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(54) Title: HETEROAROMATIC DERIVATIVES AND PHARMACEUTICAL APPLICATIONS THEREOF

(57) **Abstract:** Provided herein are novel heteroaromatic derivatives, or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, a prodrug, a pharmaceutically acceptable salt or a prodrug thereof, and pharmaceutical compositions containing such compounds. Also provided herein are uses of such compounds or pharmaceutical compositions thereof in the manufacture of a medicament for treating respiratory diseases, especially chronic obstructive pulmonary disease (COPD).



HETEROAROMATIC DERIVATIVES AND PHARMACEUTICAL APPLICATIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to Chinese Patent Application Serial No. 201410172733.3, filed with the State Intellectual Property Office of China on April 25, 2014, which is hereby incorporated by reference in its entirety and for all purposes as if specifically and fully set forth herein.

FIELD

[0002] The invention belongs to the pharmaceutical field, and it specially relates to novel heteroaromatic compounds, and pharmaceutical compositions, applications and methods of uses thereof. Especially, these compounds described herein are PDE-4 inhibitors used for treating chronic obstructive pulmonary disease (COPD).

BACKGROUND

[0003] Cyclic nucleotide phosphodiesterases (PDEs) are an important super-family of enzymes, which effectively control the intracellular concentrations of cAMP and cGMP by hydrolyzing the cAMP and cGMP, thereby regulate the biochemical reaction mediated by the second messengers in vivo. PDEs are widely distributed in mammalian tissues, and their diversity causes that different PDE enzymes in cells and sub-cellular levels have specific distributions. PDEs can selectively regulate a variety of cellular functions, which are good therapeutic targets for drug design.

[0004] Phosphodiesterase-4 (PDE-4) has been shown to be the predominant regulator of cyclic AMP in respiratory smooth muscle and inflammatory cells. Inhibitors of PDE-4 are useful in treating a variety of diseases, including allergic and inflammatory diseases, diabetes, central nervous system diseases, pain, and viruses that produce TNF.

[0005] It is known that cyclic adenosine 3',5'-monophosphate (cAMP) exhibits an important role of acting as an intracellular secondary messenger (Sutherland and Roll, *Pharmacol. Rev.*, 1960, 12: 265). Intracellular hydrolysis of cAMP to adenosine 5'-monophosphate (AMP) causes a number of inflammatory conditions including but not limited to psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS),

eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis. The most important role in the control of cAMP (as well as of cGMP) levels is played by cyclic nucleotide phosphodiesterases (PDE), which represent a biochemically and functionally, highly variable superfamily of the enzyme. Eleven distinct families of phosphodiesterases with more than 25 gene expression products have been recognized. Although all of PDE-1, PDE-2, PDE-3, PDE-4, and PDE-7 use cAMP as a substrate, only PDE-4 and PDE-7 types are highly selective for hydrolysis of cAMP. Inhibitors of PDE, particularly PDE-4 inhibitors, such as rolipram or Ro-1724 are therefore known as cAMP-enhancers. Immune cells contain PDE-3 and PDE-4, and PDE-4 is prevalent in human mononuclear cells. Thus the inhibition of phosphodiesterase type 4 has been a target for modulation and, accordingly, for therapeutic intervention in a range of disease processes. Studies have shown that the administration of PDE-4 inhibitors can have a restorative effect on memory loss in animal models including those of Alzheimer's disease (*Expert Opin. Ther. Targets*, 2005, 9 (6): 1283-1305; *Drug Discover Today*, 2005, 10 (22): 1503-19, incorporated herein by reference).

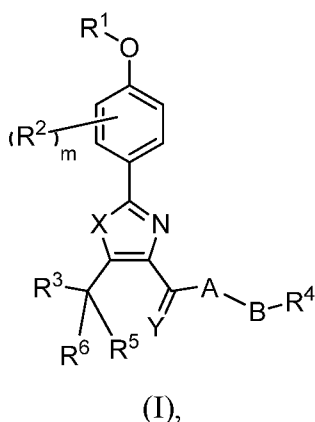
[0006] The initial observation that xanthine derivatives, theophylline and caffeine inhibit the hydrolysis of cAMP led to the discovery of the required hydrolytic activity in the cyclic nucleotide phosphodiesterase (PDE) enzymes. More recently, distinct classes of PDEs have been recognized (Beavo and Reifsnnyder, *Trends Pharmacol Sci.*, 1990; 11: 150, incorporated herein by reference), and their selective inhibition has led to improved drug therapy (Nicholus, Challiss and Shahid, *Trends Pharmacol. Sci.*, (1991); 12: 19, incorporated herein by reference). Thus it was recognized that inhibition of PDE-4 could lead to inhibition of inflammatory mediator release (Verghese et al, *J Mol. Cell. Cardiol.*, 1989, 12 (Suppl. II) : S 61, incorporated herein by reference).

[0007] WO 2004046095 discloses certain arylthiourea derivatives and related compounds, which possess antiviral activity. WO 00/35891 discloses certain morpholinone and morpholine derivatives, which are selective antagonists for human α_{1a} receptor. WO 2004050024 discloses 3-aminopyrrolidine derivatives and their use as modulators of chemokine receptors. WO 2005/21515 relates to isoxazoline derivatives, which can be used as selective inhibitors of phosphodiesterase (PDE) type IV. WO 2005/051931 discloses novel phosphodiesterase type IV inhibitors.

SUMMARY OF THE INVENTION

[0008] The invention relates to novel heteroaromatic derivatives and the methods of treating chronic obstructive pulmonary disease. The compounds or pharmaceutical compositions thereof provided herein have good affinities for PDE-4, especially have good therapeutic effects on chronic obstructive pulmonary disease.

[0009] In one aspect, provided herein are compounds having Formula (I), or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein

m is 0, 1, 2, 3 or 4;

p is 0, 1 or 2;

each *e* is independently 0, 1 or 2;

each *f* is independently 0, 1 or 2;

X is -N(R⁸)-, -O- or -S-;

Y is O or S;

A is a bond or -N(R⁷)-;

B is -(CR^aR^b)_{*p*}-;

*R*¹ is D, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₁₋₆ haloalkyl, R^{9a}R⁹N-C₁₋₆-alkyl-, C₁₋₆ alkyl-C(=O)-, -C(=O)OR^{9c}, -C(=O)-NR⁹R^{9a}, R⁹R^{9a}N-S(=O)₂-, R^{9d}-S(=O)₂-, R^{9d}-S(=O)-C₁₋₆-alkyl-, R⁹R^{9a}N-C(=O)-C₁₋₆-alkyl-, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl or C₁₋₉ heteroaryl-C₁₋₆-alkyl;

each *R*² is independently H, D, F, Cl, Br, I, CN, NO₂, OH, NH₂, -S(=O)₂Cl, R^{9a}R⁹N-, -C(=O)-R^{9d}, -C(=O)-NR⁹R^{9a}, -OC(=O)-NR⁹R^{9a}, -OC(=O)OR^{9c}, -N(R⁹)-C(=O)-NR⁹R^{9a},

-N(R⁹)-C(=O)OR^{9c}, R^{9d}-S(=O)₂-, R^{9d}-S(=O)₂-N(R^{9a})-, HOC(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-NH-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₃₋₈ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₆₋₁₀ aryl-(CR^cR^d)_f-NH-C₁₋₆-alkoxy-, C₁₋₆ alkyl-NH-C(=O)-C₁₋₆-alkoxy-, R^eR^fN-C(=O)-C₁₋₆-alkoxy-, C₁₋₉ heteroaryl-C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₃₋₈ cycloalkyl-C(=O)-C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-O-C(=O)-C₁₋₆-alkoxy-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₁₋₆ alkoxy, amino-substituted C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₃₋₈ cycloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₁₀ heterocyclyloxy, C₆₋₁₀ aryl-C₁₋₆-alkoxy, C₃₋₈ cycloalkoxy or C₃₋₈ cycloalkyl-C₁₋₆-alkoxy, and wherein optionally each R² is independently substituted with one or more R¹²;

R³ is D, F, Cl, Br, I, CN, NO₂, NH₂, OH, COOH, C₁₋₆ alkylamino, NH₂-C₁₋₆ alkyl-C₁₋₉-heteroaryl-, NH₂-C₁₋₆ alkyl-C₁₋₉ heteroaryl-C₁₋₆-alkyl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀-aryl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀ aryl-C₁₋₆-alkyl-, C₁₋₆ alkyl-C(=O)-NH-, R¹³O-C(=O)-C₁₋₆-alkyl-C(=O)-NH-, C₃₋₈ cycloalkyl-C(=O)-NH- or -C(=O)-NR^{9a};

each of R⁵ and R⁶ is independently H, D, F, Cl, Br, I, CN, NO₂, NH₂, OH, COOH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkylamino, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, hydroxy-substituted C₁₋₆ alkyl, mercapto-substituted C₁₋₆ alkyl, carboxy-substituted C₁₋₆ alkyl, NH₂-C₁₋₆ alkyl-C₁₋₉-heteroaryl-, NH₂-C₁₋₆ alkyl-C₁₋₉ heteroaryl-C₁₋₆-alkyl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀-aryl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀ aryl-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₁₋₉ heteroaryl-C₁₋₆-alkyl, C₃₋₈ cycloalkyl-C(=O)-NH-, -C(=O)-NR^{9a}, C₆₋₁₀ aryl or C₁₋₉ heteroaryl;

or optionally two groups selected from R³, R⁵ and R⁶, together with the carbon atom to which they are attached, form C=O;

R⁴ is C₆₋₁₀ aryl, C₆₋₁₀ aryl-S(=O)₂-, C₁₋₉ heteroaryl, C₁₋₉ heteroaryl-S(=O)₂-, C₆₋₁₀ aryl-C₁₋₆-alkyl or C₁₋₉ heteroaryl-C₁₋₆-alkyl, and wherein R⁴ is optionally substituted with one or more R¹⁴;

each of R⁷ and R⁸ is independently H, D or C₁₋₆ alkyl;

each R^a and R^b is independently H, D, F, Cl, Br, I, CN, OH, NO₂, NH₂, -COOR^{9c}, C₁₋₆ alkyl, -C(=O)-NR^{9a}, -C₁₋₆-alkyl-C(=O)-NR^{9a}, -C(=S)-NH₂, amino-substituted C₁₋₆ alkyl, -NH-C(=O)-R^{9b}, -C₁₋₆-alkyl-NH-C(=O)-R^{9b}, -NH-S(=O)₂-C₁₋₆ alkyl, -C₁₋₆-alkyl-NH-S(=O)₂-C₁₋₆ alkyl, -NH-S(=O)₂-C₃₋₈-cycloalkyl, -C₁₋₆-alkyl-NH-S(=O)₂-C₃₋₈ cycloalkyl, -S(=O)₂-C₁₋₆ alkyl,

-C₁₋₆-alkyl-S(=O)₂-C₁₋₆ alkyl, C₆₋₁₀ aryl or C₁₋₉ heteroaryl; or R^a and R^b, together with the carbon atom to which they are attached, form a 3- to 8-membered ring;

each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₆ alkyl;

each R^e and R^f is independently H, OH or C₁₋₆ alkyl;

each R^g, R^{9a}, R^{9b} and R^{9d} is independently H, D, OH, NH₂, -S(=O)₂-NH₂, -C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₆-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₆ alkyl, -S(=O)₂-C₁₋₆ alkyl, -S(=O)₂-C₃₋₈ cycloalkyl, C₁₋₆ haloalkyl, amino-substituted C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₆₋₁₀ aryl, C₂₋₁₀ heterocyclyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₆-alkylamino, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₆₋₁₀ aryloxy, C₂₋₁₀ heterocyclyloxy, C₃₋₈ cycloalkoxy, C₆₋₁₀ arylamino, C₂₋₁₀ heterocyclylamino, C₃₋₈ cycloalkylamino, C₁₋₉ heteroaryl or C₃₋₈ carbocyclyl; or R^g and R^{9a}, together with the nitrogen atom to which they are attached, form a 3- to 8-membered ring, and wherein optionally each 3- to 8-membered ring, R^g, R^{9a}, R^{9b} and R^{9d} is independently substituted with one or more R¹⁵;

each R^{9c} is independently H, D, -C₁₋₆-alkyl-C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₆-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, amino-substituted C₁₋₆ alkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl or C₃₋₈ carbocyclyl;

each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ haloalkylamino, hydroxy-substituted C₁₋₆ alkyl, hydroxy-substituted C₁₋₆ alkoxy or hydroxy-substituted C₁₋₆ alkylamino;

R¹³ is H, D or C₁₋₆ alkyl;

each R¹⁴ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, -C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₆-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ haloalkylamino, hydroxy-substituted C₁₋₆ alkyl, hydroxy-substituted C₁₋₆ alkoxy, hydroxy-substituted C₁₋₆ alkylamino or C₃₋₆ cycloalkyl;

each R¹⁵ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₆ alkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₁₋₉ heteroaryl-C₁₋₆-alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl, C₃₋₈ cycloalkylcarbonyl, C₂₋₁₀ heterocyclylcarbonyl, C₆₋₁₀ arylcarbonyl or C₁₋₉ heteroarylcarbonyl; and

wherein optionally each R¹, R³, R⁵, R⁶, R⁷, R⁸, R^{9c}, R^a, R^b, R^c, R^d, R^e, R^f, R¹², R¹³, R¹⁴ and R¹⁵ is independently substituted with one or more R, and wherein each R is independently H, D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₆ alkyl or C₁₋₆ alkoxy.

[0010] In certain embodiments, wherein R¹ is D, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆

cycloalkyl, C₂₋₆ heterocyclyl, C₂₋₆ heterocyclyl-C₁₋₄-alkyl, C₁₋₄ haloalkyl, -C(=O)-C₁₋₄ alkyl, -C(=O)OR^{9c}, -C(=O)-NR⁹R^{9a}, R⁹R^{9a}N-C(=O)-C₁₋₄-alkyl-, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₁₋₉ heteroaryl or C₃₋₆ cycloalkyl-C₁₋₄-alkyl.

[0011] In certain embodiments, wherein each R² is independently H, D, F, Cl, Br, I, CN, NO₂, OH, NH₂, HOC(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkoxy-, C₂₋₆ heterocyclyl-NH-C₁₋₆-alkoxy-, C₂₋₆ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkoxy-, C₂₋₆ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₃₋₆ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₆₋₁₀ aryl-(CR^cR^d)_f-NH-C₁₋₆-alkoxy-, C₁₋₄ alkyl-NH-C(=O)-C₁₋₆-alkoxy-, R^eR^fN-C(=O)-C₁₋₆-alkoxy-, C₁₋₅ heteroaryl-C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₃₋₆ cycloalkyl-C(=O)-C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkyl-O-C(=O)-C₁₋₆-alkoxy-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₆₋₁₀ aryl, C₁₋₅ heteroaryl, C₁₋₆ alkoxy, amino-substituted C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₄ alkylamino, C₃₋₆ cycloalkyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₆ heterocyclyloxy, C₆₋₁₀ aryl-C₁₋₄-alkoxy, C₃₋₆ cycloalkoxy or C₃₋₆ cycloalkyl-C₁₋₄-alkoxy, and wherein optionally each R² is independently substituted with one or more R¹²;

each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₄ alkyl;

each R^e and R^f is independently H, OH or C₁₋₄ alkyl; and

each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylamino, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ haloalkylamino, hydroxy-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkoxy or hydroxy-substituted C₁₋₄ alkylamino.

[0012] In certain embodiments, wherein R³ is D, F, Cl, Br, I, CN, NO₂, NH₂, OH, COOH, C₁₋₄ alkylamino, NH₂-C₁₋₄ alkyl-C₁₋₅-heteroaryl-, NH₂-C₁₋₄ alkyl-C₁₋₅ heteroaryl-C₁₋₄-alkyl-, NH₂-C₁₋₄ alkyl-C₆₋₁₀-aryl-, NH₂-C₁₋₄ alkyl-C₆₋₁₀ aryl-C₁₋₄-alkyl-, C₁₋₄ alkyl-C(=O)-NH-, R¹³O-C(=O)-C₁₋₄ alkyl-C(=O)-NH-, C₃₋₆ cycloalkyl-C(=O)-NH- or -C(=O)-NR⁹R^{9a},

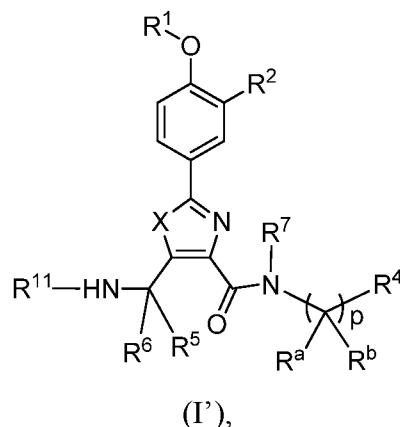
each of R⁵ and R⁶ is independently H, D, F, Cl, Br, I, CN, NO₂, NH₂, OH, COOH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkylamino, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, hydroxy-substituted C₁₋₄ alkyl, mercapto-substituted C₁₋₄ alkyl, carboxy-substituted C₁₋₄ alkyl, NH₂-C₁₋₄ alkyl-C₁₋₅-heteroaryl-, NH₂-C₁₋₄ alkyl-C₁₋₅ heteroaryl-C₁₋₄-alkyl-, NH₂-C₁₋₄ alkyl-C₆₋₁₀-aryl-, NH₂-C₁₋₄ alkyl-C₆₋₁₀ aryl-C₁₋₄-alkyl-, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₃₋₆ cycloalkyl-C(=O)-NH-, -C(=O)-NR⁹R^{9a}, C₆₋₁₀ aryl or C₁₋₅ heteroaryl;

or optionally two groups selected from R^3 , R^5 and R^6 , together with the carbon atom to which they are attached, form $C=O$;

each of R^7 and R^8 is independently H, D or C_{1-4} alkyl; and

R^{13} is H, D or C_{1-4} alkyl.

[0013] In certain embodiments, provided herein are compounds having Formula (I'), or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,

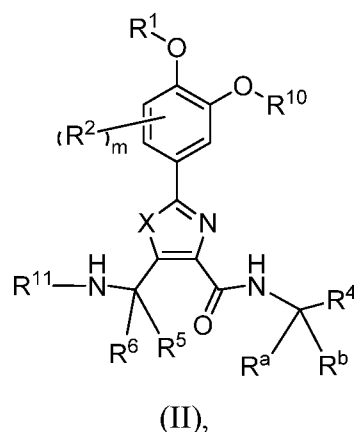


wherein

each of X, R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^a , R^b and p is as defined herein;

R^{11} is H, C_{1-4} alkyl, C_{1-4} alkyl- $C(=O)-$, $R^{13}O-C(=O)-C_{1-4}$ alkyl- $C(=O)-$ or C_{3-6} cycloalkyl- $C(=O)-$.

[0014] In certain embodiments, provided herein are compounds having Formula (II), or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein

each X, R^1 , R^2 , R^4 , R^5 , R^6 , R^a and R^b is as defined herein;

m is 0, 1, 2 or 3;

R^{10} is H, $\text{HOC(=O)-C}_{1-6}\text{-alkyl-}$, C_{1-6} alkoxy- $(\text{CH}_2)_e\text{-C(=O)-C}_{1-6}\text{-alkyl-}$, C_{2-10} heterocyclyl-NH- $\text{C}_{1-6}\text{-alkyl-}$, C_{2-10} heterocyclyl- $(\text{CH}_2)_e\text{-OC(=O)-C}_{1-6}\text{-alkyl-}$, C_{2-10} heterocyclyl- $(\text{CH}_2)_e\text{-NH-C(=O)-C}_{1-6}\text{-alkyl-}$, C_{3-8} cycloalkyl- $(\text{CH}_2)_e\text{-NH-C(=O)-C}_{1-6}\text{-alkyl-}$, C_{6-10} aryl- $(\text{CR}^c\text{R}^d)_f\text{-NH-C}_{1-6}\text{-alkyl-}$, C_{1-6} alkyl-NH- $\text{C(=O)-C}_{1-6}\text{-alkyl-}$, $\text{R}^e\text{R}^f\text{N-C(=O)-C}_{1-6}\text{-alkyl-}$, C_{1-9} heteroaryl- C_{2-10} heterocyclyl- $\text{C(=O)-C}_{1-6}\text{-alkyl-}$, C_{3-8} cycloalkyl- C(=O)-C_{2-10} heterocyclyl- $\text{C(=O)-C}_{1-6}\text{-alkyl-}$, $\text{NH}_2\text{-C(=O)-C}_{1-6}\text{-alkyl-}$, C_{1-6} alkyl- $\text{OC(=O)-C(=O)-C}_{1-6}\text{-alkyl-}$, $\text{NH}_2\text{-NH-C(=O)-C}_{1-6}\text{-alkyl-}$, $\text{NH}_2\text{-C(=O)-C(=O)-C}_{1-6}\text{-alkyl-}$, C_{1-6} alkyl- $\text{S(=O)}_2\text{-NH-C(=O)-C}_{1-6}\text{-alkyl-}$, C_{1-6} alkyl- $\text{O-C(=O)-C}_{1-6}\text{-alkyl-}$, $\text{NH}_2\text{-S(=O)}_2\text{-NH-C(=O)-C}_{1-6}\text{-alkyl-}$, C_{2-10} heterocyclyl- $\text{C(=O)-C}_{1-6}\text{-alkyl-}$, amino-substituted C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{2-10} heterocyclyl, C_{6-10} aryl- $\text{C}_{1-6}\text{-alkyl}$, C_{3-8} cycloalkyl or C_{3-8} cycloalkyl- $\text{C}_{1-6}\text{-alkyl}$, and wherein R^{10} is optionally substituted with one or more R^{12} ; and

R^{11} is H, C_{1-4} alkyl, C_{1-4} alkyl- C(=O)- , $\text{R}^{13}\text{O-C(=O)-C}_{1-4}$ alkyl- C(=O)- or C_{3-6} cycloalkyl- C(=O)- .

[0015] In certain embodiments, wherein the pharmaceutically acceptable salt is hydrochloride, hydrobromide, sulfate, nitrate, phosphate, acetate, maleate, succinate, mandelate, fumarate, malonate, malate, 2-hydroxy propionate, pyruvate, oxalate, 2-hydroxy acetate, salicylate, glucuronate, galacturonate, citrate, tartrate, aspartate, glutamate, benzoate, cinnamate, *p*-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, trifluoromethanesulfonate or a combination thereof.

[0016] In certain embodiments, wherein R^1 is methyl, ethyl, propyl, *i*-propyl, halogenated methyl, halogenated ethyl, halogenated propyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, oxetanylmethyl, oxetanylethyl, tetrahydrofuryl, tetrahydrofurylmethyl, tetrahydrofurylethyl, phenyl, benzyl, phenylethyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

[0017] In certain embodiments, wherein each R^2 is independently H, D, F, Cl, Br, I, CN, NO_2 , OH, NH_2 , methoxy, ethoxy, propoxy, *i*-propoxy, butoxy, *i*-butoxy, *t*-butoxy, cyclopropoxy, cyclobutoxy, cyclopentoxo, cyclohexoxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutylmethoxy, cyclobutylethoxy, cyclopentylmethoxy, cyclopentylethoxy, cyclohexylmethoxy, cyclohexylethoxy, oxetanyloxy, tetrahydrofuryloxy, benzyloxy, phenylethoxy, $\text{HOC(=O)-C}_{1-6}\text{-alkoxy-}$, C_{1-3} alkoxy- $(\text{CH}_2)_e\text{-C(=O)-C}_{1-6}\text{-alkoxy-}$, C_{1-4}

alkyl-O-C(=O)-C₁₋₆-alkoxy-, C₂₋₄ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkoxy-, C₂₋₄
heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ heteroaryl-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₃₋₆
cycloalkyl-C(=O)-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-C₁₋₆-alkoxy-,
NH₂-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-,
R^eR^fN-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkyl-OC(=O)-(CR^cR^d)_f-NH-C₁₋₆-alkoxy-,
NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₃ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₃₋₆
cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₂₋₄ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-,
amino-substituted C₁₋₆ alkoxy, C₂₋₄ heterocyclyl-NH-C₁₋₆-alkoxy- or
phenyl-(CR^cR^d)_f-NH-C₁₋₆-alkoxy-, and wherein optionally each R² is independently substituted
with one or more R¹²;

each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₃ alkyl;

each R^e and R^f is independently H, OH or C₁₋₃ alkyl; and

each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, methyl, ethyl, propyl,
methoxy, ethoxy, propoxy, hydroxy-substituted methyl or halogenated methyl.

[0018] In certain embodiments, wherein each of R⁵ and R⁶ is independently H, D, F, Cl, Br, I,
NH₂, methyl, ethyl, propyl, *i*-propyl, hydroxy-substituted methyl, phenyl, benzyl or phenylethyl.

[0019] In certain embodiments, wherein R⁴ is C₆₋₁₀ aryl, C₆₋₁₀ aryl-S(=O)₂-, C₁₋₉ heteroaryl, C₁₋₉
heteroaryl-S(=O)₂-, C₆₋₁₀ aryl-C₁₋₄-alkyl or C₁₋₉ heteroaryl-C₁₋₄-alkyl, and wherein R⁴ is
optionally substituted with one or more R¹⁴; and

each R¹⁴ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, -C(=O)-NH₂,
-C₁₋₄-alkyl-C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)O-C₁₋₄ alkyl, -C₁₋₄-alkyl-O-C(=O)-C₁₋₄ alkyl, C₁₋₄
alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylamino, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ haloalkylamino,
hydroxy-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkoxy, hydroxy-substituted C₁₋₄
alkylamino or C₃₋₆ cycloalkyl.

[0020] In other embodiments, wherein R⁴ is phenyl, naphthyl, thiazolyl, thienyl, isothiazolyl,
pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, oxadiazolyl, pyridyl, pyrid-2-yl-*N*-oxide,
pyrid-4-yl-*N*-oxide, pyrimidyl, pyrazinyl, quinolyl, isoquinolyl, quinazolyl, naphthyridinyl,
furo[3,2-*c*]pyridinyl, furo[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[2,3-*c*]pyridinyl,
benzoxadiazolyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, quinoxalinyl, benzofuranyl,
pyridopyrazinyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, 1,3-benzodioxolanyl,
2,3-dihydrobenzofuranyl, thieno[3,2-*b*]pyridinyl, thieno[2,3-*c*]pyridinyl, thieno[2,3-*b*]pyridinyl,

1,4-benzodioxanyl, 1,2,3,4-tetrahydroquinolin-2-yl or benzenesulfonyl, and wherein R^4 is optionally substituted with one or more R^{14} ; and

each R^{14} is independently D, F, Cl, Br, I, CN, NO_2 , OH, NH_2 , $COOH$, $-C(=O)-NH_2$, $-C_{1-3}$ -alkyl- $C(=O)-NH_2$, $-C_{1-3}$ -alkyl- $C(=O)O-C_{1-4}$ alkyl, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, methamino or ethylamino.

[0021] In certain embodiments, wherein each R^a and R^b is independently H, D, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , $-COOR^{9c}$, C_{1-4} alkyl, $-C(=O)-NR^9R^{9a}$, $-C_{1-4}$ -alkyl- $C(=O)-NR^9R^{9a}$, $-C(=S)-NH_2$, amino-substituted C_{1-4} alkyl, $-NH-C(=O)-R^{9b}$, $-C_{1-4}$ -alkyl- $NH-C(=O)-R^{9b}$, $-NH-S(=O)_2-C_{1-4}$ alkyl, $-C_{1-4}$ -alkyl- $NH-S(=O)_2-C_{1-4}$ alkyl, $-NH-S(=O)_2-C_{3-6}$ cycloalkyl, $-C_{1-4}$ -alkyl- $NH-S(=O)_2-C_{3-6}$ cycloalkyl, $-S(=O)_2-C_{1-4}$ alkyl, $-C_{1-4}$ -alkyl- $S(=O)_2-C_{1-4}$ alkyl, C_{6-10} aryl or C_{1-5} heteroaryl; or R^a and R^b , together with the carbon atom to which they are attached, form a 3- to 6-membered ring;

each R^9 , R^{9a} and R^{9b} is independently H, D, OH, NH_2 , $-S(=O)_2-NH_2$, $-C(=O)-NH_2$, $-C_{1-4}$ alkyl- $C(=O)-NH_2$, $-C_{1-4}$ -alkyl- $C(=O)O-C_{1-6}$ alkyl, $-C_{1-4}$ -alkyl- $O-C(=O)-C_{1-6}$ alkyl, C_{1-4} alkyl, $-S(=O)_2-C_{1-4}$ alkyl, $-S(=O)_2-C_{3-6}$ cycloalkyl, C_{1-4} haloalkyl, amino-substituted C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-6} alkylamino, C_{6-10} aryl, C_{2-6} heterocyclyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} -alkylamino, C_{3-6} cycloalkyl- C_{1-4} -alkyl, C_{6-10} aryl- C_{1-4} -alkyl, C_{6-10} aryloxy, C_{2-6} heterocyclyloxy, C_{3-6} cycloalkoxy, C_{6-10} arylamino, C_{2-6} heterocyclylamino, C_{3-6} cycloalkylamino, C_{1-5} heteroaryl or C_{3-6} carbocyclyl; or R^9 and R^{9a} , together with the nitrogen atom to which they are attached, form a 3- to 6-membered ring, and wherein optionally each 3- to 6-membered ring, R^9 , R^{9a} and R^{9b} is independently substituted with one or more R^{15} ;

each R^{9c} is independently H, D, $-C_{1-4}$ -alkyl- $C(=O)-NH_2$, $-C_{1-4}$ -alkyl- $C(=O)O-C_{1-4}$ alkyl, $-C_{1-4}$ -alkyl- $O-C(=O)-C_{1-6}$ alkyl, C_{1-5} alkyl, C_{1-4} haloalkyl, amino-substituted C_{1-4} alkyl, C_{6-10} aryl, C_{1-5} heteroaryl, C_{3-6} cycloalkyl, C_{2-6} heterocyclyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, C_{6-10} aryl- C_{1-4} alkyl or C_{3-6} carbocyclyl; and

each R^{15} is independently D, F, Cl, Br, I, CN, NO_2 , OH, NH_2 , $COOH$, C_{1-4} alkyl, C_{6-10} aryl, C_{1-5} heteroaryl, C_{6-10} aryl- C_{1-4} -alkyl, C_{1-5} heteroaryl- C_{1-4} -alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} -alkyl, C_{2-6} heterocyclyl, C_{2-6} heterocyclyl- C_{1-4} -alkyl, C_{3-6} cycloalkylcarbonyl, C_{2-6} heterocyclylcarbonyl, C_{6-10} arylcarbonyl or C_{1-5} heteroarylcarbonyl.

[0022] In other embodiments, wherein each R^a and R^b is independently H, D, F, Cl, Br, I, CN, OH, NO_2 , NH_2 , $-COOR^{9c}$, methyl, ethyl, propyl, isopropyl, $-C(=O)-NR^9R^{9a}$, $-C(=S)-NH_2$, aminomethyl, aminoethyl, $-C_{1-3}$ -alkyl- $NH-C(=O)-R^{9b}$, $-C_{1-3}$ -alkyl- $NH-S(=O)_2-C_{3-6}$ cycloalkyl, $-C_{1-3}$ -alkyl- $S(=O)_2-C_{1-3}$ alkyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl,

oxadiazolyl, phenyl, pyridyl or pyrimidyl; or R^a and R^b, together with the carbon atom to which they are attached, form oxetane or 1,3-dioxacyclopentane;

each R⁹, R^{9a} and R^{9b} is independently H, D, OH, NH₂, -S(=O)₂-NH₂, -C(=O)-NH₂, -C₁₋₃-alkyl-C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)O-C₁₋₄ alkyl, -C₁₋₃-alkyl-O-C(=O)-C₁₋₃ alkyl, methyl, ethyl, propyl, isopropyl, -S(=O)₂-C₁₋₃ alkyl, -S(=O)₂-cyclopropyl, -S(=O)₂-cyclobutyl, -S(=O)₂-cyclopentyl, -S(=O)₂-cyclohexyl, C₁₋₄ haloalkyl, amino-substituted C₁₋₄ alkyl, methoxy, ethoxy, propoxy, *i*-propoxy, methylamino, dimethylamino, ethylamino, propylamino, isopropylamino, phenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylmethylamino, cyclobutylmethylamino, cyclopentylmethylamino, benzyl, phenylethyl, phenoxy, cyclopropoxy, cyclobutoxy, cyclopentoxo, phenylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; or R⁹ and R^{9a}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered ring selected from azetidine, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, and wherein optionally each 3- to 6-membered ring, R⁹, R^{9a} and R^{9b} is independently substituted with one or more R¹⁵;

each R^{9c} is independently H, D, -C₁₋₃-alkyl-C(=O)-NH₂, -C₁₋₃-alkyl-C(=O)O-C₁₋₃ alkyl, -C₁₋₃-alkyl-O-C(=O)-C₁₋₄ alkyl, methyl, ethyl, propyl, isopropyl, C₁₋₄ haloalkyl, amino-substituted C₁₋₄ alkyl, phenyl, benzyl, phenylethyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; and

each R¹⁵ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, methyl, ethyl, propyl, phenyl, pyridyl, pyrimidyl, thiazolyl, thienyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, oxadiazolyl, benzyl, phenylethyl, pyridylmethyl, pyrimidylmethyl, pyridylethyl, pyrimidylethyl, benzoyl, cyclopropylcarbonyl, cyclobutylcarbonyl or cyclopentylcarbonyl.

[0023] In other embodiments, wherein R¹⁰ is H, HOC(=O)-C₁₋₆-alkyl-, C₁₋₄ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-NH-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₆₋₁₀ aryl-(CR^cR^d)_f-NH-C₁₋₆-alkyl-, C₁₋₄ alkyl-NH-C(=O)-C₁₋₆ alkyl-, R^eR^fN-C(=O)-C₁₋₆-alkyl-, C₁₋₅ heteroaryl-C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl-C(=O)-C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-C₁₋₆ alkyl-, C₁₋₆ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, NH₂-NH-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-O-C(=O)-C₁₋₄-alkyl-,

NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkyl-, amino-substituted C₁₋₆ alkyl, C₁₋₆ haloalkyl, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, C₂₋₆ heterocyclyl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₃₋₆ cycloalkyl or C₃₋₆ cycloalkyl-C₁₋₄-alkyl, and wherein R¹⁰ is optionally substituted with one or more R¹²;

each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₃ alkyl;

each of R^e and R^f is independently H, OH or C₁₋₃ alkyl; and

each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkylamino, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, C₁₋₃ haloalkylamino, hydroxy-substituted C₁₋₃ alkyl, hydroxy-substituted C₁₋₃ alkoxy or hydroxy-substituted C₁₋₃ alkylamino.

[0024] In other embodiments, wherein R¹⁰ is H, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, oxetanyl, tetrahydrofuranyl, benzyl, phenylethyl, HOC(=O)-C₁₋₆-alkyl-, C₁₋₃ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkyl-, C₂₋₄ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-O-C(=O)-C₁₋₄-alkyl-, C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkyl-, C₁₋₄ heteroaryl-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl-C(=O)-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-C₁₋₆-alkyl-, NH₂-NH-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, R^eR^fN-C(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₃ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₂₋₄ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, amino-substituted C₁₋₆ alkyl, C₂₋₄ heterocyclyl-NH-C₁₋₆-alkyl- or phenyl-(CR^cR^d)_f-NH-C₁₋₆-alkyl-, and wherein R¹⁰ is optionally substituted with one or more R¹²;

each R^c and R^d is independently H, OH, CN, F, Cl, Br, I, methyl, ethyl or propyl;

each of R^e and R^f is independently H, OH, methyl, ethyl or propyl; and

each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, hydroxy-substituted methyl or halogenated methyl.

[0025] In one aspect, provided herein is a pharmaceutical composition comprising the compound disclosed herein.

[0026] In certain embodiments, the pharmaceutical composition disclosed herein further comprises at least one pharmaceutically acceptable carrier, excipient, diluent, adjuvant or

vehicle.

[0027] In certain embodiments, the pharmaceutical composition disclosed herein further comprises an additional therapeutic agent, wherein the additional therapeutic agent is a medicament, active agent, or a combination thereof, used for treating chronic obstructive pulmonary disease.

[0028] In other embodiments, the pharmaceutical composition disclosed herein, wherein the additional therapeutic agent is sodium pyruvate, doxofylline, roflumilast, apremilast, tetomilast, tielukast, theophylline, formoterol, salmeterol, fluticasone propionate, salmeterol xinafoate/fluticasone propionate, rolipram, piclamilast, cilomilast, CDP-840, indacaterol, olodaterol, QVA149, midosteine, zileuton, salbutamol, carmoxirole, budesonide and epimer thereof, beclomethasone dipropionate (BDP), triamcinolone acetonide, flunisolide, mometasone furoate, rofleponide, ciclesonide, ipratropium bromide, ipratropium bromide/albuterol, oxitropium bromide, tiotropium bromide, glycopyrronium bromide, umeclidinium bromide, vilanterol, umeclidinium/vilanterol, aclidinium bromide, aclidinium bromide/formoterol fumarate, LAS40464, LAS100977 (abediterol), AZD-8999, RPL-554, OCID-2987, CHF-6001, CR-3465, HPP-737, fluticasone furoate/vilanterol (FF/VI), benralizumab, revatroate, or a combination thereof.

[0029] In another aspect, provided herein is the use of the compound or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening a phosphodiesterase-4 (PDE-4) mediated disorder in a subject.

[0030] In certain embodiments, wherein the phosphodiesterase-4 (PDE-4) mediated disorder is respiratory disease, allergy, inflammation, a central nervous system (CNS) disorder, pulmonary fibrosis or non-insulin dependent diabetes.

[0031] In other embodiments, wherein the respiratory disease is chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, asthma, chronic pneumonia, pneumoconiosis, bronchitis, allergic bronchitis, bronchiectasis, tuberculosis fibrosis, cystic pulmonary fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, acute respiratory distress syndrome (ARDS) or respiratory inflammation.

[0032] In other embodiments, wherein the inflammation is allergic conjunctivitis, atopic dermatitis, allergic dermatitis, rheumatoid arthritis, interstitial cystitis, allergic rhinitis, ulcerative

colitis, ankylosing spondylitis, rheumatoid arthritis or psoriatic arthritis.

[0033] In another aspect, provided herein is a method for preventing, managing, treating or lessening a phosphodiesterase-4 (PDE-4) mediated disorder in a subject, comprising administering to the subject a therapeutically effective amount of the compound or the pharmaceutical composition disclosed herein.

[0034] In certain embodiments, wherein the phosphodiesterase-4 (PDE-4) mediated disorder is respiratory disease, allergy, inflammation, a central nervous system (CNS) disorder, pulmonary fibrosis or non-insulin dependent diabetes.

[0035] In other embodiments, wherein the respiratory disease is chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, asthma, chronic pneumonia, pneumoconiosis, bronchitis, allergic bronchitis, bronchiectasis, tuberculosis fibrosis, cystic pulmonary fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, acute respiratory distress syndrome (ARDS) or respiratory inflammation.

[0036] In other embodiments, wherein the inflammation is allergic conjunctivitis, atopic dermatitis, allergic dermatitis, rheumatoid arthritis, interstitial cystitis, allergic rhinitis, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis or psoriatic arthritis.

[0037] In another aspect, provided herein is the compound or the pharmaceutical composition disclosed herein for use in preventing, managing, treating or lessening a phosphodiesterase-4 (PDE-4) mediated disorder in a subject.

[0038] In certain embodiments, wherein the phosphodiesterase-4 (PDE-4) mediated disorder is respiratory disease, allergy, inflammation, a central nervous system (CNS) disorder, pulmonary fibrosis or non-insulin dependent diabetes.

[0039] In other embodiments, wherein the respiratory disease is chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, asthma, chronic pneumonia, pneumoconiosis, bronchitis, allergic bronchitis, bronchiectasis, tuberculosis fibrosis, cystic pulmonary fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, acute respiratory distress syndrome (ARDS) or respiratory inflammation.

[0040] In other embodiments, wherein the inflammation is allergic conjunctivitis, atopic dermatitis, allergic dermatitis, rheumatoid arthritis, interstitial cystitis, allergic rhinitis, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis or psoriatic arthritis.

[0041] In another aspect, provided herein are methods for preparing, separating, and purifying the compounds represented by Formula (I), (I') or (II).

[0042] The foregoing merely summarizes certain aspects disclosed herein and is not intended to be limiting in nature. These aspects and other aspects are described more fully below.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS AND GENERAL TERMINOLOGY

[0043] Reference will now be made in detail to certain embodiments disclosed herein, examples of which are illustrated in the accompanying structures and formulas. The invention is intended to cover all alternatives, modifications, and equivalents that may be included within the scope disclosed herein as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice disclosed herein. Described herein is in no way limited to the methods and materials. In the event that one or more of the incorporated literature, patents, and similar materials differ from or contradict this application, including but not limited to defined terms, term usage, described techniques, and the like, this application controls.

[0044] It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

[0045] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as is commonly understood by one skilled in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entirety.

[0046] As used herein, the following definitions shall be applied unless otherwise indicated. For purposes disclosed herein, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and *the Handbook of Chemistry and Physics*, 75th Ed. 1994. Additionally, general principles of organic chemistry are described in Sorrell et al., “*Organic Chemistry*”, University Science Books, Sausalito: 1999, and Smith et al., “*March's Advanced Organic Chemistry*”, John Wiley & Sons, New York: 2007, all of which are incorporated herein by reference in their entireties.

[0047] The grammatical articles “a”, “an” and “the”, as used herein, are intended to include “at least one” or “one or more” unless otherwise indicated herein or clearly contradicted by the context. Thus, the articles are used herein to refer to one or more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example, “a component” means one or more components, and thus, possibly, more than one component is contemplated and may be employed or used in an implementation of the described embodiments.

[0048] As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (e.g., humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

[0049] As used herein, “patient” refers to a human (including adults and children) or other animal. In one embodiment, “patient” refers to a human.

[0050] The term “comprising” is meant to be open ended, including the indicated component but not excluding other elements.

[0051] “Stereoisomers” refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include enantiomer, diastereomers, conformer (rotamer), geometric (cis/trans) isomer, atropisomer, etc.

[0052] “chirality” refers to a molecule which is non-superimposable with its mirror image; whereas “achirality” refers to a molecule which is superimposable with its mirror image.

[0053] “Enantiomers” refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0054] “Diastereomer” refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties or biological activities. Mixture of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography such as HPLC.

[0055] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., “*Stereochemistry of Organic Compounds*”, John Wiley & Sons, Inc., New York, 1994.

[0056] Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes *D* and *L*, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes *d* and *l* or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or *l* meaning that the compound is levorotatory. A compound prefixed with (+) or *d* is dextrorotatory. A specific stereoisomer may be referred to as an enantiomer, and a mixture of such stereoisomers is called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process.

[0057] Any asymmetric atom (e.g., carbon, and the like) of the compounds disclosed herein can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)-configuration. In certain embodiments, each asymmetric atom has at least 50% enantiomeric excess, at least 60% enantiomeric excess, at least 70% enantiomeric excess, at least 80% enantiomeric excess, at least 90% enantiomeric excess, at least 95% enantiomeric excess, or at least 99% enantiomeric excess in the (*R*)- or (*S*)- configuration.

[0058] Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible stereoisomers or as mixtures thereof, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be *E* or *Z* configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a *cis*- or *trans*-configuration.

[0059] Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric isomers, enantiomers, diastereomers, for example, by chromatography and/or fractional crystallization.

[0060] Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by methods known to those skilled in the art, e.g., by separation of the diastereomeric salts thereof. Racemic products can also be resolved by chiral chromatography, e.g., high performance liquid chromatography (HPLC) using a chiral adsorbent. Preferred

enantiomers can also be prepared by asymmetric syntheses. See, for example, Jacques, et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); *Principles of Asymmetric Synthesis* (2nd Ed. Robert E. Gawley, Jeffrey Aubé, Elsevier, Oxford, UK, 2012); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972); *Chiral Separation Techniques: A Practical Approach* (Subramanian, G. Ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2007).

[0061] The term “tautomer” or “tautomeric form” refers to structural isomers of different energies which are interconvertible via a low energy barrier. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. For example, protontautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(*lH*)-one tautomers. Unless otherwise stated, all tautomeric forms of the compounds disclosed herein are within the scope of the invention.

[0062] As described herein, compounds disclosed herein may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase “optionally substituted” is used interchangeably with the phrase “substituted or unsubstituted”. In general, the term “substituted” refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. Wherein the substituents include, but are not limited to, deuterium, hydroxy, amino, fluorine, chlorine, bromine, iodine, cyano, azido, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, heteroaryloxy, oxo, carboxy, haloalkyl,

hydroxy-substituted alkyl, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)₂-, hydroxy-substituted-S(=O)-, hydroxy-substituted-S(=O)₂-, carboxyalkoxy, and the like.

[0063] Unless otherwise defined herein, for a variable that occurs more than one time in any substituent or in the compound of the invention or any other formulae herein, its definition on each occurrence is independent of its definition at every other occurrence. Combinations of substituents are permissible only if such combinations result in stable compound. Stable compounds are compounds which can be isolated in a useful degree of purity from a reaction mixture.

[0064] Furthermore, what need to be explained is that the phrase “each...is independently” is used interchangeably with the phrase “each (of)...and...is independently” and “...is independently” in the invention, unless otherwise stated. It should be broadly understood that the specific options expressed by the same symbol are independent of each other in different radicals; or the specific options expressed by the same symbol are independent of each other in the same radicals. For example, the specific options of the R⁹ groups in structural formulas “-N(R⁹)-C(=O)-NR^{9a}R^{9ab}” and “R^{9a}R⁹N-C₁₋₆-alkyl-” are independent of each other. Similarly, the specific options of the R⁹ groups in structural formula “-N(R⁹)-C(=O)-NR^{9a}R^{9ab}” are independent of each other.

[0065] At various places in the present specification, substituents of compounds disclosed herein are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term “C₁-C₆ alkyl” or “C₁₋₆ alkyl” is specifically intended to individually disclose methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl.

[0066] At various places in the present specification, linking substituents are described. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists “alkyl” or “aryl”, then it is understood that the “alkyl” or “aryl” represents a linking alkylene group or arylene group, respectively.

[0067] The term “alkyl” or “alkyl group” refers to a saturated linear or branched-chain monovalent hydrocarbon radical of 1 to 20 carbon atoms, wherein the alkyl radical may be

optionally substituted with one or more substituents described herein, wherein the substituent is, deuterium, hydroxy, amino, fluorine, chlorine, bromine, iodine, cyano, azido, heteroaryl, alkoxy, alkylamino, alkylthio, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, heteroaryloxy, oxo, carboxy, haloalkyl, hydroxy-substituted alkyl, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)₂-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-S(=O)₂-, carboxyalkoxy, and the like. Unless otherwise specified, the alkyl group contains 1-20 carbon atoms. In some embodiments, the alkyl group contains 1-12 carbon atoms. In other embodiments, the alkyl group contains 1-6 carbon atoms. In still other embodiments, the alkyl group contains 1-4 carbon atoms, and in yet other embodiments, the alkyl group contains 1-3 carbon atoms.

[0068] Some non-limiting examples of alkyl group include, but are not limited to, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (*n*-Pr, *n*-propyl, -CH₂CH₂CH₃), 2-propyl (*i*-Pr, *i*-propyl, -CH(CH₃)₂), 1-butyl (*n*-Bu, *n*-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, -CH₂CH(CH₃)₂), 2-butyl (*s*-Bu, *s*-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, -C(CH₃)₃), 1-pentyl (*n*-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), 1-heptyl, 1-octyl, and the like.

[0069] The term “alkylene” refers to a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms. Unless otherwise specified, the alkylene group contains 1-12 carbon atoms. In some embodiments, the alkylene group contains 1-6 carbon atoms. In other embodiments, the alkylene group contains 1-4 carbon atoms. In other embodiments, the alkylene group contains 1-3 carbon atoms. In still other embodiments, the alkylene group contains 1-2 carbon atoms, and is exemplified by methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), isopropylene

(-CH(CH₃)CH₂-), and the like.

[0070] The term “alkenyl” refers to linear or branched-chain monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp² double bond, wherein the alkenyl radical may be optionally substituted with one or more substituents described herein, and includes radicals having “cis” and “trans” orientations, or alternatively, “E” and “Z” orientations. In some embodiments, the alkenyl group contains 2 to 8 carbon atoms; in other embodiments, the alkenyl group contains 2 to 6 carbon atoms; in still other embodiments, the alkenyl group contains 2 to 4 carbon atoms. Examples of alkenyl group include, but are not limited to, ethylenyl or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), and the like.

[0071] The term “alkynyl” refers to a linear or branched monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted with one or more substituents described herein. In some embodiments, the alkynyl group contains 2 to 8 carbon atoms; in other embodiments, the alkynyl group contains 2 to 6 carbon atoms. in still other embodiments, the alkynyl group contains 2 to 4 carbon atoms. Examples of the alkynyl group include, but are not limited to, ethynyl (-C≡CH), propargyl (-CH₂C≡CH), 1-propynyl (-C≡C-CH₃), and the like.

[0072] The terms “carboxy” or “carboxyl”, whether used alone or with other terms, such as “carboxyalkyl”, refers to -CO₂H or -COOH. The term “carbonyl”, whether used alone or with other terms, such as “aminocarbonyl” or “acyloxy”, denotes -(C=O)-. The term “cycloalkylcarboxy”, “heterocyclylcarboxy” “arylcarboxy” or “heteroarylcarboxy” respectively refers to a cycloalkyl, heterocyclyl, aryl or heteroaryl attached to the rest of molecular via carbonyl (C=O).

[0073] The term “H” refers to a single hydrogen atom. Such group can be linked with other terms, for example, linked with oxygen atom to form a hydroxy group.

[0074] The terms “D” or “²H” refers to a single deuterium atom. For example, methyl may be substituted with one such atom to form one deuterium substituted methyl (CDH₂); methyl may be substituted with two deuterium atom to form two deuteriums substituted methyl (CD₂H); and methyl may be substituted with three deuterium atom to form three deuteriums substituted methyl (CD₃).

[0075] The term “azido” or “N₃” refers to an azide moiety. This radical may be attached to

other groups, for example, to a methyl group to form azidomethane (methyl azide, MeN_3); or attached to a phenyl group to form phenyl azide (PhN_3).

[0076] The term “heteroalkyl” refers to an alkyl chain into which one or more heteroatoms can be inserted, wherein the alkyl group and heteroatom are as defined herein. Unless otherwise stated, the heteroalkyl group contains 1 to 12 carbon atoms. In some embodiments, the heteroalkyl group contains 1 to 10 carbon atoms; in other embodiments, the heteroalkyl group contains 1 to 5 carbon atoms; in still other embodiments, the heteroalkyl group contains 1 to 4 carbon atoms. Examples of heteroalkyl group include, but are not limited to, CH_3OCH_2- , $\text{CH}_3\text{CH}_2\text{OCH}_2-$, CH_3SCH_2- , $(\text{CH}_3)_2\text{NCH}_2-$, $(\text{CH}_3)_2\text{CH}_2\text{OCH}_2-$, $\text{CH}_3\text{OCH}_2\text{CH}_2-$, $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2-$, $\text{CH}_3\text{C}(=\text{O})\text{CH}_2-$, $\text{CH}_3\text{C}(=\text{O})\text{OCH}_2-$, $\text{CH}_3\text{S}(=\text{O})_2\text{OCH}_2-$, and the like.

[0077] The term “unsaturated” refers to a moiety having one or more units of unsaturation.

[0078] The term “heteroatom” refers to oxygen (O), sulfur (S), nitrogen (N), phosphorus (P), or silicon (Si), including any oxidized form of nitrogen (N), sulfur (S), or phosphorus (P); the quaternized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR (as in *N*-substituted pyrrolidinyl).

[0079] The term “halogen” refers to Fluorine (F), Chlorine (Cl), Bromine (Br), or Iodine (I).

[0080] The term “hydroxy-substituted alkyl”, “hydroxy-substituted alkoxy” or “hydroxy-substituted alkylamino” respectively refers to an alkyl, alkoxy or alkylamino substituted with one or more hydroxy groups, wherein each of the alkyl, alkoxy or alkylamino is as defined herein. Examples of such groups include, but are not limited to, hydroxymethyl, hydroxyethyl, 1,2-dihydroxyethyl, hydroxymethoxy, hydroxyethoxy, hydroxymethylamino, hydroxyethylamino, and the like.

[0081] The terms “haloalkyl”, “haloalkenyl” or “haloalkoxy” respectively refers to an alkyl, alkenyl, or alkoxy, as the case may be, substituted with one or more halogen atoms. Such examples include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, and the like.

[0082] The term “alkoxy” refers to an alkyl group, as previously defined, attached to the rest of the molecule via an oxygen atom. Unless otherwise specified, the alkoxy group contains 1-12 carbon atoms. In some embodiments, the alkoxy group contains 1-6 carbon atoms. In other

embodiments, the alkoxy group contains 1-4 carbon atoms. In still other embodiments, the alkoxy group contains 1-3 carbon atoms. The alkoxy radical is optionally substituted with one or more substituents described herein.

[0083] Some non-limiting examples of the alkoxy group include, but are not limited to, methoxy (MeO, -OCH₃), ethoxy (EtO, -OCH₂CH₃), 1-propoxy (*n*-PrO, *n*-propoxy, -OCH₂CH₂CH₃), 2-propoxy (*i*-PrO, *i*-propoxy, -OCH(CH₃)₂), 1-butoxy (*n*-BuO, *n*-butoxy, -OCH₂CH₂CH₂CH₃), 2-methyl-1-propoxy (*i*-BuO, *i*-butoxy, -OCH₂CH(CH₃)₂), 2-butoxy (*s*-BuO, *s*-butoxy, -OCH(CH₃)CH₂CH₃), 2-methyl-2-propoxy (*t*-BuO, *t*-butoxy, -OC(CH₃)₃), 1-pentoxy (*n*-pentoxy, -OCH₂CH₂CH₂CH₂CH₃), 2-pentoxy (-OCH(CH₃)CH₂CH₂CH₃), 3-pentoxy (-OCH(CH₂CH₃)₂), 2-methyl-2-butoxy (-OC(CH₃)₂CH₂CH₃), 3-methyl-2-butoxy (-OCH(CH₃)CH(CH₃)₂), 3-methyl-1-butoxy (-OCH₂CH₂CH(CH₃)₂), 2-methyl-1-butoxy (-OCH₂CH(CH₃)CH₂CH₃), and the like.

[0084] The term “alkylthio” refers to a linear or branched-chain alkyl radical of 1 to 6 carbon atoms attached to a bivalent sulfur atom. In some embodiments, the alkylthio radical is a lower C₁₋₄ alkylthio” radical, such examples include, but are not limited to, CH₃S-

[0085] The term “alkylamino” embraces “*N*-alkylamino” and “*N,N*-dialkylamino”, that is an amino group independently substituted with one or two alkyl radicals. In some embodiments, the alkylamino radical is a “lower alkylamino” radical having one or two C₁₋₆ alkyl radicals attached to a nitrogen atom. In other embodiments, the alkylamino radical is a “lower alkylamino” radical having 1-3 carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino. Examples of such groups include, but are not limited to, *N*-methylamino, *N*-ethylamino, *N,N*-dimethylamino, *N,N*-diethylamino, and the like.

[0086] The term “aminoalkyl” or “amino-substituted alkyl” refers to a linear or branched alkyl radical having one to ten carbon atoms substituted with one or more amino radicals. More preferred aminoalkyl radical is a “lower aminoalkyl” radical having 1-6 carbon atoms. Non-limiting examples of the aminoalkyl radical include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl.

[0087] The term “*n*-membered” where *n* is an integer typically describes the number of ring-forming atoms in a moiety and the number of ring-forming atoms is *n*. For example, piperidinyl is an example of a 6 membered heterocycloalkyl and 1,2,3,4-tetrahydro-naphthalene

is an example of a 10 membered carbocyclyl group.

[0088] The terms “cycle” or “ring” refer to “carbocyclic”, “heterocyclic”, “aromatic”, “heteroaromatic”, “spirocyclic”, “spiroheterocyclic”, “fused cyclic”, “fused heterocyclic”, and the like, and wherein “carbocyclic”, “heterocyclic”, “aromatic”, “heteroaromatic”, “spirocyclic”, “spiroheterocyclic”, “fused cyclic” and “fused heterocyclic” are defined as described herein.

[0089] The terms “fused bicyclic ring”, “fused cyclic”, “fused bicycyl” or “fused cyclyl” as used interchangeably herein refers to a monovalent or multivalent saturated or partially unsaturated bridged-ring system, which refers to a bicyclic ring system that is not a aromatic system. Such system may be an isolated or conjugated unsaturated system, but its core structure is not a aromatic or heteroaromatic ring (but an aromatic group can be a substituent).

[0090] The terms “spirocyclyl”, “spirocyclic”, “spiro bicycyl” or “spiro bicyclic” as used interchangeably refers to a monovalent or multivalent, saturated or partially unsaturated ring system wherein a ring originating from a particular annular carbon of another ring. For example, as depicted below, a saturated bridged ring system (ring B and B') is termed as “fused bicyclic”, whereas ring A and ring B share an atom between the two saturated ring system, which terms as a “spirocyclyl” or “spiro bicycyl”. Each ring in the fused bicycyl or the spiro bicycyl can be either a carbocyclyl or a heterocyclyl, and each ring is optionally substituted with one or more substituents described herein.

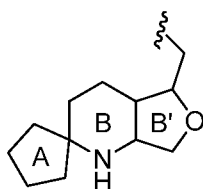


Figure a

[0091] The term “heterocycloalkyl” refers to a monovalent or multivalent saturated ring having 3 to 12 ring atoms as a monocyclic, bicyclic, or tricyclic ring system in which at least one ring atom is selected from nitrogen, sulfur and oxygen.

[0092] The term “carbocycle”, “carbocyclyl”, or “carbocyclic ring” refers to a monovalent or multivalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms as a monocyclic, bicyclic or tricyclic ring system. A carbobicyclic ring system includes a spiro carbobicycyl or a fused carbobicycyl. Suitable carbocyclyl groups include, but are not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl. Further examples of carbocyclyl group include

cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, and the like.

[0093] The term “cycloalkyl” refers to a monovalent or multivalent saturated ring having 3 to 12 carbon atoms as a monocyclic, bicyclic, or tricyclic ring system. In some embodiments, the cycloalkyl group contains 3 to 12 carbon atoms. In other embodiments, the cycloalkyl group contains 3 to 8 carbon atoms. In still other embodiments, the cycloalkyl group contains 3 to 6 carbon atoms. The cycloalkyl radical can be independently substituted with one or more substituents described herein.

[0094] The term “cycloalkylalkyl” refers to an alkyl group substituted with one or more cycloalkyl radicals, wherein the cycloalkyl and alkyl group are as defined herein. Examples of such groups include, but are not limited to, cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclobutylmethyl, cyclobutylethyl, cyclobutylpropyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, and the like.

[0095] The term “cycloalkoxy” or “carbocycloxy” respectively refers to an optionally substituted cycloalkyl group or carbocyclyl group attached to the parent molecular via an oxygen atom, wherein the cycloalkyl and carbocyclyl group are as defined herein. Examples of such group include, but are not limited to, cyclopropoxy, cyclopentoxy, cyclohexoxy, hydroxy-substituted cyclopropoxy, and the like.

[0096] The term “cycloalkylamino” refers to an amino group substituted with one or two optionally substituted cycloalkyl radicals described herein. Examples of such group include, but are not limited to, cyclopropylamino, cyclopentylamino, cyclohexylamino, hydroxy-substituted cyclopropylamino, dicyclohexylamino, dicyclopropylamino, and the like.

[0097] The term “cycloalkyl alkoxy”, “cycloalkyl-alkoxy” or “cycloalkylalkoxy” (“carbocyclylalkoxy”) refers to an alkoxy group substituted with one or more cycloalkyl (“carbocyclyl”) groups, wherein the cycloalkyl (“carbocyclyl”) and alkoxy group are as defined herein. Examples of such groups include, but are not limited to, cyclopropylmethoxy, cyclopropylethoxy, cyclopentylethoxy, cyclohexylethoxy, cyclohexylmethoxy, cyclopropylpropoxy, and the like.

[0098] The term “heterocyclic”, “heterocyclyl”, or “heterocyclic ring” as used interchangeably herein refers to a saturated or partially unsaturated monocyclic, bicyclic or tricyclic ring containing 3-12 ring atoms of which at least one ring atom is selected from nitrogen, sulfur and oxygen, and which may, unless otherwise specified, be carbon or nitrogen linked, and of which a -CH₂- group can optionally be replaced by a -C(=O)- group. Ring sulfur atoms may be optionally oxidized to form *S*-oxides. Ring nitrogen atoms maybe optionally oxidized to form *N*-oxides. Examples of heterocyclyl include, but are not limited to, oxiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrazolidinyl, imidazoliny, imidazolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, 1,3-dioxolanyl, dithiolanyl, tetrahydropyranyl, dihydropyranyl, 2*H*-pyranyl, 4*H*-pyranyl, tetrahydrothiopyranyl, piperidinyl, tetrahydropyridinyl, morpholinyl, thiomorpholinyl, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, piperazinyl, dioxanyl, dithianyl, thioxanyl, homopiperazinyl, homopiperidinyl, oxepanyl, thiepanyl, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl. Some non-limiting examples of the heterocyclyl group wherein -CH₂- group is replaced by -C(O)- moiety are 2-oxopyrrolidinyl, oxo-1,3-thiazolidinyl, 2-piperidinonyl and 3,5-dioxopiperidinyl. Some non-limiting examples of heterocyclyl wherein the ring sulfur atom is oxidized is sulfolanyl, 1,1-dioxo-thiomorpholinyl. The heterocyclyl group is optionally substituted with one or more substituents described herein.

[0099] In one embodiment, the heterocyclyl group may be 4-7 membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 4-7 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen, and which may, unless otherwise specified, be carbon or nitrogen linked, and of which a -CH₂- group can optionally be replaced by a -C(=O)- group. Ring sulfur atoms may be optionally oxidized to form *S*-oxides. Ring nitrogen atoms maybe optionally oxidized to form *N*-oxides. Examples of 4-7 membered heterocyclyl include, but are not limited to, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrazolidinyl, imidazoliny, imidazolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, 1,3-dioxolanyl, dithiolanyl, tetrahydropyranyl, dihydropyranyl, 2*H*-pyranyl, 4*H*-pyranyl, tetrahydrothiopyranyl, piperidinyl, tetrahydropyridinyl, morpholinyl, thiomorpholinyl, piperazinyl, dioxanyl, dithianyl, thioxanyl, homopiperazinyl, homopiperidinyl, oxepanyl, thiepanyl. Some non-limiting examples of heterocyclyl wherein -CH₂- group is replaced by -C(=O)- moiety are 2-oxopyrrolidinyl, oxo-1,3-thiazolidinyl,

2-piperidinonyl and 3,5-dioxopiperidinyl. Some non-limiting examples of heterocyclyl wherein the ring sulfur atom is oxidized is sulfolanyl, 1,1-dioxo-thiomorpholinyl. The 4-7 membered heterocyclyl group is optionally substituted with one or more substituents described herein.

[00100] In another embodiment, heterocyclyl may be 4-membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 4 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen, and which may, unless otherwise specified, be carbon or nitrogen linked, and of which a $-\text{CH}_2-$ group can optionally be replaced by a $-\text{C}(=\text{O})-$ group. Ring sulfur atoms may be optionally oxidized to form *S*-oxides. Ring nitrogen atoms maybe optionally oxidized to form *N*-oxides. Examples of 4-membered heterocyclyl include, but are not limited to, azetidiny, oxetanyl, thietanyl. The 4-membered heterocyclyl group is optionally substituted with one or more substituents described herein.

[00101] In another embodiment, heterocyclyl may be a 5-membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 5 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen, and which may, unless otherwise specified, be carbon or nitrogen linked, and of which a $-\text{CH}_2-$ group can optionally be replaced by a $-\text{C}(=\text{O})-$ group. Ring sulfur atoms may be optionally oxidized to form *S*-oxides. Ring nitrogen atoms maybe optionally oxidized to form *N*-oxides. Examples of 5-membered heterocyclyl include, but are not limited to, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, 1,3-dioxolanyl, dithiolanyl. Some non-limiting examples of heterocyclyl wherein $-\text{CH}_2-$ group is replaced by $-\text{C}(=\text{O})-$ moiety are 2-oxopyrrolidinyl, oxo-1,3-thiazolidinyl. A non-limiting example of heterocyclyl wherein the ring sulfur atom is oxidized is sulfolanyl. The 5-membered heterocyclyl group is optionally substituted with one or more substituents described herein.

[00102] In still another embodiment, heterocyclyl may be a 6-membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen, and which may, unless otherwise specified, be carbon or nitrogen linked, and of which a $-\text{CH}_2-$ group can optionally be replaced by a $-\text{C}(=\text{O})-$ group. Ring sulfur atoms may be optionally oxidized to form *S*-oxides. Ring nitrogen atoms maybe optionally oxidized to form *N*-oxides. Examples of 6 membered

heterocyclyl include, but are not limited to, tetrahydropyranyl, dihydropyranyl, 2*H*-pyranyl, 4*H*-pyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, dioxanyl, dithianyl, thioxanyl. Some non-limiting examples of heterocyclyl wherein -CH₂- group is replaced by -C(=O)- moiety are 2-piperidinonyl, 3,5-dioxypiperidinyl. A non-limiting example of heterocyclyl wherein the ring sulfur atom is oxidized is 1,1-dioxo-thiomorpholinyl. The 6-membered heterocyclyl group is optionally substituted with one or more substituents described herein.

[00103] In yet another embodiment, heterocyclyl refers to a 7-12 membered heterocyclyl, which refers to a saturated or partially unsaturated spiro or fused bicyclyl ring containing 7-12 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen, and which may, unless otherwise specified, be carbon or nitrogen linked, and of which a -CH₂- group can optionally be replaced by a -C(=O)- group. Ring sulfur atoms may be optionally oxidized to form *S*-oxides. Ring nitrogen atoms maybe optionally oxidized to form *N*-oxides. Examples of 7-12 membered heterocyclyl include, but are not limited to, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl. The 7-12 membered heterocyclyl group is optionally substituted with one or more substituents described herein.

[00104] The term “heterocyclylalkyl” refers to an heterocyclyl substituted alkyl, wherein the heterocyclyl radical and alkyl radical are as defined herein. Examples of the heterocyclylalkyl group include, but are not limited to thiomorpholin-4-ylmethyl, tetrahydrofuran-3-ylmethyl, oxetan-3-ylmethyl, pyrrolidin-2-ylmethyl, morpholin-4-ylmethyl, and the like.

[00105] The term “heterocyclylalkoxy” refers to a heterocyclyl substituted alkoxy, wherein the oxygen atom is attached to the rest group of molecule. The term “heterocyclylalkylamino” refers to a heterocyclyl substituted alkylamino, and wherein the nitrogen atom is attached to the rest group of molecule. Wherein the heterocyclyl, alkoxy and alkylamino are as defined herein. Examples of such group include, but are not limited to, pyrrolidin-2-ylmethoxy, morpholin-2-ylethoxy, morpholin-3-ylethoxy, piperazin-2-ylethoxy, piperidin-4-ylethamino, and the like.

[00106] The term “heterocycloxy” refers to an optionally substituted heterocyclyl described herein attached to an oxygen atom, and wherein the oxygen atom is attached to the rest group of

molecule. Examples of such group include, but are not limited to, pyrrolidin-2-oxy, pyrrolidin-3-oxy, piperidin-2-oxy, piperidin-3-oxy, piperazin-2-oxy, piperidin-4-oxy and the like.

[00107] The term “heterocyclamino” refers to an amino substituted with one or two heterocycl radicals, wherein nitrogen atom is attached to the rest group of the molecule and heterocycl is as defined herein. Examples of such group include, but are not limited to, pyrrolidin-2-amino, pyrrolidin-3-amino, piperidin-2-amino, piperidin-3-amino, piperidin-4-amino, piperazin-2-amino, and the like.

[00108] The term “aryl” refers to an monocyclic, bicyclic, or tricyclic carbocyclic ring system having a total of 6 to 14 ring members, preferably, 6 to 12 ring members, and more preferably 6 to 10 ring members, wherein at least one ring in the system is aromatic and each ring in the system contains 3 to 7 ring members and that has one or more points of attachment to the rest of the molecule. The term “aryl” may be used interchangeably with the term “aryl ring” or “aromatic.” Examples of aryl ring would include phenyl, naphthyl, and anthracene. Optionally the aryl radical is independently substituted with one or more substituents described herein.

[00109] The term “aralkyl” or “arylalkyl” refers to an aryl-substituted alkyl radical. In some embodiments, aralkyl radical or arylalkyl radical is a “lower aralkyl” radical having an aryl radical attached to an alkyl radical having one to six carbon atoms. In other embodiments, aralkyl radical or arylalkyl radical is a “phenylalkyl”, alkyl portion of which having one to four carbon atoms. Some non-limiting examples of such radical include benzyl, diphenylmethyl and phenylethyl. The aryl group of arylalkyl radical is further substituted with halogen, alkyl, alkoxy, haloalkyl and haloalkoxy.

[00110] The term “aryloxy” refers to an optionally substituted aryl group attached to the rest of the molecule via an oxygen atom, wherein the aryl group is as defined herein. Examples of such group include, but are not limited to, phenoxy, tolyloxy, ethylphenoxy, and the like.

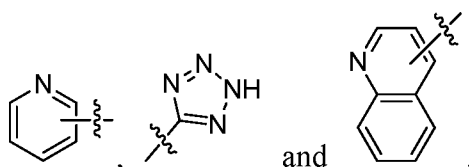
[00111] The term “arylamino” refers to an amino group substituted with one or two aryl radicals. Examples of such group include, but are not limited to, *N*-phenylamino. In some embodiments, the aryl ring of arylamino radical can further be substituted.

[00112] The term “arylalkylamino” refers to an alkylamino group substituted with one or more

optionally substituted aryl radicals, wherein the aryl and alkylamino are as defined herein. Examples of such group include, but are not limited to, phenylmethyamino, phenylethylamino, phenylpropylamino, *p*-tolylmethyamino, and the like.

[00113] The term “arylalkoxy” refers to an alkoxy group, which is substituted with one or more optionally substituted aryl radicals, wherein the aryl and alkoxy are as defined herein. Examples of such group include, but are not limited to, phenylmethoxy, phenylethoxy, *p*-tolylmethoxy, phenylpropoxy, and the like.

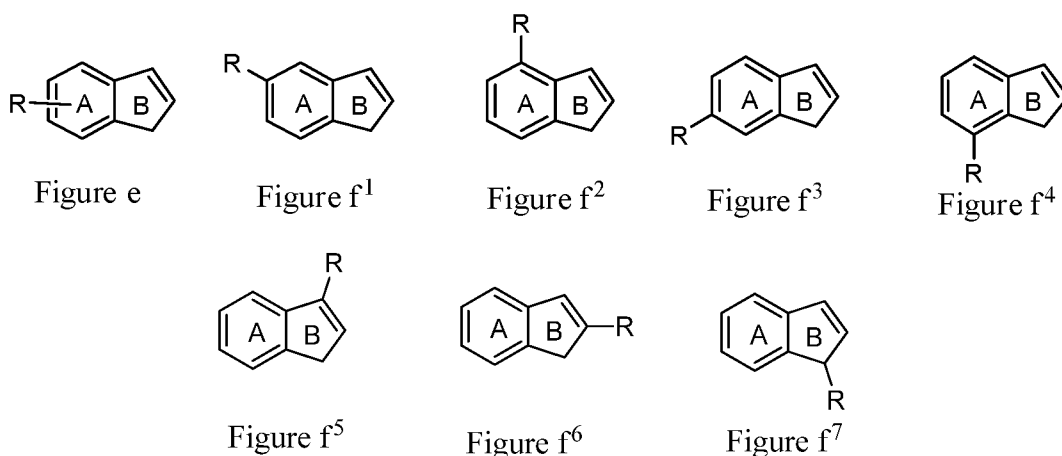
[00114] The term “heteroaryl” refers to a monocyclic, bicyclic, or tricyclic ring system having a total of 5 to 12 ring members, preferably, 5 to 10 ring members, and more preferably 5 to 6 ring members, wherein at least one ring in the system is aromatic and at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 5 to 7 ring members and the heteroaryl group has one or more points of attachment to the rest of the molecule. The term “heteroaryl” may be used interchangeably with the term “heteroaryl ring”, “aromatic heterocyclic” or the term “heteroaromatic”. The heteroaryl radicals is optionally substituted with one or more substituents described herein. In one embodiment, a 5-10 membered heteroaryl comprises 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, such as



[00115] Some non-limiting examples of heteroaryl group include 2-furanyl, 3-furanyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (e.g., 5-tetrazolyl), triazolyl (e.g., 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, pyrazolyl (e.g., 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, pyrazinyl, 1,3,5-triazinyl, pyrimidonyl, pyridonyl, and the following non-limiting bicycles: benzimidazolyl, benzofuryl, tetrahydrobenzofuryl, benzothienyl, indolyl (e.g., 2-indolyl), purinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl),

tetrahydroquinolinyl (1,2,3,4-tetrahydroquinolinyl), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl or 4-isoquinolinyl), tetrahydroisoquinolinyl (1,2,3,4-tetrahydroisoquinolinyl), imidazo[1,2-*a*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidyl, imidazo[1,2-*b*]pyridazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, or [1,2,4]triazolo[1,5-*a*]pyridyl, and the like.

[00116] As described herein, a bond drawn from a substituent to the center of one ring within a ring system (as shown below) represents substitution of the substituent at any substitutable position on the rings. For example, Figure e represents possible substitution in any of the positions on the A ring and B ring, as shown in Figure f¹-f⁷:



[00117] The term “heteroarylamino” refers to an amino group substituted with one or two optionally substituted heteroaryl radicals, wherein the heteroaryl is as defined herein. Examples of such group include, but are not limited to, *N*-thienylamino, pyridin-4-ylamino, *m*-fluoropyridylamino, dipyridylamino, and the like.

[00118] The term “heteroaryloxy” refers to an optionally substituted heteroaryl group attached to a oxygen atom, and the oxygen atom is attached to the rest group of molecule, wherein the heteroaryl group is as defined herein. Examples of such group include, but are not limited to, pyridyloxy, pyrimidyloxy, and the like.

[00119] The term “heteroarylalkyl” refers to an alkyl group substituted with one or more heteroaryl radicals, wherein the heteroaryl and alkyl are as defined herein. Examples of such group include, but are not limited to, imidazol-2-ylmethyl, furan-2-ylethyl, indol-3-ylmethyl, and the like.

[00120] The term “heteroarylalkylamino” refers to an heteroarylalkyl group contained a

nitrogen atom, and attached to the other groups via the nitrogen atom, wherein the heteroarylalkyl group is as defined herein. Examples of such group include, but are not limited to, pyridin-2-ylmethylamino, thiazol-2-ylethylamino, imidazol-2-ylethylamino, pyrimidin-2-ylpropamino, pyrimidin-2-ylmethyamino, and the like.

[00121] The term “heteroarylalkoxy” refers to an heteroarylalkyl group contained an oxygen atom, and attached to the other groups via the oxygen atom, wherein the heteroarylalkyl group is as defined herein. Examples of such group include, but are not limited to, pyridin-2-ylmethoxy, thiazol-2-ylethoxy, imidazol-2-ylethoxy, pyrimidin-2-ylpropoxy, pyrimidin-2-ylmethoxy, and the like.

[00122] The term “prodrug” refers to a compound that is transformed in vivo into a compound of formula (I), (I') or (II). Such a transformation can be affected, for example, by hydrolysis in blood or enzymatic transformation of the prodrug form to the parent form in blood or tissue. Prodrugs of the compounds disclosed herein may be, for example, esters. Esters that may be utilized as prodrugs in the present invention are phenyl esters, aliphatic (C₁-C₂₄) esters, acyloxymethyl esters, carbonates, carbamates, and amino acid esters. For example, a compound disclosed herein that contains an hydroxy group may be acylated at this position to form its prodrug. Other prodrug forms include phosphates, such as, those phosphates resulting from the phosphonation of an hydroxy group on the parent compound. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of *the A.C.S. Symposium Series*, Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, J. Rautio et al., *Prodrugs: Design and Clinical Applications*, *Nature Review Drug Discovery*, 2008, 7, 255-270, and S. J. Hecker et al., *Prodrugs of Phosphates and Phosphonates*, *Journal of Medicinal Chemistry*, 2008, 51, 2328-2345, each of which is incorporated herein by reference.

[00123] A “metabolite” is a product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzyme cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds disclosed herein,

including compounds produced by a process comprising contacting a compound disclosed herein with a mammal for a period of time sufficient to yield a metabolic product thereof.

[00124] A “pharmaceutically acceptable salts” refers to organic or inorganic salts of a compound disclosed herein. Pharmaceutically acceptable salts are well known in the art. For example, S.M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmacol Sci*, 1977, 66, 1-19, which is incorporated herein by reference. Some non-limiting examples of pharmaceutically acceptable salts formed with non-toxic acid include salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphanic acid salt, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, laurylsulfate, malate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, stearate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oilsoluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_{1-8} sulfonate or aryl sulfonate.

[00125] A “solvate” refers to an association or complex of one or more solvent molecules and a compound disclosed herein. Some non-limiting examples of solvents that form solvates include water, isopropanol, ethanol, methanol, dimethylsulfoxide, ethyl acetate, acetic acid, and

ethanolamine. The term “hydrate” refers to the complex where the solvent molecule is water.

[00126] The term “protecting group” or “PG” refers to a substituent that is commonly employed to block or protect a particular functionality while reacting with other functional groups on the compound. For example, an “amino-protecting group” is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Some non-limiting examples of suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC, Boc), benzyloxycarbonyl (CBZ, Cbz) and 9-fluorenylmethyloxycarbonyl (Fmoc). Similarly, a “hydroxy-protecting group” refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Some non-limiting examples of suitable hydroxy-protecting groups include acetyl and silyl. A “carboxy-protecting group” refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Some non-limiting examples of common carboxy-protecting groups include -CH₂CH₂SO₂Ph, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(*p*-nitrophenylsulfonyl)ethyl, 2-(diphenylphosphino)ethyl, nitroethyl, and the like. For a general description of protecting groups and their use, see Greene et al., *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991 and Kocienski et al., *Protecting Groups*, Thieme, Stuttgart, 2005.

[00127] As used herein, the term “treat”, “treating” or “treatment” of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, “treating” or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, “treating” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, “treat”, “treating” or “treatment” refers to preventing or delaying the onset or development or progression of the disease or disorder.

[00128] Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlorotheophyllinate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate,

hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, 5-sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

[00129] Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

[00130] Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, sulfosalicylic acid, and the like.

[00131] Pharmaceutically acceptable base addition salts can be formed with inorganic or organic bases.

[00132] Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

[00133] Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

[00134] The pharmaceutically acceptable salts of the present invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, and the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in

“*Remington’s Pharmaceutical Sciences*”, 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in “*Handbook of Pharmaceutical Salts: Properties, Selection, and Use*” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[00135] Furthermore, the compounds disclosed herein, including their salts, can also be obtained in the form of their hydrates, or include other solvents such as ethanol, DMSO, and the like, used for their crystallization. The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms.

[00136] Any formula given herein is also intended to represent isotopically unenriched forms as well as isotopically enriched forms of the compounds. Isotopically enriched compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chlorine, such as ^2H (deuterium, D), ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , ^{125}I , respectively.

[00137] In another aspect, the compounds of the invention include isotopically enriched compounds as defined herein, for example those into which radioactive isotopes, such as ^3H , ^{14}C and ^{18}F , or those into which non-radioactive isotopes, such as ^2H and ^{13}C are present. Such isotopically enriched compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F -enriched compound may be particularly desirable for PET or SPECT studies. Isotopically-enriched compounds of Formula (I), (I') or (II) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

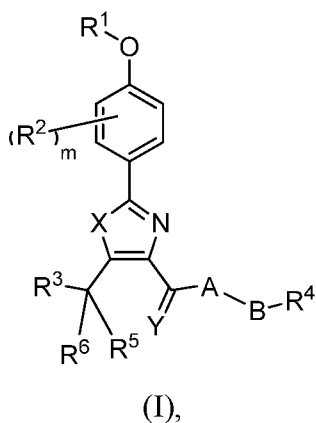
[00138] Further, substitution with heavier isotopes, particularly deuterium (i.e., ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic

index. It is understood that deuterium in this context is regarded as a substituent of a compound of Formula (I), (I') or (II). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D₂O, acetone-*d*₆, DMSO-*d*₆.

DESCRIPTION OF COMPOUNDS OF THE INVENTION

[00139] Provided herein are heteroaromatic derivatives, pharmaceutically acceptable salts, and pharmaceutical preparations thereof, which have PDE-4 antagonist activities, and especially have potential effects on the treatment of chronic respiratory obstruction.

[00140] In one aspect, provided herein are compounds having Formula (I), or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein

m is 0, 1, 2, 3 or 4;

p is 0, 1 or 2;

each e is independently 0, 1 or 2;

each f is independently 0, 1 or 2;

X is -N(R⁸)-, -O- or -S-;

Y is O or S;

A is a bond or -N(R⁷)-;

B is -(CR^aR^b)_p-;

R¹ is D, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₁₋₆ haloalkyl, R^{9a}R⁹N-C₁₋₆-alkyl-, C₁₋₆ alkyl-C(=O)-, -C(=O)OR^{9c}, -C(=O)-NR⁹R^{9a}, R⁹R^{9a}N-S(=O)₂-, R^{9d}-S(=O)₂-, R^{9d}-S(=O)-C₁₋₆-alkyl-, R⁹R^{9a}N-C(=O)-C₁₋₆-alkyl-, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl or C₁₋₉ heteroaryl-C₁₋₆-alkyl;

each R² is independently H, D, F, Cl, Br, I, CN, NO₂, OH, NH₂, -S(=O)₂Cl, R^{9a}R⁹N-, -C(=O)-R^{9d}, -C(=O)-NR⁹R^{9a}, -OC(=O)-NR⁹R^{9a}, -OC(=O)OR^{9c}, -N(R⁹)-C(=O)-NR⁹R^{9a}, -N(R⁹)-C(=O)OR^{9c}, R^{9d}-S(=O)₂-, R^{9d}-S(=O)₂-N(R^{9a})-, HOC(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-NH-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₃₋₈ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₆₋₁₀ aryl-(CR^cR^d)_f-NH-C₁₋₆-alkoxy-, C₁₋₆ alkyl-NH-C(=O)-C₁₋₆-alkoxy-, R^eR^fN-C(=O)-C₁₋₆-alkoxy-, C₁₋₉ heteroaryl-C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₃₋₈ cycloalkyl-C(=O)-C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-O-C(=O)-C₁₋₆-alkoxy-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₁₋₆ alkoxy, amino-substituted C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₃₋₈ cycloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₁₀ heterocyclyloxy, C₆₋₁₀ aryl-C₁₋₆-alkoxy, C₃₋₈ cycloalkoxy or C₃₋₈ cycloalkyl-C₁₋₆-alkoxy, and wherein optionally each R² is independently substituted with one or more R¹²;

R³ is D, F, Cl, Br, I, CN, NO₂, NH₂, OH, COOH, C₁₋₆ alkylamino, NH₂-C₁₋₆ alkyl-C₁₋₉-heteroaryl-, NH₂-C₁₋₆ alkyl-C₁₋₉ heteroaryl-C₁₋₆-alkyl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀-aryl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀ aryl-C₁₋₆-alkyl-, C₁₋₆ alkyl-C(=O)-NH-, R¹³O-C(=O)-C₁₋₆-alkyl-C(=O)-NH-, C₃₋₈ cycloalkyl-C(=O)-NH- or -C(=O)-NR⁹R^{9a};

each of R⁵ and R⁶ is independently H, D, F, Cl, Br, I, CN, NO₂, NH₂, OH, COOH, C₁₋₆ alkyl,

C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkylamino, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, hydroxy-substituted C₁₋₆ alkyl, mercapto-substituted C₁₋₆ alkyl, carboxy-substituted C₁₋₆ alkyl, NH₂-C₁₋₆ alkyl-C₁₋₉-heteroaryl-, NH₂-C₁₋₆ alkyl-C₁₋₉ heteroaryl-C₁₋₆-alkyl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀-aryl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀ aryl-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₁₋₉ heteroaryl-C₁₋₆-alkyl, C₃₋₈ cycloalkyl-C(=O)-NH-, -C(=O)-NR^{9a}, C₆₋₁₀ aryl or C₁₋₉ heteroaryl;

or optionally two groups selected from R³, R⁵ and R⁶, together with the carbon atom to which they are attached, form C=O;

R⁴ is C₆₋₁₀ aryl, C₆₋₁₀ aryl-S(=O)₂-, C₁₋₉ heteroaryl, C₁₋₉ heteroaryl-S(=O)₂-, C₆₋₁₀ aryl-C₁₋₆-alkyl or C₁₋₉ heteroaryl-C₁₋₆-alkyl, and wherein R⁴ is optionally substituted with one or more R¹⁴;

each of R⁷ and R⁸ is independently H, D or C₁₋₆ alkyl;

each R^a and R^b is independently H, D, F, Cl, Br, I, CN, OH, NO₂, NH₂, -COOR^{9c}, C₁₋₆ alkyl, -C(=O)-NR^{9a}, -C₁₋₆-alkyl-C(=O)-NR^{9a}, -C(=S)-NH₂, amino-substituted C₁₋₆ alkyl, -NH-C(=O)-R^{9b}, -C₁₋₆-alkyl-NH-C(=O)-R^{9b}, -NH-S(=O)₂-C₁₋₆ alkyl, -C₁₋₆-alkyl-NH-S(=O)₂-C₁₋₆ alkyl, -NH-S(=O)₂-C₃₋₈-cycloalkyl, -C₁₋₆-alkyl-NH-S(=O)₂-C₃₋₈ cycloalkyl, -S(=O)₂-C₁₋₆ alkyl, -C₁₋₆-alkyl-S(=O)₂-C₁₋₆ alkyl, C₆₋₁₀ aryl or C₁₋₉ heteroaryl; or R^a and R^b, together with the carbon atom to which they are attached, form a 3- to 8-membered ring;

each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₆ alkyl;

each R^e and R^f is independently H, OH or C₁₋₆ alkyl;

each R⁹, R^{9a}, R^{9b} and R^{9d} is independently H, D, OH, NH₂, -S(=O)₂-NH₂, -C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₆-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₆ alkyl, -S(=O)₂-C₁₋₆ alkyl, -S(=O)₂-C₃₋₈ cycloalkyl, C₁₋₆ haloalkyl, amino-substituted C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₆₋₁₀ aryl, C₂₋₁₀ heterocyclyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₆-alkylamino, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₆₋₁₀ aryloxy, C₂₋₁₀ heterocyclyloxy, C₃₋₈ cycloalkoxy, C₆₋₁₀ arylamino, C₂₋₁₀ heterocyclylamino, C₃₋₈ cycloalkylamino, C₁₋₉ heteroaryl or C₃₋₈ carbocyclyl; or R⁹ and R^{9a}, together with the nitrogen atom to which they are attached, form a 3- to 8-membered ring, and wherein optionally each 3- to 8-membered ring, R⁹, R^{9a}, R^{9b} and R^{9d} is independently substituted with one or more R¹⁵;

each R^{9c} is independently H, D, -C₁₋₆-alkyl-C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₆-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, amino-substituted C₁₋₆ alkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl or C₃₋₈ carbocyclyl;

each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ haloalkylamino, hydroxy-substituted C₁₋₆

alkyl, hydroxy-substituted C₁₋₆ alkoxy or hydroxy-substituted C₁₋₆ alkylamino;

R¹³ is H, D or C₁₋₆ alkyl;

each R¹⁴ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, -C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₆-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ haloalkylamino, hydroxy-substituted C₁₋₆ alkyl, hydroxy-substituted C₁₋₆ alkoxy, hydroxy-substituted C₁₋₆ alkylamino or C₃₋₆ cycloalkyl;

each R¹⁵ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₆ alkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₁₋₉ heteroaryl-C₁₋₆-alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl, C₃₋₈ cycloalkylcarbonyl, C₂₋₁₀ heterocyclylcarbonyl, C₆₋₁₀ arylcarbonyl or C₁₋₉ heteroarylcarbonyl; and

wherein optionally each R¹, R³, R⁵, R⁶, R⁷, R⁸, R^{9c}, R^a, R^b, R^c, R^d, R^e, R^f, R¹², R¹³, R¹⁴ and R¹⁵ is independently substituted with one or more R, and wherein each R is independently H, D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₆ alkyl or C₁₋₆ alkoxy.

[00141] In certain embodiments, wherein R¹ is D, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, C₂₋₆ heterocyclyl, C₂₋₆ heterocyclyl-C₁₋₄-alkyl, C₁₋₄ haloalkyl, -C(=O)-C₁₋₄ alkyl, -C(=O)OR^{9c}, -C(=O)-NR^{9a}R^{9a}, R⁹R^{9a}N-C(=O)-C₁₋₄-alkyl-, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₁₋₉ heteroaryl or C₃₋₆ cycloalkyl-C₁₋₄-alkyl.

[00142] In certain embodiments, wherein each R² is independently H, D, F, Cl, Br, I, CN, NO₂, OH, NH₂, HOC(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkoxy-, C₂₋₆ heterocyclyl-NH-C₁₋₆-alkoxy-, C₂₋₆ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkoxy-, C₂₋₆ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₃₋₆ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₆₋₁₀ aryl-(CR^cR^d)_f-NH-C₁₋₆-alkoxy-, C₁₋₄ alkyl-NH-C(=O)-C₁₋₆-alkoxy-, R^eR^fN-C(=O)-C₁₋₆-alkoxy-, C₁₋₅ heteroaryl-C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₃₋₆ cycloalkyl-C(=O)-C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkyl-O-C(=O)-C₁₋₆-alkoxy-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₆₋₁₀ aryl, C₁₋₅ heteroaryl, C₁₋₆ alkoxy, amino-substituted C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₄ alkylamino, C₃₋₆ cycloalkyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₆ heterocycliloxy, C₆₋₁₀ aryl-C₁₋₄-alkoxy, C₃₋₆ cycloalkoxy or C₃₋₆ cycloalkyl-C₁₋₄-alkoxy, and wherein optionally each R² is independently substituted with one or more R¹².

[00143] In certain embodiments, wherein each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₄ alkyl.

[00144] In certain embodiments, wherein each R^e and R^f is independently H, OH or C₁₋₄ alkyl.

[00145] In certain embodiments, wherein each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylamino, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ haloalkylamino, hydroxy-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkoxy or hydroxy-substituted C₁₋₄ alkylamino.

[00146] In certain embodiments, wherein R³ is D, F, Cl, Br, I, CN, NO₂, NH₂, OH, COOH, C₁₋₄ alkylamino, NH₂-C₁₋₄ alkyl-C₁₋₅-heteroaryl-, NH₂-C₁₋₄ alkyl-C₁₋₅ heteroaryl-C₁₋₄-alkyl-, NH₂-C₁₋₄ alkyl-C₆₋₁₀-aryl-, NH₂-C₁₋₄ alkyl-C₆₋₁₀ aryl-C₁₋₄-alkyl-, C₁₋₄ alkyl-C(=O)-NH-, R¹³O-C(=O)-C₁₋₄ alkyl-C(=O)-NH-, C₃₋₆ cycloalkyl-C(=O)-NH- or -C(=O)-NR⁹R^{9a}.

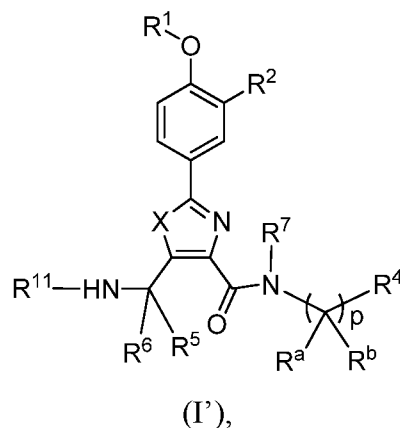
[00147] In certain embodiments, wherein each of R⁵ and R⁶ is independently H, D, F, Cl, Br, I, CN, NO₂, NH₂, OH, COOH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkylamino, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, hydroxy-substituted C₁₋₄ alkyl, mercapto-substituted C₁₋₄ alkyl, carboxy-substituted C₁₋₄ alkyl, NH₂-C₁₋₄ alkyl-C₁₋₅-heteroaryl-, NH₂-C₁₋₄ alkyl-C₁₋₅ heteroaryl-C₁₋₄-alkyl-, NH₂-C₁₋₄ alkyl-C₆₋₁₀-aryl-, NH₂-C₁₋₄ alkyl-C₆₋₁₀ aryl-C₁₋₄-alkyl-, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₃₋₆ cycloalkyl-C(=O)-NH-, -C(=O)-NR⁹R^{9a}, C₆₋₁₀ aryl or C₁₋₅ heteroaryl.

[00148] In certain embodiments, wherein optionally two groups selected from R³, R⁵ and R⁶, together with the carbon atom to which they are attached, form C=O.

[00149] In certain embodiments, wherein each of R⁷ and R⁸ is independently H, D or C₁₋₄ alkyl.

[00150] In certain embodiments, wherein R¹³ is H, D or C₁₋₄ alkyl.

[00151] In certain embodiments, provided herein are compounds having Formula (I'), or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,

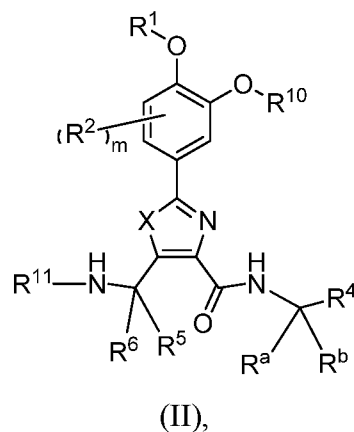


wherein

each of X, R¹, R², R⁴, R⁵, R⁶, R⁷, R^a, R^b and p is as defined herein;

R¹¹ is H, C₁₋₄ alkyl, C₁₋₄ alkyl-C(=O)-, R¹³O-C(=O)-C₁₋₄ alkyl-C(=O)- or C₃₋₆ cycloalkyl-C(=O)-.

[00152] In certain embodiments, provided herein are compounds having Formula (II), or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein

each X, R¹, R², R⁴, R⁵, R⁶, R^a and R^b is as defined herein;

m is 0, 1, 2 or 3;

R¹⁰ is H, HOC(=O)-C₁₋₆-alkyl-, C₁₋₆ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkyl-, C₂₋₁₀ heterocyclyl-NH-C₁₋₆-alkyl-, C₂₋₁₀ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkyl-, C₂₋₁₀ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₃₋₈ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₆₋₁₀ aryl-(CR^cR^d)_f-NH-C₁₋₆-alkyl-, C₁₋₆ alkyl-NH-C(=O)-C₁₋₆-alkyl-, R^eR^fN-C(=O)-C₁₋₆-alkyl-, C₁₋₉ heteroaryl-C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkyl-, C₃₋₈ cycloalkyl-C(=O)-C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-C₁₋₆-alkyl-, C₁₋₆ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, NH₂-NH-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₆ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₆

alkyl-O-C(=O)-C₁₋₆-alkyl-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkyl-, amino-substituted C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₃₋₈ cycloalkyl or C₃₋₈ cycloalkyl-C₁₋₆-alkyl, and wherein R¹⁰ is optionally substituted with one or more R¹²; and

R¹¹ is H, C₁₋₄ alkyl, C₁₋₄ alkyl-C(=O)-, R¹³O-C(=O)-C₁₋₄ alkyl-C(=O)- or C₃₋₆ cycloalkyl-C(=O)-.

[00153] In certain embodiments, wherein the pharmaceutically acceptable salt is hydrochloride, hydrobromide, sulfate, nitrate, phosphate, acetate, maleate, succinate, mandelate, fumarate, malonate, malate, 2-hydroxy propionate, pyruvate, oxalate, 2-hydroxy acetate, salicylate, glucuronate, galacturonate, citrate, tartrate, aspartate, glutamate, benzoate, cinnamate, *p*-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, trifluoromethanesulfonate or a combination thereof.

[00154] In certain embodiments, wherein R¹ is methyl, ethyl, propyl, *i*-propyl, halogenated methyl, halogenated ethyl, halogenated propyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, oxetanylmethyl, oxetanylethyl, tetrahydrofuryl, tetrahydrofurylmethyl, tetrahydrofurylethyl, phenyl, benzyl, phenylethyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

[00155] In certain embodiments, wherein each R² is independently H, D, F, Cl, Br, I, CN, NO₂, OH, NH₂, methoxy, ethoxy, propoxy, *i*-propoxy, butoxy, *i*-butoxy, *t*-butoxy, cyclopropoxy, cyclobutoxy, cyclopentoxo, cyclohexoxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutylmethoxy, cyclobutylethoxy, cyclopentylmethoxy, cyclopentylethoxy, cyclohexylmethoxy, cyclohexylethoxy, oxetanyloxy, tetrahydrofuryloxy, benzyloxy, phenylethoxy, HOC(=O)-C₁₋₆-alkoxy-, C₁₋₃ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkyl-O-C(=O)-C₁₋₆-alkoxy-, C₂₋₄ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkoxy-, C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ heteroaryl-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₃₋₆ cycloalkyl-C(=O)-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-C₁₋₆-alkoxy-, NH₂-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-(CR^eR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, R^eR^fN-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkyl-OC(=O)-(CR^eR^d)_f-NH-C₁₋₆-alkoxy-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₃ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₃₋₆ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₂₋₄ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-,

amino-substituted C₁₋₆ alkoxy, C₂₋₄ heterocyclyl-NH-C₁₋₆-alkoxy- or phenyl-(CR^cR^d)_r-NH-C₁₋₆-alkoxy-, and wherein optionally each R² is independently substituted with one or more R¹².

[00156] In certain embodiments, wherein each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₃ alkyl.

[00157] In certain embodiments, wherein each R^e and R^f is independently H, OH or C₁₋₃ alkyl.

[00158] In certain embodiments, wherein each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, hydroxy-substituted methyl or halogenated methyl.

[00159] In certain embodiments, wherein each of R⁵ and R⁶ is independently H, D, F, Cl, Br, I, NH₂, methyl, ethyl, propyl, *i*-propyl, hydroxy-substituted methyl, phenyl, benzyl or phenylethyl.

[00160] In certain embodiments, wherein R⁴ is C₆₋₁₀ aryl, C₆₋₁₀ aryl-S(=O)₂-, C₁₋₉ heteroaryl, C₁₋₉ heteroaryl-S(=O)₂-, C₆₋₁₀ aryl-C₁₋₄-alkyl or C₁₋₉ heteroaryl-C₁₋₄-alkyl, and wherein R⁴ is optionally substituted with one or more R¹⁴.

[00161] In certain embodiments, wherein each R¹⁴ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, -C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)O-C₁₋₄ alkyl, -C₁₋₄-alkyl-O-C(=O)-C₁₋₄ alkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylamino, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ haloalkylamino, hydroxy-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkoxy, hydroxy-substituted C₁₋₄ alkylamino or C₃₋₆ cycloalkyl.

[00162] In other embodiments, wherein R⁴ is phenyl, naphthyl, thiazolyl, thienyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, oxadiazolyl, pyridyl, pyrid-2-yl-*N*-oxide, pyrid-4-yl-*N*-oxide, pyrimidyl, pyrazinyl, quinolyl, isoquinolyl, quinazolyl, naphthyridinyl, furo[3,2-*c*]pyridinyl, furo[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[2,3-*c*]pyridinyl, benzoxadiazolyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, quinoxalyl, benzofuranyl, pyridopyrazinyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, 1,3-benzodioxolanyl, 2,3-dihydrobenzofuranyl, thieno[3,2-*b*]pyridinyl, thieno[2,3-*c*]pyridinyl, thieno[2,3-*b*]pyridinyl, 1,4-benzdioxanyl, 1,2,3,4-tetrahydroquinolin-2-yl or benzenesulfonyl, and wherein R⁴ is optionally substituted with one or more R¹⁴.

[00163] In other embodiments, wherein each R¹⁴ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, -C(=O)-NH₂, -C₁₋₃-alkyl-C(=O)-NH₂, -C₁₋₃-alkyl-C(=O)O-C₁₋₄ alkyl, methyl, ethyl,

propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, methamino or ethylamino.

[00164] In certain embodiments, wherein each R^a and R^b is independently H, D, F, Cl, Br, I, CN, OH, NO₂, NH₂, -COOR^{9c}, C₁₋₄ alkyl, -C(=O)-NR⁹R^{9a}, -C₁₋₄-alkyl-C(=O)-NR⁹R^{9a}, -C(=S)-NH₂, amino-substituted C₁₋₄ alkyl, -NH-C(=O)-R^{9b}, -C₁₋₄-alkyl-NH-C(=O)-R^{9b}, -NH-S(=O)₂-C₁₋₄ alkyl, -C₁₋₄-alkyl-NH-S(=O)₂-C₁₋₄ alkyl, -NH-S(=O)₂-C₃₋₆ cycloalkyl, -C₁₋₄-alkyl-NH-S(=O)₂-C₃₋₆ cycloalkyl, -S(=O)₂-C₁₋₄ alkyl, -C₁₋₄-alkyl-S(=O)₂-C₁₋₄ alkyl, C₆₋₁₀ aryl or C₁₋₅ heteroaryl.

[00165] In certain embodiments, wherein R^a and R^b , together with the carbon atom to which they are attached, form a 3- to 6-membered ring.

[00166] In certain embodiments, wherein each R^9 , R^{9a} and R^{9b} is independently H, D, OH, NH₂, -S(=O)₂-NH₂, -C(=O)-NH₂, -C₁₋₄ alkyl-C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₄-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₄ alkyl, -S(=O)₂-C₁₋₄ alkyl, -S(=O)₂-C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, amino-substituted C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₆ alkylamino, C₆₋₁₀ aryl, C₂₋₆ heterocyclyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₄-alkylamino, C₃₋₆ cycloalkyl-C₁₋₄-alkyl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₆₋₁₀ aryloxy, C₂₋₆ heterocyclyloxy, C₃₋₆ cycloalkoxy, C₆₋₁₀ arylamino, C₂₋₆ heterocyclylamino, C₃₋₆ cycloalkylamino, C₁₋₅ heteroaryl or C₃₋₆ carbocyclyl; and optionally each R^9 , R^{9a} and R^{9b} is independently substituted with one or more R^{15} .

[00167] In certain embodiments, wherein R^9 and R^{9a} , together with the nitrogen atom to which they are attached, optionally form a 3- to 6-membered ring, and wherein 3- to 6-membered ring is optionally substituted with one or more R^{15} .

[00168] In certain embodiments, wherein each R^{9c} is independently H, D, -C₁₋₄-alkyl-C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)O-C₁₋₄ alkyl, -C₁₋₄-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₅ alkyl, C₁₋₄ haloalkyl, amino-substituted C₁₋₄ alkyl, C₆₋₁₀ aryl, C₁₋₅ heteroaryl, C₃₋₆ cycloalkyl, C₂₋₆ heterocyclyl, C₃₋₆ cycloalkyl-C₁₋₄ alkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl or C₃₋₆ carbocyclyl.

[00169] In certain embodiments, wherein each R^{15} is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₄ alkyl, C₆₋₁₀ aryl, C₁₋₅ heteroaryl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₁₋₅ heteroaryl-C₁₋₄-alkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₄-alkyl, C₂₋₆ heterocyclyl, C₂₋₆ heterocyclyl-C₁₋₄-alkyl, C₃₋₆ cycloalkylcarbonyl, C₂₋₆ heterocyclylcarbonyl, C₆₋₁₀ arylcarbonyl or C₁₋₅ heteroarylcarbonyl.

[00170] In other embodiments, wherein each R^a and R^b is independently H, D, F, Cl, Br, I, CN, OH, NO₂, NH₂, -COOR^{9c}, methyl, ethyl, propyl, isopropyl, -C(=O)-NR⁹R^{9a}, -C(=S)-NH₂,

aminomethyl, aminoethyl, $-C_{1-3}\text{-alkyl-NH-C(=O)-R}^{9b}$, $-C_{1-3}\text{-alkyl-NH-S(=O)}_2\text{-C}_{3-6}$ cycloalkyl, $-C_{1-3}\text{-alkyl-S(=O)}_2\text{-C}_{1-3}$ alkyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, oxadiazolyl, phenyl, pyridyl or pyrimidyl.

[00171] In other embodiments, wherein R^a and R^b , together with the carbon atom to which they are attached, form oxetane or 1,3-dioxacyclopentane.

[00172] In other embodiments, wherein each R^9 , R^{9a} and R^{9b} is independently H, D, OH, NH_2 , $-S(=O)_2\text{-NH}_2$, $-C(=O)\text{-NH}_2$, $-C_{1-3}\text{-alkyl-C(=O)-NH}_2$, $-C_{1-4}\text{-alkyl-C(=O)O-C}_{1-4}$ alkyl, $-C_{1-3}\text{-alkyl-O-C(=O)-C}_{1-3}$ alkyl, methyl, ethyl, propyl, isopropyl, $-S(=O)_2\text{-C}_{1-3}$ alkyl, $-S(=O)_2\text{-cyclopropyl}$, $-S(=O)_2\text{-cyclobutyl}$, $-S(=O)_2\text{-cyclopentyl}$, $-S(=O)_2\text{-cyclohexyl}$, C_{1-4} haloalkyl, amino-substituted C_{1-4} alkyl, methoxy, ethoxy, propoxy, *i*-propoxy, methylamino, dimethylamino, ethylamino, propylamino, isopropylamino, phenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylmethylamino, cyclobutylmethylamino, cyclopentylmethylamino, benzyl, phenylethyl, phenoxy, cyclopropoxy, cyclobutoxy, cyclopentoxo, phenylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; and optionally each R^9 , R^{9a} and R^{9b} is independently substituted with one or more R^{15} .

[00173] In other embodiments, wherein R^9 and R^{9a} , together with the nitrogen atom to which they are attached, form a 3- to 6-membered ring selected from azetidine, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, and wherein 3- to 6-membered ring is optionally substituted with one or more R^{15} .

[00174] In other embodiments, wherein each R^{9c} is independently H, D, $-C_{1-3}\text{-alkyl-C(=O)-NH}_2$, $-C_{1-3}\text{-alkyl-C(=O)O-C}_{1-3}$ alkyl, $-C_{1-3}\text{-alkyl-O-C(=O)-C}_{1-4}$ alkyl, methyl, ethyl, propyl, isopropyl, C_{1-4} haloalkyl, amino-substituted C_{1-4} alkyl, phenyl, benzyl, phenylethyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[00175] In other embodiments, wherein each R^{15} is independently D, F, Cl, Br, I, CN, NO_2 , OH, NH_2 , COOH, methyl, ethyl, propyl, phenyl, pyridyl, pyrimidyl, thiazolyl, thienyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, oxadiazolyl, benzyl, phenylethyl, pyridylmethyl, pyrimidylmethyl, pyridylethyl, pyrimidylethyl, benzoyl, cyclopropylcarbonyl, cyclobutylcarbonyl or cyclopentylcarbonyl.

[00176] In other embodiments, wherein R^{10} is H, $HOC(=O)\text{-C}_{1-6}\text{-alkyl-}$, C_{1-4}

alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-NH-C₁₋₆-alkyl-, C₂₋₆
heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₃₋₆
cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₆₋₁₀ aryl-(CR^cR^d)_f-NH-C₁₋₆-alkyl-, C₁₋₄
alkyl-NH-C(=O)-C₁₋₆ alkyl-, R^eR^fN-C(=O)-C₁₋₆-alkyl-, C₁₋₅ heteroaryl-C₂₋₆
heterocyclyl-C(=O)-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl-C(=O)-C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkyl-,
NH₂-C(=O)-C₁₋₆ alkyl-, C₁₋₆ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-,
NH₂-NH-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₄
alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-O-C(=O)-C₁₋₄-alkyl-,
NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkyl-, amino-substituted C₁₋₆
alkyl, C₁₋₆ haloalkyl, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, C₂₋₆ heterocyclyl,
C₆₋₁₀ aryl-C₁₋₄-alkyl, C₃₋₆ cycloalkyl or C₃₋₆ cycloalkyl-C₁₋₄-alkyl, and wherein R¹⁰ is optionally
substituted with one or more R¹².

[00177] In other embodiments, wherein each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₃ alkyl.

[00178] In other embodiments, wherein each of R^e and R^f is independently H, OH or C₁₋₃ alkyl.

[00179] In other embodiments, wherein each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkylamino, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, C₁₋₃ haloalkylamino, hydroxy-substituted C₁₋₃ alkyl, hydroxy-substituted C₁₋₃ alkoxy or hydroxy-substituted C₁₋₃ alkylamino.

[00180] In other embodiments, wherein R¹⁰ is H, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, oxetanyl, tetrahydrofuranyl, benzyl, phenylethyl, HOC(=O)-C₁₋₆-alkyl-, C₁₋₃ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkyl-, C₂₋₄
heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-O-C(=O)-C₁₋₄-alkyl-, C₂₋₄
heterocyclyl-C(=O)-C₁₋₆-alkyl-, C₁₋₄ heteroaryl-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkyl-, C₃₋₆
cycloalkyl-C(=O)-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-C₁₋₆-alkyl-,
NH₂-NH-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-,
R^eR^fN-C(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-,
NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₃ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₃₋₆

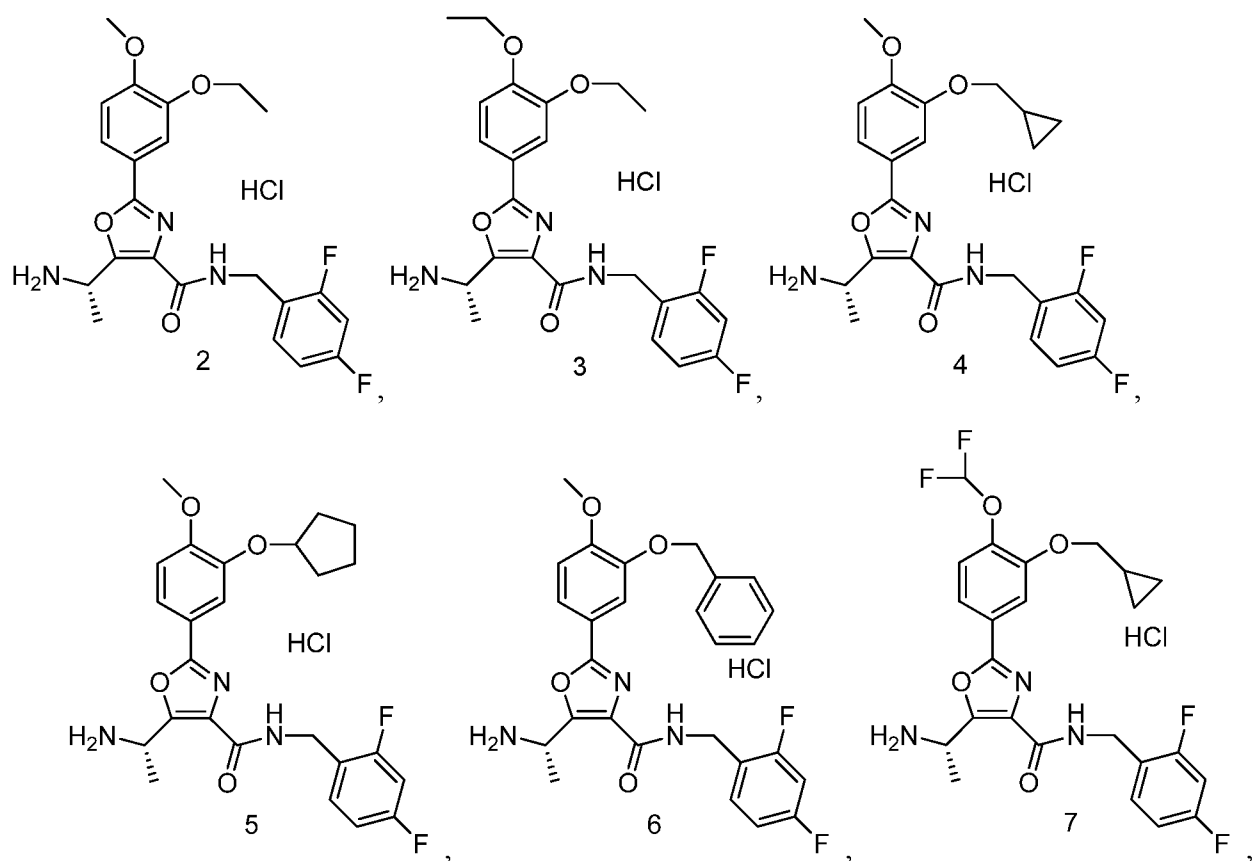
cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₂₋₄ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, amino-substituted C₁₋₆ alkyl, C₂₋₄ heterocyclyl-NH-C₁₋₆-alkyl- or phenyl-(CR^cR^d)_f-NH-C₁₋₆-alkyl-, and wherein R¹⁰ is optionally substituted with one or more R¹².

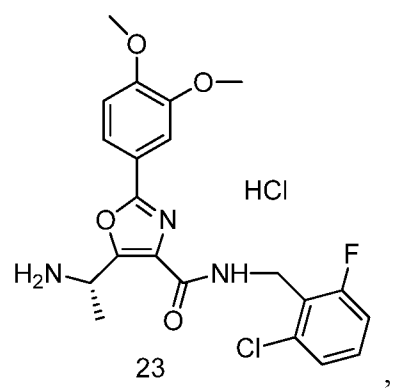
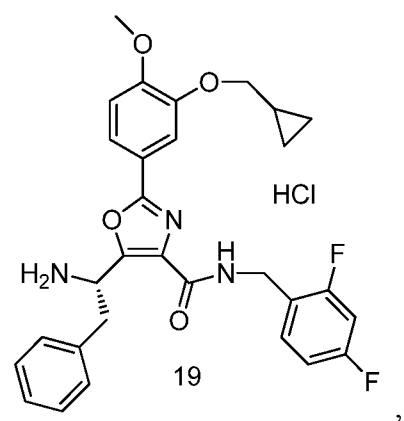
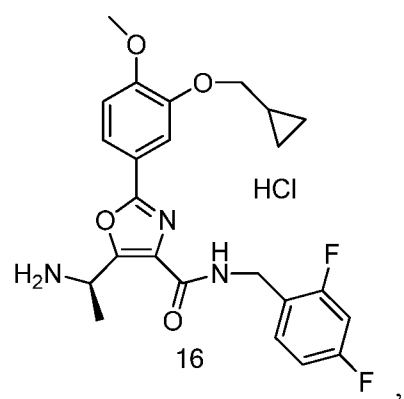
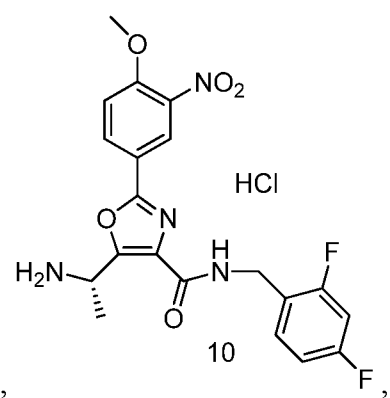
[00181] In other embodiments, wherein each R^c and R^d is independently H, OH, CN, F, Cl, Br, I, methyl, ethyl or propyl.

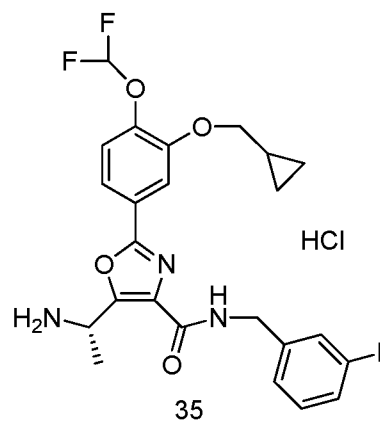
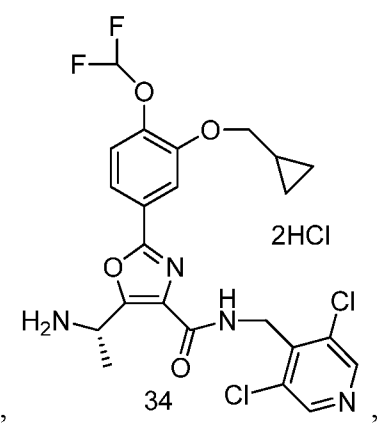
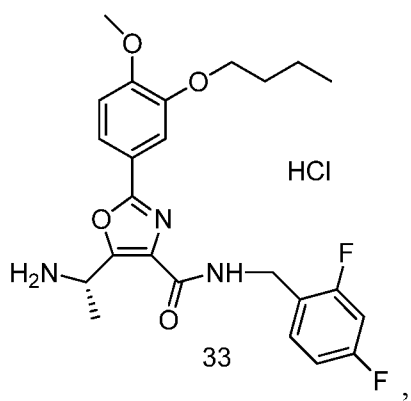
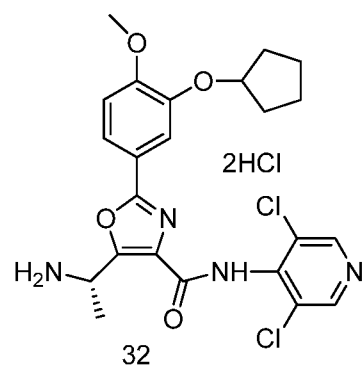
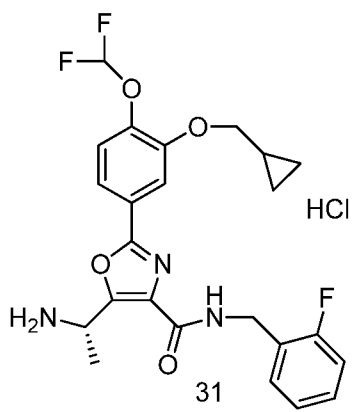
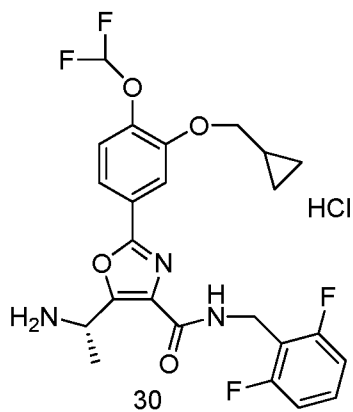
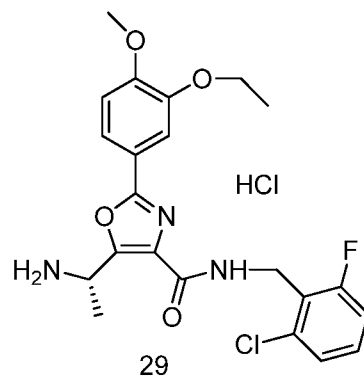
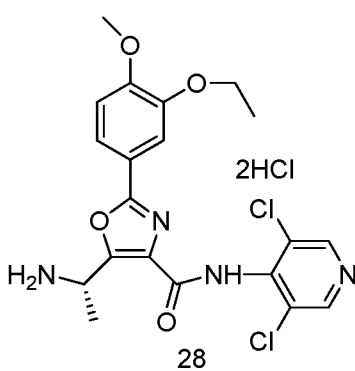
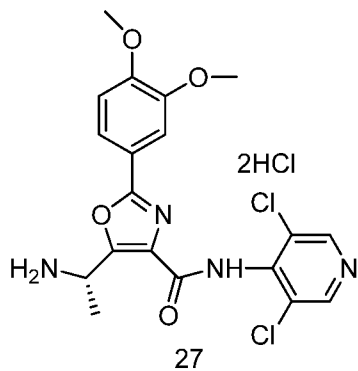
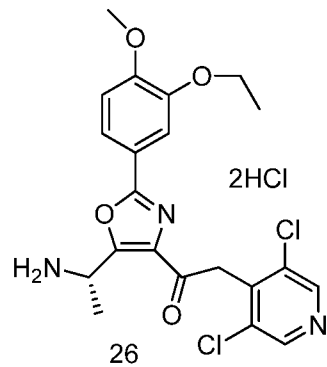
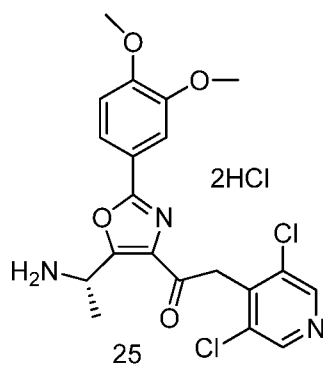
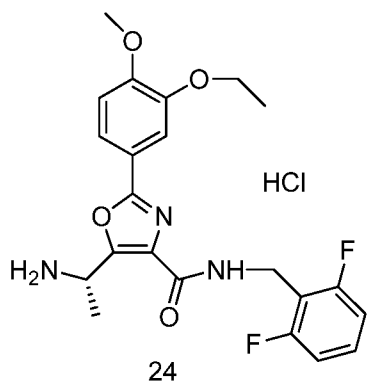
[00182] In other embodiments, wherein each of R^e and R^f is independently H, OH, methyl, ethyl or propyl.

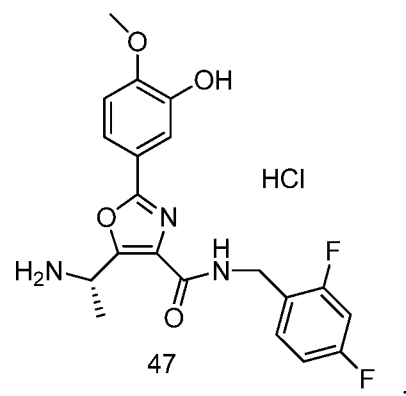
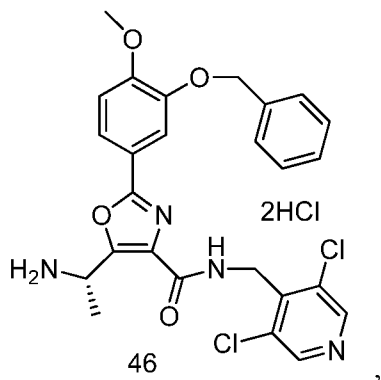
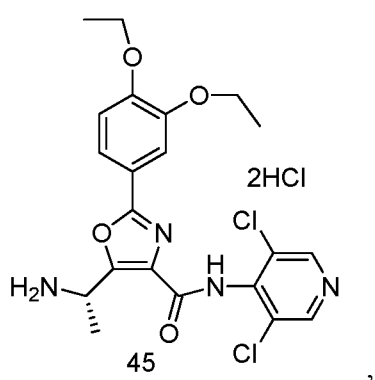
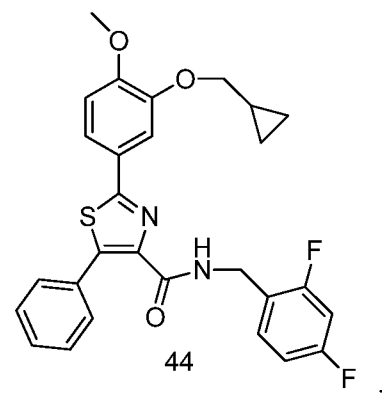
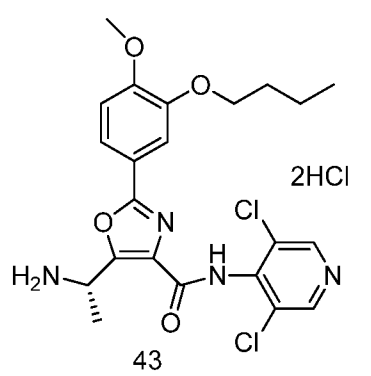
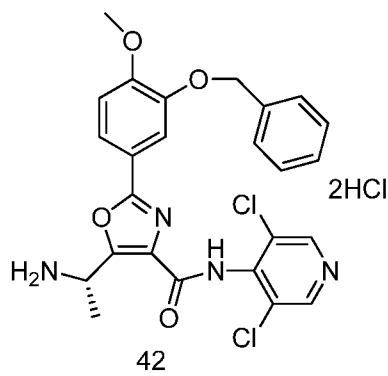
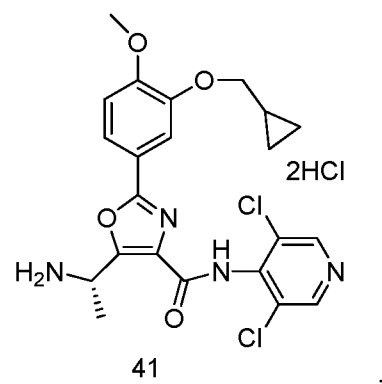
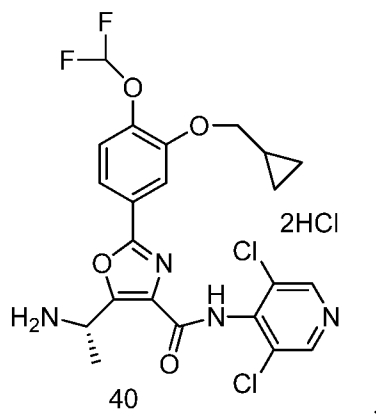
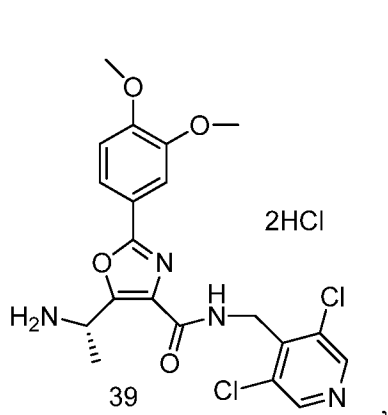
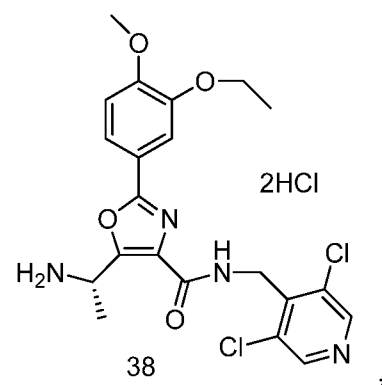
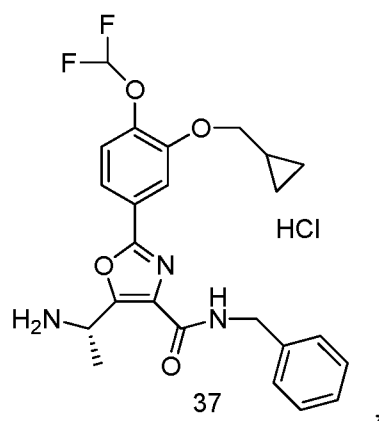
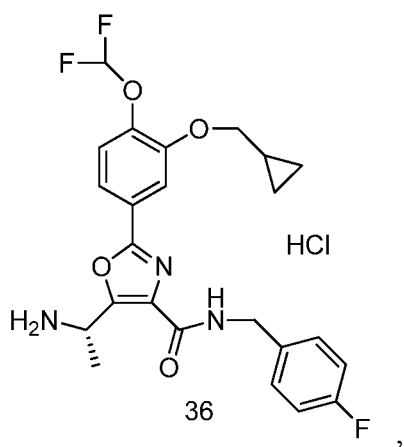
[00183] In other embodiments, wherein each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, hydroxy-substituted methyl or halogenated methyl.

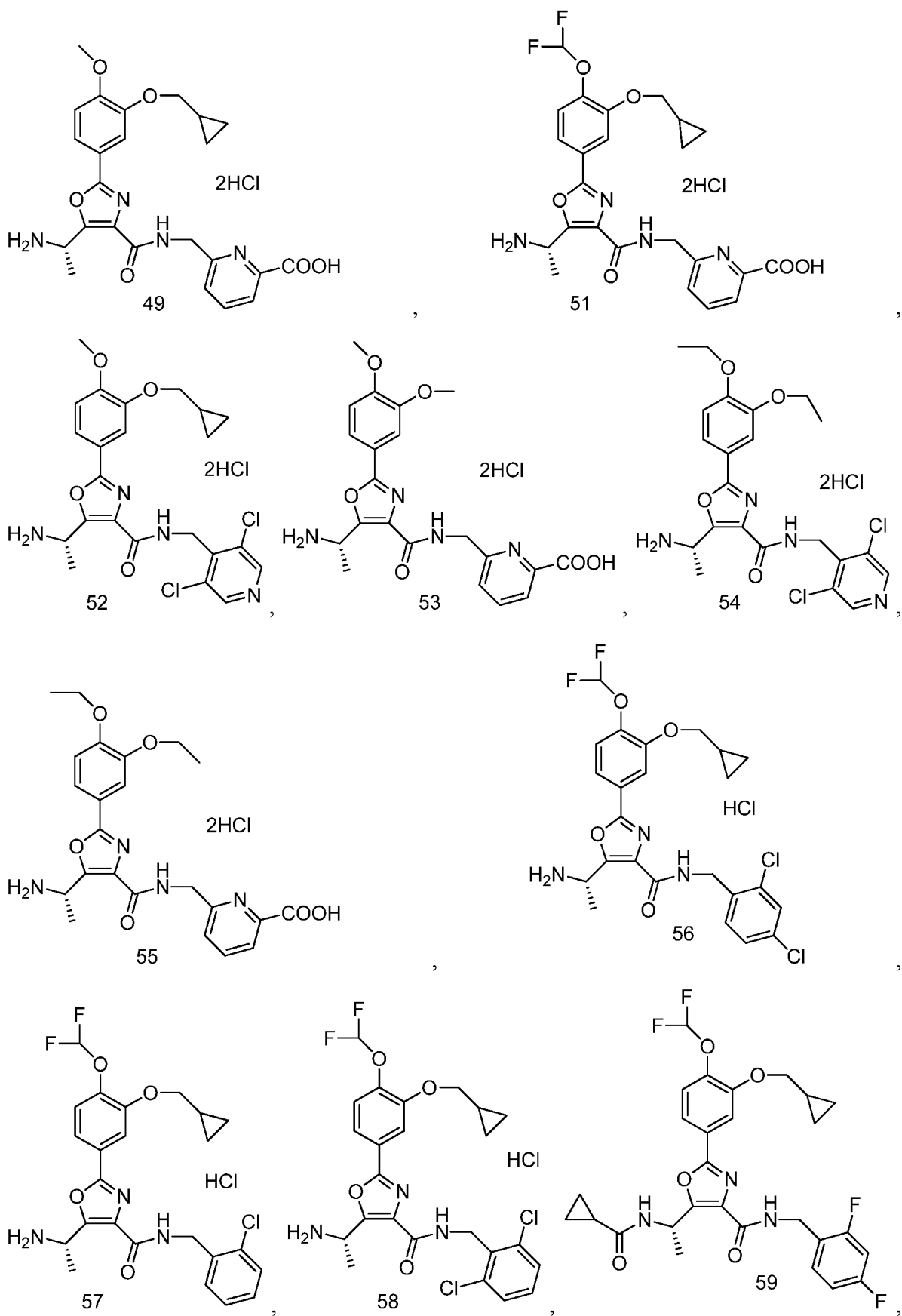
[00184] In certain embodiments, provided herein is the compound having one of the following structures, or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof, but not limited to these structures:

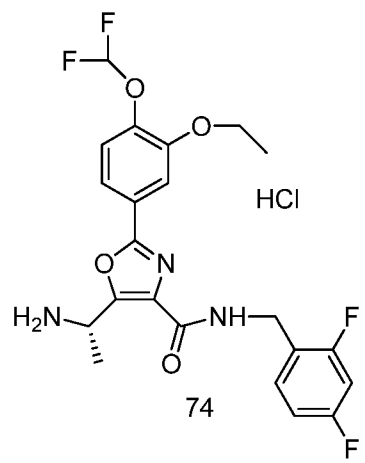
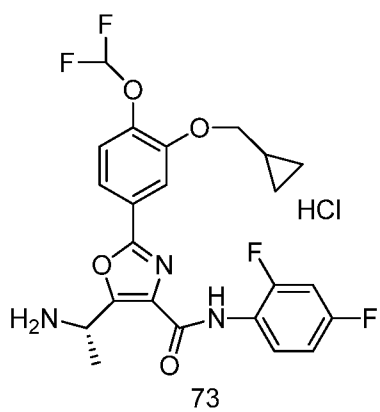
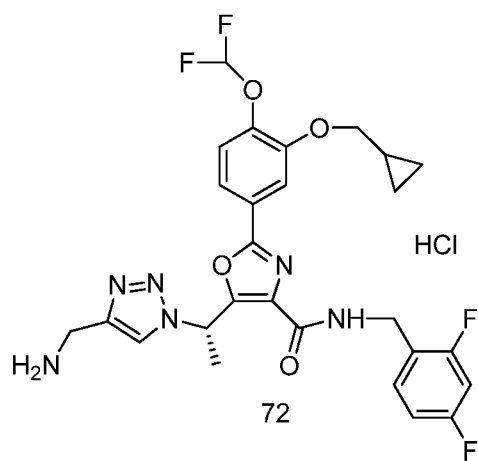
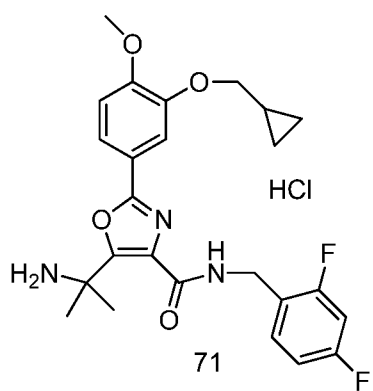
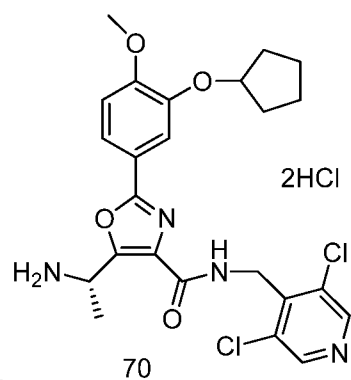
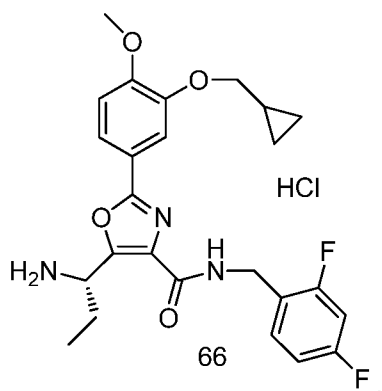
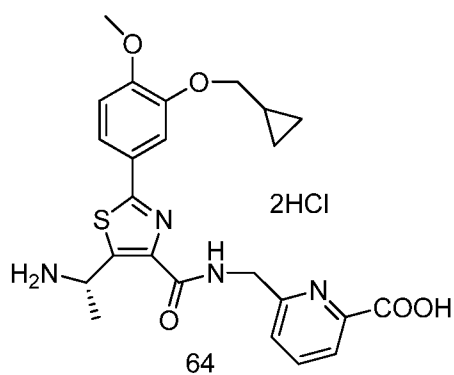
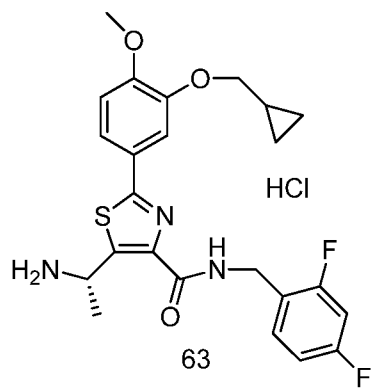
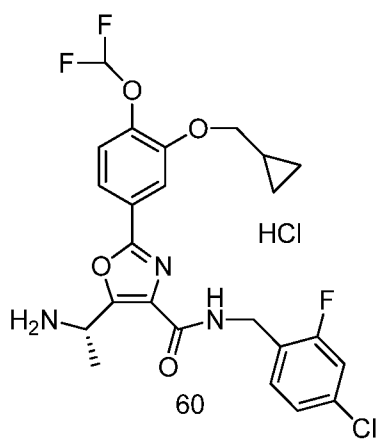


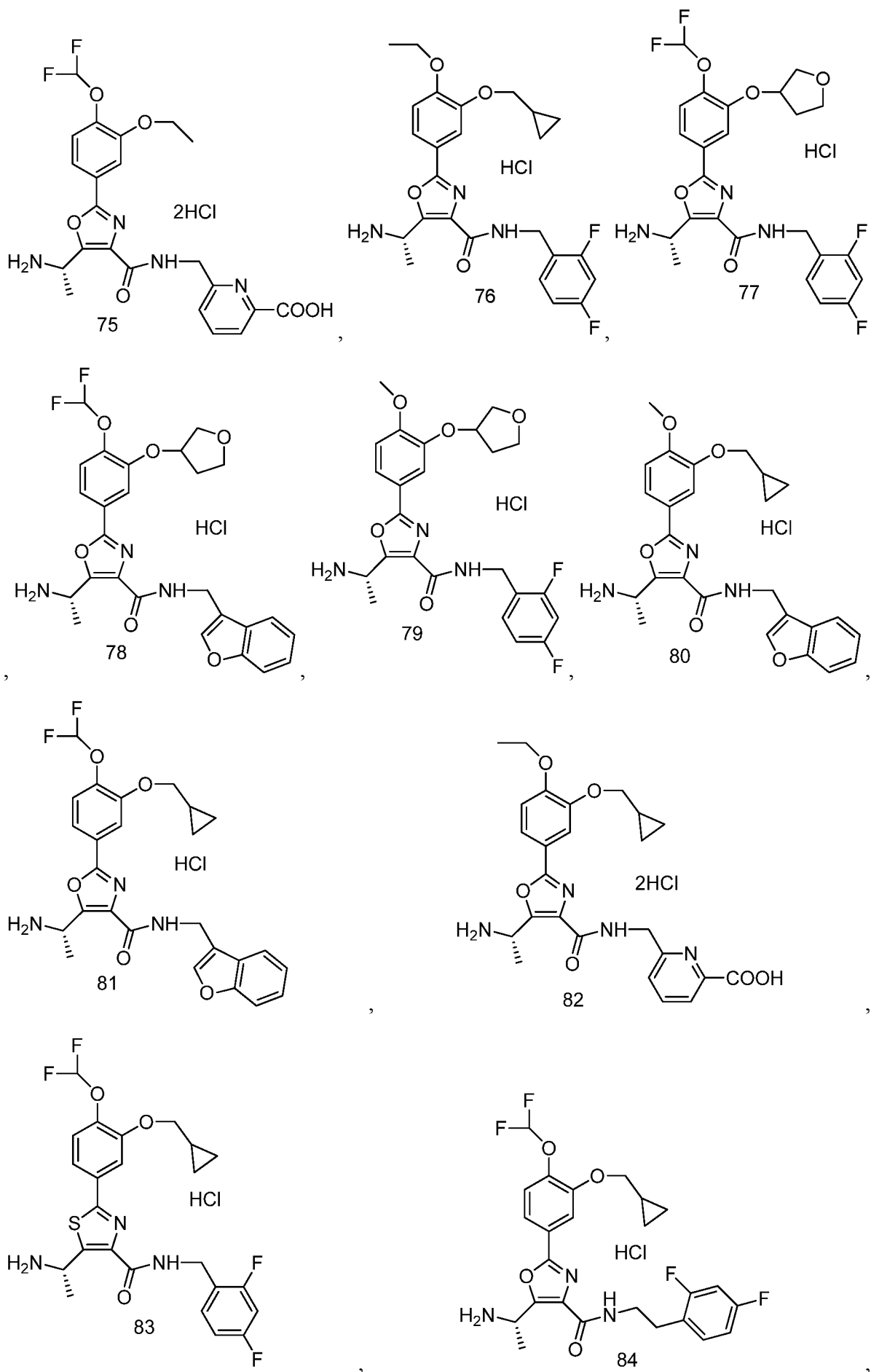


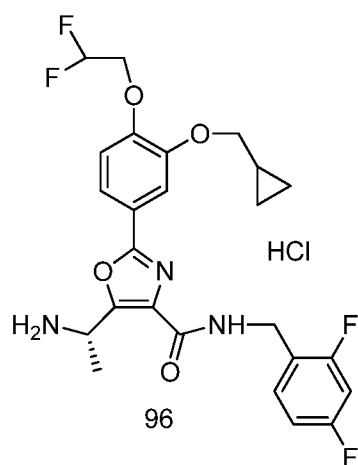
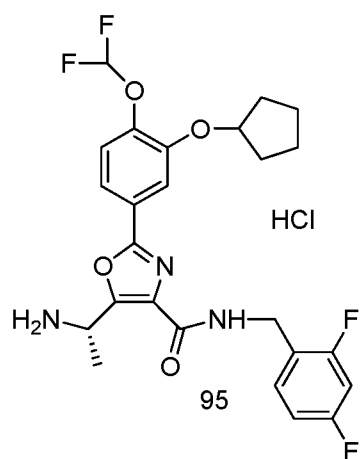
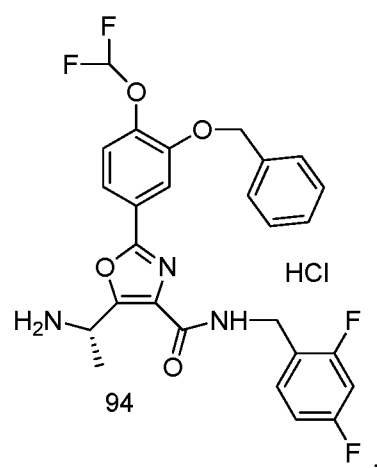
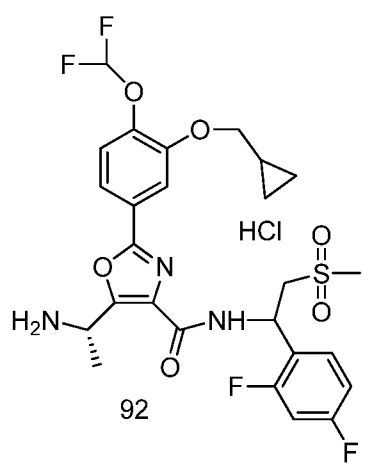
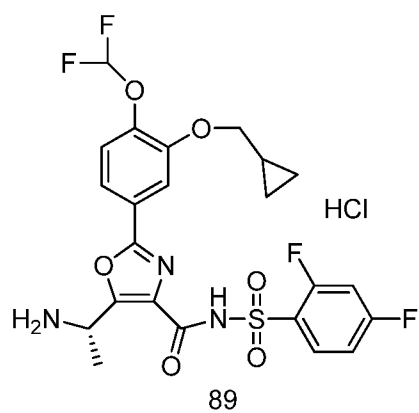
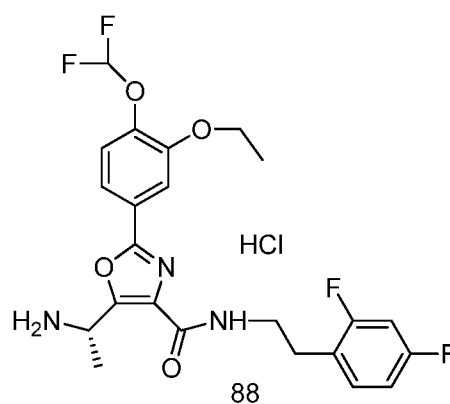
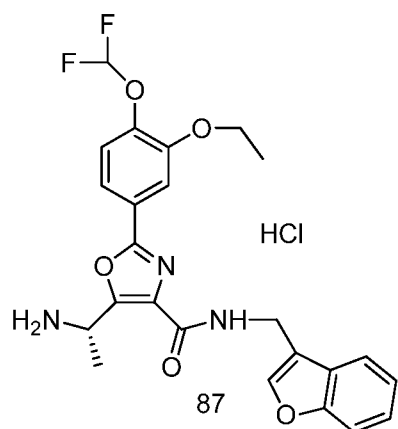
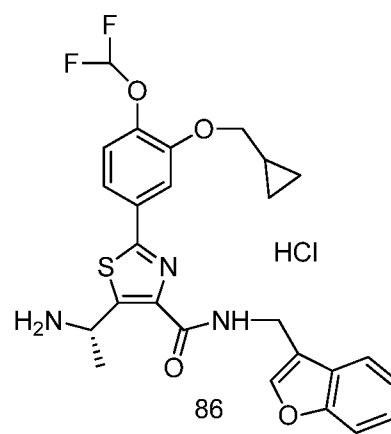
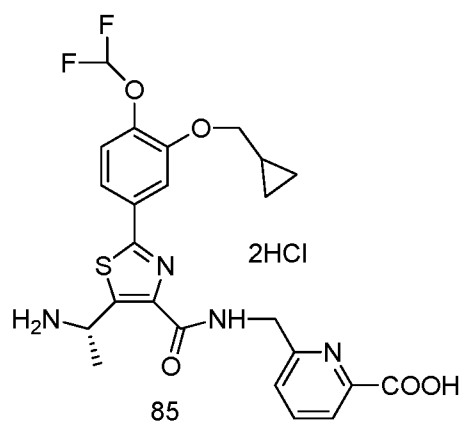


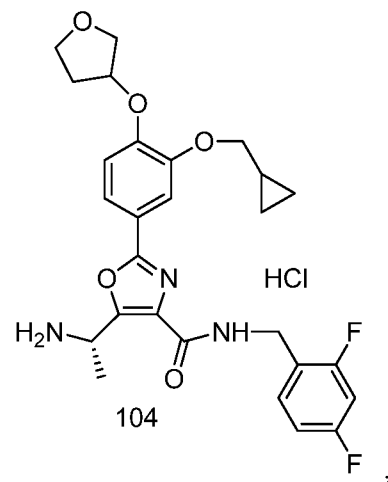
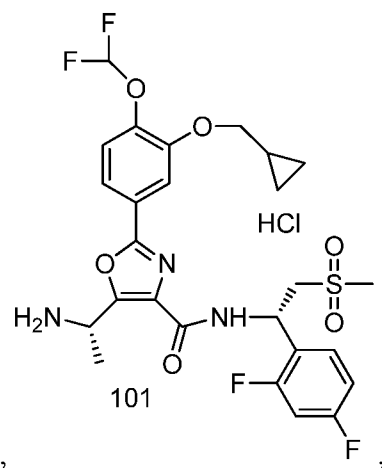
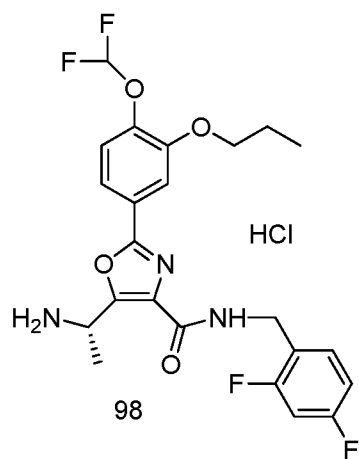


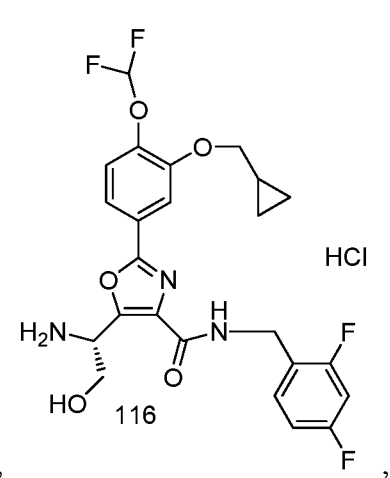
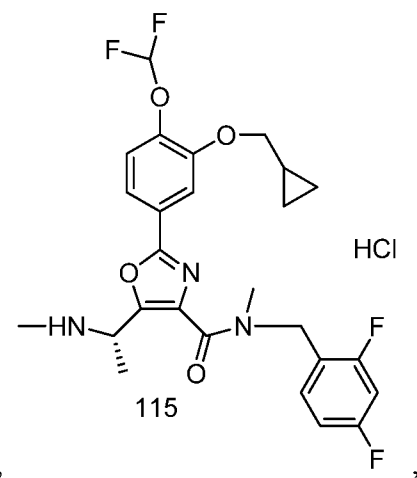
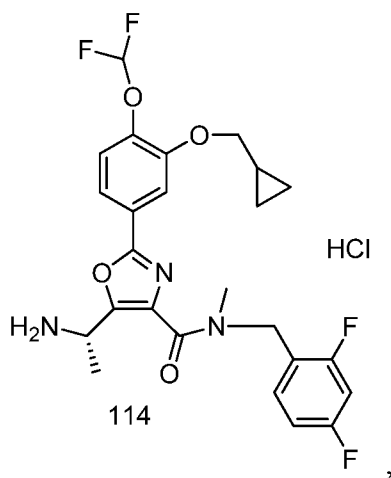
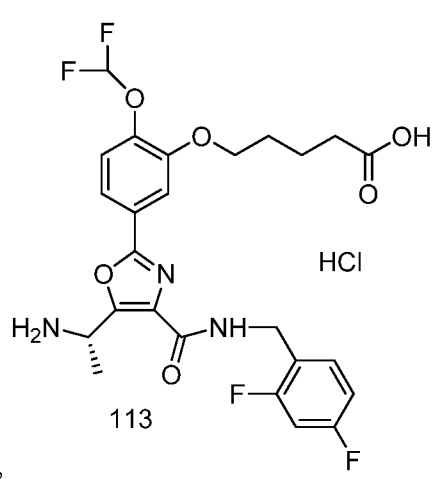
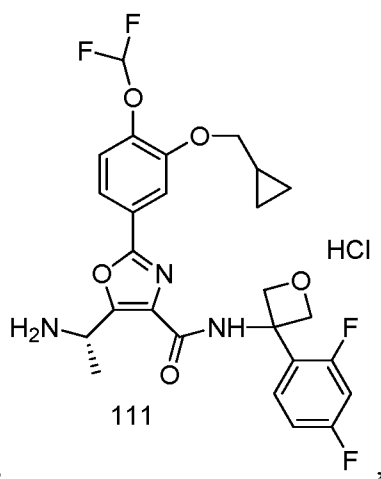
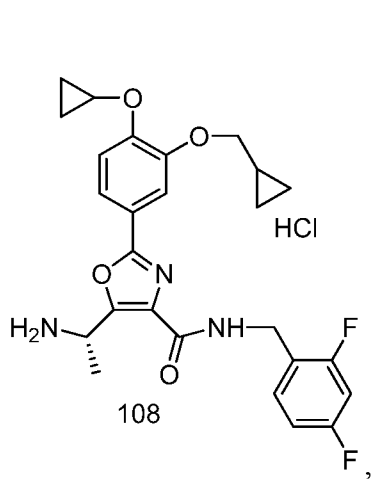
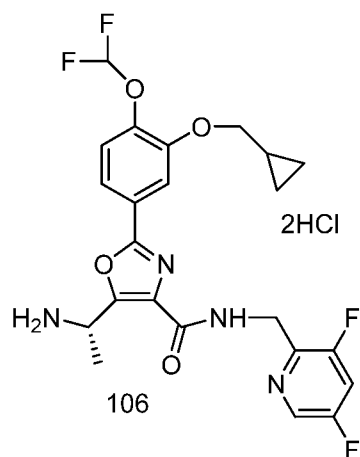
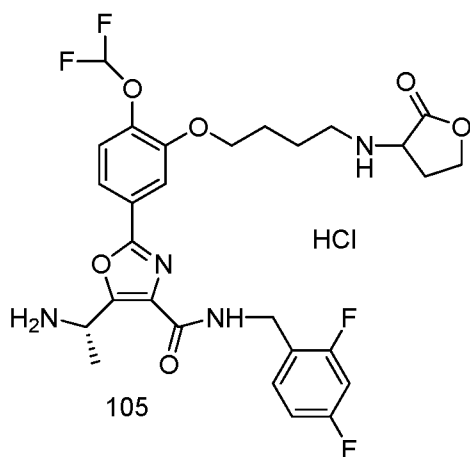


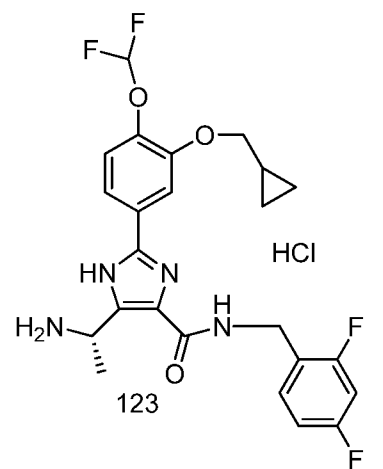
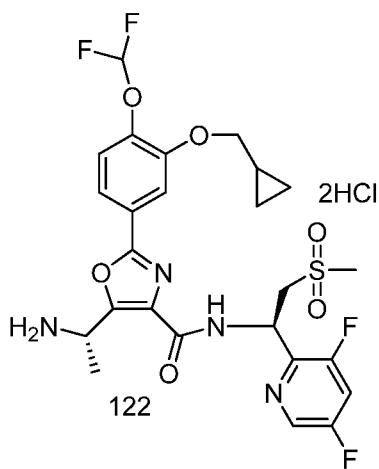
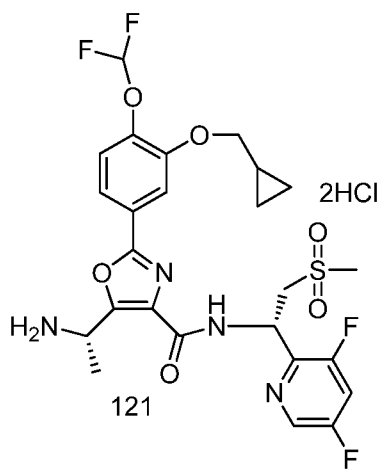
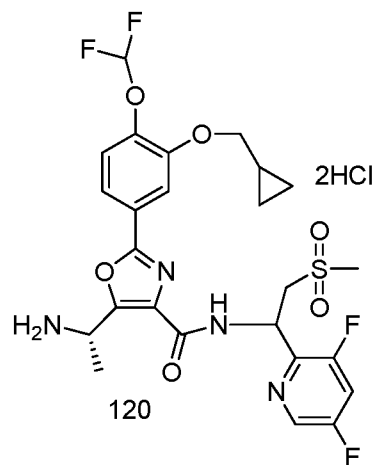
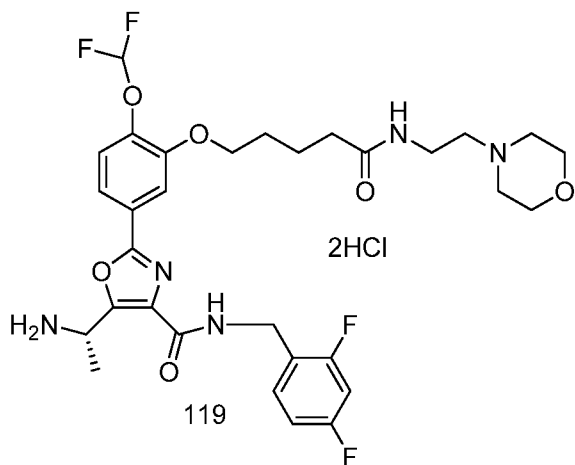
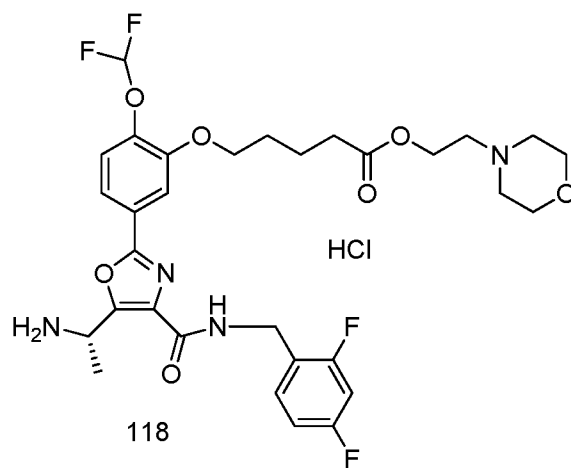
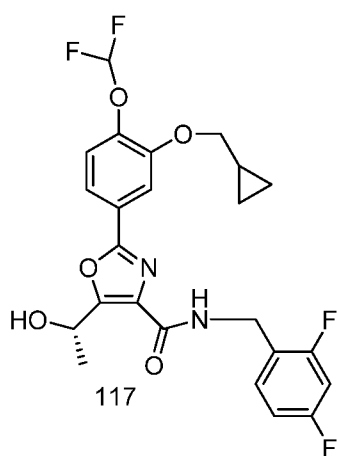


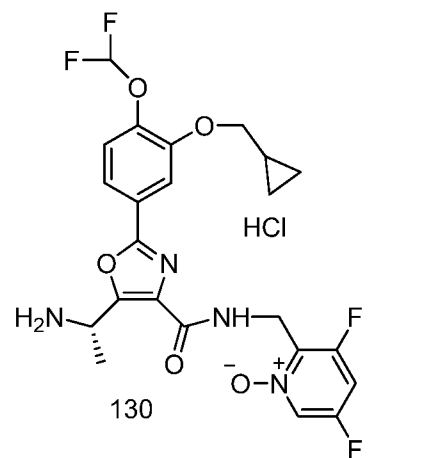
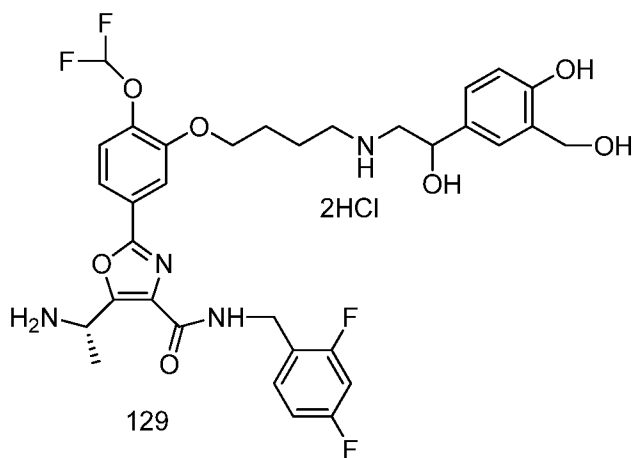
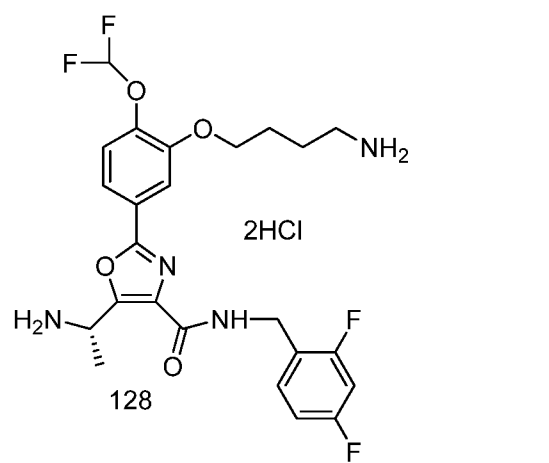
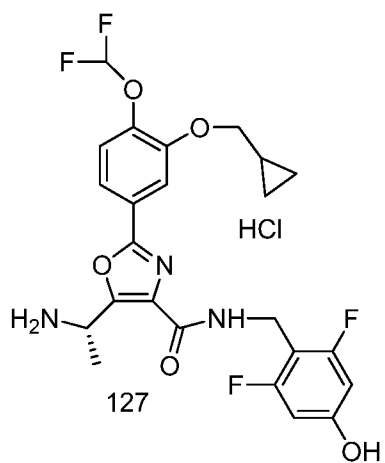
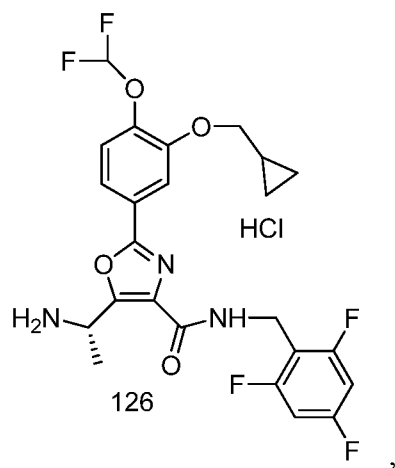
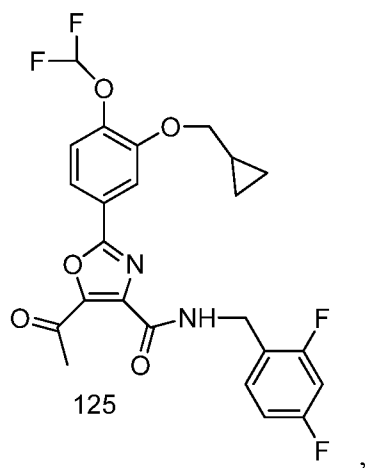
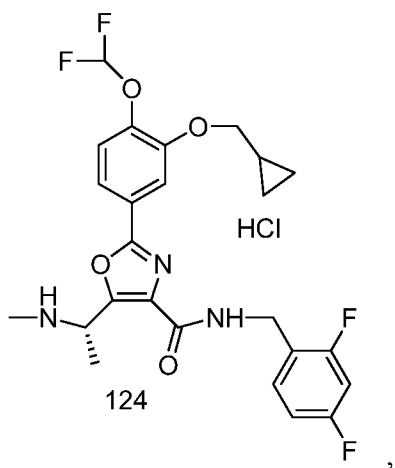


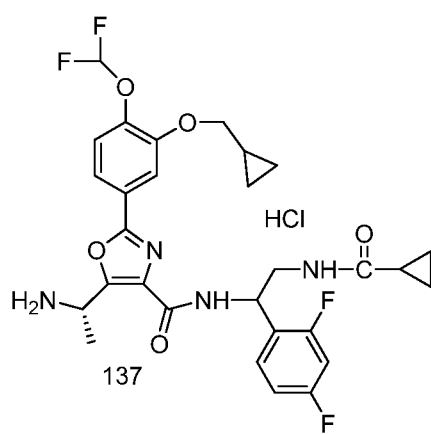
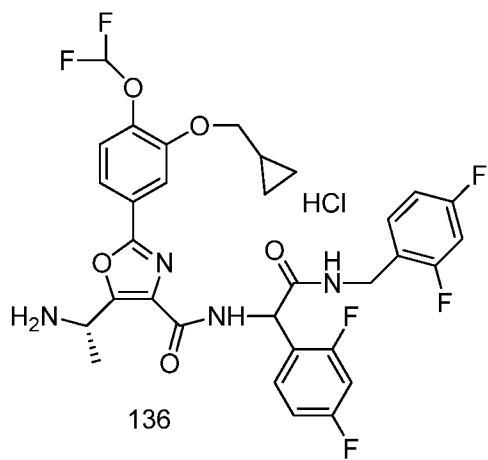
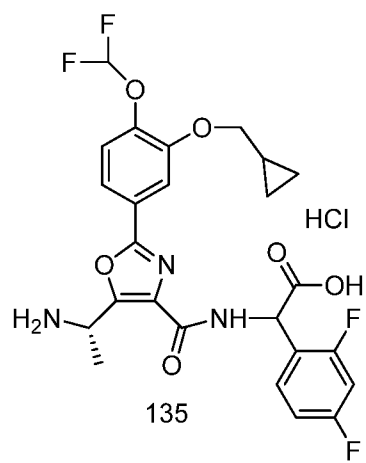
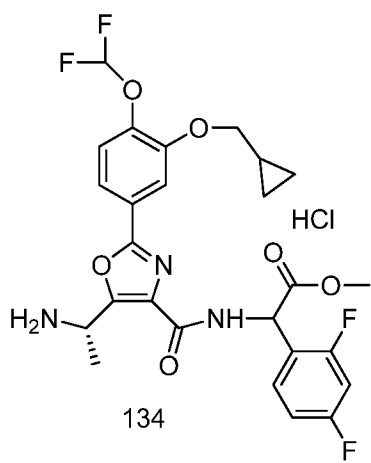
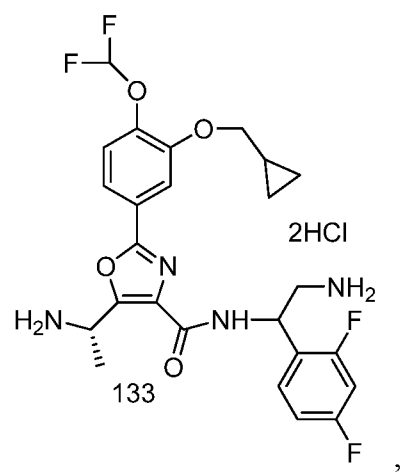
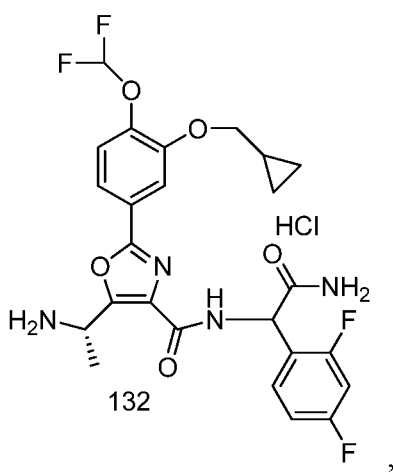
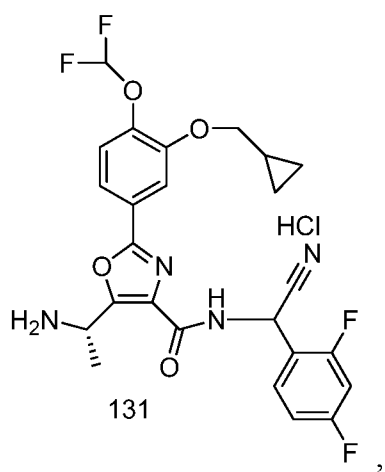


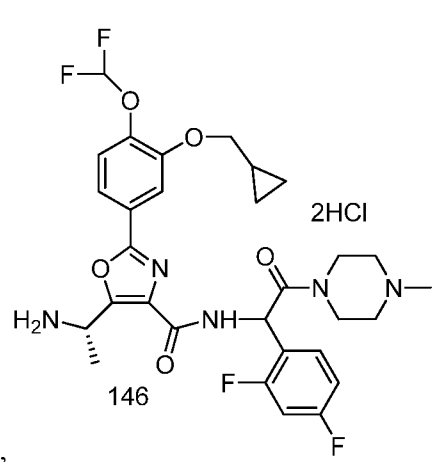
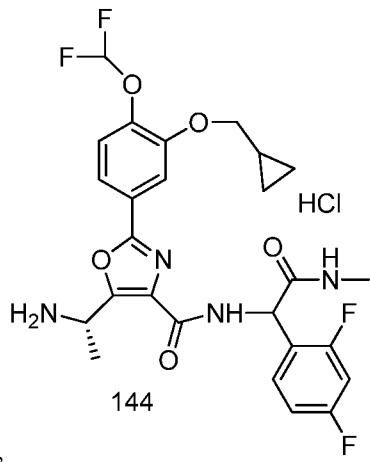
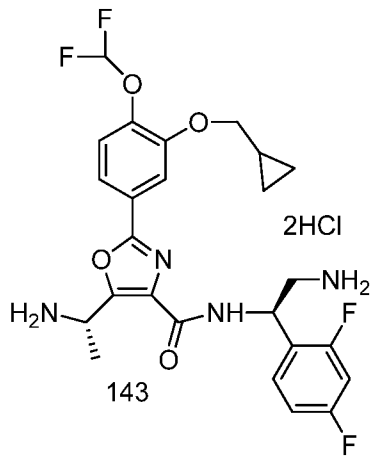
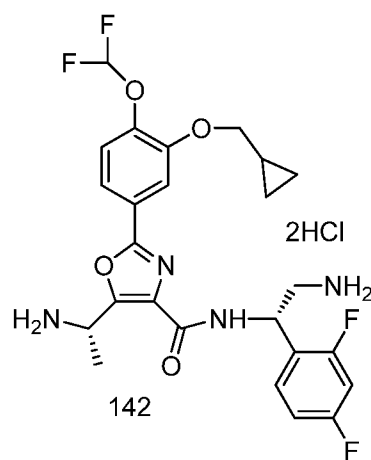
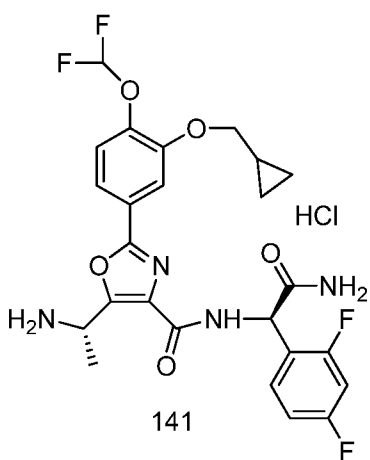
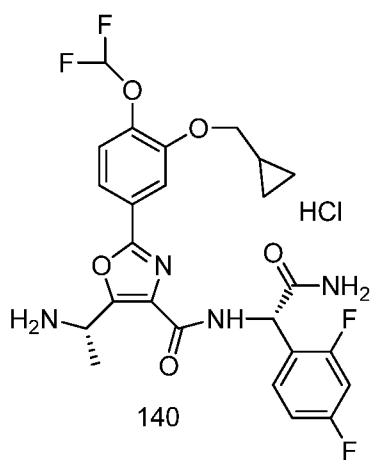
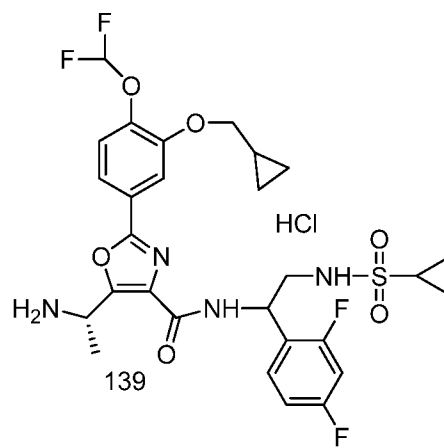
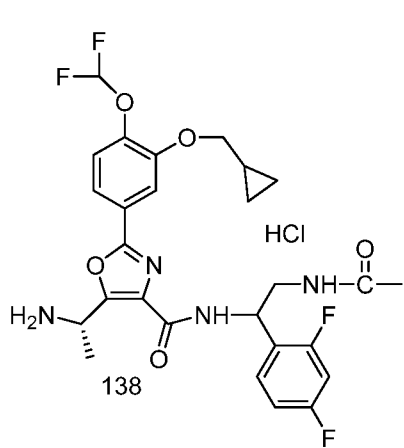




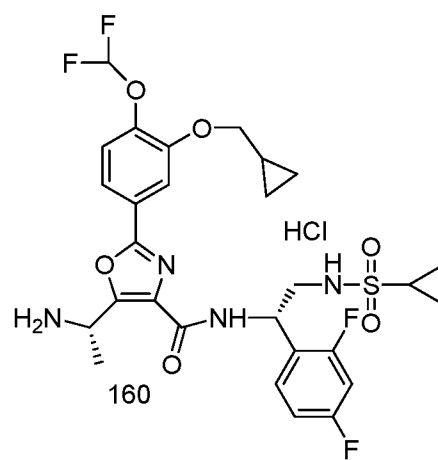
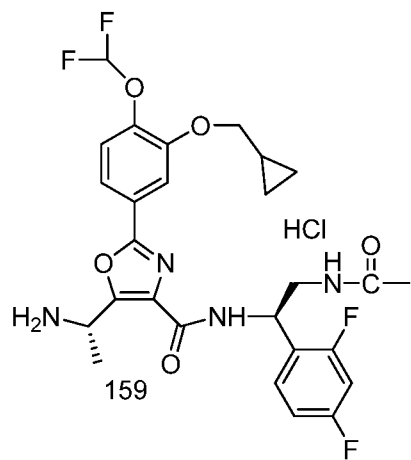
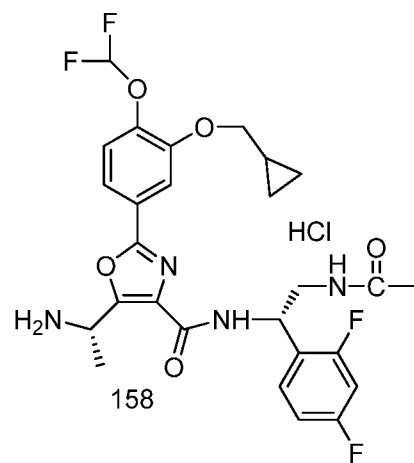
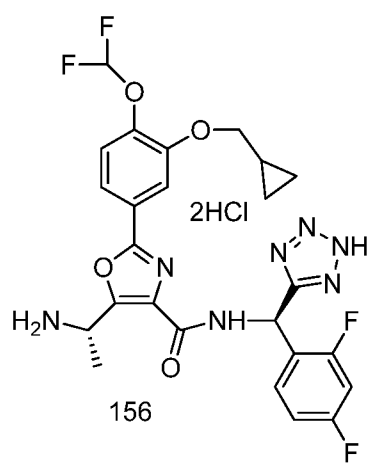
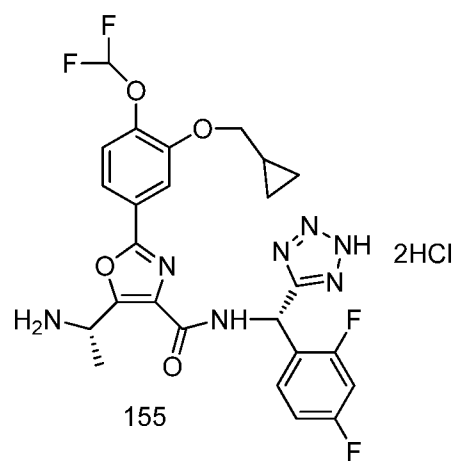
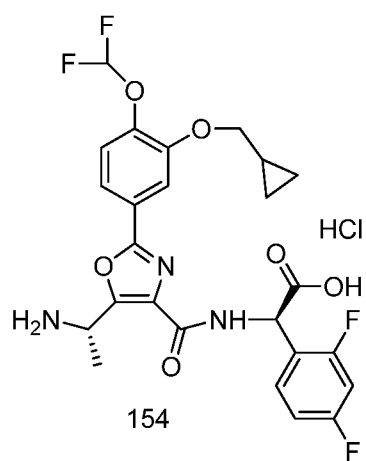


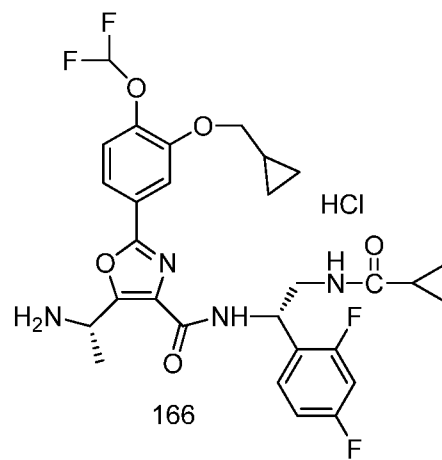
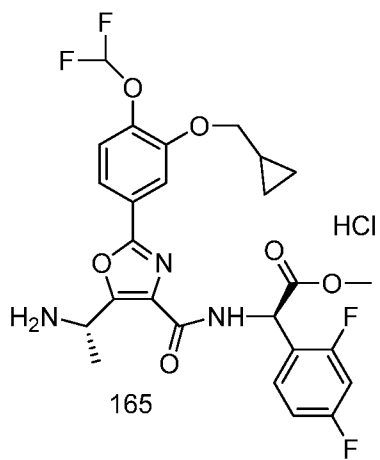
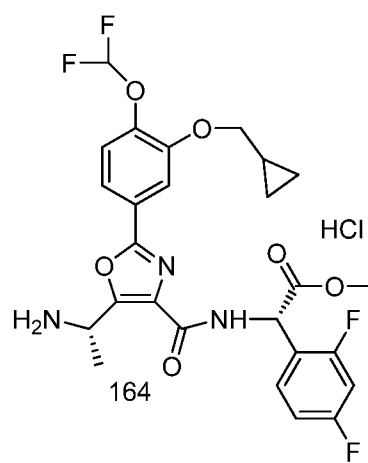
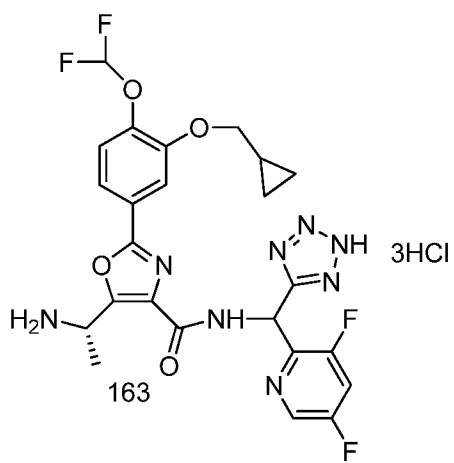
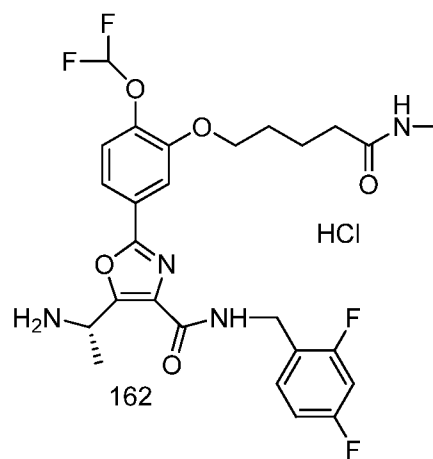
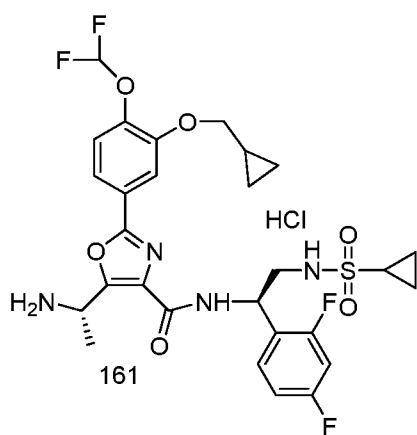


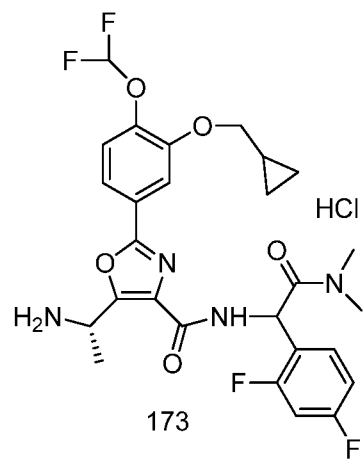
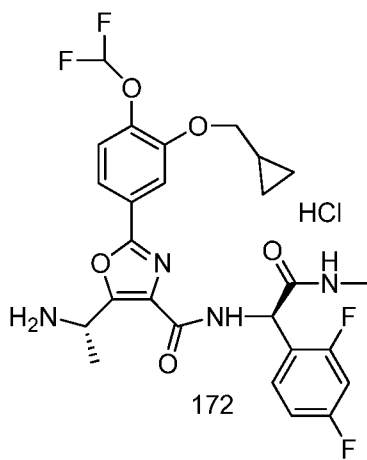
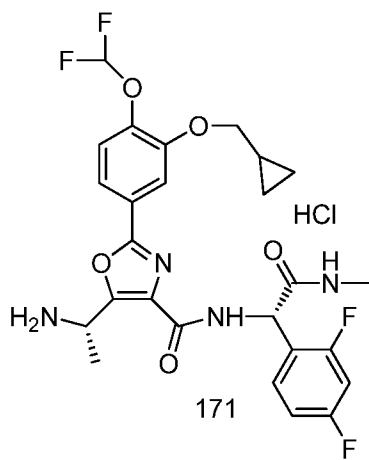
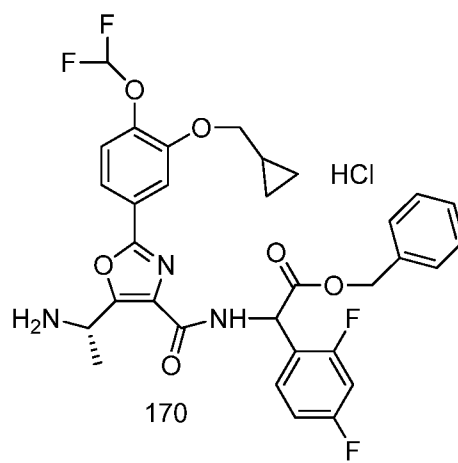
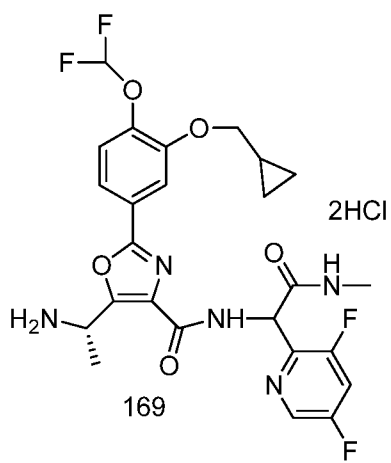
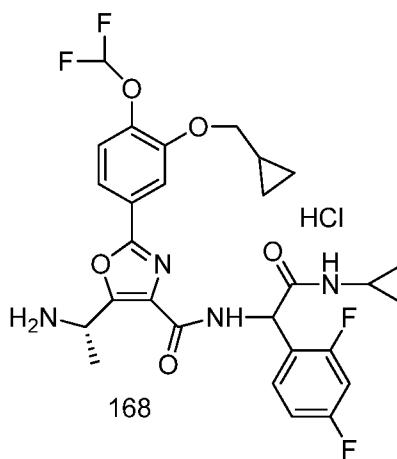
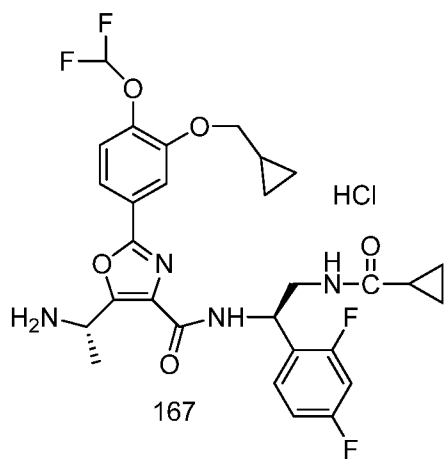


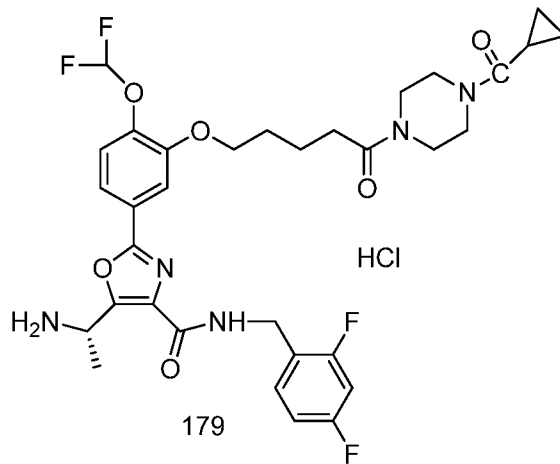
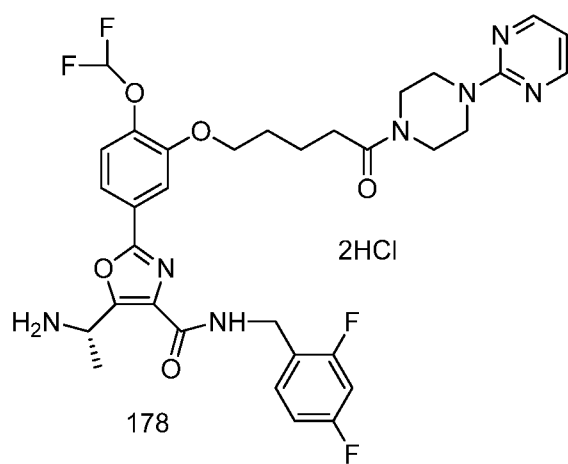
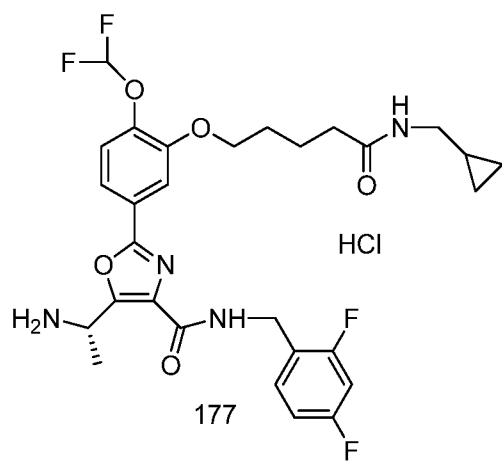
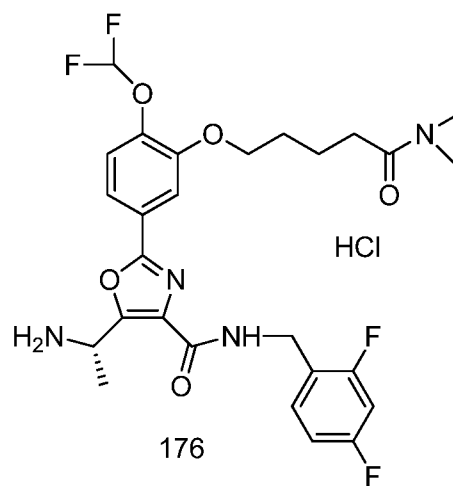
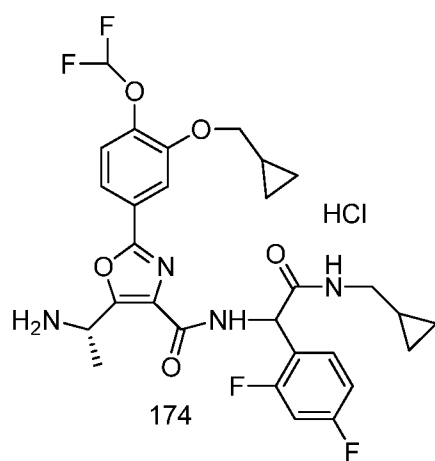


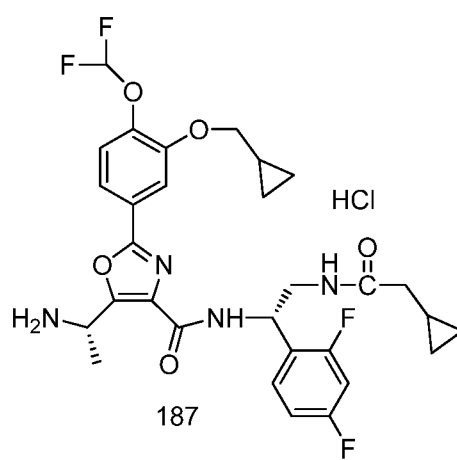
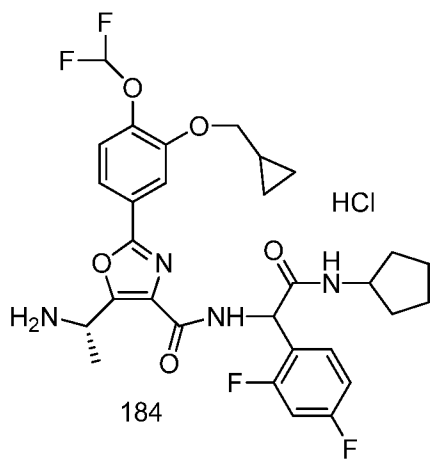
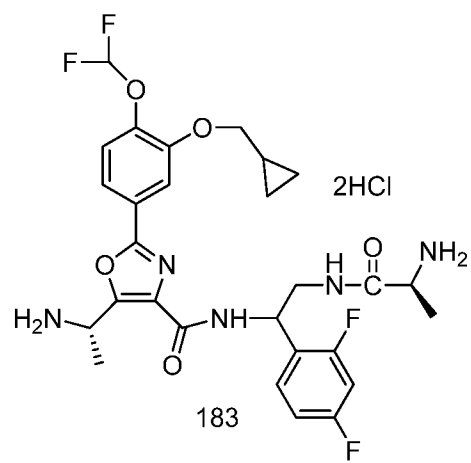
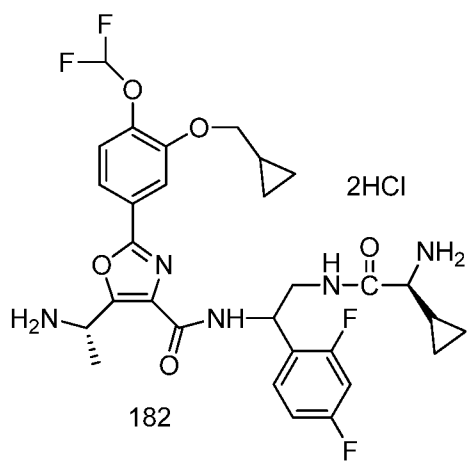
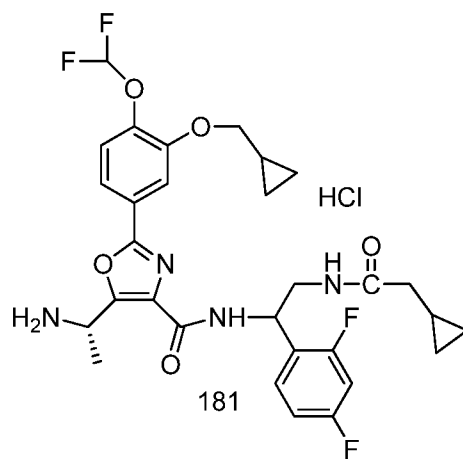
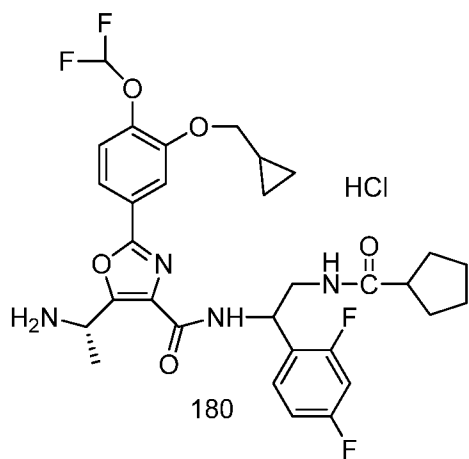


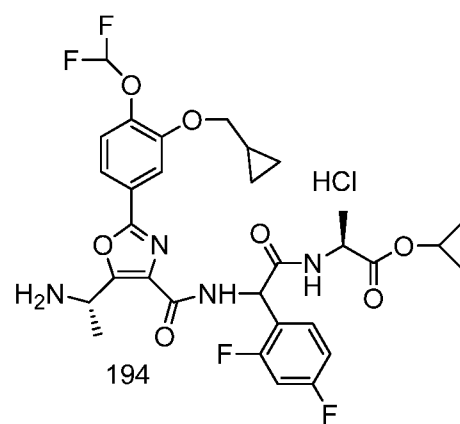
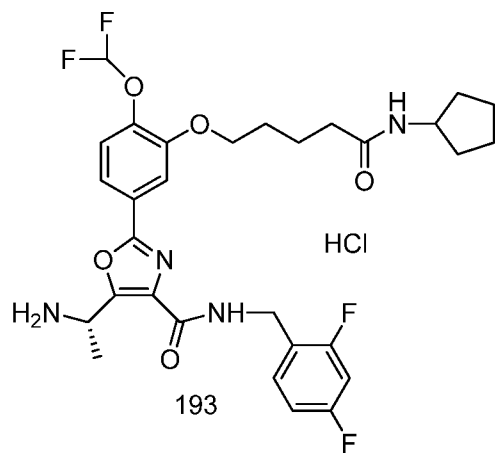
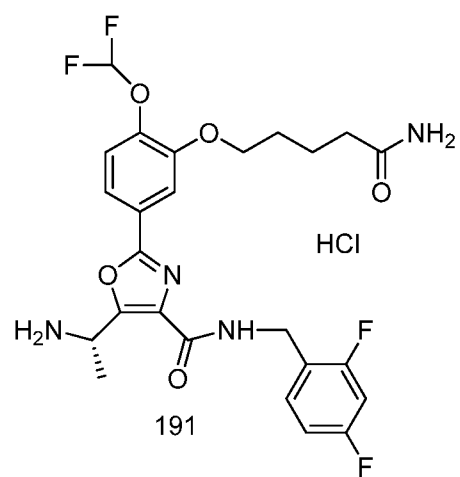
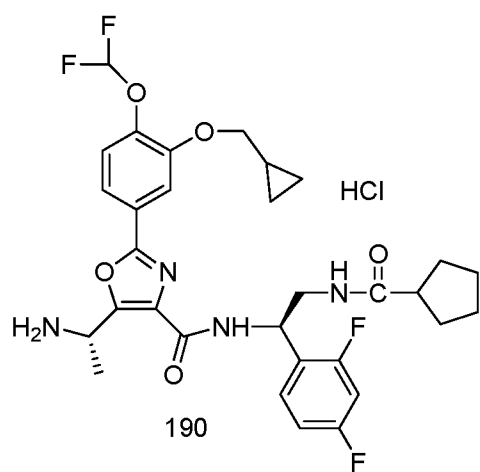
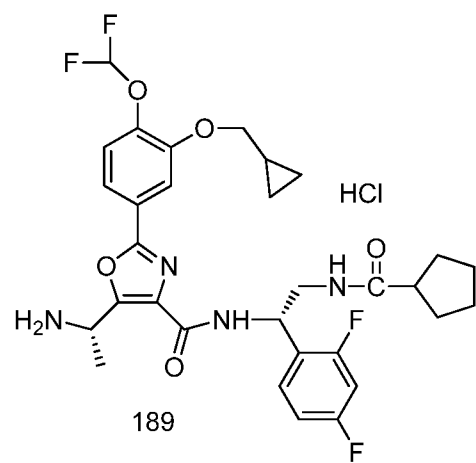
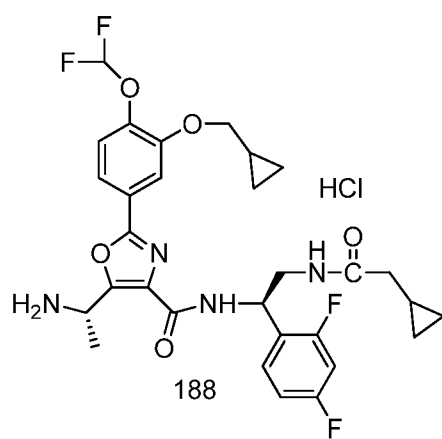


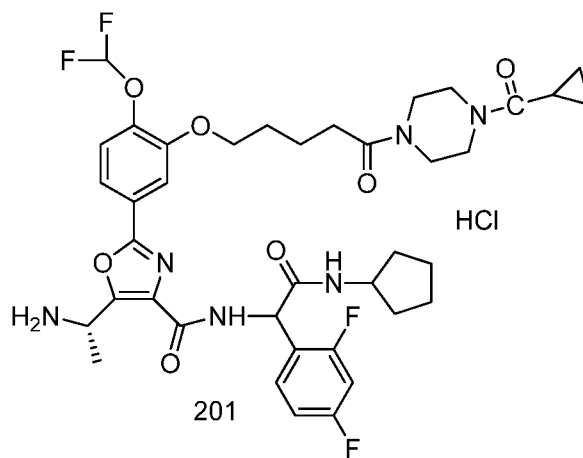
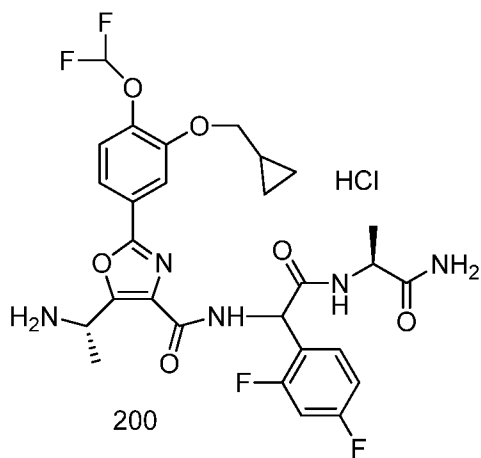
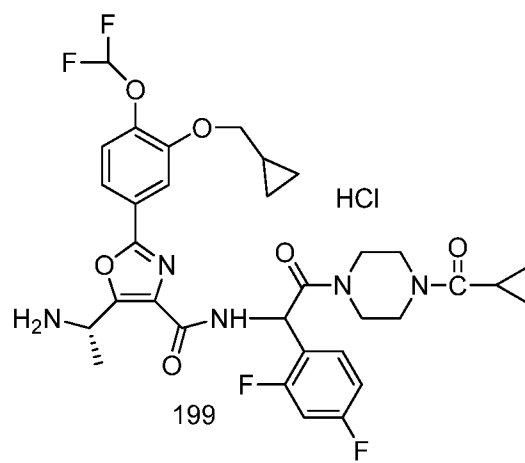
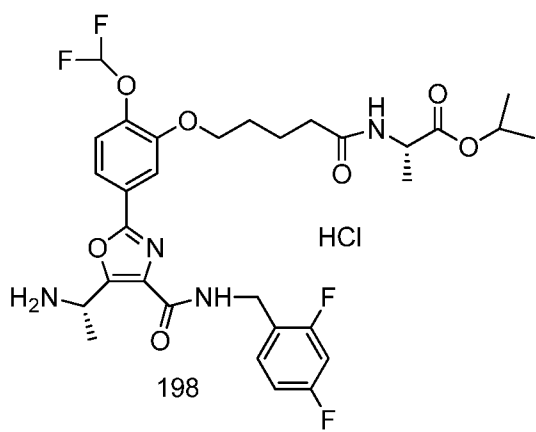
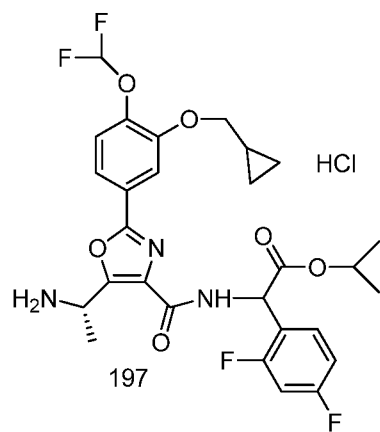
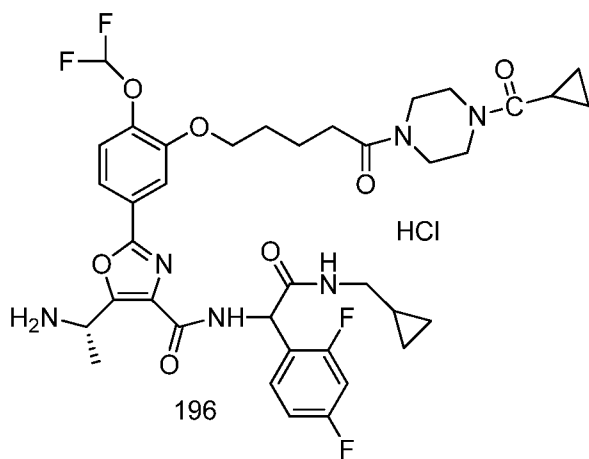


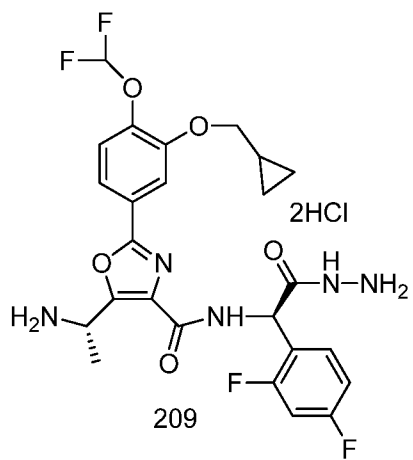
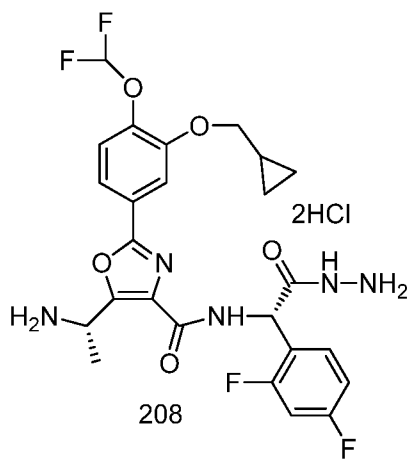
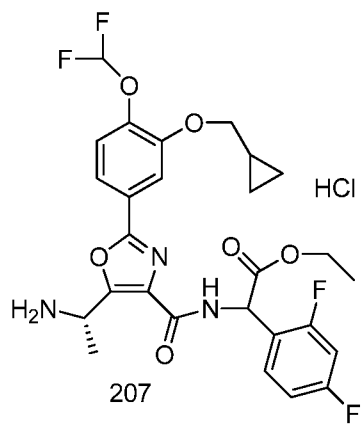
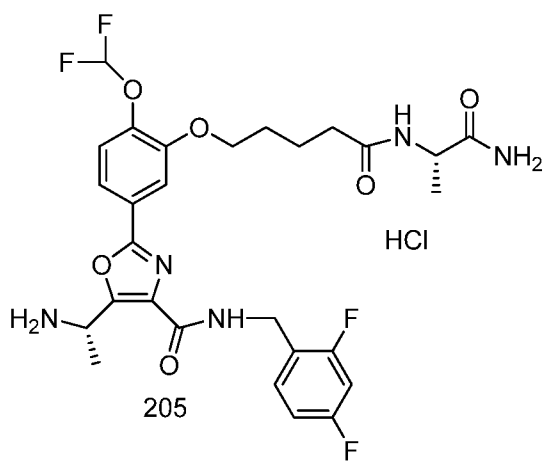
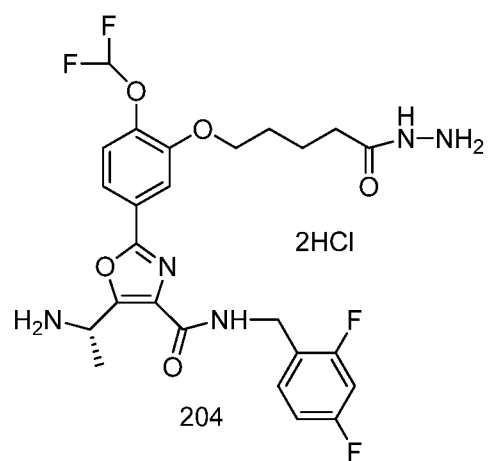
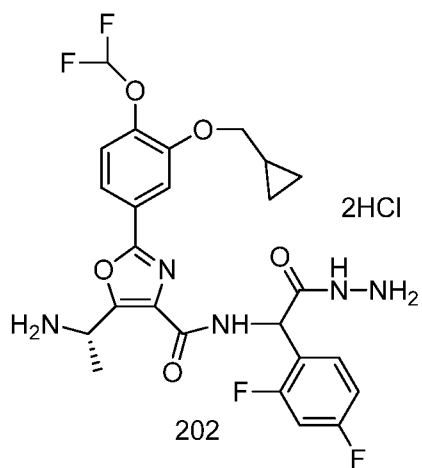


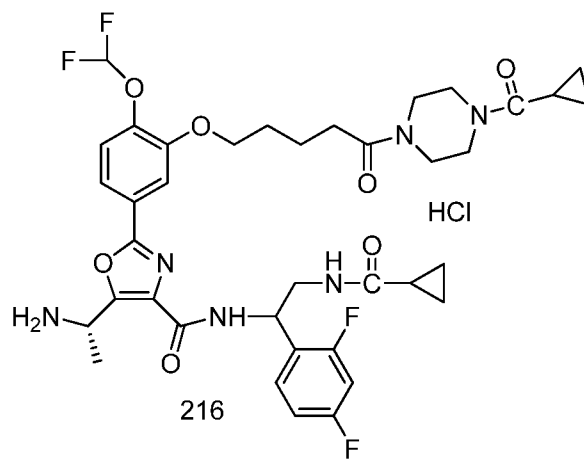
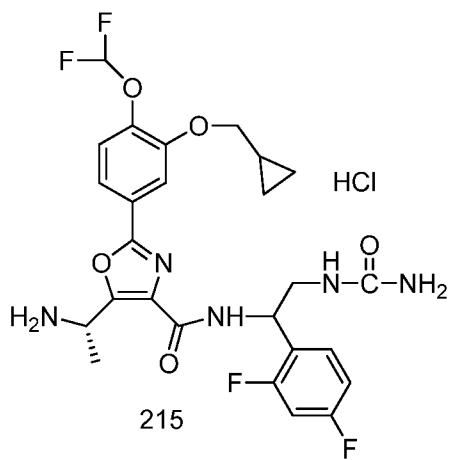
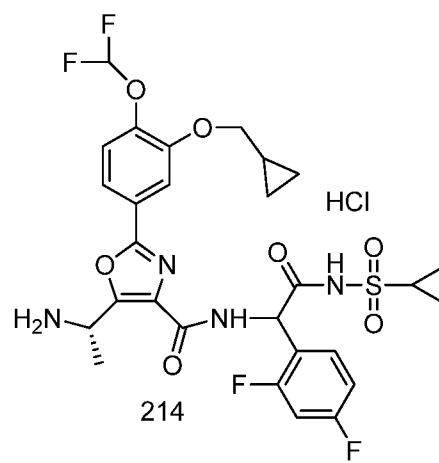
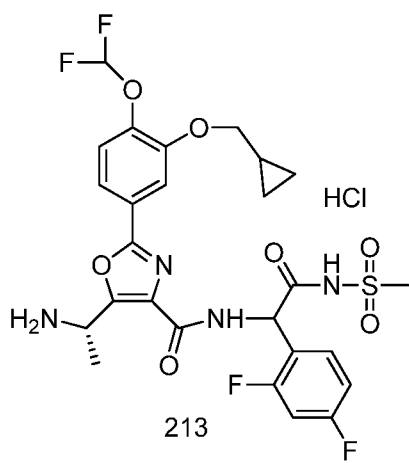
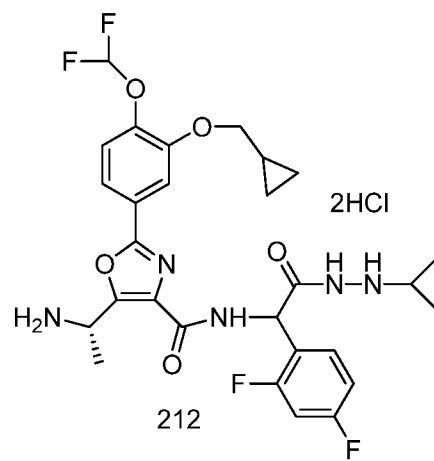
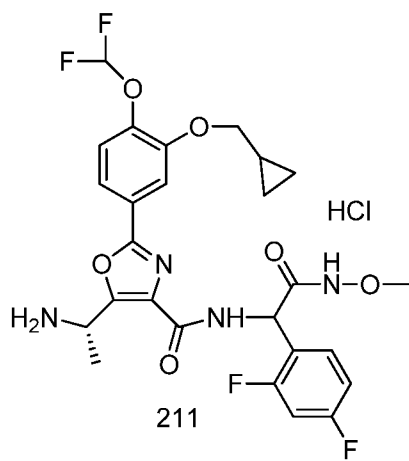


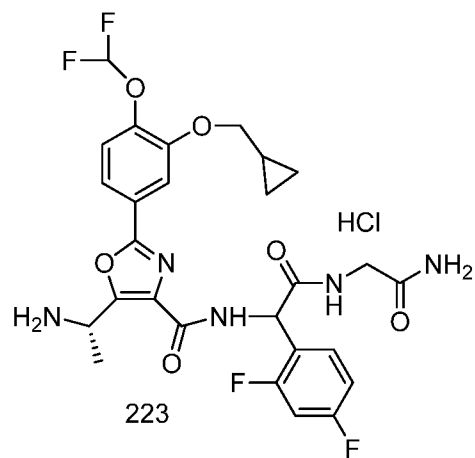
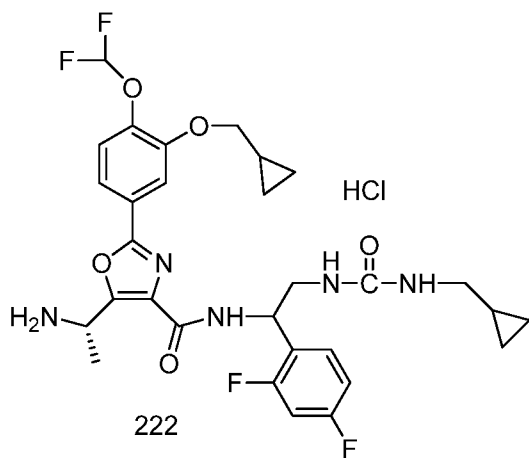
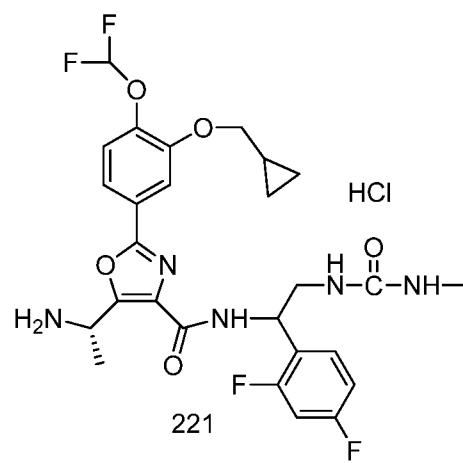
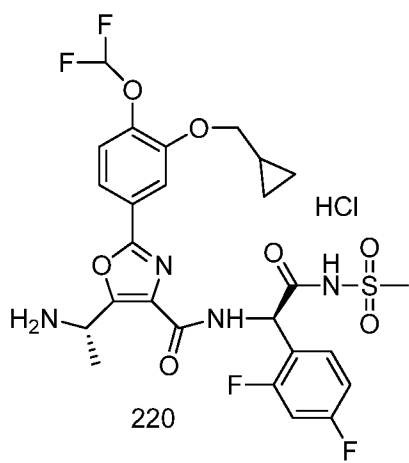
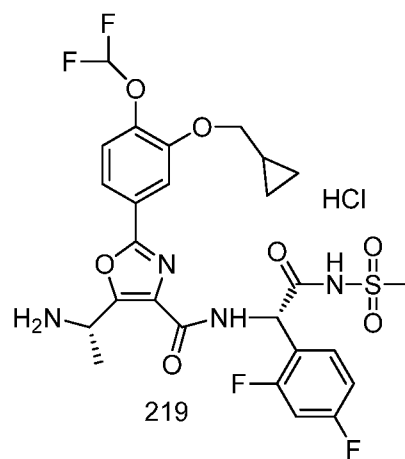
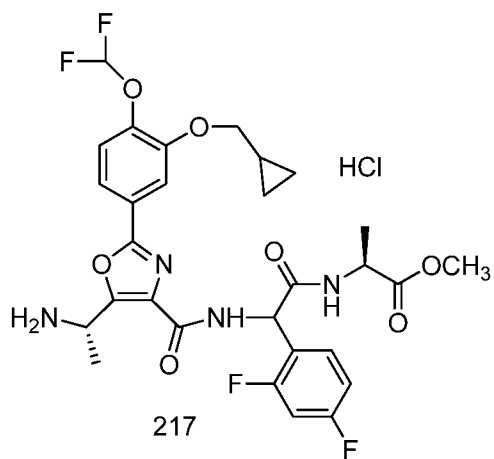


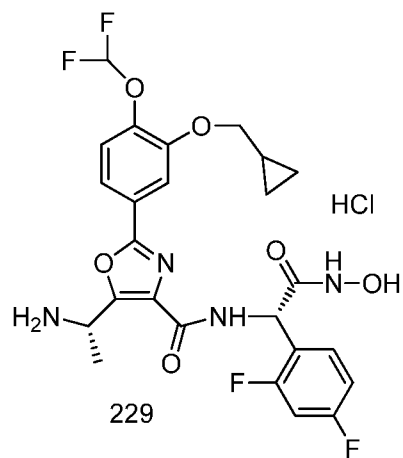
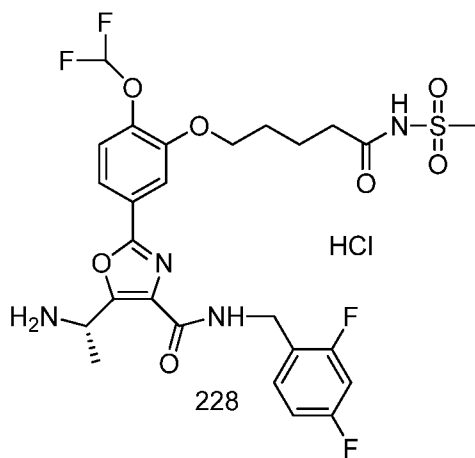
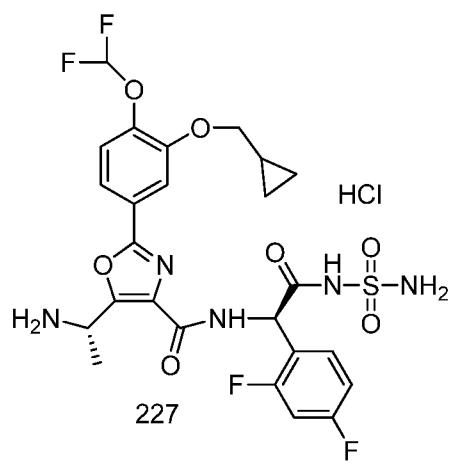
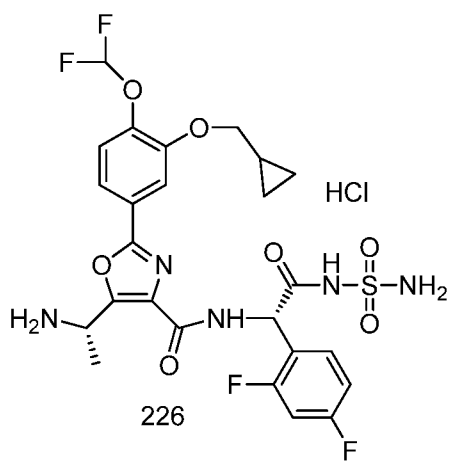
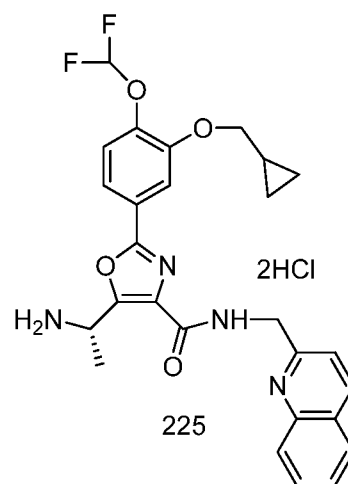
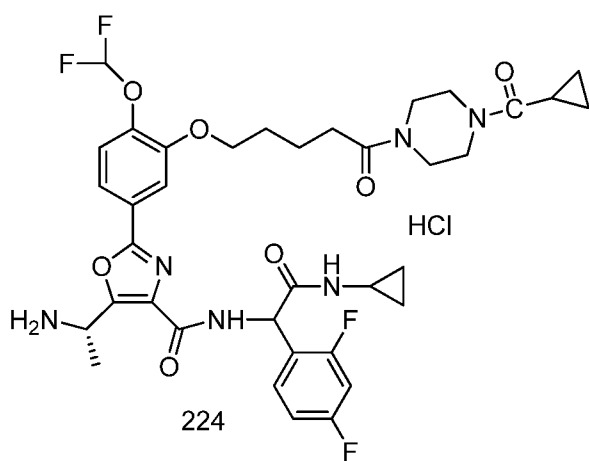


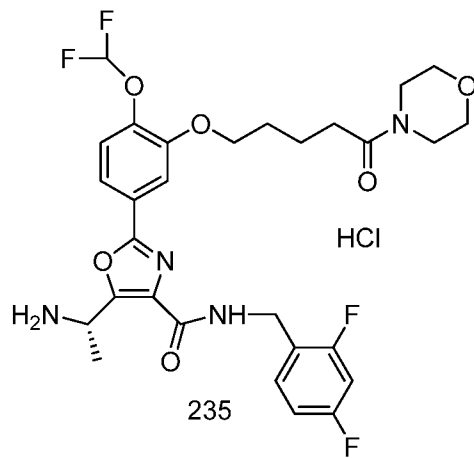
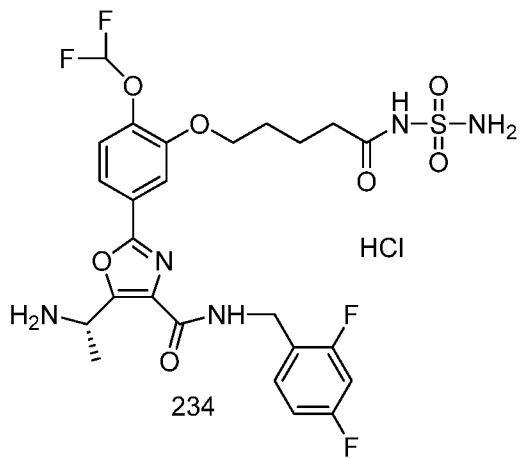
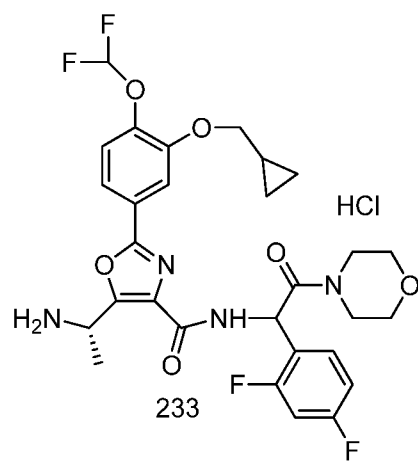
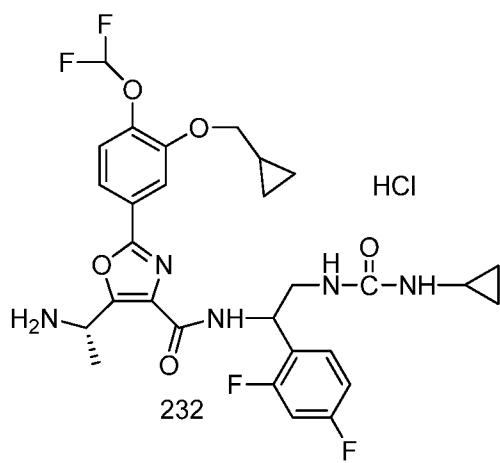
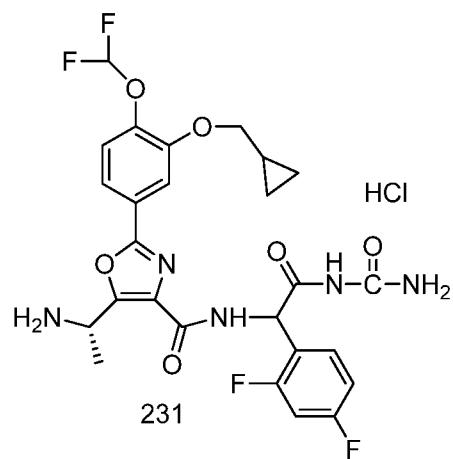
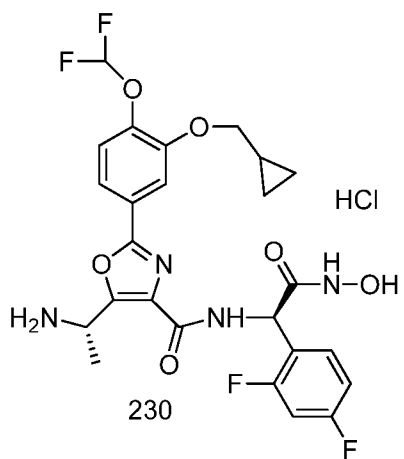


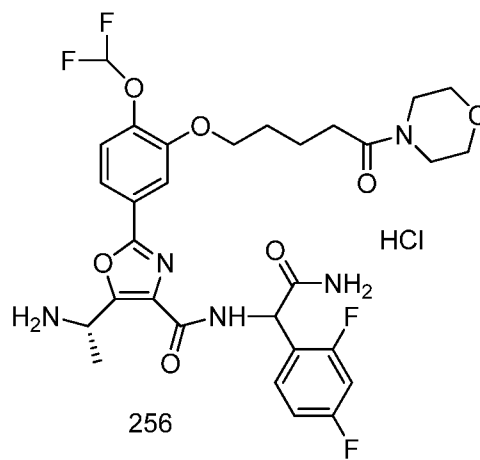
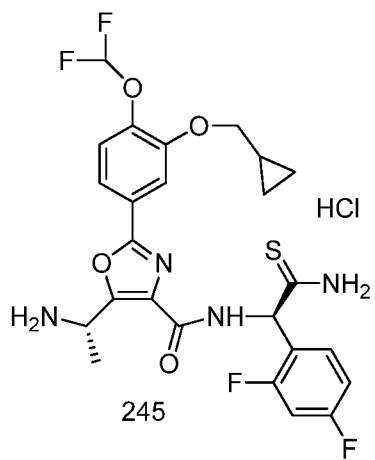
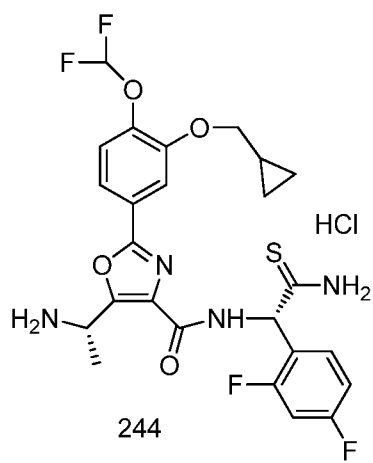
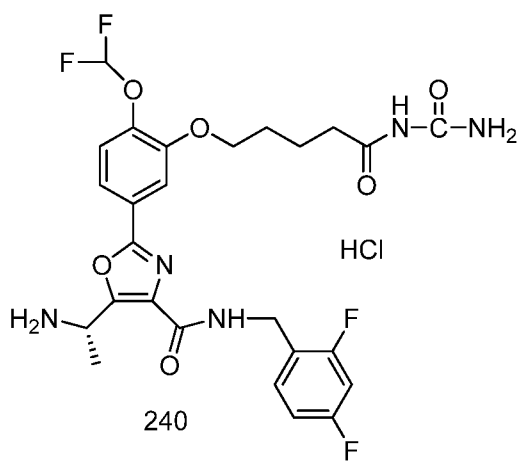
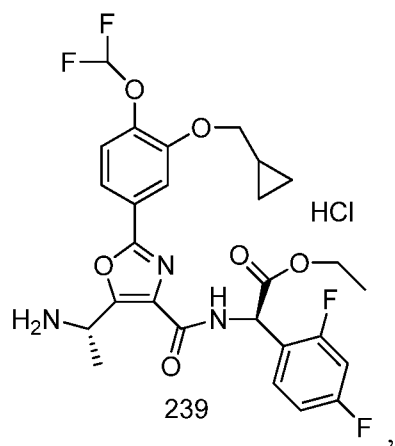
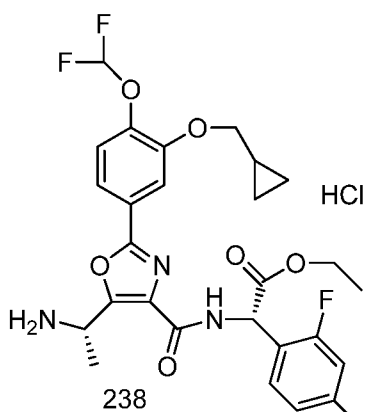
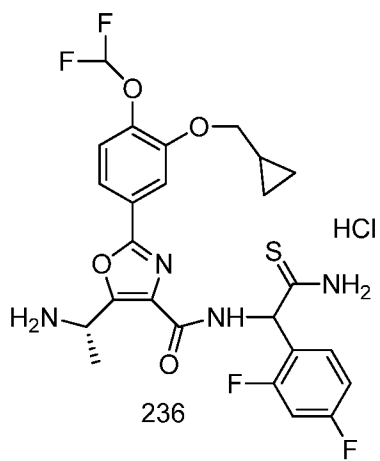


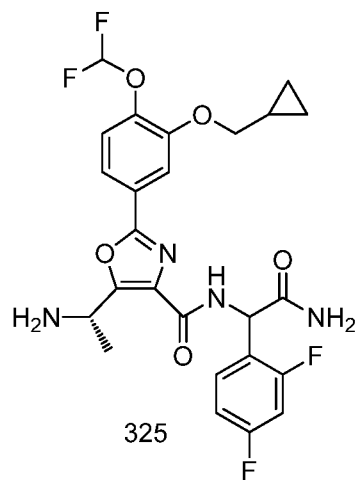
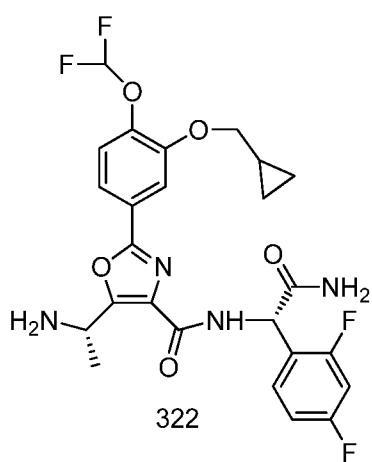
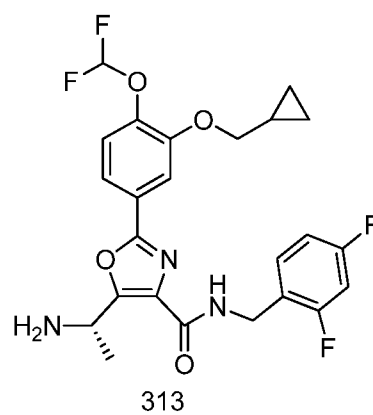
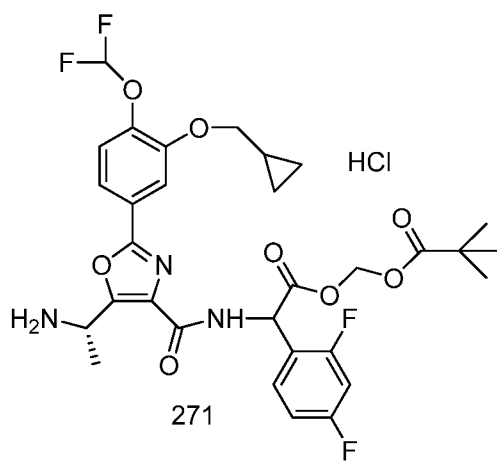
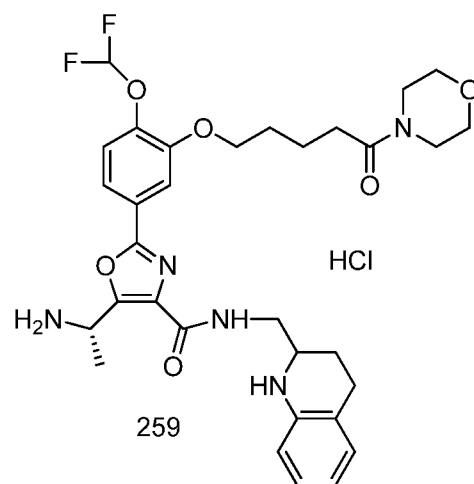
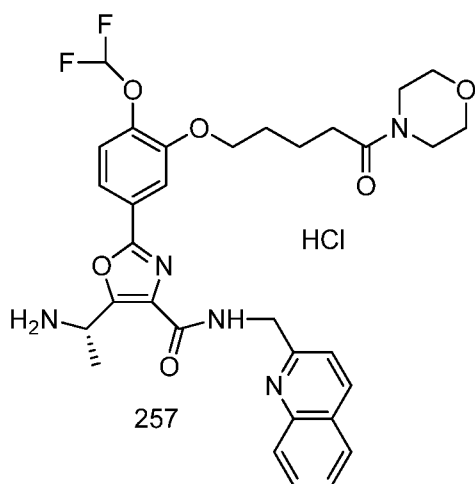


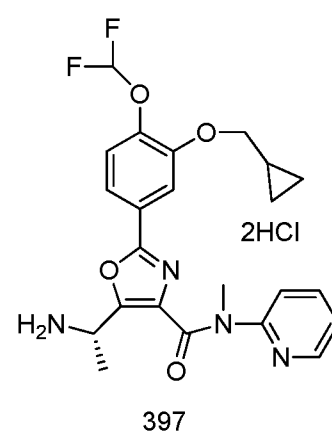
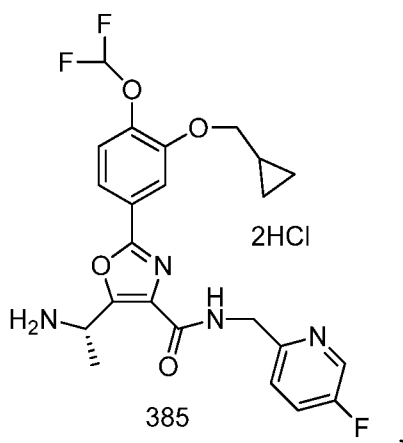
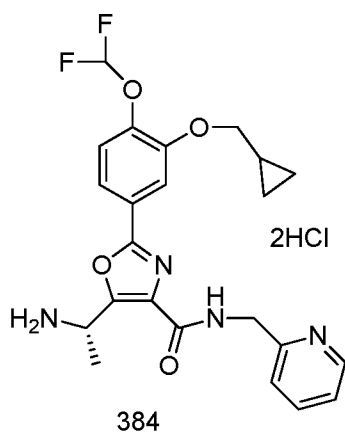
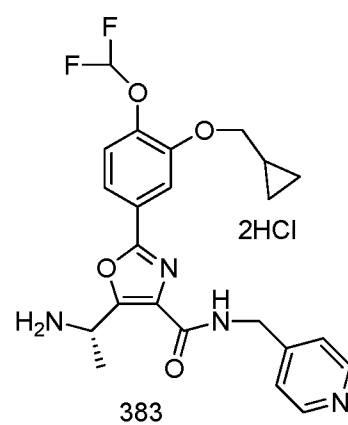
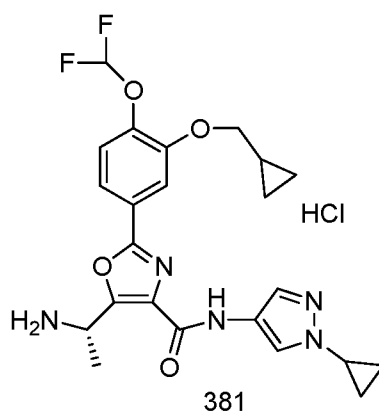
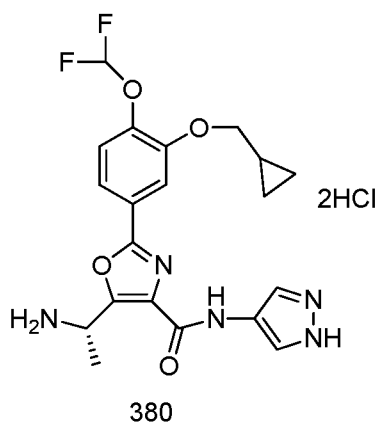
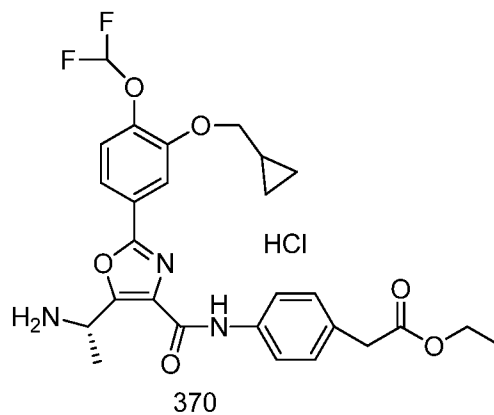
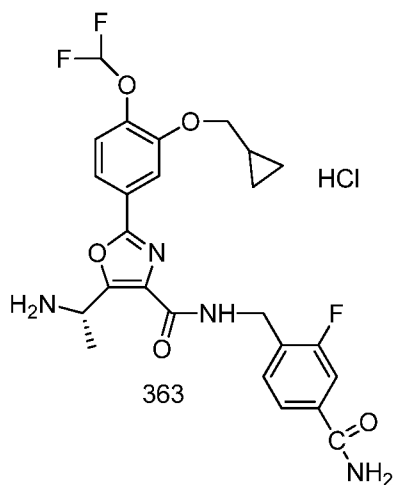
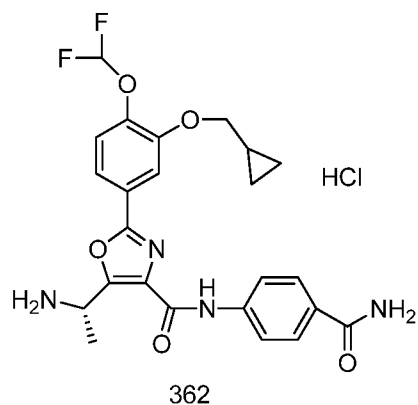
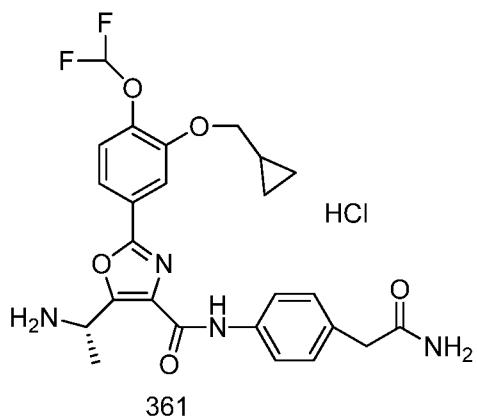


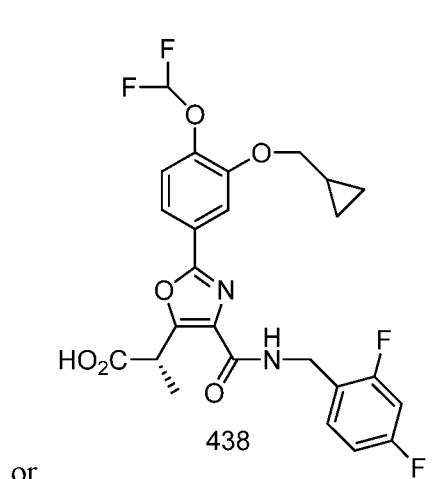
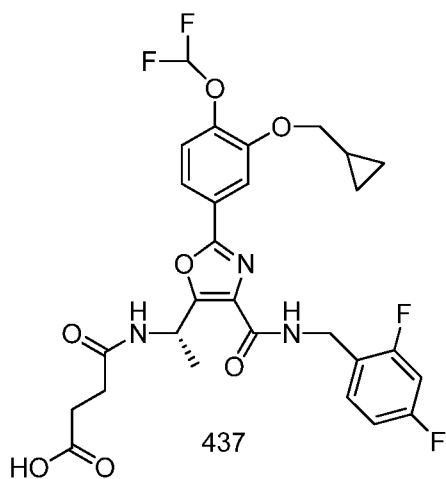
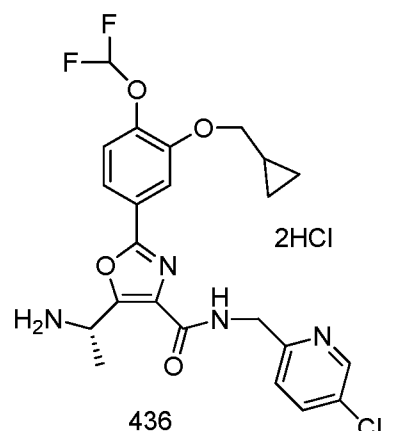
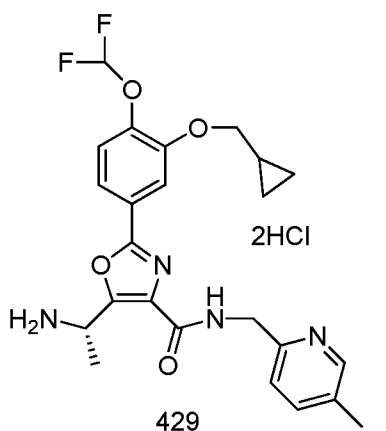
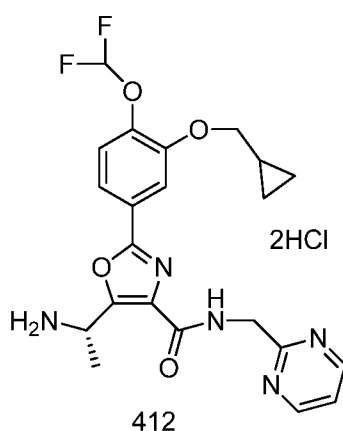
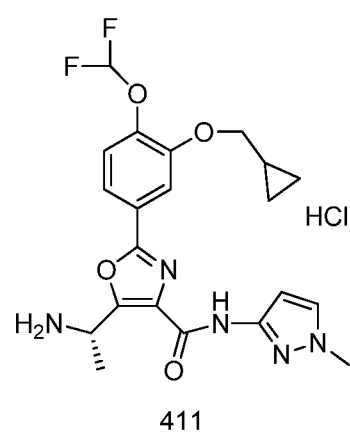
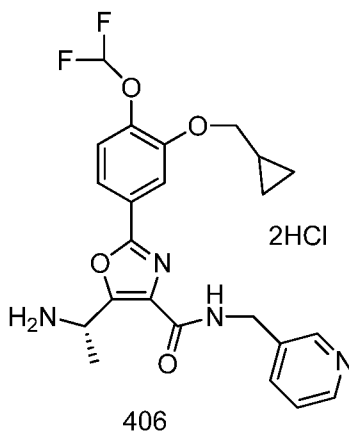
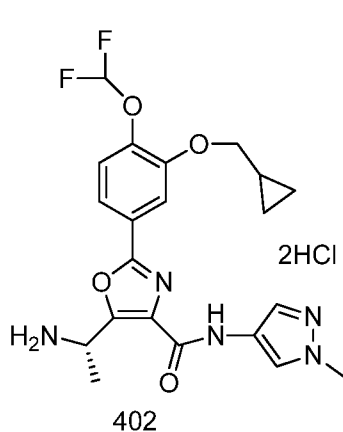












or

(Notes: the number of the compound having specific structure above is in one to one correspondence with the compound number of Example, and the compound number in “Results of inhibitory activities of compounds of the invention against PDE4B2 enzyme”. For example, compound 13 of **Example 1**, and compound 13 in “Results of inhibitory activities of compounds of the invention against PDE4B2 enzyme”, are in correspondence with the compound 13 described herein.)

[00185] Also provided herein is use of compounds disclosed herein and their pharmaceutically acceptable salts in the manufacture of a medicament for treating respiratory disease (especially

chronic obstructive pulmonary disease), allergy, inflammation, a central nervous system (CNS) disorder, pulmonary fibrosis or non-insulin dependent diabetes, Including those described in the present invention.

[00186] Also provided herein is use of compounds disclosed herein in the manufacture of a medicament for lessening, preventing, managing or treating PDE-4 mediated disorder, especially chronic obstructive pulmonary disease.

[00187] Also provided herein includes a pharmaceutical composition comprising a therapeutically effective amount of a compound having Formula (I), (I') or (II) in association with at least one pharmaceutically acceptable carrier, adjuvant or diluent.

[00188] Unless otherwise stated, all stereoisomers, geometric isomers, tautomers, *N*-oxides, hydrates, solvates, metabolites, salts, and pharmaceutically acceptable prodrugs of the compounds disclosed herein are within the scope of the invention.

[00189] Specially, the salt is a pharmaceutically acceptable salt. The phrase "pharmaceutically acceptable" refers to that the substance or composition must be chemically and/or toxicologically compatible with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[00190] The compounds disclosed herein also include salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula (I), (I') or (II) and/or for separating enantiomers of compounds of Formula (I), (I') or (II).

[00191] If the compound disclosed herein is a base, the desired salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid and salicylic acid; a pyranosidyl acid, such as glucuronic acid and galacturonic acid; an alpha hydroxy acid, such as citric acid and tartaric acid; an amino acid, such as aspartic acid or glutamic acid; an aromatic acid, such as benzoic acid and cinnamic acid; a sulfonic acid, such as *p*-toluenesulfonic acid, ethanesulfonic acid, and the like.

[00192] If the compound disclosed herein is an acid, the desired salt may be prepared by any

suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or an alkaline earth metal hydroxide, and the like. Some non-limiting examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia (primary, secondary, and tertiary amines), and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, lithium, and the like.

COMPOUNDS, COMPOSITIONS, FORMULATIONS AND ADMINISTRATION OF COMPOUNDS OR COMPOSITIONS OF THE INVENTION

[00193] The compound disclosed herein can be manufactured and formulated to a racemic mixture, an enantiomer, a diastereoisomer, a rotamer, an *N*-oxide, a polymorph, a solvate, a pharmaceutically acceptable salt or a prodrug thereof; also can be manufactured to a pharmaceutical composition comprising a compound having Formula (I), (I') or (II), or a metabolite, an enantiomer, a diastereoisomer, an *N*-oxide, a polymorph, a solvate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, and optionally excipient.

[00194] The pharmaceutical composition can be manufactured and administered in dosage units, and each unit comprises a certain amount of at least one compound and/or physiologically acceptable additional salt disclosed herein. Dosage can vary within very wide limits, it is because that the compound is effective even on low-dose levels and relatively non-toxicity. The compound can be administered in therapeutically effective low micromolar amount, and the amount can be increased to the patient's acceptable maximum dose.

[00195] Compounds having Formula (I), (I') or Formula (II) and their pharmaceutically acceptable salts can be used as chemical raw drugs being administered to patients for treatment, also can be used as active ingredients of pharmaceutical compositions. Therefore, also provided herein are pharmaceutical compositions which contain effective amount of compounds having Formula (I), (I') or Formula (II) or pharmaceutically acceptable salts thereof and one or more pharmaceutically acceptable carrier, diluent or excipient.

[00196] In practice, the compounds, or pharmaceutically acceptable salts thereof, of invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier

according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound, or pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[00197] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[00198] The term “therapeutically effective amount” in the invention means a total amount of active components which is sufficiently effective for treating the disease. When administering a single active component to a patient, term “therapeutically effective amount” means the amount of this active component. When administering the combination agents, term “therapeutically effective amount” means the total amount of active compositions, which is sufficient to effect the treatment of given disease, no matter that the dose of active composition is combined, administered simultaneously or sequentially. Compounds having Formula (I), (I') or Formula (II) or their pharmaceutically acceptable salts are described above. Considering the compatibility with other ingredients and harmless to subjects, the carrier, diluents, or excipient must be acceptable. According to another aspect described herein, also provided herein is a method of preparing the pharmaceutical preparation, which is, compounds having formula (I), (I') or formula (II) or their

pharmaceutically acceptable salts and one or more pharmaceutically acceptable carriers, diluents or excipients are mixed uniformly to form preparation. The term “pharmaceutically acceptable” refers to a compound, material, composition and/or dose form, which are in the reasonable scope of medical judgment, must be compatible with the tissue of patent, and without excessive toxicity, irritation, allergic reaction, or other problems related to reasonable benefit /risk and complications, and effectively used in the intended application.

[00199] In general, the compounds of the present invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Suitable dosage ranges are typically 1-500 mg daily, preferably 1-100 mg daily, and most preferably 1-30 mg daily, depending upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this Application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease.

[00200] Administration of the compounds of the present invention may be accomplished according to patient's needs, for example, orally, nasally, parenterally (subcutaneously, intravenously, intramuscularly, intrasternally and by infusion), by inhalation, rectally, vaginally, topically, locally, transdermally, and by ocular administration.

[00201] Various solid oral dosage forms can be used for administering of compounds of the invention including tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders. The compounds of the present invention can be administered alone or combined with various pharmaceutically acceptable carriers, diluents (such as sucrose, mannitol, lactose, starches) and excipients known in the art, including but not limited to suspending agents, solubilizers, buffering agents, binders, disintegrants, preservatives, colorants, flavorants, lubricants, and the like. Time release capsules, tablets and gels are also advantageous in administering the compounds of the present invention.

[00202] A tablet containing the compounds described herein can be prepared by compression or

molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluents. Each tablet preferably contains from about 0.1 mg to about 500 mg of the active ingredient and each cachet or capsule preferably containing from about 0.1 mg to about 500 mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1 mg, 1 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, or 500 mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

[00203] Various liquid oral dosage forms can also be used for administering compounds of the invention, including aqueous and non-aqueous solutions, emulsions, suspensions, syrups, and elixirs. Such dosage forms can also contain suitable inert diluents known in the art such as water and suitable excipients known in the art such as preservatives, lubricating agents, sweeteners, flavorants, as well as agents for emulsifying and/or suspending the compounds of the invention. The compounds of the present invention may be injected, for example, intravenously, in the form of an isotonic sterile solution. Other preparations are also possible.

[00204] Suppositories for rectal administration of the compounds of the present invention can be prepared by mixing the compound with a suitable excipient such as cocoa butter, salicylates and polyethylene glycols.

[00205] Formulations for vaginal administration can be in the form of cream, gel, paste, foam, or spray formula containing, in addition to the active ingredient, such suitable carriers as are known in the art.

[00206] For topical administration the pharmaceutical composition can be in the form of creams, ointments, liniments, lotions, emulsions, suspensions, gels, solutions, pastes, powders, sprays, and drops suitable for administration to the skin, eye, ear or nose. Topical administration may also involve transdermal administration via means such as transdermal patches.

[00207] For the treatment of the diseases of the respiratory tract, the compounds according to the invention are preferably administered by inhalation.

[00208] Inhalable preparations include inhalable powders, propellant containing metering

aerosols or propellant-free inhalable formulations. For this purpose, powder (preferably in micronized form) may be administered directly, or administered in the form of a solution or suspension containing them.

[00209] A diluent or carrier, generally non-toxic and chemically inert to the compounds of the invention, e.g. lactose or any other additive suitable for improving the respirable fraction can be added to the powdered compounds of the invention.

[00210] Inhalation aerosols containing propellant gas such as hydrofluoroalkanes may contain the compounds of the invention either in solution or in dispersed form. The propellant-driven formulations may also contain other ingredients such as co-solvents, stabilizers and optionally other excipients.

[00211] The propellant-free inhalable formulations comprising the compounds of the invention may be in form of solutions or suspensions in an aqueous, alcoholic or hydroalcoholic medium and they may be delivered by jet or ultrasonic nebulizers known from the prior art by soft-mist nebulizers such as Respimat[®].

[00212] The compounds of the invention can be administered as the sole active agent or in combination with other pharmaceutical active ingredients including those currently used in the treatment of respiratory disorders, e.g. beta2-agonists such as salbutamol, formoterol, salmeterol and carmoterol (TA2005), corticosteroids such as budesonide and its epimers, beclometasone dipropionate, triamcinolone acetonide, fluticasone propionate, flunisolide, mometasone furoate, rofleponide and ciclesonide and anticholinergic or antimuscarinic agents such as ipratropium bromide, oxitropium bromide, tiotropium bromide, glycopyrrolate bromide, revatropate or the compounds disclosed in WO 03/053966.

[00213] Preferably the compounds of general formula (I), (I') or (II) alone or combined with other active ingredients may be administered for the prevention and/or treatment of a disease of the respiratory tract characterized by airway obstruction such as asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD).

[00214] Provide herein are the methods of using compounds or pharmaceutical compositions described herein for treatment, further comprising administering an additional drug for treating chronic obstructive pulmonary disease (combination therapy). Wherein the additional drug for treating chronic obstructive pulmonary disease is sodium pyruvate, doxofylline, roflumilast,

apremilast, tetomilast, tielukast, theophylline, formoterol, salmeterol, fluticasone propionate, salmeterol xinafoate/fluticasone propionate, rolipram, piclamilast, cilomilast, CDP-840, indacaterol, olodaterol, QVA149, midesteine, zileuton, salbutamol, carmoxirole, budesonide and epimer thereof, beclomethasone dipropionate (BDP), triamcinolone acetonide, flunisolide, mometasone furoate, rofleponide, ciclesonide, ipratropium bromide, ipratropium bromide/albuterol, oxitropium bromide, tiotropium bromide, glycopyrronium bromide, umeclidinium bromide, vilanterol, umeclidinium/vilanterol, aclidinium bromide, aclidinium bromide/formoterol fumarate, LAS40464, LAS100977 (abediterol), AZD-8999, RPL-554, OCID-2987, CHF-6001, CR-3465, HPP-737, fluticasone furoate/vilanterol (FF/VI), benralizumab, revatroate, or a combination thereof.

[00215] “Combined use” or “combination” within the meaning of the present invention is to be understood as meaning that the individual components can be administered simultaneously or more or less simultaneously, or respectively in succession. As an example, one therapeutic agent could be taken in the morning and one later in the day. Or in another scenario, one therapeutic agent could be taken once daily and the other once weekly. It is understood, that if individual components are administered directly in succession, the delay in administering the second component should not be such as to lose the beneficial therapeutic effect of the combination.

[00216] Simultaneous administration can be effected by any appropriate route and, preferably, is accomplished, for example, by administering the therapeutic agents to the subject in need thereof by the oral route, or the intravenous route, or the intramuscular route, or by subcutaneous injection whereby the administration form has a fixed ratio of each therapeutic agent.

[00217] More or less simultaneous administration or administration in succession of each therapeutic agent can be effected by any appropriate route, including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, both therapeutic agents of the combination may be administered by orally.

[00218] The compound of the present invention can be contained in the pharmaceutical composition. The pharmaceutical composition disclosed herein comprise a compound of the present invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants.

Such additional therapeutic ingredients include, for example, i) Leukotriene receptor antagonists, ii) Leukotrene biosynthesis inhibitors, iii) corticosteroids, iv) H1 receptor antagonists, v) beta 2 adrenoceptor agonists, vi) COX-2 selective inhibitors, vii) statins, viii) non-steroidal anti-inflammatory drug ("NSAID"), and ix) M2/M3 antagonists.

[00219] The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00220] Creams, ointments, jellies, solutions, or suspensions containing the compound disclosed herein can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

[00221] Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[00222] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be fluid to the extent that easy syringability exists.

[00223] The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserve against the contaminating action of microorganism such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[00224] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like.

Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

[00225] This invention also provides a method of treating a pulmonary disease (e.g., COPD, asthma or cystic fibrosis) in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one compound of Formula (I), (I') or (II), or a pharmaceutically acceptable salt or solvate thereof, in combination with at least one compound selected from the group consisting of: steroid (such as glucocorticoids), 5-lipoxygenase inhibitors, β -2 adrenoceptor agonists, alpha-adrenoceptor agonists, muscarinic M1 antagonists, muscarinic M3 antagonists, muscarinic M2 agonists, NK3 antagonists, LTB4 antagonists, cysteinyl leukotriene antagonists, bronchodilators, PDE-4 inhibitors, PDE inhibitors, elastase inhibitors, MMP inhibitors, phospholipase A2 inhibitors, phospholipase D inhibitors, histamine H1 antagonists, histamine H3 antagonists, dopamine agonists, adenosine A2 agonists, NK1 and NK2 antagonists, GABA-b agonists, nociceptin agonists, expectorants, mucolytic agents, decongestants, mast cell stabilizer, antioxidants, anti-IL-8 anti-bodies, anti-IL-5 antibodies, anti-IgE antibodies, anti-TNF antibodies, IL-10, adhesion molecule inhibitors, growth hormones, and other PDE-4 inhibitors.

[00226] For use in combination with compound of Formula (I), (I') or (II), non-limiting examples of antihistamines include, astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, equitazine, mianserin, noberastine, meclizine, norastemizole, picumast, pyrillamine, promethazine, terfenadine, tripeleminamine, temelastine, trimeprazine and triprolidine.

[00227] Non-limiting examples of histamine H3 receptor antagonists include, thioperamide, impromidine, burimamide, clobenpropit, impentamine, mifetidine, *S*-sopromidine, *R*-sopromidine, SKF-91486, GR-175737, GT-2016, UCL-1199 and clozapine. Other

compounds can readily be evaluated to determine activity at H3 receptors by known methods, including the guinea pig brain membrane assay and the guinea pig neuronal ileum contraction assay, both of which are described in U.S. Patent 5,352,707. Another useful assay utilizes rat brain membranes and is described by West et al., "Identification of Two-H3-Histamine Receptor Subtypes", *Molecular Pharmacology*, 1990, Vol. 38, 610-613.

[00228] The term "leukotriene inhibitor" includes any agent or compound that inhibits, restrain, retards or otherwise interacts with the action or activity of leukotrienes. Non-limiting examples of leukotriene inhibitors include montelukast and its sodium salt; 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methyl)cyclopropaneacetic acid, and its sodium salt, described in U.S. Patent 5,270,324; 1-(((1(R)-3(3-(2-(2,3-dichlorothienol[3,2-*b*]pyridine-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropaneacetic acid, and its sodium salt, described in U.S. Patent 5,472,964; pranlukast; zafirlukast, and [2-[[2(4-*tert*-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid, described in U.S. Patent 5,296,495.

[00229] Non-limiting examples of β -adrenergic receptor agonists include, albuterol, bitolterol, isoetharine, mataproterenol, perbuterol, salmeterol, terbutaline, isoproterenol, ephedrine and epinephrine. Non-limiting examples of α -adrenergic receptor agonists include arylalkylamines, (eg., phenylpropanolamine and pseudoephedrine, imidazoles (eg., naphazoline, oxymetazoline, tetrahydrozoline and xylometazoline) and cycloalkylamines (eg., propylhexedrine).

[00230] A non-limiting example of a mast cell stabilizer is nedocromil sodium. A non-limitative example of an expectorant is guaifenesin. Non-limiting examples of decongestants are pseudoephedrine, phenylpropanolamine and phenylephrine.

[00231] Non-limiting examples of NK1, NK2 and NK3 tachykinin receptor antagonists include CP-99, 994 and SR 48968. Non-limiting examples of muscarinic antagonists include Ipratropium bromide and tiotropium bromide.

[00232] Non-limiting examples of GABA_B agonists include baclofen and 3-aminopropyl-phosphinic acid. Dopamine agonists include quinpirole, ropinirole, pramipexole, pergolide and bromocriptine.

[00233] “5-lipoxygenase inhibitors” include any agent or compound that inhibits, restrains, retards or otherwise interacts with the enzymatic action of 5-lipoxygenase, Non-limitative examples of 5-lipoxygenase inhibitors include zileuton, docebenone, piri-post, ICI-D2318, and ABT 761.

[00234] The dosages of the compounds of the present invention depend upon a variety of factors including the particular disease to be treated, the severity of the symptoms, the route of administration, the frequency of the dosage interval, the particular compound utilized, the efficacy, toxicology profile, and pharmacokinetic profile of the compound.

[00235] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may conveniently contain from about 0.5 mg to about 5 g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1 mg to about 1000 mg of the active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg or 1000 mg.

[00236] Advantageously, they are administered at a dosage comprised between 0.01 and 1000 mg/day, preferably between 0.1 and 500 mg/day.

[00237] When given by inhalation route, the compounds of the invention may be administered for example, at a dosage comprised between 0.01 and 10 mg/day, preferably between 0.05 and 5 mg/day, more preferably between 0.1 and 2 mg/day.

USE OF THE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS

[00238] Provided herein are pharmaceutical compositions containing compounds having Formula (I), (I') or (II) or the compounds described herein, and a pharmaceutically acceptable carrier, excipient, or adjuvant.

[00239] The amount of compound contained in the composition described herein is an effective and detectable amount which can against the action of PDE-4 for treating the following diseases or condition selected from the group consisting of: pain (e.g., acute pain, acute inflammatory pain, chronic inflammatory pain, and neuropathic pain), acute inflammation, chronic inflammation, rheumatoid arthritis, psoriasis, atopic dermatitis, asthma, COPD, adult

respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, ischemia reperfusion injury, renal reperfusion injury, glomerulonephritis, Parkinson's disease, Alzheimer's disease, mild cognitive impairment (MCI), depression, anxiety, graft vs. host reaction (i.e., graft vs. host disease), allograft rejections (e.g., acute allograft rejection, and chronic allograft rejection), acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral ischemia, osteoarthritis, multiple sclerosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus (i.e., Kaposi's sarcoma), meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, psoriatic arthritis, herpes, encephalitis, traumatic brain injury, CNS tumors, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute pancreatitis, chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, ocular inflammation, corneal neovascularization, polymyositis, acne, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness (i.e., airway hyperreactivity), bronchiectasis, bronchiolitis, bronchiolitis obliterans (i.e., bronchiolitis obliterans syndrome), chronic bronchitis, cystic fibrosis, dyspnea, emphysema, adult respiratory disease, acute respiratory distress syndrome, respiratory viruses, hypercapnia, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, pulmonary fibrosis, pulmonary hypertension, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, airway obstruction, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, periodontitis, cancer, transplant reperfusion injury, early transplantation rejection (e.g., acute allograft rejection), airway hyperreactivity, allergic contact dermatitis, allergic rhinitis, non-allergic rhinitis, alopecia areata, autoimmune deafness (including, for example, Meniere's disease), autoimmune hemolytic syndromes, autoimmune hepatitis, autoimmune neuropathy, autoimmune ovarian failure, autoimmune orchitis, autoimmune thrombocytopenia, chronic inflammatory demyelinating polyneuropathy, cirrhosis, dermatomyositis, diabetes, drug-induced autoimmunity, endometriosis, fibrotic diseases, gastritis, Goodpasture's syndrome, Graves' disease, Guillain-Barre disease, Hashimoto's thyroiditis, hepatitis-associated autoimmunity, HIV-related autoimmune syndromes and hematologic disorders, hypophytis, interstitial cystitis, juvenile arthritis, Langerhans' cell

histiocytosis, lichen planus, metal-induced autoimmunity, myocarditis (including viral myocarditis), myositis, neuropathies (including, for example, IgA neuropathy, membranous neuropathy and idiopathic neuropathy), nephritic syndrome, optic neuritis, pancreatitis, post-infectious autoimmunity, primary biliary cirrhosis, reactive arthritis, ankylosing spondylitis, Reiter's syndrome, reperfusion injury, scleritis, scleroderma, secondary hematologic manifestation of autoimmune diseases (such as anemias), silicone implant associated autoimmune disease, Sjogren's syndrome, systemic lupus erythematosus, transverse myelitis, tubulointerstitial nephritis, uveitis, and vitiligo in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound of Formula (I), (I') or (II), or a pharmaceutically acceptable salt or solvate thereof.

[00240] "Effective amount" or "effective dose" means an amount of a compound or a pharmaceutically acceptable composition in the invention, is sufficient for treating or lessening one or more diseases described herein. According to the invention, any dose and any route of administering the compound or composition to a subject are effective for treating or lessening the severity of disease. The accurate of the dose varies with the relative health of a subject, which depending upon numerous factors such as the age, the race, the general condition of the patient, the severity of the infection, the special factor, the route, and the like. The compound or composition described herein can be administered with one or more therapeutic agents to a subject.

GENERAL SYNTHETIC PROCEDURES

[00241] Generally, the compounds disclosed herein may be prepared by methods described herein, wherein the substituents are as defined for Formulas (I), (I') or (II), above, except where further noted. The following non-limiting schemes and examples are presented to further exemplify the invention.

[00242] Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds disclosed herein are deemed to be within the scope disclosed herein. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by utilizing other suitable reagents known in

the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds disclosed herein.

[00243] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius (°C). Reagents were purchased from commercial suppliers such as Shanghai LinkChem Co., Ltd, Aldrich Chemical Company, Inc., Arco Chemical Company and Alfa Chemical Company, and were used without further purification unless otherwise indicated. Common solvents were purchased from commercial suppliers such as Shantou XiLong Chemical Factory, Guangdong Guanghua Reagent Chemical Factory Co. Ltd., Guangzhou Reagent Chemical Factory, Tianjin YuYu Fine Chemical Ltd., Qingdao Tenglong Reagent Chemical Ltd., and Qingdao Ocean Chemical Factory.

[00244] Anhydrous tetrahydrofuran was obtained by drying tetrahydrofuran in the refluxing condition with sodium added. Anhydrous dichloromethane and anhydrous chloroform were obtained by drying dichloromethane and chloroform independently in the refluxing condition equipped with hydride calcium. Ethyl acetate, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and petrol ether were dried over anhydrous sodium sulfate before use.

[00245] Generally, the following reactions were occurred in nitrogen atmosphere or argon atmosphere or anhydrous solvents equipped with drying tubes (Unless otherwise specified), and reaction flasks were plugged with suitable rubber plugs, substrates were added via syringes. All glassware was dried before use.

[00246] Column chromatography was conducted using a silica gel column. Silica gel (300-400 mesh) was purchased from Qingdao Ocean Chemical Factory. NMR spectra were determined on Bruker 400 MHz or Bruker 600 MHz NMR spectrometer at room temperature, using CDCl₃, DMSO-*d*₆, CD₃OD or acetone-*d*₆ as solutions (reported in ppm) and TMS (0 ppm) or chloroform (7.25 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[00247] Low-resolution mass spectral (MS) data were determined on an Agilent 6320 Series

LC-MS spectrometer equipped with G1312A binary pumps and a G1316A TCC (Temperature Control of Column, maintained at 30 °C). A G1329A autosampler and a G1315B DAD detector were used in the analysis, and an ESI source was used on the LC-MS spectrometer.

[00248] Low-resolution mass spectral (MS) data were determined on an Agilent 6120 Series LC-MS spectrometer equipped with G1311A quaternary pumps and a G1316A TCC (Temperature Control of Column, maintained at 30 °C). A G1329A autosampler and a G1315D DAD detector were used in the analysis, and an ESI source was used on the LC-MS spectrometer.

[00249] Both Spectrographs were equipped with an Agilent Zorbax SB-C18 (2.1 × 30 mm, 5 µm). Injection volume was decided by the sample concentration. The flow rate was 0.6 mL/min. HPLC chromatogram was recorded using a UV-Vis wavelength detector at 210/254 nm. The mobile phase was (0.1% formic acid in CH₃CN as mobile phase A) in (0.1% formic acid in H₂O as mobile phase B). The conditions of gradient elution were described in Table 1:

Tab. 1 The conditions of gradient elution

Time (min)	A (CH ₃ CN, 0.1% HCOOH)	B (H ₂ O, 0.1% HCOOH)
0 - 3	5 - 100	95 - 0
3 - 6	100	0
6 - 6.1	100 - 5	0 - 95
6.1 - 8	5	95

[00250] Purities of compounds were assessed by Agilent 1100 Series high performance liquid chromatography (HPLC) with UV detection at 210 nm and 254 nm (Zorbax SB-C18, 2.1 × 30 mm, 4 µm), 10 min, 0.6 mL/min flow rate, 5 to 95% (0.1% formic acid in CH₃CN) in (0.1% formic acid in H₂O). Column was operated at 40 °C.

[00251] Purities of compounds were assessed by Agilent 1260 preparative high performance liquid chromatography (Pre-HPLC) or Calesep Pump 250 preparative high performance liquid chromatography (Pre-HPLC) (column type: NOVASEP, 50/80 mm, DAC) with UV detection at 210 nm /254 nm.

[00252] The following abbreviations are used throughout the specification:

HOAc acetic acid

MeCN, CH ₃ CN	acetonitrile
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
CHCl ₃	chloroform
CDCl ₃	chloroform- <i>d</i>
DMSO	dimethylsulfoxide
DMF	<i>N,N</i> -dimethylformamide
DIPEA	<i>N,N</i> -diisopropylethylamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
KHMDS	potassium bis(trimethylsilyl)amide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc, EA	ethyl acetate
EtOH	ethanol
Et ₂ O	diethyl ether, ether
Fmoc-OSU	<i>N</i> -(9-fluorenylmethoxycarbonyloxy)succinimide
Me-	methyl
Et-, CH ₃ CH ₂ -	ethyl
Ph-, C ₆ H ₅ -	phenyl
Bn-	benzyl
HCl	hydrogen chloride
HOAT	1-hydroxy-7-azabenzotriazole
HOBT	1-hydroxybenzotriazole
THF	tetrahydrofuran
MgSO ₄	magnesium sulfate
MgCl ₂	magnesium chloride
MeOH, CH ₃ OH	methanol
CD ₃ OD	deuterated methanol, methanol- <i>d</i>
HCHO	formaldehyde
CH ₂ Cl ₂ , DCM	dichloromethane
mL, m	milliliter
M	mol/L
h	hour(s)
PE	petroleum ether (60 - 90 °C)
K	potassium
RT, rt	room temperature

Rt retention time

NaBH₃CN sodium cyanoborohydride

NaOH sodium hydroxide

Na₂CO₃ sodium carbonate

K₂CO₃ potassium carbonate

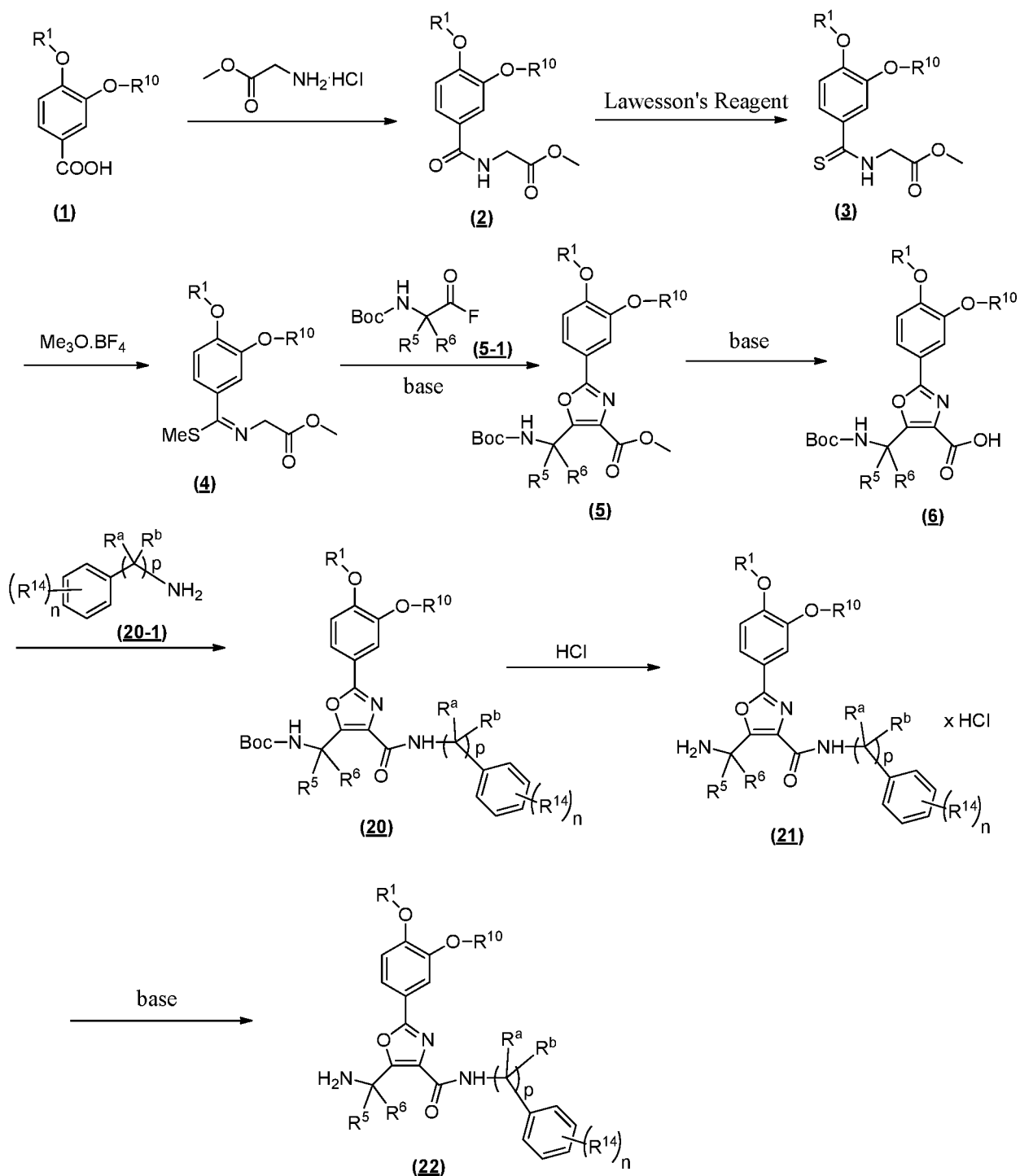
NaHCO₃ sodium bicarbonate

Na₂SO₄ sodium sulfate

H₂O water

[00253] Compounds of the invention may be prepared by methods described below, unless otherwise indicated, each p, R^a, R^b, R¹, R⁵, R⁶, R⁹, R^{9a}, R^{9b}, R^{9c}, R¹⁰, R¹¹, R¹⁴ and R¹⁵ is as defined herein.

Scheme 1

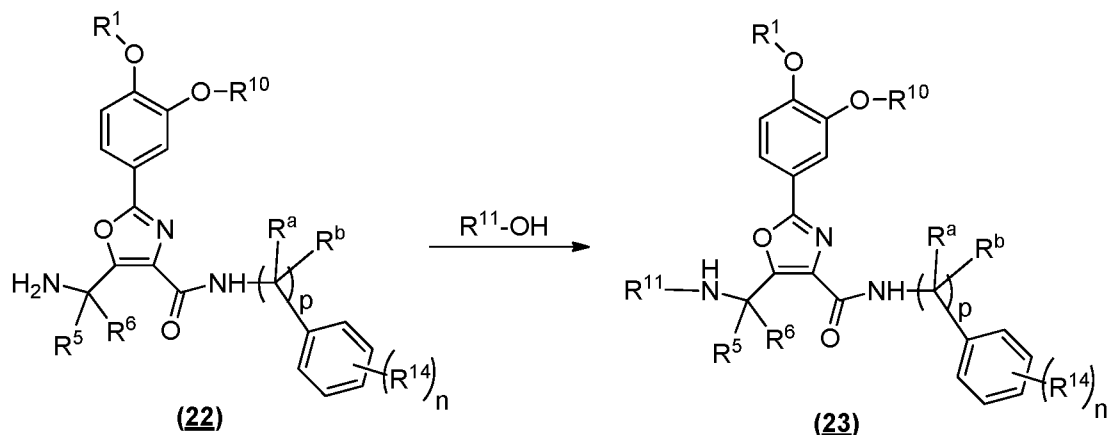


[00254] The title compound (21) and compound (22) can be prepared according to the procedure illustrated in **scheme 1**, and wherein each n is independently 0, 1, 2, 3, 4 or 5, X is 1, 2 or 3. Compound (1) can condense with glycine methyl ester hydrochloride to give compound (2). Compound (2) can be sulfurated in the presence of Lawesson's Reagent to give compound (3), which is transformed to compound (4) in the presence of trimethyloxonium tetrafluoroborate. Compound (4) can react with acyl fluoride (5-1) in the presence of a base (such as KHMDS, and the like) to give compound (5). Compound (5) can be hydrolyzed in the presence of a base (such

as $\text{LiOH}\cdot\text{H}_2\text{O}$, $\text{NH}_3\cdot\text{MeOH}$, and the like) to give compound **(6)**, which can condense with compound **(20-1)** to give compound **(20)**. Compound **(20)** can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound **(21)**.

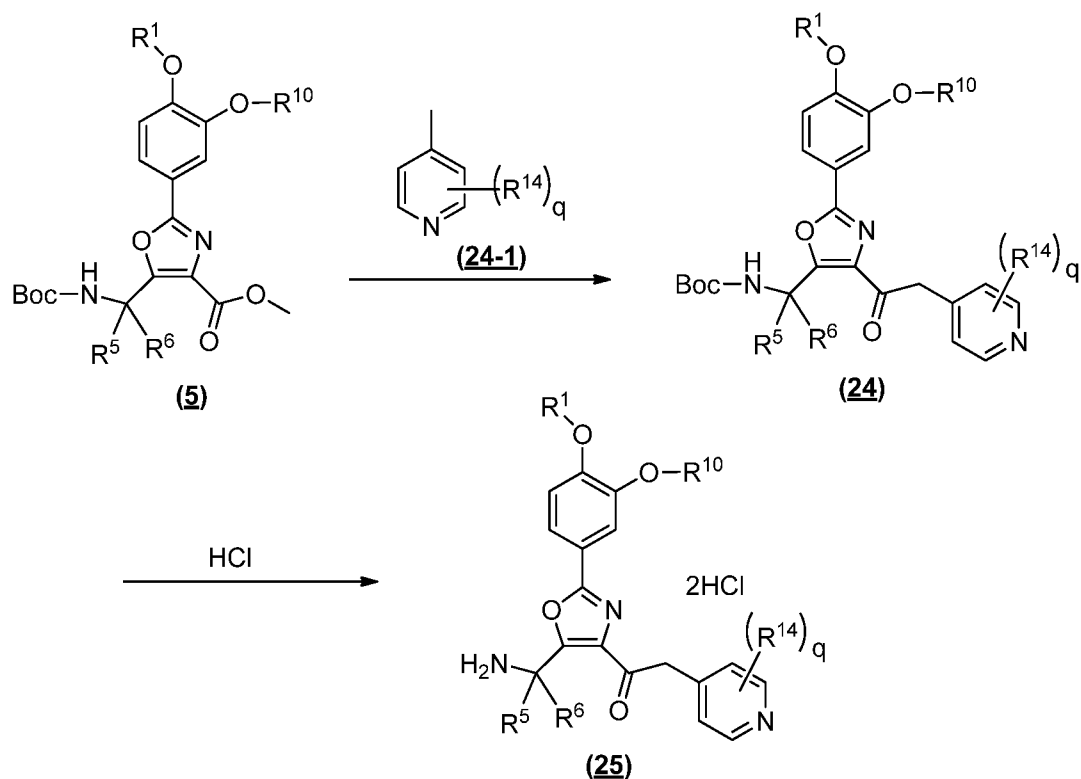
[00255] Compound **(21)** can be treated in the presence of a base (such as sodium hydroxide, and the like) to give the title compound **(22)**.

Scheme 2



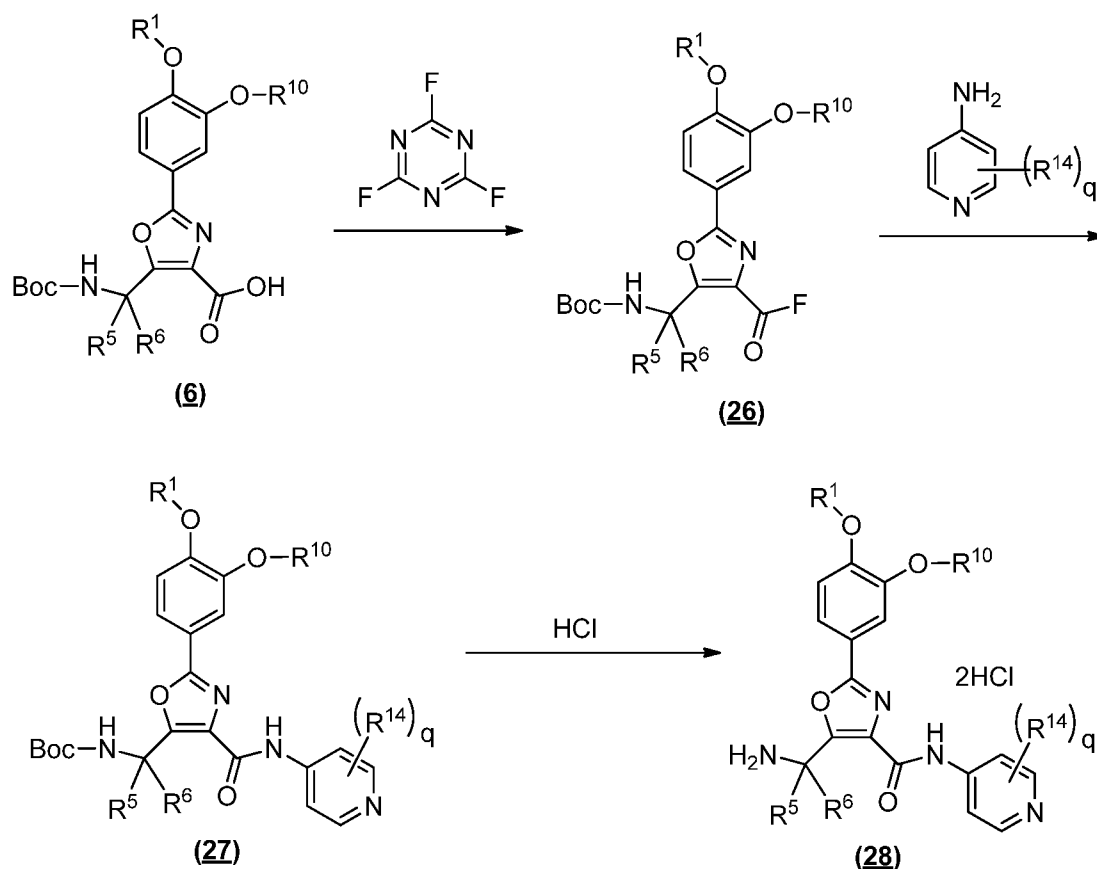
[00256] The title compound **(23)** can be prepared according to the procedure illustrated in **scheme 2**, and wherein each n is independently 0, 1, 2, 3, 4 or 5. Compound **(22)** can react with $\text{R}^{11}\text{-OH}$ to give the title compound **(23)**.

Scheme 3



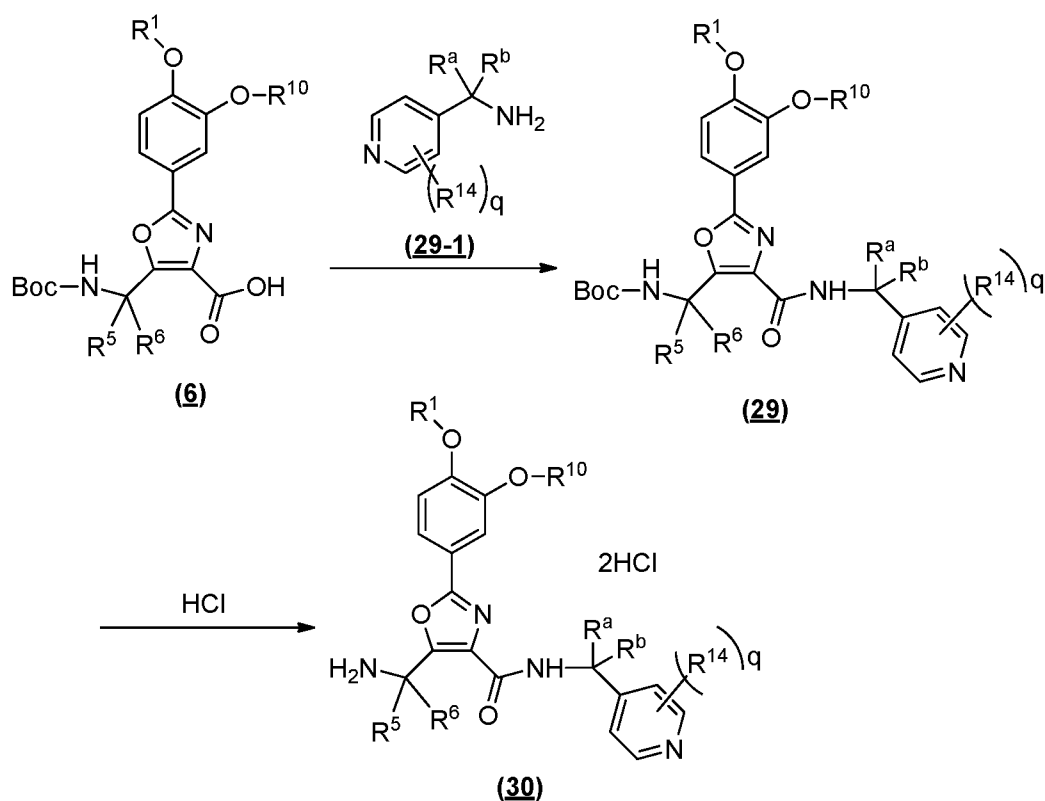
[00257] The title compound (25) can be prepared according to the procedure illustrated in **scheme 3**, and wherein each q is independently 0, 1, 2, 3 or 4. Compound (5) can react with a 4-methylpyridine derivative (24-1) to give compound (24). Compound (24) can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound (25).

Scheme 4



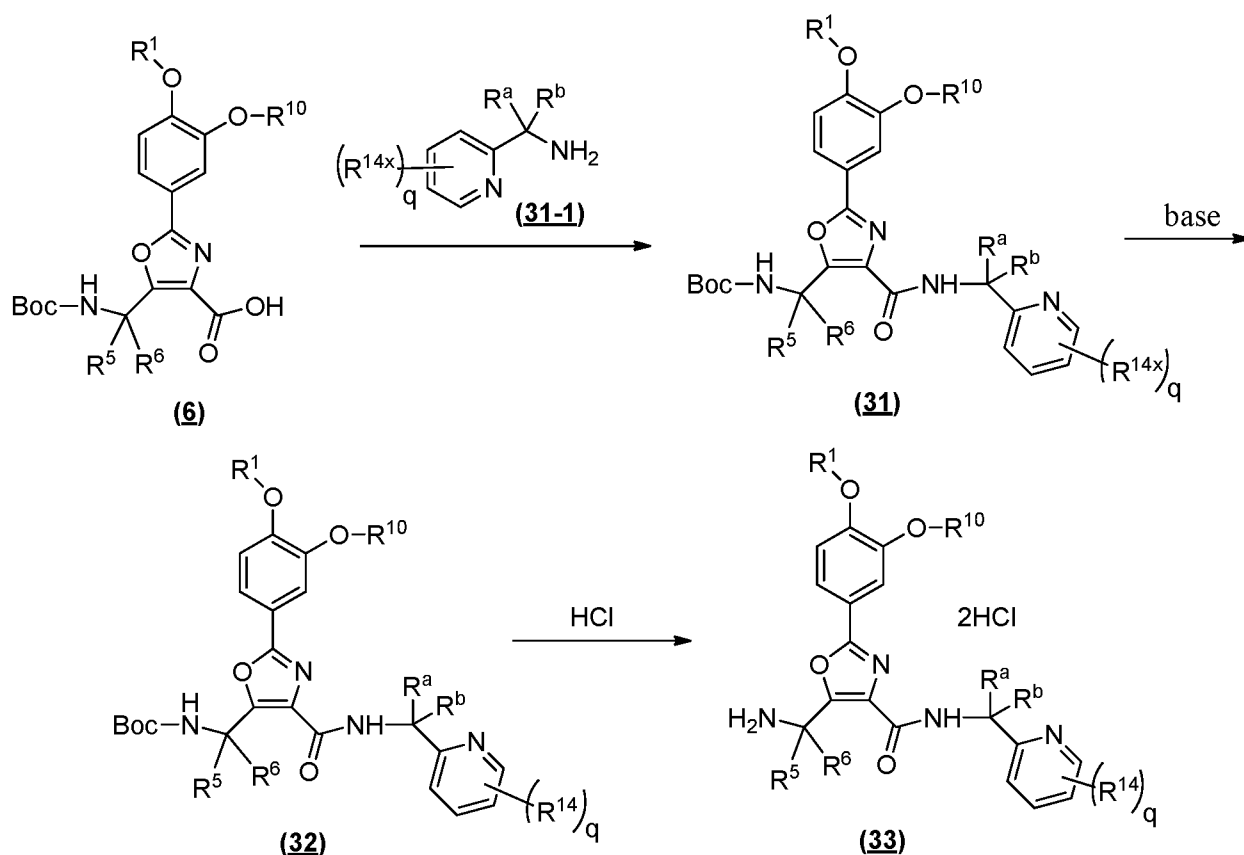
[00258] The title compound **(28)** can be prepared according to the procedure illustrated in **scheme 4**, and wherein each q is independently 0, 1, 2, 3 or 4. Compound **(6)** can react with cyanuric fluoride to give compound **(26)**, and compound **(26)** can react with a 4-aminopyridine derivative to give compound **(27)**. Compound **(27)** can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound **(28)**.

Scheme 5



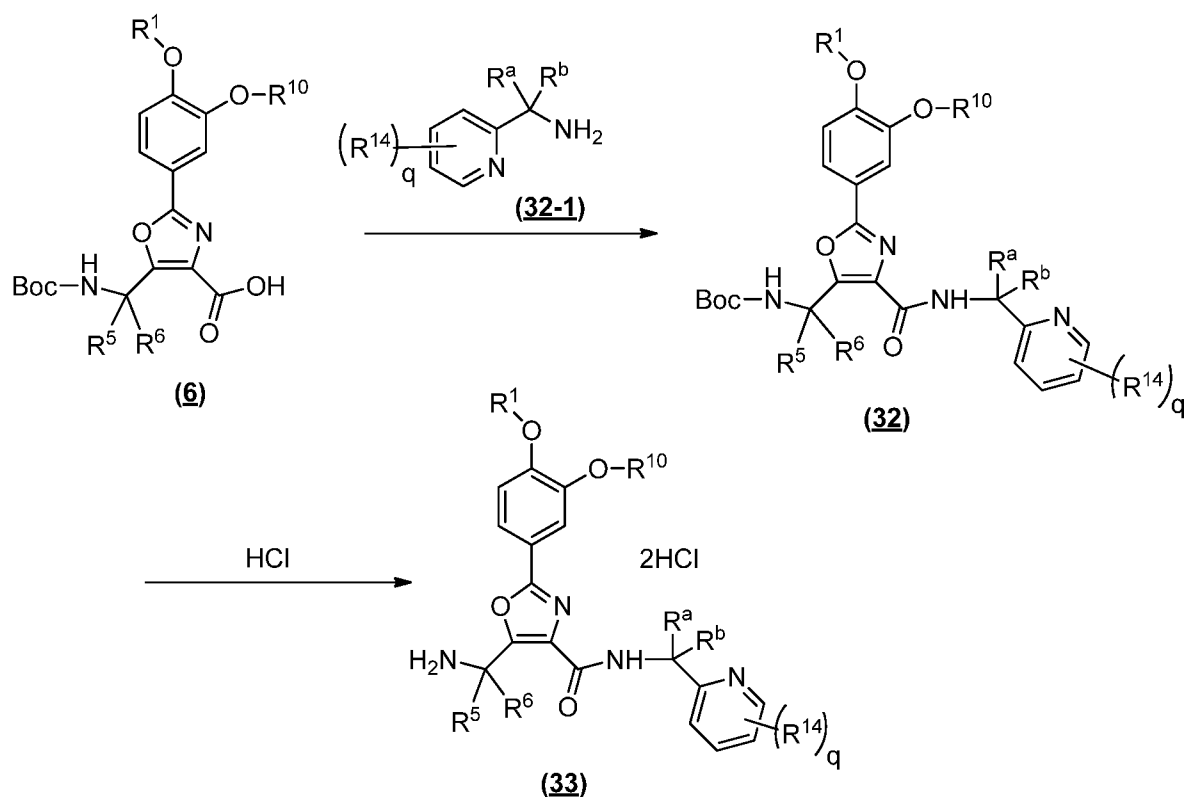
[00259] The title compound **(30)** can be prepared according to the procedure illustrated in **scheme 5**, and wherein each *q* is independently 0, 1, 2, 3 or 4. Compound **(6)** can react with compound **(29-1)** to give compound **(29)**. Compound **(29)** can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound **(30)**.

Scheme 6



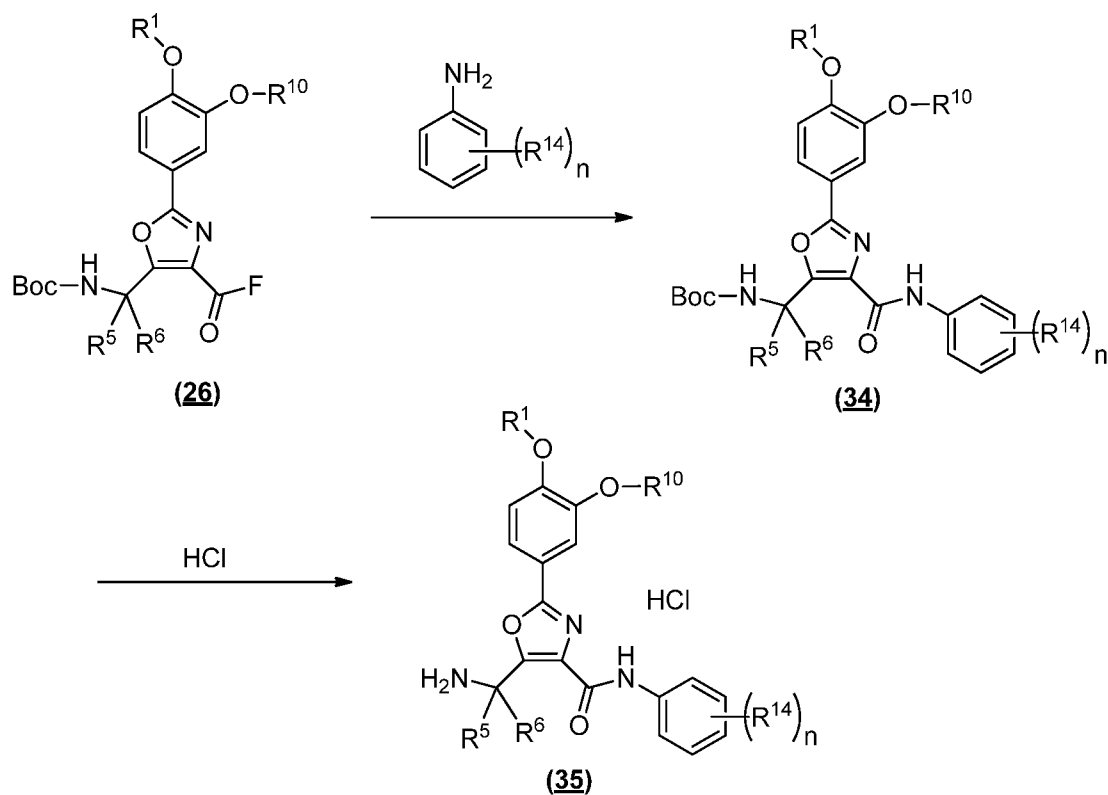
[00260] The title compound **(33)** can be prepared according to the procedure illustrated in **scheme 6**, and wherein each q is independently 0, 1, 2, 3 or 4, each R^{14x} is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, -C(=O)O-C₁₋₆ alkyl, -C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₆-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ haloalkylamino, hydroxy-substituted C₁₋₆ alkyl, hydroxy-substituted C₁₋₆ alkoxy, hydroxy-substituted C₁₋₆ alkylamino or C₃₋₆ cycloalkyl. Compound **(6)** can react with compound **(31-1)** to give compound **(31)**. Compound **(31)** can be hydrolyzed in the presence of a base to give compound **(32)**. Compound **(32)** can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound **(33)**.

Scheme 7



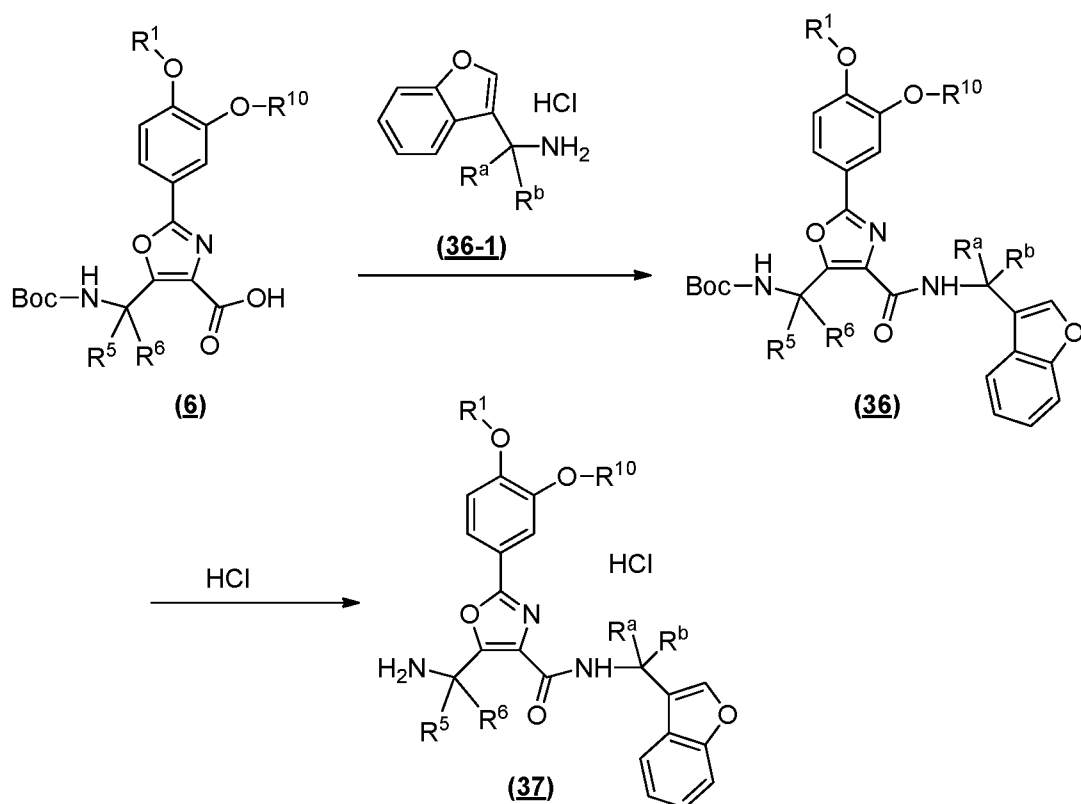
[00261] The title compound (33) can be prepared according to the procedure illustrated in scheme 7, and wherein each q is independently 0, 1, 2, 3 or 4. Compound (6) can react with compound (32-1) to give compound (32). Compound (32) can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound (33).

Scheme 8



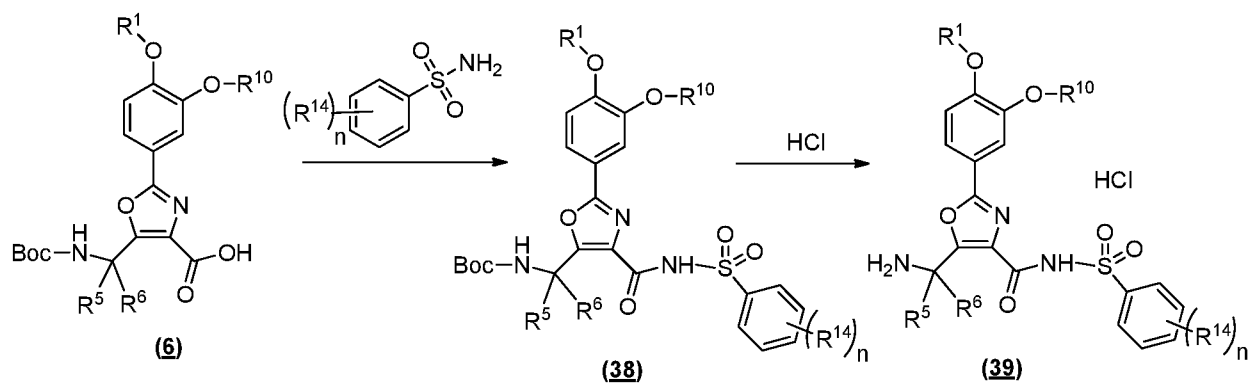
[00262] The title compound **(35)** can be prepared according to the procedure illustrated in **scheme 8**, and wherein each n is independently 0, 1, 2, 3, 4 or 5. Compound **(26)** can react with a phenylamine derivative to give compound **(34)**. Compound **(34)** can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound **(35)**.

Scheme 9



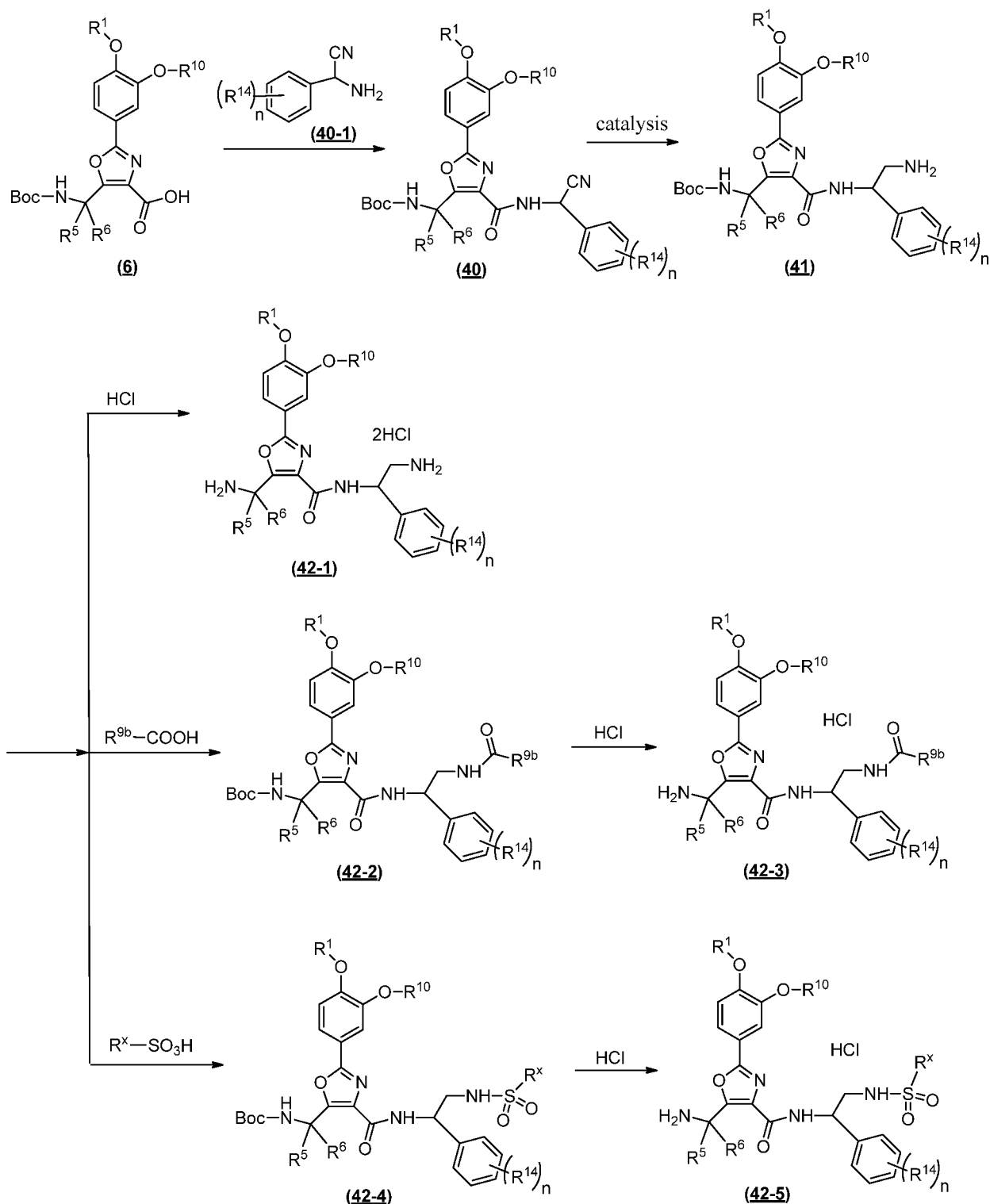
[00263] The title compound (37) can be prepared according to the procedure illustrated in **scheme 9**. Compound (6) can react with compound (36-1) to give compound (36). Compound (36) can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound (37).

Scheme 10



[00264] The title compound (39) can be prepared according to the procedure illustrated in **scheme 10**, and wherein each *n* is independently 0, 1, 2, 3, 4 or 5. Compound (6) can react with a benzenesulfonamide derivative to give compound (38). Compound (38) can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound (39).

Scheme 11



[00265] The title compound (42-1), (42-3) and (42-5) can be prepared according to the procedure illustrated in **scheme 11**, and wherein each n is independently 0, 1, 2, 3, 4 or 5, each R^x is independently C_{1-6} alkyl or C_{3-8} cycloalkyl.

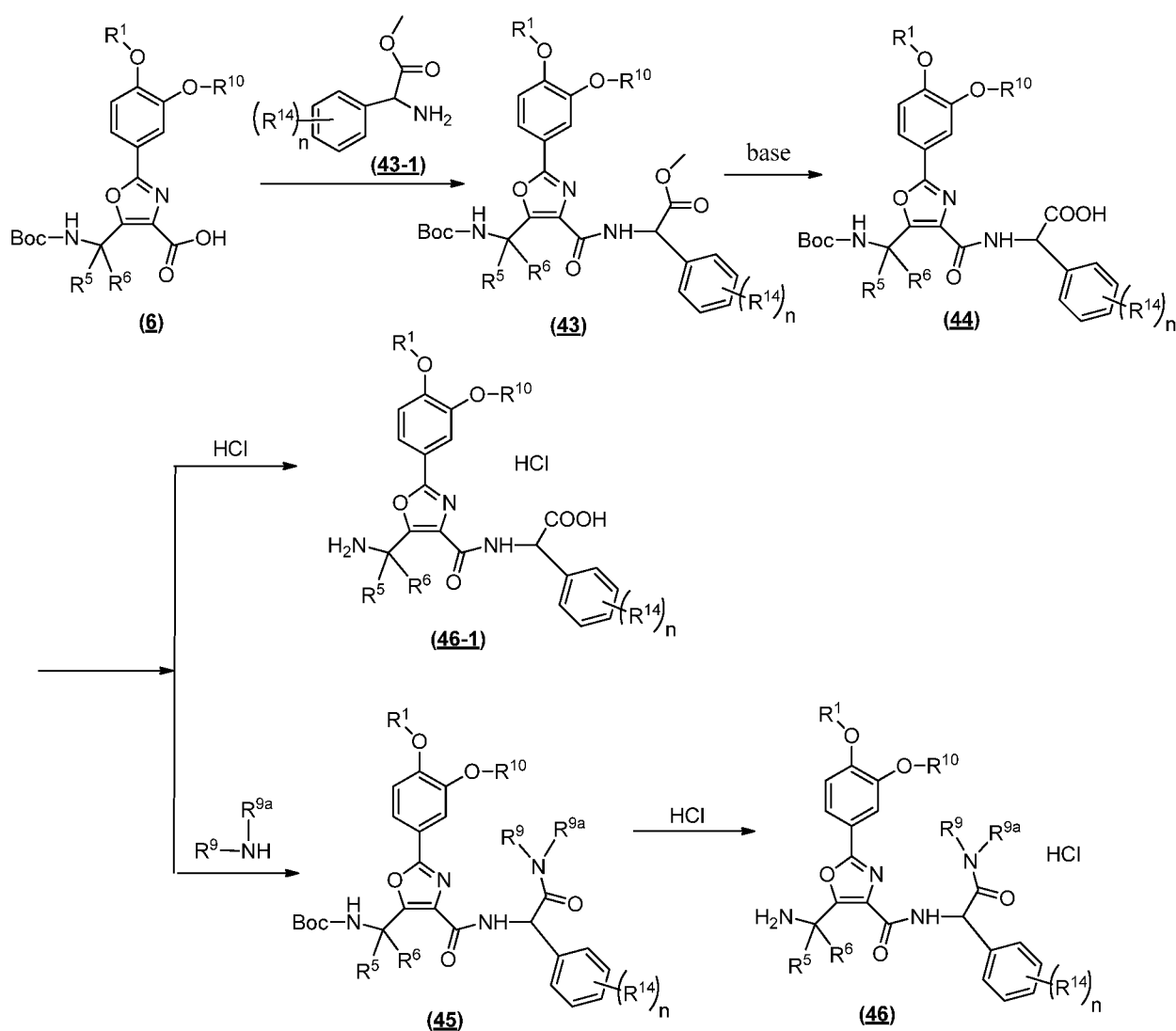
[00266] Compound (6) can react with compound (40-1) to give compound (40), and compound (40) can convert to compound (41) in the present of a catalyst. Compound (41) can be

deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound **(42-1)**.

[00267] Compound **(41)** can react with R^{9b} -COOH to give compound **(42-2)**, and compound **(42-2)** can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound **(42-3)**.

[00268] Compound **(41)** can react with R^x -SO₃H to give compound **(42-4)**, and compound **(42-4)** can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound **(42-5)**.

Scheme 12



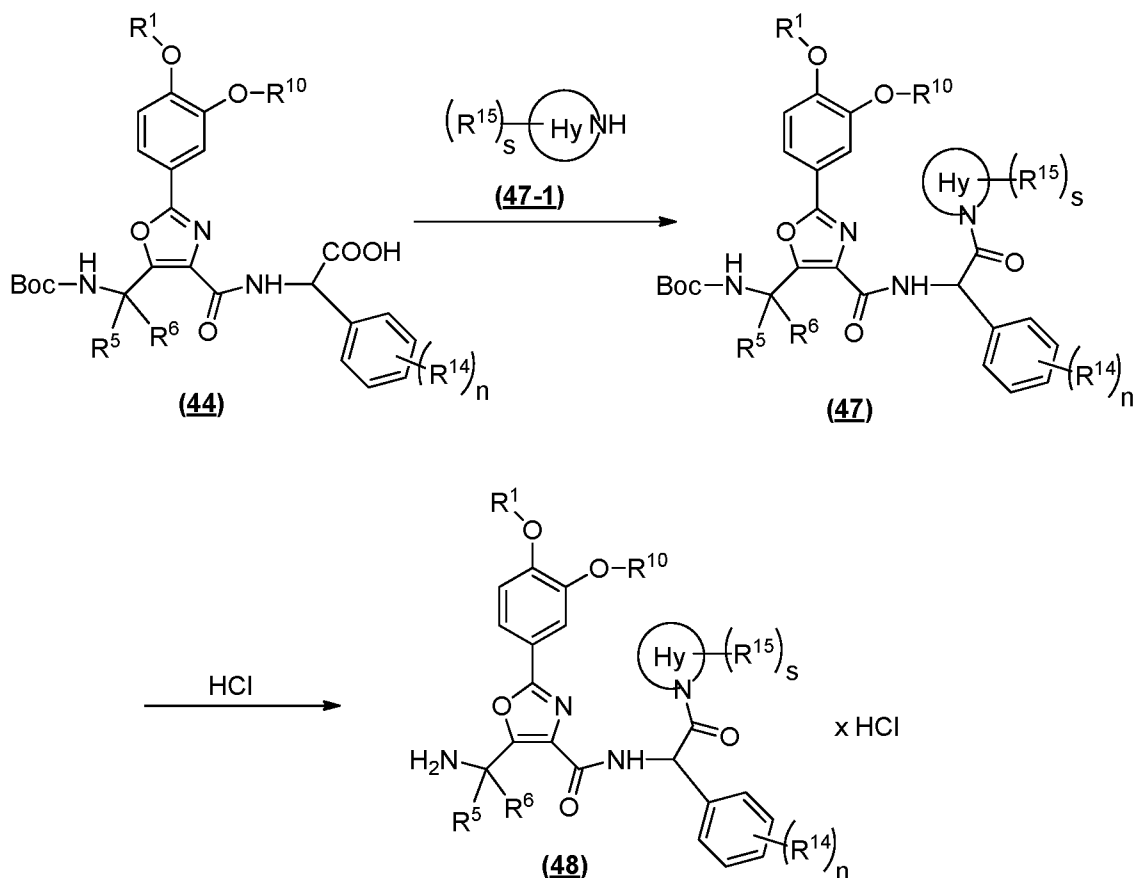
[00269] The title compound **(46-1)** and **(46)** can be prepared according to the procedure illustrated in **scheme 12**, and wherein each n is independently 0, 1, 2, 3, 4 or 5.

[00270] Compound **(6)** can react with compound **(43-1)** to give compound **(43)**, and compound

(43) can be hydrolyzed in the presence of a base to give compound (44). Compound (44) can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound (46-1).

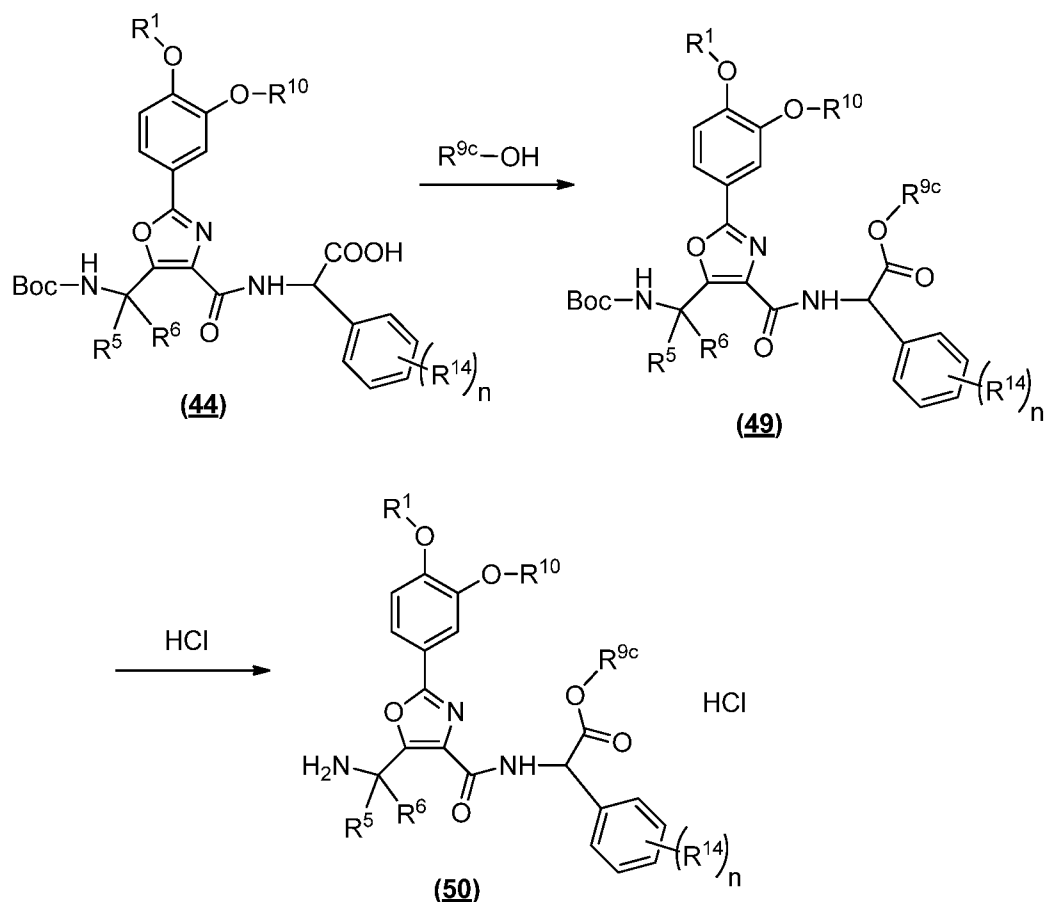
[00271] Compound (44) can react with $\text{NHR}^9\text{R}^{9a}$ to give compound (45), and compound (45) can be deprotected in a solution of hydrogen chloride in the organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound (46).

Scheme 13



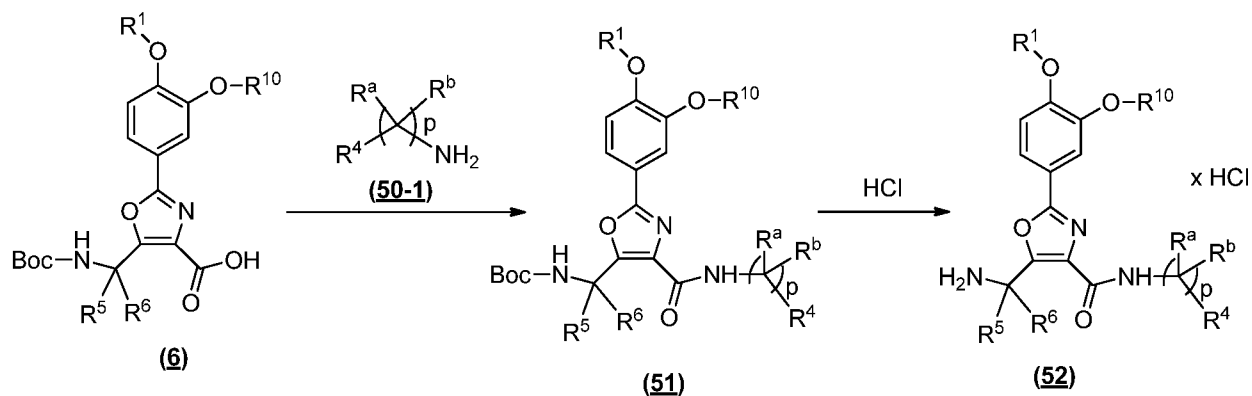
[00272] The title compound (48) can be prepared according to the procedure illustrated in **scheme 13**, and wherein each n is independently 0, 1, 2, 3, 4 or 5, each ring Hy is a 3- to 8-membered ring, each s is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14, x is 1, 2 or 3. Compound (44) can react with compound (47-1) to give compound (47), and compound (47) can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound (48).

Scheme 14



[00273] The title compound (50) can be prepared according to the procedure illustrated in **scheme 14**, and wherein each n is independently 0, 1, 2, 3, 4 or 5. Compound (44) can react with $R^{9c}-OH$ to give compound (49), and compound (49) can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound (50).

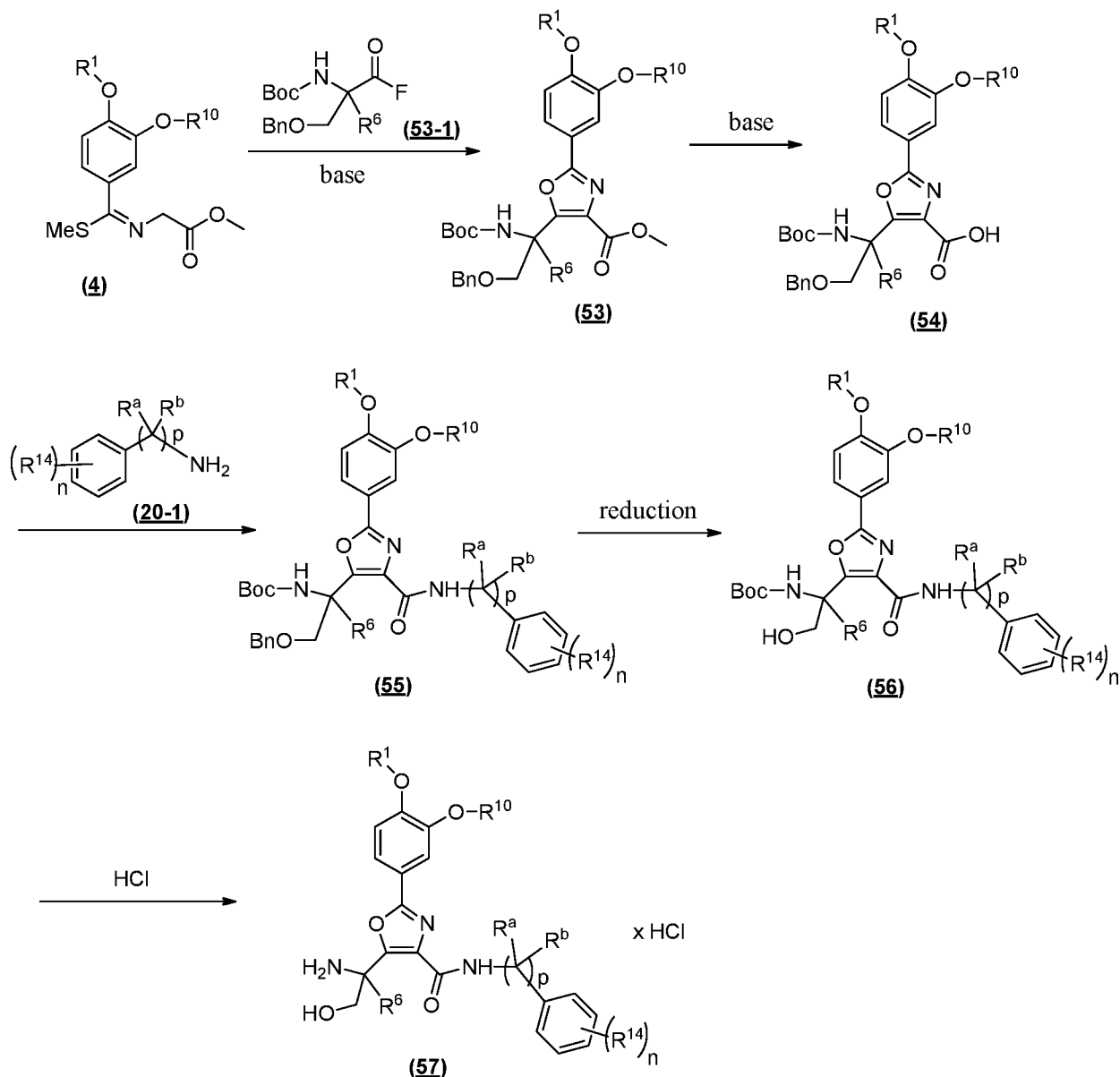
Scheme 15



[00274] The title compound (52) can be prepared according to the procedure illustrated in **scheme 15**, and wherein x is 1, 2 or 3. Compound (6) can react with compound (50-1) to give compound (51), and compound (51) can be deprotected in a solution of hydrogen chloride in an

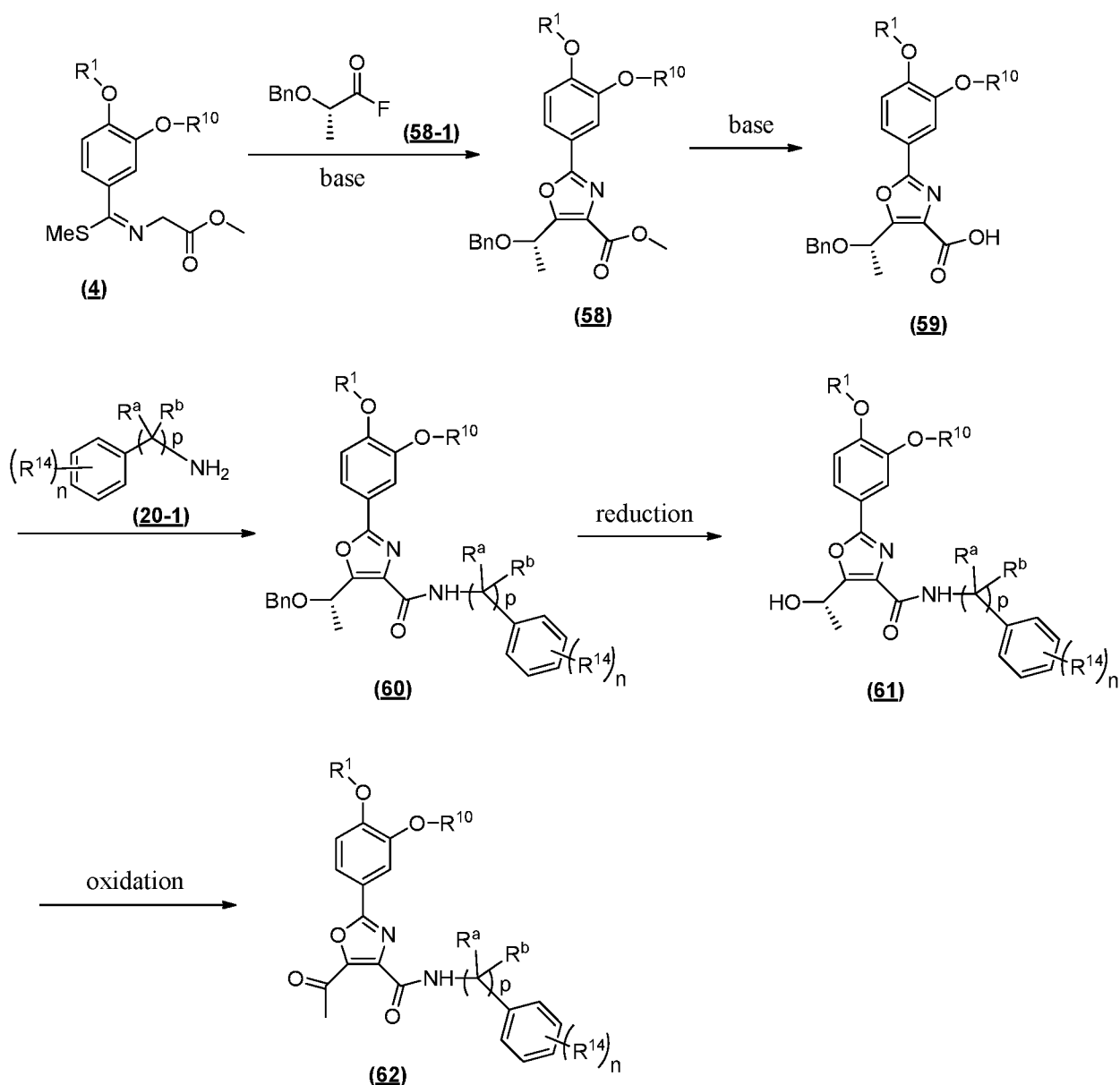
organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound **(52)**.

Scheme 16



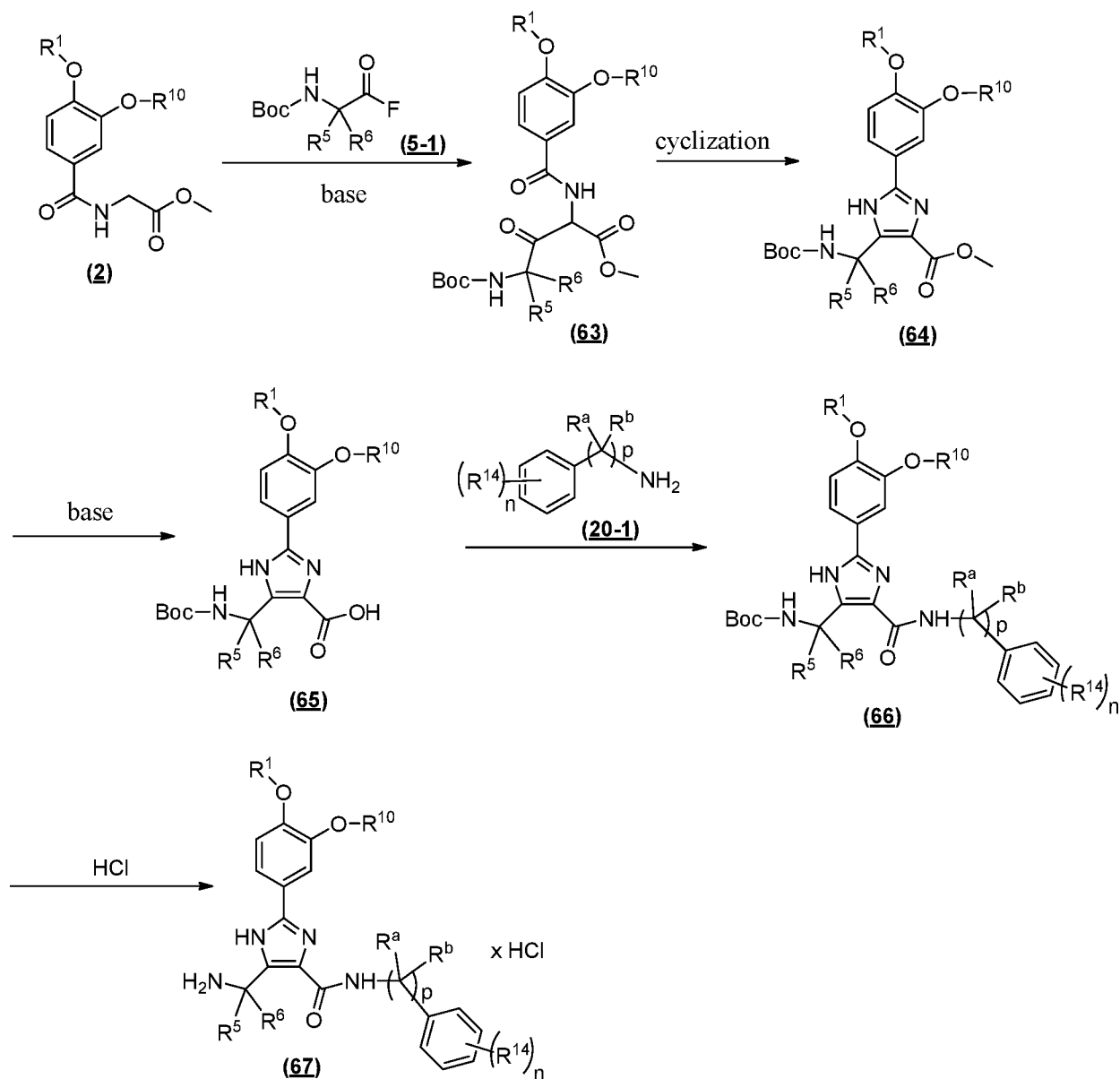
[00275] The title compound **(57)** can be prepared according to the procedure illustrated in **scheme 16**, and wherein each n is independently 0, 1, 2, 3, 4 or 5, x is 1, 2 or 3. Compound **(4)** can be cyclized with compound **(53-1)** in the presence of a base to give compound **(53)**. Compound **(53)** can be hydrolyzed in the presence of a base (such as $\text{LiOH}\cdot\text{H}_2\text{O}$, $\text{NH}_3\cdot\text{MeOH}$, and the like) to give compound **(54)**, which can condense with compound **(20-1)** to give compound **(55)**. Compound **(55)** can be reduced to remove the Bn- group and give compound **(56)**. Compound **(56)** can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound **(57)**.

Scheme 17



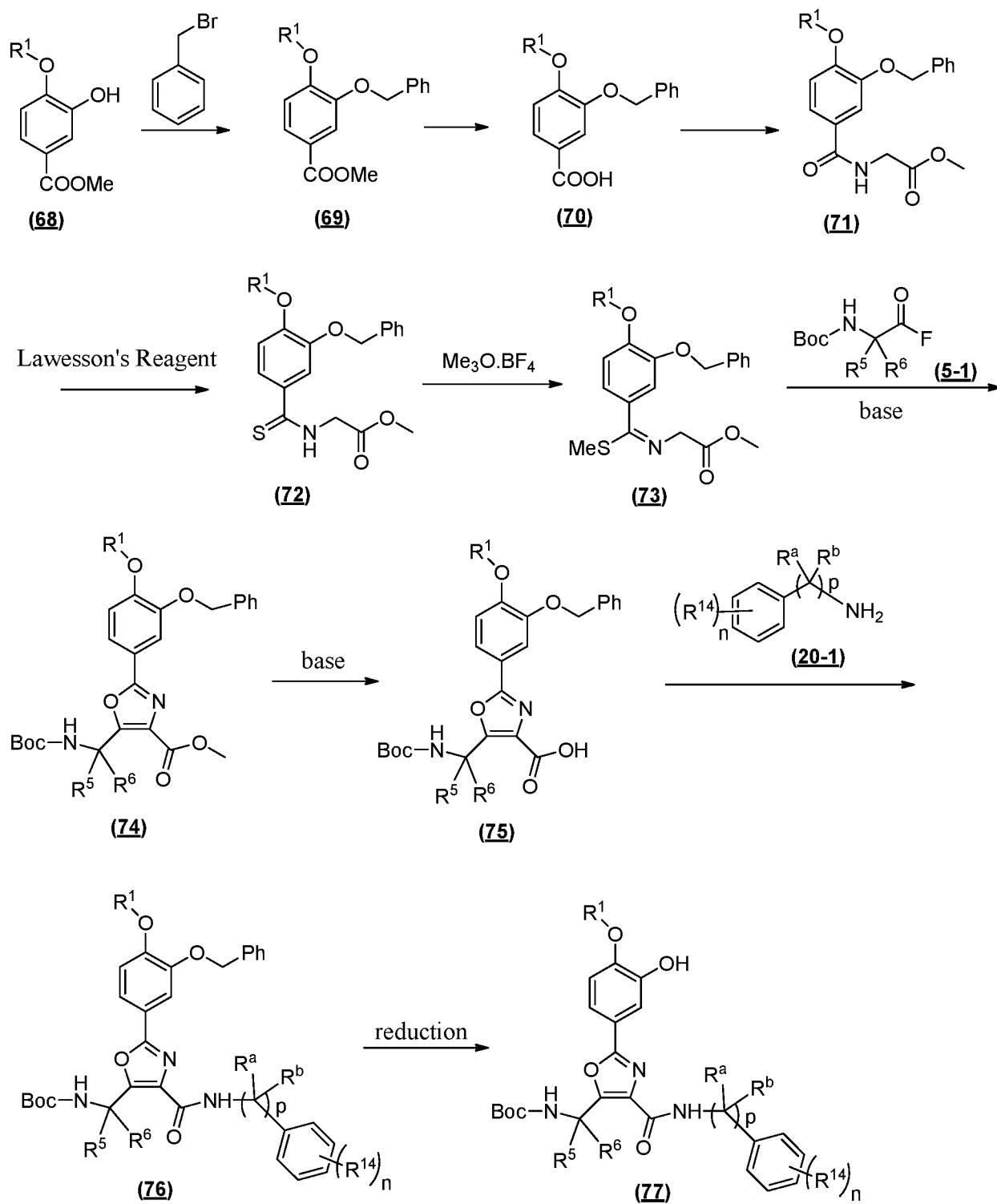
[00276] The title compound **(62)** can be prepared according to the procedure illustrated in **scheme 17**, and wherein each n is independently 0, 1, 2, 3, 4 or 5. Compound **(4)** can be cyclized with compound **(58-1)** in the presence of a base to give compound **(58)**. Compound **(58)** can be hydrolyzed in the presence of a base (such as $LiOH \cdot H_2O$, $NH_3 \cdot MeOH$, and the like) to give compound **(59)**, which can condense with compound **(20-1)** to give compound **(60)**. Compound **(60)** can be reduced to remove the Bn- group and give compound **(61)**. Compound **(61)** can be oxidized to give the title compound **(62)**.

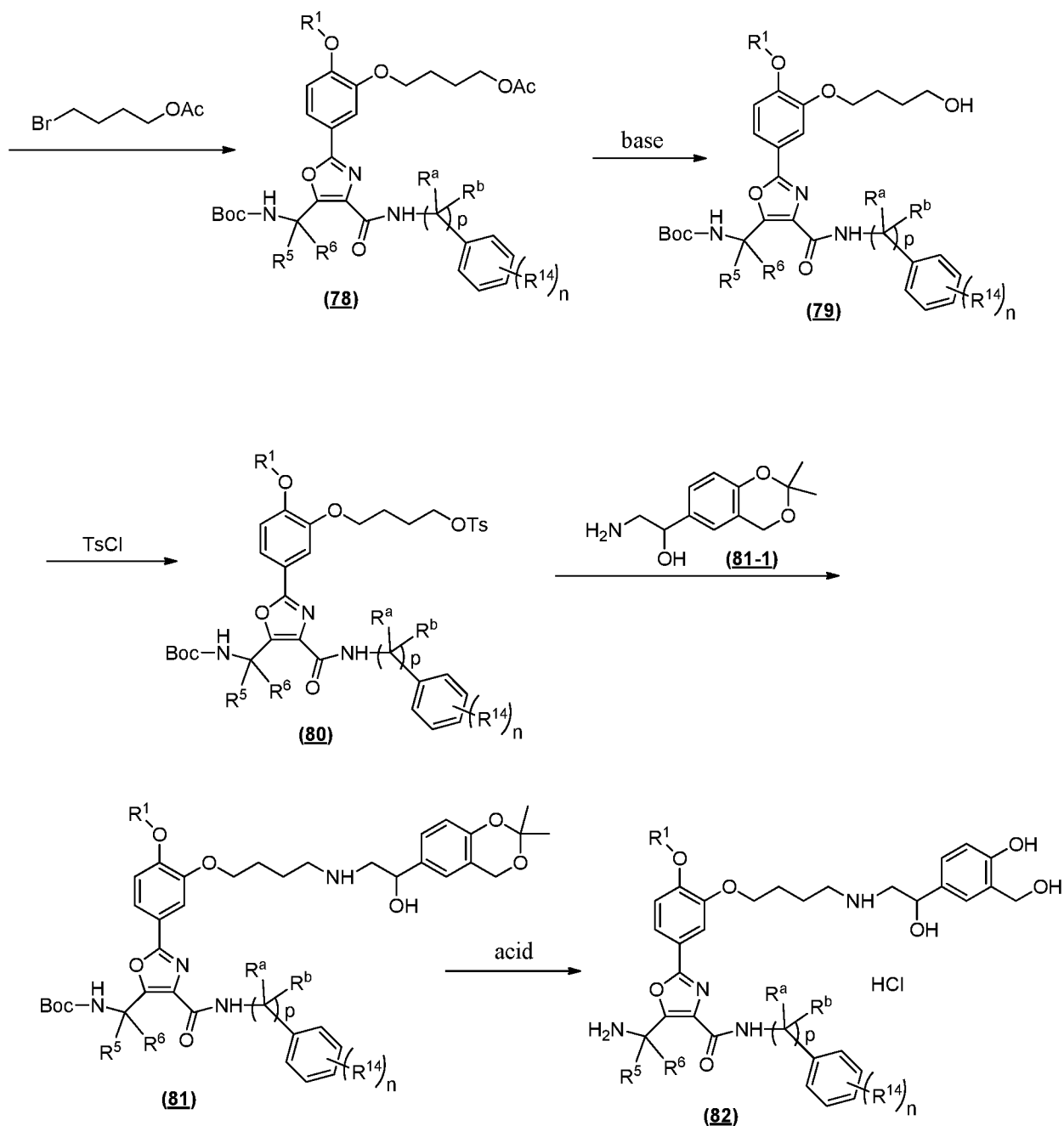
Scheme 18



[00277] The title compound (67) can be prepared according to the procedure illustrated in **scheme 18**, and wherein each n is independently 0, 1, 2, 3, 4 or 5, x is 1, 2 or 3. Compound (2) can react with compound (5-1) in the presence of a base to give compound (63). Compound (63) can be cyclized to give compound (64). Compound (64) can be hydrolyzed in the presence of a base (such as $\text{LiOH} \cdot \text{H}_2\text{O}$, $\text{NH}_3 \cdot \text{MeOH}$, and the like) to give compound (65), which can condense with compound (20-1) to give compound (66). Compound (66) can be deprotected in a solution of hydrogen chloride in an organic solvent (such as ethyl acetate, isopropanol, and the like) to give the title compound (67).

Scheme 19





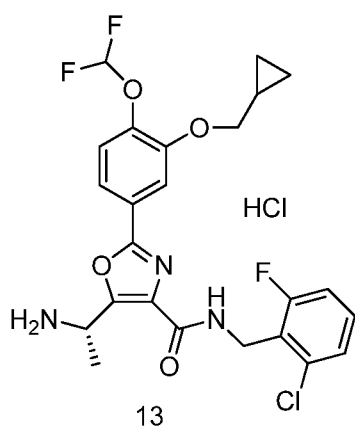
[00278] The title compound **(82)** can be prepared according to the procedure illustrated in **scheme 19**, and wherein n is 0, 1, 2, 3, 4 or 5. Compound **(68)** can react with benzyl bromide to give compound **(69)**, and compound **(69)** can be hydrolyzed in the presence of a base (such as NaOH, and the like) to give compound **(70)**. Compound **(70)** can condense with glycine methyl ester hydrochloride to give compound **(71)**. Compound **(71)** can be sulfurated in the presence of Lawesson's Reagent to give compound **(72)**, which is transformed to compound **(73)** in the presence of trimethyloxonium tetrafluoroborate. Compound **(73)** can react with acyl fluoride **(5-1)** in the presence of a base (such as KHMDS, and the like) to give compound **(74)**. Compound **(74)** can be hydrolyzed in the presence of a base (such as $\text{LiOH}\cdot\text{H}_2\text{O}$, $\text{NH}_3\cdot\text{MeOH}$,

and the like) to give compound (75), which can condense with compound (20-1) to give compound (76). Compound (76) can be reduced to give compound (77), and compound (77) can react with 4-bromobutyl acetate to give compound (78). Compound (78) can be hydrolyzed in the presence of a base to give compound (79). Compound (79) can react with *p*-tosyl chloride to give compound (80). Compound (80) can react with compound (80-1) in the presence of a base to give compound (81). The title compound (82) can be prepared from compound (81) in the presence of an acid.

[00279] Compounds, pharmaceutical compositions and applications thereof illustrated herein are further illustrated by the following examples.

EXAMPLES

Example 1: (S)-5-(1-Aminoethyl)-N-(2-chloro-6-fluorobenzyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy) phenyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzamido)acetate

[00280] To 50 mL of dichloromethane were added 3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzoic acid (10 g, 38.76 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.1 g, 58.14 mmol) and 1-hydroxy-7-azabenzotriazole (5.28 g, 38.76 mmol). The mixture was stirred at rt for 30 minutes, then methyl 2-aminoacetate hydrochloride (5.813 g, 46.51 mmol) was added. The mixture was cooled to 0 °C and *N,N*-diisopropylethylamine (27.06 mL, 155.04 mmol) was added dropwise. The resulting mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (25 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed, then the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (11.2 g, 87%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.47 (s, 1H), 7.29 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.18 (d, $J = 8.3$ Hz, 1H), 6.68 (t, $J_{F-H} = 75.0$ Hz, 1H), 4.22 (d, $J = 5.0$ Hz, 2H), 3.92 (d, $J = 7.0$ Hz, 2H), 3.80 (s, 3H), 1.25-1.32 (m, 1H), 0.62-0.67 (m, 2H), 0.33-0.37 (m, 2H); and MS-ESI: m/z 330.2 [M+H]⁺.

Step 2: Methyl 2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenylthioamido)acetate

[00281] To 50 mL of tetrahydrofuran were added methyl 2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzamido)acetate (11.12 g, 33.77 mmol) and Lawesson's Reagent (13.66 g, 33.77 mmol). The mixture was stirred at 75 °C for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (60 mL) and the resulting mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (10.5 g, 90%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.07 (s, 1H), 7.55 (d, $J = 2.0$ Hz, 1H), 7.24 (d, $J = 2.1$ Hz, 1H), 7.16 (d, $J = 8.3$ Hz, 1H), 6.68 (t, $J_{F-H} = 75.0$ Hz, 1H), 4.56 (d, $J = 4.6$ Hz, 2H), 3.94 (d, $J = 7.0$ Hz, 2H), 3.85 (s, 3H), 1.27-1.32 (m, 1H), 0.65-0.67 (m, 2H), 0.36-0.38 (m, 2H); and MS-ESI: m/z 346.2 [M+H]⁺.

Step 3: Methyl 2-(((3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)(methylthio)methylene)amino)acetate

[00282] To a solution of trimethyloxonium tetrafluoroborate (4.28 g, 28.96 mmol) in dichloromethane (20 mL) was added dropwise a solution of methyl 2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenylthioamido)acetate (5 g, 14.48 mmol) in dichloromethane (40 mL) at -78 °C. The mixture was stirred at 0 °C for 5 hours, then washed with saturated aqueous sodium bicarbonate (25 mL × 3). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed to give the title compound as yellow oil (5 g, 96%).

¹H NMR (400 MHz, CDCl₃, Z/E=1:1): δ ppm 7.16-7.20 (m, 2H), 7.10-7.13 (m, 2H), 6.83-6.87 (m, 2H), 6.65 (t, $J_{F-H} = 75.2$ Hz, 2H), 4.44 (s, 2H), 4.15 (s, 2H), 3.90 (d, $J = 6.9$ Hz, 2H), 3.85 (d, $J = 6.9$ Hz, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 2.45 (s, 3H), 2.16 (s, 3H), 1.27-1.29 (m, 2H), 0.62-0.67 (m, 4H), 0.34-0.36 (m, 4H); and MS-ESI: m/z 360.1 [M+H]⁺.

Step 4: (S)-tert-Butyl (1-fluoro-1-oxopropan-2-yl)carbamate

[00283] To 60 mL of dichloromethane were added *N*-Boc-*L*-alanine (6.5 g, 34.4 mmol) and triethylamine (5.27 mL, 37.83 mmol). To the solution was added dropwise cyanuric fluoride (5.62 mL, 68.8 mmol) at -40 °C, then the resulting mixture was stirred at -10 °C for 2 hours. The reaction mixture was washed with ice-water (20 mL × 5). The organic layer was dried over anhydrous sodium sulfate and the organic solvent was removed to give the title compound as a white solid (5.84 g, 89%).

Step 5: (*S*)-Methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylate

[00284] To 25 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)(methylthio)methylene)amino)acetate (5.2 g, 14.48 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (4.15 g, 21.72 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (36.2 mL, 36.2 mmol) at -78 °C and the reaction mixture was stirred at -78 °C for 1 hour. To the mixture was added water (20 mL) to quench the reaction and the resulting mixture was extracted with ethyl acetate (25 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a yellow solid (5.13 g, 73%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.64 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.70 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.43-5.47 (m, 1H), 3.98 (s, 3H), 3.96 (d, *J* = 7.0 Hz, 2H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 9H), 1.27-1.29 (m, 1H), 0.65-0.68 (m, 2H), 0.36-0.39 (m, 2H); and MS-ESI: *m/z* 483.1 [M+H]⁺.

Step 6: (*S*)-5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid

[00285] To a mixed solvent of tetrahydrofuran (40 mL) and water (20 mL) were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylate (5.13 g, 10.63 mmol) and lithium hydroxide monohydrate (2.23 g, 53.16 mmol). The solution was stirred at 40 °C for 2 hours, then hydrochloric acid (1 M) was added to adjust the pH of the solution to 1. The mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a yellow solid (4.8 g, 96%).

¹H NMR (600 MHz, CD₃OD): δ ppm 7.80 (d, J = 1.8 Hz, 1H), 7.66 (dd, J_1 = 8.3 Hz, J_2 = 1.9 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 6.90 (t, J_{F-H} = 74.8 Hz, 1H), 5.51 (m, 1H), 4.03 (d, J = 7.0 Hz, 2H), 1.54 (d, J = 7.1 Hz, 3H), 1.44 (s, 9H), 1.35-1.38 (m, 1H), 0.67-0.70 (m, 2H), 0.42-0.44 (m, 2H); and MS-ESI: m/z 467.3 [M-H]⁺.

Step 7: (*S*)-*tert*-Butyl (1-(4-((2-chloro-6-fluorobenzyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00286] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (183.36 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (130.56 mg, 0.96 mmol). To the resulting solution were added (2-chloro-6-fluorophenyl)methanamine (0.1 mL, 0.77 mmol) and *N,N*-diisopropylethylamine (0.33 mL, 1.92 mmol), and the mixture was stirred at rt for 22 hours. The reaction mixture was washed with water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc(v/v) = 5/1) to give the title compound as a white solid (264 mg, 67%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.59 (dd, J_1 = 8.3 Hz, J_2 = 1.9 Hz, 1H), 7.54 (d, J = 1.8 Hz, 1H), 7.47 – 7.45 (m, 1H), 7.27 (d, J = 4.6 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.10 – 7.06 (m, 1H), 6.71 (t, J_{F-H} = 75.0 Hz, 1H), 5.32 – 5.25 (m, 1H), 4.87 – 4.84 (m, 2H), 3.98 (d, J = 6.9 Hz, 2H), 1.56 (d, J = 7.0 Hz, 3H), 1.45 – 1.43 (m, 9H), 1.38 – 1.34 (m, 1H), 0.73 – 0.68 (m, 2H), 0.44 – 0.40 (m, 2H).

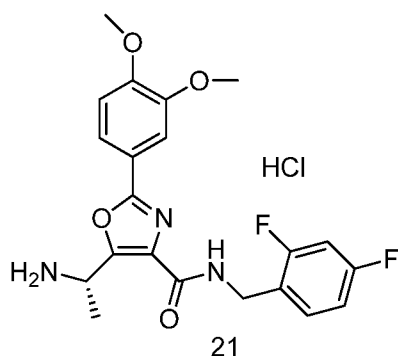
Step 8: (*S*)-5-(1-Aminoethyl)-*N*-(2-chloro-6-fluorobenzyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00287] To a solution of (*S*)-*tert*-butyl (1-(4-((2-chloro-6-fluorobenzyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.26 g, 0.43 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 16 hours and filtered. The filter cake was washed with ethyl acetate (15 mL $\times$ 3) to give the title compound as a white solid (128 mg, 55%).

Compound 13: ¹H NMR (400 MHz, CD₃OD): δ ppm 7.76 (d, J = 1.9 Hz, 1H), 7.70 (dd, J_1 =

8.4 Hz, $J_2 = 2.0$ Hz, 1H), 7.39 – 7.35 (m, 1H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.18 – 7.13 (m, 1H), 6.91 (t, $J_{F-H} = 74.8$ Hz, 1H), 5.19 – 5.14 (m, 1H), 4.81-4.82 (br.s, 2H), 4.01 (d, $J = 6.9$ Hz, 2H), 1.76 (d, $J = 7.0$ Hz, 3H), 1.34 – 1.31 (m, 1H), 0.69 – 0.66 (m, 2H), 0.43 – 0.41 (m, 2H); and MS-ESI: m/z 510.2 $[M+H-HCl]^+$.

Example 2: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 3,4-dimethoxybenzoate

[00288] To a solution of methyl 3-hydroxy-4-methoxybenzoate (10 g, 54.94 mmol) in acetone (50 mL) was added anhydrous potassium carbonate (15.2 g, 110.0 mmol) and iodomethane (6.8 mL, 109.2 mmol) in turn. The whole mixture was stirred at 60 °C in a sealed tube for 4.5 hours. To the reaction mixture was added 20 mL of saturated aqueous sodium chloride, and the mixture was extracted with ethyl acetate (25 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate for 1 hour, and the solvent was removed to give a white solid (10.23 g, 95%).

MS-ESI: m/z 197.1 $[M+H]^+$.

Step 2: 3,4-Dimethoxybenzoic acid

[00289] To a mixed solvent of ethanol (20 mL) and water (10 mL) was added methyl 3,4-dimethoxybenzoate (10.23 g, 52.17 mmol), and sodium hydroxide (10.43 g, 260.87 mmol) was added to the mixture. The mixture was stirred at 60 °C for 1.5 hours, then ethanol was removed and the residue was dissolved in water (20 mL). To the mixture was added hydrochloric acid (1 M) to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (25 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (9.16 g, 96.4%).

MS-ESI: m/z 181.1 $[M-H]^-$.

Step 3: Methyl 2-(3,4-dimethoxybenzamido)acetate

[00290] To 50 mL of dichloromethane were added 3,4-dimethoxybenzoic acid (9.16 g, 50.33 mmol), 1-hydroxy-7-azabenzotriazole (HOAT) (6.85 g, 50.33 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (14.47 g, 75.50 mmol). The mixture was stirred at rt for 30 minutes, then glycine methyl ester hydrochloride (7.58 g, 60.40 mmol) was added. The mixture was placed in an ice-bath, and *N,N*-diisopropylethylamine (35.16 mL, 201.32 mmol) was added dropwise. Then the resulting mixture was stirred overnight at rt. To the reaction mixture was added water (30 mL) and the mixture was extracted with dichloromethane (25 mL $\times$ 3). The organic layers were combined and dried over anhydrous sodium sulfate. The organic solvent was removed, then the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a white solid (10.82 g, 85%).

MS-ESI: m/z 254.1 $[M+H]^+$.

Step 4: Methyl 2-(3,4-dimethoxyphenylthioamido)acetate

[00291] To 30 mL of tetrahydrofuran were added methyl 2-(3,4-dimethoxybenzamido)acetate (2 g, 7.90 mmol) and Lawesson's Reagent (3.19 g, 7.89 mmol). The mixture was stirred at 75 °C for 2 hours and tetrahydrofuran was removed. To the residue was added saturated aqueous sodium bicarbonate (30 mL) and the mixture was extracted with ethyl acetate (25 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (1.81 g, 85%).

MS-ESI: m/z 270.1 $[M+H]^+$.

Step 5: Methyl 2-(((3,4-dimethoxyphenyl)(methylthio)methylene)amino)acetate

[00292] To a solution of trimethyloxonium tetrafluoroborate (2.20 g, 14.87 mmol) in dichloromethane (20 mL) was added dropwise a solution of methyl 2-(3,4-dimethoxyphenylthioamido)acetate (2 g, 7.43 mmol) in dichloromethane (30 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then washed with saturated aqueous sodium bicarbonate (25 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as yellow oil (1.89 g, 90%).

MS-ESI: m/z 284.1 $[M+H]^+$.

Step 6: (S)-Methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)

oxazole-4-carboxylate

[00293] To 20 mL of anhydrous tetrahydrofuran (20 mL) were added methyl 2-(((3,4-dimethoxyphenyl)(methylthio)methylene)amino)acetate (2.5 g, 8.83 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (2.53 g, 13.25 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (22.08 mL, 22.08 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice water (20 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (1.61 g, 45%).

MS-ESI: m/z 407.2 $[M+H]^+$.

Step 7: (*S*)-5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxylic acid

[00294] To a mixed solvent of tetrahydrofuran (30 mL) and water (15 mL) were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxylate (2 g, 4.92 mmol) and lithium hydroxide monohydrate (1.03 g, 24.6 mmol). The mixture was stirred at 40 °C for 3 hours and tetrahydrofuran was removed, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a yellow solid (1.8 g, 95%).

Step 8: (*S*)-*tert*-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00295] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxylic acid (0.3 g, 0.76 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (220 mg, 1.15 mmol) and 1-hydroxy-7-azabenzotriazole (156 mg, 1.15 mmol). The mixture was stirred at 0 °C for 30 minutes, then (2,4-difluorophenyl)methanamine (0.11 mL, 0.92 mmol) and *N,N*-diisopropylethylamine (0.4 mL, 2.3 mmol) were added dropwise in turn. The mixture was stirred at rt for 7 hours. The reaction mixture was washed with water (10 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and

the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as yellow oil (249 mg, 63%).

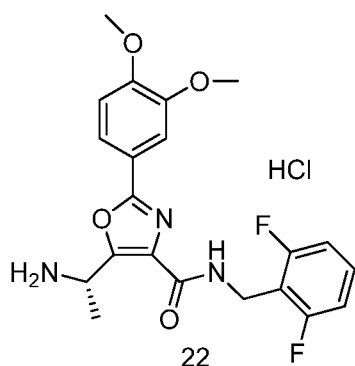
^1H NMR (400 MHz, CDCl_3): δ ppm 7.61 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.50 (d, $J = 1.9$ Hz, 1H), 7.47 – 7.41 (m, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 6.93 – 6.84 (m, 2H), 5.32 – 5.28 (m, 1H), 4.69 – 4.66 (m, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 1.56 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H); and MS-ESI: m/z 518.3 $[\text{M}+\text{H}]^+$.

Step 9: (S)-5-(1-aminoethyl)-N-(2,4-difluorobenzyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamide hydrochloride

[00296] To a solution of (S)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.24 g, 0.46 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for 2 hours and filtered, and the filter cake was washed with ethyl acetate (15 mL $\times$ 3) to give the title compound as a white solid (142 mg, 68%).

Compound 21: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.73 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.67 (d, $J = 2.0$ Hz, 1H), 7.52 – 7.46 (m, 1H), 7.13 (d, $J = 8.5$ Hz, 1H), 7.02 – 6.94 (m, 2H), 5.17 – 5.13 (m, 1H), 4.65 (s, 2H), 3.93 (d, $J = 3.3$ Hz, 6H), 1.77 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 418.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 3: (S)-5-(1-Aminoethyl)-N-(2,6-difluorobenzyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-*tert*-Butyl (1-(4-((2,6-difluorobenzyl)carbamoyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00297] To 10 mL of dichloromethane were added (S)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxylic acid (0.2 g, 0.51 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (146 mg, 0.77 mmol) and 1-hydroxy-7-azabenzotriazole (104 mg, 0.77 mmol), then the mixture was

stirred at 0 °C for 30 minutes. To the mixture were added dropwise (2,6-difluorophenyl)methanamine (0.07 mL, 0.61 mmol) and *N,N*-diisopropylethylamine (0.27 mL, 1.53 mmol), and the mixture was stirred at rt for 7 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (127 mg, 48%).

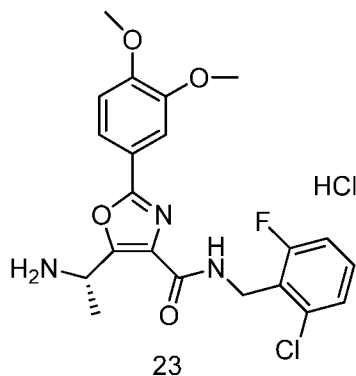
^1H NMR (400 MHz, CDCl_3): δ ppm 7.60 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.49 (d, $J = 1.9$ Hz, 1H), 7.33 – 7.29 (m, 1H), 6.99 – 6.93 (m, 3H), 5.32 – 5.26 (m, 1H), 4.83 – 4.71 (m, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H); and MS-ESI: m/z 518.3 $[\text{M}+\text{H}]^+$.

Step 2: (*S*)-5-(1-Aminoethyl)-*N*-(2,6-difluorobenzyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamide hydrochloride

[00298] To a solution of (*S*)-*tert*-butyl (1-(4-((2,6-difluorobenzyl)carbamoyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.12 g, 0.23 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 7 hours and filtered, and the filter cake was washed with ethyl acetate (15 mL $\times$ 3) to give the title compound as a white solid (85 mg, 82%).

Compound 22: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.71 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.65 (d, $J = 2.0$ Hz, 1H), 7.42 – 7.36 (m, 1H), 7.12 (d, $J = 8.5$ Hz, 1H), 7.02 (t, $J = 8.1$ Hz, 2H), 5.17 – 5.11 (m, 1H), 4.73 (s, 2H), 3.93 (d, $J = 2.9$ Hz, 6H), 1.76 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 418.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 4: (*S*)-5-(1-Aminoethyl)-*N*-(2-chloro-6-fluorobenzyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(4-((2-chloro-6-fluorobenzyl)carbamoyl)-2-(3,4-dimethoxyphenyl)oxazole-5-yl)ethyl)carbamate

oxazol-5-yl)ethyl)carbamate

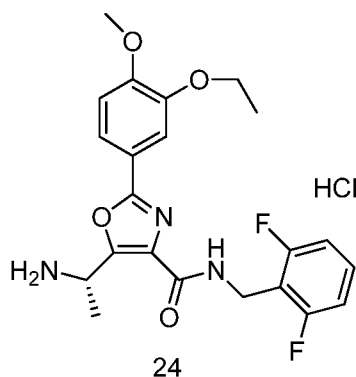
[00299] To 15 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxylic acid (0.3 g, 0.764 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (219.65 mg, 1.15 mmol) and 1-hydroxy-7-azabenzotriazole (156.4 mg, 1.15 mmol). The mixture was stirred at 0 °C for 30 minutes. To the mixture were added dropwise (2-chloro-6-fluorophenyl)methanamine (0.12 mL, 0.92 mmol) and *N,N*-diisopropylethylamine (0.4 mL, 2.3 mmol), and the mixture was stirred at rt for 12 hours. The reaction mixture was washed with water (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as a white solid (188 mg, 46%).

Step 2: (*S*)-5-(1-aminoethyl)-*N*-(2-chloro-6-fluorobenzyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamide hydrochloride

[00300] To a solution of (*S*)-*tert*-butyl (1-(4-((2-chloro-6-fluorobenzyl)carbamoyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.18 g, 0.35 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 17 hours and filtered, and the filter cake was washed with ethyl acetate (15 mL × 3) to give the title compound as a white solid (138 mg, 61%).

Compound 23: ¹H NMR (400 MHz, CD₃OD): δ ppm 7.70 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.54 – 7.52 (m, 1H), 7.31 – 7.26 (m, 1H), 7.18 – 7.13 (m, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 5.17 – 5.12 (m, 1H), 4.82 (s, 2H), 4.36 (d, *J* = 1.8 Hz, 2H), 3.92 (s, 6H), 1.76 (d, *J* = 7.0 Hz, 3H); and MS-ESI: *m/z* 434.2 [M+H-HCl]⁺.

Example 5: (*S*)-5-(1-Aminoethyl)-*N*-(2,6-difluorobenzyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 3-ethoxy-4-methoxybenzoate

[00301] To a solution of methyl 3-hydroxy-4-methoxybenzoate (10 g, 54.94 mmol) in acetone (50 mL) were added anhydrous potassium carbonate (15.2 g, 110.0 mmol) and bromoethane (6.1 mL, 82.42 mmol) in turn. The whole mixture was stirred at 60 °C in a sealed tube for 4.5 hours. To the reaction mixture was added 20 mL of saturated aqueous sodium chloride, and the mixture was extracted with ethyl acetate (25 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate for 1 hour, and the solvent was removed to give the title compound as a white solid (11.07 g, 95.9%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.65 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.12-4.17 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 1.47 (t, *J* = 7.0 Hz, 3H); and MS-ESI: *m/z* 211.2 [M+H]⁺.

Step 2: 3-Ethoxy-4-methoxybenzoic acid

[00302] To a mixed solvent of ethanol (20 mL) and water (10 mL) was added methyl 3-ethoxy-4-methoxybenzoate (11.66 g, 55.5 mmol), and sodium hydroxide (11.1g, 277.5 mmol) was added to the solution. The mixture was stirred at 60 °C for 1.5 hours, then ethanol was removed and the residue was dissolved in water (20 mL). To the mixture was added hydrochloric acid (1 M) to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (25 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (10.25 g, 94.5%).

MS-ESI: *m/z* 197.2 [M+H]⁺.

Step 3: Methyl 2-(3-ethoxy-4-methoxybenzamido)acetate

[00303] To 50 mL of dichloromethane were added 3-ethoxy-4-methoxybenzoic acid (11.86 g, 60.5 mmol), 1-hydroxy-7-azabenzotriazole (HOAT) (8.229 g, 60.51 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (17.336 g, 90.76 mmol).

The mixture was stirred at rt for 30 minutes, then glycine methyl ester hydrochloride (9.076 g, 72.61 mmol) was added. The mixture was placed in an ice-bath, and *N,N*-diisopropylethylamine (42.2 mL, 242.0 mmol) was added dropwise. The resulting mixture was stirred overnight at rt. To the reaction mixture was added water (30 mL) and the mixture was extracted with dichloromethane (25 mL $\times$ 3). The organic layers were combined and dried over anhydrous sodium sulfate. The organic solvent was removed, then the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a white solid (12.88 g, 79.7%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.42 (s, 1H), 7.33 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 4.23 (d, J = 5.0 Hz, 2H), 4.12-4.17 (m, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H); and MS-ESI: m/z 268.1 $[\text{M}+\text{H}]^+$.

Step 4: Methyl 2-(3-ethoxy-4-methoxyphenylthioamido)acetate

[00304] To 30 mL of tetrahydrofuran were added methyl 2-(3-ethoxy-4-methoxybenzamido)acetate (2 g, 7.49 mmol) and Lawesson's Reagent (3.03 g, 7.49 mmol). The mixture was stirred at 75 °C for 2 hours and tetrahydrofuran was removed. To the residue was added saturated aqueous sodium bicarbonate (30 mL) and the mixture was extracted with ethyl acetate (25 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (1.7046 g, 80.4%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.05 (s, 1H), 7.54 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.56 (d, J = 4.4 Hz, 2H), 4.13-4.18 (m, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H); and MS-ESI: m/z 284.1 $[\text{M}+\text{H}]^+$.

Step 5: Methyl 2-(((3-ethoxy-4-methoxyphenyl)(methylthio)methylene)amino)acetate

[00305] To a solution of trimethyloxonium tetrafluoroborate (2.08 g, 14.12 mmol) in dichloromethane (20 mL) was added dropwise a solution of methyl 2-(3-ethoxy-4-methoxyphenylthioamido)acetate (2 g, 7.06 mmol) in dichloromethane (30 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then washed with saturated aqueous sodium bicarbonate (25 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed to give the title compound as yellow oil (1.89 g, 90%).

Step 6: (S)-Methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-ethoxy-4-methoxyphenyl)

oxazole-4-carboxylate

[00306] To 20 mL of anhydrous tetrahydrofuran (20 mL) were added methyl 2-(((3-ethoxy-4-methoxyphenyl)(methylthio)methylene)amino)acetate (2.47 g, 8.31 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (2.38 g, 12.46 mmol). To the mixture was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (20.78 mL, 20.78 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (1.0 g, 28%).

Step 7: (*S*)-5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxylic acid

[00307] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxylate (0.73 g, 1.736 mmol) and lithium hydroxide monohydrate (364.25 g, 8.681 mmol). The solution was stirred at 40 °C for 3 hours and tetrahydrofuran was removed, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a yellow solid (668 mg, 95%).

Step 8: (*S*)-*tert*-Butyl (1-(4-((2,6-difluorobenzyl)carbamoyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00308] To 30 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxylic acid (0.7 g, 1.732 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (496.22 mg, 2.60 mmol) and 1-hydroxy-7-azabenzotriazole (HOAT) (353.33 mg, 2.60 mmol). The resulting mixture was stirred at 0 °C for 30 minutes, then to the mixture were added dropwise (2,6-difluorophenyl)methanamine (0.25 mL, 2.08 mmol) and *N,N*-diisopropylethylamine (0.91 mL, 5.2 mmol). The mixture was stirred at rt for 12 hours. The reaction mixture was washed with water (20 mL × 3) and the organic layer was dried over

anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as a white solid (834.6 mg, 91%).

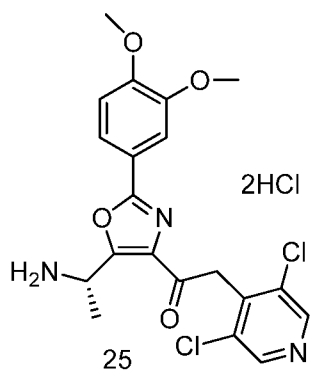
^1H NMR (400 MHz, CDCl_3): δ ppm 7.58 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.49 (d, $J = 1.9$ Hz, 1H), 7.32 – 7.30 (m, 1H), 6.98 – 6.92 (m, 3H), 5.30 – 5.25 (m, 1H), 4.83 – 4.74 (m, 2H), 4.23 – 4.17 (m, 2H), 3.94 (s, 3H), 1.55 – 1.51 (m, 6H), 1.45 (s, 9H); and MS-ESI: m/z 532.2 $[\text{M}+\text{H}]^+$.

Step 9: (S)-5-(1-Aminoethyl)-N-(2,6-difluorobenzyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxamide hydrochloride

[00309] To a solution of (*S*)-*tert*-butyl (1-(4-((2,6-difluorobenzyl)carbamoyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.83 g, 1.56 mmol) in dichloromethane (10 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for 3 hours and filtered. The filter cake was washed with ethyl acetate (20 mL $\times$ 3) to give the title compound as a white solid (699.3 mg, 96%).

Compound 24: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.70 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.63 (d, $J = 2.0$ Hz, 1H), 7.43 – 7.35 (m, 1H), 7.12 (d, $J = 8.5$ Hz, 1H), 7.02 (t, $J = 8.1$ Hz, 2H), 5.16 – 5.11 (m, 1H), 4.73 (s, 2H), 4.18 – 4.13 (m, 2H), 3.93 (s, 3H), 1.76 (d, $J = 7.0$ Hz, 3H), 1.46 (t, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 432.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 6: (S)-1-(5-(1-Aminoethyl)-2-(3,4-dimethoxyphenyl)oxazol-4-yl)-2-(3,5-dichloropyridin-4-yl)ethanone dihydrochloride



Step 1: (S)-*tert*-Butyl (1-(4-(2-(3,5-dichloropyridin-4-yl)acetyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00310] To 5 mL of tetrahydrofuran were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxylate (0.2 g, 0.49 mmol) and 3,5-dichloro-4-methylpyridine (119.6 mg, 0.74 mmol). To the solution was

added a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.476 mL, 1.476 mmol) at 0 °C, and the reaction mixture was stirred at rt for 4 hours. To the mixture was added saturated aqueous ammonium chloride (15 mL) and the resulting mixture was extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a yellow solid (120 mg, 45%).

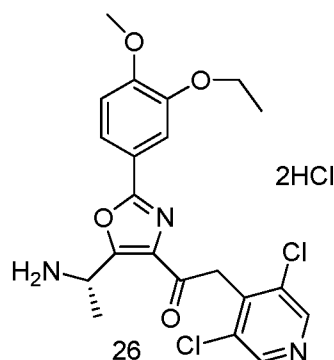
¹H NMR (400 MHz, CDCl₃): δ ppm 8.55 (s, 2H), 7.68 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.58 (d, $J = 1.9$ Hz, 1H), 6.98 (d, $J = 8.5$ Hz, 1H), 5.36 – 5.30 (m, 1H), 4.85 – 4.75 (m, 2H), 4.03 (s, 3H), 3.99 (s, 3H), 1.51 (d, $J = 7.1$ Hz, 3H), 1.42 (s, 9H); and MS-ESI: m/z 536.2 [M+H]⁺.

Step 2: (S)-1-(5-(1-Aminoethyl)-2-(3,4-dimethoxyphenyl)oxazol-4-yl)-2-(3,5-dichloropyridin-4-yl)ethanone dihydrochloride

[00311] To a solution of (*S*)-*tert*-butyl (1-(4-(2-(3,5-dichloropyridin-4-yl)acetyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.11 g, 0.21 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 5 hours and filtered, and the filter cake was washed with ethyl acetate (15 mL × 3) to give the title compound as a yellow solid (86 mg, 86%).

Compound 25: ¹H NMR (400 MHz, CD₃OD): δ ppm 8.62 (s, 2H), 7.80 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H), 7.71 (d, $J = 1.8$ Hz, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 5.21 – 5.16 (m, 1H), 5.00 – 4.92 (m, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 1.76 (d, $J = 6.9$ Hz, 3H).

Example 7: (S)-1-(5-(1-aminoethyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-4-yl)-2-(3,5-dichloropyridin-4-yl)ethanone dihydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(4-(2-(3,5-dichloropyridin-4-yl)acetyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00312] To 5 mL of tetrahydrofuran were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxylate

(0.2 g, 0.48 mmol) and 3,5-dichloro-4-methylpyridine (116.65 mg, 0.72 mmol). To the solution was added a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.44 mL, 1.44 mmol) at 0 °C, and the reaction mixture was stirred at rt for 2.5 hours. To the mixture was added saturated aqueous ammonium chloride (15 mL × 3) and the resulting mixture was extracted with dichloromethane (20 mL). The organic layer was dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a light yellow solid (0.16 g, 61%).

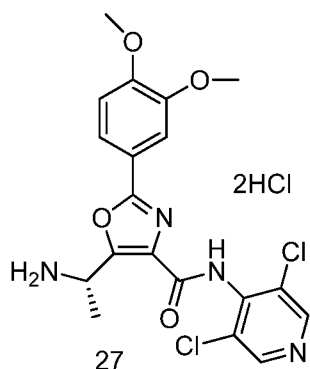
¹H NMR (400 MHz, CDCl₃): δ ppm 8.55 (s, 2H), 7.66 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 5.34 – 5.29 (m, 1H), 4.85 – 4.74 (m, 2H), 4.28 – 4.22 (m, 2H), 3.97 (s, 3H), 1.56 (t, *J* = 7.0 Hz, 3H), 1.51 (d, *J* = 7.1 Hz, 3H), 1.42 (s, 9H); and MS-ESI: *m/z* 550.1 [M+H]⁺.

Step 2: (S)-1-(5-(1-Aminoethyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-4-yl)-2-(3,5-dichloropyridin-4-yl)ethanone dihydrochloride

[00313] To a solution of (*S*)-*tert*-butyl (1-(4-(2-(3,5-dichloropyridin-4-yl)acetyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.16 g, 0.29 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 2 hours and filtered, and the filter cake was washed with ethyl acetate (15 mL × 3) to give the title compound as a yellow solid (50 mg, 40%).

Compound 26: ¹H NMR (400 MHz, CD₃OD): δ ppm 8.57 (s, 2H), 7.76 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 5.18 – 5.13 (m, 1H), 4.90 – 4.87 (m, 2H), 4.20 – 4.15 (m, 2H), 3.92 (s, 3H), 1.72 (d, *J* = 7.0 Hz, 3H), 1.46 (t, *J* = 7.0 Hz, 3H).

Example 8: (S)-5-(1-Aminoethyl)-N-(3,5-dichloropyridin-4-yl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-*tert*-Butyl (1-(2-(3,4-dimethoxyphenyl)-4-(fluorocarbonyl)oxazol-5-

yl)ethyl)carbamate

[00314] To 15 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxylic acid (0.86 g, 2.2 mmol) and triethylamine (0.34 mL, 2.42 mmol). To the solution was added cyanuric fluoride (0.36 mL, 4.4 mmol) at -40 °C, then the resulting mixture was stirred at -10 °C for 2 hours. The reaction mixture was washed with ice-water (20 mL × 4). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as a red solid (0.82 g, 95%).

¹H NMR (400 MHz, *d*₆-DMSO): δ ppm 7.61 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 5.21 – 5.16 (m, 1H), 3.86 (d, *J* = 5.1 Hz, 6H), 1.48 (d, *J* = 7.1 Hz, 3H), 1.37 (s, 9H); and MS-ESI: *m/z* 395.2 [M+H]⁺.

Step 2: (*S*)-*tert*-Butyl (1-(4-((3,5-dichloropyridin-4-yl)carbamoyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate

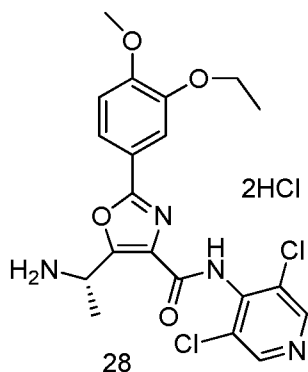
[00315] To 6 mL of tetrahydrofuran were added 3,5-dichloro-4-aminopyridine (537.9 mg, 3.3 mmol) and sodium hydride (132 mg, 3.3 mmol, 60%). The mixture was stirred at rt for 1 hour. To the mixture was added a solution of (*S*)-*tert*-butyl (1-(2-(3,4-dimethoxyphenyl)-4-(fluorocarbonyl)oxazol-5-yl)ethyl)carbamate (0.86 g, 2.2 mmol) in tetrahydrofuran (9 mL) at 0 °C, and the reaction mixture was stirred at rt for 23 hours. To the mixture was added saturated aqueous ammonium chloride (20 mL × 3) and the resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as light yellow oil (325 mg, 27%).

Step 3: (*S*)-5-(1-aminoethyl)-*N*-(3,5-dichloropyridin-4-yl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamide dihydrochloride

[00316] To a solution of (*S*)-*tert*-butyl (1-(4-((3,5-dichloropyridin-4-yl)carbamoyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.32 g, 0.59 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 1.5 hours and filtered. The filter cake was washed with ethyl acetate (20 mL × 3) to give the title compound as a yellow solid (220 mg, 81%). The product was further recrystallized from methanol/ethyl acetate (v/v = 1/20) to give the desired product as a yellow solid (110 mg).

Compound 27: ^1H NMR (400 MHz, CD_3OD): δ ppm 8.72 (s, 2H), 7.81 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.74 (d, $J = 2.0$ Hz, 1H), 7.16 (d, $J = 8.5$ Hz, 1H), 5.29 – 5.24 (m, 1H), 3.96 (d, $J = 6.8$ Hz, 6H), 1.80 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 438.2 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 9: (S)-5-(1-Aminoethyl)-N-(3,5-dichloropyridin-4-yl)-2-(3-ethoxy-4-methoxyphenyl) oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-ethoxy-4-methoxyphenyl)-4-(fluorocarbonyl)oxazol-5-yl)ethyl) carbamate

[00317] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxylic acid (0.65 g, 1.6 mmol) and triethylamine (0.25 mL, 1.76 mmol). To the resulting solution was added cyanuric fluoride (0.26 mL, 3.2 mmol) dropwise at -40°C , then the resulting mixture was reacted at -10°C for 2 hours. The reaction mixture was washed with ice-water (50 mL) for 4-5 times and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as a yellow solid (577 mg, 88%).

^1H NMR (400 MHz, d_6 -DMSO): δ ppm 7.60 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.48 (d, $J = 2.0$ Hz, 1H), 7.17 (d, $J = 8.6$ Hz, 1H), 5.26 – 5.18 (m, 1H), 4.14 – 4.06 (m, 2H), 3.85 (s, 3H), 1.47 (d, $J = 7.1$ Hz, 3H), 1.40 – 1.38 (m, 3H), 1.36 – 1.31 (m, 9H); and MS-ESI: m/z 409.3 $[\text{M}+\text{H}]^+$.

Step 2: (S)-tert-Butyl (1-(4-((3,5-dichloropyridin-4-yl)carbamoyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00318] To 6 mL of tetrahydrofuran were added 3,5-dichloro-4-aminopyridine (341.23 mg, 2.1 mmol) and sodium hydride (84 mg, 2.1 mmol, 60%), and the mixture was stirred at rt for 1 hour. To the mixture was added a solution of (S)-tert-butyl (1-(2-(3-ethoxy-4-methoxyphenyl)-4-(fluorocarbonyl)oxazol-5-yl)ethyl)carbamate (0.57 g, 1.4 mmol) in tetrahydrofuran (9 mL) at

0 °C, and the reaction mixture was stirred at rt for 14 hours. To the mixture was added saturated aqueous ammonium chloride (20 mL) and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a light yellow solid (240 mg, 31%).

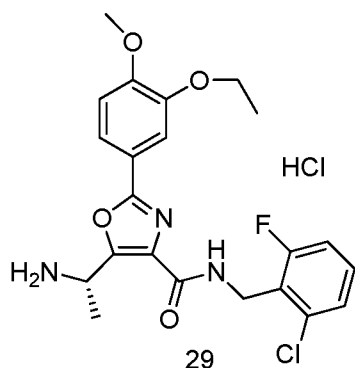
^1H NMR (400 MHz, CDCl_3): δ ppm 9.04 (s, 1H), 8.62 (s, 2H), 7.68 – 7.65 (m, 1H), 7.55 (d, J = 1.9 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 5.34 – 5.30 (m, 1H), 4.26 – 4.21 (m, 2H), 3.97 (s, 3H), 1.60 (d, J = 7.0 Hz, 3H), 1.44 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H); and MS-ESI: m/z 552.3 $[\text{M}+\text{H}]^+$.

Step 3: (*S*)-5-(1-Aminoethyl)-*N*-(3,5-dichloropyridin-4-yl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxamide dihydrochloride

[00319] To a solution of (*S*)-*tert*-butyl (1-(4-((3,5-dichloropyridin-4-yl)carbamoyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.23 g, 0.42 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 7 mL). The resulting mixture was stirred at rt for 2.5 hours and filtered. The filter cake was washed with ethyl acetate (15 mL $\times$ 3) to give a yellow solid (170 mg). The product was further recrystallized from methanol/ethyl acetate (v/v = 1/20) to give the desired product as a yellow solid (27.7 mg).

Compound 28: ^1H NMR (400 MHz, CD_3OD): δ ppm 8.70 (s, 2H), 7.79 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.72 (d, J = 1.9 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 5.28 – 5.23 (m, 1H), 4.22 – 4.17 (m, 2H), 3.95 (s, 3H), 1.79 (d, J = 7.0 Hz, 3H), 1.48 (t, J = 7.2 Hz, 3H); and MS-ESI: m/z 452.9 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 10: (*S*)-5-(1-Aminoethyl)-*N*-(2-chloro-6-fluorobenzyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(4-((2-chloro-6-fluorobenzyl)carbamoyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00320] To 10 mL of dichloromethane were added

(*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxylic acid (0.3 g, 0.74 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (212 mg, 1.11 mmol) and 1-hydroxy-7-azabenzotriazole (151 mg, 1.11 mmol), and the mixture was stirred at 0 °C for 30 minutes. To the mixture were added dropwise (2-fluoro-6-chlorophenyl)methanamine (0.11 mL, 0.89 mmol) and *N,N*-diisopropylethylamine (0.39 mL, 2.21 mmol) in turn, and the resulting mixture was stirred at rt for 12 hours. The reaction mixture was washed with water (10 mL $\times$ 3), and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as a white solid (190 mg, 47%).

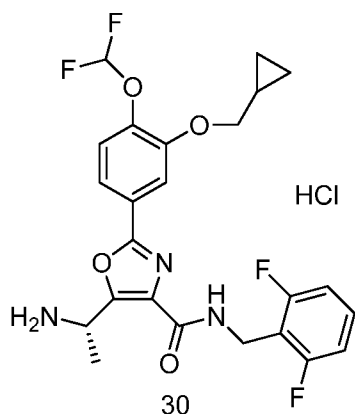
¹H NMR (400 MHz, CDCl₃): δ ppm 7.60 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.52 (d, $J = 1.8$ Hz, 1H), 7.39 – 7.29 (m, 1H), 7.27 – 7.25 (m, 1H), 7.10 – 7.05 (m, 1H), 6.94 (d, $J = 8.5$ Hz, 1H), 5.30 – 5.25 (m, 1H), 4.91 – 4.84 (m, 2H), 4.23 – 4.18 (m, 2H), 3.95 (s, 1H), 1.57 – 1.51 (m, 6H), 1.45 (s, 9H); and MS-ESI: m/z 549.2 [M+H]⁺.

Step 2: (*S*)-5-(1-Aminoethyl)-*N*-(2-chloro-6-fluorobenzyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxamide hydrochloride

[00321] To a solution of (*S*)-*tert*-butyl (1-(4-((2-chloro-6-fluorobenzyl)carbamoyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.19 g, 0.35 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for 3 hours and filtered, and the filter cake was washed with ethyl acetate (15 mL $\times$ 3) to give the title compound as a white solid (92 mg, 56%).

Compound 29: ¹H NMR (400 MHz, CD₃OD): δ ppm 7.69 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.62 (d, $J = 2.0$ Hz, 1H), 7.38 – 7.35 (m, 1H), 7.33 – 7.31 (m, 1H), 7.18 – 7.13 (m, 1H), 7.11 (d, $J = 8.5$ Hz, 1H), 5.17 – 5.12 (m, 1H), 4.81 (s, 2H), 4.17 – 4.12 (m, 2H), 3.92 (s, 3H), 1.76 (d, $J = 7.0$ Hz, 3H), 1.45 (t, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 448.2 [M+H-HCl]⁺.

Example 11: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,6-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,6-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00322] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (183.36 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (130.56 mg, 0.96 mmol). To the resulting solution were added dropwise (2,6-difluorophenyl)methanamine (0.1 mL, 0.77 mmol) and *N,N*-diisopropylethylamine (0.33 mL, 1.92 mmol) at 0 °C, and the mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (20 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (203 mg, 53%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.59 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.55 (d, $J = 1.9$ Hz, 1H), 7.35 – 7.30 (m, 1H), 7.24 (d, $J = 8.3$ Hz, 1H), 6.98 – 6.94 (m, 2H), 6.71 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.35 – 5.28 (m, 1H), 4.80 – 4.70 (m, 2H), 3.99 (d, $J = 6.9$ Hz, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.38 – 1.36 (m, 1H), 1.45 – 1.43 (m, 9H), 0.72 – 0.68 (m, 2H), 0.43 – 0.41 (m, 2H); and MS-ESI: m/z 594.2 $[\text{M}+\text{H}]^+$.

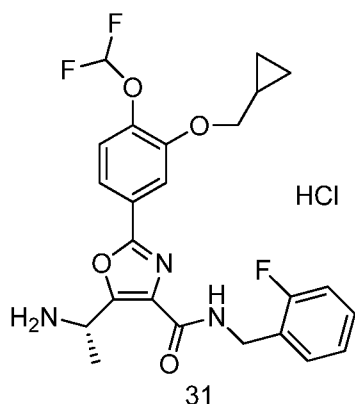
Step 2: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,6-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00323] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,6-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.2 g, 0.34 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 14 hours and filtered. The filter cake was washed with

ethyl acetate (15 mL $\times$ 3) to give the title compound as a white solid (152 mg, 83%).

Compound 30: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.69 (d, $J = 1.9$ Hz, 1H), 7.61 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.32 – 7.28 (m, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 6.93 (t, $J = 8.0$ Hz, 2H), 6.83 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.10 – 5.05 (m, 1H), 4.64 (s, 2H), 3.94 (d, $J = 7.0$ Hz, 2H), 1.67 (d, $J = 7.0$ Hz, 3H), 1.27 – 1.24 (m, 1H), 0.61 – 0.59 (m, 2H), 0.35 – 0.32 (m, 2H); and MS-ESI: m/z 494.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 12: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2-fluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2-fluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00324] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (183.36 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (130.56 mg, 0.96 mmol). To the resulting solution were added (2-fluorophenyl)methanamine (0.09 mL, 0.77 mmol) and *N,N*-diisopropylethylamine (0.33 mL, 1.92 mmol) at 0 °C, and the mixture was stirred at rt for 7 hours. The reaction mixture was washed with water (20 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (256 mg, 69%).

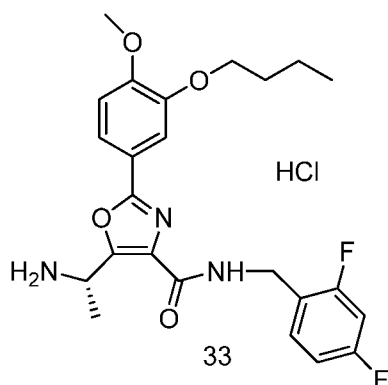
^1H NMR (400 MHz, CDCl_3): δ ppm 7.59 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.56 (d, $J = 1.8$ Hz, 1H), 7.47 – 7.43 (m, 1H), 7.33 – 7.29 (m, 1H), 7.25 (d, $J = 8.3$ Hz, 1H), 7.18 – 7.09 (m, 2H), 6.72 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.32 – 5.28 (m, 1H), 4.74 – 4.71 (m, 2H), 3.99 (d, $J = 7.0$ Hz, 2H), 1.56 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 1.41 – 1.37 (m, 1H), 0.73 – 0.68 (m, 2H), 0.44 – 0.40 (m, 2H); and MS-ESI: m/z 576.1 $[\text{M}+\text{H}]^+$.

Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2-fluorobenzyl)oxazole-4-carboxamide hydrochloride

[00325] To a solution of (S)-*tert*-butyl 1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2-fluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.25 g, 0.43 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 2 hours and filtered. The filter cake was washed with ethyl acetate (20 mL $\times$ 3) to give the title compound as a white solid (191 mg, 87%).

Compound 31: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.80 (d, $J = 1.9$ Hz, 1H), 7.73 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.45 (td, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz, 1H), 7.33 (d, $J = 8.3$ Hz, 2H), 7.19 – 7.12 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.20 – 5.14 (m, 1H), 4.69 (s, 2H), 4.03 (d, $J = 6.9$ Hz, 2H), 1.77 (d, $J = 7.0$ Hz, 3H), 1.38 – 1.34 (m, 1H), 0.71 – 0.66 (m, 2H), 0.44 – 0.41 (m, 2H); and MS-ESI: m/z 476.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 13: (S)-5-(1-Aminoethyl)-2-(3-butoxy-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 3-butoxy-4-methoxybenzoate

[00326] To *N,N*-dimethylformamide (60 mL) were added methyl 3-hydroxy-4-methoxybenzoate (10.0 g, 54.95 mmol), potassium carbonate (15.15 g, 109.78 mmol) and *n*-butyl bromide (8.85 mL, 66.07 mmol). The mixture was stirred at 60 °C for 4.5 hours. The reaction mixture was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (12.89 g, 99%).

Step 2: 3-Butoxy-4-methoxybenzoic acid

[00327] To a mixed solvent of ethanol (150 mL) and water (50 mL) were added methyl

3-butoxy-4-methoxybenzoate (12.89 g, 54.16 mmol) and sodium hydroxide (6.5 g, 162.48 mmol). The mixture was stirred at 60 °C for 1.5 hours and then concentrated to remove the ethanol. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The resulting mixture was extracted with ethyl acetate (50 mL × 3) and the combined organic layers were dried over anhydrous sodium sulfate. The organic layers was concentrated to give the title compound as a white solid (12.02 g, 99%).

Step 3: Methyl 2-(3-butoxy-4-methoxybenzamido)acetate

[00328] To 80 mL of dichloromethane were added 3-butoxy-4-methoxybenzoic acid (12.02 g, 53.66 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (15.45 g, 80.49 mmol) and 1-hydroxybenzotriazole (10.87 g, 80.49 mmol). The mixture was stirred at rt for half an hour, then glycine methyl ester hydrochloride (8.11 g, 64.39 mmol) and *N,N*-diisopropylethylamine (28.8 mL, 160.98 mmol) was added at 0 °C. The mixture was stirred at rt for 12 hours, then washed with water (40 mL × 3). The organic layer were dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a white solid (14.74 g, 93%).

Step 4: Methyl 2-(3-butoxy-4-methoxyphenylthioamido)acetate

[00329] To anhydrous tetrahydrofuran (40 mL) were added methyl 2-(3-butoxy-4-methoxybenzamido)acetate (5.0 g, 16.95 mmol) and Lawesson's Reagent (6.85 g, 16.95 mmol). The mixture was refluxed at 75 °C for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (40 mL), then the resulting mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (5.16 g, 98%).

Step 5: Methyl 2-(((3-butoxy-4-methoxyphenyl)(methylthio)methylene)amino)acetate

[00330] To a solution of trimethyloxonium tetrafluoroborate (4.88 g, 33.20 mmol) in dichloromethane (20 mL) was added dropwise a solution of methyl 2-(3-butoxy-4-methoxyphenylthioamido)acetate (5.16 g, 16.60 mmol) in dichloromethane (30 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then washed with saturated aqueous sodium bicarbonate (25 mL × 3). The organic layer was dried over anhydrous sodium sulfate.

The organic solvent was removed to give the title compound as yellow oil (5.35 g, 99%).

Step 6: (S)-Methyl 2-(3-butoxy-4-methoxyphenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylate

[00331] To 20 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-butoxy-4-methoxyphenyl)(methylthio)methylene)amino)acetate (5.35 g, 16.36 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (7.47 g, 39.1 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (32.0 mL, 32.0 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (5.02 g, 68%).

Step 7: (S)-2-(3-Butoxy-4-methoxyphenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylic acid

[00332] To a mixed solvent of tetrahydrofuran (40 mL) and water (20 mL) were added (*S*)-methyl 2-(3-butoxy-4-methoxyphenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylate (2.47 g, 5.52 mmol) and lithium hydroxide monohydrate (1.16 g, 27.27 mmol). The solution was stirred at 40 °C for 3 hours and tetrahydrofuran was removed, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (30 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a yellow solid (1.66 g, 70%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.65 (d, *J* = 8.4 Hz, 1H), 7.60 (s, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.50 - 5.42 (m, 1H), 4.12 (t, *J* = 6.8 Hz, 2H), 3.94 (s, 3H), 1.92 - 1.85 (m, 2H), 1.59 (d, *J* = 7.1 Hz, 3H), 1.57 - 1.51 (m, 2H), 1.44 (s, 9H), 1.01 (t, *J* = 7.3 Hz, 3H); and MS-ESI: *m/z* 435.2 [M+H]⁺.

Step 8: (S)-*tert*-Butyl (1-(2-(3-butoxy-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00333] To 30 mL of dichloromethane were added (*S*)-2-(3-butoxy-4-methoxyphenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylic acid (1.66 g, 3.82 mmol),

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.10 g, 5.73 mmol) and 1-hydroxy-7-azabenzotriazole (0.77 g, 5.73 mmol). The mixture was stirred at rt for half an hour. To the resulting solution were added (2,4-difluorophenyl)methanamine (0.55 mL, 0.90 mmol) and *N,N*-diisopropylethylamine (2.05 mL, 11.46 mmol) at 0 °C. The mixture was stirred at rt for 12 hours. The reaction mixture was washed with water (20 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as a white solid (694.5 mg, 40%).

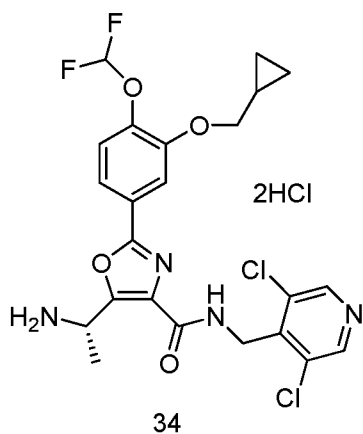
^1H NMR (400 MHz, CDCl_3): δ ppm 7.58 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.48 (d, $J = 1.9$ Hz, 1H), 7.46 - 7.40 (m, 1H), 6.93 (d, $J = 8.4$ Hz, 1H), 6.91 - 6.82 (m, 2H), 5.32 - 5.28 (m, 1H), 4.68 - 4.61 (m, 2H), 4.11 (t, $J = 6.8$ Hz, 2H), 3.93 (s, 3H), 1.92 - 1.85 (m, 2H), 1.55 (d, $J = 7.1$ Hz, 3H), 1.45 (s, 9H), 1.40 - 1.38 (m, 2H), 1.02 (t, $J = 7.4$ Hz, 3H); and MS-ESI: m/z 560.2 $[\text{M}+\text{H}]^+$.

Step 9: (*S*)-5-(1-Aminoethyl)-2-(3-butoxy-4-methoxyphenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00334] To a solution of (*S*)-*tert*-butyl (1-(2-(3-butoxy-4-methoxyphenyl)-4-((2,4-difluorobenzyl) carbamoyl)oxazol-5-yl)ethyl)carbamate (695 mg, 1.24 mmol) in dichloromethane (3 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for half an hour and concentrated to remove the solvent. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (344 mg, 60%).

Compound 33: ^1H NMR (400 MHz, d_6 -DMSO): δ ppm 7.67 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.63 (d, $J = 1.9$ Hz, 1H), 7.49 - 7.43 (m, 1H), 7.26 - 7.20 (m, 1H), 7.18 (d, $J = 8.6$ Hz, 1H), 7.08 (td, $J_1 = 8.5$ Hz, $J_2 = 1.9$ Hz, 1H), 5.12 - 5.08 (m, 1H), 4.49 (d, $J = 6.1$ Hz, 2H), 4.05 (t, $J = 6.4$ Hz, 2H), 3.86 (s, 3H), 1.78 - 1.71 (m, 2H), 1.63 (d, $J = 6.9$ Hz, 3H), 1.47 - 1.44 (m, 2H), 0.95 (t, $J = 7.4$ Hz, 3H); and MS-ESI: m/z 460.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 14: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((3,5-dichloropyridin-4-yl)methyl)oxazole-4-carboxamide dihydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00335] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (183.36 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (130.56 mg, 0.96 mmol). To the resulting solution were added dropwise a solution of (3,5-dichloropyridin-4-yl)methanamine (136 mg, 0.77 mmol) in dichloromethane (7 mL) and *N,N*-diisopropylethylamine (0.33 mL, 1.92 mmol) at 0 °C, and the mixture was stirred at rt for 17 hours. The reaction mixture was washed with water (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (263 mg, 65%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.56 (s, 2H), 7.59 (dd, *J*₁ = 8.3 Hz, *J*₂ = 1.9 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 6.71 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.32 – 5.26 (m, 1H), 4.96 (d, *J* = 5.7 Hz, 2H), 3.98 (d, *J* = 7.0 Hz, 2H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.44 (s, 9H), 1.36 – 1.32 (m, 1H), 0.71 – 0.68 (m, 2H), 0.44 – 0.41 (m, 2H).

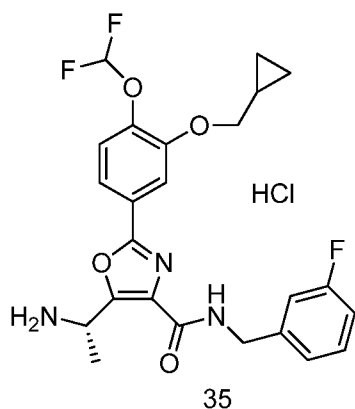
Step 2: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((3,5-dichloropyridin-4-yl)methyl)oxazole-4-carboxamide dihydrochloride

[00336] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.26 g, 0.41 mmol) in dichloromethane (5 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 17 hours and filtered. The filter cake was washed with ethyl acetate (20 mL × 3) to give the title compound as a white solid (209

mg, 85%).

Compound 34: ^1H NMR (400 MHz, CD_3OD): δ ppm 8.57 (s, 2H), 7.77 (d, $J = 1.9$ Hz, 1H), 7.70 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.32 (d, $J = 8.4$ Hz, 1H), 6.91 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.18 – 5.14 (m, 1H), 4.92 (s, 2H), 4.02 (d, $J = 6.9$ Hz, 2H), 1.76 (d, $J = 7.0$ Hz, 3H), 1.36 – 1.32 (m, 1H), 0.70 – 0.66 (m, 2H), 0.44 – 0.40 (m, 2H); and MS-ESI: m/z 528.2 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 15: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(3-fluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((3-fluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00337] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (183.36 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (130.56 mg, 0.96 mmol). To the resulting solution were added dropwise (3-fluorophenyl)methanamine (0.09 mL, 0.77 mmol) and *N,N*-diisopropylethylamine (0.33 mL, 1.92 mmol) at 0 °C, and the mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a white solid (254 mg, 69%).

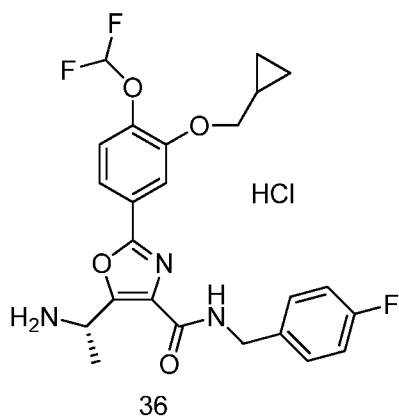
^1H NMR (400 MHz, CDCl_3): δ ppm 7.59 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.55 (d, $J = 1.9$ Hz, 1H), 7.37 – 7.33 (m, 1H), 7.25 (d, $J = 8.3$ Hz, 1H), 7.17 (d, $J = 7.7$ Hz, 1H), 7.12 – 7.09 (m, 1H), 7.04 – 7.00 (m, 1H), 6.71 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.32 – 5.28 (m, 1H), 4.67 (d, $J = 6.2$ Hz, 2H), 3.98 (d, $J = 7.0$ Hz, 2H), 1.56 (s, 3H), 1.45 (s, 9H), 1.36 – 1.32 (m, 1H), 0.71 – 0.68 (m, 2H), 0.44 – 0.41 (m, 2H).

Step 2: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(3-fluorobenzyl)oxazole-4-carboxamide hydrochloride

[00338] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((3-fluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.25 g, 0.43 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 24 hours and filtered. The filter cake was washed with ethyl acetate (20 mL $\times$ 3) to give the title compound as a white solid (149 mg, 68%).

Compound 35: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.72 (d, $J = 1.8$ Hz, 1H), 7.64 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.31 – 7.23 (m, 2H), 7.13 (d, $J = 7.7$ Hz, 1H), 7.07 – 7.04 (m, 1H), 6.95 – 6.90 (m, 1H), 6.83 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.12 – 5.06 (m, 1H), 4.54 (s, 2H), 3.95 (d, $J = 6.9$ Hz, 2H), 1.69 (d, $J = 7.0$ Hz, 3H), 1.29 – 1.25 (m, 1H), 0.62 – 0.58 (m, 2H), 0.36 – 0.32 (m, 2H); and MS-ESI: m/z 476.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 16: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(4-fluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((4-fluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00339] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (183.36 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (130.56 mg, 0.96 mmol). To the resulting solution were added dropwise (4-fluorophenyl)methanamine (0.09 mL, 0.77 mmol) and *N,N*-diisopropylethylamine (0.33 mL, 1.92 mmol) at 0 °C, the mixture was stirred at rt for 3 hours. The reaction mixture was washed

with water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as colourless oil (250 mg, 68%).

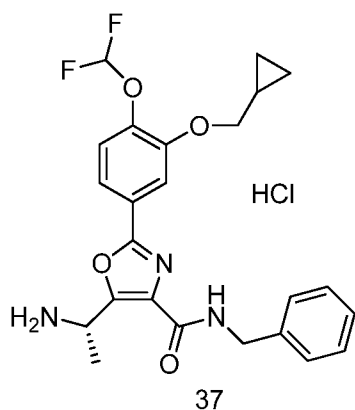
^1H NMR (400 MHz, CDCl_3): δ ppm 7.56 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.52 (d, $J = 1.9$ Hz, 1H), 7.37 – 7.33 (m, 2H), 7.22 (d, $J = 8.3$ Hz, 1H), 7.05 (t, $J = 8.7$ Hz, 2H), 6.69 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.32 – 5.26 (m, 1H), 4.61 (d, $J = 6.1$ Hz, 2H), 3.96 (d, $J = 7.0$ Hz, 2H), 1.54 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 1.36 – 1.32 (m, 1H), 0.70 – 0.65 (m, 2H), 0.41 – 0.37 (m, 2H).

Step 2: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(4-fluorobenzyl)oxazole-4-carboxamide hydrochloride

[00340] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((4-fluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.25 g, 0.43 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 24 hours and filtered. The filter cake was washed with ethyl acetate (20 mL $\times$ 3) to give the title compound as a white solid (187 mg, 78%).

Compound 36: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.79 (d, $J = 1.9$ Hz, 1H), 7.72 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.45 – 7.41 (m, 2H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.10 – 7.06 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 65.5$ Hz, 1H), 5.20 – 5.15 (m, 1H), 4.59 (s, 2H), 4.03 (d, $J = 7.0$ Hz, 2H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.32 (m, 1H), 0.70 – 0.66 (m, 2H), 0.44 – 0.42 (m, 2H); and MS-ESI: m/z 476.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 17: (*S*)-5-(1-Aminoethyl)-*N*-benzyl-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(4-(benzylcarbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00341] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g,

0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (183.36 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (130.56 mg, 0.96 mmol). To the resulting solution were added dropwise benzylamine (0.08 mL, 0.77 mmol) and *N,N*-diisopropylethylamine (0.33 mL, 1.92 mmol) at 0 °C, and the mixture was stirred at rt for 3 hours. The reaction mixture was washed with water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (200 mg, 56%).

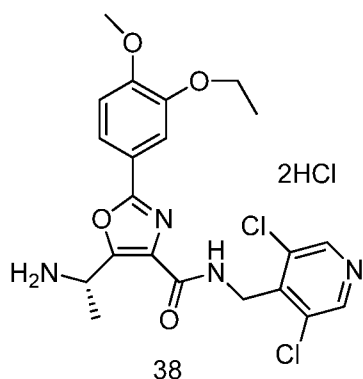
^1H NMR (400 MHz, CDCl_3): δ ppm 7.55 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.52 (d, $J = 1.8$ Hz, 1H), 7.40 – 7.38 (m, 4H), 7.36 – 7.31 (m, 1H), 7.21 (d, $J = 8.3$ Hz, 1H), 6.69 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.18 – 5.15 (m, 1H), 4.65 (d, $J = 6.0$ Hz, 2H), 3.95 (d, $J = 7.0$ Hz, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 1.36 – 1.33 (m, 1H), 0.69 – 0.65 (m, 2H), 0.41 – 0.37 (m, 2H); and MS-ESI: m/z 558.2 $[\text{M}+\text{H}]^+$.

Step 2: (*S*)-5-(1-Aminoethyl)-*N*-benzyl-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl) oxazole-4-carboxamide hydrochloride

[00342] To a solution of (*S*)-*tert*-butyl (1-(4-(benzylcarbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.2 g, 0.36 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 7 mL). The resulting mixture was stirred at rt for 18 hours and filtered. The filter cake was washed with ethyl acetate (15 mL $\times$ 3) to give the title compound as a white solid (136 mg, 77%).

Compound 37: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.80 (d, $J = 1.9$ Hz, 1H), 7.72 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.42 – 7.39 (m, 2H), 7.37 – 7.31 (m, 3H), 7.30 – 7.26 (m, 1H), 6.91 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.20 – 5.15 (m, 1H), 4.62 (s, 2H), 4.03 (d, $J = 7.0$ Hz, 2H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.32 (m, 1H), 0.71 – 0.66 (m, 2H), 0.44 – 0.40 (m, 2H); and MS-ESI: m/z 458.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 18: (*S*)-5-(1-Aminoethyl)-*N*-((3,5-dichloropyridin-4-yl)methyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxamide dihydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00343] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxylic acid (0.25 g, 0.62 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (178 mg, 0.93 mmol) and 1-hydroxy-7-azabenzotriazole (127 mg, 0.93 mmol). The mixture was stirred at 0 °C for 30 minutes, then a solution of (3,5-dichloropyridin-4-yl)methylamine (132 mg, 0.74 mmol) in dichloromethane (4 mL) and *N,N*-diisopropylethylamine (0.32 mL, 1.86 mmol) were added dropwise to the solution. The mixture was stirred at rt for 22 hours. The reaction mixture was washed with water (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a white solid (140 mg, 40%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.53 (s, 2H), 7.57 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.8 Hz, 1H), 7.47 (d, *J* = 1.7 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 5.30 – 5.24 (m, 1H), 4.93 (d, *J* = 5.5 Hz, 2H), 4.20 – 4.15 (m, 2H), 3.93 (s, 3H), 1.54 – 1.49 (m, 6H), 1.42 (s, 9H).

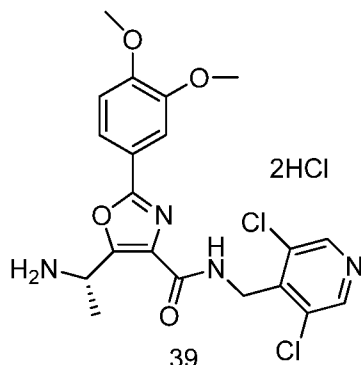
Step 2: (*S*)-5-(1-Aminoethyl)-*N*-(((3,5-dichloropyridin-4-yl)methyl)-2-(3-ethoxy-4-methoxyphenyl)oxazole-4-carboxamide dihydrochloride

[00344] To a solution of (*S*)-*tert*-butyl (1-(4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)-2-(3-ethoxy-4-methoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.14 g, 0.25 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for 3 hours and filtered. The filter cake was washed with ethyl acetate (15 mL × 3) to give the title compound as a white solid (100 mg, 75%).

Compound 38: ¹H NMR (400 MHz, CD₃OD): δ ppm 8.50 (s, 2H), 7.60 (dd, *J*₁ = 8.4 Hz, *J*₂

= 2.0 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 5.07 – 5.04 (m, 1H), 4.82 (s, 2H), 4.07 – 4.02 (m, 2H), 3.82 (s, 3H), 1.65 (d, J = 7.0 Hz, 3H), 1.35 (t, J = 7.0 Hz, 3H); and MS-ESI: m/z 466.2 $[M+H-2HCl]^+$.

Example 19: (S)-5-(1-Aminoethyl)-N-((3,5-dichloropyridin-4-yl)methyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00345] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxylic acid (0.3 g, 0.77 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (220.6 mg, 1.16 mmol) and 1-hydroxy-7-azabenzotriazole (157.1 mg, 1.16 mmol). A solution of (3,5-dichloropyridin-4-yl)methylamine (163 mg, 0.77 mmol) in dichloromethane (5 mL) and *N,N*-diisopropylethylamine (0.4 mL, 2.31 mmol) were added dropwise to the resulting mixture at 0 °C. The mixture was stirred at rt for 22 hours. The reaction mixture was washed with water (20 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc(v/v) = 2/1) to give the title compound as a white solid (378 mg, 89%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.53 (s, 2H), 7.58 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.46 (d, J = 1.9 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 5.30 – 5.24 (m, 1H), 4.93 (d, J = 5.8 Hz, 2H), 3.95 (d, J = 8.7 Hz, 6H), 1.54 (d, J = 7.0 Hz, 3H), 1.42 (s, 9H); and MS-ESI: m/z 552.1 $[M+H]^+$.

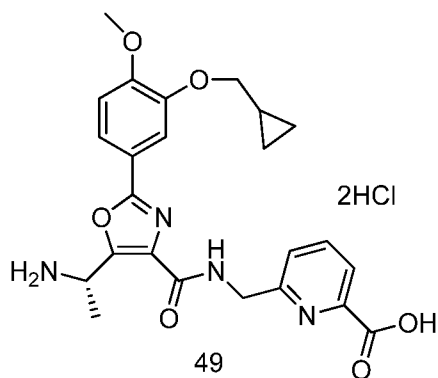
Step 2: (S)-5-(1-Aminoethyl)-N-((3,5-dichloropyridin-4-yl)methyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamide dihydrochloride

[00346] To a solution of (S)-tert-butyl (1-(4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)-2-(3,4-dimethoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.37 g, 0.67 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 9 mL). The resulting

mixture was stirred at rt for 17 hours and filtered. The filter cake was washed with ethyl acetate (20 mL $\times$ 3) to give the title compound as a white solid (326 mg, 93%).

Compound 39: ^1H NMR (400 MHz, CD_3OD): δ ppm 8.50 (s, 2H), 7.55 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.48 (d, $J = 1.9$ Hz, 1H), 6.96 (d, $J = 8.5$ Hz, 1H), 5.03 – 4.98 (m, 1H), 4.77 (s, 2H), 3.76 (s, 6H), 1.61 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 452.2 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 20: (S)-6-((5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride



Step 1: Methyl 3-(cyclopropylmethoxy)-4-methoxybenzoate

[00347] To a solution of methyl 3-hydroxy-4-methoxybenzoate (5 g, 27.4725 mmol) in *N,N*-dimethylformamide (30 mL) were added anhydrous potassium carbonate (7.58 g, 54.945 mmol) and (bromomethyl)cyclopropane (3.8 mL, 41.204 mmol) in turn. The whole mixture was stirred at 60 °C in a sealed tube for 4.5 hours. To the reaction mixture was added 20 mL of saturated aqueous sodium chloride, and the mixture was extracted with ethyl acetate (25 mL $\times$ 3). The combined organic layers were washed with water (30 mL $\times$ 3) and dried over anhydrous sodium sulfate for one hour. The organic solvent was removed to give the title compound as a white solid (6.26 g, 96.5%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.66 (d, $J = 8.4$ Hz, 1H), 7.52 (s, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 3.92 (s, 3H), 3.89 (d, $J = 7.0$ Hz, 2H), 3.87 (s, 3H), 1.32-1.36 (m, 1H), 0.62-0.67 (m, 2H), 0.34-0.38 (m, 2H); and MS-ESI: m/z 237.1 $[\text{M}+\text{H}]^+$.

Step 2: 3-(Cyclopropylmethoxy)-4-methoxybenzoic acid

[00348] To 20 mL of ethanol was added methyl 3-(cyclopropylmethoxy)-4-methoxybenzoate (2 g, 8.47 mmol), and sodium hydroxide (1.695 g, 42.37 mmol) was added to the solution. The mixture was stirred at 60 °C for 1.5 hours, then ethanol was removed and the residue was dissolved in water (20 mL). To the mixture was added hydrochloric acid (1 M) to adjust the pH

of the mixture to about 1. The resulting mixture was extracted with ethyl acetate (25 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (1.81 g, 96.2%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.65 (d, J = 8.4 Hz, 1H), 7.52 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 3.89 (s, 3H), 3.86 (d, J = 6.9 Hz, 2H), 1.24-1.27 (m, 1H), 0.58-0.63 (m, 2H), 0.33-0.37 (m, 2H); and MS-ESI: m/z 223.0 $[\text{M}+\text{H}]^+$.

Step 3: Methyl 2-(3-(cyclopropylmethoxy)-4-methoxybenzamido)acetate

[00349] To 30 mL of dichloromethane were added 3-(cyclopropylmethoxy)-4-methoxybenzoic acid (4.5 g, 20.27 mmol), 1-hydroxy-7-azabenzotriazole (HOAT) (2.759 g, 20.27mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (5.807 g, 30.405mmol). The mixture was stirred at rt for 30 minutes, then glycine methyl ester hydrochloride (3.04 g, 24.324 mmol) was added. The mixture was placed in an ice-bath, and *N,N*-diisopropylethylamine (14 mL, 81.08 mmol) was added dropwise. The resulting mixture was stirred overnight at rt. To the reaction mixture was added water (30 mL) and the mixture was extracted with dichloromethane (25 mL $\times$ 3). The organic layers were combined and dried over anhydrous sodium sulfate. The organic solvent was removed, then the residue was purified by silica gel column chromatography PE/EtOAc (v/v) = 1/1) to give the title compound as a white solid (3.68 g, 61.9%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.41 (s, 1H), 7.34 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.57 (s, 1H), 4.23 (d, J = 5.0 Hz, 2H), 3.92 (s, 3H), 3.90 (d, J = 7.0 Hz, 2H), 3.80 (s, 3H), 1.25-1.34 (m, 1H), 0.62-0.66 (m, 2H), 0.35-0.38 (m, 2H); and MS-ESI: m/z 294.2 $[\text{M}+\text{H}]^+$.

Step 4: Methyl 2-(3-(cyclopropylmethoxy)-4-methoxyphenylthioamido)acetate

[00350] To 30 mL of tetrahydrofuran were added methyl 2-(3-(cyclopropylmethoxy)-4-methoxybenzamido)acetate (4 g, 13.64 mmol) and Lawesson's Reagent (5.52 g, 13.64 mmol), and the mixture was stirred at 75 °C for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (30 mL) and the mixture was extracted with ethyl acetate (20 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (2.89 g, 68%).

Step 5: Methyl 2-(((3-(cyclopropylmethoxy)-4-methoxyphenyl)(methylthio)methylene)amino)acetate

[00351] To a solution of trimethyloxonium tetrafluoroborate (2.68 g, 18.1 mmol) in dichloromethane (15 mL) was added dropwise a solution of methyl 2-(3-(cyclopropylmethoxy)-4-methoxyphenylthioamido)acetate (2.8 g, 9.05 mmol) in dichloromethane (20 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then washed with saturated aqueous sodium bicarbonate (25 mL × 3). The organic layer was dried over anhydrous sodium sulfate and concentrated to give the title compound as yellow oil (2.8 g, 96%).

Step 6: (S)-Methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate

[00352] To 15 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-(cyclopropylmethoxy)-4-methoxyphenyl)(methylthio)methylene)amino)acetate (2.8 g, 8.66 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (3.3 g, 17.32 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (21.65 mL, 21.65 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. The reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (25 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (2.58 g, 67%).

Step 7: (S)-5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid

[00353] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate (2.58 g, 5.78 mmol) and lithium hydroxide monohydrate (1.21 g, 28.9 mmol). The solution was stirred at 40 °C for 2 hours, then hydrochloric acid (1 M) was added to adjust the pH of the solution to 1. The mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a yellow solid (1.66 g, 66%).

Step 8: (S)-Ethyl 6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxamido)methyl)picolinate

[00354] To 15 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid (0.35 g, 0.81

mmol), 6-(aminomethyl)-2-pyridinecarboxylic acid ethyl ester (175 mg, 0.97 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (232 mg, 1.21 mmol) and 1-hydroxy-7-azabenzotriazole (165 mg, 1.21 mmol). To the resulting solution were added *N,N*-diisopropylethylamine (0.42 mL, 2.43 mmol) at 0 °C, and the mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (20 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (240 mg, 50%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.18 (br.s, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.87 (t, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.60 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.9 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 5.32 – 5.29 (m, 1H), 4.90 – 4.88 (m, 2H), 4.54 – 4.49 (m, 2H), 3.98 (d, *J* = 7.0 Hz, 2H), 3.96 (s, 3H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.49 – 1.47 (m, 3H), 1.45 (s, 9H), 1.41 – 1.39 (m, 1H), 0.73 – 0.68 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: *m/z* 595.4 [M+H]⁺.

Step 9: (S)-6-((5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid

[00355] To a mixed solvent of tetrahydrofuran (10 mL) and water (5 mL) were added (*S*)-ethyl 6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxamido)methyl)picolinate (0.24 g, 0.4 mmol) and lithium hydroxide monohydrate (0.085 g, 2.0 mmol). The solution was stirred at 40 °C for 2 hours, then hydrochloric acid (1 M) was added to adjust the pH of the solution to 1. The mixture was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as yellow oil (0.22 g, 95%).

¹H NMR (400 MHz, CD₃OD): δ ppm 8.01 – 7.92 (m, 2H), 7.63 – 7.49 (m, 3H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.35 – 5.32 (m, 1H), 4.68 (s, 2H), 3.83 – 3.80 (m, 2H), 3.81 (s, 3H), 1.40 (d, *J* = 6.4 Hz, 3H), 1.31 – 1.30 (m, 9H), 1.23 – 1.22 (m, 1H), 0.57 – 0.52 (m, 2H), 0.30 – 0.26 (m, 2H); and MS-ESI: *m/z* 567.2 [M+H]⁺.

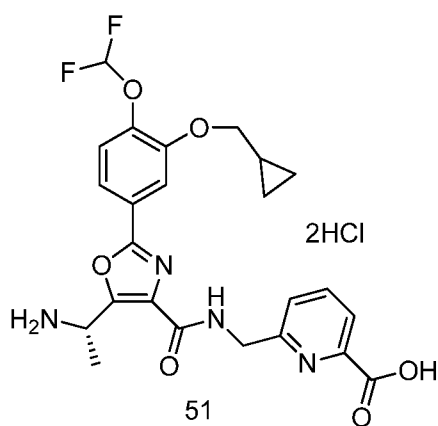
Step 10: (S)-6-((5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride

[00356] To a solution of (*S*)-6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid (0.22 g,

0.39 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 15 minutes and filtered. The filter cake was washed with ethyl acetate (20 mL $\times$ 3) to give the title compound as a white solid (90 mg, 43%).

Compound 49: ^1H NMR (400 MHz, CD_3OD): δ ppm 8.35 – 8.31 (m, 1H), 8.23 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.62 – 7.59 (m, 1H), 7.52 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 5.05 – 5.02 (m, 1H), 4.84 (s, 2H), 3.82 – 3.80 (m, 2H), 3.81 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H), 1.20 – 1.17 (m, 1H), 0.55 – 0.51 (m, 2H), 0.27 – 0.23 (m, 2H); and MS-ESI: m/z 467.3 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 21: (S)-6-((5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride



Step 1: (S)-Ethyl 6-((5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)methyl)picolinate

[00357] To 10 mL of dichloromethane was added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.35 g, 0.75 mmol), 6-(aminomethyl)-2-pyridinecarboxylic acid ethyl ester (162 mg, 0.90 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (214 mg, 1.12 mmol), 1-hydroxy-7-azabenzotriazole (152 mg, 1.12 mmol). The mixture was cooled to 0 °C, and *N,N*-diisopropylethylamine (0.4 mL, 2.24 mmol) was added dropwise. The resulting mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (20 mL $\times$ 3), and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed, then the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (250 mg, 52%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.22 (br.s, 1H), 8.08 (d, *J* = 7.5 Hz, 1H), 7.90 – 7.87 (m, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 1H), 6.73 (t, *J*_{F-H} = 75.1 Hz, 1H), 5.35 – 5.30 (m, 1H), 4.89 (s, 2H), 4.55 – 4.49 (m, 2H), 4.02 (d, *J* = 6.8 Hz, 2H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.45 (s, 9H), 1.37 – 1.34 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 1H), 0.73 – 0.68 (m, 2H), 0.46 – 0.43 (m, 2H).

Step 2: (S)-6-((5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)methyl)picolinic acid

[00358] To a mixed solvent of tetrahydrofuran (10 mL) and water (5 mL) were added (*S*)-ethyl 6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)methyl)picolinate (0.25 g, 0.4 mmol) and lithium hydroxide monohydrate (0.08 g, 2.0 mmol). The solution was stirred at 40 °C for 2 hours, then hydrochloric acid (1 M) was added to adjust the pH of the solution to 1. The mixture was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as yellow oil (0.23 g, 98%).

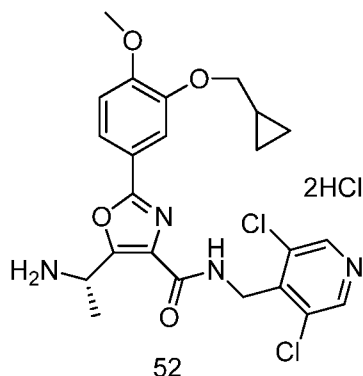
¹H NMR (400 MHz, CD₃OD): δ ppm 7.99 (d, *J* = 7.5 Hz, 1H), 7.93 – 7.90 (m, 1H), 7.63 – 7.55 (m, 3H), 7.17 (d, *J* = 9.1 Hz, 1H), 6.78 (t, *J*_{F-H} = 74.9 Hz, 1H), 5.38 – 5.32 (m, 1H), 4.67 (s, 2H), 3.90 (d, *J* = 6.9 Hz, 2H), 1.41 (d, *J* = 6.9 Hz, 3H), 1.31 – 1.28 (m, 9H), 1.26 – 1.23 (m, 1H), 0.59 – 0.54 (m, 2H), 0.33 – 0.29 (m, 2H); and MS-ESI: *m/z* 603.4 [M+H]⁺.

Step 3: (S)-6-((5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride

[00359] To a solution of (*S*)-6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)methyl)picolinic acid (0.23 g, 0.38 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for 15 minutes and filtered. The filter cake was washed with ethyl acetate (15 mL × 3) to give the title compound as a white solid (150 mg, 69%).

Compound 51: ¹H NMR (400 MHz, CD₃OD): δ ppm 8.40 (t, *J* = 7.9 Hz, 1H), 8.28 (d, *J* = 7.7 Hz, 1H), 8.19 – 8.15 (m, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.64 – 7.61 (m, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.81 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.12 – 5.07 (m, 1H), 4.89, 4.80 (s, s, 1H, 1H), 3.92 (d, *J* = 6.9 Hz, 2H), 1.66 (d, *J* = 7.0 Hz, 3H), 1.26 – 1.23 (m, 1H), 0.60 – 0.55 (m, 2H), 0.33 – 0.29 (m, 2H); and MS-ESI: *m/z* 503.3 [M+H-2HCl]⁺.

Example 22: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-((3,5-dichloropyridin-4-yl)methyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00360] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid (0.35 g, 0.81 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (232 mg, 1.21 mmol) and 1-hydroxy-7-azabenzotriazole (165 mg, 1.21 mmol). To the resulting solution were added a solution of (3,5-dichloropyridin-4-yl)methylamine (172 mg, 0.97 mmol) in dichloromethane (5 mL) and *N,N*-diisopropylethylamine (0.42 mL, 2.43 mmol) at 0 °C, then the mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (20 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (280 mg, 58%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.53 (s, 2H), 7.58 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.46 (d, $J = 1.9$ Hz, 1H), 6.93 (d, $J = 8.5$ Hz, 1H), 5.30 – 5.26 (m, 1H), 4.94 (d, $J = 5.7$ Hz, 2H), 3.94 (s, 3H), 3.92 (d, $J = 7.0$ Hz, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H), 1.39 – 1.37 (m, 1H), 0.71 – 0.66 (m, 2H), 0.42 – 0.38 (m, 2H).

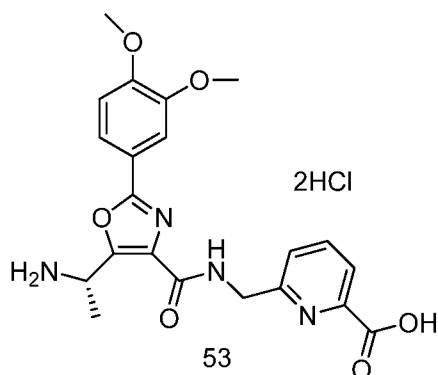
Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-((3,5-dichloropyridin-4-yl)methyl)oxazole-4-carboxamide dihydrochloride

[00361] To a solution of (S)-tert-butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.28 g, 0.47 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 23 hours and filtered. The filter cake was

washed with ethyl acetate (20 mL $\times$ 3) to give the title compound as a white solid (240 mg, 86%).

Compound 52: ^1H NMR (400 MHz, CD_3OD): δ ppm 8.62 (s, 2H), 7.70 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.12 (d, $J = 8.6$ Hz, 1H), 5.18 – 5.13 (m, 1H), 4.92 (s, 2H), 3.93 (s, 3H), 3.92 (d, $J = 7.2$ Hz, 2H), 1.76 (d, $J = 7.0$ Hz, 3H), 1.33 – 1.30 (m, 1H), 0.68 – 0.63 (m, 2H), 0.40 – 0.37 (m, 2H); and MS-ESI: m/z 492.1 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 23: (S)-6-((5-(1-Aminoethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride



Step 1: (S)-Ethyl 6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamido)methyl)picolinate

[00362] To 15 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxylic acid (0.35 g, 0.89 mmol), 6-(aminomethyl)-2-pyridinecarboxylic acid ethyl ester (193 mg, 1.07 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (256 mg, 1.34 mmol) and 1-hydroxy-7-azabenzotriazole (182 mg, 1.34 mmol). To the resulting solution was added *N,N*-diisopropylethylamine (0.47 mL, 2.68 mmol) dropwise at 0 °C, and the mixture was stirred at rt for 12 hours. The reaction mixture was washed with water (15 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as yellow oil (360 mg, 72%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.05 (d, $J = 7.6$ Hz, 1H), 7.85 (t, $J = 7.6$ Hz, 1H), 7.60 (t, $J = 8.6$ Hz, 2H), 7.54 (s, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 5.30 – 5.26 (m, 1H), 4.87 – 4.85 (m, 2H), 4.51 – 4.45 (m, 2H), 4.00 (s, 3H), 3.94 (s, 3H), 1.52 (d, $J = 7.0$ Hz, 3H), 1.44 (d, $J = 7.2$ Hz, 3H), 1.43 (s, 9H); and MS-ESI: m/z 555.4 $[\text{M}+\text{H}]^+$.

Step 2: (S)-6-((5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-

carboxamido)methyl)picolinic acid

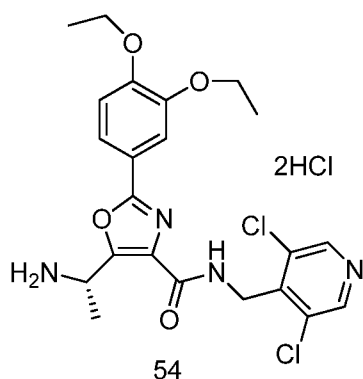
[00363] To a mixed solvent of tetrahydrofuran (14 mL) and water (7 mL) were added (*S*)-ethyl 6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamido)methyl)picolinate (0.36 g, 0.4 mmol) and lithium hydroxide monohydrate (0.14 g, 3.25 mmol). The solution was stirred at 40 °C for 2 hours, then hydrochloric acid (1 M) was added to adjust the pH of the solution to 1. The mixture was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as yellow oil (0.27 g, 79%).

¹H NMR (400 MHz, CD₃OD): δ ppm 8.09 (d, *J* = 7.4 Hz, 1H), 8.00 (t, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.67 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.8 Hz, 1H), 7.63 (s, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 5.46 – 5.44 (m, 1H), 4.79 (s, 2H), 3.92 (d, *J* = 7.2 Hz, 6H), 1.53 (d, *J* = 7.1 Hz, 3H), 1.42 (s, 9H); and MS-ESI: *m/z* 527.4 [M+H]⁺.

Step 3: (*S*)-6-((5-(1-Aminoethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride

[00364] To a solution of (*S*)-6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-dimethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid (0.27 g, 0.51 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 9 mL). The resulting mixture was stirred at rt for 15 minutes and filtered. The filter cake was washed with ethyl acetate (20 mL × 3) to give the title compound as a white solid (210 mg, 82%).

Compound 53: ¹H NMR (400 MHz, CD₃OD): δ ppm 8.57 (t, *J* = 7.9 Hz, 1H), 8.44 (d, *J* = 7.5 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.77 – 7.75 (m, 1H), 7.69 (s, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 5.21 – 5.18 (m, 1H), 3.94 (s, 6H), 3.37 (s, 2H), 1.77 (d, *J* = 7.0 Hz, 3H); and MS-ESI: *m/z* 427.3 [M+H-2HCl]⁺.

Example 24: (*S*)-5-(1-Aminoethyl)-N-((3,5-dichloropyridin-4-yl)methyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxamide dihydrochloride

Step 1: Methyl 3,4-diethoxybenzoate

[00365] To a 100 mL two-necked flask were added methyl 3,4-dihydroxybenzoate (2.0 g, 11.90 mmol), potassium carbonate (4.93 g, 35.70 mmol), *N,N*-dimethylformamide (30 mL) and bromoethane (2.22 mL, 29.75 mmol). The resulting mixture was stirred at 60 °C for 4.5 hours. The reaction mixture was extracted with ethyl acetate (50 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (2.0 g, 76%).

Step 2: 3,4-Diethoxybenzoic acid

[00366] To a 100 mL two-necked flask were added methyl 3,4-diethoxybenzoate (2.0 g, 8.92 mmol), sodium hydroxide (1.79 g, 44.64 mmol), ethanol (30 mL) and water (15 mL). The mixture was stirred at 60 °C for 1.5 hours and concentrated to remove ethanol. To the residue was added hydrochloric acid (1 M) to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (50 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (1.85 g, 99%).

¹H NMR (400 MHz, CDCl₃): δ ppm 10.95 (br.s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.59 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.17 - 4.14 (m, 4H), 1.50 - 1.45 (m, 6H); and MS-ESI: *m/z* 211.1 [M+H]⁺.

Step 3: Methyl 2-(3,4-diethoxybenzamido)acetate

[00367] To 80 mL of dichloromethane were added 3,4-diethoxybenzoic acid (6.37 g, 30.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.72 g, 45.5 mmol) and 1-hydroxybenzotriazole (6.15 g, 45.5 mmol). The mixture was stirred at rt for 30 minutes, then glycine methyl ester hydrochloride (4.57 g, 36.4 mmol) and *N,N*-diisopropylethylamine (15.9 mL, 91.0 mmol) were added at 0 °C. The resulting mixture was stirred at rt for 12 hours. The reaction mixture was washed with water (40 mL × 3). The organic layer was dried over anhydrous sodium sulfate and concentrated, then the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a white solid (6.73 g, 79%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.41 (s, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.72 (br.s, 1H), 4.19 (s, 2H), 4.14 - 4.08 (m, 4H), 3.77 (s, 3H), 1.46 - 1.41 (m, 6H); and

MS-ESI: m/z 282.1 $[M+H]^+$.

Step 4: Methyl 2-(3,4-diethoxyphenylthioamido)acetate

[00368] To 60 mL of tetrahydrofuran were added methyl 2-(3,4-diethoxybenzamido)acetate (4 g, 14.23 mmol) and Lawesson's Reagent (5.75 g, 14.23 mmol), the mixture was stirred at 75 °C for 4 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (60 mL) and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (4 g, 95%).

Step 5: Methyl 2-(((3,4-diethoxyphenyl)(methylthio)methylene)amino)acetate

[00369] To a solution of trimethyloxonium tetrafluoroborate (3.98 g, 26.90 mmol) in dichloromethane (20 mL) was added dropwise a solution of methyl 2-(3,4-diethoxyphenylthioamido)acetate (4 g, 13.45 mmol) in dichloromethane (30 mL) at -78 °C. The mixture was stirred at 0 °C for 4 hours, then washed with saturated aqueous sodium bicarbonate (25 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as yellow oil (4 g, 95%).

Step 6: (S)-Methyl 5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxylate

[00370] To 20 mL of anhydrous tetrahydrofuran were added methyl 2-(((3,4-diethoxyphenyl)(methylthio)methylene)amino)acetate (4 g, 12.85 mmol) and (S)-tert-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (4.91 g, 25.7 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (32.1 mL, 32.1 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. To the mixture was added water (30 mL) to quench the reaction and the resulting mixture was extracted with ethyl acetate (25 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (3.9 g, 70%).

Step 7: (S)-5-(1-((tert-Butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxylic acid

[00371] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added

(*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxylate (1.8 g, 4.14 mmol) and lithium hydroxide monohydrate (0.87 g, 20.71 mmol). The solution was stirred at 40 °C for 3 hours, then hydrochloric acid (1 M) was added to adjust the pH of the solution to 1. The mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a yellow solid (1.67 g, 96%).

Step 8: (*S*)-*tert*-Butyl (1-(4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)-2-(3,4-diethoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00372] To 6 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxylic acid (0.35 g, 0.83 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (239 mg, 1.25 mmol) and 1-hydroxy-7-azabenzotriazole (170 mg, 1.25 mmol). To the solution were added dropwise a solution of (3,5-dichloropyridin-4-yl)methylamine (177 mg, 1.0 mmol) in dichloromethane (9 mL) and *N,N*-diisopropylethylamine (0.44 mL, 2.5 mmol) in turn at 0 °C, the resulting mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (20 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed, and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (270 mg, 56%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.55 (s, 2H), 7.57 (dd, *J*₁ = 8.3 Hz, *J*₂ = 1.8 Hz, 2H), 7.48 (d, *J* = 1.8 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.30 – 5.26 (m, 1H), 4.95 (d, *J* = 5.6 Hz, 2H), 4.21 – 4.13 (m, 4H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.51 (td, *J*₁ = 7.0 Hz, *J*₂ = 2.4 Hz, 6H), 1.44 (s, 9H).

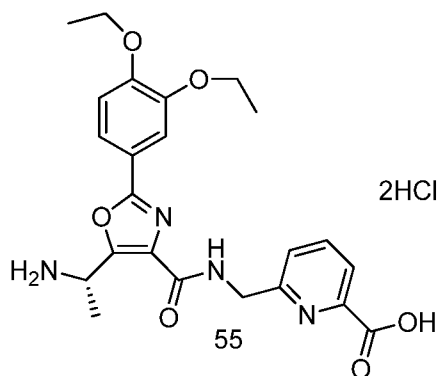
Step 9: (*S*)-5-(1-Aminoethyl)-*N*-((3,5-dichloropyridin-4-yl)methyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxamide dihydrochloride

[00373] To a solution of (*S*)-*tert*-butyl (1-(4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)-2-(3,4-diethoxyphenyl)oxazol-5-yl)ethyl)carbamate (0.27 g, 0.47 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 10 mL). The resulting mixture was stirred at rt for 20 minutes and filtered. The filter cake was washed with ethyl acetate (20 mL × 3) to give the title compound as a yellow solid (230 mg, 89%).

Compound 54: ¹H NMR (400 MHz, CD₃OD): δ ppm 8.65 (s, 2H), 7.68 (dd, *J*₁ = 8.4 Hz, *J*₂

= 2.0 Hz, 2H), 7.63 (d, $J = 2.0$ Hz, 1H), 7.09 (d, $J = 8.5$ Hz, 1H), 5.18 – 5.13 (m, 1H), 4.93 (s, 2H), 4.19 – 4.13 (m, 4H), 1.75 (d, $J = 7.0$ Hz, 3H), 1.46 (td, $J_1 = 7.0$ Hz, $J_2 = 1.3$ Hz, 6H); and MS-ESI: m/z 480.1 $[M+H-2HCl]^+$.

Example 25: (S)-6-((5-(1-Aminoethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride



Step 1: (S)-Ethyl 6-((5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxamido)methyl)picolinate

[00374] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxylic acid (0.35 g, 0.83 mmol), 6-(aminomethyl)-2-pyridinecarboxylic acid ethyl ester (180 mg, 1.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (239 mg, 1.25 mmol) and 1-hydroxy-7-azabenzotriazole (170 mg, 1.25 mmol). To the resulting solution were added *N,N*-diisopropylethylamine (0.44 mL, 2.5 mmol), and the mixture was stirred at rt for 7 hours. The reaction mixture was washed with water (20 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (270 mg, 56%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.21 (br.s, 1H), 8.08 (d, $J = 7.6$ Hz, 1H), 7.88 (t, $J = 7.7$ Hz, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.58 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H), 7.55 (d, $J = 1.7$ Hz, 1H), 6.93 (d, $J = 8.4$ Hz, 1H), 5.32 – 5.30 (m, 1H), 4.90 – 4.89 (m, 2H), 4.54 – 4.49 (m, 2H), 4.25 – 4.13 (m, 4H), 1.55 – 1.47 (m, 12H), 1.45 (s, 9H); and MS-ESI: m/z 583.4 $[M+H]^+$.

Step 2: (S)-6-((5-(1-((tert-Butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid

[00375] To a mixed solvent of tetrahydrofuran (10 mL) and water (5 mL) were added (S)-ethyl

6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxamido)methyl)picolinate (0.27 g, 0.46 mmol) and lithium hydroxide monohydrate (0.097 g, 2.32 mmol). The solution was stirred at 40 °C for 2 hours, then hydrochloric acid (1 M) was added to adjust the pH of the solution to 1. The mixture was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as yellow oil (0.24 g, 93%).

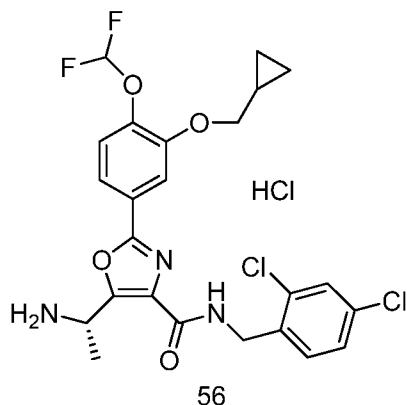
¹H NMR (400 MHz, CD₃OD): δ ppm 8.12 (d, *J* = 7.4 Hz, 1H), 8.05 (t, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.66 – 7.63 (m, 2H), 7.07 (d, *J* = 8.3 Hz, 1H), 5.45 – 5.43 (m, 1H), 4.80 (s, 2H), 4.19 – 4.13 (m, 4H), 1.54 (d, *J* = 4.5 Hz, 3H), 1.48 – 1.43 (m, 6H), 1.42 (s, 9H); and MS-ESI: *m/z* 555.2 [M+H]⁺.

Step 3: (S)-6-((5-(1-Aminoethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride

[00376] To a solution of (S)-6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid (0.24 g, 0.43 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 9 mL). The resulting mixture was stirred at rt for 15 minutes and filtered. The filter cake was washed with ethyl acetate (20 mL × 3) to give the title compound as a yellow solid (190 mg, 83%).

Compound 55: ¹H NMR (400 MHz, CD₃OD): δ ppm 8.52 (t, *J* = 7.9 Hz, 1H), 8.40 (d, *J* = 7.5 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.72 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.68 (d, *J* = 1.9 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 5.20 – 5.18 (m, 1H), 5.01 (s, 2H), 4.20 – 4.15 (m, 4H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.47 (td, *J*₁ = 6.9 Hz, *J*₂ = 1.1 Hz, 6H); and MS-ESI: *m/z* 455.3 [M+H-2HCl]⁺.

Example 26: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-dichlorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-

dichlorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00377] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.35 g, 0.75 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (214 mg, 1.12 mmol) and 1-hydroxy-7-azabenzotriazole (153 mg, 1.12 mmol). To the resulting solution were added (2,4-difluorophenyl)methanamine (0.12 mL, 0.90 mmol) and *N,N*-diisopropylethylamine (0.4 mL, 2.24 mmol), and the mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as colourless oil (350 mg, 75%).

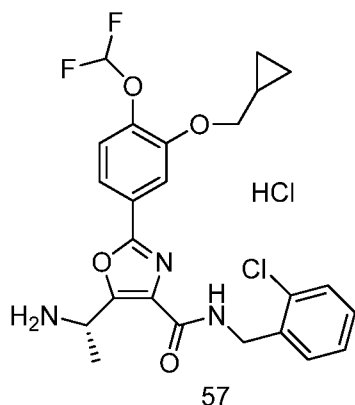
^1H NMR (400 MHz, CDCl_3): δ ppm 7.60 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.56 (d, $J = 1.9$ Hz, 1H), 7.45 (d, $J = 2.1$ Hz, 1H), 7.42 (d, $J = 8.3$ Hz, 1H), 7.27 – 7.25 (m, 1H), 6.72 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.32 – 5.28 (m, 1H), 4.73 – 4.71 (m, 2H), 3.99 (d, $J = 7.0$ Hz, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 1.38 – 1.35 (m, 1H), 0.73 – 0.69 (m, 2H), 0.44 – 0.40 (m, 2H).

Step 2: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-dichlorobenzyl)oxazole-4-carboxamide hydrochloride

[00378] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-dichlorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.35 g, 0.56 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 10 mL). The resulting mixture was stirred at rt for 20 minutes. The solvent was removed to give the title compound as a white solid (250 mg, 79%).

Compound 56: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.81 (d, $J = 1.6$ Hz, 1H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.7$ Hz, 1H), 7.47 (d, $J = 1.9$ Hz, 1H), 7.44 (d, $J = 8.4$ Hz, 1H), 7.34 – 7.31 (m, 2H), 6.93 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.21 – 5.19 (m, 1H), 4.68 (s, 2H), 4.03 (d, $J = 6.9$ Hz, 2H), 1.80 (d, $J = 7.0$ Hz, 3H), 1.64 (dd, $J_1 = 7.2$ Hz, $J_2 = 2.8$ Hz, 6H), 1.37 – 1.33 (m, 1H), 0.68 – 0.65 (m, 2H), 0.44 – 0.40 (m, 2H); and MS-ESI: m/z 527.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 27: (*S*)-5-(1-Aminoethyl)-*N*-(2-chlorobenzyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(4-((2-chlorobenzyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00379] To 10 mL of dichloromethane were added (S)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.35 g, 0.75 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (214 mg, 1.12 mmol) and 1-hydroxy-7-azabenzotriazole (153 mg, 1.12 mmol). To the resulting solution were added (2-chlorophenyl)methanamine (0.11 mL, 0.90 mmol) and *N,N*-diisopropylethylamine (0.4 mL, 2.24 mmol) at 0 °C. The resulting mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as colourless oil (310 mg, 70%).

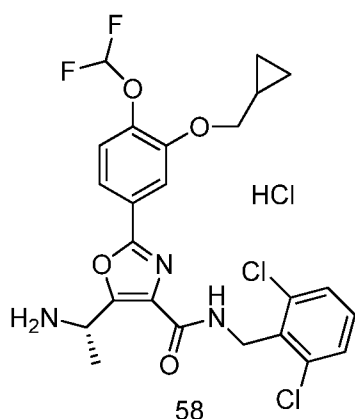
^1H NMR (400 MHz, CDCl_3): δ ppm 7.60 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.56 (d, $J = 1.9$ Hz, 1H), 7.49 – 7.47 (m, 1H), 7.44 – 7.42 (m, 1H), 7.30 – 7.28 (m, 1H), 7.25 (d, $J = 8.3$ Hz, 1H), 6.72 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.32 – 5.28 (m, 1H), 4.78 – 4.76 (m, 2H), 3.99 (d, $J = 7.0$ Hz, 2H), 1.56 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 1.39 – 1.34 (m, 1H), 0.73 – 0.68 (m, 2H), 0.44 – 0.40 (m, 2H).

Step 2: (S)-5-(1-Aminoethyl)-N-(2-chlorobenzyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00380] To a solution of (S)-tert-butyl (1-(4-((2-chlorobenzyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.31 g, 0.52 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 10 mL). The resulting mixture was stirred at rt for 20 minutes. The solvent was removed to give the title compound as a white solid (250 mg, 90%).

Compound 57: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.81 (d, $J = 1.9$ Hz, 1H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.46 – 7.42 (m, 2H), 7.33 – 7.29 (m, 3H), 6.92 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.22 – 5.17 (m, 1H), 4.72 (s, 2H), 4.03 (d, $J = 7.0$ Hz, 2H), 1.79 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.33 (m, 1H), 0.69 – 0.66 (m, 2H), 0.44 – 0.40 (m, 2H); and MS-ESI: m/z 492.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 28: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,6-dichlorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,6-dichlorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00381] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.35 g, 0.75 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (214 mg, 1.12 mmol) and 1-hydroxy-7-azabenzotriazole (153 mg, 1.12 mmol). To the resulting solution were added (2,6-dichlorophenyl)methanamine (0.12 mL, 0.90 mmol) and *N,N*-diisopropylethylamine (0.4 mL, 2.24 mmol) at 0 °C, then the mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as a white solid (337 mg, 72%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.61 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.56 (d, $J = 1.9$ Hz, 1H), 7.45 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.5$ Hz, 1H), 7.40 (dd, $J_1 = 7.7$ Hz, $J_2 = 1.5$ Hz, 1H), 7.27 – 7.22 (m, 2H), 6.73 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.32 – 5.30 (m, 1H), 4.79 – 4.77 (m, 2H), 3.99 (d, $J = 7.0$ Hz, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H), 1.37 – 1.34 (m, 1H), 0.73 – 0.68 (m, 2H), 0.44 – 0.40 (m, 2H).

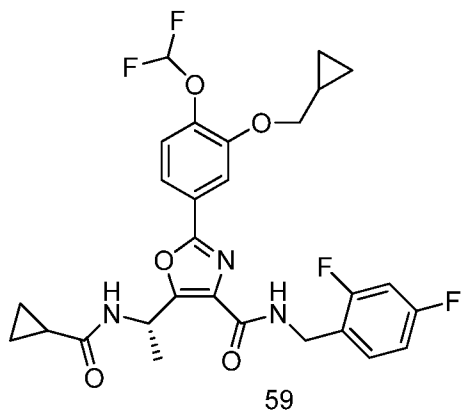
Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)

-N-(2,6-dichlorobenzyl)oxazole-4-carboxamide hydrochloride

[00382] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,6-dichlorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.33 g, 0.53 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 10 mL). The resulting mixture was stirred at rt for 20 minutes. The solvent was removed to give the title compound as a white solid (290 mg, 97%).

Compound 58: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.81 (d, $J = 1.9$ Hz, 1H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.50 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.5$ Hz, 1H), 7.41 – 7.39 (m, 1H), 7.34 – 7.29 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.21 – 5.16 (m, 1H), 4.75 (s, 2H), 4.04 (d, $J = 6.9$ Hz, 2H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.34 (m, 1H), 0.71 – 0.66 (m, 2H), 0.45 – 0.41 (m, 2H); and MS-ESI: m/z 527.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 29: (*S*)-5-(1-(Cyclopropanecarboxamido)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide



Step 1: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00383] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.5 g, 1.07 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (307.51 mg, 1.61 mmol) and 1-hydroxy-7-azabenzotriazole (219 mg, 1.61 mmol). To the resulting solution were added (2,4-difluorophenyl)methanamine (0.15 mL, 1.28 mmol) and *N,N*-diisopropylethylamine (0.56 mL, 3.21 mmol) at 0 °C, and the mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (20 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (389 mg,

61%).

Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00384] To a solution of ((S)-*tert*-butyl 1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.39 g, 0.66 mmol) in dichloromethane (3 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 12 mL). The resulting mixture was stirred at rt for 5 hours and filtered. The filter cake was washed with ethyl acetate (20 mL $\times$ 3) to give the title compound as a white solid (269 mg, 77%).

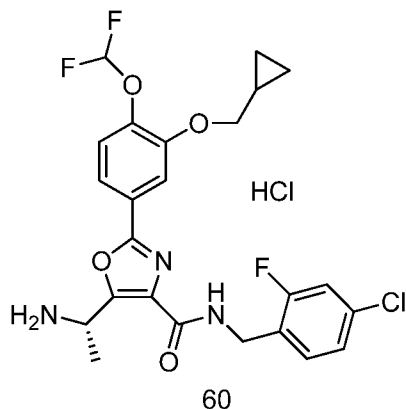
^1H NMR (400 MHz, CD_3OD): δ ppm 7.79 (d, $J = 1.9$ Hz, 1H), 7.72 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.51 – 7.45 (m, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.02 – 6.95 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.19 – 5.14 (m, 1H), 4.65 (s, 2H), 4.03 (d, $J = 7.0$ Hz, 2H), 1.77 (d, $J = 7.0$ Hz, 3H), 1.38 – 1.33 (m, 1H), 0.70 – 0.67 (m, 2H), 0.44 – 0.41 (m, 2H); and MS-ESI: m/z 494.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Step 3: (S)-5-(1-(cyclopropanecarboxamido)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide

[00385] To 10 mL of dichloromethane were added (S)-5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride (0.25 g, 0.47 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (135 mg, 0.71 mmol) and 1-hydroxy-7-azabenzotriazole (96 mg, 0.71 mmol). To the resulting solution were added cyclopropanecarboxylic acid (0.05 mL, 0.57 mmol) and *N,N*-diisopropylethylamine (0.33 mL, 1.89 mmol) at 0 °C, and the mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (20 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/2) to give the title compound as a white solid (220 mg, 83%).

Compound 59: ^1H NMR (400 MHz, CDCl_3): δ ppm 8.79 (d, $J = 9.1$ Hz, 1H), 7.65 (t, $J = 6.1$ Hz, 1H), 7.58 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.54 (d, $J = 1.8$ Hz, 1H), 7.45 – 7.39 (m, 1H), 7.25 (d, $J = 8.3$ Hz, 1H), 6.93 – 6.87 (m, 2H), 6.72 (t, $J_{\text{F-H}} = 64.4$ Hz, 1H), 5.64 – 5.60 (m, 1H), 4.68 (d, $J = 6.1$ Hz, 2H), 3.98 (d, $J = 7.0$ Hz, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.50 – 1.46 (m, 1H), 1.36 – 1.30 (m, 1H), 1.01 – 0.95 (m, 2H), 0.80 – 0.72 (m, 2H), 0.71 – 0.68 (m, 2H), 0.44 – 0.40 (m, 2H).

Example 30: (S)-5-(1-Aminoethyl)-N-(4-chloro-2-fluorobenzyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(4-((4-chloro-2-fluorobenzyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00386] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (184 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (131 mg, 0.96 mmol). To the resulting solution were added (4-chloro-2-fluorophenyl)methanamine (0.1 mL, 0.77 mmol) and *N,N*-diisopropylethylamine (0.34 mL, 1.92 mmol) at 0 °C, then the mixture was stirred at rt for 15 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as a white solid (286 mg, 73%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.59 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.56 (d, $J = 1.9$ Hz, 1H), 7.40 (t, $J = 8.2$ Hz, 1H), 7.25 (d, $J = 8.3$ Hz, 1H), 7.17 – 7.13 (m, 2H), 6.72 (t, $J_{F-H} = 75.0$ Hz, 1H), 5.32 (s, 1H), 4.69 – 4.66 (m, 2H), 3.99 (d, $J = 6.9$ Hz, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 1.37 – 1.34 (m, 1H), 0.73 – 0.68 (m, 2H), 0.44 – 0.41 (m, 2H).

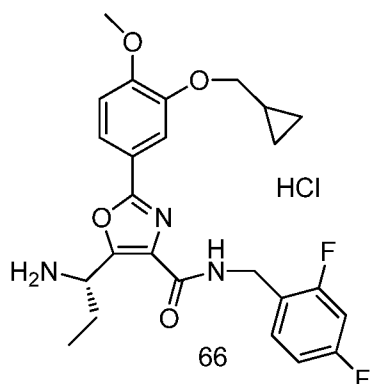
Step 2: (S)-5-(1-Aminoethyl)-N-(4-chloro-2-fluorobenzyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00387] To a solution of (S)-tert-butyl (1-(4-((4-chloro-2-fluorobenzyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.28 g, 0.46 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 10 mL). The resulting mixture was stirred at rt for 20 minutes and the solvent was removed to

give the title compound as a white solid (230 mg, 92%).

Compound 60: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.80 (d, $J = 1.9$ Hz, 1H), 7.73 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.45 (t, $J = 8.3$ Hz, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.24 – 7.20 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.18 – 5.15 (m, 1H), 4.65 (s, 2H), 4.03 (d, $J = 7.0$ Hz, 2H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.34 (m, 1H), 0.71 – 0.66 (m, 2H), 0.45 – 0.41 (m, 2H); and MS-ESI: m/z 510.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 31: (S)-5-(1-Aminopropyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-2-((tert-Butoxycarbonyl)amino)butanoic acid

[00388] To a solution of *L*-2-aminobutyric acid (2.0 g, 19.40 mmol) and di-*tert*-butyl dicarbonate (4.67 g, 21.4 mmol) in tetrahydrofuran (25 mL) was added dropwise aqueous sodium hydroxide (1 M, 23 mL) at 0 °C. The mixture was stirred at rt for 12 hours and hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The resulting mixture was extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give the title compound as a white solid (4.4 g, 99%).

^1H NMR (400 MHz, CDCl_3): δ ppm 10.52 (s, 1H), 4.32 - 4.08 (m, 1H), 1.95 - 1.89 (m, 1H), 1.78 - 1.69 (m, 1H), 1.45 (s, 9H), 1.00 - 0.96 (m, 3H).

Step 2: (S)-tert-Butyl (1-fluoro-1-oxobutan-2-yl)carbamate

[00389] To a solution of (S)-2-((tert-butoxycarbonyl)amino)butanoic acid (1.0 g, 4.93 mmol) and triethylamine (0.8 mL, 5.43 mmol) in dichloromethane (20 mL) was added dropwise slowly cyanuric fluoride (1.0 mL, 9.86 mmol) at -40 °C. The resulting mixture was stirred at -10 °C for 1 hour. The reaction mixture was washed with ice-water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate and the organic solvent was removed to give the title

compound as a white solid (0.89 g, 88%).

¹H NMR (400 MHz, *d*₆-DMSO): δ ppm 4.15 - 4.13 (m, 1H), 1.78 - 1.71 (m, 2H), 1.40 (s, 9H), 0.95 - 0.89 (m, 3H); and MS-ESI: *m/z* 206.2 [M+H]⁺.

Step 3: (*S*)-Methyl 5-(1-((*tert*-butoxycarbonyl)amino)propyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate

[00390] To 15 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-(cyclopropylmethoxy)-4-methoxyphenyl)(methylthio)methylene)amino)acetate (0.50 g, 1.55 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxobutan-2-yl)carbamate (0.89 g, 4.33 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (6.0 mL, 6.00 mmol) at -78 °C and the reaction mixture was stirred at -78 °C for 1 hour. The reaction mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a yellow solid (0.37 g, 53%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.65 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 5.31 - 5.25 (m, 1H), 4.00 (s, 3H), 3.95 (d, *J* = 7.0 Hz, 2H), 3.95 (s, 3H), 1.93 - 1.88 (m, 2H), 1.46 (s, 9H), 1.40 - 1.35 (m, 1H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.72 - 0.67 (m, 2H), 0.43 - 0.39 (m, 2H); and MS-ESI: *m/z* 461.3 [M+H]⁺.

Step 4: (*S*)-5-(1-((*tert*-Butoxycarbonyl)amino)propyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid

[00391] To a mixed solvent of tetrahydrofuran (30 mL) and water (15 mL) were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)propyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate (0.37 g, 0.81 mmol) and lithium hydroxide monohydrate (0.17 g, 0.45 mmol). The solution was stirred at 40 °C for 3 hours and concentrated to remove tetrahydrofuran. Then hydrochloric acid (1 M) was added to adjust the pH of the residue to 1. The mixture was extracted with ethyl acetate (30 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (0.34 g, 95%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.65 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.26 - 5.24 (m, 1H), 3.96 (s, 3H), 3.95 (d, *J* = 6.8 Hz, 2H), 1.96 - 1.91 (m, 2H), 1.45 (s,

9H), 1.41 - 1.36 (m, 1H), 0.99 (t, $J = 7.0$ Hz, 3H), 0.71 - 0.67 (m, 2H), 0.42 - 0.39 (m, 2H); and MS-ESI: m/z 447.1 $[M+H]^+$.

Step 5: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)propyl)carbamate

[00392] To 10 mL of dichloromethane were added (S)-5-(1-((*tert*-butoxycarbonyl)amino)propyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid (0.15 g, 0.34 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.10 g, 0.51 mmol) and 1-hydroxy-7-azabenzotriazole (0.07 g, 0.51 mmol). To the resulting solution were added (2,4-difluorophenyl)methanamine (0.05 mL, 0.41 mmol) and *N,N*-diisopropylethylamine (0.18 mL, 1.02 mmol) at 0 °C, and the mixture was stirred at rt for 12 hours. To the reaction mixture was added water (20 mL), and the resulting mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (0.15 g, 78%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.60 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.48 (d, $J = 2.0$ Hz, 1H), 7.46 - 7.40 (m, 1H), 6.95 (d, $J = 8.5$ Hz, 1H), 6.92 - 6.84 (m, 2H), 5.13 - 5.05 (m, 1H), 4.67 (t, $J = 5.8$ Hz, 2H), 3.96 (d, $J = 7.0$ Hz, 2H), 3.96 (s, 3H), 1.94 - 1.86 (m, 2H), 1.46 (s, 9H), 1.39 - 1.36 (m, 1H), 0.96 (t, $J = 7.3$ Hz, 3H), 0.72 - 0.68 (m, 2H), 0.45 - 0.41 (m, 2H); and MS-ESI: m/z 572.2 $[M+H]^+$.

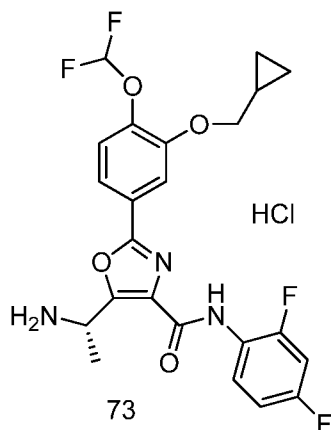
Step 6: (S)-5-(1-Aminopropyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00393] To a solution of (S)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)propyl)carbamate (0.15 g, 0.26 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for half an hour and concentrated to remove the solvent. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (117 mg, 93%).

Compound 66: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.72 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.64 (d, $J = 1.9$ Hz, 1H), 7.51 - 7.45 (m, 1H), 7.13 (d, $J = 8.5$ Hz, 1H), 7.01 - 6.94 (m, 2H), 5.04 - 5.01 (m, 1H), 4.64 (s, 2H), 3.94 (d, $J = 6.8$ Hz, 2H), 3.94 (s, 3H), 2.21 - 2.12 (m, 2H), 1.03 (t, $J =$

7.5 Hz, 3H), 0.93 - 0.86 (m, 1H), 0.68 - 0.64 (m, 2H), 0.41 - 0.37 (m, 2H); and MS-ESI: m/z 472.1 $[M+H-HCl]^+$.

Example 32: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorophenyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(fluorocarbonyl)oxazol-5-yl)ethyl)carbamate

[00394] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.48 g, 1.02 mmol) and triethylamine (0.16 mL, 1.1 mmol). To the solution was added cyanuric fluoride (0.18 mL, 2.05 mmol) at -40 °C, then the resulting mixture was stirred at -10 °C for 3 hours. The reaction mixture was washed with ice-water (20 mL $\times$ 4) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as yellow oil (0.46 g, 96%).

Step 2: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorophenyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00395] To 5 mL of tetrahydrofuran were added 2,4-difluoroaniline (0.16 mL, 1.53 mmol) and sodium hydride (61 mg, 1.53 mmol, 60%). The mixture was stirred at rt for 30 minutes. To the mixture was added a solution of (S)-tert-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(fluorocarbonyl)oxazol-5-yl)ethyl)carbamate (0.46 g, 0.98 mmol) in tetrahydrofuran (10 mL) at 0 °C, and the reaction mixture was stirred at rt for 23 hours. To the mixture was added saturated aqueous ammonium chloride (20 mL) and the resulting mixture was extracted with ethyl acetate (15 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by

silica gel column chromatography (PE/EtOAc (v/v) = 8/1) to give the title compound as a white solid (289 mg, 49 %).

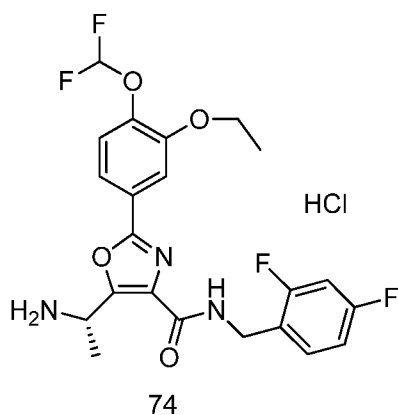
^1H NMR (400 MHz, CDCl_3): δ ppm 9.08 (s, 1H), 8.44 – 8.38 (m, 1H), 7.66 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.61 (d, $J = 1.9$ Hz, 1H), 7.29 (d, $J = 7.4$ Hz, 1H), 6.99 – 6.94 (m, 2H), 6.74 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.41 – 5.37 (m, 1H), 4.03 (d, $J = 6.9$ Hz, 2H), 1.59 (d, $J = 7.0$ Hz, 3H), 1.46 (s, 9H), 1.38 – 1.35 (m, 1H), 0.75 – 0.70 (m, 2H), 0.47 – 0.43 (m, 2H).

Step 3: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorophenyl)oxazole-4-carboxamide hydrochloride

[00396] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorophenyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.28 g, 0.48 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 12 mL). The resulting mixture was stirred at rt for 20 minutes and concentrated to give the title compound as a white solid (238 mg, 92%).

Compound 73: ^1H NMR (400 MHz, CDCl_3): δ ppm 7.82 (d, $J = 1.7$ Hz, 1H), 7.75 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.7$ Hz, 1H), 7.54 – 7.49 (m, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.34 – 7.26 (m, 1H), 7.16 – 7.11 (m, 2H), 6.91 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.26 – 5.23 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.34 – 1.31 (m, 1H), 0.68 – 0.66 (m, 2H), 0.42 – 0.41 (m, 2H); and MS-ESI: m/z 480.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 33: (*S*)-5-(1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 4-(difluoromethoxy)-3-ethoxybenzoate

[00397] To a sealed tube were added methyl 4-difluoromethoxy-3-hydroxybenzoate (5 g, 22.92 mmol), potassium carbonate (6.33 g, 45.84 mmol), bromoethane (2.58 mL, 34.38 mmol) and *N,N*'-dimethylformamide (30 mL). The whole mixture was stirred at 60 °C for 4 hours and filtered. The filtrate was concentrated to give the title product as brown oil (5.6 g, 96%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.60 – 7.58 (m, 2H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.65 (t, *J*_{F-H} = 74.8 Hz, 1H), 3.88 (s, 3H), 4.15 – 4.10 (m, 2H), 1.44 (t, *J* = 7.0 Hz, 3H).

Step 2: 4-(difluoromethoxy)-3-ethoxybenzoic acid

[00398] To a mixed solvent of ethanol (30 mL) and water (10 mL) were added methyl 4-(difluoromethoxy)-3-ethoxybenzoate (5.6 g, 22.92 mmol) and sodium hydroxide (2.73 g, 68.23 mmol). The mixture was stirred at 60 °C for 13 hours, then ethanol was removed and hydrochloric acid (1 M) was added to adjust the pH of the residue to 1. The mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated to give the title compound as a light yellow solid (4.75 g, 90%).

¹H NMR (400 MHz, CD₃OD): δ ppm 7.71 (d, *J* = 1.9 Hz, 1H), 7.65 (dd, *J*₁ = 8.3 Hz, *J*₂ = 1.9 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.87 (t, *J*_{F-H} = 74.7 Hz, 1H), 4.21 – 4.15 (m, 2H), 1.46 (t, *J* = 7.0 Hz, 3H).

Step 3: Methyl 2-(4-(difluoromethoxy)-3-ethoxybenzamido)acetate

[00399] To 35 mL of dichloromethane were added 4-(difluoromethoxy)-3-ethoxybenzoic acid (4.75 g, 20.46 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.86 g, 30.69 mmol) and 1-hydroxy-7-azabenzotriazole (4.17 g, 30.69 mmol). The mixture was stirred at rt for 30 minutes, then glycine methyl ester hydrochloride (3.08 g, 24.55 mmol) was added. The mixture was cooled to 0 °C, and *N,N*-diisopropylethylamine (11 mL, 61.38 mmol) was added dropwise. The resulting mixture was stirred at rt for 16 hours. The reaction mixture was washed with water (40 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as light yellow oil (6.2 g, 98%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.99 (s, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.31 (dd, *J*₁ = 8.3 Hz, *J*₂ = 2.0 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.62 (t, *J*_{F-H} = 74.9 Hz, 1H), 4.19 (d, *J* = 3.4 Hz, 2H), 4.14 – 4.08 (m, 2H), 1.43 (t, *J* = 7.0 Hz, 3H); and MS-ESI: *m/z* 304.0 [M+H]⁺.

Step 4: Methyl 2-(4-(difluoromethoxy)-3-ethoxyphenylthioamido)acetate

[00400] To 40 mL of tetrahydrofuran were added methyl 2-(4-(difluoromethoxy)-3-ethoxybenzamido)acetate (6 g, 19.8 mmol) and Lawesson's Reagent (8 g, 19.8 mmol). The mixture was stirred at 75 °C for 4 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (30 mL) and the resulting mixture was extracted

with ethyl acetate (20 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as yellow oil (6 g, 95%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.59 (d, J = 2.1 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.64 (t, $J_{\text{F-H}}$ = 74.9 Hz, 1H), 4.57 (d, J = 4.6 Hz, 2H), 4.21 – 4.16 (m, 2H), 3.87 (s, 3H), 1.48 (t, J = 7.0 Hz, 3H); and MS-ESI: m/z 320.2 $[\text{M}+\text{H}]^+$.

Step 5: Methyl 2-(((4-(difluoromethoxy)-3-ethoxyphenyl)(methylthio)methylene)amino)acetate

[00401] To a solution of trimethyloxonium tetrafluoroborate (5.84 g, 39.46 mmol) in dichloromethane (10 mL) was added dropwise a solution of methyl 2-(4-(difluoromethoxy)-3-ethoxyphenylthioamido)acetate (6.3 g, 19.73 mmol) in dichloromethane (30 mL) at -78°C . The mixture was stirred at 0°C for 5 hours, then washed with saturated aqueous sodium bicarbonate (25 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate and concentrated to give the title compound as yellow oil (6 g, 91%).

Step 6: (S)-Methyl 5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxylate

[00402] To 20 mL of anhydrous tetrahydrofuran were added methyl 2-(((4-(difluoromethoxy)-3-ethoxyphenyl)(methylthio)methylene)amino)acetate (6 g, 18 mmol) and (S)-tert-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (6.88 g, 36 mmol). To the stirred solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (45 mL, 45 mmol) at -78°C , and the reaction mixture was stirred at -78°C for 2 hours. To the mixture was added saturated aqueous sodium bicarbonate (35 mL) to quench the reaction and the resulting mixture was extracted with ethyl acetate (25 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as a light yellow solid (3.1 g, 38%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.66 (d, J = 1.9 Hz, 1H), 7.62 (dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 6.64 (t, $J_{\text{F-H}}$ = 74.9 Hz, 1H), 5.48 – 5.44 (m, 1H), 4.22 – 4.17 (m, 2H), 3.99 (s, 3H), 1.54 (d, J = 7.0 Hz, 3H), 1.48 (t, J = 7.0 Hz, 3H), 1.42 (s, 9H); and MS-ESI: m/z 457.3 $[\text{M}+\text{H}]^+$.

Step 7: (S)-5-(1-((tert-Butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-

ethoxyphenyl)oxazole-4-carboxylic acid

[00403] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxylate (3.17 g, 6.95 mmol) and lithium hydroxide monohydrate (1.46 g, 34.73 mmol). The solution was stirred at 40 °C for 2 hours and tetrahydrofuran was removed, then hydrochloric acid (1 M) was added to adjust the pH of the residue to 1. The mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a yellow solid (3 g, 90%).

¹H NMR (400 MHz, CD₃OD): δ ppm 7.82 (d, *J* = 1.9 Hz, 1H), 7.67 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.87 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.52 – 5.50 (m, 1H), 4.25 – 4.22 (m, 2H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.49 (t, *J* = 7.0 Hz, 3H), 1.45 (s, 9H).

Step 8: (*S*)-*tert*-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00404] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxylic acid (0.3 g, 0.68 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (194 mg, 1.02 mmol) and 1-hydroxy-7-azabenzotriazole (138 mg, 1.02 mmol). To the resulting solution were added (2,4-difluorophenyl)methanamine (0.1 mL, 0.81 mmol) and *N,N*-diisopropylethylamine (0.35 mL, 2.04 mmol), and the mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (20 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as colourless oil (264 mg, 69%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.60 – 7.57 (m, 1H), 7.58 (s, 1H), 7.56 – 7.52 (m, 1H), 7.45 – 7.41 (m, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 6.91 – 6.85 (m, 2H), 6.66 (t, *J*_{F-H} = 74.8 Hz, 1H), 5.34 – 5.31 (m, 1H), 4.68 – 4.66 (m, 2H), 4.25 – 4.19 (m, 2H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.52 (t, *J* = 7.0 Hz, 3H), 1.45 (s, 9H).

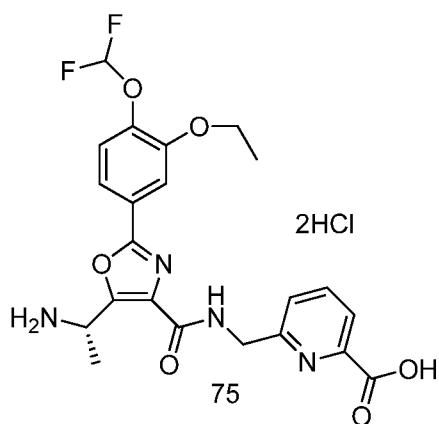
Step 9: (*S*)-5-(1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxamide hydrochloride

[00405] To a solution of (*S*)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-

(difluoromethoxy)-3-ethoxyphenyl)oxazol-5-yl)ethyl)carbamate (260 mg, 0.46 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 10 mL). The resulting mixture was stirred at rt for 20 minutes, then the solvent was removed to give the title compound as a white solid (218 mg, 94%).

Compound 74: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.81 (d, $J = 1.5$ Hz, 1H), 7.73 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.6$ Hz, 1H), 7.51 – 7.46 (m, 1H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.00 – 6.94 (m, 2H), 6.88 (t, $J_{\text{F-H}} = 74.6$ Hz, 1H), 5.20 – 5.15 (m, 1H), 4.65 (s, 2H), 4.27 – 4.22 (m, 2H), 1.78 (d, $J = 6.9$ Hz, 3H), 1.49 (t, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 468.0 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 34: (S)-6-((5-(1-Aminoethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride



Step 1: (S)-Ethyl 6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinate

[00406] To 15 mL of dichloromethane were added (S)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxylic acid (0.4 g, 0.90 mmol), ethyl 6-(2-aminoethyl)picolinate (196 mg, 1.085 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (259 mg, 1.36 mmol) and 1-hydroxy-7-azabenzotriazole (184 mg, 1.36 mmol). To the resulting solution were added *N,N*-diisopropylethylamine (0.47 mL, 2.71 mmol) at 0 °C, then the mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (15 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (279 mg, 51%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.12 (d, $J = 7.2$ Hz, 1H), 7.98 – 7.94 (m, 1H), 7.75 – 7.72 (m, 1H), 7.67 – 7.66 (m, 1H), 7.61 – 7.59 (m, 1H), 7.25 (d, $J = 8.3$ Hz, 1H), 6.67 (t, $J_{\text{F-H}} =$

74.9 Hz, 1H), 5.34 – 5.31 (m, 1H), 4.97 – 4.95 (m, 2H), 4.56 – 4.50 (m, 2H), 4.28 – 4.23 (m, 2H), 1.54 (t, $J = 6.5$ Hz, 6H), 1.47 (d, $J = 7.2$ Hz, 3H), 1.45 (s, 9H); and MS-ESI: m/z 605.3 $[M+H]^+$.

Step 2: (S)-6-((5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid

[00407] To a mixed solvent of tetrahydrofuran (10 mL) and water (5 mL) were added (S)-ethyl 6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinate (0.28 g, 0.46 mmol) and lithium hydroxide monohydrate (97 mg, 2.32 mmol). The mixture was stirred at 40 °C for 2 hours, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (10 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (0.26 g, 98%).

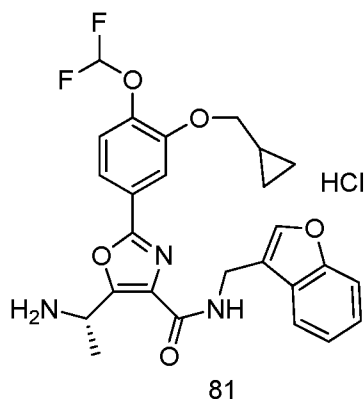
^1H NMR (400 MHz, CD_3OD): δ ppm 8.11 (d, $J = 7.6$ Hz, 1H), 8.05 – 8.02 (br, 1H), 7.74 – 7.72 (m, 2H), 7.66 (d, $J = 8.2$ Hz, 1H), 7.28 (d, $J = 8.2$ Hz, 1H), 6.86 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.47 – 5.44 (m, 1H), 4.80 (s, 2H), 4.25 – 4.20 (m, 2H), 1.53 (d, $J = 6.8$ Hz, 3H), 1.49 (t, $J = 7.1$ Hz, 3H), 1.42 (s, 9H); and MS-ESI: m/z 577.2 $[M+H]^+$.

Step 3: (S)-6-((5-(1-Aminoethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride

[00408] To a solution of (S)-6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid (260 mg, 0.45 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 10 mL). The resulting mixture was stirred at rt for 20 minutes and filtered. The filter cake was washed with ethyl acetate (20 mL $\times$ 3) to give the title compound as a white solid (210 mg, 85%).

Compound 75: ^1H NMR (400 MHz, CD_3OD): δ ppm 8.49 – 8.47 (m, 1H), 8.38 (d, $J = 7.5$ Hz, 1H), 8.08 (d, $J = 7.2$ Hz, 1H), 7.83 (d, $J = 1.7$ Hz, 1H), 7.75 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 6.90 (t, $J_{\text{F-H}} = 74.6$ Hz, 1H), 5.22 – 5.20 (m, 1H), 5.00 (s, 2H), 4.28 – 4.23 (m, 2H), 1.78 (d, $J = 6.9$ Hz, 3H), 1.50 (t, $J = 6.9$ Hz, 3H); and MS-ESI: m/z 477.1 $[M+H-2\text{HCl}]^+$.

Example 35: (S)-5-(1-Aminoethyl)-N-(benzofuran-3-ylmethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(4-((benzofuran-3-ylmethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00409] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), benzofuran-3-ylmethanamine hydrochloride (141 mg, 0.77 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (183 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (131 mg, 0.96 mmol). The mixture was stirred at 0 °C for 30 minutes and *N,N*-diisopropylethylamine (0.33 mL, 1.92 mmol) was added dropwise. The resulting mixture was stirred at rt for 22 hours, then washed with water (10 mL × 3). The organic layer was dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as a white solid (230 mg, 60%).

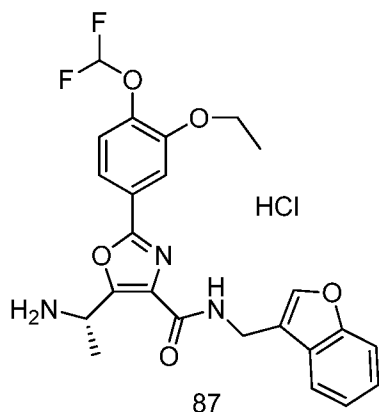
¹H NMR (400 MHz, CDCl₃): δ ppm 7.72 – 7.70 (m, 2H), 7.58 – 7.55 (m, 1H), 7.54 – 7.52 (m, 2H), 7.38 – 7.34 (m, 1H), 7.30 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.0 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.71 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.34 – 5.30 (m, 1H), 4.79 (d, *J* = 5.8 Hz, 2H), 3.96 (d, *J* = 7.0 Hz, 2H), 1.59 (d, *J* = 6.4 Hz, 3H), 1.47 (s, 9H), 1.35 – 1.32 (m, 1H), 0.71 – 0.66 (m, 2H), 0.42 – 0.38 (m, 2H).

Step 2: (*S*)-5-(1-Aminoethyl)-*N*-(benzofuran-3-ylmethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00410] To a solution of (*S*)-*tert*-butyl (1-(4-((benzofuran-3-ylmethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.23 g, 0.38 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 10 mL). The resulting mixture was stirred at rt for 20 minutes. The solvent was removed to give the title compound as a white solid (200 mg, 98%).

Compound 81: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.80 (s, 1H), 7.78 – 7.76 (m, 2H), 7.70 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.48 (d, $J = 8.2$ Hz, 1H), 7.34 – 7.30 (m, 2H), 7.27 – 7.23 (m, 1H), 6.90 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.22 – 5.17 (m, 1H), 4.75 (s, 2H), 4.01 (d, $J = 6.9$ Hz, 2H), 1.79 (d, $J = 7.0$ Hz, 3H), 1.34 – 1.30 (m, 1H), 0.69 – 0.66 (m, 2H), 0.42 – 0.40 (m, 2H); and MS-ESI: m/z 498.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 36: (S)-5-(1-Aminoethyl)-N-(benzofuran-3-ylmethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(4-(((benzofuran-3-ylmethyl)carbamoyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00411] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxylic acid (0.3 g, 0.68 mmol), benzofuran-3-ylmethanamine hydrochloride (150 mg, 0.81 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (194 mg, 1.02 mmol) and 1-hydroxy-7-azabenzotriazole (138 mg, 1.02 mmol). The mixture was stirred at 0 °C for 30 minutes and *N,N*-diisopropylethylamine (0.35 mL, 2.04 mmol) was added dropwise. The mixture was stirred at rt for 21 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as colourless oil (220 mg, 57%).

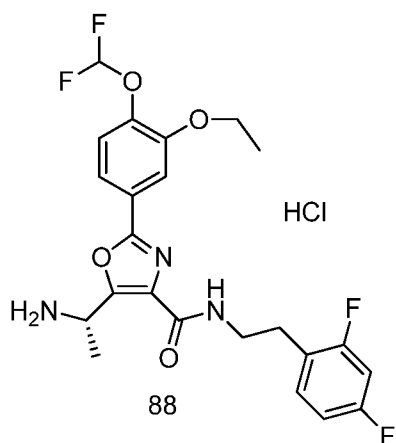
^1H NMR (400 MHz, CDCl_3): δ ppm 7.72 – 7.70 (m, 2H), 7.57 – 7.55 (m, 2H), 7.55 – 7.53 (m, 1H), 7.38 – 7.34 (m, 1H), 7.31 – 7.29 (m, 1H), 7.23 (d, $J = 8.8$ Hz, 1H), 6.65 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.36 – 5.32 (m, 1H), 4.80 (d, $J = 5.7$ Hz, 2H), 4.22 – 4.17 (m, 2H), 1.59 (d, $J = 7.0$ Hz, 3H), 1.48 (s, 9H), 1.28 (t, $J = 7.1$ Hz, 3H).

Step 2: (S)-5-(1-Aminoethyl)-N-(benzofuran-3-ylmethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxamide hydrochloride

[00412] To a solution of (*S*)-*tert*-butyl (1-(4-((benzofuran-3-ylmethyl)carbamoyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazol-5-yl)ethyl)carbamate (220 mg, 0.38 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 20 minutes. The solvent was removed to give the title compound as a light yellow solid (190 mg, 97%).

Compound 87: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.80 (s, 1H), 7.77 – 7.75 (m, 2H), 7.69 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.6$ Hz, 1H), 7.46 (d, $J = 8.1$ Hz, 1H), 7.31 – 7.28 (m, 2H), 7.24 (td, $J_1 = 7.5$ Hz, $J_2 = 0.9$ Hz, 1H), 6.87 (t, $J_{\text{F-H}} = 74.6$ Hz, 1H), 5.22 – 5.20 (m, 1H), 4.74 (s, 2H), 4.22 – 4.17 (m, 2H), 1.81 (d, $J = 6.9$ Hz, 3H), 1.46 (t, $J = 6.9$ Hz, 3H); and MS-ESI: m/z 472.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 37: (*S*)-5-(1-Aminoethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)-*N*-(2,4-difluorophenethyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(2-(4-(difluoromethoxy)-3-ethoxyphenyl)-4-((2,4-difluorophenethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00413] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)oxazole-4-carboxylic acid (0.3 g, 0.68 mmol), 2-(2,4-difluorophenyl)ethanamine (128 mg, 0.81 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (194 mg, 1.02 mmol) and 1-hydroxy-7-azabenzotriazole (138 mg, 1.02 mmol). The mixture was stirred at 0 °C for 30 minutes and *N,N*-diisopropylethylamine (0.35 mL, 2.04 mmol) was added dropwise. The resulting mixture was stirred at rt for 17 hours and washed with water (10 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the

title compound as yellow oil (230 mg, 58%).

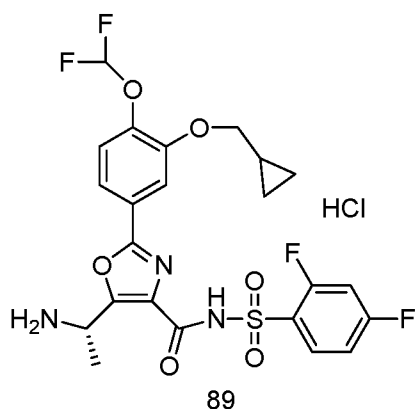
^1H NMR (400 MHz, CDCl_3): δ ppm 7.59 – 7.57 (m, 2H), 7.27 – 7.22 (m, 2H), 6.87 – 6.81 (m, 2H), 6.67 (t, $J_{\text{F-H}} = 70.0$ Hz, 1H), 5.29 – 5.25 (m, 1H), 4.25 – 4.20 (m, 2H), 3.71 – 3.67 (m, 2H), 2.99 (t, $J = 7.0$ Hz, 2H), 1.53 (t, $J = 7.5$ Hz, 6H), 1.46 (s, 9H); and MS-ESI: m/z 582.3 $[\text{M}+\text{H}]^+$.

Step 2: (S)-5-(1-Aminoethyl)-2-(4-(difluoromethoxy)-3-ethoxyphenyl)-N-(2,4-difluorophenethyl)oxazole-4-carboxamide hydrochloride

[00414] To a solution of (*S*)-*tert*-butyl (1-(2-(4-(difluoromethoxy)-3-ethoxyphenyl)-4-((2,4-difluorophenethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (230 mg, 0.40 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 20 minutes, then the solvent was removed to give the title compound as a white solid (180 mg, 88%).

Compound 88: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.79 (d, $J = 1.9$ Hz, 1H), 7.71 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.36 – 7.32 (m, 2H), 6.93 – 6.90 (m, 2H), 6.89 (t, $J_{\text{F-H}} = 74.6$ Hz, 1H), 5.12 – 5.11 (m, 1H), 4.27 – 4.22 (m, 2H), 3.66 (t, $J = 7.1$ Hz, 2H), 2.99 (t, $J = 7.1$ Hz, 2H), 1.75 (d, $J = 7.0$ Hz, 3H), 1.50 (t, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 482.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 38: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-((2,4-difluorophenyl)sulfonyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((2,4-difluorophenyl)sulfonyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00415] To 10 mL of anhydrous tetrahydrofuran were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol) and 1,1'-carbonyldiimidazole (312 mg, 1.92 mmol). The mixture was stirred at 60 °C for 30 minutes. The reaction mixture was cooled to rt, degassed and refilled with

nitrogen, then a solution of 2,4-difluorobenzenesulfonamide (247 mg, 1.28 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.14 mL, 0.96 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise. After addition, the mixture was stirred at 60 °C for 12 hours. To the reaction mixture was added saturated aqueous ammonium chloride (15 mL). The resulting mixture was extracted with ethyl acetate (15 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give the title compound as a yellow solid (0.4 g, 99%).

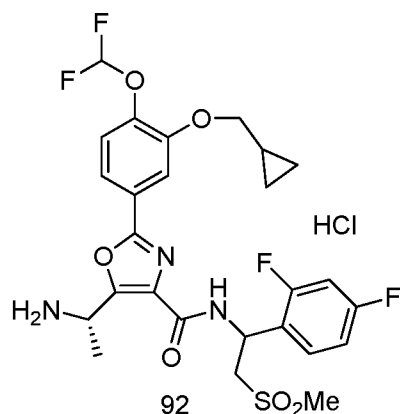
^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.26 – 8.22 (m, 1H), 7.59 – 7.54 (m, 2H), 7.27 – 7.26 (m, 1H), 7.14 – 7.10 (m, 1H), 7.02 – 6.97 (m, 1H), 6.75 (t, $J_{\text{F-H}} = 74.9$ Hz, 1H), 5.28 – 5.25 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 1.50 (d, $J = 7.1$ Hz, 3H), 1.39 (s, 9H), 1.34 – 1.33 (m, 1H), 0.74 – 0.72 (m, 2H), 0.49 – 0.45 (m, 2H).

Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-((2,4-difluorophenyl)sulfonyl)oxazole-4-carboxamide hydrochloride

[00416] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((2,4-difluorophenyl)sulfonyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.12 g, 0.19 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for 20 minutes and the solvent was removed to give the title compound as a light yellow solid (100 mg, 93%).

Compound 89: ^1H NMR (400 MHz, CD_3OD): δ (ppm) 8.22 – 8.18 (m, 1H), 7.85 (d, $J = 1.8$ Hz, 1H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.30 – 7.23 (m, 2H), 6.93 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.14 – 5.12 (m, 1H), 4.06 (d, $J = 7.0$ Hz, 2H), 1.70 (d, $J = 7.0$ Hz, 3H), 1.38 – 1.35 (m, 1H), 0.73 – 0.68 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: m/z 544.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 39: 5-((S)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(1-(2,4-difluorophenyl)-2-(methylsulfonyl)ethyl)oxazole-4-carboxamide hydrochloride



Step 1: 1-(2,4-Difluorophenyl)-2-(methylsulfonyl)ethanamine hydrochloride

[00417] To a solution of methyl sulfone (1.59 g, 16.9 mmol) in anhydrous tetrahydrofuran (30 mL) was added dropwise a solution of *n*-butyllithium in *n*-hexane (7 mL, 16.9 mmol, 2.4 M) at -78 °C, and the mixture was stirred at -78 °C for 30 minutes. To a solution of 2,4-difluorobenzaldehyde (2 g, 14.07 mmol) in tetrahydrofuran (15 mL) was added a solution of lithium bis(trimethylsilyl)azanide in tetrahydrofuran (16.9 mL, 16.9 mmol, 1M) at 0 °C, the mixture was stirred for 15 minutes and boron trifluoride etherate (3.82 mL, 31 mmol) was added dropwise at 0 °C. Then the resulting mixture was stirred for additional 10 minutes and added dropwise to the -78 °C solution of methyl sulfone and *n*-butyllithium in tetrahydrofuran said before. The mixture was stirred at rt for 24 hours, then the reaction was completed. The mixture was placed into an ice-bath, then 30 mL of water and potassium carbonate (3 g, 21.7 mmol) were added. The resulting mixture was extracted with ethyl acetate (20 mL × 3), and the organic layers were combined, dried over anhydrous sodium sulfate and concentrated. To the residue were added 6 mL of dichloromethane and a solution of hydrogen chloride in ethyl acetate (4 M, 12 mL), then the mixture was stirred at rt for 20 minutes and the solvent was removed. To the residue was added water (20 mL), and the mixture was washed with petroleum ether (15 mL). The aqueous layer was adjusted with aqueous sodium hydroxide (1 M) to pH to about 12. The resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give 0.9 g of brown oil. To the residue was added a solution of hydrogen chloride in ethyl acetate (4 M, 10 mL) and the mixture was stirred at rt for 20 minutes. The solvent was removed to give the title compound as brown oil (1 g, 27%).

¹H NMR (400 MHz, CD₃OD): δ (ppm) 7.71 – 7.65 (m, 1H), 7.22 – 7.14 (m, 2H), 5.23 –

5.19 (m, 1H), 4.00 – 3.89 (m, 2H), 3.09 (s, 3H); and MS-ESI: m/z 236.2 $[M+H-HCl]^+$.

Step 2: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(methylsulfonyl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00418] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.25 g, 0.53 mmol), 1-(2,4-difluorophenyl)-2-(methylsulfonyl)ethanamine hydrochloride (174 mg, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (109 mg, 0.80 mmol), and the mixture was stirred at 0 °C for 30 minutes. Then *N,N*-diisopropylethylamine (0.28 mL, 1.60 mmol) was added and the mixture was stirred at rt for 17 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as yellow oil (94 mg, 26%).

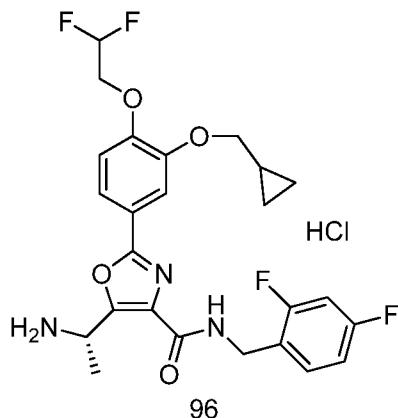
^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 – 7.61 (m, 1H), 7.60 – 7.58 (m, 2H), 7.54 – 7.51 (m, 1H), 7.26 (d, J = 8.3 Hz, 1H), 6.98 – 6.91 (m, 2H), 6.73 (t, J_{F-H} = 75.0 Hz, 1H), 5.95 – 5.91 (m, 1H), 5.37 – 5.31 (m, 1H), 4.01 – 3.99 (m, 2H), 3.86 – 3.81 (m, 1H), 3.63 – 3.56 (m, 1H), 2.87 – 2.84 (m, 3H), 1.56 – 1.50 (m, 3H), 1.45 (s, 9H), 1.36 – 1.33 (m, 1H), 0.73 – 0.70 (m, 2H), 0.46 – 0.43 (m, 2H).

Step 3: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(methylsulfonyl)ethyl)oxazole-4-carboxamide hydrochloride

[00419] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(methylsulfonyl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (94 mg, 0.14 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 30 minutes, then the solvent was removed to give a light yellow solid (77 mg, 91%).

Compound 92: ^1H NMR (400 MHz, CD_3OD): δ (ppm) 7.81 (d, J = 1.9 Hz, 1H), 7.74 (dd, J_1 = 8.4 Hz, J_2 = 1.9 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.07 – 7.02 (m, 2H), 6.92 (t, J_{F-H} = 74.7 Hz, 1H), 6.11 – 6.06 (m, 1H), 5.19 – 5.14 (m, 1H), 3.72 – 3.68 (m, 1H), 3.08 – 3.05 (m, 3H), 2.01 (s, 3H), 1.76 (d, J = 7.0 Hz, 3H), 1.40 – 1.34 (m, 1H), 0.72 – 0.67 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: m/z 586.3 $[M+H-HCl]^+$.

Example 40: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)

phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride**Step 1: Methyl 3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)benzoate**

[00420] To a sealed tube was added methyl 3-(cyclopropylmethoxy)-4-hydroxybenzoate (5 g, 22.5 mmol), 1-bromo-2,2-difluoroethane (4.89 g, 33.75 mmol), potassium carbonate (6.22 g, 45 mmol) and *N,N*-dimethylformamide (30 mL). The whole mixture was stirred at 60 °C for 7 hours and filtered. The filtrate was concentrated to give brown fluid (5.5 g, 85%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.62 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.9 Hz, 1H), 7.56 (d, *J* = 1.9 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.31 – 6.01 (m, 1H), 4.28 (td, *J*₁ = 13.1 Hz, *J*₂ = 4.2 Hz, 2H), 3.89 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 1.35 – 1.25 (m, 1H), 0.67 – 0.60 (m, 2H), 0.38 – 0.34 (m, 2H); and MS-ESI: *m/z* 287.2 [M+H]⁺.

Step 2: 3-(Cyclopropylmethoxy)-4-(2,2-difluoroethoxy)benzoic acid

[00421] To a mixed solvent of ethanol (30 mL) and water (15 mL) were added methyl 3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)benzoate (5.5 g, 19.21 mmol) and sodium hydroxide (2.31 g, 57.64 mmol). The mixture was stirred at 60 °C for 3 hours, then ethanol was removed. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The mixture was extracted with ethyl acetate (25 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated to give a white solid (5.2 g, 98%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.75 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.35 – 6.05 (m, 1H), 4.34 (td, *J*₁ = 13.0 Hz, *J*₂ = 4.2 Hz, 2H), 3.94 (d, *J* = 6.9 Hz, 2H), 1.36 – 1.30 (m, 1H), 0.71 – 0.66 (m, 2H), 0.42 – 0.37 (m, 2H); and MS-ESI: *m/z* 273.2 [M+H]⁺.

Step 3: Methyl 2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)benzamido)acetate

[00422] To 40 mL of dichloromethane were added

3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)benzoic acid (5.2 g, 19.1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.47 g, 28.65 mmol) and 1-hydroxy-7-azabenzotriazole (3.9 g, 28.65 mmol). The mixture was stirred at rt for 30 minutes, then glycine methyl ester hydrochloride (2.88 g, 22.92 mmol) was added. To the mixture was added dropwise *N,N*-diisopropylethylamine (10 mL, 57.30 mmol) at 0 °C, and the resulting mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (30 mL) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (6.19 g, 94%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.45 (d, *J* = 2.0 Hz, 1H), 7.33 (dd, *J*₁ = 8.3 Hz, *J*₂ = 2.1 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.67 – 6.63 (m, 1H), 6.33 – 6.03 (m, 1H), 4.30 (td, *J*₁ = 13.1 Hz, *J*₂ = 4.2 Hz, 2H), 4.24 (d, *J* = 5.1 Hz, 2H), 3.92 (d, *J* = 6.9 Hz, 2H), 3.82 (s, 3H), 1.34 – 1.29 (m, 1H), 0.69 – 0.64 (m, 2H), 0.39 – 0.35 (m, 2H); and MS-ESI: *m/z* 344.1 [M+H]⁺.

Step 4: Methyl 2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenylthioamido)acetate

[00423] To 35 mL of tetrahydrofuran were added methyl 2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)benzamido)acetate (6.2 g, 18.06 mmol) and Lawesson's Reagent (7.3 g, 18.06 mmol), the solution was stirred at 75 °C for 2 hours. To the reaction solution was added saturated aqueous sodium bicarbonate (30 mL) and the resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a yellow solid (6.49 g, 92%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.09 (br.s, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.32 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.2 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.32 – 6.02 (m, 1H), 4.58 (d, *J* = 4.5 Hz, 2H), 4.29 (td, *J*₁ = 13.1 Hz, *J*₂ = 4.2 Hz, 2H), 3.93 (d, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 1.34 – 1.29 (m, 1H), 0.69 – 0.64 (m, 2H), 0.40 – 0.37 (m, 2H); and MS-ESI: *m/z* 360.2 [M+H]⁺.

Step 5: Methyl 2-(((3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenyl)(methylthio)methylene)amino)acetate

[00424] To a solution of trimethyloxonium tetrafluoroborate (3.1 g, 20.87 mmol) in dichloromethane (10 mL) was added dropwise a solution of methyl 2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenylthioamido)acetate (3 g, 8.35 mmol) in

dichloromethane (20 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then washed with saturated aqueous sodium bicarbonate (25 mL) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give yellow oil (3 g, 98%).

Step 6: (S)-Methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenyl)oxazole-4-carboxylate

[00425] To 15 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenyl)(methylthio)methylene)amino)acetate (3.1 g, 8.3 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (4 g, 20.75 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (29.05 mL, 29.05 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. To the mixture was added saturated aqueous sodium chloride (30 mL) and the resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a yellow solid (1.91 g, 48%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.64 – 7.61 (m, 2H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.34 – 6.04 (m, 1H), 5.49 – 5.45 (m, 1H), 4.32 (td, *J*₁ = 13.1 Hz, *J*₂ = 4.2 Hz, 2H), 4.00 (s, 3H), 3.96 (d, *J* = 7.0 Hz, 2H), 1.57 (d, *J* = 2.8 Hz, 3H), 1.45 (s, 9H), 1.35 – 1.30 (m, 1H), 0.71 – 0.66 (m, 2H), 0.42 – 0.38 (m, 2H); and MS-ESI: *m/z* 497.2 [M+H]⁺.

Step 7: (S)-5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenyl)oxazole-4-carboxylic acid

[00426] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenyl)oxazole-4-carboxylate (1.91 g, 3.85 mmol) and lithium hydroxide monohydrate (0.81 g, 19.23 mmol). The solution was stirred at 40 °C for 2 hours, then hydrochloric acid (1 M) was added to adjust the pH to 1. The mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed to give a yellow solid (1.62 g, 87%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.71 (d, *J* = 2.0 Hz, 1H), 7.65 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.39 – 6.11 (m, 1H), 5.50 – 5.48 (m, 1H), 4.34 (td, *J*₁ = 13.7 Hz, *J*₂ = 3.9 Hz, 2H), 3.98 (d, *J* = 6.9 Hz, 2H), 1.53 (d, *J* = 7.1 Hz, 3H), 1.45 (s, 9H), 1.34 –

1.32 (m, 1H), 0.69 – 0.64 (m, 2H), 0.43 – 0.39 (m, 2H); and MS-ESI: m/z 481.6 [M-H]⁺.

Step 8: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00427] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.62 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (178 mg, 0.93 mmol) and 1-hydroxy-7-azabenzotriazole (127 mg, 0.93 mmol). The solution was stirred at 0 °C for 30 minutes, then (2,4-difluorophenyl)methanamine (0.09 mL, 0.75 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 30 minutes, then *N,N*-diisopropylethylamine (0.33 mL, 1.87 mmol) was added dropwise. The mixture was stirred at rt for 12 hours. The reaction mixture was washed with water (20 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a yellow solid (230 mg, 61%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.57 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.51 (d, $J = 1.9$ Hz, 1H), 7.46 – 7.40 (m, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 6.91 – 6.83 (m, 2H), 6.33 – 6.04 (m, 1H), 5.32 – 5.30 (m, 1H), 4.67 – 4.65 (m, 2H), 4.31 (td, $J_1 = 13.1$ Hz, $J_2 = 4.2$ Hz, 2H), 3.95 (d, $J = 7.0$ Hz, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 1.36 – 1.32 (m, 1H), 0.71 – 0.67 (m, 2H), 0.43 – 0.39 (m, 2H).

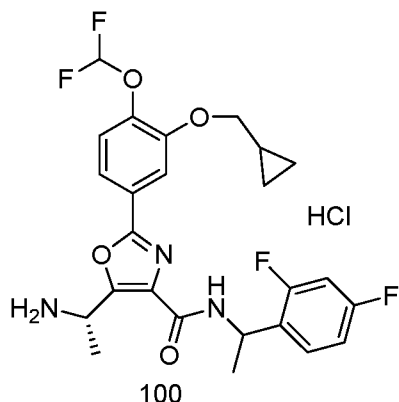
Step 9: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00428] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(2,2-difluoroethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (220 mg, 0.36 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 5 mL). The resulting mixture was stirred at rt for 15 minutes and filtered, and the filter cake was washed with ethyl acetate (15 mL × 3) to give a white solid (76 mg, 40%).

Compound 96: ¹H NMR (400 MHz, CD₃OD): δ (ppm) 7.66 – 7.64 (m, 2H), 7.45 – 7.39 (m, 1H), 7.12 (d, $J = 8.8$ Hz, 1H), 6.95 – 6.88 (m, 2H), 6.33 – 6.05 (m, 1H), 5.12 – 5.07 (m, 1H), 4.58 (s, 2H), 4.30 (td, $J_1 = 13.7$ Hz, $J_2 = 3.8$ Hz, 2H), 3.92 (d, $J = 6.9$ Hz, 2H), 1.71 (d, $J = 6.9$ Hz, 3H), 1.29 – 1.24 (m, 1H), 0.62 – 0.58 (m, 2H), 0.36 – 0.32 (m, 2H); and MS-ESI: m/z 508.1

$[M-HCl+H]^+$.

Example 41: 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)ethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00429] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), 1-(2,4-difluorophenyl)ethanamine (121 mg, 0.77 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (183.36 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (131 mg, 0.96 mmol). The mixture was stirred at 0 °C for 30 minutes and *N,N*-diisopropylethylamine (0.34 mL, 1.92 mmol) was added dropwise. The resulting mixture was stirred at rt for 14 hours. The reaction mixture was washed with water (10 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give colourless oil (270 mg, 69%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.63 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.57 (d, $J = 1.8$ Hz, 1H), 7.38 – 7.36 (m, 1H), 7.26 (d, $J = 8.4$ Hz, 1H), 6.92 – 6.83 (m, 2H), 6.73 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.45 – 5.42 (m, 1H), 4.60 – 4.54 (m, 1H), 4.01 (d, $J = 6.9$ Hz, 2H), 1.65 – 1.64 (m, 3H), 1.55 – 1.49 (m, 3H), 1.46 (s, 9H), 1.32 – 1.30 (m, 1H), 0.74 – 0.69 (m, 2H), 0.46 – 0.42 (m, 2H).

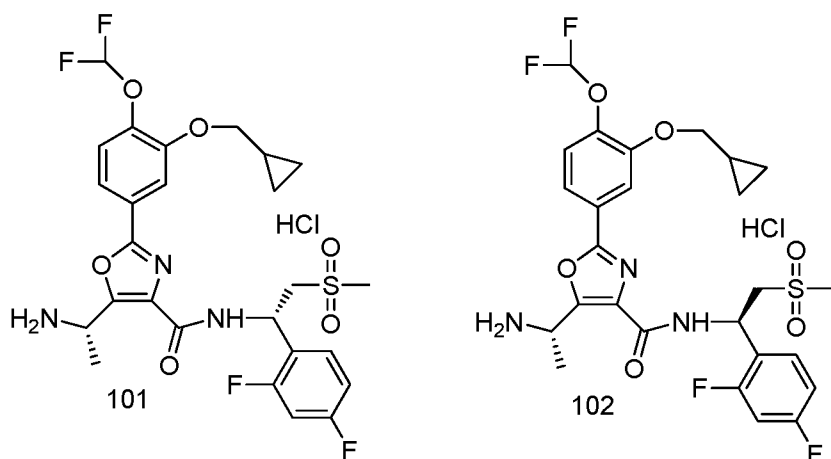
Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)ethyl)oxazole-4-carboxamide hydrochloride

[00430] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

carbamate (270 mg, 0.44 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 5 mL). The resulting mixture was stirred at rt for 2 hours and the solvent was removed to give a white solid (230 mg, 95%).

Compound 100: ^1H NMR (400 MHz, CD_3OD): δ (ppm) 7.83 (d, $J = 1.7$ Hz, 1H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.7$ Hz, 1H), 7.55 – 7.53 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 6.99 – 6.93 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.52 – 5.50 (m, 1H), 5.16 – 5.11 (m, 1H), 4.06 (d, $J = 6.9$ Hz, 2H), 1.76 (dd, $J_1 = 7.0$ Hz, $J_2 = 2.7$ Hz, 3H), 1.63 (d, $J = 7.0$ Hz, 3H), 1.36 – 1.32 (m, 1H), 0.71 – 0.67 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: m/z 508.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 42: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-(methylsulfonyl)ethyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-(methylsulfonyl)ethyl)oxazole-4-carboxamide hydrochloride



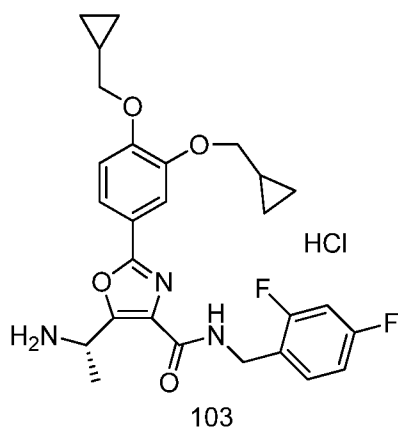
[00431] The compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(methylsulfonyl)ethyl)oxazole-4-carboxamide hydrochloride prepared from **Example 39** was further separated and purified to give compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-(methylsulfonyl)ethyl)oxazole-4-carboxamide hydrochloride as a light yellow solid and compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-(methylsulfonyl)ethyl)oxazole-4-carboxamide hydrochloride as a pink solid.

Compound 101: ^1H NMR (400 MHz, CD_3OD): δ (ppm) 7.81 (d, $J = 1.9$ Hz, 1H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.66 – 7.60 (m, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.08 – 7.02 (m, 2H),

6.92 (t, $J_{F-H} = 74.7$ Hz, 1H), 6.11 – 6.07 (m, 1H), 5.19 – 5.14 (m, 1H), 4.07 – 4.01 (m, 1H), 4.05 (d, $J = 6.9$ Hz, 2H), 3.73 – 3.68 (m, 1H), 3.06 (s, 3H), 1.75 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.33 (m, 1H), 0.72 – 0.68 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: m/z 586.2 $[M+H-HCl]^+$;

Compound 102: ^1H NMR (400 MHz, CD_3OD): δ (ppm) 7.81 (d, $J = 1.8$ Hz, 1H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.63 – 7.61 (m, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.08 – 7.02 (m, 2H), 6.92 (t, $J_{F-H} = 74.7$ Hz, 1H), 6.12 – 6.08 (m, 1H), 5.17 – 5.15 (m, 1H), 4.08 – 4.02 (m, 1H), 4.05 (d, $J = 6.9$ Hz, 2H), 3.72 – 3.68 (m, 1H), 3.07 (s, 3H), 1.76 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.33 (m, 1H), 0.72 – 0.68 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: m/z 586.3 $[M+H-HCl]^+$.

Example 43: (S)-5-(1-aminoethyl)-2-(3,4-bis(cyclopropylmethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 3,4-bis(cyclopropylmethoxy)benzoate

[00432] To a sealed tube were added methyl 3-(cyclopropylmethoxy)-4-hydroxybenzoate (5 g, 22.5 mmol), (bromomethyl)cyclopropane (4.56 g, 33.75 mmol), potassium carbonate (6.22 g, 45 mmol) and *N,N*-dimethylformamide (30 mL). The whole mixture was stirred at 60 °C for 4.5 hours and filtered. The filtrate was concentrated to give a white solid (5.47 g, 88%).

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.57 (d, $J = 2.0$ Hz, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 3.94 – 3.91 (m, 4H), 3.89 (s, 3H), 1.38 – 1.31 (m, 2H), 0.68 – 0.62 (m, 4H), 0.41 – 0.37 (m, 4H); and MS-ESI: m/z 277.1 $[M+H]^+$.

Step 2: 3,4-Bis(cyclopropylmethoxy)benzoic acid

[00433] To a mixed solvent of ethanol (40 mL) and water (20 mL) were added methyl 3,4-bis(cyclopropylmethoxy)benzoate (5.47 g, 19.8 mmol) and sodium hydroxide (2.38 g, 59.4 mmol). The mixture was stirred at 60 °C for 3 hours, then ethanol was removed. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The mixture was extracted with ethyl

acetate (25 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed to give a white solid (4.75 g, 91%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.63 (d, $J = 2.0$ Hz, 1H), 6.93 (d, $J = 8.5$ Hz, 1H), 3.98 – 3.94 (m, 4H), 1.38 – 1.33 (m, 2H), 0.70 – 0.64 (m, 4H), 0.43 – 0.38 (m, 4H); and MS-ESI: m/z 263.2 $[\text{M}+\text{H}]^+$.

Step 3: Methyl 2-(3,4-bis(cyclopropylmethoxy)benzamido)acetate

[00434] To 35 mL of dichloromethane was added 3,4-bis(cyclopropylmethoxy)benzoic acid (4.75 g, 18.1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.21 g, 27.2 mmol) and 1-hydroxy-7-azabenzotriazole (3.7 g, 27.2 mmol). The mixture was stirred at rt for 30 minutes, then glycine methyl ester hydrochloride (2.73 g, 21.7 mmol) was added. To the mixture was added *N,N*-diisopropylethylamine (13 mL, 72.4 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (20 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (5.56 g, 92%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.45 (d, $J = 2.1$ Hz, 1H), 7.35 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.1$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 6.59 (br.s, 1H), 4.25 (d, $J = 4.8$ Hz, 2H), 3.93 (d, $J = 6.9$ Hz, 4H), 3.82 (s, 3H), 1.38 – 1.31 (m, 2H), 0.68 – 0.62 (m, 4H), 0.41 – 0.36 (m, 4H); and MS-ESI: m/z 334.3 $[\text{M}+\text{H}]^+$.

Step 4: Methyl 2-(3,4-bis(cyclopropylmethoxy)phenylthioamido)acetate

[00435] To 35 mL of tetrahydrofuran were added methyl 2-(3,4-bis(cyclopropylmethoxy)benzamido)acetate (5.56 g, 16.7 mmol) and Lawesson's Reagent (6.75 g, 16.7 mmol), and the mixture was stirred at 75 °C for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (40 mL) and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a yellow solid (5.8 g, 99%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.06 (br.s, 1H), 7.56 (d, $J = 2.2$ Hz, 1H), 7.37 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 4.59 (d, $J = 4.5$ Hz, 2H), 3.95 – 3.92 (m, 4H), 3.87 (s, 3H), 1.38 – 1.31 (m, 2H), 0.68 – 0.63 (m, 4H), 0.41 – 0.37 (m, 4H); and MS-ESI:

m/z 350.2 $[M+H]^+$.

Step 5: Methyl 2-(((3,4-bis(cyclopropylmethoxy)phenyl)(methylthio)methylene)amino)acetate

[00436] To a solution of trimethyloxonium tetrafluoroborate (3.0 g, 20 mmol) in dichloromethane (10 mL) was added dropwise a solution of methyl 2-(3,4-bis(cyclopropylmethoxy)phenylthioamido)acetate (2.55 g, 7.30 mmol) in dichloromethane (20 mL) at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 3 hours, then washed with saturated aqueous sodium bicarbonate (45 mL) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give yellow oil (2.39 g, 90%).

Step 6: (S)-Methyl 2-(3,4-bis(cyclopropylmethoxy)phenyl)-5-(1-((tert-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylate

[00437] To 10 mL of anhydrous tetrahydrofuran were added methyl 2-(((3,4-bis(cyclopropylmethoxy)phenyl)(methylthio)methylene)amino)acetate (2.38 g, 6.55 mmol) and (S)-tert-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (3.6 g, 19 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (26 mL, 26 mmol) at $-78\text{ }^{\circ}\text{C}$, and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2.5 hours. To the mixture was added saturated aqueous sodium chloride (30 mL) to quench to reaction and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a yellow solid (1 g, 31%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.63 (dd, $J_1 = 8.4\text{ Hz}$, $J_2 = 2.0\text{ Hz}$, 1H), 7.59 (d, $J = 2.0\text{ Hz}$, 1H), 6.94 (d, $J = 8.4\text{ Hz}$, 1H), 5.47 – 5.40 (m 1H), 3.99 (s, 3H), 3.95 (t, $J = 6.6\text{ Hz}$, 4H), 1.55 (d, $J = 7.0\text{ Hz}$, 3H), 1.45 (s, 9H), 1.34 – 1.30 (m, 2H), 0.71 – 0.64 (m, 4H), 0.41 – 0.39 (m, 4H); and MS-ESI: m/z 487.2 $[M+H]^+$.

Step 7: (S)-2-(3,4-Bis(cyclopropylmethoxy)phenyl)-5-(1-((tert-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylic acid

[00438] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added (S)-methyl 2-(3,4-bis(cyclopropylmethoxy)phenyl)-5-(1-((tert-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylate (1 g, 2.1 mmol) and lithium hydroxide monohydrate (0.43 g, 10 mmol). The resulting mixture was stirred at $40\text{ }^{\circ}\text{C}$ for 2 hours and then a solution of hydrogen chloride in

ethyl acetate (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (20 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed to give a yellow solid (0.97 g, 81%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.59 – 7.55 (m, 2H), 6.99 (d, $J = 8.4$ Hz, 1H), 5.42 – 5.41 (m, 1H), 3.90 – 3.87 (m, 4H), 1.46 (d, $J = 7.1$ Hz, 3H), 1.39 (s, 9H), 1.29 – 1.26 (m, 2H), 0.60 – 0.56 (m, 4H), 0.34 – 0.33 (m, 4H); and MS-ESI: m/z 471.1 $[\text{M-H}]^-$.

Step 8: (*S*)-*tert*-Butyl (1-(2-(3,4-bis(cyclopropylmethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00439] To 13 mL of dichloromethane were added (*S*)-2-(3,4-bis(cyclopropylmethoxy)phenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylic acid (0.34 g, 0.73 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (183 mg, 0.95 mmol) and 1-hydroxy-7-azabenzotriazole (130 mg, 0.95 mmol). The mixture was stirred at 0 °C for 30 minutes, then (2,4-difluorophenyl)methanamine (0.1 mL, 0.76 mmol) and *N,N*-diisopropylethylamine (0.33 mL, 1.90 mmol) were added dropwise in turn. The resulting mixture was warmed to rt and stirred for 4 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give yellow oil (230 mg, 52%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.56 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.51 (d, $J = 1.9$ Hz, 1H), 7.44 – 7.40 (m, 1H), 6.94 (d, $J = 8.5$ Hz, 1H), 6.91 – 6.84 (m, 2H), 5.32 – 5.26 (m, 1H), 4.66 (t, $J = 5.2$ Hz, 2H), 3.95 (t, $J = 6.9$ Hz, 4H), 1.54 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 1.37 – 1.32 (m, 2H), 0.69 – 0.65 (m, 4H), 0.42 – 0.38 (m, 4H).

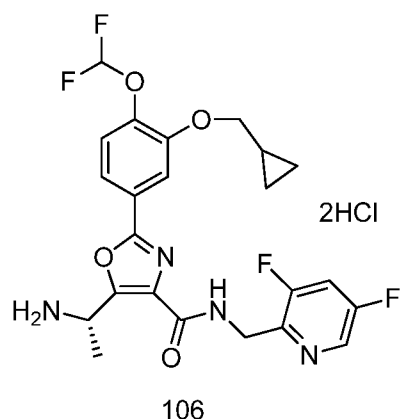
Step 9: (*S*)-5-(1-Aminoethyl)-2-(3,4-bis(cyclopropylmethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00440] To a solution of (*S*)-*tert*-butyl (1-(2-(3,4-bis(cyclopropylmethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.23 g, 0.38 mmol) in dichloromethane (1.5 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 40 minutes, then the solvent was removed to give a white solid (100 mg, 47%).

Compound 103: ^1H NMR (400 MHz, CD_3OD): δ (ppm) 7.69 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz,

1H), 7.66 (d, $J = 1.9$ Hz, 1H), 7.51 – 7.47 (m, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.01 – 6.94 (m, 2H), 5.15 – 5.13 (m, 1H), 4.64 (s, 2H), 3.97 – 3.95 (m, 4H), 1.76 (d, $J = 7.0$ Hz, 3H), 1.35 – 1.30 (m, 2H), 0.68 – 0.64 (m, 4H), 0.43 – 0.38 (m, 2H); and MS-ESI: m/z 498.3 $[M-HCl+H]^+$.

Example 44: (S)-5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-((3,5-difluoropyridin-2-yl)methyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((3,5-difluoropyridin-2-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00441] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), 3,5-difluoropyridin-2-methanamine hydrochloride (139 mg, 0.77 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (183 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (131 mg, 0.96 mmol). The mixture was stirred at 0 °C for 30 minutes, then *N,N*-diisopropylethylamine (0.45 mL, 2.56 mmol) was added dropwise. The mixture was stirred at rt for 14 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a white solid (120 mg, 32%).

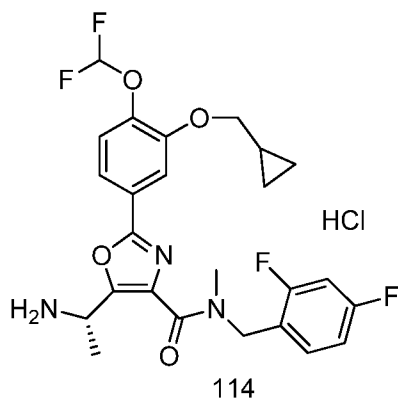
^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.38 (d, $J = 2.3$ Hz, 1H), 8.13 – 8.11 (m, 1H), 7.64 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.60 (d, $J = 1.9$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 6.73 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.32 – 5.30 (m, 1H), 4.86 – 4.83 (m, 2H), 4.01 (d, $J = 6.9$ Hz, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 1.36 – 1.33 (m, 1H), 0.74 – 0.69 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: m/z 595.1 $[M+H]^+$.

Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-

((3,5-difluoropyridin-2-yl)methyl)oxazole-4-carboxamide dihydrochloride

[00442] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((3,5-difluoropyridin-2-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (120 mg, 0.20 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 2 hours and then the solvent was removed to give a white solid (65 mg, 61%).

Compound 106: ^1H NMR (400 MHz, CD_3OD): δ (ppm) 8.34 (d, $J = 2.2$ Hz, 1H), 7.77 (d, $J = 1.5$ Hz, 1H), 7.70 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.5$ Hz, 1H), 7.63 – 7.58 (m, 1H), 7.30 (d, $J = 8.3$ Hz, 1H), 6.89 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.17 – 5.12 (m, 1H), 4.78 (s, 2H), 4.01 (d, $J = 6.9$ Hz, 2H), 1.75 (d, $J = 7.0$ Hz, 3H), 1.36 – 1.29 (m, 1H), 0.68 – 0.63 (m, 2H), 0.42 – 0.38 (m, 2H); and MS-ESI: m/z 495.1 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 45: (*S*)-5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)-*N*-methyloxazole-4-carboxamide hydrochloride**Step 1: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate**

[00443] To 20 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (1.17 g, 2.5 mmol), 2,4-difluorobenzylamine (0.536 g, 3.75 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.72 g, 3.75 mmol) and 1-hydroxy-7-azabenzotriazole (0.51 g, 3.75 mmol). The mixture was stirred at 0 °C for 30 minutes, then *N,N*-diisopropylethylamine (1.31 mL, 7.5 mmol) was added dropwise. The mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (20 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give yellow

oil (800 mg, 54%).

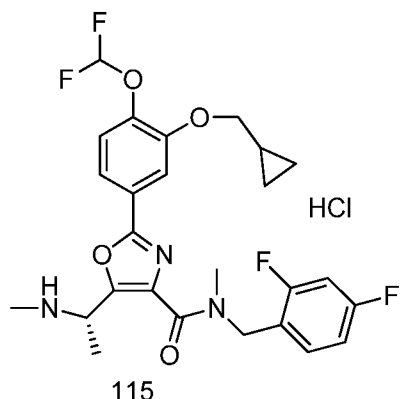
Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)-N-methyloxazole-4-carboxamide hydrochloride

[00444] To 10 mL of anhydrous tetrahydrofuran were added (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.3 g, 0.51 mmol) and sodium hydride (30 mg, 0.76 mmol, 60%). The mixture was stirred at 0 °C for 1 hours, then the mixture was warmed to rt and a solution of idomethane in tetrahydrofuran (10 mL, 0.76 mmol) was added dropwise. The reaction mixture was stirred at rt for 5 hours. To the mixture was added water (30 mL) and the resulting mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a light yellow solid (227 mg, 74%).

[00445] To a solution of the product obtained from the previous step (227 mg) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for 1.5 hours and terminated. The solvent was removed to give a white solid (200 mg, 99%) which was a mixture of two compounds. The product was further separated and purified to give the desired product (*S*)-5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)-N-methyloxazole-4-carboxamide hydrochloride as a light yellow solid (20 mg).

Compound 114: ¹H NMR (400 MHz, CD₃OD): δ (ppm) 7.70 – 7.67 (m, 1H), 7.58 – 7.46 (m, 2H), 7.31 – 7.26 (m, 1H), 7.07 – 6.98 (m, 2H), 7.02 – 6.67 (m, 1H), 5.22 – 5.21 (m, 1H), 4.56 – 4.54 (m, 2H), 3.99 (d, *J* = 6.7 Hz, 1H), 3.87 (d, *J* = 7.0 Hz, 1H), 3.45 (s, 3H), 1.75 (d, *J* = 6.9 Hz, 3H), 1.19 – 1.15 (m, 1H), 0.66 – 0.64 (m, 2H), 0.41 – 0.37 (m, 2H); and MS-ESI: *m/z* 508.3 [M+H-HCl]⁺.

Example 46: (S)-2-(3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)-N-methyl-5-(1-(methylamino)ethyl)oxazole-4-carboxamide hydrochloride

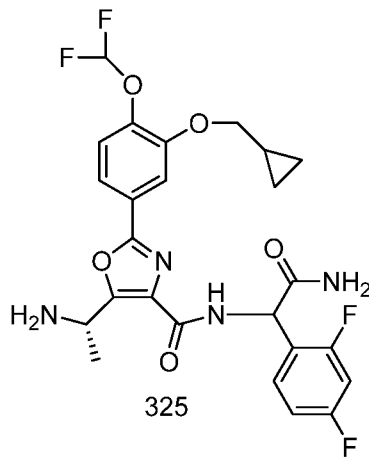
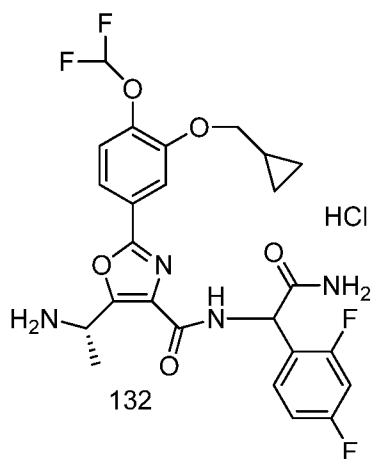


[00446] To 10 mL of anhydrous tetrahydrofuran were added (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.3 g, 0.51 mmol) and sodium hydride (30 mg, 0.76 mmol, 60%). The mixture was stirred at 0 °C for 1 hour, then the mixture was warmed to rt and a solution of idomethane in tetrahydrofuran (10 mL, 0.76 mmol) was added dropwise. The reaction mixture was stirred at rt for 5 hours. To the mixture was added water (30 mL) and the resulting mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a light yellow solid (227 mg, 74%).

[00447] To a solution of the light yellow solid obtained from the previous step (227 mg) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for 1.5 hours and terminated. The solvent was removed to give a white solid (200 mg, 99%) which was a mixture of two compounds. The product was further separated and purified to give the desired product (*S*)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)-*N*-methyl-5-(1-(methylamino)ethyl)oxazole-4-carboxamide hydrochloride as a light yellow solid (20 mg).

Compound 115: ¹H NMR (400 MHz, CD₃OD): δ (ppm) 7.74 – 7.71 (m, 1H), 7.63 – 7.49 (m, 2H), 7.34 – 7.29 (m, 1H), 7.10 – 7.01 (m, 2H), 7.08 – 6.70 (m, 1H), 5.25 – 5.24 (m, 1H), 5.07 – 4.97 (m, 2H), 4.03 (d, *J* = 6.9 Hz, 1H), 3.91 (d, *J* = 7.0 Hz, 1H), 3.48 (s, 3H), 2.76 (s, 3H), 1.79 (d, *J* = 7.0 Hz, 3H), 1.42 – 1.39 (m, 1H), 0.69 – 0.67 (m, 2H), 0.44 – 0.40 (m, 2H); and MS-ESI: *m/z* 522.2 [M+H-HCl]⁺.

Example 47: *N*-(2-Amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and *N*-(2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-

(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide**Step 1: 2-Amino-2-(2,4-difluorophenyl)acetamide**

[00448] To a mixture of 2,4-difluorobenzaldehyde (1 g, 7.04 mmol) and trimethylsilyl cyanide (0.91 g, 9.2 mmol) was added zinc iodide (0.22 g, 0.70 mmol). The resulting mixture was stirred at rt for 15 minutes, then added a solution of ammonia in methanol (7 M, 10 mL) under an ice-bath condition. The mixture was stirred at 40 °C for 4 hours under nitrogen protection, then the solvent was removed. To the residue was added ethyl acetate (20 mL), and the mixture was washed with water (10 mL × 3). The organic layer was dried over anhydrous sodium sulfate and concentrated. To the residue was added a solution of hydrogen chloride in ethyl acetate (4 M, 5 mL) and a solid was precipitated, then 15 mL of ethyl acetate was added. The mixture was filtered and the filter cake was washed with petroleum ether three times to give a white solid (0.78 g, 66%).

¹H NMR (600 MHz, CD₃OD): δ ppm 7.81 – 7.77 (m, 1H), 7.31 – 7.22 (m, 2H), 6.03 (s, 1H); and MS-ESI: *m/z* 169.1 [M+H]⁺.

[00449] To a mixture of water (0.1 g) and concentrated sulfuric acid (2 g) was added the white solid (0.25 g, 1.49 mmol) described above under an ice-bath condition. The resulting mixture was stirred at 55 °C for 4 hours, then placed into ice-bath, and ammonium hydroxide (15 mL), water (10 mL) were added dropwise in turn. To the mixture was added ethyl acetate (15 mL), and the resulting mixture was separated. The organic layer was washed with saturated aqueous sodium chloride (10 mL × 3), dried over anhydrous sodium sulfate and concentrated to give a yellow solid (190 mg, 72%).

¹H NMR (600 MHz, CD₃OD): δ ppm 7.39 – 7.35 (m, 1H), 7.02 (br.s, 1H), 6.92 – 6.89 (m, 1H), 6.88 – 6.84 (m, 1H), 5.75 (br.s, 1H), 4.73 (s, 1H); and MS-ESI: *m/z* 187.0 [M+H]⁺.

Step 2: *tert*-Butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00450] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.25 g, 0.53 mmol), 2-amino-2-(2,4-difluorophenyl)acetamide (180 mg, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (154 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (109 mg, 0.80 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.28 mL, 1.60 mmol) dropwise at 0 °C. The mixture was stirred at rt for 20 hours. The reaction mixture was washed with water (10 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (184 mg, 54%).

¹H NMR (600 MHz, CDCl₃): δ ppm 7.64 (dt, *J*₁ = 8.3 Hz, *J*₂ = 2.0 Hz, 1H), 7.61 (s, 1H), 7.54 – 7.49 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 6.96 – 6.92 (m, 2H), 6.74 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.94 – 5.93 (m, 1H), 5.60 (br.s, 1H), 5.34 – 5.30 (m, 1H), 4.03 (d, *J* = 7.0 Hz, 2H), 1.53 – 1.48 (m, 3H), 1.45 – 1.37 (m, 9H), 1.36 – 1.33 (m, 1H), 0.73 – 0.70 (m, 2H), 0.46 – 0.44 (m, 2H); and MS-ESI: *m/z* 637.1 [M+H]⁺.

Step 3: *N*-(2-Amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00451] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.18 g, 0.29 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 20 minutes and then the solvent was removed to give a white solid (160 mg, 97%).

Compound 132: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.79 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.61 – 7.58 (m, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.06 – 7.02 (m, 2H), 6.92 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.92 (s, 1H), 5.19 – 5.17 (m, 1H), 4.04 – 4.03 (m, 2H), 1.76 (d, *J* = 6.8 Hz, 3H), 1.36 – 1.32 (m, 1H), 0.69 – 0.68 (m, 2H), 0.44 – 0.43 (m, 2H); and MS-ESI: *m/z* 537.9 [M+H-HCl]⁺.

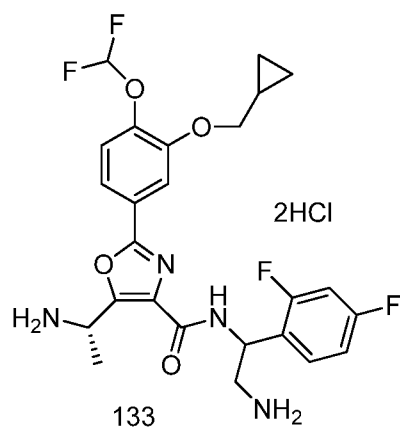
Step 4: *N*-(2-Amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide

[00452] To a solution of *N*-(2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)

-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride (85 mg, 0.15 mmol) in water (10 mL) was added sodium hydroxide (1.0 M) to adjust the pH of the solution to 9. The mixture was extracted with dichloromethane (10 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed to give a white solid (75 mg, 94%).

Compound 325: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.67 (s, 1H), 7.59 (d, $J = 8.3$ Hz, 1H), 7.46 (m, 1H), 7.21 (d, $J = 8.3$ Hz, 1H), 6.92 (m, 2H), 6.81 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.82 (s, 1H), 4.65 (m, 1H), 3.91 (m, 2H), 1.45 (d, $J = 6.9$ Hz, 3H), 1.23 (m, 1H), 0.54 – 0.63 (m, 2H), 0.28 – 0.37 (m, 2H); and MS-ESI: m/z 509.15 $[\text{M}+\text{H}]^+$.

Example 48: *N*-(2-Amino-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide dihydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(4-((cyano(2,4-difluorophenyl)methyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00453] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.4 g, 0.85 mmol), 2-amino-(2,4-difluorophenyl)acetonitrile (210 mg, 1.03 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (245 mg, 1.28 mmol) and 1-hydroxy-7-azabenzotriazole (174 mg, 1.28 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.6 mL, 3.42 mmol) dropwise at 0 °C. The mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give a white solid (218 mg, 41%).

^1H NMR (600 MHz, CDCl_3): δ ppm 7.69 – 7.66 (m, 1H), 7.60 – 7.57 (m, 2H), 7.26 (d, $J = 8.2$ Hz, 1H), 7.04 – 6.96 (m, 2H), 6.73 (t, $J_{\text{F-H}} = 74.9$ Hz, 1H), 6.40 (d, $J = 8.6$ Hz, 1H), 5.32 –

5.30 (m, 1H), 4.56 – 4.53 (m, 1H), 4.04 – 3.99 (m, 2H), 1.58 – 1.54 (m, 3H), 1.45 (s, 9H), 1.34 – 1.32 (m, 1H), 0.73 – 0.71 (m, 2H), 0.45 – 0.42 (m, 2H).

Step 2: *tert*-Butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00454] To a solution of *tert*-butyl ((1*S*)-1-(4-((cyano(2,4-difluorophenyl)methyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (215 mg, 0.35 mmol) and nickel chloride (45 mg, 0.35 mmol) in ethanol (15 mL) was added dropwise a solution of sodium borohydride (42 mg, 1.04 mmol) in ethanol (10 mL) under an ice-bath condition. The mixture was stirred at rt for 8 hours. Then hydrochloric acid (1 M, 10 mL) was added to adjust pH to about 1, and aqueous sodium hydroxide (2 M) was added to the resulting mixture to adjust pH to about 12. To the mixture were added ethyl acetate (15 mL). Then the mixture was allowed to keep standing. The upper layer was separated and concentrated to remove the organic solvent. The residue was extracted with ethyl acetate (15 mL × 3). The combined organic layers were dried and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give a light yellow solid (82 mg, 38%).

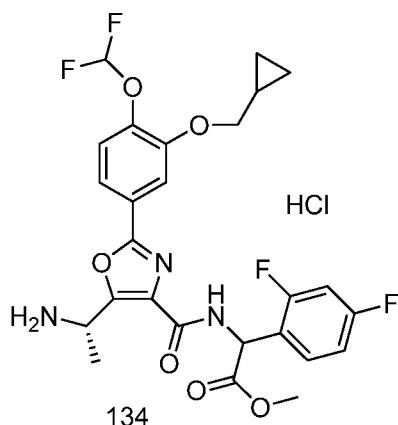
¹H NMR (600 MHz, CDCl₃): δ ppm 7.61 – 7.56 (m, 2H), 7.46 – 7.42 (m, 1H), 7.25 – 7.21 (m, 1H), 6.88 – 6.84 (m, 2H), 6.85 – 6.60 (m, 1H), 5.40 – 5.35 (m, 1H), 4.16 – 4.12 (m, 1H), 4.00 – 3.95 (m, 2H), 1.53 – 1.50 (m, 3H), 1.44 – 1.35 (m, 9H), 1.34 – 1.31 (m, 1H), 0.70 – 0.67 (m, 2H), 0.43 – 0.40 (m, 2H); and MS-ESI: *m/z* 623.2 [M+H]⁺.

Step 3: *N*-(2-Amino-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide dihydrochloride

[00455] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.08 g, 0.12 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 1 mL). The resulting mixture was stirred at rt for 20 minutes and then the solvent was removed to give a white solid (70 mg, 97%).

Compound 133: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.85 – 7.83 (m, 1H), 7.76 – 7.75 (m, 1H), 7.66 – 7.65 (m, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.11 – 7.05 (m, 2H), 6.93 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.81 – 5.78 (m, 1H), 5.23 – 5.16 (m, 1H), 4.07 (d, *J* = 6.8 Hz, 2H), 3.65 – 3.62 (m, 1H), 3.46 – 3.44 (m, 1H), 1.77 (t, *J* = 5.6 Hz, 3H), 1.42 – 1.37 (m, 1H), 0.70 – 0.69 (m, 2H), 0.45 – 0.44 (m, 2H).

Example 49: Methyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride



Step 1: Methyl 2-amino-2-(2,4-difluorophenyl)acetate hydrochloride

[00456] To a solution of 2-amino-2-(2,4-difluorophenyl)acetonitrile (0.35 g, 2.08 mmol) in methanol (20 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The mixture was stirred at rt for 7 hours and then refluxed for 24 hours. The solvent was removed to give a yellow solid (0.4 g, 95%).

^1H NMR (600 MHz, CD_3OD): δ ppm 7.60 – 7.56 (m, 1H), 7.21 – 7.13 (m, 2H), 3.85 (s, 3H); and MS-ESI: m/z 202.1 $[\text{M}+\text{H}]^+$.

Step 2: Methyl 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate

[00457] To 25 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.73 g, 1.56 mmol), methyl 2-amino-(2,4-difluorophenyl)acetate hydrochloride (410 mg, 1.73 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (430 mg, 2.24 mmol) and 1-hydroxy-7-azabenzotriazole (310 mg, 2.24 mmol). To the mixture was added *N,N*-diisopropylethylamine (1 mL, 5.98 mmol) dropwise at 0 °C. The mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give a white solid (290 mg, 29%).

^1H NMR (600 MHz, CDCl_3): δ ppm 8.15 (br.s, 1H), 7.64 – 7.62 (m, 1H), 7.59 (s, 1H), 7.51 – 7.46 (m, 1H), 7.26 (d, J = 8.3 Hz, 1H), 6.94 – 6.88 (m, 2H), 6.73 (t, $J_{\text{F-H}}$ = 75.0 Hz, 1H), 5.99 (t, J = 6.5 Hz, 1H), 5.32 – 5.29 (m, 1H), 4.03 – 4.01 (m, 2H), 3.82 (s, 3H), 1.54 – 1.49 (m, 3H),

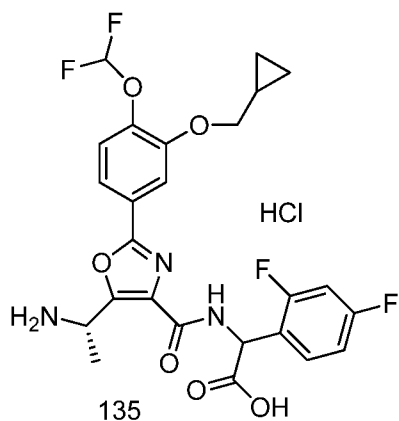
1.45 (s, 9H), 1.37 – 1.34 (m, 1H), 0.73 – 0.70 (m, 2H), 0.46 – 0.43 (m, 2H).

Step 3: Methyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride

[00458] To a solution of methyl 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate (0.1 g, 0.15 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 1.5 hours and then the solvent was removed to give a white solid (90 mg, 99%).

Compound 134: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.80 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.09 – 7.02 (m, 2H), 6.93 (t, *J*_{F-H} = 74.7 Hz, 1H), 6.05 (s, 1H), 5.20 – 5.17 (m, 1H), 4.04 (d, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 1.76 (d, *J* = 7.0 Hz, 3H), 1.38 – 1.34 (m, 1H), 0.71 – 0.68 (m, 2H), 0.45 – 0.43 (m, 2H); and MS-ESI: *m/z* 552.9 [M+H-HCl]⁺.

Example 50: 2-(5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid hydrochloride



Step 1: 2-(5-((*S*)-1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid

[00459] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added methyl 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate (190 mg, 0.29 mmol) and lithium hydroxide monohydrate (61 mg, 1.46 mmol). The solution was stirred at 40 °C for 2 hours, then hydrochloric acid (1 M) was added to adjust the pH of the solution to 1. The mixture was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, dried over

anhydrous sodium sulfate, and the solvent was removed to give a yellow solid (185 mg, 99%).

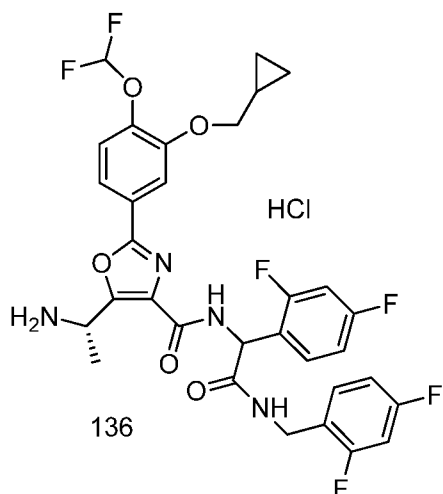
^1H NMR (600 MHz, CD_3OD): δ ppm 7.75 (s, 1H), 7.69 – 7.67 (m, 1H), 7.58 – 7.56 (m, 1H), 7.30 (d, $J = 8.3$ Hz, 1H), 7.05 – 7.00 (m, 2H), 6.90 (t, $J_{\text{F-H}} = 74.9$ Hz, 1H), 5.93 – 5.91 (m, 1H), 5.41 – 5.40 (m, 1H), 4.02 (d, $J = 6.9$ Hz, 2H), 1.50 (d, $J = 7.1$ Hz, 3H), 1.46 – 1.36 (m, 9H), 1.34 – 1.32 (m, 1H), 0.70 – 0.67 (m, 2H), 0.43 – 0.41 (m, 2H).

Step 2: 2-(5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid hydrochloride

[00460] To a solution of 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.185 g, 0.29 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 1.5 hours and then the solvent was removed to give a white solid (165 mg, 99%).

Compound 135: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.74 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.5$ Hz, 1H), 7.60 – 7.56 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.06 – 7.02 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.95 (d, $J = 2.2$ Hz, 1H), 5.20 – 5.15 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 1.76 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.33 (m, 1H), 0.70 – 0.67 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: m/z 538.9 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 51: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2-((2,4-difluorobenzyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2-((2,4-difluorobenzyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00461] To 10 mL of dichloromethane were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.24 g, 0.38 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (108 mg, 0.56 mmol) and 1-hydroxy-7-azabenzotriazole (77 mg, 0.56 mmol). To the mixture were added dropwise (2,4-difluorophenyl)methanamine (0.06 mL, 0.45 mmol) and *N,N*-diisopropylethylamine (0.2 mL, 1.13 mmol) in turn at 0 °C. The mixture was stirred at rt for 15 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a white solid (210 mg, 74%).

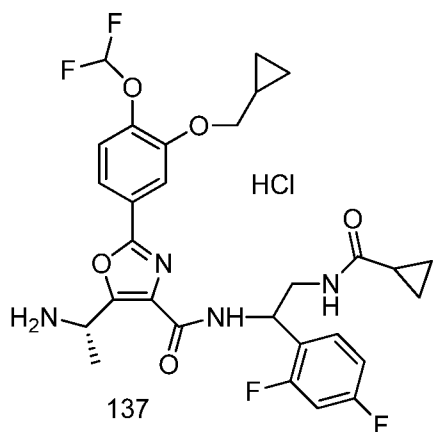
¹H NMR (600 MHz, CDCl₃): δ ppm 7.62 (d, *J* = 8.3 Hz, 1H), 7.60 (s, 1H), 7.50 – 7.48 (m, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.26 – 7.24 (m, 1H), 6.94 – 6.89 (m, 2H), 6.86 – 6.79 (m, 2H), 6.74 (t, *J*_{F-H} = 74.7 Hz, 1H), 6.40 – 6.36 (m, 1H), 5.89 (d, *J* = 6.8 Hz, 1H), 5.33 – 5.29 (m, 1H), 4.49 – 4.49 (m, 2H), 4.02 (d, *J* = 6.8 Hz, 2H), 1.52 – 1.47 (m, 3H), 1.44 – 1.38 (m, 9H), 1.36 – 1.30 (m, 1H), 0.73 – 0.70 (m, 2H), 0.46 – 0.45 (m, 2H).

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2-((2,4-difluorobenzyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)oxazole-4-carboxamide hydrochloride

[00462] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2-((2,4-difluorobenzyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.21 g, 0.27 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 20 minutes and then the solvent was removed to give a white solid (190 mg, 99%).

Compound 136: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.78 (d, *J* = 1.4 Hz, 1H), 7.72 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.8 Hz, 1H), 7.55 – 7.52 (m, 1H), 7.34 – 7.32 (m, 2H), 7.06 – 7.00 (m, 2H), 6.94 – 6.90 (m, 2H), 6.92 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.96 (s, 1H), 5.20 – 5.17 (m, 1H), 4.51 – 4.40 (m, 2H), 4.02 (d, *J* = 6.9 Hz, 2H), 1.76 (t, *J* = 6.9 Hz, 3H), 1.36 – 1.32 (m, 1H), 0.70 – 0.66 (m, 2H), 0.44 – 0.41 (m, 2H); and MS-ESI: *m/z* 663.9 [M+H-HCl]⁺.

Example 52: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopropanecarboxamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(4-((2-(cyclopropanecarboxamido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00463] To 10 mL of dichloromethane were added *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.16 g, 0.26 mmol), cyclopropanecarboxylic acid (0.03 mL, 0.31 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (74 mg, 0.39 mmol) and 1-hydroxy-7-azabenzotriazole (53 mg, 0.39 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.13 mL, 0.77 mmol) dropwise at 0 °C. The mixture was stirred at rt for 12 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (100 mg, 56%).

¹H NMR (600 MHz, CDCl₃): δ ppm 7.65 – 7.58 (m, 2H), 7.41 – 7.37 (m, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 6.92 – 6.86 (m, 2H), 6.73 (t, *J*_{F-H} = 75.0 Hz, 1H), 6.17 – 6.15 (m, 1H), 5.48 – 5.46 (m, 1H), 5.32 – 5.30 (m, 1H), 4.04 – 3.99 (m, 2H), 3.87 – 3.85 (m, 1H), 3.68 – 3.65 (m, 1H), 1.67 – 0.61 (m, 1H), 1.56 – 1.48 (m, 3H), 1.45 – 1.35 (m, 9H), 1.09 – 1.05 (m, 1H), 0.96 – 0.90 (m, 2H), 0.76 – 0.70 (m, 4H), 0.45 – 0.44 (m, 2H); and MS-ESI: *m/z* 691.2 [M+H]⁺.

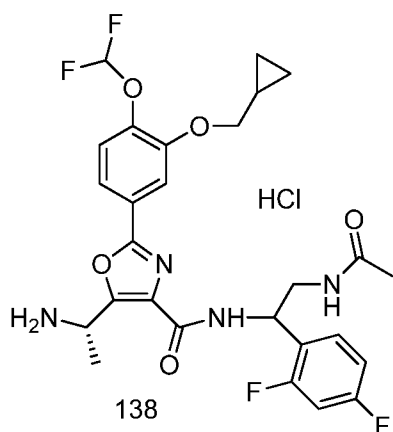
Step 2: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopropanecarboxamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00464] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-(cyclopropanecarboxamido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.10 g, 0.14 mmol) in dichloromethane (2 mL) was added a solution of

hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 40 minutes and then the solvent was removed to give a white solid (90 mg, 99%).

Compound 137: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.84 (s, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.48 – 7.46 (m, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.04 – 6.97 (m, 2H), 6.93 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.49 – 5.47 (m, 1H), 5.13 – 5.06 (m, 1H), 4.08 (d, $J = 6.9$ Hz, 2H), 3.79 – 3.63 (m, 2H), 1.74 – 1.72 (m, 3H), 1.60 – 1.55 (m, 1H), 1.38 – 1.36 (m, 1H), 0.92 – 0.88 (m, 2H), 0.77 – 0.69 (m, 4H), 0.48 – 0.44 (m, 2H); and MS-ESI: m/z 591.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 53: *N*-(2-Acetamido-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(4-((2-acetamido-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00465] To 10 mL of dichloromethane were added *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.20 g, 0.32 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (92 mg, 0.48 mmol) and 1-hydroxy-7-azabenzotriazole (66 mg, 0.48 mmol). To the mixture were added dropwise acetic acid (30 mg, 0.39 mmol) and *N,N*-diisopropylethylamine (0.17 mL, 0.96 mmol) in turn at 0 °C. The mixture was stirred at rt for 15 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give yellow oil (90 mg, 42%).

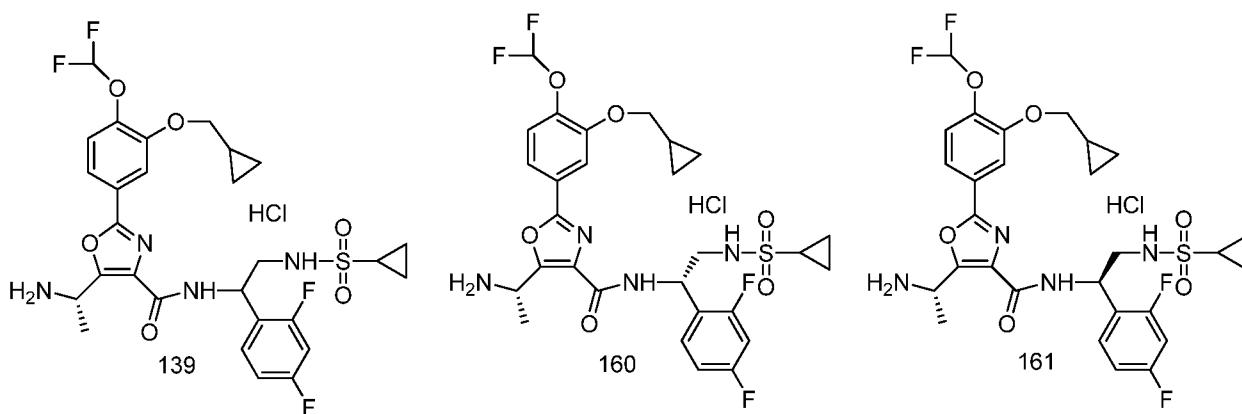
^1H NMR (600 MHz, CDCl_3): δ ppm 7.64 – 7.63 (m, 2H), 7.39-7.41 (m, 1H), 7.26 (d, $J = 8.7$ Hz, 1H), 6.93 – 6.87 (m, 2H), 6.73 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 6.13 – 6.10 (m, 1H), 5.49 – 5.48 (m, 1H), 5.32 – 5.28 (m, 1H), 4.02 (d, $J = 6.8$ Hz, 2H), 3.84 – 3.82 (m, 1H), 3.68 – 3.66 (m, 1H), 2.00 (s, 3H), 1.54 – 1.50 (m, 3H), 1.44 – 1.41 (m, 9H), 1.39 – 1.37 (m, 1H), 0.73 – 0.70 (m, 2H), 0.45 – 0.43 (m, 2H).

Step 2: *N*-(2-Acetamido-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00466] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-acetamido-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl) carbamate (0.09 g, 0.13 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 20 minutes and then the solvent was removed to give a light yellow solid (80 mg, 98%).

Compound 138: ¹H NMR (400 MHz, CD₃OD): δ ppm 7.85 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.48 (m, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.03 – 6.98 (m, 2H), 6.93 (t, *J*_{F-H} = 74.8 Hz, 1H), 5.53 – 5.50 (m, 1H), 5.15 – 5.10 (m, 1H), 4.08 (d, *J* = 6.9 Hz, 2H), 3.76 – 3.62 (m, 2H), 1.95 (s, 3H), 1.75 (d, *J* = 6.2 Hz, 3H), 1.42 – 1.37 (m, 1H), 0.72 – 0.67 (m, 2H), 0.47 – 0.43 (m, 2H); and MS-ESI: *m/z* 565.2 [M+H-HCl]⁺.

Example 54: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride, 5-((*S*)-1-aminoethyl)-*N*-((*S*)-2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-*N*-((*R*)-2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: 2-Amino-2-(2,4-difluorophenyl)acetonitrile hydrochloride

[00467] To a mixture of zinc iodide (0.68 g, 2.11 mmol) and a solution of ammonia in methanol (7 M, 30 mL) were added 2,4-difluorobenzaldehyde (3.0 g, 21.1 mmol) and trimethylsilylcyanide (2.8 g, 27.4 mmol) under nitrogen protection at 0 °C. The mixture was stirred at 40 °C for 4 hours, then the solvent was removed. The residue was extracted with ethyl

acetate (10 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed and a solution of hydrogen chloride in ethyl acetate (4 M, 5 mL) was added to the residue, then the solid was precipitated. The mixture was filtered and the filter cake was washed with ethyl acetate (5 mL $\times$ 3) to give a light yellow solid (2.9 g, 68%).

^1H NMR (400 MHz, CD_3OD): δ ppm 7.76 – 7.82 (m, 1H), 7.21 – 7.31 (m, 2H), 6.03 (s, 1H); and MS-ESI: m/z 169.15 $[\text{M}+\text{H}-\text{HCl}]^+$.

Step 2: *tert*-Butyl ((1*S*)-1-(4-((cyano(2,4-difluorophenyl)methyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00468] To 20 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.60 g, 1.28 mmol), 2-amino-(2,4-difluorophenyl)acetonitrile hydrochloride (320 mg, 1.56 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (380 mg, 2.00 mmol) and 1-hydroxy-7-azabenzotriazole (270 mg, 2.00 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.91 mL, 5.20 mmol) dropwise at 0 °C. The mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give a white solid (330 mg, 42%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.63 – 7.69 (m, 1H), 7.58 (d, J = 9.5 Hz, 2H), 7.25 (d, J = 8.2 Hz, 1H), 6.94 – 7.03 (m, 2H), 6.72 (t, $J_{\text{F-H}}$ = 75.0 Hz, 1H), 6.40 (d, J = 8.5 Hz, 1H), 5.25 – 5.35 (m, 1H), 4.00 (d, J = 6.7 Hz, 2H), 1.53 – 1.58 (m, 3H), 1.45 (s, 9H), 1.30 – 1.34 (m, 1H), 0.68 – 0.72 (m, 2H), 0.40 – 0.43 (m, 2H); and MS-ESI: m/z 641.15 $[\text{M}+\text{Na}]^+$.

Step 3: *tert*-Butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00469] To a stirred mixture of *tert*-butyl ((1*S*)-1-(4-((cyano(2,4-difluorophenyl)methyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (330 mg, 0.53 mmol) and nickel chloride (68 mg, 0.53 mmol) in anhydrous ethanol (15 mL) were added a mixture of sodium borohydride (101 mg, 2.67 mmol) and anhydrous ethanol (10 mL) at 0 °C. The resulting mixture was stirred at rt for 4 hours and then dilute hydrochloric acid was added to adjust the pH to 1. The mixture was stirred until the mixture was

clear. To the mixture was added aqueous sodium hydroxide (1 M) to adjust the pH to 9. The mixture was extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed to give a white solid (300 mg, 91%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.00 (br.s, 1H), 7.65 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz, 1H), 7.59 (d, $J = 1.6$ Hz, 1H), 7.33 – 7.42 (m, 1H), 7.27 (d, $J = 10.2$ Hz, 1H), 6.86 – 6.90 (m, 2H), 6.73 (t, $J_{\text{F-H}} = 74.9$ Hz, 1H), 5.30 – 5.41 (m, 1H), 5.25 – 5.30 (m, 1H), 4.02 (d, $J = 6.9$ Hz, 2H), 1.57 – 1.78 (m, 2H), 1.49 – 1.55 (m, 3H), 1.41 – 1.44 (m, 9H), 1.31 – 1.37 (m, 1H), 0.69 – 0.74 (m, 2H), 0.42 – 0.46 (m, 2H); and MS-ESI: m/z 623.20 $[\text{M}+\text{H}]^+$.

Step 4: *tert*-Butyl ((1*S*)-1-(4-((2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00470] To 15 mL of dichloromethane were added *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (300 mg, 0.48 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (138 mg, 0.72 mmol) and 1-hydroxy-7-azabenzotriazole (98 mg, 0.72 mmol). To the mixture were added dropwise cyclopropanesulfonic acid (71 mg, 0.58 mmol) and *N,N*-diisopropylethylamine (0.25 mL, 1.44 mmol) at 0 °C. The mixture was stirred at rt for 12 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (90 mg, 26%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.15 (br.s, 1H), 7.59 – 7.63 (m, 2H), 7.43 – 7.45 (m, 2H), 7.26 (d, $J = 8.3$ Hz, 1H), 6.91 – 6.95 (m, 2H), 6.73 (t, $J_{\text{F-H}} = 75$ Hz, 1H), 5.50 – 5.56 (m, 1H), 5.27 – 5.34 (m, 1H), 4.01 (d, $J = 6.9$ Hz, 2H), 3.65 – 3.70 (m, 2H), 2.42 – 2.50 (m, 1H), 1.50 – 1.55 (m, 3H), 1.42 – 1.45 (m, 9H), 1.18 – 1.22 (m, 1H), 1.00 – 1.06 (m, 2H), 0.85 – 0.91 (m, 2H), 0.68 – 0.73 (m, 2H), 0.41 – 0.45 (m, 2H); and MS-ESI: m/z 749.20 $[\text{M}+\text{Na}]^+$.

Step 5: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00471] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol

-5-yl)ethyl)carbamate (90 mg, 0.124 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give a white solid (70 mg, 85%).

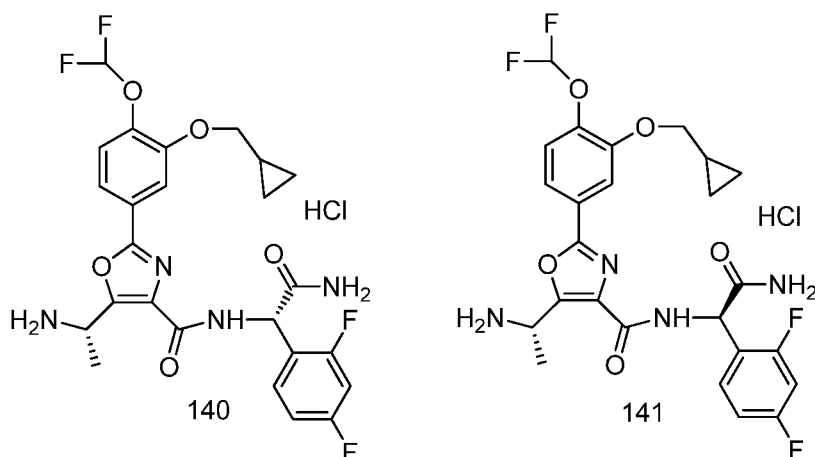
Compound 139: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.86 (s, 1H), 7.73 (d, $J = 8.2$ Hz, 1H), 7.51 – 7.58 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 6.97 – 7.06 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.51 (t, $J = 6.2$ Hz, 1H), 5.09 – 6.18 (m, 1H), 4.05 (d, $J = 6.8$ Hz, 2H), 3.67 – 3.59 (m, 2H), 2.55 – 2.63 (m, 1H), 1.75 (d, $J = 6.5$ Hz, 3H), 1.07 – 1.09 (m, 1H), 0.99 – 1.05 (m, 2H), 0.86 – 0.94 (m, 2H), 0.67 – 0.73 (m, 2H), 0.43 – 0.47 (m, 2H); and MS-ESI: m/z 627.15 $[\text{M}+\text{H}-\text{HCl}]^+$.

Step 6: 5-((*S*)-1-Aminoethyl)-*N*-((*S*)-2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-*N*-((*R*)-2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00472] The compound 5-((*S*)-1-aminoethyl)-*N*-(2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride (300 mg, 0.45 mmol) was further separated and purified by pre-HPLC, and each preparative solution of compound of *R* configuration and compound of *S* configuration was independently concentrated. To each residue was added aqueous sodium hydroxide (1 M) to adjust the pH to 9 and each mixture was extracted with ethyl acetate (10 mL $\times$ 3). Each combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed. To each residue was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL) to give a desired product 5-((*S*)-1-aminoethyl)-*N*-((*S*)-2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride as a light yellow solid (90 mg) and another desired product 5-((*S*)-1-aminoethyl)-*N*-((*R*)-2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride as a light yellow solid (85 mg).

Example 55: *N*-((*S*)-2-Amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and *N*-((*R*)-2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)

-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

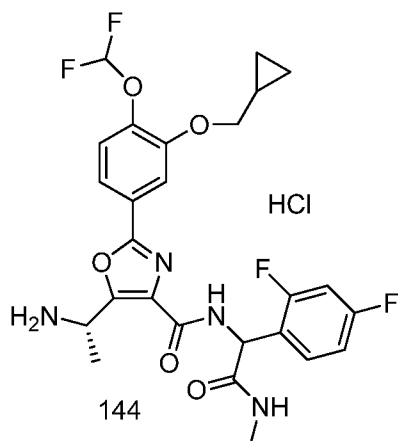


[00473] The compound *N*-(2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride prepared from **Example 47** was further separated and purified to give compound *N*-((*S*)-2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and *N*-((*R*)-2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride.

Compound 140: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.79 (d, $J = 1.9$ Hz, 1H), 7.73 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.62 – 7.58 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.07 – 7.02 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.92 (s, 1H), 5.20 – 5.17 (m, 1H), 4.04 (d, $J = 7.0$ Hz, 2H), 1.76 (d, $J = 6.8$ Hz, 3H), 1.38 – 1.33 (m, 1H), 0.71 – 0.68 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: m/z 537.2 $[\text{M}+\text{H}-\text{HCl}]^+$;

Compound 141: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.79 (d, $J = 1.9$ Hz, 1H), 7.73 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.61 – 7.59 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.07 – 7.03 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.92 (s, 1H), 5.18 – 5.14 (m, 1H), 4.03 (d, $J = 7.0$ Hz, 2H), 1.75 (d, $J = 6.8$ Hz, 3H), 1.37 – 1.33 (m, 1H), 0.71 – 0.67 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: m/z 537.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 56: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(methylamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(methylamino)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00474] To 10 mL of dichloromethane were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.23 g, 0.36 mmol), methylamine hydrochloride (29 mg, 0.43 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (104 mg, 0.54 mmol) and 1-hydroxy-7-azabenzotriazole (74 mg, 0.54 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.25 mL, 1.44 mmol) dropwise at 0 °C. The mixture was stirred at rt for 15 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (133 mg, 56%).

¹H NMR (600 MHz, CDCl₃): δ ppm 7.55 – 7.53 (m, 1H), 7.52 (s, 1H), 7.44 – 7.39 (m, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 6.86 – 6.81 (m, 2H), 6.65 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.86 – 5.85 (m, 1H), 5.79 – 5.77 (m, 1H), 5.24 – 5.20 (m, 1H), 3.94 (d, *J* = 6.8 Hz, 2H), 2.82 – 2.80 (m, 3H), 1.44 – 1.39 (m, 3H), 1.36 – 1.28 (m, 9H), 1.27 – 1.24 (m, 1H), 0.64 – 0.61 (m, 2H), 0.38 – 0.33 (m, 2H); and MS-ESI: *m/z* 651.9 [M+H]⁺.

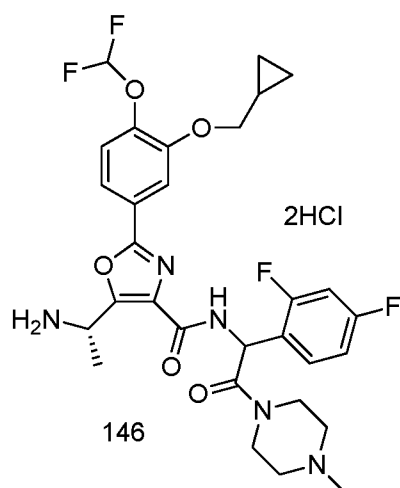
Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(methylamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride

[00475] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(methylamino)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.13 g, 0.20 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 20 minutes and

then the solvent was removed to give a white solid (110 mg, 94%). The crude product was further purified by prep-HPLC to give the title compound as a white solid (80 mg).

Compound 144: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.72 (d, $J = 8.3$ Hz, 1H), 7.59 – 7.55 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.07 – 7.02 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.90 (s, 1H), 5.19 – 5.15 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 2.80 (s, 3H), 1.75 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.34 (m, 1H), 0.71 – 0.68 (m, 2H), 0.45 – 0.43 (m, 2H); and MS-ESI: m/z 551.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 57: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)oxazole-4-carboxamide dihydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl) carbamate

[00476] To 10 mL of dichloromethane were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.16 g, 0.25 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (72 mg, 0.38 mmol) and 1-hydroxy-7-azabenzotriazole (60 mg, 0.38 mmol). To the mixture were added dropwise 1-methylpiperidine (0.03 mL, 0.30 mmol) and *N,N*-diisopropylethylamine (0.13 mL, 0.75 mmol) in turn at 0 °C. The mixture was stirred at rt for 15 hours. The solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give a white solid (60 mg, 33%).

^1H NMR (600 MHz, CDCl_3): δ ppm 7.60 – 7.58 (m, 1H), 7.57 – 7.56 (m, 1H), 7.53 – 7.49 (m, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 6.95 (t, $J = 7.2$ Hz, 1H), 6.90 (t, $J = 9.3$ Hz, 1H), 6.71 (t, $J_{\text{F-H}} =$

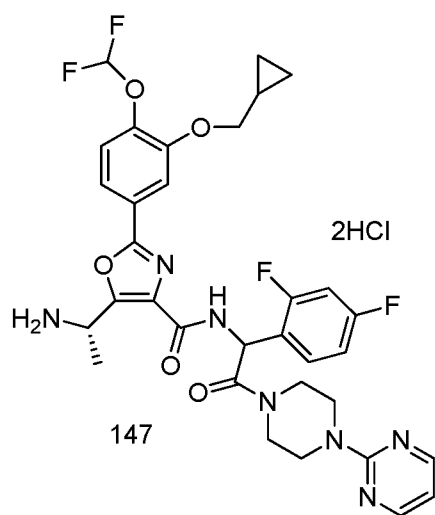
75.0 Hz, 1H), 6.29 – 6.26 (m, 1H), 5.30 – 5.25 (m, 2H), 3.98 (d, $J = 6.9$ Hz, 2H), 3.85 – 3.75 (m, 2H), 2.85 – 2.75 (m, 2H), 2.62 – 2.50 (m, 4H), 1.51 – 1.47 (m, 3H), 1.42 – 1.38 (m, 9H), 1.35 – 1.33 (m, 1H), 0.71 – 0.68 (m, 2H), 0.43 – 0.41 (m, 2H).

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)oxazole-4-carboxamide dihydrochloride

[00477] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.06 g, 0.08 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 20 minutes and then the solvent was removed to give a white solid (50 mg, 91%).

Compound 146: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.79 (d, $J = 1.8$ Hz, 1H), 7.73 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.5$ Hz, 1H), 7.60 – 7.57 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.14 – 7.08 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 6.34 (s, 1H), 5.21 – 5.17 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 3.70 – 3.40 (m, 4H), 3.30 – 3.10 (m, 4H), 2.93 (s, 3H), 1.75 (d, $J = 6.8$ Hz, 3H), 1.36 – 1.33 (m, 1H), 0.71 – 0.68 (m, 2H), 0.45 – 0.43 (m, 2H); and MS-ESI: m/z 620.2 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 58: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethyl)oxazole-4-carboxamide dihydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00478] To 10 mL of dichloromethane were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.19 g, 0.30 mmol), 2-(piperazin-1-yl)pyrimidine (60 mg, 0.36 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (86 mg, 0.45 mmol) and 1-hydroxy-7-azabenzotriazole (61 mg, 0.45 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.16 mL, 0.89 mmol) dropwise at 0 °C. The mixture was stirred at rt for 15 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give colourless oil (220 mg, 94%).

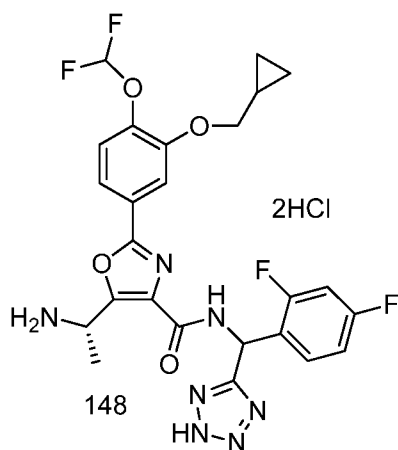
¹H NMR (600 MHz, CDCl₃): δ ppm 8.56 (d, *J* = 7.3 Hz, 1H), 8.33 (d, *J* = 4.7 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.60 (s, 1H), 7.56 – 7.55 (m, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 6.94 – 6.91 (m, 2H), 6.73 (t, *J*_{F-H} = 75.0 Hz, 1H), 6.57 (t, *J* = 4.7 Hz, 1H), 6.34 (d, *J* = 7.1 Hz, 1H), 5.32 – 5.29 (m, 1H), 4.02 (d, *J* = 6.9 Hz, 2H), 4.00 – 3.85 (m, 4H), 3.72 – 3.70 (m, 2H), 3.66 – 3.42 (m, 4H), 1.53 – 1.49 (m, 3H), 1.45 – 1.38 (m, 9H), 1.39 – 1.37 (m, 1H), 0.73 – 0.70 (m, 2H), 0.46 – 0.44 (m, 2H); and MS-ESI: *m/z* 684.1 [M+H-100]⁺.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethyl)oxazole-4-carboxamide dihydrochloride

[00479] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.22 g, 0.28 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 20 minutes and then the solvent was removed to give a white solid (200 mg, 99%).

Compound 147: ¹H NMR (600 MHz, CD₃OD): δ ppm 8.56 (d, *J* = 4.5 Hz, 2H), 7.79 (d, *J* = 1.8 Hz, 1H), 7.73 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.7 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.14 – 7.09 (m, 2H), 6.96 – 6.94 (m, 1H), 6.92 (t, *J*_{F-H} = 74.7 Hz, 1H), 6.35 – 6.34 (m, 1H), 5.20 – 5.16 (m, 1H), 4.10 – 3.99 (m, 4H), 3.87 – 3.83 (m, 4H), 3.58 – 3.56 (m, 2H), 1.76 (d, *J* = 6.9 Hz, 3H), 1.41 – 1.39 (m, 1H), 0.72 – 0.67 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: *m/z* 342.7 [M+2H-2HCl]²⁺.

Example 59: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((2,4-difluorophenyl)(2*H*-tetrazol-5-yl)methyl)oxazole-4-carboxamide dihydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((2,4-difluorophenyl)(2*H*-tetrazol-5-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00480] To a solution of *tert*-butyl ((1*S*)-1-(4-((cyano(2,4-difluorophenyl)methyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (160 mg, 0.26 mmol) and ammonium chloride (20 mg, 0.31 mmol) in *N,N*-dimethylformamide (15 mL) was added sodium azide (20 mg, 0.31 mmol). The mixture was stirred at 100 °C for 8 hours and then the solvent was removed. To the residue were added water (10 mL), and the resulting mixture was adjusted with diluted hydrochloric acid (1M) to pH to about 1. The mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give yellow oil (160 mg, 93%).

¹H NMR (600 MHz, CDCl₃): δ ppm 7.59 – 7.57 (m, 3H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.96 – 6.84 (m, 2H), 6.73 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.61 – 5.51 (m, 1H), 5.25 – 5.10 (m, 1H), 3.99 (d, *J* = 6.9 Hz, 2H), 1.59 – 1.51 (m, 3H), 1.41 – 1.39 (m, 9H), 1.35 – 1.33 (m, 1H), 0.71 – 0.69 (m, 2H), 0.44 – 0.43 (m, 2H); and MS-ESI: *m/z* 562.1 [M-100+H]⁺.

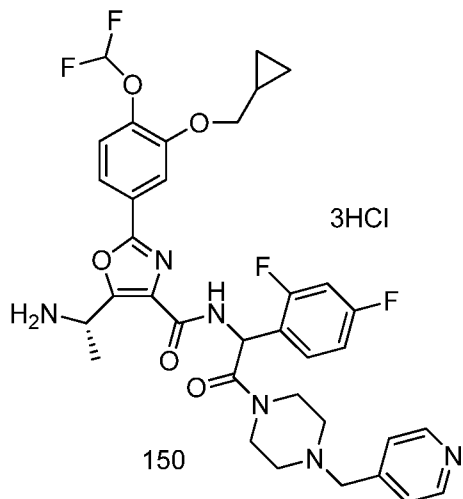
Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((2,4-difluorophenyl)(2*H*-tetrazol-5-yl)methyl)oxazole-4-carboxamide dihydrochloride

[00481] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((2,4-difluorophenyl)(2*H*-tetrazol-5-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.16 g, 0.24 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 40 minutes and then the solvent was removed to give a yellow solid (140 mg, 96%).

Compound 148: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.71 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.02 – 6.96 (m, 2H), 6.91 (s, 1H), 6.82 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.14 – 5.11 (m, 1H), 3.93 (d, *J* = 6.8 Hz, 2H), 1.68 (d, *J* = 6.5 Hz, 3H), 0.82 – 0.77

(m, 1H), 0.60 – 0.57 (m, 2H), 0.33 – 0.32 (m, 2H); and MS-ESI: m/z 562.1 $[M+H-2HCl]^+$.

Example 60: 5-((S)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyridin-4-ylmethyl)piperazin-1-yl)ethyl)oxazole-4-carboxamide trihydrochloride



Step 1: *tert*-Butyl ((1S)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyridin-4-ylmethyl)piperazin-1-yl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00482] To 10 mL of dichloromethane were added 2-(5-((S)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.23 g, 0.36 mmol), 1-(pyridin-4-ylmethyl)piperazine (77 mg, 0.43 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (103 mg, 0.54 mmol) and 1-hydroxy-7-azabenzotriazole (74 mg, 0.54 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.19 mL, 1.08 mmol) dropwise at 0 °C. The mixture was stirred at rt for 11 hours. The solvent was removed and the residue was purified by silica gel column chromatography (EtOAc/MeOH (v/v) = 20/1) to give colourless oil (260 mg, 90%).

^1H NMR (600 MHz, $CDCl_3$): δ ppm 8.60 (d, J = 4.1 Hz, 2H), 8.52 (d, J = 6.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H), 7.55 – 7.49 (m, 1H), 7.36 (d, J = 3.8 Hz, 2H), 7.25 (d, J = 8.3 Hz, 1H), 6.96 – 6.86 (m, 2H), 6.73 (t, J_{F-H} = 75.0 Hz, 1H), 6.28 (d, J = 7.5 Hz, 1H), 5.32 – 5.29 (m, 1H), 4.01 (d, J = 6.9 Hz, 2H), 3.75 – 3.72 (m, 2H), 3.66 – 3.63 (m, 1H), 3.57 (s, 2H), 3.50 – 3.45 (m, 1H), 2.53 – 2.46 (m, 4H), 1.53 – 1.48 (m, 3H), 1.44 (s, 9H), 1.33 – 1.29 (m, 1H), 0.73 – 0.68 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: m/z 797.2 $[M+H]^+$.

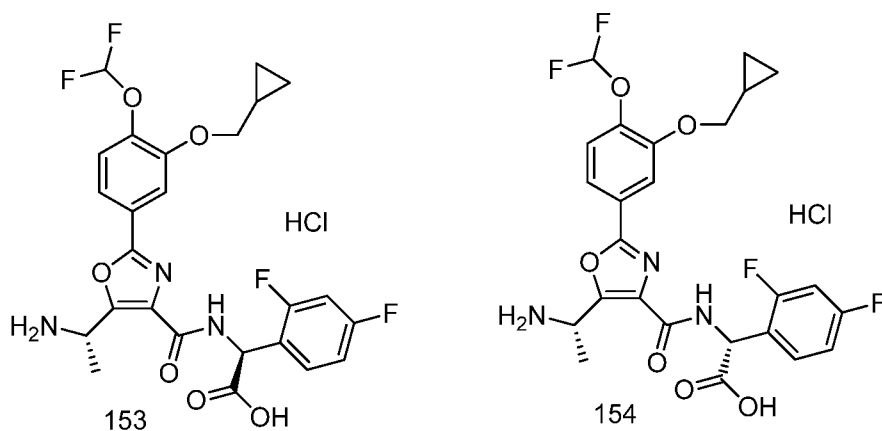
Step 2: 5-((S)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-

***N*-(1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyridin-4-ylmethyl)piperazin-1-yl)ethyl)oxazole-4-carboxamide trihydrochloride**

[00483] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyridin-4-ylmethyl)piperazin-1-yl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.26 g, 0.33 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 20 minutes and then the solvent was removed to give a white solid (220 mg, 96%).

Compound 150: ¹H NMR (400 MHz, CD₃OD): δ ppm 8.98 (s, 2H), 8.37 (d, *J* = 5.4 Hz, 2H), 7.79 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.13 – 7.07 (m, 2H), 6.92 (t, *J*_{F-H} = 70.6 Hz, 1H), 6.33 (s, 1H), 5.20 – 5.16 (m, 1H), 4.58 (s, 2H), 4.04 (d, *J* = 6.9 Hz, 2H), 3.33 – 3.20 (m, 8H), 1.75 (d, *J* = 7.0 Hz, 3H), 1.36 – 1.34 (m, 1H), 0.72 – 0.67 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: *m/z* 697.2 [M+H-3HCl]⁺.

Example 61: (*S*)-2-(5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid hydrochloride and (*R*)-2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid hydrochloride



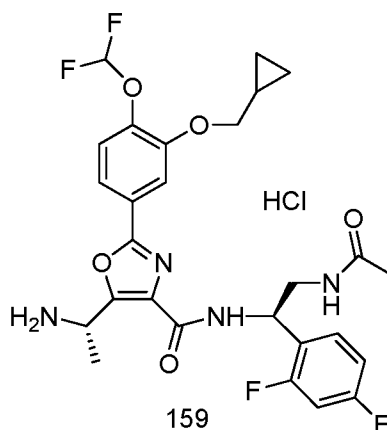
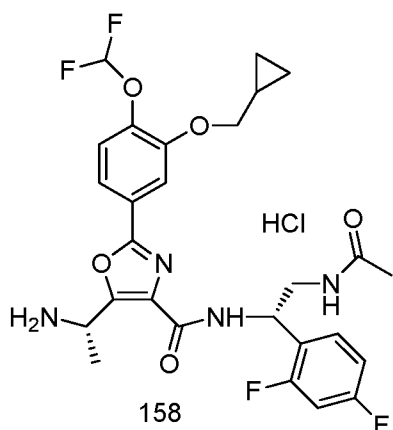
[00484] The compound 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid hydrochloride prepared from **Example 50** was further separated and purified by prep-HPLC to give compound (*S*)-2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid hydrochloride and (*R*)-2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-

difluorophenyl)acetic acid hydrochloride.

Compound 153: ^1H NMR (600 MHz, CD_3OD): δ ppm 8.76 (s, 1H), 7.71 (s, 1H), 7.68 (d, $J = 8.3$ Hz, 1H), 7.40 – 7.34 (m, 2H), 7.24 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 1H), 6.97 (t, $J = 7.7$ Hz, 1H), 5.21 (s, 1H), 5.02 – 4.98 (m, 1H), 4.02 (d, $J = 6.8$ Hz, 2H), 1.55 (d, $J = 6.7$ Hz, 3H), 1.28 – 1.24 (m, 1H), 0.61 – 0.60 (m, 2H), 0.41 – 0.40 (m, 2H); and MS-ESI: m/z 538.2 $[\text{M}+\text{H}-\text{HCl}]^+$;

Compound 154: ^1H NMR (400 MHz, d_6 -DMSO): δ ppm 8.67 (s, 1H), 7.65 – 7.63 (m, 2H), 7.35 (d, $J = 8.8$ Hz, 1H), 7.31 – 7.27 (m, 1H), 7.23 (t, $J_{\text{F-H}} = 74.0$ Hz, 1H), 7.12 (dd, $J_1 = 10.0$ Hz, $J_2 = 2.5$ Hz, 1H), 6.99 – 6.95 (m, 1H), 5.16 – 5.15 (m, 1H), 5.04 – 4.99 (m, 1H), 3.98 (d, $J = 7.0$ Hz, 2H), 1.51 (d, $J = 6.9$ Hz, 3H), 1.29 – 1.25 (m, 1H), 0.63 – 0.58 (m, 2H), 0.41 – 0.38 (m, 2H); and MS-ESI: m/z 538.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 62: *N*-((*S*)-2-Acetamido-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and *N*-((*R*)-2-acetamido-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



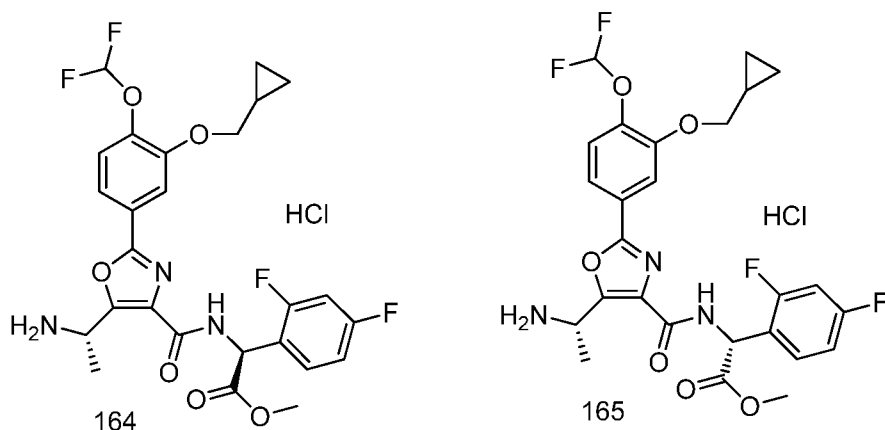
[00485] The compound *N*-(2-acetamido-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride prepared from **Example 53** was further separated and purified by pre-HPLC to give compound *N*-((*S*)-2-acetamido-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride as a light yellow solid and *N*-((*R*)-2-acetamido-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride as a light yellow solid.

Compound 158: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.78 (s, 1H), 7.71 (d, $J = 8.4$ Hz, 1H),

7.46 – 7.41 (m, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 6.98 – 6.91 (m, 2H), 6.87 (t, $J_{F-H} = 74.7$ Hz, 1H), 5.47 – 5.44 (m, 1H), 5.11 – 5.05 (m, 1H), 4.02 (d, $J = 6.9$ Hz, 2H), 3.70 – 3.56 (m, 2H), 1.89 (s, 3H), 1.68 (d, $J = 7.0$ Hz, 3H), 1.35 – 1.30 (m, 1H), 0.67 – 0.62 (m, 2H), 0.41 – 0.37 (m, 2H); and MS-ESI: m/z 565.2 $[M+H-HCl]^+$;

Compound 159: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.85 (s, 1H), 7.76 (d, $J = 8.3$ Hz, 1H), 7.50 – 7.48 (m, 1H), 7.35 (d, $J = 8.3$ Hz, 1H), 7.03 – 6.98 (m, 2H), 6.93 (t, $J_{F-H} = 74.7$ Hz, 1H), 5.53 – 5.51 (m, 1H), 5.11 – 5.08 (m, 1H), 4.07 (d, $J = 7.0$ Hz, 2H), 3.75 – 3.63 (m, 2H), 1.95 (s, 3H), 1.74 (d, $J = 7.0$ Hz, 3H), 1.39 – 1.37 (m, 1H), 0.72 – 0.69 (m, 2H), 0.46 – 0.44 (m, 2H); and MS-ESI: m/z 565.2 $[M+H-HCl]^+$.

Example 63: *(S)*-Methyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride and *(R)*-methyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride



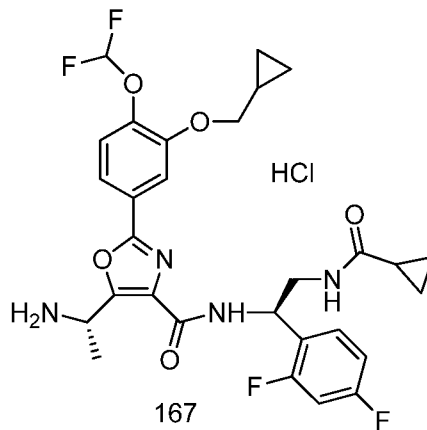
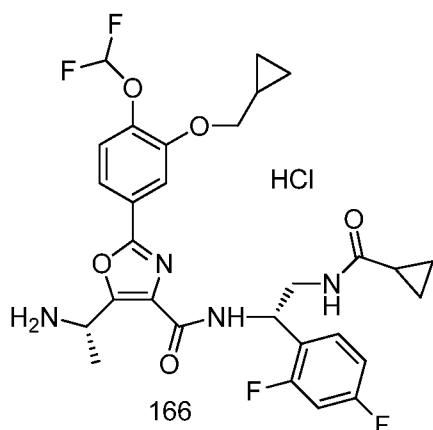
[00486] The compound methyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride prepared from **Example 49** was further separated and purified by pre-HPLC to give *(S)*-methyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride as a white solid and *(R)*-methyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride as a white solid.

Compound 164: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.80 (s, 1H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.59 – 7.55 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.10 – 7.03 (m, 2H), 6.93 (t, $J_{F-H} = 74.7$ Hz, 1H), 6.06 (s, 1H), 5.21 – 5.17 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 3.81 (s, 3H), 1.75 (d, $J = 7.0$ Hz, 3H),

1.39 – 1.36 (m, 1H), 0.71 – 0.68 (m, 2H), 0.45 – 0.43 (m, 2H); and MS-ESI: m/z 552.2 $[M+H-HCl]^+$;

Compound 165: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.80 (s, 1H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.59 – 7.55 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.10 – 7.03 (m, 2H), 6.93 (t, $J_{F-H} = 74.7$ Hz, 1H), 6.06 (s, 1H), 5.19 – 5.16 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 3.81 (s, 3H), 1.75 (d, $J = 7.0$ Hz, 3H), 1.38 – 1.35 (m, 1H), 0.71 – 0.68 (m, 2H), 0.45 – 0.43 (m, 2H); and MS-ESI: m/z 552.2 $[M+H-HCl]^+$.

Example 64: 5-((*S*)-1-Aminoethyl)-*N*-((*S*)-2-(cyclopropanecarboxamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-*N*-((*R*)-2-(cyclopropanecarboxamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



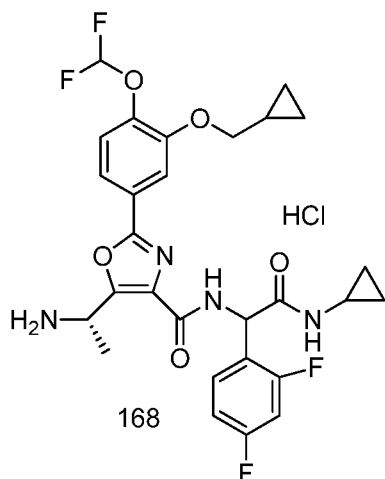
[00487] The compound 5-((*S*)-1-aminoethyl)-*N*-(2-(cyclopropanecarboxamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride prepared from **Example 52** was further separated and purified by prep-HPLC to give 5-((*S*)-1-aminoethyl)-*N*-((*S*)-2-(cyclopropanecarboxamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride as a white solid and 5-((*S*)-1-aminoethyl)-*N*-((*R*)-2-(cyclopropanecarboxamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride as a white solid.

Compound 166: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.84 (s, 1H), 7.75 (d, $J = 8.3$ Hz, 1H), 7.50 – 7.46 (m, 1H), 7.35 (d, $J = 8.3$ Hz, 1H), 7.04 – 6.98 (m, 2H), 6.94 (t, $J_{F-H} = 74.7$ Hz, 1H), 5.49 – 5.47 (m, 1H), 5.15 – 5.12 (m, 1H), 4.07 (d, $J = 7.0$ Hz, 2H), 3.79 – 3.75 (m, 1H), 3.66 – 3.63 (m, 1H), 1.72 (d, $J = 7.0$ Hz, 3H), 1.58 – 1.55 (m, 1H), 1.42 – 1.39 (m, 1H), 0.93 – 0.90 (m,

2H), 0.79 – 0.75 (m, 2H), 0.73 – 0.70 (m, 2H), 0.47 – 0.45 (m, 2H); and MS-ESI: m/z 591.2 $[M+H-HCl]^+$;

Compound 167: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.84 (s, 1H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.48 – 7.46 (m, 1H), 7.35 (d, $J = 8.3$ Hz, 1H), 7.03 – 6.98 (m, 2H), 6.94 (t, $J_{F-H} = 74.7$ Hz, 1H), 5.49 – 5.47 (m, 1H), 5.10 – 5.08 (m, 1H), 4.07 (d, $J = 7.0$ Hz, 2H), 3.77 – 3.74 (m, 1H), 3.67 – 3.65 (m, 1H), 1.73 (d, $J = 7.0$ Hz, 3H), 1.57 – 1.55 (m, 1H), 1.41 – 1.38 (m, 1H), 1.02 – 0.99 (m, 2H), 0.80 – 0.75 (m, 2H), 0.72 – 0.71 (m, 2H), 0.47 – 0.46 (m, 2H); and MS-ESI: m/z 591.2 $[M+H-HCl]^+$.

Example 65: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopropylamino)-1-(2,4-difluorophenyl)-2-oxoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 2-amino-2-(2,4-difluorophenyl)acetate

[00488] To a solution of 2-amino-2-(2,4-difluorophenyl)acetonitrile hydrochloride (1.0 g, 4.89 mmol) in anhydrous methanol (30 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The mixture was stirred at 65 °C for 24 hours, then concentrated to remove the solvent. The residue was washed with dichloromethane (10 mL $\times$ 5) to give a light yellow solid (1.05 g, 91%).

^1H NMR (600 MHz, CD_3OD): δ ppm 7.76 – 7.82 (m, 1H), 7.21 – 7.31 (m, 2H), 6.03 (s, 1H), 3.84 (s, 3H); and MS-ESI: m/z 202.20 $[M+H-HCl]^+$.

Step 2: Methyl 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate

[00489] To 20 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-

-carboxylic acid (0.50 g, 1.07 mmol), methyl 2-amino-2-(2,4-difluorophenyl)acetate (380 mg, 1.60 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (409 mg, 2.13 mmol) and 1-hydroxy-7-azabenzotriazole (218 mg, 1.60 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.75 mL, 4.28 mmol) dropwise at 0 °C. The mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (10 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give a white solid (170 mg, 25%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.16 (br.s, 1H), 7.62 – 7.64 (m, 1H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.46 – 7.51 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.88 – 6.95 (m, 2H), 6.73 (t, *J*_{F-H} = 75.1 Hz, 1H), 5.98 – 6.01 (m, 1H), 5.25 – 5.32 (m, 1H), 4.02 (dd, *J* = 6.9, 1.6 Hz, 2H), 3.82 (s, 3H), 1.49 – 1.54 (m, 3H), 1.41 – 1.45 (m, 9H), 1.34 – 1.37 (m, 1H), 0.69 – 0.74 (m, 2H), 0.43 – 0.47 (m, 2H); and MS-ESI: *m/z* 674.10 [M+Na]⁺.

Step 3: 2-(5-((*S*)-1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid

[00490] To a mixed solvent of tetrahydrofuran (10 mL) and water (5 mL) were added methyl 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate (240 mg, 0.37 mmol) and lithium hydroxide monohydrate (77 mg, 1.84 mmol). The solution was stirred at 40 °C for 30 minutes, then hydrochloric acid (1 M) was added to adjust the pH of the solution to 1. The mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give a white solid (230 mg, 98%).

¹H NMR (600 MHz, CD₃OD): δ ppm 7.70 (s, 1H), 7.61 – 7.63 (m, 1H), 7.50 – 7.54 (m, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 6.94 – 7.00 (m, 2H), 6.84 (t, *J*_{F-H} = 74.9 Hz, 1H), 5.87 (d, *J* = 13.8 Hz, 1H), 5.30 – 5.38 (m, 1H), 3.97 (dd, *J* = 6.9, 2.4 Hz, 2H), 1.45 (d, *J* = 7.1 Hz, 3H), 1.34 – 1.36 (m, 9H), 1.27 – 1.31 (m, 1H), 0.61 – 0.65 (m, 2H), 0.36 – 0.39 (m, 2H); and MS-ESI: *m/z* 660.15 [M+Na]⁺.

Step 4: *tert*-Butyl ((1*S*)-1-(4-((2-(cyclopropylamino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00491] To 15 mL of dichloromethane were added

2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (230 mg, 0.36 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (138 mg, 0.72 mmol) and 1-hydroxy-7-azabenzotriazole (74 mg, 0.54 mmol). To the mixture were added dropwise cyclopropanamine (31 mg, 0.54 mmol) and *N,N*-diisopropylethylamine (0.19 mL, 1.08 mmol) at 0 °C. The mixture was stirred at rt for 12 hours, then washed with water (10 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a white solid (180 mg, 74%).

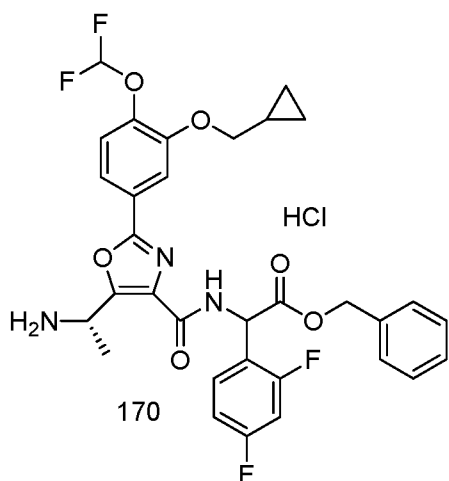
¹H NMR (600 MHz, CDCl₃): δ ppm 8.42 (br.s, 1H), 7.61 – 7.64 (m, 2H), 7.48 – 7.52 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.88 – 6.94 (m, 2H), 6.74 (t, *J*_{F-H} = 75.1 Hz, 1H), 6.07 (s, 1H), 5.80 (d, *J* = 6.8 Hz, 1H), 5.26 – 5.33 (m, 1H), 4.04 (d, *J* = 6.9 Hz, 2H), 2.70 – 2.76 (m, 1H), 1.46 – 1.53 (m, 3H), 1.40 – 1.44 (m, 9H), 1.34 – 1.39 (m, 1H), 0.77 – 0.87 (m, 2H), 0.70 – 0.73 (m, 2H), 0.48 – 0.59 (m, 2H), 0.44 – 0.47 (m, 2H); and MS-ESI: *m/z* 699.20 [M+Na]⁺.

Step 5: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopropylamino)-1-(2,4-difluorophenyl)-2-oxoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00492] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-(cyclopropylamino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (175 mg, 0.26 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give a white solid (160 mg, 99%).

Compound 168: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.79 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.54 – 7.58 (m, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.03 – 7.07 (m, 2H), 6.92 (t, *J*_{F-H} = 74.9 Hz, 1H), 5.85 (d, *J* = 4.6 Hz, 1H), 5.15 – 5.20 (m, 1H), 4.04 (d, *J* = 6.9 Hz, 2H), 2.72 – 2.75 (m, 1H), 1.75 (d, *J* = 7.0 Hz, 3H), 1.32 – 1.38 (m, 1H), 0.74 – 0.77 (m, 2H), 0.68 – 0.71 (m, 2H), 0.46 – 0.56 (m, 2H), 0.42 – 0.45 (m, 2H); and MS-ESI: *m/z* 577.20 [M+H-HCl]⁺.

Example 66: Benzyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride



Step 1: Benzyl 2-(5-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate

[00493] To 15 mL of dichloromethane were added 2-(5-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (230 mg, 0.36 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (138 mg, 0.72 mmol) and 1-hydroxy-7-azabenzotriazole (74 mg, 0.54 mmol). To the mixture were added dropwise benzyl alcohol (58 mg, 0.54 mmol) and *N,N*-diisopropylethylamine (0.19 mL, 1.08 mmol) at 0 °C. The mixture was stirred at rt for 12 hours. The mixture was washed with water (10 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (EtOAc/PE (v/v) = 8/1) to give a white solid (63 mg, 24%).

¹H NMR (600 MHz, CDCl₃): δ ppm 8.20 (br.s, 1H), 7.60 – 7.63 (m, 1H), 7.58 – 7.59 (m, 1H), 7.31 – 7.35 (m, 5H), 7.24 – 7.26 (m, 2H), 6.87 – 6.91 (m, 2H), 6.73 (t, *J*_{F-H} = 74.9 Hz, 1H), 6.03 (d, *J* = 7.7 Hz, 1H), 5.27 – 5.30 (m, 1H), 5.25 (s, 2H), 4.01 (d, *J* = 6.9 Hz, 2H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.46 (s, 9H), 1.31 – 1.39 (m, 1H), 0.70 – 0.74 (m, 2H), 0.42 – 0.45 (m, 2H); and MS-ESI: *m/z* 750.20 [M+Na]⁺.

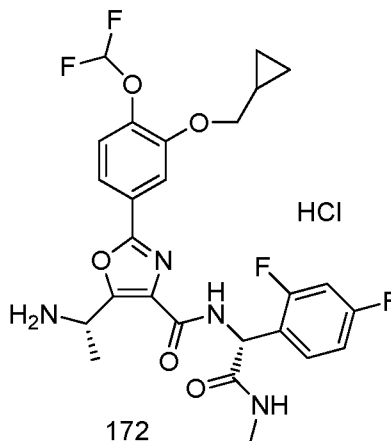
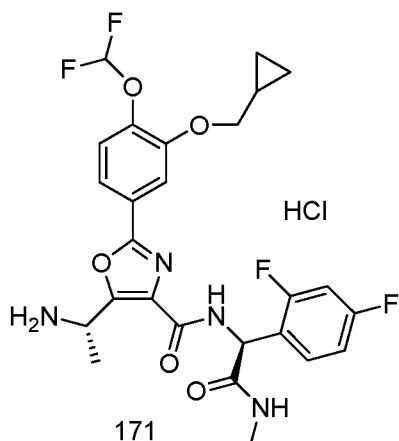
Step 2: Benzyl 2-(5-((S)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride

[00494] To a solution of benzyl 2-(5-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate (63 mg, 0.087 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 30

minutes and then the solvent was removed to give a white solid (55 mg, 96%).

Compound 170: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.80 (s, 1H), 7.72 – 7.74 (m, 1H), 7.50 – 7.56 (m, 1H), 7.28 – 7.35 (m, 5H), 6.97 – 7.08 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 6.08 (s, 1H), 5.21 – 5.32 (m, 2H), 5.15 – 5.21 (m, 1H), 4.05 (d, $J = 6.8$ Hz, 2H), 1.75 (d, $J = 6.6$ Hz, 3H), 1.31 – 1.35 (m, 1H), 0.66 – 0.72 (m, 2H), 0.41 – 0.45 (m, 2H); and MS-ESI: m/z 628.10 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 67: 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-(methylamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-(methylamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride

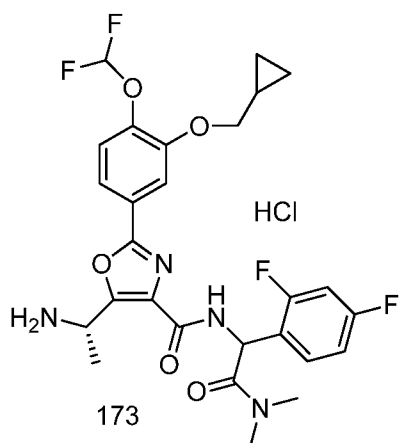


[00495] The compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(methylamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride prepared from **Example 56** was further separated by preparative chiral HPLC to give 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-(methylamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride as a white solid and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-(methylamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride as a white solid.

Compound 171: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.58 – 7.55 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.07 – 7.02 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.90 (s, 1H), 5.20 – 5.16 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 2.80 (s, 3H), 1.75 (d, $J = 7.0$ Hz, 3H), 1.38 – 1.35 (m, 1H), 0.71 – 0.68 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: m/z 551.2 $[\text{M}+\text{H}-\text{HCl}]^+$;

Compound 172: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.72 (d, $J = 8.3$ Hz, 1H), 7.58 – 7.55 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.08 – 7.03 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.89 (s, 1H), 5.17 – 5.14 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 2.80 (s, 3H), 1.75 (d, $J = 7.0$ Hz, 3H), 1.36 – 1.34 (m, 1H), 0.71 – 0.68 (m, 2H), 0.45 – 0.43 (m, 2H); and MS-ESI: m/z 551.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 68: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00496] To 15 mL of dichloromethane were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.35 g, 0.55 mmol), dimethylamine hydrochloride (54 mg, 0.66 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (158 mg, 0.82 mmol) and 1-hydroxy-7-azabenzotriazole (112 mg, 0.82 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.38 mL, 2.20 mmol) dropwise at 0 °C. The mixture was stirred at rt for 4 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give colourless oil (140 mg, 38%).

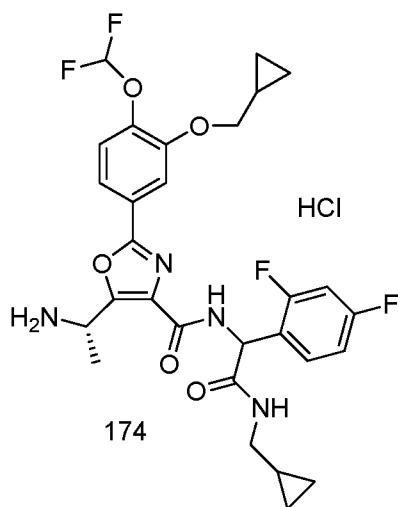
^1H NMR (600 MHz, CDCl_3): δ ppm 7.62 (d, $J = 8.4$ Hz, 1H), 7.60 (s, 1H), 7.55 – 7.51 (m, 1H), 7.24 (d, $J = 8.3$ Hz, 1H), 6.94 – 6.87 (m, 2H), 6.73 (t, $J_{\text{F-H}} = 75.1$ Hz, 1H), 6.30 – 6.28 (m, 1H), 5.32 – 5.28 (m, 1H), 4.02 (d, $J = 7.0$ Hz, 2H), 3.05 – 3.04 (m, 6H), 1.55 – 1.48 (m, 3H), 1.37 – 1.34 (m, 1H), 0.73 – 0.70 (m, 2H), 0.44 – 0.40 (m, 2H); and MS-ESI: m/z 665.2 $[\text{M}+\text{H}]^+$.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride

[00497] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.13 g, 0.20 mmol) in dichloromethane (5 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 1.5 hours and then the solvent was removed to give a white solid (110 mg, 99%).

Compound 173: ¹H NMR (400 MHz, CD₃OD): δ ppm 7.78 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.10 – 7.03 (m, 2H), 6.92 (t, *J*_{F-H} = 74.7 Hz, 1H), 6.26 (s, 1H), 5.18 – 5.14 (m, 1H), 4.04 (d, *J* = 6.9 Hz, 2H), 3.03 – 3.01 (m, 6H), 1.75 (d, *J* = 6.9 Hz, 3H), 1.35 – 1.32 (m, 1H), 0.71 – 0.66 (m, 2H), 0.45 – 0.43 (m, 2H); and MS-ESI: *m/z* 565.2 [M+H-HCl]⁺.

Example 69: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00498] To 15 mL of dichloromethane were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.35 g, 0.55 mmol), cyclopropylmethanamine (0.06 mL, 0.66

mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (158 mg, 0.82 mmol) and 1-hydroxy-7-azabenzotriazole (112 mg, 0.82 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.29 mL, 1.65 mmol) dropwise at 0 °C. The mixture was stirred at rt for 4 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a light yellow solid (145 mg, 38%).

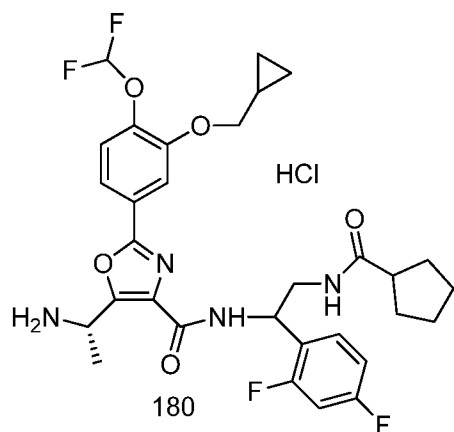
¹H NMR (600 MHz, CDCl₃): δ ppm 7.63 (d, *J* = 8.3 Hz, 1H), 7.61 (m, 1H), 7.53 – 7.50 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.95 – 6.90 (m, 2H), 6.74 (t, *J*_{F-H} = 75.0 Hz, 1H), 6.02 – 6.00 (m, 1H), 5.88 – 5.87 (m, 1H), 5.33 – 5.29 (m, 1H), 4.03 (d, *J* = 7.0 Hz, 2H), 3.24 – 3.21 (m, 1H), 3.15 – 3.11 (m, 1H), 1.53 – 1.48 (m, 3H), 1.45 – 1.40 (m, 9H), 1.37 – 1.34 (m, 1H), 0.98 – 0.94 (m, 1H), 0.73 – 0.70 (m, 2H), 0.54 – 0.52 (m, 2H), 0.47 – 0.44 (m, 2H), 0.21 – 0.20 (m, 2H); and MS-ESI: *m/z* 691.2 [M+H]⁺.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)oxazole-4-carboxamide hydrochloride

[00499] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.13 g, 0.20 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 2.5 hours and then the solvent was removed to give a white solid (110 mg, 95%).

Compound 174: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.79 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.08 – 7.03 (m, 2H), 6.92 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.92 (d, *J* = 2.7 Hz, 1H), 5.19 – 5.15 (m, 1H), 4.04 (d, *J* = 6.9 Hz, 2H), 3.15 – 3.09 (m, 2H), 1.75 (d, *J* = 7.0 Hz, 3H), 1.36 – 1.33 (m, 1H), 1.00 – 0.97 (m, 1H), 0.71 – 0.68 (m, 2H), 0.49 – 0.47 (m, 2H), 0.45 – 0.42 (m, 2H), 0.22 – 0.20 (m, 2H); and MS-ESI: *m/z* 591.2 [M+H-HCl]⁺.

Example 70: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopentanecarboxamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(4-((2-(cyclopentanecarboxamido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00500] To 15 mL of dichloromethane were added *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.30 g, 0.48 mmol), cyclopentanecarboxylic acid (66 mg, 0.58 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (140 mg, 0.72 mmol) and 1-hydroxy-7-azabenzotriazole (100 mg, 0.72 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.34 mL, 1.93 mmol) dropwise at 0 °C. The mixture was stirred at rt for 15 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give colourless oil (190 mg, 54%).

¹H NMR (600 MHz, CDCl₃): δ ppm 7.65 – 7.64 (m, 2H), 7.40 – 7.37 (m, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 6.92 – 6.86 (m, 2H), 6.74 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.95 – 5.93 (m, 1H), 5.49 – 5.48 (m, 1H), 5.31 – 5.28 (m, 1H), 4.03 (d, *J* = 6.9 Hz, 2H), 3.85 – 3.81 (m, 2H), 2.53 – 2.50 (m, 1H), 1.84 – 1.73 (m, 4H), 1.58 – 1.55 (m, 2H), 1.53 – 1.52 (m, 2H), 1.49 – 1.47 (m, 3H), 1.46 (s, 9H), 1.38 – 1.35 (m, 1H), 0.73 – 0.70 (m, 2H), 0.44 – 0.43 (m, 2H); and MS-ESI: *m/z* 719.2 [M+H]⁺.

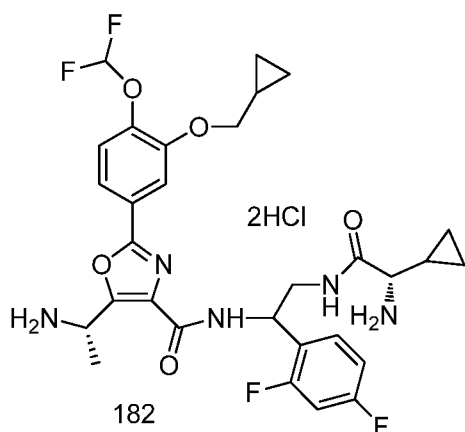
Step 2: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopentanecarboxamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00501] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-(cyclopentanecarboxamido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.19 g, 0.26 mmol) in dichloromethane (4 mL) was added a solution of

hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 1 hour and then the solvent was removed to give a white solid (170 mg, 99%).

Compound 180: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.85 (s, 1H), 7.76 (d, $J = 8.3$ Hz, 1H), 7.50 – 7.45 (m, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.03 – 7.03 (m, 2H), 6.93 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.52 – 5.48 (m, 1H), 5.15 – 5.08 (m, 1H), 4.08 (d, $J = 7.0$ Hz, 2H), 3.80 – 3.72 (m, 1H), 3.67 – 3.62 (m, 1H), 2.63 – 2.60 (m, 1H), 1.83 – 1.79 (m, 2H), 1.74 – 1.73 (m, 3H), 1.72 – 1.69 (m, 4H), 1.60 – 1.56 (m, 2H), 1.41 – 1.38 (m, 1H), 0.73 – 0.68 (m, 2H), 0.47 – 0.43 (m, 2H); and MS-ESI: m/z 619.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 71: *N*-(2-((*S*)-2-Amino-2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide dihydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-cyclopropyl-2-((2-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-5-((*S*)-1-(*tert*-butoxycarbonylamino)ethyl)oxazol-4-carboxamido)-2-(2,4-difluorophenyl)ethyl)amino)-2-oxoethyl)carbamate

[00502] To 15 mL of dichloromethane were added *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyle)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.30 g, 0.48 mmol), Boc-*L*-cyclopropylglycine (124 mg, 0.58 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (138 mg, 0.72 mmol) and 1-hydroxy-7-azabenzotriazole (98 mg, 0.72 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.25 mL, 1.45 mmol) dropwise at 0 °C. The mixture was stirred at rt for 4 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a white solid (210 mg, 53%).

^1H NMR (600 MHz, CDCl_3): δ ppm 7.65 – 7.62 (m, 2H), 7.43 – 7.37 (m, 1H), 7.27 (d, $J =$

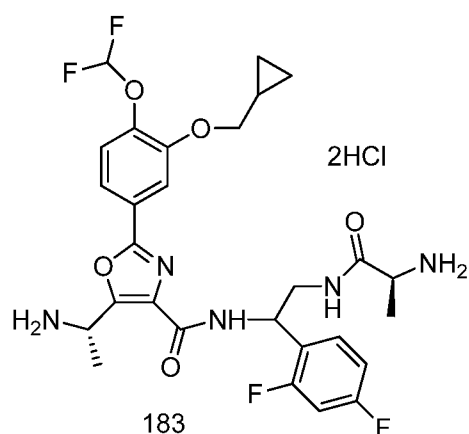
8.3 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.73 (t, $J_{F-H} = 75.0$ Hz, 1H), 5.54 – 5.50 (m, 1H), 5.32 – 5.20 (m, 2H), 4.02 (d, $J = 6.9$ Hz, 2H), 3.86 – 3.71 (m, 3H), 3.45 – 3.41 (m, 1H), 1.55 – 1.49 (m, 3H), 1.46 – 1.41 (m, 18H), 1.36 – 1.32 (m, 1H), 1.29 – 1.27 (m, 2H), 0.73 – 0.70 (m, 2H); and MS-ESI: m/z 820.2 $[M+H]^+$.

Step 2: *N*-(2-((*S*)-2-Amino-2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide dihydrochloride

[00503] To a solution of *tert*-butyl ((1*S*)-1-cyclopropyl-2-((2-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-5-((*S*)-1-(*tert*-butoxycarbonylamino)ethyl)oxazol-4-carboxamido)-2-(2,4-difluorophenyl)ethyl)amino)-2-oxoethyl)carbamate (0.21 g, 0.25 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 1 hours and then the solvent was removed to give a white solid (170 mg, 98%).

Compound 182: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.84 (s, 1H), 7.77 (d, $J = 8.3$ Hz, 1H), 7.59 – 7.57 (m, 1H), 7.35 (d, $J = 8.2$ Hz, 1H), 7.05 – 6.99 (m, 2H), 6.93 (t, $J_{F-H} = 74.7$ Hz, 1H), 5.66 – 5.61 (m, 1H), 5.19 – 5.11 (m, 1H), 4.07 (d, $J = 6.8$ Hz, 2H), 4.03 – 3.94 (m, 1H), 3.70 – 3.63 (m, 1H), 3.20 – 3.17 (m, 1H), 1.75 (d, $J = 7.0$ Hz, 3H), 1.36 – 1.32 (m, 1H), 0.93 – 0.87 (m, 1H), 0.71 – 0.68 (m, 2H), 0.65 – 0.60 (m, 2H), 0.53 – 0.50 (m, 1H), 0.47 – 0.43 (m, 2H); and MS-ESI: m/z 620.2 $[M+H-2HCl]^+$.

Example 72: 5-((*S*)-1-Aminoethyl)-*N*-(2-((*S*)-2-aminopropanamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide dihydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-((*S*)-2-(*tert*-butoxycarbonylamino)propionamido)ethyl)carbamoyl

oxazol-5-yl)ethyl)carbamate

[00504] To 15 mL of dichloromethane were added *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.30 g, 0.48 mmol), Boc-*L*-alanine (109 mg, 0.58 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (140 mg, 0.72 mmol) and 1-hydroxy-7-azabenzotriazole (100 mg, 0.72 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.34 mL, 1.93 mmol) dropwise at 0 °C. The mixture was stirred at rt for 20 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (195 mg, 51%).

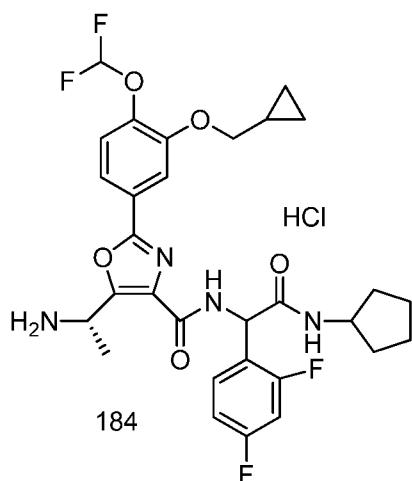
¹H NMR (400 MHz, CDCl₃): δ ppm 7.65 – 7.63 (m, 2H), 7.40 – 7.37 (m, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 6.92 – 6.86 (m, 2H), 6.73 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.50 – 5.48 (m, 1H), 5.34 – 5.30 (m, 1H), 4.17 – 4.12 (m, 1H), 4.02 (d, *J* = 6.9 Hz, 2H), 3.81 – 3.77 (m, 1H), 1.46 – 1.45 (m, 3H), 1.41 – 1.40 (m, 9H), 1.38 – 1.35 (m, 1H), 1.33 – 1.30 (m, 3H), 1.28 – 1.23 (m, 9H), 0.74 – 0.69 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: *m/z* 794.2 [M+H]⁺.

Step 2: 5-((*S*)-1-Aminoethyl)-*N*-(2-((*S*)-2-aminopropanamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide dihydrochloride

[00505] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-((*S*)-2-(*tert*-butoxycarbonylamino)propionamido)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.19 g, 0.24 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give a white solid (159 mg, 99%).

Compound 183: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.84 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.58 – 7.57 (m, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.06 – 7.01 (m, 2H), 6.93 (t, *J*_{F-H} = 74.8 Hz, 1H), 5.64 – 5.60 (m, 1H), 5.16 – 5.11 (m, 1H), 4.07 (d, *J* = 6.9 Hz, 2H), 3.95 – 3.89 (m, 2H), 3.70 – 3.65 (m, 1H), 1.75 (d, *J* = 5.9 Hz, 3H), 1.44 – 1.40 (m, 3H), 1.38 – 1.36 (m, 1H), 0.72 – 0.67 (m, 2H), 0.46 – 0.44 (m, 2H); and MS-ESI: *m/z* 594.2 [M+H-2HCl]⁺.

Example 73: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopentylamino)-1-(2,4-difluorophenyl)-2-oxoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(4-((2-(cyclopentylamino)-1-(2,4-difluorophenyl)-2-oxoethyl) carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl) carbamate

[00506] To 25 mL of dichloromethane were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (280 mg, 0.44 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (253 mg, 1.32 mmol) and 1-hydroxy-7-azabenzotriazole (89 mg, 0.66 mmol). To the mixture were added dropwise cyclopentanamine (75 mg, 0.88 mmol) and *N,N*-diisopropylethylamine (0.23 mL, 1.32 mmol) at 0 °C. The mixture was stirred at rt for 12 hours. The reaction mixture was washed with water (10 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (EtOAc/PE (v/v) = 4/1) to give a white solid (130 mg, 42%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.40 – 8.43 (m, 1H), 7.60 – 7.65 (m, 2H), 7.47 – 7.53 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.87 – 6.95 (m, 2H), 6.72 (t, *J*_{F-H} = 75.1 Hz, 1H), 5.81 (d, *J* = 6.8 Hz, 1H), 5.27 – 5.35 (m, 1H), 4.17 – 4.25 (m, 1H), 4.04 (d, *J* = 6.9 Hz, 2H), 1.90 – 2.06 (m, 2H), 1.56 – 1.72 (m, 6H), 1.44 – 1.53 (m, 3H), 1.40 – 1.44 (m, 9H), 1.31 – 1.37 (m, 1H), 0.69 – 0.74 (m, 2H), 0.43 – 0.47 (m, 2H); and MS-ESI: *m/z* 727.20 [M+Na]⁺.

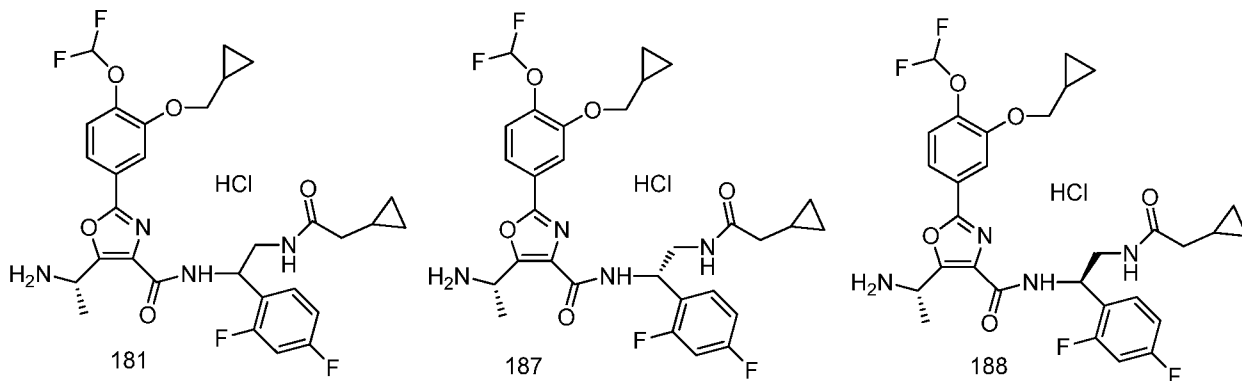
Step 2: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopentylamino)-1-(2,4-difluorophenyl)-2-oxoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00507] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-(cyclopentylamino)-1-(2,4-

difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (130 mg, 0.18 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give a white solid (115 mg, 97%).

Compound 184: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.78 (s, 1H), 7.71 – 7.73 (m, 1H), 7.54 – 7.58 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.04 – 7.07 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.90 (d, $J = 4.6$ Hz, 1H), 5.15 – 5.20 (m, 1H), 4.15 – 4.20 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 1.90 – 2.06 (m, 2H), 1.75 (d, $J = 7.0$ Hz, 3H), 1.51– 1.74 (m, 5H), 1.39– 1.44 (m, 1H), 1.37– 1.43 (m, 1H), 0.68 – 0.71 (m, 2H), 0.42 – 0.45 (m, 2H); and MS-ESI: m/z 605.20 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 74: 5-((*S*)-1-Aminoethyl)-*N*-(2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride, 5-((*S*)-1-aminoethyl)-*N*-((*S*)-2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-*N*-((*R*)-2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(4-((2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00508] To 15 mL of dichloromethane were added *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.30 g, 0.48 mmol), 2-cyclopropylacetic acid (58 mg, 0.58 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (140 mg, 0.72 mmol) and 1-hydroxy-7-azabenzotriazole (100 mg, 0.72 mmol). To the mixture was

added *N,N*-diisopropylethylamine (0.34 mL, 1.93 mmol) dropwise at 0 °C. The mixture was stirred at rt for 15 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a white solid (168 mg, 49%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.65 – 7.63 (m, 2H), 7.42 – 7.38 (m, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.73 (t, *J*_{F-H} = 75.0 Hz, 1H), 6.36 – 6.34 (m, 1H), 5.53 – 5.50 (m, 1H), 5.32 – 5.28 (m, 1H), 4.03 (d, *J* = 7.0 Hz, 2H), 3.85 – 3.81 (m, 1H), 3.76 – 3.71 (m, 1H), 2.18 – 2.14 (m, 2H), 1.55 – 1.48 (m, 3H), 1.45 – 1.41 (m, 9H), 1.37 – 1.34 (m, 1H), 1.33 – 1.30 (m, 1H), 0.92 – 0.88 (m, 2H), 0.74 – 0.69 (m, 2H), 0.57 – 0.55 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: *m/z* 705.2 [M+H]⁺.

Step 2: 5-((*S*)-1-Aminoethyl)-*N*-(2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride, 5-((*S*)-1-aminoethyl)-*N*-((*S*)-2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-*N*-((*R*)-2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00509] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.16 g, 0.23 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give compound 5-((*S*)-1-aminoethyl)-*N*-(2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride as a white solid (170 mg, 99%).

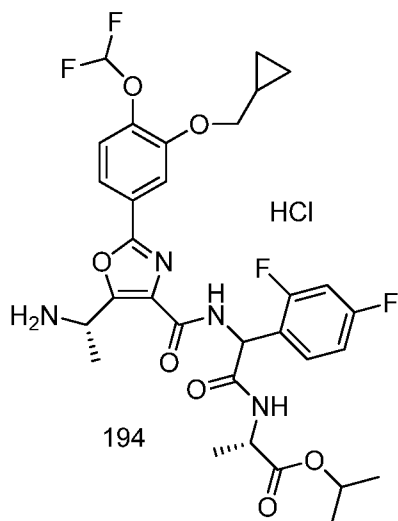
[00510] The compound 5-((*S*)-1-aminoethyl)-*N*-(2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride was further separated by preparative chiral HPLC to give compound 5-((*S*)-1-aminoethyl)-*N*-((*S*)-2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride as a light yellow solid and 5-((*S*)-1-aminoethyl)-*N*-((*R*)-2-(2-cyclopropylacetamido)-1-(2,4-difluorophenyl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-

carboxamide hydrochloride as a white solid.

Compound 187: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.71 (d, $J = 8.4$ Hz, 1H), 7.46 – 7.40 (m, 1H), 7.29 (d, $J = 8.3$ Hz, 1H), 6.98 – 6.91 (m, 2H), 6.87 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.49 – 5.46 (m, 1H), 5.06 – 5.01 (m, 1H), 4.02 (d, $J = 6.9$ Hz, 2H), 3.72 – 3.62 (m, 2H), 2.04 (d, $J = 7.1$ Hz, 2H), 1.68 (d, $J = 6.9$ Hz, 3H), 1.35 – 1.30 (m, 1H), 1.30 – 1.26 (m, 1H), 0.67 – 0.62 (m, 2H), 0.45 – 0.37 (m, 4H), 0.10 – 0.06 (m, 2H); and MS-ESI: m/z 605.2 $[\text{M}+\text{H}-\text{HCl}]^+$;

Compound 188: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.71 (d, $J = 8.4$ Hz, 1H), 7.46 – 7.40 (m, 1H), 7.29 (d, $J = 8.3$ Hz, 1H), 6.98 – 6.91 (m, 2H), 6.87 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.49 – 5.46 (m, 1H), 5.06 – 5.01 (m, 1H), 4.02 (d, $J = 6.9$ Hz, 2H), 3.72 – 3.62 (m, 2H), 2.04 (d, $J = 7.1$ Hz, 2H), 1.68 (d, $J = 6.9$ Hz, 3H), 1.35 – 1.30 (m, 1H), 1.30 – 1.26 (m, 1H), 0.67 – 0.62 (m, 2H), 0.45 – 0.37 (m, 4H), 0.10 – 0.06 (m, 2H); and MS-ESI: m/z 605.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 75: (2S)-Isopropyl 2-(2-(5-((S)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetamido)propanoate hydrochloride



Step 1: L-Alanine isopropyl ester hydrochloride

[00511] To 20 mL of dichloromethane were added Boc-*L*-alanine (1 g, 5.29 mmol), isopropanol (0.49 mL, 6.34 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.52 g, 7.93 mmol) and 1-hydroxy-7-azabenzotriazole (1.08 g, 7.93 mmol). To the mixture was added *N,N*-diisopropylethylamine (3.7 mL, 21.14 mmol) dropwise at 0 °C. The mixture was stirred at rt for 16 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 10/1) to give the compound *N*-Boc-*L*-Alanine isopropyl ester as colourless oil (630 mg, 51%).

¹H NMR (400 MHz, CDCl₃): δ ppm 5.05 – 5.01 (m, 1H), 4.24 – 4.21 (m, 1H), 1.44 (s, 9H), 1.34 (d, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 6.6 Hz, 6H); and MS-ESI: *m/z* 254.1 [M+23].

[00512] To a solution of *N*-Boc-*L*-Alanine isopropyl ester (0.25 g, 1.08 mmol) in dichloromethane (3 mL) was added a solution of hydrogen chloride in ethyl acetate (4M, 8 mL). The mixture was stirred at rt for 5 hours. The solvent was removed to give colourless oil (181mg, 99%).

¹H NMR (400 MHz, CD₃OD): δ ppm 5.06 – 5.00 (m, 1H), 4.00 – 3.94 (m, 1H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.24 – 1.22 (m, 6H); and MS-ESI: *m/z* 132.2 [M+H-HCl]⁺.

Step 2: (2*S*)-Isopropyl 2-(2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetamido)propanoate

[00513] To 15 mL of dichloromethane were added (2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.23 g, 0.36 mmol), *L*-alanine isopropyl ester hydrochloride (72 mg, 0.43 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (104 mg, 0.54 mmol) and 1-hydroxy-7-azabenzotriazole (74 mg, 0.54 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.25 mL, 1.44 mmol) dropwise at 0 °C. The mixture was stirred at rt for 12 hours. The solvent was removed and the residue was purified by silica gel column chromatography (developing solvent: PE/EtOAc (v/v) = 3/1) to give a light yellow solid (118 mg, 43%).

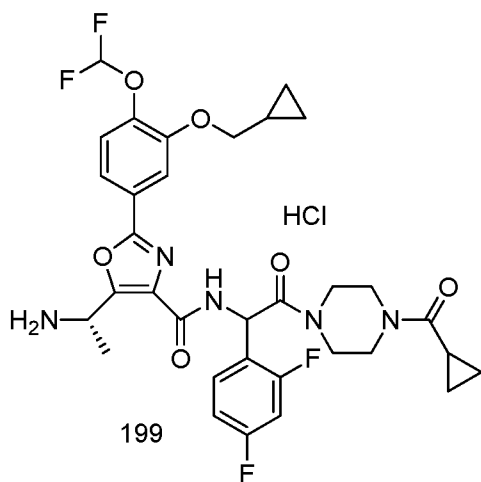
¹H NMR (400 MHz, CDCl₃): δ ppm 7.65 – 7.62 (m, 1H), 7.61 – 7.60 (m, 1H), 7.52 – 7.48 (m, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 6.95 – 6.90 (m, 2H), 6.73 (t, *J*_{F-H} = 74.5 Hz, 1H), 6.53 – 6.52 (m, 1H), 5.92 (d, *J* = 7.2 Hz, 1H), 5.33 – 5.29 (m, 1H), 5.09 – 4.99 (m, 1H), 4.57 – 4.49 (m, 1H), 4.03 (d, *J* = 6.9 Hz, 2H), 1.53 – 1.50 (m, 3H), 1.42 – 1.36 (m, 9H), 1.28 (t, *J* = 7.1 Hz, 6H), 1.24 – 1.20 (m, 3H), 0.74 – 0.69 (m, 2H), 0.47 – 0.43 (m, 2H); and MS-ESI: *m/z* 751.2 [M+H]⁺.

Step 3: (2*S*)-Isopropyl 2-(2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetamido)propanoate hydrochloride

[00514] To a solution of (2*S*)-isopropyl 2-(2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetamido)propanoate (0.11 g, 0.15 mmol) in dichloromethane (3 mL) was added

a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 3 hours and then the solvent was removed to give a light yellow solid (100 mg, 97%).

Example 76: 5-((S)-1-aminoethyl)-N-(2-(4-(cyclopropanecarbonyl)piperazin-1-yl)-1-(2,4-difluorophenyl)-2-oxoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1S)-1-(4-((2-(4-(cyclopropanecarbonyl)piperazin-1-yl)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00515] To 15 mL of dichloromethane were added 2-(5-((S)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (210 mg, 0.33 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (126 mg, 0.66 mmol) and 1-hydroxy-7-azabenzotriazole (67 mg, 0.49 mmol). To the mixture were added dropwise cyclopropyl(piperazin-1-yl)methanone hydrochloride (94 mg, 0.49 mmol) and *N,N*-diisopropylethylamine (0.23 mL, 0.99 mmol) at 0 °C. The mixture was stirred at rt for 12 hours. The mixture was washed with water (10 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (160 mg, 63%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.51 (d, *J* = 6.6 Hz, 1H), 7.60 – 7.64 (m, 2H), 7.52 – 7.57 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.88 – 6.95 (m, 2H), 6.73 (t, *J*_{F-H} = 75.1 Hz, 1H), 6.32 (d, *J* = 7.3 Hz, 1H), 5.27 – 5.34 (m, 1H), 4.02 (d, *J* = 6.9 Hz, 2H), 3.35 – 3.82 (m, 8H), 1.67 – 1.74 (m, 1H), 1.48 – 1.53 (m, 3H), 1.40 – 1.45 (m, 9H), 1.32 – 1.36 (m, 1H), 0.86 – 0.93 (m, 2H),

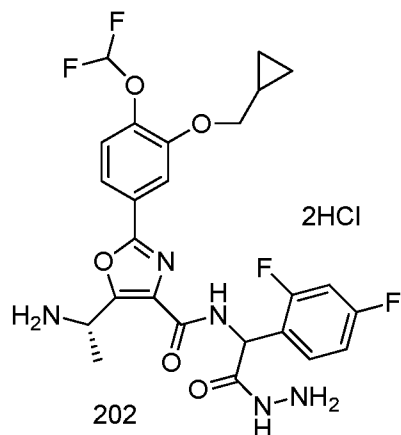
0.78 – 0.83 (m, 2H), 0.69 – 0.73 (m, 2H), 0.42 – 0.47 (m, 2H); and MS-ESI: m/z 796.20 $[M+Na]^+$.

Step 2: 5-((*S*)-1-Aminoethyl)-*N*-(2-(4-(cyclopropanecarbonyl)piperazin-1-yl)-1-(2,4-difluorophenyl)-2-oxoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00516] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-(4-(cyclopropanecarbonyl)piperazin-1-yl)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (85 mg, 0.11 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give a white solid (75 mg, 96%).

Compound 199: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.77 – 7.79 (m, 1H), 7.71 – 7.74 (m, 1H), 7.61 – 7.55 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.08 – 7.14 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 75.1$ Hz, 1H), 6.31 (s, 1H), 5.14 – 5.21 (m, 1H), 4.04 (d, $J = 6.8$ Hz, 2H), 3.18 – 3.87 (m, 8H), 1.89 – 2.00 (m, 1H), 1.76 (d, $J = 6.8$ Hz, 3H), 1.34 – 1.39 (m, 1H), 0.81 – 0.91 (m, 4H), 0.67 – 0.71 (m, 2H), 0.42 – 0.46 (m, 2H); and MS-ESI: m/z 674.20 $[M+H-\text{HCl}]^+$.

Example 77: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-hydrazinyl-2-oxoethyl)oxazole-4-carboxamide dihydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-hydrazinyl-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00517] To a solution of methyl 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate (250 mg, 0.38 mmol) in methanol (20 mL) was added hydrazinium hydroxide (80%, 1 mL). The mixture was stirred at 60 °C for 2.5 hours, then the solvent was removed to

give a white solid (240 mg, 96%).

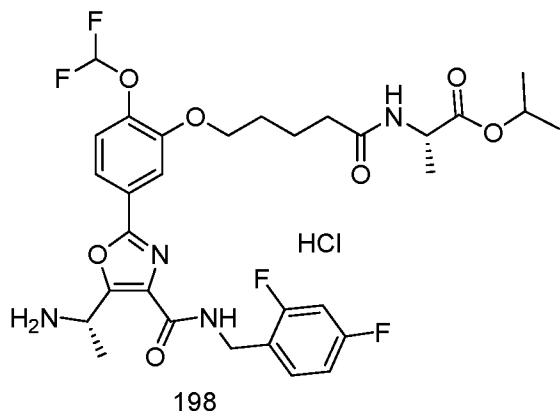
^1H NMR (600 MHz, CDCl_3): δ ppm 7.63 – 7.61 (m, 1H), 7.60 (s, 1H), 7.53 – 7.48 (m, 1H), 7.26 (d, $J = 8.3$ Hz, 1H), 6.95 – 6.88 (m, 2H), 6.74 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.92 (d, $J = 7.6$ Hz, 1H), 5.35 – 5.30 (m, 1H), 4.02 – 4.01 (m, 2H), 1.54 – 1.47 (m, 3H), 1.46 – 1.41 (m, 9H), 1.37 – 1.34 (m, 1H), 0.73 – 0.70 (m, 2H), 0.46 – 0.40 (m, 2H); and MS-ESI: m/z 552.2 $[\text{M}+\text{H}-100]^+$.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-hydrazinyl-2-oxoethyl)oxazole-4-carboxamide dihydrochloride

[00518] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-hydrazinyl-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl) carbamate (0.24 g, 0.37 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 4 mL). The resulting mixture was stirred at rt for 1.5 hours and then the solvent was removed to give a light yellow solid (220 mg, 95%).

Compound 202: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.80 – 7.79 (m, 1H), 7.75 – 7.72 (m, 1H), 7.68 – 7.63 (m, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.14 – 7.07 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 6.09 – 6.08 (m, 1H), 5.24 – 5.19 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 1.79 – 1.76 (m, 3H), 1.38 – 1.33 (m, 1H), 0.71 – 0.66 (m, 2H), 0.45 – 0.41 (m, 2H); and MS-ESI: m/z 552.2 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 78: (*S*)-Isopropyl 2-(5-(5-(5-((*S*)-1-aminoethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanamido)propanoate hydrochloride



Step 1: Methyl 3-(benzyloxy)-4-(difluoromethoxy)benzoate

[00519] To 60 mL of *N,N*-dimethylformamide were added methyl 4-(difluoromethoxy)-3-hydroxybenzoate (5.0 g, 22.94 mmol), potassium carbonate (6.33 g, 45.88 mmol) and benzyl bromide (3.3 mL, 27.53 mmol). The whole mixture was stirred at 60 °C for 4.5 hours. To the reaction mixture was added water (40 mL) and the resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were dried over

anhydrous sodium sulfate, and the solvent was removed. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a white solid (6.99 g, 99%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.75 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.48 - 7.38 (m, 5H), 7.24 (d, *J* = 8.3 Hz, 1H), 6.67 (t, *J*_{F-H} = 74.6 Hz, 1H), 5.20 (s, 2H), 3.93 (s, 3H); and MS-ESI: 309.0 [M+H]⁺.

Step 2: 3-(Benzyloxy)-4-(difluoromethoxy)benzoic acid

[00520] To a mixed solvent of ethanol (60 mL) and water (30 mL) were added methyl 3-(benzyloxy)-4-(difluoromethoxy)benzoate (6.99 g, 22.69 mmol) and sodium hydroxide (2.27 g, 56.74 mmol). The mixture was stirred at 60 °C for 1.5 hours, then ethanol was removed. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The mixture was extracted with ethyl acetate (50 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give a white solid (6.70 g, 99%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.80 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 7.0 Hz, 2H), 7.43 - 7.35 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 1H), 6.88 (t, *J*_{F-H} = 74.5 Hz, 1H), 5.23 (s, 2H); and MS-ESI: 293.1 [M-H]⁻.

Step 3: Methyl 2-(3-(benzyloxy)-4-(difluoromethoxy)benzamido)acetate

[00521] To 60 mL of dichloromethane were added 3-(benzyloxy)-4-(difluoromethoxy)benzoic acid (6.70 g, 22.79 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.60 g, 34.19 mmol) and 1-hydroxy-7-azabenzotriazole (4.62 g, 34.19 mmol). The mixture was stirred at rt for 30 minutes, then glycine methyl ester hydrochloride (3.44 g, 27.35 mmol) and *N,N*-diisopropylethylamine (12.25 mL, 68.37 mmol) were added dropwise at 0 °C. The resulting mixture was stirred at rt for 12 hours. The reaction mixture was washed with water (40 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed, then the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (7.95 g, 96%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.62 (s, 1H), 7.47 - 7.33 (m, 6H), 7.24 (d, *J* = 8.3 Hz, 1H), 6.67 (br.s, 1H), 6.65 (t, *J*_{F-H} = 74.5 Hz, 1H), 5.20 (s, 2H), 4.25 (d, *J* = 5.0 Hz, 2H), 3.83 (s, 3H); and MS-ESI: *m/z* 366.2 [M+H]⁺.

Step 4: Methyl 2-(3-(benzyloxy)-4-(difluoromethoxy)phenylthioamido)acetate

[00522] To 60 mL of tetrahydrofuran were added methyl

2-(3-(benzyloxy)-4-(difluoromethoxy)benzamido)acetate (7.95 g, 21.80 mmol) and Lawesson's Reagent (8.80 g, 21.80 mmol). The mixture was refluxed at 75 °C for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (40 mL). The resulting mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a yellow solid (8.33 g, 99%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.08 (br.s, 1H), 7.69 (s, 1H), 7.50 - 7.28 (m, 6H), 7.21 (d, *J* = 8.3 Hz, 1H), 6.64 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.21 (s, 2H), 4.57 (d, *J* = 4.5 Hz, 2H), 3.88 (s, 3H); and MS-ESI: *m/z* 380.0 [M-H]⁻.

Step 5: Methyl 2-(((3-(benzyloxy)-4-(difluoromethoxy)phenyl)(methylthio)methylene)amino)acetate

[00523] To a solution of trimethyloxonium tetrafluoroborate (6.47 g, 43.74 mmol) in dichloromethane (30 mL) was added dropwise a solution of methyl 2-(3-(benzyloxy)-4-(difluoromethoxy)phenylthioamido)acetate (8.33 g, 21.87 mmol) in dichloromethane (30 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then washed with saturated aqueous sodium bicarbonate (25 mL × 3). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed to give yellow oil (8.55 g, 99%).

MS-ESI: *m/z* 396.2 [M+H]⁺.

Step 6: (S)-Methyl 2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylate

[00524] To 30 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-(benzyloxy)-4-(difluoromethoxy)phenyl)(methylthio)methylene)amino)acetate (3.45 g, 8.74 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (4.45 g, 23.30 mmol). To the mixture was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (30.00 mL, 30.00 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a yellow solid (3.78 g, 83%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.80 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.50 - 7.36 (m,

5H), 7.29 (d, $J = 8.3$ Hz, 1H), 6.66 (t, $J_{F-H} = 74.7$ Hz, 1H), 5.68 (br.s, 1H), 5.53 - 5.45 (m, 1H), 5.23 (s, 2H), 4.01 (s, 3H), 1.57 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H).

Step 7: (*S*)-2-(3-(Benzyloxy)-4-(difluoromethoxy)phenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylic acid

[00525] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added (*S*)-methyl 2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylate (0.55 g, 1.06 mmol) and lithium hydroxide monohydrate (0.22 g, 5.30 mmol). The solution was stirred at 40 °C for 3 hours and tetrahydrofuran was removed, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (30 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give a white solid (0.53 g, 99%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.80 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.51 – 7.35 (m, 5H), 7.29 (d, $J = 8.4$ Hz, 1H), 6.66 (t, $J_{F-H} = 74.7$ Hz, 1H), 5.68 (br.s, 1H), 5.53 – 5.46 (m, 1H), 5.23 (s, 2H), 1.57 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H); and MS-ESI: m/z 449.2 [M-55].

Step 8: (*S*)-*tert*-Butyl (1-(2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00526] To 15 mL of dichloromethane were added (*S*)-2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylic acid (0.53 g, 1.05 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.31 g, 1.60 mmol) and 1-hydroxy-7-azabenzotriazole (0.22 g, 1.60 mmol). The mixture was stirred at rt for 30 minutes, then (2,4-difluorophenyl)methanamine (0.15 mL, 1.26 mmol) and *N,N*-diisopropylethylamine (0.58 mL, 3.20 mmol) were added dropwise at 0 °C. The resulting mixture was stirred at rt for 12 hours. To the reaction mixture was added water (15 mL), and the resulting mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a white solid (211.0 mg, 38%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.69 (s, 1H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.56 (br.s, 1H), 7.50 - 7.36 (m, 6H), 7.28 (d, $J = 8.3$ Hz, 1H), 6.92 - 6.85 (m, 2H), 6.56 (t, $J_{F-H} = 74.6$ Hz, 1H), 5.32 (br.s, 1H), 5.24 (s, 2H), 4.73 - 4.63 (m, 2H), 1.56 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H); and

MS-ESI: m/z 574.1 $[M-55]^+$.

Step 9: (*S*)-*tert*-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-hydroxyphenyl)oxazol-5-yl)ethyl)carbamate

[00527] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (2.53 g, 4.02 mmol) and nickel chloride (782 mg, 6.03 mmol) in ethanol (20 mL) was added a solution of sodium borohydride (688 mg, 18.09 mmol) in ethanol (20 mL). The mixture was stirred at rt for 3 hours. The mixture was adjusted to pH 1 with hydrochloric acid (1 M) and then to pH 14 with sodium hydroxide. The mixture was filtered and the filtrate was concentrated to remove ethanol. The residue was extracted with ethyl acetate (20 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a white solid (1.719 g, 80%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.60 - 7.57 (m, 2H), 7.45 - 7.38 (m, 2H), 7.16 (d, J = 8.3 Hz, 1H), 6.88 - 6.84 (m, 2H), 6.65 (t, $J_{\text{F-H}}$ = 73.6 Hz, 1H), 5.31 (s, 1H), 4.69 - 4.59 (m, 2H), 1.53 (d, J = 7.0 Hz, 3H), 1.44 (s, 9H); and MS-ESI: 540.3 $[M+H]^+$.

Step 10: (*S*)-Methyl 5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate

[00528] To a solution of (*S*)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-hydroxyphenyl)oxazol-5-yl)ethyl)carbamate (560 mg, 1.04 mmol) and methyl 5-bromovalerate (304 mg, 1.56 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (290 mg, 2.07 mmol). The mixture was stirred at 60 °C in a sealed tube for 5 hours. The solvent was removed and to the residue was added water (10 mL). The mixture was extracted with ethyl acetate (15 mL) and the organic layer was dried over anhydrous sodium sulfate. The organic layer was concentrated and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give colourless oil (448 mg, 66%).

Step 11: (*S*)-5-(5-(5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid

[00529] To a solution of (*S*)-methyl 5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate (250 mg, 0.38 mmol) in a mixed solvent of tetrahydrofuran (16 mL) and water (8 mL) was added lithium

hydroxide monohydrate (80 mg, 1.91 mmol). The mixture was stirred at 40 °C for 2 hours, and hydrochloric acid (1 M) was added to adjust the pH to about 1. The resulting mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give colourless oil (240 mg, 98%).

Step 12: (S)-Isopropyl 2-(5-(5-(5-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanamido)propanoate

[00530] To 15 mL of dichloromethane were added (S)-5-(5-(5-(1-((tert-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (0.25 g, 0.39 mmol), *L*-alanine isopropyl ester hydrochloride (80 mg, 0.47 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (112 mg, 0.59 mmol) and 1-hydroxy-7-azabenzotriazole (80 mg, 0.59 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.27 mL, 1.56 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 4 hours. The reaction mixture was washed with water (10 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give colourless oil (235 mg, 80%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.60 – 7.58 (m, 2H), 7.47 - 7.41 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.65 (t, *J*_{F-H} = 74.5 Hz, 1H), 6.14 – 6.12 (m, 1H), 5.09 – 5.03 (m, 1H), 4.69 – 4.67 (m, 2H), 4.58 – 4.54 (m, 1H), 4.17 – 4.13 (m, 2H), 2.36 (t, *J* = 6.9 Hz, 2H), 1.95 – 1.89 (m, 4H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.45 (s, 9H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 5.8 Hz, 6H); and MS-ESI: *m/z* 753.2 [M+H]⁺.

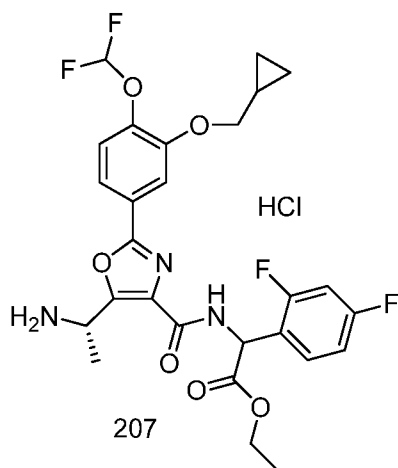
Step 13: (S)-Isopropyl 2-(5-(5-(5-((S)-1-aminoethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanamido)propanoate hydrochloride

[00531] To a solution of (S)-isopropyl 2-(5-(5-(5-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanamido)propanoate (0.22 g, 0.29 mmol) in dichloromethane (3 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 40 minutes, then the solvent was removed to give a white solid (192 mg, 94%).

Compound 198: ¹H NMR (400 MHz, CD₃OD): δ ppm 7.82 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H),

7.52 – 7.46 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.01 – 6.94 (m, 2H), 6.89 (t, $J_{F-H} = 74.5$ Hz, 1H), 5.21 – 5.15 (m, 1H), 5.01 – 4.95 (m, 1H), 4.65 (s, 2H), 4.36 – 4.30 (m, 1H), 4.20 (t, $J = 6.0$ Hz, 2H), 2.38 – 2.34 (m, 2H), 1.94 – 1.83 (m, 4H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.37 (d, $J = 7.3$ Hz, 3H), 1.24 (t, $J = 6.6$ Hz, 6H); and MS-ESI: m/z 653.3 $[M+H-HCl]^+$.

Example 79: Ethyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride



Step 1: Ethyl 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate

[00532] To 20 mL of anhydrous tetrahydrofuran were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.25 g, 0.39 mmol) and 1,1'-carbonyldiimidazole (197 mg, 1.17 mmol). The solution was stirred at 60 °C for 30 minutes, then cooled to rt. To the mixture were added anhydrous ethanol (22 mg, 0.47 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.09 mL, 0.59 mmol). After addition, the mixture was stirred at 60 °C for 8 hours. To the reaction mixture was added saturated aqueous ammonium chloride (15 mL) and the resulting mixture was extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a white solid (200 mg, 76%).

^1H NMR (600 MHz, CDCl_3): δ ppm 7.63 (d, $J = 8.3$ Hz, 1H), 7.59 (s, 1H), 7.51 – 7.48 (m, 1H), 7.26 (d, $J = 8.3$ Hz, 1H), 6.94 – 6.88 (m, 2H), 6.73 (t, $J_{F-H} = 75.0$ Hz, 1H), 5.98 – 5.96 (m, 1H), 5.32 – 5.30 (m, 1H), 5.20 – 5.18 (m, 1H), 4.56 – 4.54 (m, 1H), 4.32 – 4.25 (m, 2H), 4.02 (d, $J = 6.7$ Hz, 2H), 1.56 – 1.49 (m, 3H), 1.46 (s, 9H), 1.38 – 1.35 (m, 1H), 1.28 – 1.27 (m, 3H),

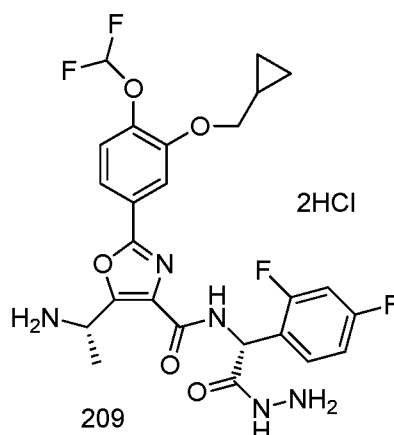
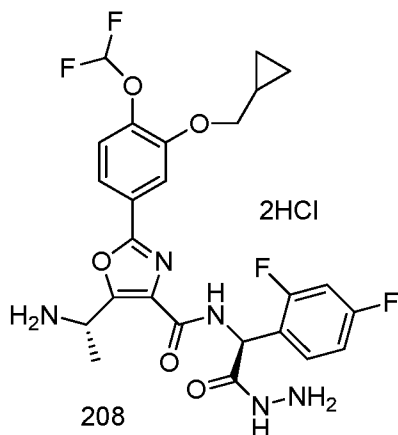
0.73 – 0.70 (m, 2H), 0.46 – 0.45 (m, 2H); and MS-ESI: m/z 566.2 $[M+H-100]^+$.

Step 2: Ethyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride

[00533] To a solution of ethyl 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate (0.2 g, 0.30 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 2 mL). The mixture was stirred at rt for 40 minutes and then the solvent was removed to give a white solid (180 mg, 99%).

Compound 207: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.80 (s, 1H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.60 – 7.56 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.09 – 7.03 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 6.01 (s, 1H), 5.20 – 5.18 (m, 1H), 4.63 – 4.62 (m, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 4.05 (d, $J = 6.9$ Hz, 2H), 1.76 (d, $J = 6.7$ Hz, 3H), 1.62 (d, $J = 7.2$ Hz, 3H), 1.36 – 1.34 (m, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 0.70 – 0.67 (m, 2H), 0.45 – 0.43 (m, 2H); and MS-ESI: m/z 566.2 $[M+H-\text{HCl}]^+$.

Example 80: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-hydrazinyl-2-oxoethyl)oxazole-4-carboxamide dihydrochloride and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-hydrazinyl-2-oxoethyl)oxazole-4-carboxamide dihydrochloride



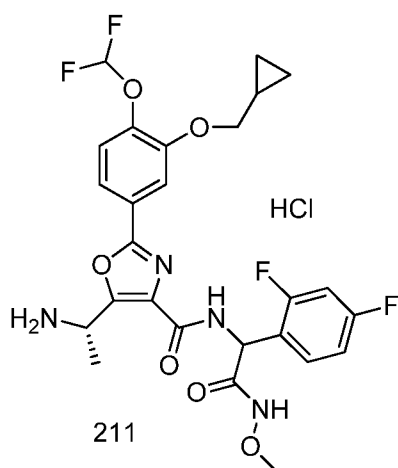
[00534] The compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-hydrazinyl-2-oxoethyl)oxazole-4-carboxamide dihydrochloride prepared from **Example 77** was further separated by preparative chiral HPLC to give 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-hydrazinyl-2-oxoethyl)oxazole-4-carboxamide dihydrochloride as a white solid and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-

N-((*R*)-1-(2,4-difluorophenyl)-2-hydrazinyl-2-oxoethyl)oxazole-4-carboxamide dihydrochloride as a light yellow solid.

Compound 208: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.66 – 7.62 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.13 – 7.08 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 6.08 (s, 1H), 5.25 – 5.23 (m, 1H), 4.03 (d, $J = 6.9$ Hz, 2H), 1.76 (d, $J = 7.0$ Hz, 3H), 1.36 – 1.33 (m, 1H), 0.71 – 0.68 (m, 2H), 0.44 – 0.42 (m, 2H); and MS-ESI: m/z 552.2 $[\text{M}+\text{H}-2\text{HCl}]^+$;

Compound 209: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.67 – 7.63 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.13 – 7.08 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 6.07 (s, 1H), 5.21 – 5.17 (m, 1H), 4.03 (d, $J = 6.9$ Hz, 2H), 1.76 (d, $J = 6.8$ Hz, 3H), 1.35 – 1.31 (m, 1H), 0.70 – 0.67 (m, 2H), 0.44 – 0.42 (m, 2H); and MS-ESI: m/z 552.2 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 81: 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(methoxyamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(methoxyamino)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate [00535] To 15 mL of dichloromethane were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.25 g, 0.39 mmol), methoxyamine hydrochloride (40 mg, 0.47 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (112 mg, 0.59 mmol) and 1-hydroxy-7-azabenzotriazole (80 mg, 0.59 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.27 mL, 1.57 mmol) dropwise at 0 °C. The mixture was stirred at rt for 15 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give colourless oil (130 mg, 49%).

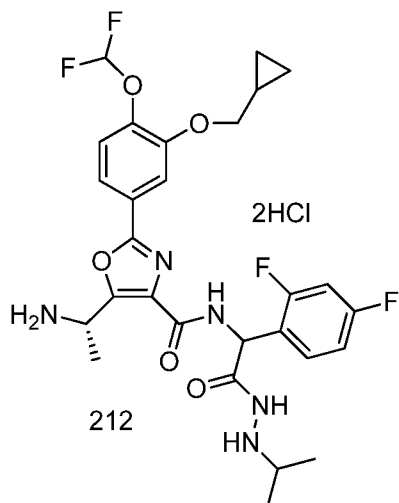
^1H NMR (600 MHz, CDCl_3): δ ppm 7.63 – 7.60 (m, 2H), 7.56 – 7.55 (m, 1H), 7.26 (d, J = 8.2 Hz, 1H), 6.96 – 6.88 (m, 2H), 6.74 (t, $J_{\text{F-H}}$ = 75.0 Hz, 1H), 5.87 – 5.84 (m, 1H), 5.36 – 5.31 (m, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.81 (s, 3H), 1.54 – 1.49 (m, 3H), 1.45 – 1.41 (m, 9H), 1.36 – 1.33 (m, 1H), 0.73 – 0.70 (m, 2H), 0.45 – 0.44 (m, 2H); and MS-ESI: m/z 567.1 $[\text{M}+\text{H}-100]^+$.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(methoxyamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride

[00536] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(methoxyamino)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.13 g, 0.19 mmol) in dichloromethane (3 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 2 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give a light yellow solid (110 mg, 95%). The crude product was further purified to give the desired product as a white solid (80 mg).

Compound 211: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.63 – 7.61 (m, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.07 – 7.03 (m, 2H), 6.92 (t, $J_{\text{F-H}}$ = 74.7 Hz, 1H), 5.87 – 5.86 (m, 1H), 5.20 – 5.17 (m, 1H), 4.04 (d, J = 6.8 Hz, 2H), 3.72 (s, 3H), 1.77 – 1.75 (m, 3H), 1.36 – 1.31 (m, 1H), 0.70 – 0.67 (m, 2H), 0.44 – 0.43 (m, 2H); and MS-ESI: m/z 567.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 82: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(2-isopropylhydrazinyl)-2-oxoethyl)oxazole-4-carboxamide dihydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(2-isopropylhydrazinyl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00537] To 15 mL of dichloromethane were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.25 g, 0.39 mmol), isopropylhydrazine hydrochloride (59 mg, 0.47 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (112 mg, 0.59 mmol) and 1-hydroxy-7-azabenzotriazole (80 mg, 0.59 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.27 mL, 1.57 mmol) dropwise at 0 °C. The mixture was stirred at rt for 20 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give colourless oil (148 mg, 54%).

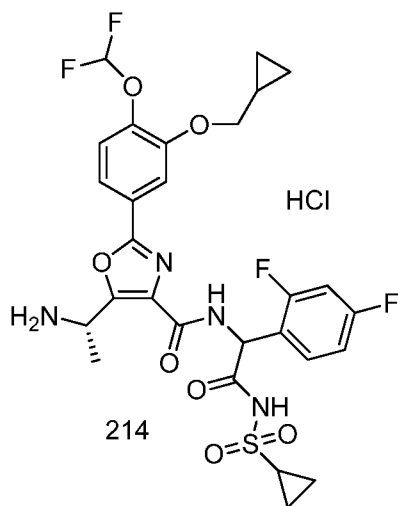
¹H NMR (600 MHz, CDCl₃): δ ppm 7.63 (d, *J* = 8.3 Hz, 1H), 7.60 (s, 1H), 7.55 – 7.51 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.74 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.89 (d, *J* = 7.4 Hz, 1H), 5.34 – 5.31 (m, 1H), 4.02 (d, *J* = 6.7 Hz, 2H), 1.53 – 1.49 (m, 3H), 1.45 – 1.41 (m, 9H), 1.35-1.38 (m, 1H), 1.04 (d, *J* = 5.9 Hz, 3H), 0.99 (d, *J* = 6.2 Hz, 3H), 0.73 – 0.70 (m, 2H), 0.46 – 0.43 (m, 2H); and MS-ESI: *m/z* 694.2 [M+H]⁺.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(2-isopropylhydrazinyl)-2-oxoethyl)oxazole-4-carboxamide dihydrochloride

[00538] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(2-isopropylhydrazinyl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.14 g, 0.21 mmol) in dichloromethane (3 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 2 mL). The resulting mixture was stirred at rt for 40 minutes and then the solvent was removed to give a white solid (120 mg, 92%). The crude product was further purified to give the desired product as a white solid (63 mg).

Compound 212: ¹H NMR (400 MHz, CD₃OD): δ ppm 7.79 (s, 1H), 7.74 – 7.66 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.13 – 7.10 (m, 2H), 6.91 (t, *J*_{F-H} = 74.7 Hz, 1H), 6.06 – 6.05 (m, 1H), 5.21 – 5.18 (m, 1H), 4.03 (d, *J* = 6.6 Hz, 2H), 3.70 – 3.67 (m, 1H), 1.78 – 1.76 (m, 3H), 1.35 – 1.33 (m, 1H), 1.33 – 1.30 (m, 6H), 0.69 – 0.67 (m, 2H), 0.43 – 0.42 (m, 2H); and MS-ESI: *m/z* 594.3 [M+H-2HCl]⁺.

Example 83: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)-2-oxoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(4-((2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00539] To 15 mL of anhydrous tetrahydrofuran were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.3 g, 0.47 mmol) and 1,1'-carbonyldiimidazole (236 mg, 1.41 mmol). The solution was stirred at 60 °C for 30 minutes, then cooled to rt. To the mixture were added cyclopropanesulfonamide (114 mg, 0.94 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.11 mL, 0.71 mmol) at rt. After addition, the mixture was stirred at 60 °C for 15 hours. To the reaction mixture was added saturated aqueous ammonium chloride (15 mL) and the resulting mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give yellow oil (340 mg, 97%).

¹H NMR (600 MHz, CDCl₃): δ ppm 7.61 – 7.58 (m, 2H), 7.53 – 7.50 (m, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.25 – 7.21 (m, 2H), 6.80 – 6.78 (m, 1H), 6.85 – 6.59 (m, 1H), 5.73 – 5.72 (m, 1H), 5.37 – 5.36 (m, 1H), 4.03 – 3.98 (m, 2H), 2.61 – 2.58 (m, 1H), 1.50 (d, *J* = 6.9 Hz, 3H), 1.42 – 1.39 (m, 9H), 1.33 – 1.30 (m, 1H), 1.21 – 1.19 (m, 2H), 1.15 – 1.13 (m, 1H), 1.05 – 1.03 (m, 2H), 0.70 – 0.66 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: *m/z* 641.1 [M+H-100]⁺.

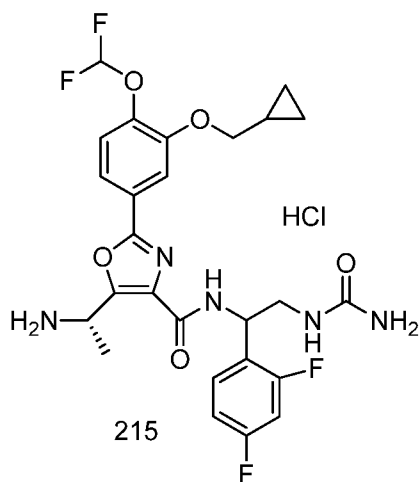
Step 2: 5-((*S*)-1-Aminoethyl)-*N*-(2-(cyclopropanesulfonamido)-1-(2,4-difluorophenyl)-2-oxoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00540] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-(cyclopropanesulfonamido)-1-

(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.34 g, 0.46 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 3 mL). The resulting mixture was stirred at rt for 1.5 hours and then the solvent was removed to give colourless oil (310 mg, 99%). The crude product was further purified by prep-HPLC to give a white solid (100 mg).

Compound 214: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.78 (s, 1H), 7.72 (d, $J = 8.3$ Hz, 1H), 7.59 – 7.55 (m, 1H), 7.32 (d, $J = 8.3$ Hz, 1H), 7.12 – 7.08 (m, 2H), 6.91 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.97 (d, $J = 7.0$ Hz, 1H), 5.23 – 5.19 (m, 1H), 4.02 (d, $J = 6.8$ Hz, 2H), 3.03 – 2.99 (m, 1H), 1.77 (d, $J = 6.7$ Hz, 3H), 1.35 – 1.32 (m, 1H), 1.30 – 1.29 (m, 2H), 1.23 – 1.19 (m, 1H), 1.18 – 1.14 (m, 2H), 0.69 – 0.66 (m, 2H), 0.42 – 0.41 (m, 2H); and MS-ESI: m/z 641.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 84: 5-((1S)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(1-(2,4-difluorophenyl)-2-ureidoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1S)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-ureidoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00541] To a solution of *tert*-butyl ((1S)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (200 mg, 0.32 mmol) and triethylamine (0.44 mL, 3.2 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise trimethylsilyl isocyanate (0.43 mL, 3.2 mmol). The mixture was stirred at rt for 2 hours and then ice-water was added. The mixture was extracted with ethyl acetate (10 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 40/1) to give a white solid (90 mg, 42%).

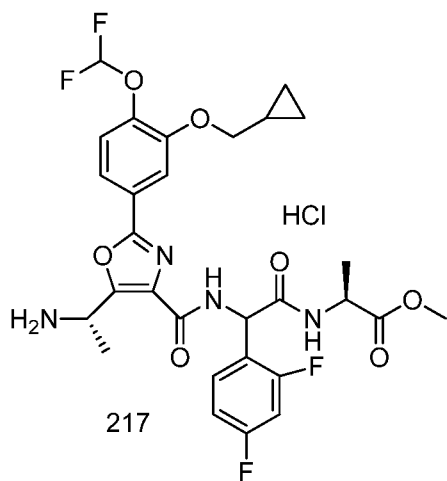
^1H NMR (600 MHz, CDCl_3): δ ppm 7.75 – 7.78 (m, 1H), 7.69 – 7.71 (m, 1H), 7.50 – 7.54 (m, 1H), 7.30 (d, $J = 8.3$ Hz, 1H), 6.98 – 7.03 (m, 2H), 6.90 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.36 – 5.45 (m, 2H), 4.03 – 4.06 (m, 2H), 3.58 – 3.72 (m, 2H), 1.47 – 1.50 (m, 3H), 1.42 (s, 9H), 1.31 – 1.37 (m, 1H), 0.68 – 0.71 (m, 2H), 0.43 – 0.46 (m, 2H); MS-ESI: m/z 666.20 $[\text{M}+\text{H}]^+$.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-ureidoethyl)oxazole-4-carboxamide hydrochloride

[00542] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-ureidoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (190 mg, 0.31 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (3.7 M, 2 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give a white solid (170 mg, 99%).

Compound 215: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.84 (s, 1H), 7.77 – 7.79 (m, 1H), 7.49 – 7.53 (m, 1H), 7.33 – 7.35 (m, 1H), 6.98 – 7.02 (m, 2H), 6.93 (t, $J_{\text{F-H}} = 75.1$ Hz, 1H), 5.45 – 5.48 (m, 1H), 5.09 – 5.16 (m, 1H), 4.08 (d, $J = 6.8$ Hz, 2H), 3.58 – 3.68 (m, 2H), 1.73 – 1.75 (m, 3H), 1.35 – 1.39 (m, 1H), 0.68 – 0.71 (m, 2H), 0.44 – 0.47 (m, 2H); and MS-ESI: m/z 566.20 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 85: (2*S*)-Methyl 2-(2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetamido)propanoate hydrochloride



Step 1: (2*S*)-Methyl 2-(2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetamido)propanoate

[00543] To 15 mL of dichloromethane were added 2-(5-(((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (230 mg, 0.36 mmol), *L*-alanine methyl ester hydrochloride (75 mg, 0.54 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (138 mg, 0.72 mmol) and 1-hydroxy-7-azabenzotriazole (74 mg, 0.54 mmol). To the mixture was added dropwise *N,N*-diisopropylethylamine (0.19 mL, 1.08 mmol) at 0 °C. The mixture was stirred at rt for 12 hours and then washed with water (10 mL × 3). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (EtOAc/PE (v/v) = 8/1) to give a white solid (190 mg, 79%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.30 – 8.35 (m, 1H), 7.60 – 7.64 (m, 2H), 7.47 – 7.53 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.89 – 6.93 (m, 2H), 6.73 (t, *J*_{F-H} = 74.9 Hz, 1H), 5.93 (d, *J* = 7.3 Hz, 1H), 5.28 – 5.34 (m, 1H), 4.57 – 4.63 (m, 1H), 4.02 (d, *J* = 6.9 Hz, 2H), 3.78 (s, 1.5H), 3.72 (s, 1.5H), 1.77 (s, 3H), 1.46 – 1.53 (m, 3H), 1.39 – 1.44 (m, 9H), 1.27 – 1.35 (m, 1H), 0.69 – 0.73 (m, 2H), 0.43 – 0.47 (m, 2H); and MS-ESI: *m/z* 723.15 [M+H]⁺.

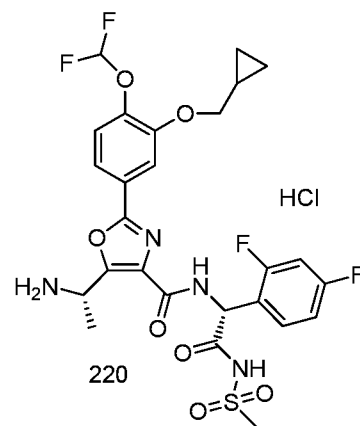
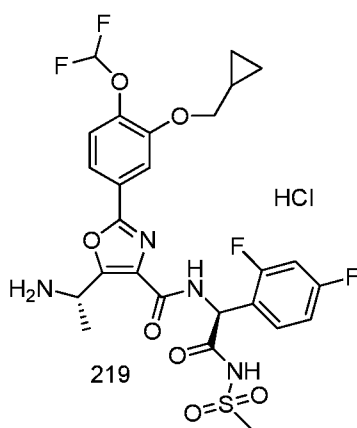
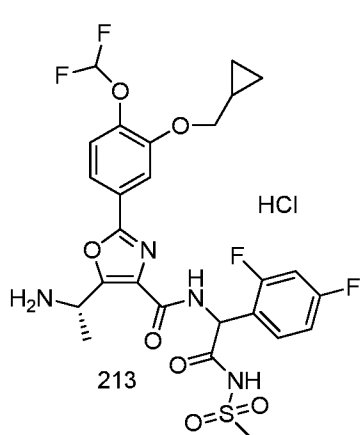
Step 2: (2*S*)-Methyl 2-(2-(5-(((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetamido)propanoate hydrochloride

[00544] To a solution of (2*S*)-methyl 2-(2-(5-(((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetamido)propanoate (190 mg, 0.26 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give a white solid (170 mg, 98%).

Compound 217: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.77 – 7.78 (m, 1H), 7.70 – 7.73 (m, 1H), 7.59 – 7.64 (m, 1H), 7.32 – 7.34 (m, 1H), 7.03 – 7.06 (m, 2H), 6.92 (td, *J* = 74.8, 3.4 Hz, 1H), 5.99 (d, *J* = 1.8 Hz, 1H), 5.16 – 5.21 (m, 1H), 4.45 – 4.51 (m, 1H), 4.02 – 4.04 (m, 2H), 3.75 (s, 1.5H), 3.69 (s, 1.5H), 1.78 (d, *J* = 6.8 Hz, 3H), 1.38 (dd, *J*₁ = 23.3 Hz, *J*₂ = 7.3 Hz, 3H), 1.32 – 1.35 (m, 1H), 0.67 – 0.70 (m, 2H), 0.41 – 0.45 (m, 2H); and MS-ESI: *m/z* 623.20 [M+H-HCl]⁺.

Example 86: 5-(((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)

-N-(1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)oxazole-4-carboxamide hydrochloride, 5-((S)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-((S)-1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)oxazole-4-carboxamide hydrochloride and 5-((S)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-((R)-1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl) carbamate

[00545] To 10 mL of anhydrous tetrahydrofuran were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.25 g, 0.39 mmol) and 1,1'-carbonyldiimidazole (197 mg, 1.17 mmol). The solution was stirred at 60 °C for 30 minutes, then cooled to rt. To the mixture were added methanesulfonamide (75 mg, 0.78 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.09 mL, 0.59 mmol) and anhydrous tetrahydrofuran (8 mL) at rt. After addition, the mixture was stirred at 60 °C for 10 hours. To the reaction mixture was added saturated aqueous ammonium chloride (15 mL) and the resulting mixture was extracted with ethyl acetate (10 mL × 3). The organic layer was dried over anhydrous sodium sulfate and concentrated to give a white solid (280 mg, 99%).

¹H NMR (600 MHz, CDCl₃): δ ppm 7.59 – 7.57 (m, 1H), 7.53 – 7.51 (m, 1H), 7.24 – 7.21 (m, 1H), 7.20 (s, 1H), 6.75 (br.s, 1H), 6.85 – 6.59 (m, 1H), 5.74 – 5.73 (m, 1H), 4.00 – 3.97 (m, 2H), 3.11 – 3.00 (m, 3H), 1.45 (d, *J* = 6.0 Hz, 3H), 1.43 – 1.39 (m, 9H), 1.33 – 1.30 (m, 1H), 0.70 – 0.65 (m, 2H), 0.42 – 0.36 (m, 2H); and MS-ESI: *m/z* 615.1 [M-100+H]⁺.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)oxazole-4-carboxamide hydrochloride, 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)oxazole-4-carboxamide hydrochloride

[00546] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.32 g, 0.45 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 3 mL). The resulting mixture was stirred at rt for 1 hour and then the solvent was removed to give compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)oxazole-4-carboxamide hydrochloride as a white solid (291 mg, 99%).

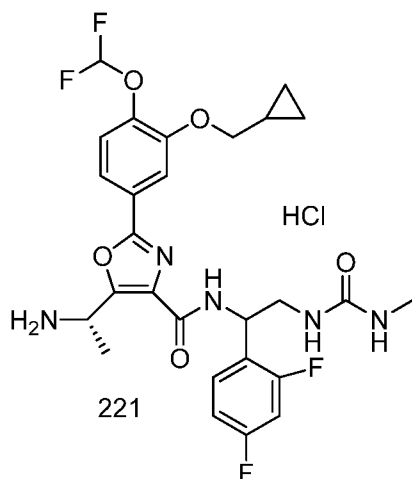
[00547] The compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)oxazole-4-carboxamide hydrochloride was further separated and purified by pre-HPLC to give 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)oxazole-4-carboxamide hydrochloride as a light yellow solid (65 mg) and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-(methylsulfonamido)-2-oxoethyl)oxazole-4-carboxamide hydrochloride as a white solid (70 mg).

Compound 219: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.78 (s, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.58 – 7.52 (m, 1H), 7.32 (d, $J = 8.3$ Hz, 1H), 7.12 – 7.06 (m, 2H), 6.91 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.97 (s, 1H), 5.23 – 5.21 (m, 1H), 4.01 (d, $J = 6.9$ Hz, 2H), 1.78 (d, $J = 6.9$ Hz, 3H), 1.35 – 1.32 (m, 1H), 0.70 – 0.65 (m, 2H), 0.43 – 0.40 (m, 2H); and MS-ESI: m/z 615.2 $[\text{M}+\text{H}-\text{HCl}]^+$;

Compound 220: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.78 (d, $J = 1.7$ Hz, 1H), 7.72 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.58 – 7.52 (m, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.13 – 7.06 (m, 2H), 6.91 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.96 (s, 1H), 5.23 – 5.18 (m, 1H), 4.01 (d, $J = 6.9$ Hz, 2H), 1.77 (d, $J = 7.0$ Hz, 3H), 1.36 – 1.32 (m, 1H), 0.70 – 0.65 (m, 2H), 0.43 – 0.39 (m, 2H); and MS-ESI: m/z

615.1 $[M+H-HCl]^+$.

Example 87: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(3-methylureido)ethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(3-methylureido)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00548] To a solution of triethylamine (39 mg, 0.39 mmol) and 1,1'-carbonyldiimidazole (CDI) (78 mg, 0.48 mmol) in anhydrous *N,N*-dimethylformamide (2 mL) was added a solution of *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (200 mg, 0.32 mmol) in anhydrous *N,N*-dimethylformamide (3 mL). The mixture was stirred at rt for 30 minutes and then methanamine hydrochloride (26 mg, 0.38 mmol) was added. The resulting mixture was stirred at 60 °C for 1 hour and then the solvent was removed. To the residue was added 5 mL of water. The mixture was extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (110 mg, 46%).

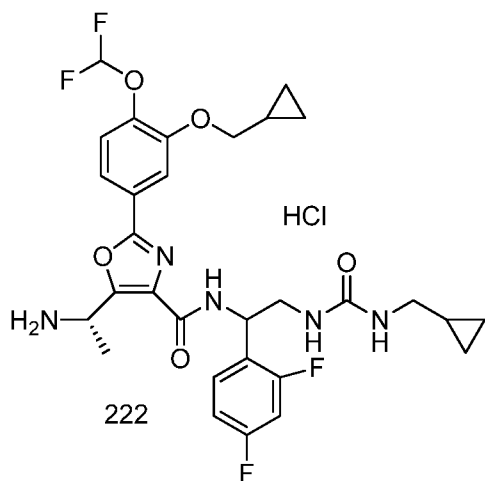
^1H NMR (400 MHz, CDCl_3): δ ppm 7.60 – 7.64 (m, 2H), 7.38 – 7.44 (m, 1H), 7.24 – 7.26 (m, 1H), 6.87 – 6.92 (m, 2H), 6.73 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.35 – 5.46 (m, 2H), 4.00 – 4.03 (m, 2H), 3.70 – 3.77 (m, 1H), 3.59 – 3.64 (m, 1H), 2.77 (d, $J = 4.7$ Hz, 3H), 1.49 – 1.54 (m, 3H), 1.41 – 1.45 (m, 9H), 1.32 – 1.36 (m, 1H), 0.69 – 0.73 (m, 2H), 0.41 – 0.45 (m, 2H); and MS-ESI: m/z 680.20 $[M+H]^+$.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-(3-methylureido)ethyl)oxazole-4-carboxamide hydrochloride

[00549] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(3-methylureido)ethyl)carbamoyl)oxazol-5-yl)ethyl) carbamate (95 mg, 0.14 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 30 minutes and the solvent was removed to give a white solid (85 mg, 99%).

Compound 221: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.86 (s, 1H), 7.77 (d, $J = 8.2$ Hz, 1H), 7.46 – 7.50 (m, 1H), 7.34 (d, $J = 8.2$ Hz, 1H), 6.96 – 7.01 (m, 2H), 6.93 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.41 – 5.44 (m, 1H), 5.08 – 5.13 (m, 1H), 4.08 (d, $J = 6.8$ Hz, 2H), 3.59 – 3.66 (m, 2H), 2.71 (s, 3H), 1.73 – 1.75 (m, 3H), 1.34 – 1.39 (m, 1H), 0.68 – 0.71 (m, 2H), 0.43 – 0.46 (m, 2H); and MS-ESI: m/z 580.20 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 88: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2-(3-(cyclopropylmethyl)ureido)-1-(2,4-difluorophenyl)ethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2-(3-(cyclopropylmethyl)ureido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)oxazol-5-yl)ethyl) carbamate

[00550] To a solution of triethylamine (0.1 mL, 0.72 mmol) and 1,1'-carbonyldiimidazole (CDI) (120 mg, 0.72 mmol) in anhydrous *N,N*-dimethylformamide (2 mL) was added a solution of *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (300 mg, 0.48 mmol) in anhydrous *N,N*-dimethylformamide (3 mL). The mixture was stirred at rt for 30 minutes and then cyclopropylmethanamine (52 mg, 0.72 mmol) was added. The resulting mixture was stirred at

60 °C for 1 hour and then the solvent was removed. To the residue was added 5 mL of water. The mixture was extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (170 mg, 49%).

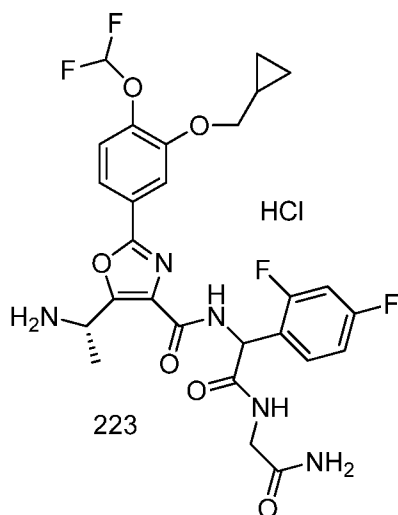
^1H NMR (400 MHz, CDCl_3): δ ppm 7.63 – 7.66 (m, 2H), 7.38 – 7.44 (m, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.81 – 6.89 (m, 2H), 6.92 (t, $J_{\text{F-H}}$ = 75.1 Hz, 1H), 5.26 – 5.46 (m, 2H), 4.02 – 4.04 (m, 2H), 3.70 – 3.77 (m, 1H), 3.59 – 3.64 (m, 1H), 3.01 – 3.10 (m, 2H), 1.49 – 1.54 (m, 3H), 1.40 – 1.45 (m, 9H), 1.31 – 1.38 (m, 2H), 0.69 – 0.73 (m, 2H), 0.40 – 0.43 (m, 4H), 0.14 – 0.17 (m, 2H).

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2-(3-(cyclopropylmethyl)ureido)-1-(2,4-difluorophenyl)ethyl)oxazole-4-carboxamide hydrochloride

[00551] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2-(3-(cyclopropylmethyl)ureido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (165 mg, 0.27 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give a white solid (150 mg, 97%).

Compound 222: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.86 (s, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.46 – 7.50 (m, 1H), 7.34 (d, J = 8.2 Hz, 1H), 6.96 – 7.01 (m, 2H), 6.93 (t, $J_{\text{F-H}}$ = 75.1 Hz, 1H), 5.40 – 5.43 (m, 1H), 5.10 – 5.16 (m, 1H), 4.08 (d, J = 6.8 Hz, 2H), 3.58 – 3.68 (m, 2H), 2.96 – 3.06 (m, 2H), 1.74 (d, J = 6.5 Hz, 3H), 1.33 – 1.40 (m, 2H), 0.68 – 0.71 (m, 2H), 0.44 – 0.47 (m, 2H), 0.37 – 0.43 (m, 2H), 0.13 – 0.17 (m, 2H); and MS-ESI: m/z 620.20 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 89: *N*-(2-((2-Amino-2-oxoethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 2-(2-(5-((S)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetamido)acetate

[00552] To 15 mL of dichloromethane were added 2-(5-((S)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.25 g, 0.39 mmol), glycine methyl ester hydrochloride (60 mg, 0.47 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (113 mg, 0.59 mmol) and 1-hydroxy-7-azabenzotriazole (80 mg, 0.59 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.27 mL, 1.57 mmol) dropwise at 0 °C. The mixture was stirred at rt for 16 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give colourless oil (187 mg, 67%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.64 – 7.61 (m, 2H), 7.53 – 7.51 (m, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 6.94 – 6.91 (m, 2H), 6.74 (t, *J*_{F-H} = 71.6 Hz, 1H), 6.48 – 6.45 (m, 1H), 5.98 – 5.96 (m, 1H), 5.32 – 5.30 (m, 1H), 4.12 – 4.08 (m, 2H), 4.03 (d, *J* = 6.8 Hz, 2H), 3.77 (s, 3H), 1.54 – 1.48 (m, 3H), 1.44 – 1.38 (m, 9H), 1.35 – 1.32 (m, 1H), 0.74 – 0.71 (m, 2H), 0.46 – 0.44 (m, 2H); and MS-ESI: *m/z* 609.2 [M+H-100]⁺.

Step 2: *tert*-Butyl ((1*S*)-1-(4-((2-((2-amino-2-oxoethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00553] To a solution of methyl 2-(2-(5-((S)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetamido)acetate (0.25 g, 0.35 mmol) in anhydrous methanol (7 mL) was

added a solution of ammonium in methanol (7 M, 8 mL). The whole mixture was stirred at 75 °C in a sealed tube for 5 hours. The solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give a light yellow solid (170 mg, 69%).

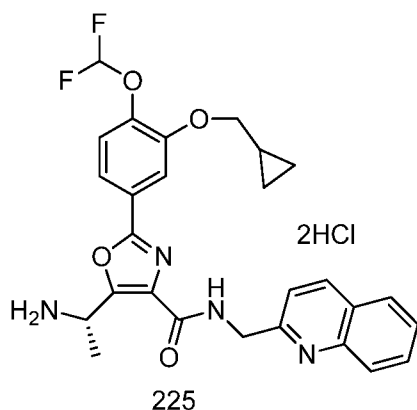
¹H NMR (600 MHz, CDCl₃): δ ppm 7.59 – 7.57 (m, 1H), 7.56 (s, 1H), 7.50 – 7.46 (m, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 6.93 – 6.89 (m, 1H), 6.86 – 6.83 (m, 1H), 6.72 (t, *J*_{F-H} = 75.0 Hz, 1H), 6.41 – 6.39 (m, 1H), 5.89 (t, *J* = 7.4 Hz, 1H), 5.65 – 5.63 (m, 1H), 5.41 – 5.39 (m, 1H), 4.04 – 3.97 (m, 2H), 3.95 – 3.93 (m, 2H), 1.56 – 1.51 (m, 3H), 1.46 – 1.41 (m, 9H), 1.34 – 1.31 (m, 1H), 0.70 – 0.69 (m, 2H), 0.41 – 0.40 (m, 2H); and MS-ESI: *m/z* 594.1 [M+H-100]⁺.

Step 3: *N*-(2-((2-Amino-2-oxoethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00554] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-((2-amino-2-oxoethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.16 g, 0.24 mmol) in a mixed solvent of dichloromethane (4 mL) and methanol (4 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 3 mL). The resulting mixture was stirred at rt for 2 hours and then the solvent was removed to give a white solid (148 mg, 97%). The crude product was further purified by prep-HPLC to give the desired product as a white solid (60 mg).

Compound 223: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.79 – 7.78 (m, 1H), 7.73 – 7.71 (m, 1H), 7.65 – 7.62 (m, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.07 – 7.03 (m, 2H), 6.92 (t, *J*_{F-H} = 74.7 Hz, 1H), 6.01 (s, 1H), 5.20 – 5.17 (m, 1H), 4.04 – 3.99 (m, 3H), 3.85 – 3.82 (m, 1H), 1.76 (d, *J* = 7.0 Hz, 3H), 1.36 – 1.33 (m, 1H), 0.70 – 0.67 (m, 2H), 0.44 – 0.41 (m, 2H); and MS-ESI: *m/z* 594.2 [M+H-HCl]⁺.

Example 90: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(quinolin-2-ylmethyl)oxazole-4-carboxamide dihydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((quinolin-2-ylmethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00555] To 15 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), quinolin-2-ylmethanamine (121 mg, 0.77 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (184 mg, 0.96 mmol) and 1-hydroxy-7-azabenzotriazole (217 mg, 1.60 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.45 mL, 2.56 mmol) dropwise at 0 °C. The mixture was stirred at rt for 16 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a white solid (366 mg, 94%).

¹H NMR (600 MHz, CDCl₃): δ ppm 8.20 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.79 – 7.76 (m, 1H), 7.66 – 7.65 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.12 – 7.11 (m, 1H), 6.74 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.34 – 5.30 (m, 1H), 4.98 – 4.97 (m, 2H), 4.03 (d, *J* = 7.0 Hz, 2H), 1.58 (d, *J* = 7.0 Hz, 3H), 1.46 (s, 9H), 1.41 – 1.37 (m, 1H), 0.74 – 0.71 (m, 2H), 0.46 – 0.44 (m, 2H); and MS-ESI: *m/z* 609.3 [M+H]⁺.

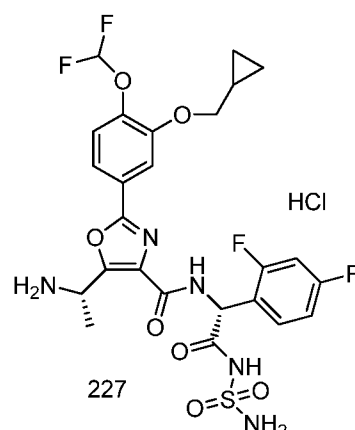
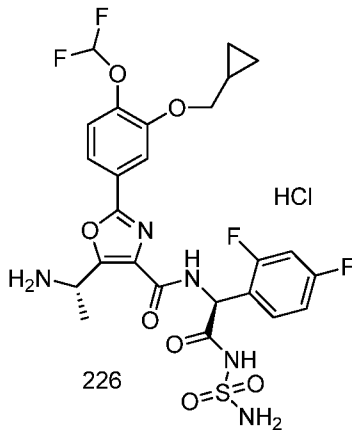
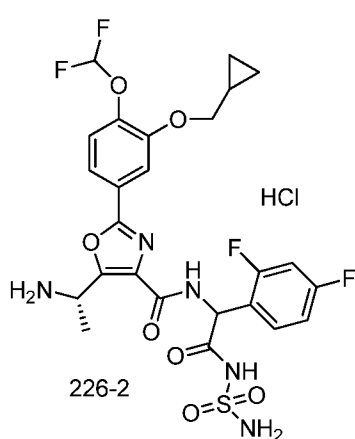
Step 2: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(quinolin-2-ylmethyl)oxazole-4-carboxamide dihydrochloride

[00556] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((quinolin-2-ylmethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.36 g, 0.59 mmol) in dichloromethane (8 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 40 minutes and then the solvent was removed to give a white solid (77 mg, 24%).

Compound 225: ¹H NMR (600 MHz, CD₃OD): δ ppm 9.15 (d, *J* = 8.5 Hz, 1H), 8.37 – 8.35 (m, 2H), 8.22 (t, *J* = 7.7 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.00 (t, *J* = 7.6 Hz, 1H), 7.84 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 6.93 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.20 – 5.19 (m, 2H), 4.05 (d, *J* = 6.8 Hz, 2H), 1.77 (d, *J* = 6.8 Hz, 3H), 1.37 – 1.34 (m, 1H), 0.71 – 0.68 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: *m/z* 509.2 [M+H-2HCl]⁺.

Example 91: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)oxazole-4-carboxamide hydrochloride, 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)

-N-((S)-1-(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)oxazole-4-carboxamide hydrochloride and 5-((S)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-((R)-1-(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00557] To 20 mL of anhydrous tetrahydrofuran were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.25 g, 0.39 mmol) and 1,1'-carbonyldiimidazole (197 mg, 1.17 mmol). The solution was stirred at 60 °C for 30 minutes, then cooled to rt. Then sulfamide (151 mg, 1.57 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.09 mL, 0.59 mmol) were added at rt. After addition, the mixture was stirred at 60 °C for 15 hours. To the reaction mixture was added saturated aqueous ammonium chloride (15 mL) and the resulting mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 40/1) to give colourless oil (212 mg, 75%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.54 - 7.60 (m, 3H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.91 (s, 1H), 6.80 - 6.85 (m, 1H), 6.72 (t, *J*_{F-H} = 74.7 Hz, 1H), 6.00 (s, 1H), 5.32 (s, 1H), 3.93 - 4.00 (m, 2H), 1.51 - 1.57 (m, 3H), 1.32 - 1.35 (m, 1H), 1.26 - 1.30 (m, 9H), 0.67 - 0.72 (m, 2H), 0.41 - 0.43 (m, 2H); and MS-ESI: *m/z* 616.0 [M+H-100]⁺.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(1-(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)oxazole-4-carboxamide hydrochloride, 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-((*S*)-1-(2,4-

difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-

(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)oxazole-4-carboxamide hydrochloride

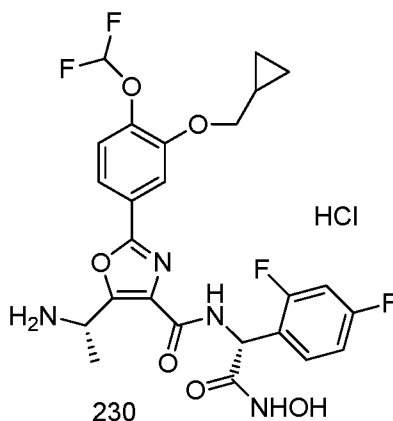
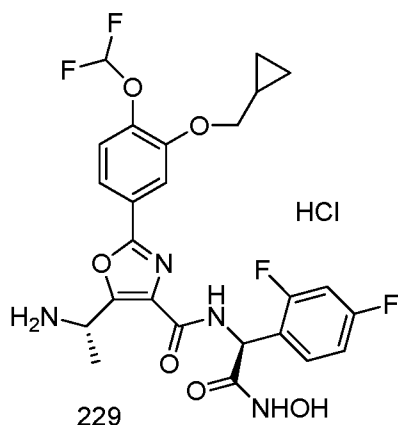
[00558] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)carbamoyl)oxazol-5-yl)ethyl) carbamate (0.20 g, 0.27 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 3 mL). The resulting mixture was stirred at rt for 3 hours and then the solvent was removed to give compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)oxazole-4-carboxamide hydrochloride as oil (167 mg, 93%).

[00559] The compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)oxazole-4-carboxamide hydrochloride was further separated and purified by prep-HPLC to give 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)oxazole-4-carboxamide hydrochloride as a white solid (54 mg) and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-oxo-2-(sulfamoylamino)ethyl)oxazole-4-carboxamide hydrochloride as a white solid (55 mg).

Compound 226: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.78 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.56 - 7.59 (m, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.05 - 7.09 (m, 2H), 6.92 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.96 (s, 1H), 5.20 - 5.22 (m, 1H), 4.01 (d, *J* = 6.9 Hz, 2H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.33 - 1.35 (m, 1H), 0.66 - 0.69 (m, 2H), 0.41 - 0.43 (m, 2H); and MS-ESI: *m/z* 616.1 [M+H-HCl]⁺;

Compound 227: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.78 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.56 - 7.58 (m, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.05 - 7.10 (m, 2H), 6.92 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.95 (s, 1H), 5.19 - 5.20 (m, 1H), 4.01 (d, *J* = 7.0 Hz, 2H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.33 - 1.36 (m, 1H), 0.66 - 0.70 (m, 2H), 0.40 - 0.43 (m, 2H); and MS-ESI: *m/z* 616.1 [M+H-HCl]⁺.

Example 92: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy) phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-(hydroxyamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy) phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-(hydroxyamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(hydroxyamino)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00560] To a solution of hydroxylamine hydrochloride (43 mg, 0.61 mmol) in methanol (20 mL) was added potassium hydroxide (52 mg, 0.92 mmol). The mixture was stirred at 40 °C for 30 minutes, then the mixture was placed in an ice-bath and methyl 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate (200 mg, 0.31 mmol) was added. The resulting mixture was stirred at 65 °C for 4 hours and then filtered. The filtrate was concentrated and hydrochloric acid (1 M) was added to the residue to adjust the pH to about 2. The mixture was extracted with ethyl acetate (10 mL × 3) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed to give a yellow solid (180 mg, 89%).

¹H NMR (600 MHz, *d*₆-DMSO): δ ppm 7.67 – 7.62 (m, 2H), 7.60 – 7.57 (m, 1H), 7.40 – 7.37 (m, 1H), 7.31 – 7.27 (m, 1H), 7.22 (t, *J*_{F-H} = 74.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 5.36 – 5.30 (m, 1H), 4.01 – 3.98 (m, 2H), 1.42 – 1.35 (m, 9H), 1.30 – 1.28 (m, 1H), 0.62 – 0.60 (m, 2H), 0.41 – 0.39 (m, 2H); and MS-ESI: *m/z* 553.2 [*M*+*H*-100]⁺.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-(hydroxyamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-(hydroxyamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride

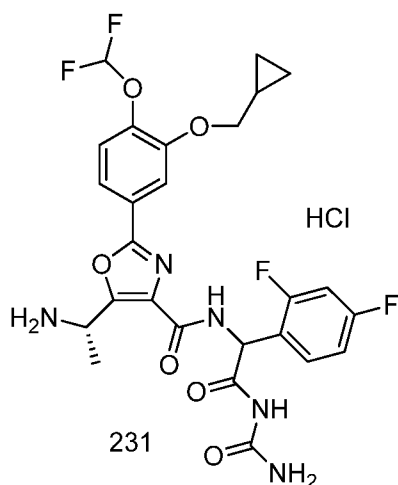
[00561] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-(hydroxyamino)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)

carbamate (0.24 g, 0.36 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 3 mL). The resulting mixture was stirred at rt for 1.5 hours and the solvent was removed to give a yellow solid (216 mg, 99%). The crude product was further separated and purified by prep-HPLC to give 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-(hydroxyamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride as a white solid (50 mg) and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-(hydroxyamino)-2-oxoethyl)oxazole-4-carboxamide hydrochloride as a yellow solid (90 mg).

Compound 229: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.64 – 7.62 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.07 – 7.02 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.90 (s, 1H), 5.20 – 5.19 (m, 1H), 4.03 (d, $J = 6.9$ Hz, 2H), 1.76 (d, $J = 6.7$ Hz, 3H), 1.36 – 1.33 (m, 1H), 0.70 – 0.67 (m, 2H), 0.45 – 0.41 (m, 2H); and MS-ESI: m/z 553.1 $[\text{M}+\text{H}-\text{HCl}]^+$;

Compound 230: MS-ESI: m/z 553.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 93: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-oxo-2-ureidoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-oxo-2-ureidoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00562] To 20 mL of anhydrous tetrahydrofuran were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.25 g, 0.39 mmol) and 1,1'-carbonyldiimidazole (197 mg, 1.17 mmol). The solution was stirred at 60 °C for 30 minutes, then cooled to rt. Then urea (94 mg, 1.57 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.09

mL, 0.59 mmol) were added. After addition, the mixture was stirred at 60 °C for 24 hours. To the reaction mixture was added saturated aqueous ammonium chloride (15 mL) and the resulting mixture was extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a yellow solid (80 mg, 30%).

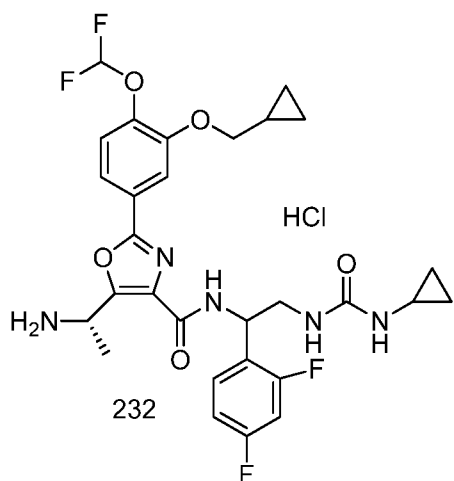
^1H NMR (400 MHz, CDCl_3): δ ppm 8.26 – 8.21 (m, 1H), 7.67 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.61 (d, $J = 1.9$ Hz, 1H), 7.31 (d, $J = 8.3$ Hz, 1H), 7.14 – 7.09 (m, 1H), 7.04 – 6.98 (m, 1H), 6.75 (t, $J_{\text{F-H}} = 74.9$ Hz, 1H), 5.38 – 5.34 (m, 1H), 4.03 (d, $J = 7.0$ Hz, 2H), 1.60 (d, $J = 7.2$ Hz, 3H), 1.44 (s, 9H), 1.38 – 1.36 (m, 1H), 0.76 – 0.71 (m, 2H), 0.48 – 0.44 (m, 2H).

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-oxo-2-ureidoethyl)oxazole-4-carboxamide hydrochloride

[00563] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-oxo-2-ureidoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.07 g, 0.11 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 3 mL). The resulting mixture was stirred at rt for 1 hour. The solvent was removed to give a light yellow solid (65 mg, 93%).

Compound 231: ^1H NMR (600 MHz, CD_3OD): δ ppm 8.02 – 7.98 (m, 1H), 7.75 (s, 1H), 7.74 – 7.72 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.27 – 7.23 (m, 1H), 7.13 (t, $J = 8.3$ Hz, 1H), 6.95 (t, $J_{\text{F-H}} = 74.6$ Hz, 1H), 5.37 – 5.34 (m, 1H), 4.04 (d, $J = 6.8$ Hz, 2H), 1.82 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.35 (m, 1H), 0.73 – 0.69 (m, 2H), 0.47 – 0.45 (m, 2H); and MS-ESI: m/z 580.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 94: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2-(3-cyclopropylureido)-1-(2,4-difluorophenyl)ethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2-(3-cyclopropylureido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00564] To 2 mL of anhydrous *N,N*-dimethylformamide were added triethylamine (101 mg, 1.01 mmol) and 1,1'-carbonyldiimidazole (CDI) (162 mg, 1.01 mmol). To the resulting solution was added a solution of *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)ethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (250 mg, 0.4 mmol) in anhydrous *N,N*-dimethylformamide (3 mL). The mixture was stirred at rt for 30 minutes, then cyclopropylamine (57 mg, 1.01 mmol) was added. The resulting mixture was stirred at 60 °C for 1 hour, then the solvent was removed. To the residue was added 5 mL of water. The mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (180 mg, 64%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.50 (br.s, 1H), 7.62 – 7.67 (m, 2H), 7.37 – 7.43 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.68 – 6.92 (m, 2H), 6.73 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.48– 5.53 (m, 1H), 5.32– 5.40 (m, 1H), 5.23– 5.34 (m, 1H), 4.74 – 4.79 (m, 1H), 4.02 (d, *J* = 6.9 Hz, 2H), 3.71 – 3.84 (m, 2H), 2.37 – 2.41 (m, 1H), 1.47 – 1.54 (m, 3H), 1.41 – 1.45 (m, 9H), 1.32 – 1.40 (m, 1H), 0.67 – 0.76 (m, 4H), 0.48 – 0.57 (m, 2H), 0.42 – 0.46 (m, 2H); and MS-ESI: *m/z* 706.25 [M+H]⁺.

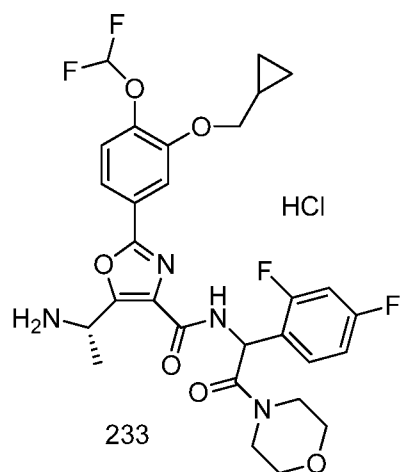
Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2-(3-cyclopropylureido)-1-(2,4-difluorophenyl)ethyl)oxazole-4-carboxamide hydrochloride

[00565] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2-(3-cyclopropylureido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

phenyl)-4-((2-(3-cyclopropylureido)-1-(2,4-difluorophenyl)ethyl)carbamoyl)oxazol-5-yl)ethyl) carbamate (170 mg, 0.24 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 30 minutes and the solvent was removed to give a white solid (150 mg, 97%).

Compound 232: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.86 (s, 1H), 7.78 (d, $J = 8.3$ Hz, 1H), 7.49 – 7.53 (m, 1H), 7.34 (d, $J = 8.2$ Hz, 1H), 6.96 – 7.02 (m, 2H), 6.93 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.47 – 5.50 (m, 1H), 5.09 – 5.16 (m, 1H), 4.08 (d, $J = 6.8$ Hz, 2H), 3.63 – 3.73 (m, 2H), 2.42 – 2.45 (m, 1H), 1.75 (d, $J = 6.6$ Hz, 3H), 1.33 – 1.39 (m, 1H), 0.66 – 0.71 (m, 4H), 0.42 – 0.47 (m, 4H); and MS-ESI: m/z 606.30 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 95: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-morpholino-2-oxoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-morpholino-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate
[00566] To 15 mL of dichloromethane were added 2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (0.25 g, 0.39 mmol), morpholine (41 mg, 0.47 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (112 mg, 0.59 mmol) and 1-hydroxy-7-azabenzotriazole (133 mg, 0.98 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.27 mL, 1.57 mmol) dropwise at 0 °C. The mixture was stirred at rt for 15 hours. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give colourless oil (267 mg, 96%).

^1H NMR (600 MHz, CDCl_3): δ ppm 8.51 (d, $J = 7.4$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.60 (s, 1H), 7.56 – 7.53 (m, 1H), 7.25 (d, $J = 8.3$ Hz, 1H), 6.96 – 6.94 (m, 1H), 6.92 – 6.88 (m, 1H),

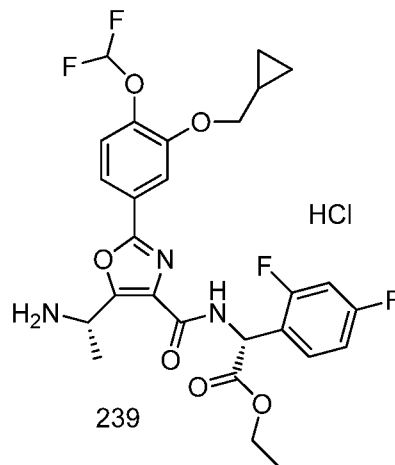
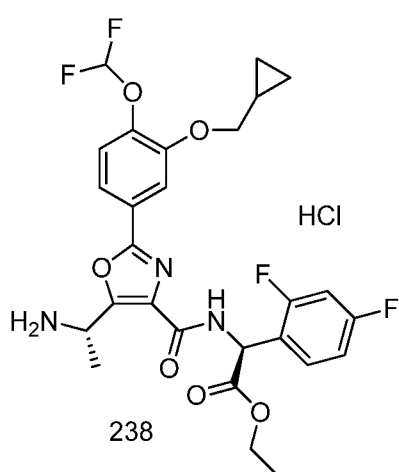
6.73 (t, $J_{F-H} = 75.1$ Hz, 1H), 6.29 – 6.28 (m, 1H), 5.32 – 5.29 (m, 1H), 4.02 (d, $J = 6.9$ Hz, 2H), 3.73 – 3.60 (m, 6H), 3.44 – 3.36 (m, 2H), 1.53 – 1.48 (m, 3H), 1.45 – 1.38 (m, 9H), 1.35 – 1.33 (m, 1H), 0.73 – 0.70 (m, 2H), 0.46 – 0.44 (m, 2H); and MS-ESI: m/z 707.3 $[M+H]^+$.

Step 2: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-morpholino-2-oxoethyl)oxazole-4-carboxamide hydrochloride

[00567] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-(2,4-difluorophenyl)-2-morpholino-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.25 g, 0.35 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 3 mL). The resulting mixture was stirred at rt for 1 hour and then the solvent was removed to give a white solid (210 mg, 91%).

Compound 233: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.78 – 7.77 (m, 1H), 7.73 – 7.71 (m, 1H), 7.58 – 7.55 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.11 – 7.06 (m, 2H), 6.92 (t, $J_{F-H} = 74.7$ Hz, 1H), 6.27 (s, 1H), 5.19 – 5.16 (m, 1H), 4.03 (d, $J = 6.9$ Hz, 2H), 3.71 – 3.58 (m, 6H), 3.37 – 3.35 (m, 1H), 3.29 – 3.27 (m, 1H), 1.77 – 1.75 (m, 3H), 1.36 – 1.34 (m, 1H), 0.70 – 0.68 (m, 2H), 0.44 – 0.43 (m, 2H); and MS-ESI: m/z 607.2 $[M+H-HCl]^+$.

Example 96: (*S*)-Ethyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride and (*R*)-ethyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride



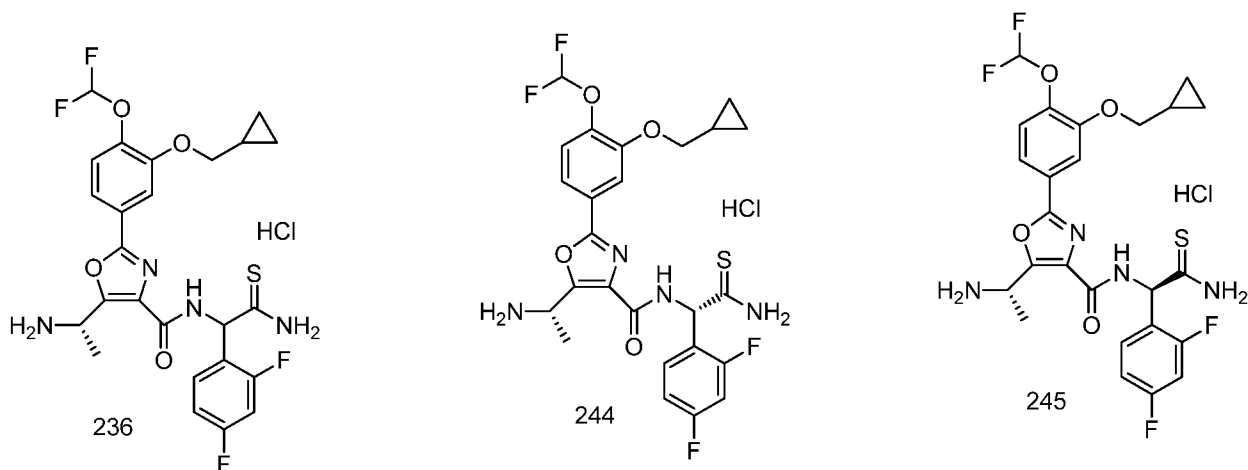
[00568] The compound ethyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride prepared from **Example 79** was further separated and purified by prep-HPLC to give (*S*)-ethyl

2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride and (*R*)-ethyl 2-(5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate hydrochloride.

Compound 238: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.80 (s, 1H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.60 – 7.56 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.07 – 7.03 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 6.02 (s, 1H), 5.20 – 5.19 (m, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 4.05 (d, $J = 6.9$ Hz, 2H), 1.76 (d, $J = 6.9$ Hz, 3H), 1.36 – 1.34 (m, 1H), 1.25 (t, $J = 7.1$ Hz, 3H), 0.71 – 0.68 (m, 2H), 0.44 – 0.43 (m, 2H); and MS-ESI: m/z 566.2 $[\text{M}+\text{H}-\text{HCl}]^+$;

Compound 239: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.80 (s, 1H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.59 – 7.57 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.09 – 7.03 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 6.02 (s, 1H), 5.18 – 5.16 (m, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 4.04 (d, $J = 6.9$ Hz, 2H), 1.76 (d, $J = 6.9$ Hz, 3H), 1.37 – 1.34 (m, 1H), 1.25 (t, $J = 7.1$ Hz, 3H), 0.71 – 0.68 (m, 2H), 0.45 – 0.43 (m, 2H); and MS-ESI: m/z 566.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 97: *N*-(2-Amino-1-(2,4-difluorophenyl)-2-thioxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride, *N*-((*S*)-2-amino-1-(2,4-difluorophenyl)-2-thioxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and *N*-((*R*)-2-amino-1-(2,4-difluorophenyl)-2-thioxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00569] To 10 mL of anhydrous methanol were added methyl

2-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetate (240 mg, 0.37 mmol) and a solution of ammonia in methanol (5.3 mL, 37 mmol, 7 M). The mixture was stirred at 60 °C for 1 hour in a 100 mL sealed tube. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (157 mg, 67%).

¹H NMR (600 MHz, CD₃OD): δ ppm 8.34 – 8.38 (m, 1H), 7.61 – 7.64 (m, 2H), 7.48 – 7.54 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 6.91 – 6.95 (m, 2H), 6.74 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.93 – 6.00 (m, 2H), 5.58 (br.s, 1H), 5.29 – 5.34 (m, 1H), 4.04 (d, *J* = 6.9 Hz, 2H), 1.48 – 1.53 (m, 3H), 1.40 – 1.45 (m, 9H), 1.28 – 1.36 (m, 1H), 0.70 – 0.74 (m, 2H), 0.44 – 0.47 (m, 2H); and MS-ESI: *m/z* 637.20 [M+H]⁺.

Step 2: *tert*-Butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-thioxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00570] To 10 mL of tetrahydrofuran were added *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (200 mg, 0.32 mmol) and Lawesson's Reagent (140 mg, 0.35 mmol). The mixture was refluxed at 75 °C for 30 minutes. The solvent was removed and to the residue was added 10 mL of water. The mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give a light yellow solid (118 mg, 58%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.78 – 8.82 (m, 1H), 7.59 – 7.67 (m, 2H), 7.28 (d, *J* = 8.3 Hz, 1H), 6.88 – 6.94 (m, 2H), 6.74 (t, *J*_{F-H} = 75.0 Hz, 1H), 6.19 – 6.26 (m, 1H), 5.30 – 5.42 (m, 1H), 4.04 (d, *J* = 6.9 Hz, 2H), 1.48 – 1.52 (m, 3H), 1.39 – 1.45 (m, 9H), 1.28 – 1.36 (m, 1H), 0.70 – 0.74 (m, 2H), 0.43 – 0.47 (m, 2H).

Step 3: *N*-(2-Amino-1-(2,4-difluorophenyl)-2-thioxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00571] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-thioxoethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (110 mg, 0.17 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 20

minutes and the solvent was removed to give a light yellow solid (95 mg, 96%).

Compound 236: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.80 (s, 1H), 7.73 – 7.75 (m, 1H), 7.66 – 7.70 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 6.98 – 7.04 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 6.19 (s, 1H), 5.14 – 5.20 (m, 1H), 4.04 (d, $J = 6.9$ Hz, 2H), 1.77 (d, $J = 7.0$ Hz, 3H), 1.32 – 1.37 (m, 1H), 0.67 – 0.70 (m, 2H), 0.42 – 0.45 (m, 2H); and MS-ESI: m/z 553.20 $[\text{M}+\text{H}-\text{HCl}]^+$.

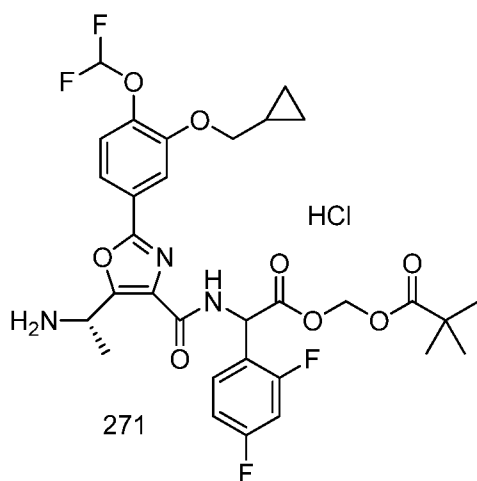
Step 4: *N*-((*S*)-2-Amino-1-(2,4-difluorophenyl)-2-thioxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride and *N*-((*R*)-2-amino-1-(2,4-difluorophenyl)-2-thioxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00572] The compound *N*-(2-amino-1-(2,4-difluorophenyl)-2-thioxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride (270 mg, 0.46 mmol) was further separated and purified by prep-HPLC, and each preparative solution of compound of *R* configuration and compound of *S* configuration was independently concentrated. To each residue was added aqueous sodium hydroxide (1 M) to adjust the pH to 9 and each resulting mixture was extracted with ethyl acetate (10 mL $\times$ 3). Each combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed. To each residue was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL) to give the product of *S* configuration named *N*-((*S*)-2-amino-1-(2,4-difluorophenyl)-2-thioxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride as a light yellow solid (68 mg) and another product of *R* configuration named *N*-((*R*)-2-amino-1-(2,4-difluorophenyl)-2-thioxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride as a light yellow solid (100 mg).

Compound 244: MS-ESI: m/z 553.20 $[\text{M}+\text{H}-\text{HCl}]^+$; and

Compound 245: MS-ESI: m/z 553.20 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 98: (2-(5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetoxy)methyl pivalate hydrochloride



Step 1: (2-(5-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetoxy)methyl pivalate

[00573] To 5 mL of anhydrous methanol were added 2-(5-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (500 mg, 0.78 mmol) and potassium hydroxide (44 mg, 0.78 mmol). The mixture was stirred at 40 °C for 15 minutes and the solvent was removed. To the residue were added *N,N*-dimethylformamide (5 mL) and chloromethyl pivalate (0.34 mL, 2.34 mmol). The mixture was stirred at rt for 4 hours and then ice-water (10 mL) was added to the mixture. The mixture was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 10/1) to give a light yellow solid (450 mg, 76%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.11 – 8.15 (m, 1H), 7.59 – 7.63 (m, 2H), 7.46 – 7.52 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.88 – 6.94 (m, 2H), 6.73 (t, *J*_{F-H} = 75.0 Hz, 1H), 6.02 – 6.03 (m, 1H), 5.93 (d, *J* = 5.5 Hz, 1H), 5.77 (d, *J* = 5.5 Hz, 1H), 5.29 – 5.33 (m, 1H), 4.01 – 4.04 (m, 2H), 1.48 – 1.54 (m, 3H), 1.41 – 1.45 (m, 9H), 1.31 – 1.35 (m, 1H), 1.16 (s, 9H), 0.69 – 0.74 (m, 2H), 0.41 – 0.47 (m, 2H); and MS-ESI: *m/z* 774.20 [M+Na]⁺.

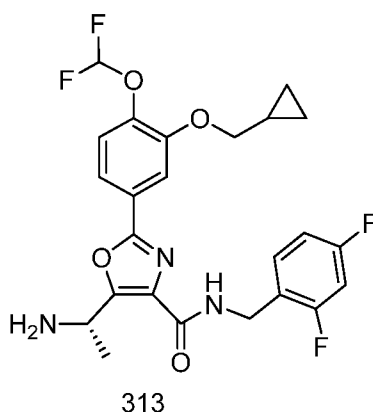
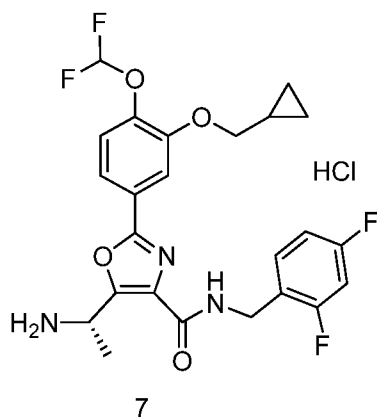
Step 2: (2-(5-((S)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetoxy)methyl pivalate hydrochloride

[00574] To a solution of (2-(5-((S)-1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)-2-(2,4-

difluorophenyl)acetoxy)methyl pivalate (260 mg, 0.35 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 30 minutes and then the solvent was removed to give a white solid (230 mg, 96%).

Compound 271: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.80 (d, $J = 1.8$ Hz, 1H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.59 (dd, $J_1 = 14.8$ Hz, $J_2 = 8.4$ Hz, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.02 – 7.10 (m, 2H), 6.92 (t, $J_{\text{F-H}} = 75.1$ Hz, 1H), 6.07 (s, 1H), 5.95 (dd, $J_1 = 5.7$ Hz, $J_2 = 1.8$ Hz, 1H), 5.75 (dd, $J_1 = 5.7$ Hz, $J_2 = 1.5$ Hz, 1H), 5.15 – 5.22 (m, 1H), 4.05 (d, $J = 6.9$ Hz, 2H), 1.76 (dd, $J_1 = 6.9$ Hz, $J_2 = 1.1$ Hz, 3H), 1.31 – 1.38 (m, 1H), 1.15 (s, 9H), 0.67 – 0.72 (m, 2H), 0.41 – 0.46 (m, 2H); and MS-ESI: m/z 652.10 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 99: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride and (*S*)-5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide



Step 1: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00575] To 25 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (0.3 g, 0.64 mmol), 1-hydroxy-7-azabenzotriazole (HOAT) (130.8 mg, 0.961 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (183.36 mg, 0.961 mmol). The mixture was stirred at rt for 30 minutes and then (2,4-difluorophenyl)methanamine (109.9 mg, 0.769 mmol) was added. To the resulting mixture was added *N,N*-diisopropylethylamine (0.35 mL, 1.923 mmol) at 0 °C and the mixture was stirred overnight

at rt. To the reaction mixture was added water (25 mL) and the mixture was extracted with dichloromethane (25 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a white solid (316.4 mg, 83.2%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.57 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.53 (d, $J = 1.8$ Hz, 1H), 7.39 - 7.44 (d, 1H), 7.23 (d, $J = 8.3$ Hz, 1H), 6.82 - 6.89 (m, 2H), 6.70 (t, $J = 75.0$ Hz, 1H), 5.27 - 5.30 (m, 1H), 4.65 (brs, 2H), 3.97 (d, $J = 6.9$ Hz, 2H), 1.53 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 1.28 - 1.29 (m, 1H), 0.66 - 0.71 (m, 2H), 0.39 - 0.42 (m, 2H); and MS-ESI: m/z 494.0 $[\text{M}-100+\text{H}]^+$.

Step 2: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00576] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (316.4 mg, 0.533 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 2 hours. The solvent was removed and an appropriate amount of dichloromethane was added to dissolve the residue. Then a lot of ethyl acetate was added to the solution and many white solids were precipitated. The mixture was filtered and the filter cake was dried to give a white solid (250 mg, 88.6%).

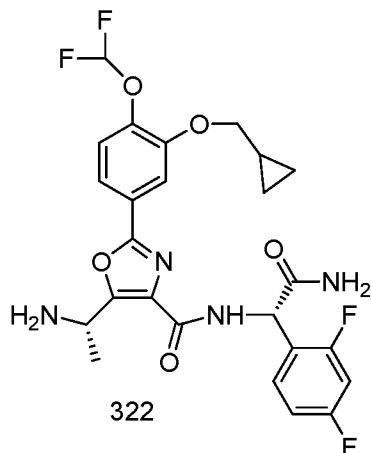
Compound 7: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.70 (s, 1H), 7.63 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.37 - 7.41 (m, 1H), 7.24 (d, $J = 8.3$ Hz, 1H), 6.86 - 6.92 (m, 2H), 6.82 (t, $J = 75.0$ Hz, 1H), 5.07 (q, $J = 7.0$ Hz, 1H), 4.55 (s, 2H), 3.94 (d, $J = 7.0$ Hz, 2H), 1.68 (d, $J = 7.0$ Hz, 3H), 1.24 - 1.28 (m, 1H), 0.58 - 0.61 (m, 2H), 0.32 - 0.34 (m, 2H); and MS-ESI: m/z 494.0 $[\text{M}-\text{HCl}+\text{H}]^+$.

Step 3: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide

[00577] To a solution of (*S*)-5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride (150 mg, 0.28 mmol) in water (10 mL) was added aqueous sodium hydroxide (1.0 M) to adjust the pH to 9. The mixture was extracted with ethyl acetate (10 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed to give a white solid (130 mg, 94%).

Compound 313: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.66 (d, $J = 1.9$ Hz, 1H), 7.58 (dd, $J_1 = 8.3$ Hz, $J_2 = 2.0$ Hz, 1H), 7.33 – 7.37 (m, 1H), 7.18 (d, $J = 8.3$ Hz, 1H), 6.83 – 6.89 (m, 2H), 6.78 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 4.65 (q, $J = 6.9$ Hz, 1H), 4.50 (s, 2H), 3.91 (d, $J = 6.9$ Hz, 2H), 1.44 (d, $J = 6.9$ Hz, 3H), 1.21 – 1.27 (m, 1H), 0.55 – 0.59 (m, 2H), 0.29 – 0.33 (m, 2H); and MS-ESI: m/z 494.30 $[\text{M}+\text{H}]^+$.

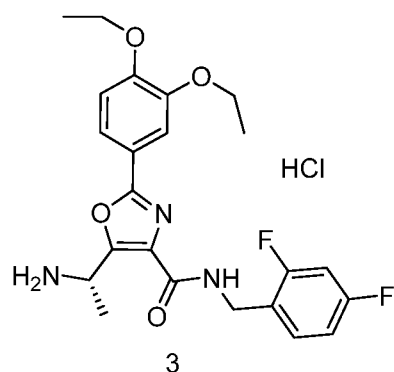
Example 100: *N*-((*S*)-2-Amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide



[00578] To a solution of *N*-((*S*)-2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride (150 mg, 0.28 mmol) in water (10 mL) was added aqueous sodium hydroxide (1.0 M) to adjust the pH to 9. The mixture was extracted with dichloromethane (10 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed to give a white solid (110 mg, 79%).

Compound 322: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.57 – 7.69 (m, 2H), 7.41 – 7.52 (m, 1H), 7.17 – 7.24 (m, 1H), 6.87 – 6.97 (m, 2H), 6.81 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.82 (s, 1H), 4.85 – 4.90 (m, 1H), 3.88 – 3.93 (m, 2H), 1.58 (d, $J = 6.6$ Hz, 3H), 1.17 – 1.30 (m, 1H), 0.54 – 0.63 (m, 2H), 0.28 – 0.37 (m, 2H); and MS-ESI: m/z 536.95 $[\text{M}+\text{H}]^+$.

Example 101: (*S*)-5-(1-Aminoethyl)-2-(3,4-diethoxyphenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3,4-diethoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00579] To 10 mL of dichloromethane were added (S)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxylic acid (176 mg, 0.41 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (118.8 mg, 0.62 mmol), 1-hydroxy-7-azabenzotriazole (83.8 mg, 0.62 mmol). The mixture was stirred at rt for 30 minutes, then 2,4-difluorobenzylamine (0.06 mL, 0.49 mmol) and *N,N*-diisopropylethylamine (0.22 mL, 1.23 mmol) were added dropwise at 0 °C. The resulting mixture was stirred at rt for 12 hours. To the reaction mixture was added water (20 mL), and the resulting mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed, and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a white solid (149 mg, 67%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.52 (d, J = 8.4 Hz, 1H), 7.46 (s, 1H), 7.41 - 7.35 (m, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.86 - 6.78 (m, 2H), 5.29 - 5.25 (m, 1H), 4.63 - 4.60 (m, 2H), 4.16 - 4.10 (m, 4H), 1.52 (d, J = 7.0 Hz, 3H), 1.48 - 1.44 (m, 6H), 1.42 (s, 9H); and MS-ESI: m/z 546.2 $[\text{M}+\text{H}]^+$.

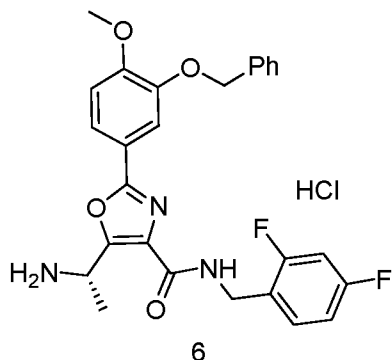
Step 2: (S)-5-(1-Aminoethyl)-2-(3,4-diethoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00580] To a solution of (S)-tert-butyl (1-(2-(3,4-diethoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (100 mg, 0.18 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 5 mL). The resulting mixture was stirred at rt for 30 minutes and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give a white solid (75 mg, 92%).

Compound 3: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.67 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H),

7.48 - 7.42 (m, 1H), 7.07 (d, $J = 8.4$ Hz, 1H), 6.98 - 6.91 (m, 2H), 5.12 - 5.09 (m, 1H), 4.62 (s, 2H), 4.17 - 4.11 (m, 4H), 1.74 (d, $J = 6.6$ Hz, 3H), 1.46 - 1.42 (m, 6H); and MS-ESI: m/z 446.2 $[M+H-HCl]^+$.

Example 102: (S)-5-(1-Aminoethyl)-2-(3-(benzyloxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 3-(benzyloxy)-4-methoxybenzoate

[00581] To *N,N*-dimethylformamide (60 mL) were added methyl 3-hydroxy-4-methoxybenzoate (10.0 g, 54.93 mmol), potassium carbonate (15.66 g, 113.30 mmol) and benzyl bromide (7.8 mL, 66.07 mmol). The mixture was stirred at 60 °C for 4.5 hours. To the mixture was added water (40 mL) and the resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (11.2 g, 75%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.69 (d, $J = 8.4$ Hz, 1H), 7.62 (s, 1H), 7.46 (d, $J = 7.3$ Hz, 2H), 7.40 - 7.31 (m, 3H), 6.91 (d, $J = 8.4$ Hz, 1H), 5.18 (s, 2H), 3.93 (s, 3H), 3.85 (s, 3H); and MS-ESI: m/z 273.1 $[M+H]^+$.

Step 2: 3-(Benzyloxy)-4-methoxybenzoic acid

[00582] To a mixed solvent of ethanol (150 mL) and water (50 mL) were added methyl 3-(benzyloxy)-4-methoxybenzoate (11.2 g, 41.18 mmol) and sodium hydroxide (8.89 g, 222.3 mmol). The mixture was stirred at 60 °C for 1.5 hours and then concentrated to remove the ethanol. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The organic layers was concentrated to give the title compound as a white solid (8.51 g, 80%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.69 (d, $J = 8.4$ Hz, 1H), 7.62 (s, 1H), 7.46 (d, $J = 7.3$ Hz, 2H), 7.40 - 7.31 (m, 3H), 6.91 (d, $J = 8.4$ Hz, 1H), 5.18 (s, 2H), 3.85 (s, 3H); and MS-ESI: m/z 259.2 $[\text{M}+\text{H}]^+$.

Step 3: Methyl 2-(3-(benzyloxy)-4-methoxybenzamido)acetate

[00583] To 80 mL of dichloromethane were added 3-(benzyloxy)-4-methoxybenzoic acid (8.51 g, 33.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (9.62 g, 50.2 mmol) and 1-hydroxybenzotriazole (6.69 g, 49.5 mmol). The mixture was stirred at rt for half an hour, then glycine methyl ester hydrochloride (4.97 g, 39.6 mmol) and *N,N*-diisopropylethylamine (17.8 mL, 102.3 mmol) were added at 0 °C. The mixture was stirred at rt for 12 hours, then washed with water (40 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a white solid (9.88 g, 91%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.47 - 7.44 (m, 3H), 7.38 - 7.35 (m, 3H), 7.32 - 7.28 (m, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 6.57 (br.s, 1H), 5.16 (s, 2H), 4.20 (d, $J = 5.0$ Hz, 2H), 3.91 (s, 3H), 3.80 (s, 3H); and MS-ESI: m/z 330.2 $[\text{M}+\text{H}]^+$.

Step 4: Methyl 2-(3-(benzyloxy)-4-methoxyphenylthioamido)acetate

[00584] To tetrahydrofuran (40 mL) were added methyl 2-(3-(benzyloxy)-4-methoxybenzamido)acetate (2.5 g, 7.59 mmol) and Lawesson's Reagent (3.07 g, 7.59 mmol). The mixture was refluxed at 75 °C for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (40 mL), and the resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (2.55 g, 97%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.02 (br.s, 1H), 7.59 (s, 1H), 7.47 - 7.45 (m, 2H), 7.39 - 7.28 (m, 4H), 6.84 (d, $J = 8.4$ Hz, 1H), 5.17 (s, 2H), 4.54 (m, $J = 4.6$ Hz, 2H), 3.90 (s, 3H), 3.83 (s, 3H); and MS-ESI: m/z 346.2 $[\text{M}+\text{H}]^+$.

Step 5: Methyl 2-(((3-(benzyloxy)-4-methoxyphenyl)(methylthio)methylene) amino)acetate

[00585] To a solution of trimethyloxonium tetrafluoroborate (1.31 g, 8.87 mmol) in dichloromethane (30 mL) was added dropwise a solution of methyl

2-(3-(benzyloxy)-4-methoxyphenylthioamido)acetate (2.55 g, 7.39 mmol) in dichloromethane (30 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then washed with saturated aqueous sodium bicarbonate (25 mL × 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as yellow oil (2.1 g, 80%).

MS-ESI: m/z 360.1 $[M+H]^+$.

Step 6: (S)-Methyl 2-(3-(benzyloxy)-4-methoxyphenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylate

[00586] To 20 mL of anhydrous tetrahydrofuran (20 mL) were added methyl 2-(((3-(benzyloxy)-4-methoxyphenyl)(methylthio)methylene)amino)acetate (2.47 g, 8.31 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (2.38 g, 12.46 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (20.78 mL, 20.78 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (1 g, 28%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.68 - 7.64 (m, 2H), 7.50 - 7.48 (m, 2H), 7.41 - 7.30 (m, 3H), 6.95 (d, J = 8.4 Hz, 1H), 5.69 (br.s, 1H), 5.47 - 5.43 (m, 1H), 5.20 (s, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 1.53 (d, J = 7.0 Hz, 3H), 1.39 (s, 9H); and MS-ESI: m/z 483.1 $[M+H]^+$.

Step 7: (S)-2-(3-(Benzyloxy)-4-methoxyphenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylic acid

[00587] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added (*S*)-methyl 2-(3-(benzyloxy)-4-methoxyphenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl) oxazole-4-carboxylate (390 mg, 0.81 mmol) and lithium hydroxide monohydrate (172 mg, 4.1 mmol). The solution was stirred at 40 °C for 3 hours and tetrahydrofuran was removed, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (30 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (352 mg, 93%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.69 - 7.66 (m, 2H), 7.51 (d, J = 7.2 Hz, 1H), 7.42 -

7.34 (m, 3H), 6.97 (d, $J = 8.3$ Hz, 1H), 5.72 (br.s, 1H), 5.43 - 5.41 (m, 1H), 5.22 (s, 2H), 3.95 (s, 3H), 1.58 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H); and MS-ESI: m/z 467.2 $[M-H]^+$.

Step 8: (*S*)-*tert*-Butyl (1-(2-(3-(benzyloxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00588] To 10 mL of dichloromethane were added (*S*)-2-(3-(benzyloxy)-4-methoxyphenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylic acid (352 mg, 0.75 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (215.7 mg, 1.13 mmol) and 1-hydroxy-7-azabenzotriazole (152.7 mg, 1.13 mmol). The mixture was stirred at rt for half an hour. To the mixture were added 2,4-difluorobenzylamine (0.10 mL, 0.90 mmol) and *N,N*-diisopropylethylamine (0.40 mL, 2.25 mmol). The mixture was stirred at rt for 12 hours. To the reaction mixture was added water (20 mL), and the resulting mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as a white solid (320 mg, 72%).

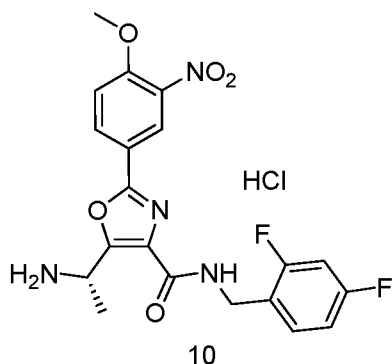
^1H NMR (400 MHz, CDCl_3): δ ppm 7.60 - 7.54 (m, 2H), 7.48 (d, $J = 7.2$ Hz, 2H), 7.44 - 7.36 (m, 3H), 7.32 (d, $J = 7.2$ Hz, 1H), 6.94 (d, $J = 8.5$ Hz, 1H), 6.90 - 6.82 (m, 2H), 5.28 - 5.26 (m, 1H), 5.25 (s, 2H), 4.66 - 4.63 (m, 2H), 3.93 (s, 3H), 1.52 (d, $J = 7.0$ Hz, 3H), 1.25 (s, 9H); and MS-ESI: m/z 594.0 $[M+H]^+$.

Step 9: (*S*)-5-(1-Aminoethyl)-2-(3-(benzyloxy)-4-methoxyphenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00589] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(benzyloxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (300 mg, 0.51 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 5 mL). The resulting mixture was stirred at rt for half an hour and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (230 mg, 92%).

Compound 6: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.73 - 7.71 (m, 2H), 7.48 - 7.44 (m, 3H), 7.39 - 7.31 (m, 3H), 7.13 (d, $J = 8.1$ Hz, 1H), 6.99 - 6.92 (m, 2H), 5.17 (s, 2H), 5.13 - 5.08 (m, 1H), 4.62 (s, 2H), 3.92 (s, 3H), 1.73 (d, $J = 7.0$ Hz, 3H).

Example 103: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(4-methoxy-3-nitrophenyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 2-(4-methoxy-3-nitrobenzamido)acetate

[00590] To 30 mL of dichloromethane were added 4-methoxy-3-nitrobenzoic acid (5.0 g, 25.4 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (7.3 g, 38.1 mmol) and 1-hydroxybenzotriazole (5.15 g, 38.1 mmol). The mixture was stirred at rt for half an hour, then glycine methyl ester hydrochloride (3.83 g, 30.5 mmol) and *N,N*-diisopropylethylamine (13.3 mL, 76.2 mmol) were added at 0 °C. The mixture was stirred at rt for 12 hours, then water (30 mL) was added. The resulting mixture was extracted with dichloromethane (40 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a white solid (6.34 g, 95%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.28 (s, 1H), 8.04 - 8.00 (m, 1H), 7.14 - 6.99 (m, 1H), 6.88 (br.s, 1H), 4.24 - 4.21 (m, 2H), 4.00 (s, 3H), 3.80 (s, 3H); and MS-ESI: m/z 269.0 $[\text{M}+\text{H}]^+$.

Step 2: Methyl 2-(4-methoxy-3-nitrophenylthioamido)acetate

[00591] To tetrahydrofuran (20 mL) were added methyl 2-(4-methoxy-3-nitrobenzamido)acetate (2.0 g, 7.46 mmol) and Lawesson's Reagent (3.02 g, 7.46 mmol). The mixture was refluxed at 75 °C for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (30 mL), and the mixture was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (2.1 g, 98%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.33 (s, 1H), 8.10 (d, J = 8.9 Hz, 1H), 7.11 (d, J = 8.9 Hz, 1H), 4.57 (d, J = 4.6 Hz, 2H), 4.02 (s, 3H), 3.86 (s, 3H); and MS-ESI: m/z 285.1 $[\text{M}+\text{H}]^+$.

Step 3: Methyl 2-(((4-methoxy-3-nitrophenyl)(methylthio)methylene)amino)acetate

[00592] To a solution of trimethyloxonium tetrafluoroborate (0.39 g, 2.64 mmol) in dichloromethane (20 mL) was added dropwise a solution of methyl 2-(4-methoxy-3-nitrophenylthioamido)acetate (0.5 g, 1.76 mmol) in dichloromethane (20 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then washed with saturated aqueous sodium bicarbonate (25 mL × 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as yellow oil (0.495 g, 95%).

MS-ESI: m/z 299.0 $[M+H]^+$.

Step 4: (S)-Methyl 5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(4-methoxy-3-nitrophenyl)oxazole-4-carboxylate

[00593] To 20 mL of anhydrous tetrahydrofuran (20 mL) were added methyl 2-(((4-methoxy-3-nitrophenyl)(methylthio)methylene)amino)acetate (0.495 g, 1.66 mmol) and (S)-tert-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (0.476 g, 2.49 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (6.6 mL, 6.6 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a yellow solid (0.213 g, 32%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.51 (s, 1H), 8.27 (d, J = 8.9 Hz, 1H), 7.18 (d, J = 8.9 Hz, 1H), 5.59 (br.s, 1H), 5.49 - 5.45 (m, 1H), 4.04 (s, 3H), 3.98 (s, 3H), 1.55 (d, J = 7.0 Hz, 3H), 1.42 (s, 9H); and MS-ESI: m/z 422.1 $[M+H]^+$.

Step 5: (S)-5-(1-((tert-Butoxycarbonyl)amino)ethyl)-2-(4-methoxy-3-nitrophenyl)oxazole-4-carboxylic acid

[00594] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added (S)-methyl 5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(4-methoxy-3-nitrophenyl)oxazole-4-carboxylate (0.24 g, 0.57 mmol) and lithium hydroxide monohydrate (0.068 g, 2.85 mmol). The solution was stirred at 40 °C for 3 hours and tetrahydrofuran was removed, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (30 mL × 3). The organic layers were combined, dried over

anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (0.211 mg, 91%).

Step 6: (*S*)-*tert*-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-methoxy-3-nitrophenyl)oxazol-5-yl)ethyl)carbamate

[00595] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-methoxy-3-nitrophenyl)oxazole-4-carboxylic acid (211 mg, 0.52 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (149.5 mg, 0.78 mmol) and 1-hydroxy-7-azabenzotriazole (105.4 mg, 0.78 mmol). The mixture was stirred at rt for half an hour. To the resulting solution were added dropwise 2,4-difluorobenzylamine (0.08 mL, 0.63 mmol) and *N,N*-diisopropylethylamine (0.27 mL, 1.56 mmol) at 0 °C. The mixture was stirred at rt for 12 hours, and water (15 mL) was added. The resulting mixture was extracted with dichloromethane (20 mL × 3) and the combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give the title compound as a white solid (190 mg, 70%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.48 (s, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.17 (d, *J* = 8.9 Hz, 1H), 6.89 - 6.82 (m, 2H), 6.74 (br.s, 1H), 5.30 (t, *J* = 7.0 Hz, 1H), 4.64 (d, *J* = 4.2 Hz, 2H), 4.03 (s, 3H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.42 (s, 9H); and MS-ESI: *m/z* 533.0 [M+H]⁺.

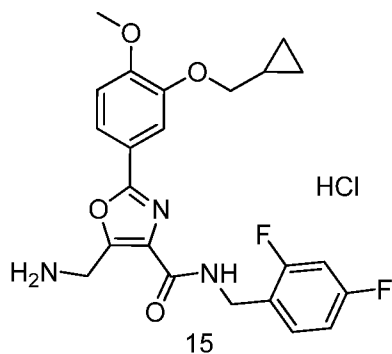
Step 7: (*S*)-5-(1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-methoxy-3-nitrophenyl)oxazole-4-carboxamide hydrochloride

[00596] To a solution of (*S*)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-methoxy-3-nitrophenyl)oxazol-5-yl)ethyl)carbamate (190 mg, 0.36 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for half an hour and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (144 mg, 93%).

Compound 10: ¹H NMR (400 MHz, CDCl₃): δ ppm 8.49 (s, 1H), 8.16 (d, *J* = 8.7 Hz, 1H), 7.62 - 7.58 (m, 1H), 7.41 - 7.39 (m, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 6.90 - 6.87 (m, 1H), 4.99 - 4.96 (m, 1H), 4.63 (d, *J* = 6.0 Hz, 2H), 4.05 (s, 3H), 1.74 (d, *J* = 7.0 Hz, 3H); and MS-ESI: *m/z*

433.2 [M+H-HCl]⁺.

Example 104: 5-(Aminomethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl (2-fluoro-2-oxoethyl)carbamate

[00597] To 20 mL of dichloromethane were added *N*-Boc-glycine (2.5 g, 14.29 mmol) and triethylamine (2.15 mL, 15.72 mmol). To the solution was added cyanuric fluoride (2.7 mL, 28.58 mmol) at -40 °C, then the resulting mixture was stirred at -10 °C for 1 hour. The reaction mixture was washed with ice-water (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate and the organic solvent was removed to give the title compound as a white solid (2.12 g, 84%).

¹H NMR (400 MHz, *d*₆-DMSO): δ ppm 7.54 - 7.51 (m, 1H), 4.03 - 4.00 (m, 2H), 1.39 (s, 9H).

Step 2: Methyl 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate

[00598] To 30 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-(cyclopropylmethoxy)-4-(methoxy)phenyl)(methylthio)methylene)amino)acetate (1.99 g, 6.16 mmol) and *tert*-butyl (2-fluoro-2-oxoethyl)carbamate (2.18 g, 12.32 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (18.48 mL, 18.48 mmol) at -78 °C and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a yellow solid (0.57 g, 25%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.66 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.55 (d, *J* = 2.0

Hz, 1H), 6.92 (d, $J = 8.5$ Hz, 1H), 5.28 (br.s, 1H), 4.72 (d, $J = 5.7$ Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 3.92 (d, $J = 6.0$ Hz, 2H), 1.46 (s, 9H), 1.39 - 1.35 (m, 1H), 0.69 - 0.64 (m, 2H), 0.40 - 0.36 (m, 2H); and MS-ESI: m/z 433.3 $[M+H]^+$.

Step 3: 5-(((*tert*-Butoxycarbonyl)amino)methyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid

[00599] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added methyl 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate (0.57 g, 1.32 mmol) and lithium hydroxide monohydrate (0.28 g, 6.60 mmol). The solution was stirred at 40 °C for 3 hours, then concentrated to remove tetrahydrofuran. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The mixture was extracted with ethyl acetate (30 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (0.54 g, 99%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.64 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.56 (s, 1H), 6.93 (d, $J = 8.5$ Hz, 1H), 5.36 (br.s, 1H), 4.71 - 4.64 (m, 2H), 3.94 (s, 3H), 3.93 (d, $J = 7.1$ Hz, 2H), 1.47 (s, 9H), 1.37 - 1.35 (m, 1H), 0.69 - 0.65 (m, 2H), 0.40 - 0.38 (m, 2H); and MS-ESI: m/z 419.1 $[M+H]^+$.

Step 4: *tert*-Butyl ((2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)methyl)carbamate

[00600] To 10 mL of dichloromethane were added 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid (0.21 g, 0.48 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.14 g, 0.72 mmol) and 1-hydroxy-7-azabenzotriazole (0.10 g, 0.72 mmol), and the resulting mixture was stirred at 0 °C for 30 minutes. To the mixture were added 2,4-difluorobenzylamine (0.06 mL, 0.58 mmol) and *N,N*-diisopropylethylamine (0.25 mL, 1.44 mmol) at 0 °C, and the mixture was stirred at rt for 12 hours. To the reaction mixture was added water (15 mL), the resulting mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc(v/v) = 3/1) to give the title compound as a white solid (0.26 g, 97%).

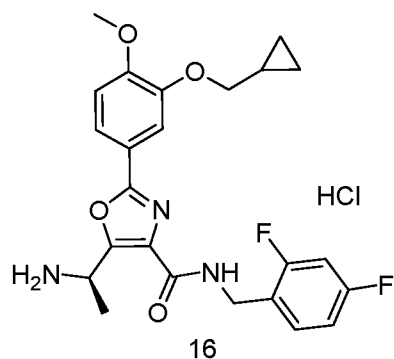
^1H NMR (400 MHz, CDCl_3): δ ppm 7.59 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.46 (d, $J = 2.0$ Hz, 1H), 7.43 - 7.37 (m, 1H), 6.92 (d, $J = 8.5$ Hz, 1H), 6.89 - 6.81 (m, 2H), 4.70 (d, $J = 6.2$ Hz, 2H), 4.63 (d, $J = 6.2$ Hz, 2H), 3.93 (s, 3H), 3.92 (d, $J = 6.9$ Hz, 2H), 1.46 (s, 9H), 1.38 - 1.35 (m, 1H), 0.70 - 0.65 (m, 2H), 0.41 - 0.38 (m, 2H); and MS-ESI: m/z 544.2 $[\text{M}+\text{H}]^+$.

Step 5: 5-(Aminomethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00601] To a solution of *tert*-butyl ((2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)methyl)carbamate (0.26 g, 0.48 mmol) in dichloromethane (3 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 30 minutes and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (210 mg, 91%).

Compound 15: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.69 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.48 - 7.42 (m, 1H), 7.09 (d, $J = 8.5$ Hz, 1H), 6.98 - 6.90 (m, 2H), 4.61 (s, 2H), 4.58 (s, 2H), 3.91 (d, $J = 6.9$ Hz, 2H), 3.91 (s, 3H), 1.34 - 1.26 (m, 1H), 0.65 - 0.61 (m, 2H), 0.38 - 0.34 (m, 2H); and MS-ESI: m/z 444.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 105: (R)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (R)-*tert*-Butyl (1-fluoro-1-oxopropan-2-yl)carbamate

[00602] To 20 mL of dichloromethane were added *N*-Boc-*R*-alanine (1.0 g, 5.29 mmol) and triethylamine (0.8 mL, 5.82 mmol). To the solution was added dropwise cyanuric fluoride (1.0 mL, 10.58 mmol) at -40 $^{\circ}\text{C}$, then the resulting mixture was stirred at -10 $^{\circ}\text{C}$ for 1 hour. The reaction mixture was washed with ice-water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate and the organic solvent was removed to give the title compound as a

white solid (0.82 g, 81%).

¹H NMR (400 MHz, *d*₆-DMSO): δ ppm 4.33 - 4.26 (m, 1H), 1.39 (s, 9H), 1.35 (d, *J* = 7.2 Hz, 3H).

Step 2: (*R*)-Methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate

[00603] To 20 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-(cyclopropylmethoxy)-4-(methoxy)phenyl)(methylthio)methylene)amino)acetate (0.5 g, 1.55 mmol) and (*R*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (0.59 g, 3.1 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (6.2 mL, 6.2 mmol) at -78 °C and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a yellow solid (0.34 g, 50%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.63 (d, *J* = 8.4 Hz, 1H), 7.54 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.46 - 5.42 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.93 (d, *J* = 7.0 Hz, 2H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.42 (s, 9H), 1.27 - 1.24 (m, 1H), 0.69 - 0.65 (m, 2H), 0.40 - 0.37 (m, 2H); and MS-ESI: *m/z* 447.3 [M+H]⁺.

Step 3: (*R*)-5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid

[00604] To a mixed solvent of tetrahydrofuran (20 mL) and water (10 mL) were added (*R*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate (0.34 g, 0.76 mmol) and lithium hydroxide monohydrate (0.16 g, 3.8 mmol). The solution was stirred at 40 °C for 3 hours, then concentrated to remove tetrahydrofuran. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The mixture was extracted with ethyl acetate (30 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (310 mg, 94%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.62 (d, *J* = 8.4 Hz, 1H), 7.54 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.40 - 5.36 (m, 1H), 3.94 (s, 3H), 3.93 (d, *J* = 7.0 Hz, 2H), 1.57 (d, *J* = 7.1 Hz, 3H),

1.44 (s, 9H), 1.27 - 1.25 (m, 1H), 0.68 - 0.66 (m, 2H), 0.40 - 0.38 (m, 2H); and MS-ESI: m/z 433.3 $[M+H]^+$.

Step 4: (R)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00605] To 10 mL of dichloromethane were added (R)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid (0.31 g, 0.72 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.21 g, 1.08 mmol) and 1-hydroxy-7-azabenzotriazole (0.15 g, 1.08 mmol), and the resulting mixture was stirred at rt for 30 minutes. To the mixture were added dropwise 2,4-difluorobenzylamine (0.10 mL, 0.86 mmol) and *N,N*-diisopropylethylamine (0.38 mL, 2.16 mmol) at 0 °C, and the mixture was stirred at rt for 12 hours. To the reaction mixture was added water (15 mL), and the mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc(v/v) = 5/1) to give the title compound as a white solid (0.29 g, 73%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.57 (d, $J = 8.4$ Hz, 1H), 7.54 (br.s, 1H), 7.45 - 7.38 (m, 2H), 6.93 - 6.80 (m, 2H), 5.29 - 5.27 (m, 1H), 4.65 - 4.62 (m, 2H), 3.93 (s, 3H), 3.92 (d, $J = 6.9$ Hz, 2H), 1.52 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 1.25 - 1.23 (m, 1H), 0.69 - 0.66 (m, 2H), 0.42 - 0.38 (m, 2H); and MS-ESI: m/z 558.2 $[M+H]^+$.

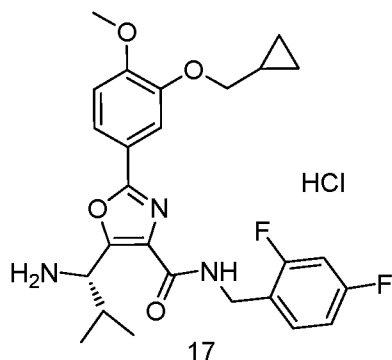
Step 5: (R)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00606] To a solution of (R)-tert-butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.29 g, 0.52 mmol) in dichloromethane (3 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 5 mL). The resulting mixture was stirred at rt for 30 minutes and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (184 mg, 78%).

Compound 16: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.69 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.48 - 7.42 (m, 1H), 7.10 (d, $J = 8.5$ Hz, 1H), 6.99 - 6.91 (m, 2H), 5.14 - 5.09 (m, 1H), 4.61 (s, 2H), 3.91 (s, 3H), 3.91 (d, $J = 6.9$ Hz, 2H), 1.73 (d, $J = 7.0$ Hz, 3H), 1.32 -

1.28 (m, 1H), 0.66 - 0.61 (m, 2H), 0.38 - 0.34 (m, 2H); and MS-ESI: m/z 458.1 $[M+H-HCl]^+$.

Example 106: (S)-5-(1-Amino-2-methylpropyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-fluoro-3-methyl-1-oxobutan-2-yl)carbamate

[00607] To 20 mL of dichloromethane were added *N*-Boc-*L*-valine (3.1 g, 14.29 mmol) and triethylamine (2.2 mL, 15.72 mmol). To the solution was added cyanuric fluoride (2.7 mL, 28.58 mmol) at -40 °C, then the resulting mixture was stirred at -10 °C for 1 hour. The reaction mixture was washed with ice-water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate and the organic solvent was removed to give the title compound as a white solid (3.01 g, 96%).

^1H NMR (400 MHz, d_6 -DMSO): δ ppm 4.10 - 4.06 (m, 1H), 2.12 - 2.03 (m, 1H), 1.45 (s, 9H), 0.97 - 0.94 (m, 6H).

Step 2: (S)-Methyl 5-(1-((tert-butoxycarbonyl)amino)-2-methylpropyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate

[00608] To 40 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-(cyclopropylmethoxy)-4-(methoxy)phenyl)(methylthio)methylene)amino)acetate (2.2 g, 6.80 mmol) and (S)-tert-butyl (1-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (2.98 g, 13.60 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (20.4 mL, 20.40 mmol) at -78 °C and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give a yellow solid (1.13 g, 38%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.63 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.54 (d, $J = 2.0$

Hz, 1H), 6.93 (d, $J = 8.5$ Hz, 1H), 5.11 - 5.07 (m, 1H), 3.94 (d, $J = 6.9$ Hz, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 1.44 (s, 9H), 1.36 - 1.33 (m, 1H), 1.04 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.7$ Hz, 3H), 0.68 - 0.63 (m, 2H), 0.40 - 0.35 (m, 2H); and MS-ESI: m/z 475.3 $[M+H]^+$.

Step 3: (*S*)-5-(1-((*tert*-Butoxycarbonyl)amino)-2-methylpropyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid

[00609] To a mixed solvent of tetrahydrofuran (40 mL) and water (20 mL) were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)-2-methylpropyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate (1.13 g, 2.38 mmol) and lithium hydroxide monohydrate (0.50 g, 11.92 mmol). The solution was stirred at 40 °C for 3 hours, then concentrated to remove tetrahydrofuran. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The mixture was extracted with ethyl acetate (30 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (0.47 g, 43%).

MS-ESI: m/z 461.3 $[M+H]^+$.

Step 4: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)-2-methylpropyl)carbamate

[00610] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)-2-methylpropyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid (0.20 g, 0.43 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.12 g, 0.65 mmol) and 1-hydroxy-7-azabenzotriazole (0.09 g, 0.65 mmol), and the resulting mixture was stirred at rt for 30 minutes. To the mixture were added dropwise 2,4-difluorobenzylamine (0.06 mL, 0.52 mmol) and *N,N*-diisopropylethylamine (0.23 mL, 1.30 mmol) at 0 °C, and the mixture was stirred at rt for 12 hours. To the reaction mixture was added water (15 mL), and the mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc(v/v) = 5/1) to give the title compound as a white solid (0.23 g, 93%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.57 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.45 (d, $J = 2.0$ Hz, 1H), 7.42 - 7.38 (m, 1H), 6.92 (d, $J = 8.5$ Hz, 1H), 6.89 - 6.82 (m, 2H), 4.90 - 4.85 (m, 1H), 4.66 - 4.64 (m, 2H), 3.93 (s, 3H), 3.94 (d, $J = 5.3$ Hz, 2H), 2.20 - 2.11 (m, 1H), 1.44 (s, 9H), 1.36

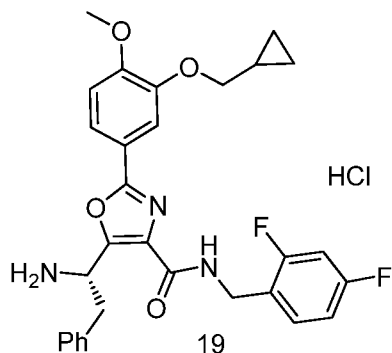
- 1.35 (m, 1H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 6.7$ Hz, 3H), 0.71 - 0.66 (m, 2H), 0.43 - 0.39 (m, 2H); and MS-ESI: m/z 586.2 $[M+H]^+$.

Step 5: (*S*)-5-(1-Amino-2-methylpropyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00611] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)-2-methylpropyl)carbamate (0.29 g, 0.50 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for 30 minutes and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (246 mg, 94%).

Compound 17: ^1H NMR (400 MHz, CDCl_3): δ ppm 7.74 - 7.71 (m, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 7.46 (s, 1H), 7.44 - 7.40 (m, 1H), 6.94 - 6.91 (m, 1H), 6.89 - 6.84 (m, 1H), 4.80 - 4.75 (m, 1H), 4.66 - 4.63 (m, 2H), 3.95 (s, 3H), 3.94 (d, $J = 7.0$ Hz, 2H), 2.70 - 2.68 (m, 1H), 1.41 - 1.34 (m, 1H), 1.13 (d, $J = 5.7$ Hz, 3H), 1.00 (d, $J = 5.6$ Hz, 3H), 0.72 - 0.67 (m, 2H), 0.44 - 0.41 (m, 2H); and MS-ESI: m/z 486.1 $[M+H-\text{HCl}]^+$.

Example 107: (*S*)-5-(1-Amino-2-phenylethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-fluoro-1-oxo-3-phenylpropan-2-yl)carbamate

[00612] To 20 mL of dichloromethane were added *N*-Boc-*L*-phenylalanine (3.6 g, 14.29 mmol) and triethylamine (2.2 mL, 15.72 mmol). To the solution was added dropwise cyanuric fluoride (2.7 mL, 28.58 mmol) at -40 °C, then the resulting mixture was stirred at -10 °C for 1 hour. The reaction mixture was washed with ice-water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate and the organic solvent was removed to give the title compound as a white solid (3.07 g, 85%).

^1H NMR (400 MHz, d_6 -DMSO): δ ppm 7.32 - 7.22 (m, 5H), 4.50 - 4.44 (m, 1H), 3.11 - 2.98 (m, 2H), 1.35 (s, 9H); and MS-ESI: m/z 266.0 $[\text{M-H}]^-$.

Step 2: (S)-Methyl 5-(1-((*tert*-butoxycarbonyl)amino)-2-phenylethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate

[00613] To 40 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-(cyclopropylmethoxy)-4-(methoxy)phenyl)(methylthio)methylene)amino)acetate (2.1 g, 6.50 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxo-3-phenylpropan-2-yl)carbamate (3.47 g, 13.00 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (19.5 mL, 19.50 mmol) at -78°C and the reaction mixture was stirred at -78°C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a yellow solid (0.95 g, 28%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.51 (d, $J = 6.7$ Hz, 1H), 7.42 (s, 1H), 7.23 - 7.11 (m, 5H), 6.90 (d, $J = 8.5$ Hz, 1H), 5.63 - 5.57 (m, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.90 (d, $J = 7.0$ Hz, 2H), 3.15 - 3.10 (m, 2H), 1.40 (s, 9H), 1.34 - 1.31 (m, 1H), 0.70 - 0.64 (m, 2H), 0.40 - 0.36 (m, 2H); and MS-ESI: m/z 523.3 $[\text{M+H}]^+$.

Step 3: (S)-5-(1-((*tert*-Butoxycarbonyl)amino)-2-phenylethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid

[00614] To a mixed solvent of tetrahydrofuran (40 mL) and water (20 mL) were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)-2-phenylethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate (0.95 g, 1.82 mmol) and lithium hydroxide monohydrate (0.38 g, 9.10 mmol). The solution was stirred at 40°C for 3 hours, then concentrated to remove tetrahydrofuran. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The mixture was extracted with ethyl acetate (30 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (0.90 g, 97%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.25 - 7.14 (m, 7H), 6.90 (d, $J = 8.5$ Hz, 1H), 5.94 (br.s, 1H), 5.57 - 5.55 (m, 1H), 3.93 (s, 3H), 3.91 (d, $J = 7.1$ Hz, 2H), 3.21 - 3.18 (m, 2H), 1.39 (s, 9H), 1.34 - 1.31 (m, 1H), 0.70 - 0.65 (m, 2H), 0.41 - 0.37 (m, 2H); and MS-ESI: m/z 509.2 $[\text{M+H}]^+$.

Step 4: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)-2-phenylethyl)carbamate

[00615] To 10 mL of dichloromethane were added (S)-5-(1-((*tert*-butoxycarbonyl)amino)-2-phenylethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid (0.20 g, 0.40 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.14 g, 0.72 mmol) and 1-hydroxy-7-azabenzotriazole (0.10 g, 0.72 mmol), and the resulting mixture was stirred at rt for 30 minutes. To the mixture were added dropwise 2,4-difluorobenzylamine (0.06 mL, 0.48 mmol) and *N,N*-diisopropylethylamine (0.25 mL, 1.44 mmol), and the mixture was stirred at rt for 12 hours. To the reaction mixture was added water (15 mL), and the mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc(v/v) = 5/1) to give the title compound as a white solid (0.24 g, 94%).

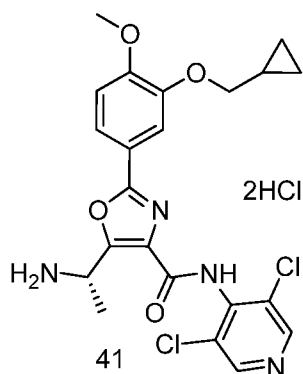
^1H NMR (400 MHz, CDCl_3): δ ppm 7.53 - 7.48 (m, 1H), 7.43 - 7.37 (m, 2H), 7.22 - 7.18 (m, 2H), 7.15 - 7.11 (m, 3H), 6.91 - 6.83 (m, 3H), 5.43 - 5.37 (m, 1H), 4.71 - 4.60 (m, 2H), 3.92 (s, 3H), 3.89 (d, J = 7.0 Hz, 2H), 3.23 - 3.10 (m, 2H), 1.40 (s, 9H), 1.36 - 1.34 (m, 1H), 0.71 - 0.66 (m, 2H), 0.42 - 0.38 (m, 2H); and MS-ESI: m/z 534.1 $[\text{M}+\text{H}-100]^+$.

Step 5: (S)-5-(1-Amino-2-phenylethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00616] To a solution of (S)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)-2-phenylethyl)carbamate (0.24 g, 0.38 mmol) in dichloromethane (3 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 30 minutes and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (150 mg, 70%).

Compound 19: ^1H NMR (400 MHz, CD_3OD) δ ppm 7.58 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.39 - 7.33 (m, 1H), 7.26 - 7.20 (m, 3H), 7.15 - 7.13 (m, 2H), 7.07 (d, J = 8.5 Hz, 1H), 6.99 - 6.91 (m, 2H), 5.32 - 5.29 (m, 1H), 4.56 (s, 2H), 3.90 (s, 3H), 3.88 (d, J = 7.0 Hz, 2H), 3.44 - 3.34 (m, 2H), 1.33 - 1.25 (m, 1H), 0.66 - 0.61 (m, 2H), 0.38 - 0.34 (m, 2H); and MS-ESI: m/z 534.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 108: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(3,5-dichloropyridin-4-yl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-(fluorocarbonyl)oxazol-5-yl)ethyl)carbamate

[00617] To 10 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid (0.30 g, 0.70 mmol) and triethylamine (0.10 mL, 0.77 mmol). To the solution was added dropwise cyanuric fluoride (0.2 mL, 1.40 mmol) at -40 °C, then the resulting mixture was stirred at -10 °C for 1 hour. The reaction mixture was washed with ice-water (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate and the organic solvent was removed to give the title compound as a white solid (282 mg, 93%).

¹H NMR (400 MHz, *d*₆-DMSO): δ ppm 7.59 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.9 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 5.22 – 5.18 (m, 1H), 3.90 (d, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 9H), 1.27 – 1.25 (m, 1H), 0.62 – 0.58 (m, 2H), 0.38 – 0.35 (m, 2H); and MS-ESI: *m/z* 435.2 [M+H]⁺.

Step 2: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((3,5-dichloropyridin-4-yl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00618] To 5 mL of tetrahydrofuran were added 3,5-dichloro-4-aminopyridine (162 mg, 1.00 mmol) and sodium hydride (80 mg, 2.00 mmol, 60%). The mixture was stirred at rt for 1 hour. To the mixture was added a solution of (S)-tert-butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-(fluorocarbonyl)oxazol-5-yl)ethyl)carbamate (282 mg, 0.65 mmol) in tetrahydrofuran (9 mL) at 0 °C, and the reaction mixture was stirred at rt for 12 hours. To the reaction mixture was added saturated aqueous ammonium chloride (20 mL), and the resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried

over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (40 mg, 11%).

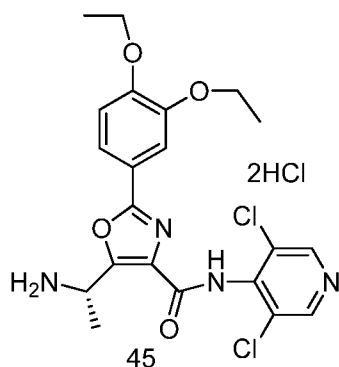
^1H NMR (400 MHz, CDCl_3): δ ppm 8.78 (s, 2H), 7.74 – 7.65 (m, 2H), 7.21 (d, J = 8.4 Hz, 1H), 5.18 – 4.95 (m, 1H), 3.93 – 3.88 (m, 5H), 1.65 (d, J = 7.0 Hz, 3H), 1.37 (s, 9H), 1.24 – 1.22 (s, 1H), 0.65 – 0.54 (m, 2H), 0.41 – 0.30 (m, 2H); and MS-ESI: m/z 577.1 $[\text{M}+\text{H}]^+$.

Step 3: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(3,5-dichloropyridin-4-yl)oxazole-4-carboxamide dihydrochloride

[00619] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((3,5-dichloropyridin-4-yl)carbamoyl)oxazol-5-yl)ethyl)carbamate (316 mg, 0.55 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for 30 minutes and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (135 mg, 52%).

Compound 41: ^1H NMR (400 MHz, d_6 -DMSO): δ ppm 8.78 (s, 2H), 7.73 (d, J = 8.5 Hz, 1H), 7.66 (s, 1H), 7.21 (d, J = 8.6 Hz, 1H), 5.11 – 5.07 (m, 1H), 3.92 (d, J = 7.0 Hz, 2H), 3.88 (s, 3H), 1.65 (d, J = 7.0 Hz, 3H), 1.30 – 1.26 (m, 1H), 0.63 – 0.58 (m, 2H), 0.38 – 0.35 (m, 2H); and MS-ESI: m/z 477.0 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 109: (S)-5-(1-Aminoethyl)-N-(3,5-dichloropyridin-4-yl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-*tert*-Butyl (1-(2-(3,4-diethoxyphenyl)-4-(fluorocarbonyl)oxazol-5-yl)ethyl)carbamate

[00620] To 20 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxylic acid

(1.02 g, 2.42 mmol) and triethylamine (0.37 mL, 2.66 mmol). To the solution was added dropwise cyanuric fluoride (0.46 mL, 4.84 mmol) at -40 °C, then the resulting mixture was stirred at -10 °C for 1 hour. The reaction mixture was washed with ice-water (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as a white solid (1.00 g, 97%).

¹H NMR (400 MHz, *d*₆-DMSO): δ ppm 7.57 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.9 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 5.21 – 5.19 (m, 1H), 4.28 – 3.97 (m, 4H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.39 – 1.23 (m, 15H); and MS-ESI: *m/z* 423.3 [M+H]⁺.

Step 2: (*S*)-*tert*-Butyl (1-(4-((3,5-dichloropyridin-4-yl)carbamoyl)-2-(3,4-diethoxyphenyl)oxazol-5-yl)ethyl)carbamate

[00621] To 5 mL of tetrahydrofuran were added 3,5-dichloro-4-aminopyridine (469 mg, 2.84 mmol) and sodium hydride (114 mg, 2.84 mmol, 60%). The mixture was stirred at rt for 1 hour. To the mixture was added a solution of (*S*)-*tert*-butyl (1-(2-(3,4-diethoxyphenyl)-4-(fluorocarbonyl)oxazol-5-yl)ethyl)carbamate (1.00 g, 2.37 mmol) in tetrahydrofuran (10 mL) at 0 °C, and the reaction mixture was stirred at rt for 12 hours. The mixture was washed with saturated aqueous ammonium chloride (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (264 mg, 20%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.63 (s, 2H), 7.65 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 5.40 – 5.27 (m, 1H), 4.26 – 4.18 (m, 4H), 1.60 (d, *J* = 7.0 Hz, 3H), 1.55 – 1.51 (m, 6H), 1.44 (s, 9H); and MS-ESI: *m/z* 565.1 [M+H]⁺.

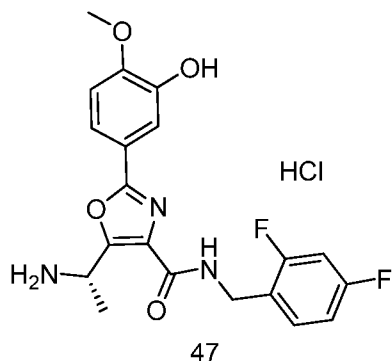
Step 3: (*S*)-5-(1-Aminoethyl)-*N*-(3,5-dichloropyridin-4-yl)-2-(3,4-diethoxyphenyl)oxazole-4-carboxamide dihydrochloride

[00622] To a solution of (*S*)-*tert*-butyl (1-(4-((3,5-dichloropyridin-4-yl)carbamoyl)-2-(3,4-diethoxyphenyl)oxazol-5-yl)ethyl)carbamate (264 mg, 0.47 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 6 mL). The resulting mixture was stirred at rt for 30 minutes and the solvent was removed. The residue was recrystallized from methanol/ethyl acetate (v/v = 1/20) to give the desired product as a white solid (161 mg, 74%).

Compound 45: ¹H NMR (400 MHz, *d*₆-DMSO): δ ppm 8.77 (s, 2H), 7.71 (s, 1H), 7.72 (d, *J*

= 6.9 Hz, 1H), 7.19 (d, J = 9.0 Hz, 1H), 5.14 – 5.04 (m, 1H), 4.20 – 4.06 (m, 4H), 1.65 (d, J = 7.0 Hz, 3H), 1.40 – 1.35 (m, 6H); and MS-ESI: m/z 465.2 $[M+H-2HCl]^+$.

Example 110: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(3-hydroxy-4-methoxyphenyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 4-methoxy-3-((4-methoxybenzyl)oxy)benzoate

[00623] To *N,N*-dimethylformamide (60 mL) were added methyl 3-hydroxy-4-methoxybenzoate (10.0 g, 54.95 mmol), potassium carbonate (32.80 g, 238.00 mmol) and *p*-methoxybenzyl bromide (23.70 g, 166.00 mmol). The mixture was stirred at 60 °C for 4.5 hours. To the mixture was added water (40 mL) and the resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a light yellow solid (16.2 g, 97%).

MS-ESI: m/z 303.3 $[M+H]^+$.

Step 2: 4-Methoxy-3-((4-methoxybenzyl)oxy)benzoic acid

[00624] To a mixed solvent of tetrahydrofuran (60 mL) and water (30 mL) were added methyl 4-methoxy-3-((4-methoxybenzyl)oxy)benzoate (16.20 g, 53.64 mmol) and lithium hydroxide monohydrate (6.80 g, 162.00 mmol). The mixture was stirred at 40 °C for 1.5 hours and then concentrated to remove the tetrahydrofuran. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The organic layer was concentrated to give the title compound as a white solid (15.01 g, 97%).

^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.78 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.69 (d, J = 1.9 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 6.95 – 6.92 (m, 3H), 5.14 (s, 2H), 3.83 (s, 6H); and MS-ESI: m/z 287.3 $[M-H]^-$.

Step 3: Methyl 2-(4-methoxy-3-((4-methoxybenzyl)oxy)benzamido)acetate

[00625] To 80 mL of dichloromethane were added 4-methoxy-3-((4-methoxybenzyl)oxy)benzoic acid (13.0 g, 45.10 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (13.0 g, 67.65 mmol) and 1-hydroxybenzotriazole (9.13 g, 67.65 mmol). The mixture was stirred at rt for half an hour, then glycine methyl ester hydrochloride (6.83 g, 54.20 mmol) and *N,N*-diisopropylethylamine (24.3 mL, 135.30 mmol) were added at 0 °C. The mixture was stirred at rt for 12 hours, then washed with water (40 mL × 3). The organic layer was dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a white solid (9.5 g, 62%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.47 (s, 1H), 7.38 - 7.34 (m, 3H), 6.90 - 6.86 (m, 3H), 6.60 (br.s, 1H), 5.08 (s, 2H), 4.21 (d, *J* = 5.0 Hz, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H); and MS-ESI: *m/z* 360.2 [M+H]⁺.

Step 4: Methyl 2-(4-methoxy-3-((4-methoxybenzyl)oxy)phenylthioamido)acetate

[00626] To tetrahydrofuran (40 mL) were added methyl 2-(4-methoxy-3-((4-methoxybenzyl)oxy)benzamido)acetate (2.0 g, 5.57 mmol) and Lawesson's Reagent (2.25 g, 5.57 mmol). The mixture was refluxed at 75 °C for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (40 mL), and the mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as yellow viscous liquid (2.05 g, 98%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.63 (s, 1H), 7.43 - 7.39 (m, 3H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 2H), 4.58 (d, *J* = 4.5 Hz, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H); and MS-ESI: *m/z* 376.2 [M+H]⁺.

Step 5: Methyl 2-(((4-methoxy-3-((4-methoxybenzyl)oxy)phenyl)(methylthio)methylene)amino)acetate

[00627] To a solution of trimethyloxonium tetrafluoroborate (1.62 g, 10.94 mmol) in dichloromethane (20 mL) was added dropwise a solution of methyl 2-(4-methoxy-3-((4-methoxybenzyl)oxy)phenylthioamido)acetate (2.05 g, 5.47 mmol) in

dichloromethane (30 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then washed with saturated aqueous sodium bicarbonate (25 mL × 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as yellow oil (2.24 g, 99%).

MS-ESI: m/z 390.1 $[M+H]^+$.

Step 6: (S)-Methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-methoxy-3-((4-methoxybenzyl)oxy)phenyl)oxazole-4-carboxylate

[00628] To 20 mL of anhydrous tetrahydrofuran (20 mL) were added methyl 2-(((4-methoxy-3-((4-methoxybenzyl)oxy)phenyl)(methylthio) methylene)amino)acetate (2.24 g, 5.47 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (2.34 g, 12.25 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (16.4 mL, 16.4 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (347 mg, 14%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.69 - 7.67 (m, 2H), 7.42 (d, J = 8.6 Hz, 2H), 6.96 - 6.90 (m, 3H), 5.49 - 5.45 (m, 1H), 5.14 (s, 2H), 3.99 (s, 3H), 3.93 (s, 3H), 3.83 (s, 3H), 1.55 (d, J = 7.0 Hz, 3H), 1.45 (s, 9H); and MS-ESI: m/z 513.3 $[M+H]^+$.

Step 7: (S)-5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(4-methoxy-3-((4-methoxybenzyl)oxy)phenyl)oxazole-4-carboxylic acid

[00629] To a mixed solvent of tetrahydrofuran (30 mL) and water (15 mL) were added (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-methoxy-3-((4-methoxybenzyl)oxy)phenyl)oxazole-4-carboxylate (374 mg, 0.73 mmol) and lithium hydroxide monohydrate (153 mg, 0.95 mmol). The solution was stirred at 40 °C for 3 hours and tetrahydrofuran was removed, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (30 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (230 mg, 64%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.68 - 7.66 (m, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.00 -

6.89 (m, 3H), 5.44 - 5.40 (m, 1H), 5.15 (s, 2H), 3.94 (s, 3H), 3.83 (s, 3H), 1.59 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H); and MS-ESI: m/z 499.3 $[M+H]^+$.

Step 8: (S)-tert-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-methoxy-3-((4-methoxybenzyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00630] To 15 mL of dichloromethane were added (S)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-methoxy-3-((4-methoxybenzyl)oxy)phenyl)oxazole-4-carboxylic acid (230 mg, 0.46 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (133 mg, 0.69 mmol) and 1-hydroxy-7-azabenzotriazole (93 mg, 0.69 mmol). The mixture was stirred at rt for half an hour. To the resulting solution were added 2,4-difluorobenzylamine (0.07 mL, 0.55 mmol) and *N,N*-diisopropylethylamine (0.25 mL, 1.38 mmol). The mixture was stirred at rt for 12 hours. To the reaction mixture was added water (15 mL), and the resulting mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a white solid (154 mg, 55%).

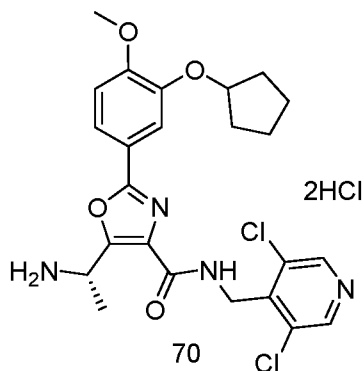
^1H NMR (400 MHz, CDCl_3): δ ppm 7.60 (dd, $J_1 = 8.3$ Hz, $J_2 = 2.0$ Hz, 1H), 7.58 (d, $J = 1.8$ Hz, 1H), 7.44 - 7.41 (m, 3H), 6.96 - 6.84 (m, 5H), 5.32 - 5.28 (m, 1H), 5.15 (s, 2H), 4.68 - 4.65 (m, 2H), 3.94 (s, 3H), 3.83 (s, 3H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.46 (s, 9H); and MS-ESI: m/z 624.3 $[M+H]^+$.

Step 9: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(3-hydroxy-4-methoxyphenyl)oxazole-4-carboxamide hydrochloride

[00631] To a solution of (S)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-methoxy-3-((4-methoxybenzyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate (154 mg, 0.25 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for half an hour and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (81 mg, 62%).

Compound 47: ^1H NMR (400 MHz, CDCl_3): δ ppm 7.74 - 7.70 (m, 1H), 7.55 (s, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.43 - 7.38 (m, 1H), 6.90 - 6.81 (m, 2H), 5.03 (br.s, 1H), 4.60 (d, $J = 5.3$ Hz, 2H), 3.89 (s, 3H), 1.89 (d, $J = 5.2$ Hz, 3H); and MS-ESI: m/z 404.1 $[M+H-\text{HCl}]^+$.

Example 111: (S)-5-(1-Aminoethyl)-2-(3-(cyclopentyloxy)-4-methoxyphenyl)-N-((3,5-dichloropyridin-4-yl)methyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopentyloxy)-4-methoxyphenyl)-4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00632] To 15 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopentyloxy)-4-methoxyphenyl)oxazole-4-carboxylic acid (0.30 g, 0.67 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.19 g, 1.00 mmol) and 1-hydroxybenzotriazole (0.14 g, 1.00 mmol). The mixture was stirred at rt for half an hour, then (3,5-dichloropyridin-4-yl)methanamine (0.14 g, 0.81 mmol) and *N,N*-diisopropylethylamine (0.18 mL, 2.01 mmol) were added dropwise at 0 °C. The mixture was stirred at rt for 12 hours, then water (15 mL) was added. The resulting mixture was extracted with dichloromethane (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (330 mg, 82%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.54 (s, 2H), 7.56 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 5.30 – 5.28 (m, 1H), 4.95 (d, *J* = 5.8 Hz, 2H), 4.91 – 4.82 (m, 1H), 3.91 (s, 3H), 1.99 – 1.84 (m, 6H), 1.70 – 1.60 (m, 2H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.44 (s, 9H); and MS-ESI: *m/z* 605.2 [M+H]⁺.

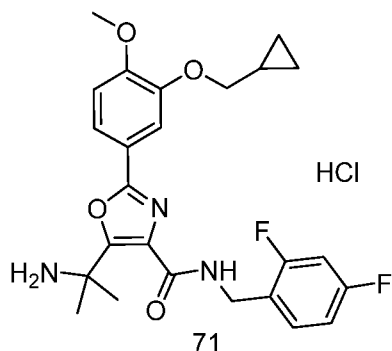
Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopentyloxy)-4-methoxyphenyl)-N-((3,5-dichloropyridin-4-yl)methyl)oxazole-4-carboxamide dihydrochloride

[00633] To a solution of (S)-tert-butyl (1-(2-(3-(cyclopentyloxy)-4-methoxyphenyl)-4-(((3,5-dichloropyridin-4-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (330 mg, 0.55 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 8 mL). The resulting mixture was stirred at rt for half an hour and the solvent was removed.

The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (242 mg, 88%).

Compound 70: ^1H NMR (400 MHz, CD_3OD): δ ppm 8.71 (s, 2H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.61 (s, 1H), 7.11 (d, $J = 8.5$ Hz, 1H), 5.19 – 5.14 (m, 1H), 4.94 (s, 2H), 4.93 – 4.90 (m, 1H), 3.91 (s, 3H), 2.04 – 1.80 (m, 6H), 1.77 (d, $J = 7.0$ Hz, 3H), 1.69 – 1.65 (s, 2H); and MS-ESI: m/z 505.1 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 112: 5-(2-Aminopropan-2-yl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl (1-fluoro-2-methyl-1-oxopropan-2-yl)carbamate

[00634] To 30 mL of dichloromethane were added *N*-Boc-*L*-2-aminoisobutyric acid (3.5 g, 14.97 mmol) and triethylamine (2.3 mL, 16.50 mmol). To the solution was added cyanuric fluoride (2.5 mL, 29.94 mmol) at -40 $^{\circ}\text{C}$, then the resulting mixture was stirred at -10 $^{\circ}\text{C}$ for 1 hour. The reaction mixture was washed with ice-water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate and the organic solvent was removed to give the title compound as a white solid (2.80 g, 91%).

^1H NMR (400 MHz, d_6 -DMSO): δ ppm 1.40 (s, 6H), 1.39 (s, 9H).

Step 2: Methyl 5-(2-(((*tert*-butoxycarbonyl)amino)propan-2-yl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate

[00635] To 30 mL of anhydrous tetrahydrofuran were added methyl 2-(((3-(cyclopropylmethoxy)-4-(methoxy)phenyl)(methylthio)methylene)amino)acetate (1.85 g, 5.73 mmol) and *tert*-butyl (1-fluoro-2-methyl-1-oxopropan-2-yl)carbamate (2.80 g, 13.66 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (20.00 mL, 20.00 mmol) at -78 $^{\circ}\text{C}$ and the reaction mixture was stirred at -78 $^{\circ}\text{C}$ for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL $\times$ 3). The

organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a yellow solid (323 mg, 15%).

MS-ESI: m/z 461.3 $[M+H]^+$.

Step 3: 5-(2-((*tert*-Butoxycarbonyl)amino)propan-2-yl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid

[00636] To a mixed solvent of tetrahydrofuran (30 mL) and water (15 mL) were added methyl 5-(2-((*tert*-butoxycarbonyl)amino)propan-2-yl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylate (323 mg, 0.70 mmol) and lithium hydroxide monohydrate (147 mg, 3.5 mmol). The solution was stirred at 40 °C for 3 hours, then concentrated to remove tetrahydrofuran. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The mixture was extracted with ethyl acetate (30 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (309 mg, 99%).

MS-ESI: m/z 445.3 $[M-H]^-$.

Step 4: *tert*-Butyl (2-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)propan-2-yl)carbamate

[00637] To 20 mL of dichloromethane were added 5-(2-((*tert*-butoxycarbonyl)amino)propan-2-yl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)oxazole-4-carboxylic acid (309 mg, 0.70 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (203 mg, 1.05 mmol) and 1-hydroxy-7-azabenzotriazole (142 mg, 1.05 mmol), and the resulting mixture was stirred at rt for 30 minutes. To the mixture were added 2,4-difluorobenzylamine (0.10 mL, 0.84 mmol) and *N,N*-diisopropylethylamine (0.38 mL, 2.10 mmol), and the mixture was stirred at rt for 12 hours. To the reaction mixture was added water (15 mL), and the resulting mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc(v/v) = 5/1) to give the title compound as a white solid (30 mg, 7.5%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.60 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.51 (d, $J = 1.9$ Hz, 1H), 7.47 – 7.40 (m, 1H), 6.94 (d, $J = 8.5$ Hz, 1H), 6.90 – 6.82 (m, 2H), 4.65 (d, $J = 6.2$ Hz,

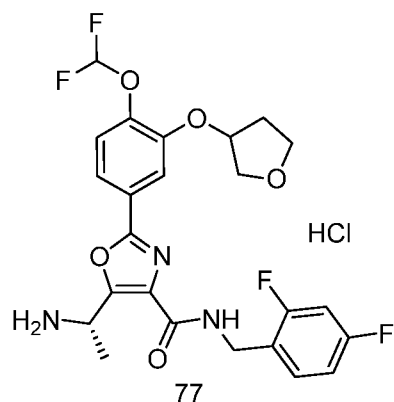
2H), 3.96 (d, $J = 6.9$ Hz, 2H), 3.96 (s, 3H), 1.83 (s, 6H), 1.43 – 1.38 (m, 1H), 1.35 (s, 9H), 0.72 – 0.68 (m, 2H), 0.44 – 0.40 (m, 2H); and MS-ESI: m/z 572.2 $[M+H]^+$.

Step 5: 5-(2-Aminopropan-2-yl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00638] To a solution of *tert*-butyl 2-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)propan-2-yl)carbamate (36 mg, 0.06 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 30 minutes and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (18.5 mg, 66%).

Compound 71: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.70 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.63 (d, $J = 2.0$ Hz, 1H), 7.51 – 7.45 (m, 1H), 7.13 (d, $J = 8.5$ Hz, 1H), 7.02 – 6.94 (m, 2H), 4.67 (s, 2H), 3.94 (s, 3H), 3.94 (d, $J = 6.9$ Hz, 2H), 1.85 (s, 6H), 1.35 – 1.32 (m, 1H), 0.71 – 0.62 (m, 2H), 0.43 – 0.32 (m, 2H); and MS-ESI: m/z 472.2 $[M+H-\text{HCl}]^+$.

Example 113: 5-((S)-1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)benzoate

[00639] To *N,N*-dimethylformamide (50 mL) were added methyl 3-hydroxy-4-(difluoromethoxy)benzoate (2.0 g, 9.18 mmol), potassium carbonate (2.54 g, 18.38 mmol) and 3-bromotetrahydrofuran (2.1 g, 13.9 mmol). The mixture was stirred at 60 °C for 4.5 hours. To the mixture was added water (40 mL) and the resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (2.48 g, 94%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.68 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.60 (d, $J = 1.9$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 6.63 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.08 - 5.04 (m, 1H), 4.06 - 3.99 (m, 3H), 3.97 - 3.95 (m, 1H), 3.93 (s, 3H), 2.33 - 2.17 (m, 2H); and MS-ESI: 289.2 $[\text{M}+\text{H}]^+$.

Step 2: 4-(Difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)benzoic acid

[00640] To a mixed solvent of ethanol (40 mL) and water (20 mL) were added methyl 4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)benzoate (2.48 g, 8.62 mmol) and sodium hydroxide (0.83 g, 20.65 mmol). The mixture was stirred at 60 °C for 1.5 hours and then concentrated to remove the ethanol. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The combined organic layers were concentrated to give the title compound as a white solid (2.24 g, 95%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.76 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.65 (d, $J = 1.9$ Hz, 1H), 7.26 (d, $J = 8.4$ Hz, 1H), 6.65 (t, $J_{\text{F-H}} = 74.2$ Hz, 1H), 5.10 - 5.07 (m, 1H), 4.08 - 4.02 (m, 3H), 4.01 - 3.97 (m, 1H), 2.33 - 2.20 (m, 2H); and MS-ESI: 273.0 $[\text{M}-\text{H}]^-$.

Step 3: Methyl 2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)benzamido)acetate

[00641] To 40 mL of dichloromethane were added 4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)benzoic acid (2.24 g, 8.20 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.37 g, 12.30 mmol) and 1-hydroxybenzotriazole (1.67 g, 12.30 mmol). The mixture was stirred at rt for half an hour, then glycine methyl ester hydrochloride (1.33 g, 9.84 mmol) and *N,N*-diisopropylethylamine (4.4 mL, 24.60 mmol) were added at 0 °C. The mixture was stirred at rt for 12 hours, then washed with water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as colourless oil (2.56 g, 91%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.48 (d, $J = 1.9$ Hz, 1H), 7.33 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.20 (d, $J = 8.3$ Hz, 1H), 6.85 (br.s, 1H), 6.60 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.07 - 5.04 (m, 1H), 4.23 (d, $J = 4.9$ Hz, 2H), 4.01 - 3.97 (m, 3H), 3.95 - 3.90 (m, 1H), 3.81 (s, 3H), 2.30 - 2.14 (m, 2H); and MS-ESI: m/z 346.0 $[\text{M}+\text{H}]^+$.

Step 4: Methyl 2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenylthioamido)

acetate

[00642] To tetrahydrofuran (40 mL) were added methyl 2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)benzamido)acetate (2.56 g, 7.42 mmol) and Lawesson's Reagent (2.98 g, 7.42 mmol). The mixture was refluxed at 75 °C for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (30 mL), and the resulting mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a yellow solid (2.45 g, 92%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.59 (d, *J* = 2.0 Hz, 1H), 7.29 (dd, *J*₁ = 8.3 Hz, *J*₂ = 2.1 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 6.60 (t, *J*_{F-H} = 74.6 Hz, 1H), 5.09 - 5.07 (m, 1H), 4.58 (d, *J* = 4.4 Hz, 2H), 4.05 - 3.99 (m, 3H), 3.97 - 3.94 (m, 1H), 3.88 (s, 3H), 2.33 - 2.17 (m, 2H); and MS-ESI: *m/z* 362.0 [M+H]⁺.

Step 5: Methyl 2-(((4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)(methylthio)methylene)amino)acetate

[00643] To a solution of trimethyloxonium tetrafluoroborate (2.00 g, 13.58 mmol) in dichloromethane (20 mL) was added dropwise a solution of methyl 2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenylthioamido)acetate (2.45 g, 6.79 mmol) in dichloromethane (30 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then washed with saturated aqueous sodium bicarbonate (25 mL × 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as yellow oil (2.53 g, 99%).

MS-ESI: *m/z* 376.2 [M+H]⁺.

Step 6: Methyl 5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)oxazole-4-carboxylate

[00644] To 30 mL of anhydrous tetrahydrofuran were added methyl 2-(((4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)(methylthio)methylene)amino)acetate (2.53 g, 6.75 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (2.60 g, 13.5 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (27.0 mL, 27.0 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C

for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a yellow solid (1.45 g, 45%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.68 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.65 (s, 1H), 7.27 (d, $J = 8.3$ Hz, 1H), 6.62 (t, $J_{\text{F-H}} = 74.5$ Hz, 1H), 5.50 - 5.46 (m, 1H), 5.15 - 5.13 (m, 1H), 4.06 - 4.03 (m, 3H), 4.01 (s, 3H), 3.98 - 3.94 (m, 1H), 2.34 - 2.20 (m, 2H), 1.57 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H); and MS-ESI: m/z 499.3 $[\text{M}+\text{H}]^+$.

Step 7: 5-((*S*)-1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)oxazole-4-carboxylic acid

[00645] To a mixed solvent of tetrahydrofuran (50 mL) and water (25 mL) were added methyl 5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)oxazole-4-carboxylate (1.45 g, 2.92 mmol) and lithium hydroxide monohydrate (0.62 g, 14.6 mmol). The solution was stirred at 40 °C for 3 hours and tetrahydrofuran was removed, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (30 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (1.29 g, 92%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.68 - 7.66 (m, 2H), 7.28 (d, $J = 8.7$ Hz, 1H), 6.62 (t, $J_{\text{F-H}} = 74.6$ Hz, 1H), 5.63 (br.s, 1H), 5.47 - 5.44 (m, 1H), 5.16 - 5.18 (m, 1H), 4.06 - 3.94 (m, 4H), 2.36 - 2.20 (m, 2H), 1.61 (d, $J = 4.8$ Hz, 3H), 1.45 (s, 9H).

Step 8: *tert*-Butyl ((1*S*)-1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00646] To 15 mL of dichloromethane were added 5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)oxazole-4-carboxylic acid (0.20 g, 0.42 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.12 g, 0.63 mmol) and 1-hydroxy-7-azabenzotriazole (0.09 g, 0.63 mmol). The mixture was stirred at rt for half an hour. To the resulting solution were added dropwise 2,4-difluorobenzylamine (0.06 mL, 0.51 mmol) and *N,N*-diisopropylethylamine (0.23 mL, 1.26 mmol) at 0 °C. The mixture was stirred at rt for

12 hours, then water (15 mL) was added. The resulting mixture was extracted with dichloromethane (20 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a white solid (183.0 mg, 72%).

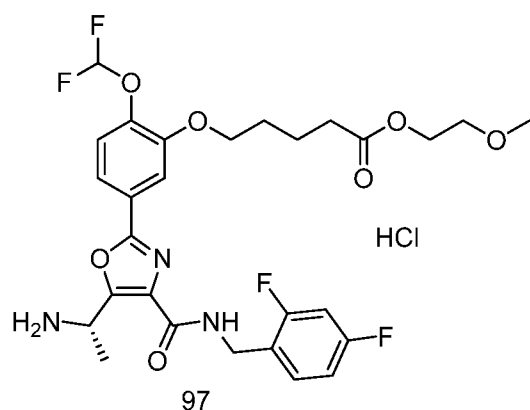
^1H NMR (400 MHz, CDCl_3): δ ppm 7.63 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.55 (br.s, 1H), 7.49 - 7.42 (m, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 6.92 - 6.84 (m, 2H), 6.62 (t, $J_{\text{F-H}} = 74.5$ Hz, 1H), 5.32 (br.s, 1H), 5.14 - 5.11 (m, 1H), 4.73 - 4.63 (m, 2H), 4.10 - 3.95 (m, 4H), 2.34 - 2.20 (m, 2H), 1.56 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H); and MS-ESI: m/z 610.2 $[\text{M}+\text{H}]^+$.

Step 9: 5-((*S*)-1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)oxazole-4-carboxamide hydrochloride

[00647] To a solution of *tert*-butyl ((1*S*)-1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((tetrahydrofuran-3-yl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate (183 mg, 0.30 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for half an hour and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (160 mg, 95%).

Compound 77: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.79 - 7.75 (m, 2H), 7.52 - 7.46 (m, 1H), 7.36 (d, $J = 8.3$ Hz, 1H), 6.99 - 6.94 (m, 2H), 6.88 (t, $J_{\text{F-H}} = 74.3$ Hz, 1H), 5.24 - 5.22 (m, 1H), 5.19 - 5.14 (m, 1H), 4.66 (s, 2H), 4.07 - 3.99 (m, 3H), 3.97 - 3.92 (m, 1H), 2.38 - 2.30 (m, 1H), 2.23 - 2.17 (m, 1H), 1.78 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 510.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 114: (*S*)-2-Methoxyethyl 5-(5-(5-(1-aminoethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate hydrochloride



Step 1: (*S*)-2-Methoxyethyl 5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4

-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate

[00648] To 10 mL of dichloromethane were added (*S*)-5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (253 mg, 0.40 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (116 mg, 0.60 mmol) and 1-hydroxy-7-azabenzotriazole (82 mg, 0.60 mmol). The mixture was stirred at rt for half an hour, then 2-methoxyethanol (0.05 mL, 0.60 mmol) and *N,N*-diisopropylethylamine (0.22 mL, 1.20 mmol) were added dropwise at 0 °C. The mixture was stirred at rt for 12 hours, then water (15 mL) was added. The resulting mixture was extracted with dichloromethane (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a white solid (190 mg, 68%).

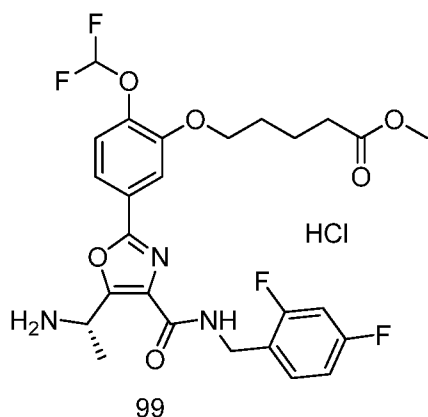
^1H NMR (400 MHz, CDCl_3): δ ppm 7.60 – 7.57 (m, 1H), 7.57 (s, 1H), 7.47 – 7.41 (m, 1H), 7.24 (d, $J = 8.2$ Hz, 1H), 6.91 – 6.84 (m, 2H), 6.64 (t, $J_{\text{F-H}} = 74.6$ Hz, 1H), 5.33 – 5.28 (m, 1H), 4.68 – 4.66 (m, 2H), 4.27 – 4.24 (m, 2H), 4.16 – 4.13 (m, 2H), 3.62 – 3.60 (m, 2H), 3.40 (s, 3H), 2.49 (t, $J = 6.9$ Hz, 2H), 1.95 – 1.87 (m, 4H), 1.56 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H); and MS-ESI: m/z 698.3 $[\text{M}+\text{H}]^+$.

Step 2: (*S*)-2-Methoxyethyl 5-(5-(5-(1-aminoethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate hydrochloride

[00649] To a solution of (*S*)-2-methoxyethyl 5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate (190 mg, 0.27 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for half an hour and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (139 mg, 82%).

Compound 97: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.81 (d, $J = 1.9$ Hz, 1H), 7.73 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.52 – 7.46 (m, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.02 – 6.94 (m, 2H), 6.88 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.20 – 5.14 (m, 1H), 4.65 (s, 2H), 4.24 – 4.18 (m, 4H), 3.62 – 3.60 (m, 2H), 3.37 (s, 3H), 2.49 (t, $J = 7.0$ Hz, 2H), 1.95 – 1.85 (m, 4H), 1.78 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 598.2 $[\text{M}+\text{H}-\text{HCl}]^+$.

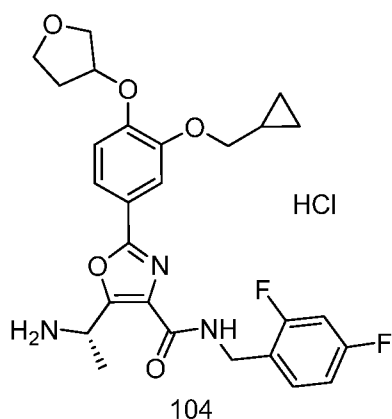
Example 115: (S)-Methyl 5-(5-(5-(1-aminoethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate hydrochloride



[00650] To a solution of (S)-methyl 5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate (90 mg, 0.14 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for half an hour and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (70 mg, 92%).

Compound 99: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.79 (s, 1H), 7.71 (d, $J = 8.2$ Hz, 1H), 7.50 – 7.44 (m, 1H), 7.31 (d, $J = 8.3$ Hz, 1H), 7.01 – 6.89 (m, 2H), 6.86 (t, $J_{\text{F-H}} = 74.5$ Hz, 1H), 5.17 – 5.15 (m, 1H), 4.63 (s, 2H), 4.25 – 4.11 (m, 2H), 3.66 (s, 3H), 2.45 (t, $J = 7.1$ Hz, 2H), 1.94 – 1.79 (m, 4H), 1.76 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 554.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 116: 5-((S)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)benzoate

[00651] To *N,N*-dimethylformamide (40 mL) were added methyl

3-(cyclopropylmethoxy)-4-hydroxybenzoate (2.0 g, 9.00 mmol), potassium carbonate (3.73 g, 27.00 mmol) and 3-bromotetrahydrofuran (2.72 g, 18.00 mmol). The mixture was stirred at 60 °C for 4.5 hours. To the mixture was added water (40 mL) and the resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (2.87 g, 100%).

^1H NMR (400 MHz, CDCl_3) δ ppm 7.63 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.56 (d, $J = 1.9$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 5.05 – 5.02 (m, 1H), 4.06 – 4.00 (m, 3H), 3.95 – 3.91 (m, 1H), 3.89 (s, 3H), 3.88 (d, $J = 6.7$ Hz, 2H), 2.23 – 2.19 (m, 2H), 1.34 – 1.28 (m, 1H), 0.66 – 0.61 (m, 2H), 0.38 – 0.34 (m, 2H); and MS-ESI: 293.3[M+H] $^+$.

Step 2: 3-(Cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)benzoic acid

[00652] To a mixed solvent of ethanol (40 mL) and water (20 mL) were added methyl 3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)benzoate (2.87 g, 9.83 mmol) and sodium hydroxide (0.98 g, 24.5 mmol). The mixture was stirred at 60 °C for 1.5 hours and then concentrated to remove the ethanol. To the residue was added hydrochloric acid (1 M) to adjust the pH to 1. The resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The organic layers was concentrated to give the title compound as a white solid (2.66 g, 97%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.74 (d, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.63 (d, $J = 2.0$ Hz, 1H), 6.89 (d, $J = 8.5$ Hz, 1H), 5.09 – 5.05 (m, 1H), 4.09 – 4.03 (m, 3H), 3.98 – 3.93 (m, 1H), 3.91 (d, $J = 6.8$ Hz, 2H), 2.27 – 2.22 (m, 2H), 1.36 – 1.29 (m, 1H), 0.68 – 0.63 (m, 2H), 0.40 – 0.37 (m, 2H); and MS-ESI: 279.0 [M+H] $^+$.

Step 3: Methyl 2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)benzamido)acetate

[00653] To 40 mL of dichloromethane were added 3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)benzoic acid (2.66 g, 9.57 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.77 g, 14.36 mmol) and 1-hydroxybenzotriazole (1.94 g, 14.36 mmol). The mixture was stirred at rt for half an hour, then glycine methyl ester hydrochloride (1.44 g, 11.48 mmol) and *N,N*-diisopropylethylamine (5.15 mL, 28.72 mmol) were added at 0 °C. The mixture was stirred at rt for 12 hours, then washed

with water (20 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate and concentrated to remove the solvent. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a white solid (2.87 g, 86%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.43 (d, J = 2.0 Hz, 1H), 7.34 (dd, J_1 = 8.3 Hz, J_2 = 2.1 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.68 (br.s, 1H), 5.04 – 5.01 (m, 1H), 4.23 (d, J = 5.1 Hz, 2H), 4.07 – 4.00 (m, 3H), 3.96 – 3.93 (m, 1H), 3.89 (d, J = 6.8 Hz, 2H), 3.81 (s, 3H), 2.23 – 2.18 (m, 2H), 1.34 – 1.27 (m, 1H), 0.66 – 0.61 (m, 2H), 0.37 – 0.34 (m, 2H); and MS-ESI: m/z 350.1 $[\text{M}+\text{H}]^+$.

Step 4: Methyl 2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenylthioamido)acetate

[00654] To tetrahydrofuran (40 mL) were added methyl 2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)benzamido)acetate (2.87 g, 8.22 mmol) and Lawesson's Reagent (3.32 g, 8.22 mmol). The mixture was refluxed at 75 °C for 2 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (30 mL), and the resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a yellow solid (2.22 g, 74%).

^1H NMR (400 MHz, CDCl_3): δ ppm 8.11 (br.s, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.34 (dd, J_1 = 8.4 Hz, J_2 = 2.2 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 5.04 – 5.00 (m, 1H), 4.58 (d, J = 4.6 Hz, 2H), 4.06 – 3.99 (m, 3H), 3.95 – 3.92 (m, 1H), 3.90 (d, J = 6.9 Hz, 2H), 3.85 (s, 3H), 2.22 – 2.17 (m, 2H), 1.34 – 1.28 (m, 1H), 0.66 – 0.61 (m, 2H), 0.38 – 0.35 (m, 2H); and MS-ESI: m/z 366.2 $[\text{M}+\text{H}]^+$.

Step 5: Methyl 2-(((3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenyl)(methylthio)methylene)amino)acetate

[00655] To a solution of trimethyloxonium tetrafluoroborate (1.80 g, 12.20 mmol) in dichloromethane (20 mL) was added dropwise a solution of methyl 2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenylthioamido)acetate (2.22 g, 6.08 mmol) in dichloromethane (30 mL) at -78 °C. The mixture was stirred at 0 °C for 3 hours, then

washed with saturated aqueous sodium bicarbonate (25 mL $\times$ 3). The organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed to give the title compound as yellow oil (2.31 g, 93%).

MS-ESI: m/z 380.1 $[M+H]^+$.

Step 6: Methyl 5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenyl)oxazole-4-carboxylate

[00656] To 30 mL of tetrahydrofuran were added methyl 2-(((3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenyl)(methylthio)methylene)amino)acetate (2.31 g, 6.09 mmol) and (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (2.85 g, 12.20 mmol). To the solution was added a solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (25.0 mL, 25.00 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 1 hour. The mixture was quenched with ice-water (20 mL) and extracted with ethyl acetate (15 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (1.39 g, 45%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.62 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.9$ Hz, 1H), 7.59 (d, $J = 2.2$ Hz, 1H), 6.90 (d, $J = 8.3$ Hz, 1H), 5.50 - 5.42 (m, 1H), 5.06 - 5.02 (m, 1H), 4.06 - 4.04 (m, 3H), 3.99 (s, 3H), 3.95 - 3.92 (m, 1H), 3.93 (d, $J = 6.8$ Hz, 2H), 2.24 - 2.19 (m, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H), 1.32 - 1.29 (m, 1H), 0.68 - 0.63 (m, 2H), 0.40 - 0.36 (m, 2H); and MS-ESI: m/z 503.2 $[M+H]^+$.

Step 7: 5-((*S*)-1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenyl)oxazole-4-carboxylic acid

[00657] To a mixed solvent of tetrahydrofuran (30 mL) and water (15 mL) were added methyl 5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenyl)oxazole-4-carboxylate (1.39 g, 2.77 mmol) and lithium hydroxide monohydrate (0.59 g, 13.80 mmol). The solution was stirred at 40 °C for 3 hours and tetrahydrofuran was removed, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (30 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give the title compound as a white solid (1.35 g, 96%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.64 – 7.61 (m, 2H), 6.91 (d, $J = 8.2$ Hz, 1H), 5.46 – 5.44 (m, 1H), 5.06 – 5.03 (m, 1H), 4.10 – 4.00 (m, 3H), 3.99 – 3.90 (m, 1H), 3.89 (d, $J = 6.8$ Hz, 2H), 2.32 – 2.15 (m, 2H), 1.58 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H), 1.34 – 1.32 (m, 1H), 0.67 – 0.64 (m, 2H), 0.40 – 0.37 (m, 2H); and MS-ESI: m/z 487.3 $[\text{M}-\text{H}]^-$.

Step 8: *tert*-Butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00658] To 15 mL of dichloromethane were added 5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenyl)oxazole-4-carboxylic acid (0.32 g, 0.65 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.19 g, 0.99 mmol) and 1-hydroxy-7-azabenzotriazole (0.14 g, 1.02 mmol). The mixture was stirred at rt for half an hour. To the resulting solution were added 2,4-difluorobenzylamine (0.10 mL, 0.90 mmol) and *N,N*-diisopropylethylamine (0.40 mL, 2.25 mmol). The mixture was stirred at rt for 12 hours, and water (15 mL) was added. The resulting mixture was extracted with dichloromethane (20 mL $\times$ 3) and the combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give the title compound as a white solid (302 mg, 75%).

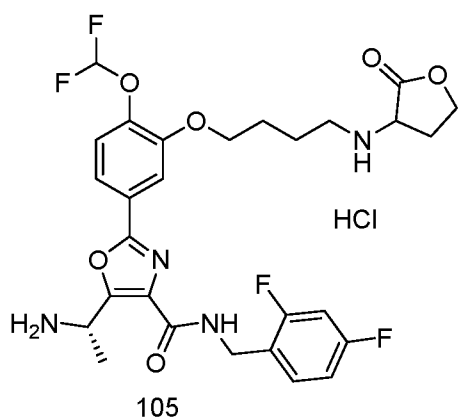
^1H NMR (400 MHz, CDCl_3): δ ppm 7.57 (d, $J = 8.4$ Hz, 1H), 7.51 (s, 1H), 7.46 – 7.40 (m, 1H), 7.01 – 6.77 (m, 3H), 5.30 – 5.28 (m, 1H), 5.06 – 5.02 (m, 1H), 4.72 – 4.58 (m, 2H), 4.10 – 4.00 (m, 3H), 3.98 – 3.92 (m, 1H), 3.89 (d, $J = 6.8$ Hz, 2H), 2.25 – 2.20 (m, 2H), 1.54 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H), 0.93 – 0.82 (m, 1H), 0.70 – 0.60 (m, 2H), 0.41 – 0.37 (m, 2H); and MS-ESI: m/z 614.3 $[\text{M}+\text{H}]^+$.

Step 9: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00659] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-(cyclopropylmethoxy)-4-((tetrahydrofuran-3-yl)oxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (302 mg, 0.49 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for half an hour and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (235 mg, 87%).

Compound 104: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.82 – 7.59 (m, 2H), 7.51 – 7.46 (m, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.00 – 6.94 (m, 2H), 5.20 – 5.12 (m, 2H), 4.64 (s, 2H), 4.08 – 3.81 (m, 6H), 2.38 – 2.09 (m, 2H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.34 – 1.28 (m, 1H), 0.72 – 0.51 (m, 2H), 0.41 – 0.36 (m, 2H); and MS-ESI: m/z 514.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 117: 5-((*S*)-1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-(4-((2-oxotetrahydrofuran-3-yl)amino)butoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-4-(5-(5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)butyl acetate

[00660] To *N,N*-dimethylformamide (20 mL) were added (*S*)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-hydroxyphenyl)oxazol-5-yl)ethyl)carbamate (1.30 g, 2.4 mmol), potassium carbonate (0.65 g, 4.7 mmol) and 4-bromobutyl acetate (0.40 mL, 3.0 mmol). The mixture was stirred at 60 °C for 4.5 hours. To the mixture was added water (30 mL) and the resulting mixture was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (1.50 g, 95%).

^1H NMR (400 MHz, CDCl_3): δ ppm 7.59 – 7.56 (m, 2H), 7.45 – 7.39 (m, 1H), 7.23 (d, $J = 8.1$ Hz, 1H), 6.89 – 6.84 (m, 2H), 6.61 (t, $J_{\text{F-H}} = 74.5$ Hz, 1H), 5.34 – 5.29 (m, 1H), 4.70 – 4.60 (m, 2H), 4.18 – 4.13 (m, 6H), 2.05 (s, 3H), 1.96 – 1.93 (m, 2H), 1.89 – 1.83 (m, 2H), 1.53 (t, $J = 7.0$ Hz, 3H), 1.43 (s, 9H); and MS-ESI: 654.2 $[\text{M}+\text{H}]^+$.

Step 2: (*S*)-*tert*-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-(4-hydroxybutoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00661] To a mixed solvent of tetrahydrofuran (40 mL) and water (20 mL) were added

(*S*)-4-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)butyl acetate (1.50 g, 2.29 mmol) and lithium hydroxide monohydrate (0.6 g, 14.29 mmol). The solution was stirred at 40 °C for 6 hours and tetrahydrofuran was removed. The residue was extracted with ethyl acetate (30 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (1.34 g, 95%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.60 – 7.57 (m, 2H), 7.46 – 7.40 (m, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.90 – 6.86 (m, 2H), 6.63 (t, *J*_{F-H} = 74.5 Hz, 1H), 5.33 – 5.31 (m, 1H), 4.71 – 4.62 (m, 2H), 4.18 (t, *J* = 6.2 Hz, 2H), 3.77 (t, *J* = 6.3 Hz, 2H), 2.02 – 1.95 (m, 2H), 1.87 – 1.77 (m, 2H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.44 (s, 9H); and MS-ESI: 610.1 [M-H]⁻.

Step 3: (*S*)-4-(5-(5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)butyl 4-methylbenzenesulfonate

[00662] To 40 mL of dichloromethane were added (*S*)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-(4-hydroxybutoxy)phenyl)oxazol-5-yl)ethyl)carbamate (1.32 g, 2.16 mmol) and tosyl chloride (1.20 g, 6.29 mmol). To the mixture was added dropwise triethylamine (0.9 mL, 6.5 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 6 hours. The reaction mixture was extracted with dichloromethane (30 mL × 3) and the combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (1.60 g, 96%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.80 (d, *J* = 8.3 Hz, 2H), 7.59 (dd, *J*₁ = 8.3 Hz, *J*₂ = 1.9 Hz, 1H), 7.56 (d, *J* = 1.8 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.90 – 6.84 (m, 2H), 6.56 (t, *J*_{F-H} = 74.3 Hz, 1H), 5.34 – 5.30 (m, 1H), 4.71 – 4.61 (m, 2H), 4.17 – 4.10 (m, 4H), 2.45 (s, 3H), 1.95 – 1.89 (m, 4H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.44 (s, 9H); and MS-ESI: 766.2 [M+H]⁺.

Step 4: (*S*)-*tert*-Butyl (1-(2-(3-(4-azidobutoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00663] To a mixed solvent of acetone (30 mL) and water (10 mL) were added (*S*)-4-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-

-2-yl)-2-(difluoromethoxy)phenoxy)butyl 4-methylbenzenesulfonate (1.60 g, 2.09 mmol) and sodium azide (0.7 g, 10.0 mmol). The solution was stirred at 80 °C for 6 hours and acetone was removed. The residue was extracted with ethyl acetate (30 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (1.30 g, 97%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.60 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.58 (d, $J = 1.7$ Hz, 1H), 7.47 – 7.41 (m, 1H), 7.25 (d, $J = 8.2$ Hz, 1H), 6.92 – 6.84 (m, 2H), 6.61 (t, $J_{F-H} = 74.4$ Hz, 1H), 5.33 – 5.28 (m, 1H), 4.72 – 4.62 (m, 2H), 4.17 (t, $J = 6.0$ Hz, 2H), 3.43 (t, $J = 6.6$ Hz, 2H), 2.02 – 1.95 (m, 2H), 1.89 – 1.82 (m, 2H), 1.56 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H); and MS-ESI: 637.3 [M+H]⁺.

Step 5: (S)-tert-Butyl (1-(2-(3-(4-aminobutoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00664] To a mixed solvent of ethyl acetate (25 mL) and water (5 mL) were added (S)-tert-butyl (1-(2-(3-(4-azidobutoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (1.298 g, 2.039 mmol) and triphenylphosphine (0.85 g, 3.2 mmol). The solution was stirred at rt for 6 hours. The mixture was extracted with ethyl acetate (30 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (MeOH/DCM (v/v) = 10/1) to give the title compound as a white solid (1.177 g, 94%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.58 – 7.53 (m, 2H), 7.44 – 7.39 (m, 1H), 7.20 (d, $J = 8.3$ Hz, 1H), 6.88 – 6.83 (m, 2H), 6.67 (t, $J = 74.1$ Hz, 1H), 5.31 – 5.22 (m, 1H), 4.66 – 4.64 (m, 2H), 4.17 – 4.12 (m, 2H), 3.11 – 3.06 (m, 2H), 1.98 – 1.89 (m, 4H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H); and MS-ESI: 611.3 [M+H]⁺.

Step 6: tert-Butyl ((1S)-1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-(4-((2-oxotetrahydrofuran-3-yl)amino)butoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00665] To anhydrous *N,N*-dimethylformamide (10 mL) were added (S)-tert-butyl (1-(2-(3-(4-aminobutoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (500 mg, 0.82 mmol), alpha-bromo-gamma-butyrolactone (201.6 mg, 1.23 mmol) and potassium carbonate (250 mg, 1.81 mmol). The mixture was stirred at 90 °C for 1

hour. To the mixture was added water (20 mL) and the resulting mixture was extracted with ethyl acetate (30 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a white solid (216 mg, 38%).

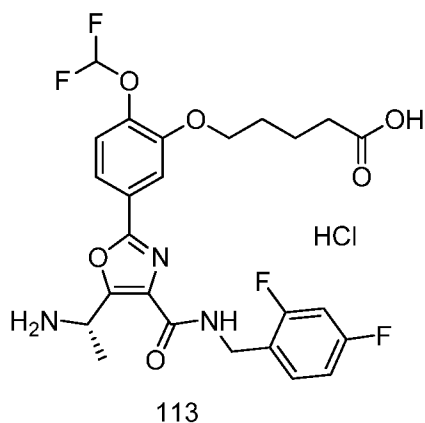
^1H NMR (400 MHz, CDCl_3): δ ppm 7.59 – 7.57 (m, 2H), 7.46 – 7.41 (m, 1H), 7.25 – 7.22 (m, 1H), 6.89 – 6.84 (m, 2H), 6.64 (t, $J_{\text{F-H}} = 74.6$ Hz, 1H), 5.39 – 5.25 (m, 1H), 4.71 – 4.63 (m, 2H), 4.50 – 4.46 (m, 1H), 4.29 – 4.23 (m, 1H), 4.18 – 4.10 (m, 2H), 3.84 – 3.76 (m, 1H), 3.13 – 3.05 (m, 1H), 2.98 – 2.86 (m, 1H), 2.66 – 2.58 (m, 1H), 2.42 – 2.35 (m, 1H), 2.00 – 1.89 (m, 4H), 1.56 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H); and MS-ESI: 695.9 $[\text{M}+\text{H}]^+$.

Step 7: 5-((*S*)-1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-(4-((2-oxotetrahydrofuran-3-yl)amino)butoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00666] To a solution of *tert*-butyl ((1*S*)-1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-(4-((2-oxotetrahydrofuran-3-yl)amino)butoxy)phenyl)oxazol-5-yl)ethyl)carbamate (206 mg, 0.29 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for half an hour and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (116 mg, 62%).

Compound 105: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.58 – 7.55 (m, 2H), 7.46 – 7.41 (m, 1H), 7.25 – 7.22 (m, 1H), 6.89 – 6.84 (m, 2H), 6.64 (t, $J_{\text{F-H}} = 74.6$ Hz, 1H), 5.42 – 5.22 (m, 1H), 4.75 – 4.58 (m, 2H), 4.50 – 4.46 (m, 1H), 4.33 – 4.08 (m, 3H), 3.84 – 3.76 (m, 1H), 3.15 – 3.00 (m, 1H), 2.92 – 2.86 (m, 1H), 2.66 – 2.58 (m, 1H), 2.42 – 2.35 (m, 1H), 2.01 – 1.83 (m, 4H), 1.56 (d, $J = 7.0$ Hz, 3H); and MS-ESI: 595.1 $[\text{M}+\text{H}-\text{HCl}]^+$.

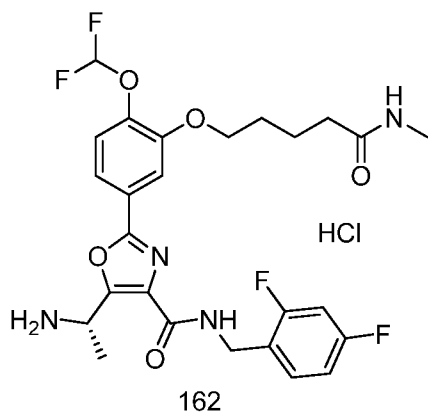
Example 118: (*S*)-5-(5-(5-(1-Aminoethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid hydrochloride



[00667] To a solution of (*S*)-5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (194 mg, 0.30 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for half an hour and the solvent was removed. The residue was recrystallized from MeOH/EtOAc (v/v = 1/20) to give the title compound as a white solid (70 mg, 92%).

Compound 113: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.82 (d, $J = 1.8$ Hz, 1H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.50 – 7.47 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.00 – 6.96 (m, 2H), 6.88 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.20 – 5.17 (m, 1H), 4.65 (s, 2H), 4.20 (t, $J = 6.1$ Hz, 2H), 2.43 (t, $J = 7.2$ Hz, 2H), 1.94 – 1.90 (m, 2H), 1.87 – 1.83 (m, 2H), 1.78 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 540.9 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 119: (*S*)-5-(1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-(methylamino)-5-oxopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-(methylamino)-5-oxopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00668] To 20 mL of dichloromethane were added

(*S*)-5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (300 mg, 0.496 mmol), methylamine hydrochloride (38 mg, 0.563 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (134 mg, 0.704 mmol) and 1-hydroxy-7-azabenzotriazole (96 mg, 0.704 mmol), and the resulting mixture was stirred at rt for 30 minutes. To the mixture was added *N,N*-diisopropylethylamine (0.33 mL, 1.876 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 10 hours. To the reaction mixture was added water (25 mL) and the resulting mixture was extracted with dichloromethane (25 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give a white solid (255 mg, 83.3%).

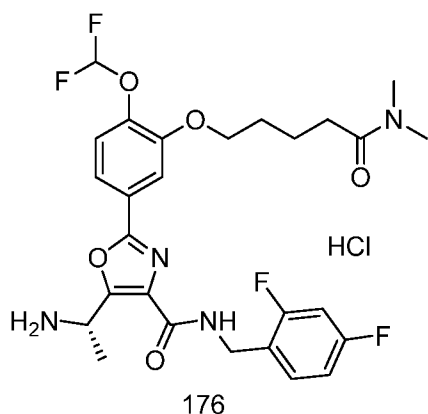
¹H NMR (600 MHz, CDCl₃): δ ppm 7.58 - 7.60 (m, 2H), 7.42 - 7.46 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.85 - 6.91 (m, 2H), 6.63 (t, *J*_{F-H} = 74.4 Hz, 1H), 5.65 (br.s, 1H), 5.31 - 5.32 (m, 1H), 4.66 - 4.69 (m, 2H), 4.12 - 4.17 (m, 2H), 2.83 (s, 3H), 2.30 - 2.35 (m, 2H), 1.86 - 1.99 (m, 4H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.45 (s, 9H); and MS-ESI: *m/z* 653.20 [M+H]⁺.

Step 2: (S)-5-(1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-(methylamino)-5-oxopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride

[00669] To a solution of (*S*)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-(methylamino)-5-oxopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate (250 mg, 0.383 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 30 minutes, then the solvent was removed to give a white solid (225.6 mg, 100%).

Compound 162: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.82 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.47 - 7.49 (m, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 6.95 - 7.0 (m, 2H), 6.87 (t, *J*_{F-H} = 74.4 Hz, 1H), 5.15 - 5.19 (m, 1H), 4.63 (s, 2H), 4.19 (m, 2H), 2.77 (s, 3H), 2.37 (m, 2H), 1.86 - 1.99 (m, 4H), 1.78 (d, *J* = 7.0 Hz, 3H); and MS-ESI: *m/z* 553.20 [M+H-HCl]⁺.

Example 120: (S)-5-(1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-(dimethylamino)-5-oxopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-(dimethylamino)-5-oxopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00670] To 20 mL of dichloromethane were added (S)-5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (334 mg, 0.5222 mmol), dimethylamine hydrochloride (52 mg, 0.6266 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (151 mg, 0.7833 mmol) and 1-hydroxy-7-azabenzotriazole (107 mg, 0.7833 mmol). The mixture was stirred at rt for 30 minutes. To the mixture was added *N,N*-diisopropylethylamine (0.36 mL, 2.089 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 10 hours. To the reaction mixture was added water (25 mL) and the resulting mixture was extracted with dichloromethane (25 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give a white solid (252 mg, 72.38%).

¹H NMR (600 MHz, CDCl₃): δ ppm 7.58 - 7.59 (m, 2H), 7.42 - 7.46 (m, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 6.85 - 6.91 (m, 2H), 6.64 (t, *J*_{F-H} = 74.6 Hz, 1H), 5.29 - 5.34 (m, 1H), 4.67 - 4.69 (m, 2H), 4.15 - 4.18 (m, 2H), 3.04 (s, 3H), 2.97 (s, 3H), 2.44 - 2.47 (m, 2H), 1.93 - 1.98 (m, 2H), 1.86 - 1.91 (m, 2H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.45 (s, 9H); and MS-ESI: *m/z* 667.2 [M+H]⁺.

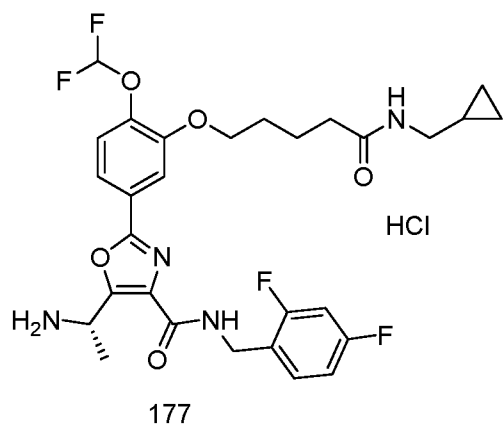
Step 2: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-(dimethylamino)-5-oxopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride

[00671] To a solution of (S)-tert-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-(dimethylamino)-5-oxopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate (252 mg, 0.378 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in

ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 40 minutes, then the solvent was removed to give a white solid (233 mg, 102.2%).

Compound 176: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.81 (d, $J = 1.8$ Hz, 1H), 7.72 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.46 - 7.50 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 6.95 - 7.0 (m, 2H), 6.89 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.15 - 5.19 (m, 1H), 4.65 (s, 2H), 4.19 - 4.21 (m, 1H), 3.01 (s, 3H), 2.94 (s, 3H), 2.51 - 2.53 (m, 1H), 1.91 - 1.96 (m, 2H), 1.81 - 1.86 (m, 2H), 1.77 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 567.20 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 121: (S)-5-(1-Aminoethyl)-2-(3-((5-((cyclopropylmethyl)amino)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-((5-((cyclopropylmethyl)amino)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00672] To 20 mL of dichloromethane were added (S)-5-(5-(5-(1-((tert-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (300 mg, 0.469 mmol), cyclopropanemethanamine (40 mg, 0.563 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (135 mg, 0.7036 mmol) and 1-hydroxy-7-azabenzotriazole (96 mg, 0.7036 mmol). The mixture was stirred at rt for 30 minutes. To the mixture was added *N,N*-diisopropylethylamine (0.25 mL, 1.407 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 10 hours. To the reaction mixture was added water (25 mL) and the resulting mixture was extracted with dichloromethane (25 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give a white solid (322 mg, 99.11%).

^1H NMR (600 MHz, CDCl_3): δ ppm 7.58 - 7.60 (m, 2H), 7.43 - 7.46 (m, 1H), 7.25 (d, $J =$

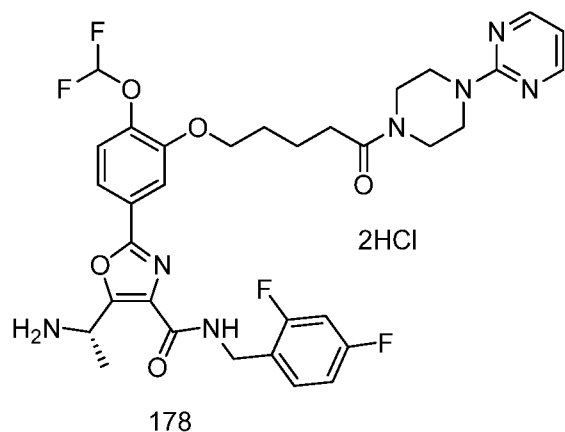
6.0 Hz, 1H), 6.85 - 6.91 (m, 2H), 6.64 (t, $J_{F-H} = 74.4$ Hz, 1H), 5.67 (br.s, 1H), 5.28 - 5.32 (m, 1H), 4.64 - 4.71 (m, 2H), 4.13 - 4.18 (m, 2H), 3.13 - 3.15 (m, 2H), 2.33 (t, $J = 6.6$ Hz, 2H), 1.90 - 1.96 (m, 4H), 1.56 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 0.94 - 0.99 (m, 1H), 0.51 - 0.54 (m, 2H), 0.20 - 0.23 (m, 2H); and MS-ESI: m/z 693.2 $[M+H]^+$.

Step 2: (S)-5-(1-Aminoethyl)-2-(3-((5-((cyclopropylmethyl)amino)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00673] To a solution of (*S*)-*tert*-butyl (1-(2-(3-((5-((cyclopropylmethyl)amino)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (322 mg, 0.4648 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 40 minutes, then the solvent was removed to give a white solid (285 mg, 97.47%).

Compound 177: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.82 (d, $J = 1.8$ Hz, 1H), 7.72 (dd, $J_1 = 1.8$ Hz, $J_2 = 8.4$ Hz, 1H), 7.46 - 7.52 (m, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 6.94 - 7.01 (m, 2H), 6.88 (t, $J_{F-H} = 74.5$ Hz, 1H), 5.15 - 5.20 (m, 1H), 4.65 (s, 2H), 4.19 - 4.22 (m, 2H), 3.06 (d, $J = 7.0$ Hz, 2H), 2.33 - 2.36 (m, 2H), 1.86 - 1.92 (m, 4H), 1.78 (d, $J = 7.2$ Hz, 3H), 0.94 - 1.02 (m, 1H), 0.47-0.52 (m, 2H), 0.19 - 0.23 (m, 2H); and MS-ESI: m/z 593.20 $[M+H-HCl]^+$.

Example 122: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-oxo-5-(4-(pyrimidin-2-yl)piperazin-1-yl)pentyl)oxy)phenyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-*tert*-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-oxo-5-(4-(pyrimidin-2-yl)piperazin-1-yl)pentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate
 [00674] To 20 mL of dichloromethane were added (*S*)-5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)

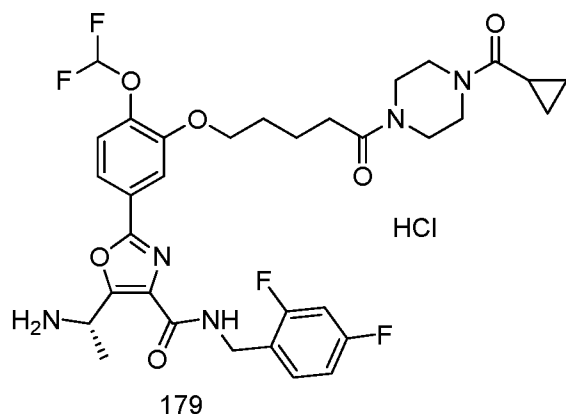
pentanoic acid (300 mg, 0.469 mmol), 1-(2-pyrimidinyl)piperazine (93 mg, 0.469 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (135 mg, 0.7036 mmol) and 1-hydroxy-7-azabenzotriazole (96 mg, 0.7036 mmol). The mixture was stirred at rt for 30 minutes. To the mixture was added *N,N*-diisopropylethylamine (0.25 mL, 1.407 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 10 hours. To the reaction mixture was added water (25 mL × 3) and the resulting mixture was extracted with dichloromethane (25 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give a white solid (284 mg, 77.05%).

¹H NMR (400 MHz, CDCl₃): δ ppm 8.35 (d, *J* = 4.8 Hz, 2H), 7.58 - 7.60 (m, 2H), 7.41 - 7.45 (m, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.84 - 6.92 (m, 2H), 6.64 (t, *J*_{F-H} = 74.8 Hz, 1H), 6.56 (t, *J* = 4.8 Hz, 1H), 5.30 - 5.35 (m, 1H), 4.66 - 4.69 (m, 2H), 4.17 - 4.20 (m, 2H), 3.83 - 3.89 (m, 4H), 3.71 - 3.74 (m, 2H), 3.57 - 3.60 (m, 2H), 2.51 - 2.55 (m, 2H), 1.90 - 1.98 (m, 4H), 1.56 (d, *J* = 7.2 Hz, 3H), 1.45 (s, 9H); and MS-ESI: *m/z* 786.20 [M+H]⁺.

Step 2: (*S*)-5-(1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-oxo-5-(4-(pyrimidin-2-yl)piperazin-1-yl)pentyl)oxy)phenyl)oxazole-4-carboxamide dihydrochloride [00675] To a solution of (*S*)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-oxo-5-(4-(pyrimidin-2-yl)piperazin-1-yl)pentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate (284 mg, 0.3614 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 40 minutes, then the solvent was removed to give a white solid (271.1 mg, 99%).

Compound 178: ¹H NMR (400 MHz, CD₃OD): δ ppm 8.65 (d, *J* = 5.2 Hz, 2H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.73 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.9 Hz, 1H), 7.46 - 7.52 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 5.2 Hz, 1H), 6.94 - 7.01 (m, 2H), 6.90 (t, *J*_{F-H} = 74.4 Hz, 1H), 5.15 - 5.21 (m, 1H), 4.65 (s, 2H), 4.22 - 4.25 (m, 2H), 4.02 - 4.05 (m, 2H), 3.93 - 3.96 (m, 2H), 3.81 - 3.86 (m, 4H), 2.61 - 2.64 (m, 2H), 1.87 - 1.99 (m, 4H), 1.78 (d, *J* = 7.2 Hz, 3H); and MS-ESI: *m/z* 343.70 [M+2H-2HCl]²⁺.

Example 123: (*S*)-5-(1-Aminoethyl)-2-(3-((5-(4-(cyclopropanecarbonyl)piperazin-1-yl)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(2-(3-((5-(4-(cyclopropanecarbonyl)piperazin-1-yl)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00676] To 20 mL of dichloromethane were added (*S*)-5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (300 mg, 0.469 mmol), 1-(cyclopropylcarbonyl)piperazine hydrochloride (107 mg, 0.5690 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (135 mg, 0.7036 mmol) and 1-hydroxy-7-azabenzotriazole (96 mg, 0.7036 mmol). The mixture was stirred at rt for 30 minutes. To the mixture was added *N,N*-diisopropylethylamine (0.25 mL, 1.407 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 10 hours. To the reaction mixture was added water (25 mL) and the resulting mixture was partitioned. The aqueous layer was extracted with dichloromethane (25 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give a white solid (251 mg, 69.0%).

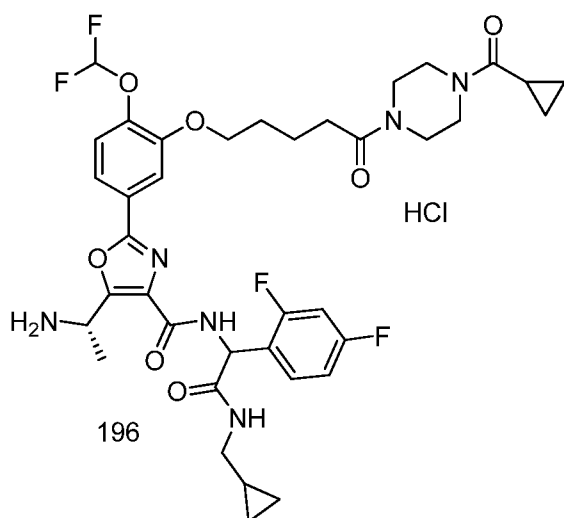
¹H NMR (400 MHz, CDCl₃): δ ppm 7.59 - 7.61 (m, 2H), 7.42 - 7.47 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.84 - 6.92 (m, 2H), 6.63 (t, *J*_{F-H} = 74.8 Hz, 1H), 5.28 - 5.33 (m, 1H), 4.66 - 4.69 (m, 2H), 4.18 (t, *J* = 6.0 Hz, 2H), 3.51 - 3.70 (m, 8H), 2.50 (t, *J* = 6.4 Hz, 2H), 1.91 - 1.97 (m, 4H), 1.56 (d, *J* = 7.2 Hz, 3H), 1.45 (s, 9H), 1.30 - 1.35 (m, 1H), 1.02 - 1.05 (m, 2H), 0.80 - 0.85 (m, 2H); and MS-ESI: *m/z* 776.25 [M+H]⁺.

Step 2: (*S*)-5-(1-Aminoethyl)-2-(3-((5-(4-(cyclopropanecarbonyl)piperazin-1-yl)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00677] To a solution of (*S*)-*tert*-butyl (1-(2-(3-((5-(4-(cyclopropanecarbonyl)piperazin-1-yl)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (251 mg, 0.3235 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 40 minutes, then the solvent was removed to give a white solid (225 mg, 97.66%).

Compound 179: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.83 (d, $J = 2.0$ Hz, 1H), 7.73 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.46 - 7.52 (m, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 6.94 - 7.02 (m, 2H), 6.90 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.15 - 5.20 (m, 1H), 4.65 (s, 2H), 4.22 (t, $J = 6.0$ Hz, 2H), 3.59 - 3.83 (m, 8H), 2.58 (t, $J = 7.2$ Hz, 2H), 1.92 - 2.04 (m, 2H), 1.85 - 1.90 (m, 2H), 1.78 (d, $J = 6.8$ Hz, 3H), 1.34 - 1.36 (m, 1H), 0.89 - 0.92 (m, 2H), 0.84 - 0.88 (m, 2H); and MS-ESI: m/z 676.20 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 124: 5-((*S*)-1-Aminoethyl)-2-(3-((5-(4-(cyclopropanecarbonyl)piperazin-1-yl)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-*N*-(2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-4-((cyano(2,4-difluorophenyl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00678] To 20 mL of dichloromethane were added (*S*)-2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylic acid (940 mg, 1.9 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (540 mg, 2.8 mmol) and 1-hydroxy-7-azabenzotriazole (380 mg, 2.8 mmol). The mixture was stirred at rt for 30 minutes, then 2-amino-2-(2,4-difluorophenyl)acetonitrile hydrochloride (460 mg, 2.2 mmol) was added. To the mixture was added *N,N*-diisopropylethylamine (1.3 mL, 7.5 mmol)

dropwise at 0 °C, and the resulting mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (25 mL × 3) and the aqueous layer was extracted with dichloromethane (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 7/1) to give a white solid (645 mg, 53%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.69 - 7.70 (m, 1H), 7.66 - 7.68 (m, 1H), 7.62 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.5 Hz, 1H), 7.38 - 7.51 (m, 5H), 7.29 (d, *J* = 7.6 Hz, 1H), 6.96 - 7.03 (m, 2H), 6.66 (t, *J*_{F-H} = 74.4 Hz, 1H), 6.39 (d, *J* = 8.8 Hz, 1H), 5.30 - 5.34 (m, 1H), 5.25 - 5.37 (d, *J* = 2.0 Hz, 1H), 1.54 - 1.58 (m, 3H), 1.46 (s, 9H); and MS-ESI: *m/z* 677.15 [M+Na]⁺.

Step 2: 2-(2-(3-(Benzyloxy)-4-(difluoromethoxy)phenyl)-5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid

[00679] To a mixed solvent of ethanol (10 mL) and water (10 mL) were added *tert*-butyl ((1*S*)-1-(2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-4-((cyano(2,4-difluorophenyl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.645 g, 0.985 mmol) and sodium hydroxide (2.244 g, 56.1 mmol). The solution was stirred at 75 °C for 4 hours and concentrated to remove ethanol, then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1. The mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give a light red solid (0.452 g, 68.1%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.71 (d, *J* = 2.0 Hz, 1H), 7.62 - 7.66 (m, 1H), 7.35 - 7.52 (m, 6H), 7.27 (d, *J* = 7.6 Hz, 1H), 6.88 - 6.96 (m, 2H), 6.66 (t, *J*_{F-H} = 74.4 Hz, 1H), 5.98 - 6.01 (m, 1H), 5.32 - 5.37 (m, 1H), 5.25 (s, 2H), 1.47 - 1.53 (m, 3H), 1.39 - 1.40 (m, 9H); and MS-ESI: *m/z* 696.15 [M+Na]⁺.

Step 3: *Tert*-butyl ((1*S*)-1-(2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00680] To 20 mL of dichloromethane were added 2-(2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxamido)-2-(2,4-difluorophenyl)acetic acid (452 mg, 0.671 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (193 mg, 1.01 mmol) and

1-hydroxy-7-azabenzotriazole (137 mg, 1.01 mmol). The mixture was stirred at rt for 30 minutes, then cyclopropanemethanamine (71.6 mg, 1.01 mmol) was added, and the resulting mixture was stirred at rt for 30 minutes. To the mixture was added *N,N*-diisopropylethylamine (0.47 mL, 2.68 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (25 mL × 3) and the aqueous layer was extracted with dichloromethane (25 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (287 mg, 58.9%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.76 (d, *J* = 2.0 Hz, 1H), 7.65 - 7.67 (m, 1H), 7.52 - 7.54 (m, 3H), 7.43 - 7.47 (m, 2H), 7.38 - 7.74 (m, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 6.90 - 6.94 (m, 2H), 6.67 (t, *J*_{F-H} = 74.8 Hz, 1H), 5.86 - 5.89 (m, 1H), 5.30 - 5.32 (m, 1H), 5.28 (s, 2H), 3.15 - 3.20 (m, 2H), 1.47 - 1.53 (m, 3H), 1.39 - 1.40 (m, 9H), 1.33 - 1.34 (m, 1H), 0.52 - 0.54 (m, 2H), 0.18 - 0.23 (m, 2H); and MS-ESI: *m/z* 727.25 [M+H]⁺.

Step 4: *tert*-Butyl ((1*S*)-1-(4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(4-(difluoromethoxy)-3-hydroxyphenyl)oxazol-5-yl)ethyl)carbamate [00681] To a mixture of *tert*-butyl ((1*S*)-1-(2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (287 mg, 0.395 mmol) and nickel chloride (51.2 mg, 0.395 mmol) in ethanol (10 mL) was added a solution of sodium borohydride (75 mg, 1.97 mmol) in ethanol (20 mL). The mixture was stirred at rt for 1.5 hours. Then hydrochloric acid (1 M) was added to adjust the pH of the mixture to 1, and the mixture was stirred until clear. Then aqueous sodium hydroxide (1 M) was added to adjust the pH of the mixture to 14. The mixture was extracted with ethyl acetate (25 mL × 3) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed to give a red brown solid (0.246 g, 97.8%).

MS-ESI: *m/z* 637.30 [M+H]⁺.

Step 5: Methyl 5-(5-(5-((1*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate

[00682] To 15 mL of *N,N*-dimethylformamide were added *tert*-butyl ((1*S*)-1-(4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(4-

(difluoromethoxy)-3-hydroxyphenyl)oxazol-5-yl)ethyl)carbamate (246 mg, 0.386 mmol), methyl 5-bromovalerate (113 mg, 0.58 mmol) and potassium carbonate (107 mg, 0.773 mmol). The mixture was stirred at 60 °C in a sealed tube for 5 hours. The mixture was filtered to remove potassium carbonate. The filtrate was concentrated and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (232 mg, 80%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.63 - 7.65 (m, 2H), 7.48 - 7.55 (m, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 6.84 - 6.95 (m, 2H), 6.65 (t, *J*_{F-H} = 74.8 Hz, 1H), 5.86 - 5.89 (m, 1H), 5.28 - 5.36 (m, 1H), 4.18 - 4.21 (m, 2H), 3.70 (s, 3H), 3.13 - 3.23 (m, 2H), 2.45 - 2.49 (m, 2H), 1.89 - 1.97 (m, 4H), 1.47 - 1.48 (m, 3H), 1.40 - 1.44 (m, 9H), 1.30 - 1.31 (m, 1H), 0.51 - 0.53 (m, 2H), 0.18 - 0.22 (m, 2H); and MS-ESI: *m/z* 751.20 [M+H]⁺.

Step 6: 5-(5-(5-((*S*)-1-((*tert*-Butoxycarbonyl)amino)ethyl)-4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid

[00683] To a mixed solvent of ethanol (20 mL) and water (10 mL) was dissolved methyl 5-(5-(5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate (232 mg, 0.309 mmol) and sodium hydroxide (61 mg, 1.55 mmol). The mixture was stirred at 60 °C for 2 hours and concentrated to remove ethanol, then hydrochloric acid (1 M) was added to adjust pH to 1. The resulting mixture was extracted with ethyl acetate (25 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give light yellow oil (210 mg, 92.2%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.82 - 7.85 (m, 1H), 7.50 - 7.59 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 6.87 - 6.95 (m, 2H), 6.64 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.86 (m, 1H), 5.35 - 5.37 (m, 1H), 4.26 - 4.29 (m, 2H), 3.13 - 3.21 (m, 2H), 2.49 (m, 2H), 1.81 - 1.90 (m, 4H), 1.49 - 1.54 (m, 3H), 1.39 - 1.49 (m, 9H), 1.31 - 1.36 (m, 1H), 0.51 - 0.53 (m, 2H), 0.20 - 0.22 (m, 2H); and MS-ESI: *m/z* 737.20 [M+H]⁺.

Step 7: *tert*-Butyl ((1*S*)-1-(2-(3-((5-(4-(cyclopropanecarbonyl)piperazin-1-yl)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00684] To 20 mL of dichloromethane were added 5-(5-(5-((*S*)-1-((*tert*-butoxycarbonyl)

amino)ethyl)-4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (210 mg, 0.28 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (80 mg, 0.42 mmol) and 1-hydroxy-7-azabenzotriazole (57 mg, 0.42 mmol). The mixture was stirred at rt for 30 minutes, then 1-(cyclopropanecarbonyl)piperazine hydrochloride (80 mg, 0.42 mmol) was added. To the mixture was added *N,N*-diisopropylethylamine (0.20 mL, 1.12 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (25 mL × 3) and the aqueous layer was extracted with dichloromethane (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give a white solid (211 mg, 86.4%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.63 - 7.65 (m, 2H), 7.48 - 7.53 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.89 - 6.95 (m, 2H), 6.64 (t, *J*_{F-H} = 74.8 Hz, 1H), 5.86 - 5.87 (m, 1H), 5.28 - 5.34 (m, 1H), 4.22 (t, *J* = 5.6 Hz, 2H), 3.53 - 3.70 (m, 8H), 3.13 - 3.24 (m, 2H), 2.52 (t, *J* = 6.8 Hz, 2H), 1.93 - 2.01 (m, 4H), 1.48 - 1.53 (m, 3H), 1.40 - 1.43 (m, 9H), 1.32 - 1.35 (m, 1H), 1.27 - 1.30 (m, 1H), 1.02 - 1.05 (m, 2H), 0.80 - 0.85 (m, 2H), 0.51 - 0.55 (m, 2H), 0.19 - 0.20 (m, 2H); and MS-ESI: *m/z* 873.30 [M+H]⁺.

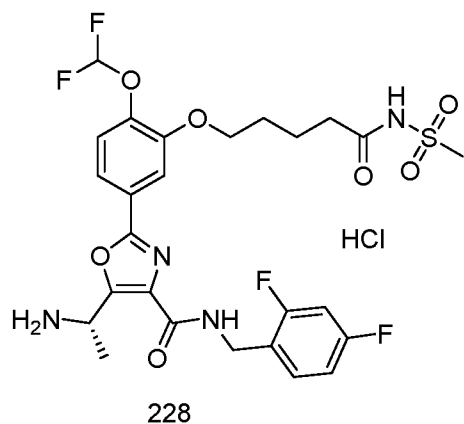
Step 8: 5-((*S*)-1-Aminoethyl)-2-(3-((5-(4-(cyclopropanecarbonyl)piperazin-1-yl)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-*N*-(2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)oxazole-4-carboxamide hydrochloride

[00685] To a solution of *tert*-butyl ((1*S*)-1-(2-(3-((5-(4-(cyclopropanecarbonyl)piperazin-1-yl)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-4-((2-((cyclopropylmethyl)amino)-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (211 mg, 0.242 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 30 minutes, then the solvent was removed to give a white solid (195 mg, 99.7%).

Compound 196: ¹H NMR (400 MHz, CD₃OD): δ ppm 7.83 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.58 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.04 - 7.09 (m, 2H), 6.90 (t, *J*_{F-H} = 74.4 Hz, 1H), 5.92 (d, *J* = 1.4 Hz, 1H), 5.16 - 5.20 (m, 1H), 4.23 (t, *J* = 6.0 Hz, 2H), 3.59 - 3.84 (m, 8H), 3.01 - 3.18 (m, 2H), 2.57 - 2.60 (t, *J* = 7.2 Hz, 2H), 1.87 - 2.01 (m, 4H), 1.76 (d, *J* = 6.8 Hz, 3H), 1.30 - 1.35 (m,

2H), 0.83 - 0.93 (m, 4H), 0.45 - 0.50 (m, 2H), 0.19 - 0.22 (m, 2H); and MS-ESI: m/z 773.25 $[M+H-HCl]^+$.

Example 125: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-(methylsulfonamido)-5-oxopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-Tert-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-(methylsulfonamido)-5-oxopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00686] To 20 mL of anhydrous tetrahydrofuran were added (S)-5-(5-(5-(1-((tert-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (200 mg, 0.313 mmol) and 1,1'-carbonyldiimidazole (152 mg, 0.938 mmol). The mixture was stirred at 60 °C for 20 minutes. The reaction mixture was cooled to rt, then methanesulfonamide (119 mg, 1.25 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (71.4 mg, 0.469 mmol) were added dropwise. After addition, the mixture was stirred at 60 °C for 3.5 hours. The reaction mixture was washed with saturated aqueous ammonium chloride (25 mL $\times$ 3) and the aqueous layer was extracted with ethyl acetate (25 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a white solid (112 mg, 50%).

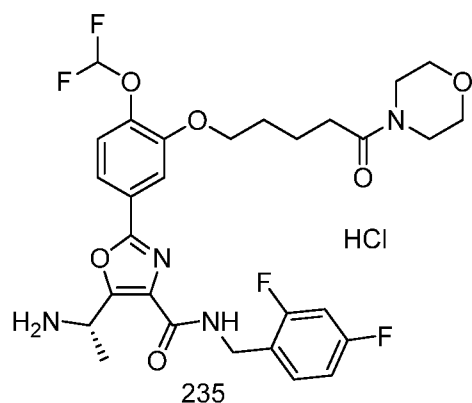
^1H NMR (400 MHz, CDCl_3): δ ppm 7.58 - 7.62 (m, 2H), 7.40 - 7.46 (m, 1H), 7.24 (d, J = 8.4 Hz, 1H), 6.83 - 6.91 (m, 2H), 6.64 (t, $J_{\text{F-H}}$ = 74.0 Hz, 1H), 5.31 - 5.33 (m, 1H), 4.66 - 4.68 (m, 2H), 4.12 - 4.17 (m, 2H), 3.31 (s, 3H), 2.51 - 2.54 (m, 2H), 1.94 - 1.96 (m, 4H), 1.56 (d, J = 6.8 Hz, 2H), 1.45 - 1.47 (m, 9H); and MS-ESI: m/z 717.30 $[M+H]^+$.

Step 2: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-(methylsulfonamido)-5-oxopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride

[00687] To a solution of (*S*)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-(methylsulfonamido)-5-oxopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate (133 mg, 0.188 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 2 mL). The resulting mixture was stirred at rt for 40 minutes and the solvent was removed to give the title compound as a white solid (121 mg, 100%).

Compound 228: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.82 (s, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.47 - 7.51 (m, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 6.97 - 7.01 (m, 2H), 6.89 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.16 - 5.19 (m, 1H), 4.65 (s, 2H), 4.19 - 4.21 (m, 2H), 3.24 (s, 3H), 2.45 - 2.47 (m, 2H), 1.87 - 1.95 (m, 4H), 1.78 (d, $J = 7.2$ Hz, 3H); and MS-ESI: m/z 617.15 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 126: (*S*)-5-(1-Aminoethyl)-*N*-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-morpholino-5-oxopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-morpholino-5-oxopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00688] To 20 mL of dichloromethane were added (*S*)-5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (150 mg, 0.235 mmol), morpholine (31 mg, 0.352 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (67 mg, 0.352 mmol) and 1-hydroxy-7-azabenzotriazole (48 mg, 0.352 mmol), and the mixture was stirred at rt for 30 minutes. Then *N,N*-diisopropylethylamine (0.12 mL, 0.704 mmol) was added dropwise at 0 °C and the mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (25 mL $\times$ 3) and the aqueous layer was extracted with dichloromethane (25 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give the title compound as a white solid (133 mg, 80%).

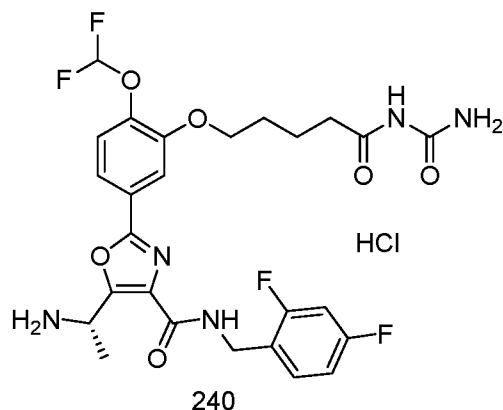
^1H NMR (400 MHz, CDCl_3): δ ppm 7.58 - 7.61 (m, 2H), 7.41 - 7.47 (m, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 6.84 - 6.92 (m, 2H), 6.62 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 5.31 - 5.33 (m, 1H), 4.66 - 4.71 (m, 2H), 4.18 (d, $J = 6.0$ Hz, 1H), 3.68 - 3.71 (m, 4H), 3.63 - 3.65 (m, 2H), 3.49 - 3.52 (m, 2H), 2.46 (t, $J = 6.8$ Hz, 2H), 1.88 - 2.01 (m, 4H), 1.56 (d, $J = 6.8$ Hz, 2H), 1.45 (s, 9H); and MS-ESI: m/z 709.30 $[\text{M}+\text{H}]^+$.

Step 2: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-morpholino-5-oxopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride

[00689] To a solution of (*S*)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-morpholino-5-oxopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate (133 mg, 0.188 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (7 M, 2 mL). The resulting mixture was stirred at rt for 40 minutes, then the solvent was removed to give a white solid (121 mg, 100%).

Compound 235: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.83 (s, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.46 - 7.52 (m, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 6.95 - 7.01 (m, 2H), 6.90 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.16 - 5.21 (m, 1H), 4.65 (s, 2H), 4.20 - 4.23 (m, 2H), 3.64 - 3.68 (m, 4H), 3.57 - 3.59 (m, 4H), 2.53 (t, $J = 6.8$ Hz, 2H), 1.83 - 1.99 (m, 4H), 1.78 (d, $J = 6.8$ Hz, 3H); and MS-ESI: m/z 609.25 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 127: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-oxo-5-ureidopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-*tert*-Butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-oxo-5-ureidopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00690] To 20 mL of anhydrous tetrahydrofuran were added (*S*)-5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (300 mg, 0.469 mmol) and

1,1'-carbonyldiimidazole (228 mg, 1.41 mmol). The mixture was stirred at 60 °C for 20 minutes. The reaction mixture was cooled to rt, then urea (214 mg, 3.563 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.305 mL, 0.315 mmol) were added. After addition, the mixture was stirred at 80 °C for 18 hours. The reaction mixture was washed with saturated aqueous ammonium chloride (25 mL × 3) and the aqueous layer was extracted with ethyl acetate (25 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give the title compound as a white solid (100 mg, 31.3%).

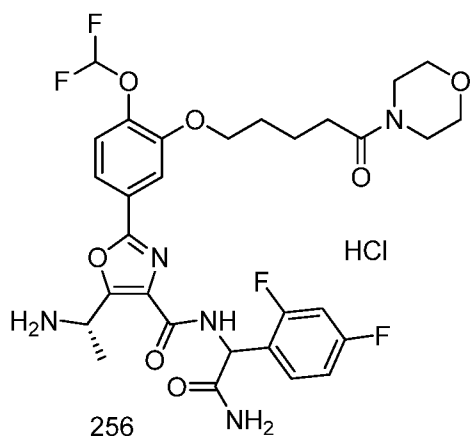
¹H NMR (400 MHz, CD₃OD): δ ppm 7.72 - 7.77 (m, 1H), 7.66 - 7.67 (m, 1H), 7.45 - 7.51 (m, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.94 - 6.99 (m, 2H), 6.86 (t, *J*_{F-H} = 74.8 Hz, 1H), 5.41 - 5.45 (m, 1H), 4.62 (s, 2H), 4.18 - 4.20 (m, 2H), 2.45 - 2.49 (m, 2H), 1.86 - 1.92 (m, 4H), 1.53 (d, *J* = 7.2 Hz, 3H), 1.42 (s, 9H); and MS-ESI: *m/z* 682.20 [M+H]⁺.

Step 2: (S)-5-(1-Aminoethyl)-N-(2,4-difluorobenzyl)-2-(4-(difluoromethoxy)-3-((5-oxo-5-ureidopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride

[00691] To a solution of (*S*)-*tert*-butyl (1-(4-((2,4-difluorobenzyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-oxo-5-ureidopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate (100 mg, 0.147 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in isopropanol (7 M, 2 mL). The resulting mixture was stirred at rt for 40 minutes and the solvent was removed to give the title compound as a white solid (91 mg, 100%).

Compound 240: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.82 (s, 1H), 7.72 - 7.76 (m, 2H), 7.62 - 7.65 (m, 1H), 7.47 - 7.51 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.95 - 7.01 (m, 2H), 6.89 (t, *J*_{F-H} = 74.4 Hz, 1H), 5.16 - 5.19 (m, 1H), 4.65 (s, 2H), 4.19 - 4.21 (m, 2H), 2.46 - 2.48 (m, 2H), 1.87 - 1.94 (m, 4H), 1.78 (d, *J* = 6.6 Hz, 3H); and MS-ESI: *m/z* 582.30 [M+H-HCl]⁺.

Example 128: N-(2-Amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((S)-1-aminoethyl)-2-(4-(difluoromethoxy)-3-((5-morpholino-5-oxopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: *tert*-Butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00692] To 20 mL of dichloromethane were added (*S*)-2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylic acid (0.30 g, 0.595 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.170 g, 0.892 mmol) and 1-hydroxy-7-azabenzotriazole (0.125 g, 0.892 mmol). The mixture was stirred at rt for 30 minutes, then 2-amino-2-(2,4-difluorophenyl)acetamide (0.159 g, 0.714 mmol) was added. To the resulting mixture was added *N,N*-diisopropylethylamine (0.45 mL, 2.38 mmol) at 0 °C and the mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (25 mL × 3). The aqueous layer was extracted with dichloromethane (25 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as a white solid (0.333 g, 81.9%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.75 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.36 - 7.55 (m, 6H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.90 - 6.96 (m, 2H), 6.67 (t, *J*_{F-H} = 74.4 Hz, 1H), 5.94 (d, *J* = 7.2 Hz, 1H), 5.31 - 5.35 (m, 1H), 5.27 (s, 2H), 1.48 - 1.53 (m, 3H), 1.41 - 1.48 (m, 9H); and MS-ESI: *m/z* 673.20 [M+H]⁺.

Step 2: *tert*-Butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(4-(difluoromethoxy)-3-hydroxyphenyl)oxazol-5-yl)ethyl)carbamate

[00693] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(3-(benzyloxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (0.333 g, 0.495 mmol) and nickel chloride (0.068 g, 0.495 mmol) in ethanol (5 mL) was added dropwise a

solution of sodium borohydride (0.098 g, 2.48 mmol) in ethanol (20 mL) at 0 °C. The mixture was stirred at rt for 10 hours, then hydrochloric acid (1 M) was added to adjust pH to 1. The mixture was stirred until clear, then aqueous sodium hydroxide (1 M) was added to adjust the pH to 14. The mixture was extracted with ethyl acetate (25 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (221 mg, 76.6%).

¹H NMR (400 MHz, CD₃OD): δ ppm 7.63 (d, *J* = 2.0 Hz, 1H), 7.48 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.00 - 7.06 (m, 2H), 6.89 (t, *J*_{F-H} = 74.8 Hz, 1H), 5.88 (d, *J* = 12.4 Hz, 1H), 5.35 - 5.40 (m, 1H), 1.50 (d, *J* = 7.2 Hz, 3H), 1.39 (s, 9H); and MS-ESI: *m/z* 583.20 [M+H]⁺.

Step 3: Methyl 5-(5-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate

[00694] To 15 mL of *N,N*-dimethylformamide were dissolved *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(4-(difluoromethoxy)-3-hydroxyphenyl)oxazol-5-yl)ethyl)carbamate (442 mg, 0.818 mmol), methyl 5-bromovalerate (239 mg, 1.23 mmol) and potassium carbonate (226 mg, 1.64 mmol). The whole mixture was stirred at 60 °C for 4 hours in a sealed tube. The reaction mixture was filtered to remove potassium carbonate and the filtrate was concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give colourless oil (454 mg, 84.8%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.63 - 7.65 (m, 2H), 7.50 - 7.56 (m, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 6.90 - 6.96 (m, 2H), 6.65 (t, *J*_{F-H} = 74.4 Hz, 1H), 5.94 (d, *J* = 6.8 Hz, 1H), 5.29 - 5.37 (m, 1H), 4.17 - 4.20 (m, 2H), 3.71 (s, 3H), 2.45 - 2.49 (m, 2H), 1.89 - 1.97 (m, 4H), 1.48 - 1.53 (m, 3H), 1.40 - 1.45 (m, 9H); and MS-ESI: *m/z* 697.25 [M+H]⁺.

Step 4: 5-(5-(4-((2-Amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid

[00695] To a mixed solvent of ethanol (20 mL) and water (10 mL) was added methyl 5-(5-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoate (220 mg, 0.316 mmol) and sodium hydroxide (64 mg, 1.58 mmol). The mixture was stirred at 60 °C for 90 minutes, then concentrated to remove ethanol. To the residue was added hydrochloric acid (1 M) to adjust the

pH to 1. The mixture was extracted with ethyl acetate (25 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give light yellow oil (179 mg, 83.0%).

^1H NMR (400 MHz, CD_3OD): δ ppm 7.44 - 7.77 (m, 1H), 7.67 (dd, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz, 1H), 7.57 - 7.61 (m, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 6.99 - 7.05 (m, 2H), 6.86 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.89 - 5.91 (m, 1H), 5.41 - 5.44 (m, 1H), 4.17 - 4.20 (m, 2H), 2.41 - 2.45 (m, 2H), 1.82 - 1.94 (m, 4H), 1.51 (d, $J = 7.2$ Hz, 3H), 1.40 (s, 9H); and MS-ESI: m/z 683.20 $[\text{M}+\text{H}]^+$.

Step 5: *tert*-Butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-morpholino-5-oxopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00696] To 20 mL of dichloromethane were added 5-(5-(4-((2-amino-1-(2,4-difluorophenyl)-2-oxoethyl)carbamoyl)-5-((*S*)-1-((*tert*-butoxycarbonyl)amino)ethyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (0.179 g, 0.262 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.076 g, 0.393 mmol) and 1-hydroxy-7-azabenzotriazole (0.054 g, 0.393 mmol). The mixture was stirred at rt for 30 minutes, then morpholine (0.027 g, 0.315 mmol) was added. To the resulting mixture was added *N,N*-diisopropylethylamine (0.15 mL, 0.787 mmol) dropwise at 0 °C. The mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (25 mL $\times$ 3) and the aqueous layer was extracted with dichloromethane (25 mL $\times$ 3). The organic layers were combined, dried over anhydrous sodium sulfate. The organic solvent was removed, then the residue was purified by silica gel column chromatography (MeOH/DCM (v/v) = 1/20) and further purified by thin-layer chromatography (MeOH/DCM (v/v) = 1/10) to give a white solid (81 mg, 41%).

^1H NMR (400 MHz, CD_3OD): δ ppm 7.77 (s, 1H), 7.66 (d, $J = 8.4$ Hz, 1H), 7.55 - 7.58 (m, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 6.98 - 7.04 (m, 2H), 6.87 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.90 (d, $J = 11.6$ Hz, 1H), 5.41 - 5.44 (m, 1H), 4.16 - 4.20 (m, 2H), 3.64 - 3.69 (m, 4H), 3.56 - 3.60 (m, 4H), 2.51 - 2.54 (m, 2H), 1.88 - 1.93 (m, 2H), 1.92 - 1.86 (m, 2H), 1.52 (d, $J = 6.8$ Hz, 3H), 1.40 (s, 9H); and MS-ESI: m/z 752.10 $[\text{M}+\text{H}]^+$.

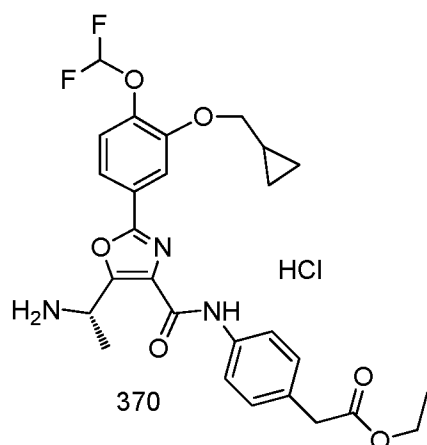
Step 6: *N*-(2-Amino-1-(2,4-difluorophenyl)-2-oxoethyl)-5-((*S*)-1-aminoethyl)-2-(4-(difluoromethoxy)-3-((5-morpholino-5-oxopentyl)oxy)phenyl)oxazole-4-carboxamide hydrochloride

[00697] To a solution of *tert*-butyl ((1*S*)-1-(4-((2-amino-1-(2,4-difluorophenyl)-2-

oxoethyl)carbamoyl)-2-(4-(difluoromethoxy)-3-((5-morpholino-5-oxopentyl)oxy)phenyl)oxazol-5-yl)ethyl)carbamate (81 mg, 0.108 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 40 minutes, then the solvent was removed to give a white solid (74 mg, 100%).

Compound 256: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.82 (s, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.58 - 7.62 (m, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.02 - 7.07 (m, 2H), 6.90 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.92 (s, 1H), 5.16 - 5.19 (m, 1H), 4.21 - 4.23 (m, 2H), 3.65 - 3.70 (m, 4H), 3.59 (m, 4H), 2.53 - 2.55 (m, 2H), 1.92 - 1.97 (m, 2H), 1.83 - 1.88 (m, 2H), 1.77 (d, $J = 7.2$ Hz, 3H); and MS-ESI: m/z 652.20 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 129: (S)-Ethyl 2-(4-(5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)phenyl)acetate hydrochloride



Step 1: Ethyl 2-(4-aminophenyl)acetate

[00698] To a solution of ethyl 4-nitrophenylacetate (500 mg, 2.39 mmol) in methanol (10 mL) was added Pd/C (64 mg). The mixture was stirred at rt for 1.5 hours under hydrogen atmosphere. The mixture was filtered and the filtrate was concentrated to give ethyl 2-(4-aminophenyl)acetate as reddish liquid (420 mg, 97%).

^1H NMR (400 MHz, CD_3OD): δ ppm 7.03 (d, $J = 8.4$ Hz, 2H), 6.71 (d, $J = 8.4$ Hz, 2H), 4.13 (q, $J = 7.1$ Hz, 1H), 3.49 (s, 2H), 1.24 (t, $J = 7.1$ Hz, 3H); and MS-ESI: m/z 180.2 $[\text{M}+\text{H}]^+$.

Step 2: (S)-Ethyl 2-(4-(5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)phenyl)acetate

[00699] To 15 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (250 mg, 0.53 mmol), ethyl 4-aminophenylacetate (115 mg,

0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (154 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (182 mg, 1.33 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.37 mL, 2.14 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 2.5 hours. The reaction mixture was washed with water (10 mL × 2) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a white solid (256 mg, 76%).

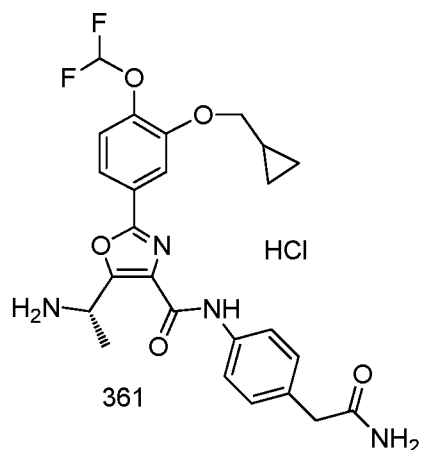
¹H NMR (400 MHz, CDCl₃): δ ppm 7.68 (d, *J* = 8.4 Hz, 2H), 7.63 (dd, *J*₁ = 8.3 Hz, *J*₂ = 1.9 Hz, 1H), 7.59 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 6.2 Hz, 1H), 6.72 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.35 – 5.30 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.01 (d, *J* = 6.9 Hz, 2H), 3.61 (s, 2H), 1.57 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 9H), 1.37 – 1.33 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.73 – 0.68 (m, 2H), 0.44 – 0.41 (m, 2H); and MS-ESI: *m/z* 574.2 [M-55]⁺.

Step 3: (*S*)-Ethyl 2-(4-(5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)phenyl)acetate hydrochloride

[00700] To a solution of (*S*)-ethyl 2-(4-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamido)phenyl)acetate (249 mg, 0.40 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 5 mL). The resulting mixture was stirred at rt for 1.5 hours, then the solvent was removed to give a white solid (220 mg, 98%).

Compound 370: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.86 (s, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.93 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.28 – 5.25 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.07 (d, *J* = 6.9 Hz, 2H), 3.65 (s, 2H), 1.82 (d, *J* = 6.9 Hz, 3H), 1.38 – 1.35 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.71 – 0.68 (m, 2H), 0.46 – 0.44 (m, 2H); and MS-ESI: *m/z* 530.8 [M+H-HCl]⁺.

Example 130: (*S*)-*N*-(4-(2-Amino-2-oxoethyl)phenyl)-5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride



Step 1: 2-(4-Aminophenyl)acetamide

[00701] To a sealed tube were added ethyl 4-nitrophenylacetate (500 mg, 2.39 mmol) and a solution of ammonia in methanol (7 M, 12 mL). The mixture was stirred at 75 °C for 24 hours, then the reaction was completed. The mixture was concentrated to remove the solvent. The residue was washed with dichloromethane (10 mL), and the mixture was filtered to give 2-(4-nitrophenyl)acetamide as a light red solid (340 mg, 78%).

¹H NMR (400 MHz, CD₃OD): δ ppm 8.22 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 3.69 (s, 2H); and MS-ESI: *m/z* 181.0 [M+H]⁺.

[00702] To a solution of 2-(4-nitrophenyl)acetamide (340 mg, 1.89 mmol) in methanol (10 mL) was added Pd/C (34 mg). The mixture was stirred at rt for 1.5 hours under hydrogen atmosphere. The mixture was filtered through a celite pad and the filtrate was concentrated to give 2-(4-aminophenyl)acetamide as a pink solid (280 mg, 98%).

¹H NMR (400 MHz, CD₃OD): δ ppm 7.06 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 3.38 (s, 2H); and MS-ESI: *m/z* 151.2 [M+H]⁺.

Step 2: (S)-*tert*-Butyl (1-(4-((4-(2-amino-2-oxoethyl)phenyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00703] To 15 mL of dichloromethane were added (S)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (250 mg, 0.53 mmol), 2-(4-aminophenyl)acetamide (96 mg, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (154 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (182 mg, 1.33 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.37 mL, 2.14 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 3 hours. The reaction mixture was washed with water (10 mL × 2) and the

organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 40/1) to give a white solid (220 mg, 68%).

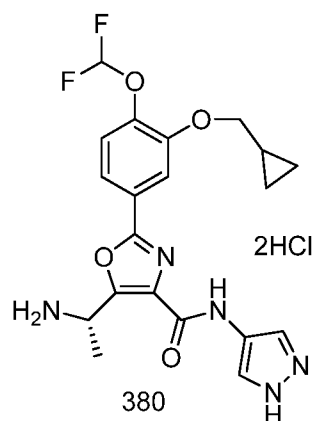
^1H NMR (400 MHz, CDCl_3): δ ppm 7.72 (d, $J = 8.2$ Hz, 2H), 7.63 (d, $J = 8.3$ Hz, 1H), 7.59 (s, 1H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.26 (d, $J = 8.2$ Hz, 1H), 6.72 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.52 – 5.44 (m, 2H), 5.37 – 5.33 (m, 1H), 4.00 (d, $J = 6.9$ Hz, 2H), 3.59 (s, 2H), 1.57 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 1.37 – 1.33 (m, 1H), 0.72 – 0.68 (m, 2H), 0.43 – 0.41 (m, 2H); and MS-ESI: m/z 545.7 $[\text{M}-55]^+$.

Step 3: (S)-N-(4-(2-Amino-2-oxoethyl)phenyl)-5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide hydrochloride

[00704] To a solution of (S)-tert-butyl (1-(4-((4-(2-amino-2-oxoethyl)phenyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (220 mg, 0.37 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 1.5 hours, then the solvent was removed to give a white solid (196 mg, 99%).

Compound 361: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.86 (s, 1H), 7.77 (d, $J = 9.8$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.37 (s, 1H), 7.34 (d, $J = 7.9$ Hz, 2H), 6.93 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.27 – 5.24 (m, 1H), 4.07 (d, $J = 6.9$ Hz, 2H), 3.55 (s, 2H), 1.81 (d, $J = 6.9$ Hz, 3H), 1.38 – 1.36 (m, 1H), 0.71 – 0.68 (m, 2H), 0.46 – 0.44 (m, 2H); and MS-ESI: m/z 501.3 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 131: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(1H-pyrazol-4-yl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-Tert-butyl (1-(4-((1H-pyrazol-4-yl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00705] To 15 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (250 mg, 0.53 mmol), 4-aminopyrazole (53 mg, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (182 mg, 1.33 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.37 mL, 2.14 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (10 mL × 2) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (138 mg, 47%).

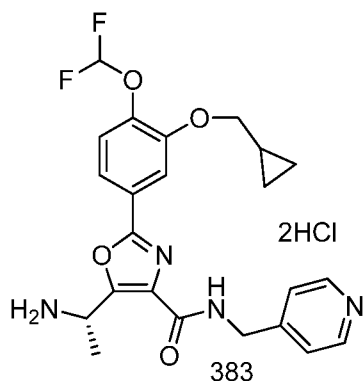
¹H NMR (400 MHz, CDCl₃): δ ppm 7.96 (s, 2H), 7.62 – 7.59 (m, 1H), 7.58 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.70 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.36 – 5.32 (m, 1H), 3.98 (d, *J* = 6.9 Hz, 2H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 9H), 1.35 – 1.32 (m, 1H), 0.71 – 0.66 (m, 2H), 0.43 – 0.39 (m, 2H); and MS-ESI: *m/z* 478.8 [M-55]⁺.

Step 2: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1*H*-pyrazol-4-yl)oxazole-4-carboxamide dihydrochloride

[00706] To a solution of (*S*)-*tert*-butyl (1-(4-((1*H*-pyrazol-4-yl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (117 mg, 0.22 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 1.5 hours, then the solvent was removed to give a white solid (87 mg, 78%).

Compound 380: ¹H NMR (600 MHz, CD₃OD): δ ppm 8.30 (s, 2H), 7.85 (d, *J* = 1.6 Hz, 1H), 7.78 (dd, *J*₁ = 8.3 Hz, *J*₂ = 1.6 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 6.93 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.29 – 5.26 (m, 1H), 4.07 (d, *J* = 6.9 Hz, 2H), 1.82 (d, *J* = 7.0 Hz, 3H), 1.39 – 1.35 (m, 1H), 0.72 – 0.69 (m, 2H), 0.44 – 0.42 (m, 2H); and MS-ESI: *m/z* 434.9 [M+H-2HCl]⁺.

Example 132: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(pyridin-4-ylmethyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((pyridin-4-ylmethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00707] To 15 mL of dichloromethane were added (S)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (250 mg, 0.53 mmol), pyridin-4-ylmethanamine hydrochloride (93 mg, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (182 mg, 1.33 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.37 mL, 2.14 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 3.5 hours. The reaction mixture was washed with water (10 mL × 2) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give a white solid (194 mg, 65%).

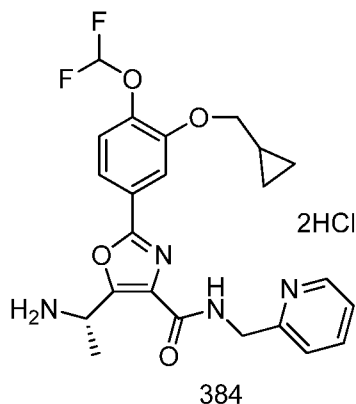
¹H NMR (400 MHz, CDCl₃): δ ppm 8.55 (d, *J* = 4.7 Hz, 2H), 7.53 (dd, *J*₁ = 8.3 Hz, *J*₂ = 1.8 Hz, 1H), 7.49 (d, *J* = 1.7 Hz, 1H), 7.25 (d, *J* = 5.6 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.66 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.29 – 5.25 (m, 1H), 4.63 (d, *J* = 6.3 Hz, 2H), 3.92 (d, *J* = 6.9 Hz, 2H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.38 (s, 9H), 1.30 – 1.26 (m, 1H), 0.66 – 0.62 (m, 2H), 0.37 – 0.33 (m, 2H); and MS-ESI: *m/z* 559.3 [M+H]⁺.

Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(pyridin-4-ylmethyl)oxazole-4-carboxamide dihydrochloride

[00708] To a solution of (S)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((pyridin-4-ylmethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (188 mg, 0.34 mmol) in dichloromethane (6 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 1 hour, then the solvent was removed to give a white solid (178 mg, 99%).

Compound 383: ^1H NMR (600 MHz, CD_3OD): δ ppm 8.86 (d, $J = 6.1$ Hz, 2H), 8.13 (d, $J = 6.1$ Hz, 2H), 7.84 (d, $J = 1.4$ Hz, 1H), 7.76 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.4$ Hz, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 6.93 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.23 – 5.20 (m, 1H), 4.95 (s, 2H), 4.05 (d, $J = 6.9$ Hz, 2H), 1.80 (d, $J = 6.9$ Hz, 3H), 1.38 – 1.35 (m, 1H), 0.70 – 0.67 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: m/z 457.8 $[\text{M-H-2HCl}]^-$.

Example 133: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(pyridin-2-ylmethyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((pyridin-2-ylmethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00709] To 15 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (250 mg, 0.53 mmol), 2-(aminomethyl)pyridine (69 mg, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (182 mg, 1.33 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.37 mL, 2.14 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 12 hours. The reaction mixture was washed with water (10 mL $\times$ 2) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (223 mg, 74%).

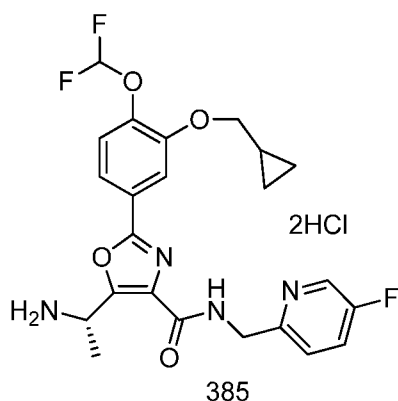
^1H NMR (400 MHz, CDCl_3): δ ppm 8.61 (d, $J = 4.4$ Hz, 1H), 8.11 (br.s, 1H), 7.70 (td, $J_1 = 7.7$ Hz, $J_2 = 1.7$ Hz, 1H), 7.60 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.57 (s, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.25 – 7.23 (m, 2H), 6.70 (t, $J_{\text{F-H}} = 75.1$ Hz, 1H), 5.31 – 5.28 (m, 1H), 4.76 (d, $J = 5.5$ Hz, 2H), 3.98 (d, $J = 7.0$ Hz, 2H), 1.53 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 1.35 – 1.30 (m, 1H), 0.71 – 0.66 (m, 2H), 0.43 – 0.39 (m, 2H); and MS-ESI: m/z 559.8 $[\text{M+H}]^+$.

Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(pyridin-2-ylmethyl)oxazole-4-carboxamide dihydrochloride

[00710] To a solution of (S)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((pyridin-2-ylmethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (216 mg, 0.39 mmol) in dichloromethane (6 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 1 hour, then the solvent was removed to give a white solid (205 mg, 99%).

Compound 384: ^1H NMR (600 MHz, CD_3OD): δ ppm 8.85 (d, $J = 5.6$ Hz, 1H), 8.65 (t, $J = 7.7$ Hz, 1H), 8.15 (d, $J = 8.0$ Hz, 1H), 8.05 (t, $J = 6.6$ Hz, 1H), 7.84 (s, 1H), 7.76 (d, $J = 8.3$ Hz, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 6.93 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.24 – 5.20 (m, 1H), 5.03 (s, 2H), 4.05 (d, $J = 6.8$ Hz, 2H), 1.79 (d, $J = 6.9$ Hz, 3H), 1.37 – 1.34 (m, 1H), 0.70 – 0.66 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: m/z 459.9 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 134: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-((5-fluoropyridin-2-yl)methyl)oxazole-4-carboxamide dihydrochloride



Step 1: (5-Fluoropyridin-2-yl)methanamine

[00711] To a solution of 5-fluoropicolinaldehyde (300 mg, 2.40 mmol) in acetonitrile (15 mL) was added hydroxylamine hydrochloride (333 mg, 4.80 mmol). The mixture was stirred at rt, then triethylamine (1.33 mL, 9.60 mmol) was added. The resulting mixture was stirred at 80 °C for 3 hours, then the solvent was removed. To the residue was added ethyl acetate (15 mL), then the resulting mixture was washed with water (10 mL $\times$ 2). The organic layer was dried over anhydrous sodium sulfate and concentrated to give 5-fluoropicolinaldehyde oxime as a white solid (336 mg, 98%).

^1H NMR (400 MHz, CD_3OD): δ ppm 8.38 (s, 1H), 8.14 (s, 1H), 7.82 – 7.75 (m, 1H), 7.48 – 7.36 (m, 1H); and MS-ESI: m/z 141.1 $[\text{M}+\text{H}]^+$.

[00712] To a solution of 5-fluoropicolinaldehyde oxime (333 mg, 2.38 mmol) and nickel chloride (308 mg, 2.38 mmol) in anhydrous ethanol (18 mL) was added sodium borohydride (476 mg, 11.88 mmol) under an ice-bath condition accompanying intense heat, then the mixture was stirred for additional 40 minutes under the ice-bath condition. The mixture was stirred at rt for 20 minutes, then hydrochloric acid solution was added to adjust the pH to about 1. The resulting mixture was stirred until clear, then sodium hydroxide was added to adjust the pH to about 14 and a white solid was precipitated. The upper layer of the suspension was separated and the solvent of the upper layer was removed. To the residue was added dichloromethane (25 mL), and the mixture was filtered. The filtrate was dried over anhydrous sodium sulfate and concentrated to give a light yellow solid (150 mg, 50%).

^1H NMR (600 MHz, CD_3OD): δ ppm 8.51 (d, $J = 2.7$ Hz, 1H), 7.66 (td, $J_1 = 8.5$ Hz, $J_2 = 2.8$ Hz, 1H), 7.51 (dd, $J_1 = 8.6$ Hz, $J_2 = 4.2$ Hz, 1H), 4.27 (s, 2H); and MS-ESI: m/z 127.2 $[\text{M}+\text{H}]^+$.

Step 2: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((5-fluoropyridin-2-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00713] To 20 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (250 mg, 0.53 mmol), (5-fluoropyridin-2-yl)methanamine (81 mg, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (182 mg, 1.33 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.37 mL, 2.14 mmol) dropwise at 0 °C. The mixture was stirred at rt for 7.5 hours. The reaction mixture was washed with water (10 mL $\times$ 2) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a white solid (130 mg, 41%).

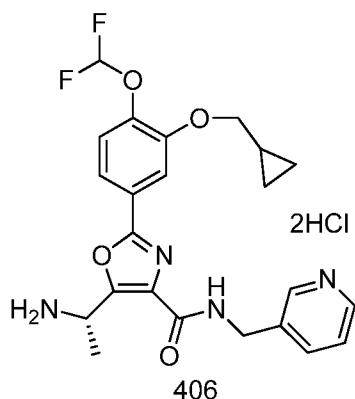
^1H NMR (400 MHz, CDCl_3): δ ppm 8.48 (d, $J = 2.4$ Hz, 1H), 8.05 (br.s, 1H), 7.62 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.59 (d, $J = 1.7$ Hz, 1H), 7.44 – 7.40 (m, 2H), 7.26 (d, $J = 8.3$ Hz, 1H), 6.72 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.34 – 5.30 (m, 1H), 4.76 (d, $J = 5.5$ Hz, 2H), 4.00 (d, $J = 7.0$ Hz, 2H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 1.36 – 1.32 (m, 1H), 0.74 – 0.69 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: m/z 577.3 $[\text{M}+\text{H}]^+$.

Step 3: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(((5-fluoropyridin-2-yl)methyl)oxazole-4-carboxamide dihydrochloride

[00714] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((5-fluoropyridin-2-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (128 mg, 0.22 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 1.5 hours and then the solvent was removed to give a white solid (118 mg, 96%).

Compound 385: ¹H NMR (600 MHz, CD₃OD): δ ppm 8.83 (br.s, 1H), 8.27 (t, *J* = 8.1 Hz, 1H), 8.00 – 7.99 (m, 1H), 7.82 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.33 (m, 1H), 7.05 – 6.80 (m, 1H), 5.21 – 5.20 (m, 1H), 4.93 (s, 2H), 4.05 – 4.04 (m, 2H), 1.80 – 1.79 (m, 3H), 1.37 – 1.34 (m, 1H), 0.69 – 0.68 (m, 2H), 0.44 – 0.42 (m, 2H); and MS-ESI: *m/z* 477.8 [M+H-2HCl]⁺.

Example 135: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(pyridin-3-ylmethyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((pyridin-3-ylmethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00715] To 15 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (250 mg, 0.53 mmol), 3-(aminomethyl)pyridine (69 mg, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (182 mg, 1.33 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.37 mL, 2.14 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (10 mL × 2) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/2) to give a

white solid (254 mg, 85%).

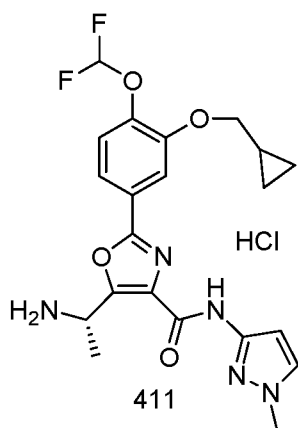
^1H NMR (400 MHz, CDCl_3): δ ppm 8.65 (br.s, 1H), 8.56 (d, $J = 4.3$ Hz, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.57 – 7.55 (m, 1H), 7.52 (s, 1H), 7.32 – 7.29 (m, 1H), 7.22 (d, $J = 8.3$ Hz, 1H), 6.69 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.32 – 5.30 (m, 1H), 4.68 – 4.65 (m, 2H), 3.96 (d, $J = 6.9$ Hz, 2H), 1.54 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 1.34 – 1.30 (m, 1H), 0.70 – 0.65 (m, 2H), 0.41 – 0.37 (m, 2H); and MS-ESI: m/z 559.3 $[\text{M}+\text{H}]^+$.

Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(pyridin-3-ylmethyl)oxazole-4-carboxamide dihydrochloride

[00716] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((pyridin-3-ylmethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (250 mg, 0.45 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 2 hours, then the solvent was removed to give a white solid (220 mg, 92%).

Compound 406: ^1H NMR (600 MHz, CD_3OD): δ ppm 8.97 (s, 1H), 8.84 (d, $J = 5.5$ Hz, 1H), 8.72 (d, $J = 8.1$ Hz, 1H), 8.15 – 8.13 (m, 1H), 7.81 (d, $J = 1.7$ Hz, 1H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.7$ Hz, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 6.92 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.23 – 5.19 (m, 1H), 4.86 – 4.85 (m, 2H), 4.04 (d, $J = 6.9$ Hz, 2H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.37 – 1.34 (m, 1H), 0.70 – 0.67 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: m/z 459.3 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 136: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(1-methyl-1H-pyrazol-3-yl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-methyl-1H-pyrazol-3-yl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00717] To 15 mL of dichloromethane were added

(*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (250 mg, 0.53 mmol), 3-amino-1-methylpyrazole (62 mg, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (182 mg, 1.33 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.37 mL, 2.14 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 3.5 hours. The reaction mixture was washed with water (10 mL × 2) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (260 mg, 85%).

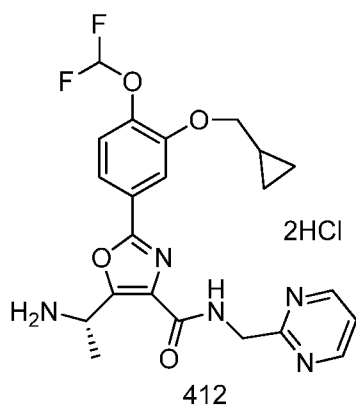
¹H NMR (400 MHz, CDCl₃): δ ppm 7.59 (s, 1H), 7.58 – 7.55 (m, 1H), 7.31 (d, *J* = 2.1 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 6.79 (d, *J* = 2.2 Hz, 1H), 6.71 (t, *J*_{F-H} = 75.1 Hz, 1H), 5.36 – 5.32 (m, 1H), 4.00 (d, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 9H), 1.37 – 1.32 (m, 1H), 0.73 – 0.68 (m, 2H), 0.46 – 0.42 (m, 2H); and MS-ESI: *m/z* 548.8 [M+H]⁺.

Step 2: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-methyl-1*H*-pyrazol-3-yl)oxazole-4-carboxamide hydrochloride

[00718] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-methyl-1*H*-pyrazol-3-yl)carbamoyl)oxazol-5-yl)ethyl)carbamate (265 mg, 0.48 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 1 hour, then the solvent was removed to give a white solid (231 mg, 98%).

Compound 411: ¹H NMR (400 MHz, CD₃OD): δ ppm 7.84 (d, *J* = 1.6 Hz, 1H), 7.77 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.6 Hz, 1H), 7.73 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 6.93 (t, *J*_{F-H} = 74.7 Hz, 1H), 6.66 (d, *J* = 2.2 Hz, 1H), 5.31 – 5.28 (m, 1H), 4.07 (d, *J* = 6.9 Hz, 2H), 3.94 (s, 3H), 1.83 (d, *J* = 6.9 Hz, 3H), 1.39 – 1.34 (m, 1H), 0.72 – 0.68 (m, 2H), 0.47 – 0.43 (m, 2H); and MS-ESI: *m/z* 448.3 [M+H-HCl]⁺.

Example 137: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(pyrimidin-2-ylmethyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((pyrimidin-2-ylmethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00719] (S)-5-(1-(((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (250 mg, 0.53 mmol), 2-(aminomethyl)pyrimidine hydrochloride (93 mg, 0.64 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) and 1-hydroxy-7-azabenzotriazole (182 mg, 1.33 mmol) were dissolved in 15 mL of dichloromethane. To the mixture was added *N,N*-diisopropylethylamine (0.37 mL, 2.14 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 17 hours. The reaction mixture was washed with water (10 mL × 2) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (225 mg, 73%).

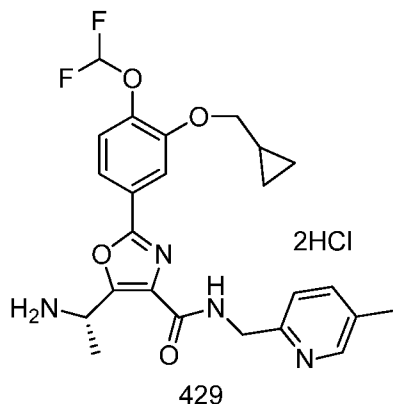
¹H NMR (400 MHz, CDCl₃): δ ppm 8.77 (d, *J* = 4.9 Hz, 2H), 8.24 (br.s, 1H), 7.64 (dd, *J*₁ = 8.3 Hz, *J*₂ = 1.9 Hz, 1H), 7.59 (d, *J* = 1.7 Hz, 1H), 7.25 – 7.24 (m, 1H), 6.71 (t, *J*_{F-H} = 75.0 Hz, 1H), 5.32 – 5.28 (m, 1H), 4.91 (d, *J* = 5.2 Hz, 2H), 3.99 (d, *J* = 6.9 Hz, 2H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 9H), 1.36 – 1.31 (m, 1H), 0.72 – 0.67 (m, 2H), 0.43 – 0.39 (m, 2H); and MS-ESI: *m/z* 560.8 [M+H]⁺.

Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(pyrimidin-2-ylmethyl)oxazole-4-carboxamide dihydrochloride

[00720] To a solution of (S)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((pyrimidin-2-ylmethyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (218 mg, 0.39 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 1 hour, then the solvent was removed to give a white solid (207 mg, 99%).

Compound 412: ^1H NMR (600 MHz, CD_3OD): δ ppm 9.01 (d, $J = 4.9$ Hz, 2H), 7.82 (s, 1H), 7.76 (d, $J = 8.3$ Hz, 1H), 7.71 – 7.69 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 6.93 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.20 – 5.17 (m, 1H), 4.96 – 4.95 (m, 2H), 4.04 (d, $J = 6.8$ Hz, 2H), 1.79 (d, $J = 6.7$ Hz, 3H), 1.37 – 1.35 (m, 1H), 0.70 – 0.67 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: m/z 460.2 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 138: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-((5-methylpyridin-2-yl)methyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((5-methylpyridin-2-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00721] To 16 mL of dichloromethane were added (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (220 mg, 0.47 mmol), (5-methylpyridin-2-yl)methanamine (69 mg, 0.56 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (135 mg, 0.70 mmol) and 1-hydroxy-7-azabenzotriazole (160 mg, 1.17 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.33 mL, 1.88 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 14 hours. The reaction mixture was washed with water (10 mL $\times$ 2) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (202 mg, 75%).

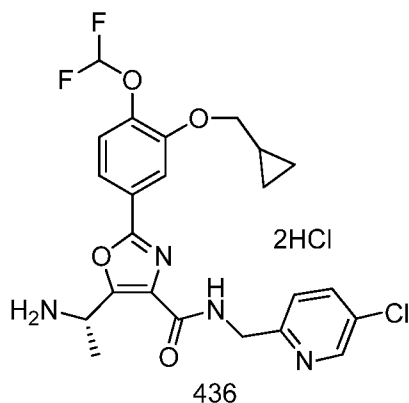
^1H NMR (400 MHz, CDCl_3): δ ppm 8.44 (s, 1H), 8.06 (br.s, 1H), 7.62 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.59 (d, $J = 1.7$ Hz, 1H), 7.52 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.7$ Hz, 1H), 7.27 (s, 1H), 7.23 (d, $J = 8.7$ Hz, 1H), 6.70 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.31 – 5.27 (m, 1H), 4.72 (d, $J = 5.5$ Hz, 2H), 3.98 (d, $J = 6.9$ Hz, 2H), 2.34 (s, 3H), 1.53 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 1.35 – 1.31 (m, 1H), 0.71 – 0.67 (m, 2H), 0.44 – 0.40 (m, 2H); and MS-ESI: m/z 573.3 $[\text{M}+\text{H}]^+$.

Step 2: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-((5-methylpyridin-2-yl)methyl)oxazole-4-carboxamide dihydrochloride

[00722] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-(((5-methylpyridin-2-yl)methyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (200 mg, 0.35 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 2 hours, then the solvent was removed to give a white solid (190 mg, 99%).

Compound 429: ¹H NMR (600 MHz, CD₃OD): δ ppm 8.69 (s, 1H), 8.46 (d, *J* = 5.5 Hz, 1H), 7.99 (d, *J* = 5.5 Hz, 1H), 7.82 (d, *J* = 1.8 Hz, 1H), 7.75 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.9 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 6.93 (t, *J*_{F-H} = 74.7 Hz, 1H), 5.23 – 5.19 (m, 1H), 4.95 (d, *J* = 6.4 Hz, 2H), 4.04 (d, *J* = 7.0 Hz, 2H), 2.58 (s, 3H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.37 – 1.34 (m, 1H), 0.71 – 0.68 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: *m/z* 473.3 [M+H-2HCl]⁺.

Example 139: (S)-5-(1-Aminoethyl)-N-((5-chloropyridin-2-yl)methyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide dihydrochloride



Step 1: (S)-tert-Butyl (1-(4-(((5-chloropyridin-2-yl)methyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate

[00723] To 16 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (220 mg, 0.47 mmol), 2-(aminomethyl)-5-chloropyridine hydrochloride (101 mg, 0.56 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (135 mg, 0.70 mmol) and 1-hydroxy-7-azabenzotriazole (160 mg, 1.17 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.33 mL, 1.88 mmol) dropwise at 0 °C. The resulting mixture was stirred at rt for 10 hours. The reaction mixture was washed with water (10 mL × 2) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent

was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a white solid (223 mg, 80%).

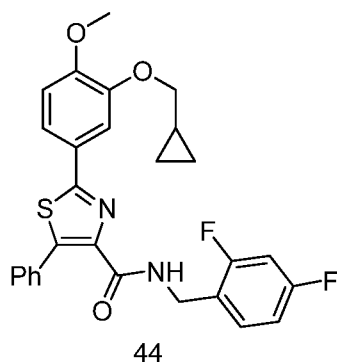
^1H NMR (400 MHz, CDCl_3): δ ppm 8.56 (d, $J = 2.3$ Hz, 1H), 8.01 (br.s, 1H), 7.67 (dd, $J_1 = 8.3$ Hz, $J_2 = 2.4$ Hz, 1H), 7.60 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.56 (d, $J = 1.7$ Hz, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.24 (d, $J = 8.4$ Hz, 1H), 6.70 (t, $J_{\text{F-H}} = 75.0$ Hz, 1H), 5.32 – 5.27 (m, 1H), 4.74 – 4.73 (m, 2H), 3.98 (d, $J = 7.0$ Hz, 2H), 1.53 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 1.34 – 1.31 (m, 1H), 0.72 – 0.67 (m, 2H), 0.43 – 0.40 (m, 2H); and MS-ESI: m/z 594.3 $[\text{M}+\text{H}]^+$.

Step 2: (*S*)-5-(1-Aminoethyl)-*N*-((5-chloropyridin-2-yl)methyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxamide dihydrochloride

[00724] To a solution of (*S*)-*tert*-butyl (1-(4-(((5-chloropyridin-2-yl)methyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazol-5-yl)ethyl)carbamate (219 mg, 0.37 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 3 hours, then the solvent was removed to give a white solid (207 mg, 99%).

Compound 436: ^1H NMR (600 MHz, CD_3OD): δ ppm 8.82 (s, 1H), 8.32 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.6$ Hz, 1H), 7.82 (s, 1H), 7.75 (d, $J = 8.3$ Hz, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 6.93 (t, $J_{\text{F-H}} = 74.7$ Hz, 1H), 5.22 – 5.18 (m, 1H), 4.87 (s, 2H), 4.04 (d, $J = 6.9$ Hz, 2H), 1.78 (d, $J = 6.9$ Hz, 3H), 1.36 – 1.34 (m, 1H), 0.70 – 0.68 (m, 2H), 0.45 – 0.42 (m, 2H); and MS-ESI: m/z 493.3 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 140: 2-(3-(Cyclopropylmethoxy)-4-methoxyphenyl)-*N*-(2,4-difluorobenzyl)-5-phenylthiazole-4-carboxamide



Step 1: O-ethyl benzothioate

[00725] To a solution of benzoic acid (5.73 g, 46.97 mmol) in ethanol (60 mL) was added concentrated hydrochloric acid (3 mL). The mixture was stirred at 86 °C for 3 hours. The

mixture was concentrated to give the crude product. To the crude product was added saturated aqueous sodium bicarbonate to adjust pH to 7, and the mixture was extracted with dichloromethane (100 mL $\times$ 3). The combined organic layers were washed with water (50 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated to give ethyl benzoate as colorless oil (5.2 g, 74%).

[00726] To a solution of ethyl benzoate (3 g, 20 mmol) in anhydrous xylene (25 mL) was added Lawesson's Reagent (8.08 g, 20 mmol). The mixture was stirred at 140 °C for 10 hours. To the reaction mixture was added Et₂O (25 mL) and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 20/1) to give light yellow oil (2.85 g, 86%).

Step 2: Methyl 2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-5-phenylthiazole-4-carboxylate

[00727] To a solution of methyl 2-(((3-(cyclopropylmethoxy)-4-methoxyphenyl)(methylthio)methylene)amino)acetate (1.183 g, 3.663 mmol) in anhydrous tetrahydrofuran (40 mL) were added O-ethyl benzothioate (2.8 g, 16.87 mmol) and DBU (2.784 g, 18.32 mmol). The mixture was stirred at 80 °C for 15.5 hours. To the reaction mixture was added water (40 mL) and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with saturated brine (40 mL $\times$ 3), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a yellow solid (347 mg, 24%).

MS (ESI, pos. ion) m/z : 396.1 [M+H]⁺.

Step 3: 2-(3-(Cyclopropylmethoxy)-4-methoxyphenyl)-5-phenylthiazole-4-carboxylic acid

[00728] To a solution of methyl 2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-5-phenylthiazole-4-carboxylate (160 mg, 0.4046 mmol) in a mixed solvent of THF/H₂O (v/v = 2/1, 6 mL) were added a solution of lithium hydroxide (48.4 mg, 2.023 mmol) in water (0.5 mL). The mixture was stirred at 40 °C for 3 hours. To the reaction mixture was added hydrochloric acid (1.2 M, 2 mL) to adjust pH to 1-2, and the resulting mixture was extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were washed with saturated brine (10 mL $\times$ 3), dried over anhydrous sodium sulfate and concentrated to give a yellow solid (120 mg, 78%).

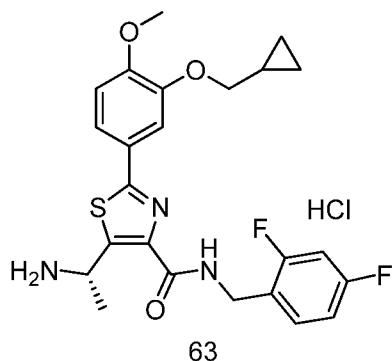
MS-ESI (pos. ion) m/z : 382.0 [M+H]⁺.

Step 4: 2-(3-(Cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)-5-phenylthiazole-4-carboxamide

[00729] To a solution of 2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-5-phenylthiazole-4-carboxylic acid (90 mg, 0.2344 mmol) in anhydrous dichloromethane (15 mL) were added EDCI (67.5 mg, 0.3516 mmol) and HOBt (47.5 mg, 0.3516 mmol). The mixture was stirred at rt for 30 minutes, then (2,4-difluorophenyl)methanamine (40.2 mg, 0.2812 mmol) and DIPEA (126 μ L, 0.7032 mmol) were added. The mixture was stirred at 25 °C for 16 hours. To the reaction mixture was added water (15 mL) and the resulting mixture was extracted with dichloromethane (10 mL $\times$ 3). The combined organic layers were washed with saturated brine (15 mL $\times$ 3), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a light yellow solid (92 mg, 77.5%).

Compound 44: ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.97 (br.s, 1H), 7.68 - 7.60 (m, 2H), 7.51 - 7.35 (m, 6H), 6.93 (d, J = 8.8 Hz, 1H), 6.87 - 6.77 (m, 2H), 4.62 (d, J = 5.6 Hz, 2H), 3.98 - 3.91 (m, 5H), 1.43 - 1.31 (m, 1H), 0.72 - 0.65 (m, 2H), 0.43 - 0.37 (m, 2H); and MS-ESI (pos. ion) m/z : 507.1 $[\text{M}+\text{H}]^+$.

Example 141: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)thiazole-4-carboxamide hydrochloride



Step 1: (S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)propanoic acid

[00730] To a solution of *L*-alanine (5 g, 56.18 mmol) in a mixed solvent of H_2O /dioxane (v/v = 1/1, 400 mL) were added sodium carbonate (29.8 g, 280.9 mmol) and *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (28.4 g, 84.27 mmol). The mixture was stirred at rt for 18 hours. The mixture was filtered, and the filtrate was extracted with ethyl ether (100 mL $\times$ 3). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with

ethyl acetate (150 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give a white solid (17.3 g, 99%).

MS-ESI (pos. ion) m/z : 334.2 $[M+Na]^+$.

Step 2: (*S*)-(9*H*-Fluoren-9-yl)methyl (1-fluoro-1-oxopropan-2-yl)carbamate

[00731] To a solution of (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)propanoic acid (5 g, 14.38 mmol) in anhydrous dichloromethane (100 mL) were added triethylamine (2.2 mL, 15.82 mmol) and cyanuric fluoride (2.4 mL, 28.76 mmol). The mixture was stirred at -40 °C for 2 hours. The mixture was washed with ice-water (50 mL × 5). The organic layer was dried over anhydrous sodium sulfate and concentrated to give a white solid (4.2 g, 93%).

MS-ESI (pos. ion) m/z : 326.2 $[M-F+OCH_3]^+$.

Step 3: (4*S*)-Ethyl 4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-amino-3-oxopentanoate hydrochloride

[00732] To a solution of *N*-(diphenylmethylene)glycine ethyl ester (3.67 g, 13.72 mmol) in anhydrous tetrahydrofuran (80 mL) was added KHMDS (1 M, 13.7 mL) at -78 °C. The mixture was stirred at -78 °C for 1 hour, then a solution of (*S*)-(9*H*-fluoren-9-yl)methyl (1-fluoro-1-oxopropan-2-yl)carbamate (4.3 g, 13.72 mmol) in anhydrous tetrahydrofuran (20 mL) was added. The resulting mixture was stirred at -78 °C for 1 hour, then hydrochloric acid (3 M, 34.3 mL) was added at -78 °C. The mixture was stirred at 25 °C for 20 minutes and concentrated. The residue was washed with ethyl ether (100 mL × 2). The solvent of the residue was removed by co-evaporation with toluene at a temperature below 40 °C to give a white solid (4.75 g, 79%).

MS (ESI, pos. ion) m/z : 397.3 $[M+H]^+$.

Step 4: 3-(Cyclopropylmethoxy)-4-methoxybenzoyl chloride

[00733] To a solution of 3-(cyclopropylmethoxy)-4-methoxybenzoic acid (3 g, 13.50 mmol) in anhydrous dichloromethane (100 mL) were added oxalyl dichloride (1.41 mL, 14.85 mmol) and DMF (104 μL, 1.35 mmol) at 0 °C. The mixture was stirred at 25 °C for 15.5 hours. The resulting mixture was concentrated *in vacuo* to give the crude product as a white solid (3.25 g, 100.3%).

MS (ESI, pos. ion) m/z : 237.2 $[M-Cl+OCH_3]^+$.

Step 5: (4*S*)-Ethyl 4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-(3-(cyclopropylmethoxy)-4-methoxybenzamido)-3-oxopentanoate

[00734] To a solution of 3-(cyclopropylmethoxy)-4-methoxybenzoyl chloride (3.17 g, 13.17

mmol) in anhydrous THF (100 mL) were added a solution of (4*S*)-ethyl 4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-amino-3-oxopentanoate hydrochloride (4.75 g, 10.97 mmol) in anhydrous DMF (50 mL) and triethylamine (3.04 mL, 21.94 mmol) at -78 °C. The reaction mixture was stirred at 25 °C for 3.5 hours, then concentrated. The residue was dissolved in EtOAc/Et₂O (1/1, 100 mL). The resulting mixture was washed with hydrochloric acid (1 M), aqueous sodium bicarbonate (10%, 70 mL × 2) and saturated brine (70 mL × 2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give white powder (3.4 g, 43%).

¹HNMR (400 MHz, CDCl₃): δ (ppm) 7.79 - 7.72 (m, 2H), 7.64 - 7.56 (m, 2H), 7.45 - 7.35 (m, 3H), 7.35 - 7.27 (m, 2H), 7.19 (d, *J* = 6.0 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.89 (d, *J* = 7.6 Hz, 1H), 5.66 - 5.57 (m, 1H), 5.02 - 4.90 (m, 1H), 4.48 - 4.18 (m, 4H), 3.97 - 3.86 (m, 5H), 1.56 (d, *J* = 7.6 Hz, 3H), 1.37 - 1.23 (m, 4H), 0.70 - 0.60 (m, 2H), 0.40 - 0.30 (m, 2H); and MS (ESI, pos. ion) *m/z*: 601.2 [M+H]⁺.

Step 6: (S)-Ethyl 5-(1-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxylate

[00735] To a solution of (4*S*)-ethyl 4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-(3-(cyclopropylmethoxy)-4-methoxybenzamido)-3-oxopentanoate (2.7 g, 4.5 mmol) in anhydrous THF (100 mL) was added Lawesson's reagent (3.64 g, 9 mmol). The reaction mixture was stirred at 80 °C for 10.5 hours, then water (100 mL) was added. The resulting mixture was extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with saturated brine (100 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1.5/1) to give a light yellow solid (2.6 g).

MS (ESI, pos. ion) *m/z*: 599.2 [M+H]⁺.

Step 7: (S)-5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxylic acid

[00736] To a solution of (S)-ethyl 5-(1-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxylate (2.1 g, 3.5 mmol) in a mixed solvent of THF/H₂O (v/v = 1/1, 210 mL) was added aqueous sodium hydroxide (1 M, 15.4 mmol). The mixture was stirred at 80 °C for 3.5 hours, then di-*tert*-butyl dicarbonate (916.7 mg, 4.2 mmol) was added. The mixture was stirred at 33 °C for 4 hours. To the reaction mixture

was added hydrochloric acid (1 M) to adjust pH to 2-3 and the resulting mixture was extracted with ethyl acetate (150 mL $\times$ 3). The combined organic layers were washed with saturated brine (30 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a yellow solid (1.08 g, 68%).

MS (ESI, pos. ion) m/z : 449.3 $[M+H]^+$.

Step 8: (S)-tert-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)thiazol-5-yl)ethyl)carbamate

[00737] To a solution of (S)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxylic acid (200 mg, 0.4464 mmol) in dichloromethane (15 mL) were added EDCI (128 mg, 0.6696 mmol) and HOBT (90.4 mg, 0.6696 mmol). The mixture was stirred at 25 °C for 30 minutes, then (2,4-difluorophenyl)methanamine (76.6 mg, 0.5357 mmol) and DIPEA (240 μ L, 1.339 mmol) were added. The resulting mixture was stirred at 25 °C for 15 hours, then water (20 mL) was added and the resulting mixture was extracted with dichloromethane (15 mL $\times$ 2). The combined organic layers were washed with saturated aqueous sodium carbonate (30 mL $\times$ 2) and saturated brine (30 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a white solid (131 mg, 43.6%).

MS (ESI, pos. ion) m/z : 574.2 $[M+H]^+$.

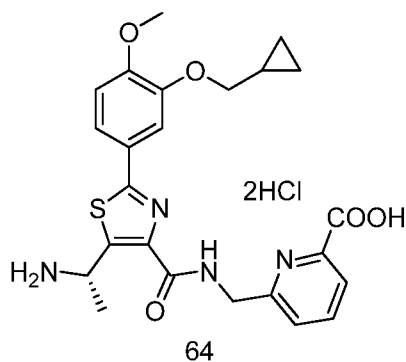
Step 9: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-N-(2,4-difluorobenzyl)thiazole-4-carboxamide hydrochloride

[00738] To a solution of (S)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)thiazol-5-yl)ethyl)carbamate (131 mg, 0.1947 mmol) in dichloromethane (1 mL) was added a solution of hydrochloric acid in ethyl acetate (4 M, 3 mL). The mixture was stirred at rt for 30 minutes, then filtered. The filter cake was washed with ethyl acetate (0.5 mL $\times$ 6), dissolved in methanol (5 mL) and concentrated to give a white solid (83 mg, 74%).

Compound 63: ^1H NMR (400 MHz, CD_3OD): δ (ppm) 7.65 (d, J = 2.4 Hz, 1H), 7.56 (dd, J = 8.4 Hz, 1H), 7.50 - 7.42 (m, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.00 - 6.90 (m, 2H), 5.35 - 5.27 (m, 1H), 4.66 (s, 2H), 3.93 (d, J = 6.8 Hz, 2H), 3.90 (s, 3H), 1.75 (d, J = 6.4 Hz, 3H), 1.35 - 1.24 (m,

1H), 0.66 - 0.60 (m, 2H), 0.39 - 0.33 (m, 2H); and MS-ESI (pos. ion) m/z : 474.1 $[M+H-HCl]^+$.

Example 142: (S)-6-((5-(1-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxamido)methyl)picolinic acid dihydrochloride



Step 1: (S)-Ethyl 6-((5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxamido)methyl)picolinate

[00739] To a solution of (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxylic acid (250 mg, 0.5580 mmol) in dichloromethane (20 mL) were added EDCI (214 mg, 1.117 mmol) and HOBT (151 mg, 1.117 mmol). The mixture was stirred at 25 °C for 30 minutes, then ethyl 6-(aminomethyl)picolinate (121 mg, 0.6696 mmol) and DIPEA (300 μ L, 1.675 mmol) were added. The resulting mixture was stirred at 25 °C for 18 hours, then water (30 mL) was added and the mixture was extracted with dichloromethane (20 mL $\times$ 2). The combined organic layers were washed with saturated aqueous sodium carbonate (30 mL $\times$ 2) and saturated brine (30 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white foamy solid (200 mg, 58.7%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.46 (br.s, 1H), 8.04 (d, J = 7.2 Hz, 1H), 7.87 - 7.80 (m, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.44 - 7.39 (m, 2H), 6.89 (d, J = 8.8 Hz, 1H), 6.27 (br.s, 1H), 5.65 - 5.40 (m, 1H), 4.91 - 4.83 (m, 2H), 4.54 - 4.42 (m, 2H), 3.98 (d, J = 7.6 Hz, 2H), 3.92 (s, 3H), 1.98 - 1.76 (m, 3H), 1.58 (d, J = 6.8 Hz, 3H), 1.37 - 1.32 (m, 1H), 0.70 - 0.62 (m, 2H), 0.43 - 0.38 (m, 2H), 0.06 (s, 9H); and MS-ESI (pos. ion) m/z : 611.2 $[M+H]^+$.

Step 2: (S)-6-((5-(1-((tert-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxamido)methyl)picolinic acid

[00740] To a solution of (S)-ethyl 6-((5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxamido)methyl)picolinate (200 mg,

0.3275 mmol) in a mixed solvent of THF/H₂O (v/v = 2/1, 9 mL) was added lithium hydroxide monohydrate (69 mg, 1.637 mmol). The mixture was stirred at 40 °C for 3.5 hours. To the mixture was added hydrochloric acid (1.2 M) to adjust pH to 2-3 and the resulting mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with saturated brine (15 mL × 2), dried over anhydrous sodium sulfate and concentrated to give a white solid (174 mg, 91.2%).

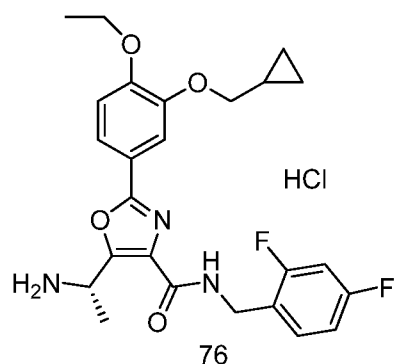
¹HNMR (400 MHz, CDCl₃): δ (ppm) 8.44 (br.s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.98 - 7.91 (m, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.46 - 7.38 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.07 (br.s, 1H), 5.65 - 5.50 (m, 1H), 4.89 - 4.83 (m, 2H), 3.98 - 3.87 (m, 5H), 1.58 (d, *J* = 7.2 Hz, 3H), 1.37 - 1.30 (m, 1H), 0.70 - 0.63 (m, 2H), 0.43 - 0.36 (m, 2H), 0.07 (s, 9H); and MS-ESI (pos. ion) *m/z*: 583.2 [M+H]⁺.

Step 3: (S)-6-((5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxamido)methyl)picolinic acid dihydrochloride

[00741] To a solution of (S)-6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-methoxyphenyl)thiazole-4-carboxamido)methyl)picolinic acid (174 mg, 0.2918 mmol) in dichloromethane (1 mL) was added a solution of hydrochloric acid in ethyl acetate (4 M, 3 mL). The mixture was stirred at rt for 40 minutes, then filtered. The filter cake was washed with ethyl acetate (0.5 mL × 6), and then dissolved in methanol (5 mL). The solution was concentrated to give a yellow solid (128 mg, 91%).

Compound 64: ¹HNMR (400 MHz, CD₃OD): δ (ppm) 8.47 - 8.42 (m, 1H), 8.35 (d, *J* = 7.6 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.59 (dd, *J* = 4.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 5.43 - 5.35 (m, 1H), 5.00 (d, *J* = 3.2 Hz, 2H), 3.94 (d, *J* = 6.8 Hz, 2H), 3.91 (s, 3H), 1.77 (d, *J* = 7.6 Hz, 3H), 1.35 - 1.24 (m, 1H), 0.66 - 0.59 (m, 2H), 0.40 - 0.34 (m, 2H); and MS-ESI (pos. ion) *m/z*: 483.2 [M+H-2HCl]⁺.

Example 143: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: Methyl 3-(cyclopropylmethoxy)-4-ethoxybenzoate

[00742] To a solution of methyl 3-(cyclopropylmethoxy)-4-hydroxybenzoate (5 g, 22.50 mmol) in DMF (100 mL) were added potassium carbonate (7.77 g, 56.25 mmol) and bromoethane (2.02 mL, 27 mmol). The mixture was stirred at 60 °C for 10.5 hours, then filtered. The filtrate was concentrated and to the residue was added water (50 mL). The resulting mixture was extracted with dichloromethane (100 mL $\times$ 3). The combined organic layers were washed with saturated brine (100 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated to give reddish liquid (5.5 g, 97.7%).

MS (ESI, pos. ion) m/z : 251.2[M+H]⁺.

Step 2: 3-(Cyclopropylmethoxy)-4-ethoxybenzoic acid

[00743] To a solution of methyl 3-(cyclopropylmethoxy)-4-ethoxybenzoate (5.5 g, 21.97 mmol) in a mixed solvent of THF/H₂O (v/v = 2/1, 150 mL) was added a solution of sodium hydroxide (2.2 g, 54.93 mmol) in water (15 mL). The mixture was stirred at 60 °C for 2 hours, then concentrated. To the residue was added concentrated hydrochloric acid to adjust pH to 2-3. The resulting mixture was extracted with dichloromethane (100 mL $\times$ 3). The combined organic layers were washed with saturated brine (100 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated to give a white solid (5.02 g, 96.3%).

¹HNMR (400 MHz, CDCl₃): δ (ppm) 7.78 - 7.70 (m, 1H), 7.60 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.22 - 4.14 (m, 2H), 3.91 (d, J = 6.8 Hz, 2H), 1.53 - 1.45 (m, 3H), 1.39 - 1.28 (m, 1H), 0.69 - 0.61 (m, 2H), 0.41 - 0.34 (m, 2H); and MS-ESI (pos. ion) m/z : 237.3 [M+H]⁺.

Step 3: Methyl 2-(3-(cyclopropylmethoxy)-4-ethoxybenzamido)acetate

[00744] To a solution of 3-(cyclopropylmethoxy)-4-ethoxybenzoic acid (5 g, 21.16 mmol) in anhydrous dichloromethane (150 mL) were added EDCI (6.094 g, 31.74 mmol) and HOBT (4.285 g, 31.74 mmol). The mixture was stirred at 25 °C for 30 minutes, then glycine methyl

ester hydrochloride (3.188 g, 25.40 mmol) was added. To the resulting mixture was added dropwise slowly DIPEA (11.4 mL, 63.48 mmol) in an ice-bath. The mixture was stirred at rt for 16.5 hours. To the reaction mixture was added water (100 mL) and the resulting mixture was extracted with dichloromethane (100 mL $\times$ 2). The combined organic layers were washed with saturated brine (100 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give a white solid (3.93 g, 61.6%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.41 (d, J = 2.0 Hz, 1H), 7.33 (dd, J = 8.2 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.61 (br.s, 1H), 4.22 (d, J = 5.2 Hz, 2H), 4.17 – 4.09 (m, 2H), 3.89 (d, J = 6.8 Hz, 2H), 3.79 (s, 3H), 1.50 - 1.43 (m, 3H), 1.36 - 1.26 (m, 1H), 0.65 - 0.58 (m, 2H), 0.38 - 0.31 (m, 2H); and MS-ESI (pos. ion) m/z : 308.1 $[\text{M}+\text{H}]^+$.

Step 4: Methyl 2-(3-(cyclopropylmethoxy)-4-ethoxyphenylthioamido)acetate

[00745] To a solution of methyl 2-(3-(cyclopropylmethoxy)-4-ethoxybenzamido)acetate (3.93 g, 12.8 mmol) in anhydrous tetrahydrofuran (130 mL) was added Lawesson' reagent (5.18 g, 12.8 mmol). The reaction mixture was stirred at 75 °C for 2 hours. To the reaction mixture was added water (100 mL) and the resulting mixture was extracted with ethyl acetate (100 mL $\times$ 3). The combined organic layers were washed with saturated aqueous sodium carbonate (100 mL $\times$ 3) and saturated brine (100 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a yellow solid (3.704 g, 89.5%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.03 (br.s, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.57 (d, J = 4.4 Hz, 2H), 4.18 – 4.10 (m, 2H), 3.91 (d, J = 6.8 Hz, 2H), 3.84 (s, 3H), 1.50 - 1.43 (m, 3H), 1.38 - 1.23 (m, 1H), 0.66 - 0.60 (m, 2H), 0.39 - 0.33 (m, 2H); and MS-ESI (pos. ion) m/z : 324.2 $[\text{M}+\text{H}]^+$.

Step 5: Methyl 2-(((3-(cyclopropylmethoxy)-4-ethoxyphenyl)(methylthio)methylene)amino)acetate

[00746] To a suspension of trimethyloxonium tetrafluoroborate (3.39 g, 22.90 mmol) in anhydrous dichloromethane (50 mL) was added a solution of methyl 2-(3-(cyclopropylmethoxy)-4-ethoxyphenylthioamido)acetate (3.704 g, 11.45 mmol) in anhydrous dichloromethane (100 mL) at -78 °C. The reaction mixture was stirred at 0 °C for 2

hours, then saturated aqueous sodium bicarbonate (100 mL) was added. The resulting mixture was extracted with dichloromethane (100 mL $\times$ 2). The combined organic layers were washed with ice-water (100 mL $\times$ 3), dried over anhydrous sodium sulfate and concentrated to give reddish liquid (3.86 g, 100%).

MS (ESI, pos. ion) m/z : 338.2 $[M+H]^+$.

Step 6: (S)-Methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxylate

[00747] To a solution of (*S*)-*tert*-butyl (1-fluoro-1-oxopropan-2-yl)carbamate (4.38 g, 22.9 mmol) in anhydrous tetrahydrofuran (50 mL) were added a solution of methyl 2-(((3-(cyclopropylmethoxy)-4-ethoxyphenyl)(methylthio)methylene)amino)acetate (3.86 g, 11.45 mmol) in anhydrous tetrahydrofuran (50 mL) and potassium hexamethyldisilazide (45.8 mL, 1 M in THF) at -78 °C. The mixture was stirred at -78 °C for 1.5 hours, then water (70 mL) was added. The mixture was stirred at 25 °C for 10 minutes and extracted with ethyl acetate (100 mL $\times$ 3). The combined organic layers were washed with brine (100 mL $\times$ 2, 10%), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a light yellow solid (2.69 g, 51%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.57 (dd, J = 8.4 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 5.75 - 5.57 (m, 1H), 4.14 - 4.07 (m, 2H), 3.92 (s, 3H), 3.88 (d, J = 7.2 Hz, 2H), 1.55 (d, J = 6.8 Hz, 3H), 1.52 - 1.49 (m, 3H), 1.28 - 1.22 (m, 1H), 0.67 - 0.60 (m, 2H), 0.40 - 0.34 (m, 2H), 0.06 (s, 9H); MS-ESI (pos. ion) m/z : 461.2 $[M+H]^+$.

Step 7: (S)-5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxylic acid

[00748] To a solution of (*S*)-methyl 5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxylate (1.344 g, 2.918 mmol) in a mixed solvent of THF/ H_2O (v/v = 2/1, 60 mL) was added lithium hydroxide monohydrate (0.613 g, 14.59 mmol). The mixture was stirred at 40 °C for 4.5 hours. To the mixture was added hydrochloric acid (1 M) to adjust pH to 2-3 and the resulting mixture was extracted with ethyl acetate (100 mL $\times$ 3). The combined organic layers were washed with saturated brine (100 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated to give a white solid (1.1 g, 84.5%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.61 (dd, J = 8.4 Hz, 1H), 7.56 (s, 1H), 6.91 (d, J =

8.4 Hz, 1H), 5.50 - 5.35 (m, 1H), 4.19 - 4.09 (m, 2H), 3.92 (d, $J = 7.2$ Hz, 2H), 1.55 (d, $J = 6.8$ Hz, 3H), 1.52 - 1.49 (m, 3H), 1.28 - 1.22 (m, 1H), 0.67 - 0.60 (m, 2H), 0.40 - 0.34 (m, 2H), 0.06 (s, 9H); and MS-ESI (pos. ion) m/z : 447.1 $[M+H]^+$.

Step 8: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00749] To a solution of (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxylic acid (300 mg, 0.6721 mmol) in dichloromethane (20 mL) were added EDCI (193.6 mg, 1.008 mmol) and HOBT (136.1 mg, 1.117 mmol). The mixture was stirred at 25 °C for 30 minutes, then (2,4-difluorophenyl)methanamine (115.3 mg, 0.8065 mmol) and DIPEA (361 μ L, 2.016 mmol) were added. The resulting mixture was stirred at 25 °C for 3 hours. To the reaction mixture was added water (20 mL) and the mixture was extracted with dichloromethane (20 mL $\times$ 2). The combined organic layers were washed with saturated brine (30 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 6/1) to give colorless colloidal liquid (144 mg, 37.5%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.68 (br.s, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.51 (s, 1H), 7.46 - 7.37 (m, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 6.90 - 6.82 (m, 2H), 5.22 - 5.04 (m, 1H), 4.67 - 4.62 (m, 2H), 4.20 - 4.12 (m, 2H), 3.94 (d, $J = 6.8$ Hz, 2H), 1.53 (d, $J = 6.8$ Hz, 3H), 1.51 - 1.46 (m, 3H), 1.36 - 1.32 (m, 1H), 0.69 - 0.62 (m, 2H), 0.42 - 0.37 (m, 2H), 0.07 (s, 9H).

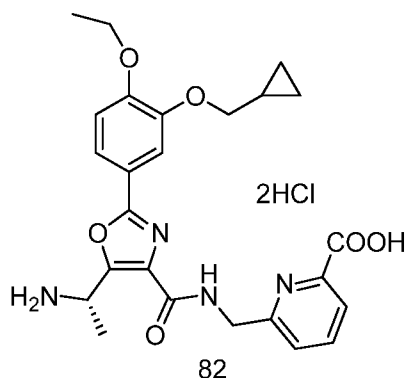
Step 9: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00750] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (140 mg, 0.2449 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The mixture was stirred at rt for 40 minutes, then concentrated. To the residue was added ethyl acetate and the mixture was filtered. The filter cake was washed with ethyl acetate (20 mL $\times$ 5), and then dissolved in methanol (5 mL). The mixture was concentrated to give a white solid (100 mg, 80.4%).

Compound 76: ^1H NMR (400 MHz, CD_3OD): δ (ppm) 7.67 (dd, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 2.4$ Hz, 1H), 7.49 - 7.41 (m, 1H), 7.08 (d, $J = 8.8$ Hz, 1H), 7.00 - 6.90 (m, 2H), 5.15 - 5.07 (m,

1H), 4.61 (s, 2H), 4.19 - 4.11 (m, 2H), 3.92 (d, $J = 6.8$ Hz, 2H), 1.73 (d, $J = 6.4$ Hz, 3H), 1.58 (d, $J = 7.2$ Hz, 3H), 1.47 - 1.41 (m, 3H), 1.35 - 1.25 (m, 1H), 0.66 - 0.60 (m, 2H), 0.39 - 0.33 (m, 2H); and MS-ESI (pos. ion) m/z : 472.2 $[M+H-HCl]^+$.

Example 144: (S)-6-((5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride



Step 1: (S)-Ethyl 6-((5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinate

[00751] To a solution of (S)-5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxylic acid (560 mg, 1.255 mmol) in dichloromethane (30 mL) were added EDCI (361 mg, 1.883 mmol) and HOBT (256 mg, 1.883 mmol). The mixture was stirred at 25 °C for 30 minutes, then ethyl 6-(aminomethyl)picolinate (271 mg, 1.506 mmol) and DIPEA (675 μ L, 3.765 mmol) were added. The resulting mixture was stirred at 25 °C for 3 hours, then water (30 mL) was added. The mixture was extracted with dichloromethane (30 mL $\times$ 2). The combined organic layers were washed with saturated brine (30 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a white solid (319 mg, 99%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.50 (br.s, 1H), 8.17 (d, $J = 6.4$ Hz, 1H), 8.11 - 8.03 (m, 1H), 7.94 - 7.84 (m, 1H), 7.60 (d, $J = 8.4$ Hz, 1H), 7.55 (s, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 5.35 - 5.25 (m, 1H), 5.15 - 5.08 (m, 2H), 4.60 - 4.50 (m, 2H), 4.20 - 4.13 (m, 2H), 3.96 (d, $J = 6.8$ Hz, 2H), 1.60 (d, $J = 7.2$ Hz, 3H), 1.52 - 1.43 (m, 6H), 1.39 - 1.33 (m, 1H), 0.69 - 0.61 (m, 2H), 0.45 - 0.37 (m, 2H), 0.07 (s, 9H); and MS-ESI (pos. ion) m/z : 609.4 $[M+H]^+$.

Step 2: (S)-6-((5-(1-((tert-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid

[00752] To a solution of (S)-ethyl 6-((5-(1-((tert-butoxycarbonyl)amino)ethyl)-2-(3-

(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinate (319 mg, 0.5241 mmol) in a mixed solvent of THF/H₂O (v/v = 2/1, 9 mL) was added lithium hydroxide monohydrate (110 mg, 2.620 mmol). The mixture was stirred at 40 °C for 4.5 hours. To the mixture was added hydrochloric acid (1 M) to adjust pH to 2-3 and the resulting mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with saturated brine (20 mL × 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give a white solid (102 mg, 33.5%).

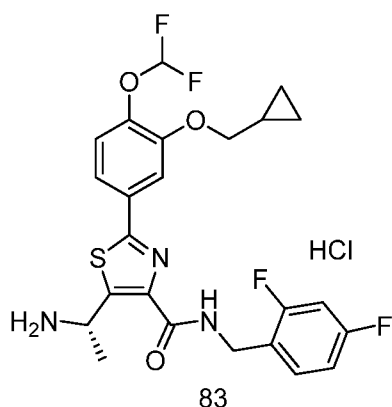
¹HNMR (400 MHz, CDCl₃): δ (ppm) 8.30 (br.s, 1H), 8.18 (d, *J* = 6.8 Hz, 1H), 8.02 – 7.93 (m, 1H), 7.72 - 7.65 (m, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.56 (s, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.66 (br.s, 1H), 5.40 - 5.25 (m, 1H), 4.97 - 4.75 (m, 2H), 4.22 - 4.12 (m, 2H), 4.00 - 3.90 (m, 2H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.52 - 1.46 (m, 3H), 1.39 - 1.30 (m, 1H), 0.70 - 0.60 (m, 2H), 0.45 - 0.36 (m, 2H), 0.07 (s, 9H); and MS-ESI (pos. ion) *m/z*: 581.1 [M+H]⁺.

Step 3: (S)-6-((5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid dihydrochloride

[00753] To a solution of (S)-6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-ethoxyphenyl)oxazole-4-carboxamido)methyl)picolinic acid (102 mg, 0.1756 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The mixture was stirred at rt for 40 minutes, then concentrated. To the residue was added ethyl acetate and the mixture was filtered. The filter cake was washed with ethyl acetate (2 mL × 5), and then dissolved in methanol (5 mL). The solution was concentrated to give a yellow solid (59 mg, 65%).

Compound 82: ¹HNMR (400 MHz, CD₃OD): δ (ppm) 8.22 - 8.07 (m, 2H), 7.85 - 7.75 (m, 1H), 7.69 (dd, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 5.18 - 5.09 (m, 1H), 4.94 - 4.85 (m, 2H), 4.20 - 4.12 (m, 2H), 3.93 (d, *J* = 6.8 Hz, 2H), 1.74 (d, *J* = 6.8 Hz, 3H), 1.49 - 1.41 (m, 3H), 1.39 - 1.23 (m, 1H), 0.67 - 0.60 (m, 2H), 0.40 - 0.34 (m, 2H); and MS-ESI (pos. ion) *m/z*: 481.1 [M+H-2HCl]⁺.

Example 145: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)thiazole-4-carboxamide hydrochloride



Step 1: 3-(Cyclopropylmethoxy)-4-(difluoromethoxy)benzoyl chloride

[00754] To a solution of 3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzoic acid (3.82 g, 14.79 mmol) in anhydrous dichloromethane (100 mL) were added oxalyl dichloride (1.55 mL, 16.27 mmol) and DMF (114 μ L, 1.48 mmol). The mixture was stirred at 25 °C for 3 hours, then concentrated *in vacuo* to give a white solid (4.09 g, 100%).

MS (ESI, pos. ion) m/z : 273.1 $[M-Cl+OCH_3]^+$.

Step 2: (4S)-Ethyl 4-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzamido)-3-oxopentanoate

[00755] To a solution of 3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzoyl chloride (4.09 g, 14.79 mmol) in anhydrous tetrahydrofuran (100 mL) were added (4S)-ethyl 4-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-amino-3-oxopentanoate hydrochloride (5.31 g, 13.40 mmol) in anhydrous DMF (50 mL) and triethylamine (3.72 mL, 26.80 mmol) at -78 °C. The reaction mixture was stirred at 25 °C for 3 hours, then concentrated. The residue was dissolved in EtOAc/Et₂O (v/v = 1/1, 100 mL). The mixture was washed with hydrochloric acid (1 M), aqueous sodium bicarbonate (70 mL $\times$ 2, 10%) and saturated brine (70 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (3.24 g, 38%).

¹HNMR (400 MHz, CDCl₃): δ (ppm) 7.79 - 7.73 (m, 2H), 7.63 - 7.52 (m, 2H), 7.48 (s, 1H), 7.44 - 7.34 (m, 3H), 7.34 - 7.27 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H), 6.88 - 6.51 (m, 1H), 5.74 (d, J = 8.4 Hz, 1H), 5.61 (d, J = 6.4 Hz, 1H), 5.02 - 4.90 (m, 1H), 4.49 - 4.16 (m, 4H), 3.96 - 3.85 (m, 2H), 1.55 (d, J = 7.2 Hz, 3H), 1.36 - 1.24 (m, 4H), 0.69 - 0.56 (m, 2H), 0.38 - 0.28 (m, 2H).

Step 3: (S)-Ethyl 5-(1-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxylate

[00756] To a solution of (4S)-ethyl 4-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(3-

(cyclopropylmethoxy)-4-(difluoromethoxy)benzamido)-3-oxopentanoate (2.6 g, 4.084 mmol) in anhydrous tetrahydrofuran (100 mL) was added Lawesson's reagent (3.3 g, 8.168 mmol). The reaction mixture was stirred at 80 °C for 21 hours. To the mixture was added water (100 mL) and the resulting mixture was extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with saturated brine (100 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a light blue solid (1.86 g).

¹HNMR (400 MHz, CD₃OD): δ (ppm) 7.79 - 7.53 (m, 5H), 7.40 - 7.15 (m, 5H), 7.13 - 6.97 (m, 1H), 6.96 - 6.50 (m, 1H), 5.70 - 5.55 (m, 1H), 4.52 - 4.37 (m, 2H), 4.37 - 4.24 (m, 1H), 4.23 - 4.12 (m, 1H), 3.98 (d, *J* = 6.8 Hz, 2H), 3.88 - 3.76 (m, 2H), 1.55 (d, *J* = 6.0 Hz, 2H), 1.47 - 1.36 (m, 3H), 1.36 - 1.24 (m, 4H), 0.70 - 0.56 (m, 2H), 0.45 - 0.30 (m, 2H).

Step 4: (S)-5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxylic acid

[00757] To a solution of (*S*)-ethyl 5-(1-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxylate (1.86 g, 2.931 mmol) in a mixed solvent of THF/H₂O (v/v = 1/1, 210 mL) was added aqueous sodium hydroxide (1 M, 12.89 mL). The mixture was stirred at 80 °C for 3 hours, then di-*tert*-butyl dicarbonate (768 mg, 3.517 mmol) was added. The resulting mixture was stirred at 33 °C for 4 hours. To the reaction mixture was added hydrochloric acid (1 M) to adjust pH to 2-3, and the mixture was extracted with ethyl acetate (150 mL × 3). The combined organic layers were washed with saturated brine (30 mL × 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a white solid (1.145 g, 80.6%).

¹HNMR (400 MHz, CDCl₃): δ (ppm) 7.50 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.90 - 6.49 (m, 1H), 5.65 - 5.55 (m, 1H), 3.97 (d, *J* = 6.8 Hz, 2H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.36 - 1.28 (m, 1H), 0.72 - 0.65 (m, 2H), 0.43 - 0.36 (m, 2H), 0.07 (s, 9H); and MS-ESI (pos. ion) *m/z*: 485.1 [M+H]⁺.

Step 5: (S)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)thiazol-5-yl)ethyl)carbamate

[00758] To a solution of (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-

(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxylic acid (300 mg, 0.6192 mmol) in dichloromethane (20 mL) were added EDCI (178 mg, 0.9288 mmol) and HOBT (126 mg, 0.9288 mmol). The mixture was stirred at 25 °C for 30 minutes, then (2,4-difluorophenyl)methanamine (106 mg, 0.7430 mmol) and DIPEA (333 µL, 1.858 mmol) were added. The resulting mixture was stirred at 25 °C for 3 hours. To the mixture was added water (20 mL), and the resulting mixture was extracted with dichloromethane (15 mL × 2). The combined organic layers were washed with saturated aqueous sodium carbonate (30 mL × 2) and saturated brine (30 mL × 2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a white solid (285 mg, 75.5%).

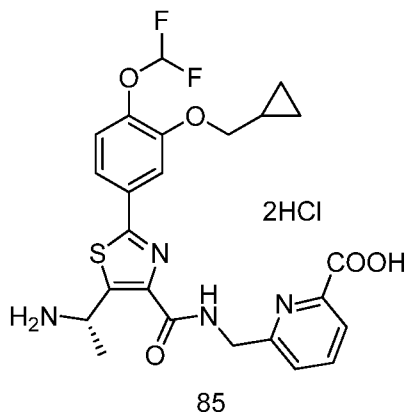
¹HNMR (400 MHz, CDCl₃): δ (ppm) 8.56 (br.s, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.90 - 7.83 (m, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 2 Hz, 1H), 7.41 (dd, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 6.89 - 6.49 (m, 1H), 6.16 (br.s, 1H), 5.65 - 5.45 (m, 1H), 4.55 - 4.45 (m, 2H), 4.01 (d, *J* = 6.8 Hz, 2H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.35 - 1.27 (m, 1H), 0.71 - 0.62 (m, 2H), 0.46 - 0.39 (m, 2H), 0.07 (s, 9H).

Step 6: (S)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)thiazole-4-carboxamide hydrochloride

[00759] To a solution of (S)-tert-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)thiazol-5-yl)ethyl)carbamate (285 mg, 0.4680 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The mixture was stirred at rt for 40 minutes, then concentrated. To the residue was added ethyl acetate and the mixture was filtered. The filter cake was washed with ethyl acetate (1 mL × 6), and then dissolved in methanol (5 mL). The mixture was concentrated to give a white solid (230 mg, 90%).

Compound 83: ¹HNMR (400 MHz, CD₃OD): δ (ppm) 7.81 (d, *J* = 1.6 Hz, 1H), 7.59 (dd, *J* = 8.4 Hz, 1H), 7.51 - 7.43 (m, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.07 - 6.67 (m, 1H), 7.00 - 6.90 (m, 1H), 5.38 - 5.30 (m, 1H), 4.72 - 4.62 (m, 2H), 4.02 (d, *J* = 6.8 Hz, 2H), 1.77 (d, *J* = 6.8 Hz, 3H), 1.38 - 1.26 (m, 1H), 0.69 - 0.62 (m, 2H), 0.43 - 0.37 (m, 2H); and MS-ESI (pos. ion) *m/z*: 510.1 [M+H-HCl]⁺.

Example 146: (S)-6-((5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)

phenyl)thiazole-4-carboxamido)methyl)picolinic acid dihydrochloride**Step 1: (S)-Ethyl 6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxamido)methyl)picolinate**

[00760] To a solution of (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxylic acid (300 mg, 0.6192 mmol) in dichloromethane (20 mL) were added EDCI (178 mg, 0.9288 mmol) and HOBT (126 mg, 0.9288 mmol). The mixture was stirred at 25 °C for 30 minutes, then ethyl 6-(aminomethyl)picolinate (134 mg, 0.7430 mmol) and DIPEA (333 μ L, 1.858 mmol) were added. The resulting mixture was stirred at 25 °C for 3 hours. To the mixture was added water (20 mL) and the resulting mixture was extracted with dichloromethane (15 mL $\times$ 2). The combined organic layers were washed with saturated aqueous sodium carbonate (30 mL $\times$ 2) and saturated brine (30 mL $\times$ 2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a white solid (332 mg, 82.9%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.59 (br.s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.93 - 7.85 (m, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.43 (dd, J = 8.6 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.87 - 6.50 (m, 1H), 6.18 (br.s, 1H), 5.66 - 5.50 (m, 1H), 4.98 - 4.84 (m, 2H), 4.56 - 4.46 (m, 2H), 4.04 (d, J = 7.2 Hz, 2H), 1.61 (d, J = 7.2 Hz, 3H), 1.49 - 1.43 (m, 3H), 1.38 - 1.30 (m, 1H), 0.75 - 0.66 (m, 2H), 0.48 - 0.42 (m, 2H), 0.09 (s, 9H); and MS-ESI (pos. ion) m/z : 647.3 $[\text{M}+\text{H}]^+$.

Step 2: (S)-6-((5-(1-((*tert*-Butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxamido)methyl)picolinic acid

[00761] To a solution of (*S*)-ethyl 6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-

(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxamido)methyl)picolinate (320 mg, 0.4949 mmol) in a mixed solvent of THF/H₂O ((v/v = 2/1, 9 mL) was added lithium hydroxide monohydrate (104 mg, 2.474 mmol). The mixture was stirred at 40 °C for 4.5 hours. To the mixture was added hydrochloric acid (1 M) to adjust pH to 2-3 and the resulting mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with saturated brine (15 mL × 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (petroleum ether) to give a white solid (230 mg, 75%).

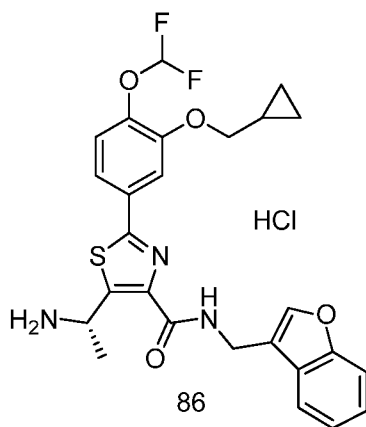
¹HNMR (400 MHz, CDCl₃): δ (ppm) 8.55 (br.s, 1H), 8.19 (d, *J* = 6.4 Hz, 1H), 8.07 - 8.00 (m, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.53 (s, 1H), 7.42 (dd, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.92 - 6.50 (m, 1H), 5.97 (br.s, 1H), 5.70 - 5.55 (m, 1H), 4.94 (d, *J* = 5.2 Hz, 2H), 4.01 (d, *J* = 7.2 Hz, 2H), 1.61 (d, *J* = 6.4 Hz, 3H), 1.38 - 1.30 (m, 1H), 0.72 - 0.64 (m, 2H), 0.47 - 0.39 (m, 2H), 0.09 (s, 9H); and MS-ESI (pos. ion) *m/z*: 619.3 [M+H]⁺.

Step 3: (*S*)-6-((5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxamido)methyl)picolinic acid dihydrochloride

[00762] To a solution of (*S*)-6-((5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxamido)methyl)picolinic acid (220 mg, 0.3557 mmol) in dichloromethane (1 mL) was added hydrogen chloride in ethyl acetate (4 M, 3 mL). The mixture was stirred at rt for 40 minutes. To the mixture was added ethyl acetate and the resulting mixture was filtered. The filter cake was washed with ethyl acetate (1 mL × 6), and then dissolved in methanol (5 mL). The mixture was concentrated to give a light yellow solid (150 mg, 87.8%).

Compound 85: ¹HNMR (400 MHz, CD₃OD): δ (ppm) 8.36 - 8.25 (m, 2H), 8.03 - 7.92 (m, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 7.63 (dd, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.09 - 6.70 (m, 1H), 5.45 - 5.38 (m, 1H), 4.97 (s, 2H), 4.06 (d, *J* = 7.2 Hz, 2H), 1.81 (d, *J* = 5.6 Hz, 3H), 1.41 - 1.30 (m, 1H), 0.72 - 0.65 (m, 2H), 0.46 - 0.42 (m, 2H); and MS-ESI (pos. ion) *m/z*: 519.3 [M+H-2HCl]⁺.

Example 147: (*S*)-5-(1-Aminoethyl)-*N*-(benzofuran-3-ylmethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(4-((benzofuran-3-ylmethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazol-5-yl)ethyl)carbamate

[00763] To a solution of (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxylic acid (200 mg, 0.4129 mmol) in dichloromethane (20 mL) were added EDCI (119 mg, 0.6194 mmol) and HOBT (85 mg, 0.6194 mmol). The mixture was stirred at 25 °C for 30 minutes, then benzofuran-3-ylmethanamine hydrochloride (91 mg, 0.4953 mmol) and DIPEA (259 μ L, 1.445 mmol) were added. The resulting was stirred at 25 °C for 3 hours. To the mixture was added water (20 mL) and the resulting mixture was extracted with dichloromethane (15 mL $\times$ 2). The combined organic layers were washed with saturated aqueous sodium carbonate (30 mL $\times$ 2) and saturated brine (30 mL $\times$ 2), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give a white solid (147 mg, 58%).

^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.72 - 7.66 (m, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 7.38 - 7.30 (m, 2H), 7.29 - 7.23 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.86 - 6.46 (m, 1H), 5.67 - 5.47 (m, 1H), 4.78 (d, J = 6.0 Hz, 2H), 3.91 (d, J = 6.4 Hz, 2H), 1.63 (d, J = 7.2 Hz, 3H), 1.33 - 1.27 (m, 1H), 0.68 - 0.62 (m, 2H), 0.39 - 0.33 (m, 2H), 0.07 (s, 9H); and MS-ESI (pos. ion) m/z : 614.3 $[\text{M}+\text{H}]^+$.

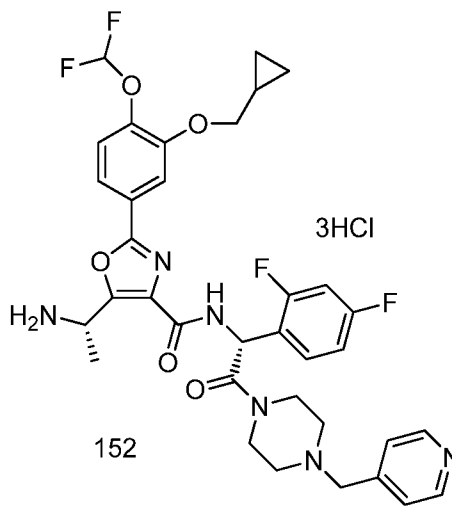
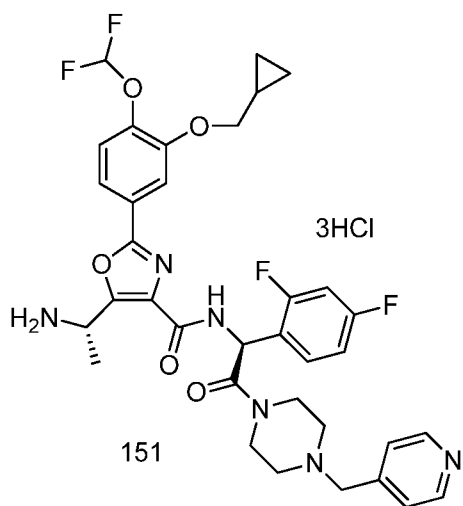
Step 2: (*S*)-5-(1-Aminoethyl)-*N*-(benzofuran-3-ylmethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazole-4-carboxamide hydrochloride

[00764] To a solution of (*S*)-*tert*-butyl (1-(4-((benzofuran-3-ylmethyl)carbamoyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)thiazol-5-yl)ethyl)carbamate (147 mg, 0.2395 mmol) in dichloromethane (1 mL) was added a solution of hydrogen chloride in ethyl acetate (4

M, 3 mL). The mixture was stirred at rt for 40 minutes. To the mixture was added ethyl acetate and the resulting mixture was filtered. The filter cake was washed with ethyl acetate (1 mL $\times$ 6), and then dissolved in CH₃OH (5 mL). The mixture was concentrated to give a white solid (125 mg, 95%).

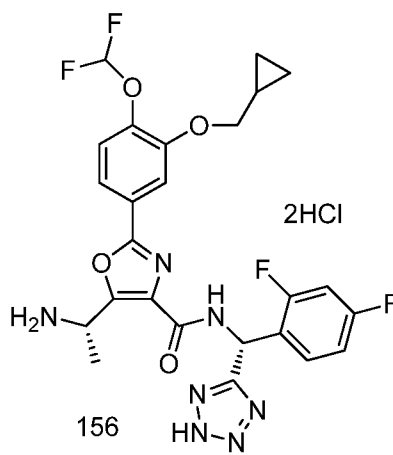
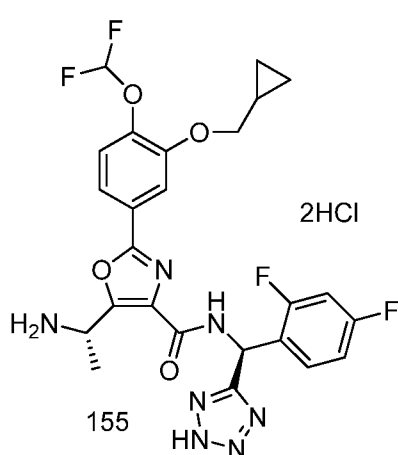
Compound 86: ¹HNMR (400 MHz, CD₃OD): δ (ppm) 7.83 - 7.77 (m, 3H), 7.58 (dd, J = 8.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.35 - 7.23 (m, 3H), 7.08 - 6.69 (m, 1H), 5.43 - 5.35 (m, 1H), 4.81 - 4.77 (m, 2H), 4.02 (d, J = 6.8 Hz, 2H), 1.82 (d, J = 7.2 Hz, 3H), 1.38 - 1.28 (m, 1H), 0.71 - 0.63 (m, 2H), 0.45 - 0.38 (m, 2H); and MS-ESI (pos. ion) m/z : 514.3 [M+H-HCl]⁺.

Example 148: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyridin-4-ylmethyl)piperazin-1-yl)ethyl)oxazole-4-carboxamide trihydrochloride and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyridin-4-ylmethyl)piperazin-1-yl)ethyl)oxazole-4-carboxamide trihydrochloride



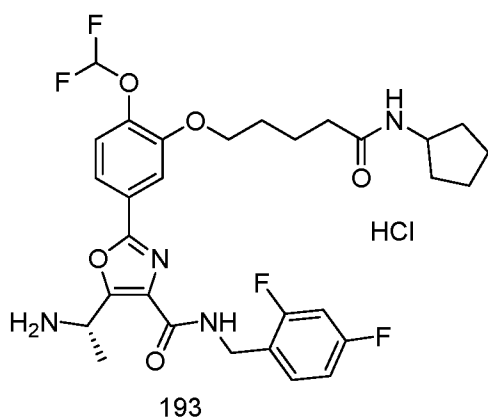
[00765] The compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyridin-4-ylmethyl)piperazin-1-yl)ethyl)oxazole-4-carboxamide trihydrochloride prepared from **Example 60** was further separated and purified to give compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyridin-4-ylmethyl)piperazin-1-yl)ethyl)oxazole-4-carboxamide trihydrochloride as a white solid and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-1-(2,4-difluorophenyl)-2-oxo-2-(4-(pyridin-4-ylmethyl)piperazin-1-yl)ethyl)oxazole-4-carboxamide trihydrochloride as a white solid.

Example 149: 5-((*S*)-1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-(2,4-difluorophenyl)(2*H*-tetrazol-5-yl)methyl)oxazole-4-carboxamide dihydrochloride and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-(2,4-difluorophenyl)(2*H*-tetrazol-5-yl)methyl)oxazole-4-carboxamide dihydrochloride



[00766] The compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((2,4-difluorophenyl)(2*H*-tetrazol-5-yl)methyl)oxazole-4-carboxamide dihydrochloride prepared from **Example 59** was further separated and purified to give compound 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*S*)-(2,4-difluorophenyl)(2*H*-tetrazol-5-yl)methyl)oxazole-4-carboxamide dihydrochloride as a white solid and 5-((*S*)-1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-((*R*)-(2,4-difluorophenyl)(2*H*-tetrazol-5-yl)methyl)oxazole-4-carboxamide dihydrochloride as a white solid.

Example 150: (*S*)-5-(1-Aminoethyl)-2-(3-((5-(cyclopentylamino)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (*S*)-*tert*-Butyl (1-(2-(3-((5-(cyclopentylamino)-5-oxopentyl)oxy)-4-

(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00767] To 15 mL of dichloromethane were added (*S*)-5-(5-(5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-2-yl)-2-(difluoromethoxy)phenoxy)pentanoic acid (0.25 g, 0.39 mmol), cyclopropylamine (40 mg, 0.47 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (112 mg, 0.59 mmol) and 1-hydroxy-7-azabenzotriazole (80 mg, 0.59 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.27 mL, 1.56 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (10 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (240 mg, 86%).

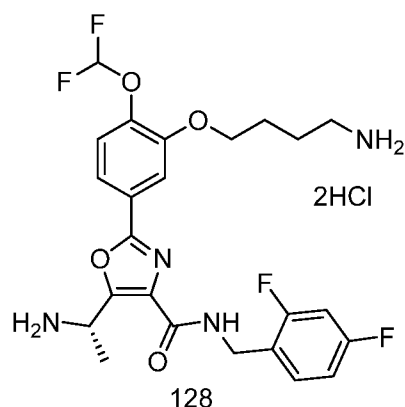
¹H NMR (400 MHz, CDCl₃): δ ppm 7.60 – 7.58 (m, 2H), 7.47 – 7.41 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.91 – 6.86 (m, 2H), 6.63 (t, *J*_{F-H} = 74.5 Hz, 1H), 5.53 – 5.51 (m, 1H), 5.32 – 5.30 (m, 1H), 4.68 – 4.67 (m, 2H), 4.25 – 4.19 (m, 1H), 4.17 – 4.14 (m, 2H), 2.28 (t, *J* = 7.0 Hz, 2H), 2.03 – 1.96 (m, 2H), 1.92 – 1.86 (m, 4H), 1.68 – 1.58 (m, 4H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.45 (s, 9H), 1.38 – 1.35 (m, 1H); and MS-ESI: *m/z* 707.2 [M+H]⁺.

Step 2: (S)-5-(1-Aminoethyl)-2-(3-((5-(cyclopentylamino)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00768] To a solution of (*S*)-*tert*-butyl (1-(2-(3-((5-(cyclopentylamino)-5-oxopentyl)oxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (0.23 g, 0.33 mmol) in dichloromethane (3 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 2 mL). The resulting mixture was stirred at rt for 1.5 hours, then the solvent was removed to give a white solid (209 mg, 99%).

Compound 193: ¹H NMR (400 MHz, CD₃OD): δ ppm 7.82 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.01 – 6.94 (m, 2H), 6.88 (t, *J*_{F-H} = 74.5 Hz, 1H), 5.18 – 5.17 (m, 1H), 4.65 (s, 2H), 4.19 (t, *J* = 5.6 Hz, 2H), 4.13 – 4.09 (m, 1H), 2.31 (t, *J* = 6.8 Hz, 2H), 1.95 – 1.84 (m, 6H), 1.78 (d, *J* = 6.9 Hz, 3H), 1.74 – 1.68 (m, 2H), 1.64 – 1.59 (m, 2H), 1.50 – 1.40 (m, 2H); and MS-ESI: *m/z* 607.2 [M+H-HCl]⁺.

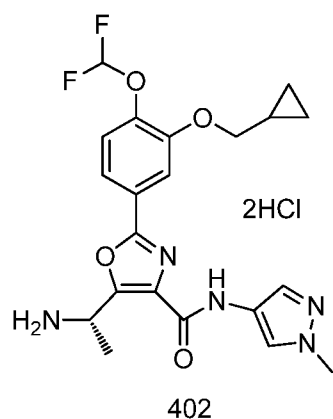
Example 151: (S)-2-(3-(4-Aminobutoxy)-4-(difluoromethoxy)phenyl)-5-(1-aminoethyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide dihydrochloride



[00769] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(4-aminobutoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)carbamate (160 mg, 0.26 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 3 mL). The resulting mixture was stirred at rt for 1 hour, then the solvent was removed to give a white solid (140 mg, 87%). The crude product was further purified by prep-HPLC to give a white solid (53 mg, 36%).

Compound 128: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.86 (d, $J = 1.8$ Hz, 1H), 7.76 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H), 7.52 – 7.48 (m, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.01 – 6.85 (m, 2H), 6.91 (t, $J_{\text{F-H}} = 74.1$ Hz, 1H), 5.20 – 5.16 (m, 1H), 4.65 (s, 2H), 4.25 (t, $J = 5.7$ Hz, 2H), 3.09 (t, $J = 7.5$ Hz, 2H), 2.03 – 1.93 (m, 4H), 1.78 (d, $J = 7.0$ Hz, 3H); and MS-ESI: 511.0 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 152: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)oxazole-4-carboxamide dihydrochloride



Step 1: 1-Methyl-1*H*-pyrazol-4-amine

[00770] To 10 mL of methanol were added 1-methyl-4-nitro-1*H*-pyrazole (500 mg, 3.93 mmol) and Pd/C (10%, 50 mg). The mixture was stirred at rt for 6 hours under hydrogen atmosphere at ordinary pressure, then filtered. The filtrate was concentrated to give red liquid (305 mg, 80%).

^1H NMR (600 MHz, CDCl_3): δ ppm 7.18 (s, 1H), 7.14 (s, 1H), 3.78 (s, 3H); and MS-ESI: m/z 98.20 $[\text{M}+\text{H}]^+$.

Step 2: (*S*)-*tert*-Butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-methyl-1*H*-pyrazol-4-yl)carbamoyl)oxazol-5-yl)ethyl)carbamate

[00771] To 10 mL of dichloromethane were added (*S*)-5-(1-((*tert*-butoxycarbonyl)amino)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)oxazole-4-carboxylic acid (300 mg, 0.64 mmol), 1-methyl-1*H*-pyrazol-4-amine (75 mg, 0.77 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (245 mg, 1.28 mmol) and 1-hydroxy-7-azabenzotriazole (130 mg, 0.96 mmol). To the mixture was added *N,N*-diisopropylethylamine (0.33 mL, 1.92 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 5 hours. The reaction mixture was washed with water (10 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give a light yellow solid (232 mg, 66%).

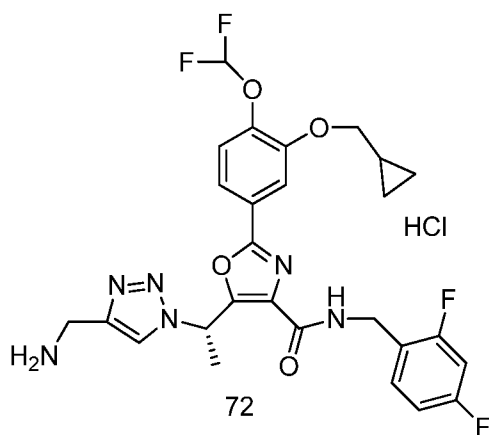
^1H NMR (600 MHz, CDCl_3): δ ppm 7.89 (br.s, 1H), 8.05 (s, 1H), 7.61 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.57 (d, $J = 12.2$ Hz, 2H), 7.25 (d, $J = 8.3$ Hz, 1H), 6.71 (t, $J_{\text{F-H}} = 75.1$ Hz, 1H), 5.32 – 5.35 (m, 1H), 3.99 (d, $J = 6.9$ Hz, 2H), 3.91 (s, 3H), 1.56 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H), 1.31 – 1.36 (m, 1H), 0.68 – 0.71 (m, 2H), 0.40 – 0.43 (m, 2H); and MS-ESI: m/z 546.70 $[\text{M}-\text{H}]^-$.

Step 3: (*S*)-5-(1-Aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)oxazole-4-carboxamide dihydrochloride

[00772] To a solution of (*S*)-*tert*-butyl (1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((1-methyl-1*H*-pyrazol-4-yl)carbamoyl)oxazol-5-yl)ethyl)carbamate (225 mg, 0.41 mmol) in dichloromethane (4 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 4 mL). The resulting mixture was stirred at rt for 30 minutes, then the solvent was removed to give a white solid (212 mg, 97%).

Compound 402: ^1H NMR (600 MHz, CD_3OD): δ ppm 8.20 – 8.23 (m, 1H), 7.95 – 7.99 (m, 1H), 7.81 (s, 1H), 7.73 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz, 1H), 7.31 (d, $J = 8.3$ Hz, 1H), 6.89 (t, $J_{\text{F-H}} = 75.1$ Hz, 1H), 5.20 – 5.24 (m, 1H), 4.03 (d, $J = 6.9$ Hz, 2H), 3.97 (s, 3H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.31 – 1.37 (m, 1H), 0.65 – 0.68 (m, 2H), 0.40 – 0.43 (m, 2H); and MS-ESI: m/z 448.10 $[\text{M}+\text{H}-2\text{HCl}]^+$.

Example 153: (S)-5-(1-(4-(Aminomethyl)-1H-1,2,3-triazol-1-yl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride



Step 1: (S)-5-(1-Azidoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide

[00773] To methanol (25 mL) were added (S)-5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride (312.4 mg, 0.59 mmol), copper(II) sulfate pentahydrate (1.476 mg, 0.059 mmol) and potassium carbonate (244.5 mg, 1.77 mmol). To the mixture was added dropwise slowly a solution of 1H-imidazole-1-sulfonyl azide (204.3 mg, 1.18 mmol) in methanol (5 mL). The resulting mixture was stirred at rt for 12 hours, then concentrated to remove the methanol. To the residue was added saturated aqueous ammonium chloride (20 mL), and the mixture was extracted with ethyl acetate (25 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate for 1 hour. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 3/1) to give a white solid (274 mg, 89.4%).

Step 2: (S)-tert-Butyl ((1-(1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)carbamate

[00774] To 25 mL double-necked round bottom flask were added N-Boc-propargylamine (98.2 mg, 0.633 mmol), anhydrous copper sulfate (13 mg, 0.05 mmol) and sodium ascorbate (20.9 mg, 0.105 mmol). The double-necked round bottom flask was degassed and filled with nitrogen, then a solution of (S)-5-(1-azidoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-N-(2,4-difluorobenzyl)oxazole-4-carboxamide (274 mg, 0.528 mmol) in tetrahydrofuran (16 mL) and distilled water (4 mL) were added in turn. The resulting mixture was stirred at 60 °C for 1

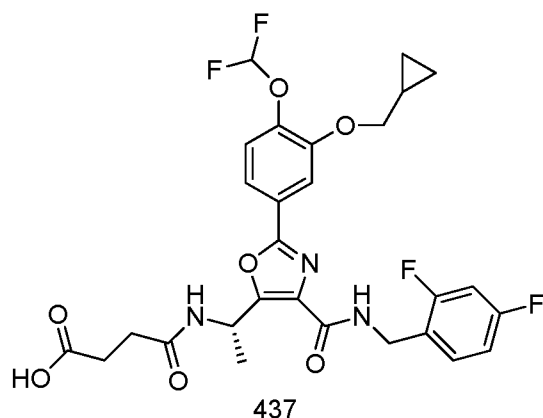
hour. The mixture was concentrated to remove tetrahydrofuran. To the residue was added saturated aqueous ammonium chloride (25 mL), and the mixture was extracted with dichloromethane (25 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate. The organic solvent was removed and the residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (320 mg, 89.9%).

Step 3: (S)-5-(1-(4-(Aminomethyl)-1*H*-1,2,3-triazol-1-yl)ethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4-difluorobenzyl)oxazole-4-carboxamide hydrochloride

[00775] To a solution of (*S*)-*tert*-butyl ((1-(1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)carbamate (385 mg, 0.571 mmol) in dichloromethane (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M, 5 mL). The resulting mixture was stirred overnight at rt, then the solvent was removed to give a white solid (328.4 mg, 94.2%).

Compound 72: ^1H NMR (400 MHz, CD_3OD): δ ppm 8.93 – 8.96 (m, 1H), 8.32 (s, 1H), 7.77 (d, $J = 1.6$ Hz, 1H), 7.69 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.7$ Hz, 1H), 7.43 – 7.49 (m, 1H), 7.32 (d, $J = 8.1$ Hz, 1H), 6.94 – 7.01 (m, 2H), 6.91 (t, $J_{\text{F-H}} = 74.8$ Hz, 1H), 6.82 – 6.87 (m, 1H), 4.60 – 4.63 (m, 2H), 4.27 (s, 2H), 4.03 (d, $J = 6.9$ Hz, 2H), 2.12 (d, $J = 7.2$ Hz, 3H), 1.31 – 1.37 (m, 1H), 0.67 – 0.71 (m, 2H), 0.41 – 0.45 (m, 2H); and MS-ESI: m/z 575.45 $[\text{M}+\text{H}-\text{HCl}]^+$.

Example 154: (S)-4-((1-(2-(3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)amino)-4-oxobutanoic acid



Step 1: (S)-Methyl 4-((1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)amino)-4-oxobutanoate

[00776] To 15 mL of dichloromethane were added (*S*)-5-(1-aminoethyl)-2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-*N*-(2,4

-difluorobenzyl)oxazole-4-carboxamide hydrochloride (250 mg, 0.47 mmol), mono-methyl succinate (74 mg, 0.56 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (135 mg, 0.71 mmol) and 1-hydroxy-7-azabenzotriazole (96 mg, 0.71 mmol). The mixture was stirred at rt for 30 minutes. To the mixture was added *N,N*-diisopropylethylamine (0.33 mL, 1.88 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 15 hours. The reaction mixture was concentrated to remove the organic solvent. The residue was purified by silica gel column chromatography (PE/EtOAc (v/v) = 1/1) to give a white solid (204 mg, 71%).

¹H NMR (400 MHz, CDCl₃): δ ppm 7.59 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.0 Hz, 1H), 7.54 (s, 1H), 7.41 - 7.46 (m, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 6.85 - 6.93 (m, 2H), 6.72 (t, *J*_{F-H} = 74.9 Hz, 1H), 5.57 - 5.61 (m, 1H), 4.67 (d, *J* = 6.2 Hz, 2H), 3.99 (d, *J* = 7.0 Hz, 2H), 3.69 (s, 3H), 2.66 - 2.70 (m, 2H), 2.52 - 2.63 (m, 2H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.31 - 1.37 (m, 1H), 0.68 - 0.73 (m, 2H), 0.40 - 0.44 (m, 2H); and MS-ESI: *m/z* 608.2 [M+H]⁺.

Step 2: (S)-4-((1-(2-(3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)amino)-4-oxobutanoic acid

[00777] To a mixed solvent of ethanol (20 mL) and water (10 mL) were added (*S*)-methyl 4-((1-(2-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-4-((2,4-difluorobenzyl)carbamoyl)oxazol-5-yl)ethyl)amino)-4-oxobutanoate (150 mg, 10.63 mmol) and sodium hydroxide (50 mg, 1.23 mmol). The mixture was stirred at 60 °C for 2 hours, then ethanol was removed. To the residue was added hydrochloric acid (1 M) to adjust the pH to about 1. The mixture was extracted with ethyl acetate (10 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvent was removed to give a white solid (146 mg, 99%).

Compound 437: ¹H NMR (600 MHz, CD₃OD): δ ppm 7.69 (s, 1H), 7.61 (dd, *J*₁ = 8.3 Hz, *J*₂ = 1.7 Hz, 1H), 7.42 - 7.46 (m, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 6.90 - 6.93 (m, 2H), 6.87 (t, *J*_{F-H} = 74.9 Hz, 1H), 5.68 - 5.71 (m, 1H), 4.55 - 4.63 (m, 2H), 3.95 (d, *J* = 7.0 Hz, 2H), 2.58 - 2.61 (m, 2H), 2.51 - 2.55 (m, 2H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.29 - 1.35 (m, 1H), 0.63 - 0.66 (m, 2H), 0.37 - 0.39 (m, 2H); and MS-ESI: *m/z* 594.1 [M+H]⁺.

[00778] The compound number in **Table 2-20** is in one to one correspondence with the number of the compound having specific structure depicted in “**DESCRIPTION OF COMPOUNDS**

OF THE INVENTION”, which is one part of “DETAILED DESCRIPTION OF THE INVENTION”.

[00779] The following compounds in **Table 2** were prepared according to the similar procedure as synthesizing method of the compound of **Example 102** using suitable materials, and parts of spectral data thereof were shown below.

Table 2 Compounds and characterizations of the compounds

Example number	Compound number	Characterizations of the compound
155	9	Compound 9: ^1H NMR (400 MHz, d_6 -DMSO): δ ppm 8.29 (d, $J = 8.6$ Hz, 2H), 7.81 – 7.77 (m, 3H), 7.74 – 7.71 (m, 1H), 7.49 – 7.43 (m, 1H), 7.26 – 7.20 (m, 2H), 7.10 – 7.06 (m, 1H), 5.36 (s, 2H), 5.13 – 5.08 (m, 1H), 4.50 (d, $J = 5.8$ Hz, 2H), 3.90 (s, 3H), 1.63 (d, $J = 6.9$ Hz, 3H); and MS-ESI: m/z 539.1 $[\text{M}+\text{H}-\text{HCl}]^+$.
156	46	Compound 46: ^1H NMR (400 MHz, d_6 -DMSO): δ ppm 8.63 (s, 2H), 7.79 (d, $J = 1.8$ Hz, 1H), 7.69 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.52 – 7.51 (m, 2H), 7.43 – 7.39 (m, 2H), 7.37 – 7.34 (m, 1H), 7.20 (d, $J = 8.6$ Hz, 1H), 5.17 (s, 2H), 5.14 – 5.09 (m, 1H), 4.71 (d, $J = 5.6$ Hz, 2H), 3.86 (s, 3H), 1.64 (d, $J = 6.9$ Hz, 3H); and MS-ESI: m/z 527.2 $[\text{M}+\text{H}-2\text{HCl}]^+$.
157	79	Compound 79: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.76 (dd, $J_1 = 8.5$ Hz, $J_2 = 2.1$ Hz, 1H), 7.64 (d, $J = 2.0$ Hz, 1H), 7.51 – 7.45 (m, 1H), 7.16 (d, $J = 8.6$ Hz, 1H), 7.02 – 6.94 (m, 2H), 5.17 – 5.12 (m, 2H), 4.65 (s, 2H), 4.05 – 3.99 (m, 3H), 3.96 – 3.89 (m, 1H), 3.94 (s, 3H), 2.31 – 2.17 (m, 2H), 1.77 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 474.1 $[\text{M}+\text{H}-\text{HCl}]^+$.
158	80	Compound 80: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.80 (s, 1H), 7.77 (d, $J = 7.6$ Hz, 1H), 7.70 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.62 (d, $J = 2.0$ Hz, 1H), 7.49 (d, $J = 8.2$ Hz, 1H), 7.34 – 7.30 (m, 1H), 7.27 – 7.23 (m, 1H), 7.11 (d, $J = 8.5$ Hz, 1H), 5.19 – 5.14 (m, 1H), 4.75 (s, 2H), 3.93 (s, 3H), 3.95 – 3.92 (m, 2H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.35 – 1.30

Example number	Compound number	Characterizations of the compound
		(m, 1H), 0.70 – 0.56 (m, 2H), 0.47 – 0.32 (m, 2H); and MS-ESI: m/z 462.1 [M+H-HCl] ⁺ .

[00780] The following compounds in **Table 3** were prepared according to the similar procedure as synthesizing method of the compound of **Example 108** using suitable materials, and parts of spectral data thereof were shown below.

Table 3 Compounds and characterizations of the compounds

Example number	Compound number	Characterizations of the compound
159	42	Compound 42: ¹ H NMR (400 MHz, <i>d</i> ₆ -DMSO): δ ppm 8.68 (s, 2H), 7.68 (d, J = 1.9 Hz, 1H), 7.66 (dd, J_1 = 8.4 Hz, J_2 = 1.9 Hz, 1H), 7.52 – 7.51 (m, 2H), 7.44 - 7.40 (m, 2H), 7.38 – 7.34 (m, 1H), 7.19 (d, J = 8.4 Hz, 1H), 5.19 (s, 2H), 4.62 - 4.57 (m, 1H), 3.87 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H); and MS-ESI: m/z 513.1 [M+H-2HCl] ⁺ .
160	43	Compound 43: ¹ H NMR (400 MHz, <i>d</i> ₆ -DMSO): δ ppm 8.68 (s, 2H), 7.62 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 4.62 – 4.57 (m, 1H), 4.06 (t, J = 6.4 Hz, 2H), 3.86 (s, 3H), 1.81 – 1.67 (m, 2H), 1.52 – 1.41 (m, 5H), 0.95 (t, J = 7.3 Hz, 3H); and MS-ESI: m/z 479.0 [M+H-2HCl] ⁺ .

[00781] The following compounds in **Table 4** were prepared according to the similar procedure as synthesizing method of the compound of **Example 1** using suitable materials, and parts of spectral data thereof were shown below.

Table 4 Compounds and characterizations of the compounds

Example number	Compound number	Characterizations of the compound
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Example number	Compound number	Characterizations of the compound
161	2	Compound 2: MS-ESI: m/z 432.17 $[M+H-HCl]^+$.
162	4	Compound 4: MS-ESI: m/z 458.18 $[M+H-HCl]^+$.
163	5	Compound 5: MS-ESI: m/z 472.20 $[M+H-HCl]^+$.
164	8	Compound 8: MS-ESI: m/z 524.19 $[M+H-HCl]^+$.
165	32	Compound 32: MS-ESI: m/z 491.12 $[M+H-2HCl]^+$.
166	78	Compound 78: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.81 (s, 1H), 7.78 - 7.76 (m, 2H), 7.74 (dd, $J_1 = 8.3$ Hz, $J_2 = 2.0$ Hz, 1H), 7.50 - 7.48 (m, 1H), 7.36 - 7.30 (m, 2H), 7.25 (td, $J_1 = 7.5$ Hz, $J_2 = 1.0$ Hz, 1H), 6.86 (t, $J_{F-H} = 74.2$ Hz, 1H), 5.22 - 5.17 (m, 2H), 4.76 (s, 2H), 4.05 - 4.00 (m, 3H), 3.96 - 3.91 (m, 1H), 2.37 - 2.28 (m, 1H), 2.22 - 2.16 (m, 1H), 1.79 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 514.1 $[M+H-HCl]^+$.
167	94	Compound 94: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.91 (s, 1H), 7.75 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H), 7.52 - 7.50 (m, 2H), 7.48 - 7.44 (m, 1H), 7.42 - 7.40 (m, 1H), 7.38 - 7.34 (m, 2H), 7.02 - 6.95 (m, 2H), 6.90 (t, $J_{F-H} = 74.4$ Hz, 1H), 5.29 (s, 2H), 5.18 - 5.13 (m, 1H), 4.66 (s, 2H), 1.77 (d, $J = 7.0$ Hz, 3H); and MS-ESI: m/z 530.2 $[M+H-HCl]^+$.
168	95	Compound 95: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.80 (d, $J = 1.9$ Hz, 1H), 7.71 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.52 - 7.46 (m, 1H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.04 - 6.92 (m, 2H), 6.83 (t, $J_{F-H} = 74.6$ Hz, 1H), 5.20 - 5.14 (m, 1H), 5.08 - 4.97 (m, 1H), 4.65 (s, 2H), 2.12 - 1.80 (m, 6H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.74 - 1.70 (m, 2H); and MS-ESI: m/z 508.2 $[M+H-HCl]^+$.
169	98	Compound 98: ^1H NMR (400 MHz, CD_3OD): δ ppm 7.81 (d, $J = 1.8$ Hz, 1H), 7.72 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.9$ Hz, 1H), 7.52 - 7.46 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.02 - 6.95 (m, 2H), 6.87 (t, $J_{F-H} = 74.6$ Hz, 1H), 5.20 - 5.14 (m, 1H), 4.65 (s, 2H), 4.13 (t, $J = 6.4$ Hz, 2H), 1.96 -

Example number	Compound number	Characterizations of the compound
		1.86 (m, 2H), 1.78 (d, $J = 7.0$ Hz, 3H), 1.11 (t, $J = 7.4$ Hz, 3H); and MS-ESI: m/z 482.1 $[M+H-HCl]^+$.

[00782] The following compounds in **Table 5** were prepared according to the similar procedure as synthesizing method of the compound of **Example 124** using suitable materials, and parts of spectral data thereof were shown below.

Table 5 Compounds and characterizations of the compounds

Example number	Compound number	Characterizations of the compound
170	201	Compound 201: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.83 (s, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.54 - 7.58 (m, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.03 - 7.07 (m, 2H), 6.90 (t, $J_{F-H} = 74.4$ Hz, 1H), 5.90 (d, $J = 3.6$ Hz, 1H), 5.16 - 5.21 (m, 1H), 4.21 - 4.23 (m, 2H), 4.15 - 4.19 (m, 1H), 3.59 - 3.84 (m, 8H), 2.57 - 2.60 (m, 2H), 1.86 - 1.98 (m, 8H), 1.76 (d, $J = 6.6$ Hz, 3H), 1.54 - 1.65 (m, 4H), 1.53 - 1.36 (m, 1H), 0.90 - 0.92 (m, 2H), 0.84 - 0.87 (m, 2H); and MS-ESI: m/z 787.25 $[M+H-HCl]^+$.
171	216	Compound 216: MS-ESI: m/z 773.32 $[M+H-HCl]^+$.
172	224	Compound 224: ^1H NMR (600 MHz, CD_3OD): δ ppm 7.83 (s, 1H), 7.73 (d, $J = 7.9$ Hz, 1H), 7.55 - 7.58 (m, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.01 - 7.08 (m, 2H), 6.91 (t, $J_{F-H} = 74.5$ Hz, 1H), 5.86 (s, 1H), 5.16 - 5.20 (m, 1H), 4.20 - 4.25 (m, 2H), 3.59 - 3.90 (m, 8H), 2.73 (m, 1H), 2.58 (m, 2H), 1.87 - 1.96 (m, 4H), 1.77 (d, $J = 6.3$ Hz, 3H), 1.35 - 1.40 (m, 1H), 0.91 (m, 2H), 0.86 (m, 2H), 0.75 - 0.76 (m, 2H), 0.50 - 0.53 (m, 2H); MS-ESI: m/z 759.25 $[M+H-HCl]^+$.

[00783] The following compounds in **Table 6** were prepared according to the similar procedure

as synthesizing method of the compound of **Example 125** using suitable materials, and parts of spectral data thereof were shown below.

Table 6 Compounds and characterizations of the compounds

Example number	Compound number	Characterizations of the compound
173	234	Compound 234: ^1H NMR (800 MHz, CD_3OD): δ ppm 7.81 (s, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.47 - 7.51 (m, 1H), 7.33 (d, $J = 7.8$ Hz, 1H), 6.95 - 7.00 (m, 2H), 6.88 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.16 - 5.19 (m, 1H), 4.65 (s, 2H), 4.18 - 4.20 (m, 2H), 2.39 - 2.42 (m, 2H), 1.88 - 1.94 (m, 4H), 1.78 (d, $J = 6.6$ Hz, 3H); and MS-ESI: m/z 618.10 $[\text{M}+\text{H}-\text{HCl}]^+$.
174	257	Compound 257: ^1H NMR (600 MHz, CD_3OD): δ ppm 9.18 (d, $J = 7.8$ Hz, 1H), 8.37 - 8.38 (m, 2H), 8.22 - 8.24 (m, 1H), 8.13 (d, $J = 7.8$ Hz, 1H), 8.00 - 8.03 (m, 1H), 7.87 (s, 1H), 7.78 (d, $J = 7.8$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 6.91 (t, $J_{\text{F-H}} = 74.4$ Hz, 1H), 5.17 - 5.23 (m, 2H), 4.24 (s, 2H), 3.64 - 3.69 (m, 6H), 3.58 - 3.59 (m, 2H), 2.53 - 2.56 (m, 2H), 1.96 (s, 2H), 1.86 - 1.87 (m, 2H), 1.78 (d, $J = 5.4$ Hz, 3H); and MS-ESI: m/z 624.30 $[\text{M}+\text{H}-\text{HCl}]^+$.

[00784] The following compounds in **Table 7** were prepared according to the similar procedure as synthesizing method of the compound of **Example 39** using suitable materials, and parts of spectral data thereof were shown below.

Table 7 Compounds and characterizations of the compounds

Example number	Compound number	Characterization of the compound
175	120	Compound 120 : MS-ESI: m/z 587.15 $[\text{M}+\text{H}-2\text{HCl}]^+$.
176	121	Compound 121: MS-ESI: m/z 587.15 $[\text{M}+\text{H}-2\text{HCl}]^+$.
177	122	Compound 122: MS-ESI: m/z 587.15 $[\text{M}+\text{H}-2\text{HCl}]^+$.

[00785] The following compound in **Table 8** was prepared according to the similar procedure as synthesizing method of the compound of **Example 40** using suitable materials, and part of spectral data thereof was shown below.

Table 8 Compound and characterization of the compound

Example number	Compound number	Characterization of the compound
178	108	Compound 108: MS-ESI: m/z 484.20 $[M+H-HCl]^+$.

[00786] The following compound in **Table 9** was prepared according to the similar procedure as synthesizing method of the compound of **Example 65** using suitable materials, and part of spectral data thereof was shown below.

Table 9 Compound and characterization of the compound

Example number	Compound number	Characterization of the compound
179	169	Compound 169: MS-ESI: m/z 552.18 $[M+H-2HCl]^+$.

[00787] The following compounds in **Table 10** were prepared according to the similar procedure as synthesizing method of the compound of **Example 74** using suitable materials, and parts of spectral data thereof were shown below.

Table 10 Compounds and characterizations of the compounds

Example number	Compound number	Characterization of the compound
180	189	Compound 189: MS-ESI: m/z 619.25 $[M+H-HCl]^+$.
181	190	Compound 190: MS-ESI: m/z 619.25 $[M+H-HCl]^+$.

[00788] The following compound in **Table 11** was prepared according to the similar procedure as synthesizing method of the compound of **Example 76** using suitable materials, and part of spectral data thereof was shown below.

Table 11 Compound and characterization of the compound

Example number	Compound number	Characterization of the compound
182	200	Compound 200: MS-ESI: m/z 608.21 $[M+H-HCl]^+$.

[00789] The following compound in **Table 12** was prepared according to the similar procedure as synthesizing method of the compound of **Example 79** using suitable materials, and part of spectral data thereof was shown below.

Table 12 Compound and characterization of the compound

Example number	Compound number	Characterization of the compound
183	197	Compound 197: MS-ESI: m/z 580.20 $[M+H-HCl]^+$.

[00790] The following compounds in **Table 13** were prepared according to the similar procedure as synthesizing method of the compound of **Example 99** using suitable materials, and parts of spectral data thereof were shown below.

Table 13 Compounds and characterizations of the compounds

Example number	Compound number	Characterization of the compound
184	40	Compound 40: MS-ESI: m/z 513.08 $[M+H-2HCl]^+$.
185	84	Compound 84: MS-ESI: m/z 508.18 $[M+H-HCl]^+$.
186	111	Compound 111: MS-ESI: m/z 536.17 $[M+H-HCl]^+$.
187	124	Compound 124: MS-ESI: m/z 508.18 $[M+H-HCl]^+$.
188	126	Compound 126: MS-ESI: m/z 512.15 $[M+H-HCl]^+$.
189	127	Compound 127: MS-ESI: m/z 510.16 $[M+H-HCl]^+$.
190	130	Compound 130: MS-ESI: m/z 511.15 $[M+H-HCl]^+$.
191	131	Compound 131: MS-ESI: m/z 519.16 $[M+H-HCl]^+$.
192	142	Compound 142: MS-ESI: m/z 523.19 $[M+H-2HCl]^+$.
193	143	Compound 143: MS-ESI: m/z 523.19 $[M+H-2HCl]^+$.
194	362	Compound 362: MS-ESI: m/z 487.17 $[M+H-HCl]^+$.
195	363	Compound 363: MS-ESI: m/z 519.18 $[M+H-HCl]^+$.
196	381	Compound 381: MS-ESI: m/z 474.19 $[M+H-HCl]^+$.

Example number	Compound number	Characterization of the compound
197	397	Compound 397: MS-ESI: m/z 459.18 $[M+H-2HCl]^+$.

[00791] The following compounds in **Table 14** were prepared according to the similar procedure as synthesizing method of the compound of **Example 119** using suitable materials, and parts of spectral data thereof were shown below.

Table 14 Compounds and characterizations of the compounds

Example number	Compound number	Characterization of the compound
198	118	Compound 118: MS-ESI: m/z 653.25 $[M+H-HCl]^+$.
199	119	Compound 119: MS-ESI: m/z 652.27 $[M+H-2HCl]^+$.
200	259	Compound 259: MS-ESI: m/z 628.29 $[M+H-HCl]^+$.

[00792] The following compounds in **Table 15** were prepared according to the similar procedure as synthesizing method of the compound of **Example 120** using suitable materials, and parts of spectral data thereof were shown below.

Table 15 Compounds and characterizations of the compounds

Example number	Compound number	Characterization of the compound
201	191	Compound 191: MS-ESI: m/z 539.18 $[M+H-HCl]^+$.
202	204	Compound 204: MS-ESI: m/z 554.19 $[M+H-2HCl]^+$.
203	205	Compound 205: MS-ESI: m/z 610.22 $[M+H-HCl]^+$.

[00793] The following compound in **Table 16** was prepared according to the similar procedure as synthesizing method of the compound of **Example 59** using suitable materials, and part of spectral data thereof was shown below.

Table 16 Compound and characterization of the compound

Example number	Compound number	Characterization of the compound
204	163	Compound 163: MS-ESI: m/z 563.17 $[M+H-3HCl]^+$.

[00794] The following compounds in **Table 17** were prepared according to the procedure described in **Scheme 16** using suitable materials, and parts of spectral data thereof were shown below.

Table 17 Compounds and characterizations of the compounds

Example number	Compound number	Characterization of the compound
205	18	Compound 18: MS-ESI: m/z 474.18 $[M+H-HCl]^+$.
206	116	Compound 116: MS-ESI: m/z 510.16 $[M+H-HCl]^+$.

[00795] The following compounds in **Table 18** were prepared according to the procedure described in **Scheme 17** using suitable materials, and parts of spectral data thereof were shown below.

Table 18 Compounds and characterizations of the compounds

Example number	Compound number	Characterization of the compound
207	117	Compound 117: MS-ESI: m/z 495.15 $[M+H]^+$.
208	125	Compound 125: MS-ESI: m/z 493.13 $[M+H]^+$.

[00796] The following compound in **Table 19** was prepared according to the procedure described in **Scheme 18** using suitable materials, and part of spectral data thereof was shown below.

Table 19 Compound and characterization of the compound

Example number	Compound number	Characterization of the compound
209	123	Compound 123: MS-ESI: m/z 493.18 $[M+H-HCl]^+$.

[00797] The following compound in **Table 20** was prepared according to the procedure described in **Scheme 19** using suitable materials, and part of spectral data thereof was shown below.

Table 20 Compound and characterization of the compound

Example number	Compound number	Characterization of the compound
210	129	Compound 129: MS-ESI: m/z 677.25 $[M+H-2HCl]^+$.

Biological test

[00798] The following methods were used to carry out the biological tests of compounds having formula (I), (I') or (II) of the invention:

[00799] 1. The inhibitory activities of compounds against PDE4B2 enzyme were evaluated by fluorescence polarization. Kits purchased from BPS (BPS, 603343) were used in the experiments, and the experiments were carried out according to the instructions provided by BPS Bioscience, Inc.

[00800] 2. A stocking solution of PDE4B2 enzyme with concentration of 83.33 pg/ μ L was prepared and the final concentration of PDE4B2 enzyme was 27.78 pg/ μ L; a stocking solution of substrate FAM- -Cyclic-3', 5'-AMP with concentration of 300 nM was prepared and the final concentration of substrate FAM- -Cyclic-3', 5'-AMP was 100 nM; each of the PDE4B2 enzyme and substrate was diluted with the BPS kits' own PDE assay buffer; Binding Agent was diluted with the BPS kits' own Binding Agent Diluent to 100-fold. All solutions were prepared before use. The reaction system was shown in **Table 21**:

Table 21 The detection system of IC₅₀ values of compounds against PDE4B2 enzyme

	Test sample	Positive Control	Substrate Control	Blank Negative Control
PDE4B2 enzyme	5 μ L	5 μ L	0 μ L	0 μ L
FAM- -Cyclic-3', 5'-AMP substrate	5 μ L	5 μ L	5 μ L	0 μ L
Tested compound	5 μ L	0 μ L	0 μ L	0 μ L
PDE assay buffer	0 μ L	5 μ L	10 μ L	15 μ L
Incubation at 25 °C for 1 h in incubator				
Binding Agent	15 μ L	15 μ L	15 μ L	15 μ L
Vibration at 25 °C for 1 h in constant temperature vibrator				

[00801] 3. 384-Well plates (Corning, 3575) were used for the test, and test sample wells, positive control wells, substrate control wells and blank negative control wells were set up. PDE4B2 enzyme and substrate FAM-Cyclic-3', 5'-AMP substrate were added to the positive

control well as positive control, FAM-Cyclic-3', 5'-AMP substrate was added to the substrate control well as substrate control, and PDE assay buffer was added to the blank negative control well as blank negative control. All samples and controls were tested at 10 doses in duplicate. After adding the corresponding tested compound, enzyme, substrate and assay buffer according to the sequence in **Table 21**, each well was incubated for 1 h in an incubator at 25 °C. And then, 15 µL of prepared Binding Agent was added to each well and each well was vibrated for 1 h in a constant temperature vibrator at 25 °C. The inhibitory activity of each compound with a different concentration against PDE4B2 enzyme was detected at the wave length of FP485/525 by PHER Astar FS multifunctional microplate reader (BMG). IC₅₀ values were calculated from plots of competitive inhibition curves using Graph Pad Prism 5 software based on several inhibition ratios and the corresponding compound concentrations.

[00802] The inhibitory activities of compounds of the invention against PDE4B2 enzyme were evaluated by the methods described above, and the results were shown in **Table 22**. The compound number in **Table 22** is in one to one correspondence with the number of the compound having specific structure depicted in “**DESCRIPTION OF COMPOUNDS OF THE INVENTION**”, which is one part of “**DETAILED DESCRIPTION OF THE INVENTION**”.

Table 22 Results of inhibitory activities of compounds of the invention against PDE4B2 enzyme

Compound number	IC ₅₀ (nM)	Compound	IC ₅₀ (nM)	Compound number	IC ₅₀ (nM)
Roflumilast	0.60	Compound 2	0.50	Compound 3	2.40
Compound 4	1.58	Compound 5	4.70	Compound 6	19.50
Compound 7	6.50	Compound 9	101.68	Compound 10	29.74
Compound 13	4.25	Compound 15	39.50	Compound 16	33.89
Compound 17	3.31	Compound 21	19.87	Compound 22	3.51
Compound 23	1.86	Compound 24	0.64	Compound 28	101.88
Compound 29	0.40	Compound 30	3.41	Compound 31	2.66
Compound 32	38.12	Compound 33	15.42	Compound 34	3.22
Compound 35	7.20	Compound 36	5.66	Compound 37	1.68

Compound number	IC ₅₀ (nM)	Compound	IC ₅₀ (nM)	Compound number	IC ₅₀ (nM)
Compound 38	3.78	Compound 39	18.28	Compound 41	7.30
Compound 43	146.85	Compound 46	70.74	Compound 49	36.66
Compound 51	3.05	Compound 52	28.83	Compound 54	3.25
Compound 57	4.26	Compound 70	1.75	Compound 73	13.85
Compound 74	4.28	Compound 75	1.60	Compound 76	0.69
Compound 77	0.57	Compound 78	4.01	Compound 79	3.03
Compound 80	6.90	Compound 81	1.39	Compound 82	104.90
Compound 84	6.70	Compound 87	1.66	Compound 88	9.59
Compound 89	0.86	Compound 92	5.00	Compound 95	5.54
Compound 96	34.10	Compound 97	5.52	Compound 98	28.99
Compound 99	4.54	Compound 100	3.55	Compound 101	0.16
Compound 102	1.50	Compound 106	0.29	Compound 113	8.04
Compound 114	10.05	Compound 132	2.98	Compound 133	2.28
Compound 134	8.02	Compound 135	0.32	Compound 137	1.09
Compound 138	2.20	Compound 139	2.51	Compound 140	1.49
Compound 141	4.53	Compound 144	6.21	Compound 146	14.44
Compound 147	52.22	Compound 148	0.36	Compound 150	3.49
Compound 151	12.66	Compound 152	3.47	Compound 154	1.09
Compound 155	0.34	Compound 156	3.75	Compound 158	1.54
Compound 159	5.40	Compound 160	2.24	Compound 161	15.6
Compound 162	3.51	Compound 164	15.97	Compound 165	15.9
Compound 166	1.57	Compound 167	9.59	Compound 168	13.68
Compound 170	31.48	Compound 171	4.09	Compound 172	4.98
Compound 173	15.22	Compound 174	15.41	Compound 176	10.72
Compound 177	6.71	Compound 178	3.15	Compound 179	1.21
Compound 180	5.45	Compound 182	6.10	Compound 183	7.13
Compound 184	17.47	Compound 187	1.77	Compound 188	11.35

Compound number	IC ₅₀ (nM)	Compound	IC ₅₀ (nM)	Compound number	IC ₅₀ (nM)
Compound 193	34.29	Compound 194	24.64	Compound 196	7.39
Compound 198	8.03	Compound 199	25.74	Compound 200	1.84
Compound 201	11.82	Compound 202	0.60	Compound 207	13.32
Compound 208	1.38	Compound 209	6.16	Compound 211	5.83
Compound 212	7.32	Compound 214	0.48	Compound 217	29.81
Compound 219	0.51	Compound 220	0.53	Compound 221	2.29
Compound 222	17.54	Compound 223	6.71	Compound 224	10.48
Compound 225	18.82	Compound 226	0.51	Compound 227	1.32
Compound 228	15.00	Compound 229	5.39	Compound 231	88.73
Compound 232	4.65	Compound 233	33.45	Compound 234	12.37
Compound 235	6.78	Compound 236	26.88	Compound 238	15.41
Compound 239	35.50	Compound 240	73.84	Compound 244	6.61
Compound 256	23.92	Compound 257	13.29	Compound 271	27.13
Compound 313	14.97	Compound 325	8.91	Compound 380	5.32
Compound 383	3.28	Compound 384	0.81	Compound 385	1.73
Compound 402	54.32	Compound 406	0.76	Compound 411	30.56
Compound 412	0.22	Compound 429	0.65	Compound 436	1.39

[00803] It was shown in **Table 22** that, the compounds of the invention had good inhibitory activities against PDE4B2 enzyme in an in vitro screening experiment.

[00804] It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

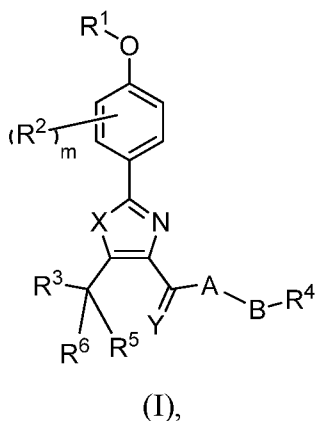
[00805] Reference throughout this specification to “one embodiment”, “an embodiment”, “some embodiments”, “explanatory embodiment”, “an example”, “a specific example” or “some examples”, means that a particular feature, structure, material or characteristic described in

connection with the embodiment or example is included in at least one embodiment or example of the present disclosure. Thus, the appearances of the phrases such as “in some embodiments”, “in one embodiment”, “in an embodiment”, “in another example”, “in an example”, “in a specific examples”, or “in some examples” in various places throughout this specification are not necessarily referring to the same embodiment or example of the present disclosure. Furthermore, the particular features, structures, materials or characteristics may be combined in any suitable manner in one or more embodiments or examples.

[00806] Finally, it should be noted that, other methods can also be used to practice the invention. Although explanatory embodiments have been shown and described, it would be appreciated by those skilled in the art that the above embodiments can not be construed to limit the present disclosure, and changes, equivalent alternatives, and modifications can be made without departing from the scope of the present disclosure. All publications or patents are incorporated herein by reference.

What is claimed is:

1. A compound having Formula (I), or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein

m is 0, 1, 2, 3 or 4;

p is 0, 1 or 2;

each *e* is independently 0, 1 or 2;

each *f* is independently 0, 1 or 2;

X is -N(R⁸)-, -O- or -S-;

Y is O or S;

A is a bond or -N(R⁷)-;

B is -(CR^aR^b)_{*p*};

R¹ is D, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₁₋₆ haloalkyl, R^{9a}R⁹N-C₁₋₆-alkyl-, C₁₋₆ alkyl-C(=O)-, -C(=O)OR^{9c}, -C(=O)-NR⁹R^{9a}, R⁹R^{9a}N-S(=O)₂-, R^{9d}-S(=O)₂-, R^{9d}-S(=O)-C₁₋₆-alkyl-, R⁹R^{9a}N-C(=O)-C₁₋₆-alkyl-, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl or C₁₋₉ heteroaryl-C₁₋₆-alkyl;

each R² is independently H, D, F, Cl, Br, I, CN, NO₂, OH, NH₂, -S(=O)₂Cl, R^{9a}R⁹N-, -C(=O)-R^{9d}, -C(=O)-NR⁹R^{9a}, -OC(=O)-NR⁹R^{9a}, -OC(=O)OR^{9c}, -N(R⁹)-C(=O)-NR⁹R^{9a}, -N(R⁹)-C(=O)OR^{9c}, R^{9d}-S(=O)₂-, R^{9d}-S(=O)₂-N(R^{9a})-, HOC(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkoxy-(CH₂)_{*e*}-C(=O)-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-NH-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-(CH₂)_{*e*}-OC(=O)-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-(CH₂)_{*e*}-NH-C(=O)-C₁₋₆-alkoxy-,

C₃₋₈ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₆₋₁₀ aryl-(CR^cR^d)_f-NH-C₁₋₆-alkoxy-, C₁₋₆ alkyl-NH-C(=O)-C₁₋₆-alkoxy-, R^eR^fN-C(=O)-C₁₋₆-alkoxy-, C₁₋₉ heteroaryl-C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₃₋₈ cycloalkyl-C(=O)-C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₆ alkyl-O-C(=O)-C₁₋₆-alkoxy-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₁₋₆ alkoxy, amino-substituted C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₃₋₈ cycloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₁₀ heterocyclyloxy, C₆₋₁₀ aryl-C₁₋₆-alkoxy, C₃₋₈ cycloalkoxy or C₃₋₈ cycloalkyl-C₁₋₆-alkoxy, and wherein optionally each R² is independently substituted with one or more R¹²;

R³ is D, F, Cl, Br, I, CN, NO₂, NH₂, OH, COOH, C₁₋₆ alkylamino, NH₂-C₁₋₆ alkyl-C₁₋₉-heteroaryl-, NH₂-C₁₋₆ alkyl-C₁₋₉ heteroaryl-C₁₋₆-alkyl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀-aryl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀ aryl-C₁₋₆-alkyl-, C₁₋₆ alkyl-C(=O)-NH-, R¹³O-C(=O)-C₁₋₆-alkyl-C(=O)-NH-, C₃₋₈ cycloalkyl-C(=O)-NH- or -C(=O)-NR⁹R^{9a};

each of R⁵ and R⁶ is independently H, D, F, Cl, Br, I, CN, NO₂, NH₂, OH, COOH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkylamino, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, hydroxy-substituted C₁₋₆ alkyl, mercapto-substituted C₁₋₆ alkyl, carboxy-substituted C₁₋₆ alkyl, NH₂-C₁₋₆ alkyl-C₁₋₉-heteroaryl-, NH₂-C₁₋₆ alkyl-C₁₋₉ heteroaryl-C₁₋₆-alkyl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀-aryl-, NH₂-C₁₋₆ alkyl-C₆₋₁₀ aryl-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₁₋₉ heteroaryl-C₁₋₆-alkyl, C₃₋₈ cycloalkyl-C(=O)-NH-, -C(=O)-NR⁹R^{9a}, C₆₋₁₀ aryl or C₁₋₉ heteroaryl;

or optionally two groups selected from R³, R⁵ and R⁶, together with the carbon atom to which they are attached, form C=O;

R⁴ is C₆₋₁₀ aryl, C₆₋₁₀ aryl-S(=O)₂-, C₁₋₉ heteroaryl, C₁₋₉ heteroaryl-S(=O)₂-, C₆₋₁₀ aryl-C₁₋₆-alkyl or C₁₋₉ heteroaryl-C₁₋₆-alkyl, and wherein R⁴ is optionally substituted with one or more R¹⁴;

each of R⁷ and R⁸ is independently H, D or C₁₋₆ alkyl;

each R^a and R^b is independently H, D, F, Cl, Br, I, CN, OH, NO₂, NH₂, -COOR^{9c}, C₁₋₆ alkyl, -C(=O)-NR⁹R^{9a}, -C₁₋₆-alkyl-C(=O)-NR⁹R^{9a}, -C(=S)-NH₂, amino-substituted C₁₋₆ alkyl, -NH-C(=O)-R^{9b}, -C₁₋₆-alkyl-NH-C(=O)-R^{9b}, -NH-S(=O)₂-C₁₋₆ alkyl, -C₁₋₆-alkyl-NH-S(=O)₂-C₁₋₆ alkyl, -NH-S(=O)₂-C₃₋₈-cycloalkyl, -C₁₋₆-alkyl-NH-S(=O)₂-C₃₋₈ cycloalkyl, -S(=O)₂-C₁₋₆ alkyl, -C₁₋₆-alkyl-S(=O)₂-C₁₋₆ alkyl, C₆₋₁₀ aryl or C₁₋₉ heteroaryl; or R^a and R^b, together with the carbon atom to which they are attached, form a 3- to 8-membered ring;

each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₆ alkyl;

each R^e and R^f is independently H, OH or C₁₋₆ alkyl;

each R⁹, R^{9a}, R^{9b} and R^{9d} is independently H, D, OH, NH₂, -S(=O)₂-NH₂, -C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₆-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₆ alkyl, -S(=O)₂-C₁₋₆ alkyl, -S(=O)₂-C₃₋₈ cycloalkyl, C₁₋₆ haloalkyl, amino-substituted C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₆₋₁₀ aryl, C₂₋₁₀ heterocyclyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₆-alkylamino, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₆₋₁₀ aryloxy, C₂₋₁₀ heterocyclyloxy, C₃₋₈ cycloalkoxy, C₆₋₁₀ arylamino, C₂₋₁₀ heterocyclylamino, C₃₋₈ cycloalkylamino, C₁₋₉ heteroaryl or C₃₋₈ carbocyclyl; or R⁹ and R^{9a}, together with the nitrogen atom to which they are attached, form a 3- to 8-membered ring, and wherein optionally each 3- to 8-membered ring, R⁹, R^{9a}, R^{9b} and R^{9d} is independently substituted with one or more R¹⁵;

each R^{9c} is independently H, D, -C₁₋₆-alkyl-C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₆-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, amino-substituted C₁₋₆ alkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₃₋₈ cycloalkyl, C₂₋₁₀ heterocyclyl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₆₋₁₀ aryl-C₁₋₆-alkyl or C₃₋₈ carbocyclyl;

each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ haloalkylamino, hydroxy-substituted C₁₋₆ alkyl, hydroxy-substituted C₁₋₆ alkoxy or hydroxy-substituted C₁₋₆ alkylamino;

R¹³ is H, D or C₁₋₆ alkyl;

each R¹⁴ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, -C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)-NH₂, -C₁₋₆-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₆-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ haloalkylamino, hydroxy-substituted C₁₋₆ alkyl, hydroxy-substituted C₁₋₆ alkoxy, hydroxy-substituted C₁₋₆ alkylamino or C₃₋₆ cycloalkyl;

each R¹⁵ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₆ alkyl, C₆₋₁₀ aryl, C₁₋₉ heteroaryl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₁₋₉ heteroaryl-C₁₋₆-alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₆-alkyl, C₂₋₁₀ heterocyclyl, C₂₋₁₀ heterocyclyl-C₁₋₆-alkyl, C₃₋₈ cycloalkylcarbonyl, C₂₋₁₀ heterocyclylcarbonyl, C₆₋₁₀ arylcarbonyl or C₁₋₉ heteroarylcarbonyl; and

wherein optionally each R¹, R³, R⁵, R⁶, R⁷, R⁸, R^{9c}, R^a, R^b, R^c, R^d, R^e, R^f, R¹², R¹³, R¹⁴ and R¹⁵ is independently substituted with one or more R, and wherein each R is independently H, D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₆ alkyl or C₁₋₆ alkoxy.

2. The compound according to claim 1, wherein R¹ is D, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, C₂₋₆ heterocyclyl, C₂₋₆ heterocyclyl-C₁₋₄-alkyl, C₁₋₄ haloalkyl, -C(=O)-C₁₋₄ alkyl, -C(=O)OR^{9c}, -C(=O)-NR^{9a}R^{9a}, R^{9a}R^{9a}N-C(=O)-C₁₋₄-alkyl-, C₆₋₁₀ aryl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₁₋₉ heteroaryl or C₃₋₆ cycloalkyl-C₁₋₄-alkyl.

3. The compound according to claim 1, wherein each R^2 is independently H, D, F, Cl, Br, I, CN, NO_2 , OH, NH_2 , $HOC(=O)-C_{1-6}$ -alkoxy-, C_{1-4} alkoxy- $(CH_2)_e-C(=O)-C_{1-6}$ -alkoxy-, C_{2-6} heterocyclyl- $NH-C_{1-6}$ -alkoxy-, C_{2-6} heterocyclyl- $(CH_2)_e-OC(=O)-C_{1-6}$ -alkoxy-, C_{2-6} heterocyclyl- $(CH_2)_e-NH-C(=O)-C_{1-6}$ -alkoxy-, C_{3-6} cycloalkyl- $(CH_2)_e-NH-C(=O)-C_{1-6}$ -alkoxy-, C_{6-10} aryl- $(CR^cR^d)_f-NH-C_{1-6}$ -alkoxy-, C_{1-4} alkyl- $NH-C(=O)-C_{1-6}$ -alkoxy-, $R^eR^fN-C(=O)-C_{1-6}$ -alkoxy-, C_{1-5} heteroaryl- C_{2-6} heterocyclyl- $C(=O)-C_{1-6}$ -alkoxy-, C_{3-6} cycloalkyl- $C(=O)-C_{2-6}$ heterocyclyl- $C(=O)-C_{1-6}$ -alkoxy-, $NH_2-C(=O)-C_{1-6}$ -alkoxy-, C_{1-6} alkyl- $OC(=O)-(CR^cR^d)_f-NH-C(=O)-C_{1-6}$ -alkoxy-, $NH_2-NH-C(=O)-C_{1-6}$ -alkoxy-, $NH_2-C(=O)-(CR^cR^d)_f-NH-C(=O)-C_{1-6}$ -alkoxy-, C_{1-4} alkyl- $S(=O)_2-NH-C(=O)-C_{1-6}$ -alkoxy-, C_{1-4} alkyl- $O-C(=O)-C_{1-6}$ -alkoxy-, $NH_2-S(=O)_2-NH-C(=O)-C_{1-6}$ -alkoxy-, C_{2-6} heterocyclyl- $C(=O)-C_{1-6}$ -alkoxy-, C_{6-10} aryl, C_{1-5} heteroaryl, C_{1-6} alkoxy, amino-substituted C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-4} alkylamino, C_{3-6} cycloalkyl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} heterocyclyloxy, C_{6-10} aryl- C_{1-4} -alkoxy, C_{3-6} cycloalkoxy or C_{3-6} cycloalkyl- C_{1-4} -alkoxy, and wherein optionally each R^2 is independently substituted with one or more R^{12} ;

each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C_{1-4} alkyl;

each R^e and R^f is independently H, OH or C_{1-4} alkyl; and

each R^{12} is independently D, F, Cl, Br, I, CN, NO_2 , OH, NH_2 , COOH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylamino, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkylamino, hydroxy-substituted C_{1-4} alkyl, hydroxy-substituted C_{1-4} alkoxy or hydroxy-substituted C_{1-4} alkylamino.

4. The compound according to claim 1, wherein R^3 is D, F, Cl, Br, I, CN, NO_2 , NH_2 , OH, COOH, C_{1-4} alkylamino, NH_2-C_{1-4} alkyl- C_{1-5} -heteroaryl-, NH_2-C_{1-4} alkyl- C_{1-5} heteroaryl- C_{1-4} -alkyl-, NH_2-C_{1-4} alkyl- C_{6-10} -aryl-, NH_2-C_{1-4} alkyl- C_{6-10} aryl- C_{1-4} -alkyl-, C_{1-4} alkyl- $C(=O)-NH-$, $R^{13}O-C(=O)-C_{1-4}$ alkyl- $C(=O)-NH-$, C_{3-6} cycloalkyl- $C(=O)-NH-$ or $-C(=O)-NR^9R^{9a}$;

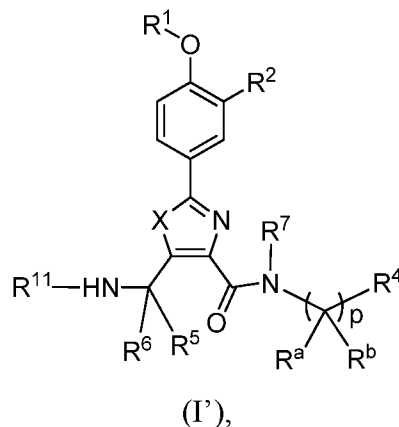
each of R^5 and R^6 is independently H, D, F, Cl, Br, I, CN, NO_2 , NH_2 , OH, COOH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkylamino, C_{1-4} alkoxy, C_{1-4} haloalkoxy, hydroxy-substituted C_{1-4} alkyl, mercapto-substituted C_{1-4} alkyl, carboxy-substituted C_{1-4} alkyl, NH_2-C_{1-4} alkyl- C_{1-5} -heteroaryl-, NH_2-C_{1-4} alkyl- C_{1-5} heteroaryl- C_{1-4} -alkyl-, NH_2-C_{1-4} alkyl- C_{6-10} -aryl-, NH_2-C_{1-4} alkyl- C_{6-10} aryl- C_{1-4} -alkyl-, C_{3-6} cycloalkyl, C_{6-10} aryl- C_{1-4} -alkyl, C_{3-6} cycloalkyl- $C(=O)-NH-$, $-C(=O)-NR^9R^{9a}$, C_{6-10} aryl or C_{1-5} heteroaryl;

or optionally two groups selected from R^3 , R^5 and R^6 , together with the carbon atom to which they are attached, form $C=O$;

each of R^7 and R^8 is independently H, D or C_{1-4} alkyl; and

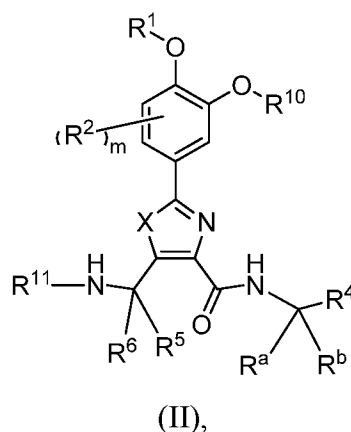
R^{13} is H, D or C_{1-4} alkyl.

5. The compound according to claim 1 having Formula (I'), or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein R^{11} is H, C_{1-4} alkyl, C_{1-4} alkyl-C(=O)-, $R^{13}O-C(=O)-C_{1-4}$ alkyl-C(=O)- or C_{3-6} cycloalkyl-C(=O)-.

6. The compound according to claim 1 having Formula (II), or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



wherein

m is 0, 1, 2 or 3;

R^{10} is H, $HOC(=O)-C_{1-6}$ -alkyl-, C_{1-6} alkoxy- $(CH_2)_e-C(=O)-C_{1-6}$ -alkyl-, C_{2-10} heterocyclyl-NH- C_{1-6} -alkyl-, C_{2-10} heterocyclyl- $(CH_2)_e-OC(=O)-C_{1-6}$ -alkyl-, C_{2-10} heterocyclyl- $(CH_2)_e-NH-C(=O)-C_{1-6}$ -alkyl-, C_{3-8} cycloalkyl- $(CH_2)_e-NH-C(=O)-C_{1-6}$ -alkyl-, C_{6-10} aryl- $(CR^cR^d)_f-NH-C_{1-6}$ -alkyl-, C_{1-6} alkyl-NH-C(=O)- C_{1-6} -alkyl-, $R^eR^fN-C(=O)-C_{1-6}$ -alkyl-, C_{1-9} heteroaryl- C_{2-10} heterocyclyl-C(=O)- C_{1-6} -alkyl-, C_{3-8} cycloalkyl-C(=O)- C_{2-10} heterocyclyl-C(=O)- C_{1-6} -alkyl-, $NH_2-C(=O)-C_{1-6}$ -alkyl-, C_{1-6} alkyl-OC(=O)- $(CR^cR^d)_f-NH-C(=O)-C_{1-6}$ -alkyl-, $NH_2-NH-C(=O)-C_{1-6}$ -alkyl-,

NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₆ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₆ alkyl-O-C(=O)-C₁₋₆-alkyl-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₂₋₁₀ heterocyclyl-C(=O)-C₁₋₆-alkyl-, amino-substituted C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl, C₂₋₁₀ heterocyclyl, C₆₋₁₀ aryl-C₁₋₆-alkyl, C₃₋₈ cycloalkyl or C₃₋₈ cycloalkyl-C₁₋₆-alkyl, and wherein R¹⁰ is optionally substituted with one or more R¹²; and

R¹¹ is H, C₁₋₄ alkyl, C₁₋₄ alkyl-C(=O)-, R¹³O-C(=O)-C₁₋₄ alkyl-C(=O)- or C₃₋₆ cycloalkyl-C(=O)-.

7. The compound according to claim 1, 5 or 6, wherein the pharmaceutically acceptable salt is hydrochloride, hydrobromide, sulfate, nitrate, phosphate, acetate, maleate, succinate, mandelate, fumarate, malonate, malate, 2-hydroxy propionate, pyruvate, oxalate, 2-hydroxy acetate, salicylate, glucuronate, galacturonate, citrate, tartrate, aspartate, glutamate, benzoate, cinnamate, *p*-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, trifluoromethanesulfonate or a combination thereof.

8. The compound according to claim 1, 5 or 6, wherein R¹ is methyl, ethyl, propyl, *i*-propyl, halogenated methyl, halogenated ethyl, halogenated propyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, oxetanylmethyl, oxetanylethyl, tetrahydrofuryl, tetrahydrofurylmethyl, tetrahydrofurylethyl, phenyl, benzyl, phenylethyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

9. The compound according to claim 1, 5 or 6, wherein each R² is independently H, D, F, Cl, Br, I, CN, NO₂, OH, NH₂, methoxy, ethoxy, propoxy, *i*-propoxy, butoxy, *i*-butoxy, *t*-butoxy, cyclopropoxy, cyclobutoxy, cyclopentoxo, cyclohexoxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutylmethoxy, cyclobutylethoxy, cyclopentylmethoxy, cyclopentylethoxy, cyclohexylmethoxy, cyclohexylethoxy, oxetanyloxy, tetrahydrofuryloxy, benzyloxy, phenylethoxy, HOC(=O)-C₁₋₆-alkoxy-, C₁₋₃ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkyl-O-C(=O)-C₁₋₆-alkoxy-, C₂₋₄ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkoxy-, C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ heteroaryl-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, C₃₋₆ cycloalkyl-C(=O)-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-C₁₋₆-alkoxy-, NH₂-NH-C(=O)-C₁₋₆-alkoxy-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkoxy-, R^eR^fN-C(=O)-C₁₋₆-alkoxy-, C₁₋₄ alkyl-OC(=O)-(CR^cR^d)_f-NH-C₁₋₆-alkoxy-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₁₋₃ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkoxy-, C₃₋₆

cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, C₂₋₄ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkoxy-, amino-substituted C₁₋₆ alkoxy, C₂₋₄ heterocyclyl-NH-C₁₋₆-alkoxy- or phenyl-(CR^cR^d)_f-NH-C₁₋₆-alkoxy-, and wherein optionally each R² is independently substituted with one or more R¹²;

each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₃ alkyl;

each R^e and R^f is independently H, OH or C₁₋₃ alkyl; and

each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, hydroxy-substituted methyl or halogenated methyl.

10. The compound according to claim 1, 5 or 6, wherein each of R⁵ and R⁶ is independently H, D, F, Cl, Br, I, NH₂, methyl, ethyl, propyl, *i*-propyl, hydroxy-substituted methyl, phenyl, benzyl or phenylethyl.

11. The compound according to claim 1, 5 or 6, wherein R⁴ is C₆₋₁₀ aryl, C₆₋₁₀ aryl-S(=O)₂-, C₁₋₉ heteroaryl, C₁₋₉ heteroaryl-S(=O)₂-, C₆₋₁₀ aryl-C₁₋₄-alkyl or C₁₋₉ heteroaryl-C₁₋₄-alkyl, and wherein R⁴ is optionally substituted with one or more R¹⁴; and

each R¹⁴ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, -C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)O-C₁₋₄ alkyl, -C₁₋₄-alkyl-O-C(=O)-C₁₋₄ alkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylamino, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, C₁₋₄ haloalkylamino, hydroxy-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkoxy, hydroxy-substituted C₁₋₄ alkylamino or C₃₋₆ cycloalkyl.

12. The compound according to claim 11, wherein R⁴ is phenyl, naphthyl, thiazolyl, thienyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, oxadiazolyl, pyridyl, pyrid-2-yl-*N*-oxide, pyrid-4-yl-*N*-oxide, pyrimidyl, pyrazinyl, quinolyl, isoquinolyl, quinazolyl, naphthyridinyl, furo[3,2-*c*]pyridinyl, furo[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[2,3-*c*]pyridinyl, benzoxadiazolyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, quinoxalinyl, benzofuranyl, pyridopyrazinyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, 1,3-benzodioxolanyl, 2,3-dihydrobenzofuranyl, thieno[3,2-*b*]pyridinyl, thieno[2,3-*c*]pyridinyl, thieno[2,3-*b*]pyridinyl, 1,4-benzdioxanyl, 1,2,3,4-tetrahydroquinolin-2-yl or benzenesulfonyl, and wherein R⁴ is optionally substituted with one or more R¹⁴; and

each R¹⁴ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, -C(=O)-NH₂, -C₁₋₃-alkyl-C(=O)-NH₂, -C₁₋₃-alkyl-C(=O)O-C₁₋₄ alkyl, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, methamino or ethylamino.

13. The compound according to claim 1, 5 or 6, wherein each R^a and R^b is independently H,

D, F, Cl, Br, I, CN, OH, NO₂, NH₂, -COOR^{9c}, C₁₋₄ alkyl, -C(=O)-NR⁹R^{9a}, -C₁₋₄-alkyl-C(=O)-NR⁹R^{9a}, -C(=S)-NH₂, amino-substituted C₁₋₄ alkyl, -NH-C(=O)-R^{9b}, -C₁₋₄-alkyl-NH-C(=O)-R^{9b}, -NH-S(=O)₂-C₁₋₄ alkyl, -C₁₋₄-alkyl-NH-S(=O)₂-C₁₋₄ alkyl, -NH-S(=O)₂-C₃₋₆ cycloalkyl, -C₁₋₄-alkyl-NH-S(=O)₂-C₃₋₆ cycloalkyl, -S(=O)₂-C₁₋₄ alkyl, -C₁₋₄-alkyl-S(=O)₂-C₁₋₄ alkyl, C₆₋₁₀ aryl or C₁₋₅ heteroaryl; or R^a and R^b, together with the carbon atom to which they are attached, form a 3- to 6-membered ring;

each R⁹, R^{9a} and R^{9b} is independently H, D, OH, NH₂, -S(=O)₂-NH₂, -C(=O)-NH₂, -C₁₋₄ alkyl-C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)O-C₁₋₆ alkyl, -C₁₋₄-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₄ alkyl, -S(=O)₂-C₁₋₄ alkyl, -S(=O)₂-C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, amino-substituted C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₆ alkylamino, C₆₋₁₀ aryl, C₂₋₆ heterocyclyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₄-alkylamino, C₃₋₆ cycloalkyl-C₁₋₄-alkyl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₆₋₁₀ aryloxy, C₂₋₆ heterocyclyloxy, C₃₋₆ cycloalkoxy, C₆₋₁₀ arylamino, C₂₋₆ heterocyclylamino, C₃₋₆ cycloalkylamino, C₁₋₅ heteroaryl or C₃₋₆ carbocyclyl; or R⁹ and R^{9a}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered ring, and wherein optionally each 3- to 6-membered ring, R⁹, R^{9a} and R^{9b} is independently substituted with one or more R¹⁵;

each R^{9c} is independently H, D, -C₁₋₄-alkyl-C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)O-C₁₋₄ alkyl, -C₁₋₄-alkyl-O-C(=O)-C₁₋₆ alkyl, C₁₋₅ alkyl, C₁₋₄ haloalkyl, amino-substituted C₁₋₄ alkyl, C₆₋₁₀ aryl, C₁₋₅ heteroaryl, C₃₋₆ cycloalkyl, C₂₋₆ heterocyclyl, C₃₋₆ cycloalkyl-C₁₋₄ alkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl or C₃₋₆ carbocyclyl; and

each R¹⁵ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₄ alkyl, C₆₋₁₀ aryl, C₁₋₅ heteroaryl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₁₋₅ heteroaryl-C₁₋₄-alkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₄-alkyl, C₂₋₆ heterocyclyl, C₂₋₆ heterocyclyl-C₁₋₄-alkyl, C₃₋₆ cycloalkylcarbonyl, C₂₋₆ heterocyclylcarbonyl, C₆₋₁₀ arylcarbonyl or C₁₋₅ heteroarylcarbonyl.

14. The compound according to claim 13, wherein each R^a and R^b is independently H, D, F, Cl, Br, I, CN, OH, NO₂, NH₂, -COOR^{9c}, methyl, ethyl, propyl, isopropyl, -C(=O)-NR⁹R^{9a}, -C(=S)-NH₂, aminomethyl, aminoethyl, -C₁₋₃-alkyl-NH-C(=O)-R^{9b}, -C₁₋₃-alkyl-NH-S(=O)₂-C₃₋₆ cycloalkyl, -C₁₋₃-alkyl-S(=O)₂-C₁₋₃ alkyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, oxadiazolyl, phenyl, pyridyl or pyrimidyl; or R^a and R^b, together with the carbon atom to which they are attached, form oxetane or 1,3-dioxacyclopentane;

each R⁹, R^{9a} and R^{9b} is independently H, D, OH, NH₂, -S(=O)₂-NH₂, -C(=O)-NH₂, -C₁₋₃-alkyl-C(=O)-NH₂, -C₁₋₄-alkyl-C(=O)O-C₁₋₄ alkyl, -C₁₋₃-alkyl-O-C(=O)-C₁₋₃ alkyl, methyl, ethyl, propyl, isopropyl, -S(=O)₂-C₁₋₃ alkyl, -S(=O)₂-cyclopropyl, -S(=O)₂-cyclobutyl, -S(=O)₂-cyclopentyl, -S(=O)₂-cyclohexyl, C₁₋₄ haloalkyl, amino-substituted C₁₋₄ alkyl, methoxy,

ethoxy, propoxy, *i*-propoxy, methylamino, dimethylamino, ethylamino, propylamino, isopropylamino, phenyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylmethylamino, cyclobutylmethylamino, cyclopentylmethylamino, benzyl, phenylethyl, phenoxy, cyclopropoxy, cyclobutoxy, cyclopentoxo, phenylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; or R⁹ and R^{9a}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered ring selected from azetidine, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, and wherein optionally each 3- to 6-membered ring, R⁹, R^{9a} and R^{9b} is independently substituted with one or more R¹⁵;

each R^{9c} is independently H, D, -C₁₋₃-alkyl-C(=O)-NH₂, -C₁₋₃-alkyl-C(=O)-O-C₁₋₃ alkyl, -C₁₋₃-alkyl-O-C(=O)-C₁₋₄ alkyl, methyl, ethyl, propyl, isopropyl, C₁₋₄ haloalkyl, amino-substituted C₁₋₄ alkyl, phenyl, benzyl, phenylethyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; and

each R¹⁵ is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, methyl, ethyl, propyl, phenyl, pyridyl, pyrimidyl, thiazolyl, thienyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, oxadiazolyl, benzyl, phenylethyl, pyridylmethyl, pyrimidylmethyl, pyridylethyl, pyrimidylethyl, benzoyl, cyclopropylcarbonyl, cyclobutylcarbonyl or cyclopentylcarbonyl.

15. The compound according to claim 6, wherein R¹⁰ is H, HOC(=O)-C₁₋₆-alkyl-, C₁₋₄ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-NH-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₆₋₁₀ aryl-(CR^cR^d)_f-NH-C₁₋₆-alkyl-, C₁₋₄ alkyl-NH-C(=O)-C₁₋₆ alkyl-, R^eR^fN-C(=O)-C₁₋₆-alkyl-, C₁₋₅ heteroaryl-C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl-C(=O)-C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-C₁₋₆ alkyl-, C₁₋₆ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, NH₂-NH-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-O-C(=O)-C₁₋₄-alkyl-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₂₋₆ heterocyclyl-C(=O)-C₁₋₆-alkyl-, amino-substituted C₁₋₆ alkyl, C₁₋₆ haloalkyl, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, C₂₋₆ heterocyclyl, C₆₋₁₀ aryl-C₁₋₄-alkyl, C₃₋₆ cycloalkyl or C₃₋₆ cycloalkyl-C₁₋₄-alkyl, and wherein R¹⁰ is optionally substituted with one or more R¹²;

each R^c and R^d is independently H, OH, CN, F, Cl, Br, I or C₁₋₃ alkyl;

each of R^e and R^f is independently H, OH or C₁₋₃ alkyl; and

each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkylamino, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, C₁₋₃ haloalkylamino, hydroxy-substituted C₁₋₃ alkyl, hydroxy-substituted C₁₋₃ alkoxy or hydroxy-substituted C₁₋₃ alkylamino.

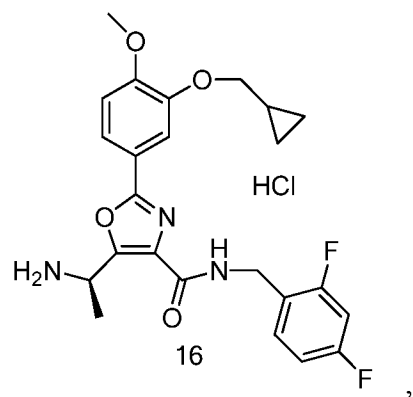
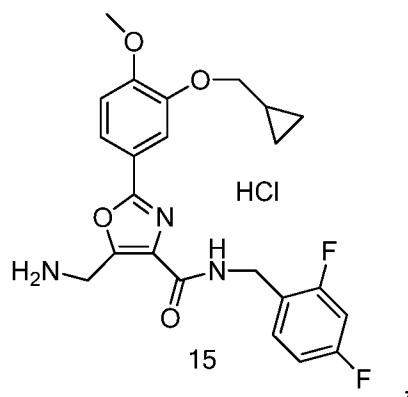
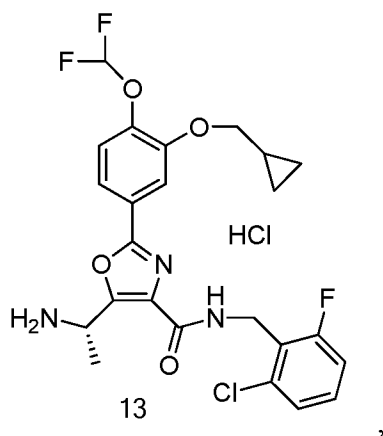
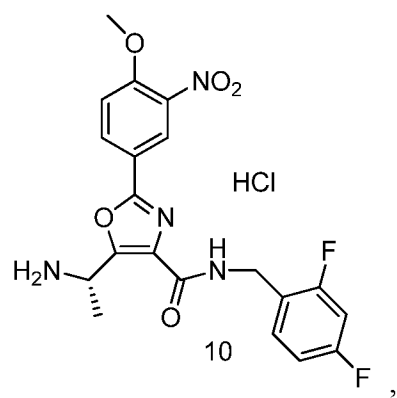
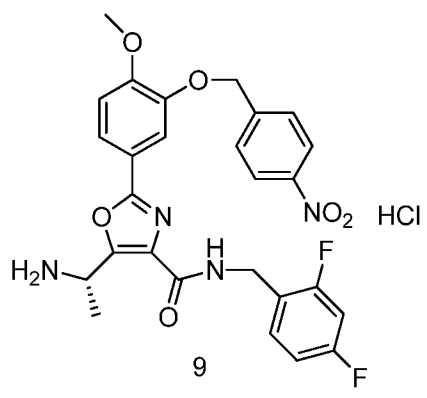
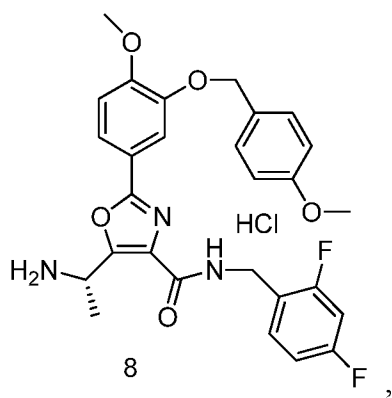
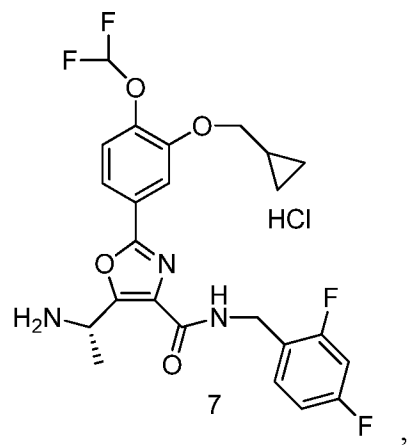
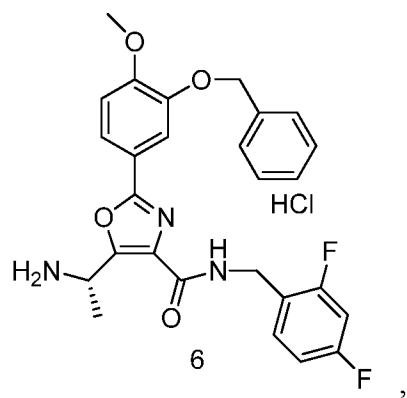
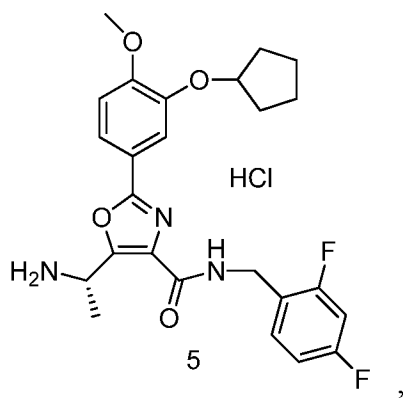
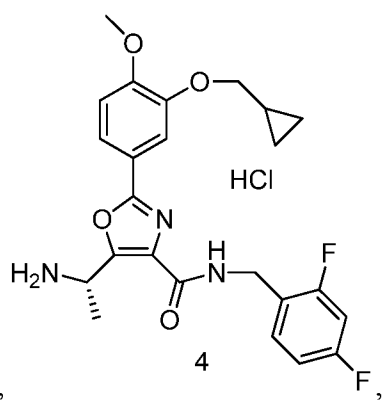
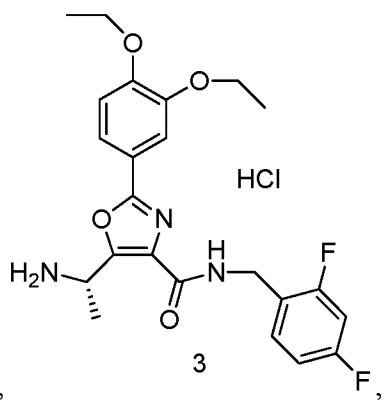
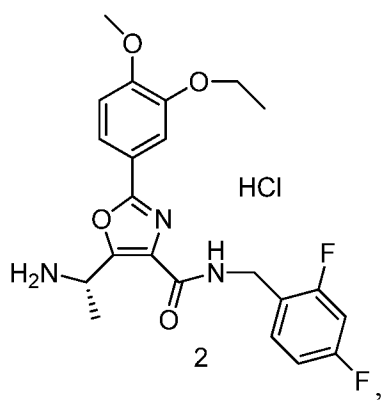
16. The compound according to claim 15, wherein R¹⁰ is H, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, oxetanyl, tetrahydrofuranyl, benzyl, phenylethyl, HOC(=O)-C₁₋₆-alkyl-, C₁₋₃ alkoxy-(CH₂)_e-C(=O)-C₁₋₆-alkyl-, C₂₋₄ heterocyclyl-(CH₂)_e-OC(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-O-C(=O)-C₁₋₄-alkyl-, C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkyl-, C₁₋₄ heteroaryl-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl-C(=O)-C₂₋₄ heterocyclyl-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-C₁₋₆-alkyl-, NH₂-NH-C(=O)-C₁₋₆-alkyl-, NH₂-C(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, R^eR^fN-C(=O)-C₁₋₆-alkyl-, C₁₋₄ alkyl-OC(=O)-(CR^cR^d)_f-NH-C(=O)-C₁₋₆-alkyl-, NH₂-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₁₋₃ alkyl-S(=O)₂-NH-C(=O)-C₁₋₆-alkyl-, C₃₋₆ cycloalkyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, C₂₋₄ heterocyclyl-(CH₂)_e-NH-C(=O)-C₁₋₆-alkyl-, amino-substituted C₁₋₆ alkyl, C₂₋₄ heterocyclyl-NH-C₁₋₆-alkyl- or phenyl-(CR^cR^d)_f-NH-C₁₋₆-alkyl-, and wherein R¹⁰ is optionally substituted with one or more R¹²;

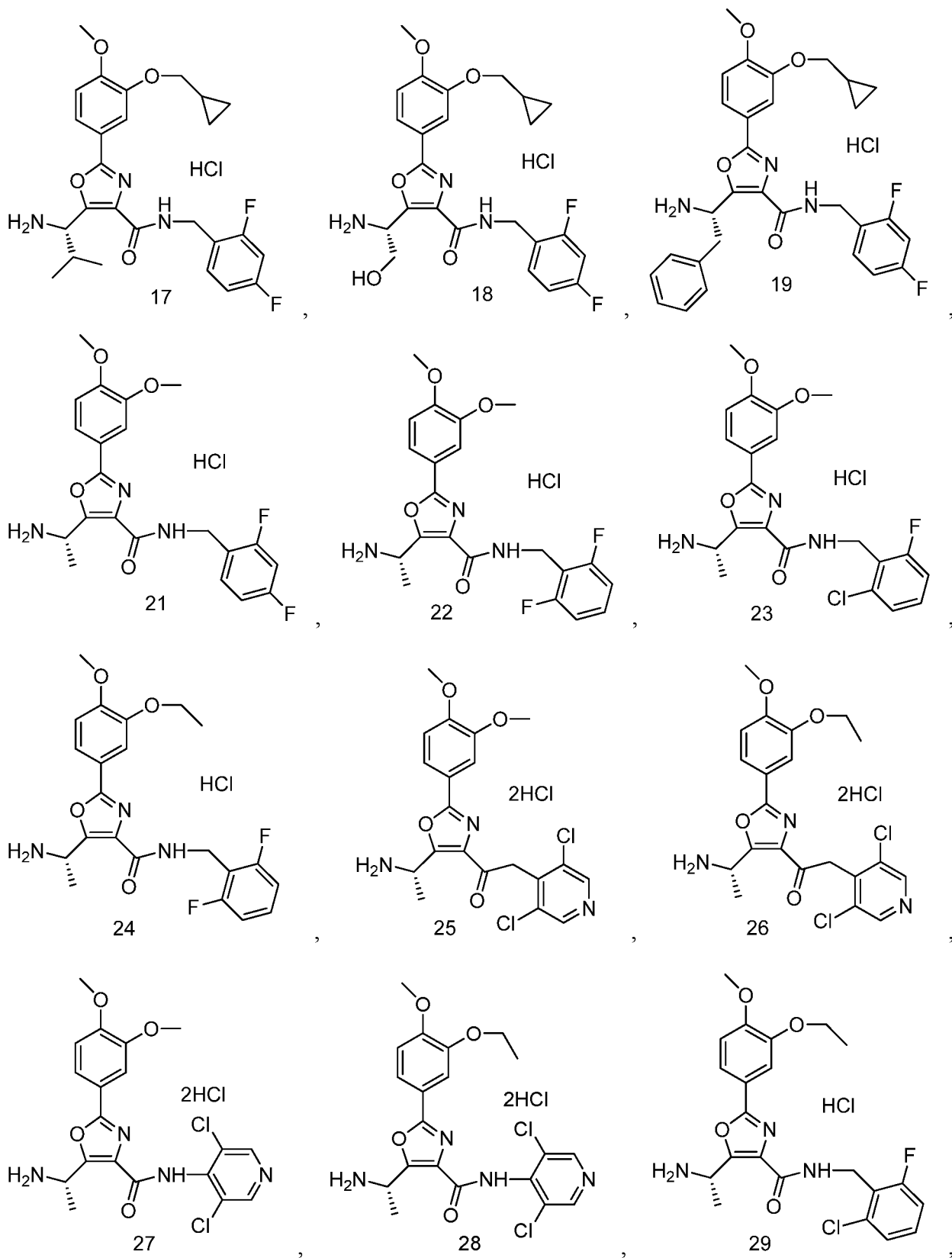
each R^c and R^d is independently H, OH, CN, F, Cl, Br, I, methyl, ethyl or propyl;

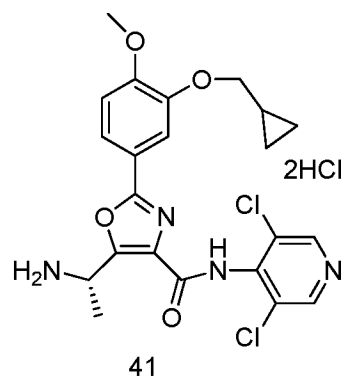
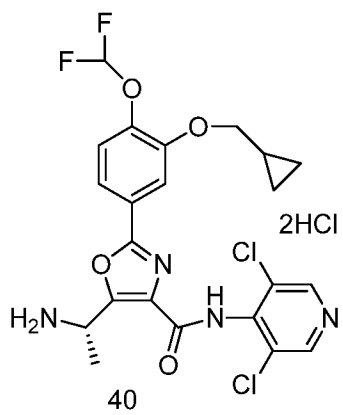
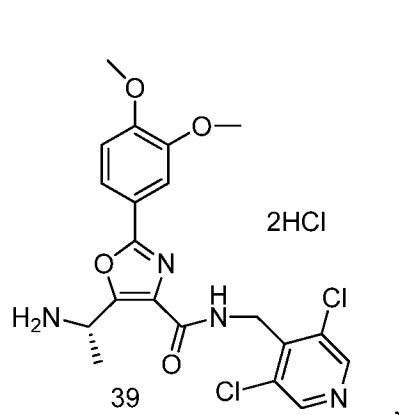
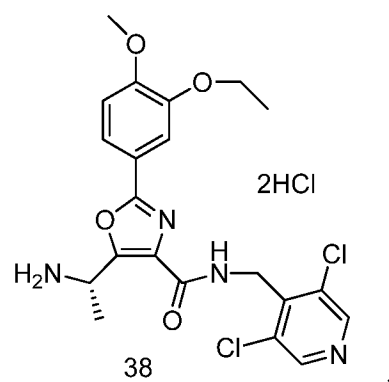
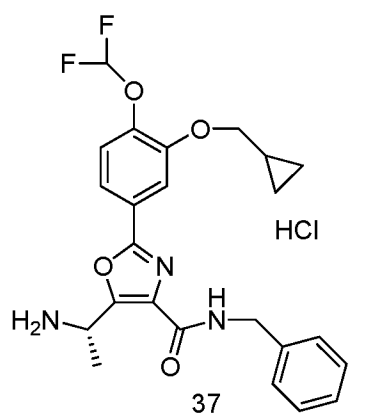
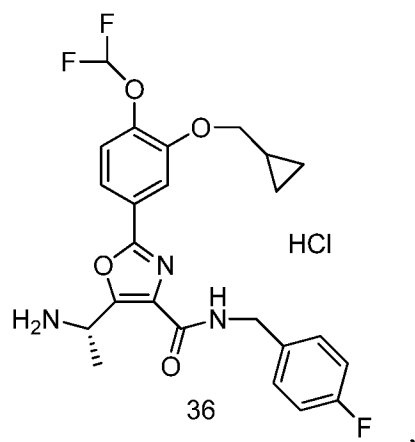
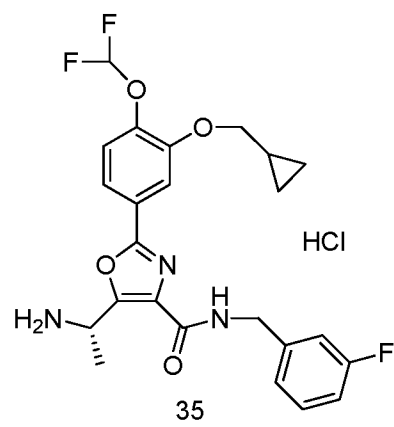
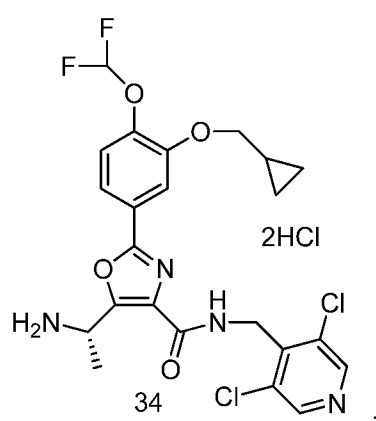
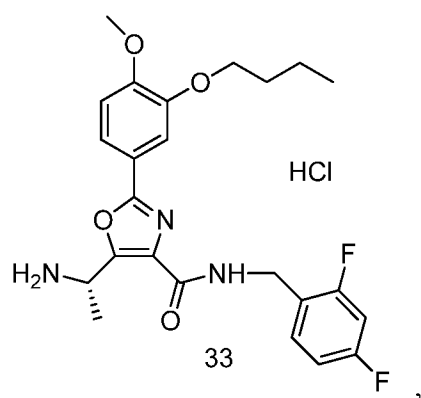
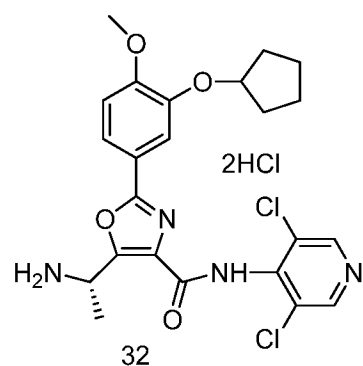
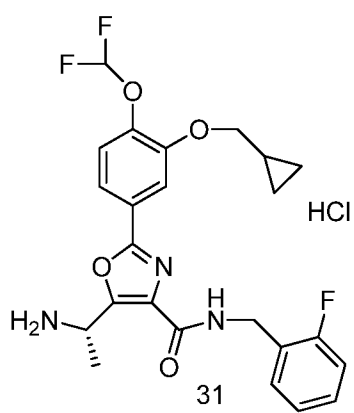
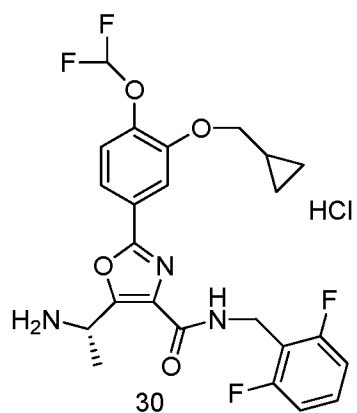
each of R^e and R^f is independently H, OH, methyl, ethyl or propyl; and

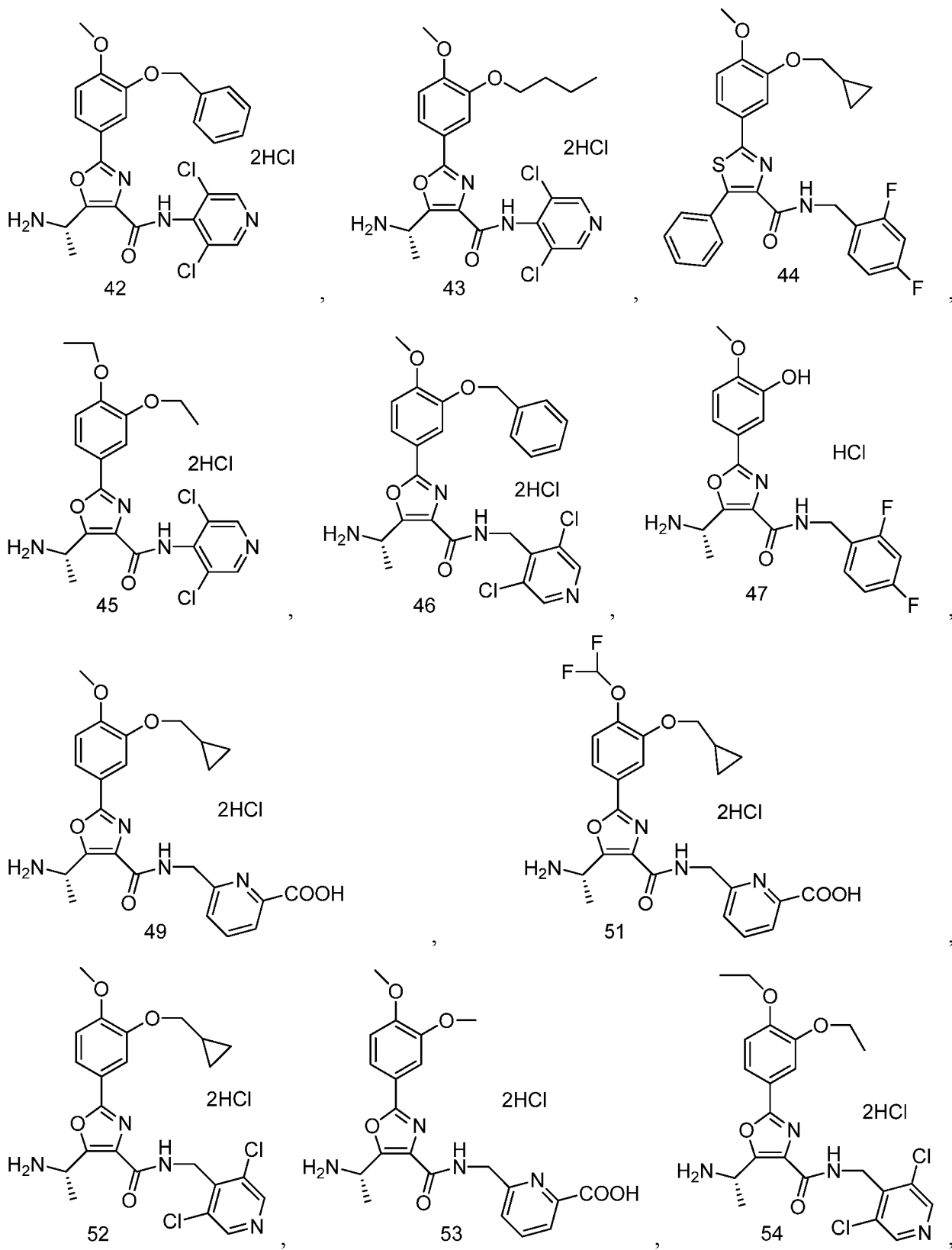
each R¹² is independently D, F, Cl, Br, I, CN, NO₂, OH, NH₂, COOH, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, hydroxy-substituted methyl or halogenated methyl.

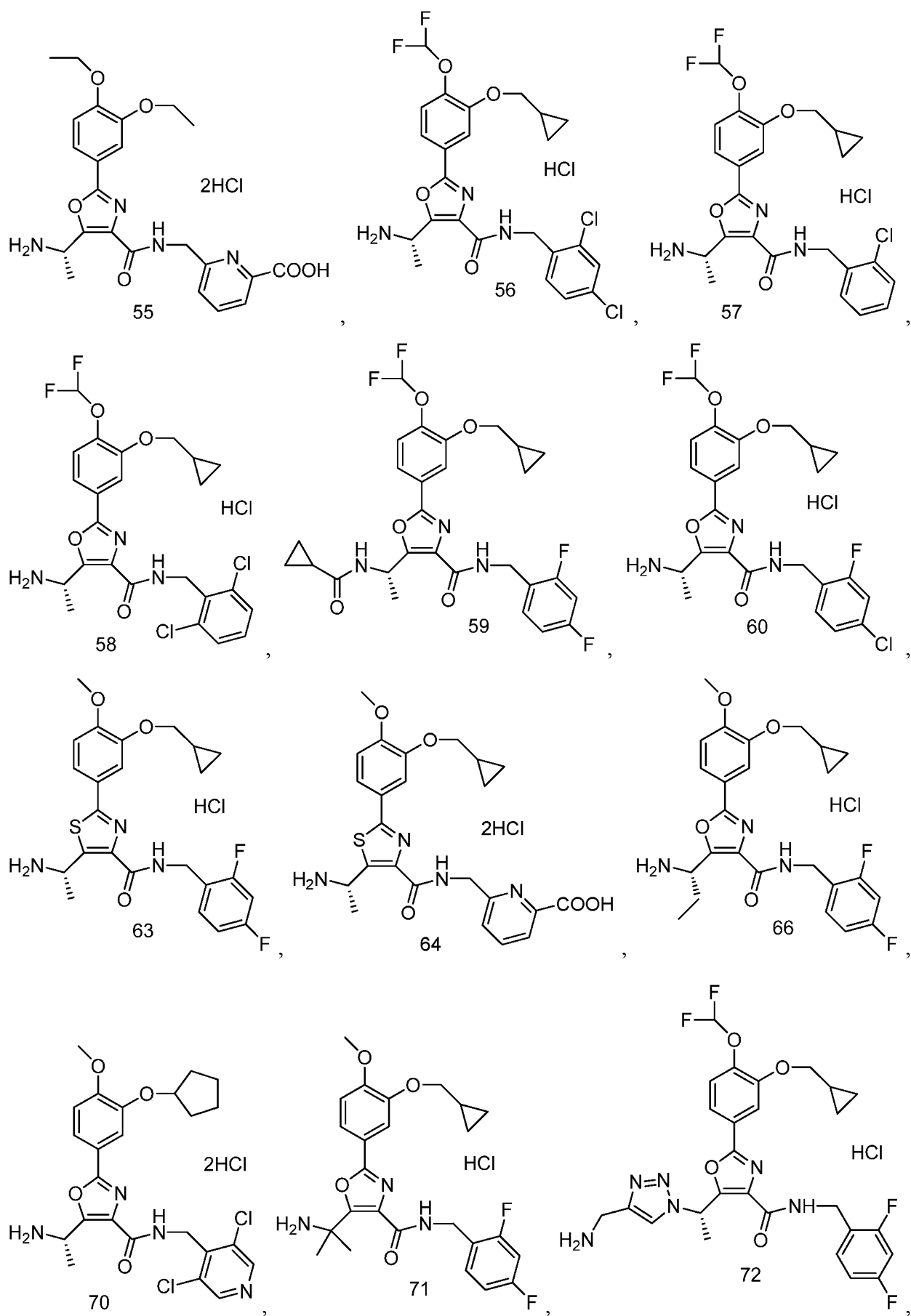
17. The compound according to claim 1 having one of the following structures, or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,

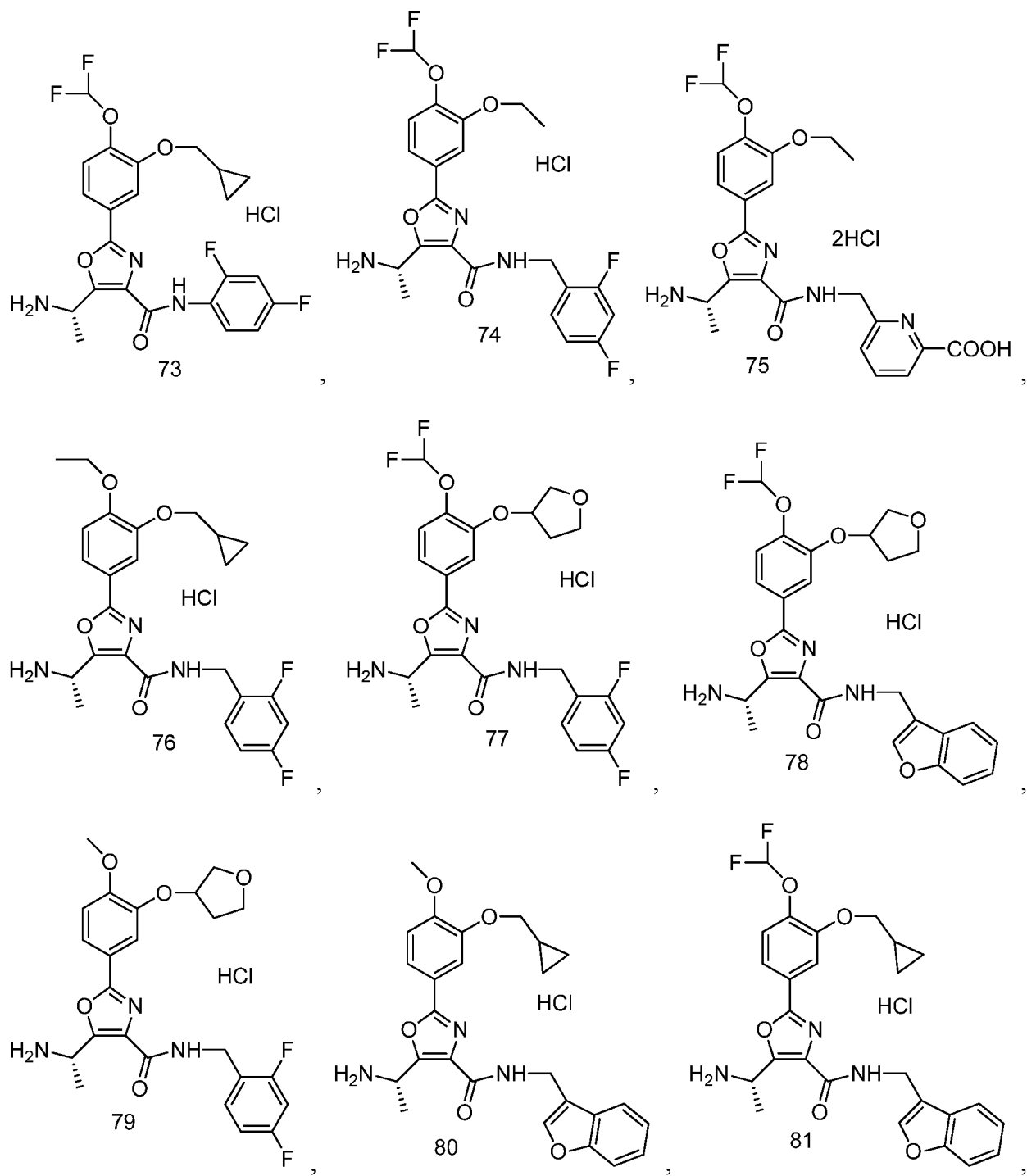


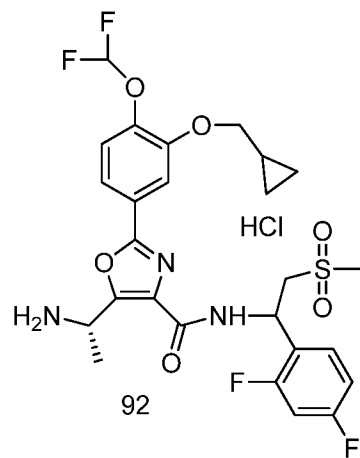
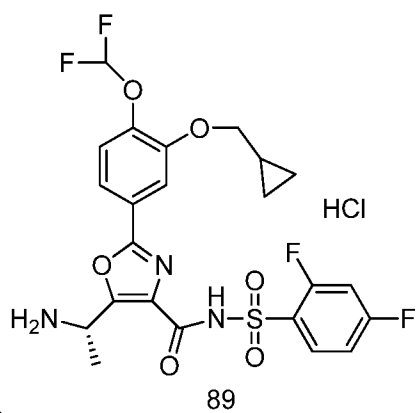
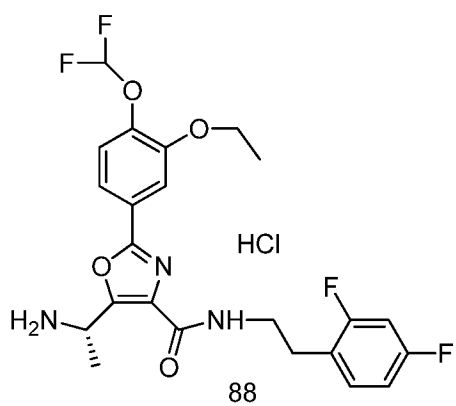
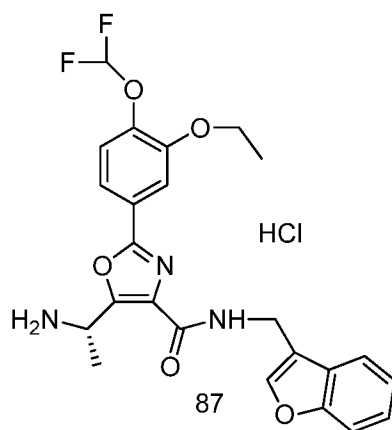
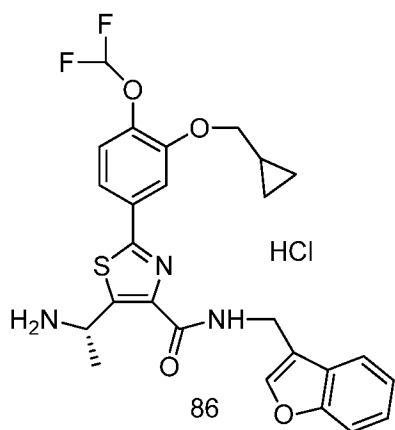
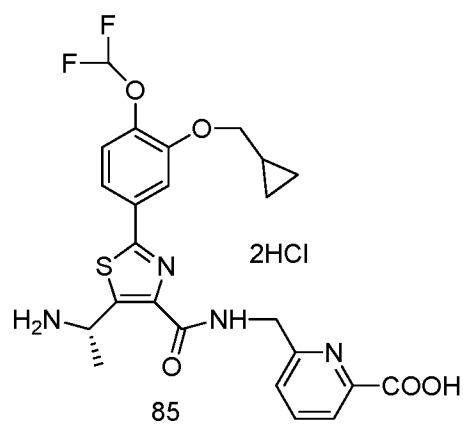
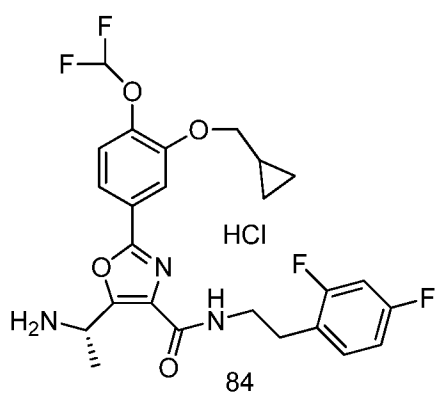
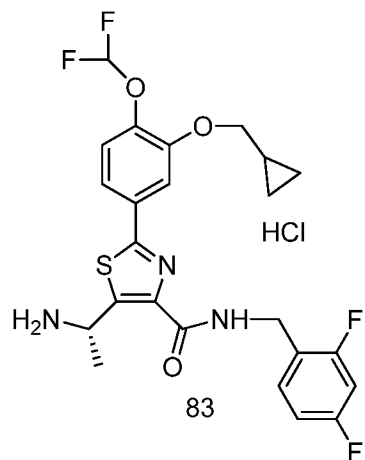
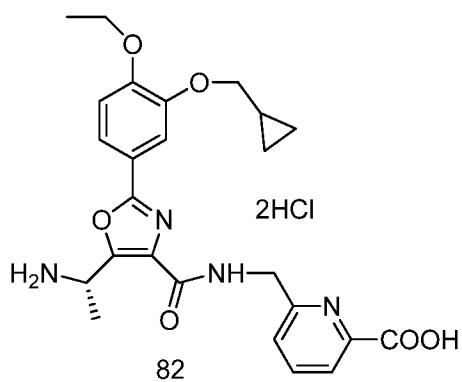


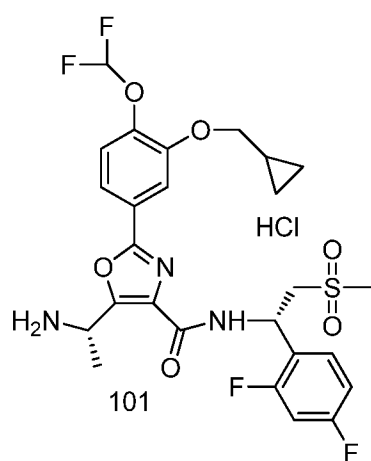
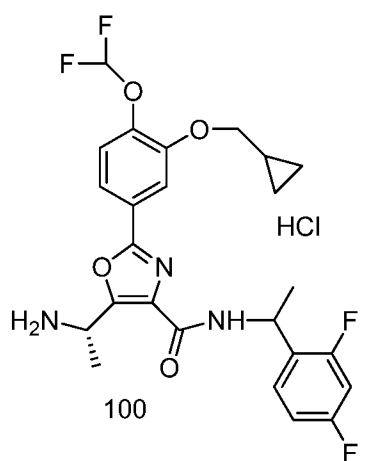
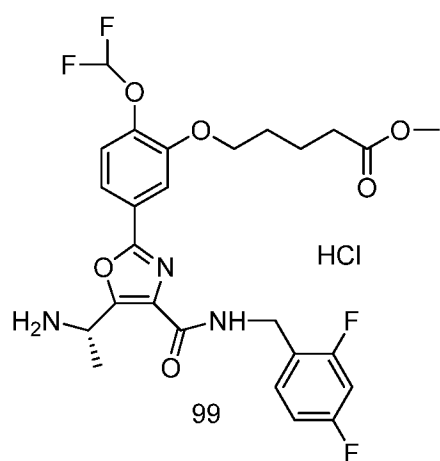
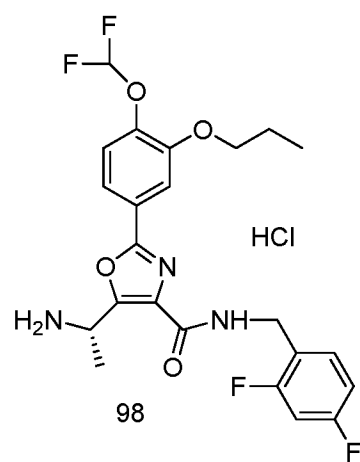
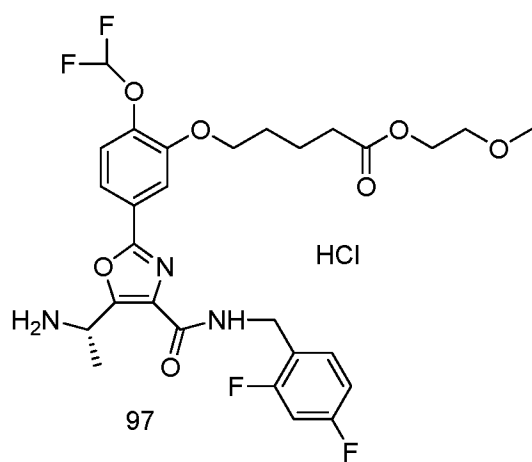
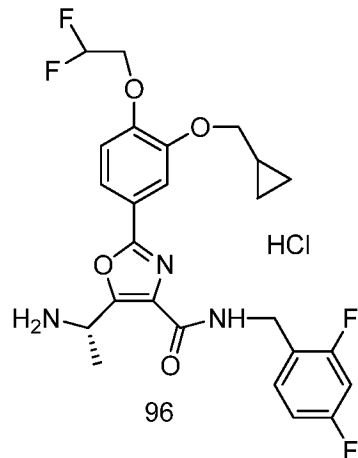
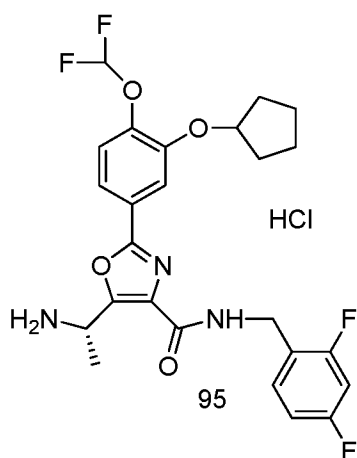
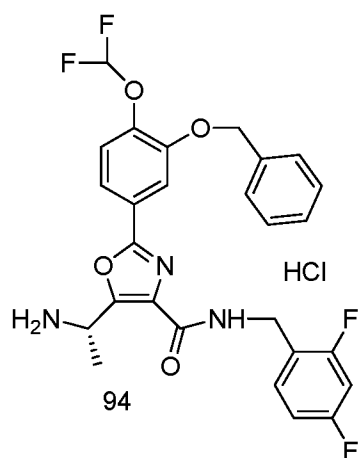


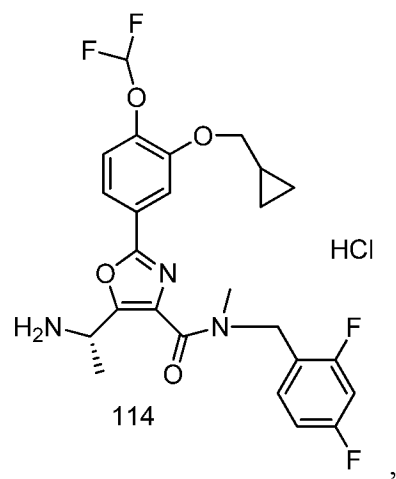
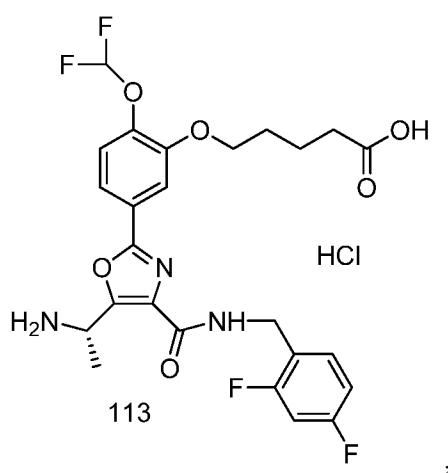
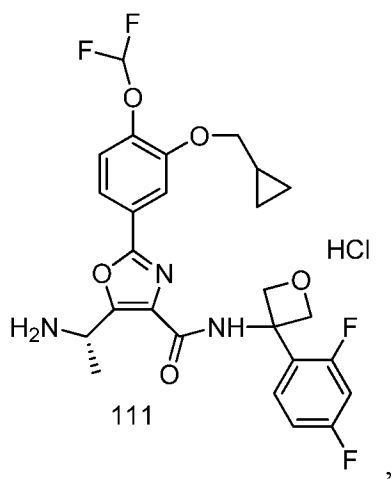
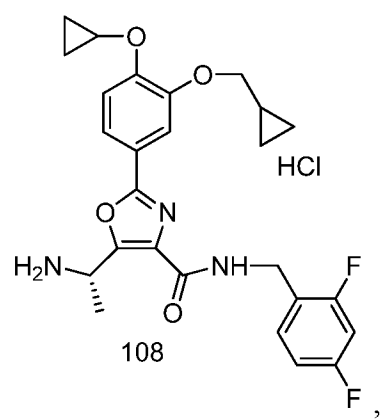
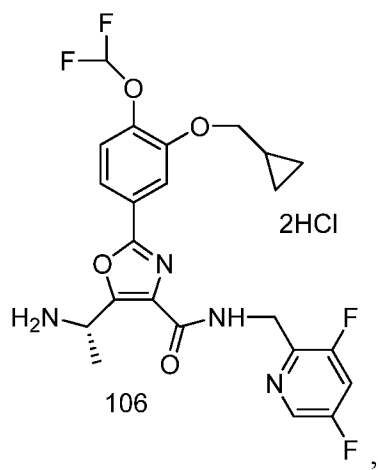
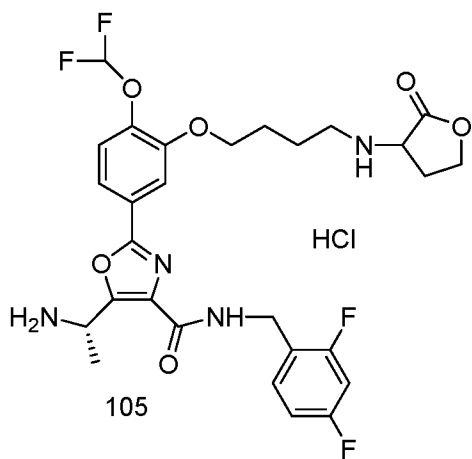
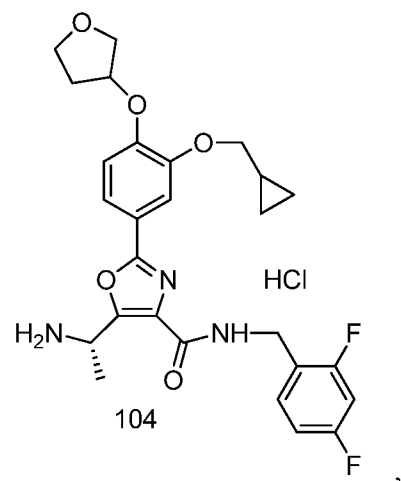
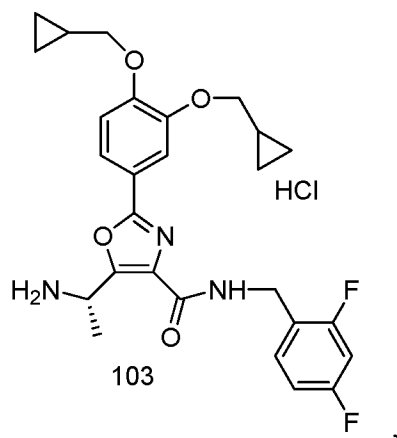
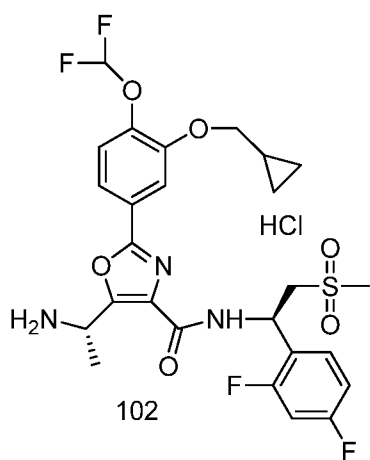


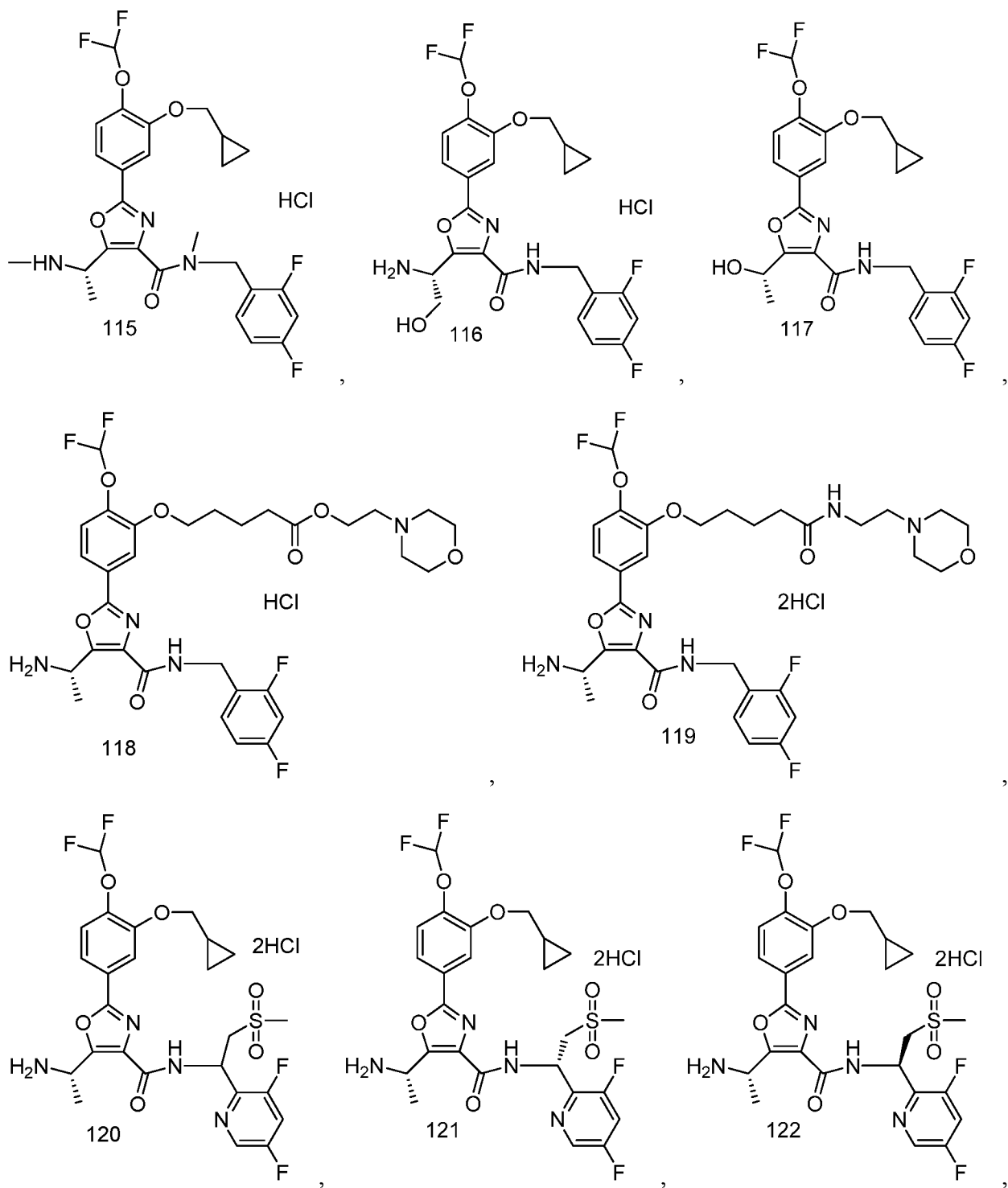


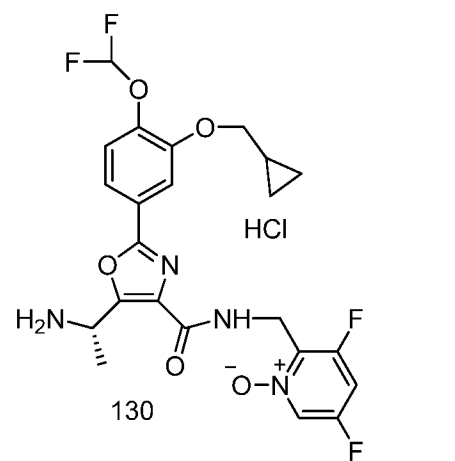
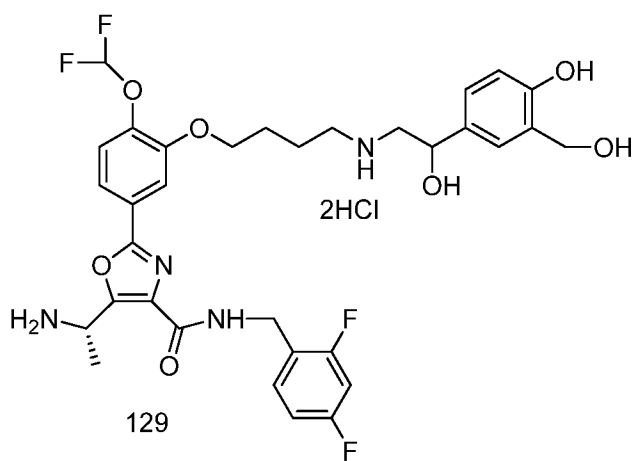
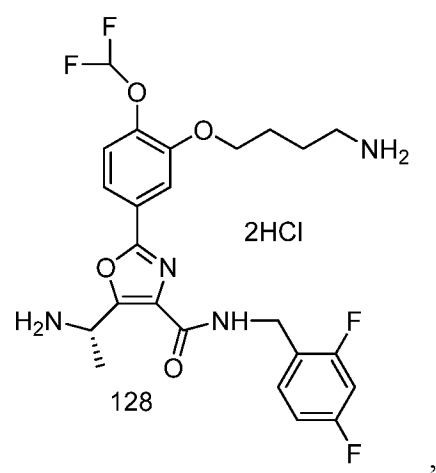
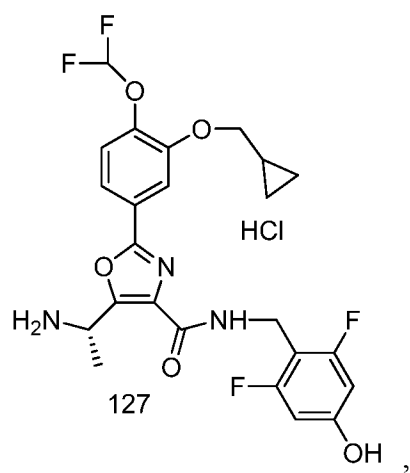
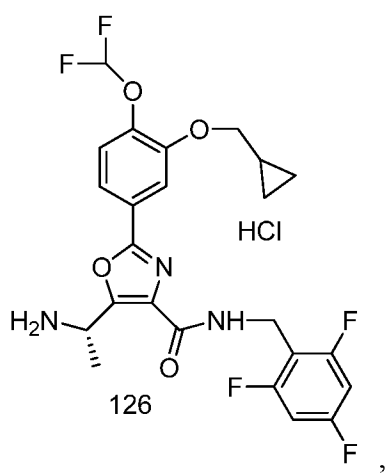
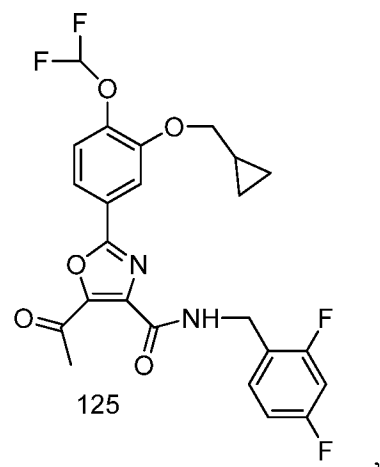
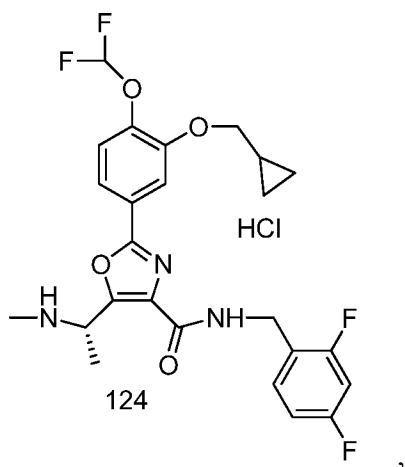
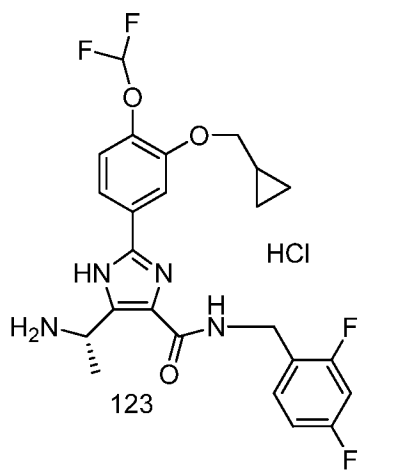


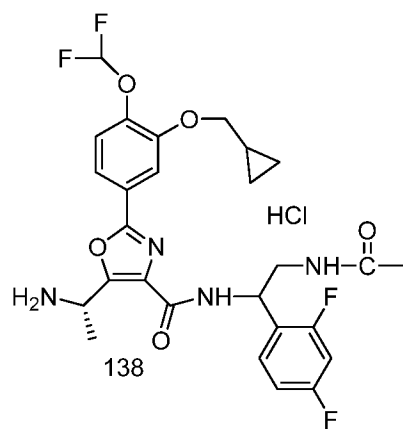
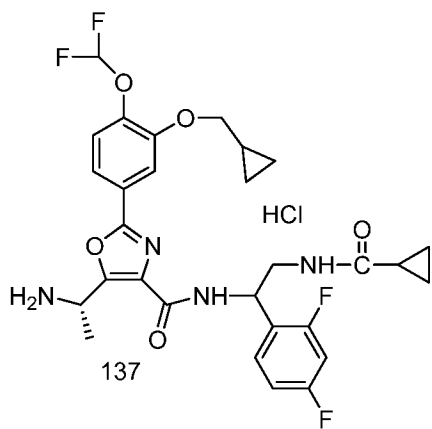
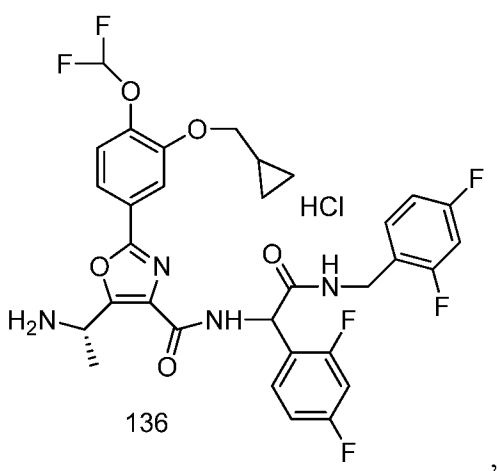
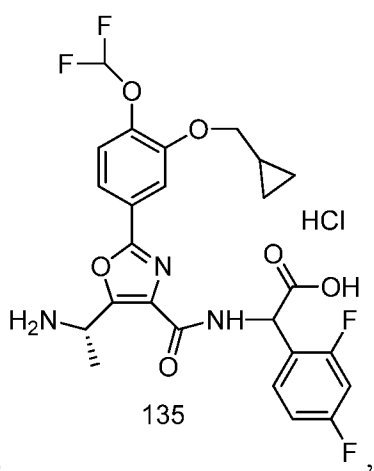
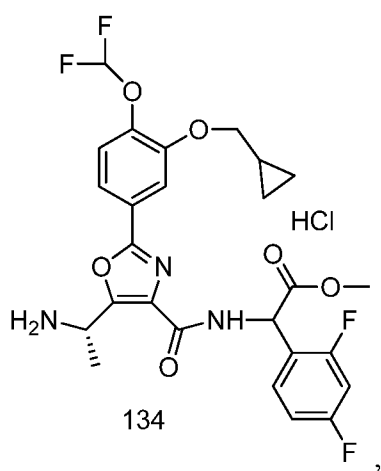
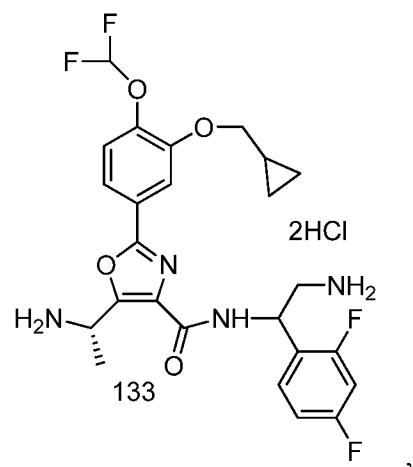
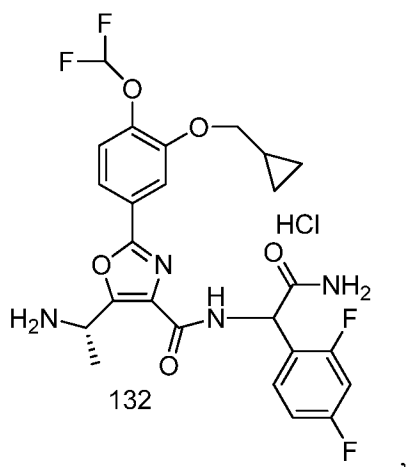
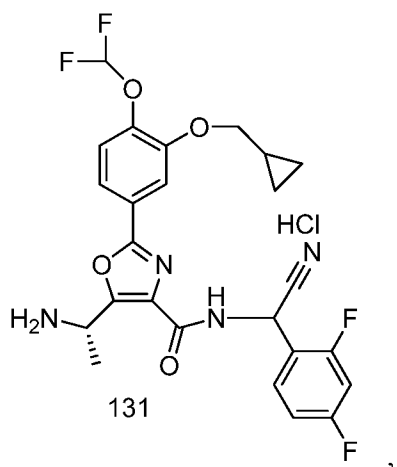


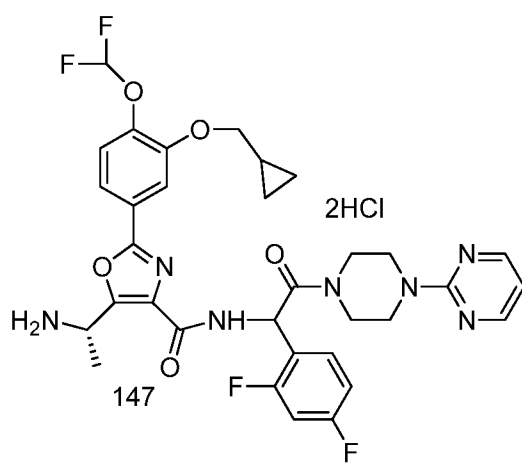
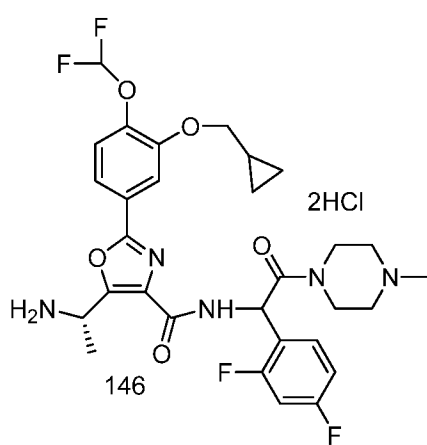
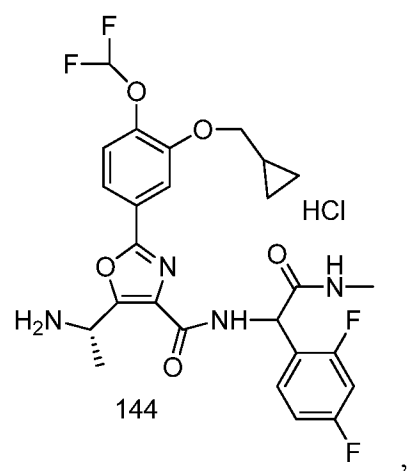
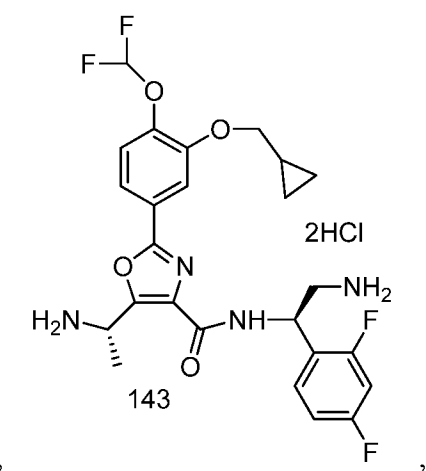
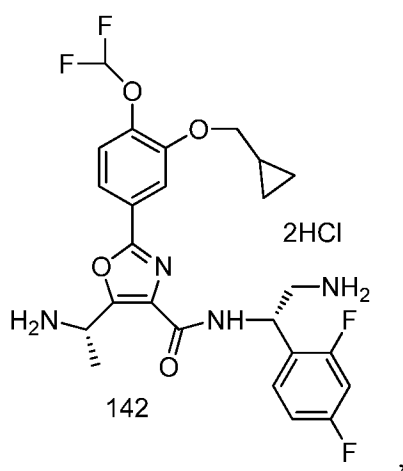
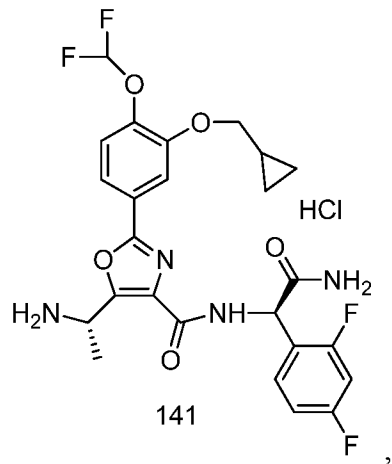
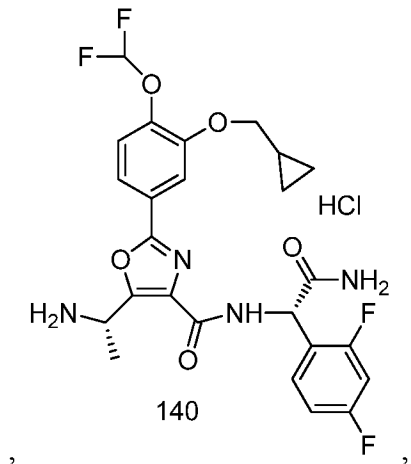
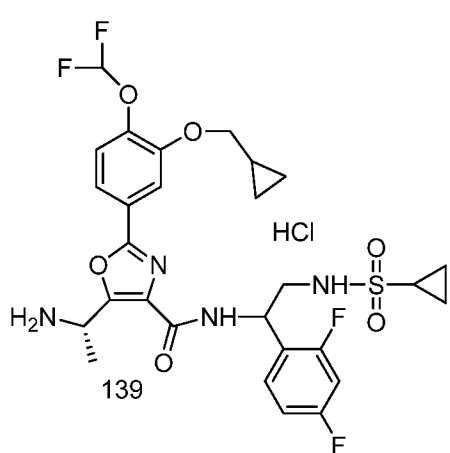


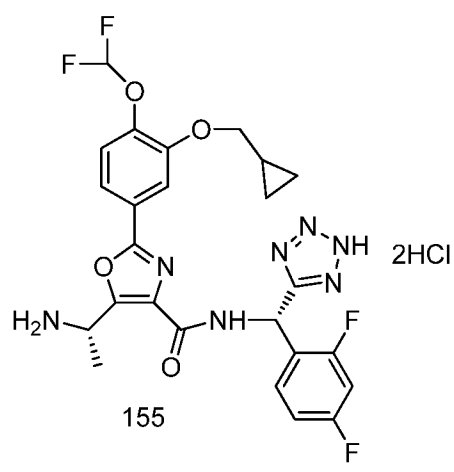
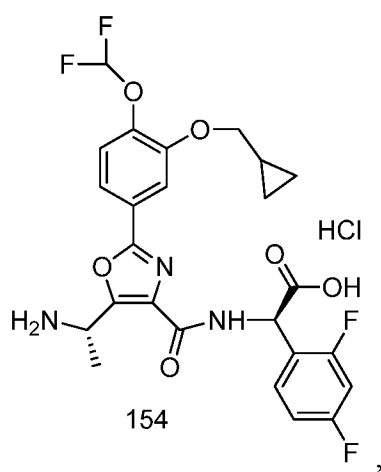
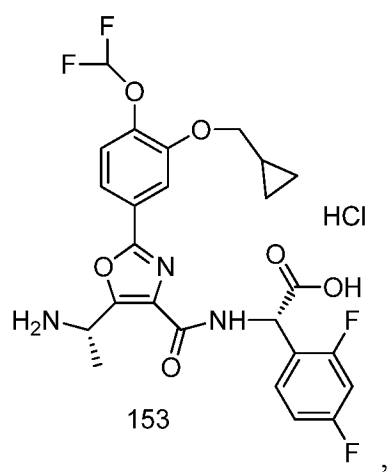
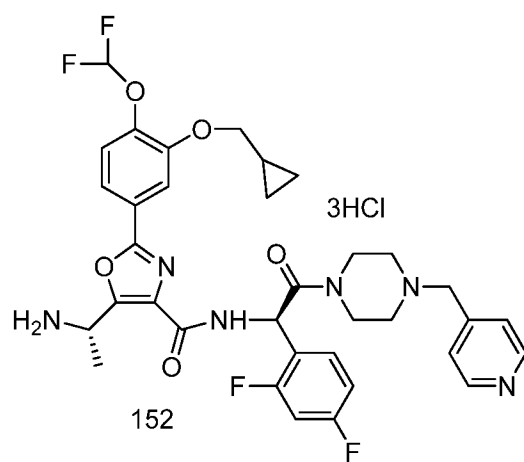
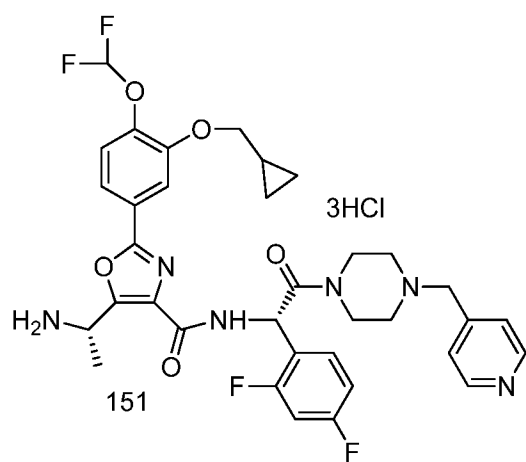
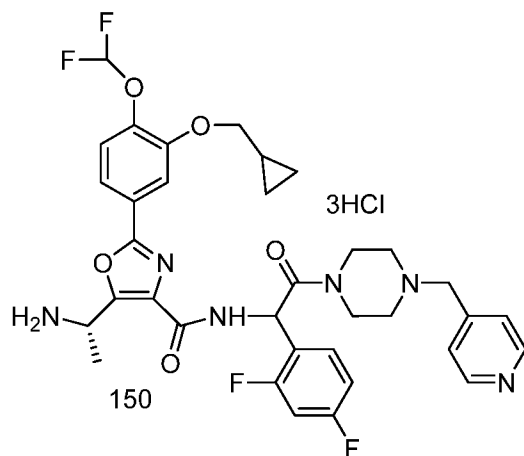
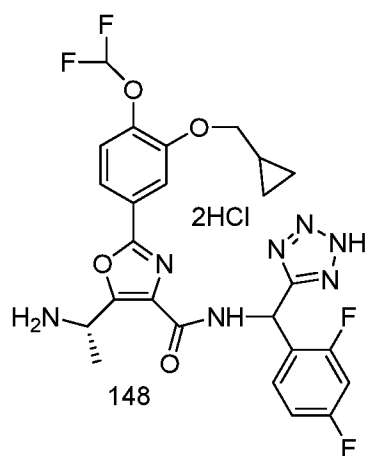


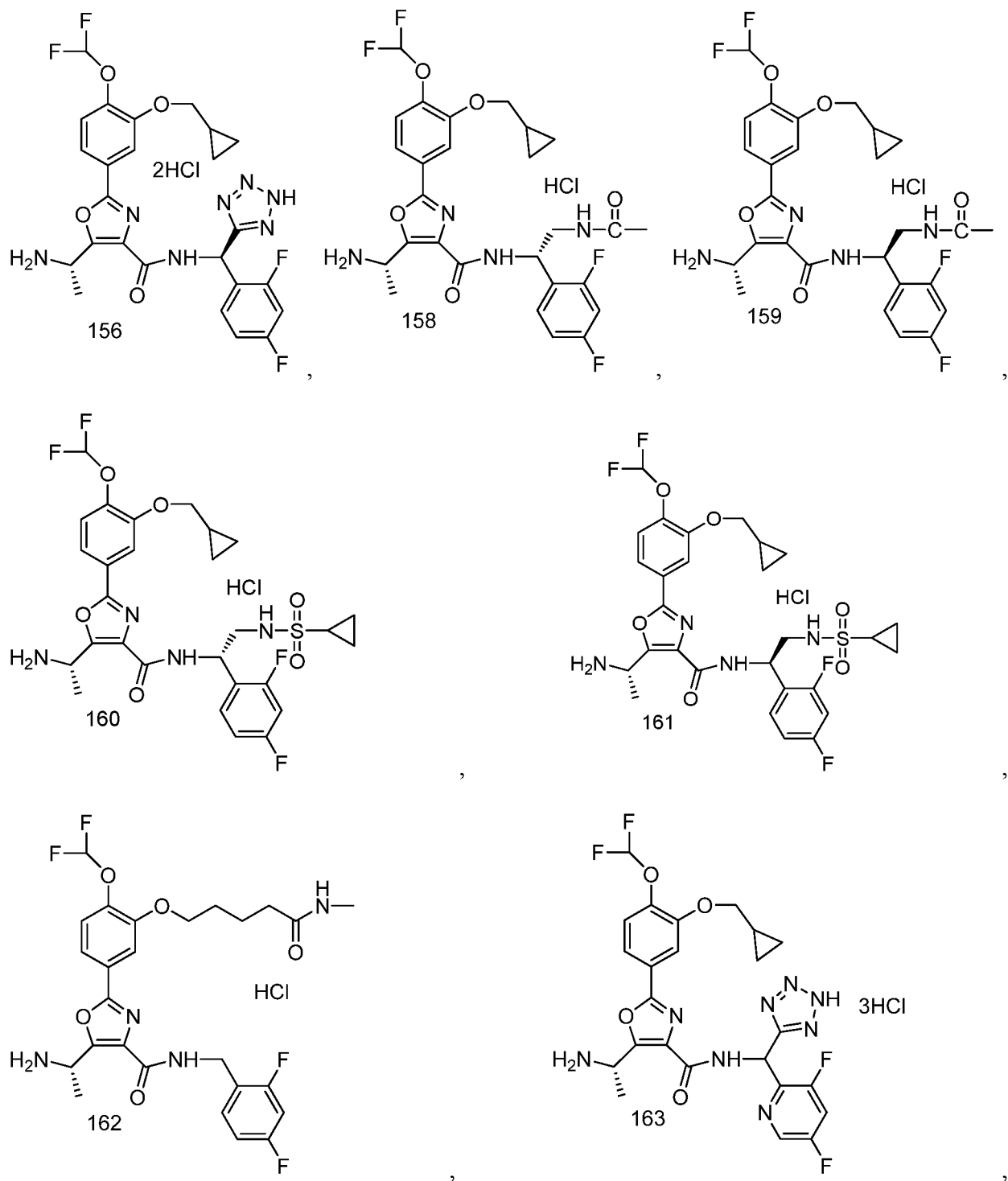


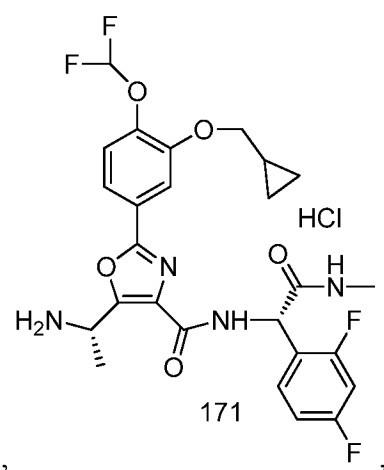
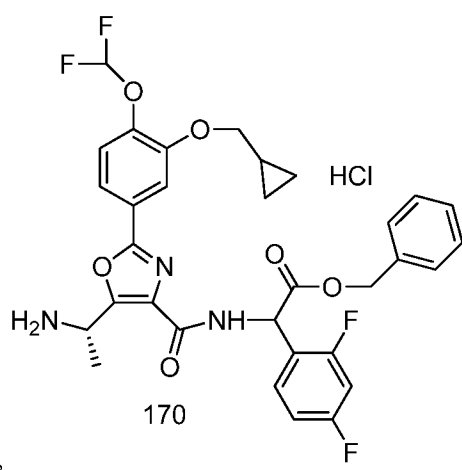
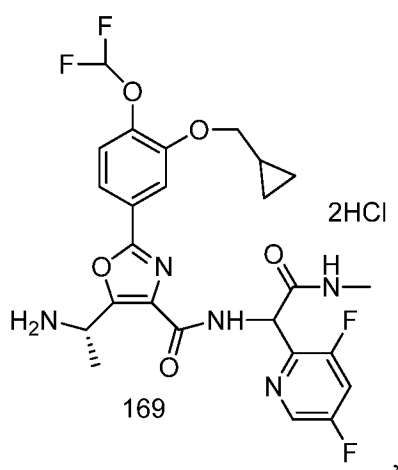
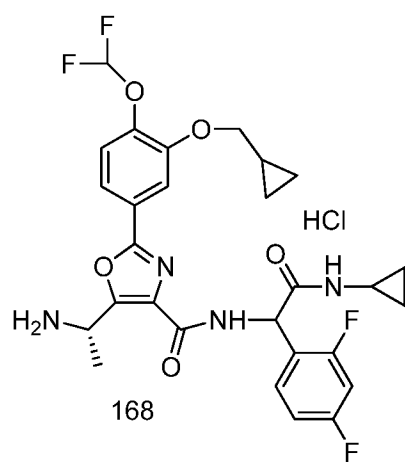
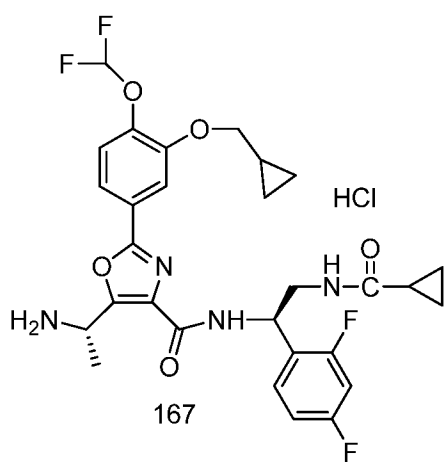
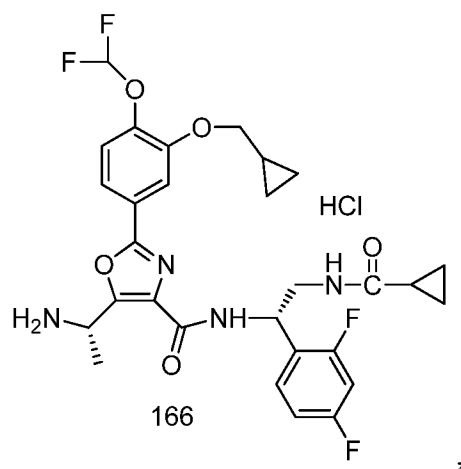
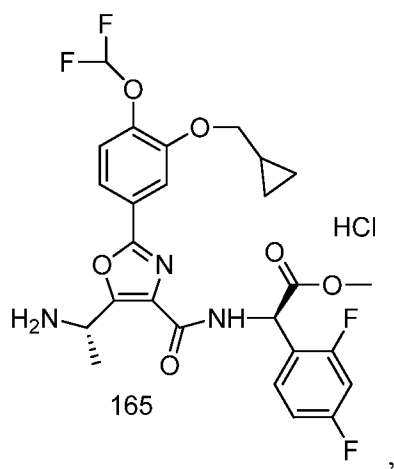
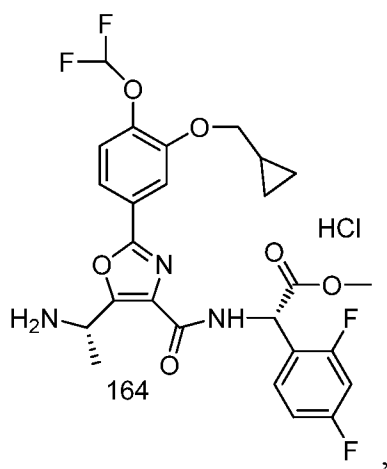


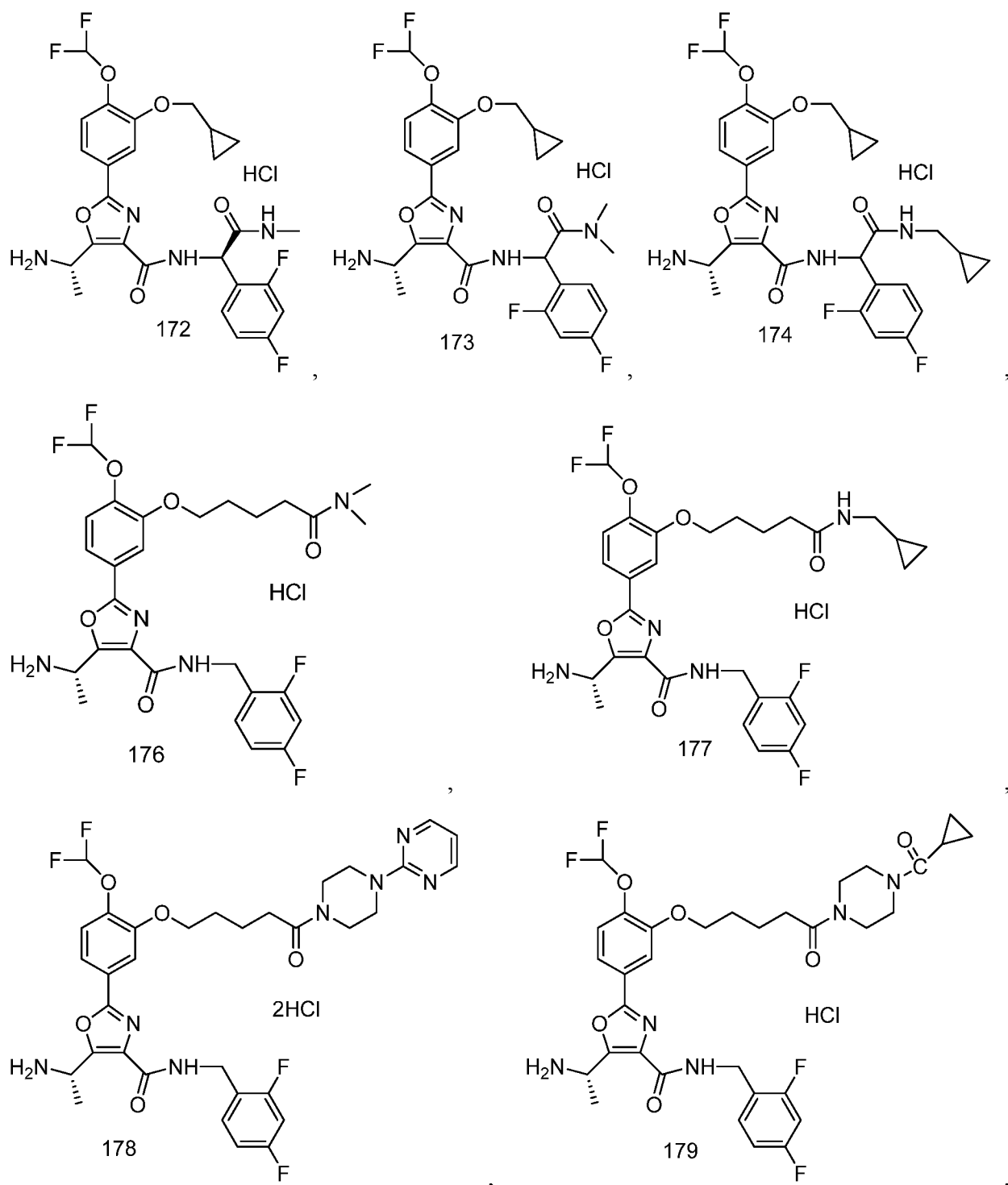


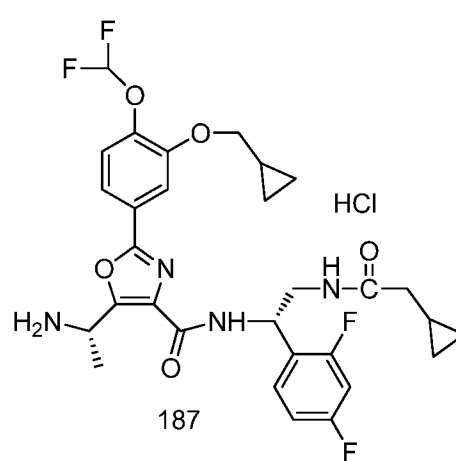
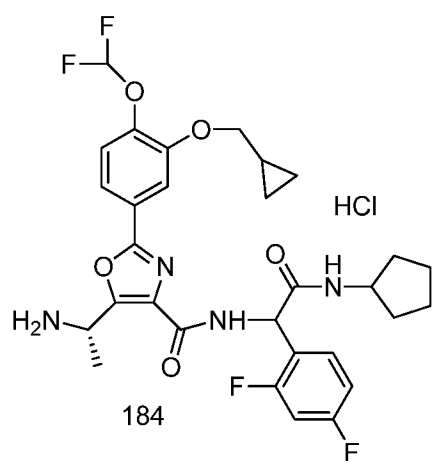
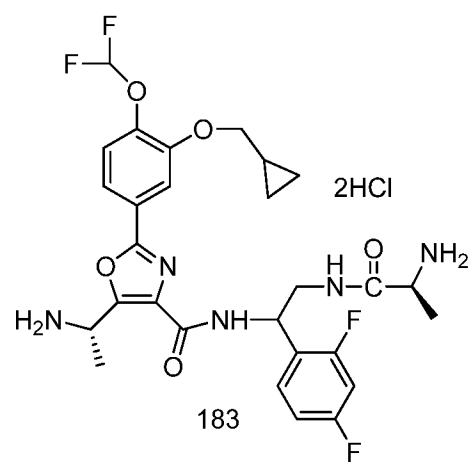
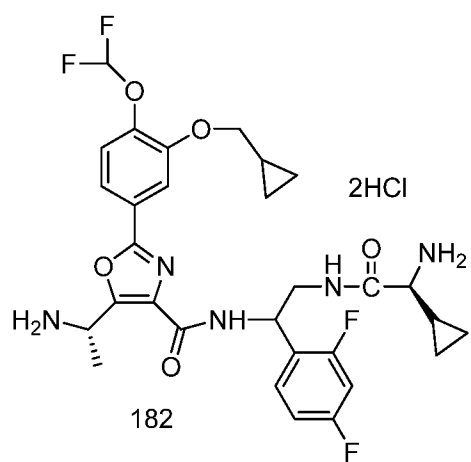
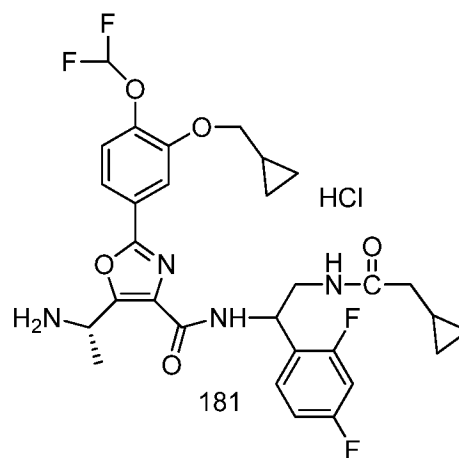
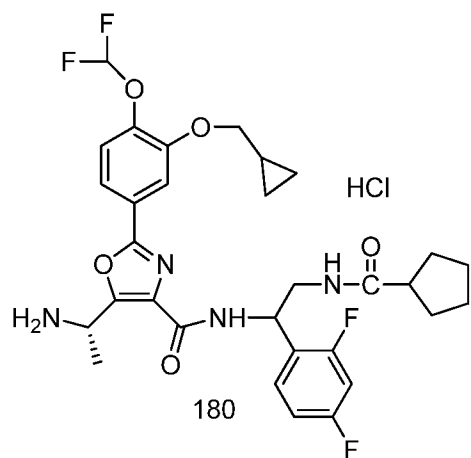


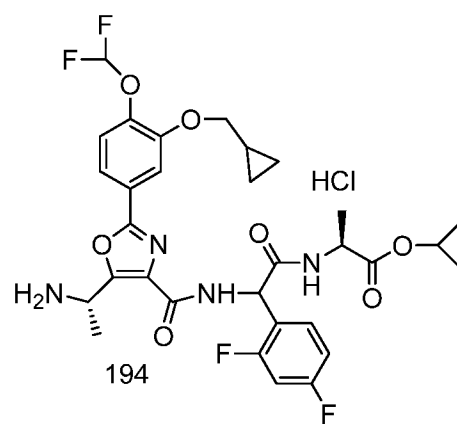
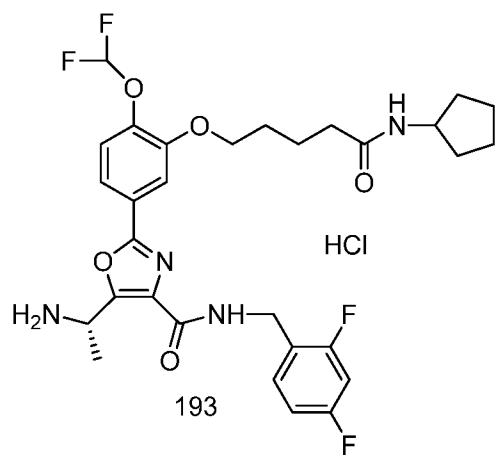
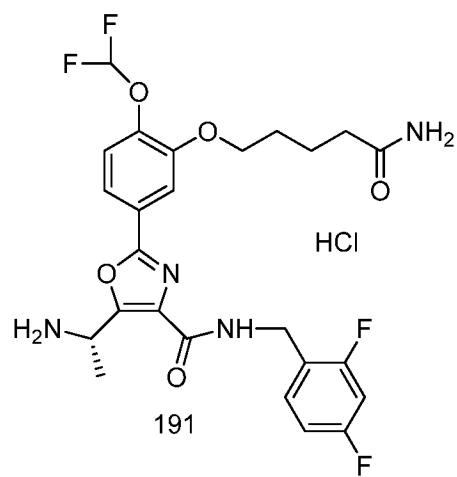
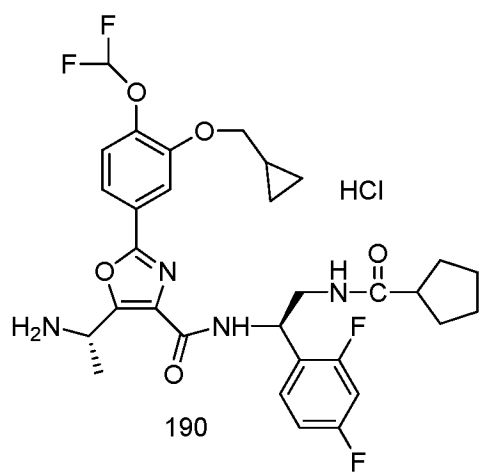
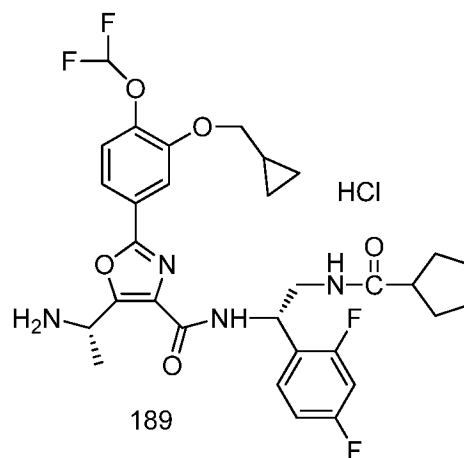
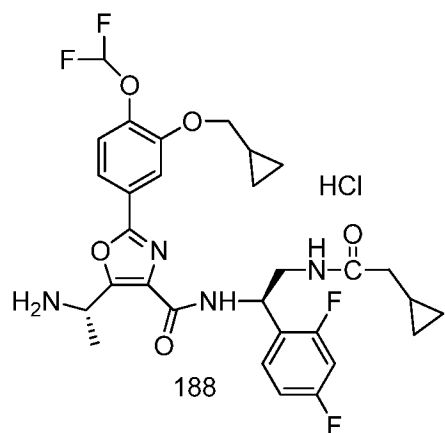


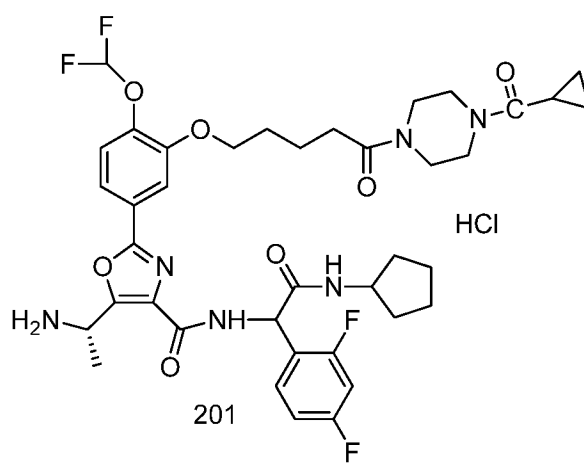
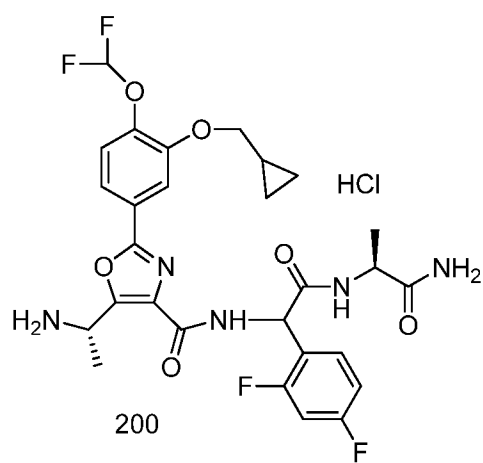
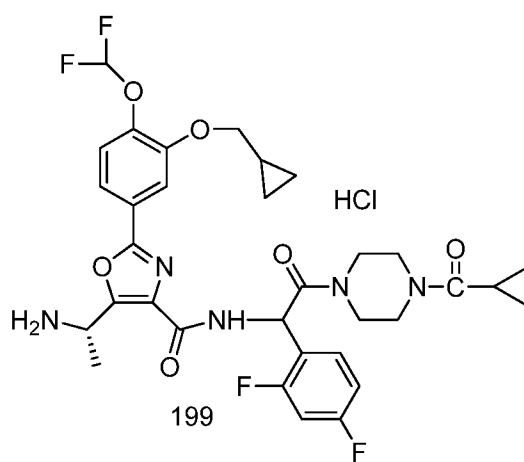
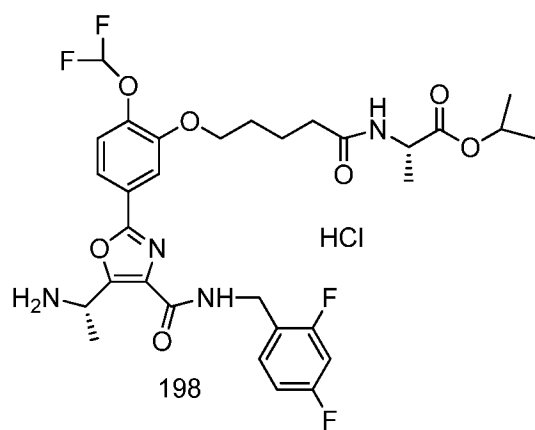
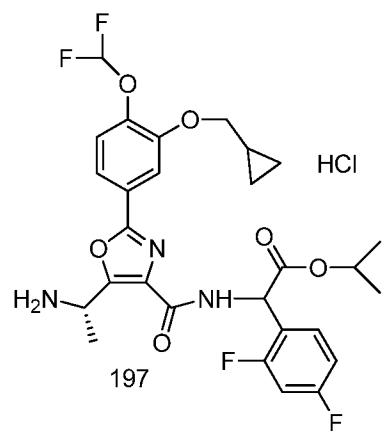
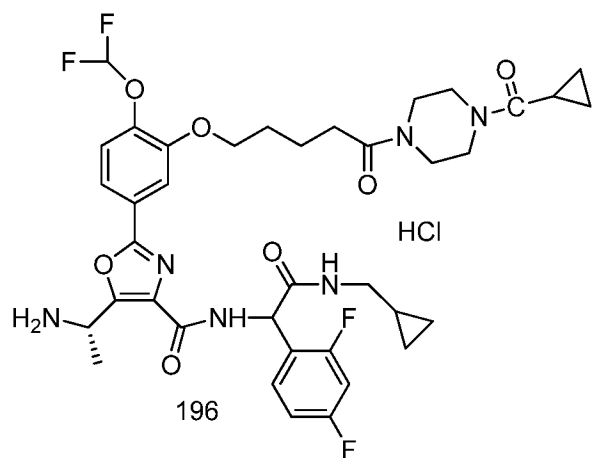


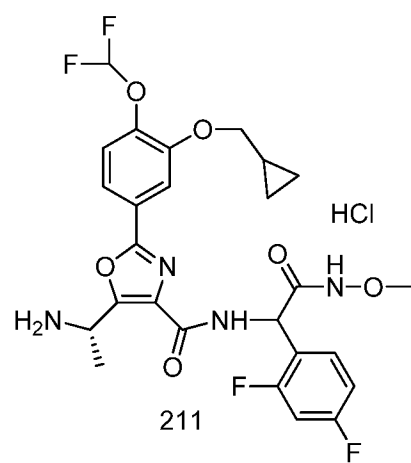
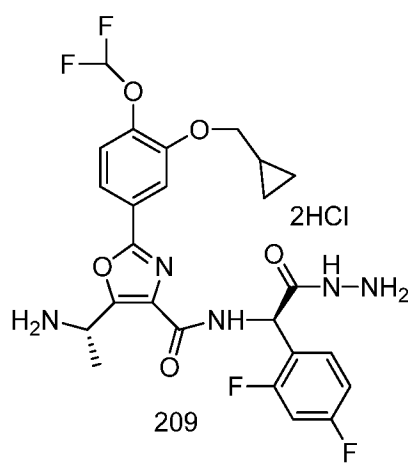
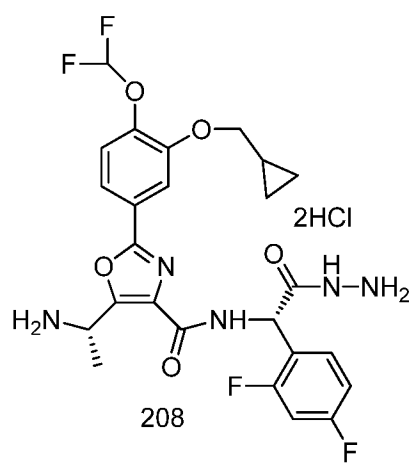
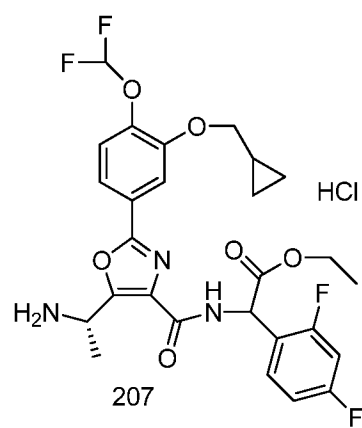
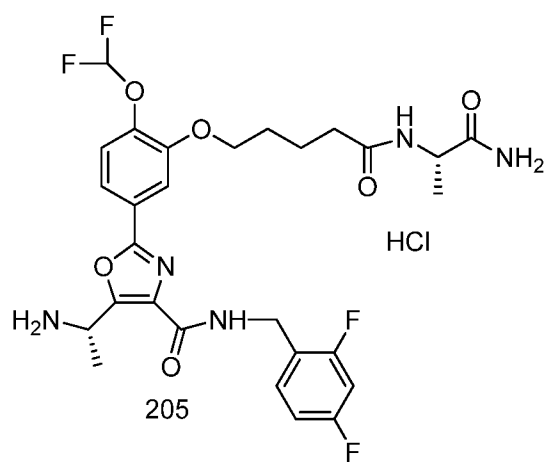
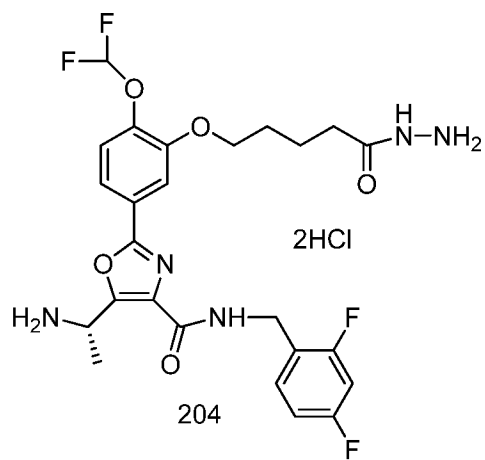
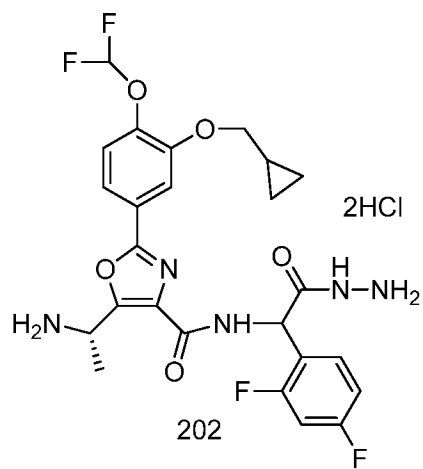


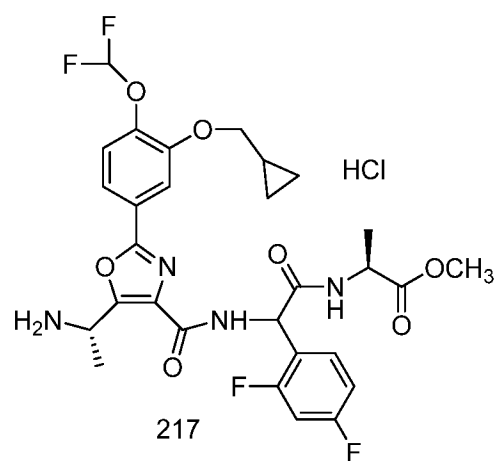
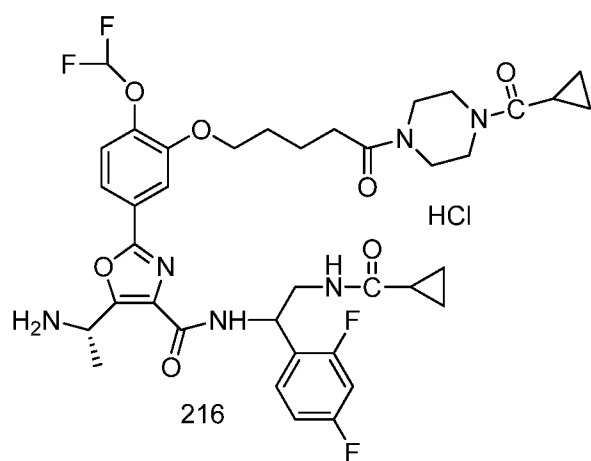
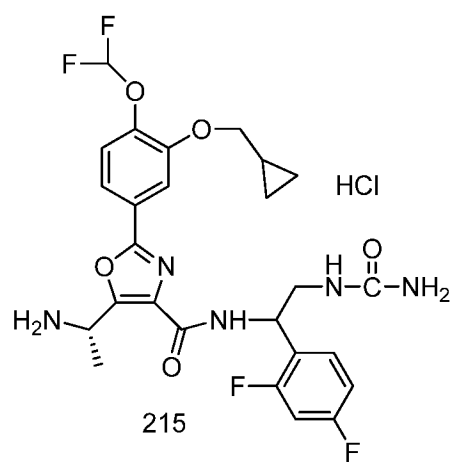
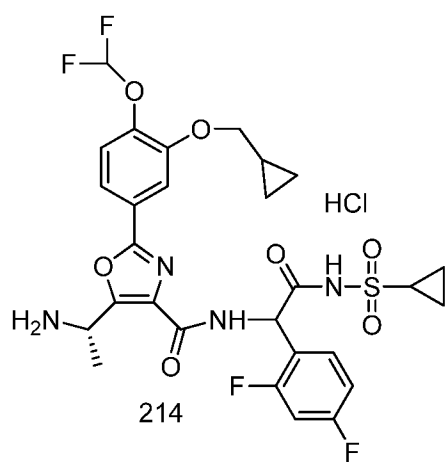
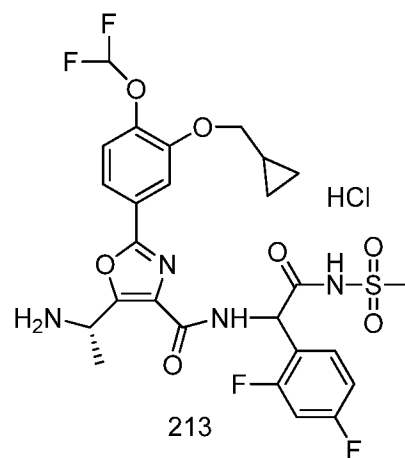
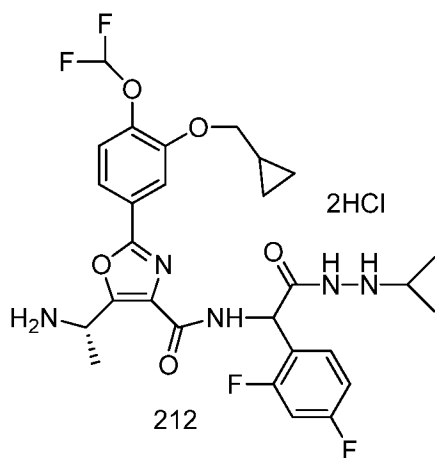


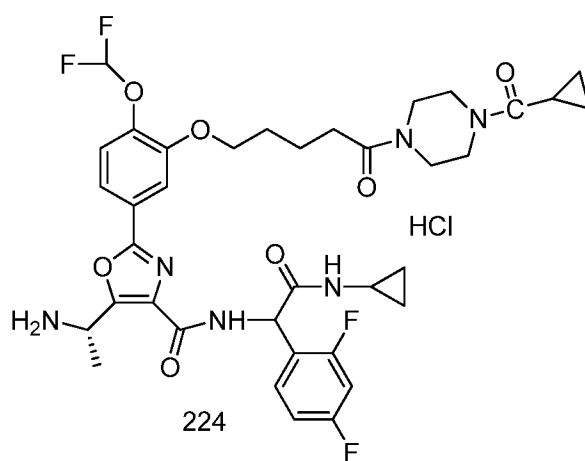
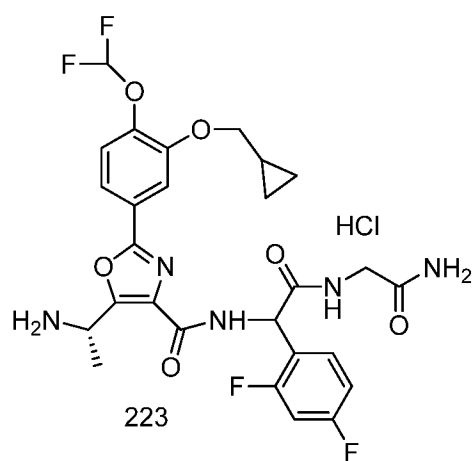
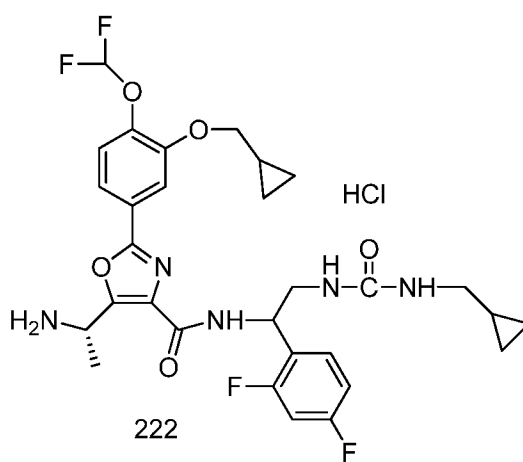
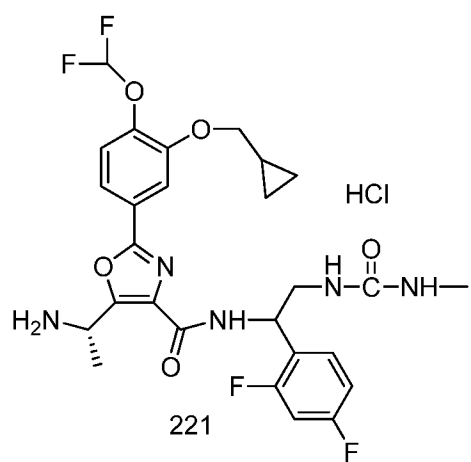
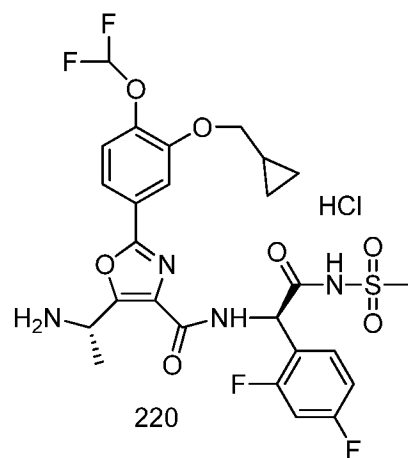
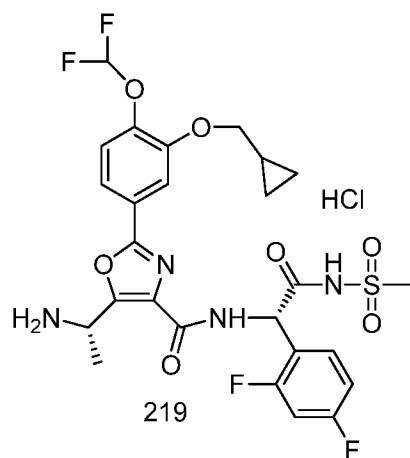


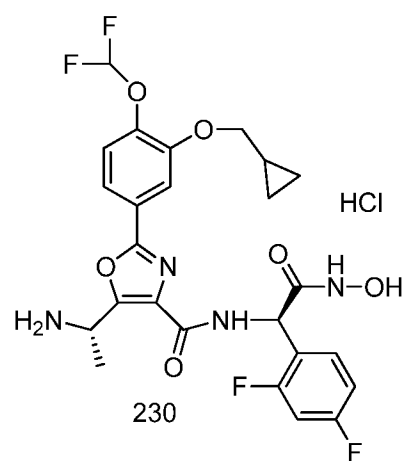
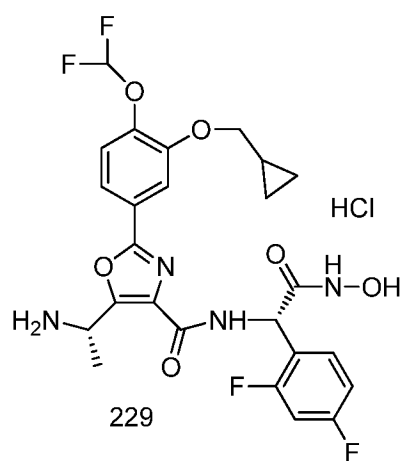
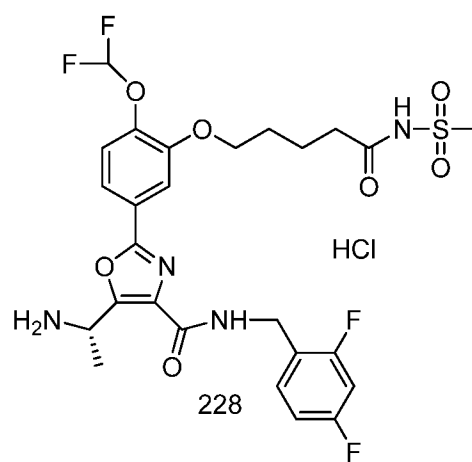
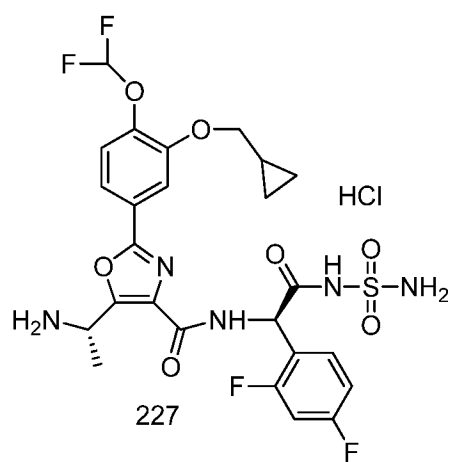
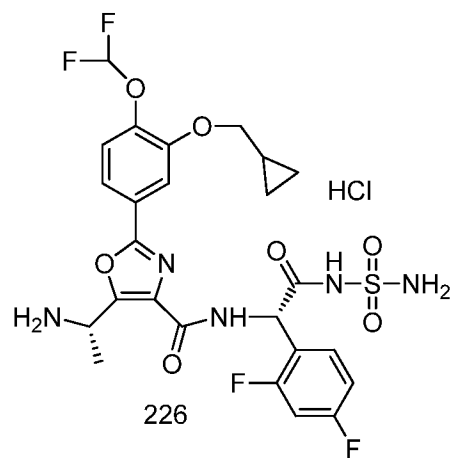
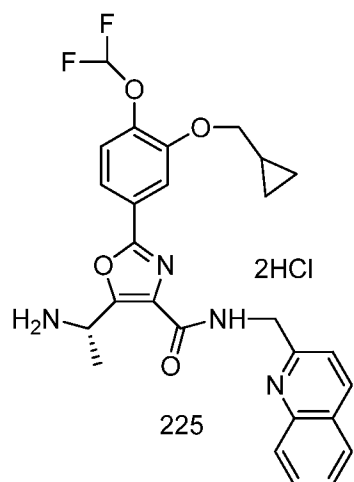


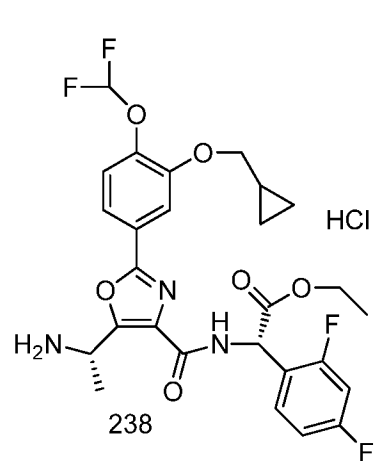
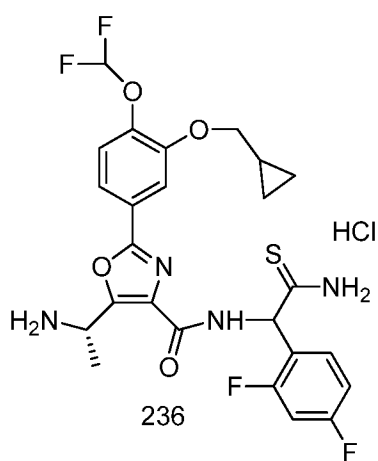
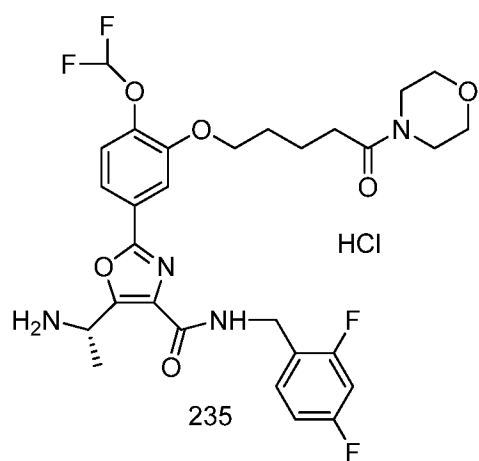
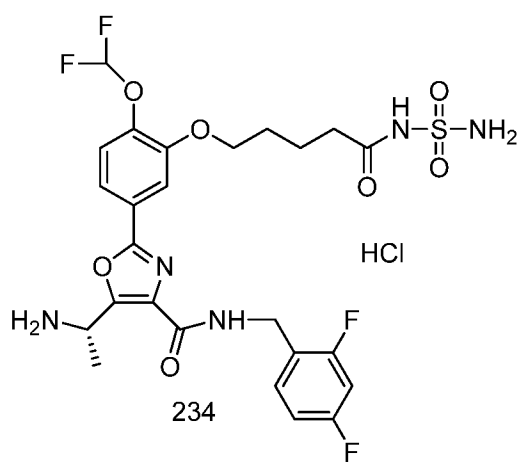
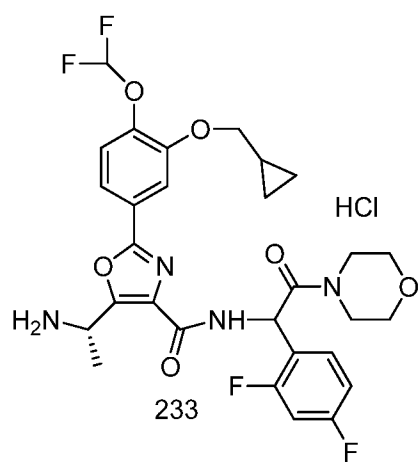
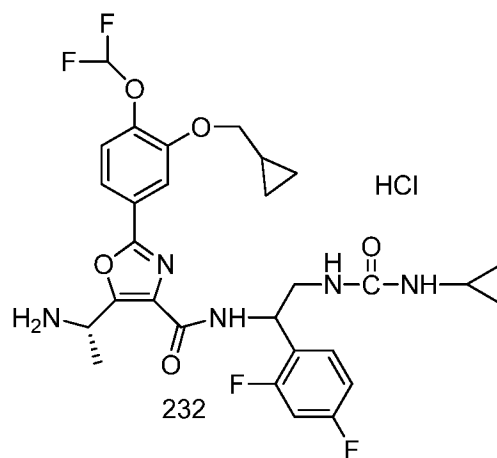
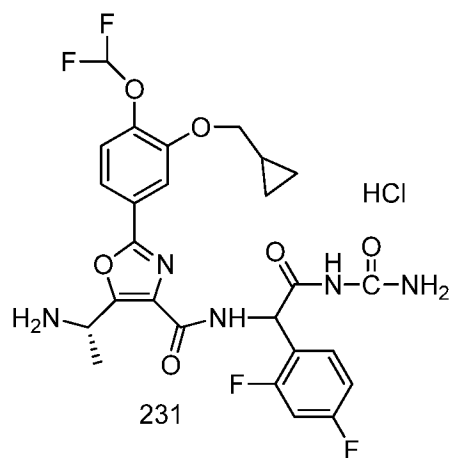


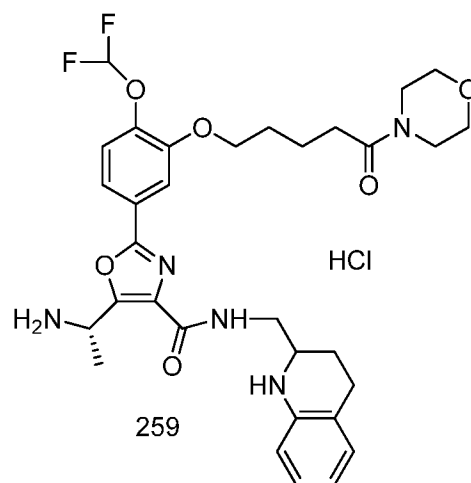
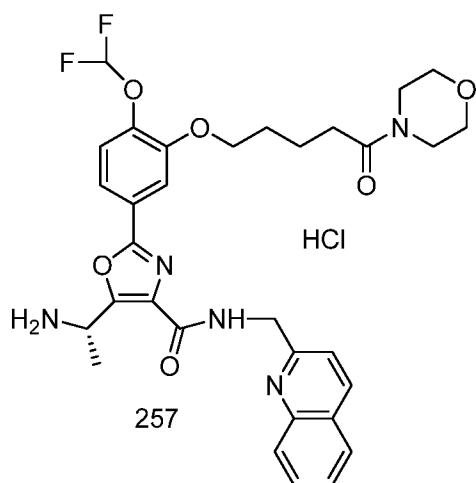
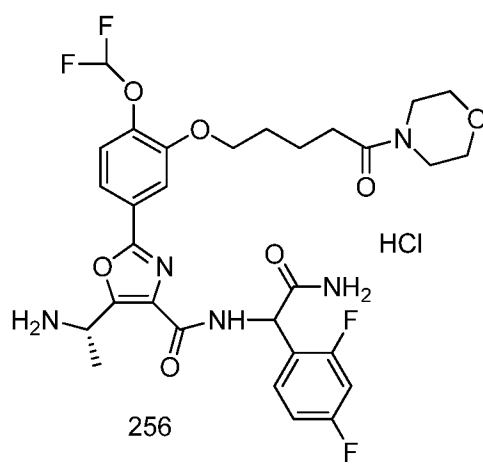
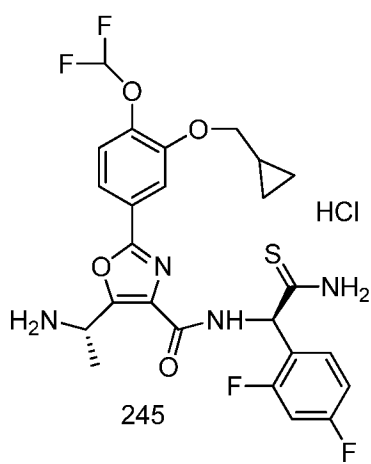
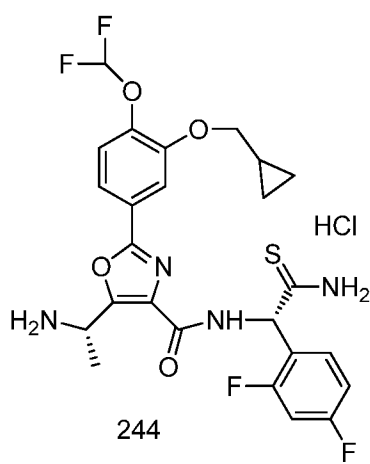
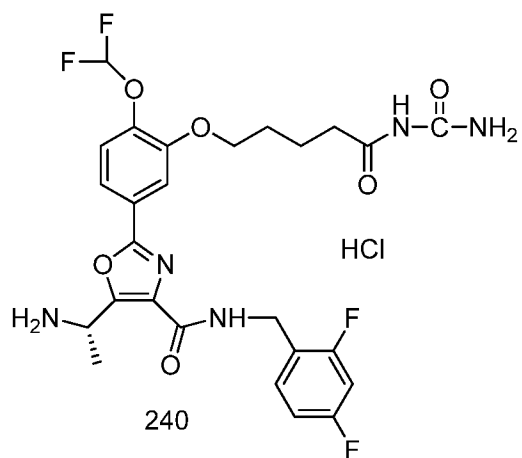
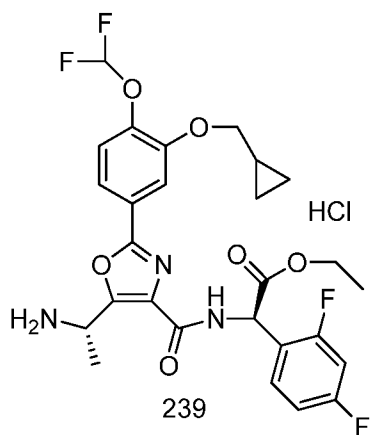


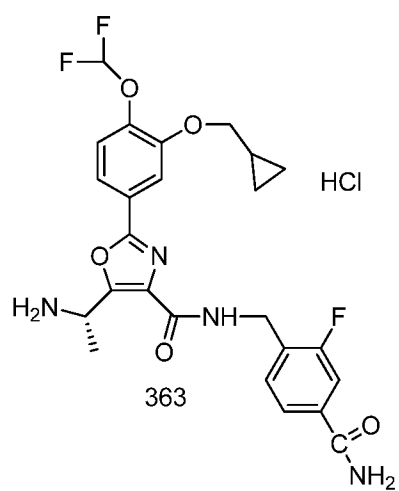
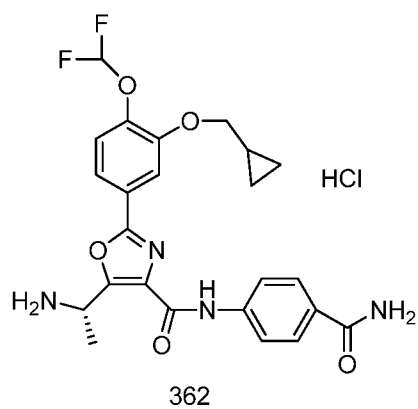
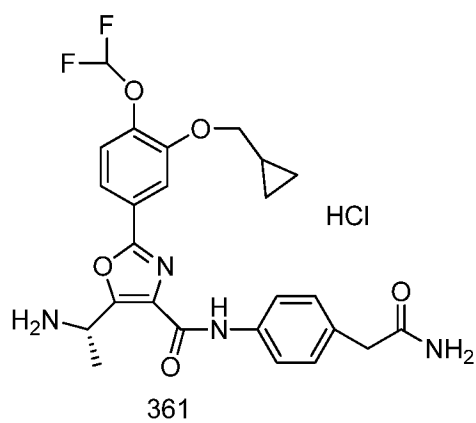
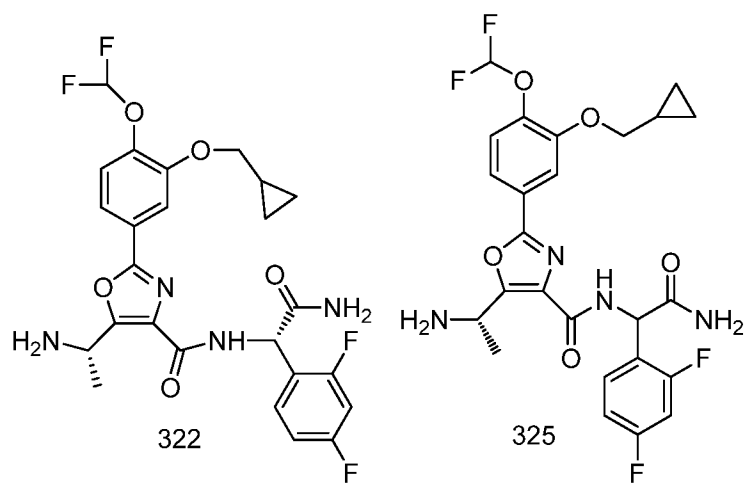
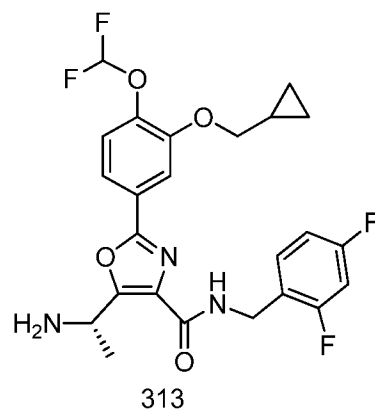
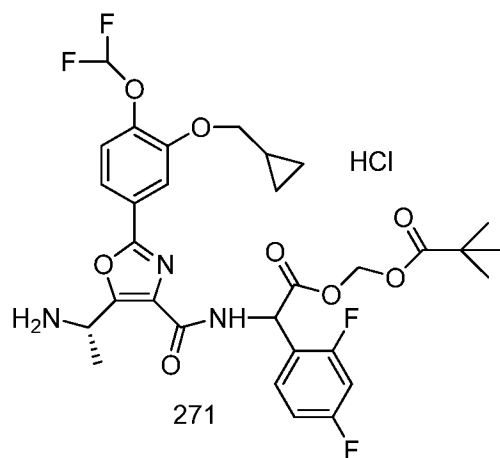


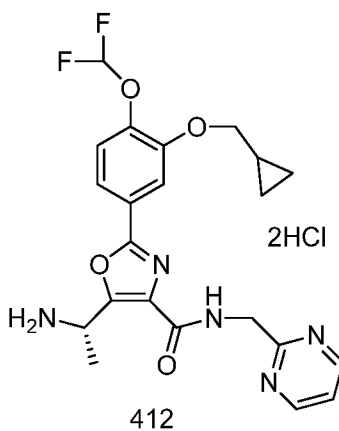
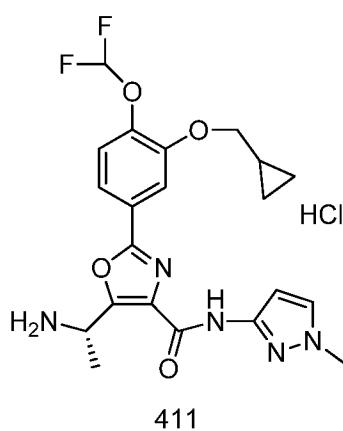
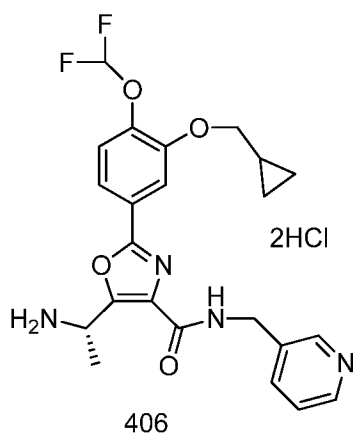
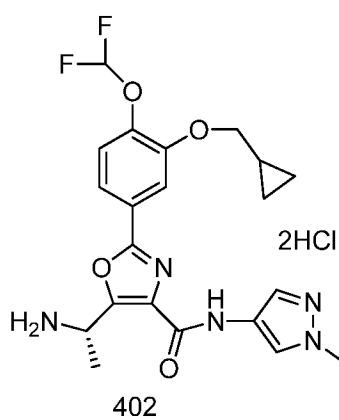
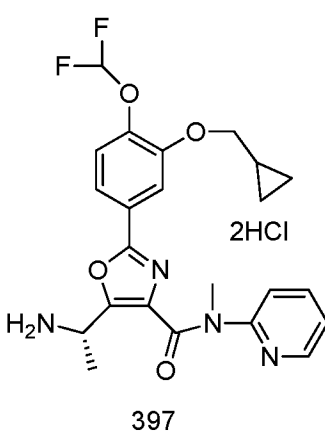
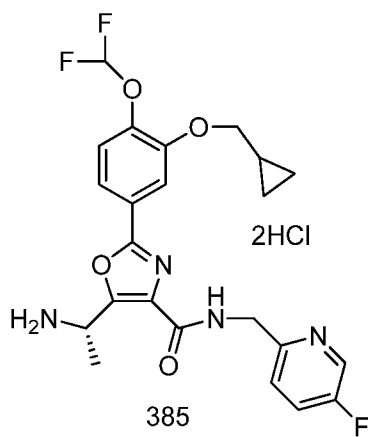
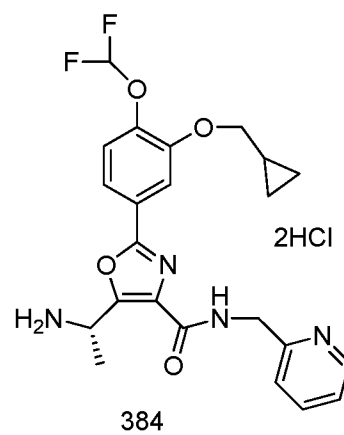
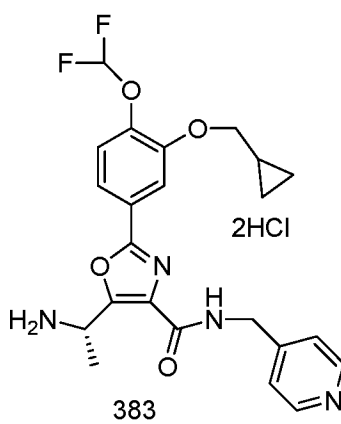
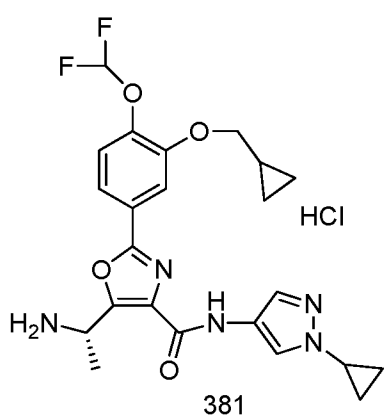
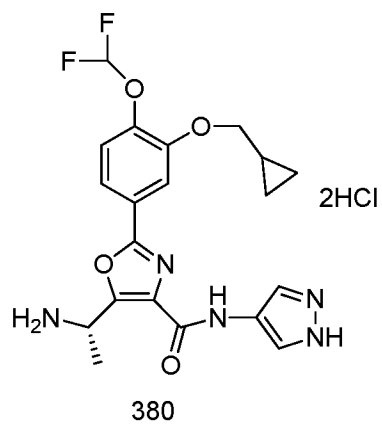
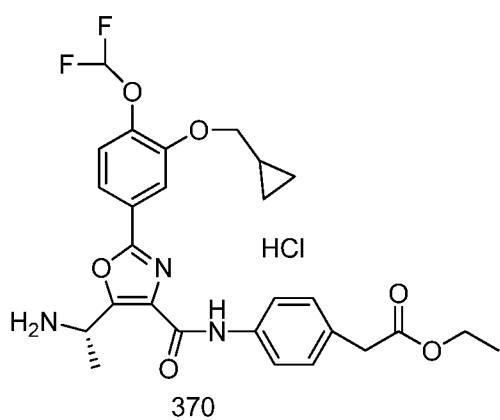


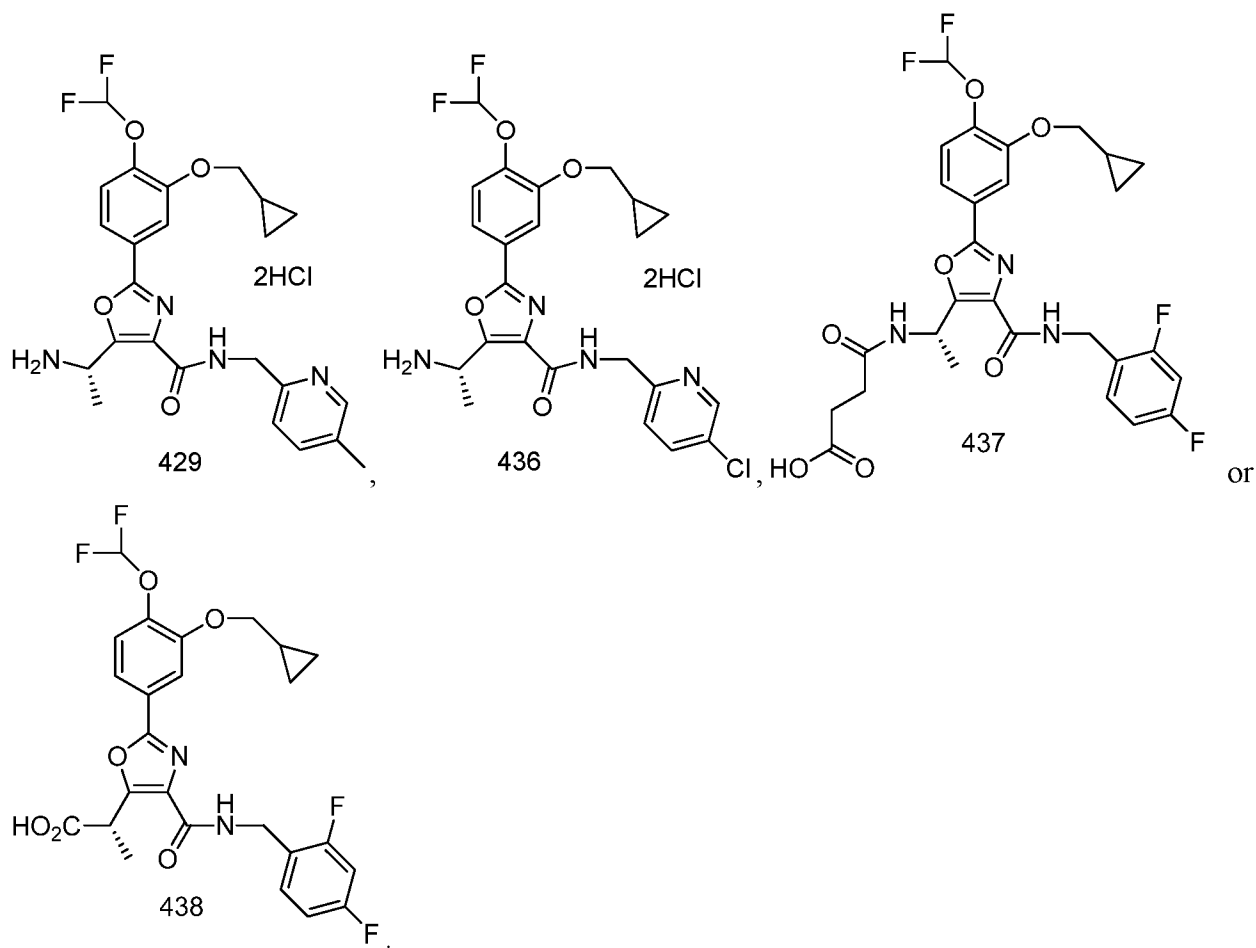












18. A pharmaceutical composition comprising the compound according to any one of claims 1-17.

19. The pharmaceutical composition according to claim 18 further comprising at least one pharmaceutically acceptable carrier, excipient, diluent, adjuvant or vehicle.

20. The pharmaceutical composition according to claim 18 or claim 19 further comprising an additional therapeutic agent, wherein the additional therapeutic agent is a medicament, active agent, or a combination thereof, used for treating chronic obstructive pulmonary disease.

21. The pharmaceutical composition according to claim 20, wherein the additional therapeutic agent is sodium pyruvate, doxofylline, roflumilast, apremilast, tetomilast, tielupkast, theophylline, formoterol, salmeterol, fluticasone propionate, salmeterol xinafoate/fluticasone propionate, rolipram, piclamilast, cilomilast, CDP-840, indacaterol, olodaterol, QVA149, midesteine, zileuton, salbutamol, carboxirole, budesonide and epimer thereof, beclomethasone dipropionate (BDP), triamcinolone acetonide, flunisolide, mometasone furoate, rofleponide, ciclesonide, ipratropium bromide, ipratropium bromide/albuterol, oxitropium bromide, tiotropium bromide, glycopyrronium bromide, umeclidinium bromide, vilanterol,

umeclidinium/vilanterol, aclidinium bromide, aclidinium bromide/formoterol fumarate, LAS40464, LAS100977 (abediterol), AZD-8999, RPL-554, OCID-2987, CHF-6001, CR-3465, HPP-737, fluticasone furoate/vilanterol (FF/VI), benralizumab, revatropate, or a combination thereof.

22. Use of the compound according to any one of claims 1-17 or the pharmaceutical composition according to any one of claims 18-21 in the manufacture of a medicament for preventing, managing, treating or lessening a phosphodiesterase-4 (PDE-4) mediated disorder in a subject.

23. The use according to claim 22, wherein the phosphodiesterase-4 (PDE-4) mediated disorder is respiratory disease, allergy, inflammation, a central nervous system (CNS) disorder, pulmonary fibrosis or non-insulin dependent diabetes.

24. The use according to claim 23, wherein the respiratory disease is chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, asthma, chronic pneumonia, pneumoconiosis, bronchitis, allergic bronchitis, bronchiectasis, tuberculosis fibrosis, cystic pulmonary fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, acute respiratory distress syndrome (ARDS) or respiratory inflammation.

25. The use according to claim 23, wherein the inflammation is allergic conjunctivitis, atopic dermatitis, allergic dermatitis, rheumatoid arthritis, interstitial cystitis, allergic rhinitis, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis or psoriatic arthritis.

26. A method for preventing, managing, treating or lessening a phosphodiesterase-4 (PDE-4) mediated disorder in a subject, comprising administering to the subject a therapeutically effective amount of the compound according to any one of claims 1-17 or the pharmaceutical composition according to any one of claims 18-21.

27. The method according to claim 26, wherein the phosphodiesterase-4 (PDE-4) mediated disorder is respiratory disease, allergy, inflammation, a central nervous system (CNS) disorder, pulmonary fibrosis or non-insulin dependent diabetes.

28. The method according to claim 27, wherein the respiratory disease is chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, asthma, chronic pneumonia, pneumoconiosis, bronchitis, allergic bronchitis, bronchiectasis, tuberculosis fibrosis, cystic pulmonary fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, acute respiratory

distress syndrome (ARDS) or respiratory inflammation.

29. The method according to claim 27, wherein the inflammation is allergic conjunctivitis, atopic dermatitis, allergic dermatitis, rheumatoid arthritis, interstitial cystitis, allergic rhinitis, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis or psoriatic arthritis.

30. The compound according to any one of claims 1-17 or the pharmaceutical composition according to any one of claims 18-21 for use in preventing, managing, treating or lessening a phosphodiesterase-4 (PDE-4) mediated disorder in a subject.

31. The compound or the pharmaceutical composition according to claim 30, wherein the phosphodiesterase-4 (PDE-4) mediated disorder is respiratory disease, allergy, inflammation, a central nervous system (CNS) disorder, pulmonary fibrosis or non-insulin dependent diabetes.

32. The compound or the pharmaceutical composition according to claim 31, wherein the respiratory disease is chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, asthma, chronic pneumonia, pneumoconiosis, bronchitis, allergic bronchitis, bronchiectasis, tuberculosis fibrosis, cystic pulmonary fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, acute respiratory distress syndrome (ARDS) or respiratory inflammation.

33. The compound or the pharmaceutical composition according to claim 31, wherein the inflammation is allergic conjunctivitis, atopic dermatitis, allergic dermatitis, rheumatoid arthritis, interstitial cystitis, allergic rhinitis, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis or psoriatic arthritis.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/077431

A. CLASSIFICATION OF SUBJECT MATTER

C07D 263/08(2006.01)i; C07D 233/04(2006.01)i; C07D 277/08(2006.01)i; A61K 31/4164(2006.01)i; A61K 31/42(2006.01)i; A61K 31/426(2006.01)i; A61P 11/00(2006.01)i

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)

C07D263/-; C07D233/-; C07D277/-; A61K31/-; A61P11/-

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)

CNPAT,CNKI,WPI,EPODOC,STN(Registry,CAplus):PULMONARY, HETEROAROMATIC, INBIHITOR?, PHOSPHODIESTERASE, OXAZOLE,DIZOLE,THIAZOLE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007058338 A2 (OTSUKA PHARMA CO LTD) 24 May 2007 (2007-05-24) claim 1, page 43 line 5-31, table26 example 248, 250, 251	1-25, 30-33
A	CN 101616901 A (RANBAXY LAB LTD) 30 December 2009 (2009-12-30) the whole document	1-25, 30-33
A	CN 101166733 A (CONTICELLO R D) 23 April 2008 (2008-04-23) the whole document	1-25, 30-33
A	CN 1805929 A (CONTICELLO R DET AL) 19 July 2006 (2006-07-19) the whole document	1-25, 30-33

☐ 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

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“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

“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

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