: Synthesis of amine building blocks.**

*Example 1.1.1: (4-methylthiazol-2-yl)methanamine*



**[0261]** Methylthiazole (1.0 g, 10.1 mmol) in tetrahydrofuran (THF) at  $-78\text{ }^{\circ}\text{C}$  was treated with n-BuLi (1.6 M, 7.56 mL) for 30 min, dimethylformamide (DMF) (1.4 mL, 18.2 mmol) was added dropwise. The resulting reaction mixture was warmed to r.t. After the starting material disappeared (by TLC), the reaction mixture was recooled to  $0\text{ }^{\circ}\text{C}$  and lithium aluminum hydride (LAH) (0.69 g, 18.5 mmol) was added. The mixture was warmed to r.t. and stirred for 1 h, the reaction was quenched with aqueous  $\text{NH}_4\text{Cl}$ , diluted with ethyl acetate (EtOAc). The organic solution was separated, extracted twice with EtOAc, dried with  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified with flash chromatography to give the corresponding alcohol as a light yellow oil.  $^1\text{H-NMR}$ : (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.89 (s, 1 H); 4.95 (s, 2 H); 2.48 (s, 3 H).

**[0262]** Methylthiazole methanol (0.57 g, 4.4 mmol) was treated with mesyl chloride (0.42 mL, 5.4 mmol) and triethyl ethylamine at  $0\text{ }^{\circ}\text{C}$  in dichloromethane. The resulting mixture was stirred for 20 minutes followed by quenching with aqueous  $\text{NH}_4\text{Cl}$ . Evaporation of the solvent from the organic layer and flash chromatography of the residue afforded the corresponding mesylate as an oil. The mesylate (0.25g, 1.2 mmol) was then dissolved in DMF and sodium azide (0.62g, 9.6 mmol) was added. The mixture was heated to reflux for 2 hours followed by cooling and washing with aqueous  $\text{NH}_4\text{Cl}$ . Evaporation of the solvent from the organic layer resulted in the corresponding azide. The azide (0.14g, 0.91mmol) was dissolved in ethyl acetate,  $\text{Pd}(\text{OH})_2$  (0.07g) was added, and the suspension was stirred under a hydrogen atmosphere for 5 hours. The suspension was filtered through Celite. Evaporation of the solvent and flash chromatography of the residue afforded the desired methylthiazole

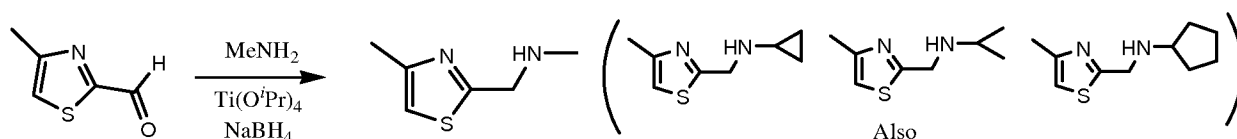
methylamine as a yellow oil.  $^1\text{H-NMR}$ : (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.74 (m, 1 H); 4.09 (m, 2 H); 2.37 (s, 3 H).

**[0263]** Using an alternative synthetic route,  $\text{NaBH}_4$  (0.75 g, 19.9 mmol, 1.3 eq) was added to a stirred solution of 4-methylthiazole-2-carbaldehyde (Aldrich, 1.7 ml, 2.0 g, 15.3 mmol, 1 eq) in 30 ml anhydrous MeOH at 0 °C. After 45 min the solvent was removed *in vacuo*. The residue was diluted with saturated aqueous  $\text{NH}_4\text{Cl}$  and extracted with EtOAc (x3). The combined organics were washed with brine (x1) and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was removed *in vacuo*. Purification via flash chromatography yielded (4-methylthiazol-2-yl)methanol in quantitative yield.

**[0264]** Diphenylphosphoryl azide (DPPA) (1.2 eq) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.2 eq) were added to a stirred solution of (4-methylthiazol-2-yl)methanol (1 eq) in 7 ml anh. toluene under Ar. After stirring overnight, the solvent was removed *in vacuo*. Purification via flash chromatography yielded 2-(azidomethyl)-4-methylthiazole.

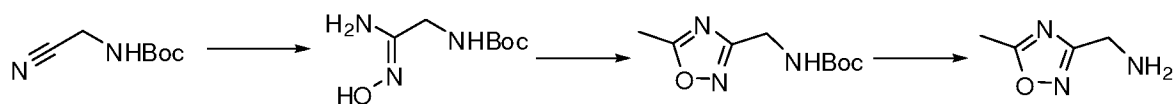
**[0265]** 2-(azidomethyl)-4-methylthiazole was dissolved in 5 ml MeOH.  $\text{Pd}(\text{OH})_2$  (20% by wt. on carbon) was added and the mixture was stirred vigorously under  $\text{H}_2$  overnight. The mixture was filtered through Celite, and the filter cake rinsed with MeOH. The solvent was removed *in vacuo* yielding (4-methylthiazol-2-yl)methanamine.

#### Example 1.1.2



**[0266]**  $\text{Ti}(\text{O}^i\text{Pr})_4$  (1.3 eq) was added with stirring to  $\text{MeNH}_2$  (2.0 M in MeOH, 3 eq) at 0 °C under Ar. After 15 min. the aldehyde (Aldrich, 1 eq) was added, and the solution was stirred for 2-3 h. The  $\text{NaBH}_4$  (1.4 eq) was added in batches, and the reaction was stirred at 0° C to room temperature overnight. The MeOH was removed via rotary evaporation. The residue was diluted with water/ $\text{CH}_2\text{Cl}_2$ , and a white ppt formed. The mixture was filtered through Celite, and the layers were separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (x3) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was removed via rotary evaporation. Purification via column chromatography yielded the product (80-85%).

## Example 1.1.3

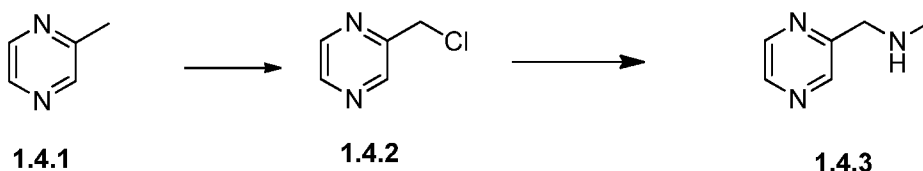


**[0267]** To a stirred solution of N-Boc-2-aminoacetonitrile (3.0g, 19.21 mmol) in a 4:1 mixture of EtOH and water (25mL) were added NaOH (860mg, 21.5mmol) and hydroxylamine hydrochloride 9 (1.44g, 20.7mmol) and the reaction was stirred for 30h. All the solvent was evaporated under reduced pressure. The solid was dissolved in water and the aqueous layer was extracted with EtOAc. The combined organic layers were dried on Na<sub>2</sub>SO<sub>4</sub> and concentrated to provide 1.8g of (Z)-tert-butyl 2-amino-2-(hydroxyimino)ethylcarbamate.

**[0268]** To a stirred solution of (Z)-tert-butyl 2-amino-2-(hydroxyimino)ethylcarbamate (945mg, 5 mmol) and EtOAc (2.0mL, 20.0 mmol) in EtOH (100mL) was added a solution of NaOEt in EtOH (13mL, 50.0mmol) and refluxed for 6h. The reaction mixture was cooled and all the solvent was evaporated under reduced pressure. The residue was dissolved in water and the aqueous layer was extracted with EtOAc. The combined organic layers were dried on Na<sub>2</sub>SO<sub>4</sub> and concentrated to provide 1.0g of tert-butyl (5-methyl-1,2,4-oxadiazol-3-yl)methylcarbamate.

**[0269]** tert-Butyl (5-methyl-1,2,4-oxadiazol-3-yl)methylcarbamate was converted into (5-methyl-1,2,4-oxadiazol-3-yl)methanamine using standard deprotection protocol of Boc group with TFA.

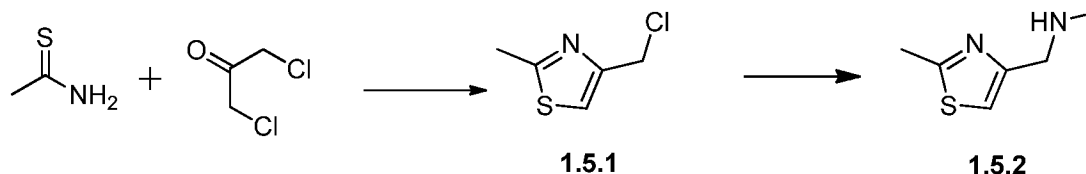
## Example 1.1.4: N-methyl-1-(pyrazin-2-yl)methanamine



**[0270]** A solution of **1.4.1** (3.0 g, 32 mmol) in CHCl<sub>3</sub> (100 mL) was heated to reflux and solid Trichloro isocyanuric acid (3.11 g, 13.4 mmol) was added in 4 portions in 1 hour and the reaction was refluxed overnight. The reaction mixture was filtered through celite and washed with 1N NaOH, dried and concentrated. The crude **1.4.2** (3.0g) was taken to the next step without purification.

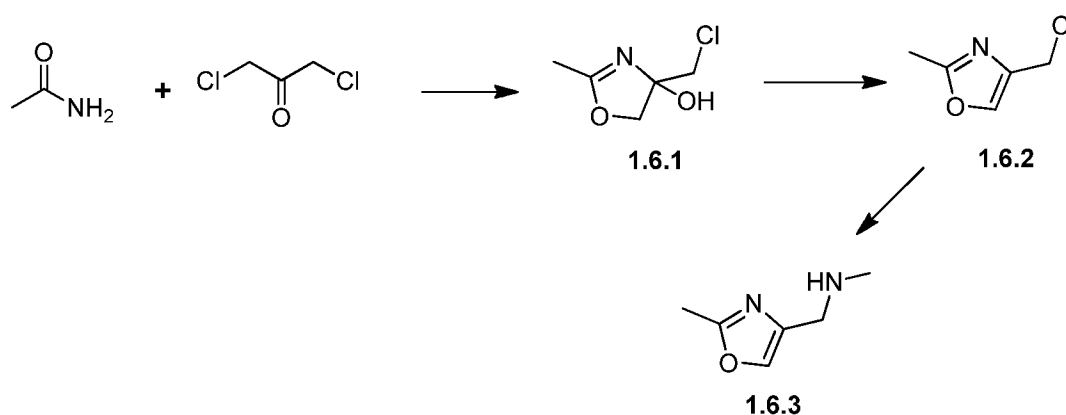
**[0271]** To an aq. solution of MeNH<sub>2</sub> (25 mL, 40% in water) was added neat **1.4.2** and stirred for 2h. Excess MeNH<sub>2</sub> was removed on rota-vapour, extracted with chloroform, dried and concentrated to give N-methyl-1-(pyrazin-2-yl)methanamine (1.8 g).



*Example 1.1.5: N-methyl-1-(2-methylthiazol-4-yl)methanamine*

**[0272]** To a solution of thioacetamide (5.0 g, 70 mmol) in EtOH( 50 mL) was added 1,3-dichloropropanone (8.5 g, 70 mmol) and the mixture was refluxed for 5.5h. Solvent was evaporated. The residue was dissolved in water and adjusted to pH ~ 8 with addition of solid NaHCO<sub>3</sub>. The mixture was extracted with ether, dried and concentrated. The crude **1.5.1** (6.0g) was taken to the next step without purification.

**[0273]** To an aq. solution of MeNH<sub>2</sub> (25 mL, 40% in water) was added neat **1.5.1** and stirred for 2h. Excess MeNH<sub>2</sub> was removed on a rota-vapour, extracted with chloroform, and dried. The residue was acidified to pH~1 and extracted with CHCl<sub>3</sub>. The aq. layer was adjusted to pH ~ 8 with addition of solid NaHCO<sub>3</sub> and extracted with CHCl<sub>3</sub> to give N-methyl-1-(2-methylthiazol-4-yl)methanamine (2.5 g).

*Example 1.1.6: N-methyl-1-(2-methyloxazol-4-yl)methanamine*

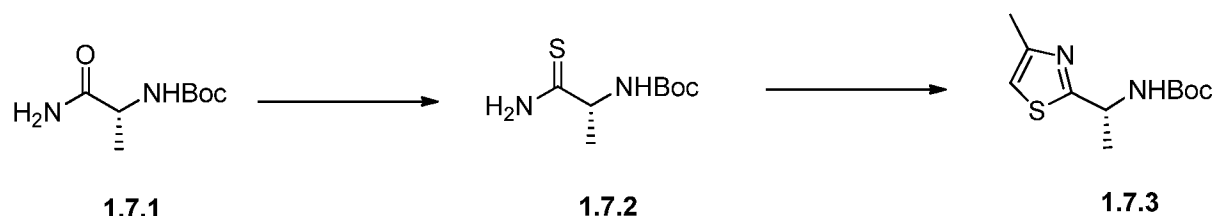
**[0274]** To a solution of acetamide (5.0 g, 85.0 mmoles) and 1,3-dichloro acetone (10.7 g, 85.0 mmoles) in acetone (100mL) were added NaHCO<sub>3</sub> (7.2 g, 85.0 mmoles) and MgSO<sub>4</sub> (13.65 g, 113 mmoles) and refluxed for 60h. The reaction mixture was filtered through Celite and concentrated, and chromatographed on silica gel (80% ether/ 20% pentane) to yield 20 % of **1.6.1**.

**[0275]** A solution of **1.6.1** (2.56 g, 17.2 mmoles) in 1,2-dichloroethane (10 mL) was added to a solution of thionyl chloride (1.5 mL, 20.6 mmoles) in 1,2-dichloroethane (40 mL) at 0°C. The solution was heated at 70 °C for 15-20 min, cooled to room temperature and concentrated. The residue was dissolved in water and brought to pH~8 with solid NaHCO<sub>3</sub>

and extracted with ether, dried, concentrated to yield 88 % of crude **1.6.2**, which was not purified.

**[0276]** To an aq. solution of MeNH<sub>2</sub> (25 mL, 40% in water) was added neat **1.6.2** and stirred for 2h. Excess MeNH<sub>2</sub> was removed on rota-vapour, extracted with chloroform, dried and concentrated to give N-methyl-1-(2-methyloxazol-4-yl)methanamine in quantitative yield.

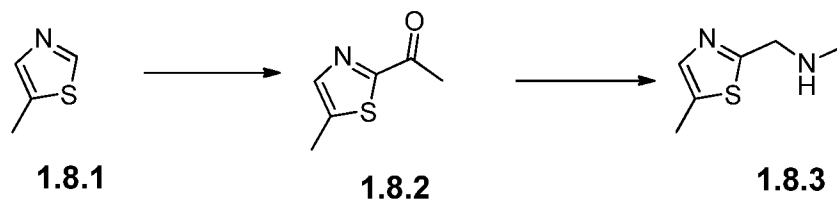
*Example 1.1.7: (R)-tert-butyl (1-(4-methylthiazol-2-yl)ethyl)carbamate*



**[0277]** To a solution of **1.7.1** (1.38 g, 7.34 mmol) in 1, 2-DME (35 mL) was added Lawesson's reagent (1.55 g, 3.82 mmol) and stirred for 4h. All solvent was evaporated, and diluted with 100 mL of saturated NaHCO<sub>3</sub> and extracted with ether (2 X 200 mL). The combined organic layers are dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was chromatographed on silica gel (35% ethyl acetate/ 75% hexane) to yield 1.5 g of **1.7.2**.

**[0278]** A mixture of Boc-D-alanine-thioamide (1.5 g, 7.35 mmol), chloroacetone (0.65 mL, 8.18 mmol) and calcium carbonate (1.0g, 10.22mmol) were refluxed in ethanol (25mL) for 4h. The reaction was cooled to room temperature and quenched with 20mL of saturated aq. NaHCO<sub>3</sub> solution. Ethanol was evaporated under reduced pressure and extracted with ethyl acetate (2 x 30mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was chromatographed on silica gel (20% ethyl acetate/ 80% hexane) to yield 600 mg of (R)-tert-butyl (1-(4-methylthiazol-2-yl)ethyl)carbamate.

*Example 1.1.8: N-methyl-1-(5-methylthiazol-2-yl)methanamine*

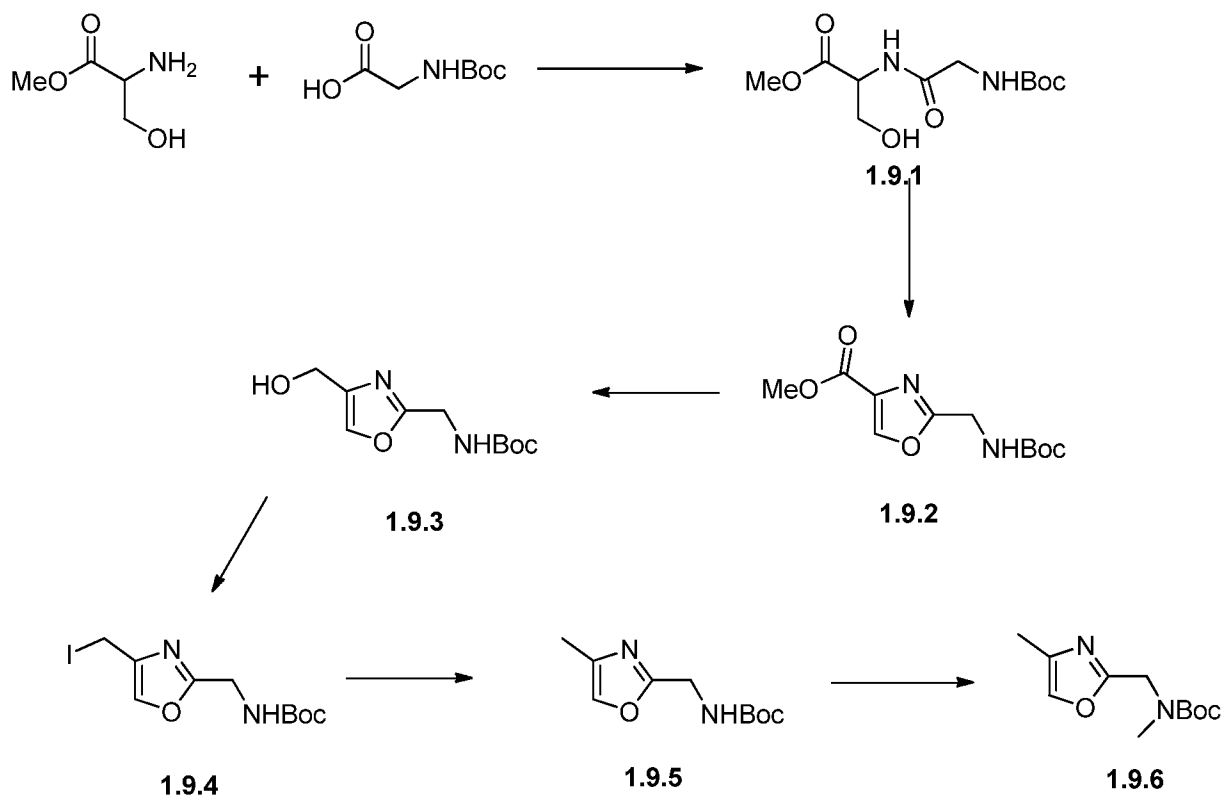


**[0279]** To a solution of BuLi (1.6 M in hexanes, 12.6 mL, 20.2 mmoles) in 25mL of diethyl ether at -78°C, was added a solution of 5-methyl thiazole **1.8.1** (2.0g, 20.2 mmoles) in ether (6mL), drop-wise and stirred at -78°C for 1.5h. Then a solution of DMF (2.33mL, 30.3 mmoles in ether (5 mL) was added at once and the reaction mixture was allowed to warm to

RT and stirred overnight. Some ice was added to the reaction mixture and 4N HCl was added slowly. This was taken up in a separating funnel, 30mL of ether was added, and the mixture shaken. The organic layer was discarded. The aqueous layer was brought to pH~7.5 with solid NaHCO<sub>3</sub> and extracted with ether twice. The ether layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated and the crude product **1.8.2** (1.6g) was carried over to the next-step without purification.

**[0280]** Ti (O<sup>i</sup>Pr)<sub>4</sub> (1.3 eq) was added with stirring to MeNH<sub>2</sub> (2.0 M in MeOH, 3 eq) under Ar. After 5 min. the aldehyde **1.8.2** (1 eq) was added, and the solution was stirred for 1-2 h. The reaction was cooled to 0° C and the NaBH<sub>4</sub> (1.3 eq) was added. The solution was stirred at 0° C to RT overnight. After quenching the reaction with water the mixture was filtered through Celite to remove the white ppt. MeOH was removed *in vacuo*. The residue was diluted with EtOAc. The resulting solution was washed with water (x3), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganic material was filtered off, and the solvent was removed *in vacuo* to give the crude product. Purification via column chromatography yielded the pure product N-methyl-1-(5-methylthiazol-2-yl)methanamine in 80 % yield.

*Example 1.1.9: tert-butyl methyl((4-methyloxazol-2-yl)methyl)carbamate*



**[0281]** To a solution of L-Serine methyl ester hydrochloride (4.76 g, 30.54 mmoles), in CH<sub>2</sub>Cl<sub>2</sub> (150mL) at 0°C, were added Et<sub>3</sub>N ( 4.65 mL, 33.59 mmoles), Boc-D-Glycine (5.35

g, 30.54 mmol), and DCC (6.92 g, 33.59 mmol) sequentially. The reaction was allowed to warm to room temperature and stirred overnight. All the solvent was evaporated and the residue was triturated with ethyl acetate and the precipitate was filtered off. The filtrate was concentrated under low pressure and chromatographed on silica gel (80% ethyl acetate/ 30% chloroform) to yield 7.5 g of **1.9.1**.

**[0282]** Deoxo-flour (5.51 mL, 29.89 mmol) was added drop-wise to a solution of **1.9.1** (7.5 g, 27.17 mmol) in  $\text{CH}_2\text{Cl}_2$  (200 mL) at  $-20^\circ\text{C}$ . The solution was stirred for 30 min and  $\text{BrCCl}_3$  (9.65 mL, 97.8 mmol) was added drop-wise. The reaction was stirred at  $2-3^\circ\text{C}$ , for 8h., quenched with satd. Aq.  $\text{NaHCO}_3$  solution and extracted with ethyl acetate. The organic layer was concentrated and chromatographed on silica gel (30% ethyl acetate/ 70% hexanes) to yield 2.95 g of **1.9.2**.

**[0283]** To a solution of **1.9.2** (2.95 g, 11.5 mmol) in THF (25 mL) at  $0^\circ\text{C}$ , was added  $\text{LiBH}_4$  (17.2 mL, 2.0M in THF, 34.5 mmol) followed by EtOH (3.4 mL, 57.5 mmol). The reaction was allowed to warm to room temperature and stirred for 3h. Ethyl acetate (11mL) was added drop-wise and stirred for 30 min. The reaction was cooled to  $0^\circ\text{C}$  and 17 mL of 1N HCl was added drop-wise and diluted with 30 mL of water. It was then extracted with ethyl acetate, dried on  $\text{Na}_2\text{SO}_4$ , concentrated, and chromatographed on silica gel (3% MeOH / 97% chloroform) to yield 1.54 g of **1.9.3**.

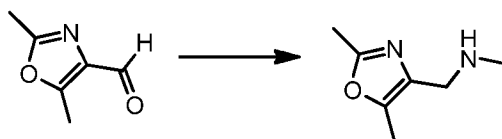
**[0284]** To a solution of TPP (3.54 g, 13.51 mmol) in  $\text{CH}_2\text{Cl}_2$  ( 30 mL), was added  $\text{I}_2$  (3.43 g, 13.51 mmol), and stirred for 10 min. Imidazole (920 mg, 13.51 mmol) was added and stirred for another 10 min and then a solution of **1.9.3** (1.54 g, 6.75 mmol), in  $\text{CH}_2\text{Cl}_2$  (40 mL), was added. After 2h, the reaction mixture was washed successively with satd. aq.  $\text{NaHCO}_3$ , aq.  $\text{Na}_2\text{S}_2\text{O}_3$ , dried on  $\text{Na}_2\text{SO}_4$  and concentrated under low pressure. The residue was chromatographed on silica gel (25% ethyl acetate/ 75% hexanes) to yield 1.81g of **1.9.4**.

**[0285]** To a solution of **1.9.4** (1.81g, 5.34 mmol) in HMPA (30 mL), was added  $\text{NaCNBH}_3$  (1.34 g, 21.36 mmol). The reaction was stirred for 4h and poured into ice-cold water and extracted with hexanes. The organic layer was dried on  $\text{Na}_2\text{SO}_4$ , concentrated, and chromatographed on silica gel (10% ethyl acetate/ 90% hexanes) to yield 580 mg of **1.9.5**.

**[0286]** To a stirred solution of **1.9.5** (380 mg, 1.78 mmol) in THF ( 8 mL ) at  $0^\circ\text{C}$ , were added 60 % NaH (86 mg, 2.14 mmol) and MeI (0.22 mL, 3.56 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with  $\text{Na}_2\text{S}_2\text{O}_3$ , brine, and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was removed via

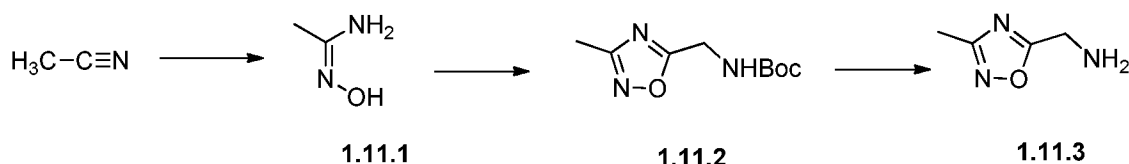
rotary evaporation. Purification via flash chromatography on silica gel yielded 175 mg of product *tert*-butyl methyl((4-methyloxazol-2-yl)methyl)carbamate.

*Example 1.1.10: 1-(2,5-dimethyloxazol-4-yl)-N-methylmethanamine*



**[0287]**  $\text{Ti}(\text{O}^i\text{PR})_4$  (1.08 mL, 3.69 mmol) was added with stirring to  $\text{MeNH}_2$  (4.3 mL, 2.0 M in MeOH, 8.5 mmol) at 0 °C under Ar. After 15 min the aldehyde (360 mg, 2.83 mmol) was added, and the reaction was stirred for 2-3 h.  $\text{NaBH}_4$  (139 mg, 3.69 mmol) was added in batches, and the reaction was stirred at 0° C to RT overnight. The solvent was removed via rotary evaporation. The residue was diluted with water/ $\text{CH}_2\text{Cl}_2$ . A white ppt formed and was removed via filtration through Celite. The layers were separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (x3) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was removed via rotary evaporation to give 300 mg of 1-(2,5-dimethyloxazol-4-yl)-N-methylmethanamine.

*Example 1.1.11: (3-methyl-1,2,4-oxadiazol-5-yl)methanamine*

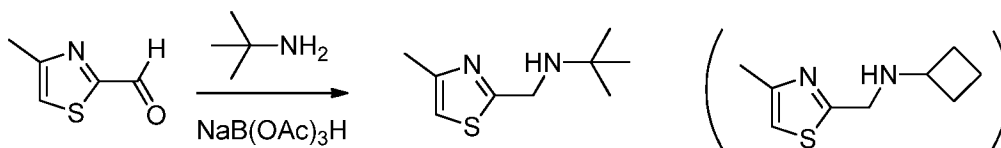


**[0288]** To a stirred solution of acetonitrile (5mL, 95 mmol) in a 4:1 mixture of EtOH and water (180mL) were added NaOH (4.26g, 107 mmol) and hydroxylamine hydrochloride (7.1g, 0.1 mmol) and the reaction was refluxed for 24h. It was then concentrated under reduced pressure. The white solid was dissolved in 150 mL of absolute EtOH and filtered to remove the inorganic salts. Concentration of the filtrate gave a crude white solid, which was recrystallized from isopropanol to obtain 3.2 g of **1.11.1**.

**[0289]** To a stirred suspension of molecular sieves ( $3\text{A}^0$ ) in anhydrous THF (200mL) was added **1.11.1** (900mg, 10.0 mmol) and stirred for 15 min. NaH (1.3g, 32.0 mmol) was added and the reaction was stirred for 45 min. Then Glycine methyl ester (1.89g, 10 mmol) was added and the reaction was refluxed overnight, cooled, filtered over celite and concentrated. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$ , washed with water, dried on  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was purified by column chromatography (40% EtOAc in hexanes) to provide 460 mg of **1.11.2**.

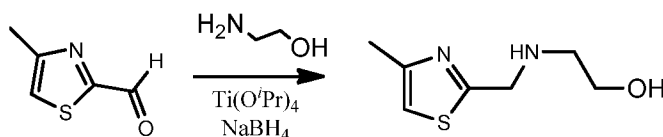
[0290] **1.11.2** was converted into (3-methyl-1,2,4-oxadiazol-5-yl)methanamine using standard deprotection protocol of a Boc group with TFA.

*Example 1.1.12*



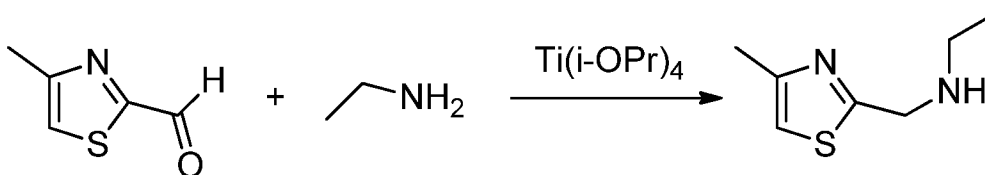
[0291] To a solution of 4-Methylthiazole-2-aldehyde (3.217 g, 25.296 mmol) in THF (100 mL) at room temperature was added t-butylamine (5.55 g, 75.89 mmol) and stirred at this temperature for overnight. The  $\text{NaB}(\text{OAc})_3\text{H}$  (10.73 g, 50.593 mmol) was then added to the reaction in portions slowly, the resulting mixture was stirred for 16 hrs, diluted with EtOAc and washed with aqueous sodium bicarbonate, saturated aqueous sodium chloride, separated, dried (sodium sulfate) and concentrated to give the product as an oil which was purified with flash chromatography to produce the amine as an oil (3.9 g, 84%).

*Example 1.1.13*



[0292] Example 1.1.4 was synthesized using the same procedure as Example 1.1.2. 2-aminoethanol was purchased from Aldrich.

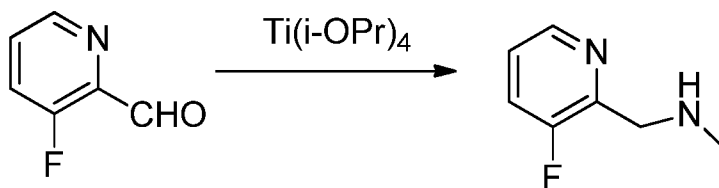
*Example 1.1.14: Synthesis of N-((4-methylthiazol-2-yl)methyl)ethanamine*



[0293]  $\text{Ti}(\text{O}^i\text{Pr})_4$  (Commercial source: sigma-aldrich) (2.9 g, 10.22 mmol) was added with stirring to  $\text{EtNH}_2$  (Commercial source: sigma-aldrich) (2.0 M in MeOH, 12 mL, 23.6 mmol) under Ar. After 5 min. the aldehyde, 4-methylthiazole-2-carbaldehyde (1.0 g, 7.86 mmol) (Commercial source: sigma-aldrich) was added, and the solution was stirred for 2 h. The reaction was cooled to 0° C and the  $\text{NaBH}_4$  (418 mg, 11.0 mmol) was added. The solution was stirred at 0° C to RT overnight. After quenching the reaction with water the mixture was filtered through celite to remove the white precipitate. Then MeOH was removed *in vacuo*. The residue was diluted with EtOAc. The resulting solution was washed with water (x3), brine (x1), and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was

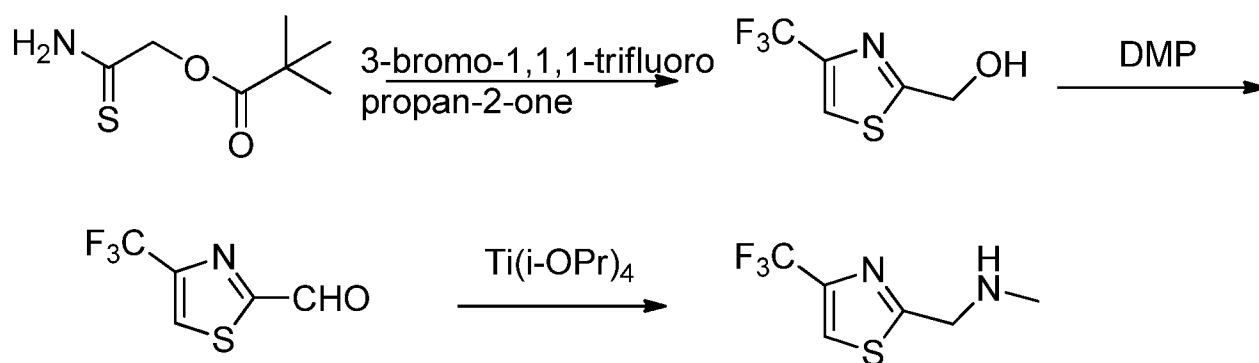
removed *in vacuo* to give the crude product. Purification via column chromatography yielded the pure N-((4-methylthiazol-2-yl)methyl)ethanamine in 50% yield.

*Example 1.1.15: Synthesis of 1-(3-fluoropyridin-2-yl)-N-methylmethanamine*



**[0294]**  $\text{Ti}(\text{O}^i\text{Pr})_4$  (Commercial source: sigma-aldrich) (2.95 g, 10.4 mmol) was added with stirring to  $\text{MeNH}_2$  (Commercial source: sigma-aldrich) (2.0 M in MeOH, 12 ml, 23.7 mmol) under Ar. After 5 min. the aldehyde, 3-fluoropyridine-2-carbaldehyde (1.0 g, 7.99 mmol) (Commercial source: sigma-aldrich) was added, and the solution was stirred for 2 h. The reaction was cooled to  $0^\circ\text{C}$  and the  $\text{NaBH}_4$  (395 mg, 10.4 mmol) was added. The solution was stirred at  $0^\circ\text{C}$  to RT overnight. After quenching the reaction with water the mixture was filtered through celite to remove the white precipitate. Then MeOH was removed *in vacuo*. The residue was diluted with EtOAc. The resulting solution was washed with water (x3), brine (x1), and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was removed *in vacuo* to give the crude product. Purification via column chromatography yielded the pure 1-(3-fluoropyridin-2-yl)-N-methylmethanamine in 67% yield.

*Example 1.1.16: Synthesis of N-methyl-1-(4-(trifluoromethyl)thiazol-2-yl)methanamine*



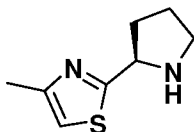
**[0295]** To the thioamide, 2-amino-2-thioxoethyl pivalate (3.0 g, 17.02 mmol) (Commercial source: Acros organics) in ethanol (10 ml), 3-bromo-1,1,1-trifluoropropan-2-one (3.23 g, 17.02 mmol) (Commercial source: Apollo scientific) was added and heated at  $60^\circ\text{C}$  for 24h. Then reaction mixture was cooled, DBU (2.59g, 17.02 mmol) was added and stirred at rt for 2d. Then volatiles were removed in vacuum, reaction mixture was partitioned between ethyl acetate and water. Organic layer was dried, evaporated and column purified to yield 4-(trifluoromethyl)thiazol-2-ylmethanol in 30% yield.

[0296] To the alcohol, 4-(trifluoromethyl)thiazol-2-yl)methanol (245 mg, 1.34 mmol) in DCM (10 ml) at 0°C, DMP (681 mg, 1.61 mmol) was added. Reaction was allowed to come to rt and stirred for 3h. Then saturated sodium bicarbonate, hypo mixture was added and stirred for 10 min. Then reaction mixture was further diluted with DCM and product was extracted into DCM. Volatiles were removed under vacuum and the resulting aldehyde, 4-(trifluoromethyl) thiazole-2-carbaldehyde was carried to the next step without further purification.

[0297]  $\text{Ti}(\text{O}^i\text{PR})_4$  (Commercial source: sigma-aldrich) (495 mg, 1.74 mmol) was added with stirring to  $\text{MeNH}_2$  (Commercial source: sigma-aldrich) (2.0 M in MeOH, 2 ml, 4.02 mmol) under Ar. After 5 min. the aldehyde, 4-(trifluoromethyl)thiazole-2-carbaldehyde (245 mg, 1.34 mmol) was added, and the solution was stirred for 2 h. The reaction was cooled to 0° C and the  $\text{NaBH}_4$  (66 mg, 1.742 mmol) was added. The solution was stirred at 0° C to RT overnight. After quenching the reaction with water the mixture was filtered through celite to remove the white precipitate. Then MeOH was removed *in vacuo*. The residue was diluted with EtOAc. The resulting solution was washed with water (x3), brine (x1), and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was removed *in vacuo* to give the crude product. Purification via column chromatography yielded the pure N-methyl-1-(4-(trifluoromethyl)thiazol-2-yl)methanamine in 37% yield overall for 2 steps.

### Example 1.2: Synthesis of cyclic amine building blocks.

#### Example 1.2.1: (R)-4-methyl-2-(pyrrolidin-2-yl)thiazole



[0298] To a solution of the commercially available (R)-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid (Synthetech, 9.97g, 40.0 mmoles) in 1, 4-dioxane (60mL) was added pyridine (2mL), di-tert-butyl dicarbonate ( $(\text{Boc})_2\text{O}$ ) ( 11.35mL, 52 mmoles) and  $\text{NH}_4\text{HCO}_3$  ( 3.98g, 50.4 mmoles) and stirred for 12h. All solvent was evaporated, diluted with EtOAc and washed with water, 5%  $\text{H}_2\text{SO}_4$  and brine. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated. (R)-benzyl 2-carbamoylpyrrolidine-1-carboxylate was generated in quantitative yield and used in the following step without further purification.

[0299] To a solution of (R)-benzyl 2-carbamoylpyrrolidine-1-carboxylate (9.97g, 40.0 mmoles) in 1,2-dimethoxyethane (1,2-DME or DME) (2000mL) was added Lawesson's reagent (8.9g, 0.55 mmoles) and stirred for 4h. All solvent was evaporated, diluted with

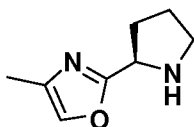


100mL of saturated  $\text{NaHCO}_3$  and extracted with ether (2x200mL). The combined organic layers was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated. Crude (R)-benzyl 2-carbamothioylpyrrolidine-1-carboxylate was carried on to the next step without further purification.

**[0300]** To a solution of (R)-benzyl 2-carbamothioylpyrrolidine-1-carboxylate (~ 40 mmoles) in EtOH ( 120mL) was added chloroacetone (4.7 mL, 60 mmoles) and heated at 75 °C for 6h. The reaction was cooled to room temperature and poured into 100 mL of saturated aq.  $\text{NaHCO}_3$  solution. Ethanol was evaporated under reduced pressure and the aqueous layer was extracted with ethyl acetate (2x200mL). The combined organic layers was dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was chromatographed on silica gel (35% ethyl acetate/ 80% hexane) to generate (R)-benzyl 2-(4-methylthiazol-2-yl)pyrrolidine-1-carboxylate in 86% yield after three steps.

**[0301]** HBr in AcOH (60mL) was added to (R)-benzyl 2-(4-methylthiazol-2-yl)pyrrolidine-1-carboxylate (neat) at room temperature. After 1h, ether (150 mL) was added slowly with vigorous strring. Stirring was continued for 10 min and allowed to settle for 5-10 min. The supernatant was decanted. This process was repeated 3-4 times until the supernatant was colourless. The semi-solid was dissolved in water (50 mL) and brought to  $\text{P}^{\text{H}} \sim 8$  with 1N LiOH and extracted with 5% MeOH/95%  $\text{CHCl}_3$  (3x100mL) to yield 4.0 g of (R)-4-methyl-2-(pyrrolidin-2-yl)thiazole.

*Example 1.2.2: (R)-4-methyl-2-(pyrrolidin-2-yl)oxazole*



**[0302]** To a solution of L-Serine methyl ester hydrochloride (Aldrich, 5.0 g, 32.0 mmoles), in  $\text{CH}_2\text{Cl}_2$  (150 mL) at 0 °C, were added  $\text{Et}_3\text{N}$  (4.88 mL, 35.2 mmoles), Cbz-D-Proline (8.01 g, 32.0 mmoles) and N,N'-dicyclohexylcarbodiimide (DCC) (7.26 g, 35.2 mmoles) sequentially. The reaction was allowed to warm to room temperature and stirred overnight. All the solvent was evaporated and the residue was triturated with ethyl acetate and the precipitate was filtered off. The filtrate was concentrated under low pressure and chromatographed on silica gel (70% ethyl acetate/ 30% chloroform) to yield 8.5g of (R)-benzyl 2-((S)-3-hydroxy-1-methoxy-1-oxopropan-2-ylcarbamoyl)pyrrolidine-1-carboxylate.

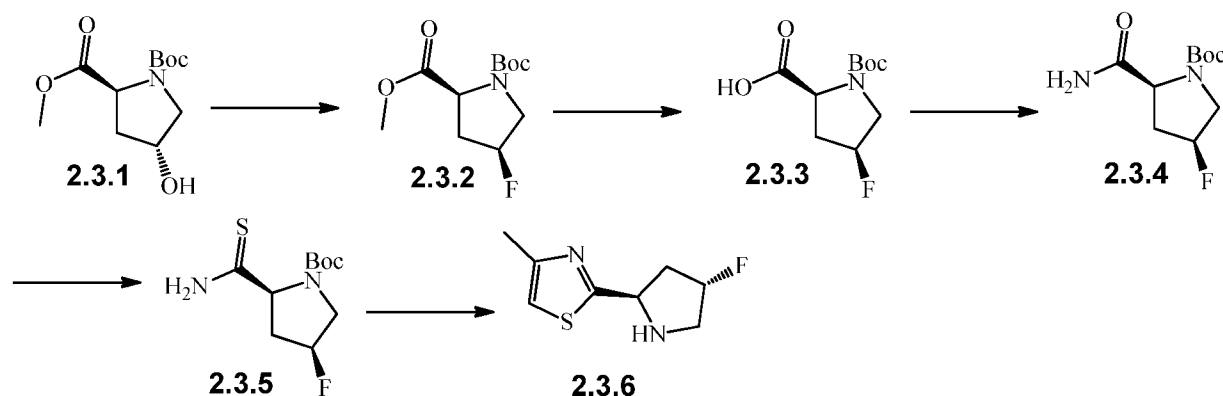
**[0303]** Deoxo-flour (4.5 mL , 24.16 mmoles) was added drop-wise to a solution of (R)-benzyl 2-((S)-3-hydroxy-1-methoxy-1-oxopropan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (8.5g, 22.0 mmoles) in  $\text{CH}_2\text{Cl}_2$  (150mL) at -20°C. The solution was stirred for 30 min and

BrCCl<sub>3</sub> (7.8 mL, 79.0 mmol) was added drop-wise followed by DBU (11.8mL, 79 mmol). The reaction was stirred at 2-3 °C, for 10h., quenched with satd. aq. NaHCO<sub>3</sub> solution and extracted with ethyl acetate. The organic layer was concentrated and chromatographed on silica gel (10% ethyl acetate/ 90% chloroform) to yield 6.95 of (R)-methyl 2-(1-(benzyloxycarbonyl)pyrrolidin-2-yl)oxazole-4-carboxylate.

**[0304]** To a solution of (R)-methyl 2-(1-(benzyloxycarbonyl)pyrrolidin-2-yl)oxazole-4-carboxylate (6.95g, 21.1 mmol) in THF (50mL) at 0°C, was added LiBH<sub>4</sub> (32 mL, 2.0M in THF, 63.2 mmol). The reaction was allowed to warm to room temperature and stirred for 3h. Ethyl acetate (25mL) was added drop-wise and stirred for 30 min. The reaction was cooled to 0°C and 50 mL of 1N HCl was added drop-wise and diluted with 100 mL of water. It was then extracted with ethyl acetate, dried on Na<sub>2</sub>SO<sub>4</sub>, concentrated, and chromatographed on silica gel (3% MeOH / 97% chloroform) to yield 4.1g of (R)-benzyl 2-(4-(hydroxymethyl)oxazol-2-yl)pyrrolidine-1-carboxylate.

**[0305]** To a solution of (R)-benzyl 2-(4-(hydroxymethyl)oxazol-2-yl)pyrrolidine-1-carboxylate (1.1g, 3.64 mmol) in HMPA (18mL), was added methyltriphenoxyposphonium iodide (3.29g, 7.28mmol) and stirred for 30min. Then NaCNBH<sub>3</sub> was added and the reaction was heated at 50 °C for 3h and poured into 100mL of ice-cold water and extracted with ether( 2X100mL). The organic layer was dried on Na<sub>2</sub>SO<sub>4</sub>, concentrated, and chromatographed on silica gel (50% ethyl acetate/ 50% hexanes) to yield 180mg of (R)-benzyl 2-(4-methyloxazol-2-yl)pyrrolidine-1-carboxylate.

**[0306]** HBr in AcOH (60mL) was added to (R)-benzyl 2-(4-methyloxazol-2-yl)pyrrolidine-1-carboxylate (neat) at room temperature. After 1h, ether (20mL) was added slowly with vigorous strring. Stirring was continued for 10 min and allowed to settle for 5-10 min. The supernatant was decanted. This process was repeated 3-4 times until the supernatant was colourless. The semi-solid was dissolved in water (50 mL) and brought to pH ~8 with 1N LiOH and extracted with 5% MeOH/95% CHCl<sub>3</sub> (3X100 mL) to yield 55 mg of (R)-4-methyl-2-(pyrrolidin-2-yl)oxazole.

*Example 1.2.3: 2-((2R,4S)-4-fluoropyrrolidin-2-yl)-4-methylthiazole*

[0307] To the alcohol **2.3.1** (5.0 g, 20.38 mmol) in dichloromethane (DCM) (50 ml) at -78°C, deoxofluor (Commercial source: sigma-aldrich) was added. Then the reaction mixture was allowed to come to room temperature (rt) and stirred at rt for 12h. Then the reaction mixture was quenched with saturated aq sodium carbonate solution at 0°C, warmed to rt. Then the reaction mixture was extracted with ethyl acetate. Organic layer was washed with water, brine and dried. Crude residue was column chromatographed to obtain 3.05 g of the ester **2.3.2**.

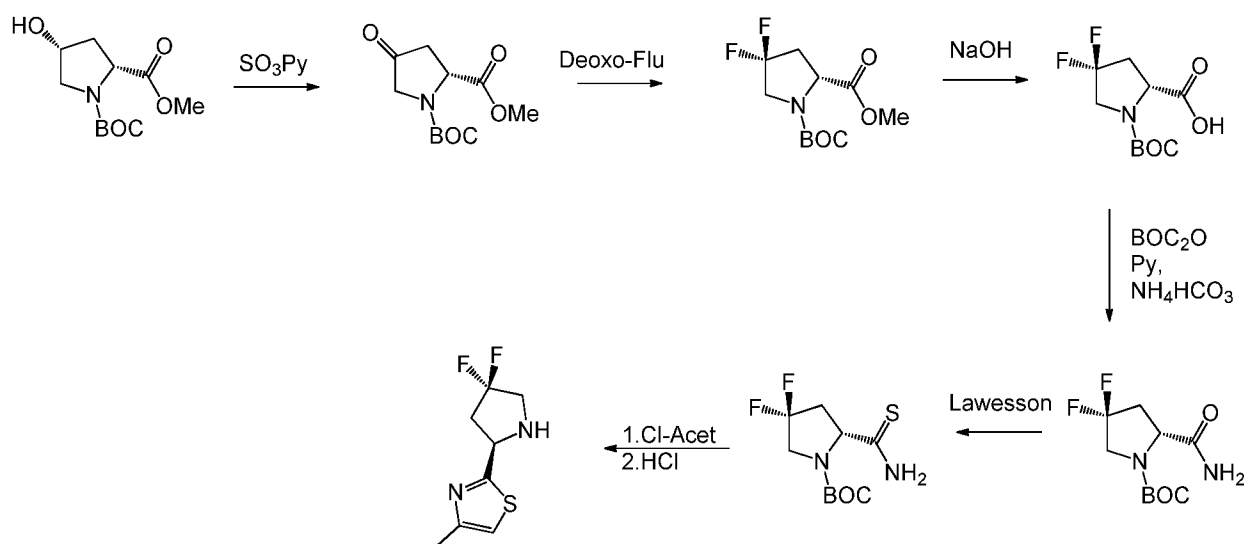
[0308] To the ester **2.3.2** (3.05, 12.33 mmol) in MeOH (20 ml), THF (20 ml), aq sodium hydroxide (986 mg, 24.66 mmol) was added. After 2h, volatiles were removed in vacuum. Aqueous layer's pH was adjusted to about 3 with concentrated HCl, and reaction mixture was extracted with MeOH/CHCl<sub>3</sub> (1:9). Combined organic layers were washed with brine, dried and concentrated to yield 2.8 g of the acid **2.3.3**.

[0309] To the acid **2.3.3** (2.07 g, 8.87 mmol) in dioxane (20 ml) pyridine (Commercial Source: sigma-aldrich) (1 ml), (Boc)<sub>2</sub>O (Commercial source: sigma-aldrich) (2.52 g, 11.53 mmol), followed by sodium bicarbonate (882 mg, 11.2 mmol). Reaction mixture was stirred overnight at rt, then volatiles were removed in vacuum. Then reaction mixture was partitioned between chloroform and water. Organic layer was dried and evaporated to obtain the amide **2.3.4** in quantitative yield.

[0310] Lawesson's reagent (Commercial source: sigma-aldrich) (1.98 g, 4.90 mmol) was added to the amide **2.3.4** (2.07 g, 8.91 mmol) in DME (Commercial source: sigma-aldrich) (30 ml) and the reaction mixture was stirred overnight at rt. Then volatiles were removed in vacuum and the reaction mixture was partitioned between ether and water. Ether layer was concentrated and column purified to obtain 1.74 g of the thioamide **2.3.5**.

[0311] To the thioamide **2.3.5** (1.7 g, 6.85 mmol) in ethanol (20 ml), calcium carbonate (2.06 g, 20.55 mmol) was added, followed by chloroacetone (Commercial source: sigma-aldrich) (955 mg, 10.27 mmol). After heating at 70°C for 5h, volatiles were removed in vacuum. Reaction mixture was filtered and partitioned between water and ether. Organic layer was dried and evaporated. To the crude residue 4N HCl/dioxane (Commercial source: sigma-aldrich) (4 ml) was added and stirred at rt for 3h. Then volatiles were removed in vacuum and reaction mixture was partitioned between chloroform and aqueous sodium bicarbonate. Organic layer was dried, evaporated and column purified to yield 900mg of the proline **2.3.6**.

Example 1.2.4: (R)-2-(4,4-difluoropyrrolidin-2-yl)-4-methylthiazole



[0312] To an ice-cold solution of 4-(R)-hydroxyl-2-(R)-hydroxymethylpyrrolidine-1-carboxylic acid tert-butyl ester (9.81 g, 40.93 mmol) in DMSO (50 mL) was added triethylamine (16.2 mL, 163.73 mmol) and sulfurtrioxide-pyridine complex (12.73 g, 81.87 mmol). The resulting mixture was stirred 30 min, warmed to room temperature and stirred 30 min, diluted with diethyl ether and washed with 5% aqueous citric acid, saturated aqueous sodium chloride, dried (sodium sulfate) and concentrated to give the title compound as an oil which was purified with flash chromatography to produce the ketone (7.5 g). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 4.818-4.673 (m, 1 H), 3.903 (s, 1 H), 3.871(s, 1 H), 3.749 (s, 3 H), 3.003-2.862 (m, 1 H), 2.605-2.542 (m, 1 H), 1.468, 1.445 (s, 9 H).

[0313] To a solution of 4-oxopyrrolidine-N-1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (7.5 g, 35.76 mmol) in dichloromethane (80 mL) at -78°C was added Deoxo-Fluor (17 mL, 1.07 mol). The resulting mixture was stirred and warmed to room temperature

for overnight, then was cooled in ice bath diluted with chloroform and quenched with saturated sodium bicarbonate solution. Warmed to room temperature, separated and dried (magnesium sulfate), concentrated and purified with silica gel chromatography to give the compound as an oil (6.47 g).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 4.568-4.422 (m, 1 H), 3.894-3.725 (m, 2 H), 3.767(s, 3 H), 2.798-2.601 (m, 1 H), 2.553-2.385 (m, 1 H), 1.470, 1.422 (s, 9 H).

**[0314]** To the ester (6.2 g, 23.37 mmol) in THF (60 ml), aq sodium hydroxide (8 ML of 1 M solution, 15 ML of water, 32 mmol) was added. After 3 h, volatiles were removed in vacuum. Aqueous layer was adjusted to about PH = 3 with 3 M HCl solution, and reaction mixture was extracted with ethyl acetate three times. Combined organic layers were washed with brine, dried and concentrated to yield a white solid (5.55 g), which was used for the next step without further purification and identification.

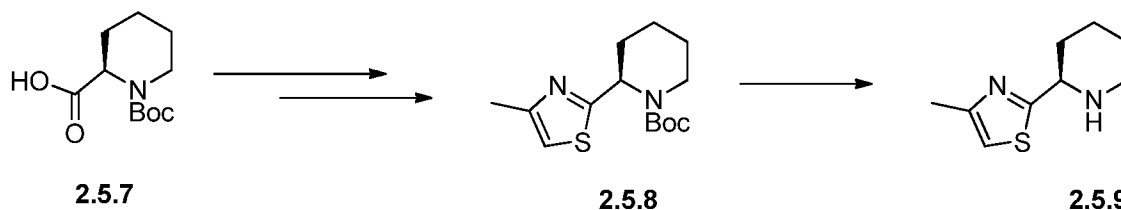
**[0315]** To the crude acid (5.55 g, 22.08 mmol) in dioxane (50 ml) were added pyridine (Commercial source: Sigma-Aldrich) (1.25 ml),  $(\text{Boc})_2\text{O}$  (Commercial source: Sigma-Aldrich) (6.75 g, 30.92 mmol), followed by ammonium bicarbonate (2.36 g, 29.82 mmol). The resulting reaction mixture was stirred overnight at rt, then volatiles were removed in vacuum. Then reaction mixture was dissolved in ethyl acetate, washed with aqueous diluted HCl (1 M), sodium bicarbonate and brine. Organic layer was dried and evaporated to obtain the amide in quantitative yield 5.6 g), which was used for the next step without further purification and identification.

**[0316]** Lawesson's reagent (Commercial source: Sigma-Aldrich) (5.41 g, 13.37 mmol) was added to the amide (5.6 g, 22.28 mmol) in DME (Commercial source: Sigma-Aldrich) (100 ml) and the reaction mixture was stirred overnight at rt. Then volatiles were removed in vacuum and the reaction mixture was partitioned between ether and water. Ether layer was concentrated and column purified to obtain 4.6 g of thioamide.

**[0317]** To the thioamide (4.6 g, 17.21 mmol) in ethanol (50 ml) was added chloroacetone (Commercial source: sigma-aldrich) (2.3 g, 25.81 mmol). After heating at 75  $^{\circ}\text{C}$  for 5h, volatiles were removed in vacuum. Reaction mixture was diluted with ethyl acetate, washed with sodium bicarbonate. Organic layer was dried and evaporated. To the crude residue 4N HCl/dioxane (Commercial source: Sigma-Aldrich) (10 ml) was added and stirred at rt for 3h. Then volatiles were removed in vacuum and reaction mixture was partitioned between chloroform and aqueous sodium bicarbonate. Organic layer was dried and evaporated to yield 1.2 g of the desired product amine.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.818 (s, 1 H), 4.733 (t, *J*

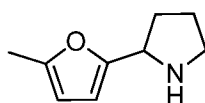
= 7.8 Hz, 1 H), 3.345-3.301 (m, 2 H), 2.861-2.710 (m, 1 H), 2.596-2.413 (m, 1 H), 2.420 (s, 3 H).

*Example 1.2.5: (R)-2-(piperidin-2-yl)-4-methylthiazole*



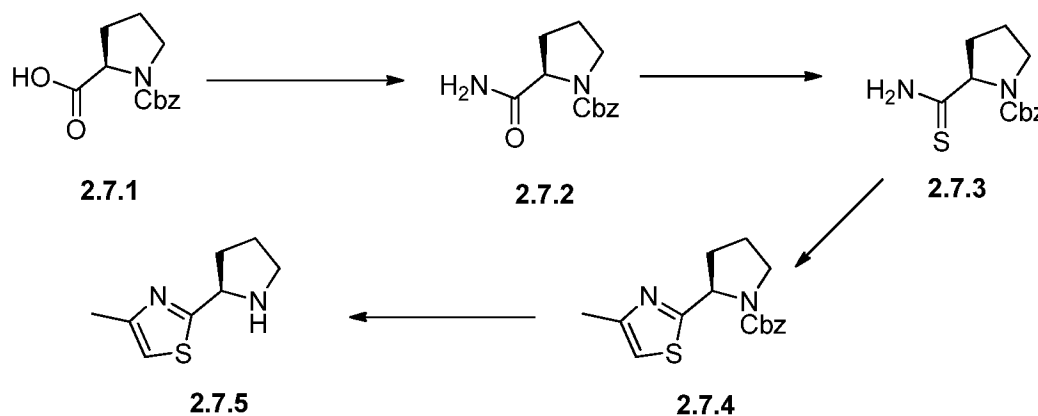
[0318] Methyl thiazole-piperidine ligand **2.5.9** was prepared following the same procedure as in the preparation of *(R)-4-methyl-2-(pyrrolidin-2-yl)thiazole* starting from the commercially available *R-N-Boc-2-piperidine* **2.5.7** (Aldrich) carboxylic acid to obtain **2.5.8** which was deprotected using standard TFA conditions to obtain **2.5.9**.

*Example 1.2.6: 2-(5-methylfuran-2-yl)pyrrolidine*



[0319] 2-(5-methylfuran-2-yl)pyrrolidine was purchased from ACB Blocks.

*Example 1.2.7: (R)-4-methyl-2-(pyrrolidin-2-yl)thiazole*



[0320] To a solution of **2.7.1** (9.97g, 40.0 mmoles) in 1, 4-dioxane (60mL) were added pyridine (2mL), (Boc)<sub>2</sub>O (11.35mL, 52 mmoles) and NH<sub>4</sub>HCO<sub>3</sub> (3.98g, 50.4 mmoles) and stirred for 12h. All solvent was evaporated, diluted with EtOAc and washed with water, 5% H<sub>2</sub>SO<sub>4</sub> and brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude yield of **2.7.2** was quantitative. This was not purified.

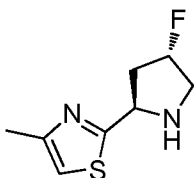
[0321] To a solution of **2.7.2** (9.97g, 40.0 mmoles) in 1, 2-DME (2000mL) was added Lawesson's reagent (8.9g, 0.55 mmoles) and stirred for 4h. All solvent was evaporated, and diluted with 100mL of saturated NaHCO<sub>3</sub> and extracted with ether (2 x 200mL). The

combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated. The crude **2.7.3** was carried on to the next step.

[0322] To a solution of **2.7.3** (~ 40 mmol) in EtOH (120mL) was added chloroacetone (4.7 mL, 60 mmol) and heated at  $75^\circ\text{C}$  for 6h. The reaction was cooled to room temperature and poured into 100 mL of saturated aq.  $\text{NaHCO}_3$  solution. Ethanol was evaporated under reduced pressure and the aqueous layer was extracted with ethyl acetate (2 x 200mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was chromatographed on silica gel (35% ethyl acetate/ 80% hexane) to yield 86% of **2.7.4** after three steps.

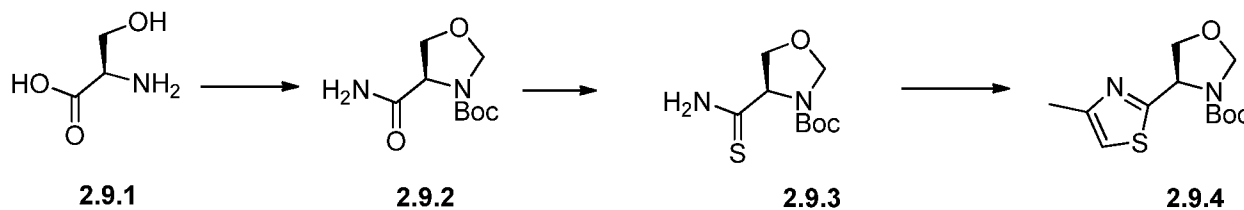
[0323] HBr in AcOH (60mL) was added to **2.7.4** (neat) at room temperature. After 1h, ether (150mL) was added slowly with vigorous stirring. Stirring was continued for 10 min and allowed to settle for 5-10 min. The supernatant was decanted. This process was repeated 3-4 times until the supernatant was colourless. The semi-solid was dissolved in water (50 mL) and brought to pH~8 with 1N LiOH and extracted with 5% MeOH/95%  $\text{CHCl}_3$  (3 x 100mL) to obtain 4.0g of (R)-4-methyl-2-(pyrrolidin-2-yl)thiazole.

*Example 1.2.8: 2-((2R,4S)-4-fluoropyrrolidin-2-yl)-4-methylthiazole*



[0324] 2-((2R,4S)-4-fluoropyrrolidin-2-yl)-4-methylthiazole was synthesized using the procedure described in Example 1.2.7.

*Example 1.2.9: (R)-4-(4-methylthiazol-2-yl)oxazolidine*

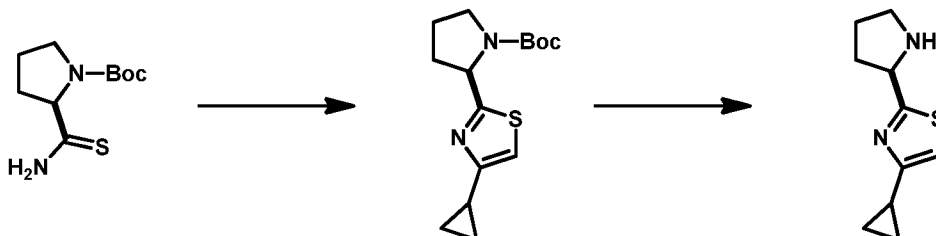


[0325] To a solution of commercially available D-Serine hydrochloride **2.9.1** (3.0g, 24.8 mmol) in  $\text{H}_2\text{O}$  (8 mL) at room temperature, was added 37% solution of formaldehyde (817mg, 27.3 mmol) and stirred for 24h. Then  $\text{NH}_2\text{OH} \cdot \text{HCl}$  (172 mg, 2.48 mmol), NaOH (50mL, 2N, 100 mmol), acetone (50mL), and  $(\text{Boc})_2\text{O}$  (6.27 mL, 27.28 mmol) were added and stirred for 12h. The reaction mixture was extracted with ether. The aqueous layer was acidified to pH~3.5 with 1N HCl and then extracted with 5% MeOH/95%  $\text{CHCl}_3$  (3 x

100mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to yield 2.49g of crude **2.9.2**.

[0326] **2.9.2** was converted into (R)-4-(4-methylthiazol-2-yl)oxazolidine using the procedure described in Example 1.2.7.

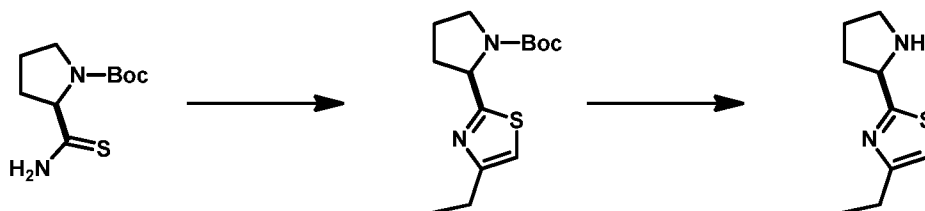
*Example 1.2.10*



[0327] **tert-Butyl (2R)-2-(4-cyclopropyl-1,3-thiazol-2-yl)pyrrolidine-1-carboxylate:** To a stirred solution of *tert*-butyl (2R)-2-carbamothioylpyrrolidine-1-carboxylate (200 mg, 0.868 mmol) in EtOH (8 ml) were added 2-bromo-1-cyclopropylethanone (315 mg, 1.74 mmol) and CaCO<sub>3</sub> (261 mg, 2.61 mmol) at rt and the mixture was stirred at 80 degree for 5 min. Volatiles were evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 0 to 66%) to give *tert*-butyl (2R)-2-(4-cyclopropyl-1,3-thiazol-2-yl)pyrrolidine-1-carboxylate (230 mg, 90% yield) as a colorless oil. MS (ESI) m/z: 295 [M+H]<sup>+</sup>.

[0328] **4-Cyclopropyl-2-[(2R)-pyrrolidin-2-yl]-1,3-thiazole:** A solution of *tert*-butyl (2R)-2-(4-cyclopropyl-1,3-thiazol-2-yl)pyrrolidine-1-carboxylate (230 mg, 0.781 mmol) and TFA (1 ml) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was left at rt for 2 hours and volatiles were evaporated to give a crude, which was dissolved in CHCl<sub>3</sub>. This mixture was washed with satd. NaHCO<sub>3</sub> aq., dried over MgSO<sub>4</sub> and evaporated to give a crude of 4-cyclopropyl-2-[(2R)-pyrrolidin-2-yl]-1,3-thiazole (120 mg, 79% yield) as a free form, which was used for the next reaction without further purification. MS (ESI) m/z: 195 [M+H]<sup>+</sup>.

*Example 1.2.11*



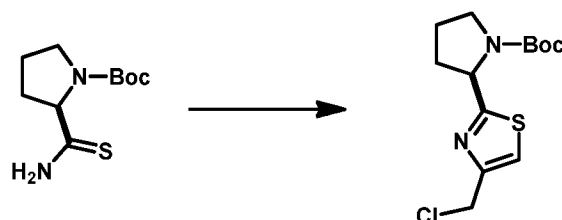
[0329] **tert-Butyl (2R)-2-(4-ethyl-1,3-thiazol-2-yl)pyrrolidine-1-carboxylate:** The desired compound was synthesized from *tert*-butyl (2R)-2-carbamothioylpyrrolidine-1-



carboxylate (220 mg, 0.955 mmol) in a similar manner to *Example 1.2.10*. (228 mg, 85% yield) MS (ESI)  $m/z$ : 283  $[M+H]^+$ .

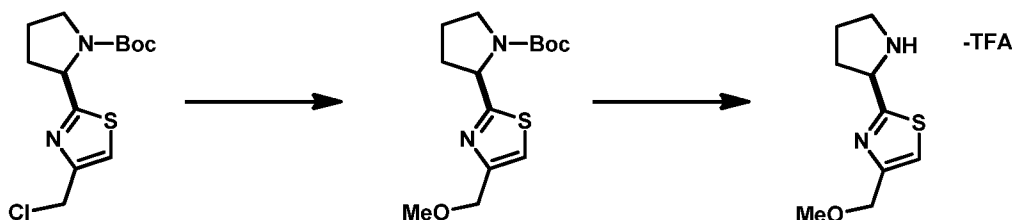
**[0330] 4-Ethyl-2-[(2*R*)-pyrrolidin-2-yl]-1,3-thiazole:** The desired compound was synthesized from *tert*-butyl (2*R*)-2-(4-ethyl-1,3-thiazol-2-yl)pyrrolidine-1-carboxylate (228 mg, 0.807 mmol) in a similar manner to *Example 1.2.10*. (103 mg, 70% yield) MS (ESI)  $m/z$ : 183  $[M+H]^+$ .

*Example 1.2.12*



**[0331] *tert*-Butyl (2*R*)-2-[4-(chloromethyl)-1,3-thiazol-2-yl]pyrrolidine-1-carboxylate:** The desired compound was synthesized from *tert*-butyl (2*R*)-2-carbamothioylpyrrolidine-1-carboxylate (200 mg, 0.868 mmol) in a similar manner to *Example 1.2.10*. (262 mg, >99% yield) MS (ESI)  $m/z$ : 303  $[M+H]^+$ .

*Example 1.2.13*



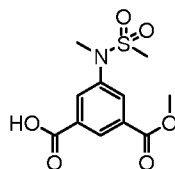
**[0332] *tert*-Butyl (2*R*)-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]pyrrolidine-1-carboxylate:** To a stirred solution of *tert*-butyl (2*R*)-2-[4-(chloromethyl)-1,3-thiazol-2-yl]pyrrolidine-1-carboxylate (262 mg, 0.865 mmol) in MeOH (5 ml) was added  $K_2CO_3$  (598 mg, 4.33 mmol) at rt and the mixture was stirred at 70 degree for 3 hours. The starting molecule was completely consumed in 3 hours and volatiles were evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 0 to 66%) to give *tert*-butyl (2*R*)-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]pyrrolidine-1-carboxylate (64 mg, 25% yield). MS (ESI)  $m/z$ : 299  $[M+H]^+$ .

**[0333] 4-(Methoxymethyl)-2-[(2*R*)-pyrrolidin-2-yl]-1,3-thiazole trifluoroacetate (1:1):** To a stirred solution of *tert*-butyl (2*R*)-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]pyrrolidine-1-carboxylate (64 mg, 0.219 mmol) in  $CH_2Cl_2$  (2 ml) was added TFA (1 ml) at rt and the mixture was left at rt for 2 hours. Volatiles were evaporated to give a crude of 4-

(methoxymethyl)-2-[(2*R*)-pyrrolidin-2-yl]-1,3-thiazole trifluoroacetate (1:1) which was used for the next reaction without further purification. MS (ESI)  $m/z$ : 199  $[M+H]^+$ .

### Example 1.3: Synthesis of isophthalate building blocks.

#### Example 1.3.1

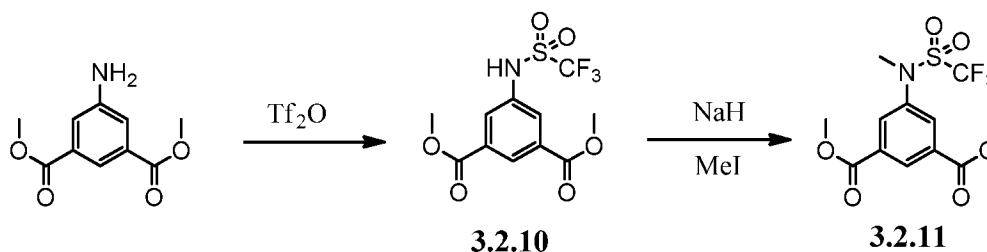


**[0334]** To a stirred solution of dimethyl 5-aminoisophthalate (Aldrich, 2.09 g, 10 mmol) in dichloromethane (30 mL), pyridine (2.43 mL, 30 mmol) was added at room temperature. At 0 °C, methanesulfonyl chloride (0.86 mL, 11 mmol) was added and the resulting mixture was stirred overnight at room temperature. The reaction mixture was then concentrated under reduced pressure and ethyl acetate (50 mL) was added. The resulting white precipitate was filtered and washed with hexanes to give dimethyl 5-(methylsulfonylamido)isophthalate in 95% (2.715 g) yield as a white solid.

**[0335]** To a stirred suspension of NaH (0.24 g, 10 mmol, 60% in oil dispersion) in 10 mL of DMF was added dimethyl 5-(methylsulfonylamido)isophthalate (1.435 g, 5 mmol) followed by iodomethane (0.62 mL, 10 mmol) at room temperature. After 5 h, the reaction was quenched by H<sub>2</sub>O (25 mL). Then the reaction mixture was extracted with EtOAc, further washed with H<sub>2</sub>O to remove excess of DMF, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product thus obtained was washed with hexanes to give dimethyl 5-(*N*-methylmethylsulfonylamido)isophthalate as a white solid in 91% (1.37 g) yield.

**[0336]** Dimethyl 5-(*N*-methylmethylsulfonylamido)isophthalate (0.842 g, 2.8 mmol) was dissolved in THF:MeOH (1:1) (8 mL) and H<sub>2</sub>O (3 mL). Solid NaOH (0.112 g, 2.8 mmol) was added and stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure. Saturated NaHCO<sub>3</sub> (10 mL) was added to the reaction mixture and extracted with toluene (to remove <10% unreacted starting material). The aqueous solution was acidified with dilute HCl (10%), extracted with EtOAc, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated and dried under reduced pressure to give 3-(methoxycarbonyl)-5-(*N*-methylmethylsulfonylamido)benzoic acid as a white solid (75%, 0.598 g), which was used without further purification.

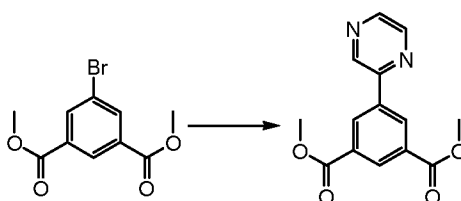
## Example 1.3.2



**[0337]** A solution of the starting material (1.0 g, 4.78 mmol, 1 eq) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 ml) was cooled to  $-78^\circ\text{C}$ .  $\text{Tf}_2\text{O}$  (0.88 ml, 1.48 g, 5.26 mmol, 1.1 eq) was added dropwise with stirring. The reaction was stirred at  $-78^\circ\text{C}$  to room temperature overnight. The reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  and diluted with EtOAc. The layers were separated. The organic layer was washed with water (x3), brine (x1), and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.8979 g (2.63 mmol, 55%) of **3.2.10**.

**[0338]** A stirred solution of **3.2.10** (0.6013 g, 1.76 mmol, 1 eq) in anhydrous DMF (5 ml) was treated with MeI (0.22 ml, 0.5 g, 3.52 mmol, 2 eq). The resulting solution was protected from light and cooled to  $0^\circ\text{C}$ . NaH (60% dispersion in oil, 0.1057 g, 2.64 mmol, 1.5 eq) was added and the reaction was stirred at  $0^\circ\text{C}$  to room temperature overnight. The reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  and the resulting mixture diluted with EtOAc/ $\text{H}_2\text{O}$ . The layers were separated. The organic layer was washed with water (x3), brine (x1), and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.5693 g (1.60 mmol, 91%) of **3.2.11**.

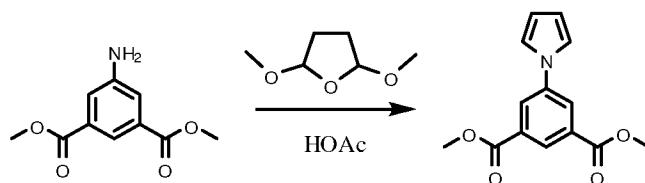
## Example 1.3.3



**[0339]** To dimethyl 5-bromoisophthalate (Matrix Scientific, 617 mg, 2.26 mmol) in toluene (10 ml), 2-tributylstannyl pyrazine (1g, 2.71 mmol) was added followed by  $\text{Pd}(\text{PPh}_3)_4$  (102 mg, 0.09 mmol). Then reaction mixture was refluxed for 22h. Then the reaction mixture was filtered through celite and volatiles were removed under vacuum. Crude residue was column

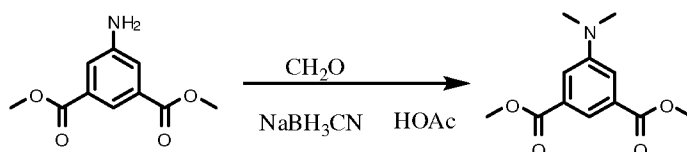
chromatographed (50% ethylacetate/50 % Hexanes) to obtain 455 mg of dimethyl 5-(pyrazin-2-yl)isophthalate as a pale yellow solid.

*Example 1.3.4*



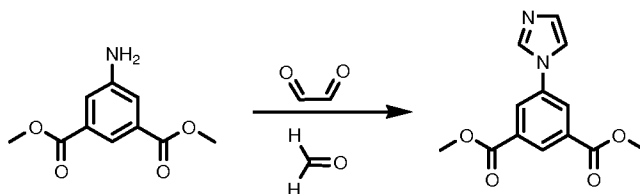
**[0340]** 2,5-dimethoxytetrahydrofuran (0.74 ml, 0.76 g, 5.74 mmol, 1.2 eq) was added to a stirred suspension of dimethyl 5-aminoisophthalate (Aldrich, 1.0 g, 4.78 mmol, 1 eq) in 7 ml acetic acid under Ar. The mixture was heated to reflux at 135 °C. After 45 min the reaction was cooled to RT, and the solvent was removed in vacuo. The residue was stirred in saturated aqueous NaHCO<sub>3</sub>/EtOAc overnight. The layers were separated. The organic layer was washed with saturated aqueous NaHCO<sub>3</sub> (x1), water (x2), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed in vacuo. Purification via flash chromatography yielded 1.00 g (4.6 mmol, 80% yield) of dimethyl 5-(1H-pyrrol-1-yl)isophthalate.

*Example 1.3.5*



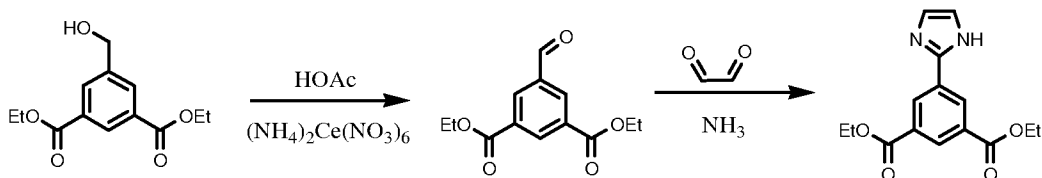
**[0341]** CH<sub>2</sub>O (aq, 37%) (3.2 ml, 3.49g, 43.0 mmol, 6 eq) was added to a stirred solution of dimethyl 5-aminoisophthalate (1.5 g, 7.17 mmol, 1 eq) in CH<sub>3</sub>CN (50 ml) at 0 °C. After 15 min NaBH<sub>3</sub>CN (1.09 g, 16.49 mmol, 2.3 eq) was added. The reaction was adjusted to pH ≈ 7 with HOAc. Stir at 0 °C to RT overnight. The solvent was removed in vacuo, and the residue was partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>. The layers were separated. The organic layer was washed with water (x3), brine(x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed in vacuo. Purification via flash chromatography yielded 1.62 g (6.83 mmol, 95% yield) of dimethyl 5-(dimethylamino)isophthalate.

## Example 1.3.6



**[0342]** The diester (1.00 g, 4.78 mmol, 1 eq) and glyoxal trimer  $\cdot 2\text{H}_2\text{O}$  (1.004 g, 4.78 mmol, 1 eq) were stirred in 6 ml EtOH overnight.  $\text{NH}_4\text{Cl}$  (0.5114 g, 9.56 mmol, 2 eq) was added. After 15 min aqueous formaldehyde (37%, 0.71 ml, 0.78 g, 9.56 mmol, 2 eq) was added and the mixture was heated to reflux at 90 °C. After 1 h the reaction was cooled to room temperature. After the dropwise addition of  $\text{H}_3\text{PO}_4$  (85%, 0.65 ml, 1.1 g, 9.56 mmol, 2 eq) the reaction was heated to reflux at 95 °C. After 6 h the reaction was cooled to room temperature and the solvent was removed *in vacuo*. The residue was stirred in  $\text{CHCl}_3$  and the mixture was filtered through cotton to remove any insoluble material. Purification via flash chromatography yielded 0.7329 g (2.82 mmol, 59% yield) of the product.

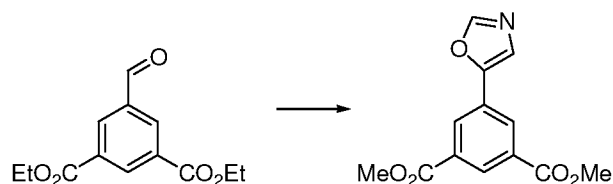
## Example 1.3.7



**[0343]** A solution of  $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$  (7.6 g, 12.6 mmol, 2 eq) in water (16 ml) was added dropwise to a stirred solution of the diester (1.6 g, 6.3 mmol, 1 eq) in HOAc (16 ml). The reaction was heated to 70 °C. After 90 min the reaction was cooled to room temperature. The reaction was diluted with water and extracted with EtOAc (x1). The organic layer was washed with saturated aqueous  $\text{NaHCO}_3$  (x4), brine (x1), and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off and the solvent was removed *in vacuo* yielding 1.3 g (5.19 mmol, 82% yield) of the product.

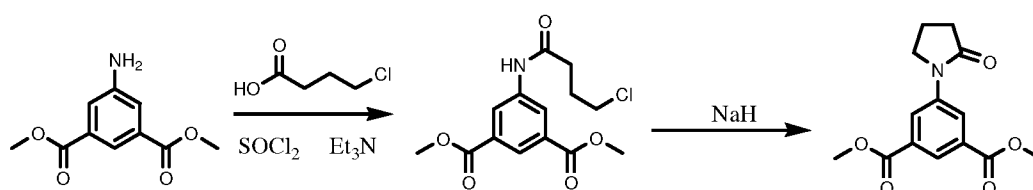
**[0344]**  $\text{NH}_3$  (2.0 M in MeOH, 4.8 ml, 9.6 mmol, 8 eq) was added to a flask charged with the diester (0.300 g, 1.2 mmol, 1 eq) and glyoxal trimer  $\cdot 2\text{H}_2\text{O}$  (0.252 g, 1.2 mmol, 1eq) at 0 °C under Ar. The reaction was stirred at 0 °C to room temperature overnight. The solvent was removed *in vacuo*. The residue was stirred in EtOAc and filtered through cotton to remove any insoluble material. Purification via flash chromatography yielded 0.1293 g (0.45 mmol, 37% yield) of the product.

## Example 1.3.8



**[0345]** To a stirred solution of the aldehyde (529 mg, 2.1 mmol) and p-toluenesulfonylmethyl isocyanide (483 mg, 2.5 mmol) in DME (15 mL) and MeOH (15 mL) was added  $K_2CO_3$ . The resulting mixture was heated to reflux for 4 h and cooled to room temperature. The solvent was removed and the residue was dissolved in EtOAc and  $H_2O$ . The layers were separated and the aqueous layer was extracted with EtOAc (2  $\times$  20 mL). The combined organic layer was washed with brine, dried with  $Na_2SO_4$  and concentrated under reduced pressure to provide 9 (103 mg, 19%).  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.63 (s, 1H), 8.49 (s, 2H), 8.00 (s, 1H), 7.54 (s, 1H), 4.00 (s, 6H).

## Example 1.3.9

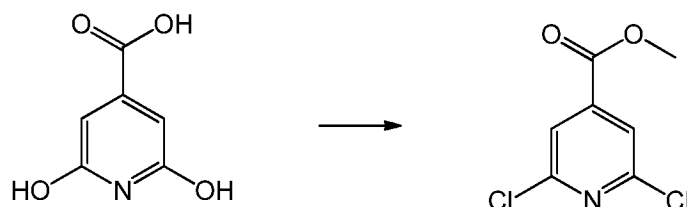


**[0346]** One drop of  $Et_3N$  (catalytic) was added to a stirred solution of 4-chlorobutanoic acid (.029 ml, 0.35 g, 2.87 mmol 1.2 eq) in  $SOCl_2$  (2 ml, 3.27 g, 27.5 mmol, 11.5 eq) and the mixture was heated to 80  $^{\circ}C$ . After 1.5 h the reaction was cooled to room temperature, and the solvent was removed in vacuo. The flask was evacuated and back-filled with Ar (x3). The residue was dissolved in 2 ml anhydrous  $CH_2Cl_2$ . The resulting solution was added dropwise to a stirred suspension of dimethyl 5-aminoisophthalate in 8 ml anhydrous  $CH_2Cl_2$ . After 1 h  $Et_3N$  (1 ml, 0.73 g, 7.17 mmol, 3 eq) was added. After 2h the solvent was removed in vacuo, and the resulting residue was dissolved EtOAc. The organic layer was washed with saturated aqueous  $NaHCO_3$  (x2), water (x3), brine (x1), and dried over  $Na_2SO_4$ . The inorganics were filtered off, and the solvent was removed in vacuo. Purification via flash chromatography yielded 0.6353 g (2.0 mmol, 85% yield) of dimethyl 5-(4-chlorobutanamido)isophthalate.

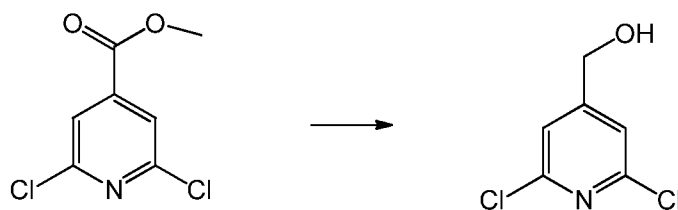
**[0347]** A solution of dimethyl 5-(4-chlorobutanamido)isophthalate (0.635 g, 2.02 mmol, 1 eq) dissolved in 5 ml anhydrous DMF was added dropwise to a stirred suspension of NaH (60% dispersion in oil, 0.101 g, 2.53 mmol, 1.25 eq) in 2 ml anhydrous DMF at 0  $^{\circ}C$  under

Ar. The reaction was stirred at 0 °C to room temperature overnight. After stirring overnight the reaction was heated to 100 °C for 19 h. After cooling to room temperature the reaction was poured into ice-water to quench. The mixture was extracted with EtOAc (x1). The organic layer was washed with water (x4), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed in vacuo. Purification via flash chromatography yielded 0.3487 g (1.26 mmol, 62% yield) of dimethyl 5-(2-oxopyrrolidin-1-yl)isophthalate.

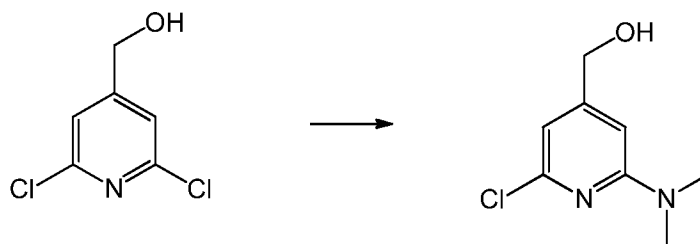
*Example 1.3.10*



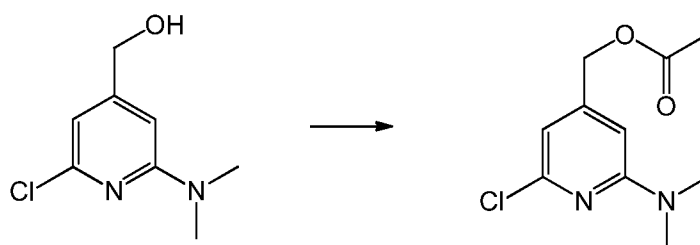
**[0348]** A mixture of 5.0 g (32.2 mmol) of citrazinic acid (Aldrich), 3.9 g (35.6 mmol) of Me<sub>4</sub>NCl, and 9 mL of POCl<sub>3</sub> was stirred with gradual heating to 130 °C under a CaCl<sub>2</sub> drying tube for about 16h. MeOH (100 mL) was added with ice bath cooling; after 1 h, solid NaHCO<sub>3</sub> was added to pH = 8. Water was added, and the aqueous layer was extracted with EtOAc (2x). The combined extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification by flash silica gel chromatography (10% EtOAc/hexanes) provided 4.27 g of the dichloride as a pink solid in 64% yield.



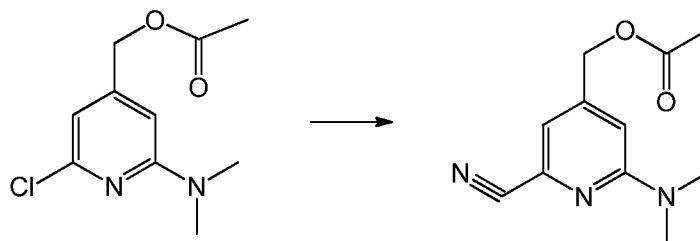
**[0349]** To a stirring solution of (7.33 mmol) of the methyl ester in 25 mL of MeOH and 5 mL of THF at 0 °C was added (21.7 mmol) of NaBH<sub>4</sub>. After 2 h the ice bath was removed and stirring was continued with warming to r.t. and after a further 15 min. 1.06 g of NaBH<sub>4</sub> was added. After another 15 min., the solution was concentrated, and EtOAc was added. The pH was adjusted to 7 with 1N HCl, and the layers were separated. The aqueous layer was extracted with EtOAc (2x), and the combined extracts were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification by flash silica gel chromatography yielded the crude alcohol.



**[0350]** A mixture of crude alcohol in 7 mL of  $(\text{CH}_3)_2\text{NH}$  (40 wt % solution in  $\text{H}_2\text{O}$ ) was stirred at r.t. for 45 min. The temperature was increased to  $50\text{ }^\circ\text{C}$ , and the solution was stirred at  $50\text{ }^\circ\text{C}$  for about 24 h. Ethyl acetate and  $\text{H}_2\text{O}$  (15 mL) were added, and the aqueous layer was extracted with EtOAc. The combined extracts were washed with brine, and the aqueous layer was extracted with EtOAc. The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification by flash silica gel chromatography (40% EtOAc/hexanes) provided 1.01 g of the N,N-dimethylaminopyridine with some impurity (unreacted starting material).



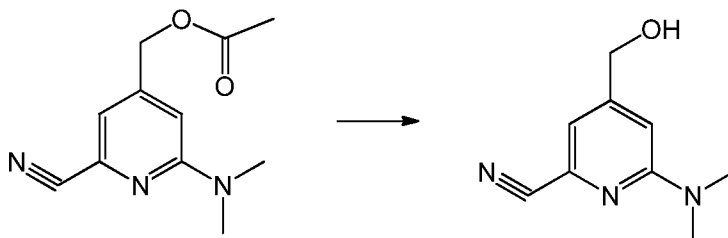
**[0351]** To a stirring solution of the N,N-dimethylaminopyridine in 7 mL of pyridine was added 1.2 mL of  $\text{Ac}_2\text{O}$ . After the solution was stirred for 12 h, the solution was concentrated, and saturated  $\text{NaHCO}_3$  solution was added to  $\text{pH} = 7$ . The aqueous layer was extracted with EtOAc, and the organic layer was washed with  $\text{H}_2\text{O}$  (15 mL) and brine (15 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification by flash silica gel chromatography (15% EtOAc/hexanes) provided the acetate as a yellow oil with some impurity.



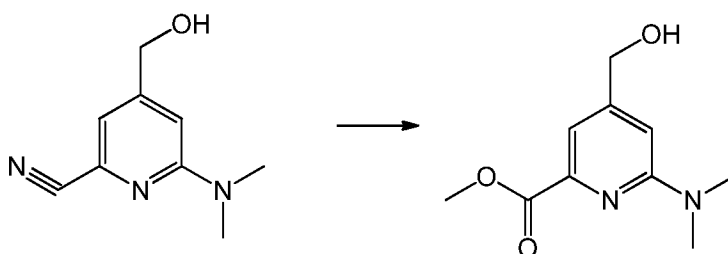
**[0352]** To a solution of 1.17 g (5.10 mmol) of the acetate in 10 mL of DMF (degassed) was added 488 mg (4.16 mmol) of  $\text{Zn}(\text{CN})_2$  and 519 mg (0.449 mmol) of  $\text{Pd}(\text{PPh}_3)_4$ . The mixture was stirred at  $80\text{ }^\circ\text{C}$  and more  $\text{Pd}(\text{PPh}_3)_4$  was added in the following quantities at various intervals in a period of 10 h: 486 mg (50 min.), 708 mg (3 h), 657 mg (6 h). The temperature was increased to  $100\text{ }^\circ\text{C}$  and stirring was continued for about 11 h. Ethyl acetate and 50 mL



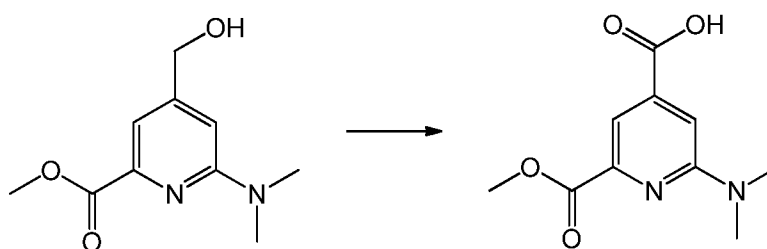
of 10%  $\text{NH}_4\text{OH}$  solution were added. The aqueous layer was extracted with EtOAc, and the combined extracts were washed with brine. The aqueous layer (brine) was extracted with EtOAc, and the combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification by flash silica gel chromatography (30% EtOAc/hexanes) provided 284 mg of the cyanide as a pale yellow solid.



**[0353]** To a stirring solution of 364 mg (1.66 mmol) of the acetate in 7 mL of MeOH was added 365 mg (2.64 mmol) of  $\text{K}_2\text{CO}_3$ . After 1 h, the mixture was filtered through Celite with MeOH and EtOAc. More EtOAc and  $\text{H}_2\text{O}$  (30 mL) were added; the aqueous layer was extracted with EtOAc (4x). The combined extracts were washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification by flash silica gel chromatography (50% EtOAc/hexanes) provided 253 mg of the pale yellow solid in 86% yield.

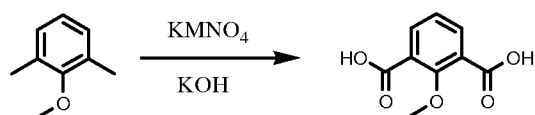


**[0354]** A mixture of 440 mg of the cyanide in 3 mL of concentrated  $\text{H}_2\text{SO}_4$  and 1.8 mL of  $\text{H}_2\text{O}$  was stirred at 135 °C for 12 h. The temperature was decreased to 95 °C, 6 mL of MeOH was added, and the solution was stirred at 95 °C for 1 h. The solution was added to ice with  $\text{H}_2\text{O}$  and EtOAc. Solid  $\text{NaHCO}_3$  and sat.  $\text{NaHCO}_3$  solution were added to a pH=8. The aqueous layer was extracted with EtOAc (2x). The combined extracts washed with brine (40 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give the methyl ester which was used without further purification.

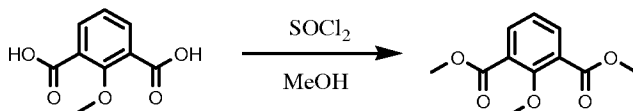


[0355] A mixture of 250 mg (1.19 mmol) of the alcohol and 1.12 g (12.8 mmol) of  $\text{MnO}_2$  in 10 mL of  $\text{CH}_2\text{Cl}_2$  was stirred at 50 °C. To the mixture was added more  $\text{MnO}_2$  in the following quantities at various intervals in a period of 75 min.: 674 mg (15 min.), 788 mg (15 min.), 924 mg (10 min.), 675 mg (15 min.), 690 mg (15 min.). The mixture was filtered through Celite with EtOAc and MeOH and concentrated. The acid was used in the next reaction without further purification.

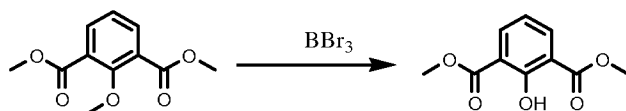
*Example 1.3.11*



[0356]  $\text{KMNO}_4$  (19.15 g, 121.2 mmol, 6.6 eq) followed by the anisole (Aldrich, 2.6 ml, 2.5 g, 18.36 mmol, 1 eq) were added to a stirred solution of KOH (3.30 g, 58.74 mmol, 3.2 eq) in 98 ml of water. The reaction was heated to 80 °C. After 3 h the reaction was cooled to room temperature. The mixture was filtered through Celite. The solution was adjusted to  $\text{pH} \approx 7$  with concentrated HCl and again the mixture was filtered through Celite. The solution was adjusted to  $\text{pH} = 2-3$  with concentrated HCl and extracted with EtOAc (x2). The combined organics were washed with brine (x1) and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off and the solvent was removed via rotary evaporation yielding 1.552 g (7.91 mmol, 43% yield) of the product.

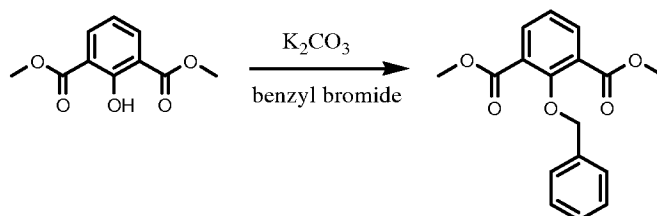


[0357]  $\text{SOCl}_2$  (1.85 ml, 3.03 g, 25.5 mmol, 10 eq) was added dropwise with stirring to a solution of the diacid (0.500 g, 2.55 mmol, 1 eq) in 10 ml anhydrous MeOH at 0 °C under Ar. The reaction was stirred at 0 °C to room temperature overnight. The solvent was removed via rotary evaporation and the residue dissolved in EtOAc. The solution was washed with saturated aqueous  $\text{NaHCO}_3$  (x2), water (x3), brine (x1), and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off and the solvent was removed via rotary evaporation yielding 0.6785 g (3.01 mmol, 118% yield) of the product with some impurities.



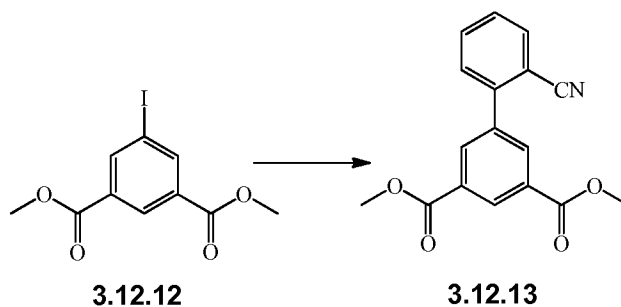
[0358]  $\text{BBr}_3$  (1.0M in  $\text{CH}_2\text{Cl}_2$ , 7.53 ml, 7.53 mmol, 2.5 eq) was added dropwise to a stirred solution of the anisole (0.6785 g, 3.01 mmol, 1 eq) in anhydrous  $\text{CH}_2\text{Cl}_2$  (4 ml) at 0 °C under Ar. After 30 min the reaction was warmed to room temperature. After 2 h the reaction was

quenched anhydrous MeOH (1 ml) and stirred overnight. The solvent was removed via rotary evaporation and the residue dissolved in EtOAc. The organic layer was washed with saturated aqueous NaHCO<sub>3</sub> (x2), water (x3), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off and the solvent was removed via rotary evaporation. Purification via flash chromatography yielded 0.4045 g (1.92 mmol, 64% yield) of the product.



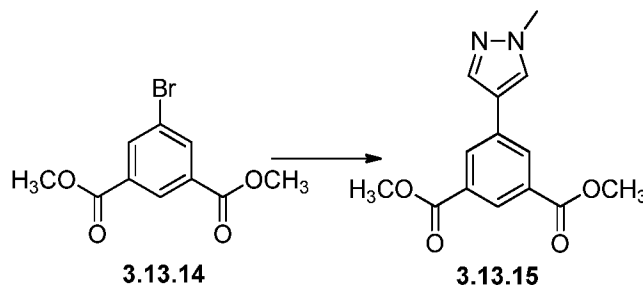
**[0359]** Benzyl bromide (0.34 ml, 0.49 g, 2.89 mmol, 1.5 eq) was added to a stirred suspension of the phenol (0.4045 g, 1.92 mmol, 1 eq) and K<sub>2</sub>CO<sub>3</sub> (0.5317 g, 3.85 mmol, 2 eq) in anhydrous DMF (2 ml) under Ar. After 48 h the reaction was diluted with Et<sub>2</sub>O. The mixture was washed with water (x4), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off and the solvent was removed via rotary evaporation. Purification via flash chromatography yielded 0.5207 g (1.73 mmol, 90% yield) of the product.

*Example 1.3.12*



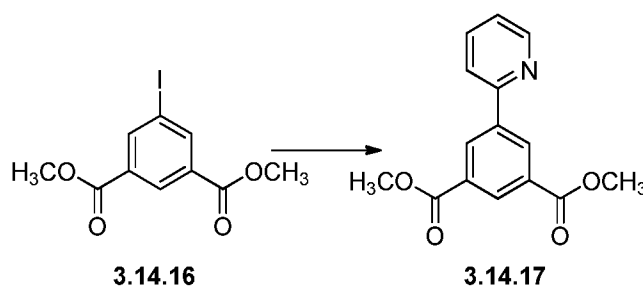
**[0360]** To a solution of dimethyl 5-iodoisophthalate **3.12.12** (Commercial source: Matrix Scientific) (2 g, 6.25 mmol) in 15 mL THF was added 2-cyano-phenyl zinc bromide (Commercial source: sigma-aldrich), (15 mL, 7.5 mmol, 0.5 M THF) and tetrakis(triphenylphosphine) palladium (Commercial source: sigma-aldrich), (71 mg, 0.06 mmol) and the reaction mixture was stirred at room temperature for 2 h. The precipitated solid was filtered, the filtrate was diluted with MeOH to provide after filtration a second crop for a total of 1.2 g of dimethyl 5-(2-cyanophenyl)isophthalate **3.12.13**.

## Example 1.3.13



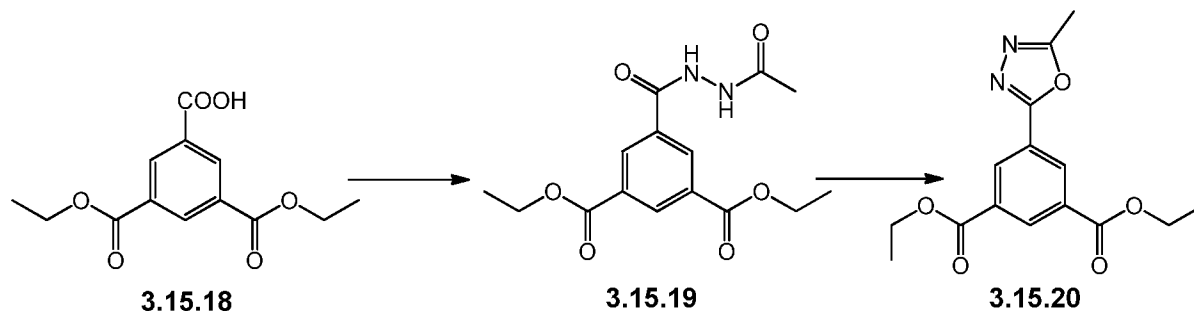
**[0361]** To a mixture of the bromo compound **3.13.14** (2.1 g, 8.0 mmol) (Commercial source: Matrix Scientific), 1-Methyl-4-pyrazolboronic acid pinacol ester (2.0 g, 9.61 mmol) (Commercial source: sigma-aldrich) and  $K_2CO_3$  (3.32 g, 24.0 mmol) (Commercial source: sigma-aldrich) in 40 ml of dioxane and 16 ml of water dichloro [1,1'-bis (diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (653 mg, 0.80 mmol) (Commercial source: sigma-aldrich) was added. The reaction mixture was heated at 80°C for 6h, then concentrated in vacuo. The residue was purified by flash column chromatography with 70% ethyl acetate/30 % Hexanes to obtain 1.3 g of **3.13.15** as a brown solid.

## Example 1.3.14



**[0362]** To the iodo compound (commercial source: Matrix Scientific) **3.14.16** (800 mg, 2.5 mmol) in THF (20 ml), 2-pyridine boronic acid N-phenyldiethanol amine ester (commercial source: Aldrich) (1.8 g, 6.6 mmol),  $K_2CO_3$  (912 mg, 6.6 mmol), triphenyl phosphine (173 mg, 0.66 mmol) were added followed by  $Pd(OAc)_2$  and cuprous iodide (251 mg, 1.32 mmol). After refluxing for 24h, reaction mixture was filtered through a pad of celite. Residual solvent was evaporated on a rotavap under reduced pressure and the crude was dissolved in ethyl acetate. Insoluble material was filtered off and the remaining residue was evaporated to dryness and column purified (60%ethylacetate/40% hexanes) to yield 400 mg of **3.14.17** as yellow solid.

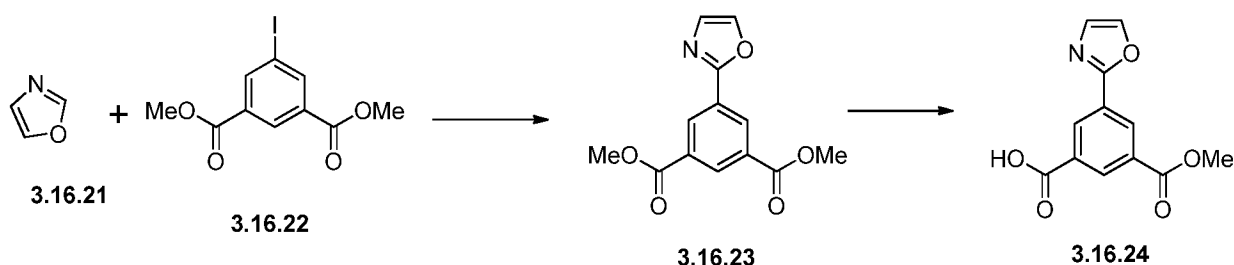
## Example 1.3.15



[0363] To the acid **3.15.18** (3.0 g, 11.28 mmol) in DCM (30 ml), 1-hydroxybenzotriazole (HOBT) (1.83 g, 13.54 mmol) and 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide (EDCI or EDC) (3.03 g, 15.79 mmol) were added. After stirring for 1h at rt, reaction mixture was cooled and acetyl hydrazide (commercial source: Sigma-Aldrich) (834 mg, 11.28 mmol) was added followed by DIPEA (0.5 ml). After stirring at rt for 16h, DCM was removed in vacuum. EtOAc was added to the crude followed by saturated aqueous sodium bicarbonate solution. White precipitate formed. The precipitate was filtered, washed with water and dried thoroughly to yield the hydrazide **3.15.19**.

[0364] To the hydrazide (1.3 g, 4.03 mmol), POCl<sub>3</sub> (commercial source: Sigma-Aldrich) (40 ml) was added and heated at 100°C for 5h. Then reaction mixture was cooled, POCl<sub>3</sub> removed in vacuum. Crude was dissolved in ethyl acetate, washed with water, aq NaHCO<sub>3</sub>, brine and dried. Crude residue was column chromatographed to yield 600mg of oxadiazole **3.15.20**.

## Example 1.3.16

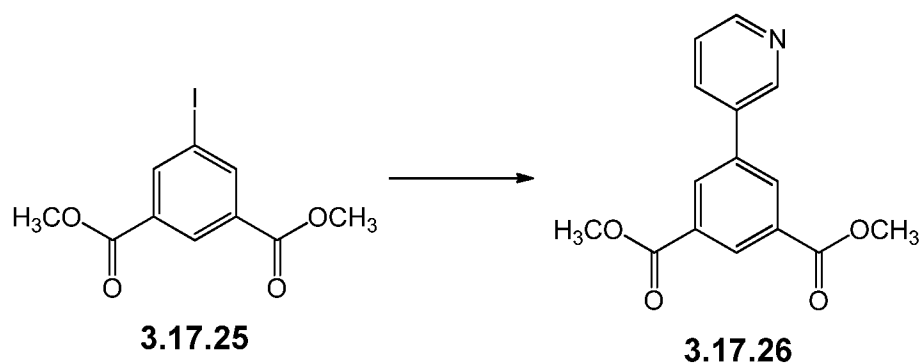


[0365] To the oxazole **3.16.21** (226 mg, 3.28 mmol) in THF (10 ml) at -78°C, n-BuLi (2.4 ml, 3.79 mmol) was added. After 0.5h, ZnCl<sub>2</sub> (21 ml, 10.33 mmol) was added. After stirring at -78 °C for 0.5h, then at 0°C for 1h, iodo-isophthalic acid **3.16.22** (1g, 3.12 mmol) was added followed by Pd(PPh<sub>3</sub>)<sub>4</sub> (191 mg, 0.16 mmol). Then the reaction mixture was refluxed for 2.5 h. The reaction mixture was cooled, diluted with water and extracted with ethylacetate. Organic layer was dried with anhydrous sodium sulfate and the volatiles were

removed on a rotavap under reduced pressure. Then crude residue was column chromatographed to obtain the diester **3.16.23** as a pale yellow solid in 50% yield.

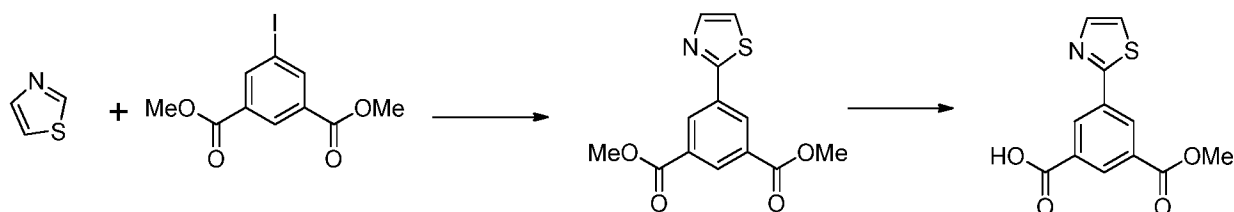
[0366] 1 N NaOH (0.9 eq) was added to a stirred solution of the diester **3.16.23** in 1:3 MeOH/THF. After stirring overnight the solvent was removed via rotary evaporation, and the residue was diluted with saturated aqueous NaHCO<sub>3</sub>. The mixture was extracted with EtOAc (x2). The aqueous layer was adjusted to pH  $\approx$  3 with concentrated HCl, and extract with EtOAc (x3). The appropriate organics were combined, washed with water (x1), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed via rotary evaporation yielding the product in 75% yield of **3.16.24**.

*Example 1.3.17*



[0367] To the iodo compound **3.17.25** (commercial source: Matrix scientific) in 1,4-dioxane (10 ml), pyridine 3-boronic acid, sodium carbonate (2M aqueous solution) and Pd(PPh<sub>3</sub>)<sub>4</sub> was added and heated at 90°C for 4h. Then reaction mixture was diluted with ether, washed with water, brine and dried. Volatiles were removed under vacuum and the crude residue was column chromatographed (60%ethylacetate/40% hexanes) to yield 450 mg of **3.17.26** as pale yellow solid.

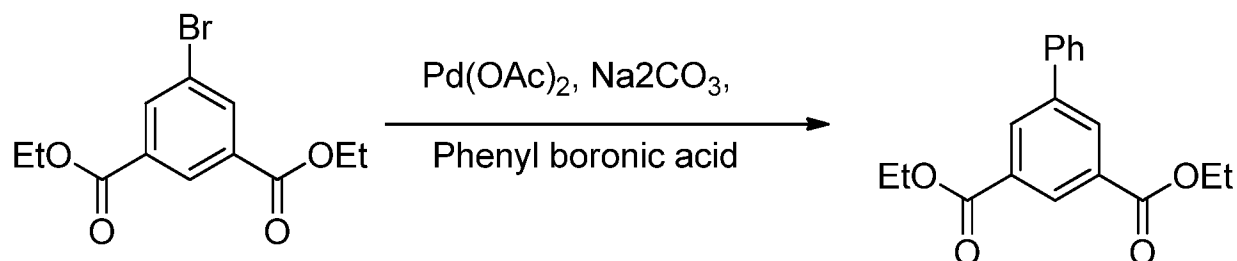
*Example 1.3.18*



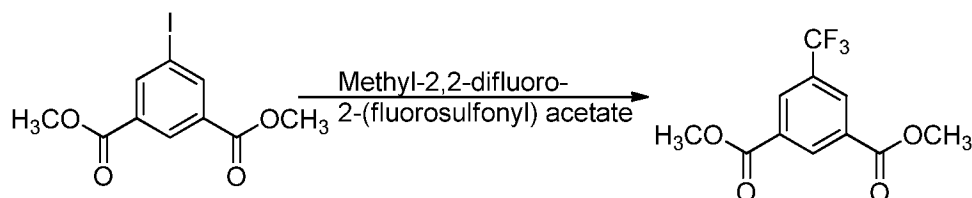
[0368] The ester was synthesized in a manner similar to that of Example 1.3.16.

Saponification was carried out in a manner similar to that for Example 1.4.4.

[0369] Synthesis of Example 1.3.18 was carried out according to the procedure of Example 1.3.16 above.

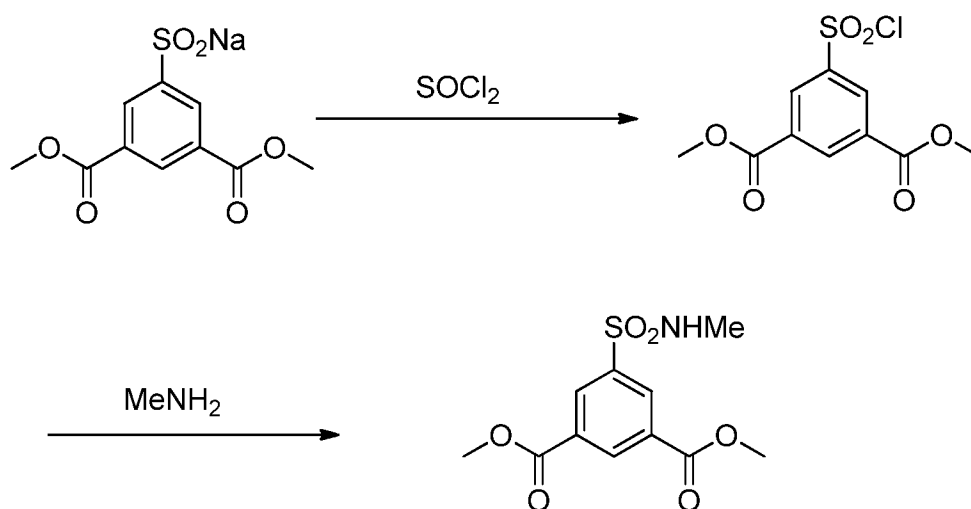
*Example 1.3.19: Synthesis of diethyl [1,1'-biphenyl]-3,5-dicarboxylate*

**[0370]** A mixture of Na<sub>2</sub>CO<sub>3</sub> (776 mg, 7.32 mmol), Pd (OAc)<sub>2</sub> (4.5 mg, 0.02 mmol), aryl halide, diethyl 5-bromoisophthalate (1gm, 3.66 mmol), phenyl boronic acid (670 mg, 5.49 mmol), distilled water (14 ml) and acetone (12 ml) was stirred at 35<sup>0</sup>C for 0.5h. Afterward, the reaction solution was extracted four times with diethyl ether (4X20 ml). The combined organic phase washed with brine, dried over sodium sulfate and then filtered. The solvent was removed under vacuum, and the crude diester, diethyl [1,1'-biphenyl]-3,5-dicarboxylate was taken to the next step without any further purification.

*Example 1.3.20: Synthesis of dimethyl 5-(trifluoromethyl)isophthalate*

**[0371]** A mixture of Methyl-2,2-difluoro-2-(fluorosulfonyl) acetate (Commercial source: sigma-aldrich) (3.5 ml, 27.49 mmol), copper iodide (Commercial source: sigma-aldrich) (2.74 g, 14.37 mmol) and the iodo compound, dimethyl 5-iodoisophthalate (Commercial source: Matrix Scientific) (4.0 g, 12.5 mmol) in DMF (25 ml) was stirred under argon atmosphere for 6h at 70<sup>0</sup>C. The reaction was then cooled to room temperature. It was diluted with DCM, the solution washed with water, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated to afford a syrup. The purification was done by column chromatography (10% ethylacetate/90 % Hexanes) to give 1.5 g of pure diester, dimethyl 5-(trifluoromethyl)isophthalate as a white solid.

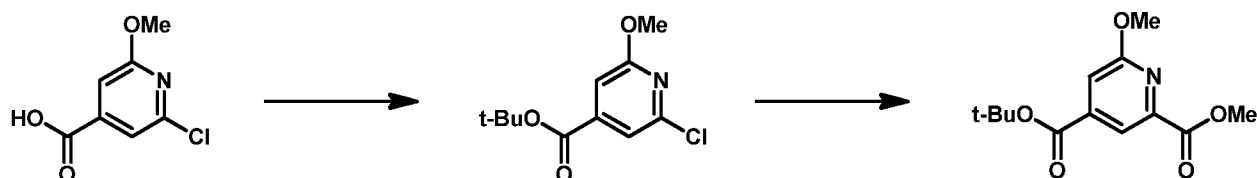
*Example 1.3.21: Synthesis of dimethyl 5-(N-methylsulfamoyl)isophthalate*



**[0372]** To the diester, sodium 3,5-bis(methoxycarbonyl)benzenesulfonate (5g, 17.12 mmol) (Commercial source: sigma-aldrich), thionyl chloride (20 ml) was added followed by couple of drops of DMF. Reaction mixture was heated at 80°C for 20h. Volatiles were then removed under vacuum. Crude was washed with water, brine, dried and column purified to yield 5g of the dimethyl 5-(chlorosulfonyl)isophthalate.

**[0373]** To the sulfonyl chloride (1.0g, 3.47 mmol) in THF (10 ml), methyl amine (2.0M, 6 ml, 12.25 mmol) was added and stirred at rt for 3h. Then volatiles were removed, reaction mixture was diluted with ethyl acetate, washed with 1N HCl, brine and dried. Crude residue was purified by column chromatography to give 700 mg of dimethyl 5-(N-methylsulfamoyl)isophthalate.

*Example 1.3.22*



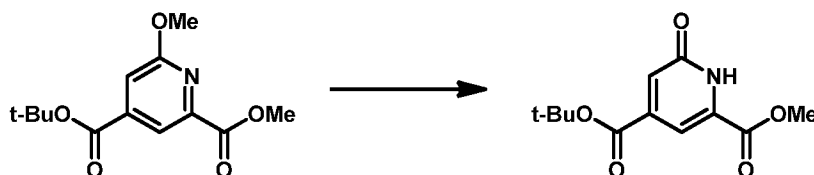
**[0374] *tert*-Butyl 2-chloro-6-methoxyisonicotinate:** To a stirred solution of 2-chloro-6-methoxyisonicotinic acid (20 g, 106.6 mmol) and Boc<sub>2</sub>O (53.5 g, 245.2 mmol) in NMP (100 ml) was added DMAP (2.60 g, 21.3 mmol) at rt and the mixture was stirred at rt overnight. The starting molecule was completely consumed and the mixture was diluted with EtOAc and H<sub>2</sub>O. The organic phase was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layer was washed with H<sub>2</sub>O (x3) and brine, dried over MgSO<sub>4</sub> and evaporated to give a crude product, which was briefly purified with column



chromatography (EtOAc in hexane = 10%, SiO<sub>2</sub> 50 g) to give *tert*-butyl 2-chloro-6-methoxyisonicotinate (22.2 g, 85% yield) as a white solid. MS (ESI) *m/z*: 244 [M+H]<sup>+</sup>.

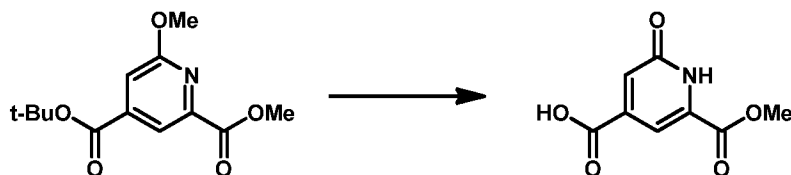
**[0375] 4-*tert*-Butyl 2-methyl 6-methoxypyridine-2,4-dicarboxylate:** To a stirred solution of *tert*-butyl 2-chloro-6-methoxyisonicotinate (22.2 g, 90.9 mmol) and Et<sub>3</sub>N (41.2 ml, 296 mmol) in MeOH (240 ml) and DMSO (240 ml) were added Pd(OAc)<sub>2</sub> (2.20 g, 9.82 mmol) and dppf (5.44 g, 9.82 mmol) at rt. CO was bubbled in the mixture for 10 min and the mixture was stirred under CO atmosphere (balloon) at 80 degree overnight, at which the starting molecule was completely consumed. The mixture was filtered through a pad of Celite and the filtrate was evaporated to some extent (to remove MeOH). The residue of DMSO solution was diluted with EtOAc and H<sub>2</sub>O. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layer was washed with H<sub>2</sub>O (x3) and brine, dried over MgSO<sub>4</sub> and evaporated to give a crude, which was briefly purified with column chromatography (EtOAc in hexane = 10 to 20%, SiO<sub>2</sub> 100 g) to give 4-*tert*-butyl 2-methyl 6-methoxypyridine-2,4-dicarboxylate (22.4 g, 92% yield) as a white solid. MS (ESI) *m/z*: 268.1 [M+H]<sup>+</sup>.

*Example 1.3.23*



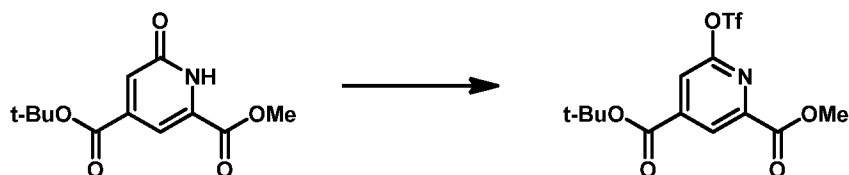
**[0376] 4-*tert*-Butyl 2-methyl 6-oxo-1,6-dihydropyridine-2,4-dicarboxylate:** To a stirred solution of 4-*tert*-butyl 2-methyl 6-methoxypyridine-2,4-dicarboxylate (15.0 g, 56.1 mmol) in MeCN (150 ml) were added NaI (25.2 g, 168 mmol) and TMSCl (21.3 ml, 168 mmol) at rt and the mixture was stirred for 18 hours at the same temperature under Ar atmosphere. The mixture was quenched with satd. NaHCO<sub>3</sub> aq. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layer was washed with satd. NaHCO<sub>3</sub> aq., and brine, dried over MgSO<sub>4</sub> and evaporated to give a crude, which was briefly purified with column chromatography (EtOAc in hexane = 20 to 100%) to give 4-*tert*-butyl 2-methyl 6-oxo-1,6-dihydropyridine-2,4-dicarboxylate (22.2 g, 85% yield) as a white solid. MS (ESI) *m/z*: 254 [M+H]<sup>+</sup>.

## Example 1.3.24



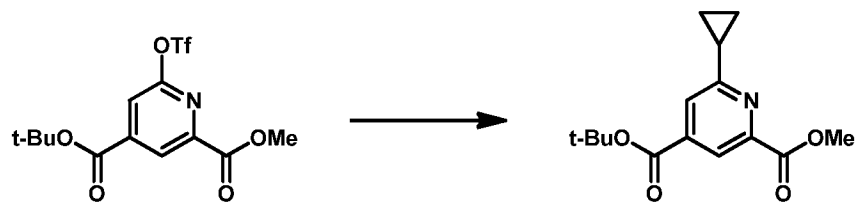
**[0377] 6-(Methoxycarbonyl)-2-oxo-1,2-dihydropyridine-4-carboxylic acid:** To a stirred solution of 4-*tert*-butyl 2-methyl 6-methoxypyridine-2,4-dicarboxylate (5.0 g, 18.7 mmol) in MeCN (50 ml) were added NaI (8.41 g, 56.1 mmol) and TMSCl (7.10 ml, 56.1 mmol) at rt and the mixture was stirred for 12 hours at the same temperature under Ar atmosphere. To this stirred mixture was added H<sub>2</sub>O (0.66 ml) at rt and the mixture was stirred for 30 min at 60 degree. The mixture was cooled to rt and it was quenched with H<sub>2</sub>O (100 ml). A precipitated solid was collected and it was washed with IPE (x3) and dried under reduced pressure to give 6-(methoxycarbonyl)-2-oxo-1,2-dihydropyridine-4-carboxylic acid (3.68 g, >99% yield) as a pale brown solid. MS (ESI) *m/z*: 198 [M+H]<sup>+</sup>.

## Example 1.3.25



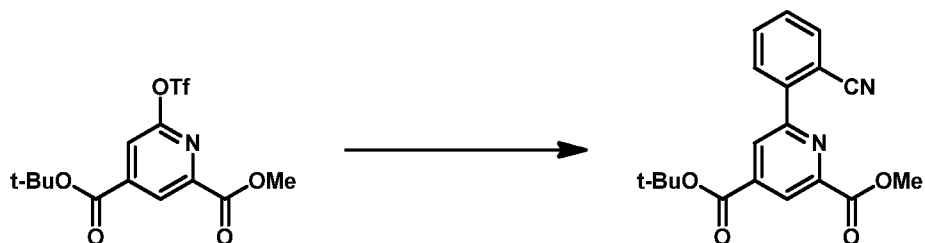
**[0378] 4-*tert*-Butyl 2-methyl 6-((trifluoromethyl)sulfonyloxy)pyridine-2,4-dicarboxylate:** To a stirred solution of 4-*tert*-butyl 2-methyl 6-oxo-1,6-dihydropyridine-2,4-dicarboxylate (2.0 g, 7.90 mmol) and *i*-Pr<sub>2</sub>NEt (2.02 ml, 11.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (80 ml) were added Tf<sub>2</sub>O (1.59 ml, 9.48 mmol) at 0 degrees drop by drop and the mixture was stirred at the same temperature for 1 hour. The starting molecule was completely consumed and it was quenched with satd. NaHCO<sub>3</sub> aq. The organic layer was separated and the aqueous layer was extracted with CHCl<sub>3</sub> (x3). The combined organic layer was washed with satd. NaHCO<sub>3</sub> aq. and brine, dried over MgSO<sub>4</sub> and evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 0 to 20%) to give 4-*tert*-butyl 2-methyl 6-((trifluoromethyl)sulfonyloxy)pyridine-2,4-dicarboxylate (2.68 g, 88% yield) as a white solid. MS (ESI) *m/z*: 386 [M+H]<sup>+</sup>.

## Example 1.3.26



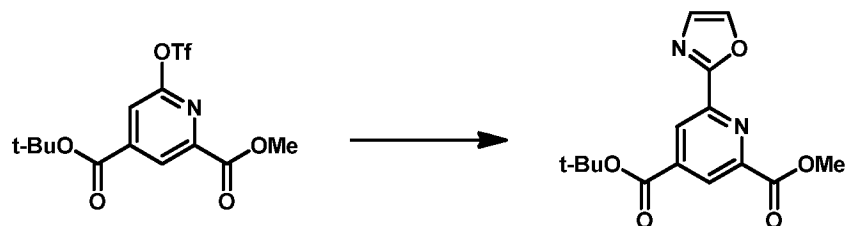
**[0379] 4-*tert*-Butyl 2-methyl 6-cyclopropylpyridine-2,4-dicarboxylate:** To a stirred solution of 4-*tert*-butyl 2-methyl 6-[[trifluoromethyl)sulfonyl]oxy]pyridine-2,4-dicarboxylate (200 mg, 0.519 mmol) and cyclopropylboronic acid (89 mg, 1.04 mmol) in toluene (2.0 ml) were added Pd<sub>2</sub>(dba)<sub>3</sub> (48 mg, 0.052 mmol), SPhos (85 mg, 0.21 mmol) and K<sub>3</sub>PO<sub>4</sub> (331 mg, 1.56 mmol) at rt and the mixture was stirred at 100 degree for 1 hour. The starting molecule was completely consumed and it was evaporated to give a purple residue. This was purified with column chromatography (EtOAc in hexane = 0 to 80%) to give 4-*tert*-butyl 2-methyl 6-cyclopropylpyridine-2,4-dicarboxylate (36 mg, 25% yield) as a pale yellow oil. MS (ESI) *m/z*: 278 [M+H]<sup>+</sup>.

## Example 1.3.27



**[0380] 4-*tert*-Butyl 2-methyl 6-(2-cyanophenyl)pyridine-2,4-dicarboxylate:** The desired compound was synthesized from 4-*tert*-butyl 2-methyl 6-[[trifluoromethyl)sulfonyl]oxy]pyridine-2,4-dicarboxylate (200 mg, 0.519 mmol) in a similar manner to *Example 1.3.26*. (35 mg, 20% yield) MS (ESI) *m/z*: 339 [M+H]<sup>+</sup>.

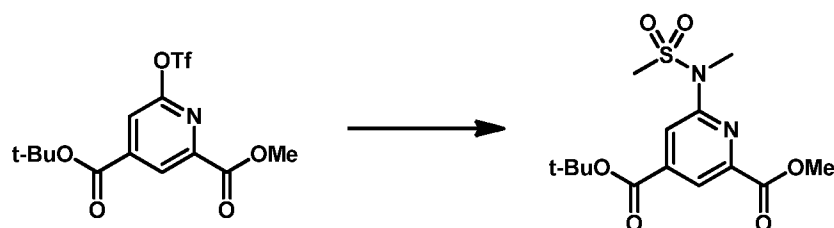
## Example 1.3.28



**[0381] 4-*tert*-Butyl 2-methyl 6-(1,3-oxazol-2-yl)pyridine-2,4-dicarboxylate:** A solution of 1,3-oxazole (0.5 M THF solution, 15.6 ml, 7.79 mmol) was placed under reduced pressure for 30 min at -78 degree for the removal of dissolved O<sub>2</sub> in THF. To this stirred oxazole/THF solution was added *n*-BuLi (1.65 M hexane solution, 2.83 ml, 4.67 mmol) at -78 degree and

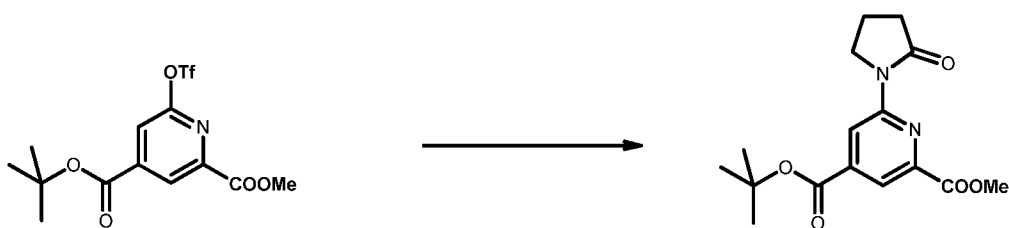
the mixture was stirred at the same temperature for 30 min.  $\text{ZnCl}_2$  (1.0 M THF solution, 4.67 ml, 4.67 mmol) was added to the mixture at the same temperature and the mixture was allowed to warm up at rt. To this stirred solution was added 4-*tert*-butyl 2-methyl 6-[[trifluoromethyl)sulfonyl]oxy]pyridine-2,4-dicarboxylate (300 mg, 0.779 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (180 mg, 0.156 mmol) and the mixture was heated at 85 degree for 1 min. The starting molecule was completely consumed and it was quenched with MeOH and volatiles were evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 20 to 100%) to give 4-*tert*-butyl 2-methyl 6-(1,3-oxazol-2-yl)pyridine-2,4-dicarboxylate (87 mg, 37% yield) as a yellow oil. MS (ESI)  $m/z$ : 305  $[\text{M}+\text{H}]^+$ .

*Example 1.3.29*



**[0382] 4-*tert*-Butyl 2-methyl 6-[methyl(methylsulfonyl)amino]pyridine-2,4-dicarboxylate:** To a stirred solution of 4-*tert*-butyl 2-methyl 6-[[trifluoromethyl)sulfonyl]oxy]pyridine-2,4-dicarboxylate (300 mg, 0.779 mmol),  $\text{CH}_3\text{SO}_2\text{NHCH}_3$  (170 mg, 1.56 mmol) and  $\text{K}_3\text{PO}_4$  (496 mg, 2.34 mmol) in dioxane (3 ml) were added  $\text{Pd}_2(\text{dba})_3$  (143 mg, 0.156 mmol) and Xantphos (270 mg, 0.467 mmol) at rt and the mixture was stirred for 1 hour at 100 degree. Volatiles were evaporated and the mixture was purified with column chromatography (EtOAc in hexane = 0 to 80%) to give 4-*tert*-butyl 2-methyl 6-[methyl(methylsulfonyl)amino]pyridine-2,4-dicarboxylate (234 mg, 87% yield) as a colorless oil. MS (ESI)  $m/z$ : 345  $[\text{M}+\text{H}]^+$ .

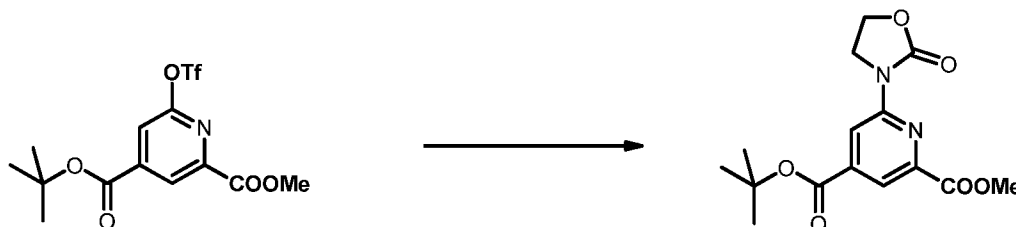
*Example 1.3.30*



**[0383] 4-*tert*-butyl 2-methyl 6-(2-oxopyrrolidin-1-yl)pyridine-2,4-dicarboxylate:** To a solution of 4-*tert*-butyl 2-methyl 6-[[trifluoromethyl)sulfonyl]oxy]pyridine-2,4-dicarboxylate (100 mg, 0.26 mmol) in toluene (3 ml), pyrrolidin-2-one (44mg, 0.52mmol),  $\text{Cs}_2\text{CO}_3$  (127 mg, 0.39 mmol), xantphos (54 mg, 0.093 mmol) were added followed by

$\text{Pd}_2(\text{dba})_3$  (14 mg, 0.016 mmol). After refluxing for 1.5 hours, reaction mixture was purified using column chromatography (EtOAc / hexane = 1:1) to yield 76 mg (91% yield) of 4-tert-butyl 2-methyl 6-(2-oxopyrrolidin-1-yl)pyridine-2,4-dicarboxylate as a white solid. MS (ESI)  $m/z$ : 321  $[\text{M}+\text{H}]^+$ .

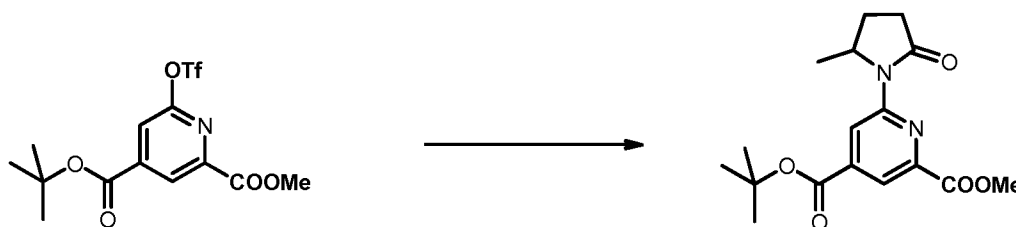
*Example 1.3.31*



**[0384] 4-tert-butyl 2-methyl 6-(2-oxo-1,3-oxazolidin-3-yl)pyridine-2,4-dicarboxylate:**

The desired compound was synthesized from 4-tert-butyl 2-methyl 6-[[[(trifluoromethyl)sulfonyl]oxy]pyridine-2,4-dicarboxylate in a similar manner to *Example 1.3.30* (62 mg, 74% yield). MS (ESI)  $m/z$ : 323  $[\text{M}+\text{H}]^+$ .

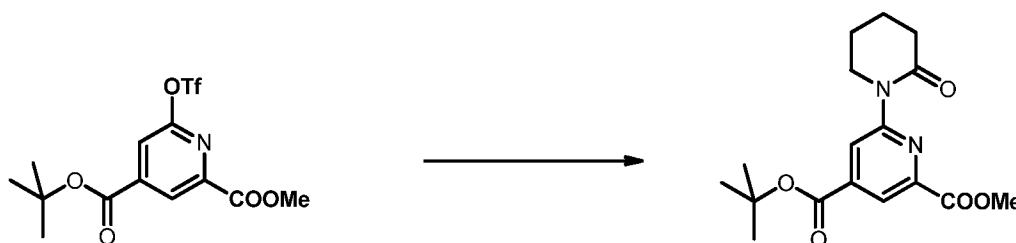
*Example 1.3.32*



**[0385] 4-tert-butyl 2-methyl 6-(2-methyl-5-oxopyrrolidin-1-yl)pyridine-2,4-**

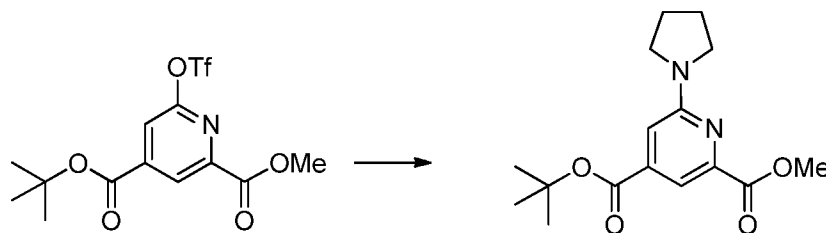
**dicarboxylate:** The desired compound was synthesized from 4-tert-butyl 2-methyl 6-[[[(trifluoromethyl)sulfonyl]oxy]pyridine-2,4-dicarboxylate in a similar manner to *Example 1.3.30* (72 mg, 83% yield). MS (ESI)  $m/z$ : 335  $[\text{M}+\text{H}]^+$ .

*Example 1.3.33*



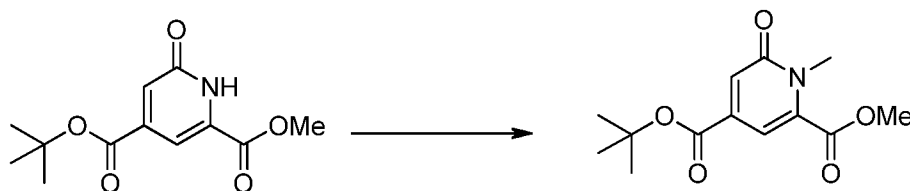
**[0386] 4-tert-butyl 2-methyl 6-(2-oxopiperidin-1-yl)pyridine-2,4-dicarboxylate:** The desired compound was synthesized from 4-tert-butyl 2-methyl 6-[[[(trifluoromethyl)sulfonyl]oxy]pyridine-2,4-dicarboxylate in a similar manner to *Example 1.3.30* (258 mg, 99% yield). MS (ESI)  $m/z$ : 335  $[\text{M}+\text{H}]^+$ .

## Example 1.3.34



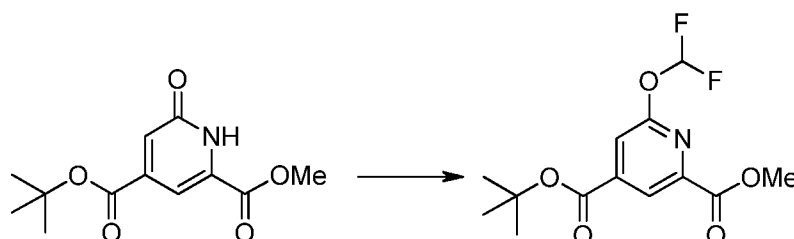
**[0387] 4-tert-butyl 2-methyl 6-(pyrrolidin-1-yl)pyridine-2,4-dicarboxylate:** To a stirred solution of 4-tert-butyl 2-methyl 6-[[trifluoromethyl)sulfonyl]oxy]pyridine-2,4-dicarboxylate (119 mg, 0.309 mmol) in dioxane (1 mL) was added pyrrolidine (0.5 mL). After stirring for 30 minutes the reaction mixture was concentrated in vacuo and the residue was purified with silica-gel column chromatography (hexane/EtOAc = 95:5 to 80:20) to give 4-tert-butyl 2-methyl 6-(pyrrolidin-1-yl)pyridine-2,4-dicarboxylate as a yellow solid. (63 mg, 67% yield) MS (APCI/ESI) M/Z: 307 [M+H]<sup>+</sup>.

## Example 1.3.35



**[0388] 4-tert-butyl 2-methyl 1-methyl-6-oxo-1,6-dihydropyridine-2,4-dicarboxylate:** To a solution of 4-tert-butyl 2-methyl 6-oxo-1,6-dihydropyridine-2,4-dicarboxylate (200 mg, 0.791 mmol) in DMF (4 mL) were added iodomethane (0.15 mL, 2.37 mmol) and potassium carbonate (218 mg, 1.58 mmol). After stirring for 14 hours at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified with silica-gel column chromatography (hexane/EtOAc 95:5 to 0:100) to give 4-tert-butyl 2-methyl 1-methyl-6-oxo-1,6-dihydropyridine-2,4-dicarboxylate as a colorless solid. (146 mg, 69% yield) MS (ESI) M/Z: 268 [M+H]<sup>+</sup>.

## Example 1.3.36

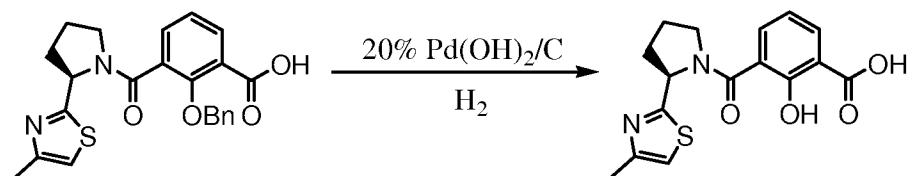


**[0389] 4-tert-butyl 2-methyl 6-(difluoromethoxy)pyridine-2,4-dicarboxylate:** To a solution of 4-tert-butyl 2-methyl 6-oxo-1,6-dihydropyridine-2,4-dicarboxylate (55 mg, 0.217)

in MeCN (1 mL) was added difluoro(fluorosulfonyl)acetic acid (0.027 mL, 0.26 mmol) and potassium carbonate (35 mg, 0.33 mmol). After stirring for 14 hours, the mixture was filtered with Celite and the filtrate was concentrated in vacuo to give crude 4-tert-butyl 2-methyl 6-(difluoromethoxy)pyridine-2,4-dicarboxylate.

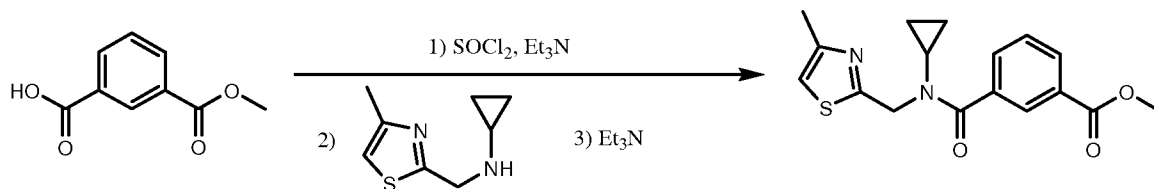
#### Example 1.4: Synthesis of isophthalamide intermediates.

##### Example 1.4.1



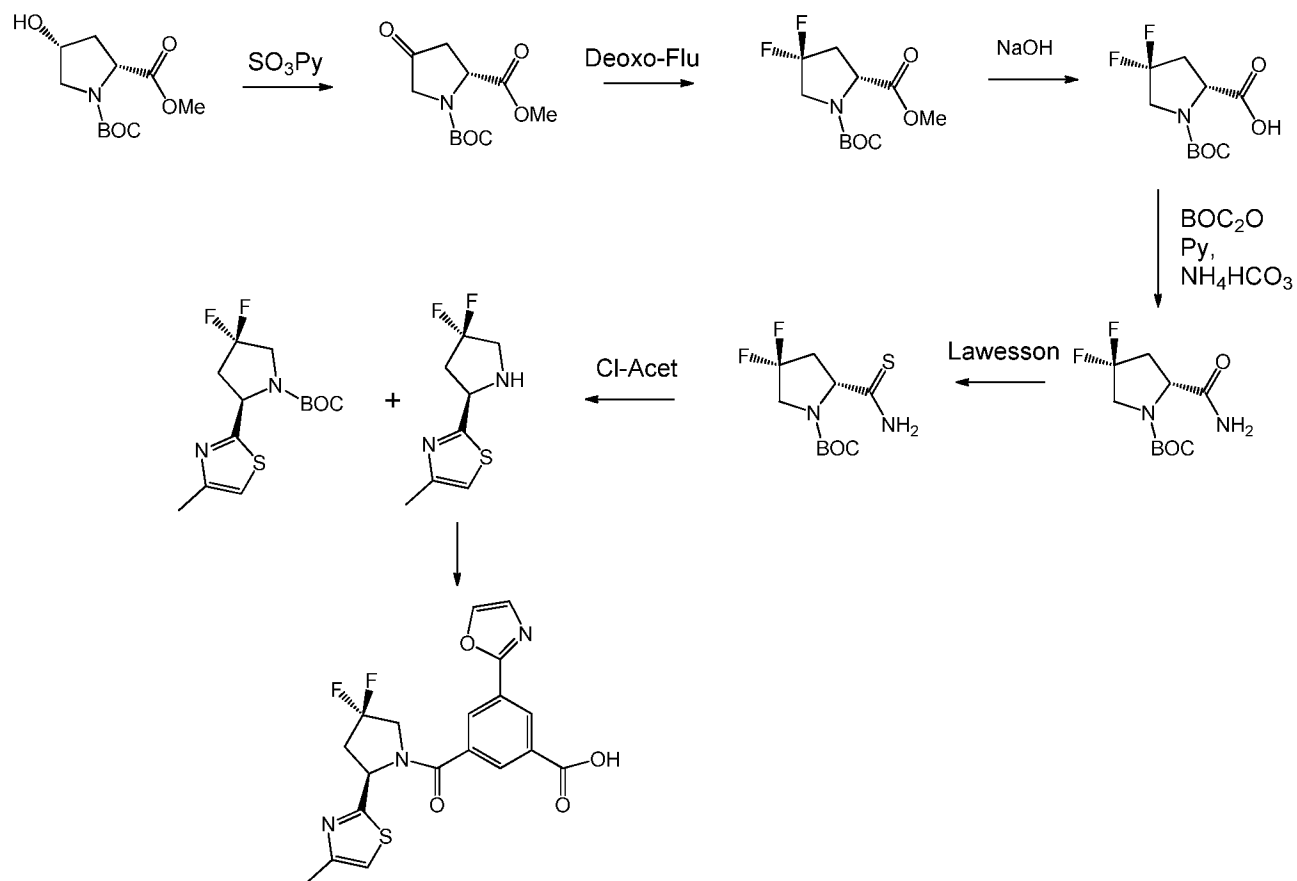
[0390] 20% Pd(OH)<sub>2</sub>/C (0.04 g, 40 wt %) was added to a stirred solution of the acid (0.1006 g, 0.24 mmol) in MeOH. The mixture was stirred under a H<sub>2</sub> (double balloon) overnight. The mixture was filtered through Celite and the solvent was removed via rotary evaporation yielding 0.0790 g (0.24 mmol, 100% yield) of the product.

##### Example 1.4.2



[0391] Et<sub>3</sub>N (1 drop, catalytic) was added to a stirred suspension of *mono*-Methyl isophthalate (0.294 mmol, 1.0 eq) in 2 ml SOCl<sub>2</sub> under Ar. The mixture was heated to reflux at 90 °C for 2h. The reaction was cooled to RT, and the solvent was removed *in vacuo*. The residue was placed under an Ar atmosphere and dissolved in 2 ml anhyd CH<sub>2</sub>Cl<sub>2</sub>. The resulting solution was treated with a solution of the amine (0.294 mmol, 1.0 eq) dissolved in 1 ml anhyd CH<sub>2</sub>Cl<sub>2</sub> under Ar. After stirring at RT for 30 min, the reaction was treated with Et<sub>3</sub>N (0.294 mmol, 1 eq). After stirring at RT for 30 min, the reaction is poured into a separatory funnel, washed with sat. NaHCO<sub>3</sub> (x1), water (x3), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were removed via filtration, and the solvent was removed *in vacuo* yielding the crude product in 93% yield.

## Example 1.4.3



**[0392]** To an ice-cold solution of 4-(R)-hydroxyl-2-(R)-hydroxymethylpyrrolidine-1-carboxylic acid tert-butyl ester (9.81 g, 40.93 mmol) in DMSO (50 mL) was added triethylamine (16.2 mL, 163.73 mmol) and sulfurtrioxide-pyridine complex (12.73 g, 81.87 mmol). The resulting mixture was stirred 30 min, warmed to room temperature and stirred 30 min, diluted with diethyl ether and washed with 5% aqueous citric acid, saturated aqueous sodium chloride, dried (sodium sulfate) and concentrated to give the title compound as an oil which was purified with flash chromatography to produce the ketone (7.5 g). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 4.818-4.673 (m, 1 H), 3.903 (s, 1 H), 3.871(s, 1 H), 3.749 (s, 3 H), 3.003-2.862 (m, 1 H), 2.605-2.542 (m, 1 H), 1.468, 1.445 (s, 9 H).

**[0393]** To a solution of 4-oxopyrrolidine-N-1,2-(R)-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (7.5 g, 35.76 mmol) in dichloromethane (80 mL) at -78°C was added Deoxo-Fluor (17 mL, 1.07 mol). The resulting mixture was stirred and warmed to room temperature for overnight, then was cooled in ice bath diluted with chloroform and quenched with saturated sodium bicarbonate solution. Warmed to room temperature, separated and dried (magnesium sulfate), concentrated and purified with silica gel chromatography to give the



compound as an oil (6.47 g).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 4.568-4.422 (m, 1 H), 3.894-3.725 (m, 2 H), 3.767(s, 3 H), 2.798-2.601 (m, 1 H), 2.553-2.385 (m, 1 H), 1.470, 1.422 (s, 9 H).

**[0394]** To the ester (6.2 g, 23.37 mmol) in THF (60 ml), aq sodium hydroxide (8 ML of 1 M solution, 15 ML of water, 32 mmol) was added. After 3 h, volatiles were removed in vacuum. Aqueous layer was adjusted to about PH = 3 with 3 M HCl solution, and reaction mixture was extracted with ethyl acetate three times. Combined organic layers were washed with brine, dried and concentrated to yield a white solid (5.55 g), which was used for the next step without further purification and identification.

**[0395]** To the crude acid (5.55 g, 22.08 mmol) in dioxane (50 ml) were added pyridine (Commercial source: sigma-aldrich) (1.25 ml),  $(\text{Boc})_2\text{O}$  (Commercial source: sigma-aldrich) (6.75 g, 30.92 mmol), followed by ammonium bicarbonate (2.36 g, 29.82 mmol). The resulting reaction mixture was stirred overnight at rt, then volatiles were removed in vacuum. Then reaction mixture was dissolved in ethyl acetate, washed with aqueous diluted HCl (1 M), sodium bicarbonate and brine. Organic layer was dried and evaporated to obtain the amide in quantitative yield 5.6 g), which was used for the next step without further purification and identification.

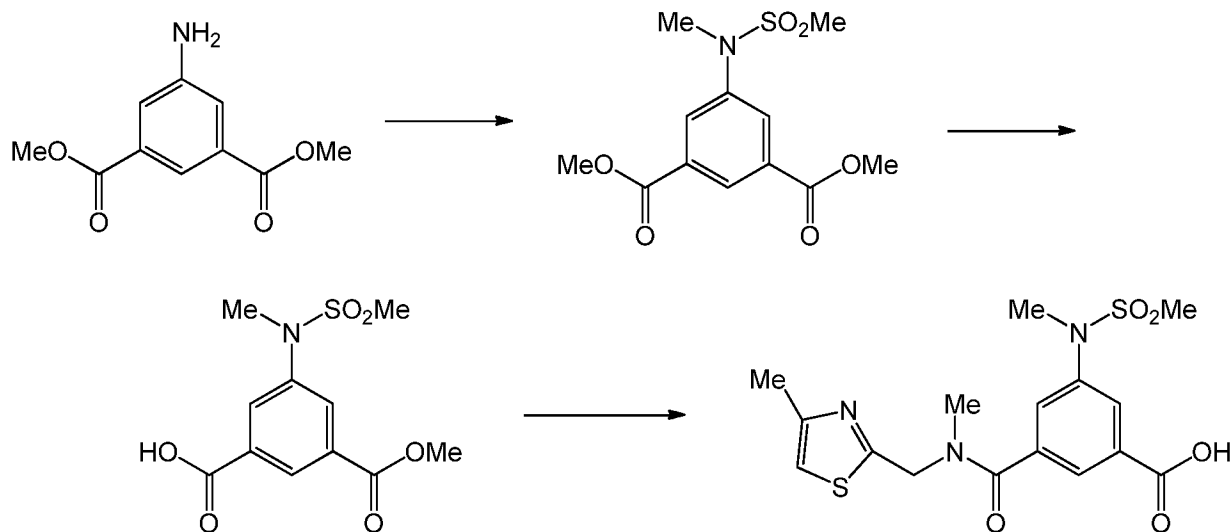
**[0396]** Lawesson's reagent (Commercial source: sigma-aldrich) (5.41 g, 13.37 mmol) was added to the amide (5.6 g, 22.28 mmol) in DME (Commercial source: sigma-aldrich) (100 ml) and the reaction mixture was stirred overnight at rt. Then volatiles were removed in vacuum and the reaction mixture was partitioned between ether and water. Ether layer was concentrated and column purified to obtain 4.6 g of thioamide.

**[0397]** To the thioamide (4.6 g, 17.21 mmol) in ethanol (50 ml) was added chloroacetone (Commercial source: sigma-aldrich) (2.3 g, 25.81 mmol). After heating at 75  $^{\circ}\text{C}$  for 5h, volatiles were removed in vacuum. Reaction mixture was diluted with ethyl acetate, washed with sodium bicarbonate. Organic layer was dried and evaporated. To the crude residue 4N HCl/dioxane (Commercial source: sigma-aldrich) (10 ml) was added and stirred at rt for 3h. Then volatiles were removed in vacuum and reaction mixture was partitioned between chloroform and aqueous sodium bicarbonate. Organic layer was dried and evaporated to yield 1.2 g of the desired product amine.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.818 (s, 1 H), 4.733 (t,  $J = 7.8$  Hz, 1 H), 3.345-3.301 (m, 2 H), 2.861-2.710 (m, 1 H), 2.596-2.413 (m, 1 H), 2.420 (s, 3 H).

**[0398]** To a stirred solution of mono acid (726.2 mg, 2.94 mmol), amine (600 mg, 2.94 mmol) in DCM were added triethylamine (1.64 mL, excess), Py-BOP (1.68 g, 3.23 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. Then aqueous saturated sodium bicarbonate was added and the reaction mixture was extracted with chloroform. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product thus obtained was purified by silica gel flash column chromatography to provide the corresponding amide (700 mg). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 8.817 (s, 1 H), 8.414 (s, 1 H), 8.286 (s, 1 H), 7.781 (s, 1 H), 7.306 (m, 1 H), 6.879 (s, 1 H), 5.918 (m, 1 H), 4.159 (m, 1 H), 3.978 (s, 3 H), 3.878 (m, 1 H), 3.175 (m, 1 H), 2.948 (m, 1 H), 2.467 (s, 3 H).

**[0399]** The ester (700 mg, 1.62 mmol) was dissolved in THF:MeOH (1:1) (15:15 mL) and H<sub>2</sub>O (3 mL). Solid NaOH (194 mg, 4.845 mmol) was added and stirred at 50 °C for 1 hour. The reaction mixture was concentrated under reduced pressure. Saturated NaHCO<sub>3</sub> (10 mL) solution was added to the reaction mixture and extracted with toluene (to remove organic impurities). The aqueous reaction mixture was acidified with diluted HCl (10%), extracted with EtOAc, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated and dried under reduced pressure to give the crude acid which can be used directly for next reaction.

*Example 1.4.4*



**[0400]** Dimethyl 5-(N-methylmethanesulfonamido)isophthalate: To a stirred solution of dimethyl 5-aminoisophthalate (2.09 g, 10 mmol) in dichloromethane (30 mL), pyridine (2.43 mL, 30 mmol) was added at room temperature. At 0°C, methanesulfonyl chloride (0.86 mL, 11 mmol) was added and the resulting mixture was stirred at room temperature for overnight. Then the reaction mixture was concentrated under reduced pressure and ethyl acetate (50 mL) was added. The resulting white precipitate was filtered and washed with

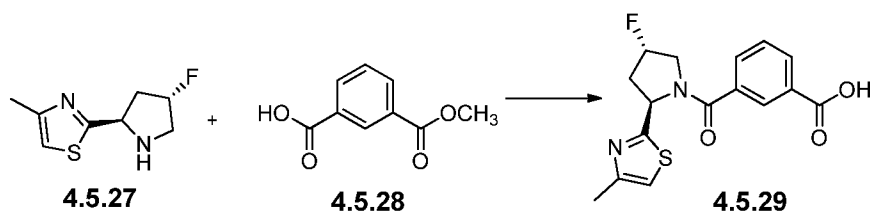
hexanes to give the sulfonamide in 95% (2.715 g) yield as a white solid. See Stachelet aL., J. Med. Chem. 2004, 47, 6447-6450.

**[0401]** To a stirred suspension of NaH (0.24 g, 10 mmol, 60% in oil dispersion) in 10 mL of DMF was added the above sulfonamide (1.435 g, 5 mmol) followed by iodomethane (0.62 mL, 10 mmol) at room temperature. After 5 hours, the reaction was quenched by H<sub>2</sub>O (25 mL). Then the reaction mixture was extracted with EtOAc, further washed with H<sub>2</sub>O to remove excess of DMF, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product thus obtained was washed with hexanes to give the diester as a white solid in 91 % (1.37 g) yield.

**[0402]** 3-(Methoxycarbonyl)-5-(N-methylmethan-5-ylsulfonamido )benzoic acid: The diester (0.842 g, 2.8 mmol) was dissolved in THF:MeOH (1:1) (8 mL) and H<sub>2</sub>O (3 mL). Solid NaOH (0.112 g, 2.8 mmol) was added and stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure. Saturated NaHCO<sub>3</sub> (10 mL) solution was added to the reaction mixture and extracted with toluene (to remove <10% unreacted starting material). The aqueous solution was acidified with dil HCl (10%), extracted with EtOAc, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated and dried under reduced pressure to give the mono acid as a white solid (75%, 0.598 g) which was used for further reaction without purification.

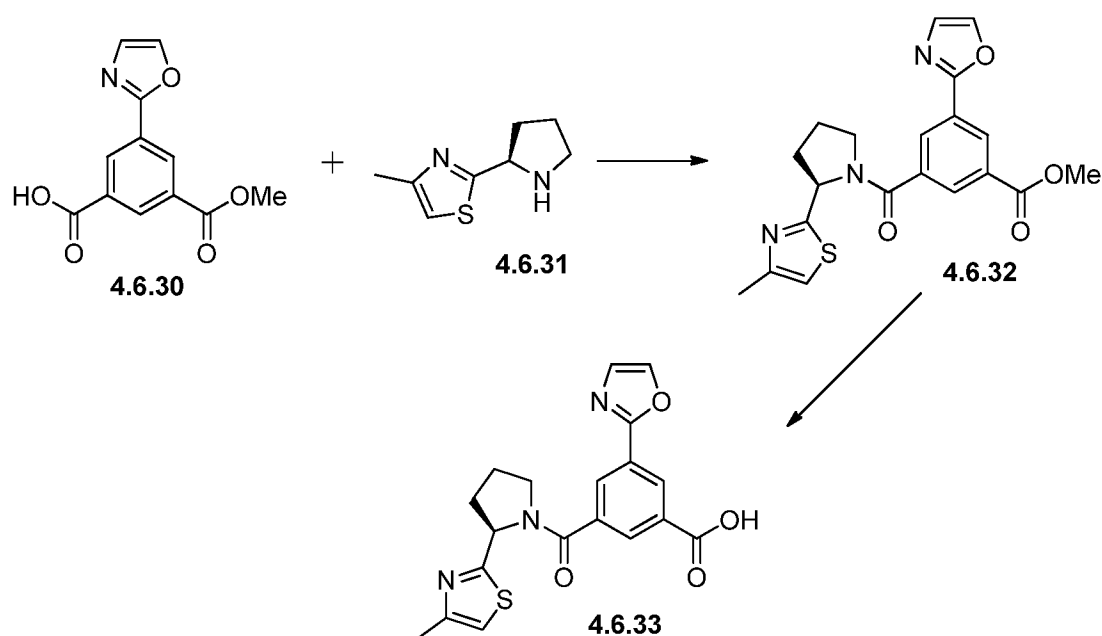
**[0403]** To a stirred solution of mono acid (0.393 g, 1.37 mmol), amine (185 mg, 1.3 mmol) in DCM were added triethylamine (1 mL, excess), Py-BOP (784 mg, 1.507 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. Then water was added and the reaction mixture was extracted with EtOAc. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product thus obtained was purified by silica gel flash column chromatography (2% MeOH in ethyl acetate) to provide the corresponding amide (0.510 g) which was dissolved in THF:MeOH (1:1) (15:15 mL) and H<sub>2</sub>O (2 mL). Solid NaOH (146 mg, 3.645 mmol) was added and stirred at 50 °C for 1 hour. The reaction mixture was concentrated under reduced pressure. Saturated NaHCO<sub>3</sub> (10 mL) solution was added to the reaction mixture and extracted with toluene (to remove organic impurities). The aqueous reaction mixture was acidified with diluted HCl (10%), extracted with EtOAc, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated and dried under reduced pressure to give the crude acid 2 which can be used directly for next reaction.

## Example 1.4.5



[0404] The amine **4.5.27** was coupled to **4.5.28** using HOBT and EDCI according to the general procedure and the so obtained ester was saponified to yield acid **4.5.29**.

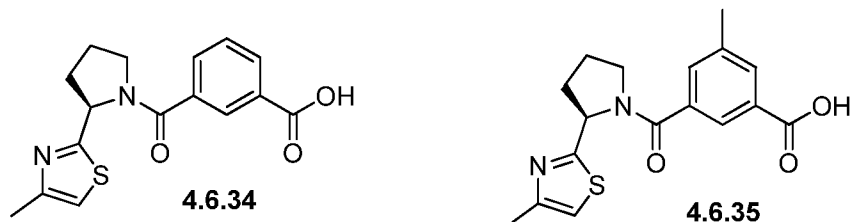
## Example 1.4.6



[0405] EDCI·HCl (0.372 g, 1.9 mmol, 1.3 eq) and HOBT·H<sub>2</sub>O (0.202 g, 1.5 mmol, 1.0 eq) were added to a stirred solution of the acid **4.6.30** (0.37g, 1.5 mmol, 1 eq) in 8 ml anhydrous CH<sub>2</sub>Cl<sub>2</sub> at 0 °C under Ar. The resulting solution was treated with a solution of DIPEA (0.78 mL, 4.5 mmol, 3.0 eq) and the amine **4.6.31** (0.252, 1.5 mmol, 1.0 eq) in 2 ml anhydrous CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred at 0 °C to room temperature overnight. The solvent was removed via rotary evaporation. The residue was quenched with water, and the resulting mixture was extracted with EtOAc (x1). The organic layer was washed with water (x2), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.8308 g (2.5 mmol, 65% yield) of the product **4.6.32**.

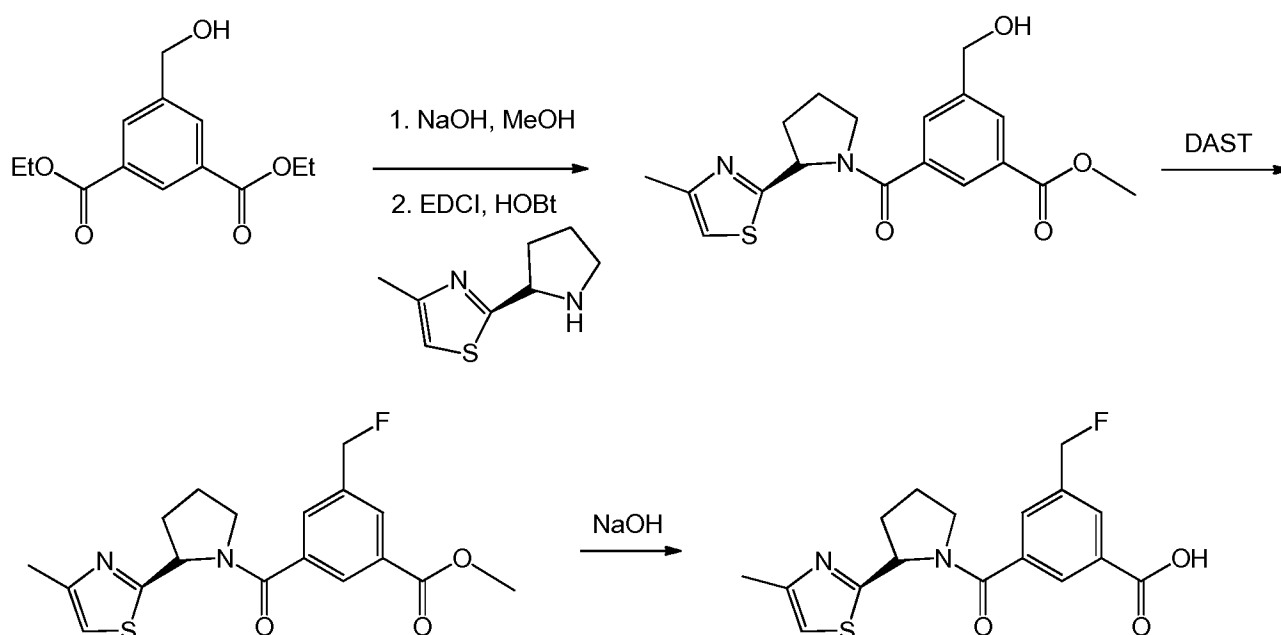
[0406] 1N LiOH (3.0 mL) was added to a stirred solution of the ester **4.6.32** (0.38 g, 2.5 mmol, 1 eq) in THF (3 ml) and. After stirring for 2 h, the medium was adjusted to pH ≈ 3 with 1N HCl and extracted with 10% MeOH/ 90% EtOAc/ (x2). The organics were

combined and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent removed via rotary evaporation yielding 0.28 g (76 % yield) of the product **4.6.33**.



[0407] Acids **4.6.34** and **4.6.35** were synthesized similar to that of **4.6.33** starting with the appropriate commercially available isophthalic acid diesters.

*Example 1.4.7*



[0408] 3-Methoxycarbonyl-5-hydroxymethylbenzoic acid: The diester (4.12 g, 16.33 mmol) was dissolved in THF:MeOH (1:1) (80 mL) and  $\text{H}_2\text{O}$  (15.52 mL). Solid NaOH (0.62 g, 15.52 mmol) was added and stirred at  $0^\circ\text{C}$  and slowly warmed to room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure. Saturated  $\text{NaHCO}_3$  (10 mL) solution was added to the reaction mixture and extracted with toluene (to remove <10% unreacted starting material). The aqueous solution was acidified with dil HCl (10%), extracted with EtOAc, dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated and dried under reduced pressure to give the mono acid as a white solid (3.32 g) which was used for further reaction without purification.

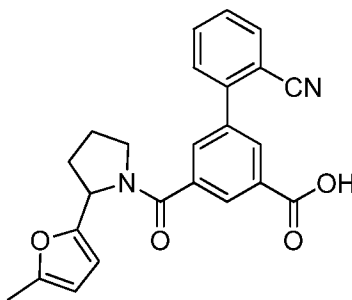
[0409] A solution of amine (1.62 g, 9.64 mmol) and acid (2.23 g, 10.6 mmol) in DCM (100 mL) were added diisopropylethylamine (6.7 mL, excess), HOBt (1.3 g, 9.64 mmol) and

EDCI (2.4 g, 12.53 mmol). The resulting solution was stirred at room temperature for overnight. The reaction mixture was diluted with chloroform, washed with sodium bicarbonate saturated aqueous solution and separated. The aqueous layer was extracted one more time with chloroform. The combined organic layers were concentrated to give a residue, which was purified with flash chromatography to produce the desired compound (2.2 g, 67%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 8.011 (m, 1.5 H), 7.876 (br, 0.5 H), 7.683 (m, 1 H), 6.749 (m, 1 H), 5.579 (m, 0.7 H), 5.061 (br, 0.3 H), 4.641 (br, 1.2 H), 4.525 (br, 0.8 H), 3.875 (m, 3 H), 3.692 (m, 1 H), 3.457 (m, 1 H), 2.345 (m, 5 H), 2.034 (m, 2 H).

**[0410]** Alcohol (2.1 g, 5.83 mmol) in dry DCM (60 mL) at  $-78^\circ\text{C}$  was added [Bis(2-methoxyethyl)amino]sulfur trifluoride (1.29 mL, 7.0 mmol) slowly and stirred at the same temperature for 2 hrs, then warmed to room temperature for overnight. The reaction was carefully quenched with aqueous saturated  $\text{NaHCO}_3$ , extracted with chloroform three times. The combined organic solvent was dried with anhydrous  $\text{Na}_2\text{SO}_4$ , removed in vacuum and the residue was purified by silica gel chromatography to afford monofluoride (1.6 g, 76%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.211-7.784 (m, 2.7 H), 7.420 (s, 0.3 H), 6.778 (s, 1 H), 5.645-5.076 (m, 3 H), 3.929-3.741 (m, 4 H), 3.519 (m, 1 H), 2.428-2.325 (m, 5 H), 2.088-1.930 (m, 2 H).

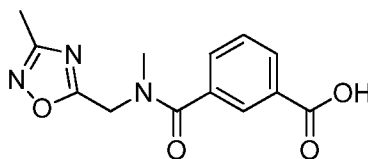
**[0411]** The ester (1.53 g, 4.22 mmol) was dissolved in THF:MeOH (1:1) (20:20 mL) and  $\text{H}_2\text{O}$  (6.5 mL). Solid NaOH (507 mg, 12.66 mmol) was added and stirred at  $50^\circ\text{C}$  for 1.5 hours. The reaction mixture was concentrated under reduced pressure. The aqueous reaction mixture was acidified with diluted HCl (10%), extracted with EtOAc, dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated and dried under reduced pressure to give the crude acid (1.5 g, quantitative yield) which can be used directly for next reaction without further purification and characterization.

*Example 1.4.8: 2'-cyano-5-(2-(5-methylfuran-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-3-carboxylic acid*



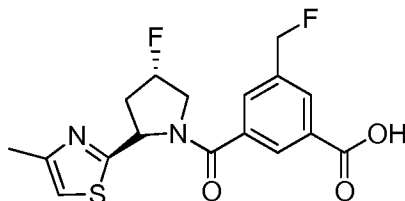
[0412] 2'-cyano-5-(2-(5-methylfuran-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-3-carboxylic acid was synthesized following a similar experimental procedure as for Example 1.4.6.

*Example 1.4.9: 3-(methyl((3-methyl-1,2,4-oxadiazol-5-yl)methyl)carbamoyl)benzoic acid*



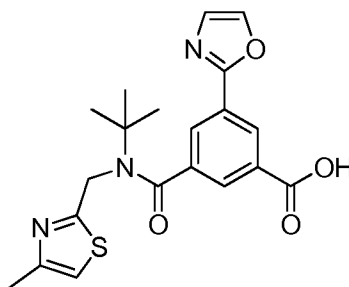
[0413] 3-(methyl((3-methyl-1,2,4-oxadiazol-5-yl)methyl)carbamoyl)benzoic acid was synthesized following a similar experimental procedure as for Example 1.4.6.

*Example 1.4.10*



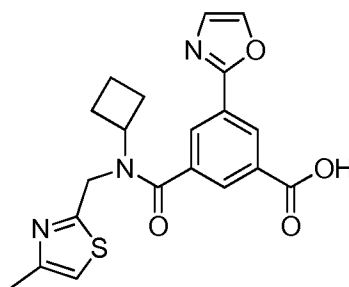
[0414] This compound was synthesized following a similar experimental procedure as for Example 1.4.7.

*Example 1.4.11*



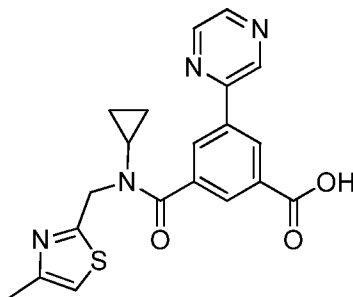
[0415] This compound was synthesized following a similar experimental procedure as for Example 1.4.6.

*Example 1.4.12*



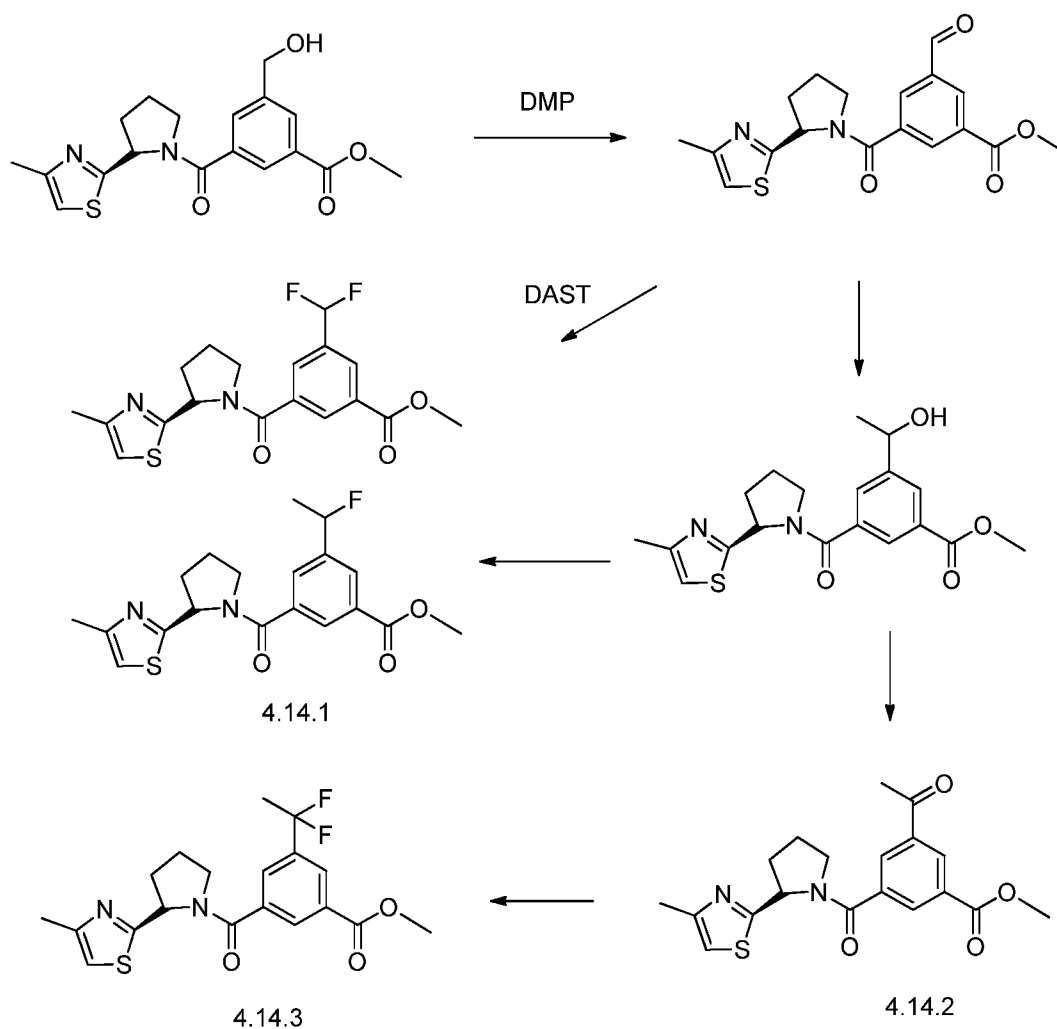
[0416] This compound was synthesized following a similar experimental procedure as for Example 1.4.6.

## Example 1.4.13



[0417] This compound was synthesized following a similar experimental procedure as for Example 1.4.6.

## Example 1.4.14



[0418] **DMP Oxidation:** To a solution of alcohol (560 mg, 1.554 mmol) in DCM (60 mL), Dess-Martin periodinane (790.8 mg, 1.864 mmol) was added at rt. After 2 hrs' stirring, the mixture was poured into a mixture of aqueous 1 M  $\text{Na}_2\text{S}_2\text{O}_3$  (30 mL) and aqueous saturated  $\text{NaHCO}_3$  (30 mL), and it was extracted with DCM three times. The combined organic layers



were concentrated in vacuum and the residue was purified by flash silica chromatography to give the product (530 mg).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  10.094, 9.933 (s,s, 1 H), 8.592-7.908 (m, 3 H), 6.796 (s, 1 H), 5.661 (m, 0.65 H), 5.083 (m, 0.35 H), 3.969-3.743 (m, 4 H), 3.515 (m, 1 H), 2.429-2.308 (m, 5 H), 2.145-1.939 (m, 2 H).

**[0419]** To a solution of aldehyde (530 mg, 1.47 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) at  $-78^\circ\text{C}$  was added [Bis(2-methoxyethyl)amino]sulfur trifluoride (0.46 mL, 2.49 mmol) slowly, then a couple drops of ethanol was added, and the mixture was stirred at same temperature for 2hr. The resulting mixture was warmed to room temperature and stirred overnight. The solution was slowly poured into saturated  $\text{NaHCO}_3$ , extracted with methylene chloride three times, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and evaporated in vacuo. Flash chromatography on silica gel afforded the pure product (442 mg).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.330-7.919 (m, 2.7 H), 7.528 (s, 0.3 H), 6.902-6.368 (m, 3 H), 5.638 (m, 0.7 H), 5.048 (m, 0.3 H), 3.946-3.746 (m, 4 H), 3.488 (m, 1 H), 2.412-2.312 (m, 5 H), 2.112-1.950 (m, 2 H).

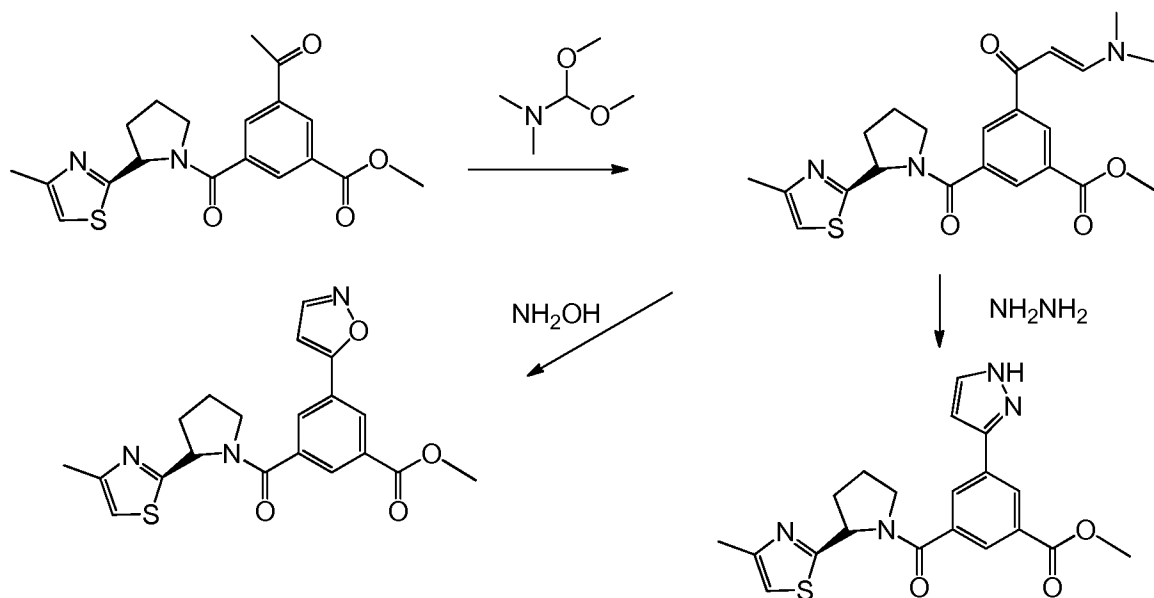
**[0420]** To a solution of aldehyde (740 mg, 2.065 mmol) in THF (40 mL) at  $-78^\circ\text{C}$  was added methyl magnesium bromide (3 M in ether, 0.69 mL), and the mixture was stirred at same temperature for 2hr. The resulting mixture was warmed to room temperature and stirred overnight. The solution was slowly poured into aqueous saturated  $\text{NH}_4\text{Cl}$ , extracted with EtOAc three times, washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and evaporated in vacuo. Flash chromatography on silica gel afforded the pure product (720 mg).

**[0421]** The second alcohol was fluorinated with Deoxo-Fluro give the product **(4.14.1)**.

**[0422]** The second alcohol was oxidized with DMP to give the product **(4.14.2)**.

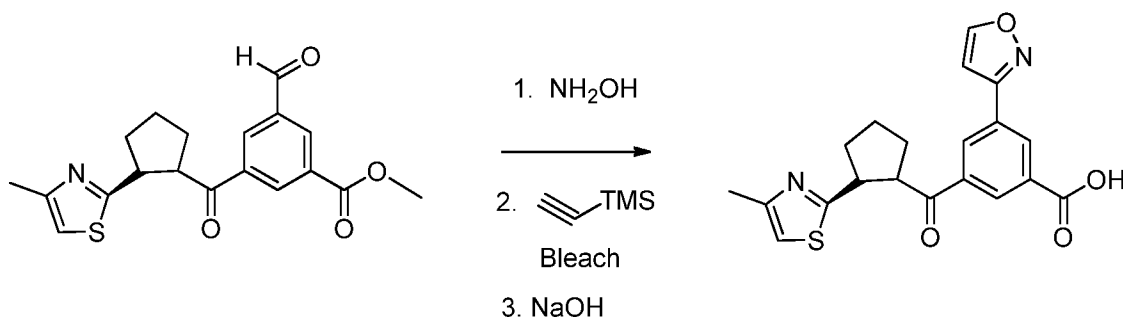
**[0423]** The ketone was fluorinated with Deoxo-Fluro give the product **(4.14.3)**.

## Example 1.4.15



**[0424]** The ketone (240 mg) was treated with N,N-dimethylformamide dimethyl acetal (5 mL, excess) at 100 °C for 17 hrs to give the crude product (170 mg), which was then treated with hydroxylamine hydrochloride (81.3 mg, 1.17 mmol) in ethanol (10 mL) at 90 °C overnight to give the crude product. Flash chromatography on silica gel afforded the pure product (50 mg). The intermediate was treated with hydrazine to give the pyrazole product.

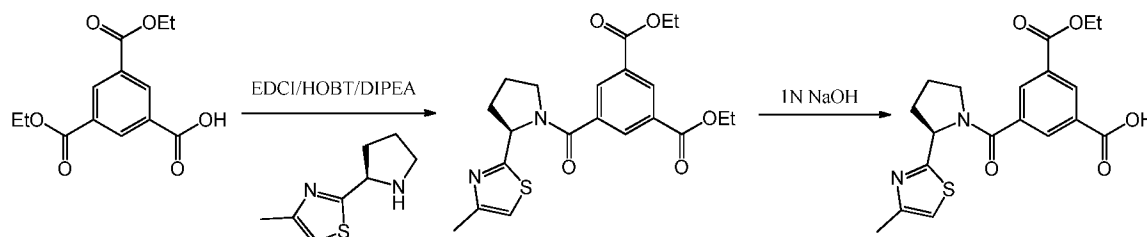
## Example 1.4.16



**[0425]** The aldehyde (610 mg, 1.702 mmol) in methanol (5 mL) was treated with hydroxylamine hydrochloride (130 mg, 1.872 mmol) and sodium acetate (237.3 mg, 2.8934 mmol) at room temperature overnight. The solvent was moved under vacuum, diluted with EtOAc, washed with saturated  $\text{NH}_4\text{Cl}$ , aqueous saturated  $\text{NaHCO}_3$ , brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and evaporated in vacuo to give the crude product, which was then treated with trimethylsilylacetylene (1 mL) and bleach (6.5 mL) in THF (6.5 mL) at room temperature overnight. The mixture was diluted with EtOAc, washed with aqueous saturated  $\text{NaHCO}_3$ , aqueous saturated  $\text{NH}_4\text{Cl}$ , brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and evaporated in vacuo. Flash chromatography on silica gel afforded the pure product (325 mg).

[0426] The general hydrolysis procedure gave the corresponding acid, meanwhile the silyl group was removed.

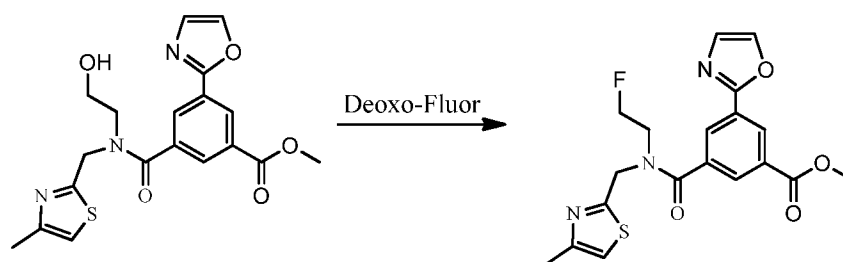
*Example 1.4.17*



[0427] EDCI·HCl (0.3946 g, 2.1 mmol, 1.1 eq) and HOBT·H<sub>2</sub>O (0.2789 g, 2.1 mmol, 1.1 eq) were added to a stirred solution of the acid (Aldrich, 0.500 g, 1.9 mmol, 1 eq) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 ml) at 0 °C under Ar. After 1 h the resulting solution was treated sequentially with the amine (0.3048 g, 1.9 mmol, 1 eq) and DIPEA (0.98 ml, 0.73 g, 5.6 mmol, 3 eq). The reaction was stirred at 0 °C to RT overnight. The reaction was quenched with water, and the volatiles were removed via rotary evaporation. The residue was partitioned between EtOAc/H<sub>2</sub>O, and the layers were separated. The organic layer was washed with water (x2), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation. Purification via flash chromatography on silica gel yielded the diester in quantitative yield.

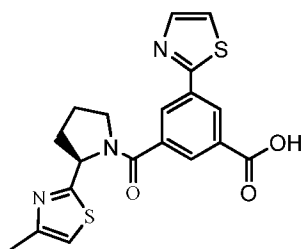
[0428] A solution of the diester (0.8097 g, 1.9 mmol, 1 eq) in 2:1 THF/MeOH (5 ml) was cooled to 0 °C with stirring. 1N NaOH (1.8 ml, 1.8 mmol 0.95 eq) was added dropwise. The reaction was stirred at 0 °C to room temperature overnight. The reaction was diluted with saturated aqueous NaHCO<sub>3</sub>, and the volatiles were removed via rotary evaporation. The resulting mixture was diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (x2). The aqueous layer was adjusted to pH ≈ 2 with HCl and extracted with EtOAc (x2). The combined EtOAc fractions were dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation to yield 0.6842 g (1.77 mmol, 95%) of the monoacid.

*Example 1.4.18*



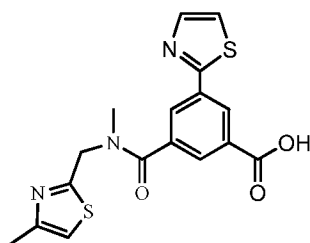
[0429] A solution of alcohol (0.0955g, 0.24 mmol, 1 eq) in anhydrous DCM (4 ml) under Ar was cooled to -78 °C under Ar. The cooled solution was treated with Deoxo-Fluor (53  $\mu$ l, 0.06 g, 0.29 mmol, 1.2 eq). The reaction was stirred at -78 °C to room temperature overnight. The reaction was diluted with saturated aqueous NaHCO<sub>3</sub>, and the layers were separated. The organic layer was washed with water (x1), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation. Purification via flash chromatography yielded 0.0204 g (0.051 mmol, 21%) of the fluoro compound. Saponification was carried out in a manner similar to that for Example 1.4.4.

*Example 1.4.19*



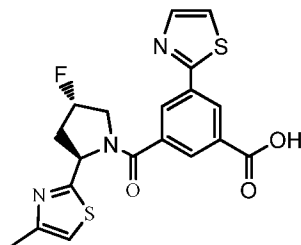
[0430] The synthesis was carried out in a manner similar to that for Example 1.4.6.

*Example 1.4.20*

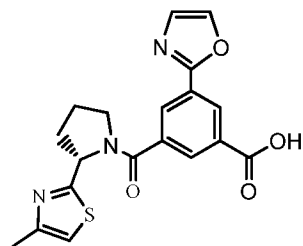


[0431] The synthesis was carried out in a manner similar to that for Example 1.4.6.

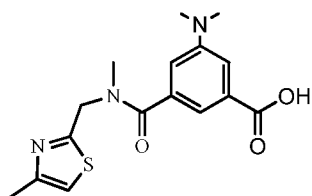
*Example 1.4.21*



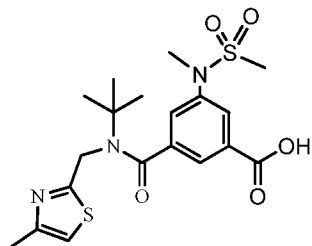
[0432] The synthesis was carried out in a manner similar to that for Example 1.4.6.

*Example 1.4.22*

The synthesis was carried out in a manner similar to that for Example 1.4.6.

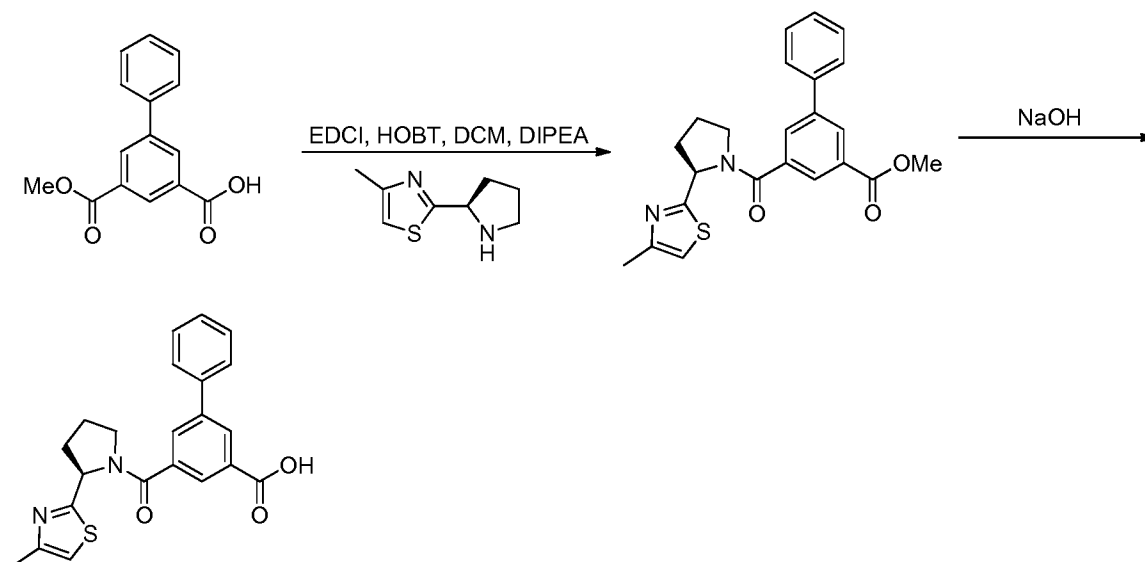
*Example 1.4.23*

[0433] The synthesis was carried out in a manner similar to that for Example 1.4.6.

*Example 1.4.24*

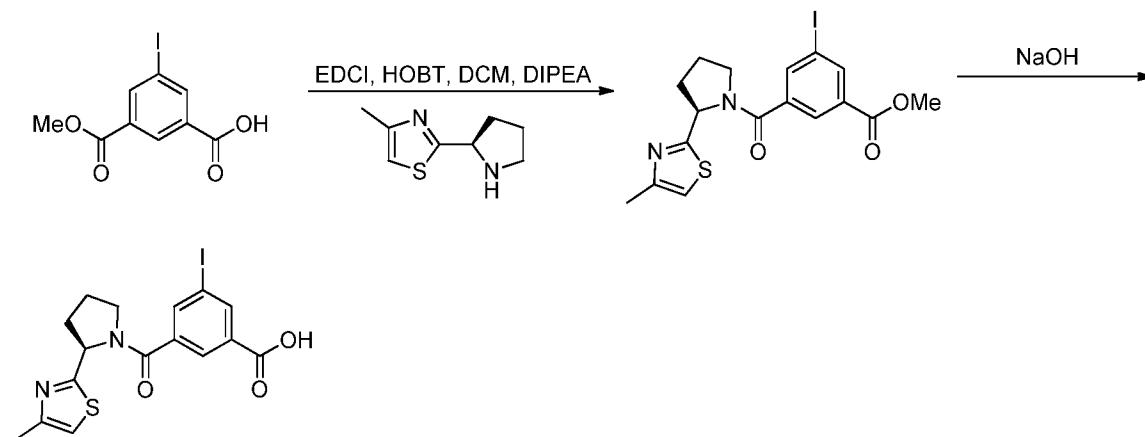
[0434] The ester was synthesized in a manner similar to that of 1.4.2 using the appropriate starting materials. Saponification was carried out in a manner similar to that for Example 1.4.4.

*Example 1.4.25: Synthesis of (R)-5-(2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-3-carboxylic acid*



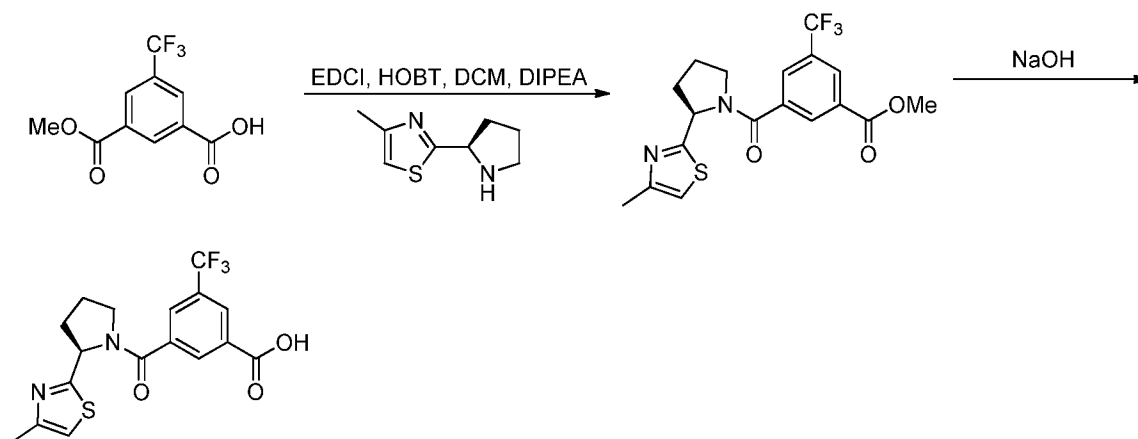
**[0435]** Ester formation followed by saponification of the resulting ester was carried out in a manner similar to that depicted in Example 1.4.6.

*Example 1.4.26: Synthesis of (R)-3-iodo-5-(2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzoic acid*



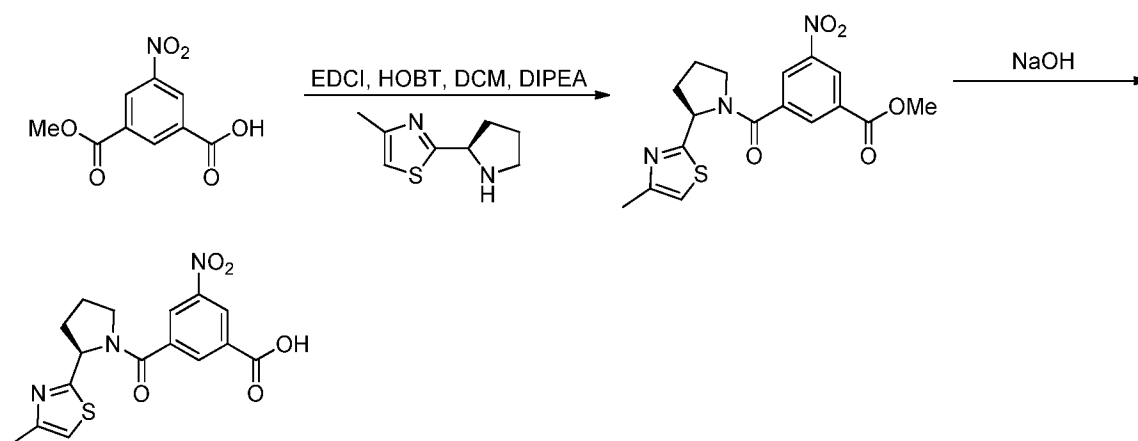
**[0436]** Ester formation followed by saponification of the resulting ester was carried out in a manner similar to that depicted in Example 1.4.6.

*Example 1.4.27: Synthesis of (R)-3-(2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-5-(trifluoromethyl)benzoic acid*



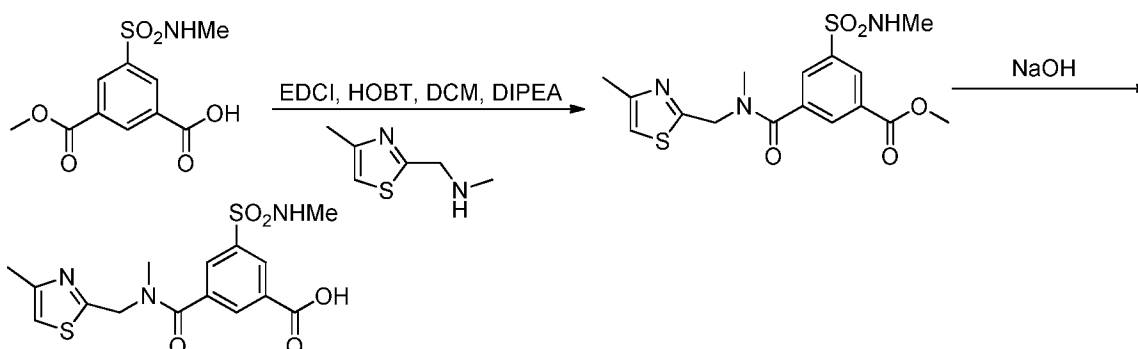
**[0437]** Ester formation followed by saponification of the resulting ester was carried out in a manner similar to that depicted in Example 1.4.6.

*Example 1.4.28: Synthesis of (R)-3-(2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-5-nitrobenzoic acid*



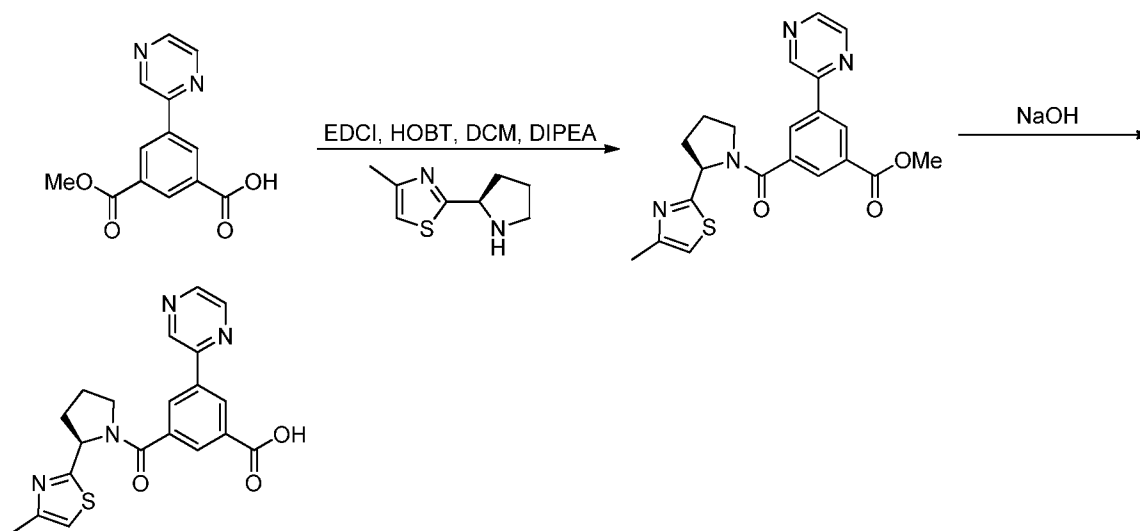
**[0438]** Ester formation followed by saponification of the resulting ester was carried out in a manner similar to that depicted in Example 1.4.6.

*Example 1.4.29: Synthesis of 3-(methyl((4-methylthiazol-2-yl)methyl)carbamoyl)-5-(N-methylsulfamoyl)benzoic acid*



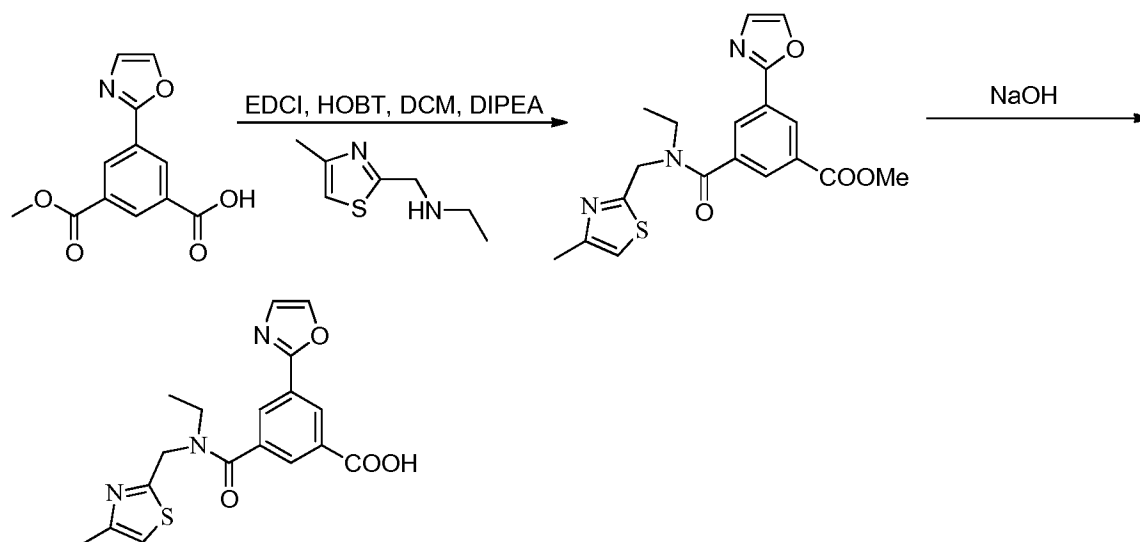
[0439] Ester formation followed by saponification of the resulting ester was carried out in a manner similar to that depicted in Example 1.4.6.

*Example 1.4.30: Synthesis of (R)-3-(2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-5-(pyrazin-2-yl)benzoic acid*



[0440] Ester formation followed by saponification of the resulting ester was carried out in a manner similar to that depicted in Example 1.4.6.

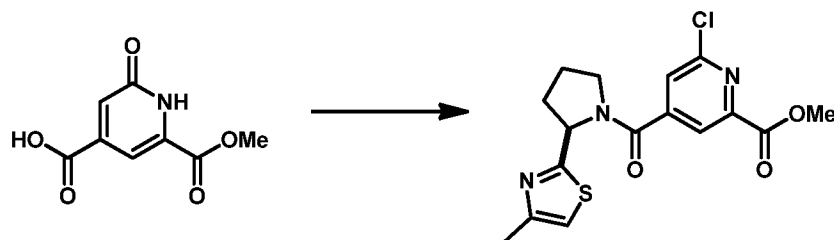
*Example 1.4.31: Synthesis of 3-(ethyl((4-methylthiazol-2-yl)methyl)carbamoyl)-5-(oxazol-2-yl)benzoic acid*



[0441] Ester formation followed by saponification of the resulting ester was carried out in a manner similar to that depicted in Example 1.4.6.

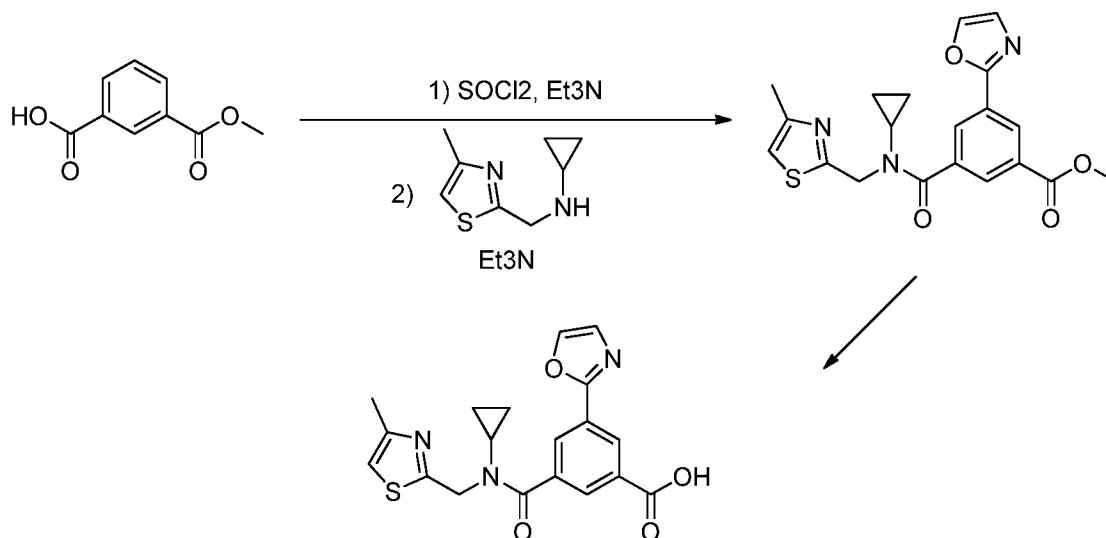


## Example 1.4.32



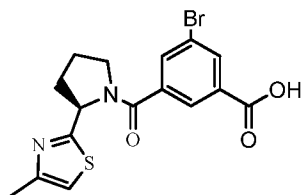
**[0442] Methyl 6-chloro-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonylpyridine-2-carboxylate:** 4-*tert*-Butyl 2-methyl 6-oxo-1,6-dihydropyridine-2,4-dicarboxylate (6.4 g, 25.3 mmol) was dissolved in  $\text{SOCl}_2$  (55 ml) and a catalytic amount of DMF (5 drops) was added. This mixture was stirred for 36 hours at 80 degree. Additional DMF (30 drops) was added and the mixture was stirred for 24 hours at 80 degree.  $\text{SOCl}_2$  was evaporated to give a residue, which was azeotroped with toluene. The obtained residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (64 ml) and  $\text{Et}_3\text{N}$  (7.05 ml, 50.5 mmol) and 4-methyl-2-[(2R)-pyrrolidin-2-yl]-1,3-thiazole (5.02 g, 29.8 mmol) was added at rt. The mixture was stirred at the same temperature for 2 hours. The reaction was quenched with 1 M HCl aq. and the organic layer was separated. The aqueous layer was extracted with  $\text{CHCl}_3$  (x3) and the combined organic layer was washed with satd.  $\text{NaHCO}_3$  aq. and brine, dried over  $\text{MgSO}_4$  and evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 30 to 100%) to give methyl 6-chloro-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonylpyridine-2-carboxylate (8.67 g, 94% yield) as a pale yellow oil. MS (ESI)  $m/z$ : 366 $[\text{M}+\text{H}]^+$ .

## Example 1.4.33



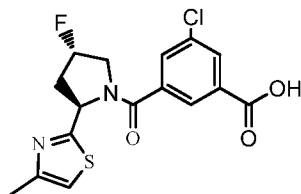
**[0443] 3-(cyclopropyl((4-methylthiazol-2-yl)methyl)carbamoyl)-5-(oxazol-2-yl)benzoic acid:** The desired compound was synthesized following a similar experimental procedure as for *Example 1.4.2*.

*Example 1.4.34*



**[0444]** The ester was synthesized in a manner similar to *Example 1.4.6* using the appropriate starting materials. Saponification was carried out in a manner similar to that for *Example 1.4.4*.

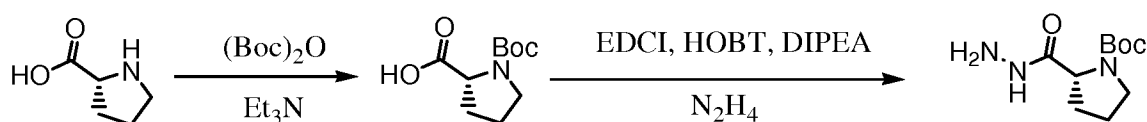
*Example 1.4.35*



**[0445]** The ester was synthesized in a manner similar *Example 1.4.6* using the appropriate starting materials. Saponification was carried out in a manner similar to that for *Example 1.4.4*.

### Example 1.5: Synthesis of acyl hydrazide intermediates.

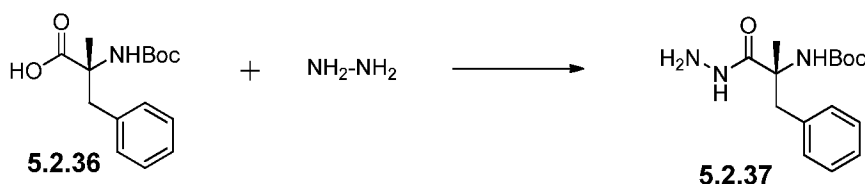
*Example 1.5.1*



**[0446]** A stirred suspension of the acid (Aldrich, 0.5 g, 4.3 mmol, 1 eq) in anhydrous  $\text{CH}_2\text{Cl}_2$  (15 ml) under Ar was cooled to 0 °C. The reaction was treated with  $\text{Et}_3\text{N}$  (0.9 ml, 0.66 g, 6.5 mmol, 1.5 eq). After 5 min  $(\text{Boc})_2\text{O}$  (1.3 ml, 1.2 g, 5.6 mmol, 1.3 eq) was added dropwise. After 3 h the reaction was quenched by the addition of aqueous citric acid (5%, 15 ml). The layers were separated, and the organic layer was dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the volatiles were removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.7386 g (3.4 mmol, 80%) of the protected acid.

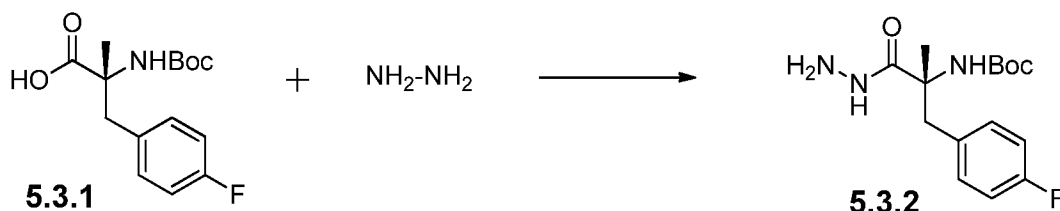
[0447] A solution of the acid (0.7386 g, 3.4 mmol, 1 eq) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 ml) under Ar was cooled to 0 °C with stirring. The solution was treated HOBT·H<sub>2</sub>O (0.5559 g, 4.1 mmol, 1.2 eq) followed by EDCI·HCl (0.7209 g, 3.8 mmol, 1.1 eq) 30 min later. After 1h anhydrous  $\text{N}_2\text{H}_4$  (0.43 ml, 0.44 g, 13.2 mmol, 4 eq) was added followed by DIPEA (2.3 ml, 1.7 g, 13.2 mmol, 4 eq) 10 min later. The reaction was stirred at 0 °C to room temperature overnight. The reaction was quenched with water and diluted with saturated aqueous  $\text{NaHCO}_3$ . The layers were separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (x3). The combined organics were dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the volatiles were removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.5616 g (2.4 mmol, 72%) of the hydrazide.

*Example 1.5.2*



[0448] To a solution of **5.2.36** (3.0g, 10.75 mmoles) in  $\text{CH}_3\text{CN}$  was added EDC (3.5g, 18.28 mmoles). After 5 min, anhydrous hydrazine was added and stirred overnight at room temperature. All the solvent was evaporated; the residue was quenched with satd.aq.  $\text{NaHCO}_3$  and was extracted with EtOAc. The organic extract was washed with brine, dried, concentrated and purified on silica gel (3% MeOH/97%  $\text{CHCl}_3$ ) to obtain 1.42g (45%) of **5.2.37**.

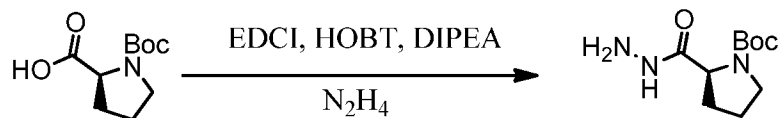
*Example 1.5.3: (R)-tert-butyl(3-(4-fluorophenyl)-1-hydrazinyl-2-methyl-1-oxopropan-2-yl)carbamate*



[0449] To a solution of **5.3.1** (2.97 g, 10 mmoles) in  $\text{CH}_3\text{CN}$  was added EDC (3.25 g, 17 mmoles). After 5 min, anhydrous hydrazine (0.79 mL, 25 mmoles) was added and stirred overnight at room temperature. All the solvent was evaporated; the residue was quenched with satd.aq.  $\text{NaHCO}_3$  and was extracted with EtOAc. The organic extract was washed with

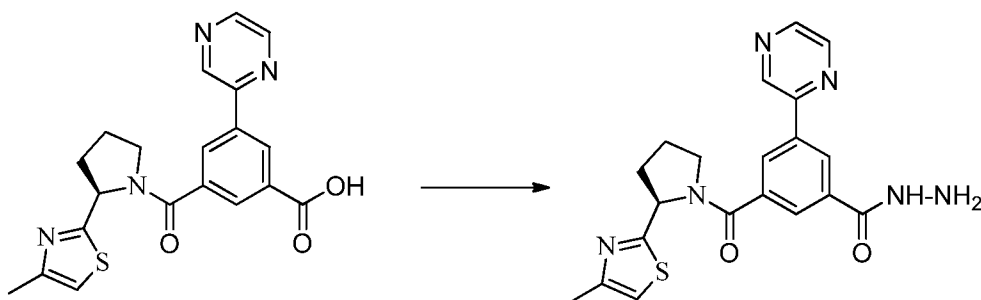
brine, dried, concentrated and purified on silica gel (3% MeOH/97% CHCl<sub>3</sub>) to obtain 2.15 g of (*R*)-tert-butyl(3-(4-fluorophenyl)-1-hydrazinyl-2-methyl-1-oxopropan-2-yl)carbamate.

*Example 1.5.4.*



**[0450]** The hydrazide was synthesized in a manner similar to that of Example 1.5.1 using the appropriate starting materials (Peptech).

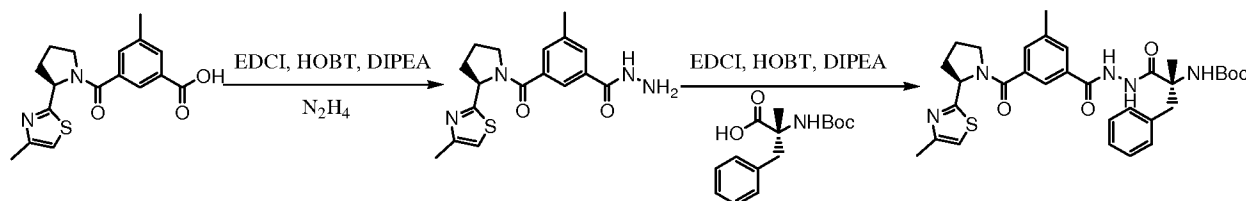
*Example 1.5.5: Synthesis of (R)-3-(2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-5-(pyrazin-2-yl)benzohydrazide*



**[0451]** To the acid, (*R*)-3-(2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-5-(pyrazin-2-yl)benzoic acid (300mg, 0.76 mmol) in DCM (5 ml), HOBT (103 mg, 0.76mmol), EDCI (146 mg, 0.76 mmol) was added and stirred at rt for 2h. Then the resulting solution was added to the hydrazine hydrate (114 mg, 2.28 mmol) in DCM at -30°C. Reaction mixture was stirred at rt for 48h and then worked up and column purified to yield (*R*)-3-(2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-5-(pyrazin-2-yl)benzohydrazide in 93% yield.

### Example 1.6: Synthesis of advanced intermediates.

*Example 1.6.1*

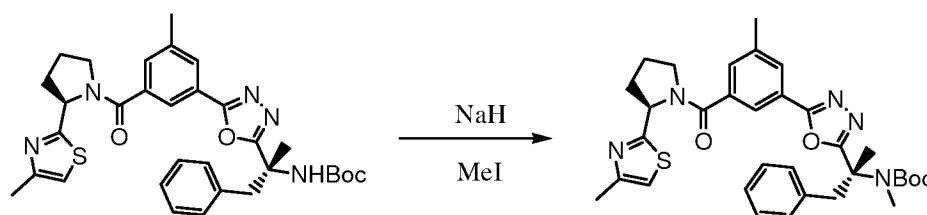


**[0452]** A solution of the acid (0.1106 g, 0.33 mmol, 1 eq) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 ml) under Ar was cooled to 0 °C with stirring. The solution was treated HOBT·H<sub>2</sub>O (0.0497 g, 0.37 mmol, 1.1 eq) followed by EDCI·HCl (0.0703 g, 0.37 mmol, 1.1 eq) 30 min later. After 1h anhydrous N<sub>2</sub>H<sub>4</sub> (0.042 ml, 0.043 g, 1.34 mmol, 4 eq) was added followed by DIPEA (0.12 ml, 0.087 g, 0.67 mmol, 2 eq) 10 min later. The reaction was stirred at 0 °C to room

temperature overnight. After stirring overnight the reaction was quenched with water and the volatiles were removed via rotary evaporation. The residue was partitioned between EtOAc/ water and the layers were separated. The organic layer was washed with water (x2), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.1223 g (0.36 mmol, 108%) of the slight crude hydrazide.

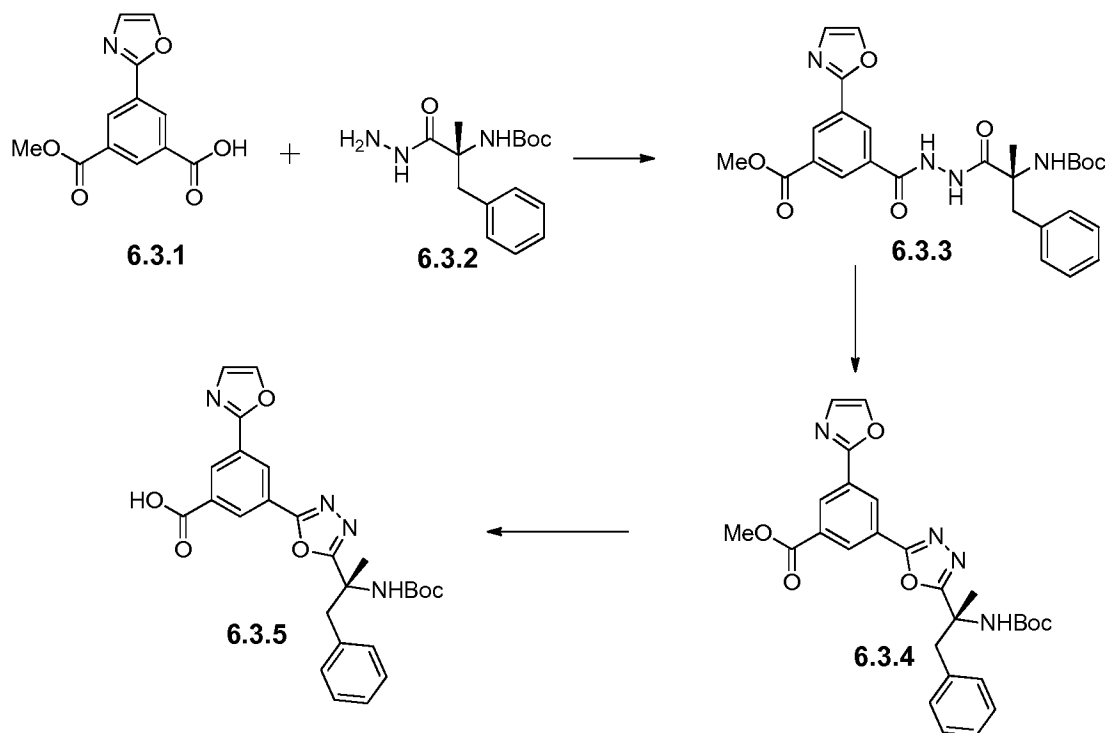
**[0453]** A solution of the acid (0.0935 g, 0.335 mmol, 1 eq) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3 ml) under Ar was cooled to 0 °C with stirring. The solution was treated HOBT·H<sub>2</sub>O (0.0542 g, 0.40 mmol, 1.2 eq) followed by EDCI·HCl (0.0703 g, 0.37 mmol, 1.1 eq) 30 min later. After 1h the reaction was treated with a solution of the crude hydrazide (0.1223 g, 0.36 mmol, ~ 1 eq) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2 ml). After 5 min DIPEA (0.22 ml, 0.17 g, 1.28 mmol, 4 eq) was added, and the reaction was stirred at 0 °C to room temperature overnight. The reaction was quenched with water and the volatiles were removed via rotary evaporation. The residue was partitioned between EtOAc/ water and the layers were separated. The organic layer was washed with water (x2), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.1507 g (0.25 mmol, 75%) of the product.

*Example 1.6.2*



**[0454]** A solution of the starting material (0.0641 g, 0.11 mmol, 1 eq) in anhydrous DMF (2 ml) under Ar was cooled to 0 °C with stirring. MeI (0.017 ml, 0.039 g, 0.27 mmol, 2.5 eq) was added, and the reaction was protected from light. NaH (60% dispersion in oil, 0.0065 g, 0.16 mmol, 1.5 eq) was added, and the reaction was stirred at 0 °C to room temperature overnight. The reaction was quenched with water and extracted with EtOAc (x1). The organic layer was washed with water (x3), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.0608 g (0.10 mmol, 92%) of the product.

*Example 1.6.3: (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)benzoic acid*

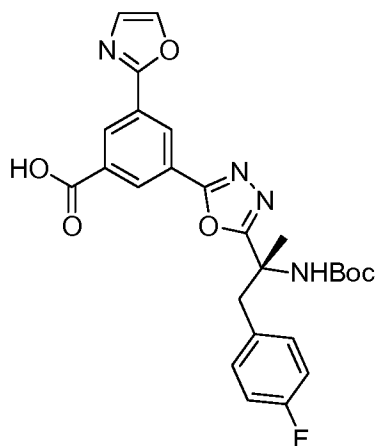


[0455] **6.3.1** and **6.3.2** were coupled using a standard coupling procedure involving HOBT, EDCI, and DIPEA in  $\text{CH}_2\text{Cl}_2$  and stirring overnight, resulting in **6.3.3** in 81% yield.

[0456] To a solution of **6.3.3** (3.51g, 6.72 mmoles) in dichloroethane (25 mL) was added Burgess' reagent (3.6g, 15.43 mmoles) and refluxed for 5h. The reaction mix was then cooled to room temperature, diluted with  $\text{CH}_2\text{Cl}_2$  and washed successively with satd.aq.  $\text{NaHCO}_3$  and brine, dried, concentrated and purified on silica gel (1% MeOH/99%  $\text{CHCl}_3$ ) to obtain 3.1g of **6.3.4**.

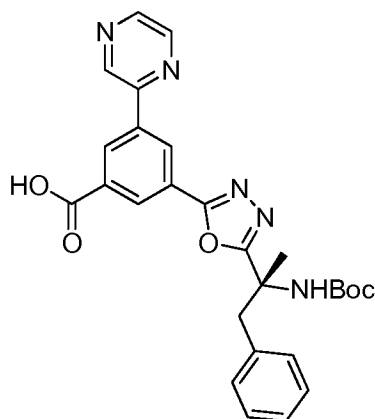
[0457] **6.3.4** was hydrolyzed using standard hydrolysis conditions using 1N LiOH in THF for 1h followed by acidic work-up to obtain (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)benzoic acid in quantitative yield.

*Example 1.6.4: (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)benzoic acid*



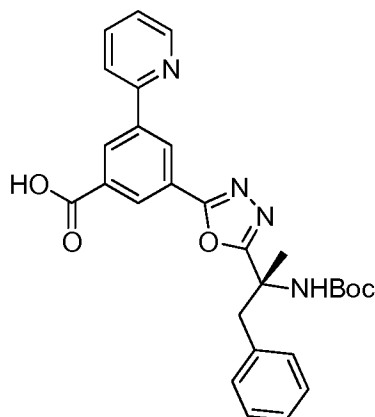
**[0458]** (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)benzoic acid was synthesized using the same procedure as in Example 1.6.3.

*Example 1.6.5: (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)benzoic acid*



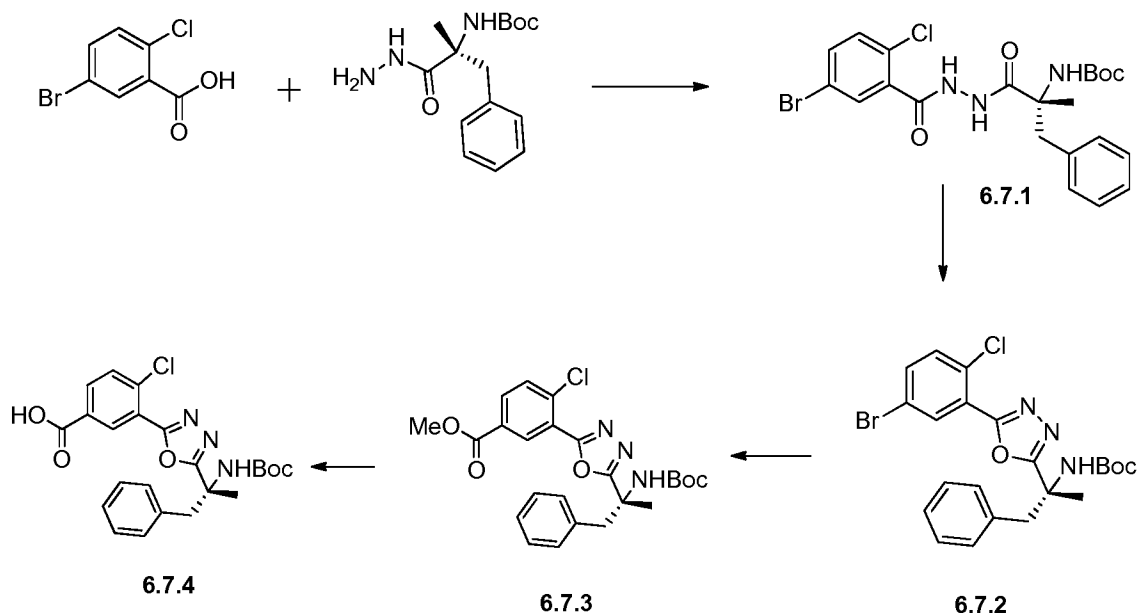
**[0459]** (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)benzoic acid was synthesized using the same procedure as in Example 1.6.3.

*Example 1.6.6: (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyridin-2-yl)benzoic acid*



**[0460]** (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyridin-2-yl)benzoic acid was synthesized using the same procedure as in Example 1.6.3.

*Example 1.6.7: (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorobenzoic acid*



**[0461]** To a solution of 5-bromo-2-chlorobenzoic acid (2 g, 8.49 mmol) and (R)-tert-butyl (1-hydrazinyl-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate (2.74 g, 9.34 mmol) in  $\text{CH}_2\text{Cl}_2$  (Volume: 50ml) was added HOBT (1.301 g, 8.49 mmol), EDC (1.954 g, 10.19 mmol) and DIPEA (4.45 ml, 25.5 mmol) and stirred overnight. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (Volume: 50ml) and washed with 0.1M HCl, sat  $\text{NaHCO}_3$  and sat NaCl. The organic layer was dried on  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified



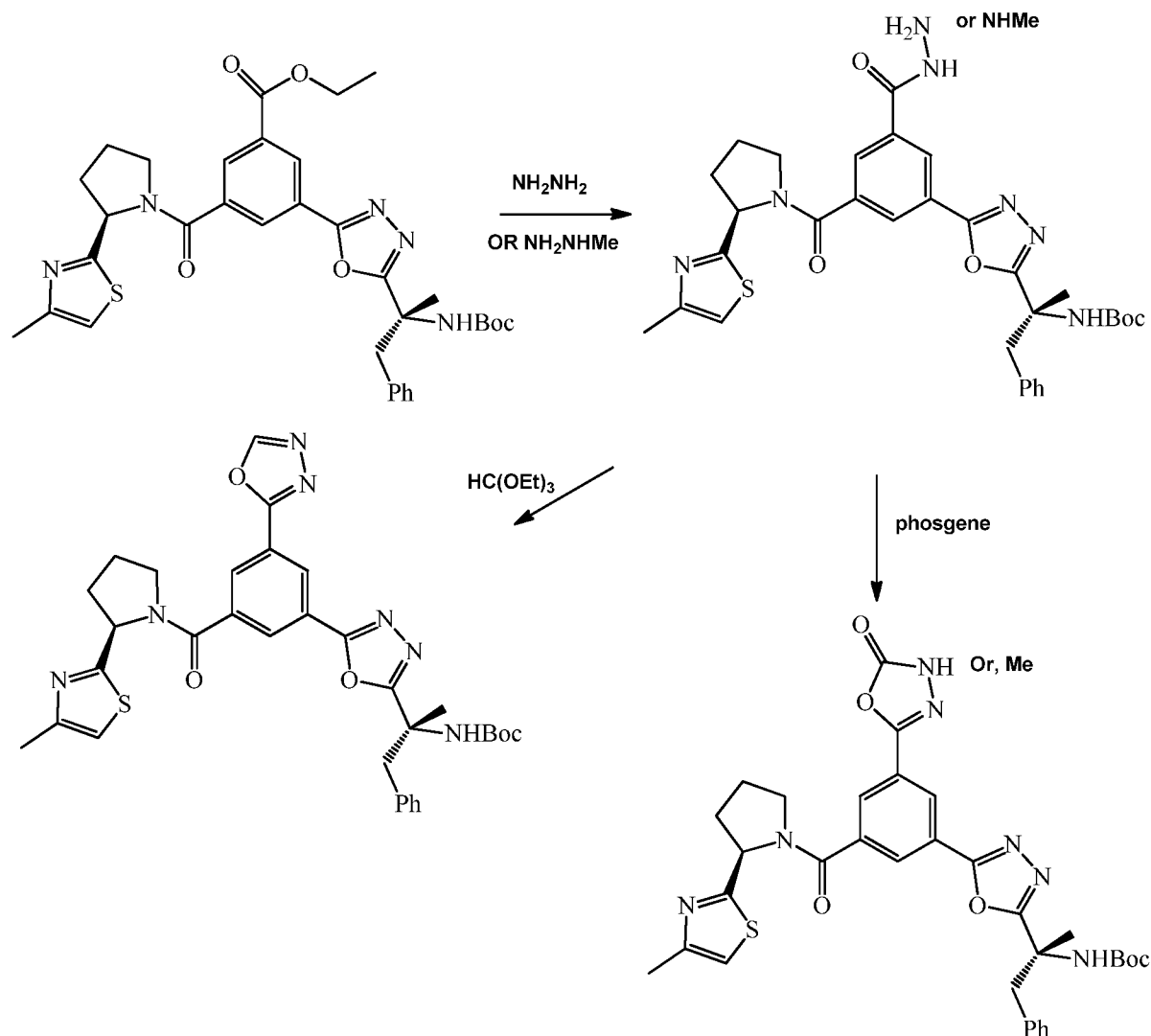
on combi-flash 0- 30% EtOAc/70% hexane to obtain 2.5 g of (R)-tert-butyl (1-(2-(5-bromo-2-chlorobenzoyl)hydrazinyl)-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate (**6.7.1**).

**[0462]** To a solution of (R)-tert-butyl (1-(2-(5-bromo-2-chlorobenzoyl)hydrazinyl)-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate (2.95 g, 5.78 mmol) in DCE (Volume: 75 ml) was added Burgess' reagent (3.44 g, 14.44 mmol), and refluxed for 4h. The reaction was cooled to room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with sat NaHCO<sub>3</sub> and sat. NaCl. The organic layer was dried on Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified on combi-flash 0- 30% EtOAc/70% hexane to obtain 2.13 g of (R)-tert-butyl (2-(5-(5-bromo-2-chlorophenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate (**6.7.2**).

**[0463]** A solution of (R)-tert-butyl (2-(5-(5-bromo-2-chlorophenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate (492.793 mg, 1.000 mmol) in Et<sub>3</sub>N (Volume: 8mL) and MeOH (1.214 mL, 30.0 mmol) (both solvents degassed) in a vial, was purged with carbon monoxide for 2 min and palladium(II) acetate (22.45 mg, 0.100 mmol) (Aldrich Lot # 83697MJV), and XANTPHOS (116 mg, 0.200 mmol) (Aldrich Lot # MKBF8281V) were added and refluxed for 2h15min. TLC shows ~95% conversion. The reaction was filtered through a cotton plug and concentrated. The residue was purified on combi-flash 0- 40% EtOAc/60% hexane to obtain 370 mg of (R)-methyl 3-(5-(2-(((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorobenzoate (**6.7.3**).

**[0464]** To a solution of (R)-methyl 3-(5-(2-(((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorobenzoate (370 mg, 0.784 mmol) in THF (Volume: 5 ml) was added LiOH (1 ml, 0.784 mmol) and stirred for 1h. TLC shows ~ 60% conversion. Continued stirring for 2h more. 1N HCl was added drop-wise to bring it to pH ~4. The mixture was diluted with EtOAc and washed with brine, dried and concentrated to obtain 347 mg of (R)-3-(5-(2-(((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorobenzoic acid (R)-3-(5-(2-(((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorobenzoic acid.

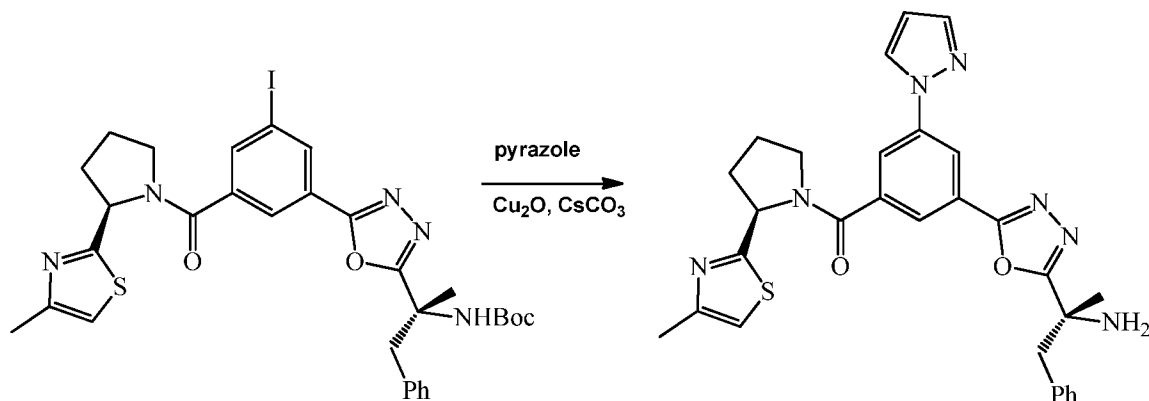
## Example 1.6.8



**[0465]** The ester (216 mg) was treated with hydrazine (0.3 mL, excess) in ethanol under microwave conditions (140 °C, 28 min) to give the product (170 mg), which was treated with triethyl orthoformate (2 mL) in toluene under microwave conditions (170 °C, 15 min) to give the crude product (90 mg).

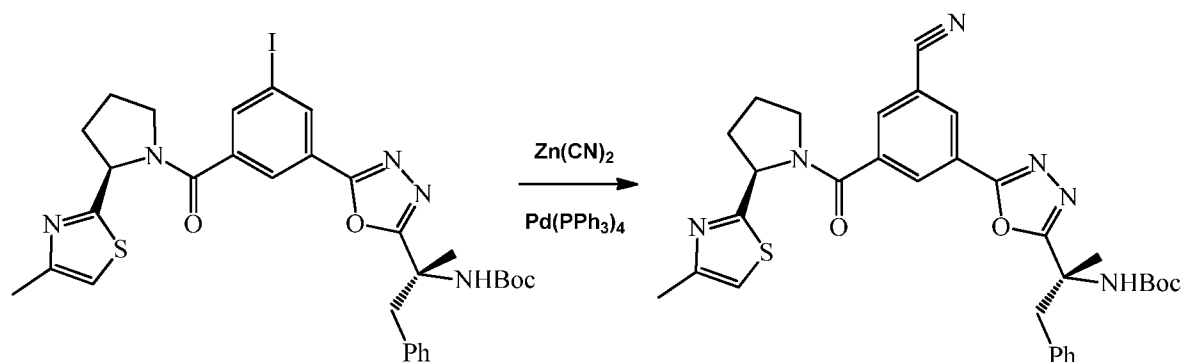
**[0466]** The hydrazide product (170 mg) in DCM (10 mL) was cooled with an ice bath, treated with phosgene (20% in toluene, 2 mL, excess) for 20 min, then warmed to room temperature and stirred one more hour. The solvent was moved under vacuum to give the crude product, which was diluted with EtOAc, washed with aqueous saturated  $\text{NH}_4\text{Cl}$ , aqueous saturated  $\text{NaHCO}_3$ , brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and evaporated in vacuo. Flash chromatography on silica gel afforded the pure product (100 mg).

## Example 1.6.9



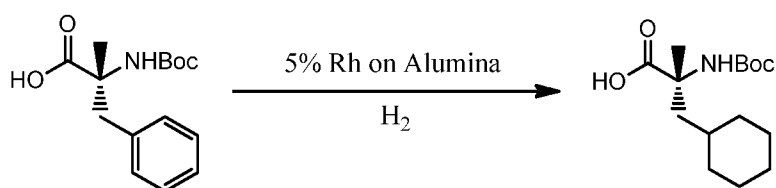
**[0467]** The iodide (150 mg, 0.2147 mmol) and pyrazole (13.2 mg, 0.1923 mmol) were treated with  $\text{Cu}_2\text{O}$  (8.25 mg, 0.0577 mmol) and  $\text{CsCO}_3$  (125.3 mg, 0.385 mmol) in DMF (4 mL) under microwave condition (140 °C, 70 min) to give the product (30 mg).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.298 (m, 1 H), 8.119 (s, 1.2 H), 8.063 (m, 0.8 H), 7.782 (m, 2 H), 8.218 (m, 3 H), 7.042 (m, 2 H), 6.805 (s, 0.8 H), 6.757 (s, 0.2 H), 6.541 (s, 0.8 H), 6.480 (s, 0.2 H), 5.675 (m, 0.8 H), 5.213 (m, 0.2 H), 3.929 (m, 1 H), 3.845 (m, 1 H), 3.634 (m, 1 H), 3.266 (m, 1 H), 3.124 (m, 1 H), 2.446 (m, 3 H), 2.130 (m, 2 H), 1.974 (m, 2 H), 1.668 (s, 3 H).

## Example 1.6.10



**[0468]** The iodide was treated with  $\text{Zn}(\text{CN})_2$  in DMF in the presence of palladium (0) to give the product.

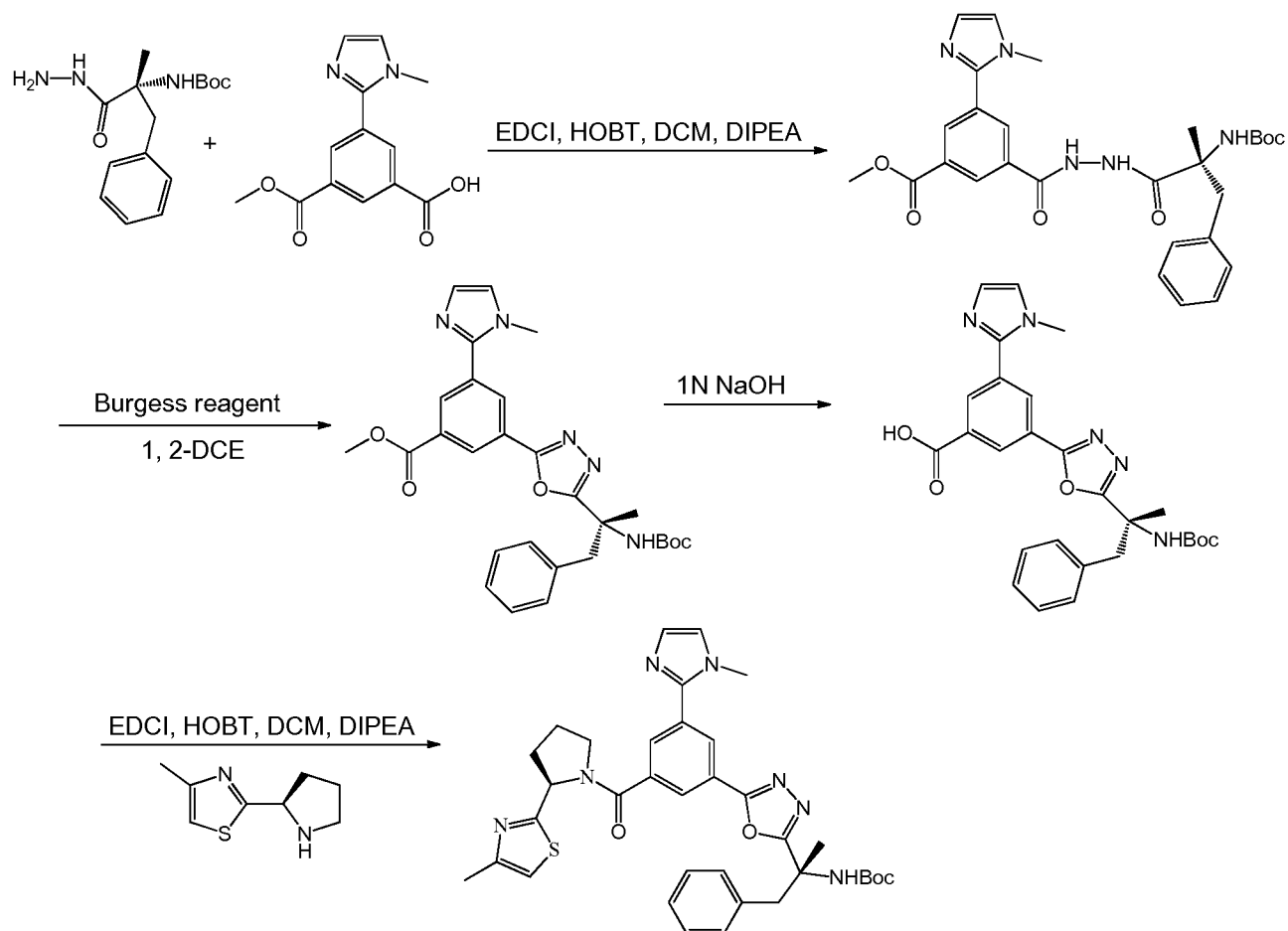
## Example 1.6.11



**[0469]** A solution of the starting material (0.4g, 1.4 mmol, 1 eq) in MeOH was purged with Ar to degas. Rh (5% on alumina, 0.4 g, 100% by wt) was added. The mixture was

hydrogenated via a Parr shaker at 55 psi and 50 °C for 60h. After cooling to room temperature the mixture was filtered through Celite. The volatiles were removed via rotary evaporation to yield 0.3502 g (88%) of the product.

*Example 1.6.12: Synthesis of tert-butyl ((R)-2-(5-(3-(1-methyl-1H-imidazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate*



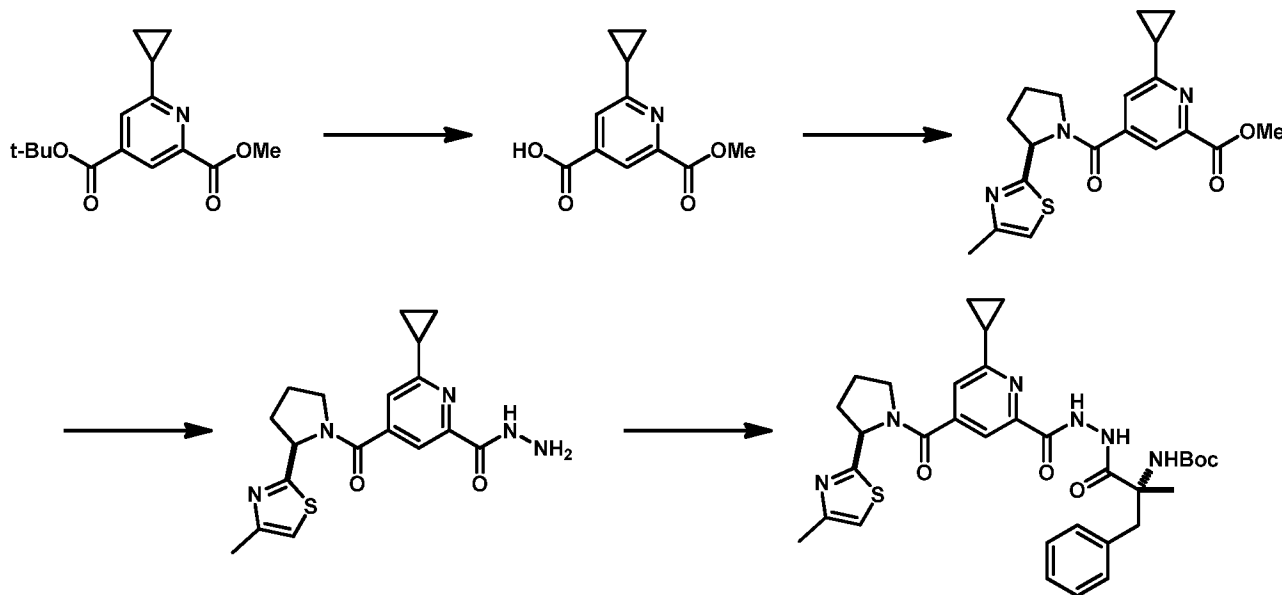
**[0470]** To the acid (400mg, 1.61 mmol) in DCM (10 ml), HOBT (261 mg, 1.93mmol), EDCI (433 mg, 2.26 mmol) was added and stirred at rt for 2h. Then to the resulting solution, hydrazide (612 mg, 2.09 mmol) was added. Reaction mixture was stirred at rt for 16h and then worked up and column purified to yield the hydrazide in 93% yield.

**[0471]** To the hydrazide (630 mg, 1.2 mmol) in 1,2 –DCE, burgess reagent (861 mg, 3.6 mmol)(commercial source: Alfa-Aesar) was added and the reaction mixture was heated at 60oC for 5h. Then reaction mixture was cooled, diluted with DCM, washed with saturated aqueous sodium bicarbonate solution, water, brine and dried. Crude residue was column chromatographed to yield the product in 75% yield.

[0472] The resulting ester was converted to acid using aqueous sodium hydroxide in a manner similar to depicted in Example 1.4.6.

[0473] To the acid (174mg, 0.35 mmol) in DCM (5 ml), HOBT (51 mg, 0.42mmol), EDCI (94 mg, 0.49 mmol) was added and stirred at rt for 2h. Then the amine, (R)-4-methyl-2-(pyrrolidin-2-yl)thiazole (59 mg, 0.35 mmol) and DIPEA (0.1 ml) was added to the reaction mixture and allowed to stir overnight and then worked up and column purified to yield the Boc compound in 30% yield.

*Example 1.6.13*



[0474] **2-Cyclopropyl-6-(methoxycarbonyl)isonicotinic acid:** 4-*tert*-Butyl 2-methyl 6-cyclopropylpyridine-2,4-dicarboxylate (236 mg, 0.85 mmol) was placed into a vessel to which TFA (4.9 ml) was added. The mixture was stirred at rt for 1 hour and volatiles were evaporated to give a crude of 2-cyclopropyl-6-(methoxycarbonyl)isonicotinic acid, which was immediately used for the next reaction without further purification.

[0475] **Methyl 6-cyclopropyl-4-[[*(2R)*-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridine-2-carboxylate:** To a stirred solution of 2-cyclopropyl-6-(methoxycarbonyl)isonicotinic acid (188 mg, 0.85 mmol), 4-methyl-2-[(*2R*)-pyrrolidin-2-yl]-1,3-thiazole (172 mg, 1.02 mmol) and Et<sub>3</sub>N (0.118 ml, 0.85 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) were added EDCI-HCl (196 mg, 1.02 mmol) and HOBT (138 mg, 1.02 mmol) at rt and the mixture was stirred at the same temperature overnight. The mixture was quenched with H<sub>2</sub>O and the organic layer was separated. The aqueous layer was extracted with CHCl<sub>3</sub> (x3) and the combined organic layer was washed with satd. NaHCO<sub>3</sub> aq. (x2), 1N HCl aq. and brine, dried

over  $\text{MgSO}_4$  and evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 0 to 66%) to give methyl 6-cyclopropyl-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate (245 mg, 78% yield) as a yellow oil. MS (ESI)  $m/z$ : 372  $[\text{M}+\text{H}]^+$ .

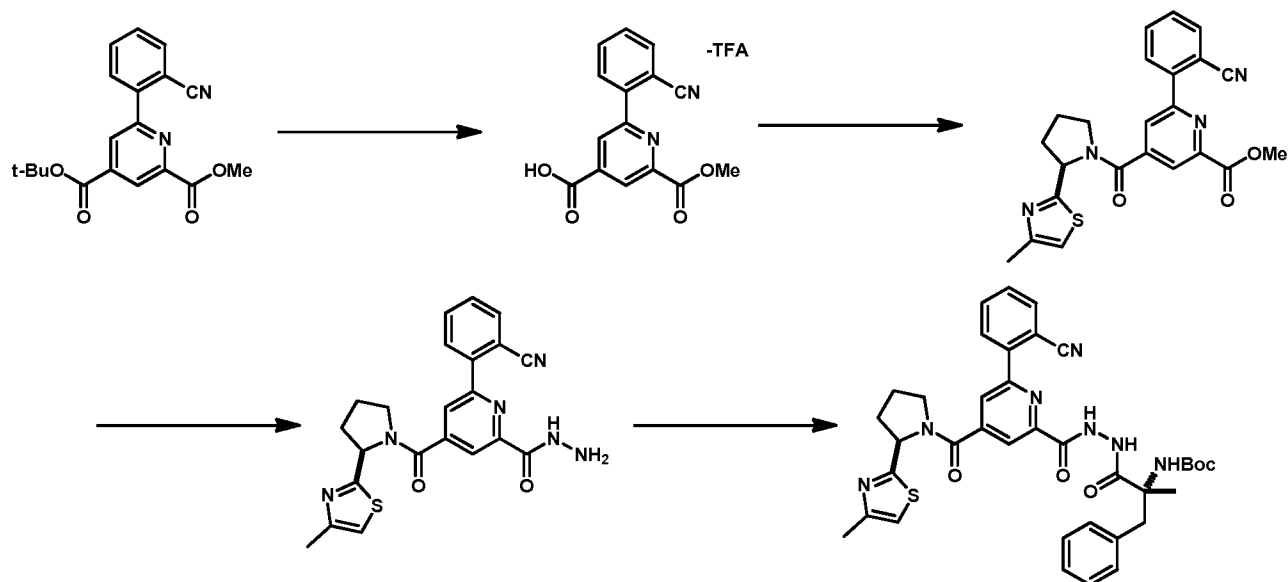
**[0476] 6-Cyclopropyl-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-**

**yl]carbonyl}pyridine-2-carbohydrazide:** To a stirred solution of methyl 6-cyclopropyl-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate (245 mg, 0.66 mmol) in EtOH was added  $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$  (0.32 ml, 6.60 mmol) at rt and the mixture was stirred at 65 degree for 1 hour. The reaction cleanly proceeded and it was diluted with  $\text{H}_2\text{O}/\text{EtOAc}$ . The organic phase was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layer was washed with  $\text{H}_2\text{O}$  (x3) and brine, dried over  $\text{MgSO}_4$  and evaporated to give a crude of 6-cyclopropyl-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carbohydrazide as a colorless oil, which was used for the next reaction without further purification.

**[0477] *tert*-Butyl [(2*R*)-1-{2-[(6-cyclopropyl-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)carbonyl]hydrazino}-2-methyl-1-oxo-3-**

**phenylpropan-2-yl]carbamate:** To a stirred solution of 6-cyclopropyl-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carbohydrazide (245 mg, 0.66 mmol) and *N*-(*tert*-butoxycarbonyl)- $\alpha$ -methyl-D-phenylalanine (221 mg, 0.79 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 ml) were added EDCI-HCl (152 mg, 0.79 mmol) and HOBT (107 mg, 0.79 mmol) at rt and the mixture was stirred at the same temperature overnight. The mixture was quenched with  $\text{H}_2\text{O}$  and the organic layer was separated. The aqueous layer was extracted with  $\text{CHCl}_3$  (x3) and the combined organic layer was washed with satd.  $\text{NaHCO}_3$  aq. (x2), 1 M HCl aq. and brine, dried over  $\text{MgSO}_4$  and evaporated to give a crude of *tert*-butyl [(2*R*)-1-{2-[(6-cyclopropyl-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)carbonyl]hydrazino}-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate which was used for the next reaction without further purification. MS (ESI)  $m/z$ : 633  $[\text{M}+\text{H}]^+$ .

## Example 1.6.14

**[0478] 2-(2-Cyanophenyl)-6-(methoxycarbonyl)isonicotinic acid trifluoroacetate (1:1):**

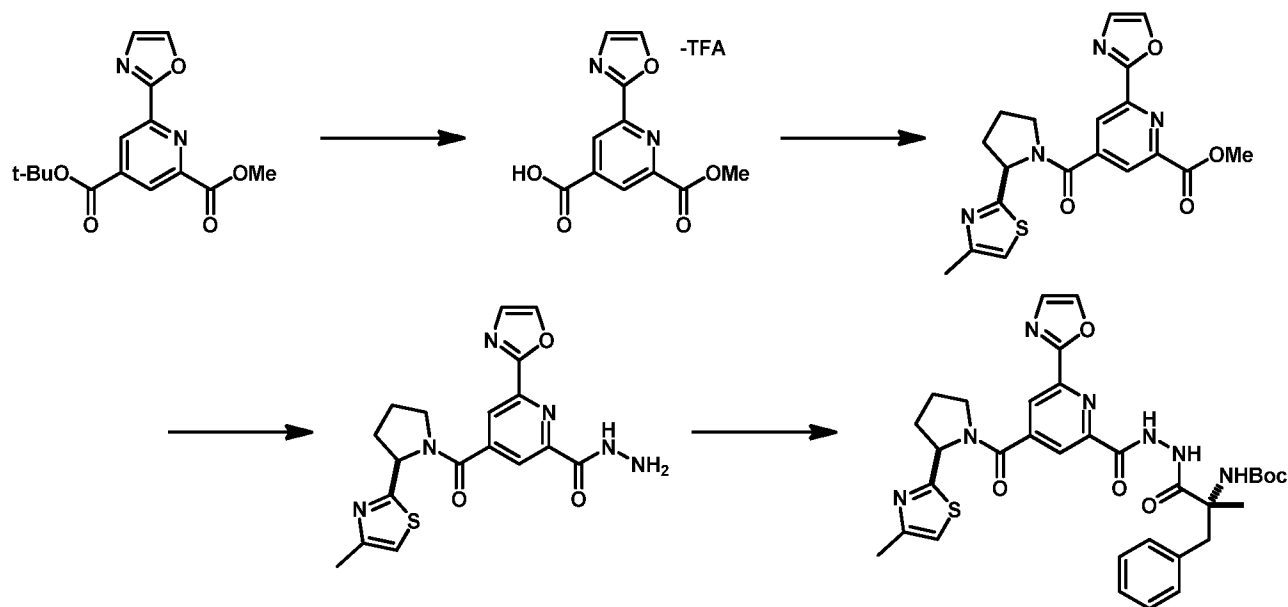
The desired compound was synthesized from 4-*tert*-butyl 2-methyl 6-(2-cyanophenyl)pyridine-2,4-dicarboxylate (95 mg, 0.281 mmol) in a similar manner to *Example 1.6.13*. MS (ESI) *m/z*: 283 [M+H]<sup>+</sup>.

**[0479] Methyl 6-(2-cyanophenyl)-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate:** The desired compound was synthesized from 2-(2-cyanophenyl)-6-(methoxycarbonyl)isonicotinic acid trifluoroacetate (1:1) (111 mg, 0.281 mmol) in a similar manner to *Example 1.6.13*. (121 mg, >99% yield) MS (ESI) *m/z*: 433 [M+H]<sup>+</sup>.

**[0480] 6-(2-Cyanophenyl)-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carbohydrazide:** The desired compound was synthesized from methyl 6-(2-cyanophenyl)-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate (121 mg, 0.281 mmol) in a similar manner to *Example 1.6.13*. MS (ESI) *m/z*: 433 [M+H]<sup>+</sup>.

**[0481] *tert*-Butyl [(2*R*)-1-(2-[[6-(2-cyanophenyl)-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]carbonyl}hydrazino)-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 6-(2-cyanophenyl)-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carbohydrazide (121 mg, 0.281 mmol) in a similar manner to *Example 1.6.13*. MS (ESI) *m/z*: 694 [M+H]<sup>+</sup>.

## Example 1.6.15

**[0482] 2-(Methoxycarbonyl)-6-(1,3-oxazol-2-yl)isonicotinic acid trifluoroacetate (1:1):**

The desired compound was synthesized from 4-*tert*-butyl 2-methyl 6-(1,3-oxazol-2-yl)pyridine-2,4-dicarboxylate (92 mg, 0.302 mmol) in a similar manner to *Example 1.6.13*.

MS (ESI)  $m/z$ : 283  $[M+H]^+$ .

**[0483] Methyl 4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1,3-oxazol-2-yl)pyridine-2-carboxylate:**

The desired compound was synthesized from 2-(methoxycarbonyl)-6-(1,3-oxazol-2-yl)isonicotinic acid trifluoroacetate (1:1) (109 mg 0.301 mmol) in a similar manner to *Example 1.6.13*. (114 mg, 95% yield) MS (ESI)  $m/z$ : 399  $[M+H]^+$ .

**[0484] 4-[[[(2R)-2-(4-Methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1,3-oxazol-2-yl)pyridine-2-carbohydrazide.**

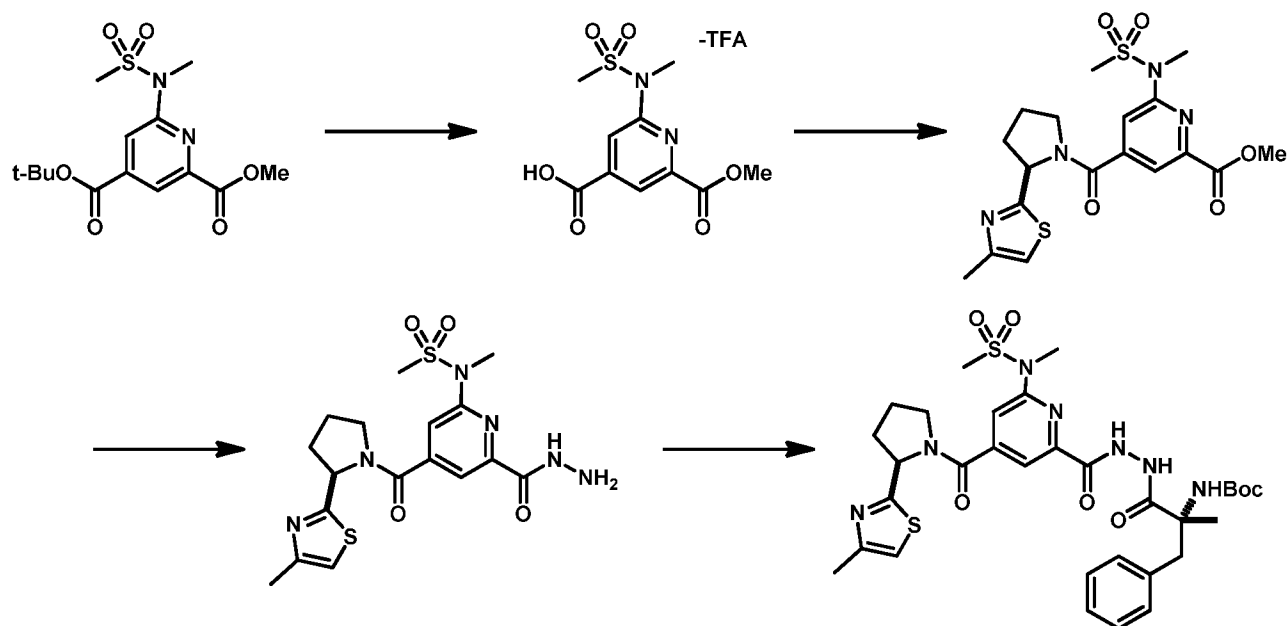
The desired compound was synthesized from methyl 4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1,3-oxazol-2-yl)pyridine-2-carboxylate (114 mg, 0.286 mmol) in a similar manner to *Example 1.6.13*. MS (ESI)  $m/z$ : 433  $[M+H]^+$ .

**[0485] *tert*-Butyl [(2R)-2-methyl-1-(2-{[4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1,3-oxazol-2-yl)pyridin-2-yl]carbonyl}hydrazino)-1-oxo-**

**3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1,3-oxazol-2-yl)pyridine-2-carbohydrazide (110 mg, 0.251 mmol) in a similar manner to *Example 1.6.13*. MS (ESI)  $m/z$ : 660  $[M+H]^+$ .



## Example 1.6.16

**[0486] 2-(Methoxycarbonyl)-6-[methyl(methylsulfonyl)amino]isonicotinic acid**

**trifluoroacetate (1:1):** The desired compound was synthesized from 4-*tert*-butyl 2-methyl-6-[methyl(methylsulfonyl)amino]pyridine-2,4-dicarboxylate (234 mg, 0.679 mmol) in a similar manner to Example 1.6.13. (247 mg, 90% yield) MS (ESI)  $m/z$ : 289  $[M+H]^+$ .

**[0487] Methyl 6-[methyl(methylsulfonyl)amino]-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate:**

The desired compound was synthesized from 2-(methoxycarbonyl)-6-[methyl(methylsulfonyl)amino]isonicotinic acid trifluoroacetate (1:1) (186 mg, 0.462 mmol) in a similar manner to Example 1.6.13. (171 mg, 84% yield) MS (ESI)  $m/z$ : 439  $[M+H]^+$ .

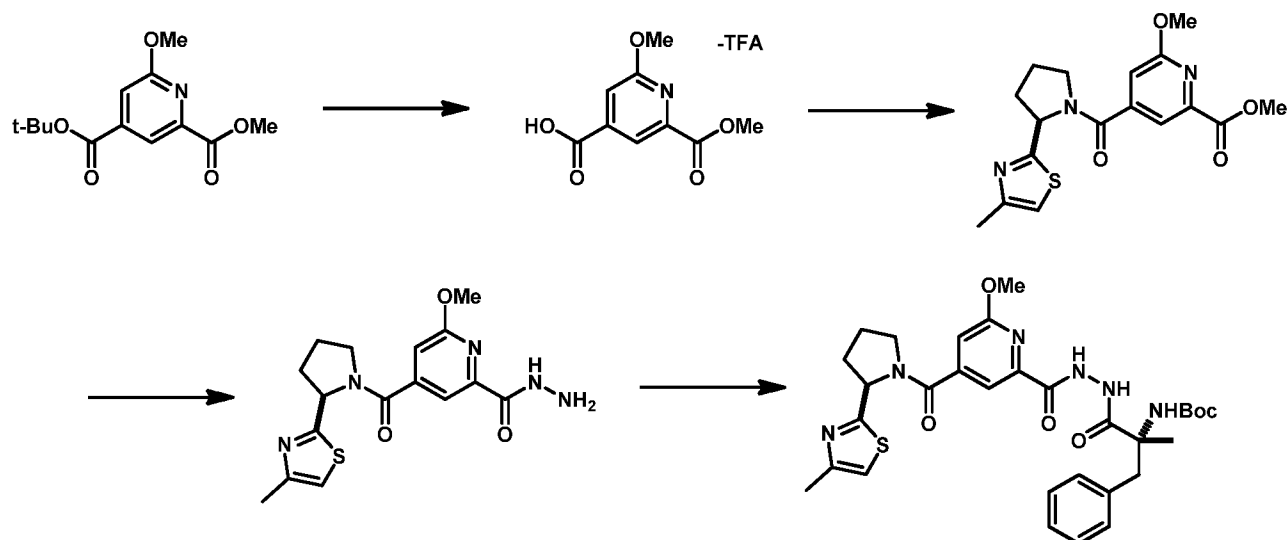
**[0488] *N*-[6-(Hydrazinocarbonyl)-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-*N*-methylethanesulfonamide:**

The desired compound was synthesized from methyl 6-[methyl(methylsulfonyl)amino]-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate (171 mg, 0.390 mmol) in a similar manner to Example 1.6.13. (156 mg, 91% yield) MS (ESI)  $m/z$ : 439  $[M+H]^+$ .

**[0489] *tert*-Butyl [(2*R*)-2-methyl-1-{2-[(6-[methyl(methylsulfonyl)amino]-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)carbonyl]hydrazino}-1-oxo-3-phenylpropan-2-yl] carbamate:**

The desired compound was synthesized from *N*-[6-(hydrazinocarbonyl)-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-*N*-methylethanesulfonamide (156 mg, 0.356 mmol) in a similar manner to Example 1.6.13. MS (ESI)  $m/z$ : 701  $[M+H]^+$ .

## Example 1.6.17



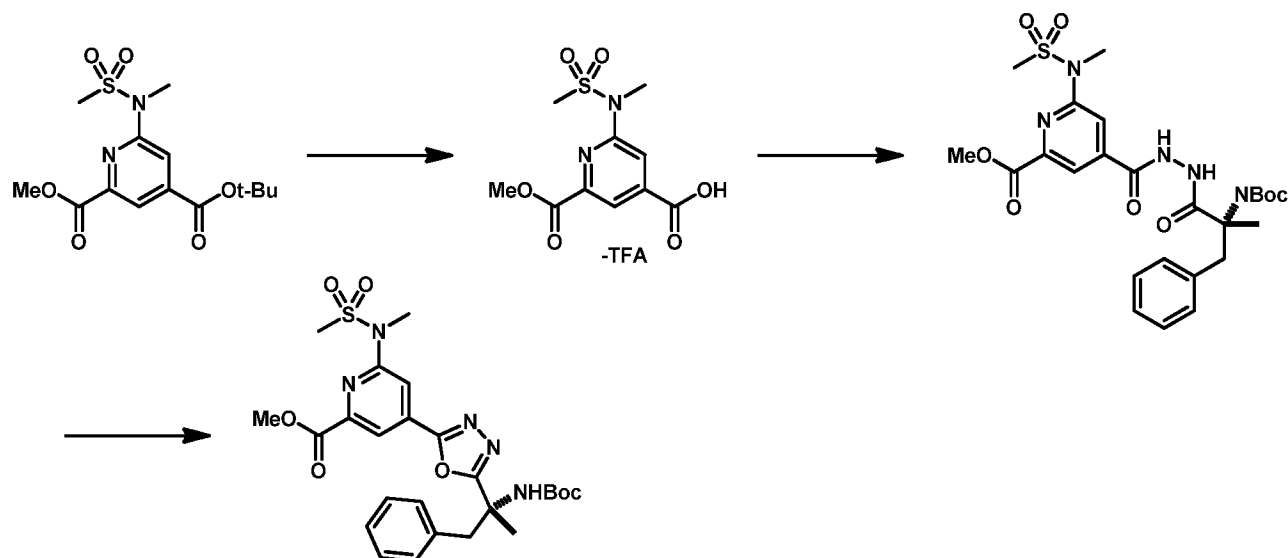
**[0490] 2-Methoxy-6-(methoxycarbonyl)isonicotinic acid trifluoroacetate (1:1):** The desired compound was synthesized from 4-*tert*-butyl 2-methyl 6-methoxypyridine-2,4-dicarboxylate (337 mg, 1.26 mmol) in a similar manner to *Example 1.6.13*. (370 mg, 90% yield) MS (ESI) *m/z*: 445 [2M+Na]<sup>+</sup>.

**[0491] Methyl 6-methoxy-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate:** The desired compound was synthesized from 2-methoxy-6-(methoxycarbonyl)isonicotinic acid trifluoroacetate (1:1) (370 mg, 1.14 mmol) in a similar manner to *Example 1.6.13*. (170 mg, 41% yield) MS (ESI) *m/z*: 362 [M+H]<sup>+</sup>.

**[0492] 6-Methoxy-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carbohydrazide:** The desired compound was synthesized from methyl 6-methoxy-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate (170 mg, 0.470 mmol) in a similar manner to *Example 1.6.13*. MS (ESI) *m/z*: 362 [M+H]<sup>+</sup>.

**[0493] *tert*-Butyl [(2*R*)-1-{2-[(6-methoxy-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)carbonyl]hydrazino}-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 6-methoxy-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carbohydrazide (170 mg, 0.470 mmol) in a similar manner to *Example 1.6.13*.

## Example 1.6.18

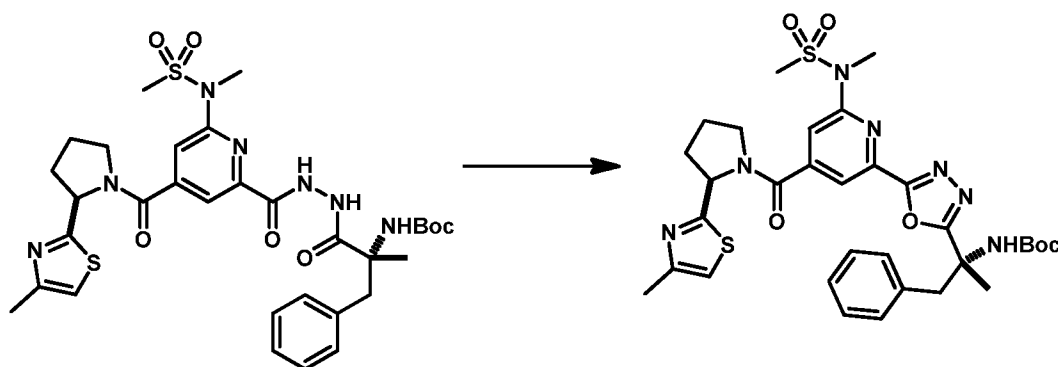


**[0494] 2-(Methoxycarbonyl)-6-[methyl(methylsulfonyl)amino]isonicotinic acid trifluoroacetate (1:1):** 4-*tert*-Butyl 2-methyl 6-[methyl(methylsulfonyl)amino]pyridine-2,4-dicarboxylate (234 mg, 0.679 mmol) was placed into a vessel to which TFA (4 ml) was added. The mixture was stirred at rt for 1 hour and volatiles were evaporated to give a crude of 2-(methoxycarbonyl)-6-[methyl(methylsulfonyl)amino]isonicotinic acid trifluoroacetate (1:1), which was immediately used for the next reaction without further purification. MS (ESI)  $m/z$ : 289  $[M+H]^+$ .

**[0495] Methyl 4-[(2R)-2-[(*tert*-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl]hydrazino)carbonyl]-6-[methyl(methylsulfonyl)amino]pyridine-2-carboxylate:** To a stirred solution of 2-(methoxycarbonyl)-6-[methyl(methylsulfonyl)amino]isonicotinic acid trifluoroacetate (1:1) (93 mg, 0.23 mmol) and *i*-Pr<sub>2</sub>NEt (0.087 ml, 0.51 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) were added *tert*-butyl [(2*R*)-1-hydrazino-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (81 mg, 0.28 mmol) and HATU (105 mg, 0.28 mmol) at rt and the mixture was stirred at the same temperature overnight. The mixture was quenched with H<sub>2</sub>O and the organic layer was separated. The aqueous layer was extracted with CHCl<sub>3</sub> (x3) and the combined organic layer was washed with aq. KHSO<sub>4</sub> (pH 4), NaHCO<sub>3</sub> aq. and brine, dried over MgSO<sub>4</sub> and evaporated to give a crude of methyl 4-[(2R)-2-[(*tert*-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl]hydrazino)carbonyl]-6-[methyl(methylsulfonyl)amino]pyridine-2-carboxylate, which was used for the next reaction without further purification.

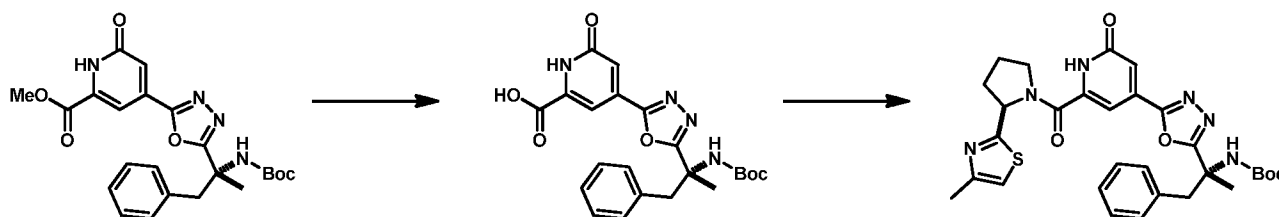
**[0496] Methyl 4-(5-((2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-[methyl(methylsulfonyl)amino]pyridine-2-carboxylate:** Methyl 4-[(2-((2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl)hydrazino)carbonyl]-6-[methyl(methylsulfonyl)amino]pyridine-2-carboxylate (130 mg, 0.23 mmol) and Burgess reagent (164 mg, 0.69 mmol) were placed into a vessel for microwave reactions. This vessel was sealed and irradiated with microwave at 120 degree for 20 min. Volatiles were evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 20 to 100%) to give methyl 4-(5-((2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-[methyl(methylsulfonyl)amino]pyridine-2-carboxylate (99 mg, 79% yield in 3 steps) as a pale yellow oil. MS (ESI)  $m/z$ : 546  $[M+H]^+$ .

*Example 1.6.19*



**[0497] *tert*-Butyl {(2*R*)-2-[5-(6-[methyl(methylsulfonyl)amino]-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from *tert*-butyl [(2*R*)-2-methyl-1-{2-[(6-[methyl(methylsulfonyl)amino]-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)carbonyl]hydrazino}-1-oxo-3-phenylpropan-2-yl] (248 mg, 0.354 mmol) in a similar manner to *Example 1.6.18*. (117 mg, 48% yield) MS (ESI)  $m/z$ : 682  $[M+H]^+$ .

*Example 1.6.20*

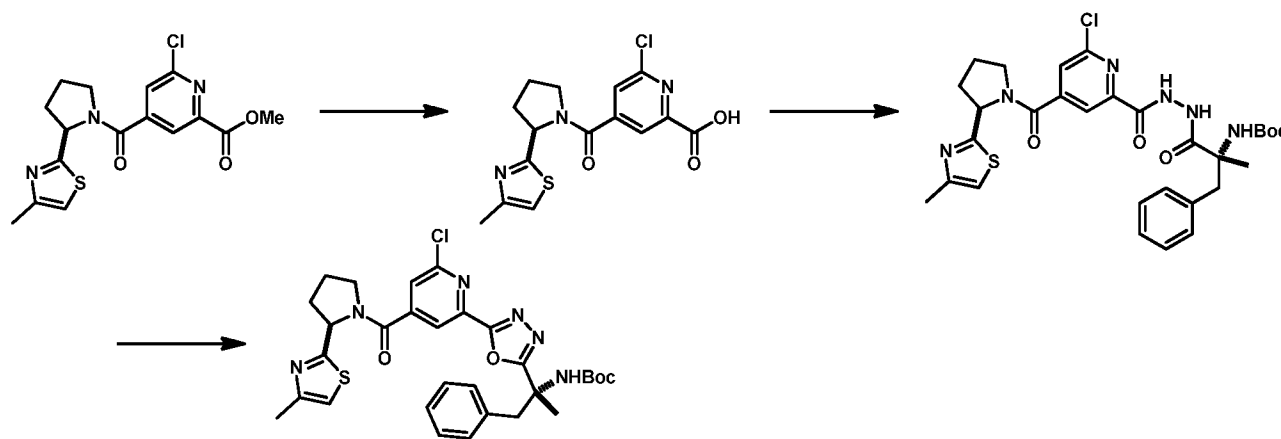


**[0498] 4-(5-((2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid:** The desired compound was

synthesized from methyl 4-(5-((2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-oxo-1,6-dihydropyridine-2-carboxylate (406 mg, 0.893 mmol) in a similar manner to *Example 1.7.56*.

**[0499] *tert*-Butyl {(2*R*)-2-[5-(6-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2-oxo-1,2-dihydropyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from 4-(5-((2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid (393 mg, 0.892 mmol) in a similar manner to *Example 1.7.56*. (268 mg, 51% yield in 2 steps) MS (ESI) *m/z*: 591 [M+H]<sup>+</sup>.

*Example 1.6.21*



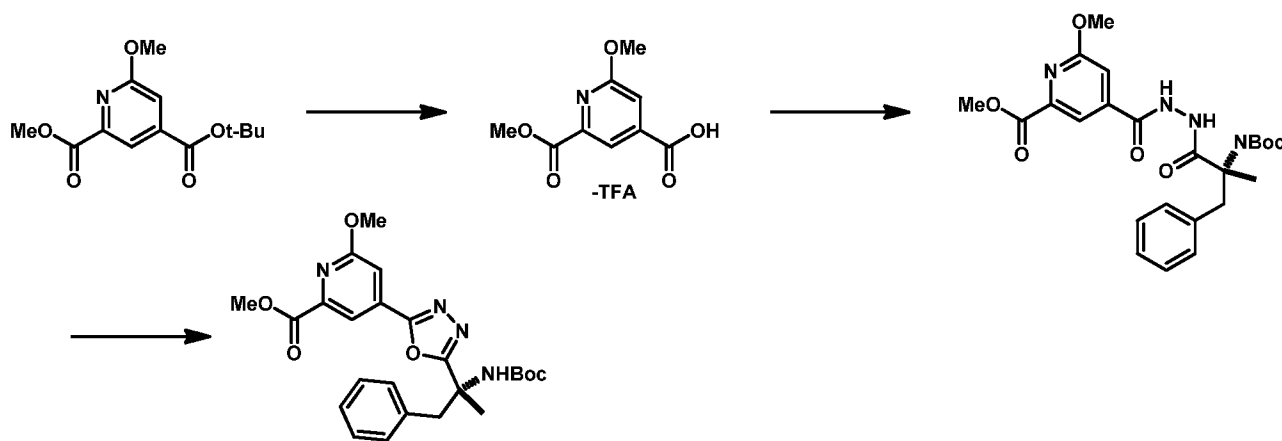
**[0500] 6-Chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonylpyridine-2-carboxylic acid:** To a stirred solution of methyl 6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonylpyridine-2-carboxylate (3.21 g, 8.77 mmol) in THF (10 ml) was added 3 M NaOH aq. (8.77 ml, 26.3 mmol) at rt and the mixture was stirred at rt for 1 hour. The mixture was quenched with 6 M HCl aq. (4.38 ml) and volatiles were evaporated to give a crude of 6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonylpyridine-2-carboxylic acid, which was used for the next reaction without further purification.

**[0501] *tert*-Butyl [(2*R*)-1-{2-[(6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)carbonyl]hydrazino}-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate:** To a stirred solution of 6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonylpyridine-2-carboxylic acid (3.09 g, 8.77 mmol) and *tert*-butyl [(2*R*)-1-hydrazino-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (2.70 g, 9.21 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml) were added HATU (3.50 g, 9.21 mmol) and *i*-Pr<sub>2</sub>NEt (1.58 ml, 9.21

mmol) at rt and the mixture was stirred at the same temperature overnight. The mixture was quenched with aqueous citric acid (pH 3) and the organic layer was separated. The aqueous layer was extracted with  $\text{CHCl}_3$  (x3) and the combined organic layer was washed with aqueous citric acid (pH 3), satd.  $\text{NaHCO}_3$  and brine, dried over  $\text{MgSO}_4$  and evaporated to give a crude, which was purified with column chromatography (NH-silica, EtOAc in hexane = 20 to 100% then MeOH in  $\text{CHCl}_3$  = 0 to 20%) to give *tert*-butyl [(2*R*)-1-{2-[(6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)carbonyl]hydrazino}-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (3.84 g, 70% yield) as a yellow oil. MS (ESI)  $m/z$ : 627  $[\text{M}+\text{H}]^+$ .

**[0502] *tert*-Butyl {(2*R*)-2-[5-(6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** *tert*-Butyl [(2*R*)-1-{2-[(6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)carbonyl]hydrazino}-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (3.84 g, 6.12 mmol) and Burgess reagent (4.38 g, 18.4 mmol) were placed into a vessel for microwave reactions. This vessel was sealed and irradiated with microwave at 120 degree for 20 min. Volatiles were evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 20 to 100%) to give *tert*-butyl {(2*R*)-2-[5-(6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (2.55 g, 68% yield) as a pale brown solid. MS (ESI)  $m/z$ : 609  $[\text{M}+\text{H}]^+$ .

#### Example 1.6.22



**[0503] 2-Methoxy-6-(methoxycarbonyl)isonicotinic acid trifluoroacetate (1:1):** 4-*tert*-Butyl 2-methyl 6-methoxypyridine-2,4-dicarboxylate (400 mg, 1.49 mmol) was placed into a vessel, to which TFA (4 ml) was added at rt. The mixture was stirred at the same temperature

for 1 hour and volatiles were evaporated to give a crude of 2-methoxy-6-(methoxycarbonyl)isonicotinic acid trifluoroacetate (1:1) as a white solid, which was used for the next reaction without further purification.

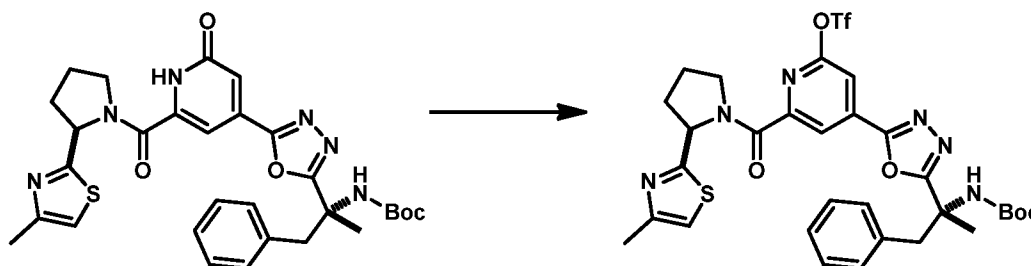
**[0504] Methyl 4-[(2-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-methyl-3-**

**phenylpropanoyl}hydrazino)carbonyl]-6-methoxypyridine-2-carboxylate:** To a stirred solution of 2-methoxy-6-(methoxycarbonyl)isonicotinic acid trifluoroacetate (1:1) (486 mg, 1.49 mmol) and *i*-Pr<sub>2</sub>NEt (0.52 ml, 3.06 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) were added HATU (597 mg, 1.57 mmol) and *tert*-butyl [(2*R*)-1-hydrazino-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (460 mg, 1.57 mmol) at rt and the mixture was stirred at the same temperature overnight. The mixture was quenched with H<sub>2</sub>O and the organic layer was separated. The aqueous layer was extracted with CHCl<sub>3</sub> (x3) and the combined organic layer was washed with satd. NaHCO<sub>3</sub> aq. (x2) and brine, dried over MgSO<sub>4</sub> and evaporated to give a crude of methyl 4-[(2-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl}hydrazino)carbonyl]-6-methoxypyridine-2-carboxylate, which was used for the next reaction without further purification. MS (ESI) *m/z*: 487 [M+H]<sup>+</sup>.

**[0505] Methyl 4-(5-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-**

**oxadiazol-2-yl)-6-methoxypyridine-2-carboxylate:** methyl 4-[(2-{(2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl}hydrazino)carbonyl]-6-methoxypyridine-2-carboxylate (727 mg, 1.49 mmol) and Burgess reagent (1.07 g, 4.48 mmol) were placed into a vessel for microwave reactions. This vessel was sealed and irradiated with microwave at 120 degree for 20 min. Volatiles were evaporated to give a crude, which was briefly purified with column chromatography (EtOAc in hexane = 33%, SiO<sub>2</sub> 10 g) to give methyl 4-(5-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-methoxypyridine-2-carboxylate containing some byproducts as a pale yellow oil. MS (ESI) *m/z*: 469 [M+H]<sup>+</sup>.

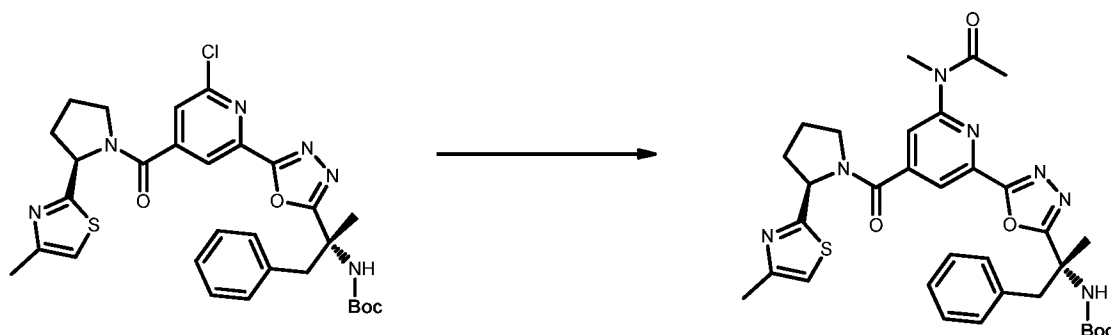
*Example 1.6.23*



**[0506] 4-(5-{(2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-**

**yl trifluoromethanesulfonate:** To a stirred solution of *tert*-butyl {(2*R*)-2-[5-(6-[[*(2R)*-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-2-oxo-1,2-dihydropyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (268 mg, 0.454 mmol) and *i*-Pr<sub>2</sub>NEt (0.116 ml, 0.68 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added Tf<sub>2</sub>O (0.091 ml, 0.54 mmol) at 0 degree. The starting molecule was completely consumed in 1 hour and it was quenched with satd. NaHCO<sub>3</sub> aq. The organic layer was separated and the aqueous layer was extracted with CHCl<sub>3</sub> (x2). The combined organic layer was washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub> and evaporated to give a crude, which was purified with column chromatography (MeOH in CHCl<sub>3</sub> = 0 to 10%) to give 4-(5-{{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-[[*(2R)*-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl trifluoromethanesulfonate (208 mg, 63% yield) as a colorless oil. MS (ESI) *m/z*: 723 [M+H]<sup>+</sup>.

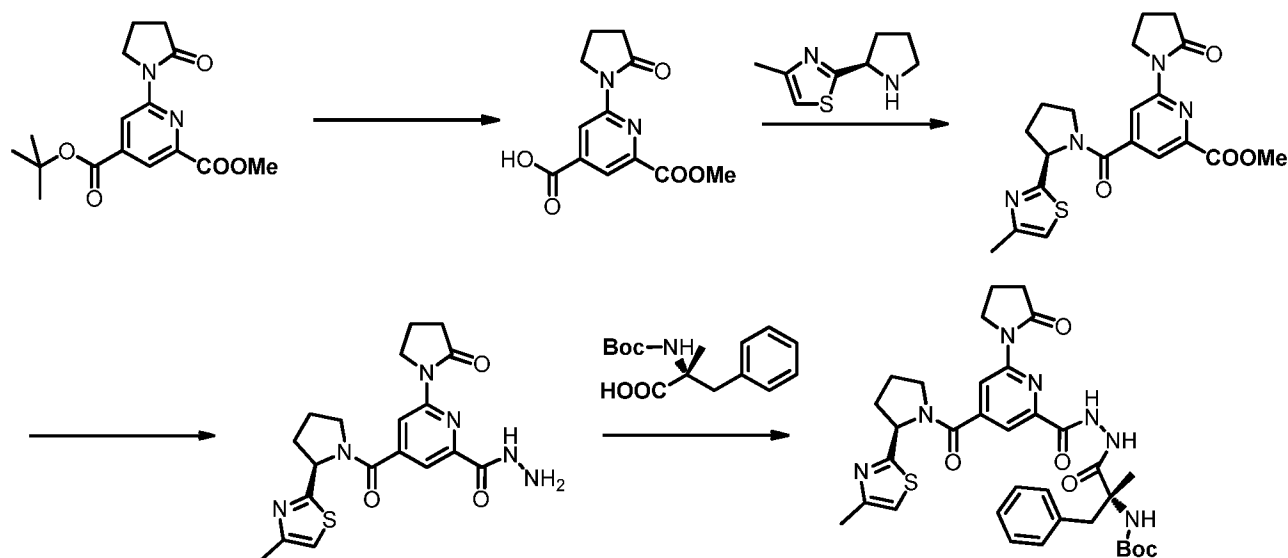
*Example 1.6.24*



**[0507] *tert*-butyl {(2*R*)-2-[5-(6-[acetyl(methyl)amino]-4-[[*(2R)*-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from *tert*-butyl {(2*R*)-2-[5-(6-chloro-4-[[*(2R)*-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate in a similar manner to *Example 1.3.21* (126 mg, 79%).



## Example 1.6.25



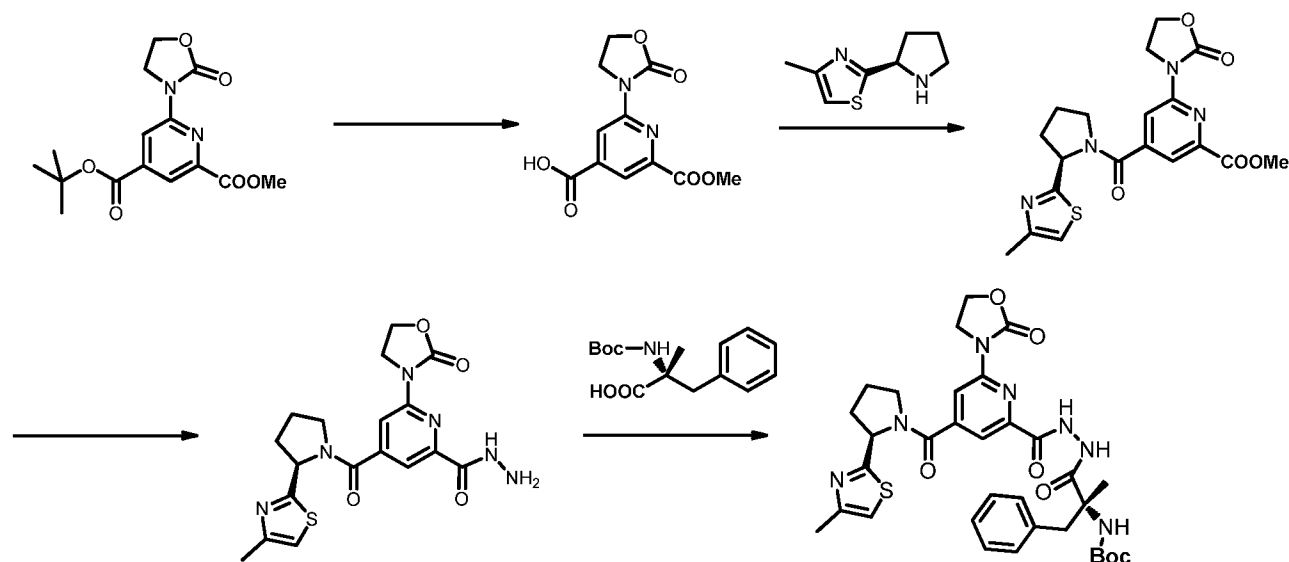
**[0508] 2-(methoxycarbonyl)-6-(2-oxopyrrolidin-1-yl)isonicotinic acid:** The desired compound was synthesized from 4-tert-butyl 2-methyl 6-(2-oxopyrrolidin-1-yl)pyridine-2,4-dicarboxylate in a similar manner to *Example 1.6.13* (60 mg).

**[0509] methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxylate:** The desired compound was synthesized from 2-(methoxycarbonyl)-6-(2-oxopyrrolidin-1-yl)isonicotinic acid in a similar manner to *Example 1.6.13* (88 mg, 94% yield; 2 steps). MS (ESI)  $m/z$ : 415  $[M+H]^+$ .

**[0510] 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxopyrrolidin-1-yl)pyridine-2-carbohydrazide:** The desired compound was synthesized from methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxylate in a similar manner to *Example 1.6.13* (86 mg).

**[0511] tert-butyl [(2R)-2-methyl-1-(2-{[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxopyrrolidin-1-yl)pyridin-2-yl]carbonyl}hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxopyrrolidin-1-yl)pyridine-2-carbohydrazide in a similar manner to *Example 1.6.13* (58 mg, 41% yield; 2 steps).

## Example 1.6.26



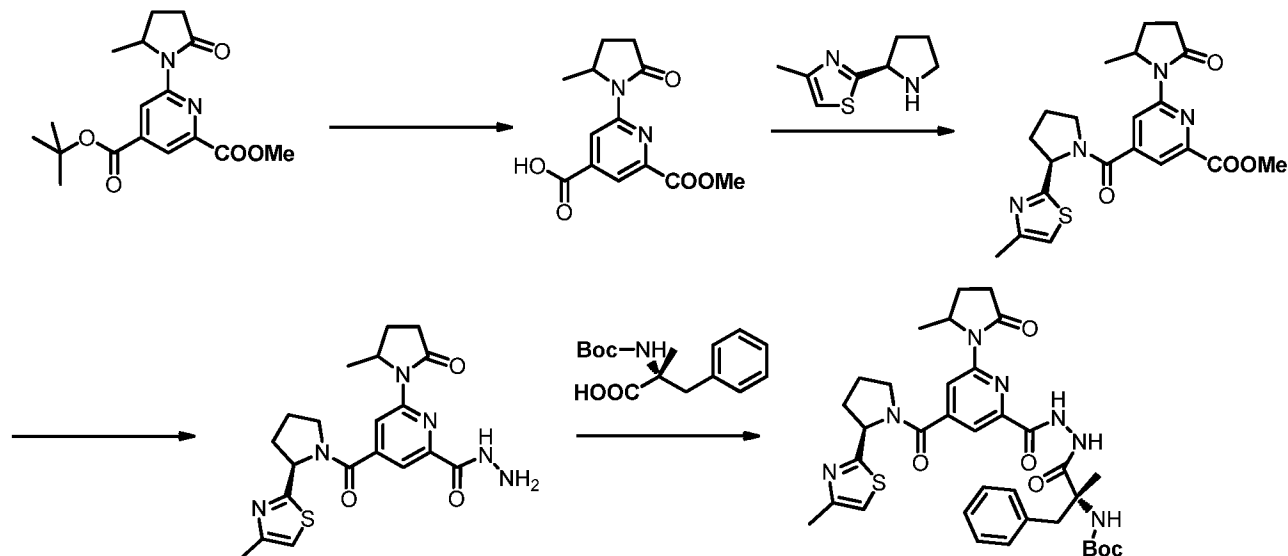
**[0512] 2-(methoxycarbonyl)-6-(2-oxo-1,3-oxazolidin-3-yl)isonicotinic acid:** The desired compound was synthesized from 4-tert-butyl 2-methyl 6-(2-oxo-1,3-oxazolidin-3-yl)pyridine-2,4-dicarboxylate in a similar manner to *Example 1.6.13* (51 mg).

**[0513] methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxo-1,3-oxazolidin-3-yl)pyridine-2-carboxylate:** The desired compound was synthesized from 2-(methoxycarbonyl)-6-(2-oxo-1,3-oxazolidin-3-yl)isonicotinic acid in a similar manner to *Example 1.6.13* (58 mg, 73% yield: 2 steps). MS (ESI)  $m/z$ : 417  $[M+H]^+$ .

**[0514] 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxo-1,3-oxazolidin-3-yl)pyridine-2-carbohydrazide:** The desired compound was synthesized from methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxo-1,3-oxazolidin-3-yl)pyridine-2-carboxylate in a similar manner to *Example 1.6.13* (58 mg).

**[0515] tert-butyl [(2R)-2-methyl-1-(2-{[4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxo-1,3-oxazolidin-3-yl)pyridin-2-yl]carbonyl}hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxo-1,3-oxazolidin-3-yl)pyridine-2-carbohydrazide in a similar manner to *Example 1.6.13* (28 mg, 30% yield: 2 steps).

## Example 1.6.27



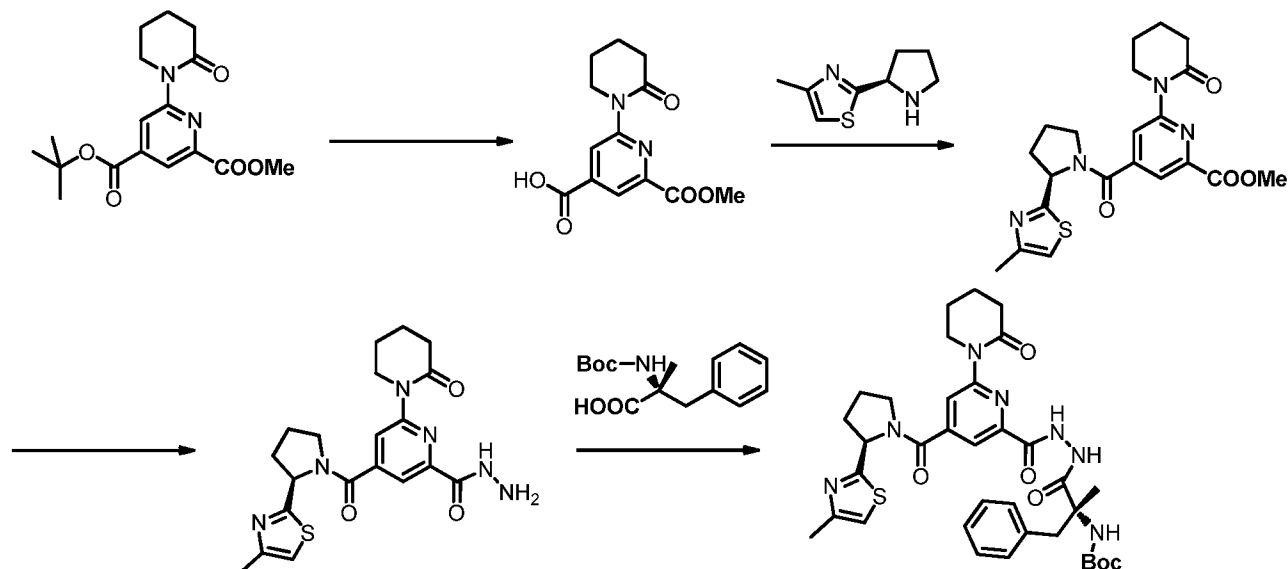
**[0516] 2-(methoxycarbonyl)-6-(2-methyl-5-oxopyrrolidin-1-yl)isonicotinic acid:** The desired compound was synthesized from 4-tert-butyl 2-methyl 6-(2-methyl-5-oxopyrrolidin-1-yl)pyridine-2,4-dicarboxylate in a similar manner to *Example 1.6.13* (58 mg).

**[0517] methyl 6-(2-methyl-5-oxopyrrolidin-1-yl)-4-[[2-(2-methyl-5-oxopyrrolidin-1-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridine-2-carboxylate:** The desired compound was synthesized from 2-(methoxycarbonyl)-6-(2-methyl-5-oxopyrrolidin-1-yl)isonicotinic acid in a similar manner to *Example 1.6.13* (70 mg, 78% yield; 2 steps). MS (ESI)  $m/z$ : 429  $[M+H]^+$ .

**[0518] 6-(2-methyl-5-oxopyrrolidin-1-yl)-4-[[2-(2-methyl-5-oxopyrrolidin-1-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridine-2-carbohydrazide:** The desired compound was synthesized from methyl 6-(2-methyl-5-oxopyrrolidin-1-yl)-4-[[2-(2-methyl-5-oxopyrrolidin-1-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridine-2-carboxylate in a similar manner to *Example 1.6.13* (70 mg).

**[0519] tert-butyl [(2R)-2-methyl-1-(2-[[6-(2-methyl-5-oxopyrrolidin-1-yl)-4-[[2-(2-methyl-5-oxopyrrolidin-1-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridine-2-carboxylate]]carbonyl]hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 6-(2-methyl-5-oxopyrrolidin-1-yl)-4-[[2-(2-methyl-5-oxopyrrolidin-1-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridine-2-carbohydrazide in a similar manner to *Example 1.6.13* (112 mg, 99% yield; 2 steps).

## Example 1.6.28



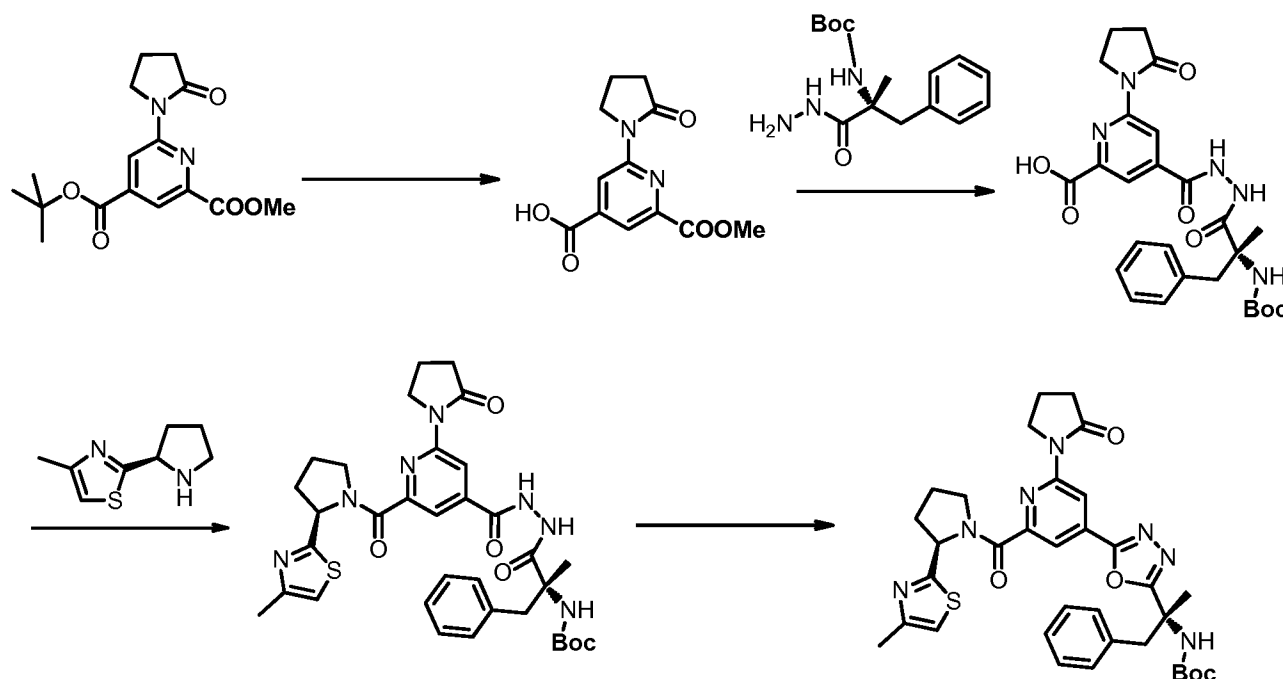
**[0520] 2-(methoxycarbonyl)-6-(2-oxopiperidin-1-yl)isonicotinic acid:** The desired compound was synthesized from 4-tert-butyl 2-methyl 6-(2-oxopiperidin-1-yl)pyridine-2,4-dicarboxylate in a similar manner to *Example 1.6.13* (211 mg).

**[0521] methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl-6-(2-oxopiperidin-1-yl)pyridine-2-carboxylate:** The desired compound was synthesized from 2-(methoxycarbonyl)-6-(2-oxopiperidin-1-yl)isonicotinic acid in a similar manner to *Example 1.6.13* (124 mg, 38% yield: 2 steps). MS (ESI)  $m/z$ : 429  $[M+H]^+$ .

**[0522] 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl-6-(2-oxopiperidin-1-yl)pyridine-2-carbohydrazide:** The desired compound was synthesized from methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl-6-(2-oxopiperidin-1-yl)pyridine-2-carboxylate in a similar manner to *Example 1.6.13* (120 mg).

**[0523] tert-butyl [(2R)-2-methyl-1-(2-[(4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl)-6-(2-oxopiperidin-1-yl)pyridin-2-yl]carbonyl)hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl-6-(2-oxopiperidin-1-yl)pyridine-2-carbohydrazide in a similar manner to *Example 1.6.13* (193 mg, 98% yield: 2 steps).

## Example 1.6.29



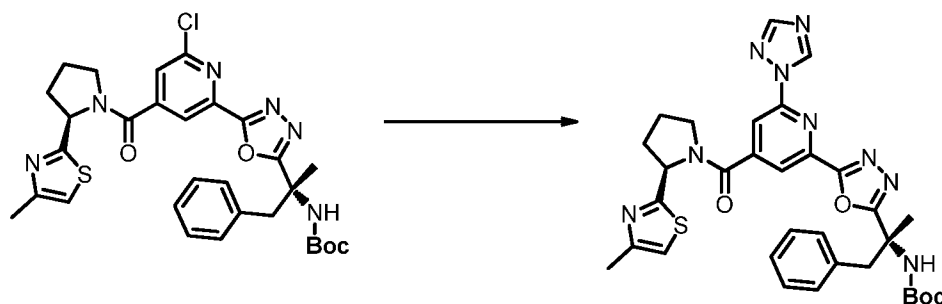
**[0524] 2-(methoxycarbonyl)-6-(2-oxopyrrolidin-1-yl)isonicotinic acid:** 4-tert-butyl 2-methyl 6-(2-oxopyrrolidin-1-yl)pyridine-2,4-dicarboxylate (228 mg, 0.71 mmol) was placed into a vessel to which TFA (3.3 ml, 43mmol) was added. The mixture was stirred at rt for 1 hour and evaporated azeotropically with toluene to give a crude of 2-(methoxycarbonyl)-6-(2-oxopyrrolidin-1-yl)isonicotinic acid (174 mg, 93%), which was immediately used for the next reaction without further purification.

**[0525] 4-[(2-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl}hydrazino)carbonyl]-6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxylic acid:** To a solution of 2-(methoxycarbonyl)-6-(2-oxopyrrolidin-1-yl)isonicotinic acid (174 mg, 0.66 mmol) and tert-butyl [(2R)-1-hydrazino-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (232 mg, 0.79 mmol) in DMF (3 ml) were added EDCI·HCl (164 mg, 0.86 mmol) and HOBt (89 mg, 0.66 mmol) at rt and the mixture was stirred at the same temperature overnight. 1M aq. NaOH and CHCl<sub>3</sub> were added to the mixture, and then the organic layer was separated. The aqueous layer was acidified with 1M aq. HCl and extracted with EtOH/CHCl<sub>3</sub>(1:5 v/v) (x3) after adding brine. The combined organic layer was dried over MgSO<sub>4</sub> and evaporated to give a crude 4-[(2-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl}hydrazino)carbonyl]-6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxylic acid (416 mg, >100% yield) as a colorless oil, which was used for the next reaction without further purification.

**[0526] tert-butyl [(2R)-2-methyl-1-{2-[2-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxopyrrolidin-1-yl)isonicotinoyl]hydrazino}-1-oxo-3-phenylpropan-2-yl]carbamate:** To a solution of 4-[(2-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl}hydrazino)carbonyl]-6-(2-oxopyrrolidin-1-yl)pyridine-2-carboxylic acid (416 mg, 0.79 mmol) and 4-methyl-2-[(2R)-pyrrolidin-2-yl]-1,3-thiazole (266 mg, 1.6 mmol) in DMF (4 ml) were added EDCI·HCl (303 mg, 1.6 mmol) and HOBt (107 mg, 0.79 mmol). After stirring at rt for 14 hours, the reaction mixture was treated with EtOAc/water. The organic layer was dried over MgSO<sub>4</sub>, and volatiles were removed under reduced pressure. Purification of the obtained residue via column chromatography (EtOH/CHCl<sub>3</sub> = 0:100 to 5:95) yielded 320 mg (60%) of tert-butyl [(2R)-2-methyl-1-{2-[2-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxopyrrolidin-1-yl)isonicotinoyl]hydrazino}-1-oxo-3-phenylpropan-2-yl]carbamate as a slightly reddish oil.

**[0527] tert-butyl [(2R)-2-{5-[2-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxopyrrolidin-1-yl)pyridin-4-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** To a stirred solution of tert-butyl [(2R)-2-methyl-1-{2-[2-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxopyrrolidin-1-yl)isonicotinoyl]hydrazino}-1-oxo-3-phenylpropan-2-yl]carbamate (320 mg, 0.47 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 ml) were added CBr<sub>4</sub> (314 mg, 0.95 mmol), PPh<sub>3</sub> (248 mg, 0.95 mmol) and imidazole (64 mg, 0.95 mmol) and the mixture was stirred at rt for 2 hours. The mixture was evaporated and the obtained residue was purified with column chromatography (EtOH/CHCl<sub>3</sub> = 0:100 to 5:95) to give tert-butyl [(2R)-2-{5-[2-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxopyrrolidin-1-yl)pyridin-4-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate as a colorless oil.

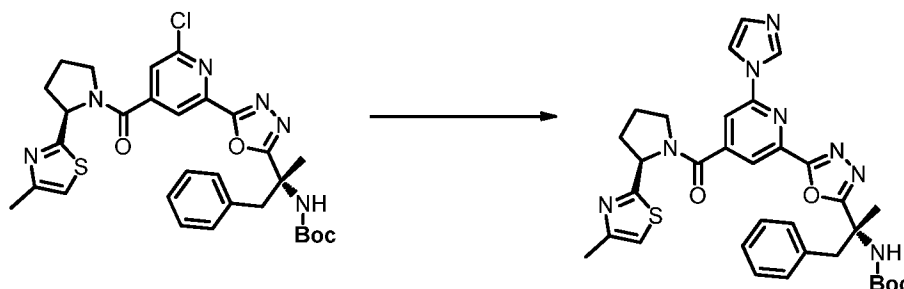
*Example 1.6.30*



**[0528] tert-butyl [(2R)-2-{5-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-**

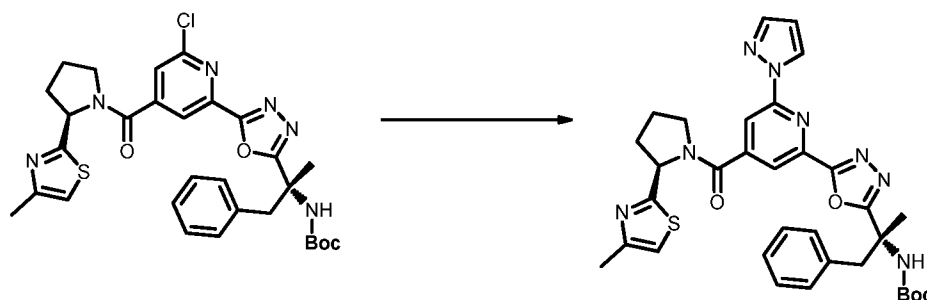
**phenylpropan-2-yl]carbamate:** A suspension of tert-butyl {(2R)-2-[5-(6-chloro-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (120 mg, 0.20 mmol), 1H-1,2,4-triazole (68 mg, 0.99 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (96 mg, 0.30 mmol) in NMP (2.4 ml) were placed into a vessel for microwave reactions. The vessel was sealed and irradiated with microwave at 150 °C for 10 min. After cooling, H<sub>2</sub>O was added and then the mixture was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The obtained residue was purified with column chromatography (EtOH / CHCl<sub>3</sub> = 0:100 to 5:95) to give tert-butyl [(2R)-2-{5-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate (32 mg, 25% yield) as a pale yellow solid.

*Example 1.6.31*



**[0529] tert-butyl [(2R)-2-{5-[6-(1H-imidazol-1-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from tert-butyl {(2R)-2-[5-(6-chloro-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate in a similar manner to *Example 1.6.30* (62 mg, 59% yield) as a pale yellow solid.

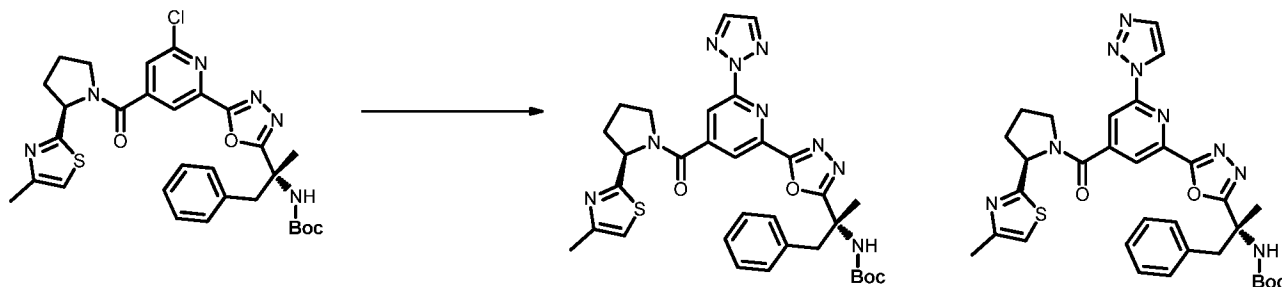
*Example 1.6.32*



**[0530] tert-butyl [(2R)-2-{5-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1H-pyrazol-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from tert-butyl {(2R)-2-[5-(6-chloro-

4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate in a similar manner to *Example 1.6.30* (144 mg, 91% yield) as a pale yellow oil.

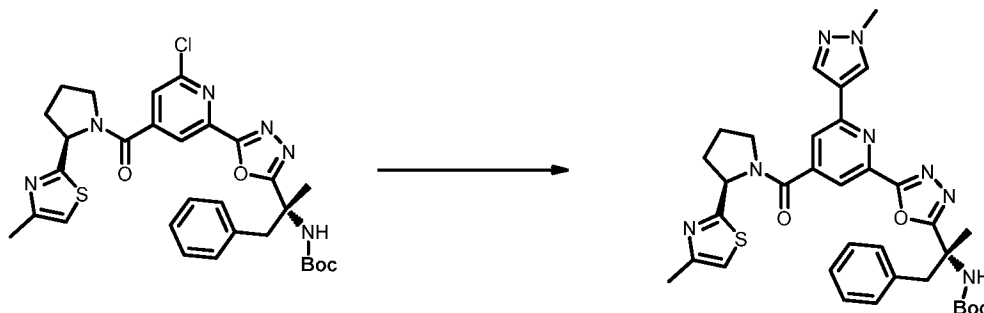
*Example 1.6.33*



**[0531] tert-butyl [(2R)-2-{5-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from tert-butyl {(2R)-2-[5-(6-chloro-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate in a similar manner to *Example 1.6.30* (116 mg, 28% yield) as a colorless oil (more polar). MS (ESI)  $m/z$ : 642  $[M+H]^+$

**[0532] tert-butyl [(2R)-2-{5-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from tert-butyl {(2R)-2-[5-(6-chloro-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate in a similar manner to *Example 1.6.30* (86 mg, 20% yield) as a colorless solid (less polar). MS (ESI)  $m/z$ : 642  $[M+H]^+$ .

*Example 1.6.34*

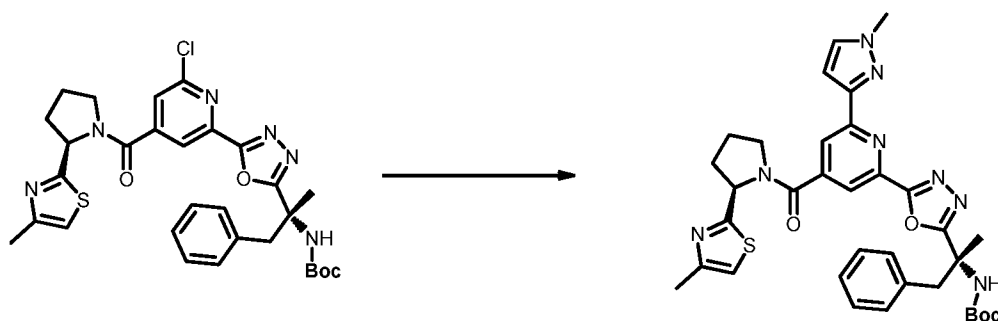


**[0533] tert-butyl [(2R)-2-{5-[6-(1-methyl-1H-pyrazol-4-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:**



**phenylpropan-2-yl]carbamate:** A suspension of tert-butyl {(2R)-2-[5-(6-chloro-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (300 mg, 0.49 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (307 mg, 1.6 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (113 mg, 0.25 mmol), SPhos (101 mg, 0.25 mmol) and K<sub>3</sub>PO<sub>4</sub> (314 mg, 1.5 mmol) in toluene (3.0 ml) were placed into a vessel for microwave reactions. The vessel was sealed and irradiated with microwave at 130 °C for 30 min. After cooling, H<sub>2</sub>O and brine were added and then the mixture was extracted with CHCl<sub>3</sub>. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The obtained residue was purified with column chromatography (NH-silica, EtOAc / hexane = 50:50 to 100:0) to give tert-butyl [(2R)-2-{5-[6-(1-methyl-1H-pyrazol-4-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (212 mg, 66% yield) as a yellow oil. MS (ESI) m/z: 655 [M+H]<sup>+</sup>

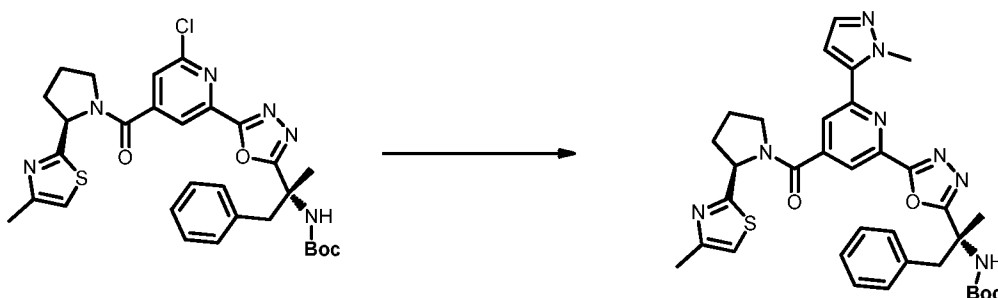
*Example 1.6.35*



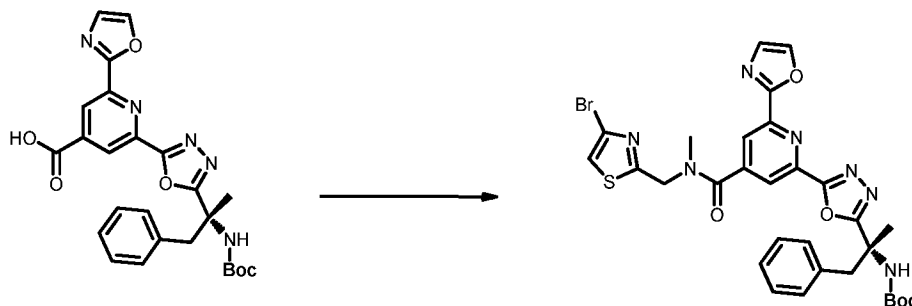
**[0534] tert-butyl [(2R)-2-{5-[6-(1-methyl-1H-pyrazol-3-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:**

The desired compound was synthesized from tert-butyl {(2R)-2-[5-(6-chloro-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate in a similar manner to *Example 1.6.34* (320 mg, 99% yield) as a yellow oil. MS (ESI) m/z: 655 [M+H]<sup>+</sup>.

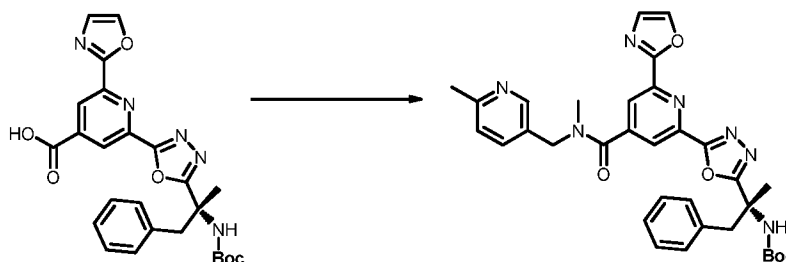
*Example 1.6.36*



[0535] **tert-butyl [(2R)-2-{5-[6-(1-methyl-1H-pyrazol-5-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from tert-butyl {(2R)-2-[5-(6-chloro-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate in a similar manner to *Example 1.6.34* (356 mg, 100% yield) as a yellow oil. MS (ESI)  $m/z$ : 655  $[M+H]^+$ .  
*Example 1.6.37*

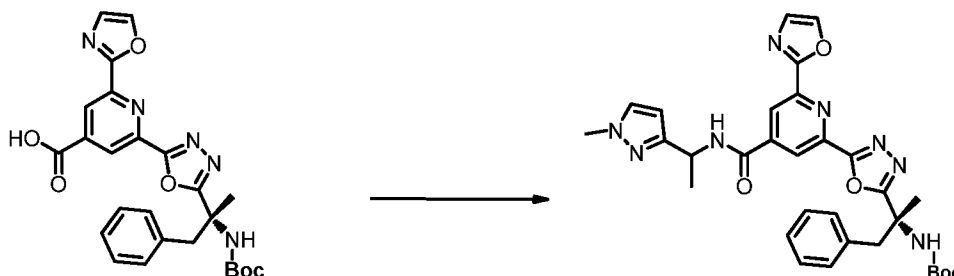


[0536] **tert-butyl [(2R)-2-{5-[4-[(4-bromo-1,3-thiazol-2-yl)methyl](methyl)carbamoyl]-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** To a stirred solution of 2-(5-{(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid (160 mg, 0.33 mmol), *i*-Pr<sub>2</sub>NEt (0.061 ml, 0.36 mmol) and 1-(4-bromo-1,3-thiazol-2-yl)-*N*-methylmethanamine (74 mg, 0.36 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4.8 ml) was added HATU (136 mg, 0.36 mmol) at rt and the mixture was stirred at the same temperature for 2 hours. The mixture was quenched with H<sub>2</sub>O and was extracted with CHCl<sub>3</sub>. The organic layer was washed with brine, dried over MgSO<sub>4</sub> and evaporated to give a crude, which was purified with column chromatography (EtOAc/hexane = 10:90 to 80:20) to give tert-butyl [(2R)-2-{5-[4-[(4-bromo-1,3-thiazol-2-yl)methyl](methyl)carbamoyl]-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate (204 mg, 92% yield) as a colorless oil. MS (ESI)  $m/z$ : 680, 682  $[M+H]^+$ .  
*Example 1.6.38*



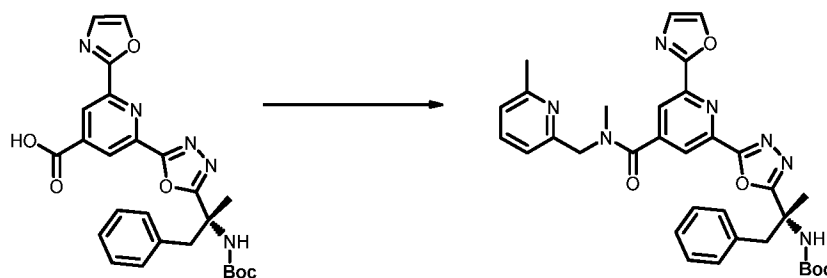
[0537] **tert-butyl [(2R)-2-{5-[4-{methyl[(6-methylpyridin-3-yl)methyl]carbamoyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 2-(5-{(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid in a similar manner to *Example 1.6.37* (86 mg, 69% yield) as a colorless oil. MS (ESI)  $m/z$ : 610  $[M+H]^+$ .

*Example 1.6.39*



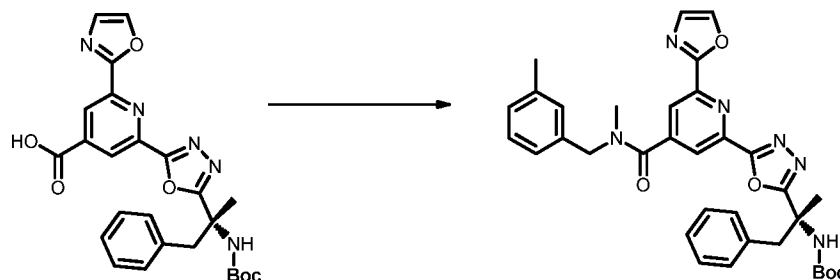
[0538] **tert-butyl [(2R)-2-{5-[4-{[1-(1-methyl-1H-pyrazol-3-yl)ethyl]carbamoyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 2-(5-{(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid and 1-(1-methyl-1H-pyrazol-3-yl) ethanamine in a similar manner to *Example 1.6.37* (80 mg, 82% yield) as a white powder. MS (ESI)  $m/z$ : 599  $[M+H]^+$

*Example 1.6.40*



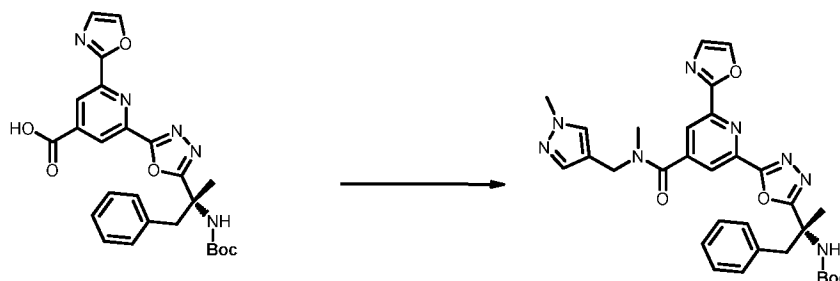
[0539] **tert-butyl [(2R)-2-{5-[4-{methyl[(6-methylpyridin-2-yl)methyl]carbamoyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 2-(5-{(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid in a similar manner to *Example 1.6.37* (90 mg, 73% yield) as a colorless oil. MS (ESI)  $m/z$ : 610  $[M+H]^+$ .

## Example 1.6.41



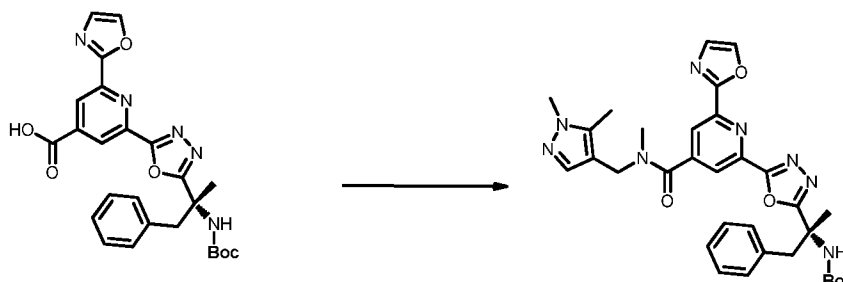
[0540] **tert-butyl [(2R)-2-(5-{4-[methyl(3-methylbenzyl)carbamoyl]-6-(1,3-oxazol-2-yl)pyridin-2-yl}-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 2-(5-{(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid in a similar manner to *Example 1.6.37* (90 mg, 91% yield) as a colorless oil. MS (ESI)  $m/z$ : 609  $[M+H]^+$ .

## Example 1.6.42



[0541] **tert-butyl [(2R)-2-{5-[4-{methyl[(1-methyl-1H-pyrazol-4-yl)methyl]carbamoyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 2-(5-{(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid in a similar manner to *Example 1.6.37* (114 mg, 94% yield) as a yellow oil.

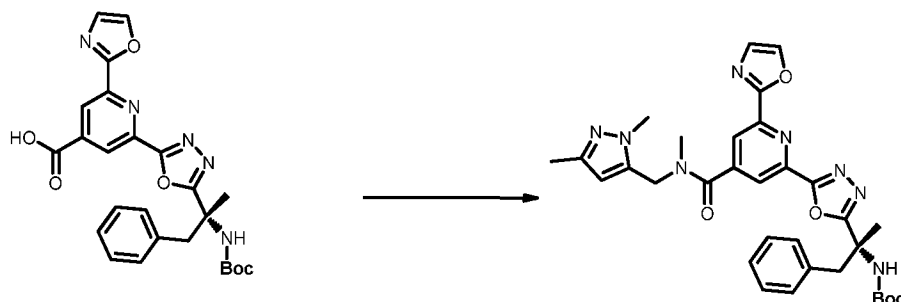
## Example 1.6.43



[0542] **tert-butyl [(2R)-2-{5-[4-{[(1,5-dimethyl-1H-pyrazol-4-yl)methyl](methyl)carbamoyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 2-(5-{(2R)-2-

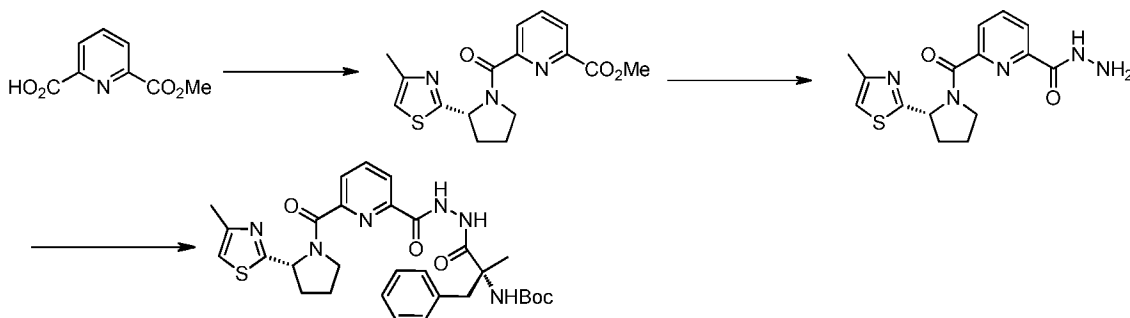
[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid in a similar manner to *Example 1.6.37* (110 mg, 88% yield) as a pale yellow oil.

*Example 1.6.44*



**[0543] tert-butyl [(2R)-2-{5-[4-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl](methyl)carbamoyl]-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 2-(5-{(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid in a similar manner to *Example 1.6.37* (118 mg, 95% yield) as a yellow oil. MS (ESI)  $m/z$ : 655  $[M+H]^+$ .

*Example 1.6.45*



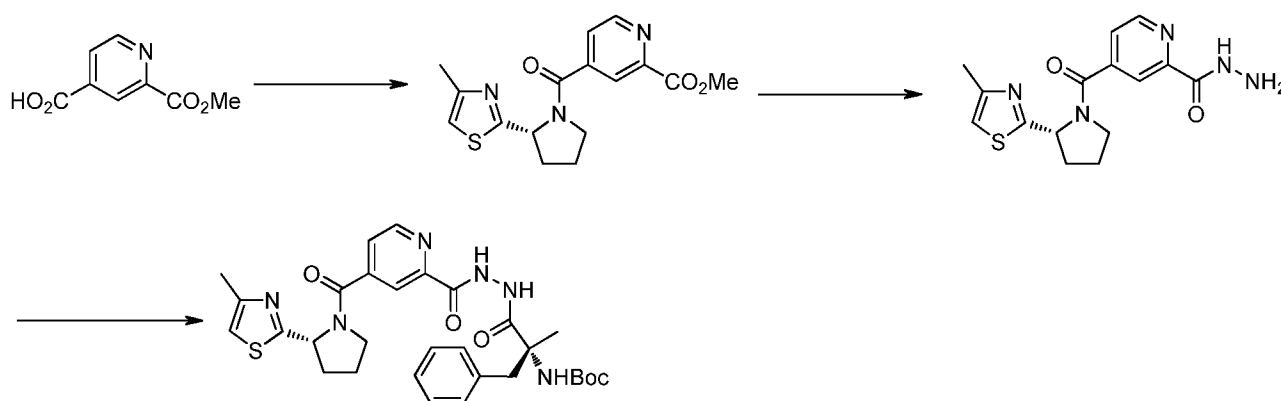
**[0544] methyl 6-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate:** The desired compound was synthesized from 6-(methoxycarbonyl)pyridine-2-carboxylic acid (237 mg, 1.31 mmol) in a similar manner to *Example 1.6.13*. (325 mg, 83% yield) MS (ESI)  $M/Z$ : 332  $[M+H]^+$ .

**[0545] 6-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carbohydrazide:** The desired compound was synthesized from methyl 6-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate (322 mg, 0.973 mmol) in a similar manner to *Example 1.6.13*. (322 mg, 100% yield) MS (ESI)  $M/Z$ : 332  $[M+H]^+$ .

**[0546] tert-butyl [(2R)-2-methyl-1-{2-[(6-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)carbonyl]hydrazino}-1-oxo-3-phenylpropan-2-**

**yl]carbamate:** To a solution of N-(tert-butoxycarbonyl)- $\alpha$ -methyl-D-phenylalanine (183 mg, 0.656 mmol) in dichloromethane (5 mL) were added HATU (272 mg, 0.716 mmol) and diisopropylethylamine (0.13 mL, 0.72 mmol). After stirring for 30 minutes at room temperature, (198 mg, 0.597 mmol) was added. After stirring for 6 hours at room temperature, the reaction mixture was diluted with ethyl acetate and washed consecutively with 0.2 M HCl-brine (1:1), sat. aq. NaHCO<sub>3</sub>-brine-H<sub>2</sub>O(1:1:1), brine. The organic layer was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give tert-butyl [(2R)-2-methyl-1-{2-[(6-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)carbonyl]hydrazino}-1-oxo-3-phenylpropan-2-yl]carbamate as a colorless amorphous. (324 mg, 92% yield) MS (ESI) M/Z: 593 [M+H]<sup>+</sup>.

*Example 1.6.46*

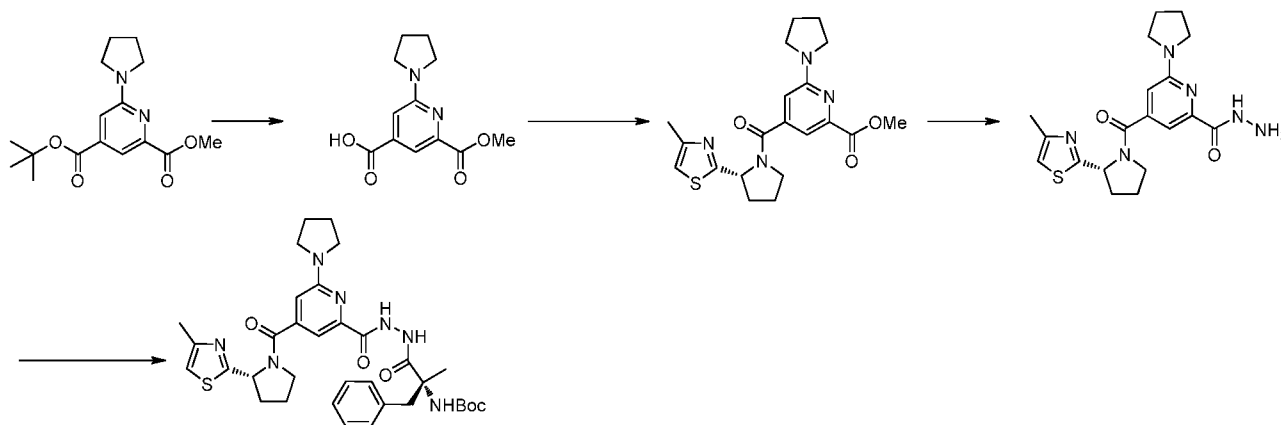


**[0547] methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate:** The desired compound was synthesized from methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate [public] (200 mg, 1.19 mmol) in a similar manner to *Example 1.6.13*. (362 mg, 92% yield) MS (ESI) M/Z: 332 [M+H]<sup>+</sup>.

**[0548] 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carbohydrazide:** The desired compound was synthesized from methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carboxylate (359 mg, 1.08 mmol) in a similar manner to *Example 1.6.13*. (244 mg, 68% yield) MS (ESI) M/Z: 332 [M+H]<sup>+</sup>.

**[0549] tert-butyl [(2R)-2-methyl-1-{2-[(4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)carbonyl]hydrazino}-1-oxo-3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridine-2-carbohydrazide (220 mg, 0.664 mmol) in a similar manner to *Example 1.6.45*. (378 mg, 96% yield) MS (ESI) M/Z: 593 [M+H]<sup>+</sup>.

## Example 1.6.47

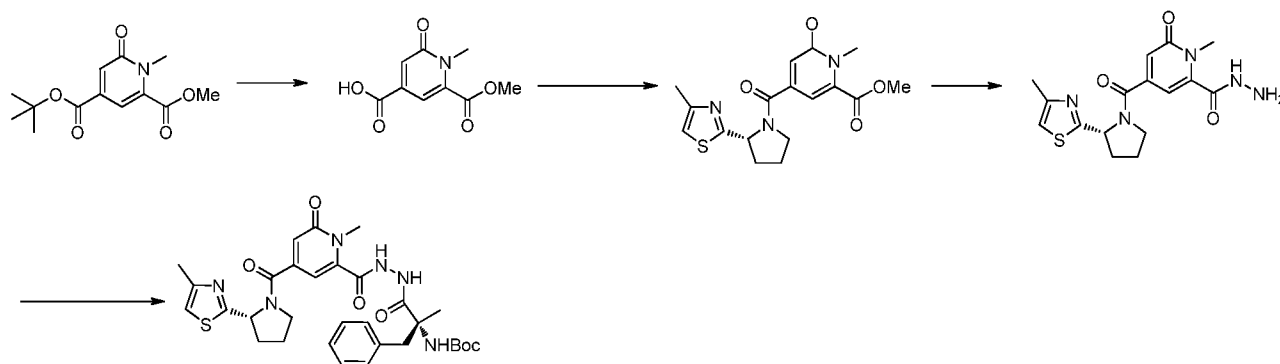


**[0550] 2-(methoxycarbonyl)-6-(pyrrolidin-1-yl)isonicotinic acid:** The desired compound was synthesized from 4-tert-butyl 2-methyl 6-(pyrrolidin-1-yl)pyridine-2,4-dicarboxylate (63 mg, 0.21 mmol) in a similar manner to *Example 1.6.13*. (51 mg, 100% yield) MS (APCI/ESI) M/Z: 251 [M+H]<sup>+</sup>.

**[0551] methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(pyrrolidin-1-yl)pyridine-2-carboxylate:** The desired compound was synthesized from 2-(methoxycarbonyl)-6-(pyrrolidin-1-yl)isonicotinic acid (51 mg, 0.206 mmol) in a similar manner to *Example 1.6.13*. (62mg, 75% yield) MS (APCI/ESI) M/Z: 401 [M+H]<sup>+</sup>.

**[0552] 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(pyrrolidin-1-yl)pyridine-2-carbohydrazide:** The desired compound was synthesized from methyl 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(pyrrolidin-1-yl)pyridine-2-carboxylate (62 mg, 0.155 mmol) in a similar manner to *Example 1.6.13*. (62mg, 100% yield) MS (APCI/ESI) M/Z: 401 [M+H]<sup>+</sup>.

**[0553] tert-butyl [(2R)-2-methyl-1-(2-{4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(pyrrolidin-1-yl)pyridin-2-yl]carbonyl}hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(pyrrolidin-1-yl)pyridine-2-carbohydrazide in a similar manner to *Example 1.6.45*. (99 mg, 100% yield) MS (APCI/ESI) M/Z: 662 [M+H]<sup>+</sup>.

*Example 1.6.48***[0554] 6-(methoxycarbonyl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid:**

The desired compound was synthesized from 4-tert-butyl 2-methyl 1-methyl-6-oxo-1,6-dihydropyridine-2,4-dicarboxylate (146 mg, 0.546 mmol) in a similar manner to *Example 1.6.13*. (115 mg, 100% yield)

**[0555] methyl 1-methyl-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl-6-oxo-1,6-dihydropyridine-2-carboxylate:**

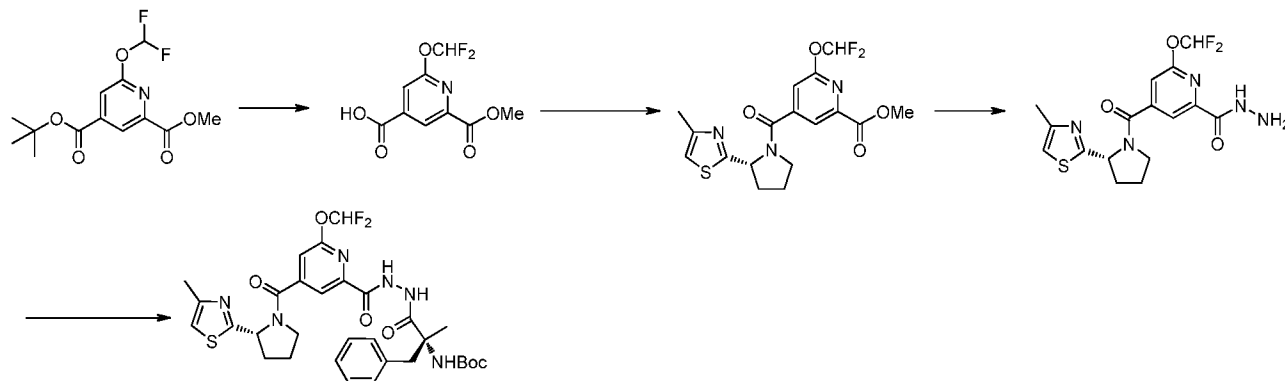
The desired compound was synthesized from 6-(methoxycarbonyl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid (115 mg, 0.546 mmol) in a similar manner to *Example 1.6.13*. (166 mg, 84% yield) MS (ESI) M/Z: 362 [M+H]<sup>+</sup>.

**[0556] 1-methyl-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl-6-oxo-1,6-dihydropyridine-2-carbohydrazide:** The desired compound was synthesized from methyl 1-methyl-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl-6-oxo-1,6-dihydropyridine-2-carboxylate (148 mg, 0.409 mmol) in a similar manner to *Example 1.6.13*. (148 mg, 100% yield) MS (ESI) M/Z: 362 [M+H]<sup>+</sup>.

**[0557] tert-butyl [(2R)-2-methyl-1-{2-[(1-methyl-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl]carbonyl}hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 1-methyl-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl-6-oxo-1,6-dihydropyridine-2-carbohydrazide (164 mg, 0.464 mmol) in a similar manner to *Example 1.6.45*. (237 mg, 84% yield) MS (ESI) M/Z: 623 [M+H]<sup>+</sup>



## Example 1.6.49



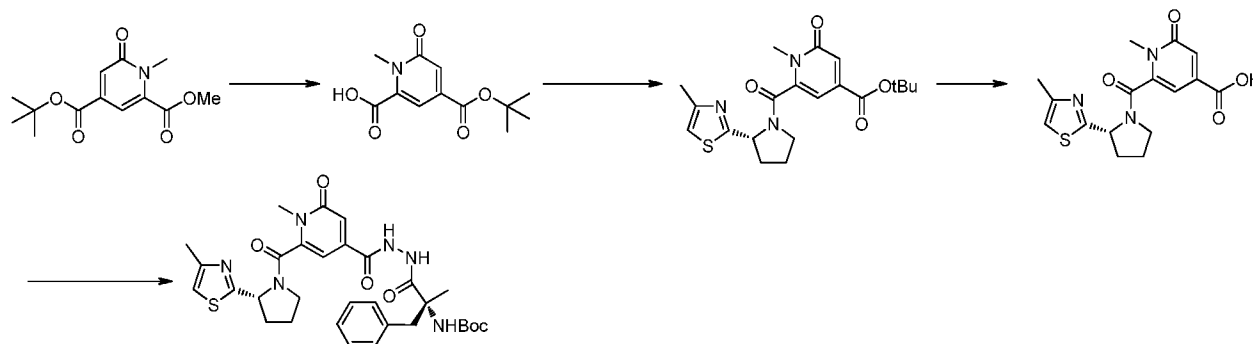
**[0558] 2-(difluoromethoxy)-6-(methoxycarbonyl)isonicotinic acid:** The desired compound was synthesized from 4-tert-butyl 2-methyl 6-(difluoromethoxy)pyridine-2,4-dicarboxylate (313 mg, 1.03 mmol) in a similar manner to *Example 1.6.13*. (255 mg, 100% yield) MS (ESI) M/Z: 248 [M+H]<sup>+</sup>.

**[0559] methyl 6-(difluoromethoxy)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonylpyridine-2-carboxylate:** The desired compound was synthesized from 2-(difluoromethoxy)-6-(methoxycarbonyl)isonicotinic acid (255 mg, 1.03 mmol) in a similar manner to *Example 1.6.13*. (385 mg, 94% yield) MS (ESI) M/Z: 398 [M+H]<sup>+</sup>.

**[0560] 6-(difluoromethoxy)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonylpyridine-2-carbohydrazide:** The desired compound was synthesized from 6-(difluoromethoxy)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonylpyridine-2-carboxylate (385 mg, 0.969 mmol) in a similar manner to *Example 1.6.13*. (385 mg, 100% yield) MS (ESI) M/Z: 398 [M+H]<sup>+</sup>.

**[0561] tert-butyl [(2R)-1-(2-[[6-(difluoromethoxy)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl]carbonyl]hydrazino)-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 6-(difluoromethoxy)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonylpyridine-2-carbohydrazide (383 mg, 0.964 mmol) in a similar manner to *Example 1.6.45*. (634 mg, 100% yield) MS (ESI) M/Z: 659 [M+H]<sup>+</sup>.

## Example 1.6.50

**[0562] 4-(tert-butoxycarbonyl)-1-methyl-6-oxo-1,6-dihydropyridine-2-carboxylic acid:**

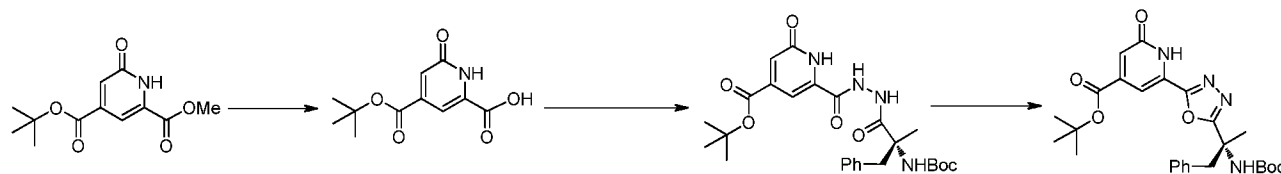
To a solution of 4-tert-butyl 2-methyl 1-methyl-6-oxo-1,6-dihydropyridine-2,4-dicarboxylate (217 mg, 0.812 mmol) in methanol (10 mL) was added 1 M aq. NaOH (1.1 mL, 1.1 mmol). After stirring for 1 hour, 1M HCl was added and brought to pH 5. The precipitate which formed was filtered off, washed with water, and dried in vacuo to give 4-(tert-butoxycarbonyl)-1-methyl-6-oxo-1,6-dihydropyridine-2-carboxylic acid as a colorless solid. (149 mg, 73% yield) MS (ESI) M/Z: 254 [M+H]<sup>+</sup>.

**[0563] 1-methyl-6-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-2-oxo-1,2-dihydropyridine-4-carboxylate:** To a solution of 4-(tert-butoxycarbonyl)-1-methyl-6-oxo-1,6-dihydropyridine-2-carboxylic acid (143 mg, 0.565 mmol) in dichloromethane (5 mL) were added HOBt (76 mg, 0.565 mmol) and EDCI.HCl (141 mg, 0.734 mmol). After stirring for 30 minutes, 4-methyl-2-[(2R)-pyrrolidin-2-yl]-1,3-thiazole (105 mg, 0.621 mmol) was added. After stirring for 5 hours, the reaction mixture was concentrated in vacuo and the residue was purified with silica-gel column chromatography (CHCl<sub>3</sub>/MeOH =99:1 to 95:5) to give tert-butyl 1-methyl-6-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-2-oxo-1,2-dihydropyridine-4-carboxylate as a colorless oil. (228 mg, 100% yield) MS (ESI) M/Z: 404 [M+H]<sup>+</sup>.

**[0564] 1-methyl-6-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-2-oxo-1,2-dihydropyridine-4-carboxylic acid:** To a solution of 1-methyl-6-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-2-oxo-1,2-dihydropyridine-4-carboxylate (228 mg, 0.565 mmol) in dichloromethane (0.5 mL) was added TFA (2 mL). The mixture was stirred for 2 hours and concentrated in vacuo to give 1-methyl-6-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-2-oxo-1,2-dihydropyridine-4-carboxylic acid as a colorless amorphous (196 mg, quant.) MS (ESI) M/Z: 348 [M+H]<sup>+</sup>.

**[0565] tert-butyl [(2R)-2-methyl-1-{2-[(1-methyl-6-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2-oxo-1,2-dihydropyridin-4-yl)carbonyl]hydrazino}-1-oxo-3-phenylpropan-2-yl]carbamate:** To a solution of 1-methyl-6-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2-oxo-1,2-dihydropyridine-4-carboxylic acid (196 mmol, 0.565 mmol) in dichloromethane (5 mL) were added HOBt (76 mg, 0.565 mmol) and EDCI.HCl (130 mg, 0.678 mmol). After stirring for 30 minutes, tert-butyl [(2R)-1-hydrazino-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (182 mmol, 0.621 mmol) was added. After stirring for 6 hours the reaction mixture was diluted with EtOAc and washed consecutively with 0.2 M HCl-brine (1:1), sat. aq. NaHCO<sub>3</sub>-brine-H<sub>2</sub>O(1:1:1), brine to give crude tert-butyl [(2R)-2-methyl-1-{2-[(1-methyl-6-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2-oxo-1,2-dihydropyridin-4-yl)carbonyl]hydrazino}-1-oxo-3-phenylpropan-2-yl]carbamate as a colorless amorphous. (212 mg, 60% yield) MS (ESI) M/Z: 623 [M+H]<sup>+</sup>.

*Example 1.6.51*



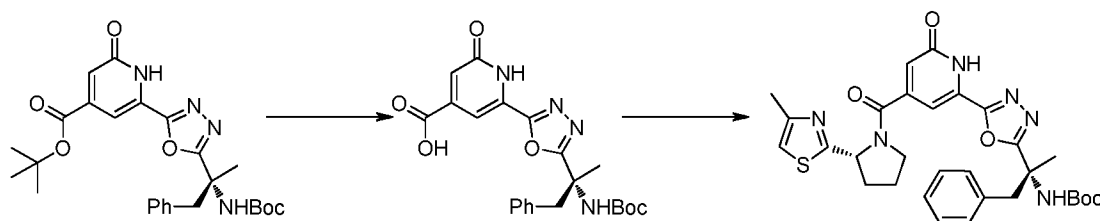
**[0566] 4-(tert-butoxycarbonyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid:** To a solution of 4-tert-butyl 2-methyl 6-oxo-1,6-dihydropyridine-2,4-dicarboxylate (320 mg, 1.26 mmol) in methanol (3 mL) was added 1M aq. NaOH (3.2 mL, 3.2 mmol). After stirring for 14 hours, 1M aq. HCl was added. The precipitate which formed was filtered off, washed with water, and dried in vacuo to give 4-(tert-butoxycarbonyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid as a colorless solid. (243 mg, 80% yield) MS (ESI) M/Z: 240 [M+H]<sup>+</sup>

**[0567] tert-butyl 6-[(2-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl}hydrazino)carbonyl]-2-oxo-1,2-dihydropyridine-4-carboxylate:** To a stirred solution of 4-(tert-butoxycarbonyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid (241 mg, 1.01 mmol) were added HOBt (136 mg, 1.01 mmol) and EDCI.HCl (232 mg, 1.21 mmol) and stirred for 30 minutes. Tert-butyl [(2R)-1-hydrazino-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (325 mg, 1.11 mmol) was added and the reaction mixture was stirred for 16 hours. The mixtures was poured into H<sub>2</sub>O and extracted with chloroform and the organic layer was concentrated in vacuo. The residue was purified with silica-gel column chromatography (CHCl<sub>3</sub>/MeOH = 99.5:0.5 to 95:5) to give tert-butyl 6-[(2-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl}hydrazino)carbonyl]-2-oxo-1,2-

dihydropyridine-4-carboxylate as a colorless amorphous. (373 mg, 73% yield) MS (ESI) M/Z: 515 [M+H]<sup>+</sup>

**[0568] tert-butyl 6-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2-oxo-1,2-dihydropyridine-4-carboxylate:** To a stirred solution of tert-butyl 6-[(2-((2R)-2-[(tert-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl}hydrazino)carbonyl]-2-oxo-1,2-dihydropyridine-4-carboxylate were added triphenylphosphine (161 mg, 0.612 mmol), imidazole (42 mg, 0.61 mmol), and carbon tetrabromide (203 mg, 0.612 mmol). After stirred for 1.5 hours at room temperature the mixture was directly loaded and purified with silica-gel column chromatography (hexane/EtOAc = 98:2 to 50:50) to give tert-butyl 6-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2-oxo-1,2-dihydropyridine-4-carboxylate as a colorless amorphous. (93 mg, 92% yield) APCI/ESI: 497 [M+H]<sup>+</sup>.

*Example 1.6.52*

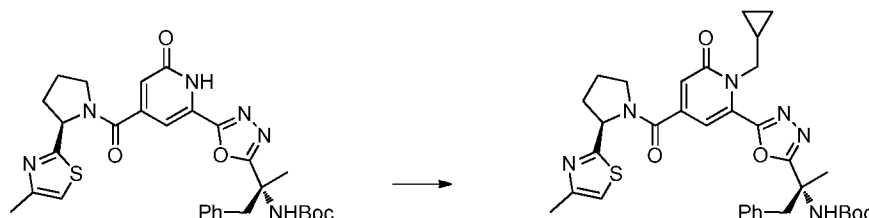


**[0569] 6-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2-oxo-1,2-dihydropyridine-4-carboxylic acid:** To a solution of tert-butyl 6-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2-oxo-1,2-dihydropyridine-4-carboxylate in MeOH (3 mL) were added H<sub>2</sub>O (1 mL) and potassium hydroxide (103 mg, 1.84 mmol). After stirred for 3 hours at 60 degC 1 M aq. HCl (2 mL) was added to the reaction mixture at 0 degC. The mixture was extracted with CHCl<sub>3</sub> and the organic layer was concentrated in vacuo to give 6-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2-oxo-1,2-dihydropyridine-4-carboxylic acid as a colorless solid. (73 mg, 99% yield) MS (ESI) M/Z: 441 [M+H]<sup>+</sup>.

**[0570] tert-butyl ((2R)-2-[5-(4-((2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl)carbonyl)-6-oxo-1,6-dihydropyridin-2-yl]-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl carbamate:** To a solution of 6-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2-oxo-1,2-dihydropyridine-4-carboxylic acid in dichloromethane (3 mL) were added HOBt and EDCI.HCl. After stirred for 30 minutes at room temperature 4-methyl-2-[(2R)-pyrrolidin-2-yl]-1,3-thiazole (30 mg, 0.18 mmol) was added. After stirred for

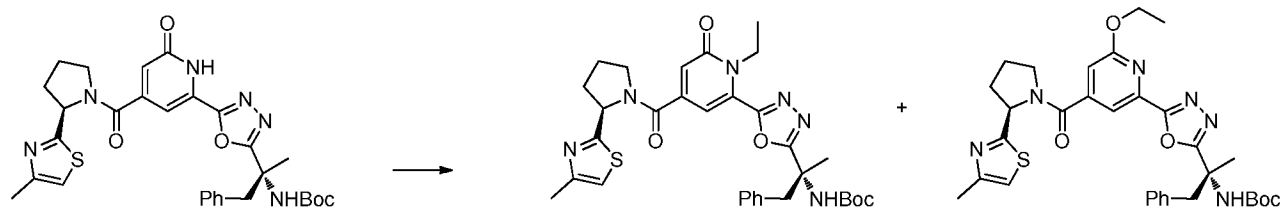
1 day, the mixtures was concentrated in vacuo and the residue was purified with silica-gel column chromatography ( $\text{CHCl}_3/\text{MeOH}$  99:1 to 90:10) to give tert-butyl {(2R)-2-[5-(4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate as a colorless solid. (72 mg, 76% yield) MS (ESI) M/Z: 591  $[\text{M}+\text{H}]^+$ .

*Example 1.6.53*



**[0571] tert-butyl [(2R)-2-{5-[1-(cyclopropylmethyl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** To a solution of tert-butyl {(2R)-2-[5-(4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (72 mg, 0.12 mmol) in MeCN (2 mL) was added cyclopropyl bromide (0.023 mL, 0.24 mmol), potassium carbonate (37 mg, 0.24 mmol), and tetra-n-butylammonium iodide (4.5 mmol, 0.012 mmol). After stirred for 7 hours at 60 degC the mixture was concentrated in vacuo and the residue was purified with silica-gel column chromatography ( $\text{CHCl}_3/\text{MeOH}$  = 99.5:0.5 to 90:10) to give tert-butyl [(2R)-2-{5-[1-(cyclopropylmethyl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate as a colorless amorphous. (29 mg, 37% yield) MS (APCI/ESI) M/Z: 645  $[\text{M}+\text{H}]^+$

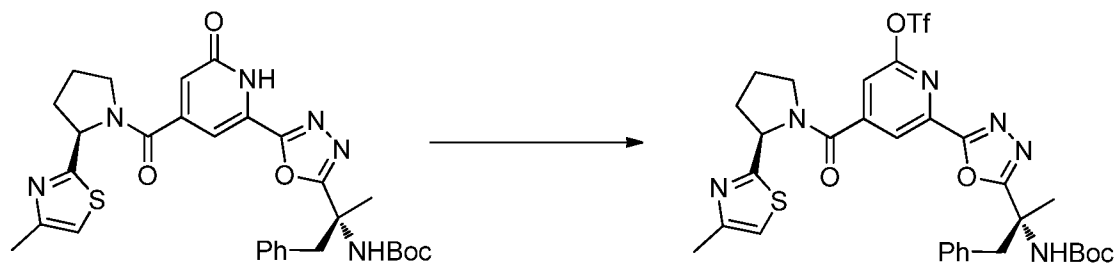
*Example 1.6.54*



**[0572] tert-butyl {(2R)-2-[5-(6-ethoxy-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate and tert-butyl {(2R)-2-[5-(1-ethyl-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from tert-butyl {(2R)-2-[5-(4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate.

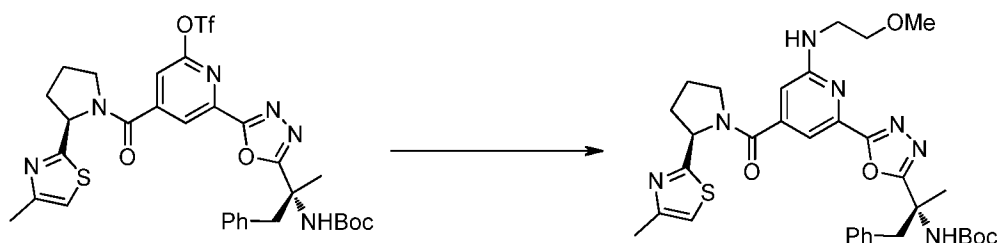
2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-oxo-1,6-dihydropyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate (150 mg, 0.254 mmol) in a similar manner to *Example 1.6.53*. (N-alkyl: 35 mg, 22% yield) MS (ESI) M/Z: 619 [M+H]<sup>+</sup>; (O-alkyl 107 mg, 68% yield) MS (ESI) M/Z: 619 [M+H]<sup>+</sup>

*Example 1.6.55*



**[0573] 6-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-(((2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl)carbonyl)pyridin-2-yl trifluoromethanesulfonate:** To a solution of tert-butyl {(2R)-2-[5-(4-((2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl)carbonyl}-6-oxo-1,6-dihydropyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate (100 mg, 0.169 mmol) in dichloromethane (2 mL) at 0 degC were added triflic anhydride (0.034 mL, 0.20 mmol) and diisopropylethylamine (0.041 mL, 0.20 mmol). After stirred at the same temperature for 1 hour, saturated aq. NaHCO<sub>3</sub> was added. The mixture was extracted with CHCl<sub>3</sub> and the organic layer was concentrated in vacuo to give crude 6-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-(((2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl)carbonyl)pyridin-2-yl trifluoromethanesulfonate. MS (ESI) M/Z: 723 [M+H]<sup>+</sup>.

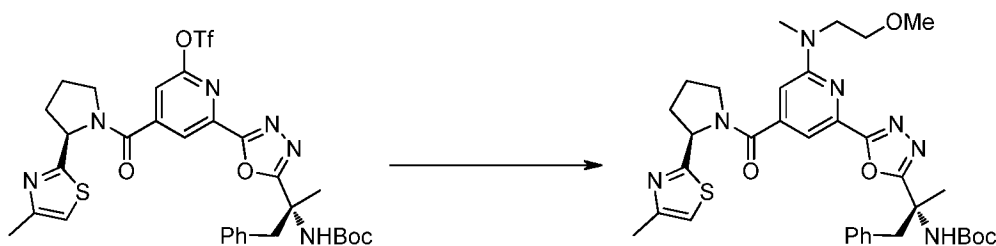
*Example 1.6.56*



**[0574] tert-butyl {(2R)-2-[5-(6-[(2-methoxyethyl)amino]-4-(((2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl)carbonyl)pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate:** To a solution of 6-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-(((2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl)carbonyl)pyridin-2-yl trifluoromethanesulfonate (60 mg,

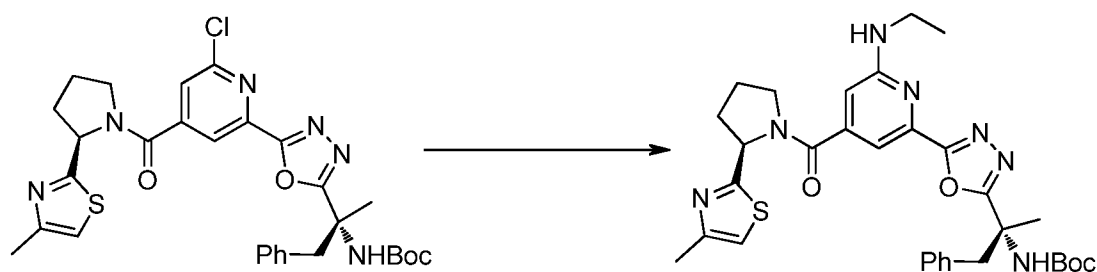
0.083 mmol) in acetonitrile (1 mL) was added 2-methoxyethylamine (0.036 mL, 0.42mmol). After stirred for 1 day, the mixture was poured into water and extracted with chloroform. The organic layer was concentrated in vacuo and the residue was purified with silica-gel chromatography (EtOAc) to give tert-butyl {(2R)-2-[5-(6-[(2-methoxyethyl)amino]-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate as a pale yellow amorphous (30 mg, 56% yield). MS (APCI/ESI) M/Z: 648 [M+H]<sup>+</sup>.

*Example 1.6.57*



**[0575] tert-butyl {(2R)-2-[5-(6-[(2-methoxyethyl)(methyl)amino]-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from 6-(5-{(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl trifluoromethanesulfonate (60 mg, 0.083 mmol) in a similar manner to *Example 1.6.56*. (52 mg, 95% yield) MS (APCI/ESI) M/Z: 662 [M+H]<sup>+</sup>.

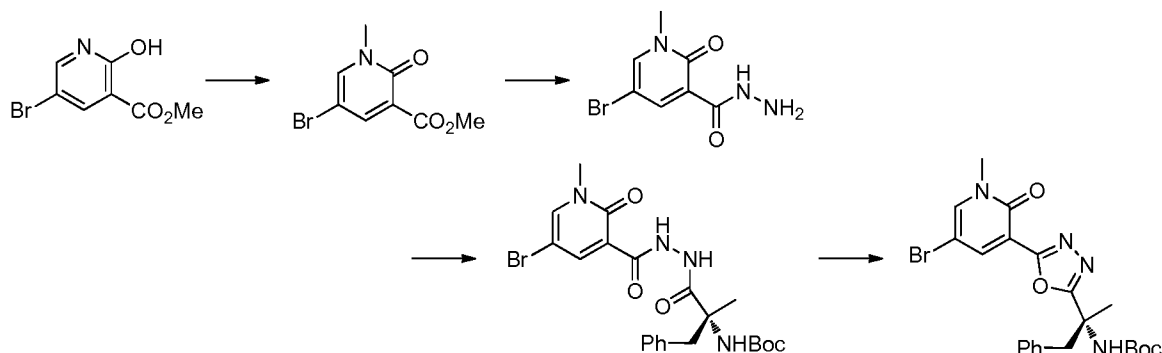
*Example 1.6.58*



**[0576] tert-butyl [(2R)-2-[5-[6-(ethylamino)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** To a solution of tert-butyl {(2R)-2-[5-(6-chloro-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (150 mg, 0.246mmol) was added ethylamine (80% yield in water; 0.1 mL, 1.2 mmol). After stirred for 4 hours under microwave irradiation at 130 degC in a sealed tube, the mixture was concentrated in vacuo and purified by silica-gel chromatography (CHCl<sub>3</sub>/MeOH

= 100:0 to 90:10) to give tert-butyl [(2R)-2-{5-[6-(ethylamino)-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate as a yellow amorphous (72 mg, 47%,). MS (APCI/ESI) M/Z: 618 [M+H]<sup>+</sup>.

*Example 1.6.59*



**[0577] methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate:** To a suspension of methyl 5-bromo-2-hydroxynicotinate (1.00 g, 4.31 mmol) in MeOH/DMF (10 + 10 mL) was added methyl iodide (0.81 mL, 13 mmol) and potassium carbonate (1.19 g, 8.62 mmol). After stirred for 14 hours at room temperature, the reaction mixture was diluted with ethyl acetate and the washed sequentially by H<sub>2</sub>O-brine (1:1), H<sub>2</sub>O-saturated aq. NaHCO<sub>3</sub> (1:1), brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified with silicagel chromatography (CHCl<sub>3</sub>/MeOH 100:0 to 90:10) to give methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate as a beige solid (745 mg, 70% yield). MS (ESI) M/Z: 246,248 [M+H]<sup>+</sup>.

**[0578] 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carbohydrazide:** To a stirred solution of methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (649 mg, 2.64 mmol) in methanol (6 mL) was added hydrazine monohydrate (198 mg, 3.96 mmol) at room temperature. The mixture was stirred for 3 hours at the same temperature and poured into water. The precipitate which formed was filtered off, washed with water, and dried in vacuo to give 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carbohydrazide (649 mg, quant.) as a beige solid. MS (ESI) M/Z: 246,248 [M+H]<sup>+</sup>.

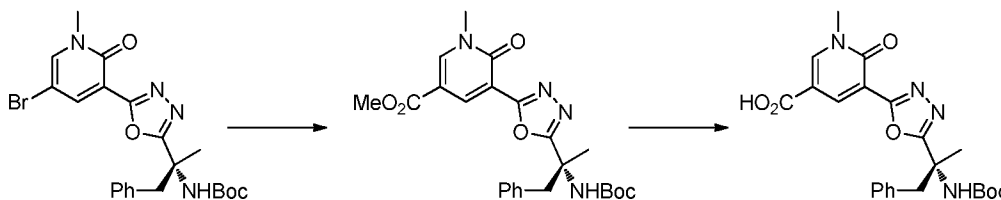
**[0579] tert-butyl [(2R)-1-{2-[(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbonyl]hydrazino}-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate:** To a solution of N-(tert-butoxycarbonyl)-alpha-methyl-D-phenylalanine (734 mg, 2.63 mmol) in dichloromethane (16 mL) was added diisopropylethylamine (0.59 mL, 3.4 mmol) and HATU (1.10 g, 2.89 mmol). The mixture was stirred for 30 minutes and 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carbohydrazide (647 mg, 2.63 mmol) were added. After stirred for 6



hours, the reaction mixture was diluted with ethyl acetate and the washed sequentially by H<sub>2</sub>O-brine (1:1), H<sub>2</sub>O-saturated aq. NaHCO<sub>3</sub> (1:1), brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, dried and concentrated in vacuo to give crude tert-butyl [(2R)-1-{2-[(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbonyl]hydrazino}-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (1.33 g, quant.). MS (ESI) M/Z: 507,509 [M+H]<sup>+</sup>.

**[0580] tert-butyl {(2R)-2-[5-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** To a stirred solution of tert-butyl [(2R)-1-{2-[(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)carbonyl]hydrazino}-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (1.33 g, 2.63 mmol) in dichloroethane (19 mL) was added Burgess reagent (1.88 g, 7.89 mmol) then stirred under microwave irradiation for 20 min at 120 degC. The crude product was directly purified by silica-gel column chromatography (hexane/EtOAc = 90:10 to 50:50) to give tert-butyl {(2R)-2-[5-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate as a beige amorphous (1.03 g, 80% yield). MS (ESI) M/Z: 489,491 [M+H]<sup>+</sup>.

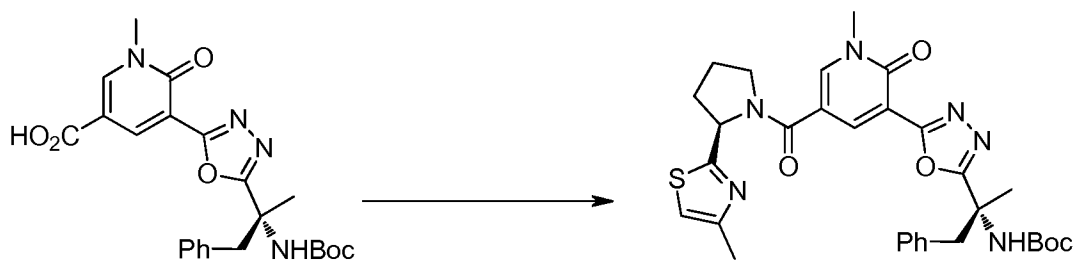
*Example 1.6.60*



**[0581] methyl 5-(5-[(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate:** To a stirred solution of tert-butyl {(2R)-2-[5-(5-bromo-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (589 mg, 1.20 mmol) in MeOH/DMSO were added palladium diacetate (135 mg, 0.602 mmol), 1,1'-Bis(diphenylphosphino)ferrocene (333 mg, 0.602 mmol), and triethylamine (0.50 mL, 3.6 mmol) at rt and the mixture was stirred at 80 degree for 8 hours under CO atmosphere. The mixture was cooled to rt and it was filtered through a pad of Celite. The filtrate was evaporated and the resulting solution was extracted three times with EtOAc. The combined organic layer was washed with H<sub>2</sub>O (x3) and brine, dried over MgSO<sub>4</sub> and evaporated to give a crude, which was purified with silica-gel column chromatography (CHCl<sub>3</sub>/MeOH = 99:1 to 80:20) to give methyl 5-(5-[(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate as beige amorphous (564 mg, 100% yield). MS (ESI) M/Z: 469 [M+H]<sup>+</sup>.

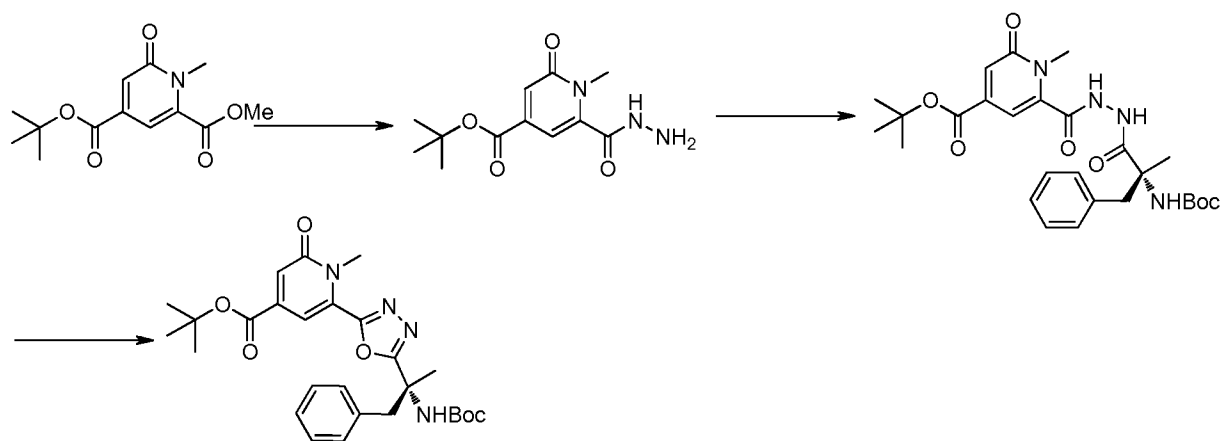
**[0582] 5-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid:** To a stirred solution of methyl 5-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (564 mg, 1.20 mmol) in MeOH/THF (3:1) was added 1 M aqueous NaOH at rt and the mixture was stirred at the same temperature for 5 hours. The mixture was acidified with 1M HCl aq. (1.57 ml) and concentrated in vacuo. The residue was suspended in CHCl<sub>3</sub>/MeOH (5:1) and the precipitate was filtered off. The filtered solution was concentrated in vacuo to give crude 5-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid as a beige amorphous (503 mg, 92% yield). MS (ESI) M/Z: 455 [M+H]<sup>+</sup>.

*Example 1.6.61*



**[0583] tert-butyl {(2R)-2-[5-(1-methyl-5-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl)-2-oxo-1,2-dihydropyridin-3-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from 5-(5-((2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (140 mg, 0.308 mmol) in a similar manner to *Example 1.6.37*. (175 mg, 94% yield).

*Example 1.6.62*

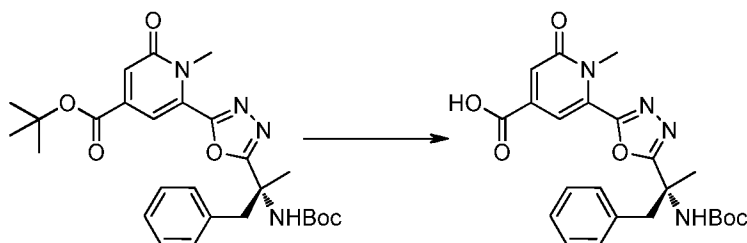


**[0584] tert-butyl 6-(hydrazinocarbonyl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylate:** The desired compound was synthesized from 4-tert-butyl 2-methyl 1-methyl-6-oxo-1,6-dihydropyridine-2,4-dicarboxylate (3.00 g, 11.2 mmol) in a similar manner to *Example 1.6.59*. (3.00 g, 100% yield) MS (ESI) M/Z: 268 [M+H]<sup>+</sup>.

**[0585] tert-butyl 6-[(2-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl}hydrazino)carbonyl]-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylate:** The desired compound was synthesized from tert-butyl 6-(hydrazinocarbonyl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylate (3.00 g, 11.2 mmol) in a similar manner to *Example 1.6.59*. (5.94 g, 100% yield).

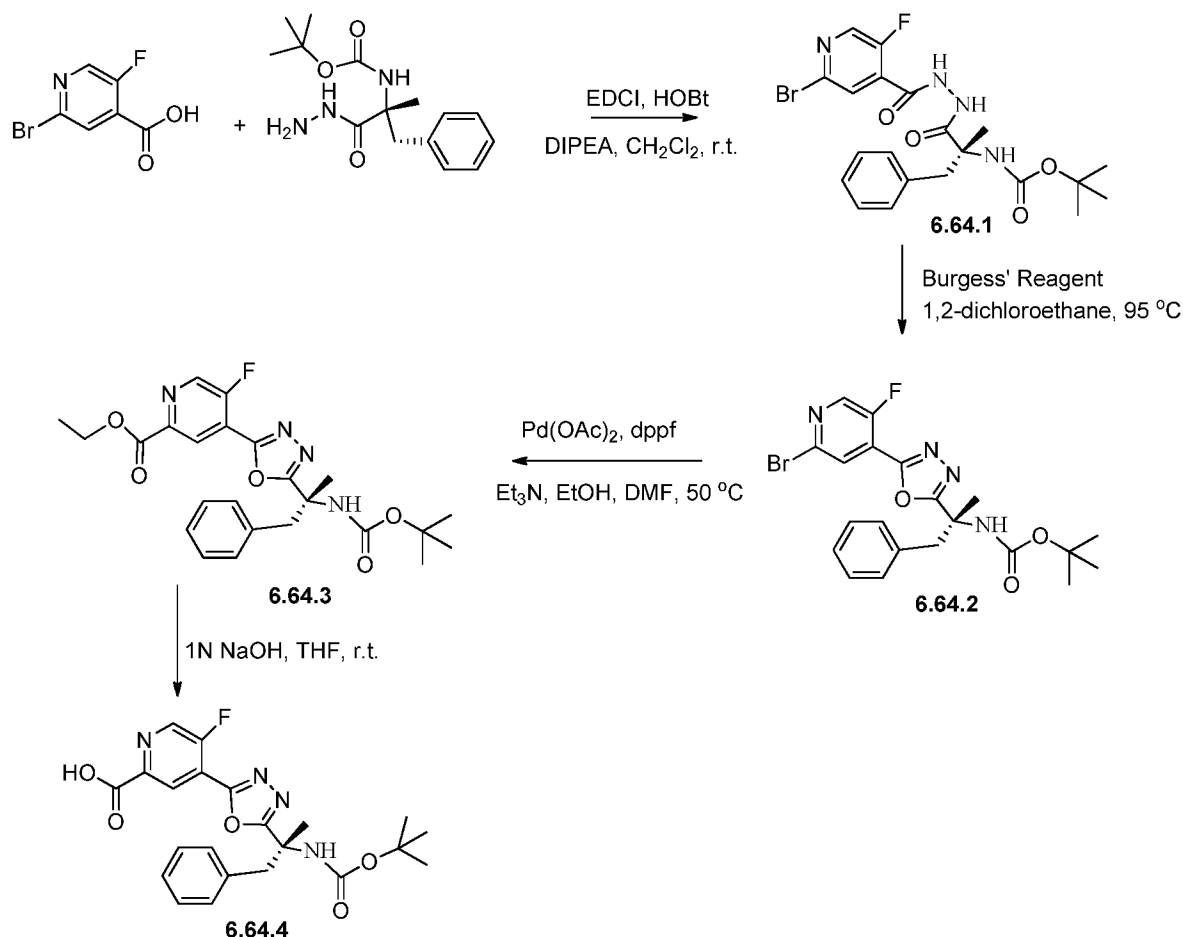
**[0586] tert-butyl 6-(5-[(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylate:** The desired compound was synthesized from tert-butyl 6-[(2-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-methyl-3-phenylpropanoyl}hydrazino)carbonyl]-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylate (5.94 g, 11.2 mmol) in a similar manner to *Example 1.6.A47* Ex A60. (5.39 g, 94% yield) MS (ESI) M/Z: 511 [M+H]<sup>+</sup>.

*Example 1.6.63*



**[0587] 6-(5-[(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid:** The desired compound was synthesized from tert-butyl 6-(5-[(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylate (5.39 g, 10.6 mmol) in a similar manner to *Example 1.6.52*. (4.80 g, quant.) MS (ESI) M/Z: 455 [M+H]<sup>+</sup>.

## Example 1.6.64



**[0588] (R)-4-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-fluoropicolinic acid:** To a stirring mixture of 0.9672g (4.4 mmol) of 2-bromo-5-fluoroisonicotinic acid, 0.9458g (4.93 mmol) of EDCI, and 0.6748 g (4.994 mmol) of HOBT in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> at r.t. was added 1.2988g (4.43 mmol) of (R)-tert-butyl (1-hydrazinyl-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate and 3.0 mL of DIPEA . After the mixture was stirred at r.t. for 15 h, H<sub>2</sub>O was added, and the aqueous layer was extracted with CHCl<sub>3</sub>. The combined extracts were washed with water 2x and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification by flash silica gel chromatography ((50-60)% EtOAc/hexanes) provided 0.9211g of (R)-tert-butyl-(1-(2-(2-bromo-5-fluoroisonicotinoyl)hydrazinyl)-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate (**6.64.1**)

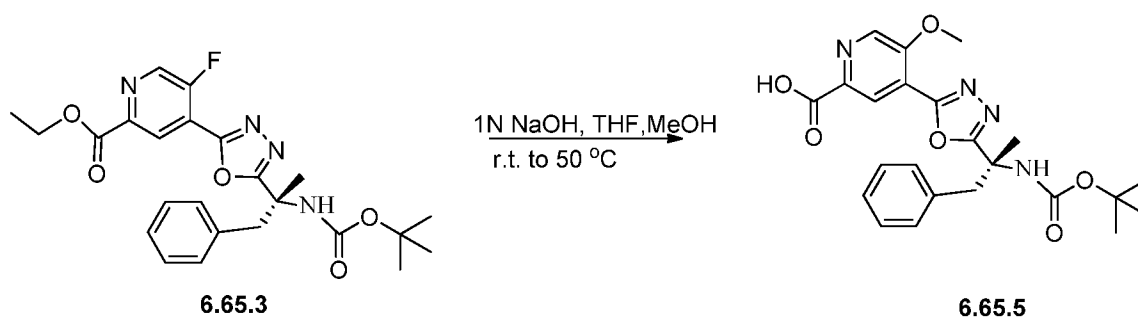
**[0589]** A solution of 0.9211 g of (R)-tert-butyl-(1-(2-(2-bromo-5-fluoroisonicotinoyl)hydrazinyl)-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate and 1.1806 g (4.95 mmol) of Burgess reagent in 10 mL of CH<sub>2</sub>ClCH<sub>2</sub>Cl was stirred at 95 °C under Ar for 25 min. Sat. NaHCO<sub>3</sub> (25 mL) and CHCl<sub>3</sub> were added, and the layers separated. The

aqueous layer was extracted with  $\text{CHCl}_3$ . The combined extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and conc. Purification by flash silica gel chromatography ((40-50)% EtOAc/hexanes) provided 0.8006 g of (R)-tert-butyl (2-(5-(2-bromo-5-fluoropyridin-4-yl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate (**6.64.2**).

**[0590]** To a degassed solution of 0.8006 g (1.677 mmol) of (R)-tert-butyl (2-(5-(2-bromo-5-fluoropyridin-4-yl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate and 0.1 mL (0.7174 mmol) of  $\text{Et}_3\text{N}$  in 4 mL of DMF and 4 mL of EtOH (solution degassed by bubbling in Ar and evacuation and backfilling 3x) was added 0.1877 g (0.3385 mmol) of dppf and 0.1892 g (0.8427 mmol) of  $\text{Pd}(\text{OAc})_2$  (evacuated and backfilled flask with Ar after each addition, 3x). The flask was evacuated and backfilled solution with CO once. The mixture stir was stirred under CO at 50 °C for ~ 3 h. Water (5 mL) and EtOAc were added, and the layers were separated. The org. layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification by flash silica gel chromatography (20% EtOAc/hexanes) provided 94 mg of (R)-ethyl 4-(5-(2-((tert-butoxycarbonyl)amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-fluoropicolinate (**6.64.3**).

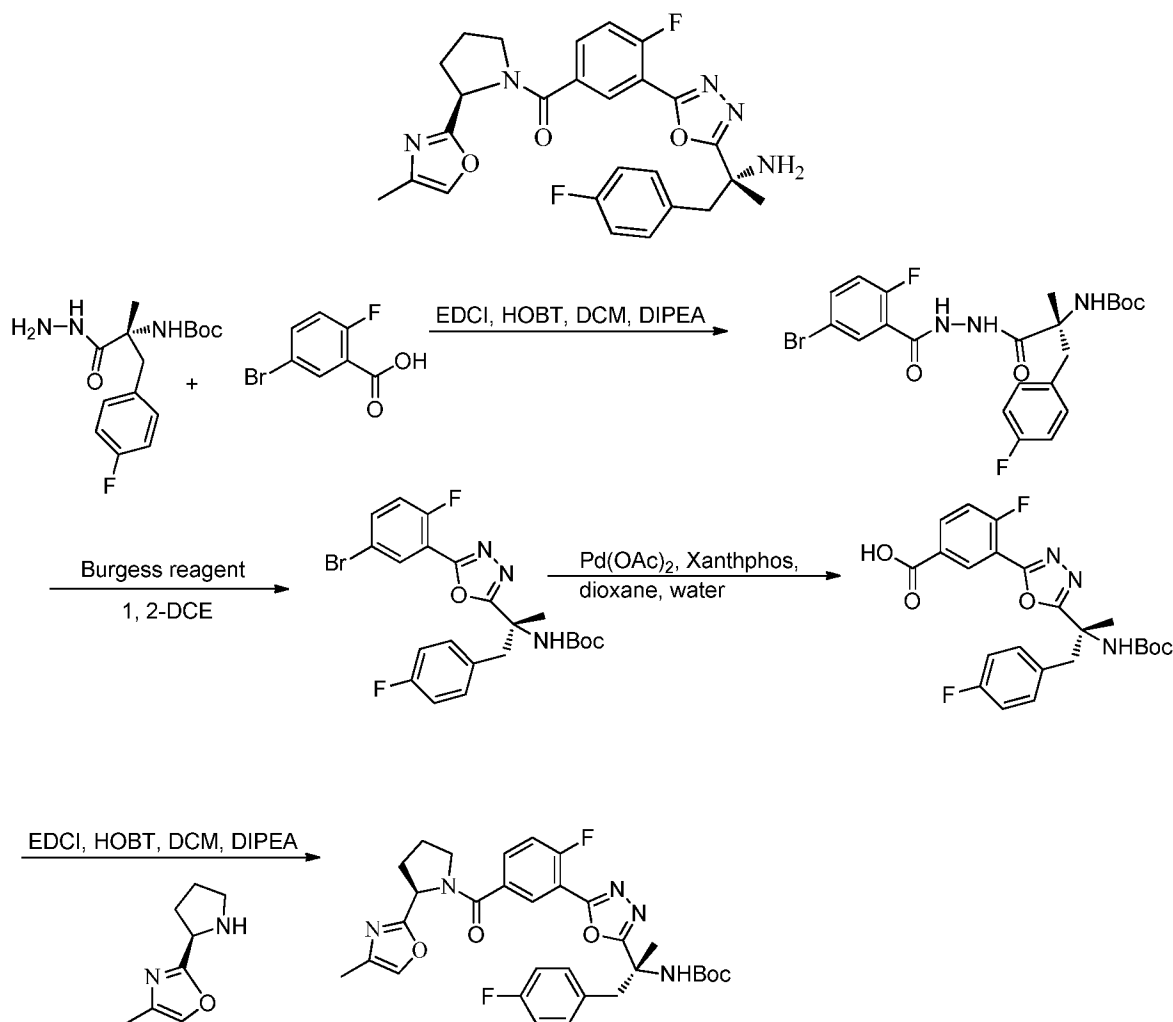
**[0591]** To a stirring solution of 112.7 mg of (R)-ethyl 4-(5-(2-((tert-butoxycarbonyl)amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-fluoropicolinate in 5 mL of THF was added 1.5 mL of 1 N NaOH. The solution was stirred at r.t. for 19.5 h. Water and  $\text{CH}_2\text{Cl}_2$  were added, and the layers partly separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . Partially sep. aqueous layer and added more  $\text{H}_2\text{O}$  and  $\text{CH}_2\text{Cl}_2$ ; separated layers. The org. layer was washed with  $\text{H}_2\text{O}$ ; 1N HCl and sat.  $\text{NaHCO}_3$  were added to pH= 2. The aqueous layer was extracted with the extract of 10%MeOH/10% $\text{H}_2\text{O}$ /80% $\text{CHCl}_3$  2x, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and conc. to provide (R)-4-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-fluoropicolinic acid (**6.64.4**).

*Example 1.6.65*



**[0592] (R)-4-(5-(2-(((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methoxypicolinic acid:** To a stirring solution of 94 mg of (R)-ethyl 4-(5-(2-(((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-fluoropicolinate in 2 mL of THF and 1 mL of MeOH was added 0.5 mL of 1 N NaOH. After 18 h, 1.0 mL of 1N NaOH was added. (Solution warmed for ~ 1h). The solution was stirred at 50 °C for 45 min. Water and CH<sub>2</sub>Cl<sub>2</sub> were added, and the layers separated but not completely. More H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub> were added, and the layers separated. The org. layer was washed with H<sub>2</sub>O. 1N HCl was added to pH= 2. The aqueous layer was extracted with the extract of 10%MeOH/10%H<sub>2</sub>O/80%CHCl<sub>3</sub> 3x. The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and conc. to provide (R)-4-(5-(2-(((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methoxypicolinic acid (**6.65.5**).

*Example 1.6.66*



**[0593]** To a solution containing the acid, 5-bromo-2-fluorobenzoic acid (391 mg, 1.784 mmol) in DCM (3 ml), HOBT (328 mg, 2.141 mmol) and EDC (479 mg, 2.498 mmol) were

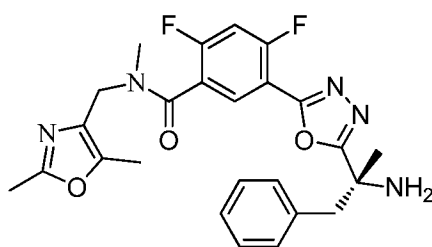
added and the reaction mixture was stirred for 1h at rt. After 1h, reaction mixture was cooled to 0°C, and (R)-tert-butyl (3-(4-fluorophenyl)-1-hydrazinyl-2-methyl-1-oxopropan-2-yl)carbamate (500 mg, 1.606 mmol) was added in DCM (1 mL) along with DIPEA (0.935 mL, 5.35 mmol). The reaction mixture color was dark brown. After stirring overnight at rt, DCM was removed in vacuum. Then reaction mixture was diluted with ethyl acetate, and saturated aq sodium bicarbonate solution was added. After stirring for 10 mins at rt, aqueous layer was extracted with ethyl acetate (2X10 mL). Combined organic layers were washed with water, brine and dried. Crude residue was carried to the next step.

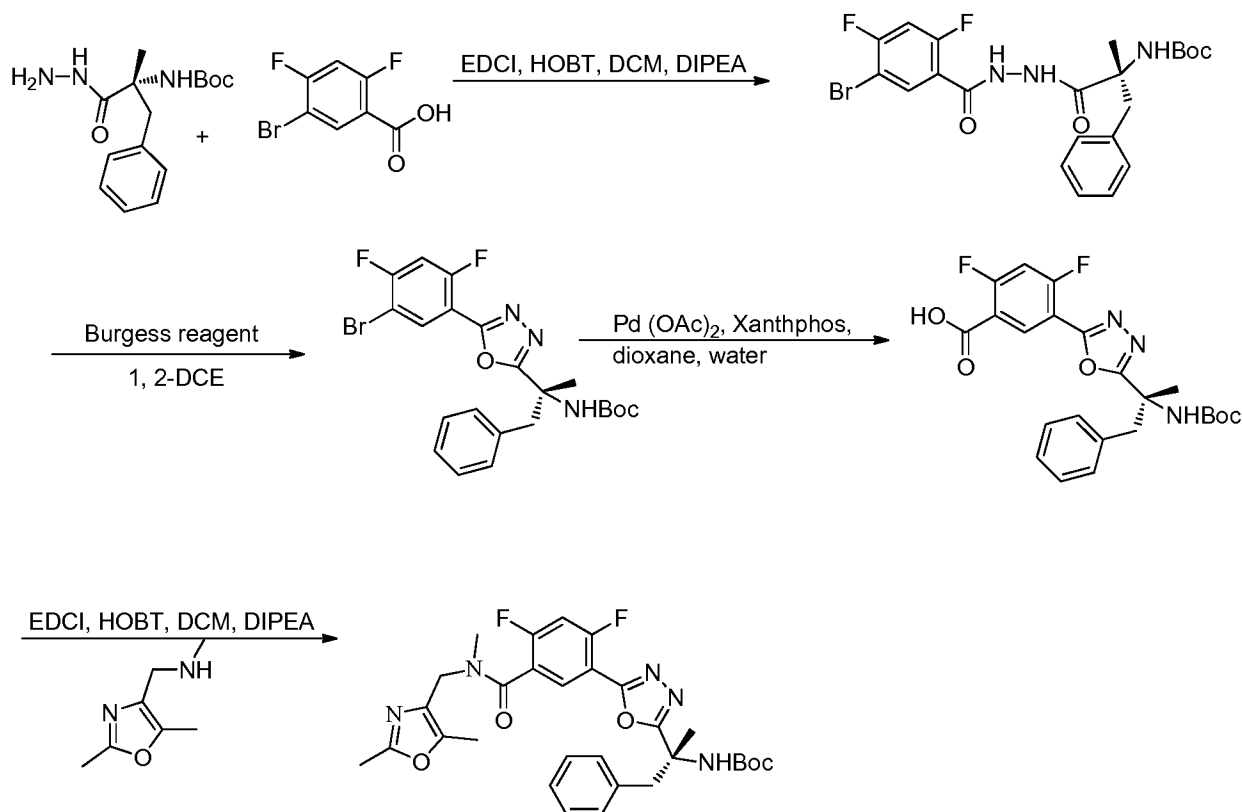
**[0594]** To the hydrazide (1.08 g, 2.11 mmol) in DCE (20 mL), Burgess reagent (1.26 g, 5.27 mmol) was added and refluxed for 3h at which time reaction color turned brown. Then reaction mixture was cooled, diluted with DCM, washed with aq sodium bicarbonate solution, water brine and dried. Crude residue was column chromatographed. (30% ethyl acetate/hexane). Product is a yellow syrup and was obtained in 67% yield.

**[0595]** To the bromo compound, (R)-tert-butyl (2-(5-(5-bromo-2-fluorophenyl)-1,3,4-oxadiazol-2-yl)-1-(4-fluorophenyl)propan-2-yl)carbamate (700 mg, 1.416 mmol) in dioxane (Ratio: 2.96, Volume: 8 mL) and Water (Ratio: 1.000, Volume: 2.7 mL), PALLADIUM(II) ACETATE (15.90 mg, 0.071 mmol) and XANTPHOS (82 mg, 0.142 mmol), Et<sub>3</sub>N (1.974 mL, 14.16 mmol) were added and the reaction mixture was purged with carbon monoxide. Then reaction mixture (a yellow suspension) was heated to 75°C for 3h by which time the suspension is greyish green. Then reaction mixture was cooled, dioxane was removed in vacuum. Water was added and filtered. Water layer was basified and extracted with ethyl acetate. Aqueous layer was then acidified and extracted with 5% MeOH/Ethyl acetate. Organic layer was dried and evaporated to yield 460 mg of acid.

**[0596]** Resulting acid is converted to the final compound in a manner similar to that as in *Example 1.7.1*.

*Example 1.6.67*





**[0597]** To a solution containing the acid, 5-bromo-2,4-difluorobenzoic acid (1.5 g, 6.33 mmol) in DCM (10 ml), HOBT (1.163 g, 7.59 mmol) and EDC (1.699 g, 8.86 mmol) were added and the reaction mixture was stirred for 1h at rt. After 1h, reaction mixture was cooled to 0°C, and (R)-tert-butyl (1-hydrazinyl-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate (1.671 g, 5.70 mmol) was added in DCM (3mL) along with DIPEA (3.32 ml, 18.99 mmol). The reaction mixture color was dark brown. After stirring overnight at rt, DCM was removed in vacuum. Then reaction mixture was diluted with ethyl acetate, and saturated aq sodium bicarbonate solution was added. After stirring for 10 mins at rt, aqueous layer was extracted with ethyl acetate (2X10 ml). Combined organic layers were washed with water, brine and dried. Crude residue was carried to the next step.

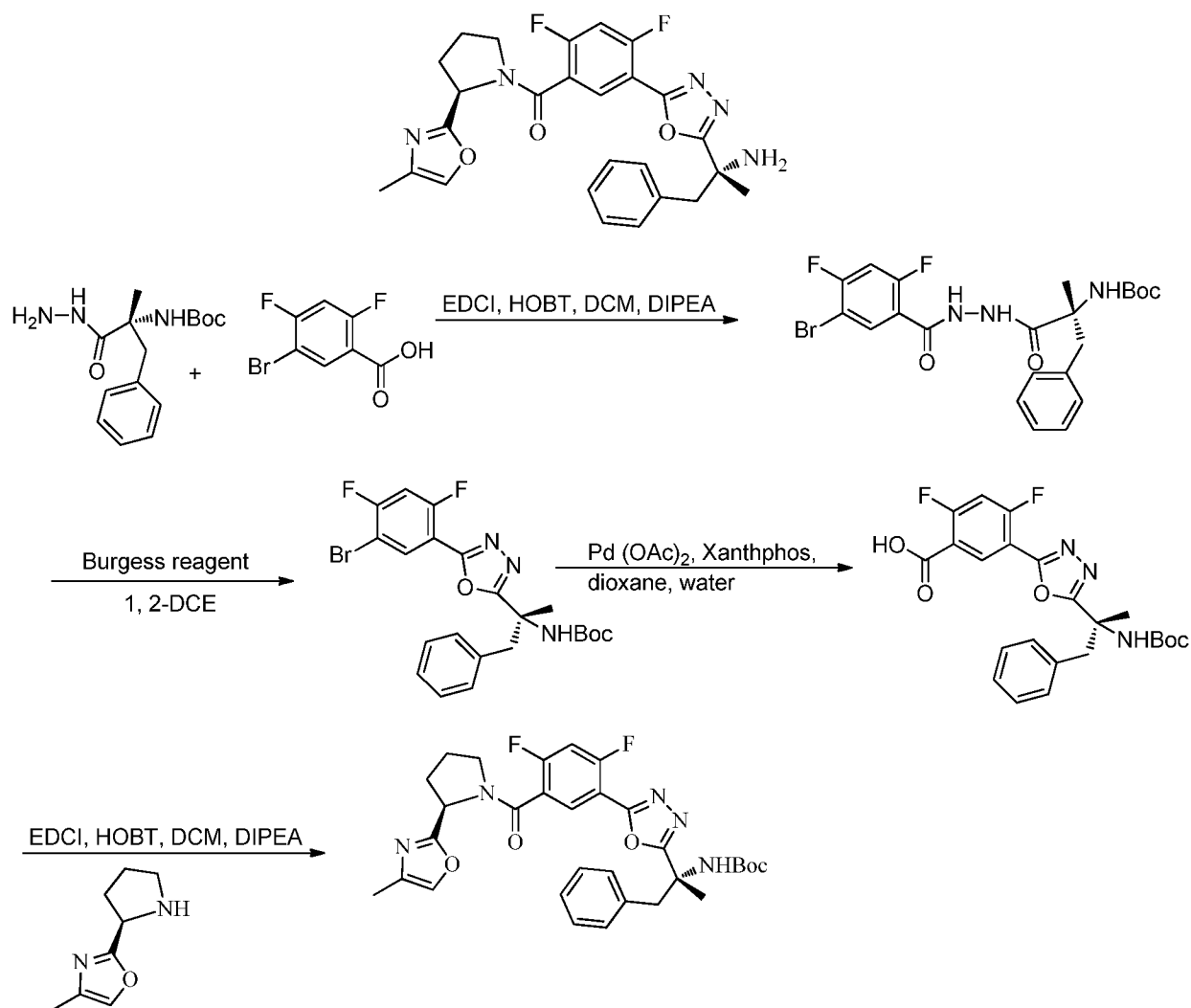
**[0598]** To the hydrazide (500 mg, 1.06 mmol) in DCE (20 ml), Burgess reagent (629 mg, 2.64 mmol) was added and refluxed for 2h at which time reaction color turned dark brown. Then reaction mixture was cooled, diluted with DCM, washed with aqueous sodium bicarbonate solution, water, and brine and dried. Crude residue was column chromatographed. (30% ethyl acetate/hexane). Product is a colorless foamy syrup and was obtained in 67% yield.



**[0599]** To the bromo compound, (R)-tert-butyl (2-(5-(5-bromo-2,4-difluorophenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate (1.0 g, 2.023 mmol) in dioxane and water, PALLADIUM(II) ACETATE (0.023 g, 0.101 mmol) and XANTPHOS (0.117 g, 0.202 mmol), Et<sub>3</sub>N (2.82 ml, 20.23 mmol) were added and the reaction mixture was purged with carbon monoxide. Then reaction mixture was heated to 75°C for 4h. Then reaction mixture was cooled, water was added and filtered. Water layer was basified and extracted with ethyl acetate. Aqueous layer was then acidified and extracted with 5%MeOH/Ethyl acetate. Organic layer was dried and evaporated to yield 360mg of acid. Organic layer also had some product along with some impurities. Partitioning the material obtained from organic layer between, aqueous( basic ) layer and 5%MeOH/ethyl acetate yielded 450 mg of acid.

**[0600]** Resulting acid is converted to the final compound in a manner similar to that as in Example 1.7.1.

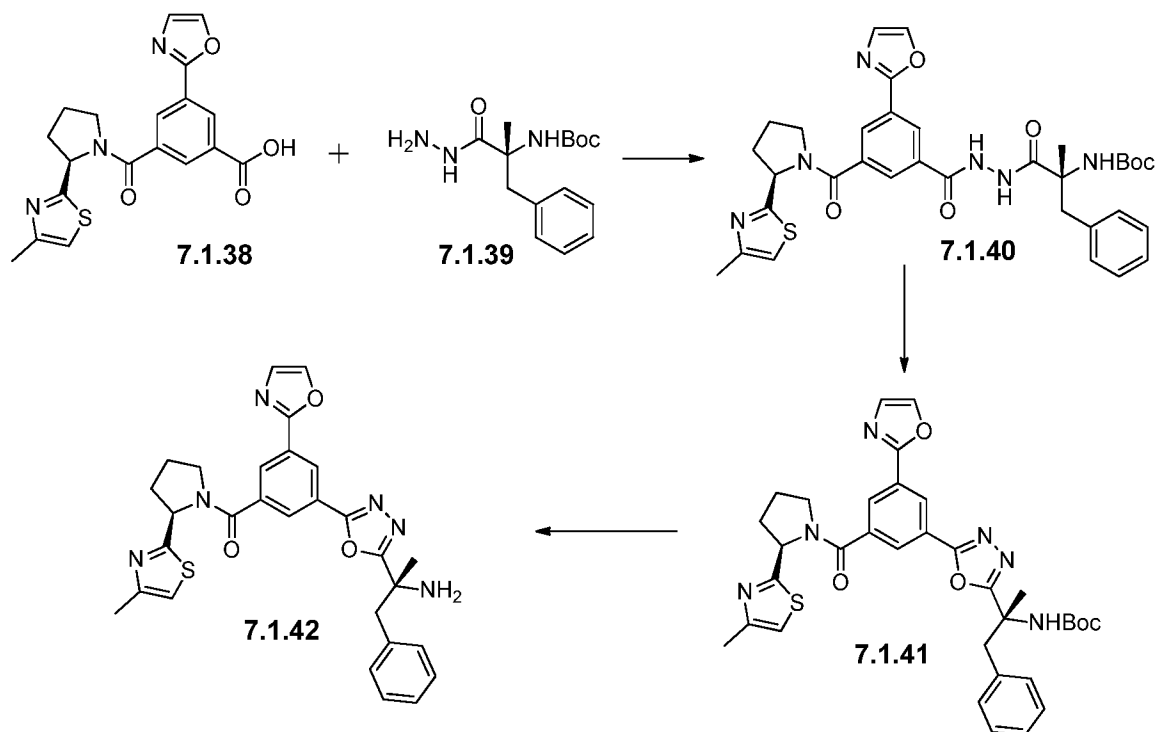
*Example 1.6.68*



[0601] The final compound was prepared using similar procedure to that of *Example 1.8.11*.

**Example 1.7: Multi-step synthesis of oxadiazole inhibitors.**

*Example 1.7.1*

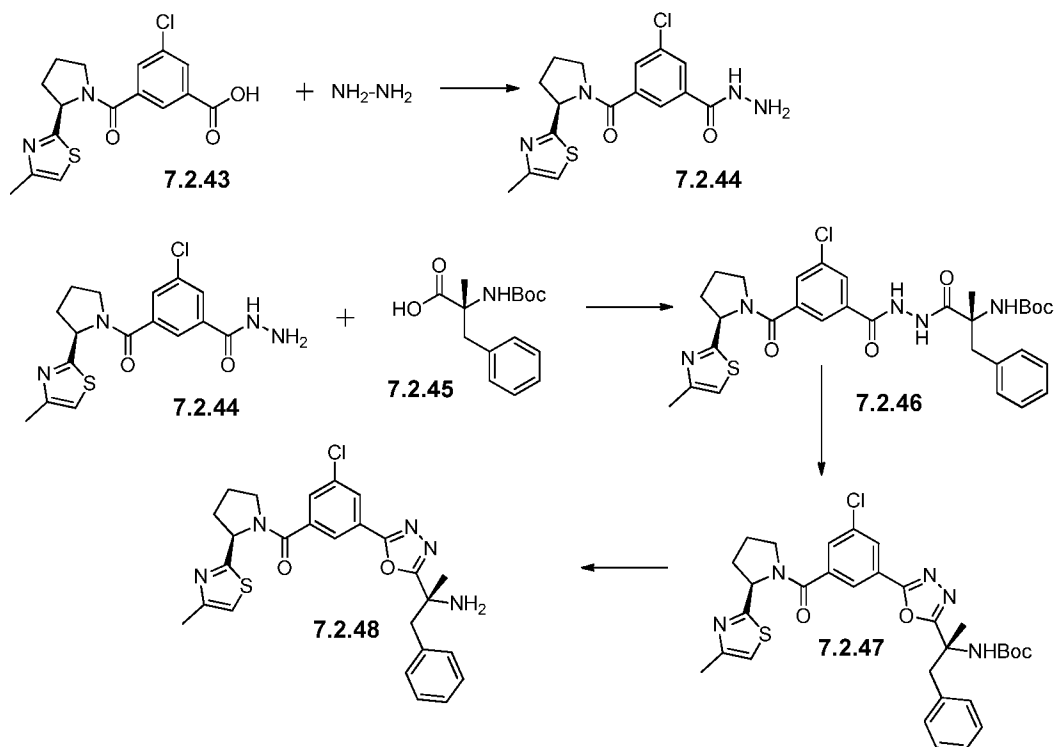


[0602] **7.1.38** and **7.1.39** were coupled using standard coupling procedure involving HOBt, EDCI DIPEA in  $\text{CH}_2\text{Cl}_2$  and stirring overnight resulted in **7.1.40** in 81% yield.

[0603] To a solution of **7.1.40** (2.37g, 3.60 mmoles) in dichloroethane (50 mL) was added Burgess' reagent (2.57g, 10.80 mmoles) and refluxed overnight (~ 16h). The reaction mix was then cooled to room temperature, diluted with  $\text{CHCl}_3$  and washed successively with satd.aq.  $\text{NaHCO}_3$  and brine, dried, concentrated and purified on silica gel (1% MeOH/99%  $\text{CHCl}_3$ ) to obtain 2.12g (92%) of **7.1.41**.

[0604] A solution of **7.1.41** (2.12g, 3.31 mmoles) in a mixture of 4N HCl in 1,4-dioxane (20mL) and 1.5N HCl in MeOH (5 mL) at 0 °C to RT was stirred for 45 min. TLC indicated the consumption of SM. All the solvent was evaporated; the residue was quenched with satd.aq.  $\text{NaHCO}_3$  and was extracted with EtOAc. The organic extract was washed with brine, dried, concentrated and purified on basic alumina (1% MeOH/99%  $\text{CHCl}_3$ ) to obtain 1.44g (80%) of compound **7.1.42**.

## Example 1.7.2



**[0605]** To a solution of **7.2.43** (150 mg, 0.43 mmoles) in  $\text{CH}_3\text{CN}$  was added EDC (commercial source: sigma-aldrich) (90 mg, 0.47 mmoles) and HOBt (commercial source: sigma-aldrich) (63 mg, 0.47 mmol). After 1h, anhydrous hydrazine (commercial source: sigma-aldrich) (55 mg, 1.72 mmol) was added and stirred overnight at room temperature. All the solvent was evaporated; the residue was quenched with satd.aq.  $\text{NaHCO}_3$  and was extracted with DCM. The organic extract was washed with brine, dried, concentrated and purified on silica gel to obtain 85 mg of **7.2.44**.

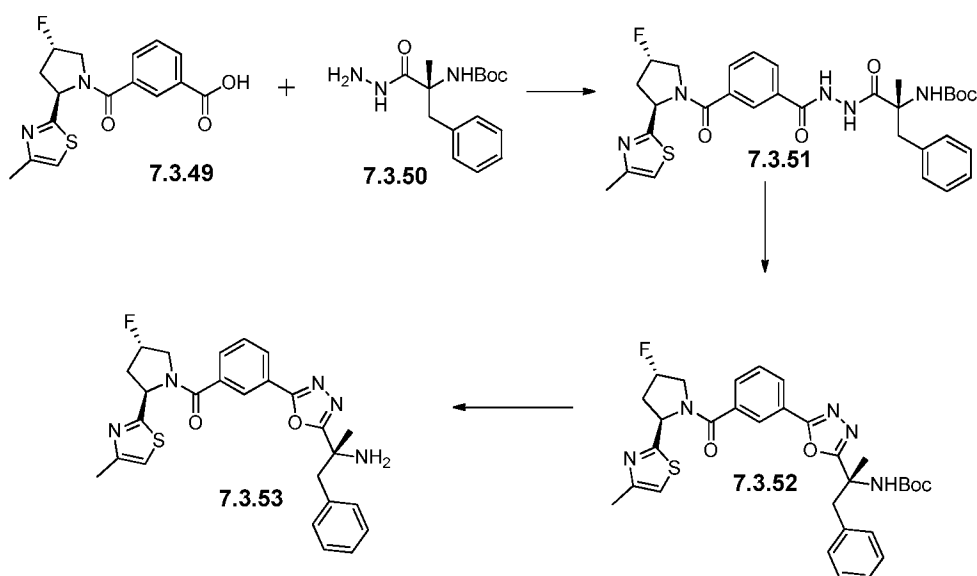
**[0606]** To a solution of **7.2.44** (85 mg, 0.23 mmoles) in DCM (5 ml) was added EDC (commercial source: sigma-aldrich) (62 mg, 0.32 mmoles) and HOBt (commercial source: sigma-aldrich) (37 mg, 0.28 mmol). After 1h, acid **7.2.45** (commercial source: Peptech) (64 mg, 0.23 mmol) was added and stirred overnight at room temperature. All the solvent was evaporated; the residue was quenched with satd.aq.  $\text{NaHCO}_3$  and was extracted with ethyl acetate. The organic extract was washed with brine, dried, concentrated and purified on basic Alumina to obtain 78 mg of **7.2.46**.

**[0607]** To a solution of **7.2.46** (78 mg, 0.12 mmoles) in dichloroethane (5 mL) was added Burgess' reagent (89 mg, 0.36 mmoles) and refluxed for 6h. The reaction mix was then cooled to room temperature, diluted with  $\text{CHCl}_3$  and washed successively with satd.aq.

NaHCO<sub>3</sub> and brine, dried, concentrated and purified on silica gel (1% MeOH/99% CHCl<sub>3</sub>) to obtain 55mg of **7.2.47**.

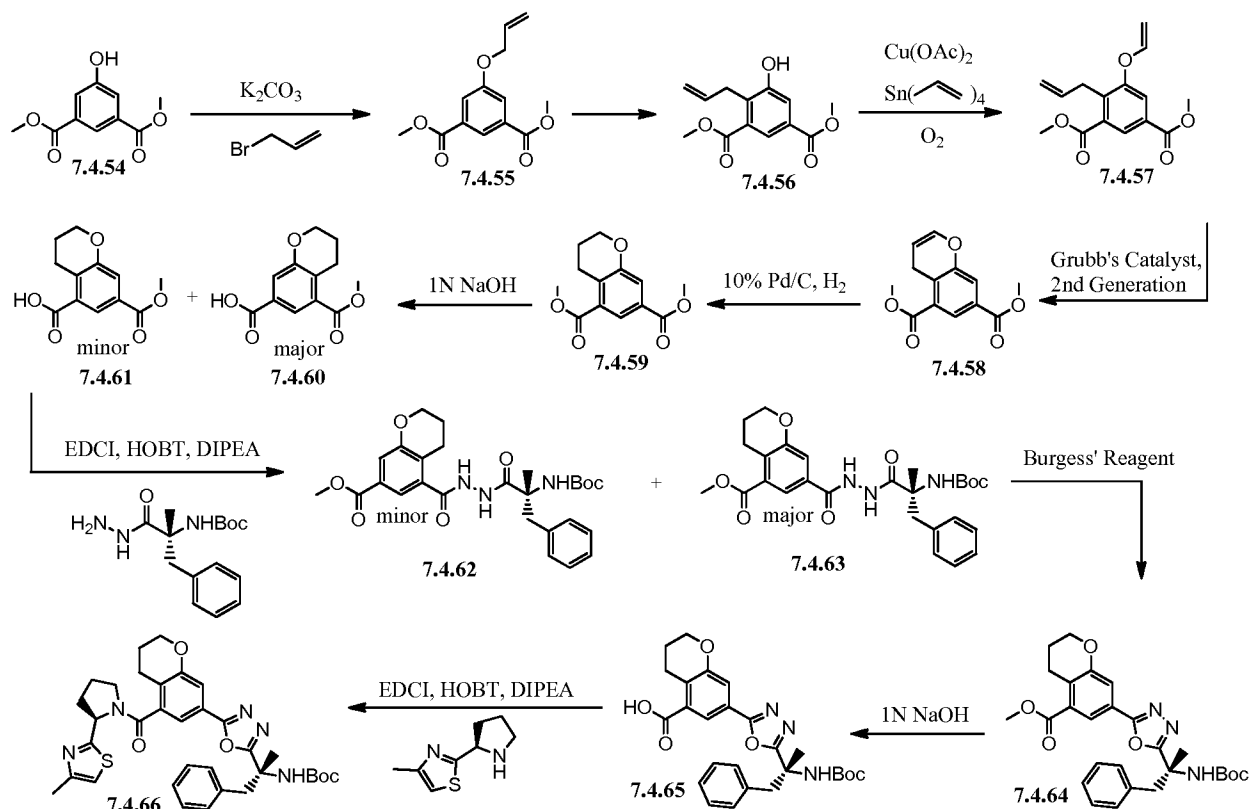
[0608] A solution of **7.2.47** (55mg, 0.09 mmoles) in a mixture of 4N HCl in 1,4-dioxane (4mL) and 1.5N HCl in MeOH (5 mL) at 0 °C to RT was stirred for 3h. TLC indicated the consumption of SM. All the solvent was evaporated; the residue was quenched with satd.aq. NaHCO<sub>3</sub> and was extracted with EtOAc. The organic extract was washed with brine, dried, concentrated and purified on basic alumina (1% MeOH/99% CHCl<sub>3</sub>) to obtain 32 mg of desired product **7.2.48**.

*Example 1.7.3*



[0609] **7.3.49** and **7.3.50** were coupled using standard coupling procedure involving HOBT, EDCI DIPEA in CH<sub>2</sub>Cl<sub>2</sub> and stirring overnight resulted in **7.3.51** in 77% yield. Final compound **7.3.53** was synthesized from ligand **7.3.51** as depicted above.

## Example 1.7.4



[0610] The bromide (1.0 ml, 1.44 g, 11.9 mmol, 1.25 eq) was added to a stirred suspension of **7.4.54** (Aldrich, 2.0 g, 9.5 mmol, 1 eq) and  $\text{K}_2\text{CO}_3$  (2.959 g, 21.4 mmol, 2.25 eq) in anhydrous DMF (10 ml) under Ar. The mixture was heated to 60 °C overnight. After cooling to room temperature the mixture was diluted with EtOAc and filtered through cotton. The organic layer was washed with water (x4), brine (x1), and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the volatiles were removed via rotary evaporation.

Purification via flash chromatography on silica gel yielded 2.14 g (8.6 mmol, 90%) of **7.4.55**.

[0611] A solution of **7.4.55** (1.04 g, 4.2 mmol, 1 eq) in diethylaniline (5 ml) was purged with Ar for 5 min to degas. The solution was heated to 195 °C with stirring. After 24 h the reaction was cooled to room temperature and diluted with  $\text{Et}_2\text{O}$ . The organic layer was washed with 1 N HCl (x2), water (x1), brine (x1), and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the volatiles were removed via rotary evaporation. Purification via flash chromatography on silica gel yielded the impure product. Recrystallization from  $\text{CH}_2\text{Cl}_2$ /hexane yielded 0.579 g (2.3 mmol, 56%) of **7.4.56**.

[0612] Anhydrous  $\text{CH}_3\text{CN}$  (10ml) was added to a flask charged with **7.4.56** (0.8369 g, 3.3 mmol, 1 eq) and  $\text{Cu}(\text{OAc})_2$  (0.7289 g, 4.0 mmol, 1.2 eq) under Ar. The flask was evacuated and back-filled with  $\text{O}_2$  (x3). Tetravinyltin (0.73 ml, 0.9 g, 4.0 mmol, 1.2 eq) was added with stirring. After stirring over the weekend the mixture was poured into aqueous  $\text{NH}_4\text{OH}$  (30%, 75 ml) with stirring. After 15 min the mixture was extracted with  $\text{EtOAc}$  (x1). The organic layer was washed with brine (x1), and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and volatiles were removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.7338 g (2.7 mmol, 80%) of the **7.4.57**.

[0613] A solution of **7.4.57** (0.2521 g, 0.9 mmol, 1 eq) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 ml) was purged with Ar to degas (5 min). 2<sup>nd</sup> generation Grubb's Catalyst (0.0772 g, 0.09 mmol, 10 mol %) was added with stirring. After stirring overnight the solvent was removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.166 g (0.677 mmol, 74%) of **7.4.58**.

[0614] A solution of **7.4.58** (0.166 g, 0.67 mmol, 1 eq) in MeOH (10 ml) was treated with 10% Pd/C (0.017 g, *ca.* 10% by wt) and placed under  $\text{H}_2$  (double balloon). After stirring vigorously overnight the mixture was filtered through Celite. The volatiles were removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.142 g (0.57 mmol, 85%) of **7.4.59**.

[0615] A solution of **7.4.59** (0.142 g, 0.57 mmol, 1 eq) in 1:1 THF/MeOH (3 ml) was cooled to 0 °C with stirring. NaOH (1 N, 0.6 ml, 0.6 mmol, 1.05 eq) was added dropwise. After 4 h at temperature the reaction was allowed to warm gradually as it stirred overnight. The reaction was diluted with saturated aqueous  $\text{NaHCO}_3$ , and the volatiles were removed via rotary evaporation. The residue was diluted with water and extracted with 3:1  $\text{CH}_2\text{Cl}_2$ /hexane (x2). The aqueous layer was adjusted to pH  $\approx$  2 with 1 N HCl. The aqueous layer was extracted with 2% MeOH in  $\text{CH}_2\text{Cl}_2$  (x2). The appropriate organics were combined and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was removed via rotary evaporation yielding 0.088 g (0.37 mmol, 65%) of a mixture of **7.4.61** and **7.4.60** (~1:2)

[0616] A solution of **7.4.61** and **7.4.60** (0.079 g, 0.33 mmol, 1 eq) in anhydrous  $\text{CH}_2\text{Cl}_2$  (5 ml) under Ar was cooled to 0 °C with stirring. The cooled solution was treated with EDCI·HCl (0.0703 g, 0.37 mmol, 1.1 eq) and HOBT· $\text{H}_2\text{O}$  (0.0497 g, 0.37 mmol, 1.1 eq). After 1 h the reaction was treated sequentially with the hydrazide (0.0981 g, 0.33 mmol, 1 eq) and DIPEA (0.23 ml, 0.17 g, 1.3 mmol, 4 eq). The reaction was stirred at 0 °C to room temperature overnight. After quenching with water the volatiles were removed via rotary

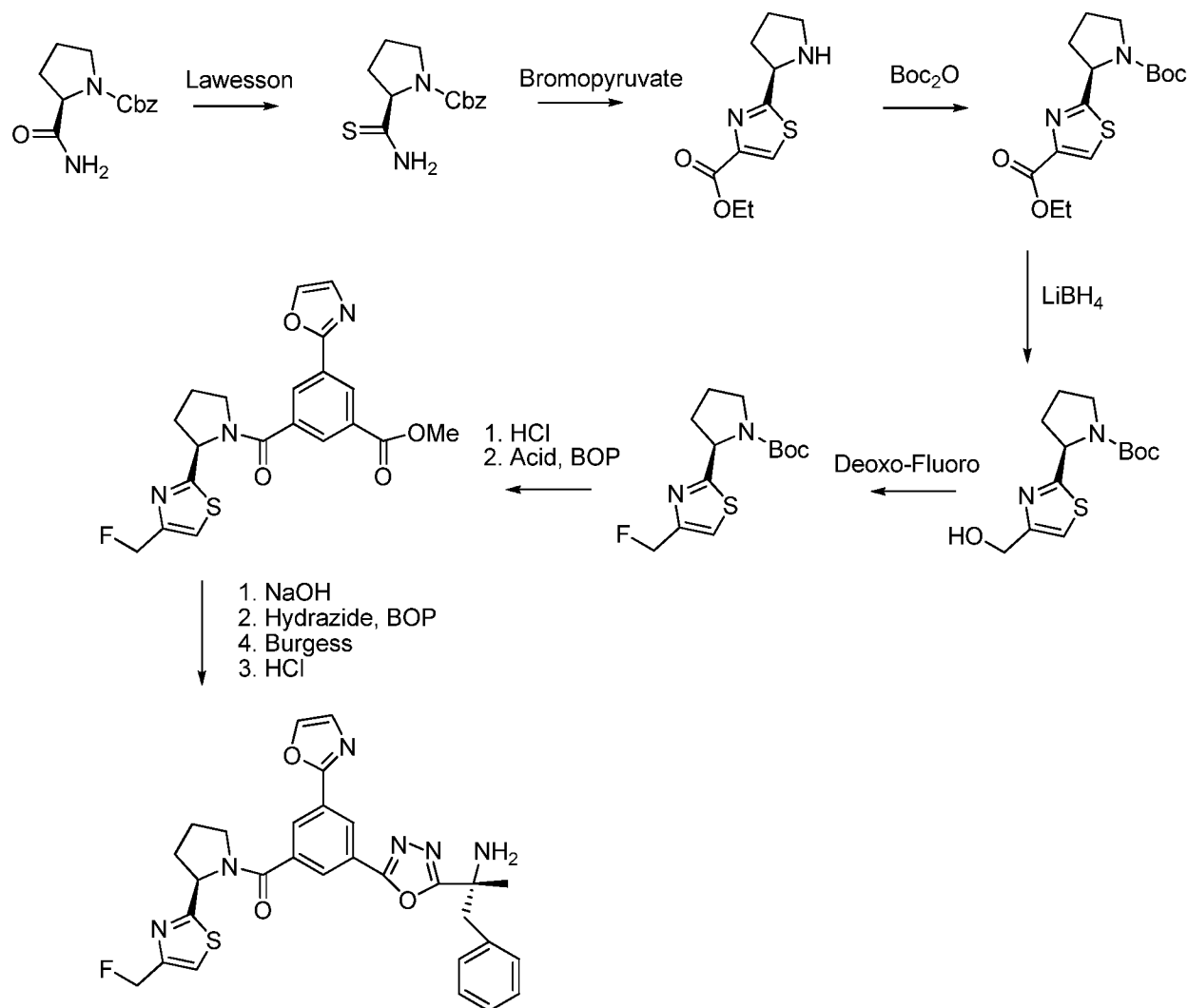
evaporation. The residue was partitioned between EtOAc/ water and the layers were separated. The organic layer was washed with water (x2), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed via rotary evaporation. Purification via flash chromatography on silica gel yielded a small amount of **7.4.62** and 0.1256 g (0.25 mmol) of **7.4.63** with some impurity. Some mixed fractions were also collected.

**[0617]** Burgess' Reagent (0.1426 g, 0.61 mmol, 2.5 eq) was added to a stirred solution of **7.4.63** (0.1256 g, 0.25 mmol, 1 eq) in anhydrous 1,2-dichloroethane (5 ml) under Ar. The solution was heated to reflux overnight. After cooling to room temperature the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with saturated aqueous NaHCO<sub>3</sub> (x1), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.0984 g (0.2 mmol, 80%) of **7.4.64**.

**[0618]** NaOH (1 N, 0.25 ml, 0.25 mmol, 1.25 eq) was added to a stirred solution of **7.4.64** (0.0984 g, 2.0 mmol, 1 eq) in 1:1 THF/MeOH (3 ml). After stirring overnight the reaction was diluted with saturated aqueous NaHCO<sub>3</sub>. The volatiles were removed via rotary evaporation. The residue was diluted with water and CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was adjusted to pH  $\approx$  2 with 1 N HCl. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (x2). The organics were combined and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed via rotary evaporation yielding 0.0887 g (0.18 mmol, 92%) of **7.4.65**.

**[0619]** A solution of **7.4.65** (0.0887 g, 0.18 mmol, 1 eq) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was cooled to 0 °C with stirring. The solution was treated with HOBT·H<sub>2</sub>O (0.0275 g, 0.2 mmol, 1.1 eq) followed by EDCI·HCl (0.0389 g, 0.2 mmol, 1.1 eq) 30 min later. After 1 h the resulting solution was treated sequentially with the amine (0.0311 g, 0.18 mmol, 1 eq) and DIPEA (0.13 ml, 0.096 g, 0.74 mmol, 4 eq). The reaction was stirred at 0 °C to room temperature overnight. After quenching with water the volatiles were removed via rotary evaporation. The residue was partitioned between EtOAc/ water and the layers were separated. The organic layer was washed with water (x2), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the solvent was removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.0864 g, (0.14 mmol, 76%) of **7.4.66**.

### Example 1.7.5



**[0620]** Lawesson's reagent (Commercial source: sigma-aldrich) (11.33 g, 280 mmol) was added to the amide (10 g, 46.67 mmol) in DME (Commercial source: sigma-aldrich) (140 ml) and the reaction mixture was stirred overnight at rt. Then the reaction mixture was diluted with ethyl acetate/Hexanes, washed with aqueous sodium bicarbonate. The organic layer was separated, dried with anhydrous sodium sulfate, concentrated to obtain pale yellow solid thioamide (9.65 g), which was used directly for the next reaction without further purification and identification.

**[0621]** To the thioamide (9.65 g, 41.91 mmol) in ethanol (150 ml) was added ethyl bromopyruvate (7.9 mL, 62.86 mmol, Commercial source: sigma-aldrich). After heating at 75 °C for 5h, then resulting mixture was kept at room temperature for overnight. The volatiles were removed in vacuum. Reaction mixture was diluted with chloroform, washed with sodium bicarbonate. Organic layer was dried and evaporated to give a residue, which



was purified through flash column to obtain the amine (6.65 g). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 8.063 (s, 1 H), 4.627 (m, 1 H), 4.397 (m, 2 H), 3.115 (m, 2 H), 2.354 (m, 1 H), 2.016 (m, 1 H), 1.852 (m, 2 H), 1.405 (m, 3 H).

**[0622]** To the amine (3.38 g, 14.91 mmol) in DCM (100 mL) at r.t, Boc<sub>2</sub>O (4.23 g, 19.39 mmol) was added, followed by pyridine (2.95 mL, 37.28 mmol). The resulting reaction mixture was stirred at r.t. overnight, then diluted with chloroform, washed with sodium bicarbonate. Organic layer was dried and evaporated to give a residue, which was purified through flash column to obtain the ester (4.0 g).

**[0623]** The ester (4 g, 12.25 mmol) in THF (50 mL) at 0 °C was added LiBH<sub>4</sub> (2.0 M solution in THF, 18.4 mL, 36.76 mmol) and stirred, slowly warmed to rt overnight. The reaction mixture was diluted with ethyl acetate, carefully quenched with 5 % aqueous citric acid. The organic layer was separated, dried and evaporated to yield product which was purified by flash column to give alcohol (2.1 g).

**[0624]** To a solution of alcohol (2.1 g, 7.38 mmol) in dichloromethane (60 mL) at -78°C was added Deoxo-Fluor (1.77 mL, 9.6 mmol). The resulting mixture was stirred and warmed to room temperature for overnight, then was cooled in ice bath diluted with chloroform and quenched with saturated sodium bicarbonate solution. The mixture was warmed to room temperature, separated and dried, concentrated and purified with silica gel chromatography to give the compound (1.1 g). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 7.239 (s, 1 H), 5.495 (s, 1 H), 5.337 (s, 1 H), 5.216 (m, 0.4 H), 5.099 (m, 0.6 H), 3.612-3.405 (m, 2 H), 2.274 (m, 2 H), 1.932 (m, 2 H), 1.468 (s, 4 H), 1.318 (s, 5 H).

**[0625]** To the fluoride (1.1 g, 3.84 mmol) in methanol (4.5 ml), 4 M HCl in dioxane (9.6 mL) was added at rt. After 1.5 h, volatiles were removed in vacuum. The resulting solid was used directly for the next reaction without further purification. To a stirred solution of the salt (400 mg, 1.8 mmol), acid (443.8 mg, 1.8 mmol) in DCM (80 mL) were added PyBOP (1.03 g, 1.8 mmol), triethylamine (1 mL, excess) at room temperature. The reaction mixture was stirred at room temperature for 16 h. Then aqueous saturated sodium bicarbonate was added and the reaction mixture was extracted with chloroform. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product thus obtained was purified by silica gel flash column chromatography to provide the corresponding amide (623 mg). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ: 8.762 (s, 1 H), 8.419 (s, 1 H), 8.295 (s, 1 H), 7.765 (s, 1 H), 7.273 (m, 2 H), 5.697-5.150 (m, 3 H), 3.957 (s, 3 H), 3.783 (m, 1 H), 3.545 (m, 1 H), 2.431 (m, 2 H), 2.171-1.920 (m, 2 H).

**[0626]** The ester (623 mg, 1.5 mmol) was dissolved in THF:MeOH (1:1) (15:15 mL) and H<sub>2</sub>O (2.3 mL). Solid NaOH (180 mg, 4.5 mmol) was added and stirred at 50 °C for 2 hours. The reaction mixture was concentrated under reduced pressure. Saturated NaHCO<sub>3</sub> (10 mL) solution was added to the reaction mixture and extracted with toluene (to remove organic impurities). The aqueous reaction mixture was acidified with diluted HCl (10%), extracted with EtOAc, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated and dried under reduced pressure to give the crude acid which can be used directly for next reaction.

*Example 1.7.6*

**[0627] 3-[5-(1-Amino-2-phenylcyclohexyl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate:** The mixture of 3-[5-(1-amino-2-phenylcyclohexyl)-1,3,4-oxadiazol-2-yl]benzoic acid (180mg, 0.5mmol), EDC (114 mg, 0.59 mmol), HOBt (80 mg, 0.59mmol), N-methyl-1-(4-methyl-1,3-thiazol-2-yl)methanamine (85 mg, 0.59 mmol) in DMF (4 mL) was stirred for 4 h at ambient temperature. After dilution with EtOAc, the organic layer was washed with H<sub>2</sub>O, sat. NaHCO<sub>3</sub> aq. and brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by silica gel chromatography (CHCl<sub>3</sub>:MeOH = 100:0-95:5) to give a free base (44 mg) as an amorphous solid, which was dissolved in EtOH and then oxalic acid (8 mg, 0.09 mmol) and trace Et<sub>2</sub>O were added. The resulting precipitate was collected by filtration, washed with Et<sub>2</sub>O and dried in vacuo to give 3-[5-(1-amino-2-phenylcyclohexyl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate as a colorless solid (13 mg, 5%). MS (ESI) m/z: 488 [M + H]<sup>+</sup>.

**[0628] 3-[5-(1-Amino-2-phenylcyclohexyl)-1,3,4-oxadiazol-2-yl]benzoic acid:** To an ice-chilled solution of methyl 3-({2-[(1-amino-2-phenylcyclohexyl)carbonyl]hydrazino}carbonyl)benzoate (161 mg, 0.41 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) were added DBU (0.304 mL, 2.04 mmol) and 2-chloro-1,3-dimethylimidazolium chloride (206 mg, 1.22 mmol). The reaction mixture was allowed to warm to room temperature. After stirring overnight at ambient temperature, the mixture was partitioned between EtOAc and H<sub>2</sub>O, the organic layer was washed with sat. NaHCO<sub>3</sub> aq. and brine, dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue (100 mg) was dissolved in dioxane (1 mL) and ethylene glycol (1mL), CsOH.H<sub>2</sub>O (226 mg, 1.35 mmol) was added to the solution. The mixture was stirred for 2 h at 150°C. After cooling to ambient temperature, 1M aq. HCl was added and then the mixture was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub> and concentrated in vacuo to give 3-[5-(1-amino-2-phenylcyclohexyl)-1,3,4-

oxadiazol-2-yl]benzoic acid (186 mg, 126%), which was used for the next step without further purification. MS (ESI)  $m/z$ : 364  $[M + H]^+$ .

**[0629] Methyl 3-({2-[(1-Amino-2-**

**phenylcyclohexyl)carbonyl]hydrazino}carbonyl)benzoate:** A mixture of 1-amino-2-phenylcyclohexanecarbohydrazide dihydrochloride (180 mg, 0.59 mmol), EDC (135 mg, 0.71 mmol), HOBt (95 mg, 0.71 mmol), Et<sub>3</sub>N (0.180 mL, 1.29 mmol) and 3-(methoxycarbonyl)benzoic acid (106 mg, 0.59 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was stirred for 4 h at ambient temperature. After dilution with EtOAc, the organic layer was washed with H<sub>2</sub>O, sat. aq. NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane:EtOAc = 100:0-50:50) to give methyl 3-({2-[(1-amino-2-phenylcyclohexyl)carbonyl]hydrazino}carbonyl)benzoate as an amorphous solid. MS (ESI)  $m/z$ : 396  $[M + H]^+$ .

**[0630] 1-Amino-2-phenylcyclohexanecarbohydrazide dihydrochloride:** tert-Butyl 2-[(1-amino-2-phenylcyclohexyl)carbonyl]hydrazinecarboxylate (160 mg, 0.48 mmol) was dissolved in 4 M HCl/EtOAc. After stirring overnight, the mixture was evaporated to give 1-amino-2-phenylcyclohexanecarbohydrazide dihydrochloride as a colorless oil. MS (ESI)  $m/z$ : 234  $[M + H]^+$ .

**[0631] tert-Butyl 2-[(1-amino-2-phenylcyclohexyl)carbonyl]hydrazinecarboxylate:** A mixture of 1-amino-2-phenylcyclohexanecarboxylic acid hydrochloride (500 mg, 1.96 mmol), EDC (450 mg, 2.35 mmol), HOBt (317 mg, 2.35 mmol) and tert-butyl hydrazinecarboxylate (620 mg, 4.69 mmol) in DMF (10 mL) was stirred overnight at ambient temperature. After dilution with EtOAc, the organic layer was washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane:EtOAc = 100:0-50:50) to give tert-butyl 2-[(1-amino-2-phenylcyclohexyl)carbonyl]hydrazinecarboxylate as a colorless solid (167 mg, 26%). MS (ESI)  $m/z$ : 334  $[M + H]^+$ .

*Example 1.7.7*

**[0632] rel-3-{5-[(1R,2R)-1-Amino-2-phenylcyclopropyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide 4-methylbenzenesulfonate:** A mixture of tert-butyl rel-[(1R,2R)-1-{[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbonyl}benzoyl)hydrazino]carbonyl}-2-phenylcyclopropyl]carbamate (55.6 mg, 0.099 mmol) and Burgess reagent (70.5 mg, 0.296 mmol) in dichloroethane (DCE) (1 mL) was stirred for 20 min at 130°C in a sealed tube under microwave irradiation. The

mixture was partitioned between  $\text{CHCl}_3$  and water. The organic layer was washed with satd. aq.  $\text{NaHCO}_3$  and brine, dried over  $\text{MgSO}_4$ , silicagel and celite, filtered off, and the filtrate was evaporated. Silicagel column chromatography ( $\text{CHCl}_3$ -MeOH, a linear gradient of MeOH from 0 to 4%) afforded a colorless gum (MS (ESI)  $m/z$ : 568.10  $[\text{M} + \text{Na}]^+$ ). The gum was dissolved in MeCN (1 mL), and to the solution was added p-toluenesulfonic acid monohydrate (56.3 mg). The mixture was stirred for 1 h at  $50^\circ\text{C}$ . The mixture was partitioned between  $\text{CHCl}_3$  and satd. aq.  $\text{NaHCO}_3$ . The organic layer was washed with brine, dried over  $\text{MgSO}_4$ , filtered, and the filtrate was evaporated. The residue was dissolved in isopropyl alcohol (IPA), and to the solution was added p-toluenesulfonic acid monohydrate (18.8 mg). The solvent was evaporated off, and the residue was triturated in EtOAc to give 3-{5-[(1R,2R)-1-amino-2-phenylcyclopropyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide 4-methylbenzenesulfonate (1:1) as a white powder, which was collected by filtration, washed with EtOAc and dried in vacuo (26.3 mg, 60.9%). MS (ESI)  $m/z$ : 446.2  $[\text{M} + \text{H}]^+$ .

**[0633] tert-Butyl rel-[(1R,2R)-1-{[2-(3-{Methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]carbonyl}-2-phenylcyclopropyl]carbamate:** A mixture of rel-(1R,2R)-1-[bis(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid (129 mg, 0.342 mmol), 3-(hydrazinocarbonyl)-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide (156 mg, 0.513 mmol), EDC (91.7 mg, 0.478 mmol) and HOBT (55.4 mg, 0.410 mmol) in DMF (2 mL) was stirred for 13 h at ambient temperature. The mixture was partitioned between EtOAc and water. The organic layer was washed with 1 N HCl, satd. aq.  $\text{NaHCO}_3$ , and brine, dried over  $\text{MgSO}_4$ , filtered, and the filtrate was evaporated. Silicagel column chromatography ( $\text{CHCl}_3$ -MeOH, a linear gradient of MeOH from 0 to 4%) afforded tert-butyl rel-[(1R,2R)-1-{[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]carbonyl}-2-phenylcyclopropyl]carbamate (55.6 mg, 28.9%) as a colourless foam.

**[0634] rel-(1R,2R)-1-[Bis(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid:** To a solution of methyl rel-(1R,2R)-1-[bis(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylate (150 mg, 0.383 mmol) in MeOH- $\text{H}_2\text{O}$  (2:1, 1.5 mL) was added 85% KOH (126 mg, 1.92 mmol). The mixture was stirred for 1.5 h at ambient temperature and 2 h at  $70^\circ\text{C}$ . The mixture was washed with  $\text{Et}_2\text{O}$  (two times), and acidified by adding 1 N HCl (pH = 3). The residue was extracted with  $\text{CHCl}_3$ -MeOH (five times). The extract was dried over  $\text{MgSO}_4$  and alumina, filtered, and the filtrate

was evaporated to give rel-(1R,2R)-1-[bis(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid as a colorless gum (129 mg). MS (ESI) m/z: 686.15 [M + Na]<sup>+</sup>.

**[0635] Methyl rel-(1R,2R)-1-[bis(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylate:** To a suspension of trimethylsulfoxonium iodide (350 mg, 1.59 mmol) in DMSO (1.5 mL) was added NaH (63.6 mg, 60% in oil, 63.6 mmol) at ambient temperature. After stirring for 1 h, to the mixture was added a solution of methyl 2-[bis(tert-butoxycarbonyl)amino]-3-phenylacrylate (300 mg, 0.795 mmol) in DMSO (1.5 mL). The mixture was stirred for 5 h at ambient temperature. The reaction was quenched by adding 10% citric acid. The mixture was partitioned between EtOAc and water. The organic layer was washed with water (two times) and brine, dried over MgSO<sub>4</sub>, filtered, and the filtrate was evaporated. Silicagel column chromatography (EtOAc-hexane, a linear gradient of EtOAc from 0 to 20%) afforded methyl rel-(1R,2R)-1-[bis(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylate as a colourless oil (150 mg, 48.2%). MS (ESI) m/z: 414.05 [M + Na]<sup>+</sup>.

*Example 1.7.8*

**[0636] rel-3-{5-[(1R,2S)-1-Amino-2-phenylcyclopropyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide 4-methylbenzenesulfonate (1:1):** The desired compound was synthesised from tert-butyl rel-[(1R,2S)-1-{[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]carbonyl}-2-phenylcyclopropyl]carbamate (283 mg) in a similar manner to Ex. 1.7.7 (143 mg, 61.6%). MS (ESI) m/z: 446.2 [M + H]<sup>+</sup>.

**[0637] tert-butyl rel-[(1R,2S)-1-{[2-(3-{Methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]carbonyl}-2-phenylcyclopropyl]carbamate:** The desired compound was synthesised from rel-(1R,2S)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid (150 mg) in a similar manner to Ex. 1.7.7 (238 mg, 78.1%). MS (ESI) m/z: 564.20 [M + H]<sup>+</sup>.

**[0638] rel-(1R,2S)-1-[(tert-Butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylic acid:** The desired compound was synthesised from ethyl rel-(1R,2S)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopropanecarboxylate (1.21 g) in a similar manner to Ex. 1.7.7 (892, 81.2%). MS (ESI) m/z: 300.11 [M + H]<sup>+</sup>.

*Example 1.7.9*

**[0639] 3-(5-(2-Amino-1-methoxy-3-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide oxalate:** tert-Butyl 2-benzyl-3-methoxy-1-[2-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazinyl]-1-oxopropan-2-ylcarbamate (40 mg, 0.069 mmol) was treated with 4N HCl/EtOAc at ambient temperature for 1 h. The reaction mixture was evaporated and neutralized with sat. aq. NaHCO<sub>3</sub>, extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, then evaporated off. The residue was dissolved in ether. To the solution was added oxalic acid (6.2 mg, 0.069 mmol), and the resulting solid was collected, washed with ether, then dried under vacuum to afford 3-[5-(2-amino-1-methoxy-3-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methylthiazol-2-yl)methyl]benzamide oxalate as a white amorphous solid (30 mg, 76%). MS (ESI) m/z: 478.2 [M + H]<sup>+</sup>.

**[0640] tert-Butyl 1-methoxy-2-(5-(3-(methyl((4-methylthiazol-2-yl)methyl)carbamoyl)phenyl)-1,3,4-oxadiazol-2-yl)-3-phenylpropan-2-ylcarbamate:** 2-Benzyl-3-methoxy-1-[2-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazinyl]-1-oxopropan-2-ylcarbamate (130 mg, 0.22 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2.6 mL) then to the solution was added Burgess reagent (156 mg, 0.655 mmol). The mixture was heated under microwave conditions (130°C, 20 min) then the reaction was diluted with CHCl<sub>3</sub>, washed with water and brine then dried over MgSO<sub>4</sub> and evaporated. The crude material was purified with silica gel column chromatography to afford tert-butyl 1-methoxy-2-[5-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}phenyl)-1,3,4-oxadiazol-2-yl]-3-phenylpropan-2-ylcarbamate as a colorless oil (90 mg, 71%). MS (ESI) m/z: 600.2 [M + Na]<sup>+</sup>.

**[0641] 2-Benzyl-3-methoxy-1-(2-(3-(methyl((4-methylthiazol-2-yl)methyl)carbamoyl)benzoyl)hydrazinyl)-1-oxopropan-2-ylcarbamate:** To a solution of 2-benzyl-2-(tert-butoxycarbonylamino)-3-methoxypropanoic acid (180 mg, 0.58 mmol) in DMF (1.8 ml) was added 3-(hydrazinecarbonyl)-N-methyl-N-[(4-methylthiazol-2-yl)methyl]benzamide (212.5 mg, 0.7 mmol), EDC (134 mg, 0.7 mmol) and HOBt (78.6 mg, 0.58 mmol) then stirred at ambient temperature overnight. After adding water, the mixture was extracted with EtOAc, washed with brine then dried over MgSO<sub>4</sub>. The crude material was purified with silica gel column chromatography to afford tert-butyl 2-benzyl-3-methoxy-1-[2-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazinyl]-1-oxopropan-2-ylcarbamate as a colorless oil (130 mg, 38%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 10.00 (s,

1H), 8.98 (s, 1H), 8.01-7.90 (m, 2H), 7.66 (m, 1H), 7.5 (m, 1H), 7.31-7.17 (m, 5H), 6.89 (s, 1H), 5.33 (m, 1H), 5.0-4.6 (m, 2H), 3.97 (m, 1H), 3.67 (m, 1H), 3.51 (s, 3H), 3.50-3.33 (m, 2H), 3.12-2.85 (m, 2H), 2.45 (s, 3H), 1.48 (s, 9H).

**[0642] 2-Benzyl-2-(tert-butoxycarbonylamino)-3-methoxypropanoic acid:** To a solution of methyl 2-benzyl-2-(tert-butoxycarbonylamino)-3-methoxypropanoate (270 mg, 0.84 mmol) in MeOH (2.8 ml) was added 3N NaOH aq. (2.8 ml) then heated at 50°C until the reaction was complete. The MeOH was evaporated off and the aqueous solution was washed with ether, acidified with KHSO<sub>4</sub> aq., extracted with EtOAc, the organic phase was washed with brine, dried over MgSO<sub>4</sub> and evaporated to give 2-benzyl-2-(tert-butoxycarbonylamino)-3-methoxypropanoic acid (200 mg, 77%). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.30-7.10 (m, 4H), 5.36 (s, 1H), 3.98-3.70 (m, 1H), 3.5-3.17 (m, 4H), 2.04 (s, 2H), 1.48 (s, 9H).

**[0643] Methyl 2-benzyl-2-(tert-butoxycarbonylamino)-3-methoxypropanoate:** A mixture of methyl 2-benzyl-2-(tert-butoxycarbonylamino)-3-hydroxypropanoate (270 mg, 0.87 mmol), methyl trifluoromethanesulfonate (573 mg, 3.5 mmol) and 2,6-di-tert-butyl-4-methylpyridine (789 mg, 3.8 mmol) in DCE (2.7 ml) was stirred at ambient temperature overnight. The solution was quenched with sat. aq. KHSO<sub>4</sub>, extracted with EtOAc, washed with sat. aq. NaHCO<sub>3</sub>, brine and dried over MgSO<sub>4</sub>. Purification with silica gel column chromatography (0 to 30% EtOAc/hexane) gave methyl 2-benzyl-2-(tert-butoxycarbonylamino)-3-methoxypropanoate (200 mg, 71%) as a colorless oil. MS (ESI) m/z: 224.15 [M - Boc + 2H]<sup>+</sup>.

#### *Example 1.7.10*

**[0644] (3-(5-(rel-(1S,2R)-1-Amino-2-phenylcyclobutyl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide) hydrochloride:** tert-Butyl rel-(1S,2R)-1-[5-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}phenyl)-1,3,4-oxadiazol-2-yl]-2-phenylcyclobutylcarbamate (180 mg, 0.32 mmol) was treated with 4N HCl/EtOAc at ambient temperature for 3 h, then evaporated to dryness. The residue was washed with ether, and then dried under vacuum to afford 3-{5-[(1S,2R)-1-amino-2-phenylcyclobutyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methylthiazol-2-yl)methyl]benzamide hydrochloride as a colorless amorphous solid. MS (ESI) m/z: 460.1 [M+ H]<sup>+</sup>.

**[0645] tert-Butyl rel-(1S,2R)-1-(5-(3-(Methyl((4-methylthiazol-2-yl)methyl)carbamoyl)phenyl)-1,3,4-oxadiazol-2-yl)-2-phenylcyclobutylcarbamate:** The desired compound was synthesized from tert-butyl (1S,2R)-1-[2-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazinecarbonyl]-2-

phenylcyclobutylcarbamate (230 mg, 0.4 mmol) in a similar manner to Ex. 1.7.9 (190 mg, 85%). MS (ESI)  $m/z$ : 560.15  $[M+H]^+$ .

**[0646] tert-Butyl rel-(1S,2R)-1-(2-(3-(Methyl((4-methylthiazol-2-yl)methyl)carbamoyl)benzoyl)hydrazinecarbonyl)-2-phenylcyclobutylcarbamate:** To a solution of rel-(1S,2R)-1-(tert-butoxycarbonylamino)-2-phenylcyclobutanecarboxylic acid (200 mg, 0.69 mmol) in DMF (2 ml) was added 3-(hydrazinecarbonyl)-N-methyl-N-[(4-methylthiazol-2-yl)methyl]benzamide (313 mg, 1 mmol), EDC (197 mg, 1 mmol) and HOBt (93 mg, 0.69 mmol), then stirred at ambient temperature overnight. After adding water, the mixture was extracted with EtOAc, washed with brine then dried over  $MgSO_4$ . The crude material was purified with silica gel column chromatography to afford tert-butyl rel-(1S,2R)-1-[2-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazinecarbonyl]-2-phenylcyclobutylcarbamate as a colorless form (230 mg, 58%). MS (ESI)  $m/z$ : 578.15  $[M+H]^+$ .

*Example 1.7.11*

**[0647] 3-{5-[rel-(1R,2R)-1-Amino-2-phenylcyclobutyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methylthiazol-2-yl)methyl]benzamide:** The desired compound was synthesised from tert-butyl rel-(1R,2R)-1-[5-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}phenyl)-1,3,4-oxadiazol-2-yl]-2-phenylcyclobutylcarbamate (390 mg, 0.7 mmol) by a similar manner to Ex.1.7.10 (220 mg, 64%). MS (ESI)  $m/z$ : 460.1  $[M+H]^+$ .

**[0648] tert-butyl rel-(1R,2R)-1-[5-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}phenyl)-1,3,4-oxadiazol-2-yl]-2-phenylcyclobutylcarbamate:** The desired compound was synthesized from tert-butyl rel-(1R,2R)-1-[2-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazinecarbonyl]-2-phenylcyclobutylcarbamate (230 mg, 0.4 mmol) in a similar manner to Ex. 1.7.9 (390 mg, 81%). MS (ESI)  $m/z$ : 560.15  $[M+H]^+$ .

**[0649] tert-Butyl rel-(1R,2R)-1-(2-(3-(Methyl((4-methylthiazol-2-yl)methyl)carbamoyl)benzoyl)hydrazinecarbonyl)-2-phenylcyclobutylcarbamate:** To a solution of rel-(1R,2R)-1-(tert-butoxycarbonylamino)-2-phenylcyclobutanecarboxylic acid (300 mg, 1 mmol) in DMF (3 ml) was added 3-(hydrazinecarbonyl)-N-methyl-N-[(4-methylthiazol-2-yl)methyl]benzamide (470 mg, 1.5 mmol), EDC (296 mmol, 1.5 mmol) and HOBt (139 mg, 1 mmol) then stirred at ambient temperature overnight. After adding water, the mixture was extracted with EtOAc, washed with brine then dried over  $MgSO_4$ . The crude material was purified with silica gel column chromatography to afford tert-butyl rel-(1R,2R)-



1-[2-(3-{methyl[(4-methylthiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazinecarbonyl]-2-phenylcyclobutylcarbamate as a colorless form (500 mg, 84%). MS (ESI)  $m/z$ : 578.15  $[M+H]^+$ .

*Example 1.7.12*

**[0650] 3-{5-[(4E)-2-Amino-1,5-diphenylpent-4-en-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1):** To a stirred solution of 3-{5-[(4E)-2-amino-1,5-diphenylpent-4-en-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide (90 mg, 0.16 mmol) in Et<sub>2</sub>O was added oxalic acid (14 mg, 0.16 mmol). The precipitate which formed was filtered off, washed with Et<sub>2</sub>O, and dried in vacuo to give 3-{5-[(4E)-2-amino-1,5-diphenylpent-4-en-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1) as a colorless solid (0.077 g, 75%). MS (ESI)  $m/z$ : 549  $[M+H]^+$ .

**[0651] 3-{5-[(4E)-2-Amino-1,5-diphenylpent-4-en-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide:** To tert-butyl {(4E)-2-[5-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}phenyl)-1,3,4-oxadiazol-2-yl]-1,5-diphenylpent-4-en-2-yl}carbamate (0.510 g, 1.21 mmol) was added 4M hydrogen chloride in dioxane (5 mL). After being stirred overnight, the reaction mixture was poured into sat. aq. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to give the title compound as a colorless oil (481 mg, quant.). MS (APCI/ESI)  $m/z$ : 550  $[M+H]^+$ .

**[0652] tert-Butyl {(4E)-2-[5-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}phenyl)-1,3,4-oxadiazol-2-yl]-1,5-diphenylpent-4-en-2-yl}carbamate:** The title compound was synthesised from tert-butyl {(4E)-2-benzyl-1-[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]-1-oxo-5-phenylpent-4-en-2-yl}carbamate (0.610 g) by a similar manner to Ex. 1.7.9 (0.510 g, 86%). MS (APCI/ESI)  $m/z$ :  $m/z$  648  $[M-H]^-$ .

**[0653] tert-Butyl {(4E)-2-benzyl-1-[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]-1-oxo-5-phenylpent-4-en-2-yl}carbamate:** To a stirred solution of N-(tert-butoxycarbonyl)-alpha-[(2E)-3-phenylprop-2-en-1-yl]phenylalanine (0.370 g, 0.970 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), were added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (0.443 g, 1.17 mmol) and iPr<sub>2</sub>NEt (0.24 mL, 1.36 mmol). The mixture was stirred for 15 minutes and 3-(hydrazinocarbonyl)-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide (0.443 g,

1.46 mmol) was added. After being stirred overnight, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed successively with sat. aq.  $\text{NaHCO}_3$  and brine, dried with anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo to give tert-butyl {(4E)-2-benzyl-1-[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]-1-oxo-5-phenylpent-4-en-2-yl}carbamate as a colorless oil (0.610 g, 94%). MS (APCI/ESI)  $m/z$ : 690  $[\text{M} + \text{Na}]^+$ .

**[0654] N-(tert-Butoxycarbonyl)-alpha-[(2E)-3-phenylprop-2-en-1-yl]phenylalanine:**

To a stirred solution of ethyl N-(tert-butoxycarbonyl)-alpha-[(2E)-3-phenylprop-2-en-1-yl]phenylalaninate (0.395 g, 0.965 mmol) in MeOH was added 3 M aq. NaOH (3.2 mL, 9.6 mmol). After being stirred for 3 days at 50°C, the reaction mixture was concentrated in vacuo. To the residue was added 1M aq. HCl and extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane 0:100 to 100:0) to give N-(tert-butoxycarbonyl)-alpha-[(2E)-3-phenylprop-2-en-1-yl]phenylalanine (0.370 g, 100%) as a colorless solid. MS (APCI/ESI)  $m/z$ : 380  $[\text{M}-\text{H}]^-$ .

**[0655] Ethyl N-(tert-butoxycarbonyl)-alpha-[(2E)-3-phenylprop-2-en-1-yl]phenylalaninate:**

To a stirred solution of ethyl alpha-[(2E)-3-phenylprop-2-en-1-yl]phenylalaninate (0.750 g, 1.02 mmol) in dioxane (5 mL) was added  $\text{Boc}_2\text{O}$  (0.635 g, 2.91 mmol). After being stirred for 1 day at 50°C, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane 0:100 to 20:80) to give ethyl N-(tert-butoxycarbonyl)-alpha-[(2E)-3-phenylprop-2-en-1-yl]phenylalaninate as colorless oil (0.400 g, 40%). MS (ESI)  $m/z$ : 410  $[\text{M} + \text{H}]^+$ .

**[0656] Ethyl alpha-[(2E)-3-phenylprop-2-en-1-yl]phenylalaninate:** To a stirred solution of ethyl (E)-N-(4-chlorobenzylidene)-L-phenylalaninate (4.00 g, 12.7 mmol) in MeCN (100 mL) were added [(1E)-3-bromoprop-1-en-1-yl]benzene (3.12 g, 15.8 mmol),  $\text{K}_2\text{CO}_3$  (4.38 g, 31.7 mmol), and tetrabutylammonium bromide (0.408 g, 1.27 mmol). After being stirred for 4 days under reflux, the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc and washed successively with water and brine. The organic layer was dried with anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The residue was dissolved in THF (40 mL) and 1 M aq. HCl (40 mL) was added. After being stirred for 1 hour, the aqueous layer was washed with  $\text{Et}_2\text{O}$ , neutralized, and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was dried with anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane 10:90 to 50:50) to give

ethyl alpha-[(2E)-3-phenylprop-2-en-1-yl]phenylalaninate as a colorless oil (0.750 g, 19%). MS (APCI/ESI)  $m/z$ : 310  $[M+H]^+$ .

*Example 1.7.13*

**[0657] 3-[5-(2-Amino-1,5-diphenylpentan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1):** A solution of 3-{5-[(4E)-2-amino-1,5-diphenylpent-4-en-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide (0.100 g, 0.331 mmol) in EtOH (10 mL) was passed through the H-Cube (registered trademark) reactor (Pd/C CatCart; 1.0 mL/min; 1 atm H<sub>2</sub>; room temperature). The eluted solution was concentrated in vacuo and purified by column chromatography on silica gel (MeOH/CHCl<sub>3</sub> 1:99 to 10:90). The residue was dissolved in Et<sub>2</sub>O and oxalic acid (0.016 g, 0.178 mmol) was added. The precipitate which formed was filtered off, washed with Et<sub>2</sub>O, and dried in vacuo to give 3-[5-(2-Amino-1,5-diphenylpentan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1) as a colorless solid (0.072 g, 62%). MS (ESI)  $m/z$ : 552  $[M - H]^-$ .

*Example 1.7.14*

**[0658] 3-[5-(2-Amino-1,3-diphenylpropan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1):** To tert-butyl {2-[5-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}phenyl)-1,3,4-oxadiazol-2-yl]-1,3-diphenylpropan-2-yl}carbamate (0.240 g, 0.385 mmol) was added 4 M hydrogen chloride in dioxane (5 mL). After being stirred overnight, the reaction mixture was poured into sat. aq. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was dissolved in Et<sub>2</sub>O and oxalic acid (0.035 g, 0.39 mmol) was added. The precipitate which formed was filtered off, washed with Et<sub>2</sub>O, and dried in vacuo to give 3-[5-(2-amino-1,3-diphenylpropan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1) as a colorless solid (0.180 g, 76%). MS (ESI)  $m/z$ : 524  $[M + H]^+$ .

**[0659] tert-Butyl {2-[5-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}phenyl)-1,3,4-oxadiazol-2-yl]-1,3-diphenylpropan-2-yl}carbamate:** The title compound was synthesised from tert-butyl {2-benzyl-1-[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]-1-oxo-3-phenylpropan-2-yl}carbamate (0.254 mg) by a similar manner to Ex. 1.7.9 (0.241 g, 98%). MS (APCI/ESI)  $m/z$ : 622  $[M - H]^-$ .

**[0660] tert-Butyl {2-benzyl-1-[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]-1-oxo-3-phenylpropan-2-yl}carbamate:** To a stirred solution of alpha-benzyl-N-(tert-butoxycarbonyl)phenylalanine (0.240 g, 0.675 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), were added HATU (0.333 g, 0.878 mmol) and iPr<sub>2</sub>NEt (0.18 mL, 1.01 mmol). The reaction mixture was stirred for 15 minutes and 3-(hydrazinocarbonyl)-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide (0.267 g, 0.877 mmol) was added. After being stirred overnight, the reaction mixture was poured into water, extracted with EtOAc and washed successively with sat. aq. NaHCO<sub>3</sub> and brine. The organic layer was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give tert-butyl {2-benzyl-1-[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]-1-oxo-3-phenylpropan-2-yl}carbamate as a pale yellow oil (0.254 g, 59%). MS (APCI/ESI) m/z: m/z 640 [M - H]<sup>-</sup>.

*Example 1.7.15*

**[0661] rel-3-{5-[(1R,2R)-1-Amino-2-phenylcyclopentyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1):** To tert-butyl rel-{(1R,2R)-1-[5-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}phenyl)-1,3,4-oxadiazol-2-yl]-2-phenylcyclopentyl}carbamate (0.214 g, 0.362 mmol) was added 4 M hydrogen chloride in dioxane (5 mL). After being stirred overnight, the reaction mixture was poured into sat. aq. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue was dissolved in Et<sub>2</sub>O, and oxalic acid (0.033 g, 0.36 mmol) was added. The precipitate which formed was filtered off, washed with Et<sub>2</sub>O, and dried in vacuo to give rel-3-{5-[(1R,2R)-1-Amino-2-phenylcyclopentyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1) as a beige solid (0.190 g, 93%). MS (ESI) m/z: 474 [M + H]<sup>+</sup>.

**[0662] tert-Butyl rel-{(1R,2R)-1-[5-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}phenyl)-1,3,4-oxadiazol-2-yl]-2-phenylcyclopentyl}carbamate:** The title compound was synthesised from tert-butyl rel-[(1R,2R)-1-{2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]carbonyl}-2-phenylcyclopentyl]carbamate (0.270 g) in a similar manner to Ex. 1.7.9 (0.214 g, 82%). MS (APCI/ESI) m/z: 4574 [M + H]<sup>+</sup>.

**[0663] tert-Butyl rel-[(1R,2R)-1-[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbamoyl}benzoyl)hydrazino]carbonyl]-2-phenylcyclopentyl]carbamate:** To

a stirred solution of *rel*-(1*R*,2*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-phenylcyclopentanecarboxylic acid (0.150 g, 0.491 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL), were added HATU (0.224 g, 0.589 mmol) and iPr<sub>2</sub>NEt (0.13 mL, 0.74 mmol). The reaction mixture was stirred for 15 minutes and 3-(hydrazinocarbonyl)-*N*-methyl-*N*-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide (0.224 g, 0.687 mmol) was added. After being stirred overnight, the reaction mixture was poured into water, extracted with EtOAc and washed successively with sat. aq. NaHCO<sub>3</sub> and brine. The organic layer was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to give *tert*-butyl *rel*-[(1*R*,2*R*)-1-{[2-(3-{methyl[(4-methyl-1,3-thiazol-2-yl)methyl]carbonyl}benzoyl)hydrazino]carbonyl}-2-phenylcyclopentyl]carbamate as a pale yellow oil (0.270 g, 93%). MS (APCI/ESI) *m/z*: 640 [M - H]<sup>-</sup>.

**[0664] *rel*-(1*R*,2*R*)-1-[(*tert*-Butoxycarbonyl)amino]-2-phenylcyclopentanecarboxylic**

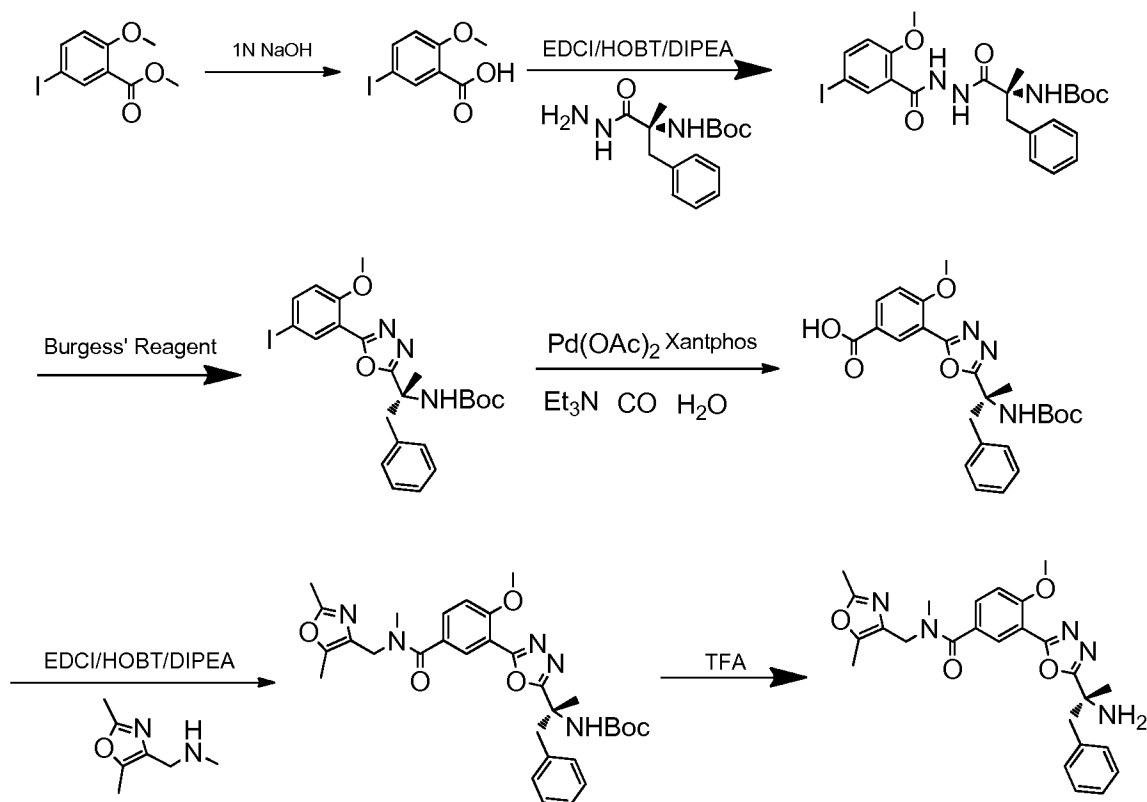
**acid:** To a solution of ethyl isocyanoacetate (2.6 mL, 23.9 mmol) in MeCN (77 mL) was added K<sub>2</sub>CO<sub>3</sub> (19.8 g, 144 mmol), Bu<sub>4</sub>NHSO<sub>4</sub> (1.63 g, 4.79 mmol) and (1,4-dibromobutyl)benzene (6.99 g, 23.9 mmol). The mixture was heated at 80°C until all of the starting electrophile had been consumed. The reaction mixture was cooled and filtered through celite to remove insoluble solid. The solid material was washed with acetonitrile and the filtrate was evaporated. The residue was taken into ether and washed with water and brine and then dried over MgSO<sub>4</sub>. The residue was purified with silica gel column chromatography (AcOEt/hexane = 0:100 to 30:70) to give a yellow oil (2.67 g) as a product.

**[0665]** To a solution of the product of the previous step in EtOH (50 mL) was added 12 M hydrogen chloride (0.91 mL, 11 mmol). The reaction mixture was stirred until complete consumption of the starting material was achieved. The reaction mixture was concentrated in vacuo, and the resulting solid was suspended in dichloroethane (110 mL) and triethylamine (2.3 mL, 16 mmol) was added. After 5 min, Boc<sub>2</sub>O (7.19 g, 32.9 mmol) was added. After being stirred at ambient temperature for 1 day, the reaction mixture was diluted with dichloroethane and washed successively with aq. KHSO<sub>4</sub>, aq. NaHCO<sub>3</sub> and brine. The organic layer was dried over MgSO<sub>4</sub> and the solvent evaporated to yield a residue, which was purified by flash column chromatography to give the Boc-protected amine as a white solid (3.21 g).

**[0666]** To a solution of the product of the previous step in EtOH (32 mL) was added 6 M aq. NaOH (5.0 mL, 30 mmol). The reaction mixture was heated under reflux for 5 h. The mixture was cooled to room temperature and water (5 mL) was added. The aqueous layer was washed with dichloromethane, acidified with KHSO<sub>4</sub> aq, and then extracted with

dichloromethane. The organic layer was concentrated in vacuo to give rel-(1R,2R)-1-[(tert-butoxycarbonyl)amino]-2-phenylcyclopentanecarboxylic acid as a colorless solid (1.49 g, 81%). MS (ESI)  $m/z$ :306  $[M + H]^+$ .

*Example 1.7.16*



**[0667]** A 100 ml round bottom flask was charged with methyl 5-iodo-2-methoxybenzoate (Aldrich, 0.5 g, 1.712 mmol) and a stir bar. A solution of THF/MeOH (7 ml: 3 ml) was added with stirring. The resulting solution was treated with NaOH (1M, 3.42 ml, 3.42 mmol). After stirring overnight, the solution was adjusted to pH = 1-2 with HCl (~ 6M) and extracted with EtOAc (x1). The layers were separated. The organic layer was washed with water (x1), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation yielding 5-iodo-2-methoxybenzoic acid (0.4599 g, 1.654 mmol, 97 % yield) as a white solid.

**[0668]** A 100 ml round bottom flask charged with 5-iodo-2-methoxybenzoic acid (0.4599 g, 1.654 mmol) and a stir bar was evacuated and back-filled with Ar (x3). Anhydrous DCM (10 mL) was added, and the solution was cooled to 0 °C with stirring. The solution was treated with EDCI·HCl (0.349 g, 1.819 mmol,) and HOBT·H<sub>2</sub>O (0.279 g, 1.819 mmol). After 1 h (R)-tert-butyl (1-hydrazinyl-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate (0.461 g, 1.571 mmol) and DIPEA (0.867 ml, 4.96 mmol) were added sequentially. The reaction was

stirred at 0 °C to room temperature overnight. After stirring overnight the volatiles were removed via rotary evaporation. The residue was partitioned between EtOAc/water, and the layers were separated. The organic layer was washed with water (x2), brine (x1), and the volatiles were removed via rotary evaporation. Purification via flash chromatography eluting with EtOAc/hexanes yielded (R)-tert-butyl (1-(2-(5-iodo-2-methoxybenzoyl)hydrazinyl)-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate (0.7363 g, 1.331 mmol, 80 % yield).

**[0669]** A 10-20 ml microwave vial was charged with (R)-tert-butyl (1-(2-(5-iodo-2-methoxybenzoyl)hydrazinyl)-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate (0.7363 g, 1.331 mmol) and a stir bar. Burgess' reagent (0.951 g, 3.99 mmol) was added. The vial was sealed with a rubber septum (14/20) and evacuated and back-filled with Ar (x3). Anhydrous 1,2-Dichloroethane (6 ml) was added. The vial was sealed with a cap, and the contents were shaken gently to dissolve. The resulting solution was irradiated at 120 °C for 12 min. After cooling to room temperature the solution was transferred to a round bottom flask, and the volatiles were removed via rotary evaporation. The residue was partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>. The layers were separated. The organic layer was washed with water (x2) and brine (x1). The volatiles were removed via rotary evaporation. Purification via flash chromatography eluting with EtOAc/hexanes yielded (R)-tert-butyl (2-(5-(5-iodo-2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate (0.6141 g, 1.147 mmol, 86 % yield) as a white foam.

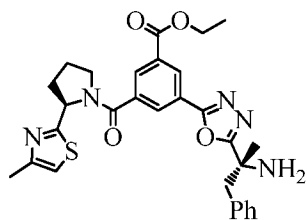
**[0670]** A 100 ml round bottom flask was charged with (R)-tert-butyl (2-(5-(5-iodo-2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate (0.6141 g, 1.147 mmol), Pd(OAc)<sub>2</sub> (0.013 g, 0.057 mmol), Xantphos (0.066 g, 0.115 mmol), and a stir bar. The flask was evacuated and back-filled with Ar (x3). Dioxane (6 ml) and water (2 ml) were combined and purged with Ar to degas, and the resulting solution was added to the flask. After stirring for 2-3 min, the resulting green-black solution was treated with Et<sub>3</sub>N (1.599 ml, 11.47 mmol) which had been degassed via Ar purge. The flask was sealed with a septum which was then secured with electrical tape. The mixture was purged with CO with stirring for 3 min, and the resulting mixture was heated to 75 °C with stirring under CO. After stirring for 4 hours the brown solution was cooled to room temperature. The dioxane was removed via rotary evaporation. The residue was diluted with water and filtered through Celite. The filter pad was rinsed with dilute NaOH (pH ~ 9). The combined aqueous fractions were adjusted to pH = 4-5 with 3 N HCl, and a white ppt was formed. The mixture was extracted with EtOAc (x1), and the layers were separated. The organic layer was washed with water

(x1), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation yielding (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-methoxybenzoic acid (0.5 g, 1.103 mmol, 96 % yield) as a white foam.

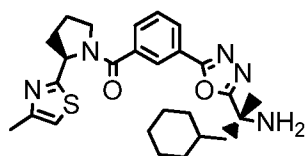
**[0671]** A 25 ml round bottom flask charged with (R)-3-(5-(2-((tert-butoxycarbonyl)amino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-methoxybenzoic acid (0.040 g, 0.088 mmol) and a stir bar was evacuated and back-filled with Ar (x3). Anhydrous DCM (5 mL) was added, and the solution was cooled to 0 °C with stirring. The solution was treated with EDCI-HCl (0.019 g, 0.097 mmol) and HOBT·H<sub>2</sub>O (0.015 g, 0.097 mmol). After 1 h 1-(2,5-dimethyloxazol-4-yl)-N-methylmethanamine (0.012 g, 0.088 mmol) and DIPEA (0.046 ml, 0.265 mmol) were added sequentially. The reaction was stirred at 0 °C to room temperature overnight. After stirring overnight, the volatiles were removed via rotary evaporation. The residue was partitioned between EtOAc/water, and the layers were separated. The organic layer was washed with water (x2), brine (x1), and the volatiles were removed via rotary evaporation. Purification via flash chromatography eluting with EtOAc/MeOH yielded (R)-tert-butyl (2-(5-(5-(((2,5-dimethyloxazol-4-yl)methyl)(methyl)carbamoyl)-2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate (0.0393 g, 0.068 mmol, 77 % yield).

**[0672]** A 25 ml round bottom flask charged with (R)-tert-butyl (2-(5-(5-(((2,5-dimethyloxazol-4-yl)methyl)(methyl)carbamoyl)-2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate (0.0393 g, 0.068 mmol) and a stir bar was evacuated and back-filled with Ar (x3). Anhydrous DCM (0.5 mL) was added with stirring. The resulting solution was treated with TFA (0.5 mL, large excess). After 1 h the volatiles were removed via rotary evaporation. The residue was partitioned between saturated aqueous NaHCO<sub>3</sub> and EtOAc. After stirring for several minutes the layers were separated. The organic layer was washed with water (x1), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation yielding (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4-methoxy-N-methylbenzamide (0.0238 g, 0.050 mmol, 73.3 % yield) as a sticky white solid.

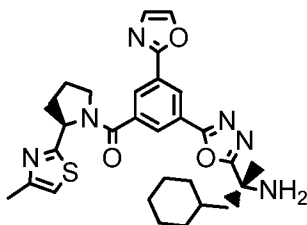


*Example 1.7.17*

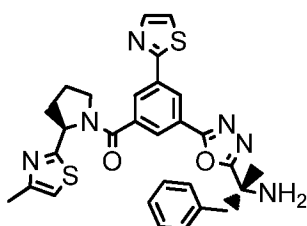
[0673] The compound was synthesized in a manner similar to that of Example 1.7.1.

*Example 1.7.18*

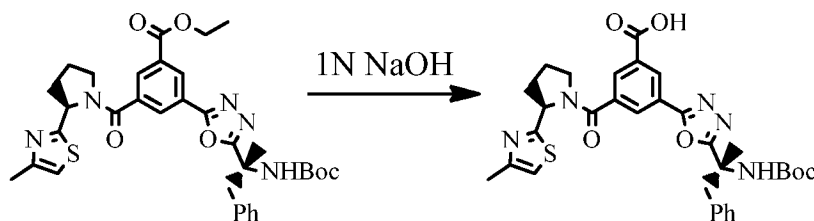
[0674] The compound was synthesized in a manner similar to that of example 1.7.2.

*Example 1.7.19*

[0675] The compound was synthesized in a manner similar to that of example 1.7.2.

*Example 1.7.20*

[0676] The compound was synthesized in a manner similar to that of example 1.7.1.

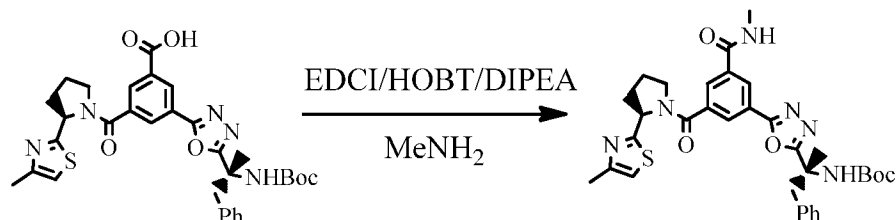
*Example 1.7.21*

[0677] 1N NaOH (0.16 ml, 0.16 mmol, 1.5 eq) was added to a stirred solution of SM (0.071 g, 0.11 mmol, 1 eq). in THF/MeOH (1 ml:0.5 ml). After 3 h the volatiles were removed via rotary evaporation. 1N HCl was added to pH = 5-6 producing a white ppt. The

mixture was extracted with EtOAc (x1), and the layers were separated. The organic layer was washed with water (x1), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation to yield the acid (100%).

**[0678]** Final deprotection was carried out in a manner similar to that of Example 1.7.1.

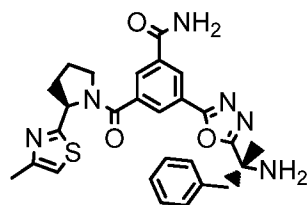
*Example 1.7.22*



**[0679]** EDCI·HCl (0.0161 g, 0.084 mmol, 1.1 eq) and HOBT·H<sub>2</sub>O (0.0114 g, 0.084 mmol, 1.1 eq) were added to a stirred solution of the acid (0.0473 g, 0.077 mmol, 1 eq) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 ml) at 0 °C. After 1 h MeNH<sub>2</sub>·HCl (Aldrich, 0.0155 g, 0.23 mmol, 3 eq) and DIPEA (0.07 ml, 0.05 g, 0.38 mmol, 5 eq) were added sequentially. The reaction was stirred at 0 °C to room temperature overnight. The reaction was quenched with water, and the volatiles were removed via rotary evaporation. The residue was partitioned between EtOAc/H<sub>2</sub>O, and the layers were separated. The organic layer was washed with water (x2), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 0.0365 g (0.058 mmol, 75%) of the amide.

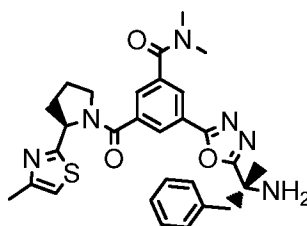
**[0680]** Final deprotection was carried out in a manner similar to that of Example 1.7.1.

*Example 1.7.23*

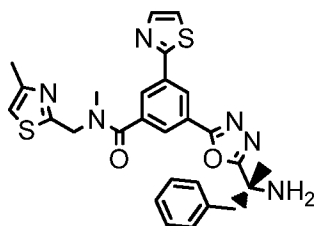


**[0681]** The compound was synthesized in a manner similar to that of example 1.7.22.

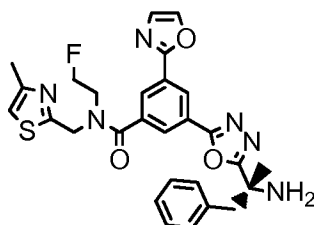
*Example 1.7.24*



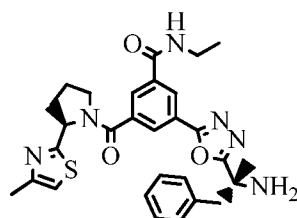
**[0682]** The compound was synthesized in a manner similar to that of example 1.7.22.

*Example 1.7.25*

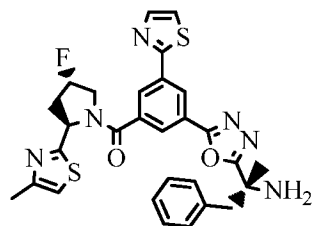
[0683] The compound was synthesized in a manner similar to that of example 1.7.1.

*Example 1.7.26*

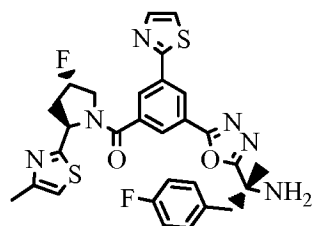
[0684] The compound was synthesized in a manner similar to that of example 1.7.1.

*Example 1.7.27*

[0685] The compound was synthesized in a manner similar to that of example 1.7.22.

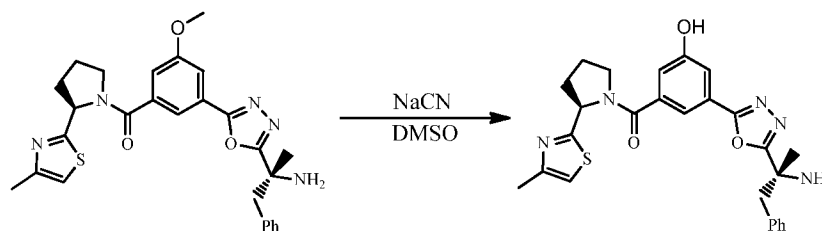
*Example 1.7.28*

[0686] The compound was synthesized in a manner similar to that of example 1.7.1.

*Example 1.7.29*

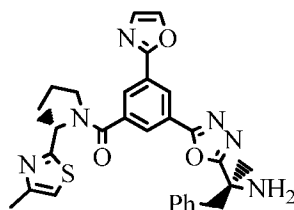
[0687] The compound was synthesized in a manner similar to that of example 1.7.1.

## Example 1.7.30



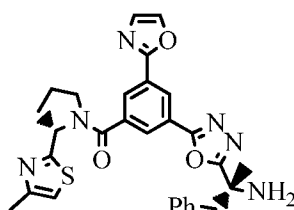
**[0688]** A flask charged with the starting material (0.0402 g, 0.08 mmol, 1 eq), NaCN (0.0196 g, 0.4 mmol, 5 eq), and a stir bar was evacuated and back-filled with Ar (x3). Anhydrous DMSO (2.5 ml) was added, and the resulting mixture was heated to 180 °C with stirring. After 5 h the reaction was cooled to room temperature. The reaction was diluted with water and extracted with EtOAc. The organic layer was washed with water (x3), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation. Purification via flash chromatography yielded 0.0207 g (0.042 mmol, 53%) of the product.

## Example 1.7.31



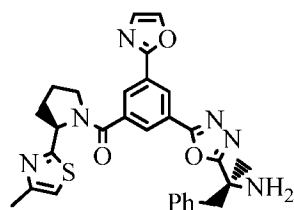
**[0689]** The compound was synthesized in a manner similar to that of example 1.7.1.

## Example 1.7.32



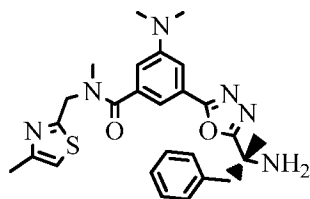
**[0690]** The compound was synthesized in a manner similar to that of example 1.7.1.

## Example 1.7.33



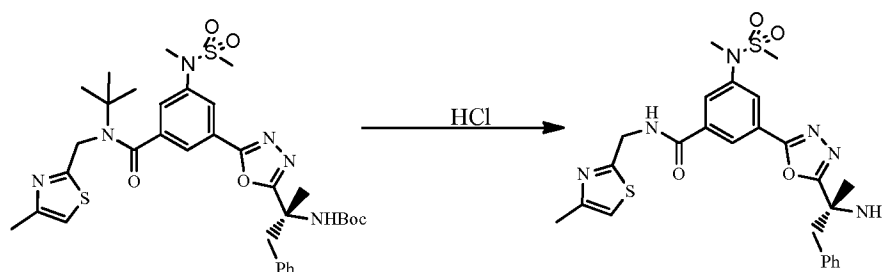
**[0691]** The compound was synthesized in a manner similar to that of example 1.7.1.

## Example 1.7.34



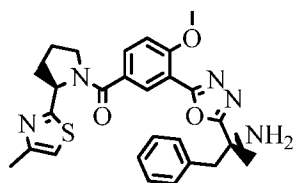
[0692] The compound was synthesized in a manner similar to that of example 1.7.1.

## Example 1.7.35



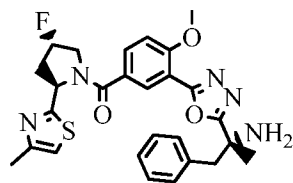
[0693] A flask charged with the starting material (0.0571 g, 0.082 mmol, 1 eq) and a stir bar was evacuated and back-filled with Ar (x3). Anhydrous DMC (0.5 ml) was added. The resulting solution was treated with HCl (4.0 M in 1,4-dioxane, 0.5 ml, large excess) with stirring. After 1 h the volatiles were removed via rotary evaporation. The residue was partitioned between with saturated aqueous NaHCO<sub>3</sub>/EtOAc, and the layers were separated. The organic layer was washed with water (x1), brine (x1), and dried over Na<sub>2</sub>SO<sub>4</sub>. The inorganics were filtered off, and the volatiles were removed via rotary evaporation. Purification via flash chromatography yielded 0.033g (0.061 mmol, 74%) of the product.

## Example 1.7.36

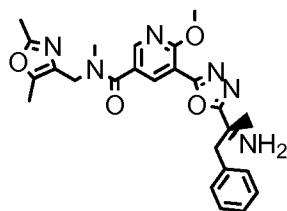


[0694] The compound was synthesized in a manner similar to that of example 1.7.17.

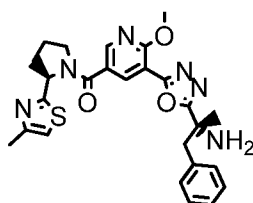
## Example 1.7.37



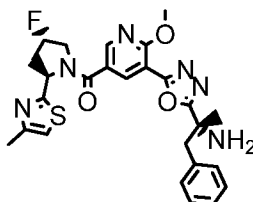
[0695] The compound was synthesized in a manner similar to that of example 1.7.17.

*Example 1.7.38*

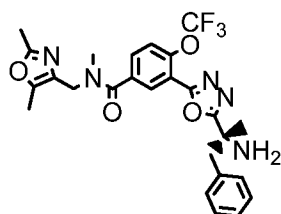
[0696] The compound was synthesized in a manner similar to that of example 1.7.17 starting with methyl 5-bromo-2-methoxynicotinate (Combi-Blocks).

*Example 1.7.39*

[0697] The compound was synthesized in a manner similar to that of example 1.7.17 starting with methyl 5-bromo-2-methoxynicotinate (Combi-Blocks).

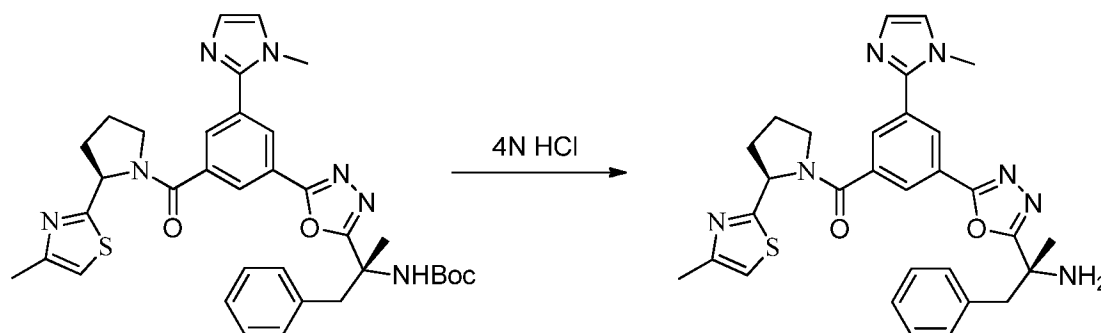
*Example 1.7.40*

[0698] The compound was synthesized in a manner similar to that of example 1.7.17 starting with methyl 5-bromo-2-methoxynicotinate (Combi-Blocks).

*Example 1.7.41*

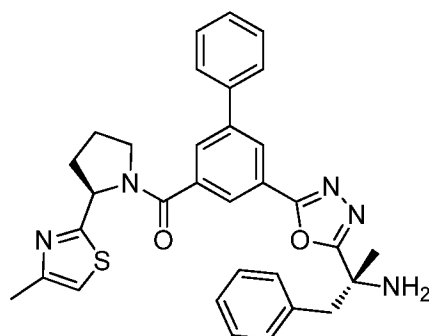
[0699] The compound was synthesized in a manner similar to that of example 1.7.17 starting with 5-bromo-2-(trifluoromethoxy)benzoic acid (Combi-Blocks).

*Example 1.7.42: Synthesis of (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-methyl-1Himidazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone*



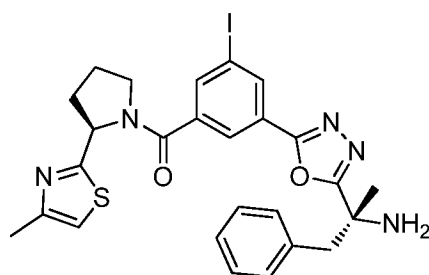
**[0700]** Deprotection of the Boc protected compound using a procedure similar to the one depicted in Example 1.7.2 yielded the final product.

*Example 1.7.43*



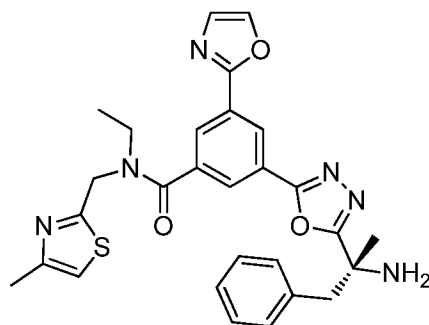
**[0701]** The compound was synthesized in a manner similar to that as in Example 1.7.1.

*Example 1.7.44*



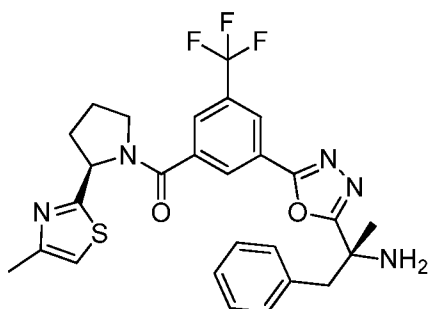
**[0702]** The compound was synthesized in a manner similar to that as in Example 1.7.1.

*Example 1.7.45*



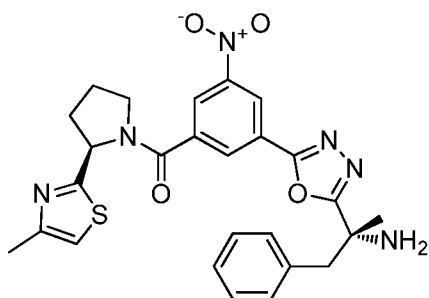
[0703] The compound was synthesized in a manner similar to that as in Example 1.7.1.

*Example 1.7.46*



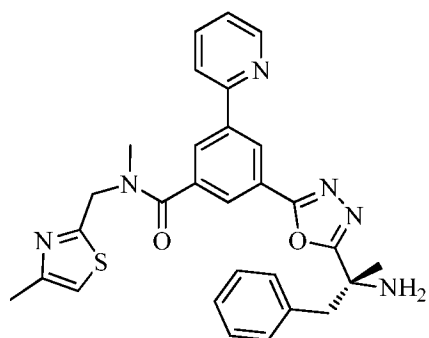
[0704] The compound was synthesized in a manner similar to that as in Example 1.7.1.

*Example 1.7.47*



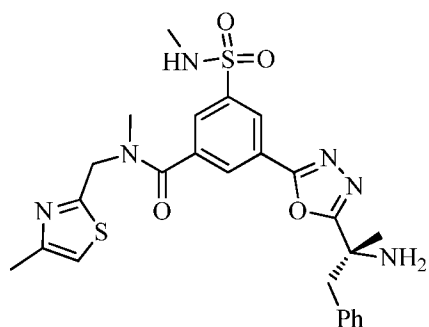
[0705] The compound was synthesized in a manner similar to that as in Example 1.7.1.

*Example 1.7.48*



[0706] The compound was synthesized in a manner similar to that as in Example 1.7.1.

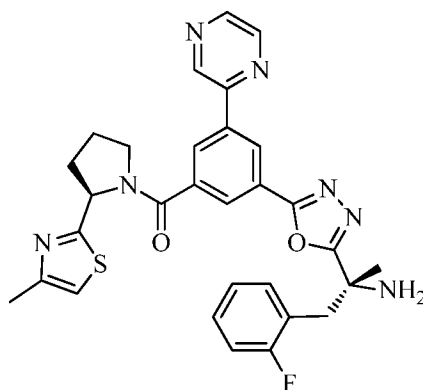
*Example 1.7.49*



[0707] The compound was synthesized in a manner similar to that as in Example 1.7.1.

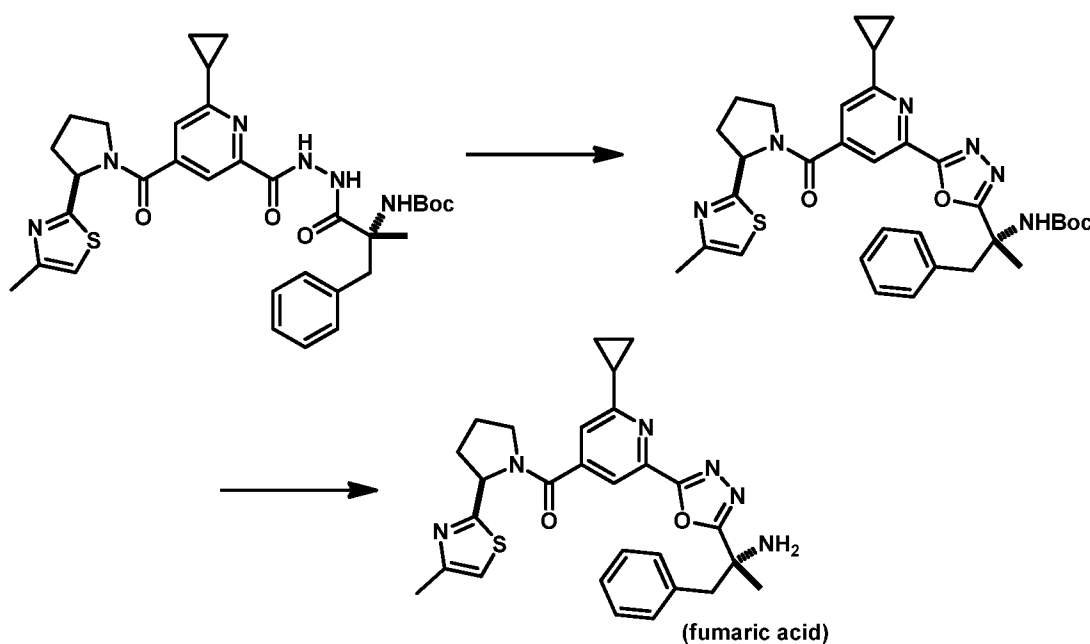


## Example 1.7.50



[0708] The compound was synthesized in a manner similar to that as in Example 1.7.1.

## Example 1.7.51

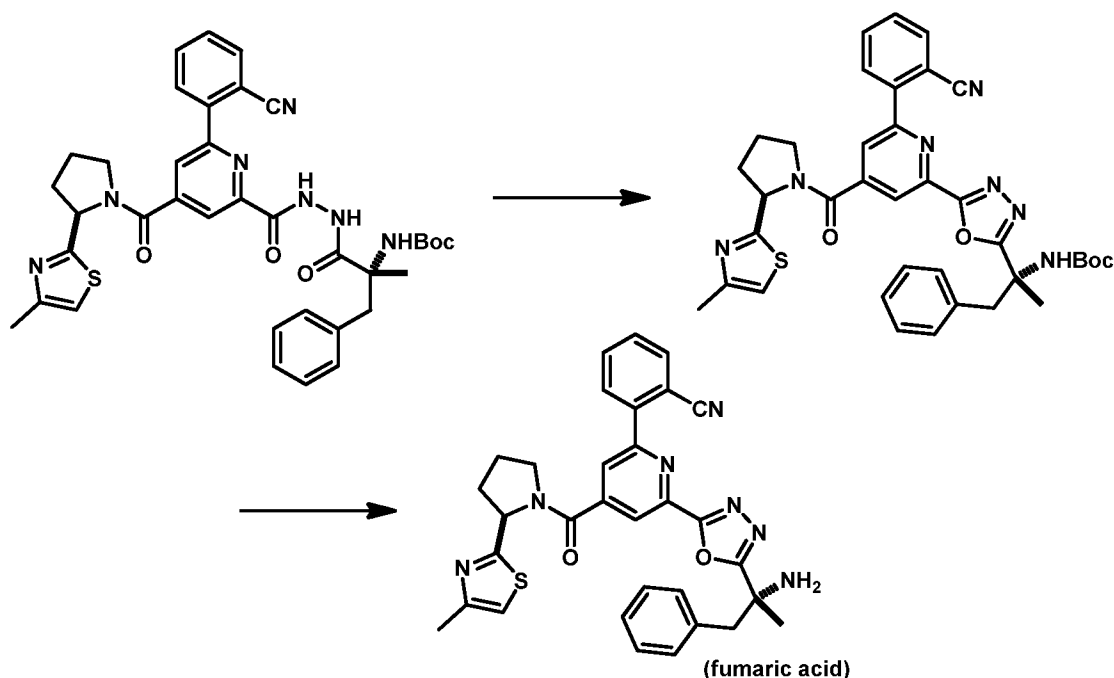


[0709] ***tert*-Butyl {(2*R*)-2-[5-(6-cyclopropyl-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** To a stirred solution of *tert*-butyl [(2*R*)-1-[2-[(6-cyclopropyl-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)carbonyl]hydrazino]-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (417 mg, 0.66 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) were added CBr<sub>4</sub> (437 mg, 1.32 mmol), PPh<sub>3</sub> (346 mg, 1.32 mmol) and imidazole (89 mg, 1.32 mmol) at 0 degree and the mixture was stirred at rt for 2 hours. The starting molecule was completely consumed and volatiles were evaporated to give a crude product. This was purified with column chromatography (EtOAc in hexane = 0 to 100%) to give *tert*-butyl {(2*R*)-2-[5-(6-cyclopropyl-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate containing a

significant amount of  $\text{O=PPh}_3$  as a white solid, which was used for the next reaction without further purification. MS (ESI)  $m/z$ : 615  $[\text{M}+\text{H}]^+$ .

**[0710] (2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-cyclopropylpyridin-4-yl)[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1):** To a stirred solution of *tert*-butyl {[(2*R*)-2-[5-(6-cyclopropyl-4-[[[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate (405 mg, 0.66 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.4 ml) was added TFA (0.8 ml) at rt and the mixture was stirred for 1 hour. Volatiles were evaporated and the residue was purified with column chromatography (NH-silica, EtOAc in hexane = 20 to 100%) to give the desired product as a free form. This was dissolved in EtOH (1 ml) and fumaric acid (1 eq. to the free form) was added. The mixture was stirred at rt for 1 hour and EtOH was evaporated to give a solid, which was collected, washed with IPE and dried under reduced pressure to give (2-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-cyclopropylpyridin-4-yl)[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) (145 mg, 35% yield in 4 steps) as an off-white solid.

*Example 1.7.52*

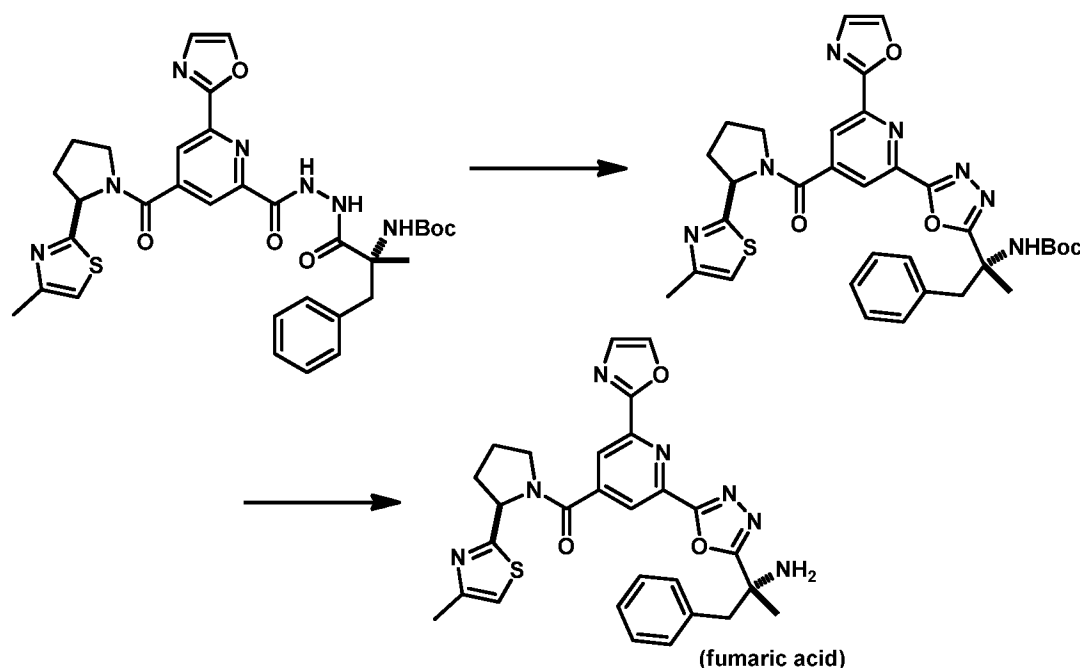


**[0711] *tert*-Butyl [(2*R*)-2-{5-[6-(2-cyanophenyl)-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from *tert*-butyl [(2*R*)-1-(2-{[6-(2-cyanophenyl)-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-

yl]carbonyl}hydrazino)-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (194 mg, 0.281 mmol) in a similar manner to *Example 1.7.51*. MS (ESI)  $m/z$ : 676  $[M+H]^+$ .

**[0712] 2-(6-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)benzonitrile (2*E*)-but-2-enedioate (1:1) :** The desired compound was synthesized from *tert*-butyl [(2*R*)-2-{5-[6-(2-cyanophenyl)-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate (188 mg, 0.278 mmol) in a similar manner to *Example 1.7.51*. (50 mg, 26% yield in 6 steps).

*Example 1.7.53*

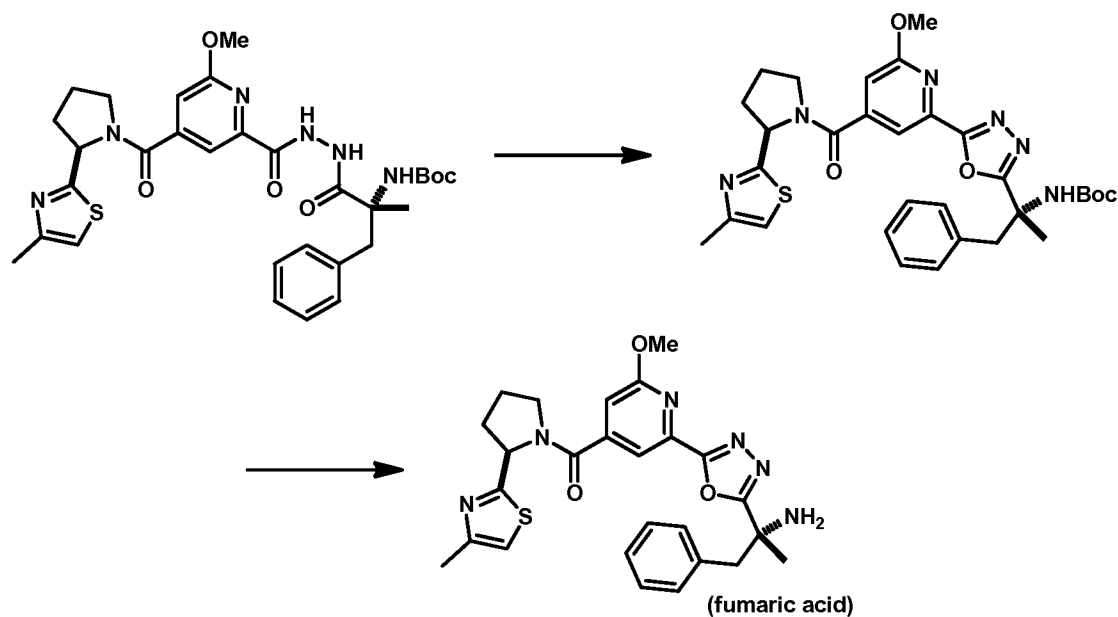


**[0713] *tert*-Butyl [(2*R*)-2-{5-[4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from *tert*-butyl [(2*R*)-2-methyl-1-(2-{[4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]carbonyl}hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate (160 mg, 0.250 mmol) in a similar manner to *Example 1.7.50*. (116 mg, 72% yield) MS (ESI)  $m/z$ : 642  $[M+H]^+$ .

**[0714] [2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :** The desired compound was synthesized from *tert*-butyl [(2*R*)-2-{5-[4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(1,3-oxazol-2-yl)pyridin-2-

yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate (116 mg, 0.180 mmol) in a similar manner to *Example 1.7.50*. (85 mg, 72% yield).

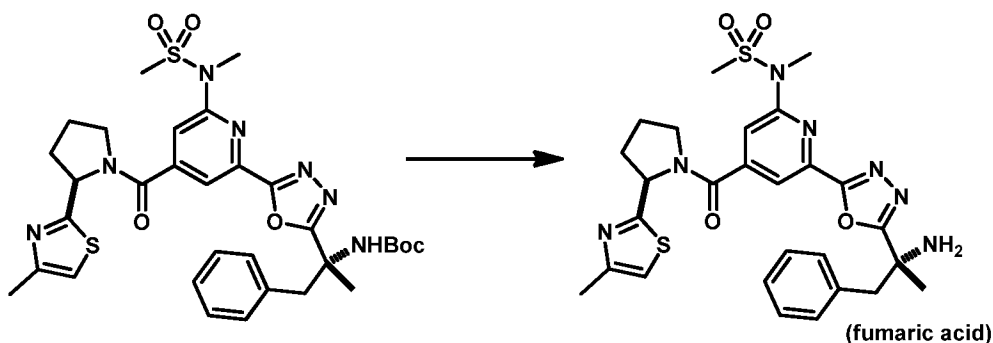
*Example 1.7.54*



[0715] ***tert*-Butyl {(2*R*)-2-[5-(6-methoxy-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from *tert*-butyl [(2*R*)-1-{2-[(6-methoxy-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)carbonyl]hydrazino}-2-methyl-1-oxo-3-phenylpropan-2-yl]carbamate (292 mg, 0.469 mmol) in a similar manner to *Example 1.7.50*. (160 mg, 56% yield) MS (ESI) *m/z*: 605 [M+H]<sup>+</sup>.

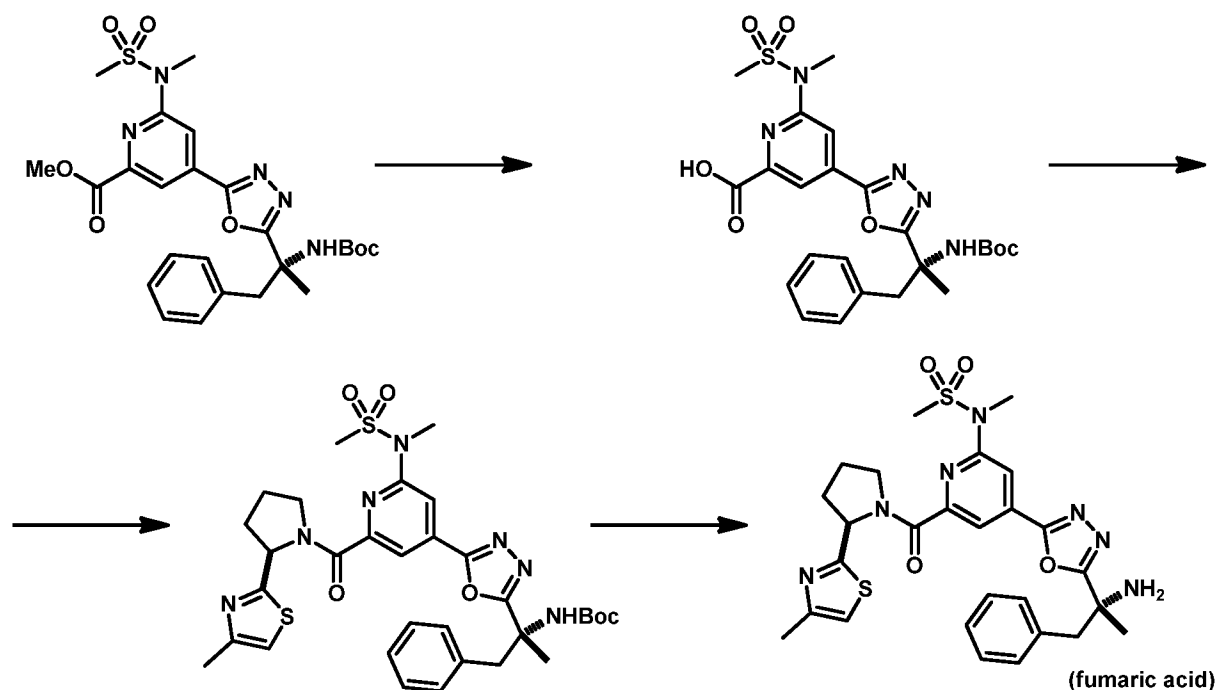
[0716] **(2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-4-yl)[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :** The desired compound was synthesized from *tert*-butyl {(2*R*)-2-[5-(6-methoxy-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (160 mg, 0.265 mmol) in a similar manner to *Example 1.7.50*. (120 mg, 73% yield).

## Example 1.7.55



[0717] ***N*-(6-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-*N*-methylmethanesulfonamide (2*E*)-but-2-enedioate (1:1)** : The desired compound was synthesized from *tert*-butyl { (2*R*)-2-[5-(6-[methyl(methylsulfonyl)amino]-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate (117 mg, 0.172 mmol) in a similar manner to *Example 1.7.50*. (67 mg, 56% yield).

## Example 1.7.56



[0718] **4-(5-{(2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-[methyl(methylsulfonyl)amino]pyridine-2-carboxylic acid**: To a stirred solution of methyl 4-(5-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-

oxadiazol-2-yl)-6-[methyl(methylsulfonyl)amino]pyridine-2-carboxylate (99 mg, 0.18 mmol) in THF (1.36 ml) was added 1 M NaOH aq. (1.36 ml) at rt and the mixture was stirred at rt for 1 hour. The reaction was quenched with 1 M HCl aq. (1.36 ml) The mixture was evaporated to give a crude of 4-(5-((2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-[methyl(methylsulfonyl)amino]pyridine-2-carboxylic acid as a white solid, which was used for the next reaction without further purification.

**[0719] *tert*-Butyl {(2*R*)-2-[5-(2-[methyl(methylsulfonyl)amino]-6-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:**

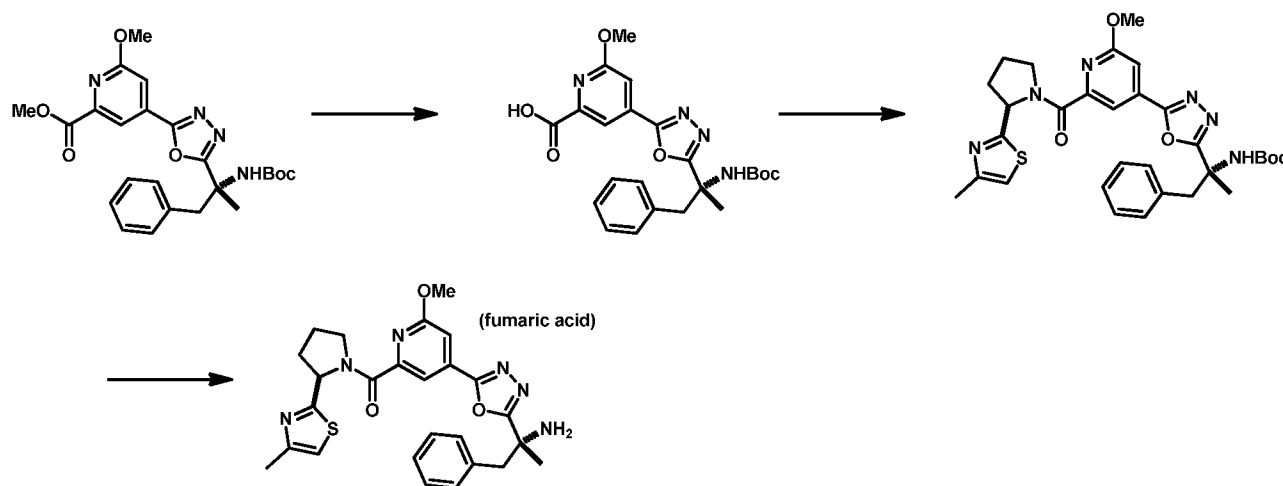
To a stirred solution of 4-(5-((2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-[methyl(methylsulfonyl)amino]pyridine-2-carboxylic acid (96 mg, 0.18 mmol), *i*-Pr<sub>2</sub>NEt (0.068 ml, 0.40 mmol) and 4-methyl-2-[(2*R*)-pyrrolidin-2-yl]-1,3-thiazole (36 mg, 0.22 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) was added HATU (82 mg, 0.22 mmol) at rt and the mixture was stirred at the same temperature overnight. The mixture was quenched with H<sub>2</sub>O and the organic layer was separated. The aqueous layer was extracted with CHCl<sub>3</sub> (x3) and the combined organic layer was washed with aq. KHSO<sub>4</sub> (pH 4), satd. NaHCO<sub>3</sub> aq and brine, dried over MgSO<sub>4</sub> and evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 20 to 80%) to give *tert*-butyl {(2*R*)-2-[5-(2-[methyl(methylsulfonyl)amino]-6-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (62 mg, 50% yield) as a yellow oil. MS (ESI) *m/z*: 682 [M+H]<sup>+</sup>.

**[0720] *N*-(4-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-*N*-methylmethanesulfonamide (2*E*)-but-2-enedioate (1:1) :**

To a stirred solution of *tert*-butyl {(2*R*)-2-[5-(2-[methyl(methylsulfonyl)amino]-6-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (62 mg, 0.090 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added TFA (4 ml) at rt and the mixture was stirred for 1 hour. Volatiles were evaporated and the residue was purified with column chromatography (NH-silica, EtOAc in hexane = 20 to 100%) to give the desired product as a free form. This was dissolved in EtOH (1 ml) and fumaric acid (1 eq. to the free form) was added. The mixture was stirred at rt for 1 hour and EtOH was evaporated to give a solid, which was collected, washed with IPE and dried under reduced pressure to give *N*-(4-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2*R*)-2-(4-methyl-1,3-

thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-*N*-methylmethanesulfonamide (2*E*)-but-2-enedioate (1:1) (25 mg, 40% yield) as an off-white solid.

*Example 1.7.57*

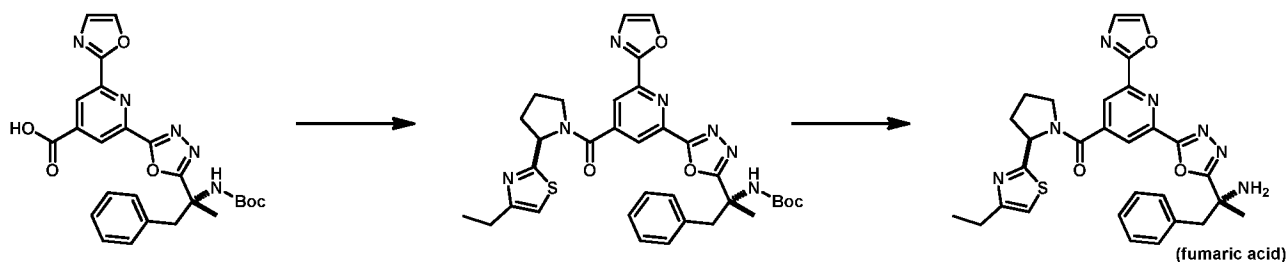


**[0721] 4-(5-((2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-methoxypyridine-2-carboxylic acid:** The desired compound was synthesized from methyl 4-(5-((2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-methoxypyridine-2-carboxylate (650 mg, 1.39 mmol) in a similar manner to *Example 1.7.56*. MS (ESI) *m/z*: 668 [M+H]<sup>+</sup>.

**[0722] *tert*-Butyl {(2*R*)-2-[5-(2-methoxy-6-[[*(2R)*-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from 4-(5-((2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-methoxypyridine-2-carboxylic acid (630 mg, 1.39 mmol) in a similar manner to *Example 1.7.56*. (677 mg, 81% yield) MS (ESI) *m/z*: 605 [M+H]<sup>+</sup>.

**[0723] (4-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-2-yl)[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :** The desired compound was synthesized from *tert*-butyl {(2*R*)-2-[5-(2-methoxy-6-[[*(2R)*-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (246 mg, 0.407 mmol) in a similar manner to *Example 1.7.56*. (125 mg, 50% yield).

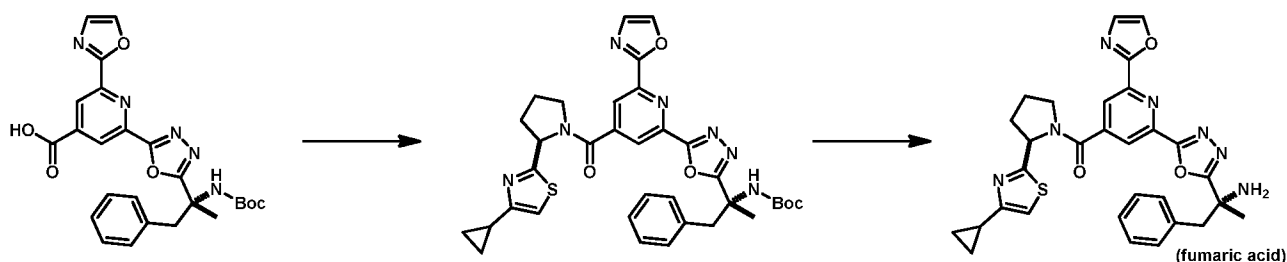
## Example 1.7.58



**[0724] *tert*-Butyl [(2*R*)-2-{5-[4-[(2*R*)-2-(4-ethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 2-(5-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid (120 mg, 0.244 mmol) in a similar manner to *Example 1.7.56*. (147 mg, 92% yield) MS (ESI) *m/z*: 657 [M+H]<sup>+</sup>.

**[0725] [2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2*R*)-2-(4-ethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :** The desired compound was synthesized from *tert*-butyl [(2*R*)-2-{5-[4-[(2*R*)-2-(4-ethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate (147 mg, 0.244 mmol) in a similar manner to *Example 1.7.56*. (91 mg, 60% yield).

## Example 1.7.59



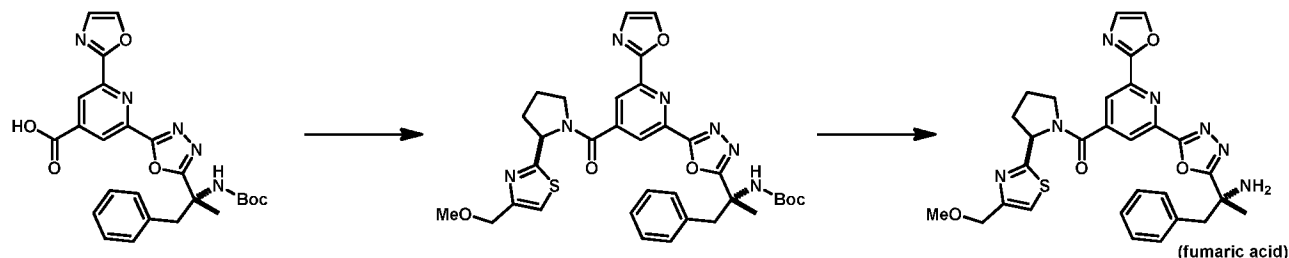
**[0726] *tert*-Butyl [(2*R*)-2-{5-[4-[(2*R*)-2-(4-cyclopropyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from 2-(5-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid (120 mg, 0.244 mmol) in a similar manner to *Example 1.7.56*. MS (ESI) *m/z*: 669 [M+H]<sup>+</sup>.

**[0727] [2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2*R*)-2-(4-cyclopropyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone**



**(2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from *tert*-butyl [(2*R*)-2-{5-[4-{{(2*R*)-2-(4-cyclopropyl-1,3-thiazol-2-yl)pyrrolidin-1-yl}carbonyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate (163 mg, 0.244 mmol) in a similar manner to *Example 1.7.56*. (94 mg, 56% yield in 2 steps).

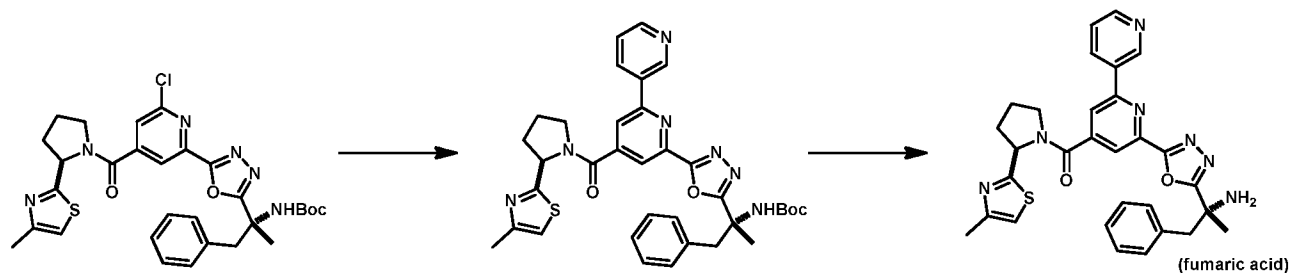
*Example 1.7.60*



**[0728] *tert*-Butyl [(2*R*)-2-{5-[4-{{(2*R*)-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}carbonyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate**: The desired compound was synthesized from 2-(5-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid (100 mg, 0.203 mmol) in a similar manner to *Example 1.7.56*.

**[0729] [2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl]{{(2*R*)-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}methanone (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from *tert*-butyl [(2*R*)-2-{5-[4-{{(2*R*)-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}carbonyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate (120 mg, 0.179 mmol) in a similar manner to *Example 1.7.56*. (12 mg, 10% yield in 2 steps).

*Example 1.7.61*

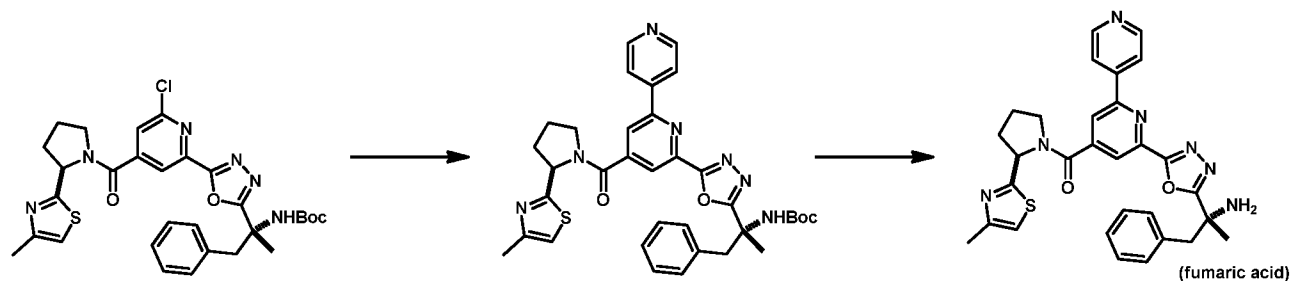


**[0730] *tert*-Butyl {(2*R*)-2-[5-(4-{{(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl}carbonyl}-2,3'-bipyridin-6-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate**: To a stirred solution of *tert*-butyl {(2*R*)-2-[5-(6-chloro-4-{{(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl}carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-

yl}carbamate (120 mg, 0.197 mmol) in toluene (1.5 ml) were added pyridin-3-ylboronic acid (73 mg, 0.59 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (36 mg, 0.039 mmol) and SPhos (65 mg, 0.158 mol) at rt and the mixture was irradiated at 150 degree for 30 min. The starting molecule was completely consumed and volatiles were evaporated to give a crude product. This was purified with column chromatography (EtOAc in hexane = 20 to 100% then MeOH in CHCl<sub>3</sub> = 0 to 10%) to give *tert*-butyl {(2*R*)-2-[5-(4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2,3'-bipyridin-6-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (74 mg, 58% yield) as a colorless oil. MS (ESI) *m/z*: 652 [M+H]<sup>+</sup>.

**[0731] (6-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-2,3'-bipyridin-4-yl)[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :** To a stirred solution of *tert*-butyl {(2*R*)-2-[5-(4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2,3'-bipyridin-6-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (74 mg, 0.114 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added TFA (4 ml) at rt and the mixture was stirred for 1 hour. Volatiles were evaporated and the residue was purified with column chromatography (NH-silica, EtOAc in hexane = 20 to 100%) to give the desired product as a free form. This was dissolved in EtOH (1 ml) and fumaric acid (1 eq. to the free product) was added. The mixture was stirred at rt for 1 hour and EtOH was evaporated to give a solid, which was collected, washed with IPE and dried under reduced pressure to give (6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-2,3'-bipyridin-4-yl)[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) (50 mg, 66% yield) as an off-white solid.

*Example 1.7.62*

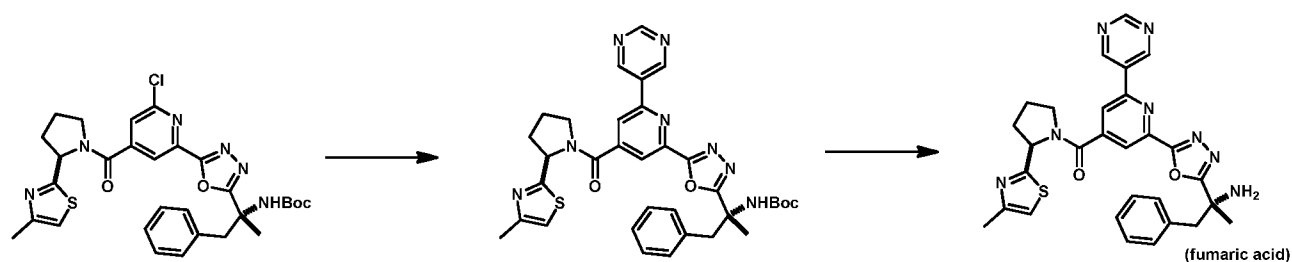


**[0732] *tert*-Butyl {(2*R*)-2-[5-(4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2,4'-bipyridin-6-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from *tert*-butyl {(2*R*)-2-[5-(6-chloro-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-

phenylpropan-2-yl}carbamate (240 mg, 0.394 mmol) in a similar manner to *Example 1.7.61*. (124 mg, 48% yield) MS (ESI)  $m/z$ : 652  $[M+H]^+$ .

**[0733] (6-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-2,4'-bipyridin-4-yl)[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :** The desired compound was synthesized from *tert*-butyl {(2*R*)-2-[5-(4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2,4'-bipyridin-6-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (124 mg, 0.190 mmol) in a similar manner to *Example 1.7.61*. (53 mg, 42% yield).

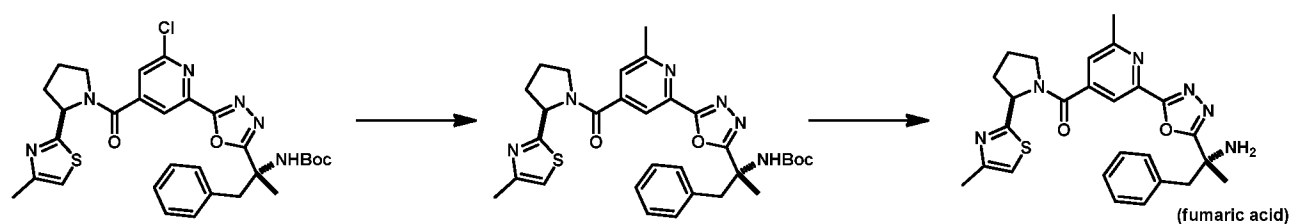
*Example 1.7.63*



**[0734] *tert*-Butyl [(2*R*)-2-{5-[4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(pyrimidin-5-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from *tert*-butyl {(2*R*)-2-[5-(6-chloro-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (200 mg, 0.328 mmol) in a similar manner to *Example 1.7.61*. (180 mg, 84% yield) MS (ESI)  $m/z$ : 597  $[M-t-Bu+H]^+$ .

**[0735] [2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(pyrimidin-5-yl)pyridin-4-yl][(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :** The desired compound was synthesized from *tert*-butyl [(2*R*)-2-{5-[4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(pyrimidin-5-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (180 mg, 0.276 mmol) in a similar manner to *Example 1.7.61*. (104 mg, 47% yield).

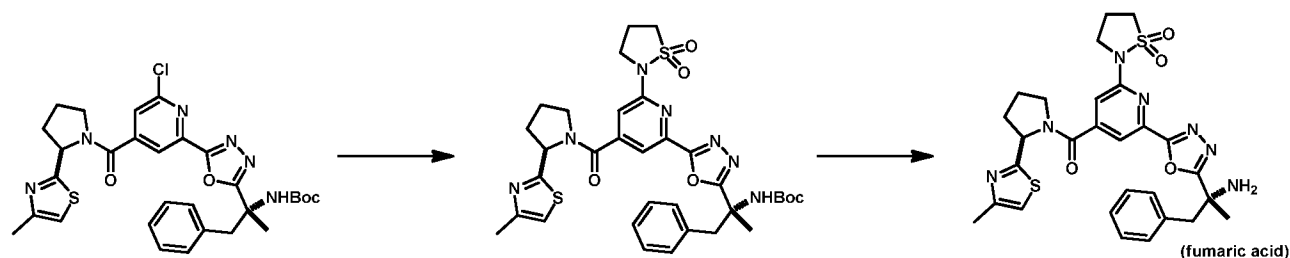
*Example 1.7.64*



**[0736] *tert*-Butyl {(2*R*)-2-[5-(6-methyl-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from *tert*-butyl {(2*R*)-2-[5-(6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (150 mg, 0.246 mmol) in a similar manner to *Example 1.7.61*. (144 mg, 99% yield) MS (ESI) *m/z*: 589 [M-*t*-Bu+H]<sup>+</sup>.

**[0737] (2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methylpyridin-4-yl)[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :** The desired compound was synthesized from *tert*-butyl {(2*R*)-2-[5-(6-methyl-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (144 mg, 0.245 mmol) in a similar manner to *Example 1.7.61*. (54 mg, 37% yield).

*Example 1.7.65*

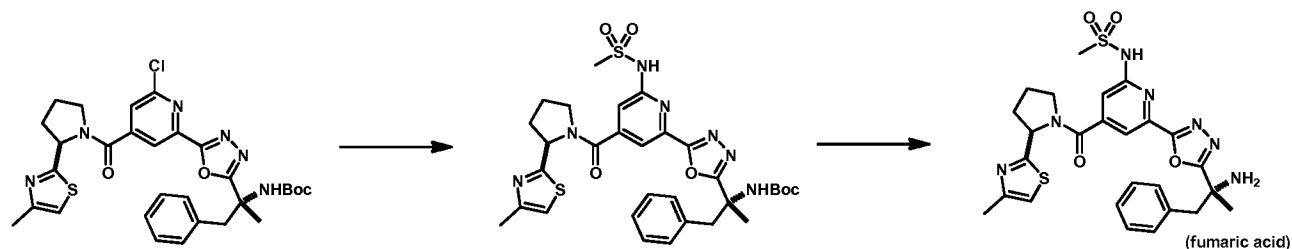


**[0738] *tert*-Butyl [(2*R*)-2-{5-[6-(1,1-dioxido-1,2-thiazolidin-2-yl)-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** To a stirred solution of *tert*-butyl {(2*R*)-2-[5-(6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (150 mg, 0.246 mmol) in dioxane (3 ml) were added 1,2-thiazolidine-1,1-dioxide (90 mg, 0.74 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (113 mg, 0.12 mmol), Xantphos (214 mg, 0.37 mmol) and K<sub>3</sub>PO<sub>4</sub> (157 mg, 0.74 mmol) at rt and the mixture was irradiated with microwave at 150 degree for 30 min. The starting molecule was completely consumed and volatiles were evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 20 to 100%) to give *tert*-butyl [(2*R*)-2-{5-[6-(1,1-dioxido-1,2-thiazolidin-2-yl)-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl}carbamate (144 mg, 84% yield) as a colorless oil. MS (ESI) *m/z*: 694 [M+H]<sup>+</sup>.

**[0739] [2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,1-dioxido-1,2-thiazolidin-2-yl)pyridin-4-yl][(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-**

**yl]methanone (2E)-but-2-enedioate (1:1)** : To a stirred solution of *tert*-butyl [(2*R*)-2-{5-[6-(1,1-dioxido-1,2-thiazolidin-2-yl)-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate (144 mg, 0.208 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added TFA (4 ml) at rt and the mixture was stirred for 1 hour. Volatiles were evaporated and the residue was purified with column chromatography (NH-silica, EtOAc in hexane = 20 to 100%) to give the desired product as a free form. This was dissolved in EtOH (1 ml) and fumaric acid (1 eq. to the free amine) was added. The mixture was stirred at rt for 1 hour and EtOH was evaporated to give a solid, which was collected, washed with IPE and dried under reduced pressure to give [2-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,1-dioxido-1,2-thiazolidin-2-yl)pyridin-4-yl][(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) (84 mg, 57% yield) as an off-white solid.

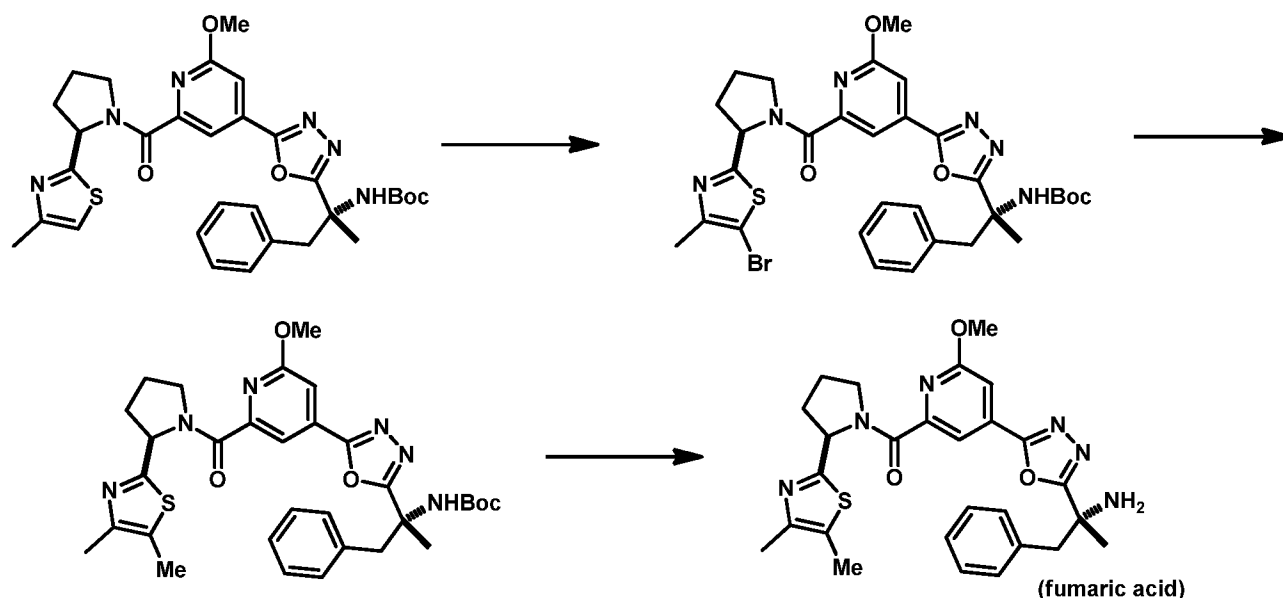
*Example 1.7.66*



**[0740] *tert*-Butyl {(2*R*)-2-[5-(6-[(methylsulfonyl)amino]-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from *tert*-butyl {(2*R*)-2-[5-(6-chloro-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (150 mg, 0.246 mmol) in a similar manner to *Example 1.7.65*. (112 mg, 68% yield) MS (ESI) *m/z*: 668 [M+H]<sup>+</sup>.

**[0741] *N*-(6-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)methanesulfonamide (2*E*)-but-2-enedioate (1:1)** : The desired compound was synthesized from *tert*-butyl {(2*R*)-2-[5-(6-[(methylsulfonyl)amino]-4-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (112 mg, 0.168 mmol) in a similar manner to *Example 1.7.65*. (51 mg, 45% yield).

## Example 1.7.67



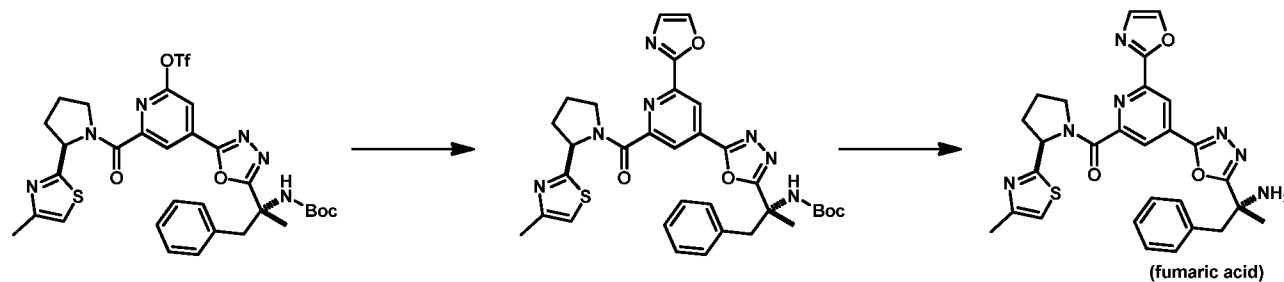
[0742] ***tert*-Butyl {(2*R*)-2-[5-(2-[[*(2R)*]-2-(5-Bromo-4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-methoxypyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** To a stirred solution of *tert*-butyl {(2*R*)-2-[5-(2-methoxy-6-[[*(2R)*]-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl)pyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate in CCl<sub>4</sub> (1.32 ml) was added NBS (94 mg) at rt and the mixture was stirred at 70 degree for 1 hour. The starting molecule was completely consumed and volatiles were evaporated. This resulting crude was purified with column chromatography (EtOAc in hexane = 0 to 66%) to give *tert*-butyl {(2*R*)-2-[5-(2-[[*(2R)*]-2-(5-bromo-4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-methoxypyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (222 mg, 74% yield) as a colorless oil, which was immediately used for the next reaction.

[0743] ***tert*-Butyl {(2*R*)-2-[5-(2-[[*(2R)*]-2-(4,5-dimethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-methoxypyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** To a stirred solution of *tert*-butyl {(2*R*)-2-[5-(2-[[*(2R)*]-2-(5-bromo-4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-methoxypyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (111 mg, 0.162 mmol) in toluene (1.39 ml) were added trimethylboroxine (102 mg, 0.81 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (74 mg, 0.081 mmol), SPhos (133 mg, 0.33 mmol) and K<sub>3</sub>PO<sub>4</sub> (103 mg, 0.49 mmol) at rt and the mixture was stirred at 110 degree for 30 min. The starting molecule was completely consumed and volatiles were evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 10 to

80%) to give *tert*-butyl {(2*R*)-2-[5-(2-[(2*R*)-2-(4,5-dimethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-methoxypyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate (98 mg, 98% yield) as a colorless oil. MS (ESI) *m/z*: 620 [M+H]<sup>+</sup>

**[0744] (4-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-2-yl)[(2*R*)-2-(4,5-dimethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :** To a stirred solution of *tert*-butyl {(2*R*)-2-[5-(2-[(2*R*)-2-(4,5-dimethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-methoxypyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate (98 mg, 0.158 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.7 ml) was added TFA (1.3 ml) at rt and the mixture was stirred for 1 hour. Volatiles were evaporated and the residue was purified with column chromatography (NH-silica, EtOAc in hexane = 20 to 80%) to give the product as a free form. This was dissolved in EtOH (1 ml) and fumaric acid (1 eq. to the free amine) was added. The mixture was stirred at rt for 1 hour and EtOH was evaporated to give a solid, which was collected, washed with IPE and dried under reduced pressure to give (4-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-2-yl)[(2*R*)-2-(4,5-dimethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) (56 mg, 56% yield) as an off-white solid.

*Example 1.7.68*

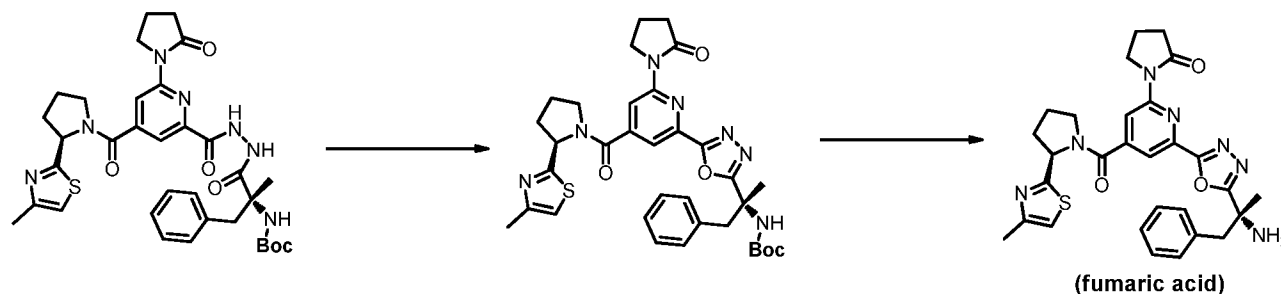


**[0745] *tert*-Butyl [(2*R*)-2-{5-[2-[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(1,3-oxazol-2-yl)pyridin-4-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate:** A solution of 1,3-oxazole (0.19 ml, 2.88 mmol) in THF (3 ml) was placed into a vessel and it was placed under reduced pressure for 30 min at -78 degree for the removal of dissolved O<sub>2</sub> in THF. To this stirred oxazole/THF solution was added *n*-BuLi (1.6 M hexane solution, 1.08 ml, 1.72 mmol) at -78 degree and the mixture was stirred at the same temperature for 1 hour. ZnCl<sub>2</sub> (1.0 M THF solution, 1.72 ml, 1.72 mmol) was added to the mixture, which was allowed to warm up to 0 degree and stirred for 15 min at this degree. To this stirred solution was added 4-(5-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-

yl]carbonyl}pyridin-2-yl trifluoromethanesulfonate (208 mg, 0.288 mmol) in THF (0.5 ml, freshly opened, not degassed) and Pd(PPh<sub>3</sub>)<sub>4</sub> (333 mg, 0.288 mmol) and the mixture was heated at 80 degree for 1 hour. The starting molecule was completely consumed and it was quenched with MeOH and volatiles were evaporated to give a crude, which was purified with column chromatography (EtOAc in hexane = 20 to 100%) to give *tert*-butyl [(2*R*)-2-{5-[2-[[[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(1,3-oxazol-2-yl)pyridin-4-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate containing some byproducts, which was used for the next reaction without further purification.

**[0746] [4-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-2-yl][(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedoate (1:1) :** To a stirred solution of *tert*-butyl [(2*R*)-2-{5-[2-[[[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(1,3-oxazol-2-yl)pyridin-4-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate (184 mg, 0.287 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added TFA (1 ml) at rt and the mixture was stirred for 1 hour. Volatiles were evaporated and the residue was purified with column chromatography (NH-silica, EtOAc in hexane = 20 to 100%) to give the product as a free form. This was dissolved in EtOH (1 ml) and fumaric acid (1 eq. to the free amine) was added. The mixture was stirred at rt for 1 hour and EtOH was evaporated to give a solid, which was collected, washed with IPE and dried under reduced pressure to give [4-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-2-yl][(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedoate (1:1) (97 mg, 51% yield) as an off-white solid.

*Example 1.7.69*



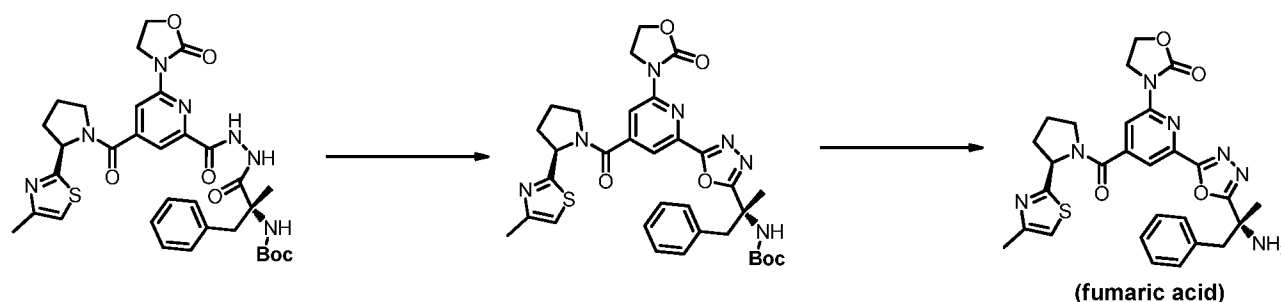
**[0747] *tert*-butyl [(2*R*)-2-{5-[4-[[[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxopyrrolidin-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from *tert*-butyl [(2*R*)-2-methyl-1-(2-{[4-[[[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-



oxopyrrolidin-1-yl)pyridin-2-yl]carbonyl}hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.51* (56 mg, 99%).

**[0748] 1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)pyrrolidin-2-one (2E)-but-2-enedioate (1:1) :** The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxopyrrolidin-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.51* (30 mg, 52% yield).

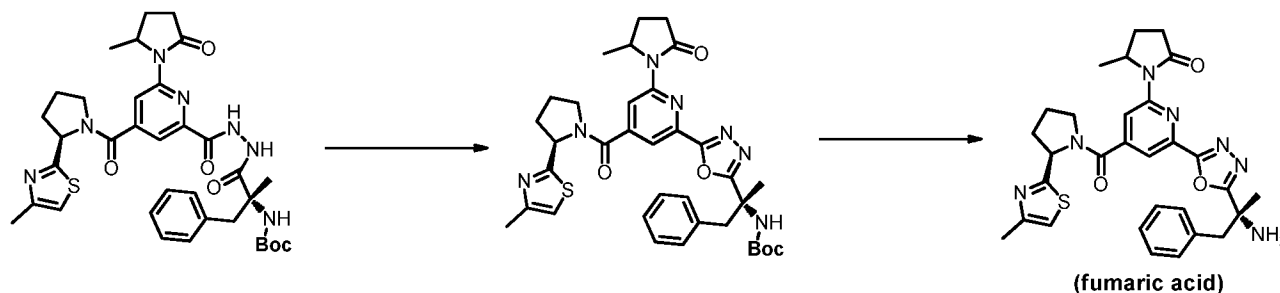
*Example 1.7.70*



**[0749] tert-butyl [(2R)-2-{5-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxo-1,3-oxazolidin-3-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from tert-butyl [(2R)-2-methyl-1-(2-{[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxo-1,3-oxazolidin-3-yl)pyridin-2-yl]carbonyl}hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.51* (27 mg, 99%).

**[0750] 3-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3-oxazolidin-2-one (2E)-but-2-enedioate (1:1) :** The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxo-1,3-oxazolidin-3-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.51* (13 mg, 47% yield).

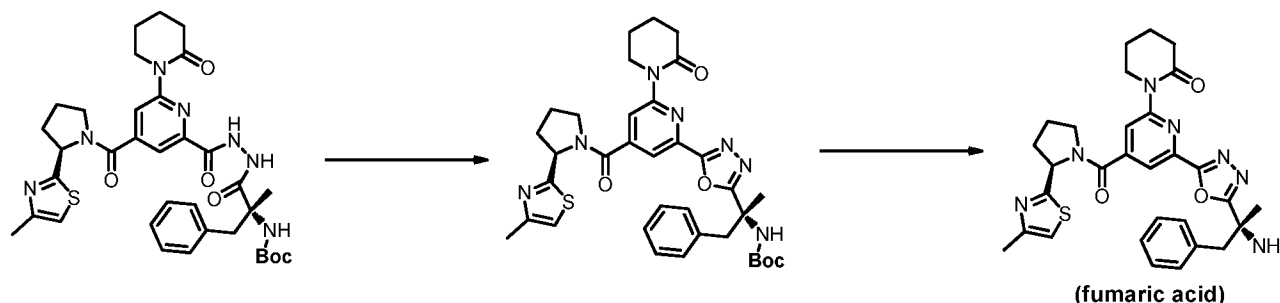
## Example 1.7.71



**[0751] tert-butyl [(2R)-2-{5-[6-(2-methyl-5-oxopyrrolidin-1-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from tert-butyl [(2R)-2-methyl-1-(2-{[6-(2-methyl-5-oxopyrrolidin-1-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]carbonyl}hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.51* (86 mg, 79% yield). MS (ESI)  $m/z$ : 672  $[M+H]^+$ .

**[0752] 1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-5-methylpyrrolidin-2-one (2E)-but-2-enedioate (1:1) :** The desired compound was synthesized from tert-butyl [(2R)-2-{5-[6-(2-methyl-5-oxopyrrolidin-1-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.A1 Ex A9* (15 mg, 26% yield).

## Example 1.7.72

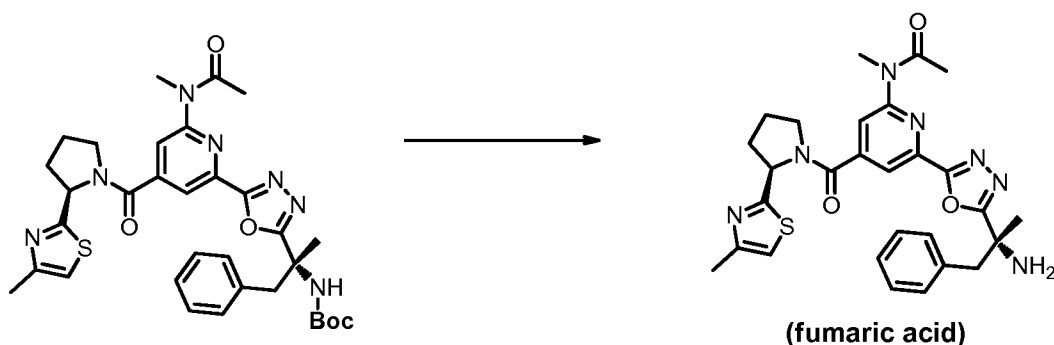


**[0753] tert-butyl [(2R)-2-{5-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxopiperidin-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate:** The desired compound was synthesized from tert-butyl [(2R)-2-methyl-1-(2-{[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxopiperidin-1-

yl)pyridin-2-yl]carbonyl}hydrazino)-1-oxo-3-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.51* (134 mg, 71% yield). MS (ESI)  $m/z$ : 672  $[M+H]^+$ .

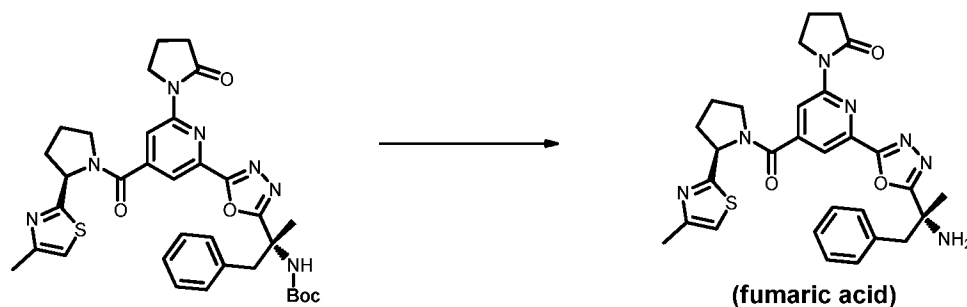
**[0754] 1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)piperidin-2-one (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2-oxopiperidin-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.51* (8.4 mg, 6.1% yield).

*Example 1.7.73*



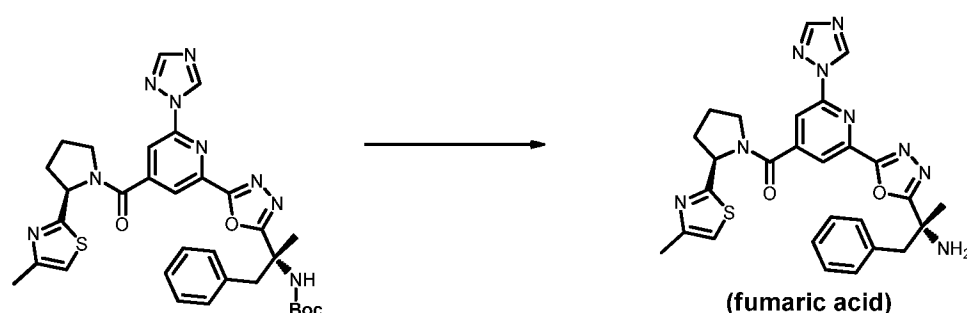
**[0755] N-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-N-methylacetamide (2E)-but-2-enedioate (1:1)** : To a solution of tert-butyl {(2R)-2-[5-(6-[acetyl(methyl)amino]-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (126mg, 0.20 mmol) in  $CH_2Cl_2$  (0.7mL), TFA (1.5ml, 19mmol) was added at 0 °C, and the mixture was stirred for 3 hours at room temperature. All the solvent was evaporated azeotropically with toluene. The residue was purified using column chromatography (NH-silica, EtOH/ $CHCl_3$  = 1:99) to obtain 60 mg of the desired compound as a colorless oil. A solidification of the compound (60mg) with fumaric acid gave N-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-N-methylacetamide (2E)-but-2-enedioate (1:1) (45mg, 35% yield) as a white powder.

## Example 1.7.74



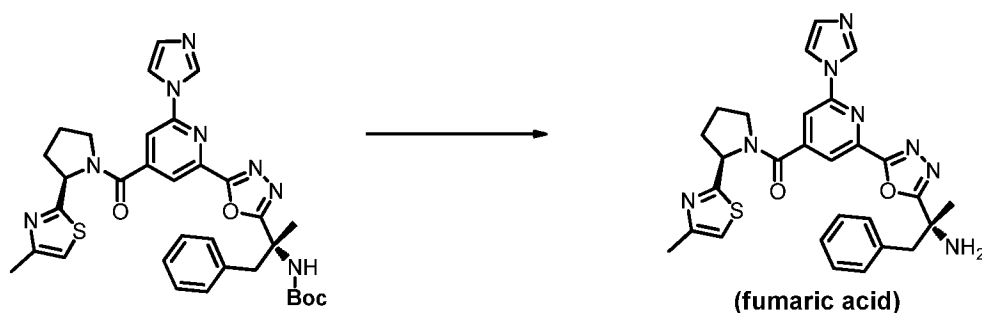
**[0756] 1-(4-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)pyrrolidin-2-one (2E)-but-2-enedioate (1:1) :** The desired compound was synthesized from tert-butyl [(2R)-2-{5-[2-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(2-oxopyrrolidin-1-yl)pyridin-4-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (60 mg, 19% yield) as a white powder.

## Example 1.7.75



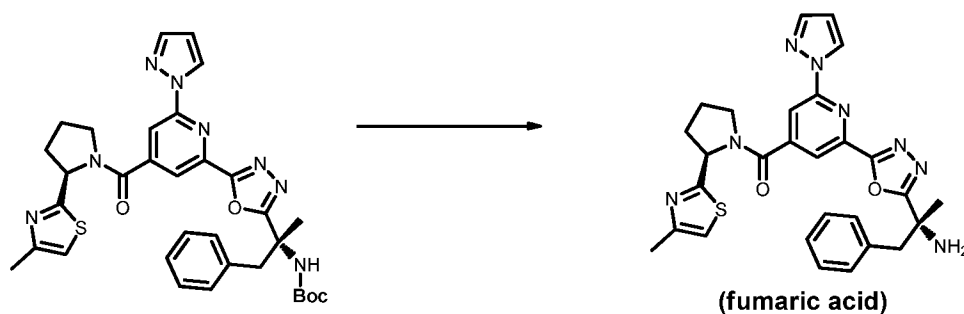
**[0757] [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-1,2,4-triazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :** The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (40 mg, 100% yield) as a white powder.

## Example 1.7.76



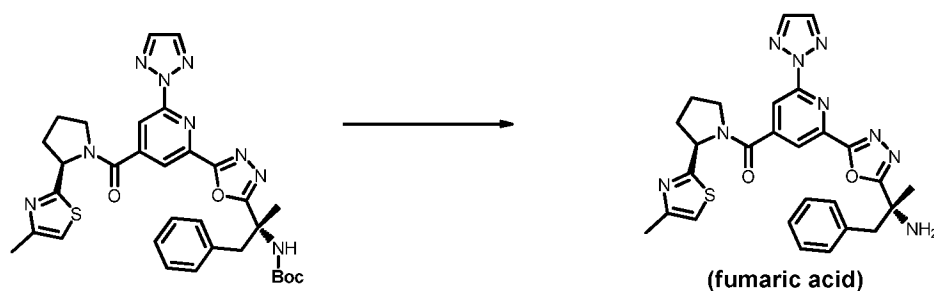
[0758] [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-imidazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[6-(1H-imidazol-1-yl)-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (21 mg, 34% yield) as a beige powder.

*Example 1.7.77*



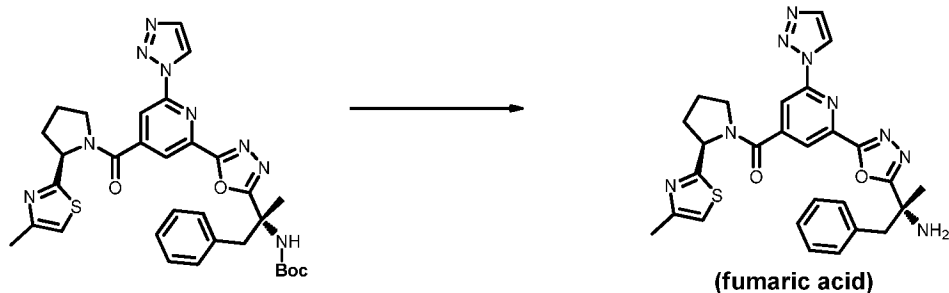
[0759] [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-pyrazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(1H-pyrazol-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (74 mg, 50% yield) as a white powder.

*Example 1.7.78*



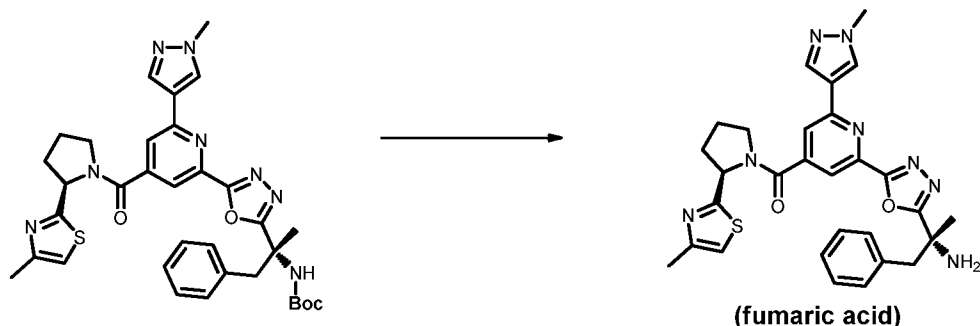
[0760] [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(2H-1,2,3-triazol-2-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (38 mg, 43% yield) as a white powder.

*Example 1.7.79*



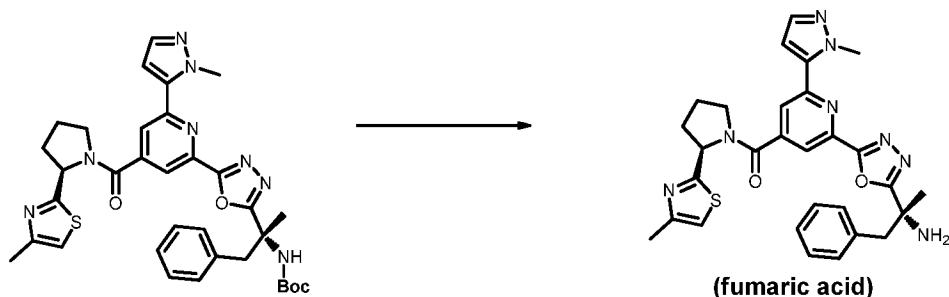
**[0761] [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-1,2,3-triazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :** The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (73 mg, 62% yield) as a beige powder.

*Example 1.7.80*



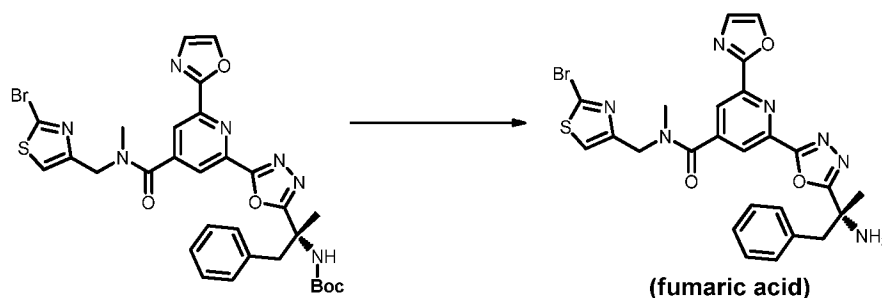
**[0762] [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :** The desired compound was synthesized from tert-butyl [(2R)-2-{5-[6-(1-methyl-1H-pyrazol-4-yl)-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (115 mg, 55% yield) as a pale yellow powder.

*Example 1.7.81*



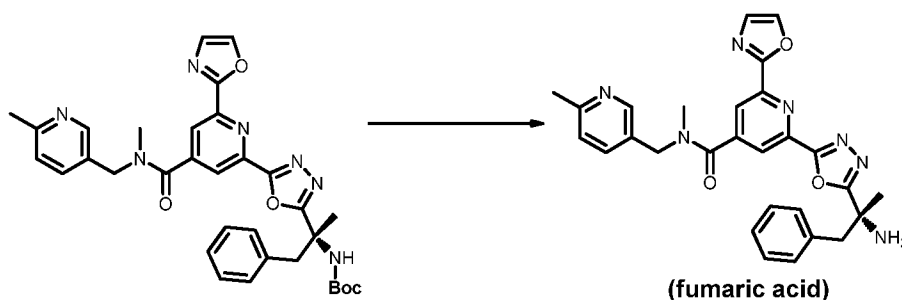
**[0763] 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yl}[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[6-(1-methyl-1H-pyrazol-5-yl)-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (202 mg, 61% yield) as a white powder.

*Example 1.7.82*



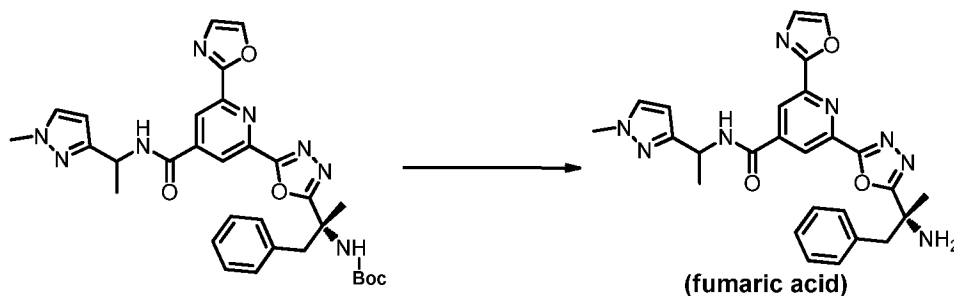
**[0764] 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(4-bromo-1,3-thiazol-2-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{[(4-bromo-1,3-thiazol-2-yl)methyl](methyl)carbonyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (56 mg, 52% yield) as a white powder.

*Example 1.7.83*



**[0765] 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(6-methylpyridin-3-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{methyl[(6-methylpyridin-3-yl)methyl]carbonyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (56 mg, 52% yield) as a white powder.

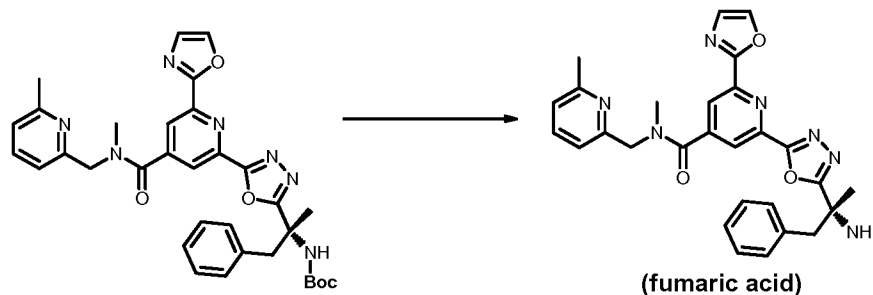
## Example 1.7.84



**[0766] 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[1-(1-methyl-1H-pyrazol-3-yl)ethyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) :**

The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{[1-(1-methyl-1H-pyrazol-3-yl)ethyl]carbamoyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate and 1-(1-methyl-1H-pyrazol-3-yl) ethanamine in a similar manner to *Example 1.7.73* (64 mg, 77% yield) as a white powder.

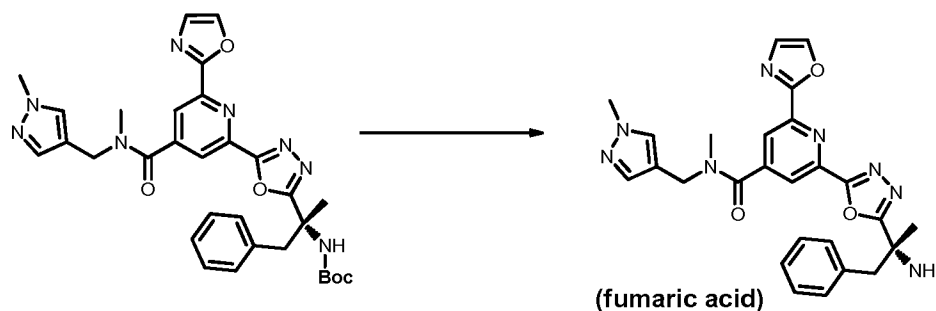
## Example 1.7.85



**[0767] 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(6-methylpyridin-2-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) :**

The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{methyl[(6-methylpyridin-2-yl)methyl]carbamoyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (75 mg, 85% yield) as a white powder.

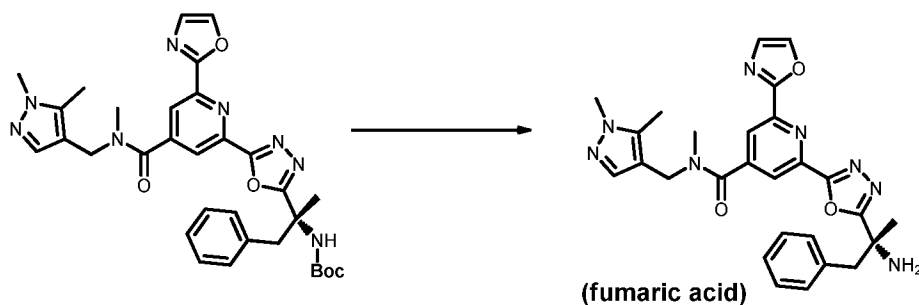
## Example 1.7.86





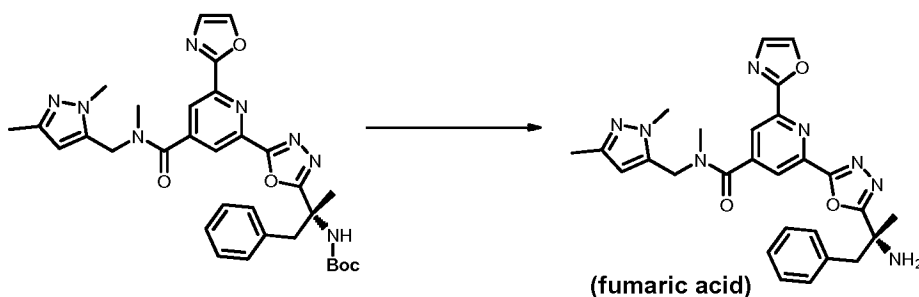
**[0768] 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(1-methyl-1H-pyrazol-4-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{methyl}[(1-methyl-1H-pyrazol-4-yl)methyl]carbamoyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (89 mg, 76% yield) as a white powder.

*Example 1.7.87*



**[0769] 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{[(1,5-dimethyl-1H-pyrazol-4-yl)methyl](methyl)carbamoyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (47 mg, 42% yield) as a white powder.

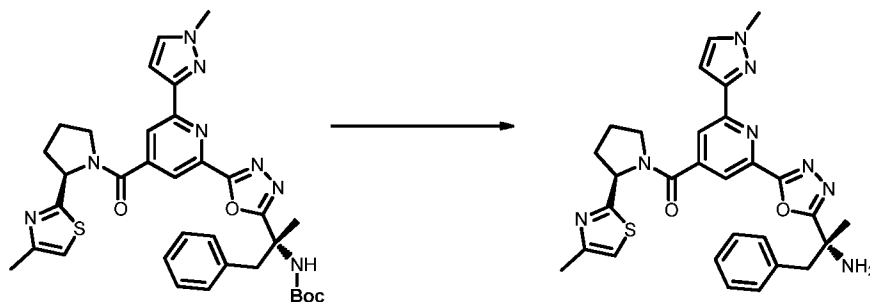
*Example 1.7.88*



**[0770] 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[4-{[(1,3-dimethyl-1H-pyrazol-5-yl)methyl](methyl)carbamoyl}-6-(1,3-oxazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (97 mg, 80% yield) as a white powder. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ: 8.43 (0.7H, s), 8.42 (0.3H, s), 8.27 (0.7H, s), 8.25 (1H, s), 8.19 (0.3H, s), 7.57 (1H, s), 7.26-7.16 (3H, m), 7.11-7.05 (2H, m), 6.61 (2H, s), 6.14 (0.7H, s), 6.09 (0.3H, s), 4.74 (1.4H, s), 4.55 (0.6H, s),

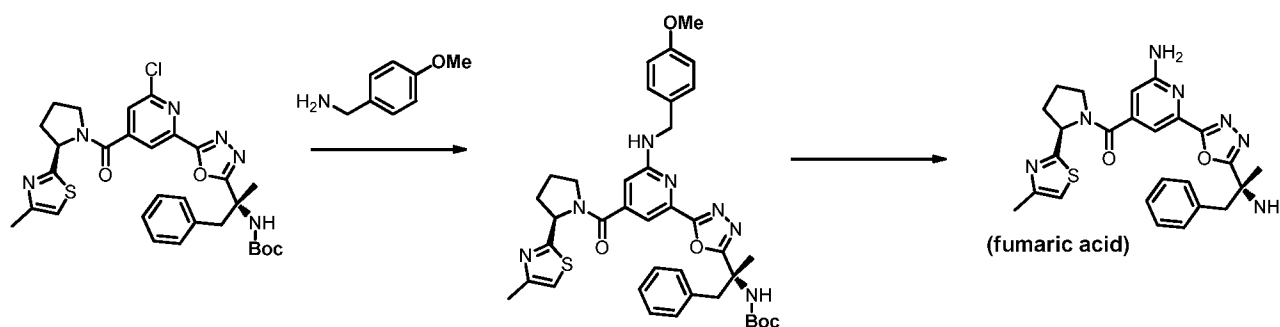
3.78-3.50 (3H, m), 3.40 (2H, br.s), 3.15 (2H, s), 3.02 (0.9H, s), 2.90 (2.1H, s), 2.14-2.10 (3H, m), 1.50-1.49 (3H, m). MS (ESI)  $m/z$ : 513  $[M+H]^+$ .

*Example 1.7.89*



**[0771] [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-3-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone** : To a solution of tert-butyl [(2R)-2-{5-[6-(1-methyl-1H-pyrazol-3-yl)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate (310mg, 0.47 mmol) in  $CH_2Cl_2$  ( 1.0mL) was added TFA ( 3.0ml, 39mmol) at 0 °C, and the mixture was stirred for 3 hours at room temperature. Volatiles were evaporated azeotropically with toluene. The residue was purified using column chromatography (NH-silica, EtOAc / hexane = 50:50 to 100:0) to give 210 mg of the desired compound as a pale yellow solid. A trituration of the solid in EtOH gave [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-3-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (96mg, 37% yield) as a white powder.  $^1H$  NMR (400 MHz,  $DMSO-d_6$ ),  $\delta$ : 8.11 (0.6H, d,  $J$  = 1.3 Hz), 8.02 (0.6H, d,  $J$  = 1.3 Hz), 7.89-7.88 (1.0H, m), 7.83 (0.4H, d,  $J$  = 2.1 Hz), 7.74 (0.4H, d,  $J$  = 0.4 Hz), 7.26-7.04 (6H, m), 6.96 (0.6H, d,  $J$  = 2.2 Hz), 6.85 (0.4H, d,  $J$  = 2.2 Hz), 5.48 (0.6H, dd,  $J$  = 8.0, 4.1 Hz), 5.23-5.18 (0.4H, m), 3.97 (1.8H, s), 3.94 (1.2H, s), 3.76-3.54 (2H, m), 3.17-3.08 (2H, m), 2.46-1.93 (9H, m), 1.50 (1.8H, s), 1.48 (1.2H, s). MS (ESI)  $m/z$ : 555  $[M+H]^+$ .

*Example 1.7.90*

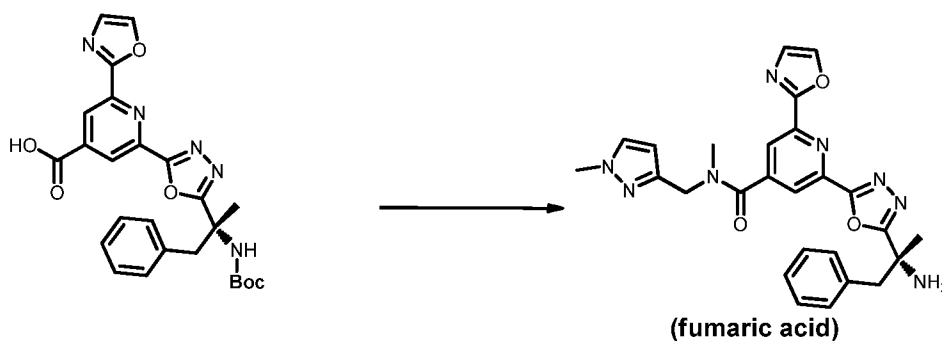


**[0772] tert-butyl {(2R)-2-[5-(6-[(4-methoxybenzyl)amino]-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-**

**phenylpropan-2-yl}carbamate:** A solution of tert-butyl {(2R)-2-[5-(6-chloro-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (300 mg, 0.49 mmol) and 1-(4-methoxyphenyl)methanamine (203 mg, 1.5 mmol) in NMP (1.5 ml) were placed into a vessel for microwave reactions. The vessel was sealed and irradiated with microwave at 140 °C for 30 min. After cooling, H<sub>2</sub>O and brine were added and then the mixture was extracted with CHCl<sub>3</sub>. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The obtained residue was purified with column chromatography (NH-silica, EtOAc / hexane = 10:90 to 100:0) to give tert-butyl {(2R)-2-[5-(6-[(4-methoxybenzyl)amino]-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (76 mg, 22% yield) as a colorless oil. MS (ESI) m/z: 710 [M+H]<sup>+</sup>.

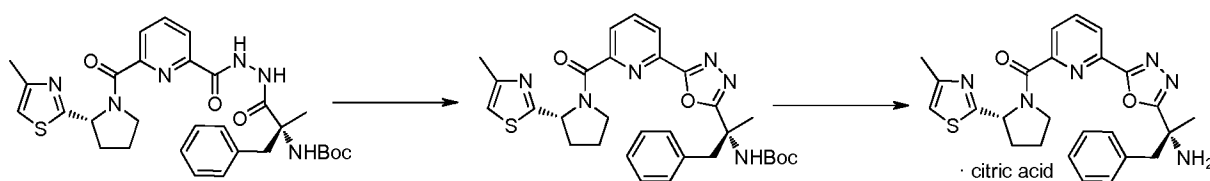
**[0773] (2-amino-6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :** To a solution of tert-butyl {(2R)-2-[5-(6-[(4-methoxybenzyl)amino]-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (73 mg, 0.10 mmol) in TFA (1.6 ml) was added anisole (0.5 ml) and the mixture was stirred at 60 °C for 8 hours. After cooling, saturated aq. NaHCO<sub>3</sub> and brine were added, and then the mixture was extracted with CHCl<sub>3</sub>. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified with column chromatography (NH-silica, EtOH / EtOAc / hexane = 0:50:50 to 5:95:0) to give the desired product (33mg) as a free form. A salt formation of the obtained white solid with fumaric acid gave (2-amino-6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) (35 mg, 56% yield in 2 steps) as a white powder.

*Example 1.7.91*



**[0774] 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(1-methyl-1H-pyrazol-3-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) :** To a solution of 2-(5-{(2R)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl}-1,3,4-oxadiazol-2-yl)-6-(1,3-oxazol-2-yl)isonicotinic acid (80 mg, 0.16 mmol) and N-methyl-1-(1-methyl-1H-pyrazol-3-yl)methanamine (31 mg, 0.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.2 ml) were added EDCI·HCl (47 mg, 0.24 mmol) and HOBT (22 mg, 0.16 mmol) at rt and the mixture was stirred at the same temperature overnight. 0.1M aq. HCl and CHCl<sub>3</sub> were added to the mixture and the organic layer was separated. The aqueous layer was extracted with CHCl<sub>3</sub>. The combined organic layer was washed with saturated aq. NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub> and evaporated. The residue was purified with column chromatography (EtOAc / hexane = 50:50 to 100:0) to give colorless solid. To a solution of the obtained solid in CH<sub>2</sub>Cl<sub>2</sub> (1.0mL) was added TFA (2.0m) at 0 °C, and the mixture was stirred for 3 hours at room temperature. Volatiles were evaporated azeotropically with toluene. The residue was purified using column chromatography (NH-silica, EtOAc / hexane = 20:80 to 100:0) to obtain 50 mg of the desired compound as a colorless oil. A solidification of the compound with fumaric acid gave 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(1-methyl-1H-pyrazol-3-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) (28mg, 28% yield) as a white powder.

*Example 1.7.92*

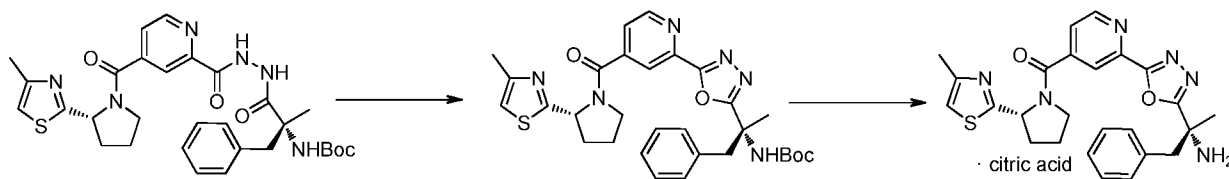


**[0775] tert-butyl rel-{(2R)-2-[5-(6-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from tert-butyl [(2R)-2-methyl-1-{2-[(6-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)carbonyl]hydrazino}-1-oxo-3-phenylpropan-2-yl]carbamate (321 mg, 0.542 mmol) in a similar manner to *Example 1.7.51*. (270 mg, 87% yield) MS (ESI) M/Z: 575 [M+H]<sup>+</sup>.

**[0776] (6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-2-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone 2-hydroxypropane-1,2,3-tricarboxylate (1:1) :** The desired compound was synthesized from tert-butyl rel-{(2R)-2-[5-(6-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-

1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate (267 mg, 0.464 mmol) in a similar manner to *Example 1.7.51*. (143 mg, 46% yield)

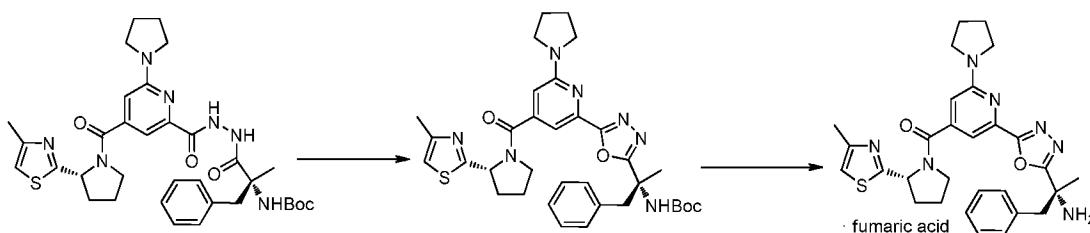
*Example 1.7.93*



**[0777] tert-butyl rel-[(2R)-2-[5-(4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate:** The desired compound was synthesized from tert-butyl [(2R)-2-methyl-1-{2-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl}carbonyl]hydrazino-1-oxo-3-phenylpropan-2-yl} carbamate (375 mg, 0.633 mmol) in a similar manner to *Example 1.7.51*. (320 mg, 88% yield) MS (ESI) M/Z: 575 [M+H]<sup>+</sup>.

**[0778] (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone 2-hydroxypropane-1,2,3-tricarboxylate (1:1) :** The desired compound was synthesized from tert-butyl rel-[(2R)-2-[5-(4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl} carbamate (317 mg, 0.552 mmol) in a similar manner to *Example 1.7.51*. (299 mg, 82% yield)

*Example 1.7.94*

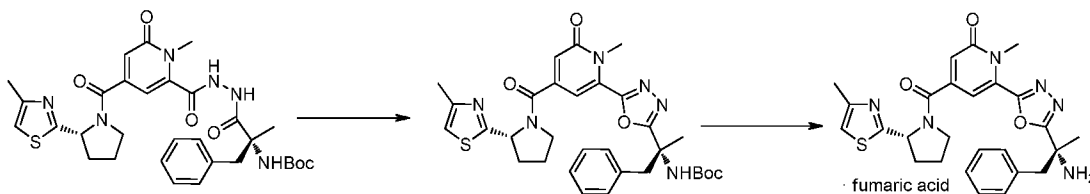


**[0779] tert-butyl rel-[(2R)-2-{5-[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(pyrrolidin-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl} carbamate:** The desired compound was synthesized from tert-butyl [(2R)-2-methyl-1-(2-{[4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(pyrrolidin-1-yl)pyridin-2-yl}carbonyl]hydrazino-1-oxo-3-phenylpropan-2-yl} carbamate (99 mg, 0.15 mmol) in a similar manner to *Example 1.7.51*. (45 mg, 47% yield) MS (APCI/ESI) M/Z: 644 [M+H]<sup>+</sup>.

**[0780] [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(pyrrolidin-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-**

**2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl rel-[(2R)-2-{5-[4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-(pyrrolidin-1-yl)pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate (45 mg, 0.070 mmol) in a similar manner to *Example 1.7.51*. (35 mg, 76% yield)

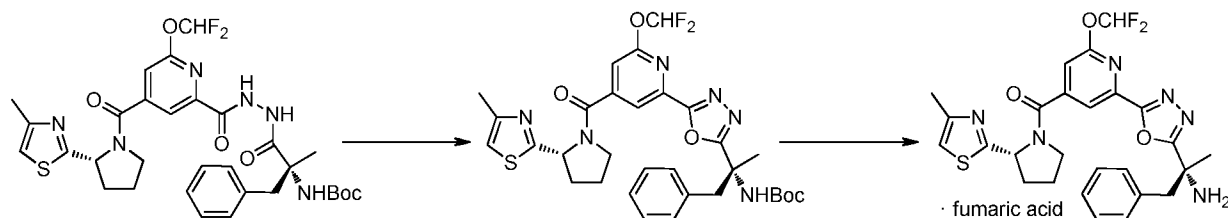
*Example 1.7.95*



**[0781] tert-butyl rel-[(2R)-2-[5-(1-methyl-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate**: The desired compound was synthesized from tert-butyl [(2R)-2-methyl-1-{2-[(1-methyl-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl]carbonyl]hydrazino}-1-oxo-3-phenylpropan-2-yl]carbamate (235 mg, 0.377 mmol) in a similar manner to *Example 1.7.51*. (228 mg, 100% yield) MS (ESI) M/Z: 605 [M+H]<sup>+</sup>.

**[0782] 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl rel-[(2R)-2-[5-(1-methyl-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate (226 mg, 0.374 mmol) in a similar manner to *Example 1.7.51*. (211 mg, 91 mmol)

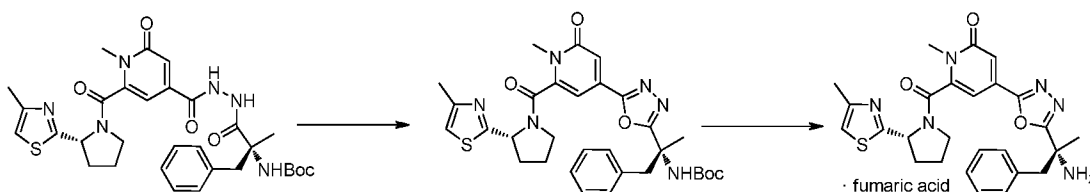
*Example 1.7.96*



**[0783] tert-butyl rel-[(2R)-2-[5-[6-(difluoromethoxy)-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl]-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate**: The desired compound was synthesized from (634 mg, 0.962 mmol) in a similar manner to *Example 1.7.51*. (480 mg, 78% yield) MS (ESI) M/Z: 641 [M+H]<sup>+</sup>.

**[0784] [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(difluoromethoxy)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :** The desired compound was synthesized from tert-butyl rel-[(2R)-2-{5-[6-(difluoromethoxy)-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-1,3,4-oxadiazol-2-yl}-1-phenylpropan-2-yl]carbamate (488 mg, 0.762 mmol) in a similar manner to *Example 1.7.51*. (386 mg, 77% yield)

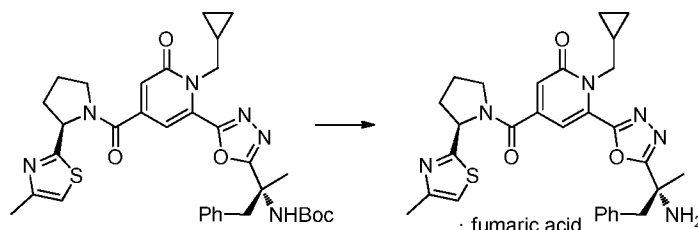
*Example 1.7.97*



**[0785] tert-butyl {(2R)-2-[5-(1-methyl-6-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2-oxo-1,2-dihydropyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate:** The desired compound was synthesized from (210 mg, 0.337 mmol) in a similar manner to *Example 1.7.51*. (86 mg, 42% yield) MS (ESI) M/Z: 605 [M+H]<sup>+</sup>.

**[0786] 4-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-6-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one (2E)-but-2-enedioate (1:1) :** The desired compound was synthesized from tert-butyl {(2R)-2-[5-(1-methyl-6-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2-oxo-1,2-dihydropyridin-4-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (86 mg, 0.14 mmol) in a similar manner to *Example 1.7.51*. (69 mg, 79% yield)

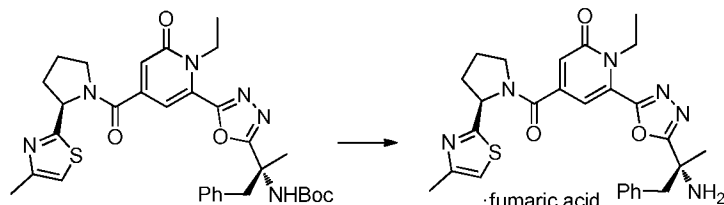
*Example 1.7.98*



**[0787] 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-(cyclopropylmethyl)-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one (2E)-but-2-enedioate (1:1) :** The desired compound was synthesized from tert-butyl [(2R)-2-{5-[1-(cyclopropylmethyl)-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-6-oxo-1,6-dihydropyridin-2-yl]-1,3,4-oxadiazol-2-yl}-

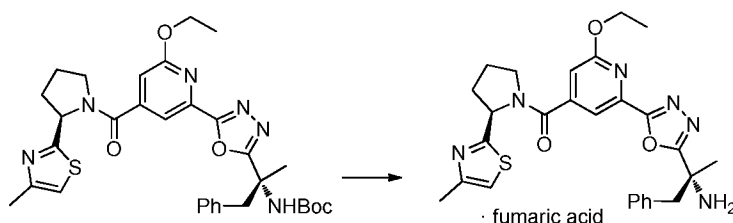
1-phenylpropan-2-yl]carbamate (55 mg, 0.085 mmol) in a similar manner to *Example 1.7.73*. (24 mg, 43% yield)

*Example 1.7.99*



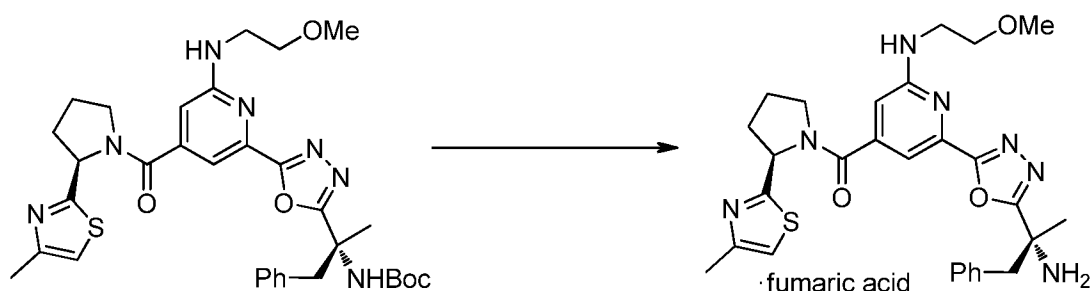
**[0788] 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-ethyl-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl {[(2R)-2-[5-(1-ethyl-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate (35 mg, 0.057 mmol) in a similar manner to *Example 1.7.73*. (24 mg, 66% yield)

*Example 1.7.100*



**[0789] (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-ethoxypyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl {[(2R)-2-[5-(6-ethoxy-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl]carbamate (106 mg, 0.171 mmol) in a similar manner to *Example 1.7.73*. (90 mg, 83% yield)

*Example 1.7.101*

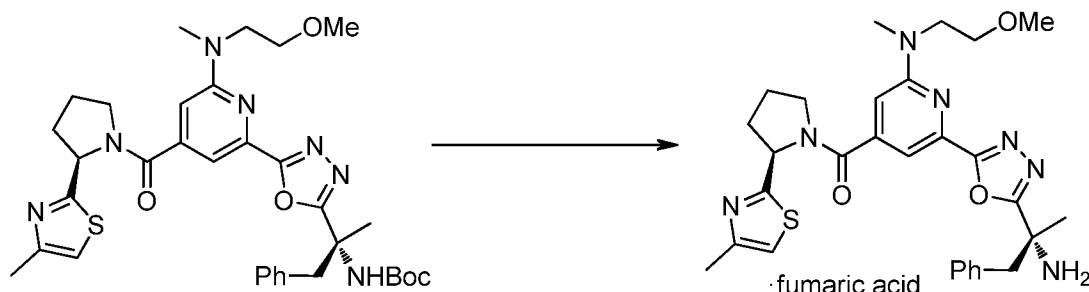


**[0790] (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2-methoxyethyl)amino]pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-**



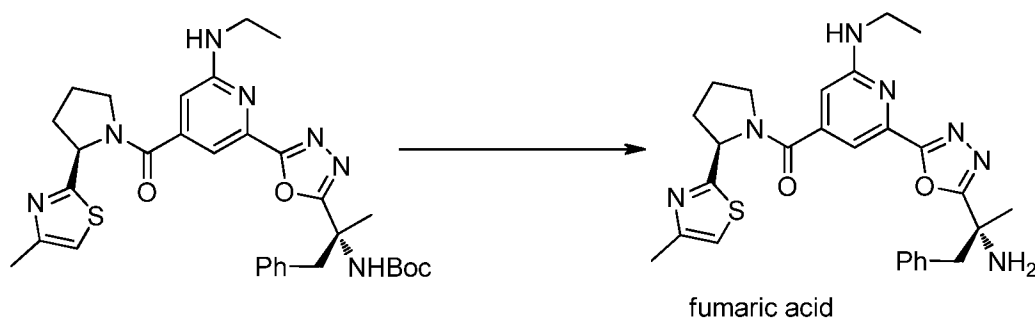
**yl]methanone (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl {(2R)-2-[5-(6-[(2-methoxyethyl)amino]-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (24 mg, 0.036 mmol) in a similar manner to *Example 1.7.73*. (20 mg, 81% yield)

*Example 1.7.102*



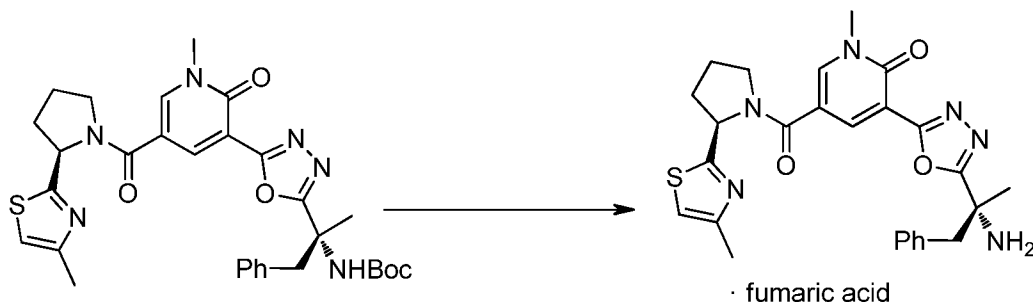
**[0791] (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2-methoxyethyl)(methyl)amino]pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl {(2R)-2-[5-(6-[(2-methoxyethyl)(methyl)amino]-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (52 mg, 0.079 mmol) in a similar manner to *Example 1.7.73*. (44mg, 82% yield)

*Example 1.7.103*



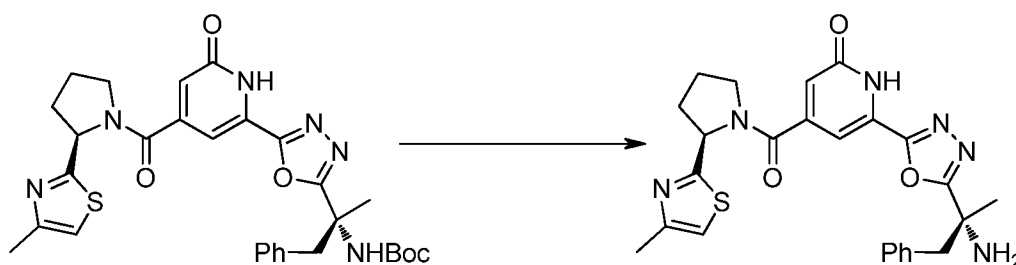
**[0792] [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(ethylamino)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl [(2R)-2-{5-[6-(ethylamino)-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (72 mg, 0.12 mmol) in a similar manner to *Example 1.7.73*. (33mg, 44% yield)

## Example 1.7.104



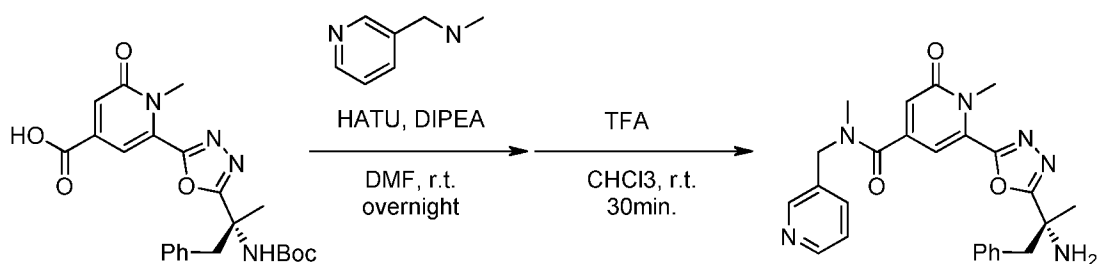
**[0793] 3-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-5-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl {(2R)-2-[5-(1-methyl-5-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}-2-oxo-1,2-dihydropyridin-3-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (173 mg, 0.286 mmol) in a similar manner to *Example 1.7.73*. (93 mg, 52% yield)

## Example 1.7.105



**[0794] 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one (2E)-but-2-enedioate (1:1)** : The desired compound was synthesized from tert-butyl {(2R)-2-[5-(4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]-6-oxo-1,6-dihydropyridin-2-yl)-1,3,4-oxadiazol-2-yl]-1-phenylpropan-2-yl}carbamate (50 mg, 0.085 mmol) in a similar manner to *Example 1.7.73*. (39 mg, 77% yield)

## Example 1.7.106



**[0795] 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-2-oxo-N-(pyridin-3-ylmethyl)-1,2-dihydropyridine-4-carboxamide** : To a solution of *N*-

methyl-*N*-(3-pyridylmethyl)amine (6.1 mg, 0.05 mmol) and 6-(5-[(2*R*)-2-[(tert-butoxycarbonyl)amino]-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid (9.1 mg, 0.02 mmol) and HATU (7.6 mg, 0.02 mmol) in DMF (0.8 mL) was added diisopropylethylamine (30.8 uL, 0.18 mmol). The reaction mixture was stirred at rt overnight, and concentrated in vacuo. The residue was dissolved in chloroform (0.5 mL) and trifluoroacetic acid (0.5 mL). The solution was stirred at r.t. for 30 min. and concentrated in vacuo. The residue was directly purified by LC-MS (5% aqueous formic acid /MeOH ) to give 6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-*N*,1-dimethyl-2-oxo-*N*-(pyridin-3-ylmethyl)-1,2-dihydropyridine-4-carboxamide.

*Example 1.7.107*

**[0796] 6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-*N*,1-dimethyl-*N*-[(6-methylpyridin-2-yl)methyl]-2-oxo-1,2-dihydropyridine-4-carboxamide :** The desired compound was synthesized from 6-methyl-2-picolylmethylamine (6.8 mg, 0.05 mmol) in a similar manner to *Example 1.7.106*.

*Example 1.7.108*

**[0797] 6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-*N*-butyl-1-methyl-2-oxo-*N*-(pyridin-4-ylmethyl)-1,2-dihydropyridine-4-carboxamide :** The desired compound was synthesized from *N*-(4-pyridinylmethyl)-1-butanamine hydrochloride (10.0 mg, 0.05 mmol) in a similar manner to *Example 1.7.106*.

*Example 1.7.109*

**[0798] 6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-4-{[2-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1*H*)-one :** The desired compound was synthesized from 3-methyl-5-(2-pyrrolidinyl)-1,2,4-oxadiazole (7.7 mg, 0.05 mmol) in a similar manner to *Example 1.7.106*.

*Example 1.7.110*

**[0799] 6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-*N*-butyl-1-methyl-2-oxo-*N*-(pyridin-3-ylmethyl)-1,2-dihydropyridine-4-carboxamide :** The desired compound was synthesized from *N*-(3-pyridinylmethyl)-1-butanamine (8.2 mg, 0.05 mmol) in a similar manner to *Example 1.7.106*.

*Example 1.7.111*

**[0800] 6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-*N*,1-dimethyl-2-oxo-*N*-(1*H*-pyrazol-5-ylmethyl)-1,2-dihydropyridine-4-carboxamide :** The desired

compound was synthesized from methyl-(2*H*-pyrazol-3-ylmethyl)-amine (5.6 mg, 0.05 mmol) in a similar manner to *Example 1.7.106*.

*Example 1.7.112*

**[0801] 6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-*N*,1-dimethyl-2-oxo-*N*-[1-(2-thienyl)ethyl]-1,2-dihydropyridine-4-carboxamide** : The desired compound was synthesized from *N*-methyl-1-(2-thienyl)ethanamine hydrochloride (8.8 mg, 0.05 mmol) in a similar manner to *Example 1.7.106*.

*Example 1.7.113*

**[0802] 6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-*N*-[(2,5-dimethyl-1,3-oxazol-4-yl)methyl]-*N*,1-dimethyl-2-oxo-1,2-dihydropyridine-4-carboxamide** : The desired compound was synthesized from *N*-[(2,5-dimethyl-1,3-oxazol-4-yl)methyl]-*N*-methylamine (7.0 mg, 0.05 mmol) in a similar manner to *Example 1.7.106*.

*Example 1.7.114*

**[0803] (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-*N*-(tert-butyl)-*N*-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide** : The desired compound was synthesized in a similar manner to *Example 1.4.11* and *Example 1.7.1*.

*Example 1.7.115*

**[0804] (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-*N*-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide**: The desired compound was synthesized in a similar manner to *Example 1.4.11* and *Example 1.7.1*. In the final step, TFA was used instead of 4*N* HCl in dioxane.

*Example 1.7.116*

**[0805] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(fluoromethyl)phenyl)((2*R*,4*S*)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone**: The desired compound was synthesized in a similar manner to *Example 1.4.10* and *Example 1.7.1*.

*Example 1.7.117*

**[0806] (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-*N*-cyclopropyl-*N*-((4-methylthiazol-2-yl)methyl)-5-(pyrazin-2-yl)benzamide** : The desired compound was synthesized in a similar manner to *Example 1.4.13* and *Example 1.7.1*.

*Example 1.7.118*

**[0807] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(difluoromethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:** The desired compound was synthesized in a similar manner to *Example 1.4.14* and *Example 1.7.1*.

*Example 1.7.119*

**[0808] (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclobutyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide :** The desired compound was synthesized in a similar manner to *Example 1.4.12* and *Example 1.7.1*.

*Example 1.7.120*

**[0809] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone :** The desired compound was synthesized in a similar manner to *Example 1.4.17*, *Example 1.7.1*, and *Example 1.6.8*.

*Example 1.7.121*

**[0810] 5-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-1,3,4-oxadiazol-2(3H)-one :** The desired compound was synthesized in a similar manner to *Example 1.4.17*, *Example 1.7.1*, and *Example 1.6.8*.

*Example 1.7.122*

**[0811] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-fluoroethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone :** The desired compound was synthesized in a similar manner to *Example 1.4.14* and *Example 1.7.1*.

*Example 1.7.123*

**[0812] 1-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)ethanone :** The desired compound was synthesized in a similar manner to *Example 1.4.14* and *Example 1.7.1*.

*Example 1.7.124*

**[0813] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone :** The desired compound was synthesized in a similar manner to *Example 1.6.9*.

*Example 1.7.125*

**[0814] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(isoxazol-5-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone** : The desired compound was synthesized in a similar manner to *Example 1.7.123* and *Example 1.4.15*.

*Example 1.7.126*

**[0815] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1,1-difluoroethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone** : The desired compound was synthesized in a similar manner to *Example 1.4.14* and *Example 1.7.1*.

*Example 1.7.127*

**[0816] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(isoxazol-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone** : The desired compound was synthesized in a similar manner to *Example 1.4.16* and *Example 1.7.1*.

*Example 1.7.128*

**[0817] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrazol-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone** : The desired compound was synthesized in a similar manner to *Example 1.7.123* and *Example 1.4.15*.

*Example 1.7.129*

**[0818] 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzonitrile** : The desired compound was synthesized in a similar manner to *Example 1.6.10* and *Example 1.7.44*.

*Example 1.7.130*

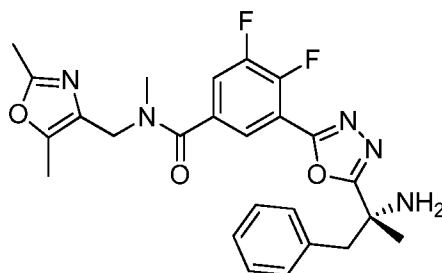
**[0819] (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide** : The final compound was prepared using similar procedure to that of *Example 1.7.1*.

*Example 1.7.131*

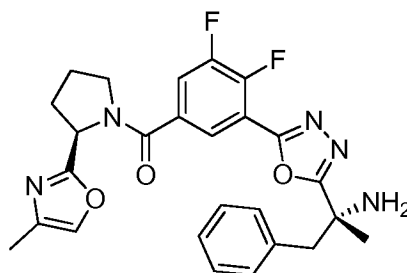
**[0820] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-bromophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone** : The compound was synthesized in a manner similar to that of *Example 1.7.1*.

*Example 1.7.132*

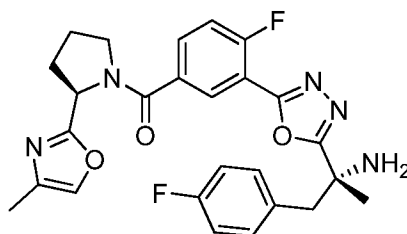
**[0821] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-chlorophenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone** : The compound was synthesized in a manner similar to that of *example 1.7.1*.

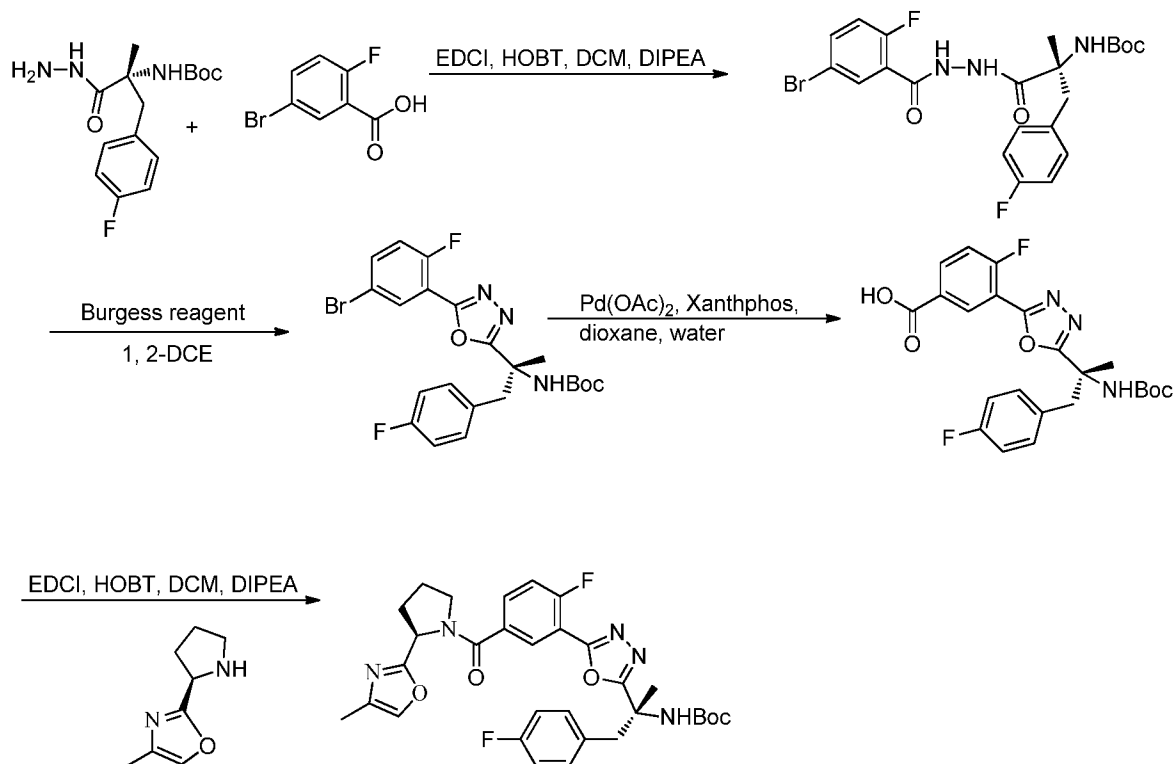
*Example 1.7.133*

**[0822]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide : Starting from the commercially available chemical, following a similar procedure to *Example 1.7.16* to make the compound.

*Example 1.7.134*

**[0823]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4,5-difluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone : Starting from the commercially available chemical, following a similar method to *Example 1.7.16* to make the compound.

*Example 1.7.135*



**[0824] (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone :** To a solution containing the acid, 5-bromo-2-fluorobenzoic acid (391 mg, 1.784 mmol) in DCM (3 ml), HOBT (328 mg, 2.141 mmol) and EDC (479 mg, 2.498 mmol) were added and the reaction mixture was stirred for 1 h at rt. After 1 h, reaction mixture was cooled to 0°C, and (R)-tert-butyl (3-(4-fluorophenyl)-1-hydrazinyl-2-methyl-1-oxopropan-2-yl)carbamate (500 mg, 1.606 mmol) was added in DCM (1 mL) along with DIPEA (0.935 ml, 5.35 mmol). The reaction mixture color was dark brown. After stirring overnight at rt, DCM was removed in vacuum. Then reaction mixture was diluted with ethyl acetate, and saturated aq sodium bicarbonate solution was added. After stirring for 10 mins at rt, aqueous layer was extracted with ethyl acetate (2X10 ml). Combined organic layers were washed with water, brine and dried. Crude residue was carried to the next step.

**[0825]** To the hydrazide (1.08 g, 2.11 mmol) in DCE (20 ml), Burgess reagent (1.26 g, 5.27 mmol) was added and refluxed for 3 h at which time reaction color turned brown. Then reaction mixture was cooled, diluted with DCM, washed with aq sodium bicarbonate solution, water brine and dried. Crude residue was column chromatographed. (30% ethyl acetate/hexane). Product is a yellow syrup and was obtained in 67% yield.

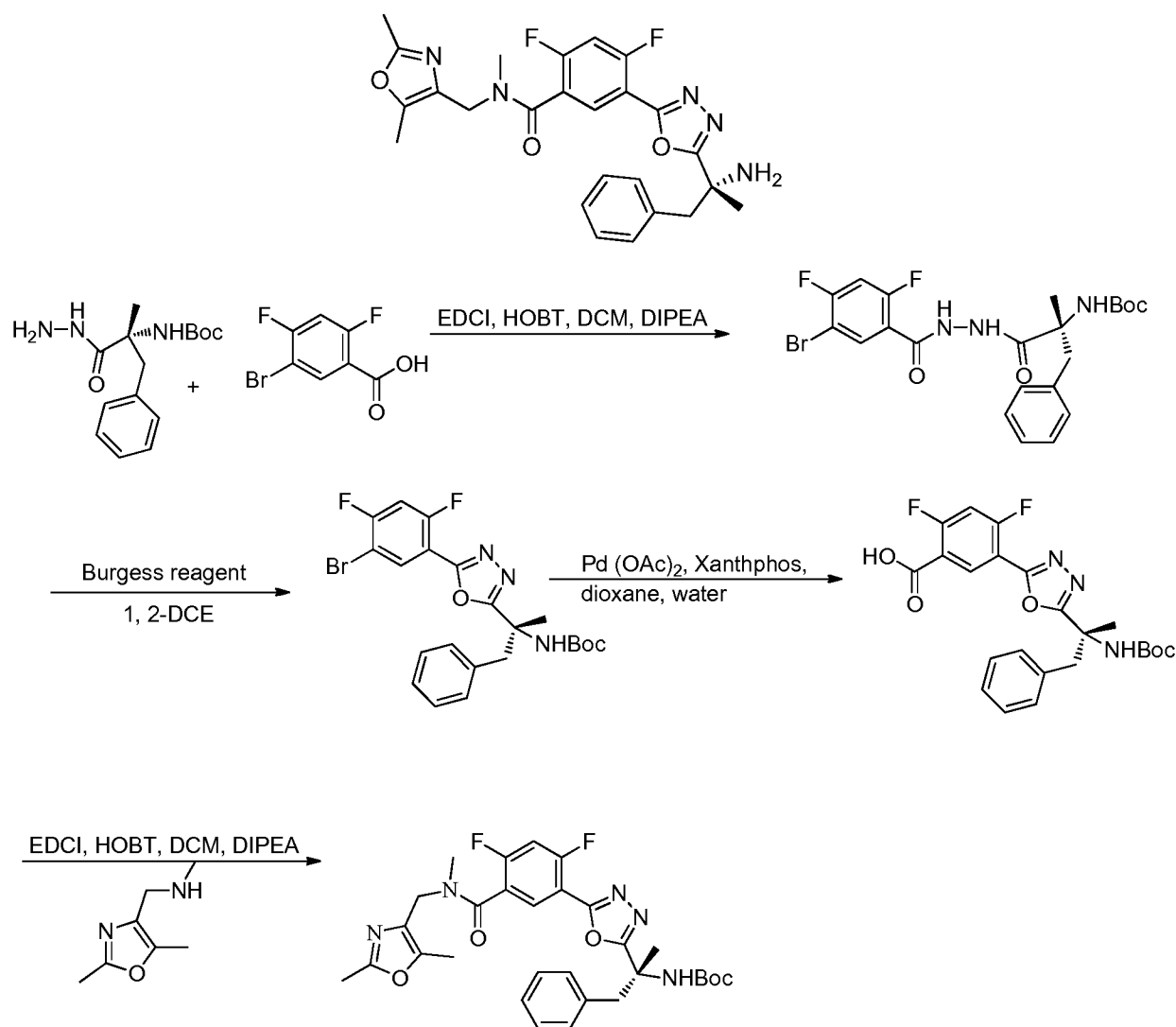
**[0826]** To the bromo compound, (R)-tert-butyl (2-(5-(5-bromo-2-fluorophenyl)-1,3,4-oxadiazol-2-yl)-1-(4-fluorophenyl)propan-2-yl)carbamate (700 mg, 1.416 mmol) in dioxane



(Ratio: 2.96, Volume: 8 ml) and Water (Ratio: 1.000, Volume: 2.7 ml), PALLADIUM(II) ACETATE (15.90 mg, 0.071 mmol) and XANTPHOS (82 mg, 0.142 mmol), Et<sub>3</sub>N (1.974 ml, 14.16 mmol) were added and the reaction mixture was purged with carbon monoxide. Then reaction mixture (a yellow suspension) was heated to 75°C for 3h by which time the suspension is greyish green. Then reaction mixture was cooled, dioxane was removed in vacuum. Water was added and filtered. Water layer was basified and extracted with ethyl acetate. Aqueous layer was then acidified and extracted with 5% MeOH/Ethyl acetate. Organic layer was dried and evaporated to yield 460mg of acid.

**[0827]** Resulting acid is converted to the final compound in a manner similar to that as in *Example 1.7.1*.

*Example 1.7.136*



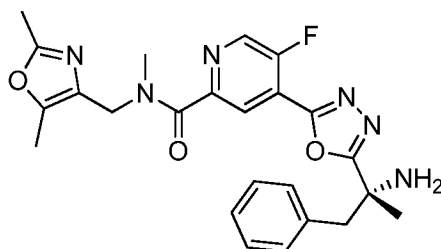
**[0828]** (R)-5-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-2,4-difluoro-N-methylbenzamide : To a solution containing the

acid, 5-bromo-2,4-difluorobenzoic acid (1.5 g, 6.33 mmol) in DCM (10 ml), HOBT (1.163 g, 7.59 mmol) and EDC (1.699 g, 8.86 mmol) were added and the reaction mixture was stirred for 1h at rt. After 1h, reaction mixture was cooled to 0°C, and (R)-tert-butyl (1-hydrazinyl-2-methyl-1-oxo-3-phenylpropan-2-yl)carbamate (1.671 g, 5.70 mmol) was added in DCM (3 mL) along with DIPEA (3.32 ml, 18.99 mmol). The reaction mixture color was dark brown. After stirring overnight at rt, DCM was removed in vacuum. Then reaction mixture was diluted with ethyl acetate, and saturated aq sodium bicarbonate solution was added. After stirring for 10 mins at rt, aqueous layer was extracted with ethyl acetate (2X10 ml). Combined organic layers were washed with water, brine and dried. Crude residue was carried to the next step.

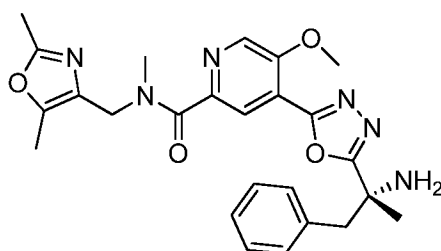
**[0829]** To the hydrazide (500 mg, 1.06 mmol) in DCE (20 ml), Burgess reagent (629 mg, 2.64 mmol) was added and refluxed for 2h at which time reaction color turned dark brown. Then reaction mixture was cooled, diluted with DCM, washed with aqueous sodium bicarbonate solution, water, and brine and dried. Crude residue was column chromatographed. (30% ethyl acetate/hexane). Product is a colorless foamy syrup and was obtained in 67% yield.

**[0830]** To the bromo compound, (R)-tert-butyl (2-(5-(5-bromo-2,4-difluorophenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate (1.0 g, 2.023 mmol) in dioxane and water, PALLADIUM(II) ACETATE (0.023 g, 0.101 mmol) and XANTPHOS (0.117 g, 0.202 mmol), Et<sub>3</sub>N (2.82 ml, 20.23 mmol) were added and the reaction mixture was purged with carbon monoxide. Then reaction mixture was heated to 75°C for 4h. Then reaction mixture was cooled, water was added and filtered. Water layer was basified and extracted with ethyl acetate. Aqueous layer was then acidified and extracted with 5% MeOH/Ethyl acetate. Organic layer was dried and evaporated to yield 360mg of acid. Organic layer also had some product along with some impurities. Partitioning the material obtained from organic layer between, aqueous (basic) layer and 5% MeOH/ethyl acetate yielded 450 mg of acid.

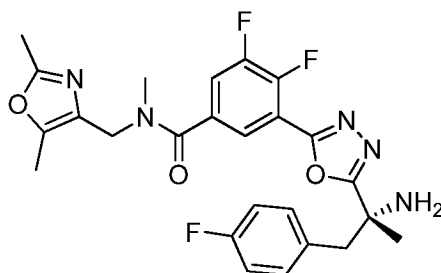
**[0831]** Resulting acid is converted to the final compound in a manner similar to that as in *Example 1.7.1*.

*Example 1.7.137*

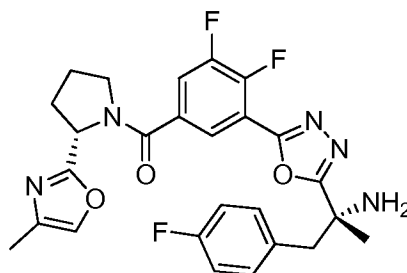
**[0832] (R)-4-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-5-fluoro-N-methylpicolinamide** : The compound was synthesized in a manner similar to that of example 1.8.2.

*Example 1.7.138*

**[0833] (R)-4-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-5-methoxy-N-methylpicolinamide** : The compound was synthesized in a manner similar to that of example 1.8.2.

*Example 1.7.139*

**[0834] (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide** : Starting from the commercially available chemical, following a similar method to *Example 1.7.16* to make the compound.

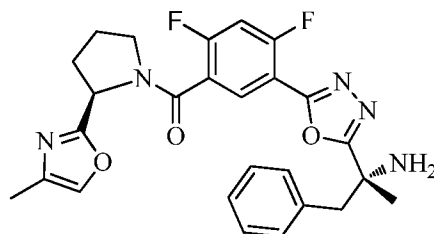
*Example 1.7.140*

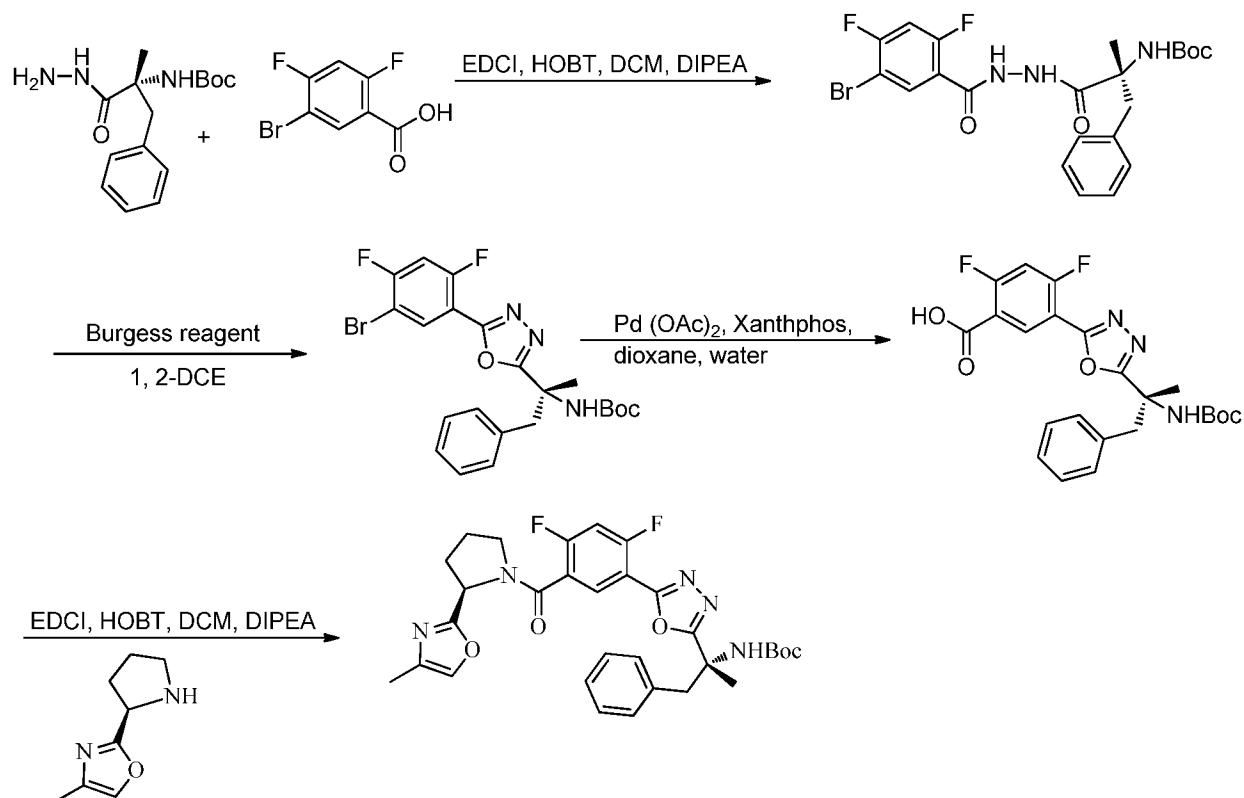
**[0835] (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-4,5-difluorophenyl)((S)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone** : Starting from the commercially available chemical, following a similar method to *Example 1.7.16* to make the compound.

*Example 1.7.141*

**[0836] 5-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-3-methyl-1,3,4-oxadiazol-2(3H)-one** :

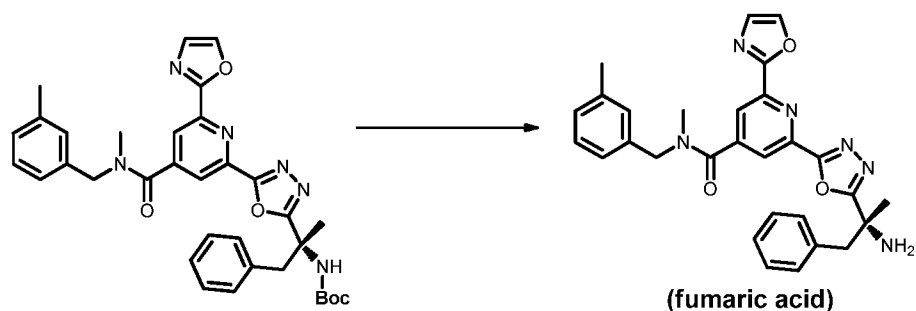
The desired compound was synthesized in a similar manner to *Example 1.4.17*, *Example 1.7.1*, and *Example 1.6.8*.

*Example 1.7.142*



**[0837]** (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2,4-difluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone: The final compound was prepared using similar procedure to that of *Example 1.8.11*.

**[0838]** *Example 1.7.143*



**[0839]**

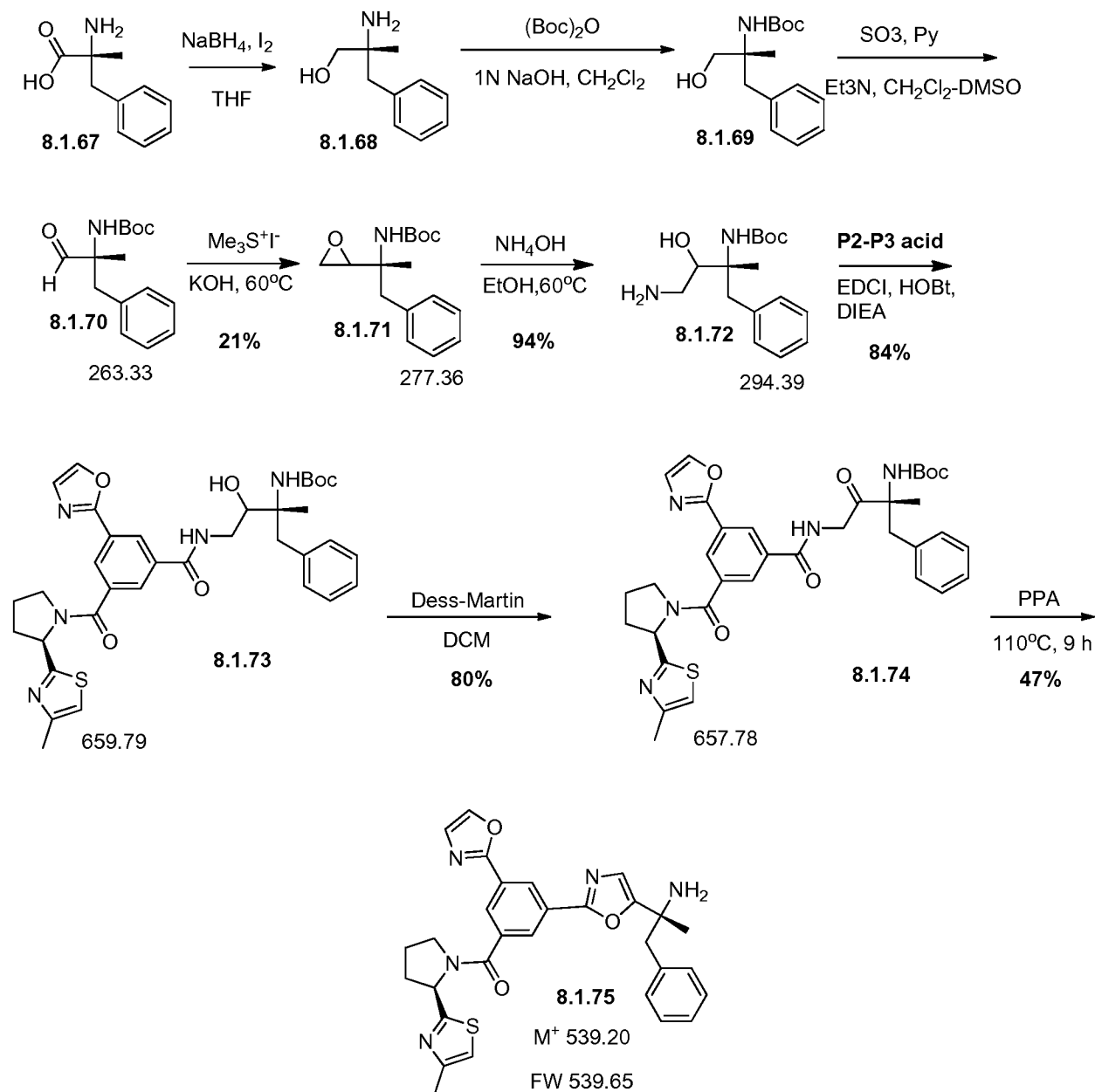
**2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-(3-methylbenzyl)-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)**

The desired compound was synthesized from tert-butyl [(2R)-2-(5-{4-[methyl(3-methylbenzyl)carbamoyl]-6-(1,3-oxazol-2-yl)pyridin-2-yl}-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (58 mg, 65% yield) as a white powder.  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$ : 8.44 (0.55H, s), 8.41 (0.45H, s), 8.28 (0.55H, s), 8.27 (0.55H, s), 8.24 (0.45H, s), 8.23 (0.45H, s), 7.57 (0.55H, s), 7.55 (0.45H, s), 7.32-7.01 (9H, m), 6.62 (2H, s), 4.69 (1.1H, s), 4.49 (0.9H, s), 3.40 (2H, br.s), 3.15 (1.1H, s),

3.12 (0.9H, s), 3.00 (1.35H, s), 2.88 (1.65H, s), 2.35 (1.65H, s), 2.27 (1.35H, s), 1.50 (1.65H, s), 1.48 (1.35H, s). MS (ESI)  $m/z$ : 509  $[M+H]^+$ .

### Example 1.8: Synthesis of oxazole inhibitors.

#### Example 1.8.1



[0840] To a solution of **8.1.67** (3.5g, 19.53mmoles) in THF (50mL) at room temperature was added  $\text{NaBH}_4$  (1.85g, 48.82mmoles) in one portion and cooled to 0 °C. Then  $\text{I}_2$  (4.96g, 19.53mmoles) in THF (10mL) was added over a period of 30 min and then refluxed for 40h. The reaction was cooled to 0 °C and quenched with slow addition of MeOH until the bubbling subsided. All the solvent was evaporated. The residue was dissolved in 15mL of 5N

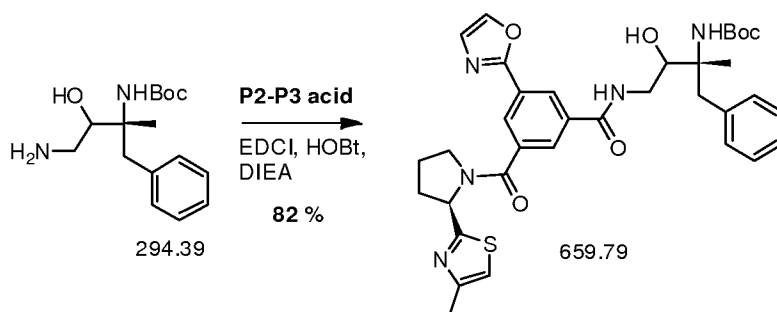
NaOH and refluxed for 2.5 h. It was then cooled to room temperature and extracted with  $\text{CH}_2\text{Cl}_2$  (4x20mL). Combined organic layers were dried on  $\text{Na}_2\text{SO}_4$  and concentrated. The crude **8.1.68** (3.2g) was carried on to the next step.

[0841]  $(\text{Boc})_2\text{O}$  (4.66g, 21.33mmoles) in  $\text{CH}_2\text{Cl}_2$  (80mL) was added to a solution of **8.1.68** (3.2g, 19.39mmoles) in  $\text{CH}_2\text{Cl}_2$  (20mL) and 1M NaOH (100mL) and the reaction was stirred overnight. The layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . Combined organic layers were dried on  $\text{Na}_2\text{SO}_4$  and concentrated. The crude was purified on silica gel (40% EtOAc/60% Hexanes) to yield 4.4g (85% for two steps) of **8.1.69**.

[0842] To a solution of **8.1.69** (4.4g, 16.60mmoles) in  $\text{CH}_2\text{Cl}_2$ -DMSO (5:1, 85mL) was added Et<sub>3</sub>N (6.9 mL, 49.81mmoles) followed by  $\text{SO}_3\cdot\text{Py}$  (6.6g, 41.51mmoles). After stirring overnight, the reaction mixture was diluted with ether and washed with 10%  $\text{NaHSO}_4$ , saturated  $\text{NaHCO}_3$ , brine, dried on  $\text{Na}_2\text{SO}_4$  and concentrated. The crude aldehyde **8.1.70** (4.1g, 94%) was used in the next step without purification.

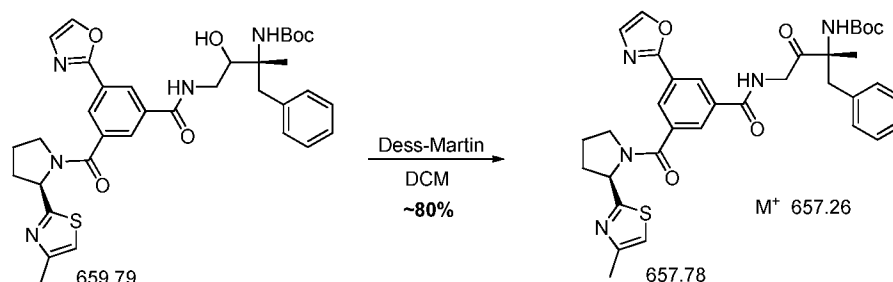
[0843] To a solution of **8.1.70** (4.1g, 15.59 mmoles) in  $\text{CH}_3\text{CN}$  (60mL) at room temperature was added water (25 drops) followed by trimethylsulfonium iodide (3.34g, 16.37 mmoles) and potassium hydroxide (2.19g, 38.97 mmoles). The reaction was stirred at in a sealed tube at 60 °C for 3h, diluted with ethylacetate and washed with water, brine dried on  $\text{Na}_2\text{SO}_4$  and concentrated. The crude was purified on silica gel (50% EtOAc/50% Hexanes) to yield 900mg (21%) of **8.1.71**.

[0844] A solution of **8.1.71** (4.1g, 15.59 mmoles) and  $\text{NH}_4\text{OH}$  (30 mL) in EtOH ( 30 mL) was stirred at 60 °C in a sealed tube for 16h. All the solvent was evaporated and purified on basic alumina (10% MeOH/90%  $\text{CHCl}_3$ ) to yield 900mg (94%) of **8.1.72**.

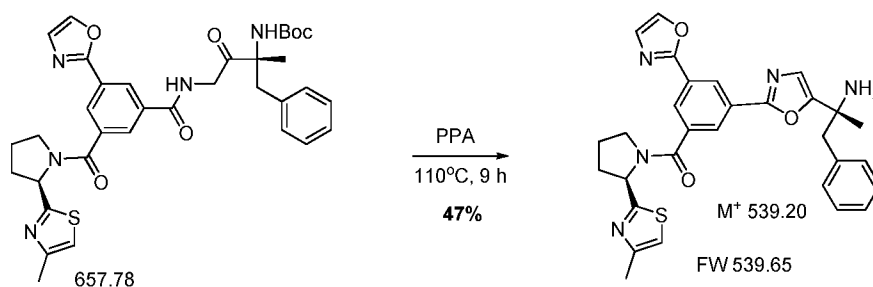


[0845] All starting materials and reagents were mixed up at r. t. in DCM then cooled to about zero in ice water bath and DIEA added and the mix was allowed warming to room overnight. Next morning TLC (MeOH/ $\text{CHCl}_3$ , 1:9) indicated clean reaction completed to show single spot of the product **8.1.73**. After bicarbonate and water wash DCM was replaced

with EtOAc and solution washed with 10% citric acid and then bicarbonate and dried over sodium sulfate. Yield 401 mg of **8.1.73** as foamy solid (82 %).



**[0846]** The above mix in 20 ml of dry DCM was stirred for 5 hours at room temperature (~21°C) then an aliquot was taken into 5 % NaOH and TLC (10 % MeOH in CHCl<sub>3</sub>) showed a new spot just slightly up of that of s. m. Proton NMR indicated reaction completion. New group of signals in 4.5 – 4.8 ppm area (CH<sub>2</sub>=O) appeared. Nevertheless, 20 ml more DCM added (because of some solids presence) and the mix was stirred overnight. Next day 5% NaOH was added (20 ml) followed by sat. NH<sub>4</sub>Cl and mix was stirred additional 1 h. Organic layer separated, washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. Solvent removed in rotor then 40 ml of toluene added and stripped in rotor to remove possible residual water. Yield of yellowish solid was 360 mg (>100% contained sole 20% of toluene by NMR). Estimated yield is 80% of **8.1.74** (single spot on TLC).

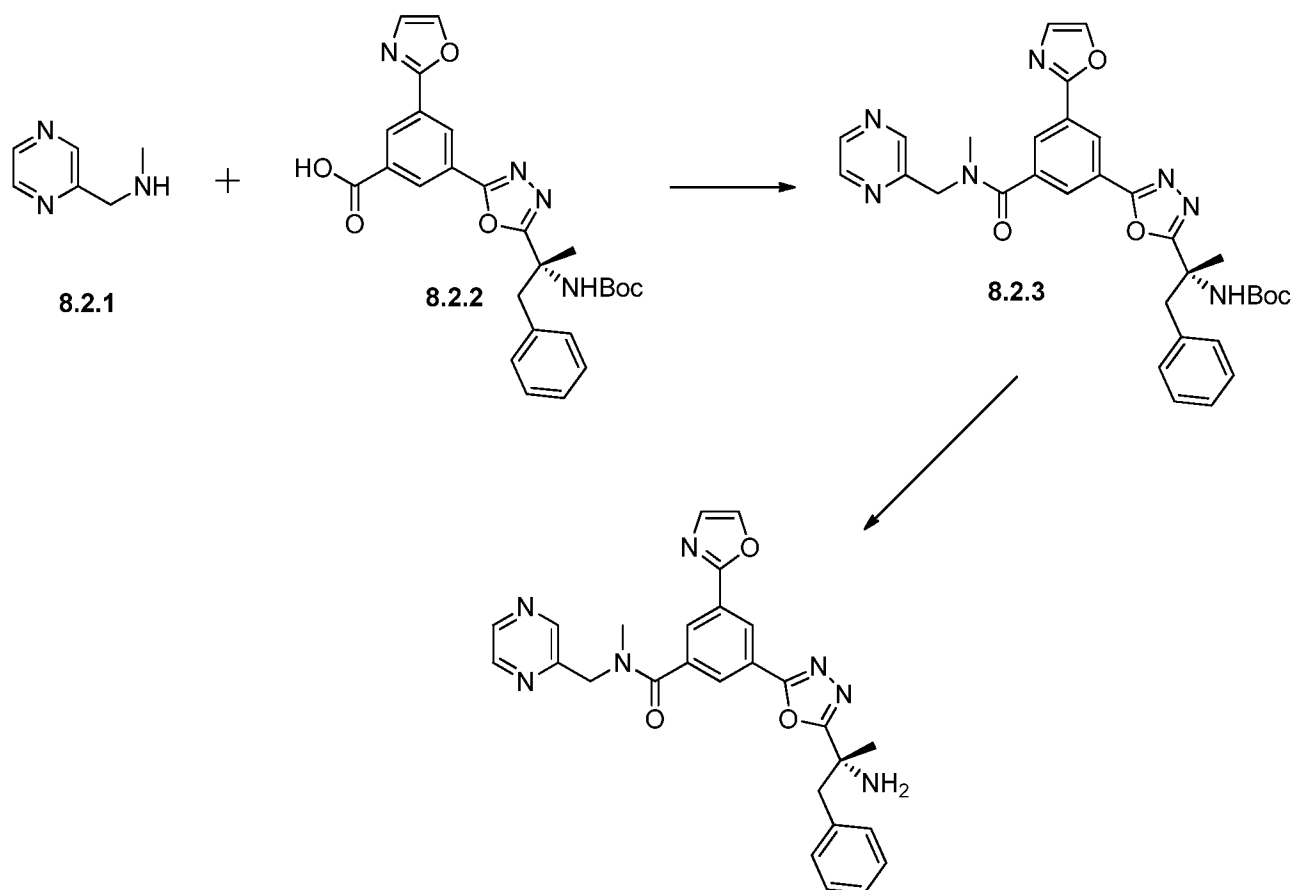


**[0847]** The ketone **8.1.74** was heated with ~ 9 g of poly phosphoric acid (PPA) at 100°C for 1 h in an opened 20 ml vial to let CO<sub>2</sub> and *t*-BuOH from Boc-decomposition out. Foaming was observed. Reaction progress was monitored by TLC (10% MeOH in CHCl<sub>3</sub>). Starting material was gone by 20 min and de-Boc amine was detected instead in a sample treated with water then 20% NaOH and EtOAc. Temperature was set to 110°C and the reaction mixture (yellow) stirred at that temperature for 9 hours in closed vial. Dark brown reaction mixture was cooled to ca. 40°C, diluted with 20 ml of water then 28 g of 20% NaOH added to pH ~ 9 and yellow turbid mixture was extracted 2 x 20 ml of EtOAc and organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>. After solvent removal in rotor 160 mg of yellow material was obtained (93 % crude). This was purified very well on 4 g CombiFlash silica gel column with 0 to 4 %

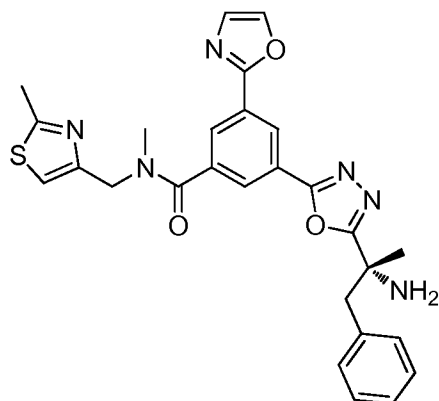


MeOH in chloroform for 35 min to isolate 81 mg of pure product **8.1.75** (47 %) as slightly yellowish foamy solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.74 and 8.62 (s, 1H); 8.32 and 8.10 (s, 2H), 7.79 and 7.71 (s, 1H); 7.22 (m, 4 H); 6.98 (m, 2H); 6.80 (m, 2H); 5.70 and 5.20 (t, 1H); 3.75 (m, 2H); 3.10 (dd, 2H,  $J = 13.5$  Hz); 2.45 (m, 4 H); 2.05 (m, 4 H); 1.71 (br. s 2H) and 1.53 (s, 3H). ESI MS: 540.20 ( $M + 1$ ). Please note that central benzene ring protons appear as two signals of amide rotamers.

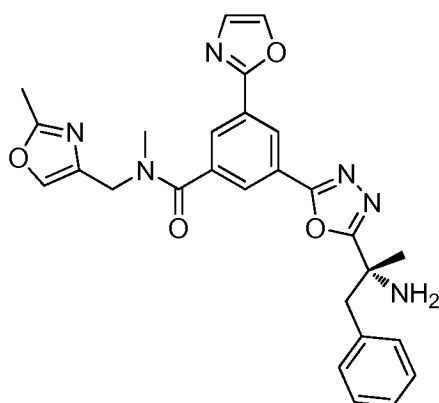
*Example 1.8.2 : (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(oxazol-2-yl)-N-(pyrazin-2-ylmethyl)benzamide*



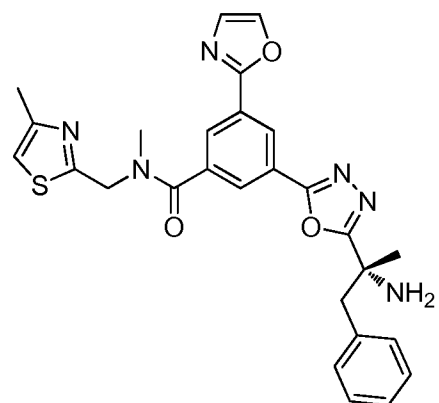
[0848] **8.2.1** and **8.2.2** were coupled using standard coupling procedure involving HOBT, EDCI, DIPEA in  $\text{CH}_2\text{Cl}_2$  and stirring overnight to obtain **8.2.3** which was deprotected using 30% TFA in  $\text{CH}_2\text{Cl}_2$  for 1h to obtain (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(oxazol-2-yl)-N-(pyrazin-2-ylmethyl)benzamide.

*Example 1.8.3*

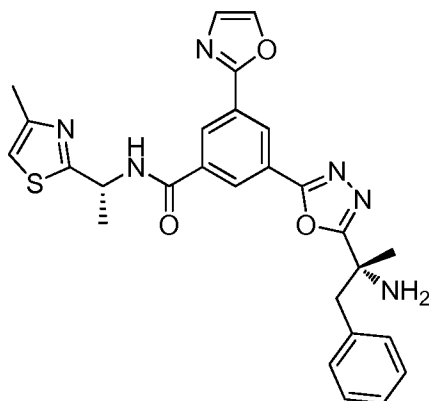
[0849] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.4*

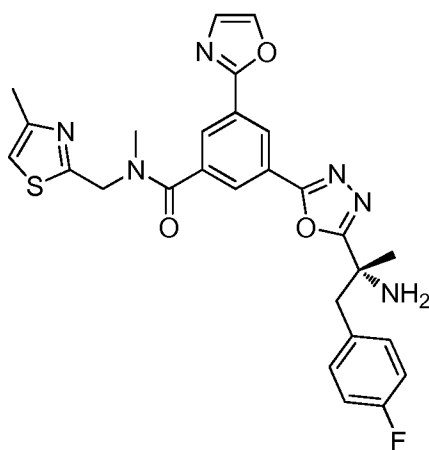
[0850] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.5*

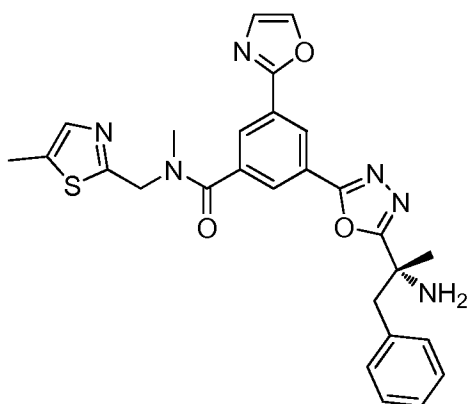
[0851] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.6*

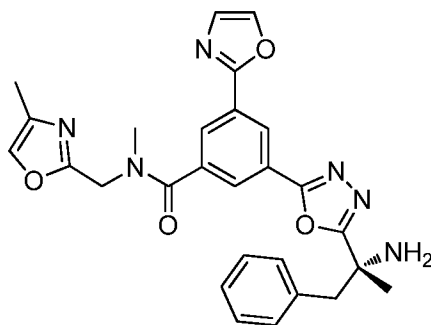
[0852] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.7*

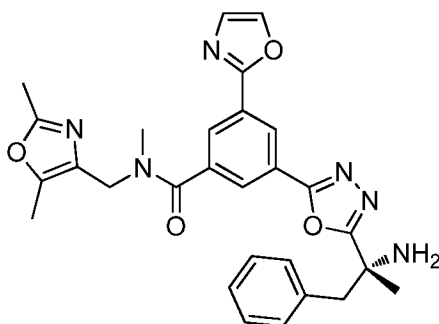
[0853] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.8*

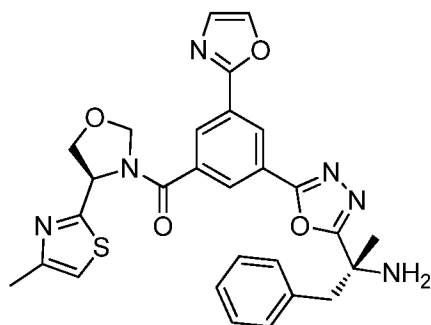
[0854] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.9*

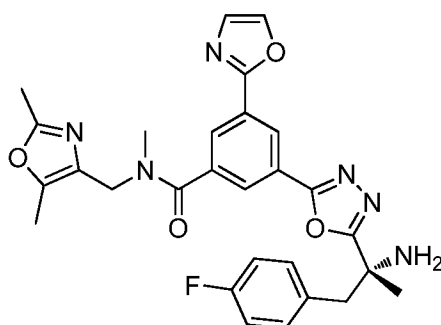
[0855] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.10*

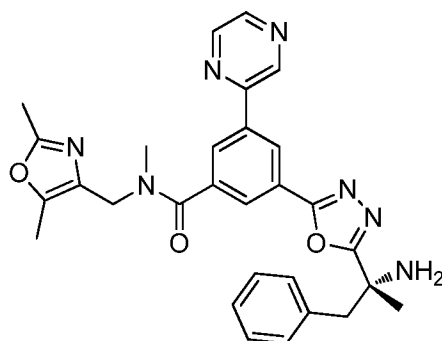
[0856] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.11*

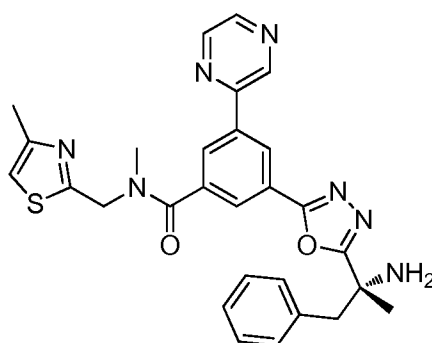
[0857] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.12*

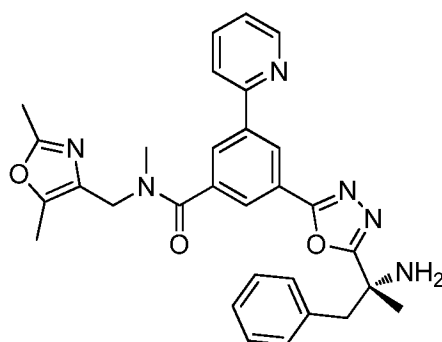
[0858] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.13*

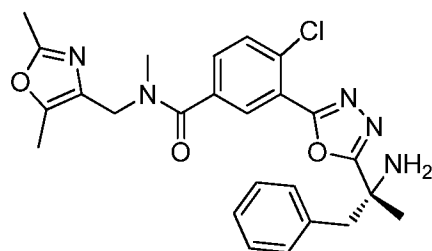
[0859] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.14*

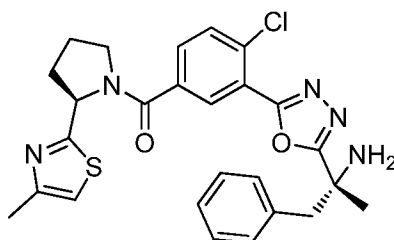
[0860] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.15*

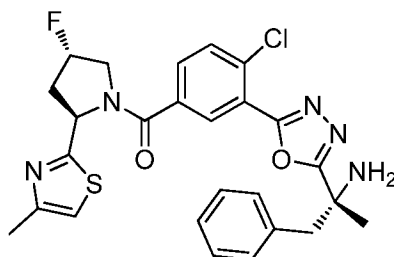
[0861] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.16*

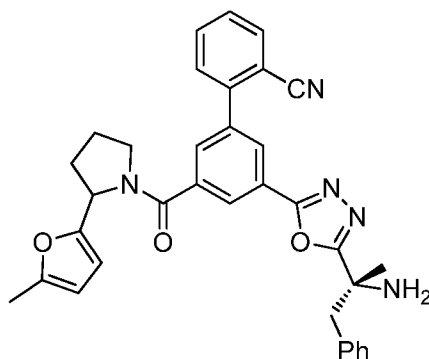
[0862] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.17*

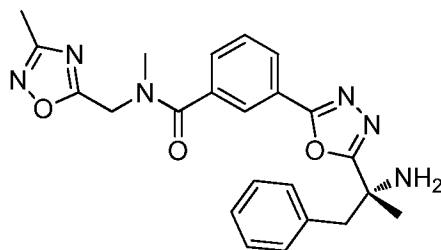
[0863] The compound was synthesized in a similar fashion of example 1.8.2.

*Example 1.8.18*

[0864] The compound was synthesized in a similar fashion of example 1.8.2.

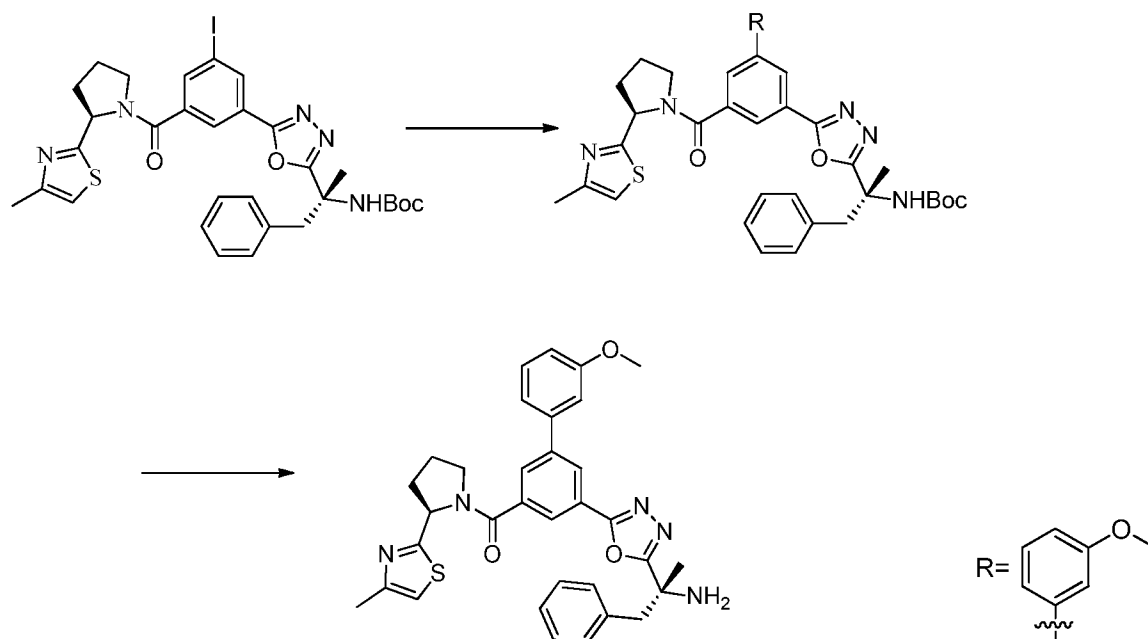
*Example 1.8.19*

[0865] The compound was synthesized in a manner similar to that as in Example 1.7.1.

*Example 1.8.20*

[0866] The compound was synthesized in a manner similar to that as in Example 1.7.1.

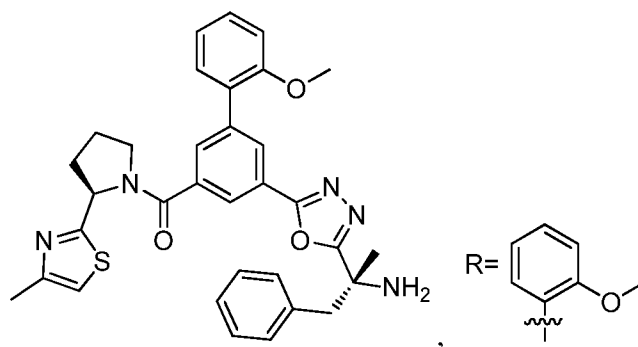
## Example 1.8.21



**[0867]** To the iodide (100mg, 0.12 mmol) in toluene (9 ml), water (3 ml) (3:1 ratio), 3-Methoxyphenylboronic Acid (21 mg, 0.14 mmol) (commercial source: Sigma-Aldrich), K<sub>3</sub>PO<sub>4</sub> (commercial source: Sigma-Aldrich) (76 mg, 0.36 mmol) was added followed by palladium acetate (0.5 mg, 0.02 mmol) (commercial source: Sigma-Aldrich) and X-phos (2.3 mg, 0.04 mmol) (commercial source: Sigma-Aldrich). Then the reaction mixture was heated under reflux for 4h. Then reaction mixture was cooled, diluted with ether and filtered through celite. Filtrate was partitioned between ether and water. Organic layer was dried evaporated and column purified to yield 50 mg of the product.

**[0868]** Deprotection of the resulting Boc compound using a procedure similar to the one depicted in Example 1.7.2 yielded the final product.

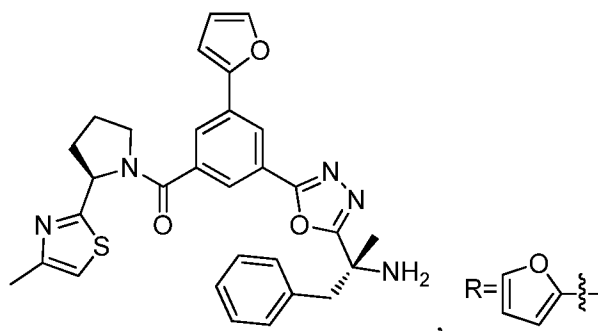
## Example 1.8.22



**[0869]** Following the above procedure, coupling of the iodo compound with 2-Methoxyphenylboronic Acid (commercial source: Sigma-Aldrich) and deprotection of the

resulting Boc compound using a procedure similar to the one depicted in Example 1.7.2 yielded the final product.

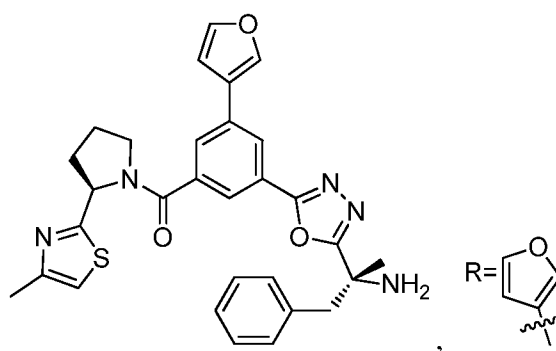
*Example 1.8.23*



**[0870]** Following the above procedure, coupling of the iodo compound with furan 2-boronic Acid (commercial source: Sigma-Aldrich) yielded the coupled product.

**[0871]** To the Boc compound (10 mg, 0.016 mmol) in DCM (1 ml), aqueous phosphoric acid (20 microlitres) was added and stirred at rt for 3h. Then reaction mixture was cooled, basified to pH 8 with 50% aqueous sodium hydroxide solution. Then the aqueous solution was extracted with DCM. Organic layer was dried, evaporated and column purified to yield final product.

*Example 1.8.24*

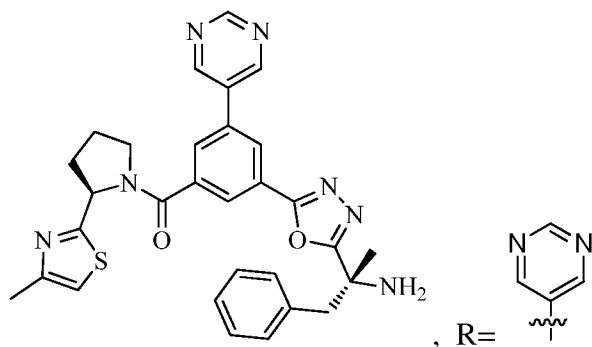


**[0872]** To the iodide (100 mg, 0.12 mmol) in dioxane (9 ml), water (3 ml) (3:1 ratio), furan-3-boronic Acid (16 mg, 0.14 mmol) (commercial source: Sigma-Aldrich),  $K_3PO_4$  (commercial source: Sigma-Aldrich) (76 mg, 0.36 mmol) was added followed by palladium acetate (0.5 mg, 0.02 mmol) (commercial source: Sigma-Aldrich) and X-phos (2.3 mg, 0.04 mmol) (commercial source: Sigma-Aldrich). Then the reaction mixture was heated to 130° for 40 min under microwave conditions. Then reaction mixture was cooled, diluted with ether and filtered through celite. Filtrate was partitioned between ether and water. Organic layer was dried, evaporated and column purified to yield the coupled product. Deprotection of



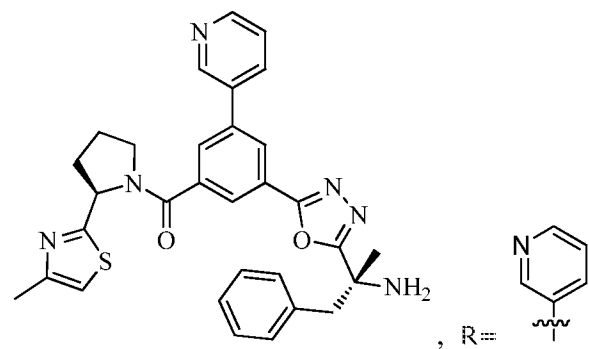
the resulting Boc compound using a procedure similar to the one depicted in Example 1.7.2 yielded the final product.

*Example 1.8.25*



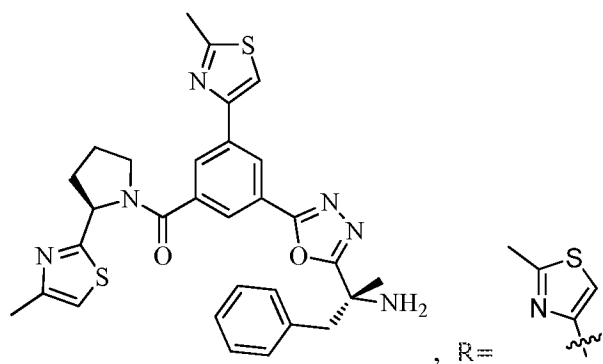
**[0873]** Following the above procedure, coupling of the iodo compound with with pyrimidine 5-Iboronic Acid(commercial source: Frontier Scientific) and deprotection of Boc group using 4N HCl using a procedure similar to Example 1.7.2 gave the final product.

*Example 1.8.26*



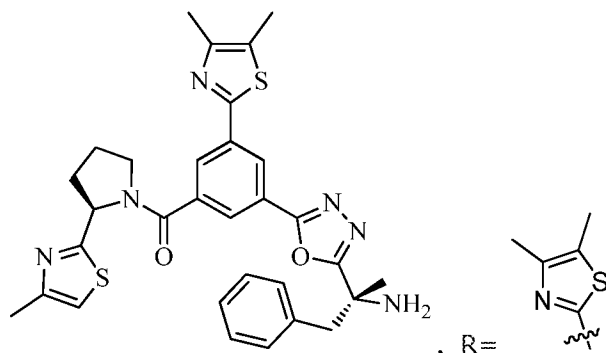
**[0874]** Following the above procedure, coupling of the iodo compound with with pyridine 3-boronic Acid(commercial source: matrix Scientific) and deprotection of Boc group using 4N HCl using a procedure similar to Example 1.7.2 gave the final product.

*Example 1.8.27*



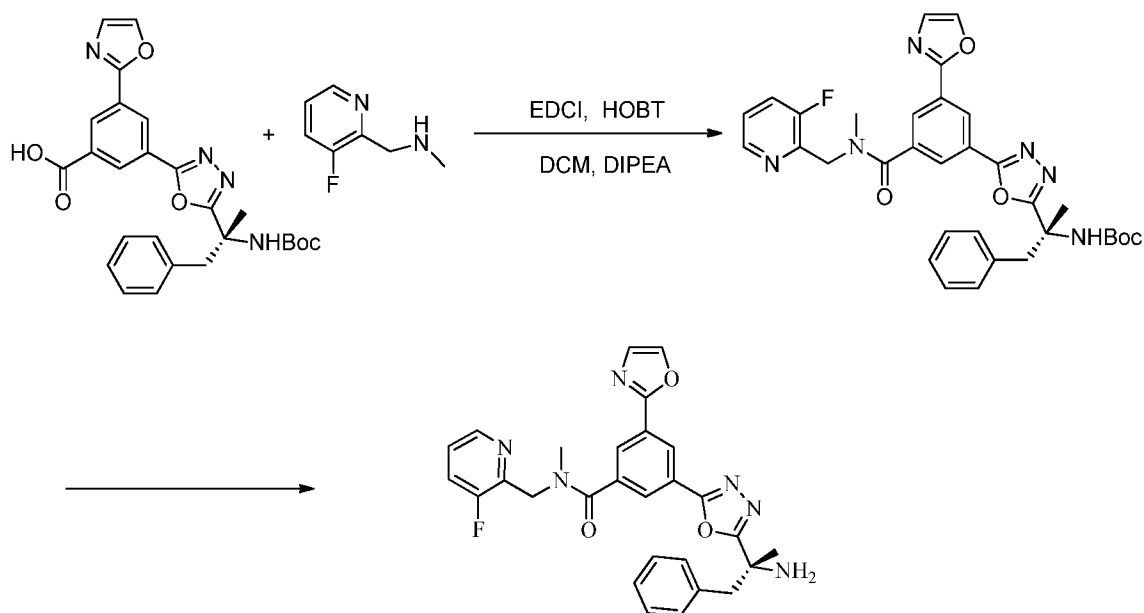
[0875] Following the above procedure, coupling of the iodo compound with pyridine 3-boronic Acid (commercial source: Combiphos catalysts) and deprotection of Boc group using 4NHCl using a procedure similar to Example 1.7.2 gave the final product.

*Example 1.8.28*



[0876] Following the above procedure, coupling of the iodo compound with pyridine 3-boronic Acid (commercial source: Synthonix) and deprotection of Boc group using 4NHCl using a procedure similar to Example 1.7.2 gave the final product.

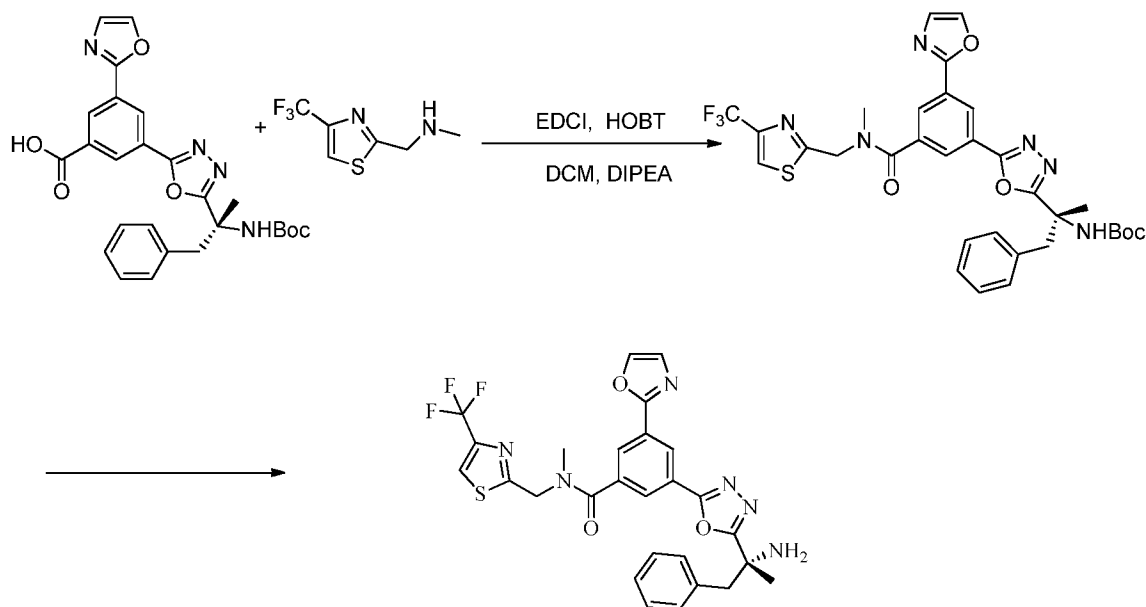
*Example 1.8.29*



[0877] To the acid (150mg, 0.30 mmol) in DCM (5 ml), HOBT (49 mg, 0.36mmol), EDCI (81 mg, 0.42 mmol) was added and stirred at rt for 2h. Then the acid (150mg, 0.30 mmol) and DIPEA (0.1 ml) was added to the reaction mixture and allowed to stir overnight and then worked up and column purified to yield the coupled product in 78% yield.

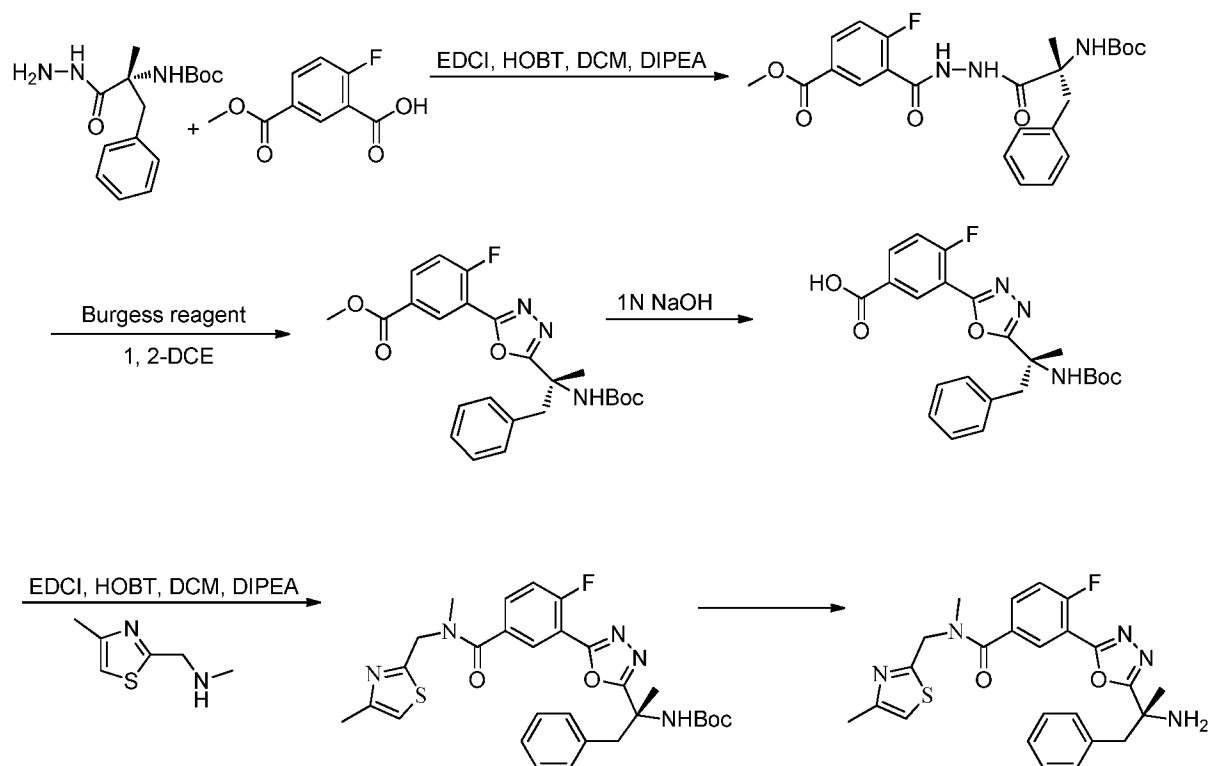
[0878] Deprotection of the resulting Boc protected compound as in Example 1.7.2 gave final product.

## Example 1.8.30



[0879] The final compound was prepared using similar procedure to that of *Example 1.8.9*.

## Example 1.8.31



[0880] To a solution containing the acid, 2-fluoro-5-(methoxycarbonyl)benzoic acid (380 mg, 1.918 mmol) in DCM (3 ml), HOBT (352 mg, 2.301 mmol) and EDC (515 mg, 2.68 mmol) were added and the reaction mixture was stirred for 1h at rt. After 1h, reaction mixture was cooled to 0°C, and (R)-tert-butyl (1-hydrazinyl-2-methyl-1-oxo-3-phenylpropan-2-

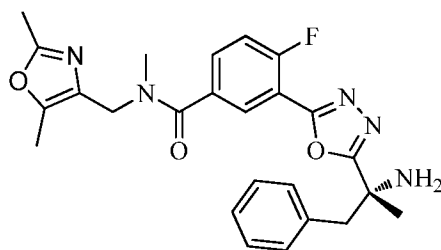
yl)carbamate (506 mg, 1.726 mmol) was added in DCM (1- mL) along with DIPEA (1.005 ml, 5.75 mmol). After stirring overnight at rt, DCM was removed in vacuum. Then reaction mixture was diluted with ethyl acetate and saturated aq sodium bicarbonate solution was added. After stirring for 10 mins at rt, aqueous layer was extracted with ethyl acetate (2X10 ml). Combined organic layers were washed with water, brine and dried. Crude residue was purified by column chromatography (100% hexane-100% ethyl acetate) to yield the hydrazide in 66% yield.

**[0881]** To the hydrazide (500 mg, 1.056 mmol) in DCE (10 ml), Burgess reagent (629 mg, 2.64 mmol) was added and refluxed for 4h at which time reaction colour turned brown. then reaction mixture was cooled, diluted with DCM, washed with aq sodium bicarbonate solution, water brine and dried. Crude residue was column chromatographed. (50% ethyl acetate/hexane). Product is a yellow syrup and was obtained in 62% yield.

**[0882]** To the ester, (R)-methyl 3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorobenzoate (300 mg, 0.844 mmol) in MeOH (Ratio: 3.00, Volume: 3 ml) and Water (Ratio: 1.000, Volume: 1 mL), sodium hydroxide (101 mg, 2.53 mmol) was added and the reaction mixture was stirred for 4h at rt. then reaction mixture was acidified and extracted with ethyl acetate. Organic layer was dried and evaporated to yield the product acid in its pure form as tan colour solid.

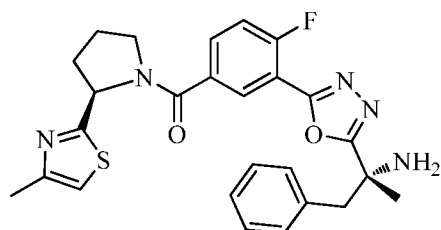
**[0883]** Resulting acid is converted to the final compound in a manner similar to that as in Example 1.7.1.

*Example 1.8.32*



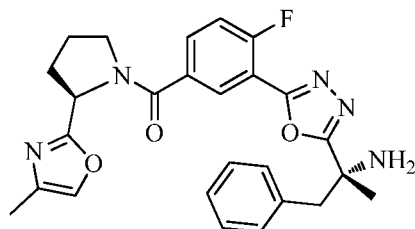
**[0884]** The final compound was prepared using similar procedure to that of *Example 1.8.31*.

*Example 1.8.33*



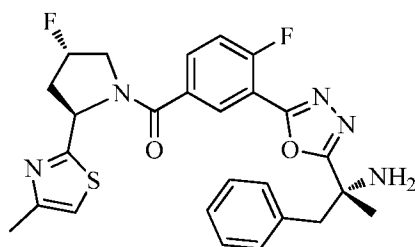
[0885] The final compound was prepared using similar procedure to that of *Example 1.8.31*.

*Example 1.8.34*



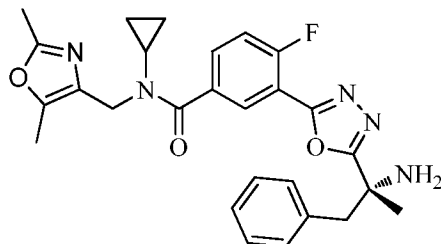
[0886] The final compound was prepared using similar procedure to that of *Example 1.8.31*.

*Example 1.8.35*



[0887] The final compound was prepared using similar procedure to that of *Example 1.8.31*.

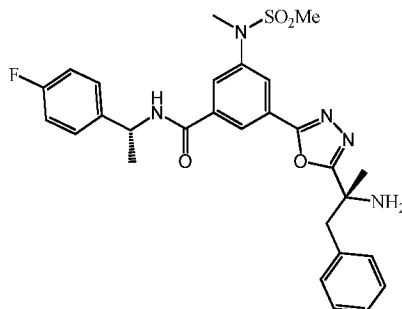
*Example 1.8.36*



[0888] The final compound was prepared using similar procedure to that of *Example 1.8.31*.

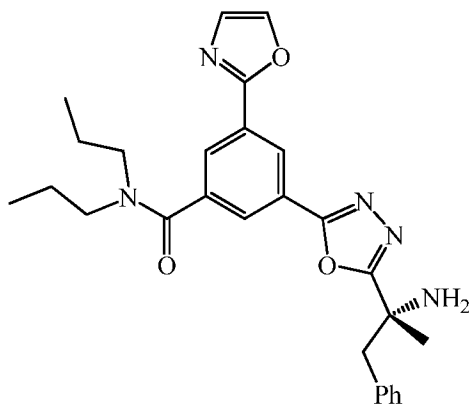
**Example 1.9: Supplemental Compounds.**

*Example 1.9.1: 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((R)-1-(4-fluorophenyl)ethyl)-5-(N-methylmethanesulfonamido)benzamide*



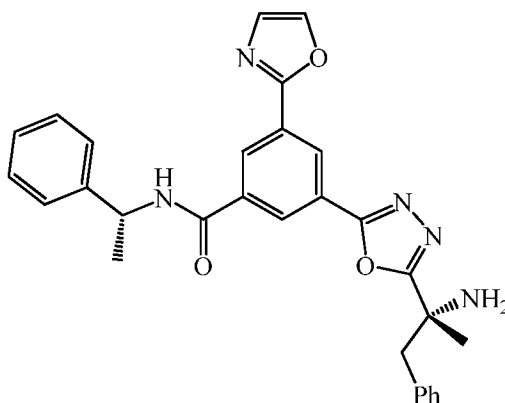
**[0889]**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.40 (br s, 1H), 8.14 (br s, 1H), 8.05 (br s, 1H), 7.82 (d,  $J = 7.5$  Hz, 1H), 7.42-7.38 (m, 2H), 7.30-7.20 (m, 3H), 7.08-7.00 (m, 4H), 5.40-5.24 (1.0H), 3.40 (s, 3H), 3.32 (d,  $J = 14$  Hz, 1H), 3.12 (d,  $J = 14$  Hz, 1H), 2.94 (s, 3H), 2.39 (s, 2H), 1.67 (s, 3H), 1.61 (d,  $J = 6.9$  Hz, 3H).

*Example 1.9.2: (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)-N,N-dipropylbenzamide*



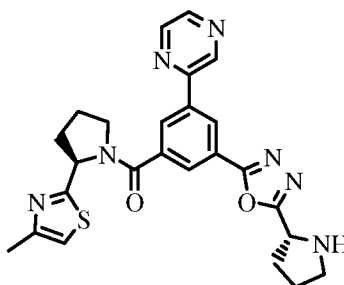
**[0890]**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.75-0.78 (m, 3H), 0.99-1.04 (m, 3H), 1.57-1.84 (m, 7H), 3.08-3.31 (m, 4H), 3.47-3.52 (m, 2H), 7.02-7.05 (m, 2H), 7.21-7.31 (m, 4H), 7.79 (s, 1H), 8.11 (t, 1H,  $J = 1.8$  Hz), 8.20 (t, 1H,  $J = 1.5$  Hz), 8.68 (t, 1H,  $J = 1.5$  Hz).

*Example 1.9.3: 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)-N-((R)-1-phenylethyl)benzamide*



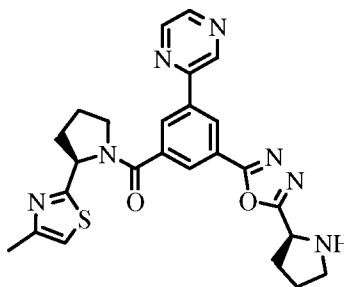
**[0891]**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.65-1.68 (m, 6H), 3.08-3.32 (m, 2H), 5.36-5.41 (m, 1H), 6.65 (d, 1H,  $J = 7.8$  Hz), 7.02-7.27 (m, 2H), 7.21-7.44 (m, 8H), 7.80 (s, 1H), 8.52 (s, 1H), 8.59 (s, 1H), 8.76 (s, 1H).

*Example 1.9.4: ((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)(3-(pyrazin-2-yl)-5-(5-((R)-pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)methanone*



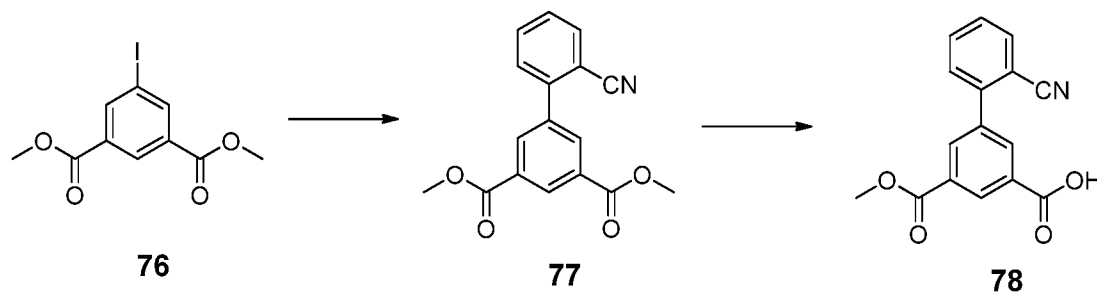
**[0892]**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.15-9.10 (m, 1H), 8.86-8.35 (m, 5H), 8.10-7.77 (m, 2H), 6.81-6.76 (m, 1H), 5.72-5.66 (m, 0.6H), 5.30-5.18 (m, 0.3H), 3.93-3.73 (m, 2H), 3.64-3.46 (m, 1H), 2.47-2.29 (m, 5H), 2.24-1.93 (m, 4H).

*Example 1.9.5: ((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)(3-(pyrazin-2-yl)-5-(5-((S)-pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)methanone*



**[0893]**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.14 (m, 1H), 8.50-8.36 (m, 5H), 8.11-8.02 (m, 1H), 6.81-6.77 (m, 1H), 5.71-5.67 (m, 0.7H), 5.20-5.18 (m, 0.3H), 4.58 (broad s, 1H), 3.98-3.73 (m, 2H), 3.64-3.47 (m, 1H), 3.18-3.12 (m, 2H), 2.45-1.87 (m, 14H).

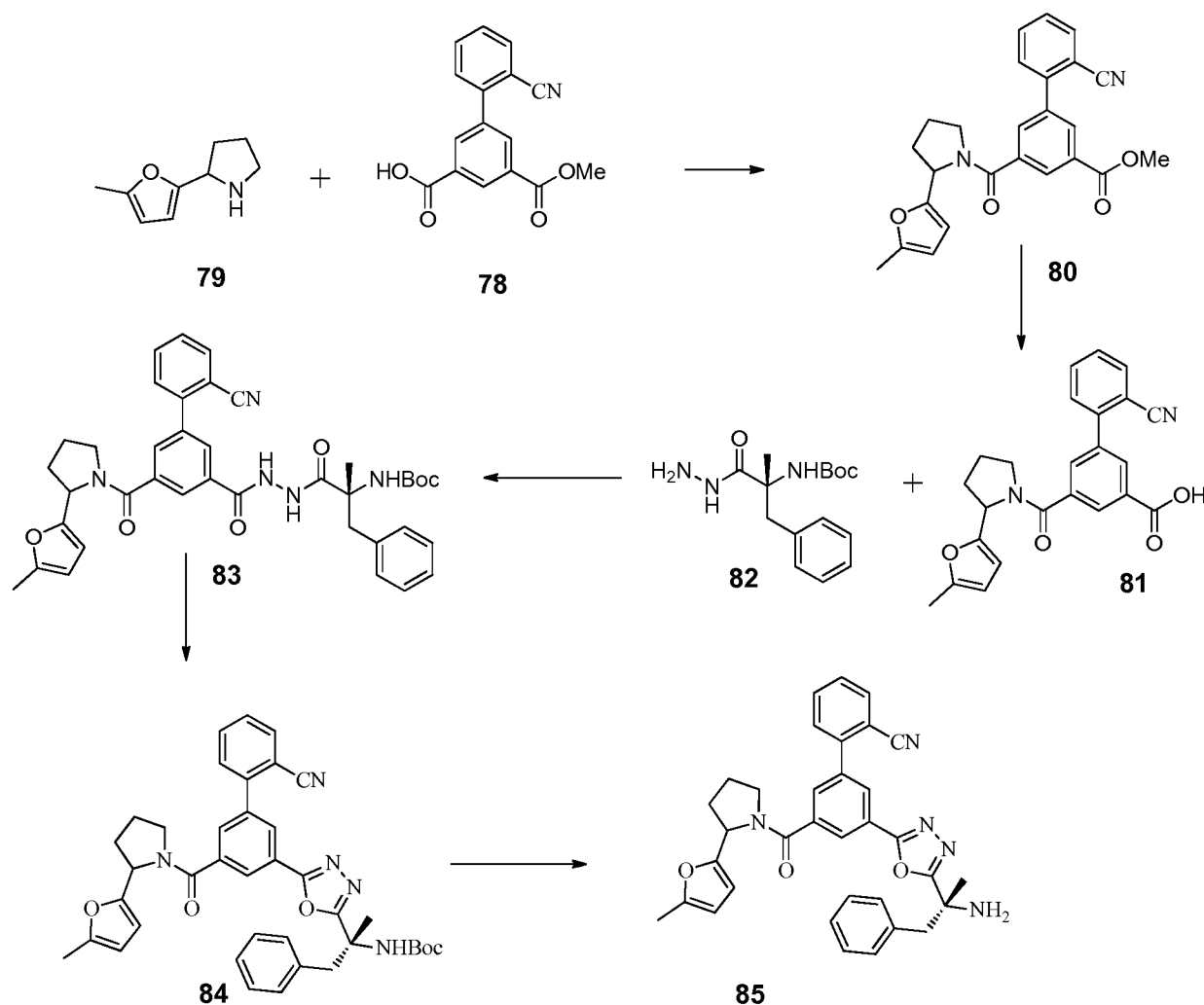
*Example 1.9.6: 3'-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5'-(2-(5-methylfuran-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carbonitrile*



**[0894]** To a solution of dimethyl 5-iodoisophthalate **76** (Commercial source: Matrix Scientific) (2 g, 6.25 mmol) in 15 mL THF was added 2-cyano-phenyl zinc bromide (Commercial source: Sigma-Aldrich), (15 mL, 7.5 mmol, 0.5 M THF) and tetrakis(triphenylphosphine) palladium (Commercial source: Sigma-Aldrich), (71 mg, 0.06 mmol) and the reaction mixture was stirred at room temperature for 2 h. The precipitated solid was filtered, was diluted with MeOH to provide after filtration a second crop for a total of 1.2 g (65 %) of dimethyl 5-(cyanophenyl)isophthalate **77**.

**[0895]** NaOH (155 mg, 3.86 mmol) was added to a stirred solution of the diester **77** (1.2 g, 4.07 mmol,) in 1:3:3  $\text{H}_2\text{O}/\text{MeOH}/\text{THF}$  (25 ml). Reaction mixture was stirred overnight at room temperature. Volatiles were removed in vacuum and the residue is partitioned between ethyl acetate and saturated aqueous  $\text{NaHCO}_3$ . Reaction mixture was extracted with EtOAc. Aqueous layer's  $\text{pH}$  was adjusted to about 3 with concentrated HCl, and reaction mixture was extracted with 10% MeOH/90%  $\text{CHCl}_3$  (x5). Combined organic layers were washed with brine, dried and concentrated to yield 0.9 g (79 %) of the mono acid **78**.





**[0896]** To a solution of 2-(5-methyl-2-furyl)pyrrolidine **79** (Commercial source: ACB Blocks Ltd.) (54 mg, 0.36mmoles) and **78** (100mg, 0.36mmoles) in  $\text{CH}_2\text{Cl}_2$  (8 mL) was added HOBT (48 mg, 0.36 mmoles) and (EDC 82mg, 0.42 mmoles) followed by DIPEA (0.186 mL, 1.07 mmoles) and stirred over night at room temperature. All the solvent was evaporated; the residue was diluted with EtOAc and washed with 0.5 N HCl and satd. aq.  $\text{NaHCO}_3$ . The organic layer was washed with brine, dried, concentrated and purified on silica gel (50% EtOAc/50% hexanes) to obtain 120 mg (77%) of **80**.

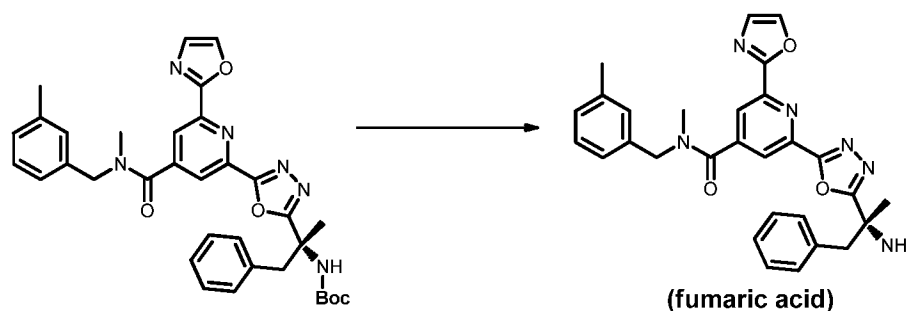
**[0897]** 1N LiOH (1.0 mL) was added to a stirred solution of the ester **80** (120 mg, 0.28 mmol) in THF (3 mL) and. After stirring for 1 h, the medium was adjusted to  $\text{pH} \approx 4$  with 1N HCl and extracted EtOAc. The organics were combined and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent removed via rotary evaporation yielding 110 mg (94 % yield) of the **81**.

[0898] To a solution of **81** (60 mg, 0.14 mmol) and **82** (42 mg, 0.14 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) was added HOBt (19 mg, 0.14 mmol), EDC (33 mg, 0.17 mmol) and DIPEA (0.075 mL, 0.43 mmol) and stirred over night at room temperature. The solvent was removed via rotary evaporation. The residue was quenched with satd. aq.  $\text{NaHCO}_3$  and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The inorganics were filtered off, and the solvent was removed via rotary evaporation. Purification via flash chromatography on silica gel yielded 80 mg (82 %) of the product **83**.

[0899] To a solution of **83** (80 mg, 0.12 mmol) in dichloromethane (5 mL) was added Burgess' reagent (85 mg, 0.35 mmol) and refluxed for 5h. The reaction mix was then cooled to room temperature, diluted with  $\text{CHCl}_3$  and washed successively with satd. aq.  $\text{NaHCO}_3$  and brine, dried, concentrated and purified on silica gel (1% MeOH/99%  $\text{CHCl}_3$ ) to obtain 60 mg (76%) of **84**.

[0900] A solution of **84** (60 mg, 0.09 mmol) in a mixture of 4N HCl in 1,4-dioxane (3 mL) and 1.5N HCl in MeOH (1 mL) at 0 °C to RT was stirred for 45 min. TLC indicated the consumption of SM. All the solvent was evaporated; the residue was quenched with satd. aq.  $\text{NaHCO}_3$  and was extracted with EtOAc. The organic extract was washed with brine, dried, concentrated and purified on silica gel (2% MeOH/98%  $\text{CHCl}_3$ ) to obtain 30 mg (59%) of **85**.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 8.32-8.17 (m, 1H), 8.00-7.80 (m, 2H), 7.80-7.60 (m, 2H), 7.60-7.44 (m, 2H), 7.38-7.20 (m, 3H), 7.12-6.98 (m, 2H), 6.20 (s, 0.5H), 5.85 (s, 0.5H), 5.72 (s, 0.5H), 5.68 (s, 0.5H), 5.40 (s, 0.5H), 5.00 (s, 0.5H), 3.96-3.70 (m, 1H), 3.70-3.22 (m, 3H), 2.30-1.80 (m, 7H), 1.67-1.66 (two s, 3H).

#### Example 1.9.7

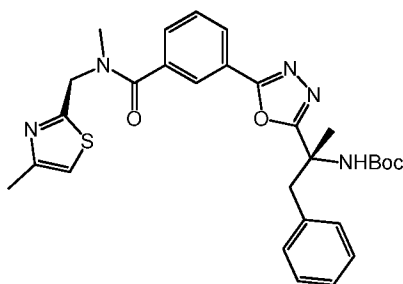


[0901] 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-(3-methylbenzyl)-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) : The desired compound was synthesized from tert-butyl [(2R)-2-(5-{4-[methyl(3-methylbenzyl)carbamoyl]-6-(1,3-oxazol-2-yl)pyridin-2-yl}-1,3,4-oxadiazol-2-yl)-1-

phenylpropan-2-yl]carbamate in a similar manner to *Example 1.7.73* (58 mg, 65% yield) as a white powder.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.44 (0.55H, s), 8.41 (0.45H, s), 8.28 (0.55H, s), 8.27 (0.55H, s), 8.24 (0.45H, s), 8.23 (0.45H, s), 7.57 (0.55H, s), 7.55 (0.45H, s), 7.32-7.01 (9H, m), 6.62 (2H, s), 4.69 (1.1H, s), 4.49 (0.9H, s), 3.40 (2H, br.s), 3.15 (1.1H, s), 3.12 (0.9H, s), 3.00 (1.35H, s), 2.88 (1.65H, s), 2.35 (1.65H, s), 2.27 (1.35H, s), 1.50 (1.65H, s), 1.48 (1.35H, s). MS (ESI)  $m/z$ : 509  $[\text{M}+\text{H}]^+$ .

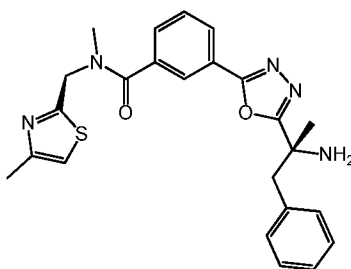
## Example 2: Inhibitor Compounds

### Example 2.1



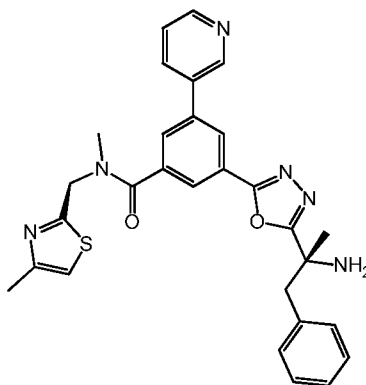
**[0902]** tert-Butyl (2-(5-(3-(methyl((4-methylthiazol-2-yl)methyl)carbamoyl)phenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30-8.12 (m, 2H), 7.80-7.54 (m, 2H), 7.40-7.20 (m, 3H), 7.18-7.00 (m, 2H), 6.92 (br s, 1H), 5.02 (br s, 2.2H), 4.78 (br s, 0.8H), 3.64-3.40 (m, 2H), 3.30-3.00 (m, 3H), 2.49 (s, 3H), 1.76 (br s, 3H), 1.44 (s, 9H).

### Example 2.2



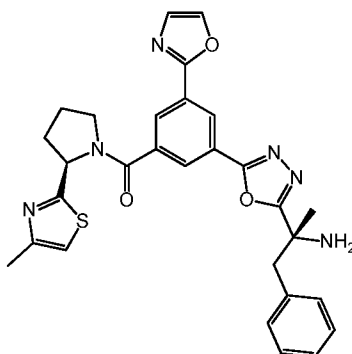
**[0903]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20-8.00 (m, 2H), 7.70-7.44 (m, 2H), 7.20-7.10 (m, 3H), 7.00-6.90 (m, 2H), 6.80 (br s, 1H), 4.92 (br s, 1.2H), 4.64 (br s, 0.8H), 3.24-2.90 (m, 5H), 2.39 (s, 3H), 1.80 (br s, 2H), 1.58 (s, 3H).

## Example 2.3



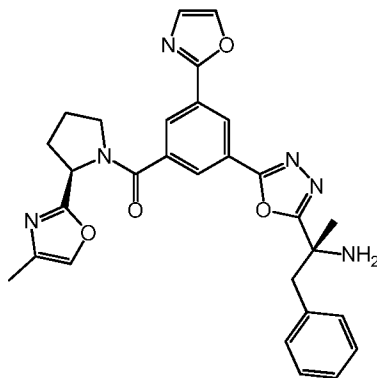
**[0904]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyridin-3-yl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.88 (br s, 1H), 8.72 (br s, 1H), 8.38-7.80 (m, 4H), 7.48 (s, 1H), 7.36-7.20 (m, 3H), 7.12-7.00 (m, 2H), 6.98 (br s, 1H), 5.04 (br s, 1.2H), 4.80 (br s, 0.8H), 3.40-3.06 (m, 5H), 2.50 (s, 3H), 1.80 (br s, 2H), 1.71 (s, 3H).

## Example 2.4



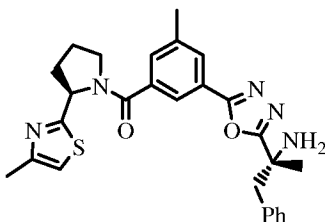
**[0905]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)-((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.80 (s, 0.6H), 8.68 (s, 0.4H), 8.42 (s, 0.6H), 8.38 (s, 0.6H), 8.14 (s, 0.4H), 8.04 (s, 0.4H), 7.82 (s, 0.6H), 7.78 (s, 0.4H), 7.39-7.19 (m, 4H), 7.12-7.00 (m, 2H), 6.83 (s, 0.6H), 6.78 (s, 0.4H), 5.76-5.70 (m, 0.6H), 5.22-5.18 (m, 0.4H), 4.02-3.84 (m, 2H), 3.70-3.58 (m, 1H), 3.40-3.24 (m, 1H), 3.20-3.06 (m, 1H), 2.57-2.40 (m, 4H), 2.24-1.80 (m, 4H), 1.74-1.62 (two s, 3H).

## Example 2.5



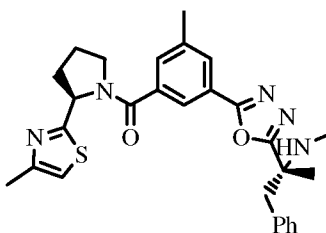
**[0906]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.76 (s, 0.6H), 8.60 (s, 0.4H), 8.42 (s, 0.6H), 8.36 (s, 0.6H), 8.02 (s, 0.4H), 8.00 (s, 0.4H), 7.82 (s, 0.6H), 7.78 (s, 0.4H), 7.39-7.19 (m, 5H), 7.04-6.96 (m, 2H), 5.40-5.32 (m, 0.6H), 4.94-4.84 (m, 0.4H), 4.00-3.80 (m, 2H), 3.64-3.54 (m, 1H), 3.38-3.20 (m, 1H), 3.18-3.04 (m, 1H), 2.43-2.04 (m, 4H), 2.04-1.70 (m, 4H), 1.67 (s, 3H).

## Example 2.6



**[0907]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methylphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99-7.72 (m, 2H), 7.55 (s, 1H), 7.29-7.19 (m, 4H), 7.05-7.00 (m, 2H), 6.80-6.77 (m, 1H), 5.69-5.65 (m, 0.6H), 5.15-5.13 (m, 0.3H), 3.93-3.87 (m, 1H), 3.81-3.74 (m, 1H), 3.59-3.49 (m, 1H), 3.30-3.21 (m, 1H), 3.11-3.03 (m, 1H), 2.47-2.26 (m, 8H), 2.24-2.03 (m, 3H), 2.00-1.74 (m, 3H), 1.65-1.59 (m, 3H).

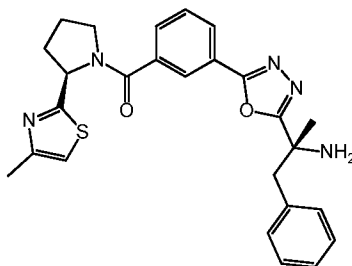
## Example 2.7



**[0908]** (3-methyl-5-(5-((R)-2-(methylamino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone  $^1\text{H}$  NMR (300 MHz,

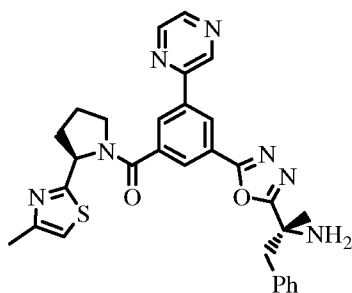
CDCl<sub>3</sub>)  $\delta$  7.96-7.69 (m, 2H), 7.54 (s, 1H), 7.29-7.16 (m, 4H), 7.02-7.00 (m, 2H), 6.80-6.76 (m, 1H), 5.69-5.65 (m, 0.7H), 5.14-5.11 (m, 0.3H), 3.90-3.89 (m, 1H), 3.80-3.72 (m, 1H), 3.58-3.49 (m, 1H), 3.19-3.16 (m, 2H), 2.46-2.25 (m, 10H), 2.21-2.04 (m, 3H), 1.99-1.90 (m, 1H), 1.77 (m, 2H), 1.61-1.55 (m, 3H).

*Example 2.8*



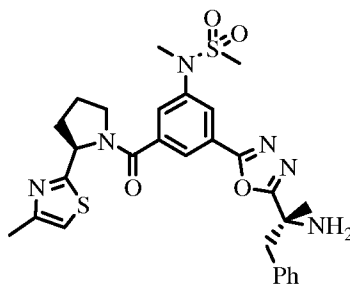
**[0909]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.99-7.72 (m, 2H), 7.55 (s, 1H), 7.29-7.19 (m, 4H), 7.05-7.00 (m, 2H), 6.80-6.77 (m, 1H), 5.69-5.65 (m, 0.6H), 5.15-5.13 (m, 0.3H), 3.93-3.87 (m, 1H), 3.81-3.74 (m, 1H), 3.59-3.49 (m, 1H), 3.30-3.21 (m, 1H), 3.11-3.03 (m, 1H), 2.47-2.26 (m, 5H), 2.24-2.03 (m, 3H), 1.65-1.59 (two s, 3H).

*Example 2.9*



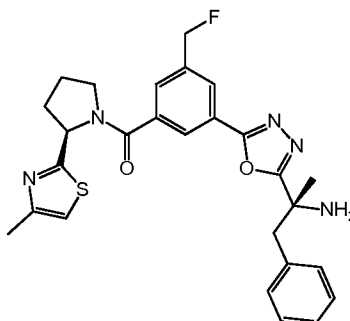
**[0910]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  9.13-8.56 (m, 4H), 8.41-8.04 (m, 2H), 7.29-7.21 (m, 3H), 7.04-7.02 (m, 2H), 6.80-6.77 (m, 1H), 5.71-5.67 (m, 0.6H), 5.20-5.18 (m, 0.3H), 3.97-3.81 (m, 2H), 3.65-3.57 (m, 1H), 3.31-3.23 (m, 1H), 3.12-3.05 (m, 1H), 2.44-2.28 (m, 7H), 2.21-2.10 (m, 2H), 2.03-1.93 (m, 3H), 1.67-1.64 (m, 3H).

## Example 2.10



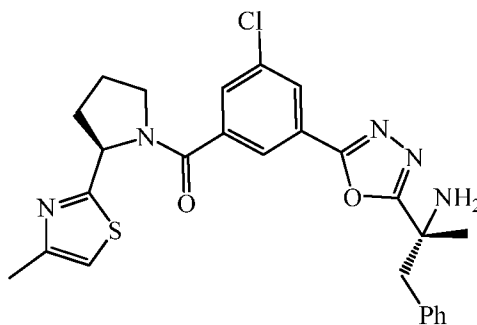
**[0911]** N-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-N-methylmethanesulfonamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.12-7.52 (m, 3H), 7.31-7.21 (m, 4H), 7.04-7.01 (m, 2H), 6.79-6.72 (m, 1H), 5.66-5.62 (m, 0.6H), 5.20-5.17 (m, 0.3H), 3.91-3.80 (m, 1H), 3.63-3.55 (m, 1H), 3.39-3.20 (m, 4H), 3.10-3.03 (m, 1H), 2.91-2.79 (m, 3H), 2.43-2.28 (m, 5H), 2.21-2.03 (m, 2H), 2.01-1.70 (m, 3H), 1.64-1.61 (m, 3H).

## Example 2.11



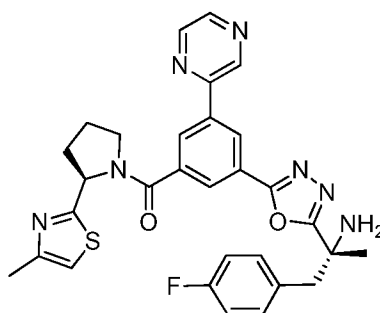
**[0912]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(fluoromethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (s, 0.6H), 8.06 (s, 0.6H), 8.00 (s, 0.4H), 7.90 (s, 0.4H), 7.78 (s, 0.6H), 7.40 (s, 0.4H), 7.29-7.19 (m, 3H), 7.05-6.90 (m, 2H), 6.80 (s, 0.6H), 6.78 (s, 0.4H), 5.69-5.60 (m, 0.6H), 5.57 (s, 1H), 5.41 (s, 1H), 5.19-5.08 (m, 0.4H), 3.98-3.84 (m, 1H), 3.84-3.74 (m, 1H), 3.59-3.48 (m, 1H), 3.30-3.18 (m, 1H), 3.16-3.00 (m, 1H), 2.47-2.06 (m, 5H), 2.24-1.80 (m, 3H), 1.72-1.60 (two s, 3H).

## Example 2.12



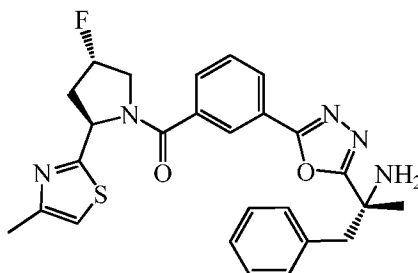
**[0913]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-chlorophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.62-2.42 (m, 10H), 3.04-3.26 (m, 2H), 3.24-3.82 (m, 2H), 5.62-5.72 (m, 1H), 6.80 (s, 1H), 6.84-7.21 (m, 5H), 7.74 (s, 1H), 8.02-8.18 (m, 2H).

## Example 2.13



**[0914]** (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.21-8.64 (m, 4H), 8.49-8.10 (m, 2H), 7.34-7.33 (m, 1H), 7.08-6.88 (m, 5H), 5.76 (m, 0.6H), 5.28 (m, 0.3H), 4.02-3.93 (m, 1H), 3.71-3.42 (m, 1H), 3.36-3.28 (m, 1H), 3.18-3.15 (m, 1H), 2.51-2.45 (m, 3H), 2.36-1.83 (m, 5H), 1.73 (m, 3H).

## Example 2.14

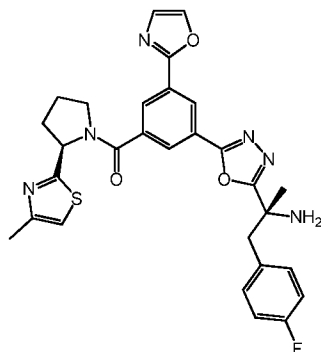


**[0915]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.42 (s, 3H), 2.42 (s, 3H), 2.68-2.86 (m, 2H), 3.02-3.26 (m, 1H), 3.61-4.14 (m, 3H), 5.28 (d,



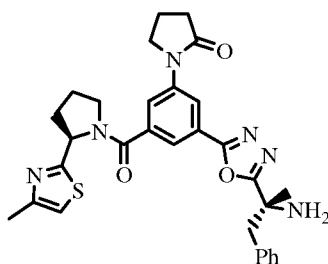
1H, J= 42 Hz), 5.62-5.72 (m, 1H), 6.81 (s, 1H), 7.01-7.06 (m, 2H), 7.21-7.28 (m, 3H), 7.51-7.60 (m, 1H), 7.72-7.74 (m, 1H), 8.10-8.22 (m, 2H).

*Example 2.15*



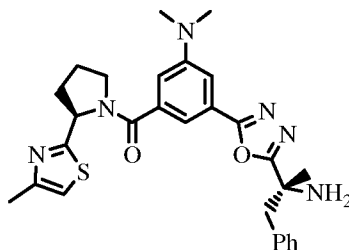
**[0916]** (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.76 (s, 0.6H), 8.60 (s, 0.4H), 8.42 (s, 0.6H), 8.36 (s, 0.6H), 8.06 (s, 0.4H), 8.02 (s, 0.4H), 7.82 (s, 0.6H), 7.78 (s, 0.4H), 7.26 (s, 0.6H), 7.22 (s, 0.4H), 7.04-6.84 (m, 4H), 6.80 (s, 0.6H), 6.76 (s, 0.4H), 5.74-5.62 (m, 0.6H), 5.20-5.18 (m, 0.4H), 3.98-3.80 (m, 2H), 3.64-3.50 (m, 1H), 3.30-3.16 (m, 1H), 3.16-3.02 (m, 1H), 2.50-2.30 (m, 4H), 2.24-1.80 (m, 4H), 1.64-1.62 (two s, 3H).

*Example 2.16*



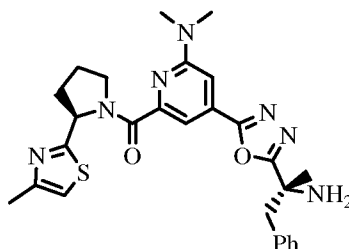
**[0917]** 1-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)pyrrolidin-2-one. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.38-8.14 (m, 2H), 7.98-7.90 (m, 1H), 7.28-7.15 (m, 4H), 7.04-7.02 (m, 2H), 6.78-6.74 (m, 1H), 5.69-5.65 (m, 0.6H), 5.23-5.21 (m, 0.3H), 3.99-3.50 (m, 4H), 3.29-3.21 (m, 1H), 3.10-3.03 (m, 1H), 2.70-2.59 (m, 2H), 2.44-2.08 (m, 8H), 2.03-1.88 (m, 3H), 1.64-1.61 (m, 3H).

## Example 2.17



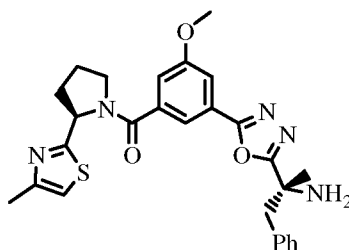
**[0918]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(dimethylamino)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43-7.33 (m, 2H), 7.30-7.16 (m, 5H), 7.05-7.02 (m, 3H), 6.80-6.68 (m, 1H), 5.69-5.65 (m, 0.6H), 5.20-5.17 (m, 0.4H), 4.15-3.74 (m, 2H), 3.62-3.54 (m, 1H), 3.33-3.21 (m, 1H), 3.11-3.03 (m, 5H), 2.86 (s, 3H), 2.48-2.16 (m, 6H), 2.14-2.05 (m, 3H), 2.01-1.73 (m, 3H), 1.68-1.60 (m, 3H).

## Example 2.18



**[0919]** (4-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(dimethylamino)pyridin-2-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65-7.61 (m, 1H), 7.27-7.20 (m, 4H), 7.12 (m, 1H), 7.02-6.99 (m, 2H), 6.76-6.68 (m, 1H), 6.21-6.19 (m, 0.5H), 5.72-5.68 (m, 0.4H), 4.21-3.89 (m, 2H), 3.28-3.14 (m, 4H), 3.09-3.05 (m, 1H), 2.91 (s, 3H), 2.43-2.31 (m, 5H), 2.17-1.75 (m, 5H), 1.63 (s, 3H).

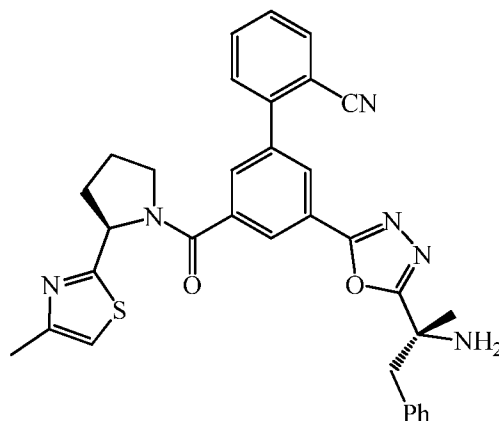
## Example 2.19



**[0920]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methoxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76-7.51 (m, 2H), 7.28-7.20 (m, 4H), 7.03-6.91 (m, 2H), 6.78-6.76 (m, 1H),

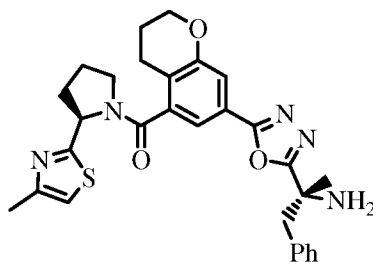
5.67-5.63 (m, 0.6H), 5.16-5.14 (m, 0.3H), 3.90-3.69 (m, 5H), 3.60-3.49 (m, 1H), 3.28-3.19 (m, 1H), 3.10-3.02 (m, 1H), 2.43-2.28 (m, 5H), 2.22-1.90 (m, 5H), 1.64-1.61 (m, 3H).

*Example 2.20*



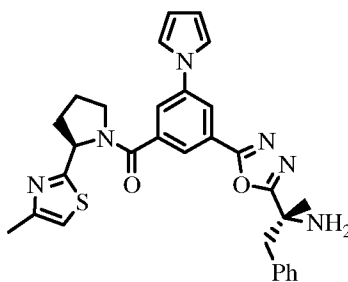
**[0921]** 3'-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5'-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carbonitrile.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.65 (s, 3H), 1.95-2.46 (m, 7H), 3.06-3.30 (m, 1H), 3.60-3.75 (m, 2H), 3.90-3.93 (m, 1H), 5.66-5.70 (m, 1H), 6.78 (s, 1H), 7.02-7.05 (m, 2H), 7.19-7.26 (m, 4H), 7.54-7.92 (m, 4H), 8.24-8.29 (m, 2H).

*Example 2.21*



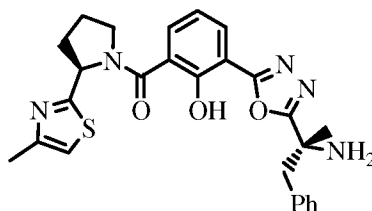
**[0922]** (7-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)chroman-5-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50-7.42 (m, 2H), 7.34-7.20 (m, 4H), 7.05-6.98 (m, 2H), 6.82-6.669 (m, 1H), 5.66-5.63 (m, 0.6H), 5.04 (m, 0.3H), 4.29-4.12 (m, 2H), 3.95-3.86 (m, 1H), 3.55-3.33 (m, 1H), 3.28-3.20 (m, 1H), 3.09-2.90 (m, 2H), 2.82-2.54 (m, 1H), 2.44-2.29 (m, 5H), 2.23-1.73 (m, 7H), 1.64-1.62 (m, 3H).

## Example 2.22



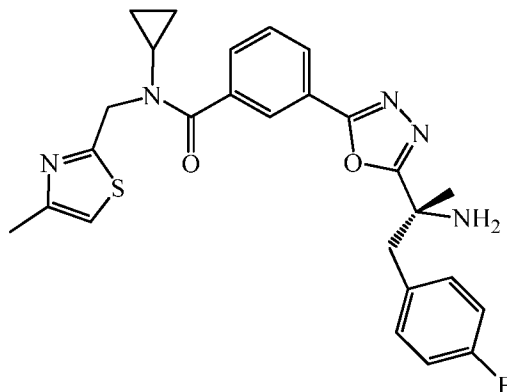
**[0923]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrrol-1-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06-8.02 (m, 2H), 7.82-7.75 (m, 1H), 7.37-7.18 (m, 5H), 7.05-6.95 (m, 3H), 6.81-6.58 (m, 1H), 6.41-6.34 (m, 2H), 5.70-5.65 (m, 0.5H), 5.19-5.17 (m, 0.4H), 3.94-3.77 (m, 2H), 3.64-3.56 (m, 1H), 3.34-3.22 (m, 1H), 3.12-3.06 (m, 1H), 2.45-2.33 (m, 4H), 2.27-2.11 (m, 2H), 2.02-1.74 (m, 3H), 1.68-1.65 (m, 3H).

## Example 2.23



**[0924]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2-hydroxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.63-10.50 (m, 1H), 7.79-7.54 (m, 2H), 7.28-7.21 (m, 4H), 7.10-6.69 (m, 4H), 5.73-5.69 (m, 0.5H), 5.21-5.19 (m, 0.4H), 3.95-3.90 (m, 1H), 3.73-3.66 (m, 1H), 3.55-3.46 (m, 1H), 3.31-3.25 (m, 1H), 3.12-3.08 (m, 1H), 2.47-2.17 (m, 5H), 2.12-1.60 (m, 3H).

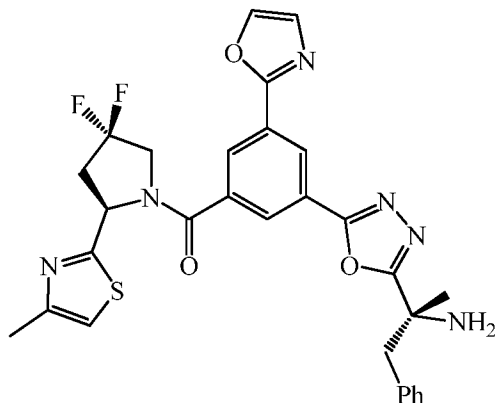
## Example 2.24



**[0925]** (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)benzamide.  $^1\text{H}$  NMR (300 MHz,

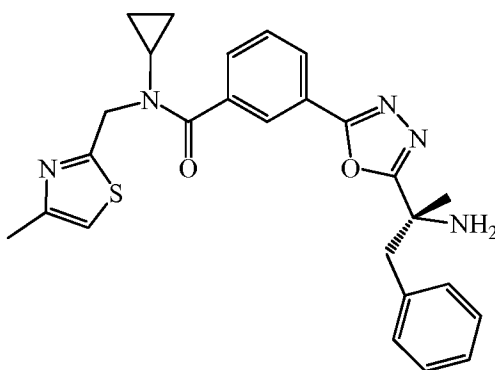
CDCl<sub>3</sub>+CD<sub>3</sub>OD)  $\delta$  8.182 (s, 1 H), 8.067 (d,  $J$  = 3.9 Hz, 1 H), 7.735 (d,  $J$  = 7.8 Hz, 1 H), 7.559 (t,  $J$  = 7.8, 15.6 Hz, 1 H), 7.024-6.861 (m, 5 H), 5.019 (s, 2 H), 3.232 (d,  $J$  = 13.5 Hz, 1 H), 3.056 (d,  $J$  = 13.5 Hz, 1 H), 2.928 (m, 1 H), 2.443 (s, 3 H), 1.625 (s, 3 H), 0.638 (m, 2 H), 0.528 (m, 2 H).

*Example 2.25*



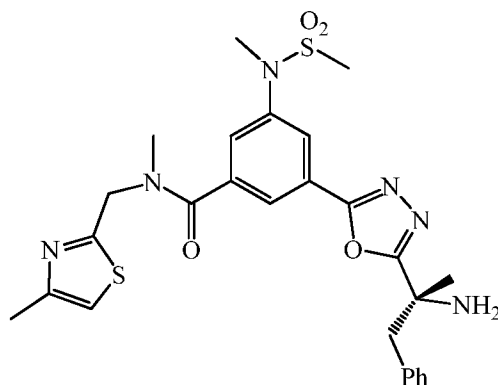
**[0926]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-4,4-difluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>+CD<sub>3</sub>OD)  $\delta$  8.738 (s, 1 H), 8.361 (s, 1 H), 8.276 (s, 1 H), 7.795 (s, 1 H), 7.7219 (m, 3 H), 7.013 (m, 2 H), 6.872 (s, 1 H), 5.886 (br, 1 H), 4.173 (m, 1 H), 3.903 (m, 1 H), 3.272 (d,  $J$  = 13.5 Hz, 1 H), 3.086 (d,  $J$  = 13.5 Hz, 1 H), 2.945 (m, 2 H), 2.443 (s, 3 H), 1.655 (s, 3 H).

*Example 2.26*



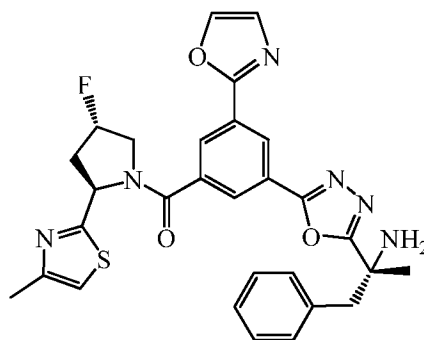
**[0927]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)benzamide. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>+CD<sub>3</sub>OD)  $\delta$  8.184 (s, 1 H), 8.068 (d,  $J$  = 7.8 Hz, 1 H), 7.756 (d,  $J$  = 7.8 Hz, 1 H), 7.557 (t,  $J$  = 7.8, 15.6 Hz, 1 H), 7.207 (m, 3 H), 7.027 (m, 2 H), 6.871 (s, 1 H), 5.029 (s, 2 H), 3.268 (d,  $J$  = 13.2 Hz, 1 H), 3.086 (d,  $J$  = 13.5 Hz, 1 H), 2.932 (m, 1 H), 2.451 (s, 3 H), 1.649 (s, 3 H), 0.675 (m, 2 H), 0.533 (m, 2 H).

## Example 2.27



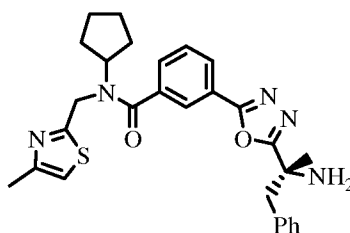
**[0928]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(N-methylmethanysulfonamido)-N-((4-methylthiazol-2-yl)methyl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  8.056 (m, 2 H), 7.791 (m, 1 H), 7.213 (m, 3 H), 7.002 (m, 2 H), 6.916 (m, 1 H), 4.973 (s, 1.4 H), 4.718 (s, 0.6 H), 3.390 (s, 3 H), 3.288-3.061 (m, 2 H), 3.105 (s, 3 H), 2.917 (s, 3 H), 2.448 (s, 3 H), 1.647 (s, 3 H).

## Example 2.28



**[0929]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.65 (s, 3H), 2.44 (s, 3H), 2.80-2.90 (m, 2H), 3.07-3.30 (m, 2H), 3.60-4.08 (m, 3H), 5.30 (d, 1H,  $J = 48$  Hz), 5.82-5.88 (m, 1H), 6.85 (s, 1H), 7.01-7.04 (m, 2H), 7.21-7.30 (m, 4H), 7.79 (s, 1H), 8.31 (s, 1H), 8.39 (s, 1H), 8.74 (s, 1H).

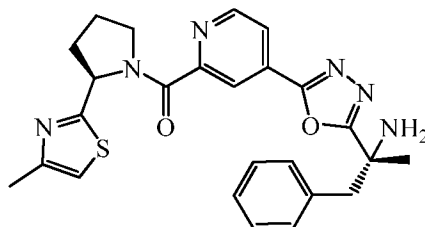
## Example 2.29



**[0930]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopentyl-N-((4-methylthiazol-2-yl)methyl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.09-8.08 (m, 2H),

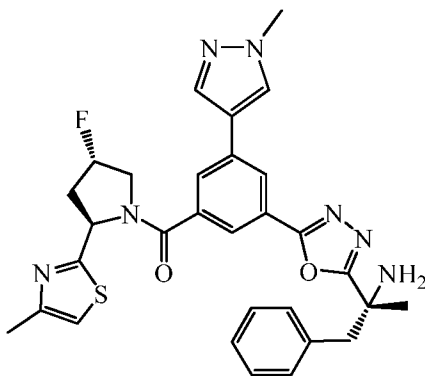
7.62-7.54 (m, 2H), 7.28-7.18 (m, 4H), 7.06-7.01 (m, 2H), 6.84 (m, 1H), 4.90 (broad s, 2H), 4.12-4.10 (m, 1H), 3.27 (d, 1H), 3.09 (d, 1H), 2.04-1.60 (m, 12H), 1.44 (m, 2H).

*Example 2.30*



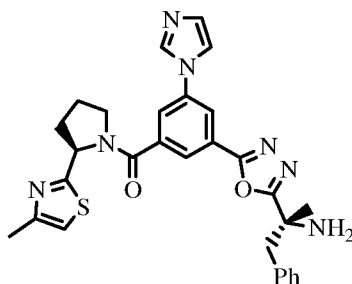
**[0931]** (4-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.62(s, 3H), 1.95-2.46 (m, 7H), 3.07-3.61 (m, 3H), 5.62-5.64 (m, 1H), 6.85 (s, 1H), 7.01-7.14 (m, 2H), 7.21-7.38 (m, 3H), 7.60 (s, 1H), 8.40 (s, 1H), 8.86 (s, 1H).

*Example 2.31*



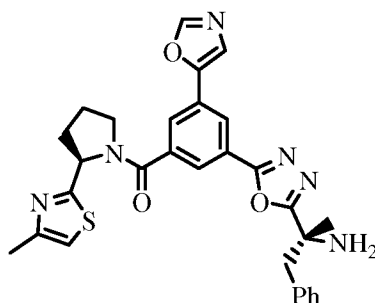
**[0932]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.65 (s, 3H), 1.84-2.20 (m, 4H), 2.44 (s, 3H), 3.01-3.36 (m, 2H), 3.54-3.92 (m, 5H), 5.62-5.65 (m, 1H), 6.83 (s, 1H), 7.01-7.04 (m, 2H), 7.18-7.22 (m, 2H), 7.48 (s, 1H), 7.71-7.82 (m, 3H), 7.98 (s, 1H), 8.14 (s, 1H).

## Example 2.32



**[0933]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-imidazol-1-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.16-7.97 (m, 2H), 7.78-7.72 (m, 1H), 7.39-7.36 (m, 1H), 7.31-7.20 (m, 5H), 7.06-7.03 (m, 2H), 6.83 (m, H), 5.70-5.65 (m, 0.5H), 5.17-5.12 (m, 0.4H), 3.95-3.81 (m, 2H), 3.64-3.59 (m, 1H), 3.35-3.23 (m, 1H), 3.13-3.07 (m, 1H), 2.46-2.28 (m, 4H), 2.23-2.08 (m, 2H), 2.05-1.72 (m, 4H), 1.69-1.66 (m, 3H).

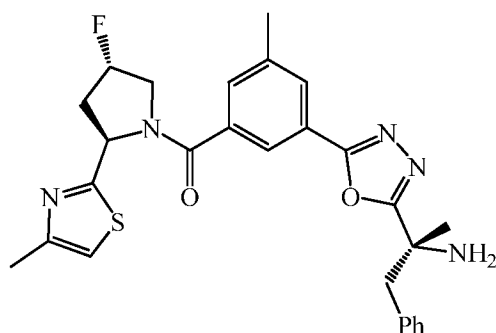
## Example 2.33



**[0934]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-5-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.32-8.26 (m, 1H), 8.01-7.91 (m, 2H), 7.62-7.53 (m, 1H), 7.30-7.19 (m, 4H), 7.06-7.03 (m, 2H), 6.82-6.79 (m, 1H), 5.70-5.66 (m, 0.6H), 5.16-5.14 (m, 0.4H), 3.96-3.78 (m, 2H), 3.63-3.55 (m, 1H), 3.31-3.23 (m, 1H), 3.13-3.06 (m, 1H), 2.45-2.30 (m, 4H), 2.22-2.11 (m, 2H), 2.05-1.82 (m, 3H), 1.68-1.65 (m, 3H).

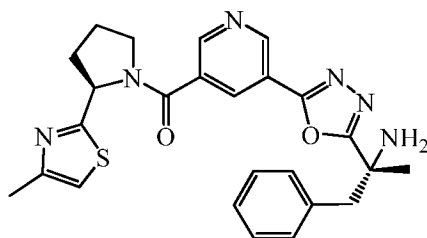


## Example 2.34



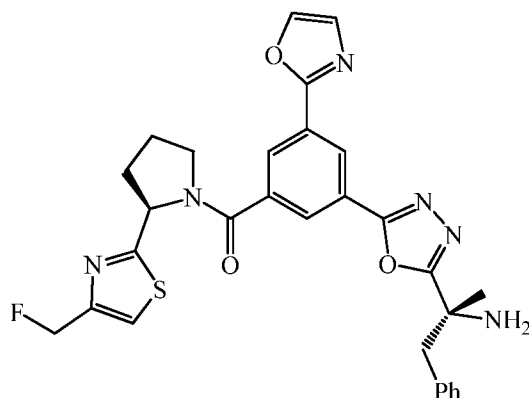
**[0935]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methylphenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  7.981 (s, 1 H), 7.914 (s, 1 H), 7.577 (s, 1 H), 7.229 (m, 3 H), 7.021 (m, 2 H), 6.841 (s, 1 H), 5.807 (m, 0.8 H), 5.329 (s, 0.2 H), 5.371 (s, 0.5 H), 5.196 (s, 0.5 H), 4.085-3.811 (m, 2 H), 3.300-3.072 (m, 2 H), 2.835 (m, 2 H), 2.465 (s, 3 H), 2.435 (s, 3 H), 1.659 (s, 3 H).

## Example 2.35



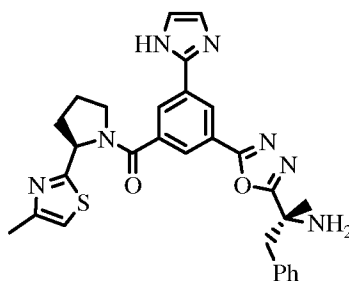
**[0936]** (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)pyridin-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.61(s, 3H), 1.82-2.47 (m, 7H), 3.06-3.32 (m, 3H), 3.51-3.92 (m, 3H), 5.62-5.64 (m, 1H), 6.82 (s, 1H), 6.88-7.10 (m, 2H), 7.21-7.38 (m, 3H), 8.42 (s, 1H), 8.88 (s, 1H), 9.30 (s, 1H).

## Example 2.36



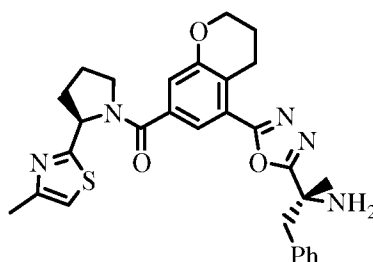
**[0937]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-(fluoromethyl)thiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  8.729 (s, 1 H), 8.405 (s, 1 H), 8.329 (s, 1 H), 7.808 (s, 1 H), 7.744-7.188 (m, 5 H), 7.038 (m, 2 H), 5.714-5.207 (m, 3 H), 3.868 (m, 1 H), 3.609 (m, 1 H), 3.27 (m, 1 H), 3.102 (m, 1 H), 2.457 (m, 2 H), 2.173 (m, 1 H), 1.999 (m, 1 H), 1.670 (s, 3 H).

## Example 2.37



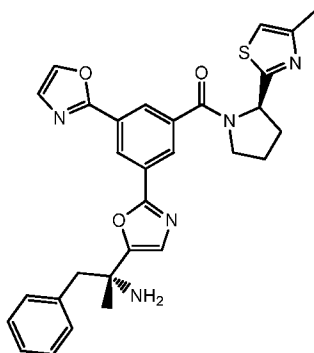
**[0938]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-imidazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.64-8.54 (m, 1H), 8.34-7.90 (m, 2H), 7.39-7.17 (m, 4H), 7.06-7.01 (m, 4H), 6.77-6.68 (m, 1H), 5.66-5.59 (m, 0.7H), 5.26-5.24 (m, 0.2H), 3.89-3.81 (m, 1H), 3.63-3.55 (m, 1H), 3.45-3.22 (m, 1H), 3.12-3.05 (m, 1H), 2.61-2.26 (m, 5H), 2.19-1.92 (m, 3H), 1.63 (broad s, 3H).

## Example 2.38



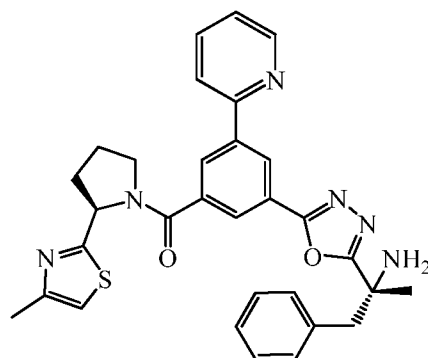
**[0939]** (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)chroman-7-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65-7.40 (m, 1H), 7.33-7.19 (m, 4H), 7.05-6.88 (m, 2H), 6.78-6.75 (m, 1H), 5.59-5.64 (m, 0.6H), 5.20-5.18 (m, 0.3H), 4.24-4.17 (m, 2H), 3.88-3.73 (m, 1H), 3.62-3.53 (m, 1H), 3.29-3.06 (m, 3H), 2.44-2.17 (m, 4H), 2.14-1.70 (m, 6H), 1.64-1.61 (m, 3H).

*Example 2.39*



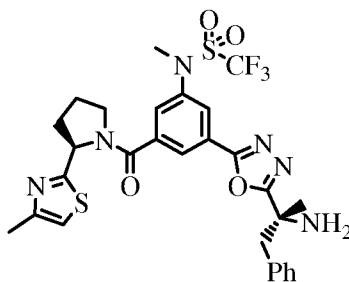
**[0940]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)oxazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.74 and 8.62 (s, 1H); 8.32 and 8.10 (s, 2H), 7.79 and 7.71 (s, 1H); 7.22 (m, 4 H); 6.98 (m, 2H); 6.80 (m, 2H); 5.70 and 5.20 (t, 1H); 3.75 (m, 2H); 3.10 (dd, 2H,  $J = 13.5$  Hz); 2.45 (m, 4 H); 2.05 (m, 4 H); 1.71 (br. s 2H) and 1.53 (s, 3H).

*Example 2.40*



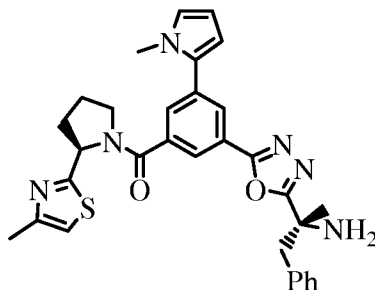
**[0941]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyridin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.67 (s, 3H), 1.84-2.47 (m, 7H), 3.06-3.32 (m, 2H), 3.57-3.92 (m, 3H), 5.62-5.64 (m, 1H), 6.81 (s, 1H), 7.03-7.05 (m, 2H), 7.22-7.34 (m, 4H), 7.83-7.85 (m, 2H), 8.27 (s, 1H), 8.40 (s, 1H), 8.70-8.75 (m, 2H).

## Example 2.41



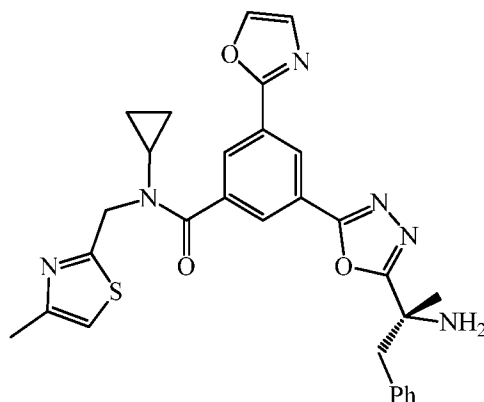
**[0942]** tert-butyl (2-(5-(3-(methyl((4-methylthiazol-2-yl)methyl)carbamoyl)phenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21-7.95 (m, 2H), 7.76-7.48 (m, 1H), 7.28-7.19 (m, 3H), 7.05-7.02 (m, 2H), 7.02-6.75 (m, 1H), 5.67-5.63 (m, 0.6H), 5.15-5.13 (m, 0.3H), 3.94-3.76 (m, 1H), 3.60-3.43 (m, 4H), 3.29-3.22 (m, 1H), 3.12-3.05 (m, 1H), 2.49-2.32 (m, 4H), 2.23-1.95 (m, 5H), 1.66-1.64 (m, 3H).

## Example 2.42



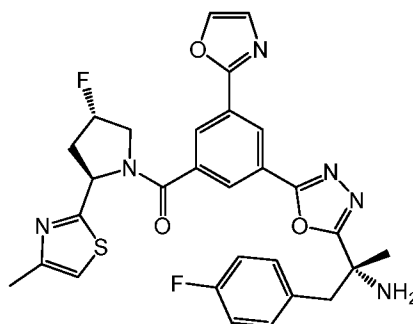
**[0943]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-methyl-1H-pyrrol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11-7.86 (m, 2H), 7.76-7.42 (m, 1H), 7.27-7.22 (m, 4H), 7.05-7.02 (m, 2H), 6.80-6.72 (m, 2H), 6.34-6.17 (m, 2H), 5.71-5.66 (m, 0.6H), 5.22-5.20 (m, 0.3H), 3.96-3.57 (m, 4H), 3.30-3.22 (m, 1H), 3.11-3.04 (m, 1H), 2.47-2.31 (m, 4H), 2.24-1.93 (m, 3H), 1.77 (broad s, 3H), 1.66-1.63 (m, 3H).

## Example 2.43



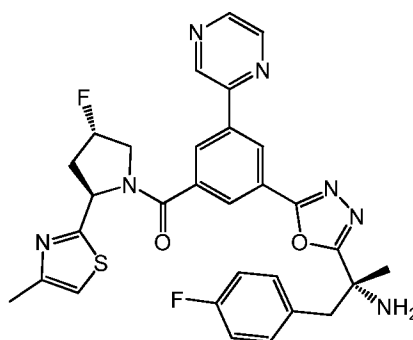
**[0944]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.707 (s, 1 H), 8.403 (s, 1 H), 8.301 (s, 1 H), 7.798 (s, 1 H), 7.303-7.199 (m, 4 H), 7.038 (m, 2 H), 6.882 (s, 1 H), 5.049 (s, 2 H), 3.319 (m, 1 H), 3.134 (m, 1 H), 3.011 (m, 1 H), 2.460 (s, 3 H), 1.674 (s, 1 H), 0.687 (m, 2 H), 0.561 (m, 2 H).

*Example 2.44*



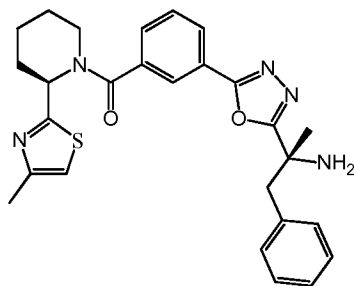
**[0945]** (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.64(s, 3H), 2.45 (s, 3H), 2.76-2.90 (m, 2H), 3.05-3.28 (m, 2H), 3.85-4.14 (m, 2H), 5.30 (d, 1H,  $J = 51$  Hz), 5.83-5.88 (m, 1H), 6.85-7.03 (m, 4H), 7.30 (s, 2H), 7.80 (s, 1H), 8.34 (s, 1H), 8.40 (s, 1H), 8.74 (s, 1H).

*Example 2.45*



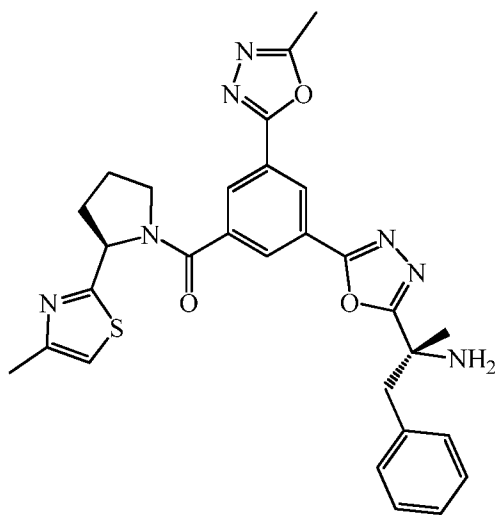
**[0946]** (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.66 (s, 3H), 2.45 (s, 3H), 2.79-2.91 (m, 2H), 3.06-3.29 (m, 2H), 3.90-4.19 (m, 2H), 5.31 (d, 1H,  $J = 51$  Hz), 5.84-5.89 (m, 1H), 6.86-7.7.05 (m, 7H), 8.33 (s, 1H), 8.43 (s, 1H), 8.61 (s, 1H), 8.69 (s, 1H), 8.76 (s, 1H), 9.15 (s, 1H).

## Example 2.46



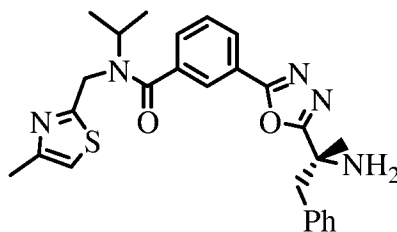
**[0947]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)piperidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.18-8.14 (m, 2H), 7.70-7.42 (m, 2H), 7.32-7.14 (m, 3H), 7.10-6.90 (m, 2H), 6.87(s, 1H), 6.30-6.18 (m, 0.6H), 5.20-5.02 (m, 0.4H), 3.70-2.60 (m, 4H), 2.44(s, 3H) 1.84(s, 3H), 1.64 (s, 3H), 2.08-1.40 (m, 5H).

## Example 2.47



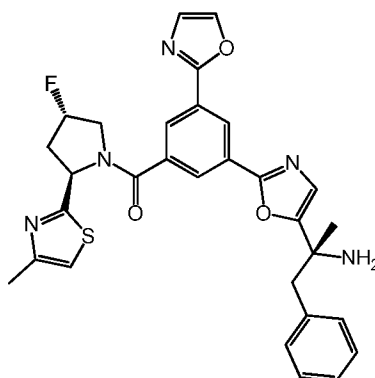
**[0948]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.24 (s, 3H), 1.69 (s, 3H), 1.93-2.42 (m, 6H), 3.04-3.28 (m, 2H), 3.51-3.56 (m, 1H), 3.77-3.93 (m, 2H), 5.63-5.67 (m, 1H), 6.74 (s, 1H), 6.99-7.01 (m, 2H), 7.20-7.25 (m, 3H), 8.20 (s, 1H), 8.33 (s, 1H), 8.47 (s, 1H).

## Example 2.48



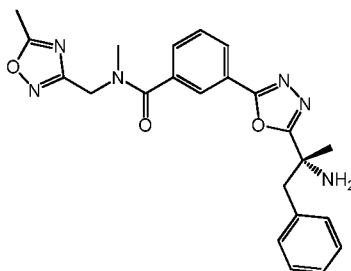
**[0949]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-isopropyl-N-((4-methylthiazol-2-yl)methyl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06-8.01 (m, 2H), 7.58-7.53 (m, 2H), 7.28-7.17 (m, 3H), 7.04-7.01 (m, 2H), 6.84 (s, 1H), 4.92-4.45 (m, 2H), 4.07 (m, 1H), 3.26 (d, 1H), 3.08 (d, 1H), 2.42 (s, 3H), 1.09 (s, 3H), 1.24-1.19 (m, 6H).

## Example 2.49



**[0950]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)oxazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.80 (s, 0.8H), 8.72 (s, 0.2H), 8.38 (two s, 1.7H), 7.98 (s, 0.3H), 7.80 (s, 1H), 7.34-7.20 (m, 4H), 7.00-6.92 (m, 2H), 6.82 (s, 1H), 6.80 (s, 1H), 5.92-5.82 (m, 1H), 5.40 (br s, 0.5H), 5.20 (br s, 0.5H), 4.17-3.84 (m, 2H), 3.20-3.00 (m, 2H), 2.94-2.84 (m, 1H), 2.84-2.78 (m, 1H), 2.46 (s, 3H), 1.78 (br s, 2H), 1.53 (s, 3H).

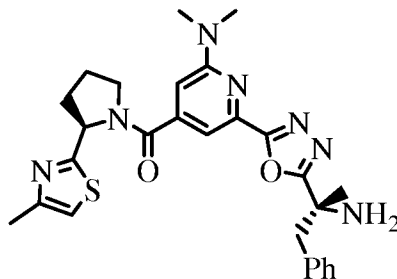
## Example 2.50



**[0951]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((5-methyl-1,2,4-oxadiazol-3-yl)methyl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.22-8.06

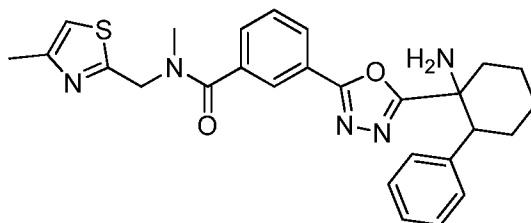
(m, 2H), 7.80-7.52 (m, 2H), 7.23-7.18 (m, 3H) 7.04- 6.96 (m, 2H), 4.86 (br s, 1.2H), 4.56 (br s, 0.8H), 3.26-3.04 (m, 5H), 2.39 (br s, 3H), 1.83 (br s 2H), 1.64 (s, 3H).

*Example 2.51*



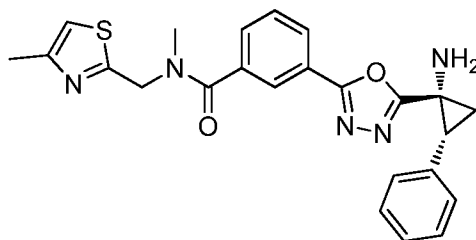
**[0952]** (2-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(dimethylamino)pyridin-4-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32-7.16 (m, 5H), 7.10-7.02 (m, 2H), 6.83-6.77 (m, 2H), 5.65-5.61 (m, 0.6H), 5.15-5.13 (m, 0.3H), 3.91-3.72 (m, 2H), 3.58-3.49 (m, 1H), 3.45-3.26 (m, 1H), 3.22-2.98 (m, 7H), 2.45-2.33 (m, 4H), 2.22-1.92 (m, 3H), 1.67-1.63 (m, 3H).

*Example 2.52*



**[0953]** 3-[5-(1-Amino-2-phenylcyclohexyl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide.

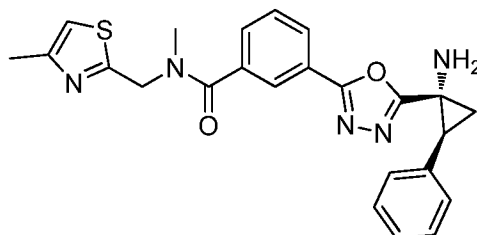
*Example 2.53*



**[0954]** *rel*-3-{5-[(1R,2R)-1-Amino-2-phenylcyclopropyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide.

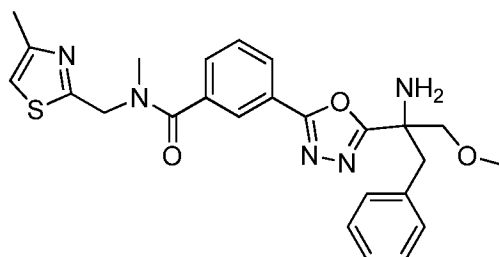


## Example 2.54



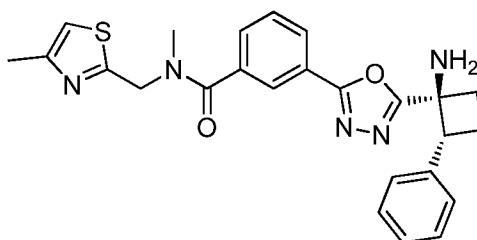
**[0955]** *rel*-3-{5-[(1R,2S)-1-Amino-2-phenylcyclopropyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide.

## Example 2.55



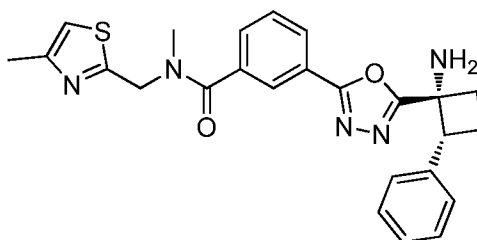
**[0956]** 3-(5-(2-Amino-1-methoxy-3-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide.

## Example 2.56



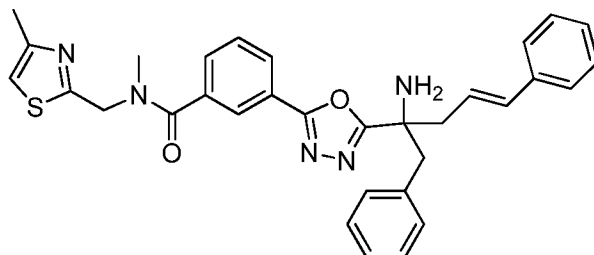
**[0957]** 3-(5-(*rel*-(1S,2R)-1-Amino-2-phenylcyclobutyl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide.

## Example 2.57



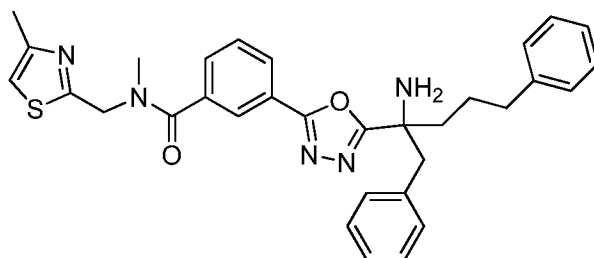
**[0958]** 3-(5-(*rel*-(1R,2R)-1-Amino-2-phenylcyclobutyl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide.

*Example 2.58*



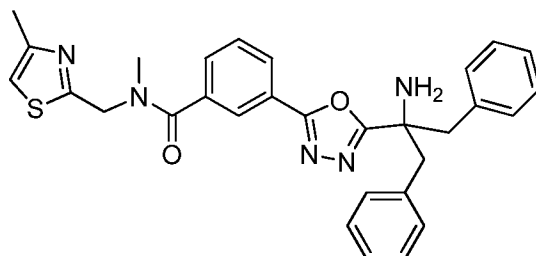
**[0959]** 3-{5-[(4E)-2-Amino-1,5-diphenylpent-4-en-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide.

*Example 2.59*



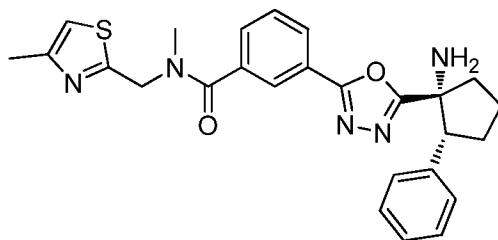
**[0960]** 3-[5-(2-Amino-1,5-diphenylpentan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide.

*Example 2.60*



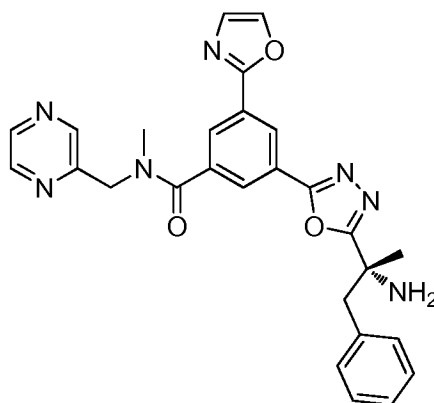
**[0961]** 3-[5-(2-Amino-1,3-diphenylpropan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide.

## Example 2.61



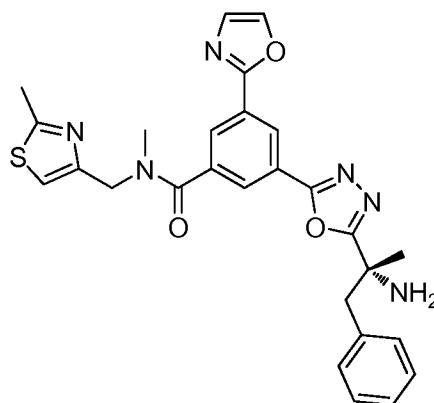
**[0962]** *rel*-3-{5-[(1R,2R)-1-Amino-2-phenylcyclopentyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide.

## Example 2.62



**[0963]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(oxazol-2-yl)-N-(pyrazin-2-ylmethyl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.78 (s, 1H), 8.72 (s, 1H), 8.64-8.50 (m, 2H), 8.34 (s, 1H), 8.12 (s, 1H), 7.80 (s, 1H), 7.30 (s, 1H), 7.28-7.00 (m, 3H), 7.04-6.98 (m, 2H), 4.96 (s, 1.4 H), 4.68 (s, 0.6 H), 3.36-3.20 (m, 1H), 3.36-3.02 (m, 4H), 1.67 (s, 3H).

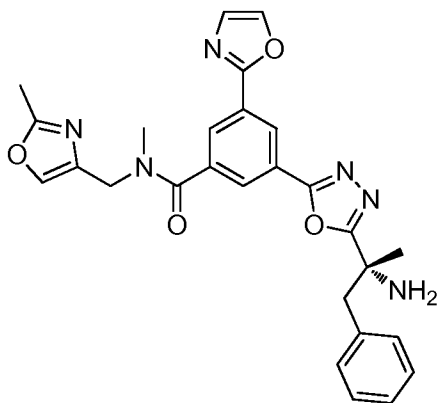
## Example 2.63



**[0964]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((2-methylthiazol-4-yl)methyl)-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.70 (s,

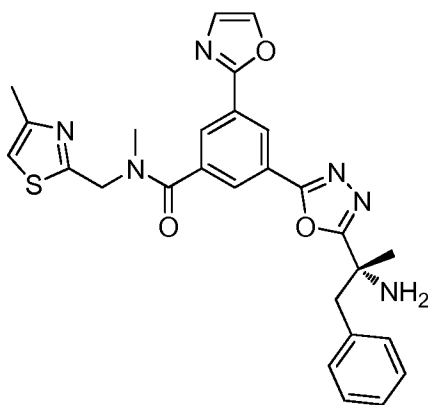
1H), 8.48-8.20 (m, 3H), 7.80 (m, 1H), 7.32 (s, 1H), 7.28-6.98 (m, 3H), 7.04-6.98 (m, 2H), 4.92 (s, 1H), 4.54 (s, 1H), 3.36-3.22 (m, 1H), 3.20-3.02 (m, 4H), 2.78-2.72 (two s, 3H), 2.00 (br s, 2H), 1.67-1.66 (two s, 3H).

*Example 2.64*



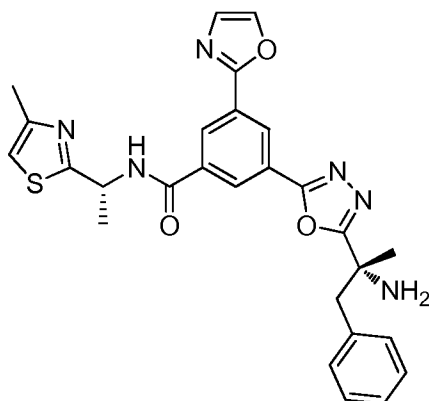
**[0965]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((2-methyloxazol-4-yl)methyl)-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.72 (s, 1H), 8.48-8.18 (m, 3H), 7.80 (m, 1H), 7.60, 7.60 (two s, 1H), 7.32-7.00 (m, 3H), 7.06-7.00 (m, 2H), 4.60 (s, 1.2H), 4.38 (s, 0.8H), 3.35-3.24 (m, 1H), 3.20-3.02 (m, 4H), 2.52-2.40 (two s, 3H), 1.80 (br s, 2H), 1.67 (s, 3H).

*Example 2.65*



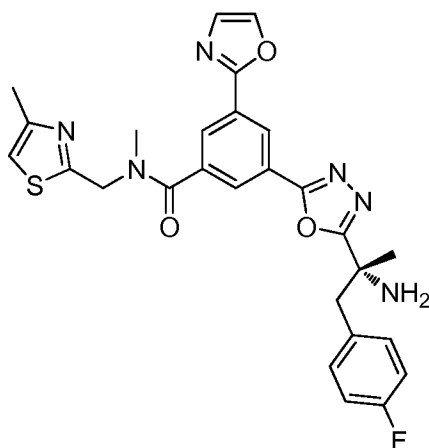
**[0966]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.72 (s, 1H), 8.42-8.00 (m, 2H), 7.80 (s, 1H), 7.36 (s, 1H), 7.30-7.00 (m, 3H), 7.08-6.98 (m, 2H), 6.92 (s, 1H), 5.00 (s, 1.3H), 4.78 (s, 0.7H), 3.37-3.22 (m, 1H), 3.22-3.00 (m, 4H), 2.42 (s, 3H), 1.90 (br s, 2H), 1.66 (s, 3H).

## Example 2.66



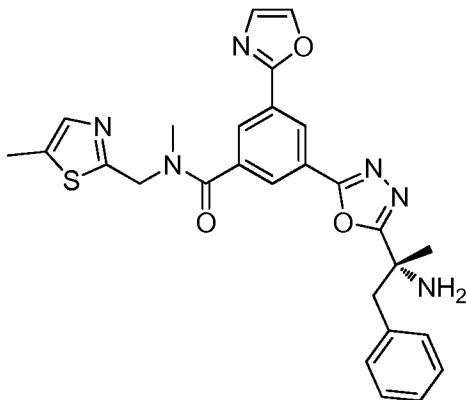
**[0967]** 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((R)-1-(4-methylthiazol-2-yl)ethyl)-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.78 (s, 1H), 8.62 (s, 1H), 8.58 (s, 1H), 7.80 (s, 1H), 7.32-7.20 (m, 3H), 7.06-7.00 (m, 2H), 6.82 (s, 1H), 5.64-5.58 (m, 1H), 3.30 (d,  $J = 14.8$  Hz, 1H), 3.10 (d,  $J = 14.8$  Hz, 1H), 2.43 (s, 3H), 2.02 (br s, 2H), 1.74 (d,  $J = 7.2$  Hz, 3H), 1.66 (s, 3H).

## Example 2.67



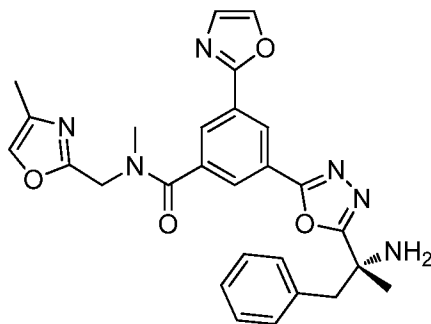
**[0968]** (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.70 (s, 1H), 8.42-8.20 (m, 2H), 7.8 (s, 1H), 7.32 (s, 1H), 7.06-6.98 (m, 2H), 6.98-6.88 (m, 3H), 5.00 (s, 1.4H), 4.78 (s, 0.6H), 3.32-3.02 (m, 5H), 2.43 (s, 3H), 1.80 (br s, 2H), 1.65 (s, 3H).

## Example 2.68



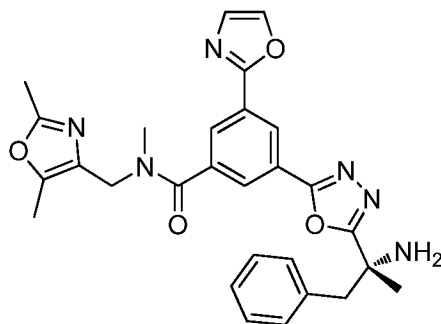
**[0969]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((5-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.77 (s, 1H), 8.40-8.00 (m, 2H), 7.80 (s, 1H), 7.40 (s, 1H) 7.32 (s, 1H), 7.30-7.00 (m, 3H), 7.06-6.98 (m, 2H), 4.97 (s, 1.4H), 4.72 (s, 0.6H), 3.37-3.24 (m, 1H), 3.20-3.00 (m, 4H), 2.44 (s, 3H), 1.90 (br s, 2H), 1.67 (s, 3H).

## Example 2.69



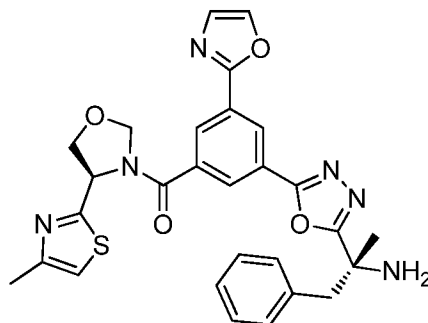
**[0970]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methyloxazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.76 (s, 1H), 8.42-8.20 (m, 2H), 7.8 (s, 1H), 7.40 (s, 1H), 7.36 (s, 1H), 7.30-7.20 (m, 3H), 7.08-6.98 (m, 2H), 4.82 (s, 1.3H), 4.56 (s, 0.7H), 3.36-3.24 (m, 1H), 3.20-3.04 (m, 4H), 2.2 (s, 3H), 1.80 (br s, 2H), 1.67 (s, 3H).

## Example 2.70



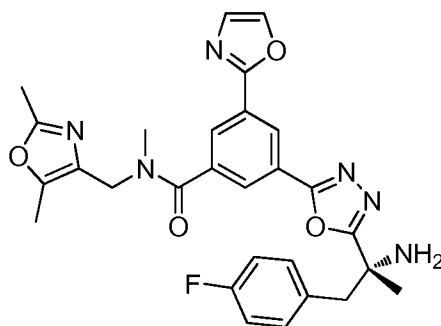
**[0971]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.70 (s, 1H), 8.22 (s, 1H), 8.18 (s, 1H), 7.79 (s, 1H), 7.31 (s, 1H), 7.30-7.20 (m, 3H), 7.04-6.98 (m, 2H), 4.58 (s, 1.2H), 4.24 (s, 0.8H), 3.30 (d,  $J = 14.8$  Hz, 1H), 3.12 (d,  $J = 14.8$  Hz, 1H), 3.12 (s, 3H), 2.42 (s, 3H), 2.41 (s, 3H), 1.80 (br s, 2H), 1.67 (s, 3H).

*Example 2.71*



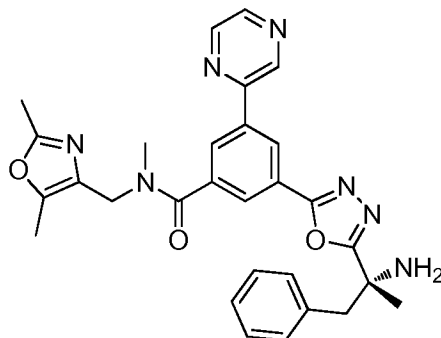
**[0972]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-4-(4-methylthiazol-2-yl)oxazolidin-3-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.92 (s, 1H), 8.82 (s, 1H), 8.70 (s, 1H), 7.82 (s, 1H), 7.80 (d,  $J = 9$  Hz, 1H), 7.33 (s, 1H), 7.26-7.20 (m, 4H), 7.06-7.00 (m, 2H), 6.92 (s, 1H), 5.8-5.72 (m, 1H), 4.77 (d,  $J = 6.2$  Hz, 2H), 3.36 (d,  $J = 14.8$  Hz, 1H), 3.16 (d,  $J = 14.8$  Hz, 1H), 2.46 (s, 3H), 1.82 (br s, 2H), 1.69 (s, 3H).

*Example 2.72*



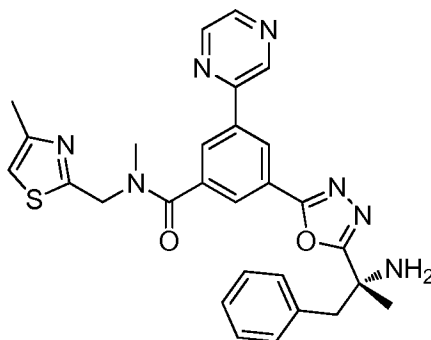
**[0973]** (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.88 (s, 1H), 8.83 (s, 1H), 8.00 (s, 1H), 7.80 (s, 1H), 7.32 (s, 1H), 7.06-6.90 (m, 4H), 4.60 (s, 1.3H), 4.24 (s, 0.7H), 3.28 (d,  $J = 14.8$  Hz, 1H), 3.08 (d,  $J = 14.8$  Hz, 1H), 3.12 (s, 3H), 2.42 (s, 3H), 2.41 (s, 3H), 1.84 (br s, 2H), 1.65 (s, 3H).

## Example 2.73



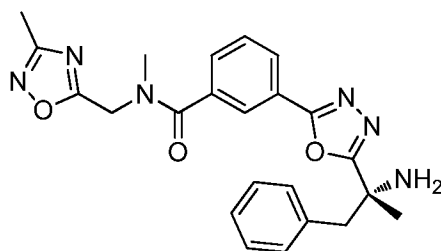
**[0974]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(pyrazin-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.34-8.18 (m, 6H), 7.34-7.00 (m, 3H), 7.20-7.00 (m, 2H), 4.58 (s, 1.1H), 4.26 (s, 0.9H), 3.32 (d,  $J = 14.8$  Hz, 1H), 3.10 (d,  $J = 14.8$  Hz, 1H), 3.14 (s, 3H), 2.42 (s, 3H), 2.41 (s, 3H), 1.68 (s, 3H).

## Example 2.74



**[0975]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyrazin-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.18 (s, 1H), 8.80-8.20 (m, 5H), 7.32-7.20 (m, 3H), 7.14-7.00 (m, 2H), 6.92 (s, 1H), 5.00 (s, 1.2H), 4.78 (s, 0.8H), 3.38-3.04 (m, 2H), 3.18 (s, 3H), 2.46 (s, 3H), 1.98 (s, 2H), 1.68 (s, 3H).

## Example 2.75

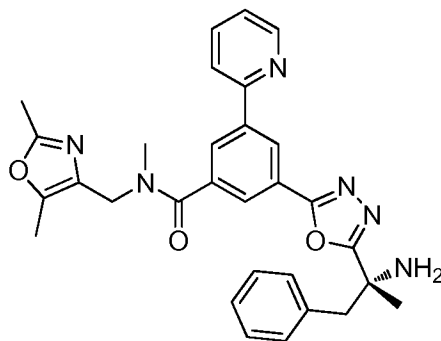


**[0976]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.18-8.10 (m,



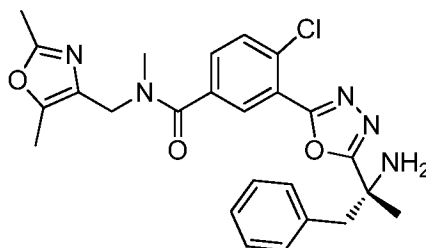
2H), 7.70-7.62 (m, 1H), 7.62-7.57 (m, 1H), 7.28-7.00 (m, 3H), 7.04-7.00 (m, 2H) 4.97 (s, 1.4H), 4.64 (s, 0.6H), 3.30 (d,  $J = 14.8$  Hz, 1H), 3.10 (d,  $J = 14.8$  Hz, 1H), 3.18 (s, 3H), 2.44 (s, 3H), 1.78 (s, 2H), 1.66 (s, 3H).

*Example 2.76*



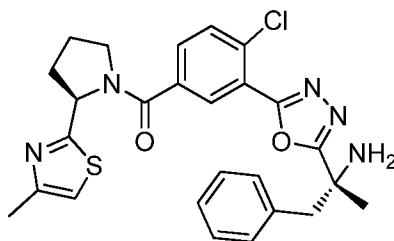
**[0977]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(pyridin-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.82-7.80 (m, 6H), 7.36-7.30 (m, 1H), 7.30-7.00 (m, 3H), 7.20-6.98 (m, 2H), 4.58 (s, 1.3H), 4.28 (s, 0.7H), 3.30 (d,  $J = 14.8$  Hz, 1H), 3.20-3.06 (m, 4H), 2.42 (s, 3H), 2.41 (s, 3H), 1.90 (br s, 2H), 1.67 (s, 3H).

*Example 2.77*



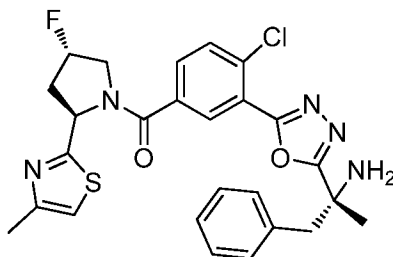
**[0978]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chloro-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methylbenzamide:  $[\text{M}+\text{H}]^+$  : 480.180.

*Example 2.78*



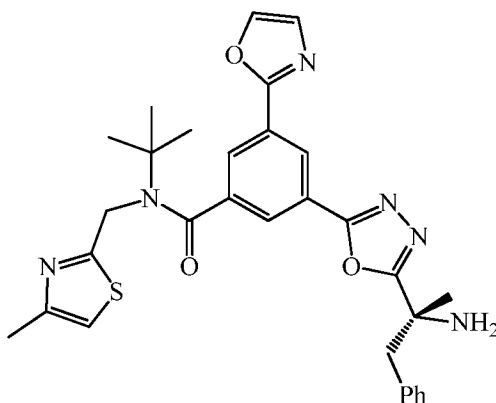
**[0979]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $[\text{M}+\text{H}]^+$  : 508.157.

## Example 2.79



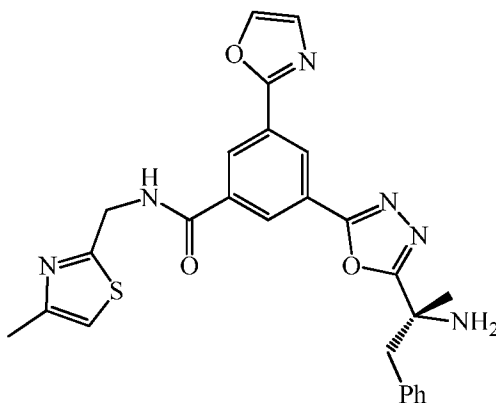
**[0980]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorophenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $[M+H]^+$  : 526.148.

## Example 2.80



**[0981]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(tert-butyl)-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide :  $^1H$  NMR (300 MHz,  $CDCl_3+CD_3OD$ )  $\delta$  8.626 (m, 1 H), 8.313 (m, 1 H), 8.223 (m, 1 H), 7.762 (s, 1 H), 7.281-7.205 (m, 4 H), 7.023-6.991 (m, 2 H), 6.787 (s, 1 H), 4.801 (s, 2 H), 3.278 (d,  $J = 13.5$  Hz, 1 H), 3.087 (d,  $J = 13.5$  Hz, 1 H), 2.360 (s, 3 H), 1.859 (br, 2 H), 1.647 (s, 3 H), 1.565 (s, 9 H).

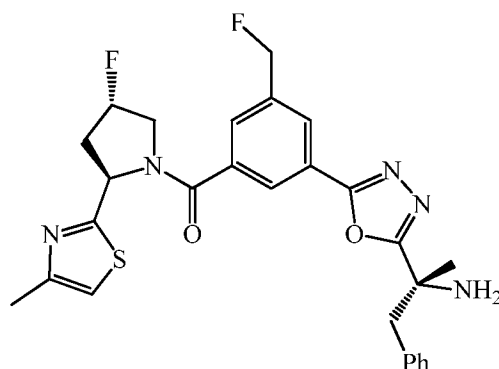
## Example 2.81



**[0982]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide:  $^1H$  NMR (300 MHz,  $CDCl_3+CD_3OD$ )  $\delta$  8.674 (s, 1

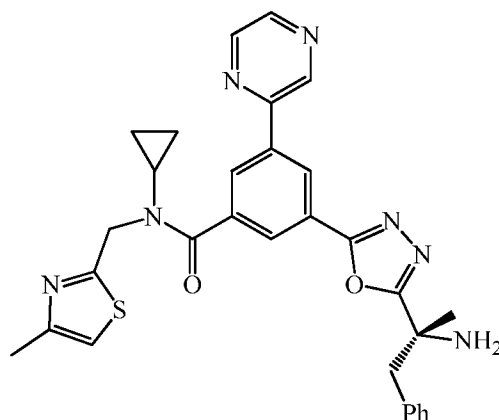
H), 8.628 (s, 1 H), 8.546 (s, 1 H), 7.731 (s, 1 H), 7.265-7.173 (m, 4 H), 6.995 (m, 2 H), 6.787 (s, 1 H), 4.888 (m, 2 H), 3.215 (d,  $J = 13.5$  Hz, 1 H), 3.088 (d,  $J = 13.5$  Hz, 1 H), 2.350 (s, 3 H), 1.623 (s, 3 H).

*Example 2.82*



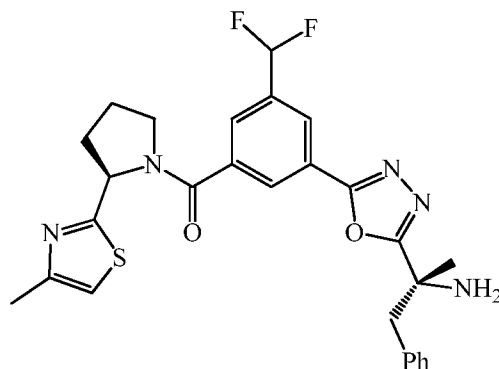
**[0983]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(fluoromethyl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  8.068 (s, 1 H), 7.955 (s, 1 H), 7.725 (s, 1 H), 7.306-7.145 (m, 5 H), 6.815 (s, 1 H), 5.742 (m, 1 H), 5.469 (s, 1 H), 5.322 (s, 2 H), 5.156 (s, 1 H), 4.006 (m, 1 H), 3.742 (m, 1 H), 3.271 (m, 2 H), 2.757 (m, 2 H), 2.409 (m, 3 H), 1.400 (s, 3 H).

*Example 2.83*



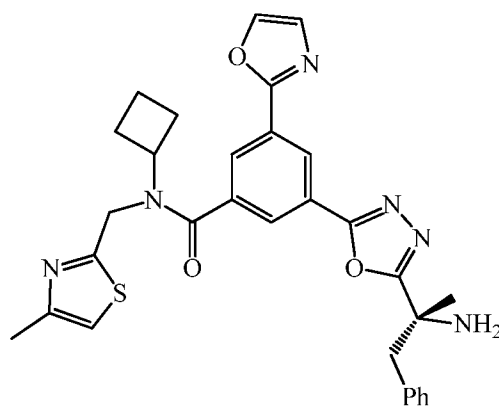
**[0984]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyrazin-2-yl)benzamide :  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  9.126 (s, 1 H), 8.712-8.674 (m, 2 H), 8.597 (s, 1 H), 8.422 (s, 1 H), 8.296 (s, 1 H), 7.262-7.186 (m, 3 H), 7.023 (m, 2 H), 6.877 (s, 1 H), 5.049 (s, 2 H), 3.264 (d,  $J = 13.2$  Hz, 1 H), 3.123 (d,  $J = 13.5$  Hz, 1 H), 3.007 (m, 1 H), 2.453 (s, 3 H), 1.671 (s, 3 H), 0.673 (m, 2 H), 0.574 (m, 2 H).

## Example 2.84



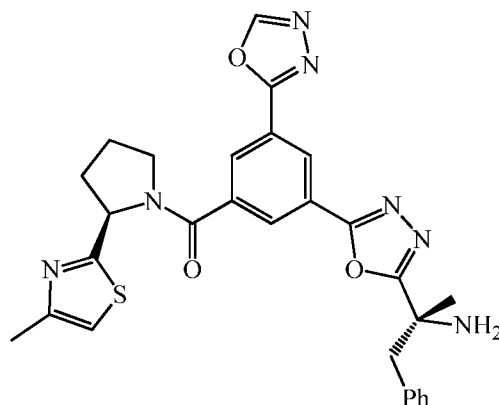
**[0985]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(difluoromethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.313 (s, 0.56 H), 8.180 (s, 0.60 H), 8.082 (s, 0.44 H), 8.035 (s, 0.40 H), 7.802 (s, 0.65 H), 7.472 (s, 0.35 H), 7.216 (m, 3 H), 7.002 (m, 2 H), 6.757 (m, 1.45 H), 6.552 (m, 0.55 H), 5.642 (m, 0.7 H), 5.074 (m, 0.3 H), 3.747 (m, 1 H), 3.524 (m, 1 H), 3.239 (m, 1 H), 3.087 (m, 1 H), 2.429 (s, 2 H), 2.295 (s, 1 H), 2.138 (m, 2 H), 1.983 (m, 2 H), 1.654 (s, 3 H).

## Example 2.85



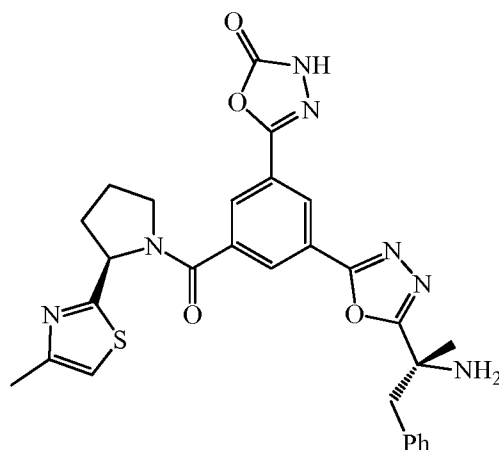
**[0986]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclobutyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide :  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.733 (s, 1 H), 8.273 (s, 1 H), 8.196 (m, 1 H), 7.806 (s, 1 H), 7.321-7.228 (m, 4 H), 7.047 (m, 2 H), 6.859 (s, 1 H), 5.108 (s, 2 H), 4.283 (br, 1 H), 3.280 (d,  $J = 13.5$  Hz, 1 H), 3.134 (d,  $J = 13.5$  Hz, 1 H), 2.451 (s, 3 H), 2.318 (m, 2 H), 2.043 (m, 2 H), 1.672 (s, 5 H).

## Example 2.86



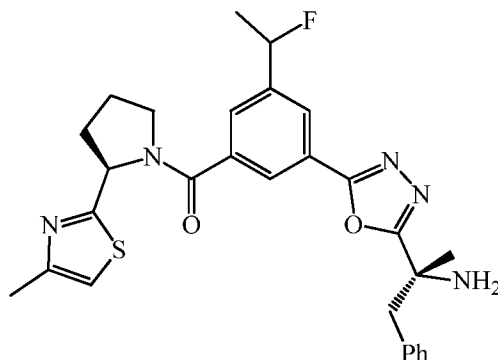
**[0987]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone :  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  9.272 (br, 0.7 H), 8.871 (br, 0.3 H), 8.507 (s, 0.7 H), 8.403 (s, 0.3 H), 8.298 (s, 0.7 H), 8.294 (s, 0.7 H), 8.018 (s, 0.3 H), 7.908 (s, 0.3 H), 7.179 (m, 3 H), 6.978 (m, 2 H), 6.703 (s, 1 H), 5.635 (m, 0.65 H), 5.162 (m, 0.35 H), 3.797 (m, 1 H), 3.535 (m, 1 H), 3.216 (m, 1 H), 3.086 (m, 1 H), 2.364 (s, 2 H), 2.268 (s, 1 H), 2.078 (m, 2 H), 1.950 (m, 2 H), 1.625 (s, 3 H).

## Example 2.87



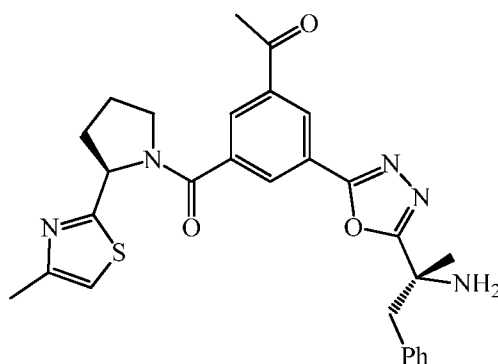
**[0988]** 5-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-1,3,4-oxadiazol-2(3H)-one :  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.462 (s, 0.7 H), 8.361 (s, 0.3 H), 8.347 (s, 0.7 H), 8.205 (s, 0.7 H), 8.005 (s, 0.3 H), 7.844 (s, 0.3 H), 7.217 (m, 3 H), 7.019 (m, 2 H), 6.819 (s, 0.7 H), 6.792 (s, 0.3 H), 5.657 (m, 0.65 H), 5.205 (m, 0.35 H), 3.927 (m, 1 H), 3.815 (m, 1 H), 3.564 (m, 1 H), 3.266 (m, 1 H), 3.112 (m, 1 H), 2.442 (s, 2 H), 2.391 (m, 1 H), 2.295 (s, 1 H), 2.161 (m, 2 H), 2.029 (m, 1 H), 1.675 (s, 2 H), 1.648 (s, 1 H).

## Example 2.88



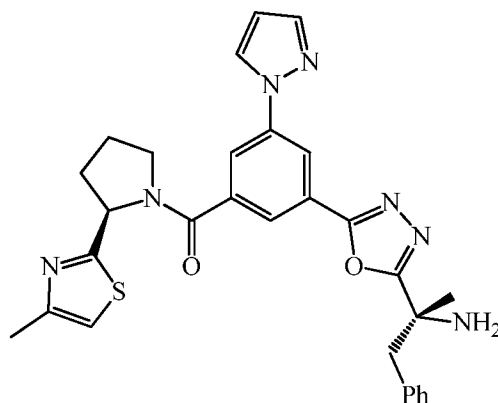
**[0989]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-fluoroethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone :  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.156 (s, 0.6 H), 8.032 (s, 0.6 H), 7.943 (s, 0.4 H), 7.888 (s, 0.4 H), 7.736 (s, 0.6 H), 7.352 (s, 0.4 H), 7.262 (m, 3 H), 7.007 (m, 2 H), 6.806 (m, 1 H), 5.804 (m, 0.3 H), 5.644 (m, 1.05 H), 5.464 (m, 0.3 H), 5.102 (m, 0.35 H), 3.916 (m, 1 H), 3.793 (m, 1 H), 3.549 (m, 1 H), 3.256 (m, 1 H), 3.109 (m, 1 H), 2.442 (s, 2 H), 2.310 (m, 1 H), 2.111 (m, 2 H), 1.966 (m, 2 H), 1.661 (s, 3 H).

## Example 2.89



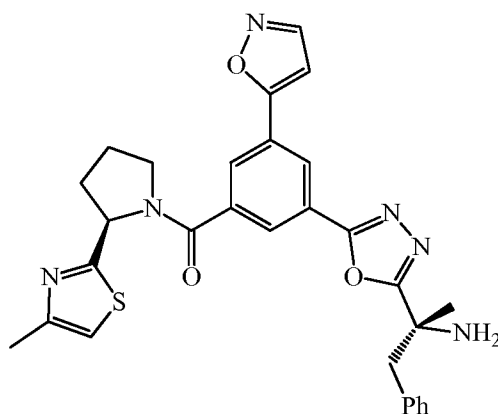
**[0990]** 1-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-acetyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)ethanone :  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.608 (s, 0.65 H), 8.515 (s, 0.35 H), 8.417 (s, 0.65 H), 8.327 (s, 0.65 H), 8.162 (s, 0.35 H), 7.938 (s, 0.35 H), 7.221 (m, 3 H), 7.021 (s, 2 H), 6.806 (s, 1 H), 5.664 (m, 0.65 H), 5.107 (m, 0.35 H), 3.928 (m, 1 H), 3.847 (m, 1 H), 3.550 (m, 1 H), 3.261 (m, 1 H), 3.112 (m, 1 H), 2.697 (s, 2 H), 2.508 (s, 1 H), 2.442 (s, 3 H), 2.311 (s, 1 H), 2.141 (m, 2 H), 1.985 (m, 1 H), 1.659 (s, 3 H).

## Example 2.90



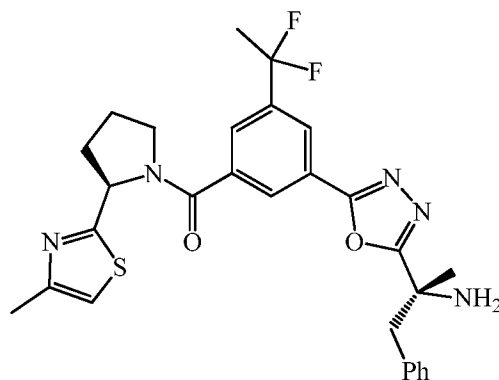
**[0991]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone :  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.298 (m, 1 H), 8.119 (s, 1.2 H), 8.063 (m, 0.8 H), 7.782 (m, 2 H), 8.218 (m, 3 H), 7.042 (m, 2 H), 6.805 (s, 0.8 H), 6.757 (s, 0.2 H), 6.541 (s, 0.8 H), 6.480 (s, 0.2 H), 5.675 (m, 0.8 H), 5.213 (m, 0.2 H), 3.929 (m, 1 H), 3.845 (m, 1 H), 3.634 (m, 1 H), 3.266 (m, 1 H), 3.124 (m, 1 H), 2.446 (m, 3 H), 2.130 (m, 2 H), 1.974 (m, 2 H), 1.668 (s, 3 H).

## Example 2.91



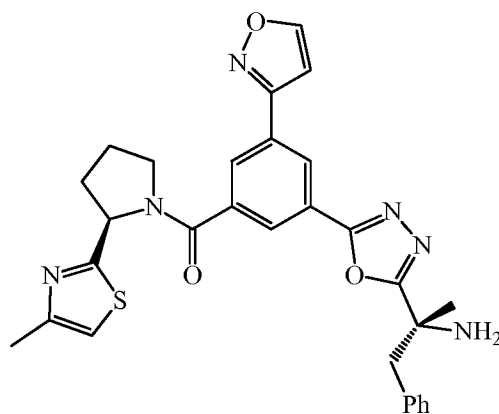
**[0992]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(isoxazol-5-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone :  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.449 (s, 0.7 H), 8.367 (s, 1 H), 8.309 (s, 0.3 H), 8.262 (s, 0.7 H), 8.160 (s, 0.7 H), 8.014 (s, 0.3 H), 7.755 (s, 0.3 H), 7.220 (m, 3 H), 7.024 (m, 2 H), 6.775 (m, 1.6 H), 6.500 (s, 0.4 H), 5.680 (m, 0.8 H), 5.159 (m, 0.2 H), 3.934 (m, 1 H), 3.820 (m, 1 H), 3.608 (m, 1 H), 3.258 (m, 1 H), 3.100 (m, 1 H), 2.445 (s, 2 H), 2.280 (s, 1 H), 2.158 (m, 2 H), 2.002 (m, 2 H), 1.669, 1.645 (m, 3 H).

## Example 2.92



**[0993]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1,1-difluoroethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone :  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.597 (s, 0.7 H), 8.507 (s, 0.3 H), 8.409 (s, 0.7 H), 8.313 (s, 0.7 H), 8.161 (s, 0.3 H), 7.932 (s, 0.3 H), 7.211 (m, 3 H), 7.029 (m, 2 H), 6.802, 6.775 (m, 1 H), 5.666 (m, 0.7 H), 5.115 (m, 0.3 H), 3.925 (m, 1 H), 3.833 (m, 1 H), 3.540 (m, 1 H), 3.251 (m, 1 H), 3.093 (m, 1 H), 2.691 (s, 2 H), 2.500 (s, 1 H), 2.440 (m, 2 H), 2.307 (m, 1 H), 2.130 (m, 2 H), 1.948 (m, 1 H), 1.658, 1.635 (m, 3 H).

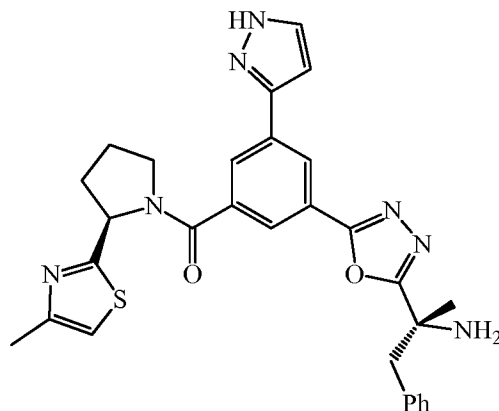
## Example 2.93



**[0994]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(isoxazol-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone :  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.509 (m, 2 H), 8.297 (m, 0.7 H), 8.231 (s, 0.7 H), 8.024 (m, 0.3 H), 7.816 (br, 0.3 H), 7.198 (m, 3 H), 7.191 (m, 2 H), 6.812 (s, 1.3 H), 6.746 (s, 0.3 H), 6.594 (s, 0.4 H), 5.626 (m, 0.8 H), 5.177 (m, 0.2 H), 3.878 (m, 2 H), 3.604 (m, 1 H), 3.258 (m, 1 H), 3.102 (m, 1 H), 2.421 (m, 3 H), 2.124 (m, 2 H), 1.977 (m, 2 H), 1.651 (s, 3 H).

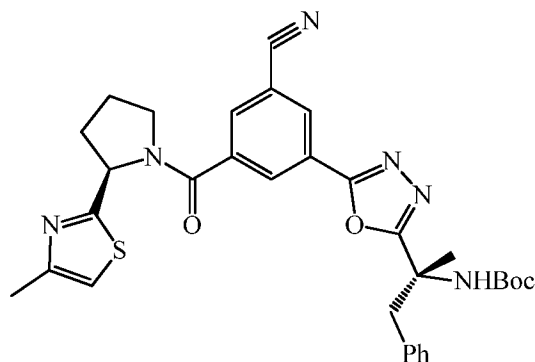


## Example 2.94



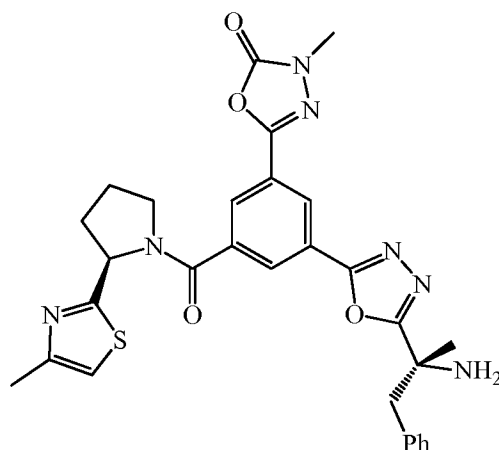
**[0995]** 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrazol-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone : LC/MS RT: 6.23, m/z 540.209.

## Example 2.95



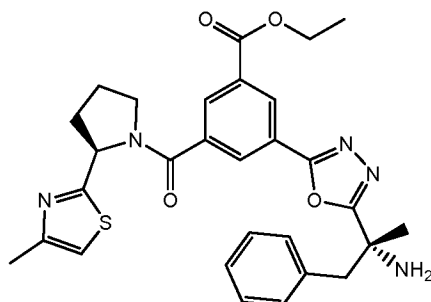
**[0996]** 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzonitrile : LC/MS RT: 5.68, m/z 499.184.

## Example 2.96



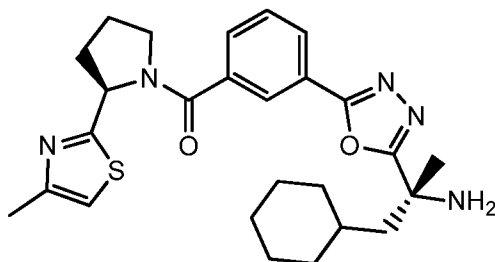
**[0997]** 5-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-3-methyl-1,3,4-oxadiazol-2(3H)-one :  
LC/MS RT: 5.63, m/z 572.200.

*Example 2.97*



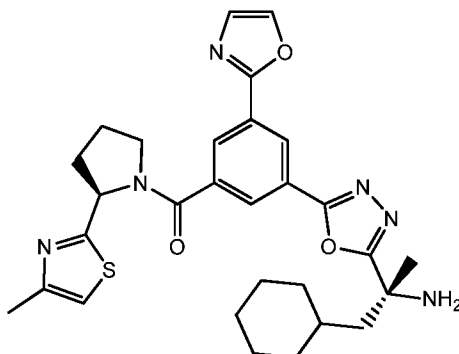
**[0998]** Ethyl 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzoate. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.80-8.60 (m, 1H), 8.41-8.07 (m, 2H), 7.29-7.19 (m, 4H), 7.05-7.02 (m, 2H), 6.91-6.71 (m, 1H), 5.70-5.66 (m, 0.6H), 5.13-5.11 (m, 0.3H), 4.49-4.34 (m, 2H), 3.99-3.77 (m, 2H), 3.59-3.51 (m, 1H), 3.31-3.23 (m, 1H), 3.12-3.05 (m, 1H), 2.45-2.31 (m, 4H), 2.23-2.03 (m, 2H), 2.04-1.85 (m, 4H), 1.67-1.64 (m, 3H), 1.46-1.36 (m, 3H).

*Example 2.98*



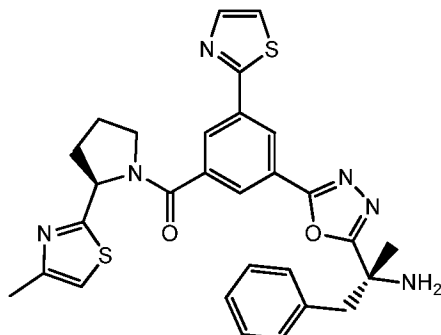
**[0999]** (3-(5-((R)-2-amino-1-cyclohexylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.80-8.60 (m, 1H), 8.24-7.94 (m, 2H), 7.76-7.41 (m, 2H), 6.79-6.75 (m, 1H), 5.69-5.65 (m, 0.7H), 5.17-5.15 (m, 0.3H), 3.91-3.76 (m, 2H), 3.60-3.52 (m, 1H), 2.48-2.26 (m, 4H), 2.22-1.70 (m, 8H), 1.62-1.49 (m, 7H), 1.42-1.32 (m, 2H), 1.27-0.81 (m, 5H).

## Example 2.99

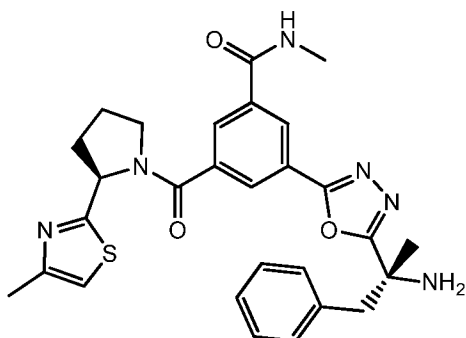


**[1000]** (3-(5-((R)-2-amino-1-cyclohexylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.76-8.64 (m, 1H), 8.41-8.04 (m, 2H), 7.81-7.74 (m, 1H), 7.32-7.27 (m, 1H), 6.81-6.74 (m, 1H), 5.71-5.67 (m, 0.7H), 5.20-5.18 (m, 0.3H), 3.97-3.75 (m, 2H), 3.65-3.56 (m, 1H), 2.46-2.26 (m, 6H), 2.22-1.70 (m, 7H), 1.62-1.34 (m, 10H), 1.42-1.32 (m, 2H), 1.27-0.83 (m, 5H).

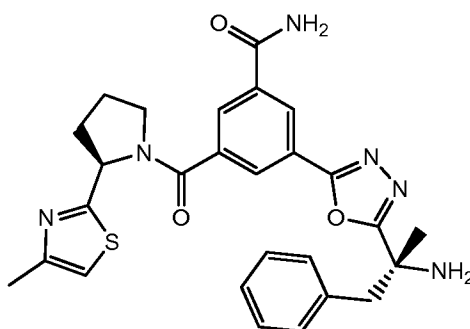
## Example 2.100



**[1001]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(thiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.63-8.60 (m, 1H), 8.41-7.88 (m, 3H), 7.46-7.7.39 (m, 1H), 7.27-7.20 (m, 3H), 7.20-7.03 (m, 2H), 6.81-6.74 (m, 1H), 5.70-5.66 (m, 0.6H), 5.20-5.18 (m, 0.3H), 3.96-3.81 (m, 2H), 3.65-3.57 (m, 1H), 3.31-3.23 (m, 1H), 3.12-3.05 (m, 1H), 2.45-2.27 (m, 4H), 2.20-2.11 (m, 5H), 1.67-1.64 (m, 3H).

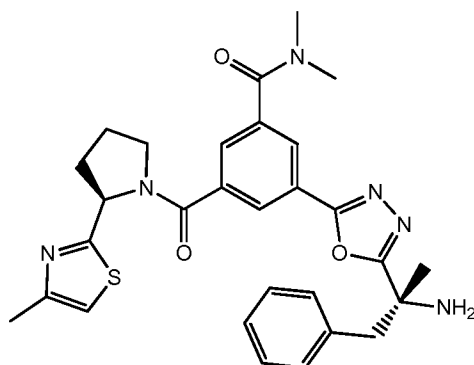
*Example 2.101*

**[1002]** 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.45-8.37 (m, 1H), 8.32-7.81 (m, 2H), 7.28-7.20 (m, 4H), 7.04-7.02 (m, 2H), 6.79-6.76 (m, 1H), 6.68-6.39 (m, 1H), 5.67-5.63 (m, 0.7H), 5.17-5.15 (m, 0.3H), 3.93-3.78 (m, 2H), 3.59-3.48 (m, 1H), 3.29-3.21 (m, 1H), 3.11-2.98 (m, 4H), 2.44-2.26 (m, 4H), 2.21-2.09 (m, 2H), 2.00-1.76 (m, 4H), 1.65-1.62 (m, 3H).

*Example 2.102*

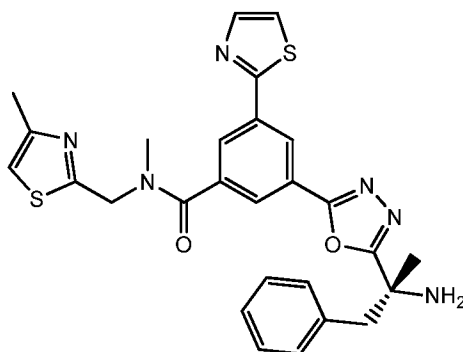
**[1003]** 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.54-8.45 (m, 1H), 8.37-7.89 (m, 2H), 7.29-7.19 (m, 4H), 7.04-7.01 (m, 2H), 6.91-6.77 (m, 2H), 6.13-6.5.80 (broad s, 1H), 5.67-5.63 (m, 0.6H), 5.18-5.16 (m, 0.3H), 3.92-3.80 (m, 2H), 3.61-3.53 (m, 1H), 3.29-3.19 (m, 1H), 3.17-3.05 (m, 1H), 2.49-2.26 (m, 4H), 2.24-1.76 (m, 6H), 1.65-1.63 (m, 3H).

## Example 2.103



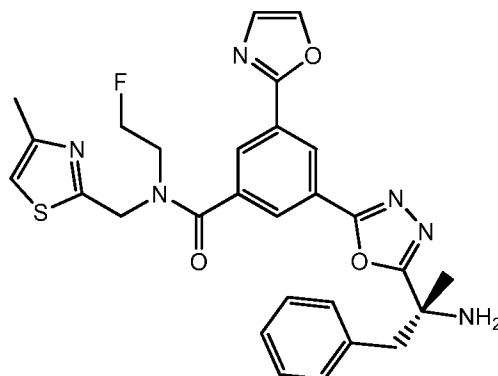
**[1004]** 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N,N-dimethyl-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25-7.98 (m, 2H), 7.78-7.51 (m, 1H), 7.33-7.15 (m, 4H), 7.03-7.01 (m, 2H), 6.79-6.74 (m, 1H), 5.68-5.63 (m, 0.7H), 5.18-5.15 (m, 0.3H), 3.91-3.75 (m, 2H), 3.59-3.51 (m, 1H), 3.29-2.91 (m, 8H), 2.44-2.26 (m, 4H), 2.23-1.92 (m, 3H), 1.90-1.70 (broad s, 3H), 1.65-1.62 (m, 3H).

## Example 2.104



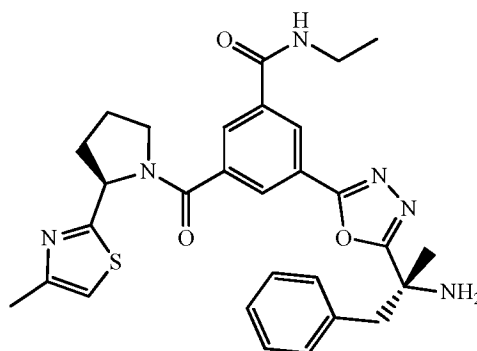
**[1005]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(thiazol-2-yl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.67-8.62 (m, 1H), 8.32-8.16 (m, 2H), 7.94-7.93 (m, 1H), 7.44 (m, 1H), 7.28-7.21 (m, 3H), 7.04-7.02 (m, 2H), 6.92-6.88 (m, 1H), 5.01 (broad s, 1.3H), 4.74 (broad s, 0.7H), 3.31-3.27 (m, 1H), 3.19-3.08 (m, 4H), 2.46 (m, 3H), 2.10-1.80 (m, 2H), 1.67 (broad s, 3H).

## Example 2.105



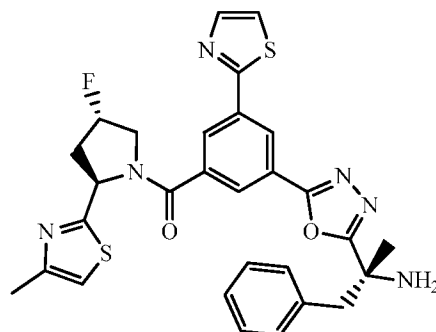
**[1006]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(2-fluoroethyl)-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.73-8.72 (m, 1H), 8.42-8.20 (m, 2H), 7.79 (s, 1H), 7.33-7.32 (m, 1H), 7.31-7.19 (m, 4H), 7.05-7.02 (m, 2H), 6.93-6.86 (m, 1H), 5.09-4.82 (m, 4H), 3.98-3.70 (m, 2H), 3.31-3.27 (m, 1H), 3.12-3.08 (m, 3H), 2.44 (broad s, 3H), 1.90-1.60 (m, 8H).

## Example 2.106



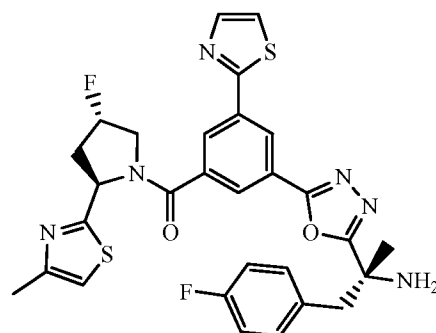
**[1007]** 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-ethyl-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.45-8.37 (m, 1H), 8.31-7.72 (m, 2H), 7.25-7.14 (m, 4H), 7.04-6.95 (m, 2H), 6.79-6.75 (m, 1H), 6.65-6.34 (m, 1H), 5.67-5.63 (m, 0.7H), 5.15-5.13 (m, 0.3H), 3.90-3.78 (m, 2H), 3.59-3.36 (m, 3H), 3.28-3.21 (m, 1H), 3.11-3.04 (m, 1H), 2.43-2.26 (m, 5H), 2.20-2.04 (m, 2H), 2.00-1.89 (m, 3H), 1.64-1.62 (m, 3H), 1.27-1.24 (m, 3H).

## Example 2.107



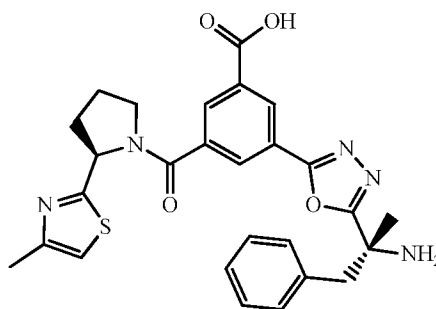
**[1008]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(thiazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.67-8.55 (m, 1H), 8.35-7.94 (m, 3H), 7.47-7.46 (m, 1H), 7.26-7.22 (m, 4H), 7.05-7.04 (m, 2H), 6.86-6.56 (m, 1H), 5.89-5.84 (m, 0.8H), 5.53-5.23 (m, 1.2H), 4.15-3.89 (m, 2H), 3.32-3.27 (m, 1H), 3.13-3.08 (m, 1H), 2.94-2.79 (m, 2H), 2.45-2.21 (m, 3H), 2.04-1.74 (m, 2H), 1.67 (broad s, 3H).

## Example 2.108



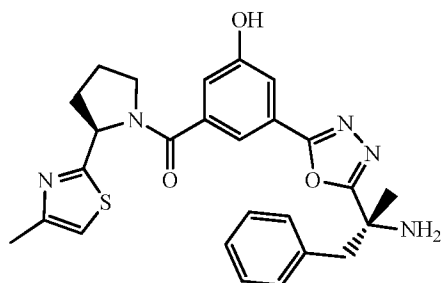
**[1009]** (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(thiazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.69-8.28 (m, 1H), 8.35-7.94 (m, 3H), 7.48-7.46 (m, 1H), 7.06-6.87 (m, 4H), 5.90-5.84 (m, 0.8H), 5.55-5.20 (m, 1.2H), 4.16-3.90 (m, 2H), 3.29-3.25 (m, 1H), 3.11-3.06 (m, 1H), 2.95-2.80 (m, 2H), 2.46-2.19 (m, 3H), 2.10-1.72 (m, 6H).

## Example 2.109



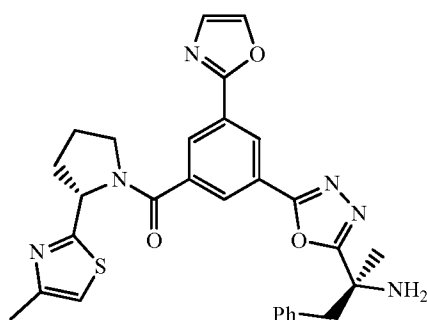
**[1010]** 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzoic acid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$  +  $\text{CD}_3\text{OD}$ )  $\delta$  8.67-8.58 (m, 1H), 8.35-7.98 (m, 2H), 7.26-7.17 (m, 5H), 6.98 (m, 2H), 6.76-6.69 (m, 1H), 5.57 (m, 0.7H), 5.13 (m, 0.2H), 3.87-3.07 (m, 5H), 2.39-1.93 (m, 7H), 1.65-1.62 (m, 3H).

*Example 2.110*



**[1011]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-hydroxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.66-7.45 (m, 2H), 7.39-7.15 (m, 4H), 7.03-6.90 (m, 2H), 6.80-6.75 (m, 1H), 5.63-5.59 (m, 0.7H), 5.23-5.21 (m, 0.3H), 3.92-3.73 (m, 2H), 3.58-3.56 (m, 1H), 3.27-3.17 (m, 1H), 3.10-3.02 (m, 1H), 2.48-2.32 (m, 5H), 2.24-1.88 (m, 3H), 1.63-1.60 (m, 3H).

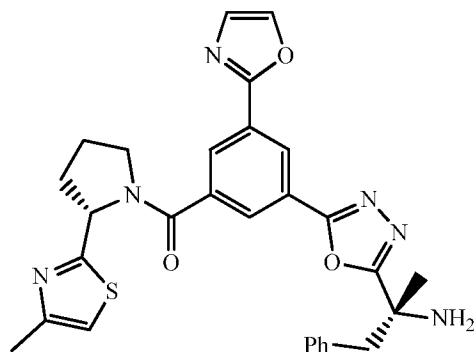
*Example 2.111*



**[1012]** (3-(5-((S)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((S)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.73-8.63 (m, 1H), 8.41-8.03 (m, 2H), 7.81-7.74 (m, 1H), 7.32-7.19 (m, 3H), 7.06-7.03 (m, 2H), 6.82-6.74 (m, 1H), 5.72-5.67 (m, 0.7H), 5.20-5.17 (m, 0.3H), 3.96-3.81 (m, 2H), 3.64-3.56 (m, 1H), 3.32-3.24 (m, 1H), 3.13-3.06 (m, 1H), 2.45-2.41 (m, 4H), 2.27-2.11 (m, 2H), 2.03-1.64 (m, 6H).

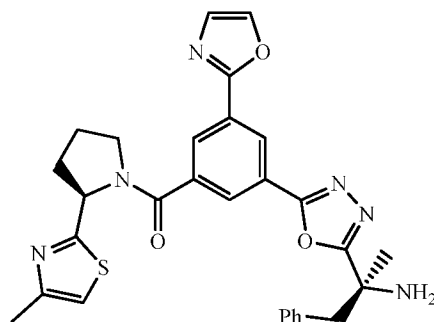


## Example 2.112



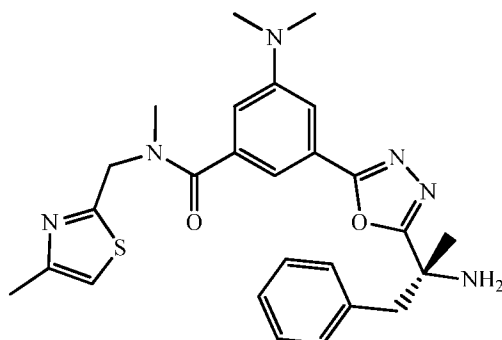
**[1013]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((S)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.71-8.61 (m, 1H), 8.39-8.00 (m, 2H), 7.79-7.73 (m, 1H), 7.30-7.20 (m, 3H), 7.01 (m, 2H), 6.79-6.72 (m, 1H), 5.69-5.65 (m, 0.7H), 5.17-5.15 (m, 0.3H), 3.91-3.81 (m, 2H), 3.59-3.57 (m, 1H), 3.30-3.22 (m, 1H), 3.11-3.06 (m, 1H), 2.44-2.41 (m, 4H), 2.25-1.91 (m, 5H), 1.65-1.62 (m, 3H).

## Example 2.113



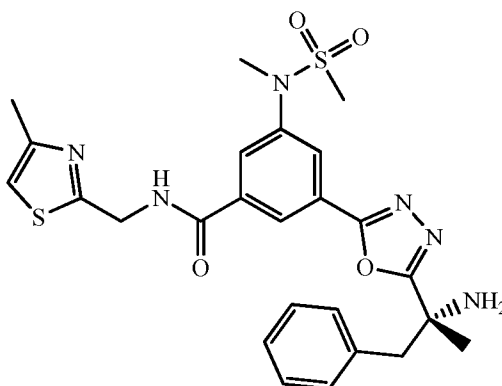
**[1014]** (3-(5-((S)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.72-8.61 (m, 1H), 8.40-8.01 (m, 2H), 7.80-7.73 (m, 1H), 7.31-7.17 (m, 3H), 7.05-7.02 (m, 2H), 6.80-6.73 (m, 1H), 5.70-5.66 (m, 0.7H), 5.18-5.16 (m, 0.3H), 3.94-3.79 (m, 2H), 3.62-3.49 (m, 1H), 3.31-3.23 (m, 1H), 3.12-3.05 (m, 1H), 2.44-2.39 (m, 4H), 2.26-1.89 (m, 5H), 1.66-1.62 (m, 3H).

## Example 2.114



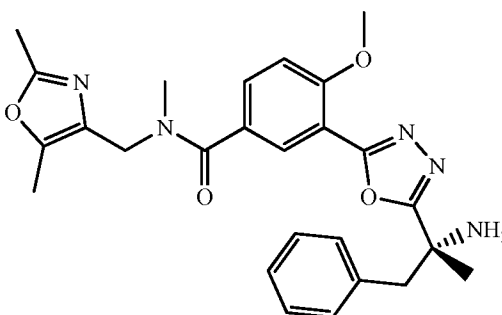
**[1015]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(dimethylamino)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.19 (m, 5H), 7.01 (m, 2H), 6.89 (m, 1H), 4.98 (broad s, 1.1H), 4.73 (broad s, 0.9H), 3.28-3.23 (m, 1H), 3.14-3.00 (m, 10H), 2.44-2.41 (m, 3H), 2.08 (broad s, 2H), 1.64 (s, 3H).

## Example 2.115



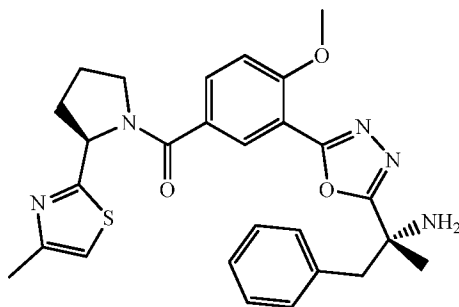
**[1016]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(N-methylmethylsulfonamido)-N-((4-methylthiazol-2-yl)methyl)benzamide.  $[\text{M}+\text{H}] = 541.1$ .

## Example 2.116



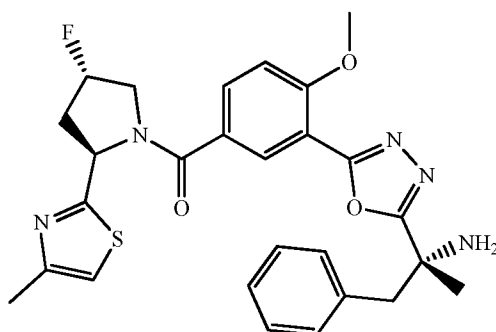
**[1017]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4-methoxy-N-methylbenzamide.  $[\text{M}+\text{H}] = 476.2$ .

## Example 2.117



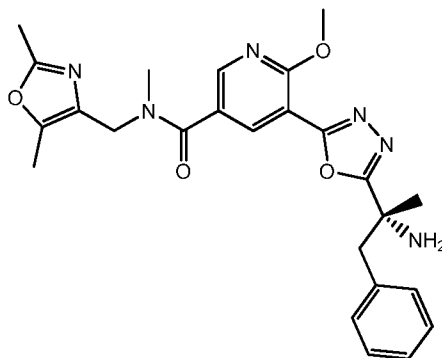
**[1018]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $[M+H] = 504.2$ .

## Example 2.118



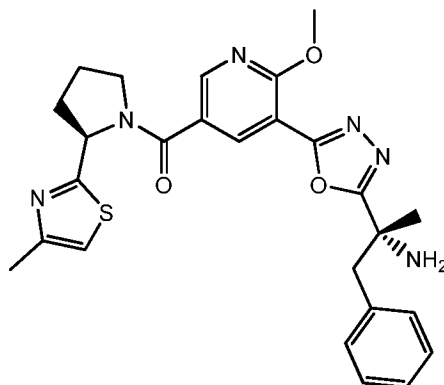
**[1019]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $[M+H] = 522.2$ .

## Example 2.119



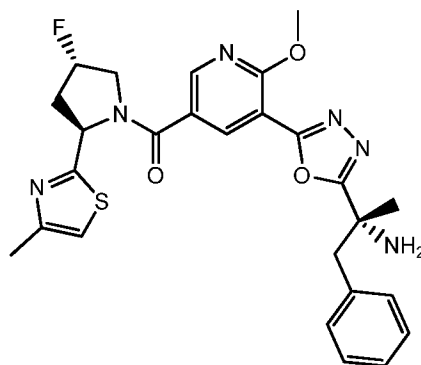
**[1020]** (R)-5-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-6-methoxy-N-methylnicotinamide.  $[M+H] = 477.2$ .

## Example 2.120



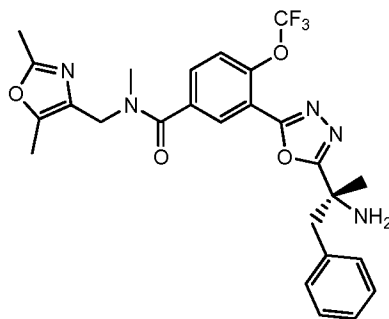
[1021] (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-methoxypyridin-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $[M+H] = 505.2$ .

## Example 2.121



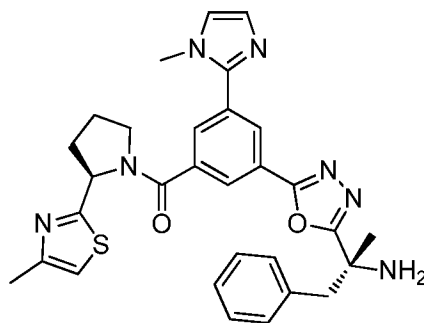
[1022] (5-(5-((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)-1,3,4-oxadiazol-2-yl)-6-methoxypyridin-3-yl)((R)-2-amino-1-phenylpropan-2-yl)methanone.  $[M+H] = 523.2$ .

## Example 2.122



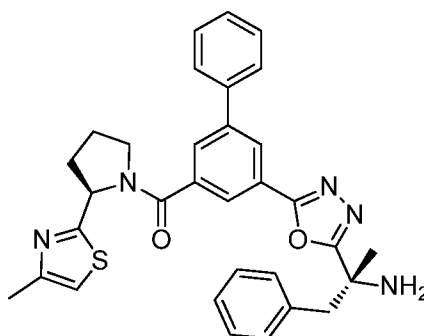
[1023] (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-4-(trifluoromethoxy)benzamide.  $[M+H] = 530.2$ .

## Example 2.123



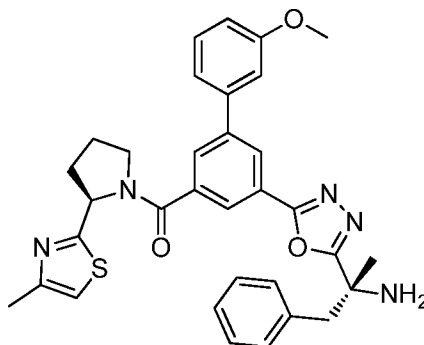
**[1024]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-methyl-1H-imidazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.60 (s, 3H), 1.78-2.42 (m, 7H), 3.16-3.38 (m, 2H), 3.58-3.86 (m, 5H), 5.64 (m, 1H), 6.80 (s, 1H), 6.86-7.38 (m, 7H), 8.40 (s, 1H), 8.22 (s, 1H), 8.40 (s, 1H).

## Example 2.124



**[1025]** (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-[1,1'-biphenyl]-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.61 (s, 3H), 1.81-2.42 (m, 6H), 3.10-3.38 (m, 2H), 3.56-3.64 (m, 1H), 3.81-3.98 (m, 2H), 5.63-5.76 (m, 1H), 6.80-8.36 (m, 14H).

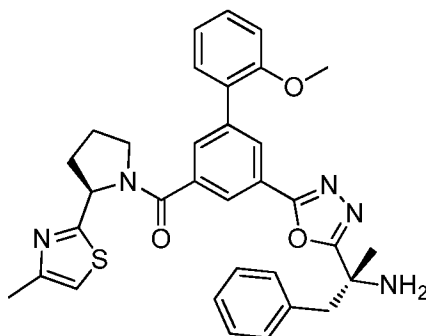
## Example 2.125



**[1026]** (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-3'-methoxy-[1,1'-biphenyl]-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,

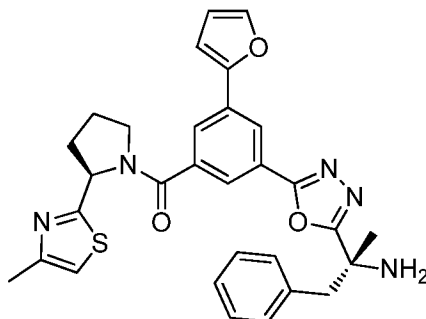
$\text{CDCl}_3$ )  $\delta$  1.62 (s, 3H), 1.82-2.54 (m, 7H), 3.10-3.38 (m, 2H), 3.56-3.64 (m, 1H), 3.78-3.98 (m, 4H), 5.61-5.76 (m, 1H), 6.76-7.60 (m, 10H), 7.96 (s, 1H), 8.16-8.22 (m, 2H).

*Example 2.126*



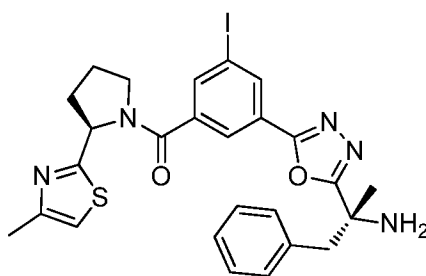
**[1027]** (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2'-methoxy-[1,1'-biphenyl]-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.61 (s, 3H), 1.83-2.42 (m, 7H), 3.0-3.24 (m, 2H), 3.61-3.96 (m, 5H), 5.61-5.72 (m, 1H), 6.81-7.42 (m, 10H), 7.98 (s, 1H), 8.18-8.22 (m, 2H).

*Example 2.127*



**[1028]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(furan-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.61 (s, 3H), 1.82-2.41 (m, 6H), 3.10-3.24 (m, 2H), 3.41-3.98 (m, 3H), 5.61-5.65 (m, 1H), 6.80 (s, 1H), 6.88-7.24 (m, 8H), 8.10-8.41 (m, 3H).

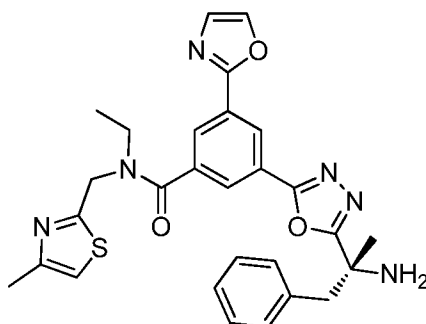
*Example 2.128*



**[1029]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-iodophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.63 (s,

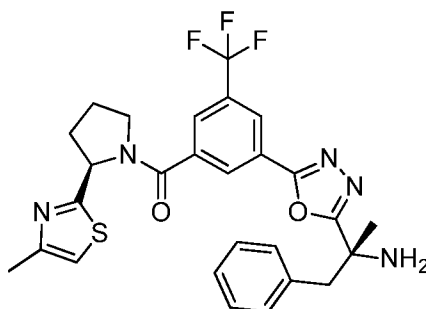
3H), 1.96-2.13 (m, 3H), 2.13-2.45 (m, 3H), 3.04-3.25 (m, 2H), 3.29-3.56 (m, 1H), 3.53-3.92 (m, 2H), 5.62-5.66 (m, 1H), 6.81 (s, 1H), 7.04-7.22 (m, 2H), 7.23-7.26 (m, 3H), 8.05 (s, 1H), 8.08 (s, 1H), 8.38 (s, 1H).

*Example 2.129*



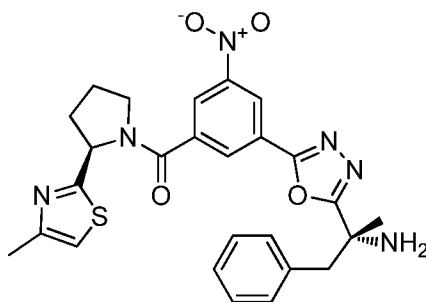
**[1030]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-ethyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.61 (s, 3H), 2.40 (s, 3H), 3.10-3.46 (m, 4H), 5.0 (br s, 2H), 6.82-7.24 (m, 8H), 7.80 (s, 1H), 8.18-8.23 (m, 1H), 8.76 (s, 1H).

*Example 2.130*



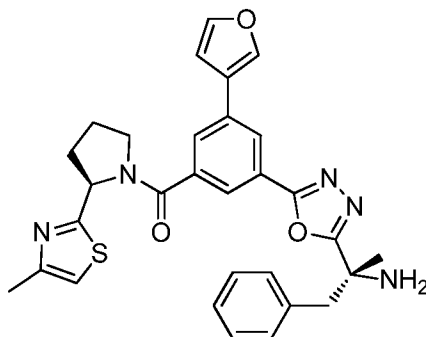
**[1031]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(trifluoromethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.60 (s, 3H), 1.82-2.42 (m, 6H), 3.20-3.84 (m, 5H), 5.61-5.72 (m, 1H), 6.78-7.22 (m, 6H), 8.0-8.41 (m, 3H).

*Example 2.131*



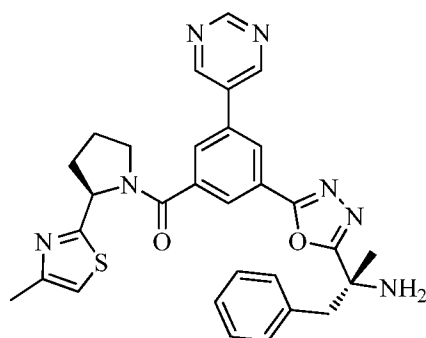
**[1032]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-nitrophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.62 (s, 3H), 1.98-2.41 (m, 6H), 3.10-3.32 (m, 2H), 3.52-3.61 (m, 1H), 3.98-4.02 (m, 2H), 5.61-5.66 (m, 1H), 6.78-7.24 (m, 6H), 8.18-8.92 (m, 3H).

*Example 2.132*



**[1033]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(furan-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.62 (s, 3H), 1.95-2.14 (m, 3H), 2.46 (s, 3H), 3.06-3.27 (m, 2H), 3.58-3.63 (m, 1H), 3.79-3.96 (m, 2H), 5.69-5.71 (m, 1H), 6.81-6.83 (m, 2H), 7.19 (br s, 2H), 7.23-7.28 (m, 2H), 7.46-7.63 (m, 2H), 7.81-7.86 (m, 2H), 8.11-8.16 (m, 2H).

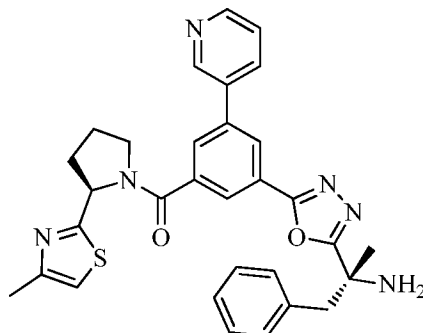
*Example 2.133*



**[1034]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrimidin-5-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.63 (s, 1H), 1.94-2.40 (m, 5H), 2.42-3.26 (m, 2H), 3.42-3.56 (m, 1H), 3.58-3.92 (m, 2H), 5.66-5.70 (m, 1H), 6.8 (s, 1H), 7.02-7.21 (m, 2H), 7.22-7.26 (m, 4H), 7.43 (s, 1H), 7.56-7.61 (m, 1H), 7.75-7.77 (m, 1H), 7.94-8.22 (m, 2H).

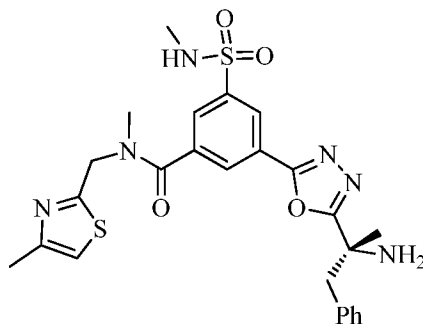


## Example 2.134



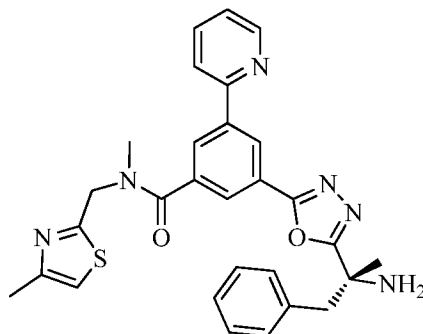
**[1035]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyridin-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.66 (s, 3H), 1.97-2.18 (m, 3H), 2.41 (s, 3H), 3.10-3.27 (m, 2H), 3.31-3.60 (m, 1H), 3.64-3.95 (m, 2H), 5.67-5.71 (m, 1H), 6.81 (s, 1H), 7.03-7.05 (br s, 2H), 7.19-7.26 (m, 3H), 7.95-8.01 (m, 2H), 8.20-8.27 (m, 2H), 8.65-8.67 (m, 2H), 8.91 (s, 1H).

## Example 2.135



**[1036]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(N-methylsulfamoyl)-N-((4-methylthiazol-2-yl)methyl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.60 (s, 3H), 2.40 (s, 3H), 2.60-2.74 (m, 3H), 3.1-3.36 (m, 5H), 5.0 (br s, 2H), 6.92-7.22 (m, 7H), 8.18-8.52 (m, 2H).

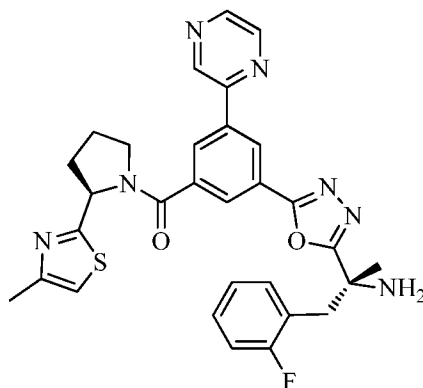
## Example 2.136



**[1037]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyridin-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.66 (s,

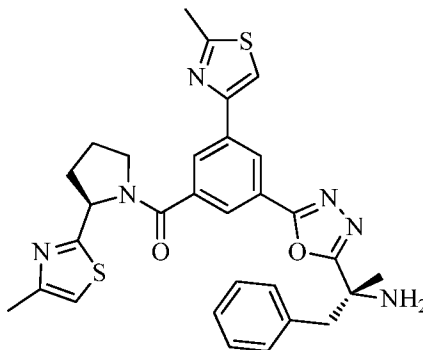
3H), 2.39 (s, 3H), 3.07-3.31 (m, 5H), 5.0 (br s, 2H), 6.91-7.32 (m, 7H), 7.82 (s, 2H), 8.15-8.21 (m, 2H), 8.68-8.72 (m, 2H).

*Example 2.137*



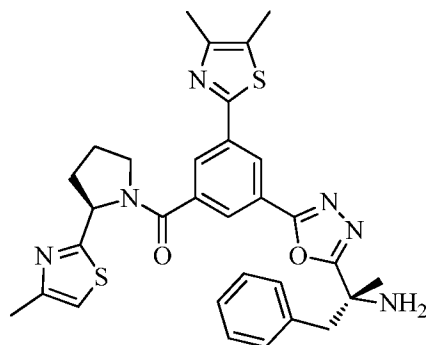
**[1038]** (3-(5-((R)-2-amino-1-(2-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.60 (s, 3H), 1.76-2.42 (m, 6H), 3.10-4.12 (m, 5H), 5.61-5.78 (m, 1H), 6.79-7.38 (m, 6H), 8.10-8.82 (m, 4H), 9.20 (s, 1H).

*Example 2.138*



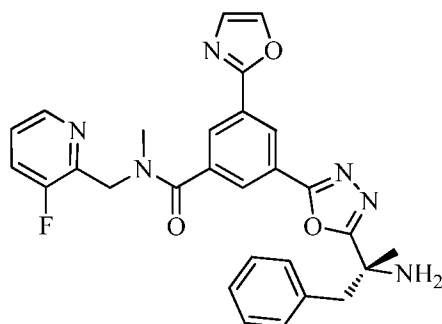
**[1039]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(2-methylthiazol-4-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.60 (s, 3H), 1.81-2.41 (m, 6H), 2.78 (s, 3H), 3.0-3.36 (m, 2H), 3.52-4.02 (m, 3H), 5.62-5.74 (m, 1H), 6.76-7.36 (m, 14H), 7.51 (s, 1H), 8.18-8.28 (m, 2H), 8.60 (s, 1H).

## Example 2.139



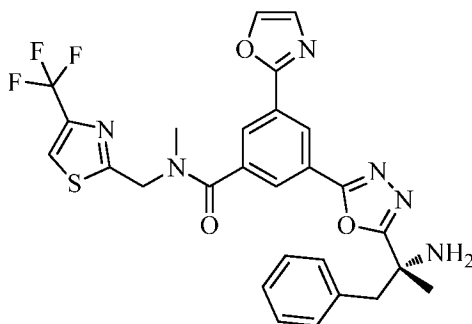
**[1040]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(4,5-dimethylthiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.60 (s, 3H), 2.01-2.42 (m, 6H), 3.10-3.32 (m, 2H), 3.58-3.62 (m, 1H), 3.92-4.02 (m, 2H), 5.68-5.82 (m, 1H), 6.72-7.31 (m, 7H), 8.20 (s, 1H), 8.44-8.60 (m, 1H).

## Example 2.140



**[1041]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((3-fluoropyridin-2-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.6 (s, 3H), 3.10-3.38 (m, 5H), 4.70 (s, 1H), 5.0 (s, 1H), 7.0 (m, 2H), 7.20-7.31 (m, 6H), 7.80 (d, 1H), 8.22-8.61 (m, 3H), 8.71 (s, 1H).

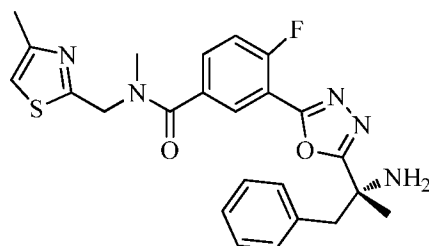
## Example 2.141



**[1042]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(oxazol-2-yl)-N-((4-(trifluoromethyl)thiazol-2-yl)methyl)benzamide:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$

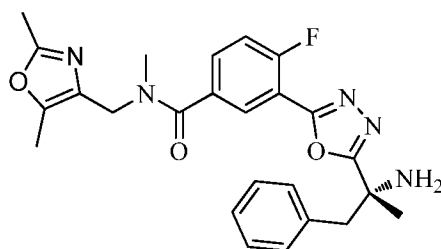
1.60 (s, 3H), 3.04-3.38 (m, 5H), 5.02 9s, 2H), 7.02-7.38 (m, 6H), 7.80-7.84 (m, 2H), 8.21-8.39 (m, 2H), 8.76 (s, 1H).

*Example 2.142*



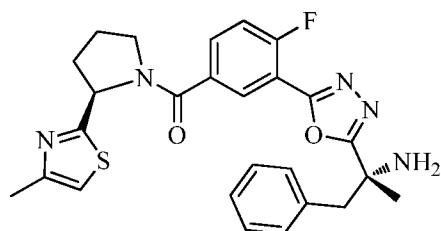
**[1043]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluoro-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide:  $m/z$ :  $M^+$ : 466.169.

*Example 2.143*



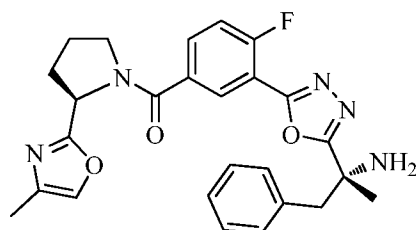
**[1044]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4-fluoro-N-methylbenzamide:  $m/z$ :  $M^+$ : 464.207.

*Example 2.144*



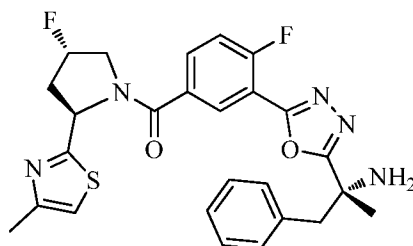
**[1045]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $m/z$ :  $M^+$ : 492.183.

*Example 2.145*



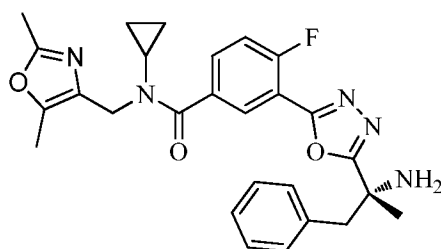
**[1046]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone:  $m/z$ :  $M^+$ : 476.206.

## Example 2.146



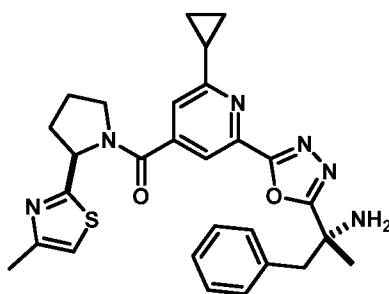
**[1047]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone:  $m/z$ :  $M^+$ : 510.174.

## Example 2.147



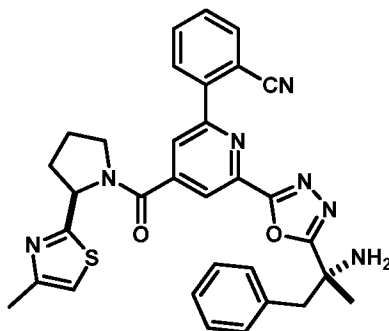
**[1048]** (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((2,5-dimethyloxazol-4-yl)methyl)-4-fluorobenzamide:  $m/z$ :  $M^+$ : 490.222.

## Example 2.148



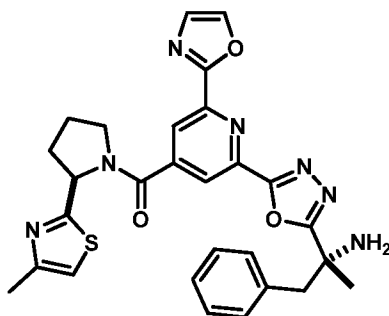
**[1049]** (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-cyclopropylpyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (0.6H, s), 7.61 (0.4H, s), 7.61 (0.6H, s), 7.21 (4.0H, m), 7.06 (2.4H, m), 6.62 (2H, s), 5.46 (0.6H, dd,  $J = 4.1$  Hz), 5.18 (0.4H, m), 3.60 (2H, m), 3.11 (2H, m), 2.40 (2H, m), 2.40 (1.8H, s), 2.22 (1.2H, s), 2.13 (1H, m), 1.97 (2H, m), 1.48 (3H, m), 1.05 (4H, m). MS (ESI)  $M/Z$ : 258.3  $[M+2H]^{(2+)}/2$ .

## Example 2.149



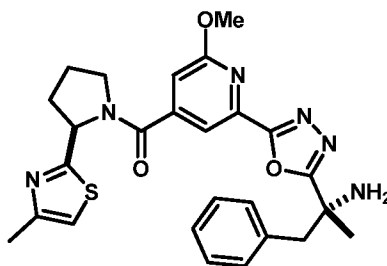
**[1050]** 2-(6-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)benzonitrile (2*E*)-but-2-enedioate (1:1):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (0.6H, s), 8.22 (0.6H, s), 8.06 (1.8H, m), 7.90 (2H, m), 7.73 (1H, m), 7.20 (3.6H, m), 7.05 (2.4H, m), 6.62 (2H, s), 5.50 (0.6H, dd,  $J = 4.4$  Hz), 5.33 (0.4H, m), 3.76 (1.2H, m), 3.61 (0.8H, m), 3.12 (2H, m), 2.41 (1H, m), 2.37 (1.8H, s), 2.16 (1H, m), 2.16 (1.2H, s), 2.01 (2H, m), 1.50 (3H, m) MS (ESI)  $M/Z$ : 288.8  $[\text{M}+2\text{H}]^{(2+)}/2$ .

## Example 2.150



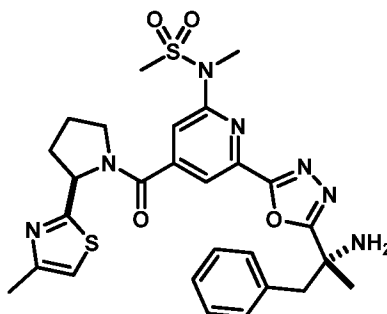
**[1051]** [2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (0.6H, s), 8.40 (0.4H, s), 8.31 (0.6H, s), 8.26 (0.6H, s), 8.03 (0.4H, s), 8.01 (0.4H, s), 7.58 (0.6H, s), 7.53 (0.4H, s), 7.22 (3.6H, m), 7.07 (2.4H, m), 6.62 (2H, s), 5.50 (0.6H, dd,  $J = 4.0$  Hz), 5.23 (0.4H, m), 3.67 (2H, m), 3.15 (2H, m), 2.41 (1H, m), 2.37 (1.8H, m), 2.16 (1.2H, m), 2.14 (1H, m), 1.99 (2H, m), 1.50 (3H, s) MS (ESI)  $M/Z$ : 271.8  $[\text{M}+2\text{H}]^{(2+)}/2$ .

## Example 2.151



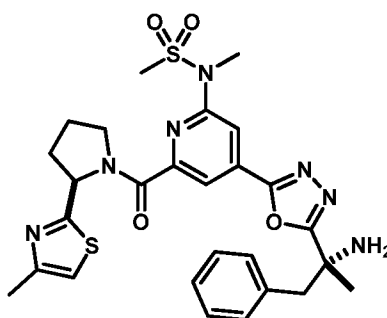
**[1052]** (2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-4-yl)[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (0.6H, s), 7.44 (0.4H, s), 7.19 (3.6H, m), 7.05 (3H, m), 6.62 (2H, s), 6.88 (0.4H, s), 5.44 (0.6H, dd,  $J = 4.0$  Hz), 5.20 (0.4H, m), 4.00 (1.8H, s), 3.92 (1.2H, s), 3.60 (2H, m), 3.11 (2H, m), 2.42 (1H, m), 2.35 (1.8H, s), 2.20 (1.2H, s), 2.12 (1H, m), 1.97 (2H, m), 1.49 (3H, m) MS (ESI)  $M/Z$ : 505.3  $[\text{M}+\text{H}]^+$ .

## Example 2.152



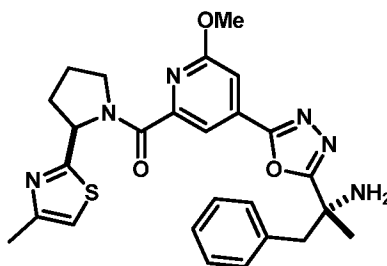
**[1053]** *N*-(6-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-*N*-methylmethanesulfonamide (2*E*)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 (0.6H, s), 7.70 (0.6H, s), 7.61 (0.4H, s), 7.42 (0.4H, s), 7.20 (3.6H, m), 7.05 (2.4H, m), 6.61 (2H, s), 5.46 (0.6H, dd,  $J = 4.0$  Hz), 5.21 (0.4H, m), 3.64 (2H, m), 3.43 (1.8H, s), 3.40 (1.2H, s), 3.33 (1.2H, s), 3.31 (1.8H, s), 3.11 (2H, m), 2.41 (1H, m), 2.34 (1.8H, s), 2.20 (1.2H, s), 2.13 (1H, m), 1.97 (2H, m), 1.48 (3H, m) MS (ESI)  $M/Z$ : 582.3  $[\text{M}+\text{H}]^+$ .

## Example 2.153



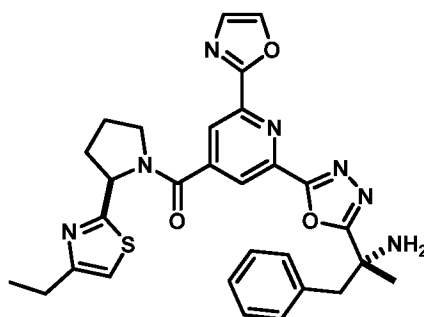
**[1054]** *N*-(4-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[[ (2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-*N*-methylmethanesulfonamide (2*E*)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.07 (0.6H, s), 8.03 (0.6H, s), 7.97 (0.4H, s), 7.90 (0.4H, s), 7.20 (3H, m), 7.14 (0.4H, s), 7.04 (2.6H, m), 6.62 (2H, s), 5.92 (0.4H, m), 5.53 (0.6H, dd,  $J = 4.0$  Hz), 4.01 (0.4H, m), 3.78 (1.6H, m), 3.45 (1.8H, s), 3.33 (1.2H, s), 3.13 (1.2H, s), 3.11 (1.8H, s), 3.12 (2H, m), 2.42 (1H, m), 2.35 (1.8H, s), 2.21 (1.2H, s), 2.05 (3H, m), 1.48 (3H, s) MS (ESI)  $M/Z$ : 582.3  $[\text{M}+\text{H}]^+$ .

*Example 2.154*



**[1055]** (4-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-2-yl)[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (0.5H, s), 7.81 (0.5H, s), 7.50 (0.5H, s), 7.36 (0.5H, s), 7.20 (3H, m), 7.14 (0.5H, s), 7.02 (2.5H, m), 6.62 (2H, s), 6.02 (0.5H, m), 5.52 (0.5H, dd,  $J = 4.0$  Hz), 4.08 (0.5H, m), 4.01 (1.5H, s), 3.91 (0.5H, m), 3.78 (1H, m), 3.65 (1.5H, s), 3.11 (2H, m), 2.42 (1H, m), 2.34 (1.5H, m), 2.23 (1.5H, m), 2.06 (2H, m), 1.83 (1H, m), 1.48 (3H, m) MS (ESI)  $M/Z$ : 505.3  $[\text{M}+\text{H}]^+$ .

*Example 2.155*

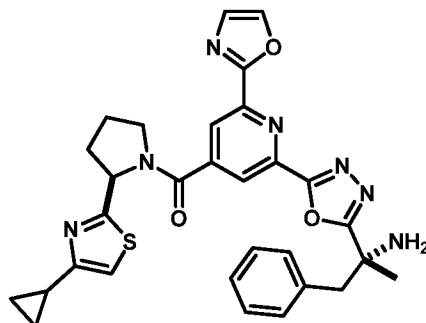


**[1056]** [2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2*R*)-2-(4-ethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.45 (0.6H, s), 8.39 (0.4H, s), 8.31 (0.6H, s), 8.27 (0.6H, s), 8.02 (0.4H, s), 7.99 (0.4H, s), 7.58 (0.6H, s), 7.52 (0.4H, s), 7.21 (3.6H, m), 7.07 (2.4H, m), 6.62 (2H, s), 5.50 (0.6H, dd,  $J = 4.0$  Hz), 5.26 (0.4H, m), 3.69 (2H, m), 3.15 (2H, m), 2.72 (1.2H, q,  $J = 7.4$  Hz), 2.47 (1H, m), 2.40 (0.8H, m), 2.15 (1H, m), 1.99 (2H, m),



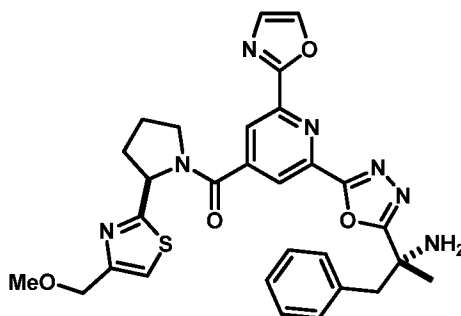
1.50 (3H, m), 1.24 (1.8H, t,  $J = 7.4$  Hz), 0.99 (1.2H, t,  $J = 7.8$  Hz) MS (ESI) M/Z: 556.4 [M+H]<sup>+</sup>.

*Example 2.156*



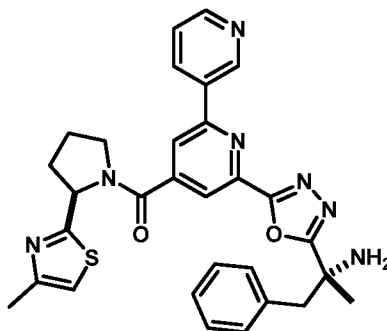
**[1057]** [2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2R)-2-(4-cyclopropyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.44 (0.6H, s), 8.40 (0.4H, s), 8.31 (0.6H, s), 8.25 (0.6H, s), 8.00 (0.4H, s), 8.00 (0.4H, s), 7.59 (0.6H, s), 7.53 (0.4H, s), 7.21 (3.6H, m), 7.08 (2.4H, m), 6.62 (2H, s), 5.47 (0.6H, dd,  $J = 4.0$  Hz), 5.24 (0.4H, m), 3.64 (2H, m), 3.15 (2H, m), 2.40 (0.6H, m), 2.07 (2H, m), 1.96 (2H, m), 1.82 (0.4H, m), 1.49 (3H, m), 0.90 (1.2H, m), 0.81 (1.2H, m), 0.70 (0.8H, m), 0.57 (0.4H, m), 0.46 (0.4H, m) MS (ESI) M/Z: 568 [M+H]<sup>+</sup>.

*Example 2.157*



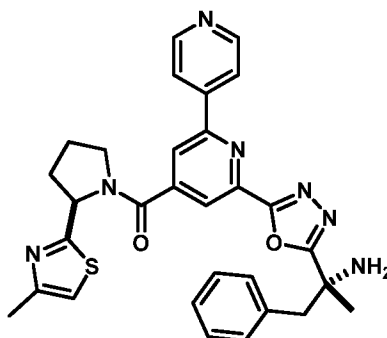
**[1058]** [2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2R)-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : MS (ESI) m/z: 572 [M+H]<sup>+</sup>.

## Example 2.158



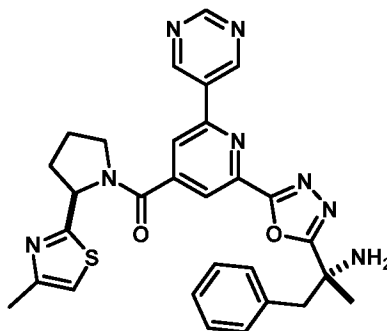
**[1059]** (6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-2,3'-bipyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.43 (0.6H, s), 9.23 (0.4H, s), 8.74 (0.6H, dd,  $J = 2.7$  Hz), 8.70 (0.4H, dd,  $J = 2.7$  Hz), 8.60 (0.6H, dt,  $J = 8.0, 1.8$  Hz), 8.42 (0.4H, dt,  $J = 8.0, 1.8$  Hz), 8.37 (0.6H, s), 8.14 (0.6H, s), 8.05 (0.4H, s), 7.87 (0.4H, s), 7.59 (1H, m), 7.21 (3.6H, m), 7.07 (2.4H, m), 6.61 (2H, s), 5.50 (0.6H, dd,  $J = 4.0$  Hz), 5.31 (0.4H, m), 3.77 (1H, m), 3.58 (1H, m), 3.15 (2H, m), 2.43 (1H, m), 2.38 (1.8H, s), 2.18 (1H, m), 2.15 (1.2H, s), 2.00 (2H, m), 1.52 (3H, m) MS (ESI)  $M/Z$ : 276.8  $[\text{M}+2\text{H}]^{(2+)}/2$ .

## Example 2.159



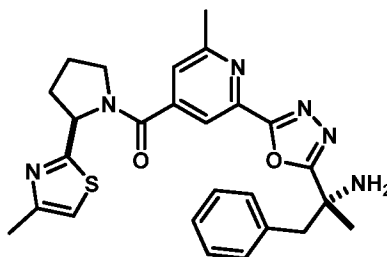
**[1060]** (6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-2,4'-bipyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.80 (0.6H, s), 8.80 (0.6H, s), 8.78 (0.4H, s), 8.76 (0.4H, s), 8.42 (0.6H, s), 8.22 (0.6H, s), 8.21 (0.6H, s), 8.20 (0.6H, s), 8.10 (0.4H, s), 8.03 (0.4H, s), 8.02 (0.4H, s), 7.93 (0.4H, s), 7.23 (3.6H, m), 7.07 (2.4H, m), 6.62 (2H, s), 5.50 (0.6H, dd,  $J = 4.0$  Hz), 5.29 (0.4H, m), 3.76 (1H, m), 3.58 (1H, m), 3.15 (2H, m), 2.44 (1H, m), 2.37 (1.8H, s), 2.17 (1H, m), 2.13 (1.2H, s), 2.01 (2H, m), 1.52 (3H, s) MS (ESI)  $M/Z$ : 276.8  $[\text{M}+2\text{H}]^{(2+)}/2$ .

## Example 2.160



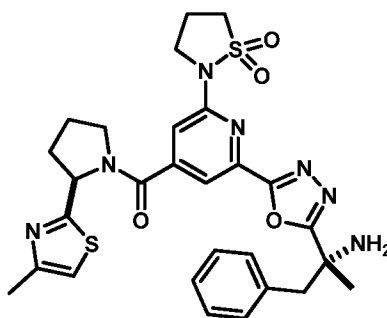
**[1061]** [2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(pyrimidin-5-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.61 (1.2H, s), 9.44 (1H, s), 9.34 (0.8H, m), 8.47 (0.6H, s), 8.19 (0.6H, s), 8.15 (0.4H, s), 7.93 (0.4H, s), 7.21 (3.6H, m), 7.07 (2.4H, m), 6.62 (2H, s), 5.51 (0.6H, dd,  $J = 4.0$  Hz), 5.33 (0.4H, m), 3.77 (1.2H, m), 3.58 (0.8H, m), 3.14 (2H, m), 2.44 (1H, m), 2.38 (1.8H, s), 2.20 (1H, m), 2.15 (1.2H, s), 1.99 (2H, m), 1.51 (3H, m) MS (ESI)  $M/Z$ : 277.3  $[\text{M}+2\text{H}]^{(2+)/2}$ .

## Example 2.161



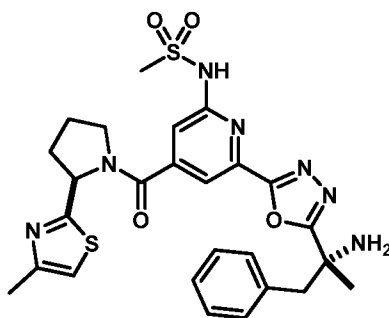
**[1062]** (2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methylpyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (0.7H, s), 7.71 (0.3H, s), 7.63 (0.7H, s), 7.21 (4H, m), 7.06 (2.3H, m), 6.62 (2H, s), 5.46 (0.7H, dd,  $J = 4.0$  Hz), 5.20 (0.3H, m), 3.56 (2H, m), 3.11 (2H, m), 2.65 (2.1H, s), 2.51 (0.9H, s), 2.39 (1H, m), 2.37 (2.1H, s), 2.21 (0.9H, s), 2.15 (1H, m), 1.98 (2H, m), 1.47 (3H, m) MS (ESI)  $M/Z$ : 489.3  $[\text{M}+\text{H}]^+$ .

## Example 2.162



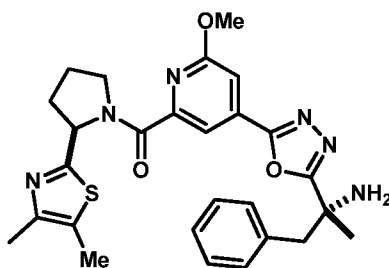
**[1063]** [2-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,1-dioxido-1,2-thiazolidin-2-yl)pyridin-4-yl][(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (0.7H, s), 7.53 (0.3H, s), 7.44 (0.7H, s), 7.21 (4H, m), 7.05 (2.3H, m), 6.61 (2H, s), 5.46 (0.7H, dd,  $J = 4.0$  Hz), 5.17 (0.3H, m), 4.05 (1.4H, m), 3.92 (0.6H, m), 3.71 (2H, m), 3.56 (2H, m), 3.12 (2H, m), 2.43 (3H, m), 2.36 (2.1H, s), 2.22 (0.9H, s), 2.13 (1H, m), 1.98 (2H, m), 1.48 (3H, m) MS (ESI)  $M/Z$ : 594.4  $[\text{M}+\text{H}]^+$ .

*Example 2.163*



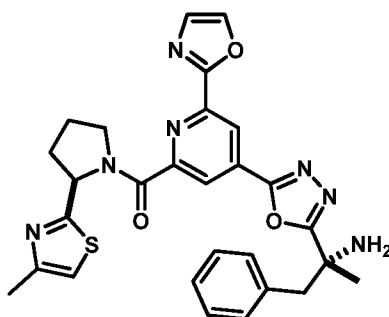
**[1064]** *N*-(6-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[[ (2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)methanesulfonamide (2*E*)-but-2-enedioate (1:1) : MS (ESI)  $m/z$ : 285  $[\text{M}+2\text{H}]^{(2+)}/2$ .

*Example 2.164*



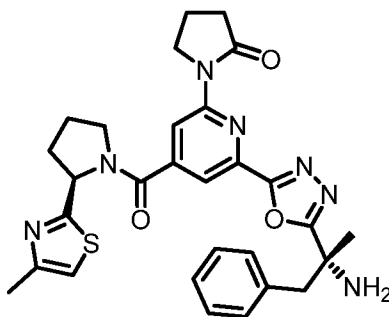
**[1065]** (4-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-2-yl)[(2*R*)-2-(4,5-dimethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) : MS (ESI)  $m/z$ : 260.3  $[\text{M}+2\text{H}]^{(2+)}/2$ .

*Example 2.165*



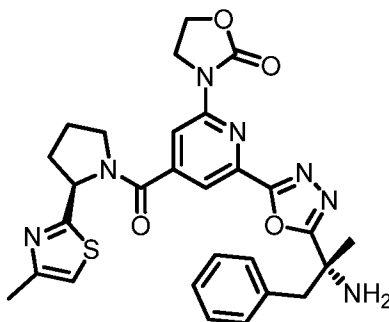
**[1066]** [4-{5-[(2*R*)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-2-yl][(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2*E*)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.67 (0.6H, s), 8.52 (0.4H, s), 8.45 (0.6H, s), 8.36 (0.4H, s), 8.34 (0.6H, s), 8.12 (0.4H, s), 7.60 (0.6H, s), 7.56 (0.4H, s), 7.23 (3H, m), 7.15 (0.6H, s), 7.06 (2.4H, m), 6.61 (2H, s), 6.03 (0.4H, m), 5.57 (0.6H, dd,  $J = 4.0$  Hz), 4.15 (0.6H, m), 3.85 (1.4H, m), 3.13 (2H, m), 2.50 (1H, m), 2.37 (1.8H, s), 2.17 (1H, m), 2.15 (1.2H, s), 2.02 (2H, m), 1.48 (3H, s) MS (ESI)  $M/Z$ : 271.7  $[\text{M}+2\text{H}]^{(2+)} / 2$ .

*Example 2.166*



**[1067]** 1-(6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)pyrrolidin-2-one (2*E*)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.62 (0.7H, d,  $J = 1.0$  Hz), 8.28 (0.3H, d,  $J = 1.0$  Hz), 7.86 (0.7H, d,  $J = 1.0$  Hz), 7.65-7.55 (1.3H, m), 7.26-7.15 (3H, m), 7.09-7.02 (2H, m), 6.62 (2H, s), 5.48 (0.7H, dd,  $J = 8.1, 4.1$  Hz), 5.16-5.12 (0.3H, m), 4.10 (1.4H, t,  $J = 7.0$  Hz), 4.05-3.99 (0.6H, m), 3.76-3.07 (6H, m), 2.68-1.90 (11H, m), 1.49 (2.1H, s), 1.48 (0.9H, s). MS (ESI)  $m/z$ : 558  $[\text{M}+\text{H}]^+$ .

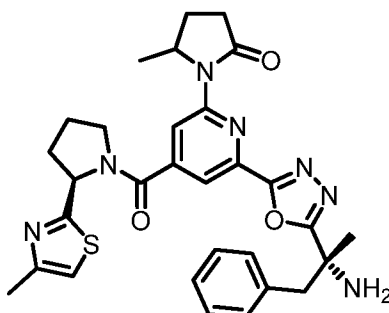
*Example 2.167*



**[1068]** 3-(6-{5-[(2*R*)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2*R*)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3-oxazolidin-2-one (2*E*)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.39 (0.7H, d,  $J = 1.1$  Hz), 8.07 (0.3H, d,  $J = 1.0$  Hz), 7.86 (0.7H, d,  $J = 1.1$  Hz), 7.66-7.52 (1.3H, m), 7.26-7.16 (3H, m), 7.09-7.01 (2H, m), 6.62 (2H, s), 5.48 (0.7H, dd,  $J = 8.1, 4.1$  Hz), 5.16-5.13 (0.3H, m), 4.56-

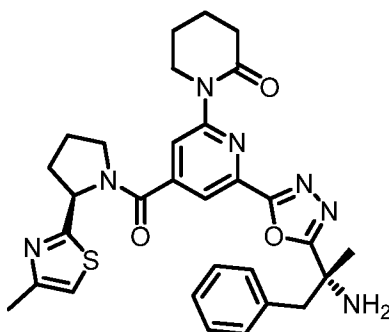
4.46 (2H, m), 4.32-4.16 (2H, m), 3.76-3.06 (6H, m), 2.56-1.90 (7H, m), 1.50 (2.1H, s), 1.48 (0.9H, s). MS (ESI)  $m/z$ : 560  $[M+H]^+$ .

*Example 2.168*



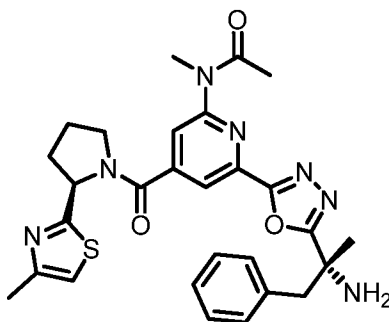
**[1069]** 1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[[2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)-5-methylpyrrolidin-2-one (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.55-8.52 (0.7H, m), 8.23-8.21 (0.15H, m), 8.13-8.10 (0.15H, m), 7.87-7.84 (0.7H, m), 7.63-7.61 (0.15H, m), 7.55-7.52 (0.15H, m), 7.24-7.15 (4H, m), 7.08-7.00 (2H, m), 6.61 (2H, s), 5.48 (0.7H, dd,  $J = 8.0, 4.1$  Hz), 5.19-5.14 (0.3H, m), 4.85-4.70 (1H, m), 3.78-3.02 (6H, m), 3.89-1.70 (11H, m), 1.50 (2.1H, s), 1.49 (0.9H, s), 1.41-1.27 (3H, m). MS (ESI)  $m/z$ : 572  $[M+H]^+$ .

*Example 2.169*



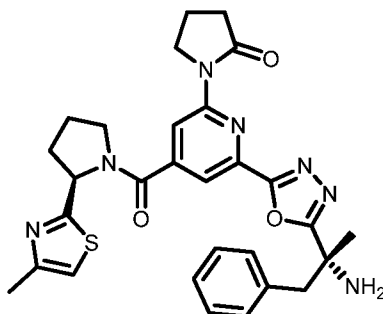
**[1070]** 1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[[2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2-yl)piperidin-2-one (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.11 (0.7H, d,  $J = 1.1$  Hz), 7.91 (0.7H, d,  $J = 1.1$  Hz), 7.80 (0.3H, d,  $J = 1.1$  Hz), 7.60 (0.3H, d,  $J = 1.1$  Hz), 7.25-7.15 (4H, m), 7.06-7.00 (2H, m), 6.62 (2H, s), 5.47 (0.7H, dd,  $J = 8.1, 4.0$  Hz), 5.23-5.17 (0.3H, m), 4.04-3.05 (8H, m), 2.67-1.80 (13H, m), 1.49 (2.1H, s), 1.47 (0.9H, s). MS (ESI)  $m/z$ : 572  $[M+H]^+$ .

## Example 2.170



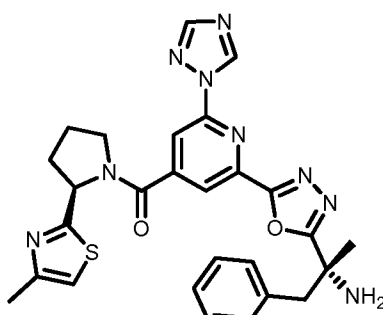
**[1071]** N-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-N-methylacetamide (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.95 (0.65H, s), 7.94 (0.65H, s), 7.63 (0.35H, s), 7.61 (0.35H, s), 7.25-7.15 (4H, m), 7.09-7.00 (2H, m), 6.62 (2H, s), 5.47 (0.65H, dd,  $J$  = 8.1, 4.0 Hz), 5.28-5.22 (0.35H, m), 3.80-2.94 (9H, m), 2.67-1.90 (10H, m), 1.49 (1.95H, s), 1.48 (1.05H, s). MS (ESI)  $m/z$ : 546  $[\text{M}+\text{H}]^+$ .

## Example 2.171



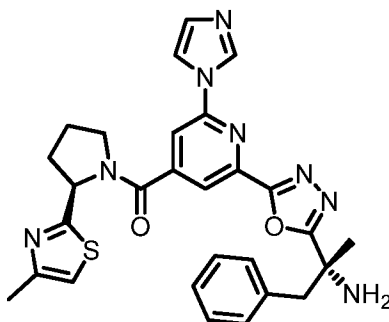
**[1072]** 1-(4-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)pyrrolidin-2-one (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.04 (0.55H, d,  $J$  = 1.4 Hz), 8.91 (0.45H, d,  $J$  = 1.4 Hz), 8.00 (0.55H, d,  $J$  = 1.4 Hz), 7.92 (0.45H, d,  $J$  = 1.4 Hz), 7.26-7.01 (6H, m), 6.62 (2H, s), 5.94 (0.45H, dd,  $J$  = 7.4, 5.4 Hz), 5.54 (0.55H, dd,  $J$  = 7.9, 3.1 Hz), 4.15-3.02 (8H, m), 2.70-1.75 (11H, m), 1.49 (1.65H, s), 1.48 (1.35H, s). MS (ESI)  $m/z$ : 558  $[\text{M}+\text{H}]^+$ .

## Example 2.172



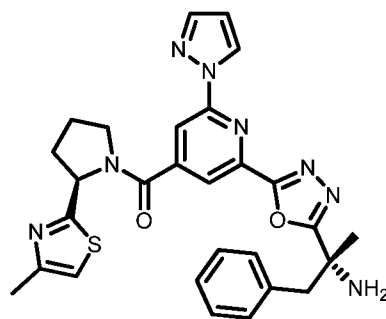
**[1073]** [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-1,2,4-triazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.52 (0.6H, s), 9.43 (0.4H, s), 8.43 (0.6H, s), 8.38 (0.4H, s), 8.18 (0.6H, d,  $J = 1.1$  Hz), 8.08 (0.6H, s), 7.94-7.93 (0.4H, m), 7.85-7.84 (0.4H, m), 7.26-7.18 (4H, m), 7.10-7.05 (2H, m), 6.62 (2H, s), 5.49 (0.6H, dd,  $J = 8.1, 4.0$  Hz), 5.26-5.23 (0.4H, m), 3.78-3.00 (6H, m), 2.73-1.88 (7H, m), 1.53-1.48 (3H, m). MS (ESI)  $m/z$ : 542  $[\text{M}+\text{H}]^+$ .

*Example 2.173*



**[1074]** [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-imidazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.74 (0.55H, s), 8.56 (0.45H, s), 8.17-7.77 (3H, m), 7.27-7.15 (5H, m), 7.10-7.02 (2H, m), 6.62 (2H, s), 5.49 (0.55H, dd,  $J = 7.9, 3.9$  Hz), 5.35-5.29 (0.45H, m), 3.82-3.05 (6H, m), 2.68-1.90 (7H, m), 1.53-1.45 (3H, m). MS (ESI)  $m/z$ : 541  $[\text{M}+\text{H}]^+$ .

*Example 2.174*

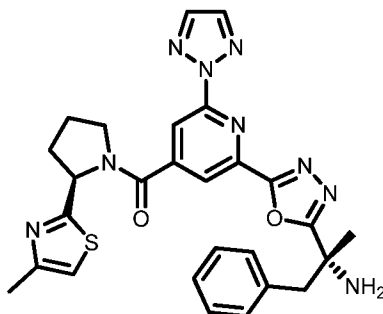


**[1075]** [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-pyrazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.73 (0.6H, d,  $J = 2.5$  Hz), 8.64 (0.4H, d,  $J = 2.6$  Hz), 8.13 (0.6H, m), 8.06 (0.6H, m), 7.95 (0.6H, m), 7.91-7.88 (0.8H, m), 7.80-7.78 (0.4H, m), 7.26-7.15 (4H, m), 7.10-7.03 (2H, m), 6.71 (0.6H, dd,  $J = 2.5, 1.7$  Hz), 6.66 (0.4H,



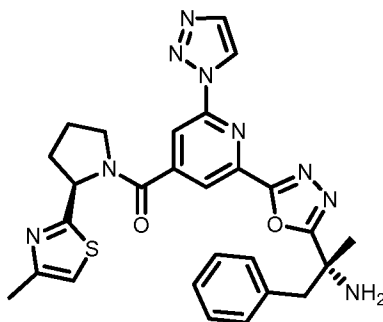
dd,  $J = 2.4, 1.8$  Hz), 6.61 (2H, s), 5.49 (0.6H, dd,  $J = 8.0, 4.0$  Hz), 5.26-5.22 (0.4H, m), 3.77-3.10 (6H, m), 2.70-1.86 (7H, m), 1.53-1.47 (3H, m). MS (ESI)  $m/z$ : 541  $[M+H]^+$ .

*Example 2.175*



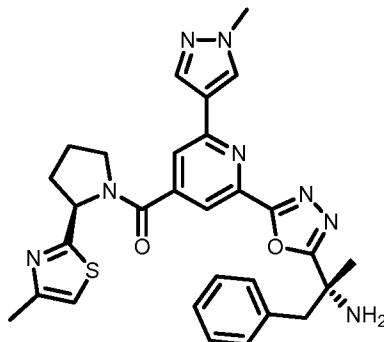
**[1076]** [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(2H-1,2,3-triazol-2-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1):  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.32 (1.2H, s), 8.26 (1.4H, s), 8.23 (0.6H, s), 8.00 (0.4H, s), 7.97 (0.4H, s), 7.26-7.18 (4H, m), 7.10-7.04 (2H, m), 6.62 (2H, s), 5.50 (0.6H, dd,  $J = 8.1, 4.0$  Hz), 5.29-5.22 (0.4H, m), 3.79-3.57 (2H, m), 3.30 (2H, t,  $J = 7.0$  Hz), 3.19-3.11 (2H, m), 2.70 (3H, s), 2.47-1.86 (4H, m), 1.51 (1.8H, s), 1.50 (1.2H, s). MS (ESI)  $m/z$ : 542  $[M+H]^+$ .

*Example 2.176*



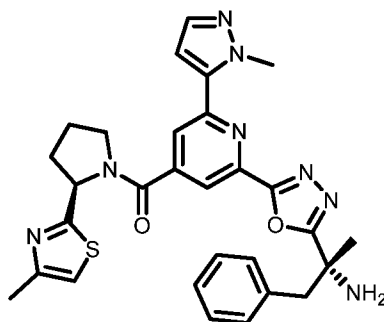
**[1077]** [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1H-1,2,3-triazol-1-yl}pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1):  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.98 (0.6H, d,  $J = 1.1$  Hz), 8.89 (0.4H, d,  $J = 1.1$  Hz), 8.36-7.97 (3H, m), 7.26-7.15 (4H, m), 7.10-7.03 (2H, m), 6.62 (2H, s), 5.50 (0.6H, dd,  $J = 8.1, 4.0$  Hz), 5.29-5.26 (0.4H, m), 3.79-3.13 (6H, m), 2.70-1.86 (7H, m), 1.51 (1.8H, s), 1.50 (1.2H, s). MS (ESI)  $m/z$ : 542  $[M+H]^+$ .

## Example 2.177



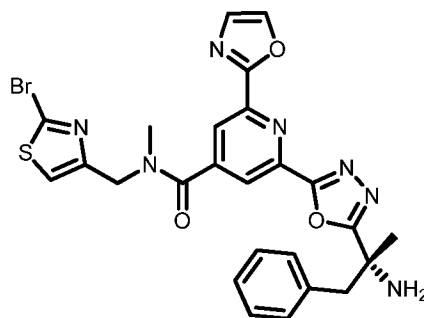
**[1078]** [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.50 (0.6H, s), 8.32 (0.4H, s), 8.20 (0.6H, s), 7.99 (0.4H, s), 7.96 (0.6H, d,  $J = 1.2$  Hz), 7.90 (0.6H, d,  $J = 1.2$  Hz), 7.28-7.02 (6.8H, m), 6.62 (2H, s), 5.49 (0.6H, dd,  $J = 8.0, 3.9$  Hz), 5.30-5.24 (0.4H, m), 3.94 (1.8H, s), 3.92 (1.2H, s), 3.80-3.52 (2H, m), 3.40 (2H, br.s), 3.21-3.11 (2H, m), 2.48-1.85 (7H, m), 1.55-1.48 (3H, m). MS (ESI)  $m/z$ : 555  $[\text{M}+\text{H}]^+$ .

## Example 2.178



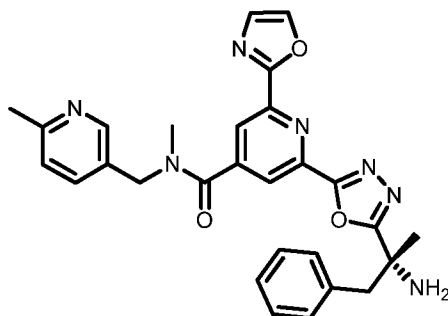
**[1079]** [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.10 (0.6H, d,  $J = 1.1$  Hz), 8.07 (0.6H, d,  $J = 1.0$  Hz), 7.82 (0.4H, d,  $J = 1.0$  Hz), 7.77 (0.4H, m), 7.57 (0.6H, d,  $J = 2.0$  Hz), 7.53 (0.4H, d,  $J = 2.0$  Hz), 7.26-7.16 (3.6H, m), 7.11 (0.6H, d,  $J = 2.0$  Hz), 7.09-7.01 (2.4H, m), 6.81 (0.4H, d,  $J = 2.0$  Hz), 6.62 (2H, s), 5.49 (0.6H, dd,  $J = 8.0, 3.8$  Hz), 5.28-5.24 (0.4H, m), 4.24 (1.8H, s), 4.17 (1.2H, s), 3.80-3.08 (6H, m), 2.46-1.86 (7H, m), 1.53-1.46 (3H, m). MS (ESI)  $m/z$ : 555  $[\text{M}+\text{H}]^+$ .

## Example 2.179



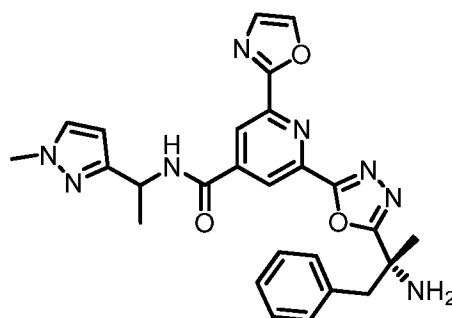
**[1080]** 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(4-bromo-1,3-thiazol-2-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.44 (0.6H, s), 8.41 (0.4H, s), 8.27-8.23 (1.6H, m), 7.89 (0.6H, s), 7.85 (0.4H, s), 7.65-7.53 (3.4H, m), 7.25-7.17 (3H, m), 7.10-7.05 (2H, m), 6.62 (2H, s), 4.99 (1.2H, s), 4.85 (0.8H, s), 3.18-3.05 (5H, m), 1.51 (1.8H, s), 1.49 (1.2H, s). MS (ESI)  $m/z$ : 580, 582  $[\text{M}+\text{H}]^+$ .

## Example 2.180



**[1081]** 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(6-methylpyridin-3-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) : MS (ESI)  $m/z$ : 510  $[\text{M}+\text{H}]^+$ .

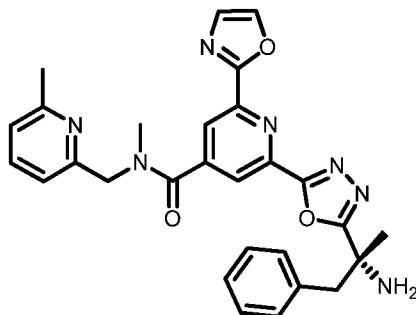
## Example 2.181



**[1082]** 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[1-(1-methyl-1H-pyrazol-3-yl)ethyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.51 (1H, d,  $J$  = 8.3 Hz), 8.73 (1H, d,  $J$  = 1.4 Hz), 8.69 (1H, d,

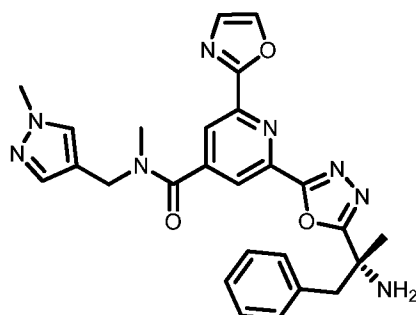
$J = 1.5$  Hz), 8.44 (1H, d,  $J = 1.0$  Hz), 7.61 (1H, d,  $J = 2.2$  Hz), 7.58 (1H, d,  $J = 0.7$  Hz), 7.25-7.17 (3H, m), 7.09-7.06 (2H, m), 6.62 (2H, s), 6.22 (1H, d,  $J = 2.2$  Hz), 5.29 (1H, qu), 3.81 (3H, s), 3.40 (2H, br.s), 3.17 (1H, d,  $J = 13.5$  Hz), 3.15 (1H, d,  $J = 13.5$  Hz), 1.55-1.50 (6H, m). MS (ESI)  $m/z$ : 499  $[M+H]^+$ .

*Example 2.182*



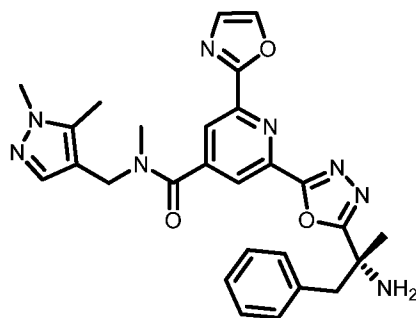
**[1083]** 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(6-methylpyridin-2-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  8.49 (0.6H, d,  $J = 1.3$  Hz), 8.44 (0.4H, m), 8.41 (0.6H, d,  $J = 1.3$  Hz), 8.40 (0.6H, m), 8.34 (0.4H, d,  $J = 1.2$  Hz), 8.31 (0.4H, d,  $J = 1.2$  Hz), 7.73 (0.4H, t,  $J = 7.6$  Hz), 7.67 (0.6H, t,  $J = 7.6$  Hz), 7.58 (0.4H, s), 7.54 (0.6H, s), 7.26-7.02 (7H, m), 6.62 (2H, s), 4.78 (0.8H, s), 4.51 (1.2H, s), 3.30 (2H, br.s), 3.16 (0.8H, s), 3.13 (1.2H, s), 2.99 (1.2H, s), 2.96 (1.8H, s), 2.54 (1.8H, s), 2.52 (1.2H, s), 1.51 (1.2H, s), 1.48 (1.8H, s). MS (ESI)  $m/z$ : 510  $[M+H]^+$ .

*Example 2.183*



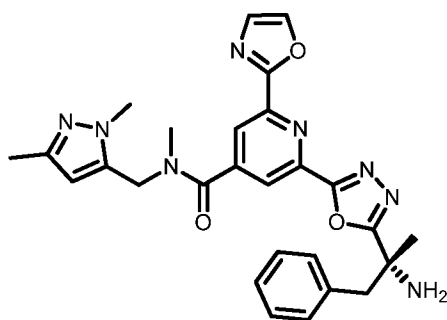
**[1084]** 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(1-methyl-1H-pyrazol-4-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) : MS (ESI)  $m/z$ : 499  $[M+H]^+$ .

## Example 2.184



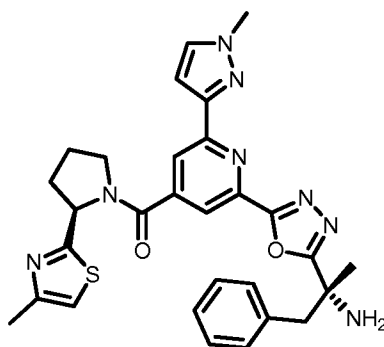
**[1085]** 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) : MS (ESI)  $m/z$ : 513  $[M+H]^+$ .

## Example 2.185



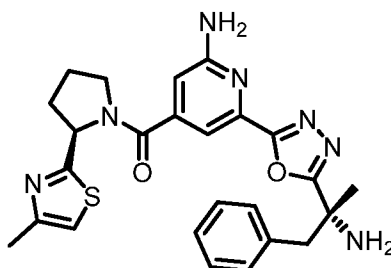
**[1086]** 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.43 (0.7H, s), 8.42 (0.3H, s), 8.27 (0.7H, s), 8.25 (1H, s), 8.19 (0.3H, s), 7.57 (1H, s), 7.26-7.16 (3H, m), 7.11-7.05 (2H, m), 6.61 (2H, s), 6.14 (0.7H, s), 6.09 (0.3H, s), 4.74 (1.4H, s), 4.55 (0.6H, s), 3.78-3.50 (3H, m), 3.40 (2H, br.s), 3.15 (2H, s), 3.02 (0.9H, s), 2.90 (2.1H, s), 2.14-2.10 (3H, m), 1.50-1.49 (3H, m). MS (ESI)  $m/z$ : 513  $[M+H]^+$ .

## Example 2.186



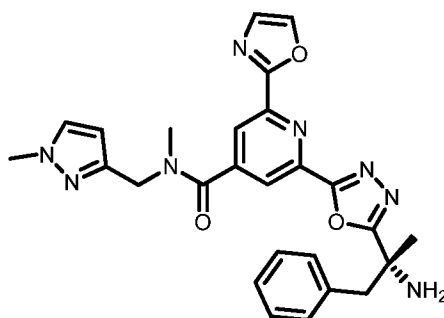
**[1087]** 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-3-yl)pyridin-4-yl[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.11 (0.6H, d,  $J = 1.3$  Hz), 8.02 (0.6H, d,  $J = 1.3$  Hz), 7.89-7.88 (1.0H, m), 7.83 (0.4H, d,  $J = 2.1$  Hz), 7.74 (0.4H, d,  $J = 0.4$  Hz), 7.26-7.04 (6H, m), 6.96 (0.6H, d,  $J = 2.2$  Hz), 6.85 (0.4H, d,  $J = 2.2$  Hz), 5.48 (0.6H, dd,  $J = 8.0, 4.1$  Hz), 5.23-5.18 (0.4H, m), 3.97 (1.8H, s), 3.94 (1.2H, s), 3.76-3.54 (2H, m), 3.17-3.08 (2H, m), 2.46-1.93 (9H, m), 1.50 (1.8H, s), 1.48 (1.2H, s). MS (ESI)  $m/z$ : 555  $[\text{M}+\text{H}]^+$ .

*Example 2.187*



**[1088]** (2-amino-6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.28-6.96 (8H, m), 6.73 (0.75H, s), 6.72 (0.75H, s), 6.62 (2H, s), 6.54 (0.25H, s), 6.45 (0.25H, s), 5.44 (0.75H, dd,  $J = 8.0, 4.2$  Hz), 5.21-5.16 (0.25H, m), 3.76-3.00 (6H, m), 2.43-1.85 (7H, m), 1.47 (2.25H, s), 1.45 (0.75H, s). MS (ESI)  $m/z$ : 490  $[\text{M}+\text{H}]^+$ .

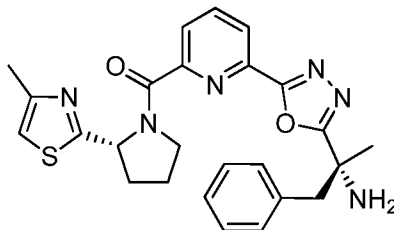
*Example 2.188*



**[1089]** 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(1-methyl-1H-pyrazol-3-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) :  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.42 (1H, d,  $J = 3.7$  Hz), 8.36 (0.6H, m), 8.32 (0.6H, m), 8.23 (0.4H, m), 8.21 (0.4H, m), 7.68 (0.4H, d,  $J = 2.0$  Hz), 7.65 (0.6H, d,  $J = 2.0$  Hz), 7.57-7.56 (1H, m), 7.25-7.17 (3H, m), 7.10-7.05 (2H, m), 6.62 (2H, s), 6.27 (0.4H, d,  $J = 2.1$  Hz), 6.21 (0.6H, d,  $J = 2.1$  Hz), 4.64 (0.8H, s), 4.38 (1.2H, s), 3.83 (1.2H, s), 3.81 (1.8H, s),

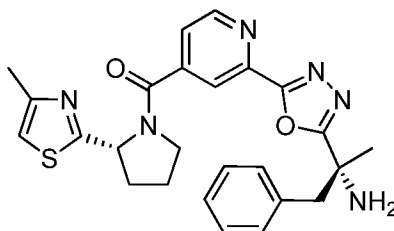
3.40 (2H, br.s), 3.17 (1H, d,  $J = 13.5$  Hz), 3.15 (1H, d,  $J = 13.5$  Hz), 3.01 (1.8H, s), 2.91 (1.2H, s), 1.51 (3H, s). MS (ESI)  $m/z$ : 499  $[M+H]^+$ .

*Example 2.189*



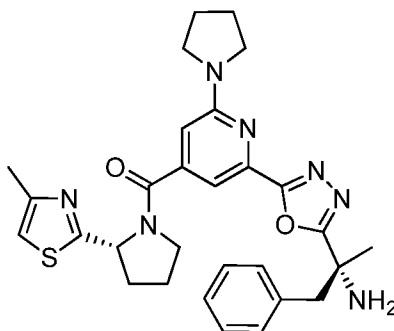
**[1090]** (6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-2-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone 2-hydroxypropane-1,2,3-tricarboxylate (1:1) : MS (ESI)  $M/Z$ : 475  $[M+H]^+$ .

*Example 2.190*



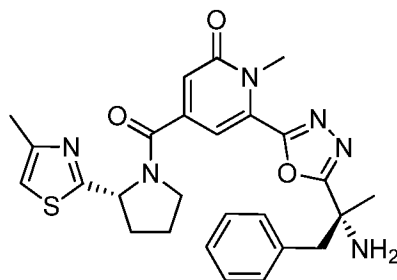
**[1091]** (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone 2-hydroxypropane-1,2,3-tricarboxylate (1:1) : MS (ESI)  $M/Z$ : 475  $[M+H]^+$ .

*Example 2.191*



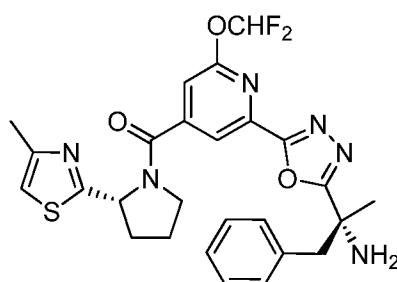
**[1092]** [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(pyrrolidin-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : MS (ESI)  $M/Z$ : 544  $[M+H]^+$ ,  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.24-7.15 (4.6H, m), 7.06-7.02 (2.4H, m), 6.66 (0.6H, br s), 6.62 (2H, s), 6.30 (0.4H, br s), 5.43 (0.6H, dd,  $J = 3.9, 8.0$  Hz), 5.18 (0.4H, m), 3.72-3.32 (6H, m), 3.23 (3H, br s), 3.15-3.06 (2H, m), 2.39-2.32 (1H, m), 2.36 (1.8H, s), 2.24 (1.2H, s), 2.12 (0.6H, m), 2.04-1.90 (6.4H, m), 1.49 (1.8H, s), 1.47 (1.2H, s).

## Example 2.192



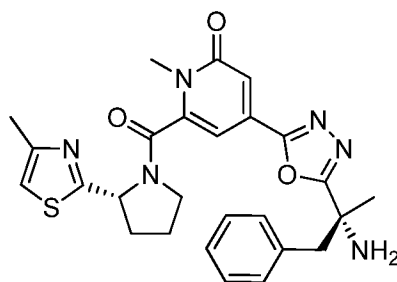
**[1093]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one (2E)-but-2-enedioate (1:1) : MS (ESI) M/Z: 505 [M+H]<sup>+</sup>.

## Example 2.193



**[1094]** [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(difluoromethoxy)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : MS (ESI) M/Z: 541 [M+H]<sup>+</sup>.

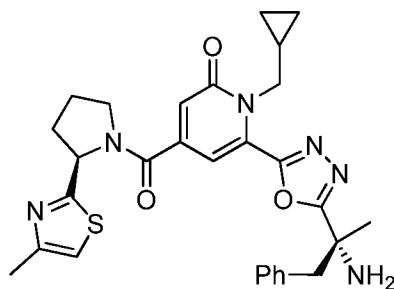
## Example 2.194



**[1095]** 4-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-6-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one (2E)-but-2-enedioate (1:1) : MS (ESI) M/Z: 505 [M+H]<sup>+</sup>.

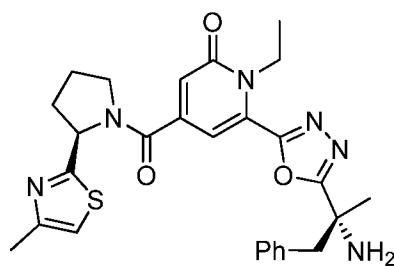


## Example 2.195



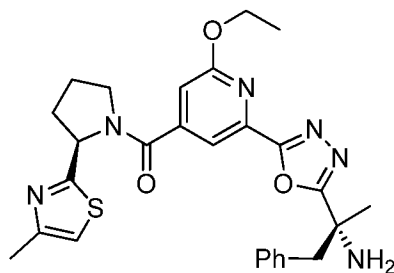
**[1096]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-(cyclopropylmethyl)-4-[[ (2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one (2E)-but-2-enedioate (1:1) : MS (ESI) M/Z: 545 [M+H]<sup>+</sup>.

## Example 2.196



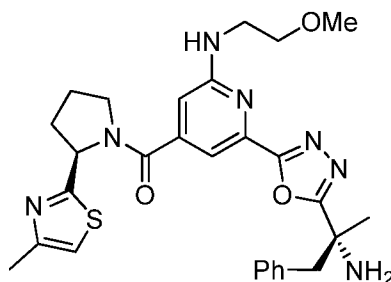
**[1097]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-ethyl-4-[[ (2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one (2E)-but-2-enedioate (1:1) : MS (ESI) M/Z: 519 [M+H]<sup>+</sup>.

## Example 2.197



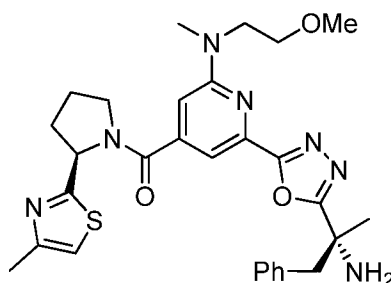
**[1098]** (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-ethoxypyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : MS (ESI) M/Z: 519 [M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 7.69 (0.6H, s), 7.41 (0.4H, s), 7.17-7.24 (3.6H, m), 7.02-7.12 (3H, m), 6.84 (0.4H, s), 6.62 (2H, s), 5.43-5.46 (0.6H, m), 5.20-5.22 (0.4H, m), 4.45 (1.2H, q, J = 7.0 Hz), 4.35 (0.8H, q, J = 7.0 Hz), 3.49-3.73 (2H, m), 3.34 (3H, br s), 3.06-3.15 (2H, m), 2.33-2.42 (1H, m), 2.36 (1.8H, s), 2.20 (1.2H, s), 2.11 (0.6H, m), 1.91-2.10 (2.4H, m), 1.49 (1.8H, s), 1.47 (1.2H, s), 1.39 (1.8H, t, J = 7.0 Hz), 1.33 (1.2H, t, J = 7.0 Hz).

## Example 2.198



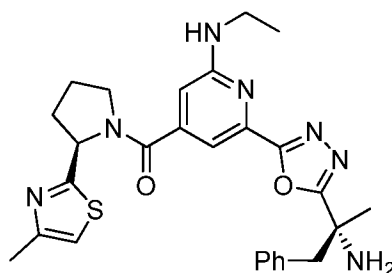
**[1099]** (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2-methoxyethyl)amino]pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : MS (ESI) M/Z: 548 [M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 7.27-7.17 (5.3H, m), 7.10-6.97 (2.7H, m), 6.83 (0.7H, s), 6.62 (2H, s), 6.51 (0.3H, s), 5.43 (0.7H, dd, J = 4.1, 8.0 Hz), 5.18 (0.3H, m), 3.71-3.40 (6H, m), 3.32 (3H, br s), 3.30 (2.1H, s), 3.27 (0.9H, s), 3.14-3.04 (2H, m), 2.38 (1H, m), 2.36 (2.1H, s), 2.24 (0.9H, s), 2.09 (0.7H, m), 2.00-1.91 (2.3H, m), 1.48 (2.1H, s), 1.46 (0.9H, s).

## Example 2.199



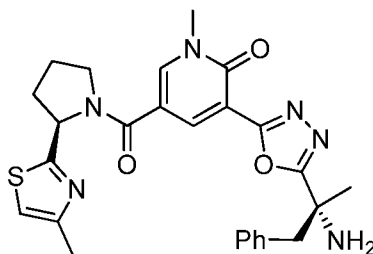
**[1100]** (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2-methoxyethyl)(methyl)amino]pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : MS (ESI) M/Z: 562 [M+H]<sup>+</sup>, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 7.23-7.13 (4.6H, m), 7.05-7.01 (2.4H, m), 6.87 (0.6H, s), 6.62 (2H, s), 6.53 (0.4H, s), 5.43 (0.6H, dd, J = 3.8, 7.0 Hz), 5.18 (0.4H, m), 3.80 (1H, m), 3.72-3.45 (5H, m), 3.40 (3H, br s), 3.27 (1.8H, s), 3.24 (1.2H, s), 3.13 (1.8H, s), 3.12-3.07 (2H, m), 2.95 (1.2H, s), 2.37 (1H, m), 2.36 (1.8H, s), 2.24 (1.2H, s), 2.13 (0.6H, m), 2.02-1.91 (2.4H, m), 1.49 (1.8H, s), 1.47 (1.2H, s).

## Example 2.200



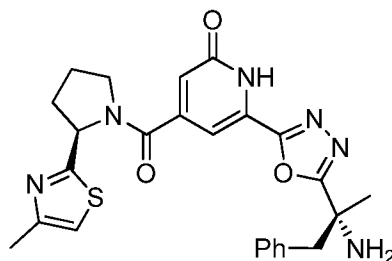
**[1101]** [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(ethylamino)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) : MS (ESI)  $M/Z$ : 518  $[M+H]^+$ ,  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.24-7.11 (5.3H, m), 7.05-6.98 (2.7H, m), 6.73 (0.7H, br s), 6.62 (2H, s), 6.40 (0.3H, br s), 5.43 (0.7H, dd,  $J = 4.1, 8.0$  Hz), 5.18 (0.3H, m), 3.70-3.48 (2H, m), 3.40 (3H, br s), 3.35 (1.4H, m), 3.21-3.05 (2.6H, m), 2.38 (1H, m), 2.36 (2.1H, s), 2.24 (0.9H, s), 2.10 (0.7H, m), 2.03-1.89 (2.3H, m), 1.49 (2.1H, s), 1.47 (0.9H, s), 1.19 (2.1H, t,  $J = 7.2$  Hz), 1.17 (0.9H, t,  $J = 7.2$  Hz).

## Example 2.201



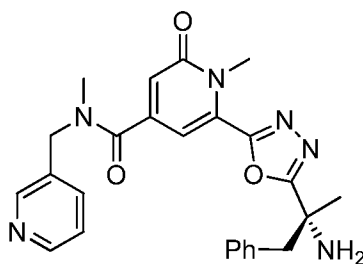
**[1102]** 3-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-5-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one (2E)-but-2-enedioate (1:1) : MS (ESI)  $M/Z$ : 505  $[M+H]^+$ .

## Example 2.202



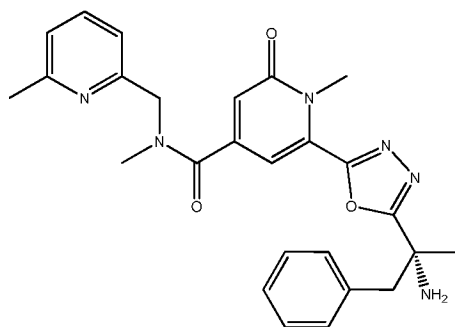
**[1103]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one (2E)-but-2-enedioate (1:1) : MS (ESI)  $M/Z$ : 491  $[M+H]^+$ .

## Example 2.203



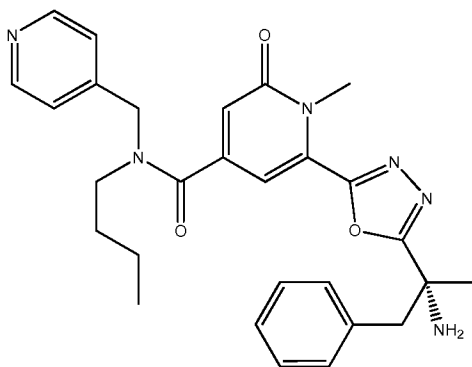
**[1104]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-2-oxo-N-(pyridin-3-ylmethyl)-1,2-dihydropyridine-4-carboxamide : MS (ESI) m/z: 459 [M+H]<sup>+</sup>.

## Example 2.204



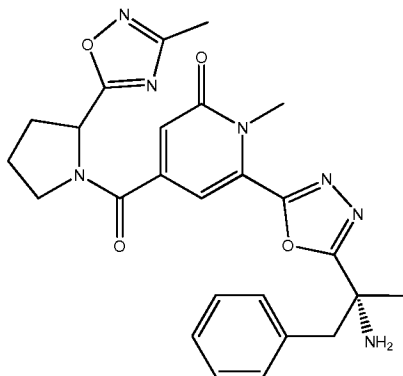
**[1105]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-N-[(6-methylpyridin-2-yl)methyl]-2-oxo-1,2-dihydropyridine-4-carboxamide : MS (ESI) M/Z: 473 [M+H]<sup>+</sup>.

## Example 2.205



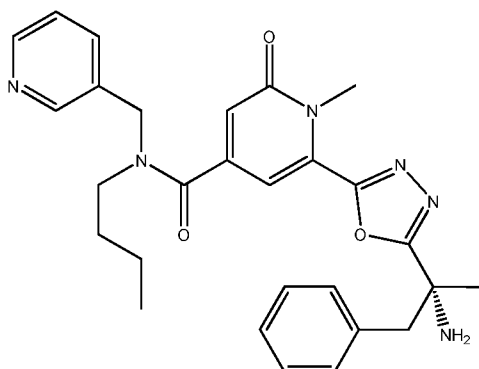
**[1106]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-butyl-1-methyl-2-oxo-N-(pyridin-4-ylmethyl)-1,2-dihydropyridine-4-carboxamide : MS (ESI) m/z: 501 [M+H]<sup>+</sup>.

## Example 2.206



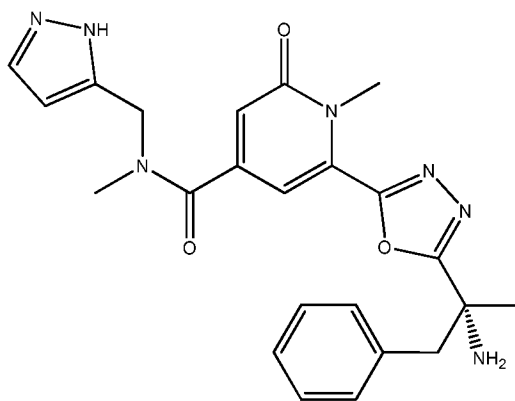
**[1107]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-4-{[2-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one : MS (ESI) m/z: 490  $[M+H]^+$ .

## Example 2.207



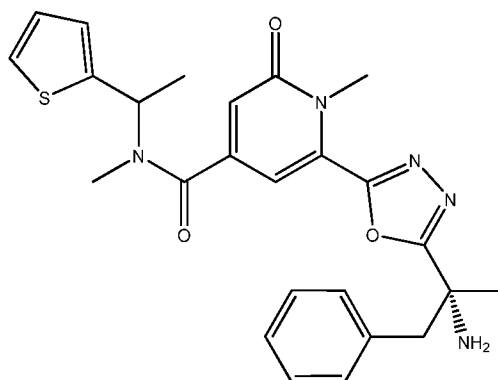
**[1108]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-butyl-1-methyl-2-oxo-N-(pyridin-3-ylmethyl)-1,2-dihydropyridine-4-carboxamide : MS (ESI) m/z: 501  $[M+H]^+$ .

## Example 2.208



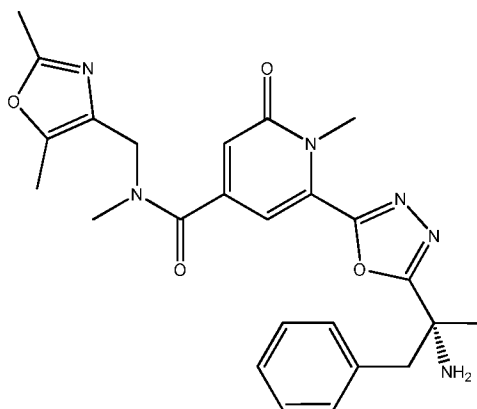
**[1109]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-2-oxo-N-(1H-pyrazol-5-ylmethyl)-1,2-dihydropyridine-4-carboxamide : MS (ESI) m/z: 448 [M+H]<sup>+</sup>.

*Example 2.209*



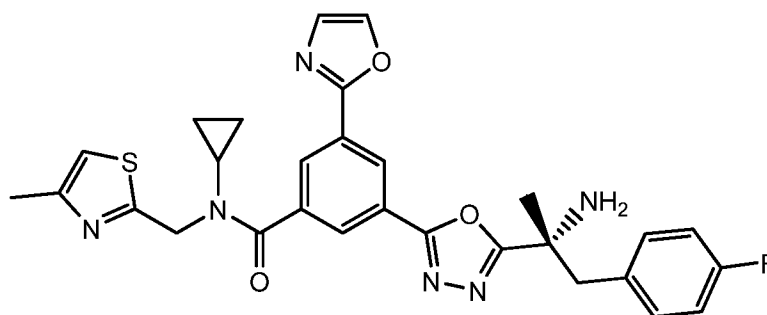
**[1110]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-2-oxo-N-[1-(2-thienyl)ethyl]-1,2-dihydropyridine-4-carboxamide : MS (ESI) m/z: 478 [M+H]<sup>+</sup>.

*Example 2.210*



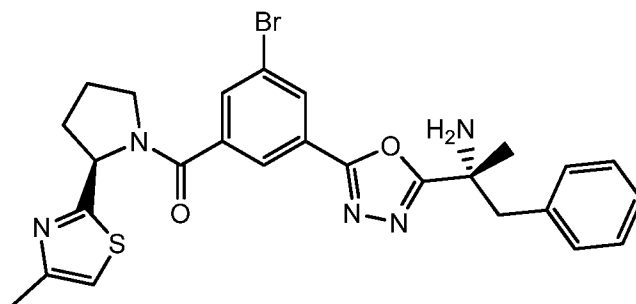
**[1111]** 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(2,5-dimethyl-1,3-oxazol-4-yl)methyl]-N,1-dimethyl-2-oxo-1,2-dihydropyridine-4-carboxamide : MS (ESI) m/z: 477 [M+H]<sup>+</sup>.

*Example 2.211*



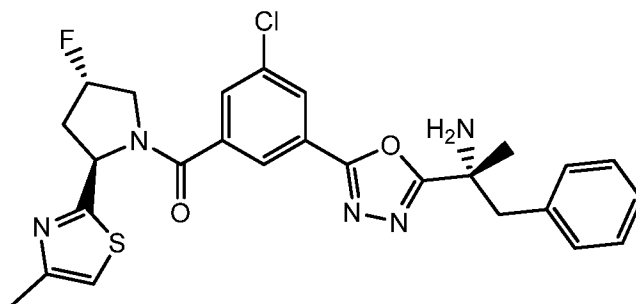
**[1112]** (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3+\text{CD}_3\text{OD}$ )  $\delta$  8.690 (s, 1 H), 8.397 (s, 1 H), 8.309 (s, 1 H), 7.787 (s, 1 H), 7.286 (m, 1 H), 7.039-6.868 (m, 5 H), 5.042 (s, 2 H), 3.270 (d,  $J = 13.5$  Hz, 1 H), 3.093 (d,  $J = 13.5$  Hz, 1 H), 2.990 (m, 1 H), 2.452 (s, 3 H), 1.905 (br, 2 H), 1.637 (s, 3 H), 0.666 (m, 2 H), 0.558 (m, 2 H).

*Example 2.212*



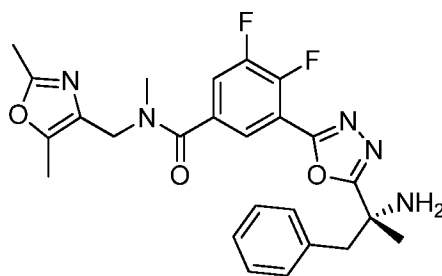
**[1113]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-bromophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20-8.11 (m, 2H), 7.86 (m, 1H), 7.33-7.21 (m, 4H), 7.03-7.01 (m, 2H), 6.81-6.79 (m, 1H), 5.67-5.63 (m, 0.6H), 5.11 (m, 0.3H), 3.98-3.70 (m, 2H), 3.59-3.54 (m, 1H), 3.29-3.21 (m, 1H), 3.11-3.07 (m, 1H), 2.45-2.34 (m, 5H), 2.18-2.07 (m, 2H), 2.02-1.94 (m, 2H), 1.67-1.64 (m, 3H).

*Example 2.213*



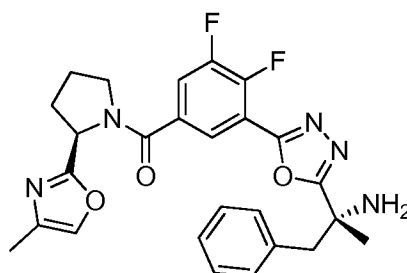
**[1114]** (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-chlorophenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.01-7.93 (m, 2H), 7.73-7.72 (m, 1H), 7.29-7.22 (m, 4H), 7.04-7.01 (m, 2H), 6.85-6.84 (m, 1H), 5.85-5.85 (m, 1H), 5.54-5.23 (m, 2H), 4.06-3.63 (m, 4H), 3.29-3.24 (m, 1H), 3.11-3.07 (m, 1H), 2.90-2.76 (m, 2H), 2.44-2.29 (m, 3H), 2.00-1.74 (m, 2H), 1.67-1.64 (m, 3H).

*Example 2.214*



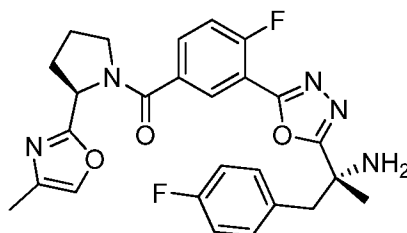
[1115] (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide : LC/MS RT: 7.30, m/z 482.201.

Example 2.215



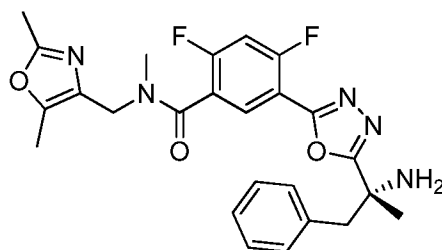
[1116] (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4,5-difluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone : LC/MS RT: 7.08-7.45, m/z 494.200.

Example 2.216



[1117] (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone : m/z: M<sup>+</sup>: 494.200.

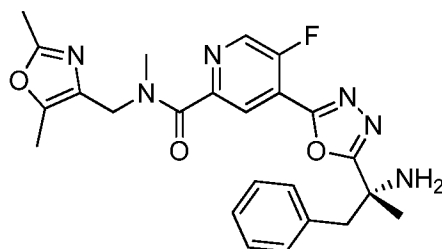
Example 2.217



[1118] (R)-5-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-2,4-difluoro-N-methylbenzamide : m/z: M<sup>+</sup>: 482.201.

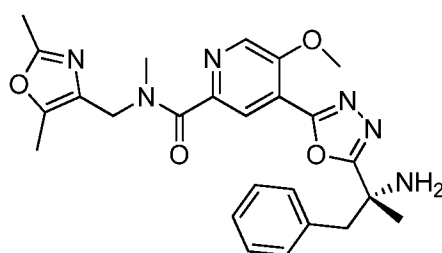


## Example 2.218



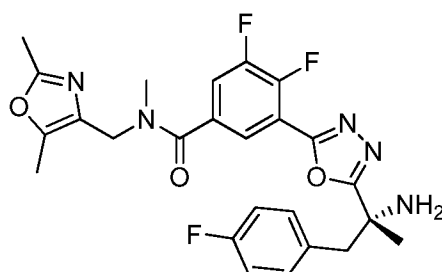
**[1119]** (R)-4-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-5-fluoro-N-methylpicolinamide : (R)-4-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-5-fluoro-N-methylpicolinamide. MS (ESI) RT 6.66, m/z: 465.204 [M+1]<sup>+</sup>.

## Example 2.219



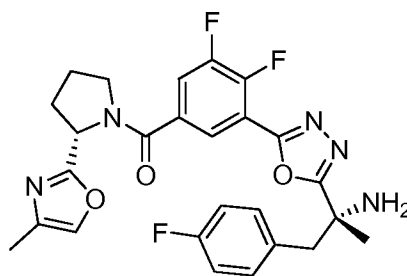
**[1120]** (R)-4-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-5-methoxy-N-methylpicolinamide : (R)-4-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-5-methoxy-N-methylpicolinamide. MS (ESI) RT 6.57, m/z: 477.224 [M+1]<sup>+</sup>.

## Example 2.220



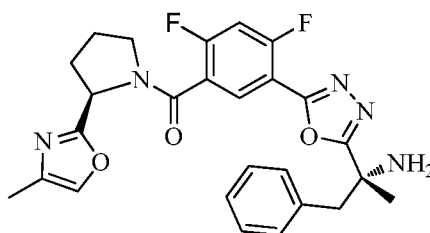
**[1121]** (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide : LC/MS RT: 7.53, m/z 500.188.

## Example 2.221



**[1122]** (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-4,5-difluorophenyl)((S)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone : LC/MS RT: 7.51, m/z 512.189.

*Example 2.222*



**[1123]** (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2,4-difluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone: m/z: M<sup>+</sup>: 494.200.

### Example 3: Inhibition of Memapsin 2 Beta-Secretase Activity

#### *Example 3.1*

**[1124]** Potency of compounds were determined by measurement of their inhibition of memapsin 2 activity toward a fluorescent substrate. Kinetic inhibition experiments were performed using the procedure as described in Ermolieff, *et al.* (*Biochemistry* 39:12450-12456 (2000), the teachings of which are incorporated hereby in their entirety). Briefly, assays were performed at pH 4, 37 °C, by pre-incubation of memapsin 2 enzyme with compound for 20 minutes. Activity measurements were initiated by addition of a fluorogenic substrate FS-2 (Bachem Americas, Torrance, CA) MCA-SEVNLDAEFK-DNP (SEQ ID NO.: 2). The substrate was derived from 10 amino acids of the human amyloid precursor protein (APP), with the Swedish variant amino acids at the beta-secretase cleavage site. The terminal amino acid was modified from arginine to lysine to facilitate derivatization with a functional group for detection by autofluorescence. The amino acid sequence of the “core” peptide of the substrate is SEVNLDAEFK (SEQ ID NO.: 3). The amino terminus was derivatized with (7-methoxycoumarin-4-yl)acetyl (MCA), and the epsilon amine of the lysine side chain of the terminal residue (K in sequence SEVNLDAEFK (SEQ ID NO.: 3)) was

derivatized with 2,4-dinitrophenyl (DNP). Results are shown in Table 1 ("BACE1 Ki"). For example, the BACE1 Ki determined using this procedure for (7-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)chroman-5-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone is about 702 nM. In additional examples, 3'-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5'-(2-(5-methylfuran-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carbonitrile is about 1562 nM, 3'-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5'-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carbonitrile is about 201 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide is about 61 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(pyrazin-2-yl)benzamide is about 101 nM, (2-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(oxazol-2-yl)pyridin-4-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone fumarate is about 139 nM, (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide is about 25 nM, (2-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone fumarate is about 124 nM, (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide is about 29 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide is about 30 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((2,5-dimethyloxazol-4-yl)methyl)-4-fluorobenzamide is about 18 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide is about 63 nM, (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone is about 101 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide is about 20 nM, (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone is about 63 nM, (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methylphenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone is about 438 nM, 1-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)pyrrolidin-2-one is about 677 nM, and (3-

(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methylphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone is about 473 nM.

### Example 3.2

**[1125]** For measurement of memapsin 2 enzyme IC<sub>50</sub>, assays were performed at pH 4.4, at room temperature, by pre-incubation of memapsin 2 enzyme with compound for 15 minutes. Fluorescence intensities were measured 60 minutes after addition of a fluorogenic substrate, MCA-SEVNLDAEFK-DNP (SEQ ID No:2) (M-2485, Bachem Americas, Torrance, CA). The values of IC<sub>50</sub> were calculated by SAS version 8.2.

### Example 3.3

**[1126]** The values of IC<sub>50</sub> were measured as described in *Example 3.2* except that calculation was conducted with Graphpad Prism version 5.

### Example 3.4

**[1127]** BACE1 % inhibition was measured as described in *Example 3.2*, at 3μM inhibitor concentration.

TABLE 1: Compound Assay data.

| Ref # | Compound Structure                                                                                                               | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-1   | tert-Butyl (2-(5-(3-(methyl((4-methylthiazol-2-yl)methyl)carbamoyl)phenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate   | +                                                                        |                                                                                               |                                                                                     |                                                                             |
| 1-2   | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide                  | ++                                                                       |                                                                                               | +                                                                                   |                                                                             |
| 1-3   | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyridin-3-yl)benzamide | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                       | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-4   | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone               | +++                                                                      |                                                                                               | +++                                                                                 | +++                                                                         |
| 1-5   | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone                | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-6   | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methylphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                      | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-7   | (3-methyl-5-(5-((R)-2-(methylamino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone              | +                                                                        |                                                                                               | N.I.                                                                                |                                                                             |
| 1-8   | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                               | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-9   | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone              | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-10  | N-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-N-methylmethanesulfonamide | ++                                                                       |                                                                                               | +                                                                                   |                                                                             |

| Ref # | Compound Structure                                                                                                                                    | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 µM<br>'+++<br>1-5 µM<br>'++<br>>5 µM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-11  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(fluoromethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone           | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-12  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-chlorophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                   | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |
| 1-13  | (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-14  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone               | ++                                                                       |                                                                                               | N.I.                                                                                |                                                                             |
| 1-15  | (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone  | +++                                                                      |                                                                                               | +++                                                                                 | ++                                                                          |
| 1-16  | 1-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)pyrrolidin-2-one         | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-17  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(dimethylamino)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone          | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                   | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-18  | (4-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(dimethylamino)pyridin-2-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone   | ++                                                                       |                                                                                               | N.I.                                                                                |                                                                             |
| 1-19  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methoxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                 | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-20  | 3'-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5'-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carbonitrile | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-21  | (7-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)chroman-5-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                     | ++                                                                       |                                                                                               | ++                                                                                  | +++                                                                         |
| 1-22  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrrol-1-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone        | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |
| 1-23  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2-hydroxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                 | +                                                                        |                                                                                               | N.I.                                                                                |                                                                             |
| 1-24  | (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)benzamide                       | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                      | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-25  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-4,4-difluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-26  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)benzamide                                    | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |
| 1-27  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(N-methylmethylsulfonamido)-N-((4-methylthiazol-2-yl)methyl)benzamide           | +++                                                                      |                                                                                               | N.I.                                                                                |                                                                             |
| 1-28  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-29  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopentyl-N-((4-methylthiazol-2-yl)methyl)benzamide                                    | ++                                                                       |                                                                                               | N.I.                                                                                |                                                                             |
| 1-30  | (4-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                        | ++                                                                       |                                                                                               | N.I.                                                                                |                                                                             |
| 1-31  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |



| Ref # | Compound Structure                                                                                                                                 | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-32  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-imidazol-1-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone    | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-33  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-5-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone         | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-34  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methylphenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone   | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-35  | (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)pyridin-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                   | ++                                                                       |                                                                                               | N.I.                                                                                |                                                                             |
| 1-36  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-(fluoromethyl)thiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-37  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-imidazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone    | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-38  | (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)chroman-7-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                   | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                                 | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-39  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)oxazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                                   | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |
| 1-40  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyridin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                        | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-41  | tert-butyl (2-(5-(3-(methyl((4-methylthiazol-2-yl)methyl)carbamoyl)phenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate                                     | +                                                                        |                                                                                               | +                                                                                   |                                                                             |
| 1-42  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-methyl-1H-pyrrol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone             | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |
| 1-43  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide                               | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-44  | (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone  | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-45  | (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                           | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-46  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)piperidin-1-yl)methanone                                    | ++                                                                       |                                                                                               | +                                                                                   |                                                                             |
| 1-47  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-48  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-isopropyl-N-((4-methylthiazol-2-yl)methyl)benzamide                                           | +                                                                        |                                                                                               | N.I.                                                                                |                                                                             |
| 1-49  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)oxazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |
| 1-50  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((5-methyl-1,2,4-oxadiazol-3-yl)methyl)benzamide                                     | +                                                                        |                                                                                               | N.I.                                                                                |                                                                             |
| 1-51  | (2-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(dimethylamino)pyridin-4-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone           | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-52  | 3-[5-(1-Amino-2-phenylcyclohexyl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate                                 |                                                                          | +                                                                                             |                                                                                     |                                                                             |

| Ref # | Compound Structure                                                                                                                                          | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-53  | rel-3-{5-[(1R,2R)-1-Amino-2-phenylcyclopropyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide 4-methylbenzenesulfonate       |                                                                          | +                                                                                             |                                                                                     |                                                                             |
| 1-54  | rel-3-{5-[(1R,2S)-1-Amino-2-phenylcyclopropyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide 4-methylbenzenesulfonate (1:1) |                                                                          | +                                                                                             |                                                                                     |                                                                             |
| 1-55  | 3-(5-(2-Amino-1-methoxy-3-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide oxalate                               |                                                                          | +                                                                                             |                                                                                     |                                                                             |
| 1-56  | (3-(5-(rel-(1S,2R)-1-Amino-2-phenylcyclobutyl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide) hydrochloride                      |                                                                          | +                                                                                             |                                                                                     |                                                                             |
| 1-57  | 3-{5-[rel-(1R,2R)-1-Amino-2-phenylcyclobutyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methylthiazol-2-yl)methyl]benzamide                                      |                                                                          | +                                                                                             |                                                                                     |                                                                             |
| 1-58  | 3-{5-[(4E)-2-Amino-1,5-diphenylpent-4-en-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1)             |                                                                          | +                                                                                             |                                                                                     |                                                                             |
| 1-59  | 3-[5-(2-Amino-1,5-diphenylpentan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1)                     |                                                                          | +                                                                                             |                                                                                     |                                                                             |

| Ref # | Compound Structure                                                                                                                              | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-60  | 3-[5-(2-Amino-1,3-diphenylpropan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1)         |                                                                          | +                                                                                             |                                                                                     |                                                                             |
| 1-61  | rel-3-{5-[(1R,2R)-1-Amino-2-phenylcyclopentyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide ethanedioate (1:1) |                                                                          | +                                                                                             |                                                                                     |                                                                             |
| 1-62  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(oxazol-2-yl)-N-(pyrazin-2-ylmethyl)benzamide                           | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |
| 1-63  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((2-methylthiazol-4-yl)methyl)-5-(oxazol-2-yl)benzamide                 | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-64  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((2-methyloxazol-4-yl)methyl)-5-(oxazol-2-yl)benzamide                  | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-65  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide                 | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-66  | 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((R)-1-(4-methylthiazol-2-yl)ethyl)-5-(oxazol-2-yl)benzamide                     | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                           | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-67  | (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide    | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-68  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((5-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide              | +                                                                        |                                                                                               | ++                                                                                  |                                                                             |
| 1-69  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methyloxazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide               | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-70  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide           | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-71  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-4-(4-methylthiazol-2-yl)oxazolidin-3-yl)methanone   | +                                                                        |                                                                                               | N.I.                                                                                |                                                                             |
| 1-72  | (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-73  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(pyrazin-2-yl)benzamide          | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                               | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 µM<br>'+++<br>1-5 µM<br>'++<br>>5 µM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-74  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyrazin-2-yl)benzamide                 | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-75  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)benzamide                         | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |
| 1-76  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(pyridin-2-yl)benzamide              | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-77  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chloro-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methylbenzamide                      | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-78  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone              | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-79  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorophenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |
| 1-80  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(tert-butyl)-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide            | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                       | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-81  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide                                   | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-82  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(fluoromethyl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +                                                                        |                                                                                               | N.I.                                                                                |                                                                             |
| 1-83  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyrazin-2-yl)benzamide                    | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-84  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(difluoromethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone            | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-85  | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclobutyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide                      | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-86  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone      | +++                                                                      |                                                                                               | N.I.                                                                                |                                                                             |
| 1-87  | 5-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-1,3,4-oxadiazol-2(3H)-one  | +++                                                                      |                                                                                               | +                                                                                   |                                                                             |



| Ref # | Compound Structure                                                                                                                               | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-88  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-fluoroethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone     | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-89  | 1-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)ethanone            | +++                                                                      |                                                                                               | +                                                                                   |                                                                             |
| 1-90  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone   | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |
| 1-91  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(isoxazol-5-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone     | +                                                                        |                                                                                               | +++                                                                                 |                                                                             |
| 1-92  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1,1-difluoroethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |
| 1-93  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(isoxazol-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone     | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-94  | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrazol-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone   | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                               | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-95  | 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzonitrile                                  | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-96  | 5-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-3-methyl-1,3,4-oxadiazol-2(3H)-one | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-97  | Ethyl 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzoate                                | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-98  | (3-(5-((R)-2-amino-1-cyclohexylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                                   | +                                                                        |                                                                                               | +                                                                                   |                                                                             |
| 1-99  | (3-(5-((R)-2-amino-1-cyclohexylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                   | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |
| 1-100 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(thiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                      | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-101 | 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide                            | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |

| Ref # | Compound Structure                                                                                                                                                 | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-102 | 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide                                       | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-103 | 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N,N-dimethyl-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide                          | +                                                                        |                                                                                               | N.I.                                                                                |                                                                             |
| 1-104 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(thiazol-2-yl)benzamide                                   | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-105 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(2-fluoroethyl)-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide                           | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-106 | 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-ethyl-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide                               | ++                                                                       |                                                                                               | N.I.                                                                                |                                                                             |
| 1-107 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(thiazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone           | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-108 | (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(thiazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                         | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 µM<br>'+++<br>1-5 µM<br>'++<br>>5 µM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-109 | 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzoic acid            | +++                                                                      |                                                                                               | N.I.                                                                                |                                                                             |
| 1-110 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-hydroxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone       | ++                                                                       |                                                                                               | +                                                                                   |                                                                             |
| 1-111 | (3-(5-((S)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((S)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +                                                                        |                                                                                               | +                                                                                   |                                                                             |
| 1-112 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((S)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +                                                                        |                                                                                               | +                                                                                   |                                                                             |
| 1-113 | (3-(5-((S)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | N.I.                                                                                |                                                                             |
| 1-114 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(dimethylamino)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide          | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-115 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(N-methylmethylsulfonamido)-N-((4-methylthiazol-2-yl)methyl)benzamide       | ++                                                                       |                                                                                               | +                                                                                   |                                                                             |

| Ref # | Compound Structure                                                                                                                                      | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-116 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4-methoxy-N-methylbenzamide                            | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-117 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                    | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-118 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone       | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-119 | (R)-5-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-6-methoxy-N-methylnicotinamide                         | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-120 | (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-methoxypyridin-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone              | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |
| 1-121 | (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-methoxypyridin-3-yl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-122 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-4-(trifluoromethoxy)benzamide                 | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                       | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-123 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-methyl-1H-imidazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +                                                                        |                                                                                               | ++                                                                                  |                                                                             |
| 1-124 | (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-[1,1'-biphenyl]-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-125 | (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-3'-methoxy-[1,1'-biphenyl]-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone     | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-126 | (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2'-methoxy-[1,1'-biphenyl]-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone     | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-127 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(furan-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-128 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-iodophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                        | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-129 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-ethyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide                           | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                             | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-130 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(trifluoromethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-131 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-nitrophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone             | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |
| 1-132 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(furan-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone      | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |
| 1-133 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrimidin-5-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone  | ++                                                                       |                                                                                               | +                                                                                   |                                                                             |
| 1-134 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyridin-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone    | ++                                                                       |                                                                                               | +++                                                                                 |                                                                             |
| 1-135 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(N-methylsulfamoyl)-N-((4-methylthiazol-2-yl)methyl)benzamide          | ++                                                                       |                                                                                               | +                                                                                   |                                                                             |
| 1-136 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyridin-2-yl)benzamide               | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                      | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-137 | (3-(5-((R)-2-amino-1-(2-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone   | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-138 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(2-methylthiazol-4-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone     | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-139 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(4,5-dimethylthiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-140 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((3-fluoropyridin-2-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide                         | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-141 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(oxazol-2-yl)-N-((4-(trifluoromethyl)thiazol-2-yl)methyl)benzamide              | ++                                                                       |                                                                                               | +                                                                                   |                                                                             |
| 1-142 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluoro-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide                                | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-143 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4-fluoro-N-methylbenzamide                             | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |



| Ref # | Compound Structure                                                                                                                                                                   | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-144 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                                                  | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-145 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone                                                   | ++                                                                       |                                                                                               |                                                                                     |                                                                             |
| 1-146 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                                     | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |
| 1-147 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((2,5-dimethyloxazol-4-yl)methyl)-4-fluorobenzamide                                                     | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-148 | (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-cyclopropylpyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)     | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-149 | 2-(6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)benzonitrile (2E)-but-2-enedioate (1:1) | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                                                                 | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-150 | [2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)             | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-151 | (2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)                       | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-152 | N-(6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-N-methylmethanesulfonamide (2E)-but-2-enedioate (1:1) | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |
| 1-153 | N-(4-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-N-methylmethanesulfonamide (2E)-but-2-enedioate (1:1) | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |
| 1-154 | (4-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-2-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)                       | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                                                              | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-155 | [2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2R)-2-(4-ethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)           | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |
| 1-156 | [2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2R)-2-(4-cyclopropyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)     | ++                                                                       | <u>++</u>                                                                                     |                                                                                     |                                                                             |
| 1-157 | [2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl]{(2R)-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}methanone (2E)-but-2-enedioate (1:1) | ++                                                                       | <u>++</u>                                                                                     |                                                                                     |                                                                             |
| 1-158 | (6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-2,3'-bipyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)                      | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-159 | (6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-2,4'-bipyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)                      | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-160 | [2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(pyrimidin-5-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)           | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                                                                      | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-161 | (2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methylpyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)                             | ++                                                                       | <u>++</u>                                                                                     |                                                                                     |                                                                             |
| 1-162 | [2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,1-dioxido-1,2-thiazolidin-2-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-163 | N-(6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)methanesulfonamide (2E)-but-2-enedioate (1:1)               | +                                                                        | ±                                                                                             |                                                                                     |                                                                             |
| 1-164 | (4-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-2-yl)[(2R)-2-(4,5-dimethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)                        | +                                                                        | ±                                                                                             |                                                                                     |                                                                             |
| 1-165 | [4-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-2-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)                  | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                                                               | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-166 | 1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)pyrrolidin-2-one (2E)-but-2-enedioate (1:1)          | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-167 | 3-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3-oxazolidin-2-one (2E)-but-2-enedioate (1:1)     | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-168 | 1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-5-methylpyrrolidin-2-one (2E)-but-2-enedioate (1:1) | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |
| 1-169 | 1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)piperidin-2-one (2E)-but-2-enedioate (1:1)           | ++                                                                       | <u>++</u>                                                                                     | ++                                                                                  |                                                                             |
| 1-170 | N-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-N-methylacetamide (2E)-but-2-enedioate (1:1)        | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                                                           | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-171 | 1-(4-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)pyrrolidin-2-one (2E)-but-2-enedioate (1:1)      | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |
| 1-172 | [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-1,2,4-triazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |
| 1-173 | [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-imidazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)      | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-174 | [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-pyrazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)       | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-175 | [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(2H-1,2,3-triazol-2-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                                                              | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-176 | [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-1,2,3-triazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)    | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-177 | [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-178 | [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) | +++                                                                      | <u>++</u>                                                                                     |                                                                                     |                                                                             |
| 1-179 | 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(4-bromo-1,3-thiazol-2-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)                       | +++                                                                      | <u>+++</u>                                                                                    |                                                                                     |                                                                             |
| 1-180 | 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(6-methylpyridin-3-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)                           |                                                                          |                                                                                               |                                                                                     |                                                                             |
| 1-181 | 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[1-(1-methyl-1H-pyrazol-3-yl)ethyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)                               | +                                                                        | ±                                                                                             |                                                                                     |                                                                             |

| Ref # | Compound Structure                                                                                                                                                            | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-182 | 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(6-methylpyridin-2-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)         | ++                                                                       | <u>++</u>                                                                                     |                                                                                     |                                                                             |
| 1-183 | 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(1-methyl-1H-pyrazol-4-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)     | +                                                                        | ±                                                                                             |                                                                                     |                                                                             |
| 1-184 | 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) |                                                                          |                                                                                               |                                                                                     |                                                                             |
| 1-185 | 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1) | +                                                                        | ±                                                                                             |                                                                                     |                                                                             |
| 1-186 | (2-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyridin-4-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                 | +++                                                                      | <u>+++</u>                                                                                    | ++                                                                                  |                                                                             |
| 1-187 | (2-amino-6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)    | ++                                                                       | <u>++</u>                                                                                     |                                                                                     |                                                                             |



| Ref # | Compound Structure                                                                                                                                                                     | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-188 | 2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(1-methyl-1H-pyrazol-3-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide (2E)-but-2-enedioate (1:1)              | ++                                                                       | <u>++</u>                                                                                     |                                                                                     |                                                                             |
| 1-189 | (6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-2-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone 2-hydroxypropane-1,2,3-tricarboxylate (1:1)    | +                                                                        | ±                                                                                             |                                                                                     |                                                                             |
| 1-190 | (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone 2-hydroxypropane-1,2,3-tricarboxylate (1:1)    | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |
| 1-191 | [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(pyrrolidin-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-192 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-4-[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one (2E)-but-2-enedioate (1:1)      | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                                                               | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-193 | [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(difluoromethoxy)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)           | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |
| 1-194 | 4-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-6-[[ (2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one (2E)-but-2-enedioate (1:1)              | ++                                                                       |                                                                                               |                                                                                     |                                                                             |
| 1-195 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-(cyclopropylmethyl)-4-[[ (2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one (2E)-but-2-enedioate (1:1) | +++                                                                      |                                                                                               |                                                                                     |                                                                             |
| 1-196 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-ethyl-4-[[ (2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one (2E)-but-2-enedioate (1:1)               | +                                                                        | <u>±</u>                                                                                      |                                                                                     |                                                                             |
| 1-197 | (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-ethoxypyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)                      | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |

| Ref # | Compound Structure                                                                                                                                                                                   | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-198 | (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2-methoxyethyl)amino]pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)         | ++                                                                       | <u>++</u>                                                                                     | +++                                                                                 |                                                                             |
| 1-199 | (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2-methoxyethyl)(methyl)amino]pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1) | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-200 | [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(ethylamino)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone (2E)-but-2-enedioate (1:1)                    | +++                                                                      | <u>+++</u>                                                                                    | +++                                                                                 |                                                                             |
| 1-201 | 3-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-5-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one (2E)-but-2-enedioate (1:1)                  |                                                                          |                                                                                               | ++                                                                                  |                                                                             |
| 1-202 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one (2E)-but-2-enedioate (1:1)                           | ++                                                                       | <u>++</u>                                                                                     |                                                                                     |                                                                             |
| 1-203 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-2-oxo-N-(pyridin-3-ylmethyl)-1,2-dihydropyridine-4-carboxamide                                                            |                                                                          | &                                                                                             |                                                                                     |                                                                             |

| Ref # | Compound Structure                                                                                                                                     | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-204 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-N-[(6-methylpyridin-2-yl)methyl]-2-oxo-1,2-dihydropyridine-4-carboxamide    |                                                                          | &                                                                                             |                                                                                     |                                                                             |
| 1-205 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-butyl-1-methyl-2-oxo-N-(pyridin-4-ylmethyl)-1,2-dihydropyridine-4-carboxamide          |                                                                          | &                                                                                             |                                                                                     |                                                                             |
| 1-206 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-4-{[2-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one |                                                                          | &&                                                                                            |                                                                                     |                                                                             |
| 1-207 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-butyl-1-methyl-2-oxo-N-(pyridin-3-ylmethyl)-1,2-dihydropyridine-4-carboxamide          |                                                                          | &&                                                                                            |                                                                                     |                                                                             |
| 1-208 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-2-oxo-N-(1H-pyrazol-5-ylmethyl)-1,2-dihydropyridine-4-carboxamide           |                                                                          | &&                                                                                            |                                                                                     |                                                                             |
| 1-209 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-2-oxo-N-[1-(2-thienyl)ethyl]-1,2-dihydropyridine-4-carboxamide              |                                                                          | &&                                                                                            |                                                                                     |                                                                             |

| Ref # | Compound Structure                                                                                                                                          | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-210 | 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(2,5-dimethyl-1,3-oxazol-4-yl)methyl]-N,1-dimethyl-2-oxo-1,2-dihydropyridine-4-carboxamide |                                                                          | <u>+++</u><br><br>&&&                                                                         |                                                                                     |                                                                             |
| 1-211 | (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide              | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-212 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-bromophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone                          | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-213 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-chlorophenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone            | +++                                                                      |                                                                                               | N.I.                                                                                |                                                                             |
| 1-214 | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide                             | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-215 | (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4,5-difluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone                      | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |

| Ref # | Compound Structure                                                                                                                               | BACE1<br>Ki *<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000<br>nM '+ | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM '+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>'+++<br>1-5 μM<br>'++<br>>5 μM '+ | Cathepsin<br>D Ki<br><500 nM<br>'+++<br>500-2000<br>nM '++<br>>2000nM<br>'+ |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1-216 | (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone     | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-217 | (R)-5-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-2,4-difluoro-N-methylbenzamide                  | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-218 | (R)-4-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-5-fluoro-N-methylpicolinamide                   | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |
| 1-219 | (R)-4-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-5-methoxy-N-methylpicolinamide                  | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-220 | (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide        | +++                                                                      |                                                                                               | +++                                                                                 |                                                                             |
| 1-221 | (3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-4,5-difluorophenyl)((S)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone | +++                                                                      |                                                                                               | ++                                                                                  |                                                                             |
| 1-222 | (5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2,4-difluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone           | ++                                                                       |                                                                                               | ++                                                                                  |                                                                             |

N.I. = no inhibition of Aβ observed using the cellular assay described in Example 5.

\* measured using assay conditions described in Example 3.1;

\*\* Entries with plusses (+) without underlining were measured using assay conditions described in Example 3.2. Entries with plusses (+) and with underlining were measured using assay conditions described in Example 3.3. Entries with ampersands (&) were measuring using assay conditions described in Example 3.4, where & = % inhibition from 26-50%, && = % inhibition from 51-75%, and &&& = % inhibition from 76-100+%.

TABLE 2: Compound Assay data – Supplemental Compounds.

| Ref # | Compound Structure                                                                                                                             | BACE1<br>Ki<br><400 nM<br>+++<br>400-2000<br>nM ++<br>>2000<br>nM + | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM<br>'+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>+++<br>1-5 μM<br>++<br>>5 μM + | Cathepsi<br>n D Ki<br><500 nM<br>+++<br>500-2000<br>nM ++<br>>2000<br>nM + |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 2-1   | 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((R)-1-(4-fluorophenyl)ethyl)-5-(N-methylmethylsulfonamido)benzamide            | ++                                                                  |                                                                                                  |                                                                                  |                                                                            |
| 2-2   | (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)-N,N-dipropylbenzamide                                             | ++                                                                  |                                                                                                  | ++                                                                               |                                                                            |
| 2-3   | 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)-N-((R)-1-phenylethyl)benzamide                                    | +                                                                   |                                                                                                  | N.I.                                                                             |                                                                            |
| 2-4   | ((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)(3-(pyrazin-2-yl)-5-(5-((S)-pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)methanone                | +                                                                   |                                                                                                  | N.I.                                                                             |                                                                            |
| 2-5   | ((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)(3-(pyrazin-2-yl)-5-(5-((R)-pyrrolidin-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)methanone                | +                                                                   |                                                                                                  | N.I.                                                                             |                                                                            |
| 2-6   | 3'-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5'-(2-(5-methylfuran-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carbonitrile | ++                                                                  |                                                                                                  | N.I.                                                                             |                                                                            |

| Ref # | Compound Structure                                                                                                               | BACE1<br>Ki<br><400 nM<br>+++<br>400-2000<br>nM ++<br>>2000<br>nM + | BACE1<br>Enzyme<br>IC <sub>50</sub> **<br><400 nM<br>'+++<br>400-2000<br>nM '++<br>>2000nM<br>'+ | BACE1<br>Cellular<br>IC <sub>50</sub><br><1 μM<br>+++<br>1-5 μM<br>++<br>>5 μM + | Cathepsi<br>n D Ki<br><500 nM<br>+++<br>500-2000<br>nM ++<br>>2000<br>nM + |
|-------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 2-7   | (R)-2-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-(3-methylbenzyl)-6-(oxazol-2-yl)isonicotinamide fumarate | ++                                                                  | <u>++</u>                                                                                        |                                                                                  |                                                                            |

N.I. = no inhibition of Aβ observed using the cellular assay described in Example 5.

\*\* Entries with plusses (+) and with underlining were measured using assay conditions described in Example 3.3.

#### Example 4: Inhibition of Memapsin 1 Beta-Secretase Activity and Cathepsin D Activity

##### *Inhibition of Memapsin 1 Activity*

[1128] Recombinant memapsin 1 (R&D Systems) is assayed for activity and inhibition by compounds using the same procedure outlined in Example 3 above.

##### *Inhibition of Cathepsin D Activity*

[1129] A fluorogenic FRET peptide substrate for cathepsin D activity (Mca-Gly-Lys-Pro-Ile-Leu-Phe-Phe-Arg-Leu-Lys(Dnp)-D-Arg-NH<sub>2</sub>), catalog number M-2455, Bachem) (SEQ ID NO.: 1) was dissolved at 75 μM in DMSO. Cathepsin D protein was obtained from rat liver homogenates. Briefly, rat livers were homogenized in PBS. The extract was acidified to pH 4 with 2 M sodium acetate, pH 4 and allowed to incubate at 4 °C overnight. Following addition of Triton X-100 to a final concentration of 1%, the extract was centrifuged at 25,000 xg and stirred overnight with pepstatin A immobilized on agarose beads (Sigma-Aldrich). Following wash with sodium acetate/1% Triton X-100 pH 4, pepstatin-A-immobilized cathepsin D was eluted with an addition of 0.1 M Tris-HCl pH 8.5. Eluent was immediately adjusted to pH 5 with 2 M sodium acetate. Assay of cathepsin D activity vs. cathepsin D substrate was performed at pH 4, 37 °C, using the same assay procedure for Memapsin 2 activity and Ki outlined in Example 3 above, in presence and absence of compound. For example, the cathepsin D Ki determined using this procedure for (7-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)chroman-5-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone is about 411 nM.



## Example 5: Cellular A $\beta$ IC<sub>50</sub> Determinations

### Example 5.1

**[1130]** The potency of compounds against intracellular memapsin 2 activity was determined in a cellular assay of A $\beta$  production. Compounds that successfully penetrate the cell membrane demonstrated their ability to inhibit intracellular memapsin 2 activity by blocking the production of A $\beta$  detected following secretion into the culture medium. Human neuroblastoma cell line SK-N-BE(2) (ATCC number CRL-2271) was seeded in 96-well plates at 10,000 cells/well in complete medium [MEM+F12 (1:1 ratio) + 1% pen/strep + 10% fetal bovine serum] and incubated at 37 °C/5% CO<sub>2</sub> for 24h. Compounds are diluted to 50  $\mu$ M in DMSO, then further diluted to a final concentration range of between 1  $\mu$ M – 0.00002  $\mu$ M into serum-limited culture medium [MEM+F12 (1:1 ratio) + 1% pen/strep + 5% fetal bovine serum] at a final DMSO concentration of 0.2%. Following a 24 hour incubation at 37 °C/5% CO<sub>2</sub>, a portion (100  $\mu$ l) of conditioned media was removed for analysis of A $\beta$ <sub>40</sub> using a sandwich ELISA (Invitrogen). The amount of A $\beta$ <sub>40</sub> over the range of concentration of compounds, expressed relative to control incubations without compound, was fit to a 4-paramter IC<sub>50</sub> model. Results are provided in Table 1 above (“Cellular IC<sub>50</sub>”). For example, the cellular A $\beta$  IC<sub>50</sub> determined using this procedure for (7-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)chroman-5-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone is about 1.5  $\mu$ M. In additional examples, 3'-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5'-(2-(5-methylfuran-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carbonitrile showed no inhibition, 3'-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5'-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carbonitrile is about 432 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide is about 23 nM, (2-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(oxazol-2-yl)pyridin-4-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone fumarate is about 75 nM, (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide is about 40 nM, (2-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone fumarate is about 90 nM, (R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide is about 50 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-

yl)methyl)-5-(oxazol-2-yl)benzamide is about 56 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((2,5-dimethyloxazol-4-yl)methyl)-4-fluorobenzamide is about 20 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide is about 78 nM, (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone is about 21 nM, (R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide is about 22 nM, and (3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone is about 30 nM.

#### *Example 5.2*

**[1131]** The potency of compounds against BACE1 activity was determined in a cellular assay of Abeta production. Human SK-N-BE(2) neuroblastoma cells were plated at 96,000 cells/well/100μL in 96-well plates in RPMI1640/10%FBS/penicilin-streptomycin and cultured for 24 hours at 37°C, 5% CO<sub>2</sub>. Test compounds were dissolved and diluted into Me<sub>2</sub>SO and further diluted into RPMI1640 /5%FBS /penicilin-streptomycin (yielding a final Me<sub>2</sub>SO concentration of 0.5%). The culture media in 96-well plates were replaced by 125 μL/well of the media containing test compounds. After incubation for 6 hours at 37°C, 5% CO<sub>2</sub>, 50 μL media were transferred into a fresh 96-well plate and used for Abeta40 assay by an ELISA kit (#27718, Immuno-Biological Laboratories, Japan). Cell viability was measured after removal of 50μL media for the Abeta assay by CellTiter-Glo™ Luminescent Cell Viability Assay (#7571, Promega). CellTiter-Glo Substrate was dissolved into CellTiter-Glo Buffer and added to the plates in 75μL/well. After 2 minutes shaking the plates, the whole sample was transferred into a white 96-well plate and luminescence was measured for ATP quantification as the cell viability. Abeta concentration measured by ELISA was normalized by the viability of the corresponding cells.

#### **Example 6: Determination of CYP3A4 Inhibition**

**[1132]** To evaluate the drug-drug interaction potential for compounds, the potency to inhibit the major metabolic cytochrome CYP450 isoform 3A4 is assessed. The inhibition constant K<sub>i</sub> is determined for inhibition of the metabolism of midazolam, a CYP3A4 substrate.

### *Assay Procedure*

[1133] CYP3A4  $K_i$  assays are performed following a recently published protocol with slight modifications (Di, L., Kerns, E.H., Li, S.Q., and Carter, G.T. (2007) Comparison of cytochrome P450 inhibition assays for drug discovery using human liver microsomes with LC-MS, rhCYP450 isozymes with fluorescence, and double cocktail with LC-MS.

International Journal of Pharmaceutics 335: 1-11). The P450 inhibition assay is performed in 96-well plates at 37.2 °C in a shaking incubator. The compounds are diluted from 5 mM stocks in 100% DMSO and incubated at seven final concentrations from 0.078 to 10  $\mu$ M (0.1% DMSO in each final incubation), with human liver microsomes (HLM) at a final protein concentration of 0.1 mg/mL protein and a substrate (midazolam) concentration ranging from 1.25 to 10 mM.

[1134] The assay is standardized for both phosphate buffer (100 mM, pH 7.4) and the NADPH regenerating system ( $MgCl_2$ , 3.3 mM; G6P, 3.3 mM; G6PD, 1 U/mL; NADP<sup>+</sup>, 1.3 mM). Eight replicate control samples (0.1% DMSO, no compound) are prepared. Assays (200  $\mu$ L) are set up by mixing HLM+substrate stock, 10 mL of test article in 2% DMSO, and the substrate before initiating the reaction with the addition of the regenerating system mixture. Reactions are quenched following incubation for 20, 30 and 40 minutes as described following.

### *Reaction Quench and MS-Prep*

[1135] After incubation for the specified time in a humidified shaking incubator, 20 mL of the reaction mixture is removed and the reactions are terminated by adding 200  $\mu$ L of cold acetonitrile. Samples are centrifuged at 1000  $\times g$  for 15 minutes in Solvinert filter plate. The receptor plate is dried via speed vacuum at 40 °C. The sample is reconstituted with a reconstitution buffer composed of 10% acetonitrile, 10% DMSO, 90% H<sub>2</sub>O with an internal standard added at a concentration of 100 ng/mL. MS-Analysis is completed using LC-MS/MS. Formation of 1'-hydroxymidazolam is measured by monitoring a specific SRM (342>203) transition for the CYP3A4 metabolite.

### *Determination of $K_i$*

[1136] Data are expressed as the quantity of midazolam metabolite relative to control incubations. Initial velocities are obtained by multiplying the relative quantity by the initial substrate concentration and dividing by the incubation duration. Data are transformed to inverse of initial velocity and expressed vs. inhibitor concentration [I] for determination of  $K_i$

by the Dixon method (Dixon, M. (1953) Biochemical Journal 55: 170-171) using where intercept  $[I] = -K_i$  is determined at multiple substrate concentrations.

### **Example 7: *In Vivo* Tests**

#### *Example 7.1 Abeta 40 reduction in rats*

##### *Formulation*

[1137] Test compounds were prepared in a vehicle of 35% HP $\beta$ CD in H<sub>2</sub>O. The test compound was formulated the same day as oral dosing. Dose and concentration were based on the free base equivalent. Sonication was used where required to facilitate the formulation.

##### *Test species*

[1138] Male Sprague-Dawley rats (200-400 grams) were obtained from Taconic Farms (Hudson, NY) and were given approximately one week of acclimation. Prior to oral dosing, animals were fasted overnight; and food returned 2 hours post administration. Water was made available *ad libitum* throughout the study. Animals were visually inspected for health before being included into the study group, and were randomly assigned to the treatment and control groups to achieve similar group mean body weights. Dosing was performed in the morning. The dosing solution (dose volume  $\leq 10$  mL/kg) was administered directly into the stomach using a 3-inch metallic rodent gavage needle. Control animals received oral administration of equivalent volume of the vehicle.

##### *Sampling methods*

[1139] Blood samples (volume  $\sim 150$   $\mu$ L) were collected from the saphenous vein. Alternatively, blood was sampled terminally by cardiocentesis (see Terminal Procedures below). Blood samples were collected into lithium-heparin tubes and placed on wet ice. Plasma was separated by centrifugation at 6,000 rpm (3,300 rcf) for 10 min at 4 °C and subsequently stored at -70 °C.

##### *Terminal Procedures*

[1140] At a fixed time post-dose (e.g., 3 h), animals were euthanized with excess of isoflurane. Blood was collected by cardiocentesis. CSF was carefully withdrawn from the cisterna magna using a 29 gauge needle after a quick dissection to expose the atlanto-occipital membrane. The CSF samples were centrifuged at 6000 rpm (3,300 rcf) for 10 min to confirm free of blood contamination and stored at -70 °C. Immediately following the CSF collection, brain hemispheres were harvested, dissected into segments (cortex, hippocampus, cerebellum), snap frozen in liquid nitrogen, and subsequently stored at -70 °C.

##### *Extraction of Brain Abeta*

[1141] Fragments of brain hemispheres (~100 mg) or hippocampus (from 1 hemisphere) were weighed while frozen. A 10-fold volume (w:v) of 0.2% diethylamine (DEA) containing 50 mM NaCl (pH 10) was added, followed by a 100-fold dilution (v:v) of Protease Inhibitor Cocktail 1 (containing AEBSF, aprotinin, E-64 protease inhibitor, EDTA, and leupeptin; catalog number 539131, Calbiochem). Brains were homogenized by sonication for 35 seconds on ice (level 10 of XL-2000 Microson cell disruptor) in microcentrifuge tube. Resulting homogenates were centrifuged at 14,000 xg for 30 min in a refrigerated benchtop centrifuge at 4 °C. Supernatants were collected and stored at -70 °C.

*Determination of Abeta*

[1142] Abeta40 in brain homogenates, plasma, and CSF were analyzed by ELISA (Human/Rat Abeta40 ELISA II, catalog number 294-64701, WAKO Chemicals, Inc., USA). Amount of Abeta40 reduction was determined by obtaining the mean concentration of Abeta40 from animals treated with test article divided by the mean Abeta40 from animals receiving vehicle alone (control group).

*Example 7.2 Cognitive function in mice*

*Animals:*

[1143] Tg2576 mice, hemizygous transgenic mice overexpressing human mutant APP (K670N/M671L) (Hsiao K, et al. Correlative memory deficits, Ab elevation, and amyloid plaques in transgenic mice. Science 1996;274:99-102) bred to normal C57BL6/SJL mice at the Charles River Japan (Atsugi, Japan). Studies were performed in Japan (including Tsukuba, Japan) using female Tg2576 mice and age-matched wild type (Wt) littermates. The mice were genotyped by PCR using DNA from tails.

*Drug treatment:*

[1144] A compound of the formula (I) was dissolved in distilled water and administered at a volume of 10 ml/kg orally. The compound of the formula (I) was administered 3 hours before the Y-maze or Morris water maze task in 6-month-old Tg2576.

*Y-maze test (YM):*

[1145] Working memory performance was examined by recording spontaneous alteration behavior in Y-maze test. Mice were placed at the end of one arm and the number of arm entries and alterations were counted for 8 minutes. Alteration was defined as entries into all three arms on consecutive occasions. Alteration rate (%) was calculated as follows:

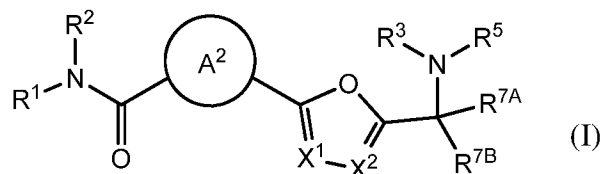
$$\text{Alteration rate (\%)} = (\text{Alterations} / \text{Total entries} - 2) \times 100$$

*Morris water maze task (MWM):*

[1146] Spatial memory was tested with the Morris water maze task, which consisted of three parts: visible platform training (day 1), hidden platform training (days 2-4), and probe trial (day 4). A circular pool (100 cm in diameter) was filled with opaque water at a temperature of  $21 \pm 1^\circ\text{C}$ , and a clear acrylic platform (9 cm in diameter) submerged 1.5 cm below the surface of the water was placed in the pool. The escape platform was kept in a constant position in the center of one of the four quadrants of the pool. During the visible platform training, the platform location was indicated by a marker rising above the water. In the first part of the test (visible), the ability of the mice to locate a visible platform was tested to exclude differences in vision and motivation with 4 trials. In the second part of the test (hidden), mice were trained to locate a hidden platform, each consisting of three consecutive trials (of 1 minute each) (designated H1-H3). When the mice found the platform, they were allowed to remain on it for 30 seconds. If the mice did not find the platform within 60 seconds, they were removed from the water and then placed on the platform for 30 seconds. In the third part of the test (probe), we examined whether the mice spent more time searching in the quadrant that used to contain the platform (target quadrant) than in the other quadrants of the pool (the platform was removed). This test was performed immediately after H6 and gave a putative measure for retention of spatial memory. Escape latency (the time to find the hidden platform) and time spent swimming in the target quadrant were recorded for each trial. The cumulative latencies of 3 days hidden platform trials were calculated in each treatment group.

## CLAIMS

1. A compound of the formula (I):



wherein

- $R^1$  is  $A^1-L^1$ - or taken together with  $R^2$  and the nitrogen to which they are attached form a 5- or 6-membered heterocycloalkyl ring substituted with  $A^1-L^1$ -,  $R^{6A}$  and  $R^{6B}$ ;
- $R^2$  is hydrogen,  $-N(R^8)R^9$ ,  $-S(O)_2R^{11}$ ,  $-C(O)R^{12}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or taken together with  $R^1$  and the nitrogen to which they are attached form a 5- or 6-membered heterocycloalkyl ring substituted with  $A^1-L^1$ -,  $R^{6A}$  and  $R^{6B}$ ;
- $A^1$  is an optionally substituted heteroaryl;
- $L^1$  is a bond,  $-N(R^{17})$ -,  $-S$ -,  $-S(O)$ -,  $-S(O)_2$ -, or an optionally substituted alkylene;
- $R^{6A}$  and  $R^{6B}$  are independently hydrogen, halogen,  $-OH$ ,  $-NO_2$ ,  $-N(R^8)R^9$ ,  $-OR^{10}$ ,  $-SH$ ,  $-SR^{11}$ ,  $-S(O)R^{11}$ ,  $-S(O)_2R^{11}$ ,  $-C(O)R^{12}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl,  $-alkyl-OR^{10}$ ,  $-alkyl-N(R^8)R^9$ , heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl;
- $A^2$  is an optionally substituted moiety selected from cycloalkylene, heterocycloalkylene, arylene and heteroarylene;
- $X^1$  and  $X^2$  are independently N or CH;
- $R^3$  is hydrogen,  $-N(R^8)R^9$ ,  $-S(O)_2R^{11}$ ,  $-C(O)R^{12}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

- $R^5$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl;
- $R^{7A}$  is an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, -alkyl-OR<sup>10</sup>, -alkyl-N(R<sup>8</sup>)R<sup>9</sup>, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl, or taken together with  $R^{7B}$  and the carbon to which they are attached form a cycloalkyl ring substituted with  $R^4-L^4$ ;
- $R^{7B}$  is  $R^4-L^4$  or taken together with  $R^{7A}$  and the carbon to which they are attached form a cycloalkyl ring substituted with  $R^4-L^4$ ;
- $R^4$  is hydrogen, halogen, -OH, -NO<sub>2</sub>, -N(R<sup>8</sup>)R<sup>9</sup>, -OR<sup>10</sup>, -SH, -SR<sup>11</sup>, -S(O)R<sup>11</sup>, -S(O)<sub>2</sub>R<sup>11</sup>, -C(O)R<sup>12</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, -alkyl-OR<sup>10</sup>, -alkyl-N(R<sup>8</sup>)R<sup>9</sup>, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl;
- $L^4$  is a bond or an optionally substituted alkylene;
- $R^8$  is independently hydrogen, -C(O)R<sup>13</sup>, -S(O)<sub>2</sub>R<sup>14</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;
- $R^9$  is independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;
- $R^{10}$  is independently -C(O)R<sup>13</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;
- $R^{11}$  is independently an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl, wherein if attached to S(O)<sub>2</sub>,  $R^{11}$  can also be -NR<sup>15</sup>R<sup>16</sup>;
- $R^{12}$  and  $R^{13}$  are each independently hydrogen, -N(R<sup>18</sup>)R<sup>19</sup>, -OR<sup>19</sup>, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-



alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^{14}$  is independently hydrogen,  $-N(R^{18})R^{19}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; and  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ , and  $R^{19}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

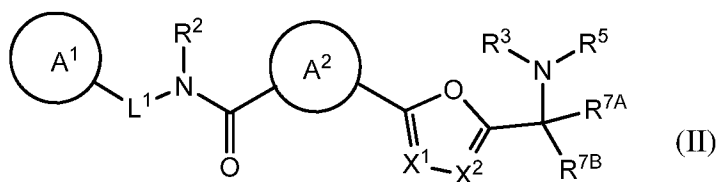
provided that when  $R^3$  and  $R^5$  are both hydrogen, one of  $R^{7A}$  and  $R^{7B}$  is methyl and the other is benzyl, each  $X^1$  and  $X^2$  is N,  $A^2$  is 5-substituted-1,3-phenylene and  $R^1$  is taken together with  $R^2$  and the nitrogen to which they are attached to form a 5-membered heterocycloalkyl ring, the 5-membered heterocycloalkyl ring formed by taking  $R^1$  together with  $R^2$  and the nitrogen to which they are attached is a moiety other than a 2-substituted-pyrrolidinyl substituted with 5-chlorofuran-2-yl, 5-methylfuran-2-yl, 3-pyridyl or 5-bromo-3-pyridyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, wherein  $A^1$  is an optionally substituted 5 to 7 membered heteroaryl; or a pharmaceutically acceptable salt or solvate thereof.
3. The compound of claim 2, wherein  $A^1$  is an optionally substituted 5-membered heteroaryl; or a pharmaceutically acceptable salt or solvate thereof.
4. The compound of claim 3, wherein  $A^1$  is an optionally substituted 5-membered heteroaryl comprising at least one ring nitrogen; or a pharmaceutically acceptable salt or solvate thereof.
5. The compound of any one of claim 1 or 2, wherein  $A^1$  is an optionally substituted moiety selected from the group consisting of pyrazolyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, thiophenyl, pyridyl, pyrimidyl, pyridazinyl, thiazolyl, triazolyl, thienyl, dihydrothieno-pyrazolyl, thianaphthenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, isoindolyl, acridinyl, benzisoxazolyl, pyrazinyl, pyrrolinyl, indolyl, and benzodiazepinyl; or a pharmaceutically acceptable salt or solvate thereof.

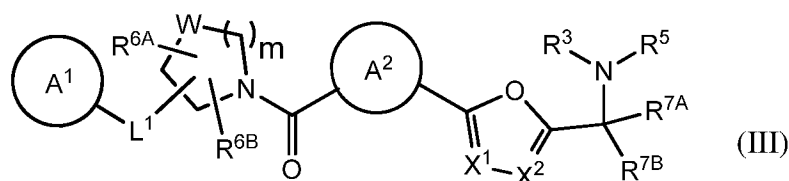
6. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted moiety selected from the group consisting of thiazolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, thiophenyl, pyridyl, pyrimidyl, oxadiazolyl, and pyranlyl; or a pharmaceutically acceptable salt or solvate thereof.
7. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted moiety selected from the group consisting thiazolyl, oxadiazolyl, and oxazolyl; or a pharmaceutically acceptable salt or solvate thereof.
8. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted thiazolyl; or a pharmaceutically acceptable salt or solvate thereof.
9. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted oxazolyl; or a pharmaceutically acceptable salt or solvate thereof.
10. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted oxadiazolyl; or a pharmaceutically acceptable salt or solvate thereof.
11. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted imidazolyl; or a pharmaceutically acceptable salt or solvate thereof.
12. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted pyrazolyl; or a pharmaceutically acceptable salt or solvate thereof.
13. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted isoxazolyl; or a pharmaceutically acceptable salt or solvate thereof.
14. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted thiophenyl; or a pharmaceutically acceptable salt or solvate thereof.
15. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted pyridyl; or a pharmaceutically acceptable salt or solvate thereof.
16. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted pyrazinyl; or a pharmaceutically acceptable salt or solvate thereof.
17. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted pyrimidyl; or a pharmaceutically acceptable salt or solvate thereof.
18. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted 2-thiazolyl; or a pharmaceutically acceptable salt or solvate thereof.
19. The compound of claim 5, wherein A<sup>1</sup> is an optionally substituted 2-oxazolyl; or a pharmaceutically acceptable salt or solvate thereof.
20. The compound of any one of claims 1-19, wherein L<sup>1</sup> is a bond, or an optionally substituted alkylene; or a pharmaceutically acceptable salt or solvate thereof.

21. The compound of claim 20, wherein  $L^1$  is a bond; or a pharmaceutically acceptable salt or solvate thereof.
22. The compound of claim 20, wherein  $L^1$  is an optionally substituted alkylene; or a pharmaceutically acceptable salt or solvate thereof.
23. The compound of claim 20, wherein  $L^1$  is an optionally substituted  $C_1$ - $C_6$  alkylene; or a pharmaceutically acceptable salt or solvate thereof.
24. The compound of claim 20, wherein  $L^1$  is optionally substituted methylene; or a pharmaceutically acceptable salt or solvate thereof.
25. The compound of claim 20, wherein  $L^1$  is methylmethylene; or a pharmaceutically acceptable salt or solvate thereof.
26. The compound of claim 20, wherein  $L^1$  is a  $C_1$ - $C_6$  alkylene; or a pharmaceutically acceptable salt or solvate thereof.
27. The compound of claim 20, wherein  $L^1$  is methylene; or a pharmaceutically acceptable salt or solvate thereof.
28. The compound of any one of claims 1-27, having the formula (II):



- or a pharmaceutically acceptable salt or solvate thereof.
29. The compound of any one of claims 1 to 28, wherein  $R^2$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; or a pharmaceutically acceptable salt or solvate thereof.
  30. The compound of claim 29, wherein  $R^2$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, and cycloalkyl-alkyl; or a pharmaceutically acceptable salt or solvate thereof.
  31. The compound of claim 29, wherein  $R^2$  is hydrogen or an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
  32. The compound of claim 29, wherein  $R^2$  is hydrogen or an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
  33. The compound of claim 29, wherein  $R^2$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.

34. The compound of claim 29, wherein  $R^2$  is an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
35. The compound of claim 29, wherein  $R^2$  is an optionally substituted  $C_1$ - $C_3$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
36. The compound of claim 29, wherein  $R^2$  is 2-fluoroethyl; or a pharmaceutically acceptable salt or solvate thereof.
37. The compound of claim 29, wherein  $R^2$  is an optionally substituted  $C_3$ - $C_6$  cycloalkyl; or a pharmaceutically acceptable salt or solvate thereof.
38. The compound of claim 29, wherein  $R^2$  is cyclopropyl; or a pharmaceutically acceptable salt or solvate thereof.
39. The compound of claim 29, wherein  $R^2$  is cyclobutyl; or a pharmaceutically acceptable salt or solvate thereof.
40. The compound of claim 29, wherein  $R^2$  is methyl; or a pharmaceutically acceptable salt or solvate thereof.
41. The compound of claim 29, wherein  $R^2$  is ethyl; or a pharmaceutically acceptable salt or solvate thereof.
42. The compound of claim 29, wherein  $R^2$  is butyl; or a pharmaceutically acceptable salt or solvate thereof.
43. The compound of any one of claims 1-27, having the formula (III):



wherein

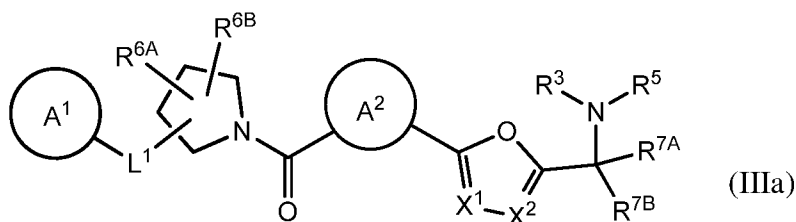
W is  $-\text{CH}_2-$ ,  $-\text{O}-$ ,  $-\text{N}(\text{R}^{17})-$ ,  $-\text{S}-$ ,  $-\text{S}(\text{O})-$ , or  $-\text{S}(\text{O})_2-$ , or where W is  $-\text{CH}-$  or  $-\text{N}-$ , and is substituted with  $\text{R}^{6A}$  or  $\text{R}^{6B}$ , or where W is  $-\text{C}-$ , and is substituted with  $\text{R}^{6A}$  and  $\text{R}^{6B}$ ; and

m is 1 or 2;

or a pharmaceutically acceptable salt or solvate thereof.

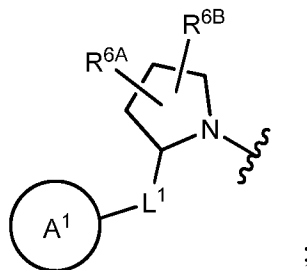
44. The compound of claim 43, wherein W is  $-\text{O}-$ ; or a pharmaceutically acceptable salt or solvate thereof.
45. The compound of claim 44, wherein m is 1; or a pharmaceutically acceptable salt or solvate thereof.

46. The compound of claim 43, wherein W is -S-, -S(O)-, or -S(O)<sub>2</sub>; or a pharmaceutically acceptable salt or solvate thereof.
47. The compound of claim 43, wherein W is -S-; or a pharmaceutically acceptable salt or solvate thereof.
48. The compound of claim 47, wherein m is 1; or a pharmaceutically acceptable salt or solvate thereof.
49. The compound of claim 43, wherein W is -N(R<sup>17</sup>)-; or a pharmaceutically acceptable salt or solvate thereof.
50. The compound of claim 43, wherein W is -CH<sub>2</sub>-; or a pharmaceutically acceptable salt or solvate thereof.
51. The compound of claim 50, wherein m is 1; or a pharmaceutically acceptable salt or solvate thereof.
52. The compound of claim 43, having the formula (IIIa):



or a pharmaceutically acceptable salt or solvate thereof.

53. The compound of claim 52, wherein the A<sup>1</sup>-L<sup>1</sup>- moiety is substituted on the pyrrolidine heterocycloalkyl ring according to the formula:

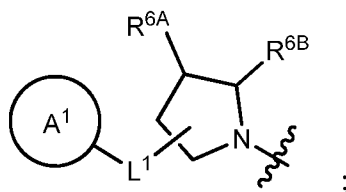


or a pharmaceutically acceptable salt or solvate thereof.

54. The compound of claim 53, wherein A<sup>1</sup> is an optionally substituted moiety selected from the group consisting of pyrazolyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, pyrimidyl, pyridazinyl, thiazolyl, triazolyl, thienyl, dihydrothieno-pyrazolyl, thianaphthenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl,

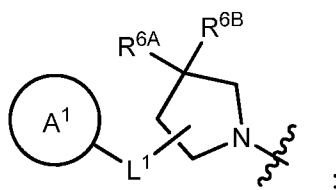
- isoquinolinyl, isoindolyl, acridinyl, benzisoxazolyl, pyrazinyl, pyrrolinyl, indolyl, and benzodiazepinyl; or a pharmaceutically acceptable salt or solvate thereof.
55. The compound of claim 53, wherein  $L^1$  is a bond;  $A^1$  is a substituted thiazolyl; or a pharmaceutically acceptable salt or solvate thereof.
56. The compound of claim 55, wherein  $A^1$  is 4-methylthiazol-2-yl; or a pharmaceutically acceptable salt or solvate thereof.
57. The compound of any one of claims 1 to 27 and 43 to 56, wherein  $R^{6A}$  and  $R^{6B}$  are independently hydrogen, halogen, -OH,  $-N(R^8)R^9$ ,  $-OR^{10}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; or a pharmaceutically acceptable salt or solvate thereof.
58. The compound of claim 57, wherein  $R^{6B}$  is hydrogen, or an optionally substituted moiety selected from aryl, aralkyl, heteroaryl, and heteroaralkyl; or a pharmaceutically acceptable salt or solvate thereof.
59. The compound of claim 57, wherein  $R^{6B}$  is hydrogen, halogen, an optionally substituted alkyl, or  $-OR^{10}$ ; or a pharmaceutically acceptable salt or solvate thereof.
60. The compound of claim 57, wherein  $R^{6B}$  is halogen; or a pharmaceutically acceptable salt or solvate thereof.
61. The compound of claim 60, wherein  $R^{6B}$  is fluoro; or a pharmaceutically acceptable salt or solvate thereof.
62. The compound of claim 57, wherein  $R^{6B}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
63. The compound of any of claims 58 to 62, wherein  $R^{6A}$  is hydrogen, halogen or an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
64. The compound of any of claims 58 to 62, wherein  $R^{6A}$  is hydrogen or halogen; or a pharmaceutically acceptable salt or solvate thereof.
65. The compound of any of claims 58 to 62, wherein  $R^{6A}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
66. The compound of any of claims 58 to 62, wherein  $R^{6A}$  is halogen; or a pharmaceutically acceptable salt or solvate thereof.
67. The compound of claim 66, wherein  $R^{6A}$  is fluoro; or a pharmaceutically acceptable salt or solvate thereof.

68. The compound of claim 57, wherein each  $R^{6A}$  and  $R^{6B}$  is fluoro; or a pharmaceutically acceptable salt or solvate thereof.
69. The compound of any one of claims 1 to 27 and 52 to 68, wherein  $R^{6A}$  and  $R^{6B}$  are substituted on the pyrrolidine heterocycloalkyl ring according to the formula:



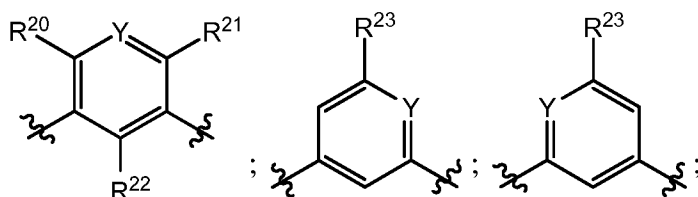
or a pharmaceutically acceptable salt or solvate thereof.

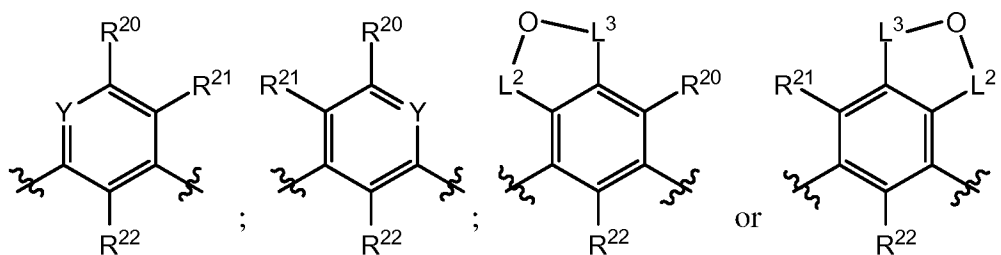
70. The compound of any one of claims 1 to 27 and 52 to 68, wherein  $R^{6A}$  and  $R^{6B}$  are substituted on the pyrrolidine heterocycloalkyl ring according to the formula:



or a pharmaceutically acceptable salt or solvate thereof.

71. The compound of any one of claims 1 to 70, wherein  $A^2$  is an optionally substituted arylene, an optionally substituted heteroarylene; or a pharmaceutically acceptable salt or solvate thereof.
72. The compound of claim 71, wherein  $A^2$  is an optionally substituted moiety selected from the group consisting of phenylene, pyridinylene, oxazolylene, thiazolylene, pyrazolylene, pyranylene, oxadiazolylene, imidazolylene, furanylene and pyridonylene; or a pharmaceutically acceptable salt or solvate thereof.
73. The compound of claim 71, wherein  $A^2$  has the formula:





wherein

$L^2$  and  $L^3$  are independently a bond or an optionally substituted  $C_1$ - $C_5$  alkylene;

$R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are independently hydrogen, halogen,  $-N(R^{24})R^{25}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

each  $R^{23}$  is independently hydrogen, halogen, cyano,  $-NO_2$ ,  $-N(R^{24})R^{25}$ ,  $-OR^{26}$ ,  $-SR^{27}$ ,  $-S(O)R^{27}$ ,  $-S(O)_2R^{27}$ , or  $-C(O)R^{28}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; and

$Y$  is  $-N=$  or  $-C(R^{23})=$ ;

wherein

$R^{24}$  and  $R^{25}$  are each independently hydrogen,  $-C(O)R^{29}$ , or  $-S(O)_2R^{30}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

$R^{29}$  is independently hydrogen,  $-N(R^{31})R^{32}$ , or  $-OR^{33}$ , an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

$R^{31}$ ,  $R^{32}$ , and  $R^{33}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; and



$R^{30}$  is independently an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^{26}$  is independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

$R^{27}$  is independently  $-N(R^{34})R^{35}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

$R^{34}$  and  $R^{35}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; and

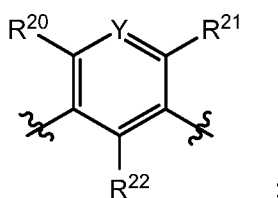
$R^{28}$  is independently  $-OR^{36}$ ,  $-N(R^{37})R^{38}$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

wherein

$R^{36}$ ,  $R^{37}$ , and  $R^{38}$  are each independently hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl;

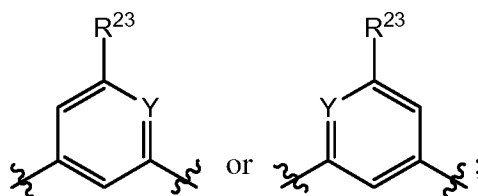
or a pharmaceutically acceptable salt or solvate thereof.

74. The compound of claim 73, wherein A2 has the formula:



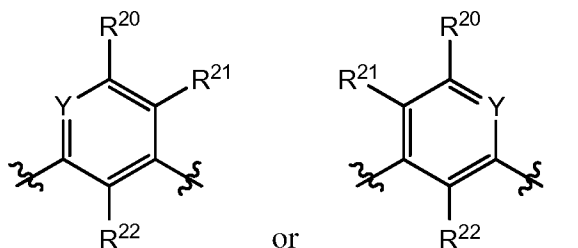
or a pharmaceutically acceptable salt or solvate thereof.

75. The compound of claim 73, wherein A2 has the formula:



or a pharmaceutically acceptable salt or solvate thereof.

76. The compound of claim 73, wherein  $A^2$  has the formula:

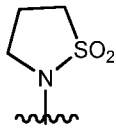
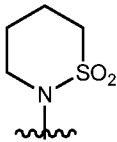


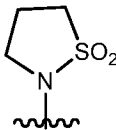
or a pharmaceutically acceptable salt or solvate thereof.

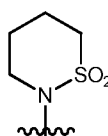
77. The compound of any one of claims 73 to 76, wherein  $Y$  is  $-C(R^{23})=$ ; or a pharmaceutically acceptable salt or solvate thereof.
78. The compound of any one of claims 73 to 76, wherein  $Y$  is  $-N=$ ; or a pharmaceutically acceptable salt or solvate thereof.
79. The compound of any one of claims 73 to 77, wherein  $R^{23}$  is hydrogen, halogen,  $-N(R^{24})R^{25}$ ,  $-OR^{26}$ ,  $-SR^{27}$ ,  $-S(O)R^{27}$ ,  $-S(O)_2R^{27}$ ,  $-C(O)R^{28}$ , or an optionally substituted heterocycloalkyl; or a pharmaceutically acceptable salt or solvate thereof.
80. The compound of claim 79, wherein  $R^{23}$  is cyano or  $-NO_2$ , or a pharmaceutically acceptable salt or solvate thereof.
81. The compound of claim 79, wherein  $R^{23}$  is hydrogen, halogen,  $-N(R^{24})R^{25}$ , or an optionally substituted heterocycloalkyl; or a pharmaceutically acceptable salt or solvate thereof.
82. The compound of claim 81, wherein  $R^{23}$  is halogen, or a pharmaceutically acceptable salt or solvate thereof.
83. The compound of claim 81, wherein  $R^{23}$  is hydrogen or  $-N(R^{24})R^{25}$ ; or a pharmaceutically acceptable salt or solvate thereof.
84. The compound of claim 83, wherein  $R^{23}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
85. The compound of claim 83, wherein  $R^{23}$  is  $-N(R^{24})R^{25}$ ; or a pharmaceutically acceptable salt or solvate thereof.

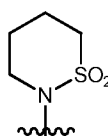
86. The compound of claim 85, wherein  $R^{23}$  is -N(alkyl)alkylsulfonamido; or a pharmaceutically acceptable salt or solvate thereof.
87. The compound of claim 86, wherein  $R^{23}$  is -N-methyl-methanesulfonamido; or a pharmaceutically acceptable salt or solvate thereof.
88. The compound of claim 79, wherein  $R^{23}$  is  $-OR^{26}$ ; or a pharmaceutically acceptable salt or solvate thereof.
89. The compound of claim 88, wherein  $R^{26}$  is hydrogen or optionally substituted alkyl, or a pharmaceutically acceptable salt or solvate thereof.
90. The compound of claim 89, wherein  $R^{26}$  is optionally substituted alkyl, or a pharmaceutically acceptable salt or solvate thereof.
91. The compound of claim 90, wherein  $R^{26}$  is difluoromethyl or trifluoromethyl, or a pharmaceutically acceptable salt or solvate thereof.
92. The compound of claim 90, wherein  $R^{26}$  is methyl or ethyl, or a pharmaceutically acceptable salt or solvate thereof.
93. The compound of claim 79, wherein  $R^{23}$  is  $-SR^{27}$ ,  $-S(O)R^{27}$  or  $-S(O)_2R^{27}$ ; or a pharmaceutically acceptable salt or solvate thereof.
94. The compound of claim 79, wherein  $R^{23}$  is  $-C(O)R^{28}$ ; or a pharmaceutically acceptable salt or solvate thereof.
95. The compound of claim 94, wherein  $R^{28}$  is  $-OR^{36}$ , or a pharmaceutically acceptable salt or solvate thereof.
96. The compound of claim 95, wherein  $R^{36}$  is  $C_1$ - $C_6$  alkyl, or a pharmaceutically acceptable salt or solvate thereof.
97. The compound of claim 94, wherein  $R^{28}$  is  $-N(R^{37})R^{38}$ , or a pharmaceutically acceptable salt or solvate thereof.
98. The compound of claim 97, wherein each  $R^{37}$  and  $R^{38}$  is independently hydrogen or methyl, or a pharmaceutically acceptable salt or solvate thereof.
99. The compound of any one of claims 73 to 77, wherein  $R^{23}$  is hydrogen, an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; or a pharmaceutically acceptable salt or solvate thereof.
100. The compound of claim 99, wherein  $R^{23}$  is an optionally substituted moiety selected from alkyl, cycloalkyl, and heterocycloalkyl; or a pharmaceutically acceptable salt or solvate thereof.

101. The compound of claim 99, wherein  $R^{23}$  is an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
102. The compound of claim 99, wherein  $R^{23}$  is an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
103. The compound of claim 99, wherein  $R^{23}$  is  $C_1$ - $C_6$  alkyl substituted with one or more halogen; or a pharmaceutically acceptable salt or solvate thereof.
104. The compound of claim 103, wherein  $R^{23}$  is selected from the group consisting of fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl and 2,2,2-trifluoroethyl; or a pharmaceutically acceptable salt or solvate thereof.
105. The compound of claim 99, wherein  $R^{23}$  is methyl; or a pharmaceutically acceptable salt or solvate thereof.
106. The compound of claim 99, wherein  $R^{23}$  is an optionally substituted cycloalkyl; or a pharmaceutically acceptable salt or solvate thereof.
107. The compound of claim 106, wherein  $R^{23}$  is cyclopropyl, or a pharmaceutically acceptable salt or solvate thereof.
108. The compound of claim 99, wherein  $R^{23}$  is an optionally substituted heterocycloalkyl; or a pharmaceutically acceptable salt or solvate thereof.
109. The compound of any one of claims 79, 81, 99, 100 or 108, wherein the optionally substituted heterocycloalkyl is an optionally substituted cyclic sulfonamido; or a pharmaceutically acceptable salt or solvate thereof.
110. The compound of claim 109, wherein the optionally substituted cyclic sulfonamido is

an optionally substituted  or ; or a pharmaceutically acceptable salt or solvate thereof.

111. The compound of claim 109, wherein  $R^{23}$  is ; or a pharmaceutically acceptable salt or solvate thereof.



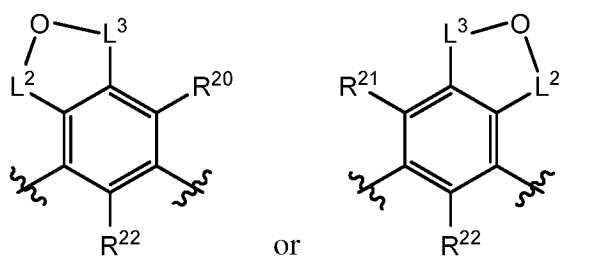
112. The compound of claim 109, wherein R<sup>23</sup> is ; or a pharmaceutically acceptable salt or solvate thereof.
113. The compound of claim 109, wherein R<sup>23</sup> is optionally substituted pyrrolidinyl, or a pharmaceutically acceptable salt or solvate thereof.
114. The compound of claim 113, wherein R<sup>23</sup> is 2-oxopyrrolidin-1-yl, or a pharmaceutically acceptable salt or solvate thereof.
115. The compound of claim 109, wherein R<sup>23</sup> is optionally substituted piperidinyl, or a pharmaceutically acceptable salt or solvate thereof.
116. The compound of claim 115, wherein R<sup>23</sup> is 2-oxopiperidin-1-yl, or a pharmaceutically acceptable salt or solvate thereof.
117. The compound of claim 109, wherein R<sup>23</sup> is oxazolidinyl, or a pharmaceutically acceptable salt or solvate thereof.
118. The compound of claim 117, wherein R<sup>23</sup> is 2-oxo-3-oxazolidinyl, or a pharmaceutically acceptable salt or solvate thereof.
119. The compound of any one of claims 73 to 77, wherein R<sup>23</sup> is an optionally substituted moiety selected from cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; or a pharmaceutically acceptable salt or solvate thereof.
120. The compound of claim 119, wherein R<sup>23</sup> is an optionally substituted moiety selected from aryl, aralkyl, heteroaryl, and heteroaralkyl; or a pharmaceutically acceptable salt or solvate thereof.
121. The compound of claim 119, wherein R<sup>23</sup> is an optionally substituted moiety selected from aryl and heteroaryl; or a pharmaceutically acceptable salt or solvate thereof.
122. The compound of claim 119, wherein R<sup>23</sup> is an optionally substituted aryl; or a pharmaceutically acceptable salt or solvate thereof.
123. The compound of claim 119, wherein R<sup>23</sup> is an optionally substituted heteroaryl; or a pharmaceutically acceptable salt or solvate thereof.
124. The compound of claim 119, wherein R<sup>23</sup> is an optionally substituted moiety selected from pyridyl, phenyl, thiazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, triazolyl, isoxazolyl, pyrimidyl, pyranyl, pyrazinyl, and furanyl; or a pharmaceutically acceptable salt or solvate thereof.

125. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted moiety selected from thiazolyl, oxadiazolyl, oxazolyl, imidazolyl, pyrazolyl, pyridyl and pyrazinyl; or a pharmaceutically acceptable salt or solvate thereof.
126. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted phenyl; or a pharmaceutically acceptable salt or solvate thereof.
127. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted pyridyl; or a pharmaceutically acceptable salt or solvate thereof.
128. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted thiazolyl; or a pharmaceutically acceptable salt or solvate thereof.
129. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted oxazolyl; or a pharmaceutically acceptable salt or solvate thereof.
130. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted oxadiazolyl; or a pharmaceutically acceptable salt or solvate thereof.
131. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted imidazolyl; or a pharmaceutically acceptable salt or solvate thereof.
132. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted pyrazolyl; or a pharmaceutically acceptable salt or solvate thereof.
133. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted isoxazolyl; or a pharmaceutically acceptable salt or solvate thereof.
134. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted pyrimidyl; or a pharmaceutically acceptable salt or solvate thereof.
135. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted pyrazinyl; or a pharmaceutically acceptable salt or solvate thereof.
136. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted furanyl; or a pharmaceutically acceptable salt or solvate thereof.
137. The compound of claim 124, wherein R<sup>23</sup> is an optionally substituted triazolyl; or a pharmaceutically acceptable salt or solvate thereof.
138. The compound of claim 137, wherein R<sup>23</sup> is an optionally substituted 1,2,3-triazolyl; or a pharmaceutically acceptable salt or solvate thereof.
139. The compound of claim 137, wherein R<sup>23</sup> is an optionally substituted 1,2,4-triazolyl; or a pharmaceutically acceptable salt or solvate thereof.
140. The compound of claim 128, wherein R<sup>23</sup> is an optionally substituted 2-thiazolyl; or a pharmaceutically acceptable salt or solvate thereof.

141. The compound of claim 129, wherein  $R^{23}$  is an optionally substituted 2-oxazolyl; or a pharmaceutically acceptable salt or solvate thereof.
142. The compound of claim 129, wherein  $R^{23}$  is an optionally substituted 5-oxazolyl; or a pharmaceutically acceptable salt or solvate thereof.
143. The compound of claim 135, wherein  $R^{23}$  is an optionally substituted 2-pyrazinyl; or a pharmaceutically acceptable salt or solvate thereof.
144. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein  $R^{24}$  and  $R^{25}$  are independently hydrogen, or an optionally substituted moiety selected from alkyl and heteroalkyl; or a pharmaceutically acceptable salt or solvate thereof.
145. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein  $R^{24}$  and  $R^{25}$  are independently hydrogen, or an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
146. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein at least one of  $R^{24}$  and  $R^{25}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
147. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein  $R^{24}$  and  $R^{25}$  are hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
148. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein at least one of  $R^{24}$  and  $R^{25}$  is an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
149. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein  $R^{24}$  and  $R^{25}$  are independently an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
150. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein at least one of  $R^{24}$  and  $R^{25}$  is methyl; or a pharmaceutically acceptable salt or solvate thereof.
151. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein  $R^{24}$  and  $R^{25}$  are independently hydrogen, an optionally substituted alkyl,  $-C(O)R^{29}$ , or  $-S(O)_2R^{30}$ ; or a pharmaceutically acceptable salt or solvate thereof.
152. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein one of  $R^{24}$  and  $R^{25}$  is  $-C(O)R^{29}$  or  $-S(O)_2R^{30}$ ; or a pharmaceutically acceptable salt or solvate thereof.
153. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein one of  $R^{24}$  and  $R^{25}$  is  $-C(O)R^{29}$ ; or a pharmaceutically acceptable salt or solvate thereof.
154. The compound of any one of claims 73 to 77, 79 to 83 and 85, wherein one of  $R^{24}$  and  $R^{25}$  is  $-S(O)_2R^{30}$ ; or a pharmaceutically acceptable salt or solvate thereof.

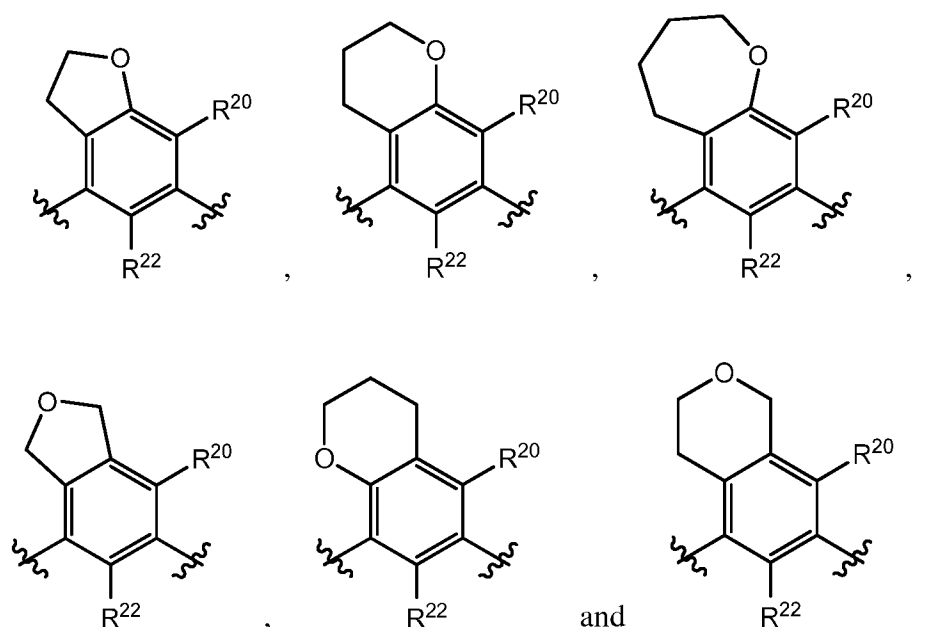
155. The compound of any one of claims 73 to 77, 79 to 83, 85 and 151 to 153, wherein  $R^{29}$  is independently hydrogen, an optionally substituted alkyl,  $-N(R^{31})R^{32}$ , or  $-OR^{33}$ ; or a pharmaceutically acceptable salt or solvate thereof.
156. The compound of any one of claims 73 to 77, 79 to 83, 85 and 151 to 153, wherein  $R^{29}$  is independently hydrogen, or an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
157. The compound of any one of claims 73 to 77, 79 to 83, 85 and 151 to 153, wherein  $R^{29}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
158. The compound of any one of claims 73 to 77, 79 to 83, 85 and 151 to 153, wherein  $R^{29}$  is an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
159. The compound of any one of claims 73 to 77, 79 to 83, 85 and 151 to 153, wherein  $R^{29}$  is methyl; or a pharmaceutically acceptable salt or solvate thereof.
160. The compound of any one of claims 73 to 77, 79 to 83, 85 and 151 to 153, wherein  $R^{29}$  is independently  $-N(R^{31})R^{32}$ , or  $-OR^{33}$ ; or a pharmaceutically acceptable salt or solvate thereof.
161. The compound of any one of claims 73 to 77, 79 to 83, 85 and 151 to 153, wherein  $R^{29}$  is  $-N(R^{31})R^{32}$ ; or a pharmaceutically acceptable salt or solvate thereof.
162. The compound of any one of claims 73 to 77, 79 to 83, 85 and 151 to 153, wherein  $R^{29}$  is  $-OR^{33}$ ; or a pharmaceutically acceptable salt or solvate thereof.
163. The compound of any one of claims 73 to 77, 79 to 83, 85, 151 to 153, 155 and 160 to 162, wherein  $R^{31}$ ,  $R^{32}$ , and  $R^{33}$  are independently hydrogen, or an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
164. The compound of any one of claims 73 to 77, 79 to 83, 85, 151, 152 and 154, wherein  $R^{30}$  is an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
165. The compound of any one of claims 73 to 77, 79 to 83, 85, 151, 152 and 154, wherein  $R^{30}$  is methyl; or a pharmaceutically acceptable salt or solvate thereof.
166. The compound of claim 73, wherein  $A^2$  has the formula:





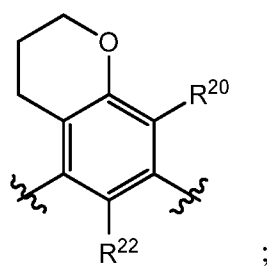
- or a pharmaceutically acceptable salt or solvate thereof.
167. The compound of claim 166, wherein  $L^2$  is an optionally substituted  $C_2$ - $C_5$  alkylene; and  $L^3$  is a bond; or a pharmaceutically acceptable salt or solvate thereof.
168. The compound of claim 166, wherein  $L^2$  is a bond; and  $L^3$  is an optionally substituted  $C_2$ - $C_5$  alkylene; or a pharmaceutically acceptable salt or solvate thereof.
169. The compound of claim 166, wherein  $L^2$  and  $L^3$  are independently an optionally substituted  $C_1$ - $C_2$  alkylene; or a pharmaceutically acceptable salt or solvate thereof.
170. The compound of claim 166, wherein  $L^2$  is an optionally substituted  $C_1$ - $C_4$  alkylene; and  $L^3$  is an optionally substituted methylene; or a pharmaceutically acceptable salt or solvate thereof.
171. The compound of claim 166, wherein  $L^2$  is an optionally substituted  $C_2$ - $C_4$  alkylene; and  $L^3$  is a bond or an optionally substituted methylene; or a pharmaceutically acceptable salt or solvate thereof.
172. The compound of any one of claims 73 to 171, wherein  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are independently hydrogen, or an optionally substituted  $C_1$ - $C_{10}$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
173. The compound of any one of claims 73 to 171, wherein  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are independently hydrogen, or an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
174. The compound of any one of claims 73 to 171, wherein at least one of  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
175. The compound of any one of claims 73 to 171, wherein  $R^{20}$ ,  $R^{21}$ , and  $R^{22}$  are hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
176. The compound of any one of claims 73 to 171, wherein at least one of  $R^{20}$ ,  $R^{21}$  and  $R^{22}$  is  $-N(R^{24})R^{25}$ ; or a pharmaceutically acceptable salt or solvate thereof.
177. The compound of any one of claims 73 to 171, wherein  $R^{20}$  is  $-N(R^{24})R^{25}$ ; or a pharmaceutically acceptable salt or solvate thereof.

178. The compound of any one of claims 73 to 171, wherein  $R^{21}$  is  $-N(R^{24})R^{25}$ ; or a pharmaceutically acceptable salt or solvate thereof.
179. The compound of any one of claims 73 to 171, wherein  $R^{22}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
180. The compound of any one of claims 73 to 171, wherein  $R^{22}$  is hydrogen and  $R^{20}$  and  $R^{21}$  are independently hydrogen, or an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
181. The compound of any one of claims 73 to 171, wherein  $R^{22}$  is hydrogen and  $R^{20}$  and  $R^{21}$  are independently hydrogen or methyl; or a pharmaceutically acceptable salt or solvate thereof.
182. The compound of any one of claims 73 to 171, wherein  $R^{22}$  is hydrogen and one of  $R^{20}$  and  $R^{21}$  is methyl; or a pharmaceutically acceptable salt or solvate thereof.
183. The compound of claim 166, wherein  $A^2$  is a moiety selected from the group consisting of



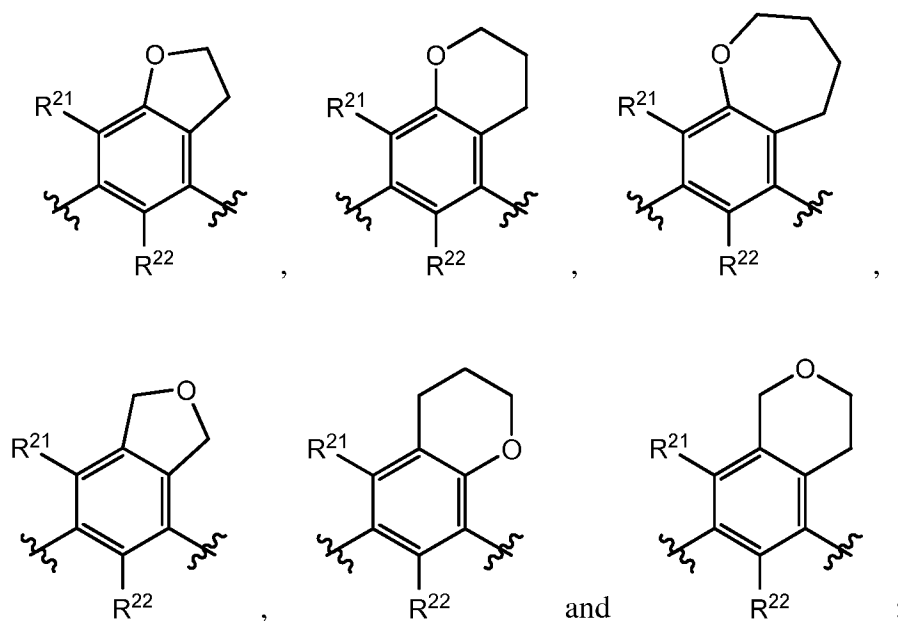
or a pharmaceutically acceptable salt or solvate thereof.

184. The compound of claim 166, wherein  $A^2$  is a moiety of the formula



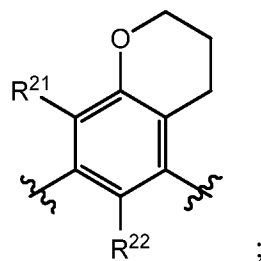
or a pharmaceutically acceptable salt or solvate thereof.

185. The compound of claim 183 or 184, wherein  $R^{20}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
186. The compound of claim 166, wherein  $A^2$  is a moiety selected from the group consisting of



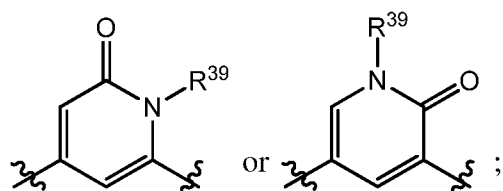
or a pharmaceutically acceptable salt or solvate thereof.

187. The compound of claim 166, wherein  $A^2$  is a moiety of the formula



or a pharmaceutically acceptable salt or solvate thereof.

188. The compound of claim 186 or 187, wherein  $R^{21}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
189. The compound of any one of claims 73 to 188, wherein  $R^{22}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
190. The compound of any one of claims 73 to 188, wherein  $R^{22}$  is  $-N(R^{24})R^{25}$ ; or a pharmaceutically acceptable salt or solvate thereof.
191. The compound of claim 71, wherein  $A^2$  has the formula:

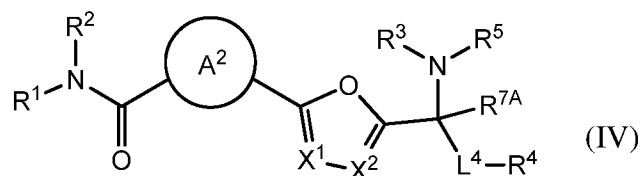


- wherein each  $R^{39}$  is independently hydrogen or an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
192. The compound of claim 191, wherein  $R^{39}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
193. The compound of claim 191, wherein  $R^{39}$  is optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
194. The compound of claim 191, wherein  $R^{39}$  is  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
195. The compound of claim 194, wherein  $R^{39}$  is methyl or ethyl; or a pharmaceutically acceptable salt or solvate thereof.
196. The compound of any one of claims 1 to 195, wherein  $X^1$  is N; or a pharmaceutically acceptable salt or solvate thereof.
197. The compound of any one of claims 1 to 195, wherein  $X^2$  is N; or a pharmaceutically acceptable salt or solvate thereof.
198. The compound of any one of claims 1 to 195, wherein both  $X^1$  and  $X^2$  are N; or a pharmaceutically acceptable salt or solvate thereof.
199. The compound of any one of claims 1 to 195, wherein both  $X^1$  and  $X^2$  are CH; or a pharmaceutically acceptable salt or solvate thereof.
200. The compound of any one of claims 1 to 195, wherein  $X^1$  is N and  $X^2$  is CH; or a pharmaceutically acceptable salt or solvate thereof.
201. The compound of any one of claims 1 to 195, wherein  $X^1$  is CH and  $X^2$  is N; or a pharmaceutically acceptable salt or solvate thereof.

202. The compound of any one of claims 1 to 201, wherein  $R^3$  is  $-N(R^8)R^9$ ,  $-S(O)_2R^{11}$  or  $-C(O)R^{12}$ ; or a pharmaceutically acceptable salt or solvate thereof.
203. The compound of any one of claims 1 to 201, wherein  $R^3$  is hydrogen,  $-C(O)Bu$ , or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl; or a pharmaceutically acceptable salt or solvate thereof.
204. The compound of claim 202, wherein  $R^3$  is  $-C(O)R^{12}$ ; or a pharmaceutically acceptable salt or solvate thereof.
205. The compound of claim 204, wherein  $R^{12}$  is an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
206. The compound of any one of claims 1 to 201, wherein  $R^3$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; or a pharmaceutically acceptable salt or solvate thereof.
207. The compound of claim 206, wherein  $R^3$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, and cycloalkyl-alkyl; or a pharmaceutically acceptable salt or solvate thereof.
208. The compound of claim 206, wherein  $R^3$  is hydrogen or an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
209. The compound of claim 206, wherein  $R^3$  is hydrogen or an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
210. The compound of claim 206, wherein  $R^3$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
211. The compound of claim 206, wherein  $R^3$  is an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
212. The compound of claim 206, wherein  $R^3$  is methyl; or a pharmaceutically acceptable salt or solvate thereof.
213. The compound of any one of claims 1 to 212, wherein  $R^4$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
214. The compound of any one of claims 1 to 212, wherein  $R^4$  is an optionally substituted moiety selected from alkyl and heteroalkyl; or a pharmaceutically acceptable salt or solvate thereof.

215. The compound of any one of claims 1 to 212, wherein  $R^4$  is an optionally substituted moiety selected from cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; or a pharmaceutically acceptable salt or solvate thereof.
216. The compound of claim 215, wherein  $R^4$  is an optionally substituted moiety selected from cycloalkyl and heterocycloalkyl; or a pharmaceutically acceptable salt or solvate thereof.
217. The compound of claim 215, wherein  $R^4$  is an optionally substituted moiety selected from aryl and heteroaryl; or a pharmaceutically acceptable salt or solvate thereof.
218. The compound of claim 215, wherein  $R^4$  is an optionally substituted aryl; or a pharmaceutically acceptable salt or solvate thereof.
219. The compound of claim 215, wherein  $R^4$  is an optionally substituted heteroaryl; or a pharmaceutically acceptable salt or solvate thereof.
220. The compound of claim 218, wherein  $R^4$  is phenyl; or a pharmaceutically acceptable salt or solvate thereof.
221. The compound of claim 218, wherein  $R^4$  is phenyl, optionally substituted with one or more halogens; or a pharmaceutically acceptable salt or solvate thereof.
222. The compound of claim 221, wherein  $R^4$  is 3,5-difluorophenyl; or a pharmaceutically acceptable salt or solvate thereof.
223. The compound of claim 221, wherein  $R^4$  is 4-fluorophenyl; or a pharmaceutically acceptable salt or solvate thereof.
224. The compound of claim 221, wherein  $R^4$  is 3-fluorophenyl; or a pharmaceutically acceptable salt or solvate thereof.
225. The compound of any one of claims 1 to 224, wherein  $L^4$  is a bond, or an optionally substituted alkylene; or a pharmaceutically acceptable salt or solvate thereof.
226. The compound of claim 225, wherein  $L^4$  is a bond; or a pharmaceutically acceptable salt or solvate thereof.
227. The compound of claim 225, wherein  $L^4$  is an optionally substituted alkylene; or a pharmaceutically acceptable salt or solvate thereof.
228. The compound of claim 225, wherein  $L^4$  is an optionally substituted  $C_1$ - $C_6$  alkylene; or a pharmaceutically acceptable salt or solvate thereof.
229. The compound of claim 225, wherein  $L^4$  is a  $C_1$ - $C_6$  alkylene; or a pharmaceutically acceptable salt or solvate thereof.

230. The compound of claim 225, wherein  $L^4$  is methylene; or a pharmaceutically acceptable salt or solvate thereof.
231. The compound of any one of claims 1 to 230, wherein  $R^5$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl, and heteroaralkyl; or a pharmaceutically acceptable salt or solvate thereof.
232. The compound of claim 231, wherein  $R^5$  is hydrogen, or an optionally substituted moiety selected from alkyl, cycloalkyl, and cycloalkyl-alkyl; or a pharmaceutically acceptable salt or solvate thereof.
233. The compound of claim 231, wherein  $R^5$  is hydrogen or an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
234. The compound of claim 231, wherein  $R^5$  is hydrogen or an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
235. The compound of claim 231, wherein  $R^5$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
236. The compound of claim 231, wherein  $R^5$  is an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
237. The compound of claim 231, wherein  $R^5$  is methyl; or a pharmaceutically acceptable salt or solvate thereof.
238. The compound of any one of claims 1-237, having the formula (IV):



- or a pharmaceutically acceptable salt or solvate thereof.
239. The compound of claim 238, wherein  $R^{7A}$  is an optionally substituted moiety selected from alkyl, cycloalkyl, cycloalkyl-alkyl, -alkyl-OR<sup>10</sup>, -alkyl-N(R<sup>8</sup>)R<sup>9</sup>, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl; or a pharmaceutically acceptable salt or solvate thereof.
240. The compound of claim 239, wherein  $R^{7A}$  is an optionally substituted moiety selected from alkyl, cycloalkyl and cycloalkyl-alkyl; or a pharmaceutically acceptable salt or solvate thereof.

241. The compound of claim 239, wherein  $R^{7A}$  is an optionally substituted alkyl; or a pharmaceutically acceptable salt or solvate thereof.
242. The compound of claim 239, wherein  $R^{7A}$  is an optionally substituted  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt or solvate thereof.
243. The compound of claim 239, wherein  $R^{7A}$  is methyl; or a pharmaceutically acceptable salt or solvate thereof.
244. The compound of claim 239, wherein  $R^{7A}$  is an optionally substituted moiety selected from -alkyl-OR<sup>10</sup> and -alkyl-N(R<sup>8</sup>)R<sup>9</sup>; or a pharmaceutically acceptable salt or solvate thereof.
245. The compound of claim 239, wherein  $R^{7A}$  is an optionally substituted -alkyl-OR<sup>10</sup>; or a pharmaceutically acceptable salt or solvate thereof.
246. The compound of claim 245, wherein  $R^{7A}$  is  $-CH_2OCH_3$ ; or a pharmaceutically acceptable salt or solvate thereof.
247. The compound of claim 239, wherein  $R^{7A}$  is an optionally substituted moiety selected from heterocycloalkyl, heterocycloalkyl-alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl; or a pharmaceutically acceptable salt or solvate thereof.
248. The compound of claim 239, wherein  $R^{7A}$  is an optionally substituted aralkyl; or a pharmaceutically acceptable salt or solvate thereof.
249. The compound of claim 239, wherein  $R^{7A}$  is an optionally substituted -alkylene-phenyl; or a pharmaceutically acceptable salt or solvate thereof.
250. The compound of claim 249, wherein  $R^{7A}$  is benzyl or 3-phenylpropyl; or a pharmaceutically acceptable salt or solvate thereof.
251. The compound of claim 239, wherein  $R^{7A}$  is an optionally substituted moiety selected from phenyl, pyrazolyl, furanyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, pyridyl, pyrimidyl, pyridazinyl, thiazolyl, triazolyl, thienyl, dihydrothienopyrazolyl, thianaphthenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, isoindolyl, acridinyl, benzisoxazolyl, dimethylhydantoin, pyrazinyl, tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, morpholinyl, indolyl, diazepinyl, azepinyl, thiepinyl, piperidinyl, and oxepinyl; or a pharmaceutically acceptable salt or solvate thereof.
252. The compound of claim 239, wherein  $R^{7A}$  is an optionally substituted moiety selected from pyridyl, phenyl, thiazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl,



isoxazolyl, pyrimidyl, pyrazinyl and furanyl; or a pharmaceutically acceptable salt or solvate thereof.

253. The compound of claim 239, wherein R<sup>7A</sup> is an optionally substituted moiety selected from pyridyl and imidazolyl; or a pharmaceutically acceptable salt or solvate thereof.
254. The compound of claim 1, wherein the compound is selected from the group consisting of:

tert-Butyl (2-(5-(3-(methyl((4-methylthiazol-2-yl)methyl)carbamoyl)phenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyridin-3-yl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methylphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-methyl-5-(5-((R)-2-(methylamino)-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

N-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-N-methylmethanesulfonamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(fluoromethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-chlorophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

1-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)pyrrolidin-2-one;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(dimethylamino)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(4-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(dimethylamino)pyridin-2-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methoxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

3'-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5'-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)-[1,1'-biphenyl]-2-carbonitrile;

(7-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)chroman-5-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrrol-1-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2-hydroxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-4,4-difluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(N-methylmethylsulfonamido)-N-((4-methylthiazol-2-yl)methyl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopentyl-N-((4-methylthiazol-2-yl)methyl)benzamide;

(4-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-imidazol-1-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-5-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-methylphenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)pyridin-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-(fluoromethyl)thiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-imidazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)chroman-7-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)oxazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyridin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

tert-butyl (2-(5-(3-(methyl((4-methylthiazol-2-yl)methyl)carbamoyl)phenyl)-1,3,4-oxadiazol-2-yl)-1-phenylpropan-2-yl)carbamate;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-methyl-1H-pyrrol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

(3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)piperidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-isopropyl-N-((4-methylthiazol-2-yl)methyl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)oxazol-2-yl)-5-(oxazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((5-methyl-1,2,4-oxadiazol-3-yl)methyl)benzamide;

(2-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(dimethylamino)pyridin-4-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

3-[5-(1-Amino-2-phenylcyclohexyl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide;

rel-3-{5-[(1R,2R)-1-Amino-2-phenylcyclopropyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide;

rel-3-{5-[(1R,2S)-1-Amino-2-phenylcyclopropyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide;

3-(5-(2-Amino-1-methoxy-3-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide;

3-(5-(rel-(1S,2R)-1-Amino-2-phenylcyclobutyl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide;

3-(5-(rel-(1R,2R)-1-Amino-2-phenylcyclobutyl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide;

3-{5-[(4E)-2-Amino-1,5-diphenylpent-4-en-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide;

3-[5-(2-Amino-1,5-diphenylpentan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide;

3-[5-(2-Amino-1,3-diphenylpropan-2-yl)-1,3,4-oxadiazol-2-yl]-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide;

rel-3-{5-[(1R,2R)-1-Amino-2-phenylcyclopentyl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(4-methyl-1,3-thiazol-2-yl)methyl]benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(oxazol-2-yl)-N-(pyrazin-2-ylmethyl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((2-methylthiazol-4-yl)methyl)-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((2-methyloxazol-4-yl)methyl)-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((R)-1-(4-methylthiazol-2-yl)ethyl)-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((5-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methyloxazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-4-(4-methylthiazol-2-yl)oxazolidin-3-yl)methanone;

(R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(pyrazin-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyrazin-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(pyridin-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chloro-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methylbenzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-chlorophenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(tert-butyl)-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(fluoromethyl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyrazin-2-yl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(difluoromethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclobutyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

5-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-1,3,4-oxadiazol-2(3H)-one;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-fluoroethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

1-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)ethanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrazol-1-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(isoxazol-5-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1,1-difluoroethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(isoxazol-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1H-pyrazol-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzonitrile;

5-(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)phenyl)-3-methyl-1,3,4-oxadiazol-2(3H)-one;

Ethyl 3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzoate;

(3-(5-((R)-2-amino-1-cyclohexylpropan-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-cyclohexylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(thiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide;

3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide;

3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N,N-dimethyl-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(thiazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-(2-fluoroethyl)-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-ethyl-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(thiazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(thiazol-2-yl)phenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-((R)-2-(4-methylthiazol-2-yl)pyrrolidine-1-carbonyl)benzoic acid;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-hydroxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((S)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((S)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((S)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((S)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(dimethylamino)-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(N-methylmethylsulfonamido)-N-((4-methylthiazol-2-yl)methyl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4-methoxy-N-methylbenzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-5-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-6-methoxy-N-methylnicotinamide;

(5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-methoxypyridin-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-methoxypyridin-3-yl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-4-(trifluoromethoxy)benzamide;



(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(1-methyl-1H-imidazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-[1,1'-biphenyl]-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-3'-methoxy-[1,1'-biphenyl]-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2'-methoxy-[1,1'-biphenyl]-3-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(furan-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-iodophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-ethyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(trifluoromethyl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-nitrophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(furan-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrimidin-5-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyridin-3-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(N-methylsulfamoyl)-N-((4-methylthiazol-2-yl)methyl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(pyridin-2-yl)benzamide;

(3-(5-((R)-2-amino-1-(2-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(pyrazin-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(2-methylthiazol-4-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(4,5-dimethylthiazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((3-fluoropyridin-2-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-5-(oxazol-2-yl)-N-((4-(trifluoromethyl)thiazol-2-yl)methyl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluoro-N-methyl-N-((4-methylthiazol-2-yl)methyl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4-fluoro-N-methylbenzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((2,5-dimethyloxazol-4-yl)methyl)-4-fluorobenzamide;

(2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-cyclopropylpyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

2-(6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)benzonitrile;

[2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

(2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

N-(6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-N-methylmethanesulfonamide;

N-(4-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-N-methylmethanesulfonamide;

(4-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-2-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2R)-2-(4-ethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl][(2R)-2-(4-cyclopropyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-4-yl]{(2R)-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}methanone;

(6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-2,3'-bipyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

(6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-2,4'-bipyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(pyrimidin-5-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

(2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methylpyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,1-dioxido-1,2-thiazolidin-2-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

N-(6-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)methanesulfonamide;

(4-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-methoxypyridin-2-yl)[(2R)-2-(4,5-dimethyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[4-{5-[(2R)-2-Amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1,3-oxazol-2-yl)pyridin-2-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)pyrrolidin-2-one;

3-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-1,3-oxazolidin-2-one;

1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[[{(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]-5-methylpyrrolidin-2-one;

1-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[[{(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]piperidin-2-one;

N-(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-[[{(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl)-N-methylacetamide;

1-(4-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[[{(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2-yl]pyrrolidin-2-one;

[2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-1,2,4-triazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-imidazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-pyrazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(2H-1,2,3-triazol-2-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1H-1,2,3-triazol-1-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(4-bromo-1,3-thiazol-2-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide;

2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(6-methylpyridin-3-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide;

2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[1-(1-methyl-1H-pyrazol-3-yl)ethyl]-6-(1,3-oxazol-2-yl)isonicotinamide;

2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(6-methylpyridin-2-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide;

2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(1-methyl-1H-pyrazol-4-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide;

2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide;

2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-N-methyl-6-(1,3-oxazol-2-yl)isonicotinamide;

2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(1-methyl-1H-pyrazol-3-yl)pyridin-4-yl}[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

(2-amino-6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-4-yl}[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-methyl-N-[(1-methyl-1H-pyrazol-3-yl)methyl]-6-(1,3-oxazol-2-yl)isonicotinamide;

(6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-2-yl}[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

(2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}pyridin-4-yl}[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

[2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(pyrrolidin-1-yl)pyridin-4-yl}[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one];

[2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-(difluoromethoxy)pyridin-4-yl}[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;

4-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-6-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one];

6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-(cyclopropylmethyl)-4-[[[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl]pyridin-2(1H)-one];

6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-ethyl-4-  
 {[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one;  
 (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-  
 ethoxypyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]methanone;  
 (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2-  
 methoxyethyl)amino]pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-  
 yl]methanone;  
 (2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-[(2-  
 methoxyethyl)(methyl)amino]pyridin-4-yl)[(2R)-2-(4-methyl-1,3-thiazol-2-  
 yl)pyrrolidin-1-yl]methanone;  
 [2-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-6-  
 (ethylamino)pyridin-4-yl][(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-  
 yl]methanone;  
 3-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-5-  
 {[(2R)-2-(4-methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one;  
 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-4-{[(2R)-2-(4-  
 methyl-1,3-thiazol-2-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one;  
 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-2-  
 oxo-N-(pyridin-3-ylmethyl)-1,2-dihydropyridine-4-carboxamide;  
 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-N-  
 [(6-methylpyridin-2-yl)methyl]-2-oxo-1,2-dihydropyridine-4-carboxamide;  
 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-butyl-1-  
 methyl-2-oxo-N-(pyridin-4-ylmethyl)-1,2-dihydropyridine-4-carboxamide;  
 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-1-methyl-4-{[2-  
 (3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl]carbonyl}pyridin-2(1H)-one;  
 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-butyl-1-  
 methyl-2-oxo-N-(pyridin-3-ylmethyl)-1,2-dihydropyridine-4-carboxamide;  
 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-2-  
 oxo-N-(1H-pyrazol-5-ylmethyl)-1,2-dihydropyridine-4-carboxamide;  
 6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N,1-dimethyl-2-  
 oxo-N-[1-(2-thienyl)ethyl]-1,2-dihydropyridine-4-carboxamide;

6-{5-[(2R)-2-amino-1-phenylpropan-2-yl]-1,3,4-oxadiazol-2-yl}-N-[(2,5-dimethyl-1,3-oxazol-4-yl)methyl]-N,1-dimethyl-2-oxo-1,2-dihydropyridine-4-carboxamide;

(R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-bromophenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-chlorophenyl)((2R,4S)-4-fluoro-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide;

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-4,5-difluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-5-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-2,4-difluoro-N-methylbenzamide;

(R)-4-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-5-fluoro-N-methylpicolinamide;

(R)-4-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-5-methoxy-N-methylpicolinamide;

(R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide;

(3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-4,5-difluorophenyl)((S)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone; and

(5-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-2,4-difluorophenyl)((R)-2-(4-methyloxazol-2-yl)pyrrolidin-1-yl)methanone;

or a pharmaceutically acceptable salt or solvate thereof.

255. The compound of claim 1, wherein the compound is selected from the group consisting of:

(3-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(3-(5-((R)-2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-5-(oxazol-2-yl)phenyl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(pyrazin-2-yl)benzamide;

(2-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(oxazol-2-yl)pyridin-4-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-N-methyl-5-(oxazol-2-yl)benzamide;

(2-(5-((R)-2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)((R)-2-(4-methylthiazol-2-yl)pyrrolidin-1-yl)methanone;

(R)-3-(5-(2-amino-1-(4-fluorophenyl)propan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

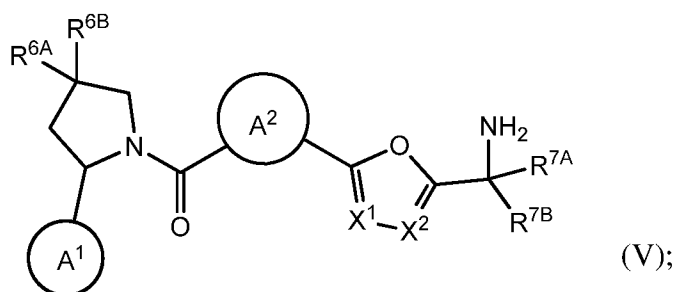
(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-methyl-N-((4-methylthiazol-2-yl)methyl)-5-(oxazol-2-yl)benzamide;

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-cyclopropyl-N-((2,5-dimethyloxazol-4-yl)methyl)-4-fluorobenzamide; and

(R)-3-(5-(2-amino-1-phenylpropan-2-yl)-1,3,4-oxadiazol-2-yl)-N-((2,5-dimethyloxazol-4-yl)methyl)-4,5-difluoro-N-methylbenzamide;

or a pharmaceutically acceptable salt or solvate thereof.

256. A compound of the formula (V):

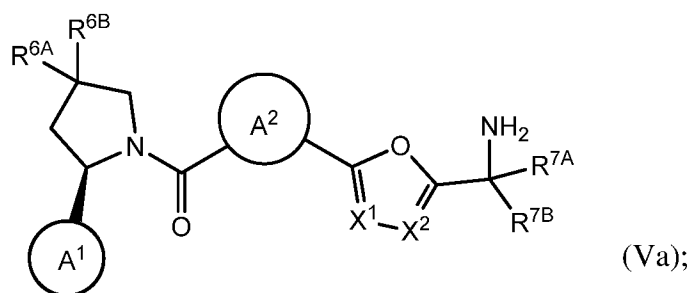


wherein  $A^1$ ,  $A^2$ ,  $X^1$ ,  $X^2$ ,  $R^{6A}$ ,  $R^{6B}$ ,  $R^{7A}$  and  $R^{7B}$  are as defined in any one of the preceeding claims, where applicable;

or a pharmaceutically acceptable salt or solvate thereof.

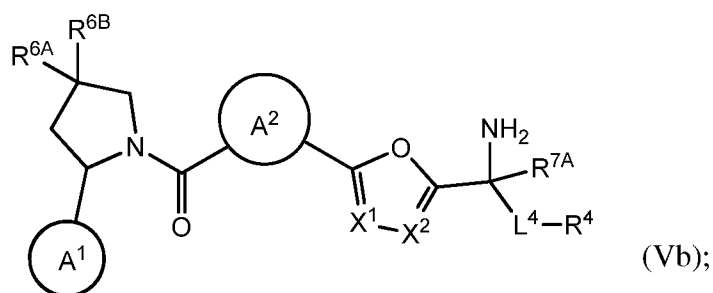
257. The compound of claim 256, wherein the compound is of the formula (Va):





or a pharmaceutically acceptable salt or solvate thereof.

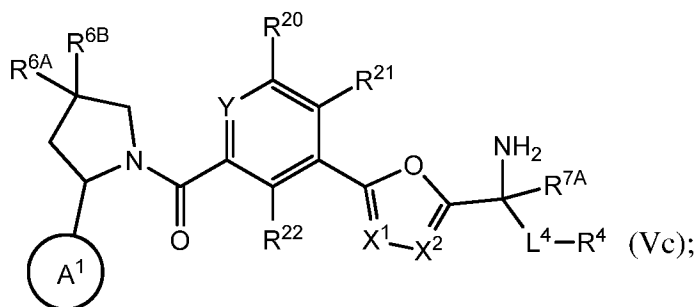
258. The compound of claim 256, wherein the compound is of the formula (Vb):



wherein L<sup>4</sup> and R<sup>4</sup> are as defined in any one of the preceeding claims, where applicable;

or a pharmaceutically acceptable salt or solvate thereof.

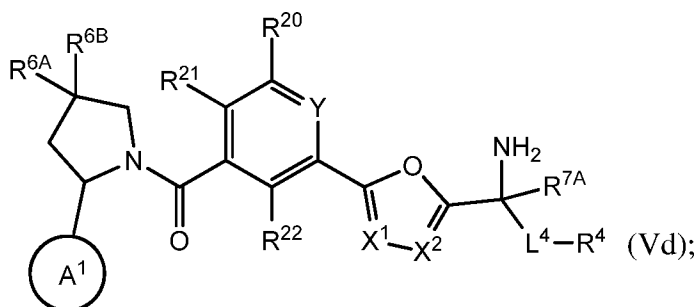
259. The compound of claim 258, wherein the compound is of the formula (Vc):



wherein Y, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> are as defined in any one of claims 73 and 77 to 190, where applicable;

or a pharmaceutically acceptable salt or solvate thereof.

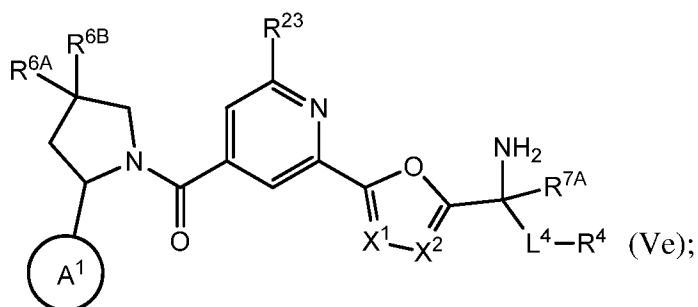
260. The compound of claim 258, wherein the compound is of the formula (Vd):



wherein Y, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> are as defined in any one of claims 73 and 77 to 190, where applicable;

or a pharmaceutically acceptable salt or solvate thereof.

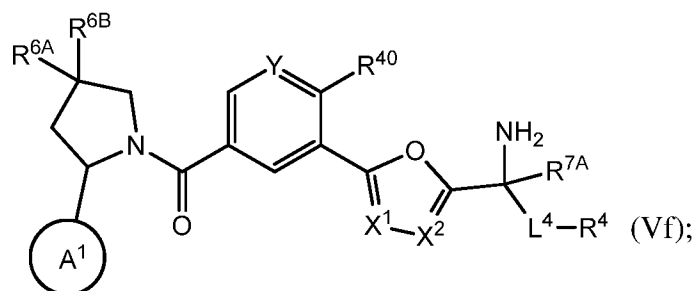
261. The compound of claim 258, wherein the compound is of the formula (Ve):



wherein R<sup>23</sup> is as defined in any one of claims 73 and 79 to 165;

or a pharmaceutically acceptable salt or solvate thereof.

262. The compound of claim 258, wherein the compound is of the formula (Vf):



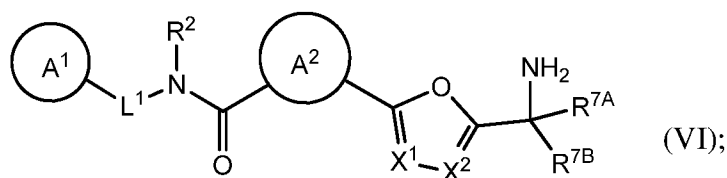
wherein Y is N or CH, and

R<sup>40</sup> is halogen or optionally substituted alkoxy;

or a pharmaceutically acceptable salt or solvate thereof.

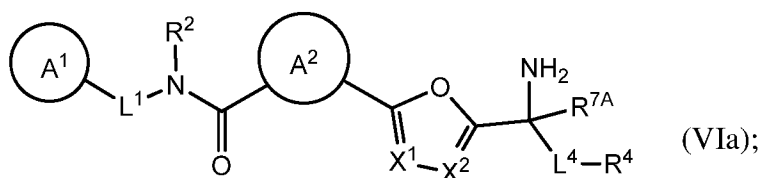
263. The compound of claim 262, wherein Y is CH, or a pharmaceutically acceptable salt or solvate thereof.
264. The compound of claim 262 or 263, wherein R<sup>40</sup> is optionally substituted methoxy, or a pharmaceutically acceptable salt or solvate thereof.
265. The compound of claim 262 or 263, wherein R<sup>40</sup> is halogen, or a pharmaceutically acceptable salt or solvate thereof.

266. The compound of claim 265, wherein  $R^{40}$  is fluoro or chloro, or a pharmaceutically acceptable salt or solvate thereof.
267. The compound of any one of claims 256 to 266, wherein  $R^{6B}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
268. The compound of any one of claims 256 to 266, wherein  $R^{6B}$  is halogen; or a pharmaceutically acceptable salt or solvate thereof.
269. The compound of claim 268, wherein  $R^{6B}$  is fluoro; or a pharmaceutically acceptable salt or solvate thereof.
270. The compound of any one of claims 256 to 269, wherein  $R^{6A}$  is hydrogen; or a pharmaceutically acceptable salt or solvate thereof.
271. The compound of any one of claims 256 to 269, wherein  $R^{6A}$  is halogen; or a pharmaceutically acceptable salt or solvate thereof.
272. The compound of claim 271, wherein  $R^{6A}$  is fluoro; or a pharmaceutically acceptable salt or solvate thereof.
273. A compound of the formula (VI):



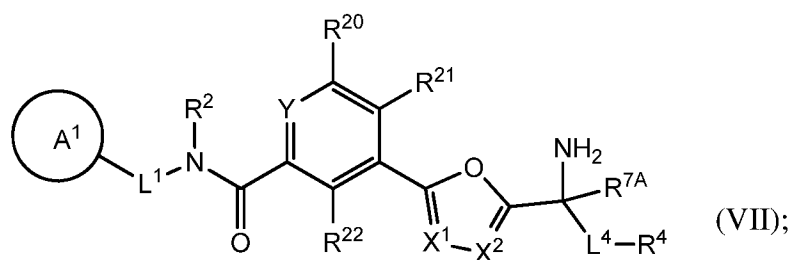
wherein  $A^1$ ,  $A^2$ ,  $X^1$ ,  $X^2$ ,  $L^1$ ,  $R^2$ ,  $R^{7A}$  and  $R^{7B}$  are as defined in any one of the preceding claims, where applicable;  
or a pharmaceutically acceptable salt or solvate thereof.

274. The compound of claim 273, wherein the compound is of the formula (VIa):



wherein  $L^4$  and  $R^4$  are as defined in any one of the preceding claims, where applicable;  
or a pharmaceutically acceptable salt or solvate thereof.

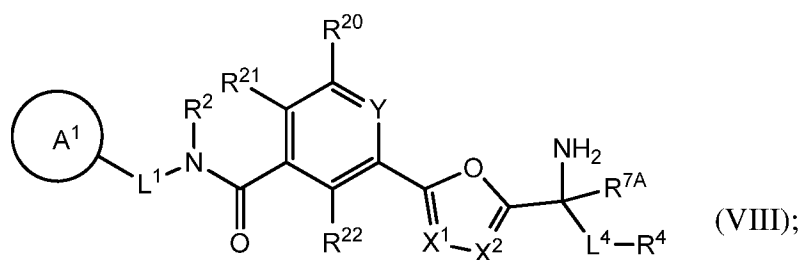
275. The compound of claim 274, wherein the compound is of the formula (VII):



wherein Y, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> are as defined in any one of claims 73 and 77 to 190, where applicable;

or a pharmaceutically acceptable salt or solvate thereof.

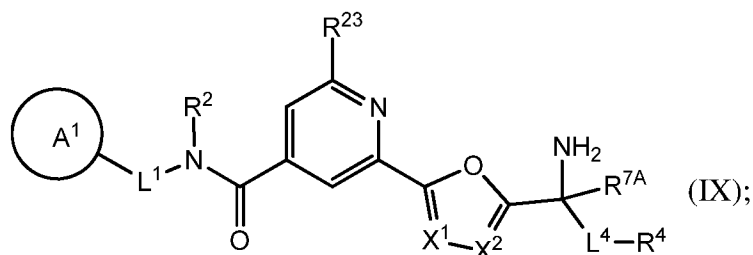
276. The compound of claim 274, wherein the compound is of the formula (VIII):



wherein Y, R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> are as defined in any one of claims 73 and 77 to 190, where applicable;

or a pharmaceutically acceptable salt or solvate thereof.

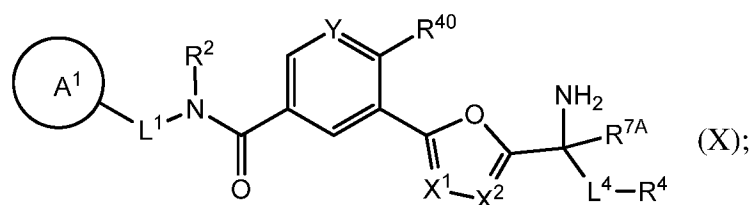
277. The compound of claim 274, wherein the compound is of the formula (IX):



wherein R<sup>23</sup> is as defined in any one of claims 73 and 79 to 165;

or a pharmaceutically acceptable salt or solvate thereof.

278. The compound of claim 274, wherein the compound is of the formula (X):



wherein Y is N or CH, and

- R<sup>40</sup> is halogen or optionally substituted alkoxy;  
or a pharmaceutically acceptable salt or solvate thereof.
279. The compound of claim 278, wherein Y is CH, or a pharmaceutically acceptable salt or solvate thereof.
280. The compound of claim 278 or 279, wherein R<sup>40</sup> is halogen, or a pharmaceutically acceptable salt or solvate thereof.
281. The compound of claim 278 or 279, wherein R<sup>40</sup> is optionally substituted alkoxy, or a pharmaceutically acceptable salt or solvate thereof.
282. The compound of claim 281, wherein R<sup>40</sup> is trifluoromethoxy, or a pharmaceutically acceptable salt or solvate thereof.
283. The compound of any one of claims 273 to 282, wherein L<sup>1</sup> is methylene; or a pharmaceutically acceptable salt or solvate thereof.
284. The compound of any one of claims 256 to 283, wherein R<sup>7A</sup> is substituted or unsubstituted alkyl or substituted or unsubstituted heteroaryl; or a pharmaceutically acceptable salt or solvate thereof.
285. The compound of claim 284, wherein R<sup>7A</sup> is methyl; or a pharmaceutically acceptable salt or solvate thereof.
286. The compound of any one of claims 256 to 285, wherein L<sup>4</sup> is methylene; or a pharmaceutically acceptable salt or solvate thereof.
287. The compound of claim 286, wherein R<sup>4</sup> is substituted or unsubstituted aryl; or a pharmaceutically acceptable salt or solvate thereof.
288. The compound of claim 287, wherein R<sup>4</sup> is phenyl; or a pharmaceutically acceptable salt or solvate thereof.
289. The compound of claim 287, wherein R<sup>4</sup> is 4-fluorophenyl; or a pharmaceutically acceptable salt or solvate thereof.
290. The compound of any one of claims 256 to 289, wherein A<sup>1</sup> is optionally substituted thiazolyl; or a pharmaceutically acceptable salt or solvate thereof.
291. The compound of claim 290, wherein A<sup>1</sup> is 4-methylthiazol-2-yl; or a pharmaceutically acceptable salt or solvate thereof.
292. The compound of claim 290, wherein A<sup>1</sup> is 4-(fluoromethyl)thiazol-2-yl; or a pharmaceutically acceptable salt or solvate thereof.
293. The compound of any one of claims 256 to 289, wherein A<sup>1</sup> is optionally substituted oxazolyl; or a pharmaceutically acceptable salt or solvate thereof.

294. The compound of claim 293, wherein A<sup>1</sup> is 4-methyloxazol-2-yl; or a pharmaceutically acceptable salt or solvate thereof.
295. The compound of any one of claims 256 to 266 and 267 to 285, wherein A<sup>1</sup> is optionally substituted thiazolyl; and R<sup>4</sup> is optionally substituted phenyl; or a pharmaceutically acceptable salt or solvate thereof.
296. The compound of claim 295, wherein A<sup>1</sup> is 4-methylthiazol-2-yl, 4-(fluoromethyl)thiazol-2-yl or 4-methyloxazol-2-yl; and R<sup>4</sup> is phenyl or 4-fluorophenyl; or a pharmaceutically acceptable salt or solvate thereof.
297. The compound of any one of claims 256 to 296, wherein X<sup>1</sup> is N; or a pharmaceutically acceptable salt or solvate thereof.
298. The compound of claim 297, wherein X<sup>2</sup> is N; or a pharmaceutically acceptable salt or solvate thereof.
299. The compound of claim 297, wherein X<sup>2</sup> is CH; or a pharmaceutically acceptable salt or solvate thereof.
300. The compound of any one of claims 256 to 296, wherein X<sup>1</sup> is CH; or a pharmaceutically acceptable salt or solvate thereof.
301. The compound of claim 300, wherein X<sup>2</sup> is CH; or a pharmaceutically acceptable salt or solvate thereof.
302. The compound of claim 300, wherein X<sup>2</sup> is N; or a pharmaceutically acceptable salt or solvate thereof.
303. The compound of any one of claims 1 to 302, wherein the compound has a memapsin 2 K<sub>i</sub> of less than about 300 nM; or a pharmaceutically acceptable salt or solvate thereof.
304. The compound of any one of claims 1 to 302, wherein the compound has an apparent memapsin 2 K<sub>i</sub> of less than about 300 nM as measured by inhibition of memapsin 2 catalytic activity toward the fluorogenic substrate FS-2 (MCA-SEVNLDAEFK-DNP; SEQ ID NO.: 2); or a pharmaceutically acceptable salt or solvate thereof.
305. The compound of any one of claims 1 to 304, wherein the compound is capable of inhibiting cellular A $\beta$  production with an IC<sub>50</sub> of less than about 500 nM; or a pharmaceutically acceptable salt or solvate thereof.
306. The compound of any one of claims 1 to 305, wherein the compound is capable of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 or cathepsin D catalytic activity; or a pharmaceutically acceptable salt or solvate thereof.

307. The compound of claim 306, wherein the compound is capable of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 or cathepsin D catalytic activity by greater than about 5-fold; or a pharmaceutically acceptable salt or solvate thereof.
308. The compound of claim 307, wherein the compound is capable of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 catalytic activity cathepsin D by greater than about 5-fold; or a pharmaceutically acceptable salt or solvate thereof.
309. The compound of any one of claims 1 to 308, wherein the compound (a) has a memapsin 2  $K_i$  of less than about 300 nM; (b) is capable of inhibiting cellular A $\beta$  production with an  $IC_{50}$  of less than about 500 nM; and (c) is capable of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 or cathepsin D catalytic activity by greater than about 5-fold; or a pharmaceutically acceptable salt or solvate thereof.
310. The compound of any one of claims 1 to 309, wherein the compound is substantially pure; or a pharmaceutically acceptable salt or solvate thereof.
311. A formulation comprising a compound of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.
312. A formulation comprising an effective amount of compound of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.
313. A method of treating Alzheimer's disease in an individual in need thereof, the method comprising administering to the individual an effective amount of a compound of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof.
314. A method of treating of a condition mediated by memapsin 2 catalytic activity in an individual in need thereof, the method comprising administering to the individual an effective amount of a compound of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof.
315. A method of reducing memapsin 2 catalytic activity, the method comprising contacting memapsin 2 with an effective amount of a compound of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof.
316. The method of claim 315, wherein said memapsin 2 is contacted in a cell.
317. A method of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 catalytic activity, the method comprising contacting a memapsin 2 with an effective

- amount of a compound of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof in the presence of memapsin 1.
318. A method of selectively reducing memapsin 2 catalytic activity relative to cathepsin D catalytic activity, the method comprising contacting a memapsin 2 protein with a therapeutically effective amount of a compound of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof in the presence of cathepsin D.
319. A method of selectively reducing memapsin 2 catalytic activity relative to memapsin 1 catalytic activity and cathepsin D catalytic activity, the method comprising contacting memapsin 2 with a therapeutically effective amount of a compound of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof in the presence of memapsin 1 and cathepsin D.
320. A compound of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof for use as a medicament.
321. Use of one or more compounds of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment or prevention of a condition mediated by memapsin 2 catalytic activity.
322. Use of one or more compounds of any one of claims 1 to 309 or a pharmaceutically acceptable salt or solvate thereof for the treatment or prevention of a condition mediated by memapsin 2 catalytic activity.
323. Use as described in claim 321 or 322, wherein the condition is Alzheimer's disease.
324. A kit for the treatment or prevention in an individual with Alzheimer's disease, comprising:
- (a) a compound of any one of claims 1 to 309, or a pharmaceutically acceptable salt or solvate thereof; and
  - (b) packaging.
325. A kit for the treatment or prevention in an individual of a condition mediated by memapsin 2 catalytic activity, comprising:
- (a) a compound of any one of claims 1 to 309, or a pharmaceutically acceptable salt or solvate thereof; and
  - (b) packaging.
326. A kit for the treatment or prevention in an individual with Alzheimer's disease, comprising:
- (a) a formulation of claim 321 or 322; and



- (b) packaging.
327. A kit for the treatment or prevention in an individual of a condition mediated by memapsin 2 catalytic activity, comprising:
- (a) a formulation of claim 321 or 322; and
  - (b) packaging.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2011/056747

## A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

*C07D 417/14* (2006.01)      *A61K 31/427* (2006.01)      *C07D 413/12* (2006.01)  
*A61K 31/422* (2006.01)      *A61K 31/4439* (2006.01)      *C07D 413/14* (2006.01)  
*A61K 31/4245* (2006.01)      *A61P 25/28* (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

STN: databases: REGISTRY, CAPLUS, substructure search based on structural formulae of claims 1, 256 and 273

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                  | Relevant to claim No. |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | WO 2005/103020 A1 (MERCK & CO., INC.) 03 November 2005<br>Example 38 on page 132, title, abstract, other examples including 57 to 61 on pages 147 and 148, page 54, claims 1 and 20 | 1-327                 |
| X         | WO 2006/078577 A1 (MERCK & CO., INC.) 27 July 2006<br>Example 89 on page 36, title, abstract, claim 1                                                                               | 1-327                 |
| A         | US 2009/0117040 A1 (WANKER <i>et al</i> ) 07 May 2009<br>Paragraph 0278 on page 15                                                                                                  |                       |
| A         | CA 2706991 A1 (BAYER SCHERING PHARMA AKTIENGESELLSCHAFT) 04 June 2009<br>Example 470 on page 478                                                                                    |                       |

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

|                                                                                                                                                                         |                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * Special categories of cited documents:                                                                                                                                |                                                                                                                                                                                                                                                  |
| "A" document defining the general state of the art which is not considered to be of particular relevance                                                                | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention                                              |
| "E" earlier application or patent but published on or after the international filing date                                                                               | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone                                                                     |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "O" document referring to an oral disclosure, use, exhibition or other means                                                                                            | "&" document member of the same patent family                                                                                                                                                                                                    |
| "P" document published prior to the international filing date but later than the priority date claimed                                                                  |                                                                                                                                                                                                                                                  |

Date of the actual completion of the international search  
09 December 2011

Date of mailing of the international search report  
22/12/2011

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**INTERNATIONAL SEARCH REPORT****International application No.**  
**PCT/US2011/056747**

| <b>C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT</b> |                                                                                                                  |                              |
|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------|
| <b>Category*</b>                                             | <b>Citation of document, with indication, where appropriate, of the relevant passages</b>                        | <b>Relevant to claim No.</b> |
| <b>A</b>                                                     | <b>WO 2007/007588 A1 (ONO PHARMACEUTICAL CO., LTD.) 18 January 2007</b><br><b>Compound at the top of page 85</b> |                              |

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2011/056747

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent Document Cited in Search Report                                                                                    |            |      |              | Patent Family Member |            |    |              |
|---------------------------------------------------------------------------------------------------------------------------|------------|------|--------------|----------------------|------------|----|--------------|
| WO                                                                                                                        | 2005103020 | AU   | 2005236020   | CA                   | 2563615    | CN | 1942457      |
|                                                                                                                           |            | EP   | 1740559      | JP                   | 2007533743 | US | 2007244119   |
|                                                                                                                           |            | US   | 7847100      |                      |            |    |              |
| WO                                                                                                                        | 2006078577 | AU   | 2006206654   | CA                   | 2594946    | CN | 101106989    |
|                                                                                                                           |            | EP   | 1841426      | JP                   | 2008526999 | US | 2008139538   |
| US                                                                                                                        | 2009117040 | EP   | 1713457      | WO                   | 2005077343 |    |              |
| CA                                                                                                                        | 2706991    | AR   | 069417       | CN                   | 101932577  | DE | 102007057718 |
|                                                                                                                           |            | DE   | 102008010221 | EP                   | 2227466    | JP | 2011504889   |
|                                                                                                                           |            | KR   | 20100114018  | PA                   | 8805201    | PE | 10262009     |
|                                                                                                                           |            | TW   | 200936135    | US                   | 2009306139 | UY | 31484        |
|                                                                                                                           |            | WO   | 2009068214   |                      |            |    |              |
| WO                                                                                                                        | 2007007588 | NONE |              |                      |            |    |              |
| Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. |            |      |              |                      |            |    |              |
| END OF ANNEX                                                                                                              |            |      |              |                      |            |    |              |