Pyrimidine and Pyridine Derivatives and Their Pharmaceutical Use and Compositions

Field of the Invention

This invention relates to pyrimidine and pyridine derivatives. Such compounds have been shown to inhibit matrix metalloproteinase enzymes. These compounds are useful for treating diseases resulting from MMP-mediated tissue breakdown such as heart disease, cardiac insufficiency, inflammatory bowel disease, multiple sclerosis, osteoarthritis, rheumatoid arthritis, arthritis other than osteo- or rheumatoid arthritis, heart failure, age-related macular degeneration, chronic obstructive pulmonary disease, asthma, periodontal diseases, psoriasis, atherosclerosis, fibrotic disorders in the kidney, lung, and/or osteoporosis.

Background of the Invention

Matrix metalloproteinases (sometimes referred to as MMPs) are naturally occurring enzymes found in most mammals. Over-expression and activation of MMPs, or an imbalance between MMPs and inhibitors of MMPs, have been suggested as factors in the pathogenesis of diseases characterized by the breakdown of extracellular matrix or connective tissues.

To date, 24 different members of the MMP family have been identified in vertebrates, 23 of which are found in human, including collagenases (MMP-1, MMP-8, MMP-13), gelatinases (MMP-2 and MMP-9), stromelysins (MMP-3, MMP-10, MMP-11), matrilysins (MMP-7 and MMP-26), membrane-type (MMT-14, MMP-15, MMP-16, MMT-17, MMP-24, MMT-25), as well as metalloelastases (MMP-12, MMP-19, MMP-20, MMP-22, MMP-23) (See Visse and Nagase (2003) *Circ. Res.* 92:827-839) These enzymes have been implicated with a number of diseases which result from breakdown of connective tissue, including such diseases as rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, multiple sclerosis, gingivitis, corneal epidermal and gastric ulceration, atherosclerosis, neointimal proliferation which leads to restenosis and ischemic heart failure, and tumor metastasis. Inhibiting matrix metalloproteinase enzymes, thereby curtailing and/or eliminating the breakdown of connective tissues that results in the disease states, is a recognized method for preventing and treating these and other diseases.

There is a catalytic zinc domain in matrix metalloproteinases that is typically the focal point for inhibitor design. The modification of substrates by introducing zinc-chelating groups has generated potent inhibitors such as peptide hydroxamates and thiol-containing peptides. Peptide hydroxamates and the natural endogenous inhibitors of MMPs (TIMPs) have been used successfully to treat animal models of cancer and inflammation. MMP inhibitors have also been used to prevent and treat congestive heart failure and other cardiovascular diseases; see, e.g., U.S. Patent No. 5,948,780.

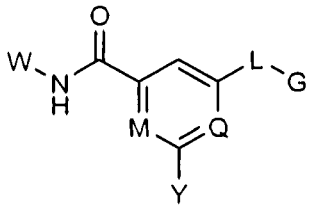
A major limitation on the use of currently known MMP inhibitors is their lack of specificity for any particular enzyme. Recent data has established that specific MMP enzymes are associated with some diseases, with no effect on others. The MMPs are generally categorized based on their substrate specificity, and indeed the collagenase subfamily of MMP-1, MMP-8, and MMP-13 selectively cleave native interstitial collagens, and thus are associated only with diseases linked to such interstitial collagen tissue. This is evidenced by the recent discovery that MMP-13 alone is over-

expressed in breast carcinoma, while MMP-1 alone is over expressed in papillary carcinoma (see Chen et al., *J. Amer. Chem. Soc.*, 2000;122:9648-54).

Selective inhibitors of MMP-13 include a compound named WAY 170523, which has been reported by Chen et al., *supra*, 2000. Other selective inhibitors of MMP-13 are reported in International Patent Application Publication No. WO 05/105760. Other selective inhibitors of MMP-13 are reported in U.S. Patent Application Publication No. US20030229103. Other selective inhibitors of MMP-13 are reported in U.S. Patent Application Publication No. US20040167120. Other selective inhibitors of MMP-13 are reported in U.S. Patent Application Publication No. US20050004111. Other selective inhibitors of MMP-13 are reported in U.S. Patent Application Publication No. US20060173183. Other selective inhibitors of MMP-13 are reported in International Patent Application Publication No. WO 06/128184. Other selective inhibitors of MMP-13 are reported in Co-assigned International Patent Application Publication No. WO 02/64572. Other selective inhibitors of MMP-13 are reported in Co-assigned International Patent Application Publication No. WO 02/64599. U.S. Patent No. 6,008,243 discloses inhibitors of MMP-13. However, no selective or nonselective inhibitor of MMP-13 has been approved and marketed for the treatment of any disease in any mammal. Accordingly, the need continues to find new low molecular weight compounds that are potent and selective MMP inhibitors, and that have an acceptable therapeutic index of toxicity/potency to make them amenable for use clinically in the prevention and treatment of the associated disease states.

Summary of the Invention

The present invention provides compounds of Formula I:



I

wherein

G is (C_{1-3} alkylenyl)-R^a or R^a, wherein said C_{1-3} alkylenyl may be substituted by one or more substituents selected from OH and F;

R^a is C_{1-6} alkyl, 3- to 7-membered heterocycloalkyl, or 3- to 8-membered cycloalkyl, wherein said C_{1-6} alkyl may be substituted by one or more substituents selected from F, $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said heterocycloalkyl and cycloalkyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

M is N or C-R^b;

Q is N or C-R^c, provided that if Q is C-R^c, M is N;

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or 9-membered heteroaryl-(C_{1-6} alkylenyl), wherein said phenyl, pyridyl, or 9-membered heteroaryl is substituted by one or more groups selected from R^{30} and R^{31};

Y is C_{1-6} alkyl, C_{1-6} haloalkyl; or C_{1-6} hydroxyalkyl;

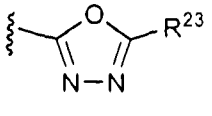
L is 5-membered heteroaryl;

R^2 is H, F, CN, $-OR^5$, R^{12}, $-C(=O)R^7$, $-NR^8R^{33}$, $-NR^8C(=O)R^9$, $-NR^8SO_2R^{36}$, or $-SO_2R^{12}$;

R^3 is H, F, CN, or $-OR^{22}$;

R^4 is H, $-(C_{1-6}$ alkylene$)R^6$, $-C(=O)R^9$, or $-SO_2R^{12}$;

R^5 is H or $-(C_{1-6}$ alkyl), wherein said C_{1-6} alkyl may be substituted by one or more R^{26} substituents;

R^6 is H, CN, $-OR^{23}$, $-SO_2R^{37}$, $-NR^{24}C(=O)R^{23}$, $-NR^{24}SO_2R^{37}$, or ;

R^7 is $-(C_{1-6}$ alkyl), $-(C_{1-6}$ haloalkyl), $-(C_{1-6}$ alkylene)OH, $-NR^{38}R^{39}$, $-NHSO_2CH_3$, or $-OR^{25}$;

R^9 is $-(C_{1-6}$ alkylene$)R^{28}$, $-NHR^{24}$, or $-OR^{25}$;

R^{10} is H, F, CN, R^{12}, or $-C(=O)R^7$;

R^{11} is H, F, CN, $-OR^5$, R^{12}, $-C(=O)R^7$, $-NR^8R^{33}$, $-NR^8C(=O)R^9$, $-NR^8SO_2R^{36}$, or $-SO_2R^{12}$;

R^{12} is $-(C_{1-6}$ alkyl), wherein said C_{1-6} alkyl may be substituted by one or more substituents selected from CN, $-OR^{23}$, $-SR^{23}$, $-SO_2R^{37}$, $-NR^8R^{33}$, $-NR^{24}C(=O)R^{23}$, and $-NR^{24}SO_2R^{23}$, provided that any one carbon atom of said C_{1-6} alkyl is not substituted by more than one CN or more than one $-OR^{23}$;

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H or $-(C_{1-6}$ alkyl);

R^{21} is H, F, or R^{12};

R^{23} is H, $-(C_{1-6}$ alkyl), or $-(C_{1-6}$ alkylene)OH;

R^{26} is H, OH, halo, NH_2, or SH;

R^{28} is H, NH_2, or $-OR^{29}$;

R^{29} is H, (C_{1-6} alkyl), or $-C(=O)(C_{1-6}$ alkyl);

R^{30} is H or F;

R^{31} is F, Cl, Br, -CN, $-C(=O)NH_2$, -OH, $-OR^{32}$, $-OCH_2CH_2OR^{25}$, R^{32}, ,or (C_{1-6} alkyl) optionally substituted by $-OR^{25}$ or $-OCH_2CH_2OR^{25}$

where R^{30} and R^{31} when adjacent may be taken together to constitute a group of the formula $-O-(CH_2)_n-$ or $-O-(CH_2)_n-O-$;

n is 1 or 2;

R^{32} is $-(C_{1-6}$ alkyl) optionally substituted with one, two, or three F;

R^{36} is $-(C_{1-6}$ alkyl) or $-(C_{3-6}$ cycloalkyl); and

R^{37} is $-(C_{1-6}$ alkyl), $-(C_{3-6}$ cycloalkyl), or $-(C_{1-6}$ alkylene)OH;

R^{38} and R^{39} are independently H, $-(C_{1-6}$ alkyl), or R^{38} and R^{39} taken together form a 5- or 6-membered heterocycloalkyl;

or a pharmaceutically-acceptable salt thereof.

This invention also includes pharmaceutically acceptable salts, solvates and hydrates of compounds of Formula I. This invention also includes all tautomers and stereochemical isomers of these compounds.

This invention also is directed, in part, to a method for treating an MMP-13 mediated disorder in a mammal. Such disorders include rheumatoid arthritis and osteoarthritis. The method comprises

administering a compound of Formula I or a pharmaceutically acceptable salt thereof, to the mammal in an amount that is therapeutically-effective to treat the condition.

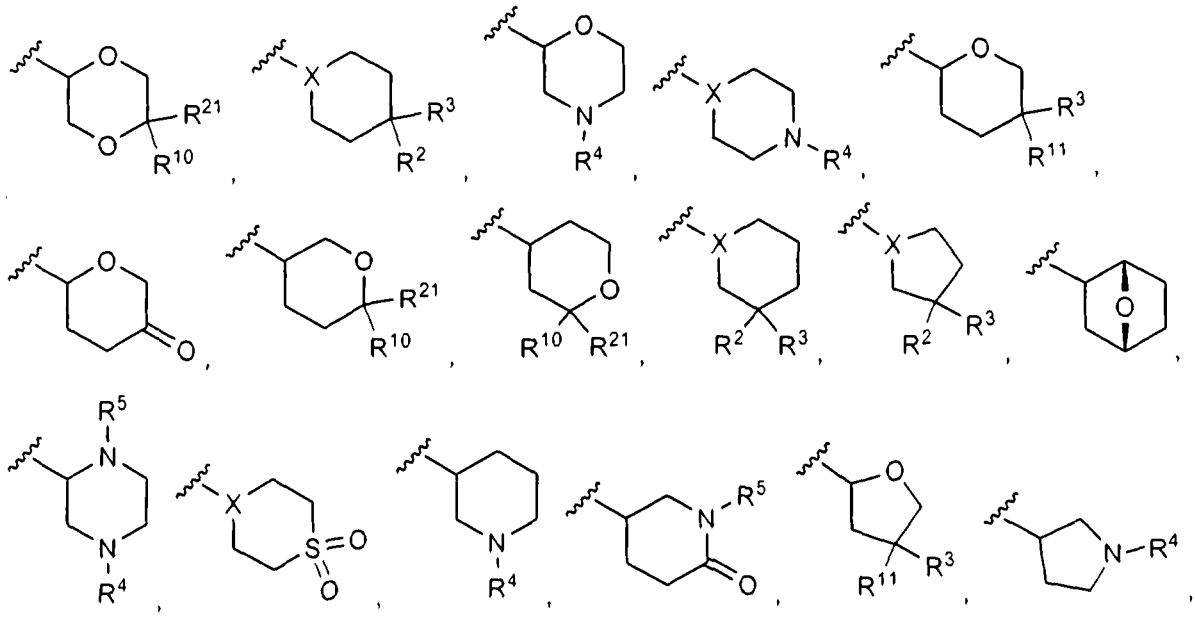
Detailed Description of the Invention

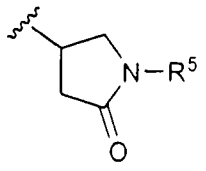
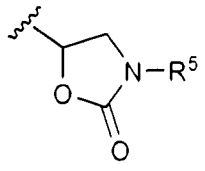
One embodiment of the invention is a compound of Formula I as shown above.

Another embodiment of the invention is a compound of Formula I wherein R^a is C_{1-6} alkyl, 1,4-dioxanyl, piperidinyl, cyclohexyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydropyranonyl, pyrrolidinyl, cyclopentyl, 7-oxa-bicyclo[2.2.1]heptanyl, piperazinyl, 1,1'-dioxothiomorpholinyl, tetrahydro-1,1'-dioxothiopyranyl, tetrahydrothiopyranyl, piperidinonyl, tetrahydrofuryl, pyrrolidinonyl, or oxazolidinonyl, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$, and wherein said 1,4-dioxyl, piperidinyl, cyclohexyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydropyranonyl, pyrrolidinyl, cyclopentyl, 7-oxa-bicyclo[2.2.1]heptanyl, piperazinyl, 1,1'-dioxothiomorpholinyl, tetrahydro-1,1'-dioxothiopyranyl, tetrahydrothiopyranyl, piperidinonyl, tetrahydrofuryl, pyrrolidinonyl, or oxazolidinonyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21}.

Another embodiment of the invention is a compound of Formula I wherein R^a is C_{1-6} alkyl, 1,4-dioxanyl substituted by R^{10} and R^{21}, piperidinyl substituted by R^2 and R^3 or by R^4, cyclohexyl substituted by R^2 and R^3 or by R^4, morpholinyl substituted by R^4, thiomorpholinyl substituted by R^{10} and R^{21}, tetrahydropyranyl substituted by R^3 and R^{11} or by R^{10} and R^{21}, tetrahydropyranonyl, pyrrolidinyl substituted by R^2 and R^3 or by R^4, cyclopentyl substituted by R^2 and R^3, 7-oxa-bicyclo[2.2.1]heptanyl, piperazinyl substituted by R^4 and R^5, 1,1'-dioxothiomorpholinyl, tetrahydro-1,1'-dioxothiopyranyl, tetrahydrothiopyranyl, piperidinonyl substituted by R^5, tetrahydrofuryl substituted by R^3 and R^{11}, pyrrolidinonyl substituted by R^5, oxazolidinonyl substituted by R^5, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

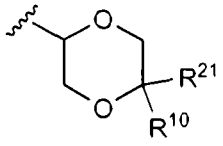
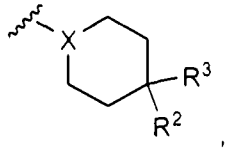
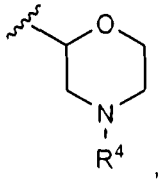
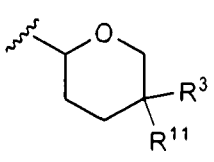
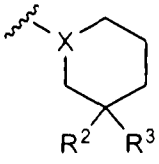
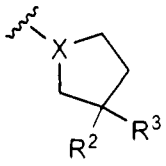
Another embodiment of the invention is a compound of Formula I wherein R^a is C_{1-6} alkyl,




, or 
, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$; and

X is N or CH, provided that when X is N, G is (C_{2-3} alkylenyl)-R^a, wherein said C_{1-3} alkylenyl may be substituted by one or more substituents selected from OH and F.

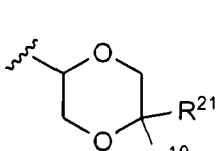
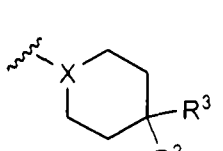
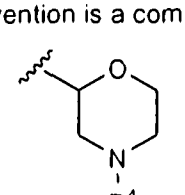
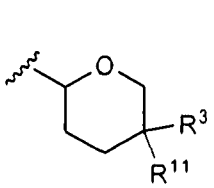
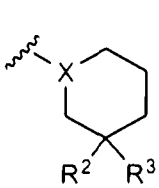
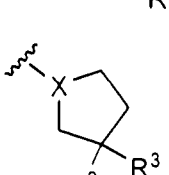
Another embodiment of the invention is a compound of Formula I wherein R^a is C_{1-6} alkyl,


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, or 
, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

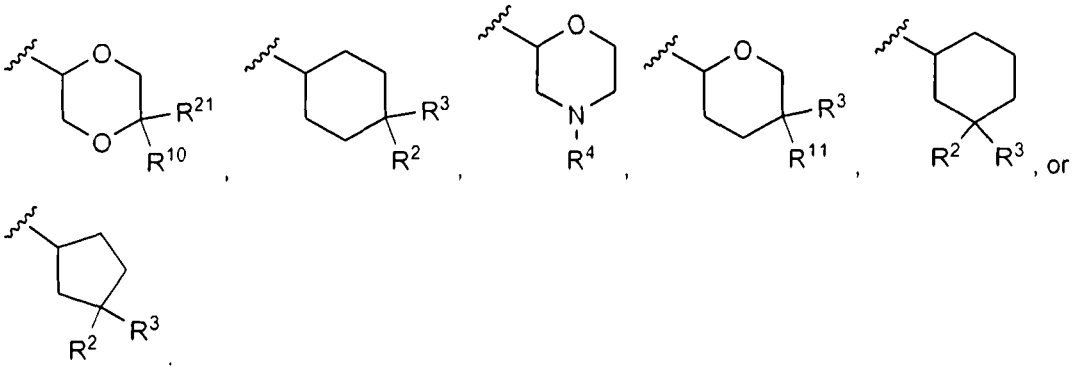
Another embodiment of the invention is a compound of Formula I wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

Another embodiment of the invention is a compound of Formula I wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more $-OR^{34}$.

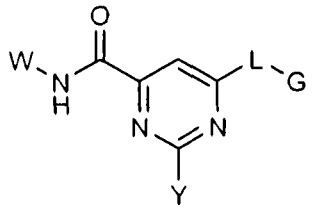
Another embodiment of the invention is a compound of Formula I wherein R^a is


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Another embodiment of the invention is a compound of Formula I wherein R^a is



Another embodiment of the invention is a compound of Formula II:



II

wherein G is (C_{1-3} alkylenyl)-R^a or R^a, wherein said C_{1-3} alkylenyl may be substituted by one or more substituents selected from OH and F;

R^a is C_{1-6} alkyl, 3- to 7-membered heterocycloalkyl, or 3- to 8-membered cycloalkyl, wherein said C_{1-6} alkyl may be substituted by one or more substituents selected from F, $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said heterocycloalkyl and cycloalkyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or 9-membered heteroaryl-(C_{1-6} alkylenyl), wherein said phenyl, pyridyl, or 9-membered heteroaryl is substituted by one or more groups selected from R^{30} and R^{31};

Y is C_{1-6} alkyl, C_{1-6} haloalkyl; or C_{1-6} hydroxyalkyl;

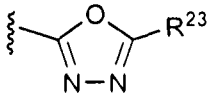
L is 5-membered heteroaryl;

R^2 is H, F, CN, $-OR^5$, R^{12}, $-C(=O)R^7$, $-NR^8R^{33}$, $-NR^8C(=O)R^9$, $-NR^8SO_2R^{36}$, or $-SO_2R^{12}$;

R^3 is H, F, CN, or $-OR^{22}$;

R^4 is H, $-(C_{1-6}$ alkylene)R^6, $-C(=O)R^9$, or $-SO_2R^{12}$;

R^5 is H or $-(C_{1-6}$ alkyl), wherein said C_{1-6} alkyl may be substituted by one or more R^{26} substituents;

R^6 is H, CN, $-OR^{23}$, $-SO_2R^{37}$, $-NR^{24}C(=O)R^{23}$, $-NR^{24}SO_2R^{37}$, or ;

R^7 is $-(C_{1-6}$ alkyl), $-(C_{1-6}$ haloalkyl), $-(C_{1-6}$ alkylene)OH, $-NR^{38}R^{39}$, $-NHSO_2CH_3$, or $-OR^{25}$;

R^9 is $-(C_{1-6}$ alkylene)R^{28}, $-NHR^{24}$, or $-OR^{25}$;

R^{10} is H, F, CN, R^{12}, or $-C(=O)R^7$;

R^{11} is H, F, CN, $-OR^5$, R^{12}, $-C(=O)R^7$, $-NR^8R^{33}$, $-NR^8C(=O)R^9$, $-NR^8SO_2R^{36}$, or $-SO_2R^{12}$;

R^{12} is -(C_{1-6} alkyl), wherein said C_{1-6} alkyl may be substituted by one or more substituents selected from CN, -OR^{23}, -SR^{23}, -SO_2R^{37}, -NR^8R^{33}, -$NR^{24}C(=O)R^{23}$, and -$NR^{24}SO_2R^{23}$, provided that any one carbon atom of said C_{1-6} alkyl is not substituted by more than one CN or more than one -OR^{23};

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H or -(C_{1-6} alkyl);

R^{21} is H, F, or R^{12};

R^{23} is H, -(C_{1-6} alkyl), or -(C_{1-6} alkylene)OH;

R^{26} is H, OH, halo, NH_2, or SH;

R^{28} is H, NH_2, or -OR^{29};

R^{29} is H, (C_{1-6} alkyl), or -C(=O)(C_{1-6} alkyl);

R^{30} is H or F;

R^{31} is F, Cl, Br, -CN, -$C(=O)NH_2$, -OH, -OR^{32}, -$OCH_2CH_2OR^{25}$, R^{32}, ,or (C_{1-6} alkyl) optionally substituted by –OR^{25} or -$OCH_2CH_2OR^{25}$

where R^{30} and R^{31} when adjacent may be taken together to constitute a group of the formula -O-$(CH_2)_n$- or -O-$(CH_2)_n$-O-;

n is 1 or 2;

R^{32} is -(C_{1-6} alkyl) optionally substituted with one, two, or three F;

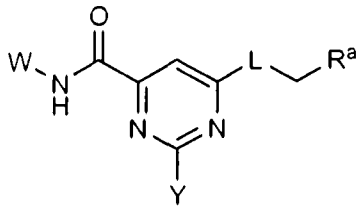
R^{36} is -(C_{1-6} alkyl) or -(C_{3-6} cycloalkyl); and

R^{37} is -(C_{1-6} alkyl), -(C_{3-6} cycloalkyl), or -(C_{1-6} alkylene)OH;

R^{38} and R^{39} are independently H, -(C_{1-6} alkyl), or R^{38} and R^{39} taken together form a 5- or 6-membered heterocycloalkyl;

or a pharmaceutically-acceptable salt thereof.

Another embodiment of the invention is a compound of Formula IIA:

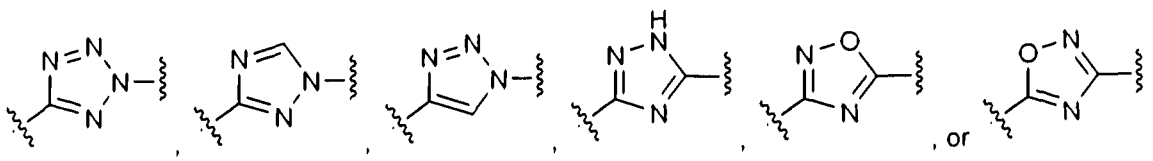


IIA

wherein R^a, W, Y, and L are as defined hereinabove for Formula II.

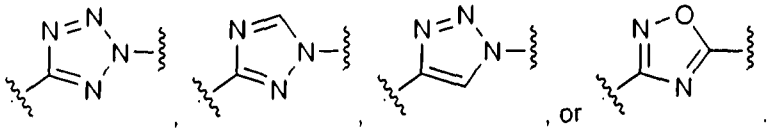
Another embodiment of the invention is a compound of Formula IIA wherein L is triazolyl, tetrazolyl, or oxadiazolyl.

Another embodiment of the invention is a compound of Formula IIA wherein L is

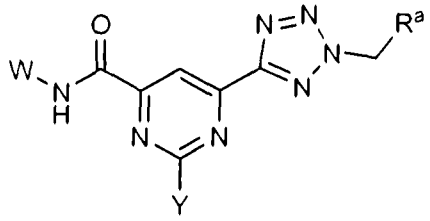


, or .

Another embodiment of the invention is a compound of Formula IIA wherein L is



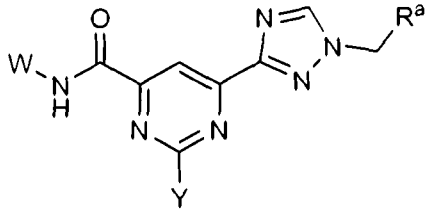
Another embodiment of the invention is a compound of Formula IIA-1



IIA-1

wherein R^a, W, and Y are as defined hereinabove for Formula II.

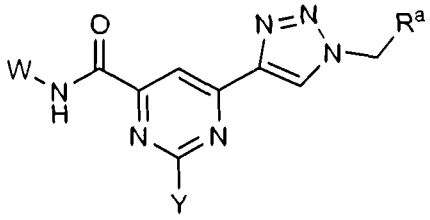
Another embodiment of the invention is a compound of Formula IIA-2



IIA-2

wherein R^a, W, and Y are as defined hereinabove for Formula II.

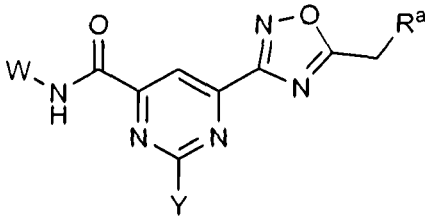
Another embodiment of the invention is a compound of Formula IIA-3



IIA-3

wherein R^a, W, and Y are as defined hereinabove for Formula II.

Another embodiment of the invention is a compound of Formula IIA-4

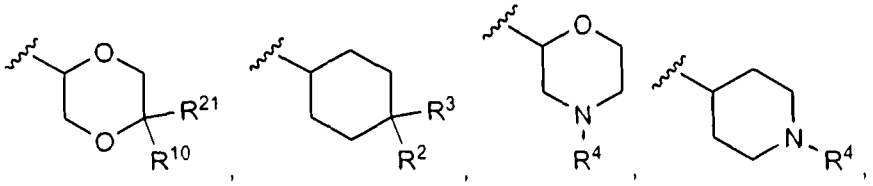


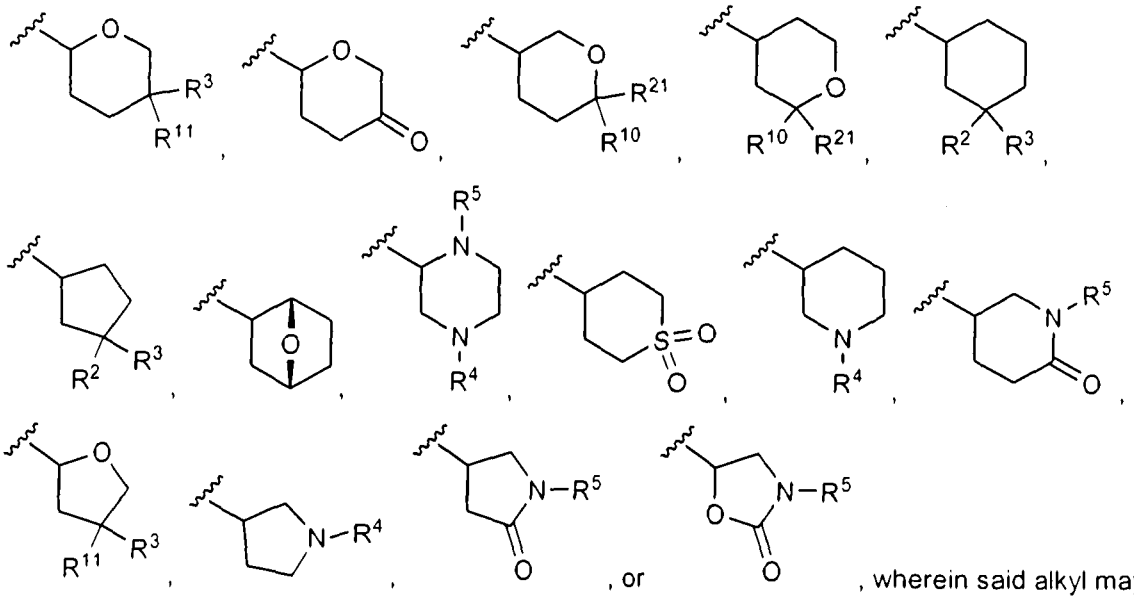
IIA-4

wherein R^a, W, and Y are as defined hereinabove for Formula II.

Another embodiment of the invention is a compound of Formula IIA, IIA-1, IIA-2, IIA-3, or IIA-4

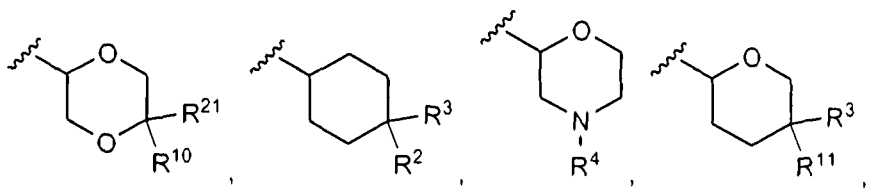
wherein R^a is C_{1-6} alkyl,

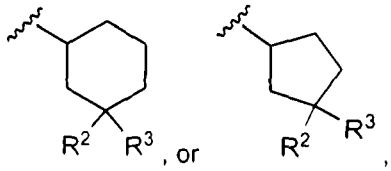




substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

Another embodiment of the invention is a compound of Formula IIA, IIA-1, IIA-2, IIA-3, or IIA-4 wherein R^a is C_{1-6} alkyl,



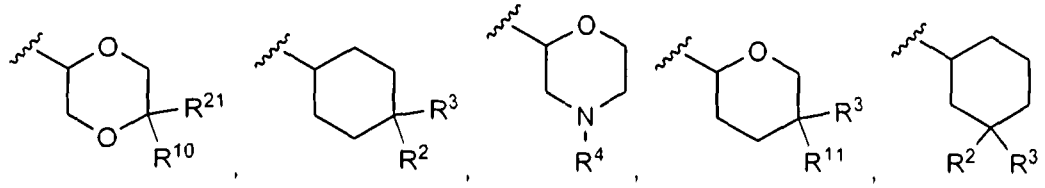


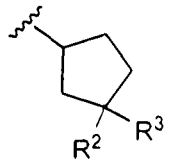
, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

Another embodiment of the invention is a compound of Formula IIA, IIA-1, IIA-2, IIA-3, or IIA-4 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

Another embodiment of the invention is a compound of Formula IIA, IIA-1, IIA-2, IIA-3, or IIA-4 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more $-OR^{34}$.

Another embodiment of the invention is a compound of Formula IIA, IIA-1, IIA-2, IIA-3, or IIA-4 wherein R^a is





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Another embodiment of the invention is a compound of Formula IIA, IIA-1, IIA-2, IIA-3, or IIA-4 wherein Y is methyl.

Another embodiment of the invention is a compound of Formula IIA, IIA-1, IIA-2, IIA-3, or IIA-4 wherein W is phenyl-(C_{1-6} alkylenyl), wherein said phenyl is substituted by one or more groups selected from R^{30} and R^{31}.

Another embodiment of the invention is a compound of Formula IIA, IIA-1, IIA-2, IIA-3, or IIA-4 wherein W is phenylmethyl, wherein said phenyl is substituted by one or more groups selected from R^{30} and R^{31}.

Another embodiment of the invention is a compound shown in Table 1.

Table 1

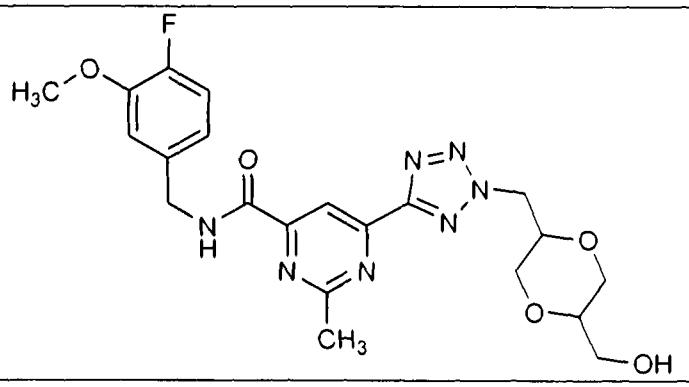
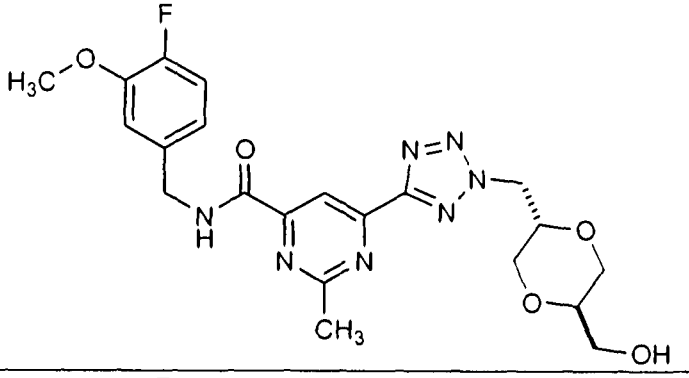
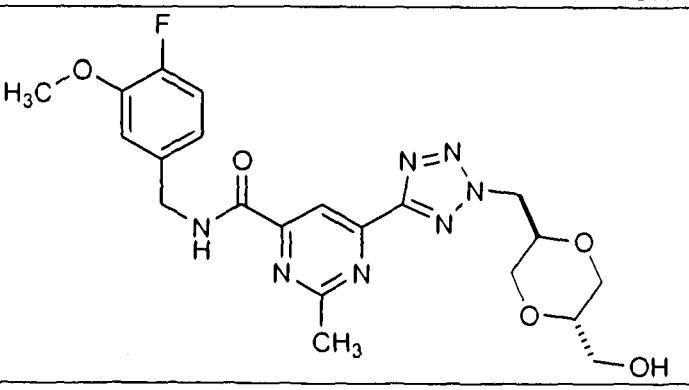
Compound Name	Structure
N-(4-fluoro-3-methoxybenzyl)-6-(2-((5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide	
N-(4-fluoro-3-methoxybenzyl)-6-(2-(((2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide	
N-(4-fluoro-3-methoxybenzyl)-6-(2-(((2R,5S)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide	

Table 1

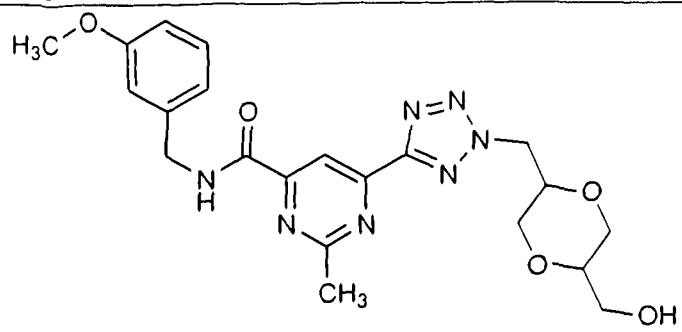
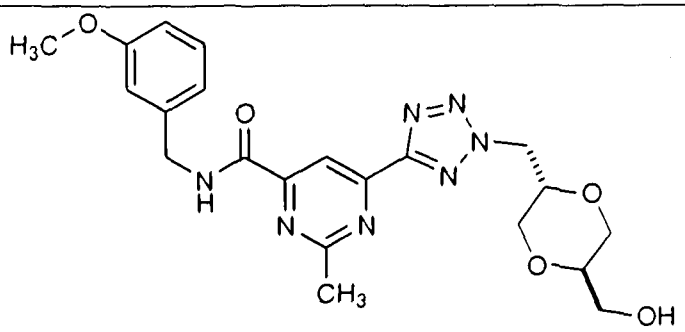
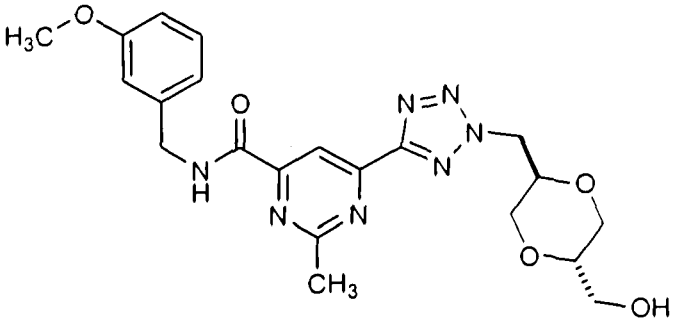
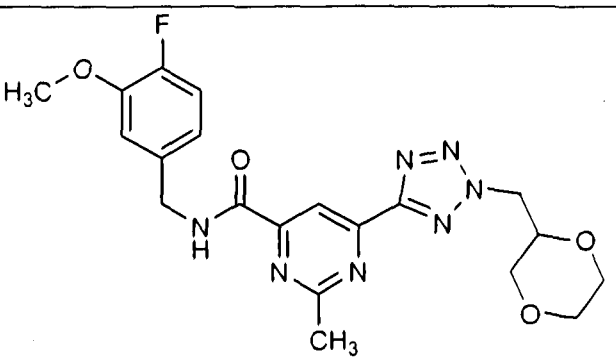
Compound Name	Structure
N-(3-methoxybenzyl)-6-(2-((5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide	
N-(3-methoxybenzyl)-6-(2-(((2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide	
N-(3-methoxybenzyl)-6-(2-(((2R,5S)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide	
6-(2-((1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-N-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide	

Table 1

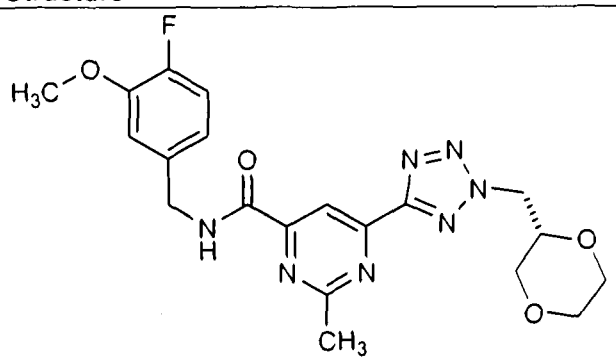
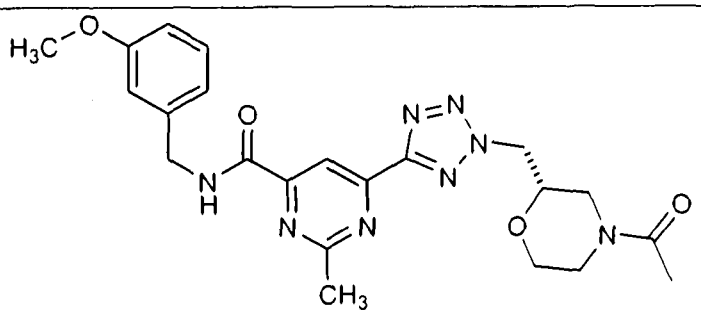
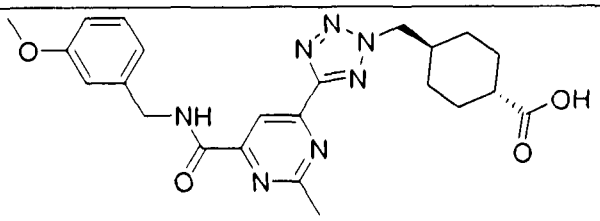
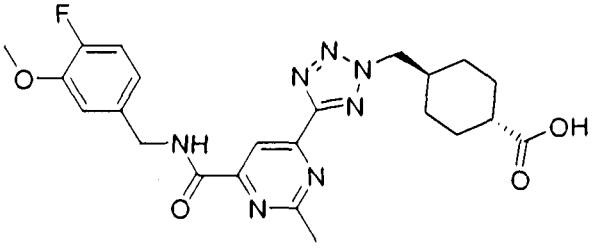
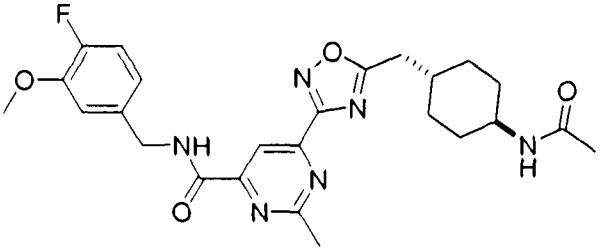
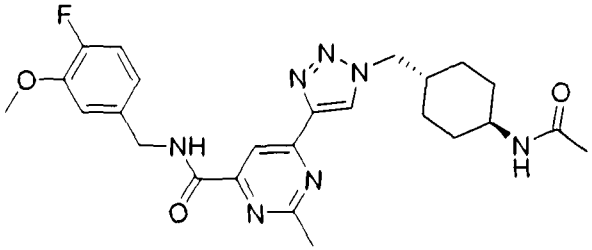
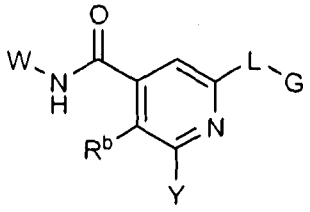
Compound Name	Structure
6-(2-(((S)-1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-N-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide	
N-(3-methoxybenzyl)-6-(2-(((S)-4-acetylmorpholin-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide	
(1r,4r)-4-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2H-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid	
(1r,4r)-4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2H-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid	
N-(4-fluoro-3-methoxybenzyl)-6-(5-((*trans*-4-acetamidocyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide	

Table 1	
Compound Name	**Structure**
N-(4-fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide	

Another embodiment of the invention is a compound of Formula III:



III

wherein G is (C_{1-3} alkylenyl)-R^a or R^a, wherein said C_{1-3} alkylenyl may be substituted by one or more substituents selected from OH and F;

R^a is C_{1-6} alkyl, 3- to 7-membered heterocycloalkyl, or 3- to 8-membered cycloalkyl, wherein said C_{1-6} alkyl may be substituted by one or more substituents selected from F, $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said heterocycloalkyl and cycloalkyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or 9-membered heteroaryl-(C_{1-6} alkylenyl), wherein said phenyl, pyridyl, or 9-membered heteroaryl is substituted by one or more groups selected from R^{30} and R^{31};

Y is C_{1-6} alkyl, C_{1-6} haloalkyl; or C_{1-6} hydroxyalkyl;

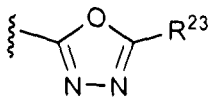
L is 5-membered heteroaryl;

R^2 is H, F, CN, $-OR^5$, R^{12}, $-C(=O)R^7$, $-NR^8R^{33}$, $-NR^8C(=O)R^9$, $-NR^8SO_2R^{36}$, or $-SO_2R^{12}$;

R^3 is H, F, CN, or $-OR^{22}$;

R^4 is H, $-(C_{1-6}$ alkylene)R^6, $-C(=O)R^9$, or $-SO_2R^{12}$;

R^5 is H or $-(C_{1-6}$ alkyl), wherein said C_{1-6} alkyl may be substituted by one or more R^{26} substituents;

R^6 is H, CN, $-OR^{23}$, $-SO_2R^{37}$, $-NR^{24}C(=O)R^{23}$, $-NR^{24}SO_2R^{37}$, or ;

R^7 is $-(C_{1-6}$ alkyl), $-(C_{1-6}$ haloalkyl), $-(C_{1-6}$ alkylene)OH, $-NR^{38}R^{39}$, $-NHSO_2CH_3$, or $-OR^{25}$;

R^9 is $-(C_{1-6}$ alkylene)R^{28}, $-NHR^{24}$, or $-OR^{25}$;

R^{10} is H, F, CN, R^{12}, or $-C(=O)R^7$;

R^{11} is H, F, CN, $-OR^5$, R^{12}, $-C(=O)R^7$, $-NR^8R^{33}$, $-NR^8C(=O)R^9$, $-NR^8SO_2R^{36}$, or $-SO_2R^{12}$;

R^{12} is -(C_{1-6} alkyl), wherein said C_{1-6} alkyl may be substituted by one or more substituents selected from CN, -OR^{23}, -SR^{23}, -SO_2R^{37}, -NR^8R^{33}, -$NR^{24}C(=O)R^{23}$, and -$NR^{24}SO_2R^{23}$, provided that any one carbon atom of said C_{1-6} alkyl is not substituted by more than one CN or more than one -OR^{23};

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H or -(C_{1-6} alkyl);

R^{21} is H, F, or R^{12};

R^{23} is H, -(C_{1-6} alkyl), or -(C_{1-6} alkylene)OH;

R^{26} is H, OH, halo, NH_2, or SH;

R^{28} is H, NH_2, or -OR^{29};

R^{29} is H, (C_{1-6} alkyl), or -C(=O)(C_{1-6} alkyl);

R^{30} is H or F;

R^{31} is F, Cl, Br, -CN, -C(=O)NH_2, -OH, -OR^{32}, -$OCH_2CH_2OR^{25}$, R^{32}, ,or (C_{1-6} alkyl) optionally substituted by –OR^{25} or -$OCH_2CH_2OR^{25}$

where R^{30} *and* R^{31} *when adjacent may be taken together to constitute a group of the formula* -O-$(CH_2)_n$- or -O-$(CH_2)_n$-O-;

n is 1 or 2;

R^{32} is -(C_{1-6} alkyl) optionally substituted with one, two, or three F;

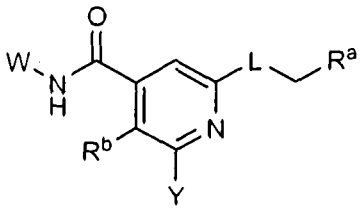
R^{36} is -(C_{1-6} alkyl) or -(C_{3-6} cycloalkyl); and

R^{37} is -(C_{1-6} alkyl), -(C_{3-6} cycloalkyl), or -(C_{1-6} alkylene)OH;

R^{38} and R^{39} are independently H, -(C_{1-6} alkyl), or R^{38} and R^{39} taken together form a 5- or 6-membered heterocycloalkyl;

or a pharmaceutically-acceptable salt thereof.

Another embodiment of the invention is a compound of Formula IIIA:

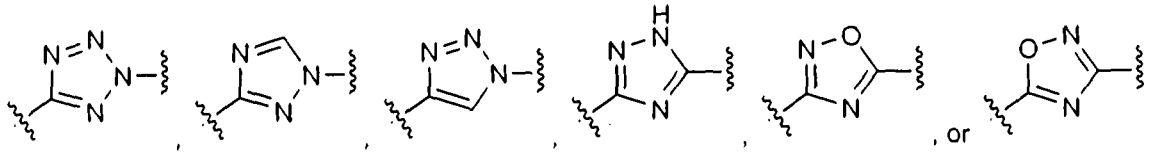


IIIA

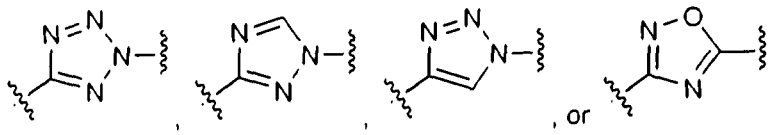
wherein R^a, R^b, W, and Y are as defined hereinabove for Formula III.

Another embodiment of the invention is a compound of Formula IIIA wherein L is triazolyl, tetrazolyl, or oxadiazolyl.

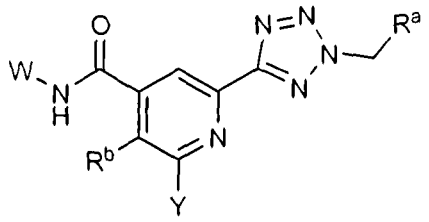
Another embodiment of the invention is a compound of Formula IIIA wherein L is



Another embodiment of the invention is a compound of Formula IIIA wherein L is



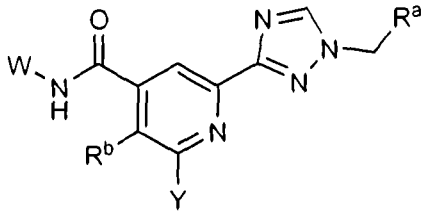
Another embodiment of the invention is a compound of Formula IIIA-1



IIIA-1

wherein R^a, R^b, W, and Y are as defined hereinabove for Formula III.

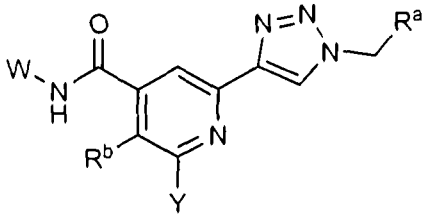
Another embodiment of the invention is a compound of Formula IIIA-2



IIIA-2

wherein R^a, R^b, W, and Y are as defined hereinabove for Formula III.

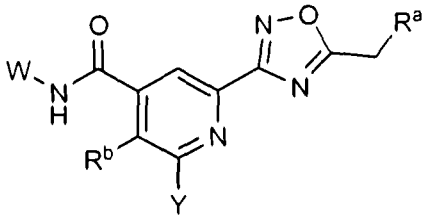
Another embodiment of the invention is a compound of Formula IIIA-3



IIIA-3

wherein R^a, R^b, W, and Y are as defined hereinabove for Formula III.

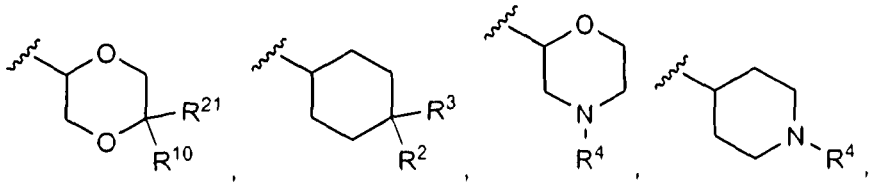
Another embodiment of the invention is a compound of Formula IIIA-4

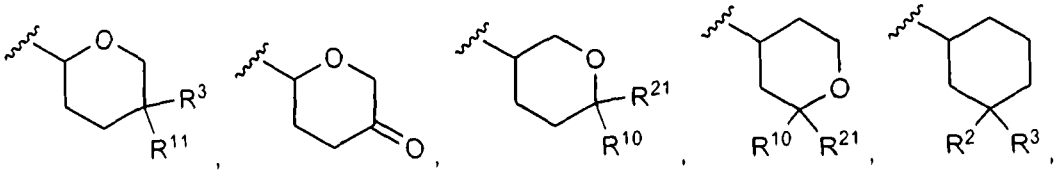


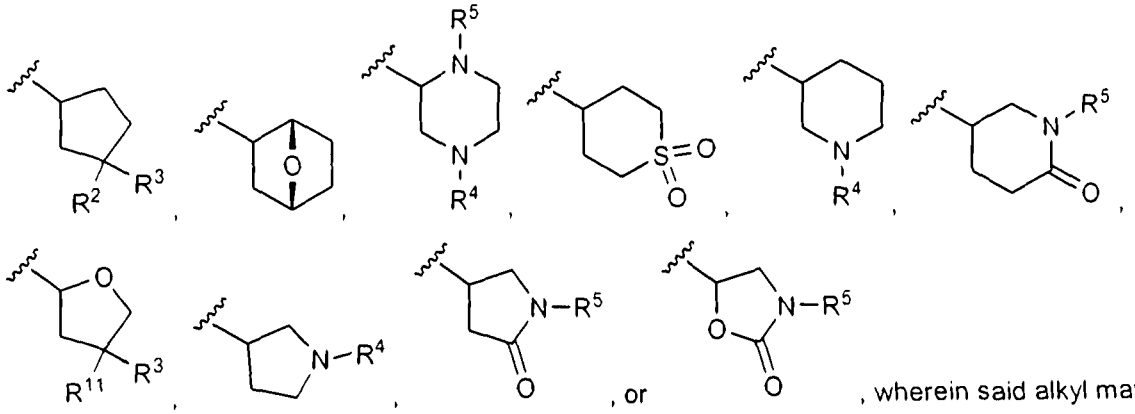
IIIA-4

wherein R^a, R^b, W, and Y are as defined hereinabove for Formula III.

Another embodiment of the invention is a compound of Formula IIIA, IIIA-1, IIIA-2, IIIA-3, or IIIA-4 wherein R^a is C_{1-6} alkyl,

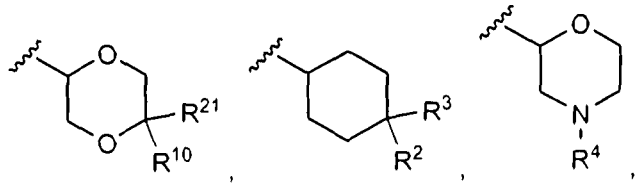


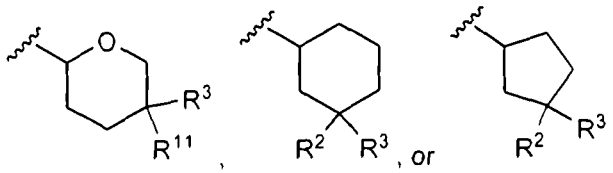




substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

Another embodiment of the invention is a compound of Formula IIIA, IIIA-1, IIIA-2, IIIA-3, or IIIA-4 wherein R^a is C_{1-6} alkyl,



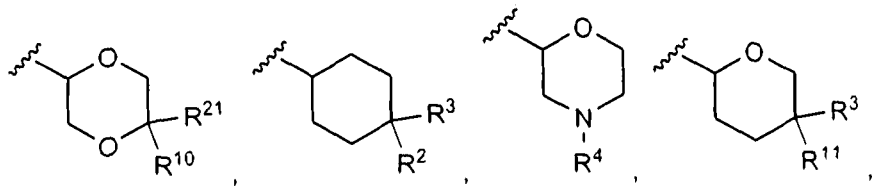


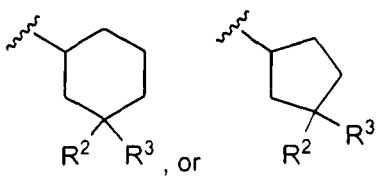
more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

Another embodiment of the invention is a compound of Formula IIIA, IIIA-1, IIIA-2, IIIA-3, or IIIA-4 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

Another embodiment of the invention is a compound of Formula IIIA, IIIA-1, IIIA-2, IIIA-3, or IIIA-4 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more $-OR^{34}$.

Another embodiment of the invention is a compound of Formula IIIA, IIIA-1, IIIA-2, IIIA-3, or IIIA-4 wherein R^a is





Another embodiment of the invention is a compound of Formula IIIA wherein:

R^a is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl,

isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or indolyl-(C_{1-6} alkylenyl), wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

Y is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein Y may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

L is triazolyl, tetrazolyl, or oxadiazolyl;

R^4 is H, $-(C_{1-6}$ alkylene$)R^6$, $-C(=O)R^9$, or $-SO_2R^{12}$, wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

R^5 is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, may be substituted by one or more R^{26} substituents;

R^7 is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, $-NHR^{24}$, or $-OR^{25}$, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

R^9 is $-(C_{1-6}$ alkylene$)R^{28}$, $-NHR^{24}$, or $-OR^{25}$;

R^{12} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{12} may be substituted by one or more substituents selected from CN, $-OR^{23}$, $-SO_2R^{37}$, $-NR^8R^{33}$, $-NR^{24}C(=O)R^{23}$, and $-NR^{24}SO_2R^{23}$, provided that any one carbon atom of R^{12} is not substituted by more than one CN or more than one $-OR^{23}$;

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl,;

R^{23} is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

R^{26} is H, OH, F, Cl, Br, NH_2, or SH;

R^{29} is H, $-C(=O)CH_3$, $-C(=O)CH_2CH_3$, $-C(=O)(CH_2)_2CH_3$, $-C(=O)CH(CH_3)_2$, $-C(=O)(CH_2)_3CH_3$, $-C(=O)CH(CH_3)CH_2CH_3$, $-C(=O)CH_2CH(CH_3)_2$, $-C(=O)(CH_2)_4CH_3$, $-C(=O)CH_2CH(CH_3)CH_2CH_3$, $-C(=O)CH_2C(CH_3)_3$, or $-C(=O)(CH_2)_5CH_3$;

R^{31} is Cl, Br, $-OR^{32}$, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, or $-OCH_2CH_2OR^{25}$;

R^{32} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{32} may be substituted with one, two, or three F;

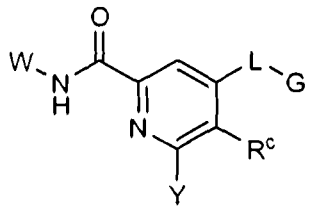
R^{36} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl; and

R^{37} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

or a pharmaceutically-acceptable salt thereof.

Another embodiment of the invention is a compound of Formula IIIA, IIIA-1, IIIA-2, IIIA-3, or IIIA-4 wherein Y is methyl.

Another embodiment of the invention is a compound of Formula IV:



IV

wherein G is (C_{1-3} alkylenyl)-R^a or R^a, wherein said C_{1-3} alkylenyl may be substituted by one or more substituents selected from OH and F;

R^a is C_{1-6} alkyl, 3- to 7-membered heterocycloalkyl, or 3- to 8-membered cycloalkyl, wherein said C_{1-6} alkyl may be substituted by one or more substituents selected from F, $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said heterocycloalkyl and cycloalkyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or 9-membered heteroaryl-(C_{1-6} alkylenyl), wherein said phenyl, pyridyl, or 9-membered heteroaryl is substituted by one or more groups selected from R^{30} and R^{31};

Y is C_{1-6} alkyl, C_{1-6} haloalkyl; or C_{1-6} hydroxyalkyl;

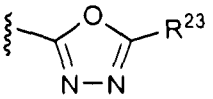
L is 5-membered heteroaryl;

R^2 is H, F, CN, $-OR^5$, R^{12}, $-C(=O)R^7$, $-NR^8R^{33}$, $-NR^8C(=O)R^9$, $-NR^8SO_2R^{36}$, or $-SO_2R^{12}$;

R^3 is H, F, CN, or $-OR^{22}$;

R^4 is H, $-(C_{1-6}$ alkylene)R^6, $-C(=O)R^9$, or $-SO_2R^{12}$;

R^5 is H or $-(C_{1-6}$ alkyl), wherein said C_{1-6} alkyl may be substituted by one or more R^{26} substituents;

R^6 is H, CN, $-OR^{23}$, $-SO_2R^{37}$, $-NR^{24}C(=O)R^{23}$, $-NR^{24}SO_2R^{37}$, or ;

R^7 is -(C_{1-6} alkyl), -(C_{1-6} haloalkyl), -(C_{1-6} alkylene)OH, $-NR^{38}R^{39}$, $-NHSO_2CH_3$, or $-OR^{25}$;

R^9 is -(C_{1-6} alkylene)R^{28}, $-NHR^{24}$, or $-OR^{25}$;

R^{10} is H, F, CN, R^{12}, or $-C(=O)R^7$;

R^{11} is H, F, CN, $-OR^5$, R^{12}, $-C(=O)R^7$, $-NR^8R^{33}$, $-NR^8C(=O)R^9$, $-NR^8SO_2R^{36}$, or $-SO_2R^{12}$;

R^{12} is -(C_{1-6} alkyl), wherein said C_{1-6} alkyl may be substituted by one or more substituents selected from CN, $-OR^{23}$, $-SR^{23}$, $-SO_2R^{37}$, $-NR^8R^{33}$, $-NR^{24}C(=O)R^{23}$, and $-NR^{24}SO_2R^{23}$, provided that any one carbon atom of said C_{1-6} alkyl is not substituted by more than one CN or more than one $-OR^{23}$;

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H or -(C_{1-6} alkyl);

R^{21} is H, F, or R^{12};

R^{23} is H, -(C_{1-6} alkyl), or -(C_{1-6} alkylene)OH;

R^{26} is H, OH, halo, NH_2, or SH;

R^{28} is H, NH_2, or $-OR^{29}$;

R^{29} is H, (C_{1-6} alkyl), or $-C(=O)(C_{1-6}$ alkyl);

R^{30} is H or F;

R^{31} is F, Cl, Br, -CN, $-C(=O)NH_2$, -OH, $-OR^{32}$, $-OCH_2CH_2OR^{25}$, R^{32}, ,or (C_{1-6} alkyl) optionally substituted by $-OR^{25}$ or $-OCH_2CH_2OR^{25}$

where R^{30} and R^{31} when adjacent may be taken together to constitute a group of the formula $-O-(CH_2)_n-$ or $-O-(CH_2)_n-O-$;

n is 1 or 2;

R^{32} is -(C_{1-6} alkyl) optionally substituted with one, two, or three F;

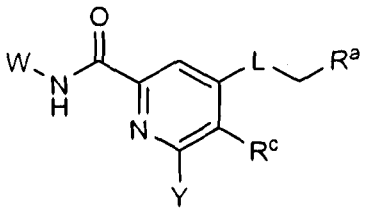
R^{36} is -(C_{1-6} alkyl) or -(C_{3-6} cycloalkyl); and

R^{37} is -(C_{1-6} alkyl), -(C_{3-6} cycloalkyl), or -(C_{1-6} alkylene)OH;

R^{38} and R^{39} are independently H, -(C_{1-6} alkyl), or R^{38} and R^{39} taken together form a 5- or 6-membered heterocycloalkyl;

or a pharmaceutically-acceptable salt thereof.

Another embodiment of the invention is a compound of Formula IVA:

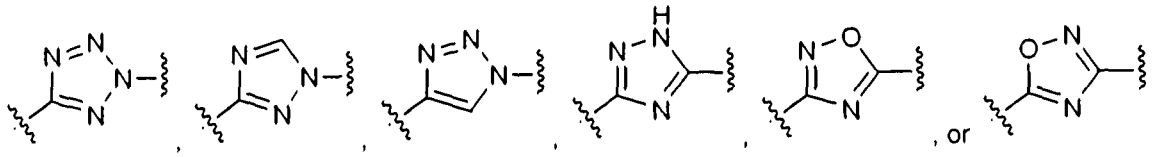


IVA

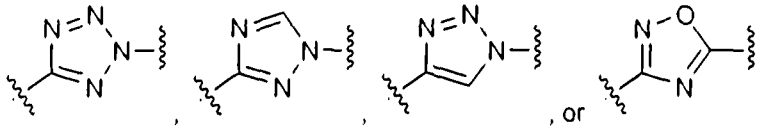
wherein R^a, R^c, W, Y, and L are as defined hereinabove for Formula IV.

Another embodiment of the invention is a compound of Formula IVA wherein L is triazolyl, tetrazolyl, or oxadiazolyl.

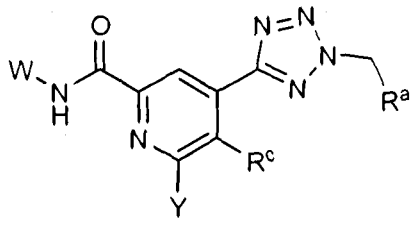
Another embodiment of the invention is a compound of Formula IVA wherein L is



Another embodiment of the invention is a compound of Formula IVA wherein L is



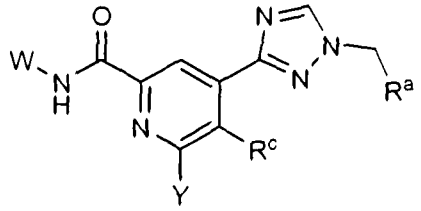
Another embodiment of the invention is a compound of Formula IVA-1



IVA-1

wherein R^a, R^c, W, Y, and L are as defined hereinabove for Formula IV.

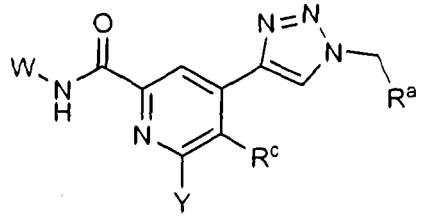
Another embodiment of the invention is a compound of Formula IVA-2



IVA-2

wherein R^a, R^c, W, Y, and L are as defined hereinabove for Formula IV.

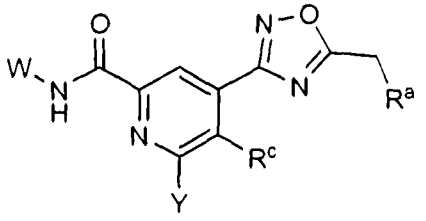
Another embodiment of the invention is a compound of Formula IVA-3



IVA-3

wherein R^a, R^c, W, Y, and L are as defined hereinabove for Formula IV.

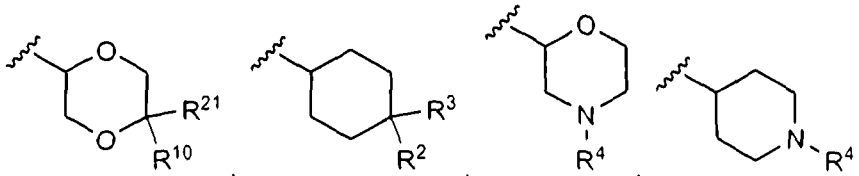
Another embodiment of the invention is a compound of Formula IVA-4

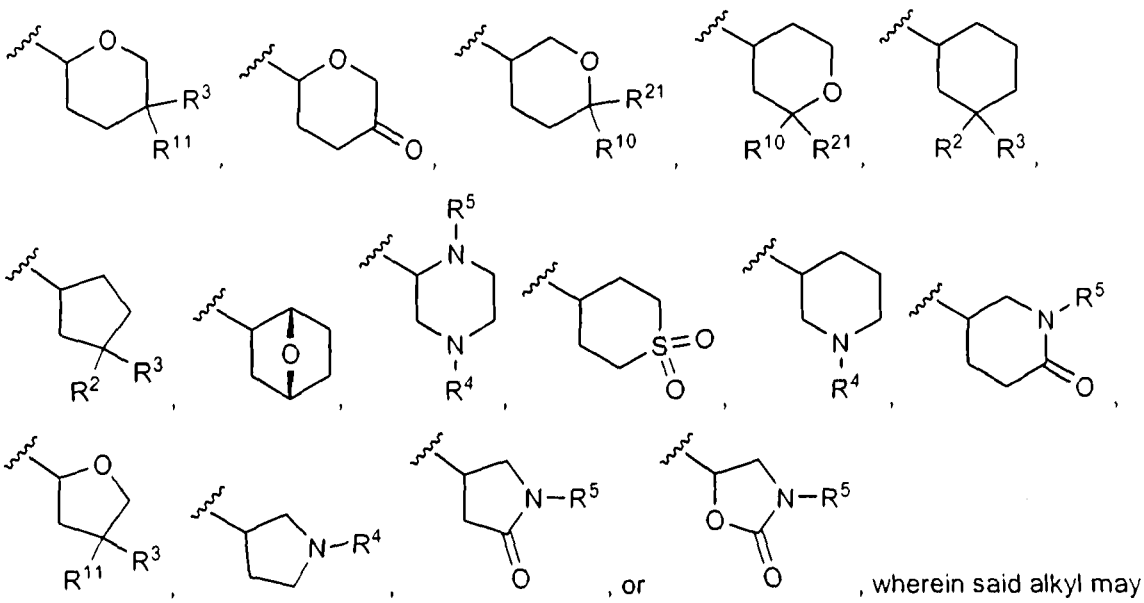


IVA-4

wherein R^a, R^c, W, Y, and L are as defined hereinabove for Formula IV.

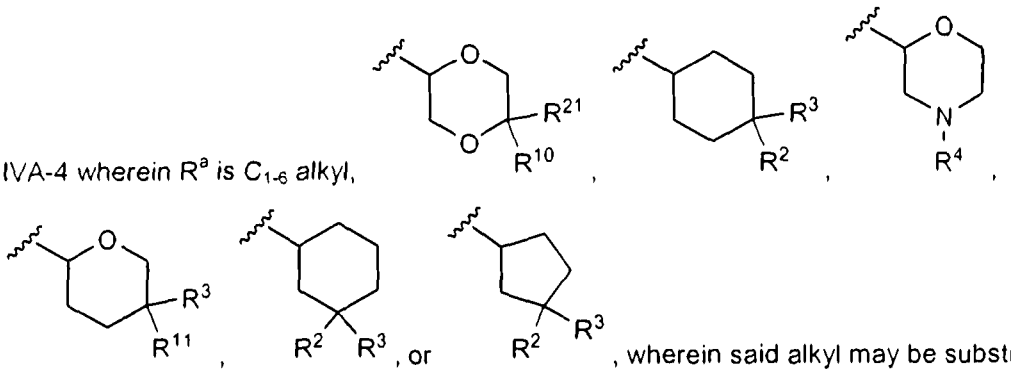
Another embodiment of the invention is a compound of Formula IVA, IVA-1, IVA-2, IVA-3, or IVA-4 wherein R^a is C_{1-6} alkyl,





substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

Another embodiment of the invention is a compound of Formula IVA, IVA-1, IVA-2, IVA-3, or IVA-4 wherein R^a is C_{1-6} alkyl,

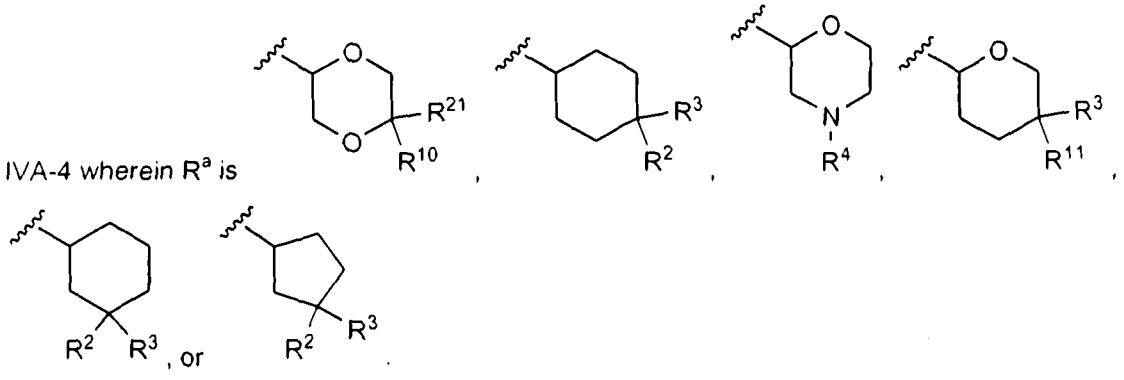


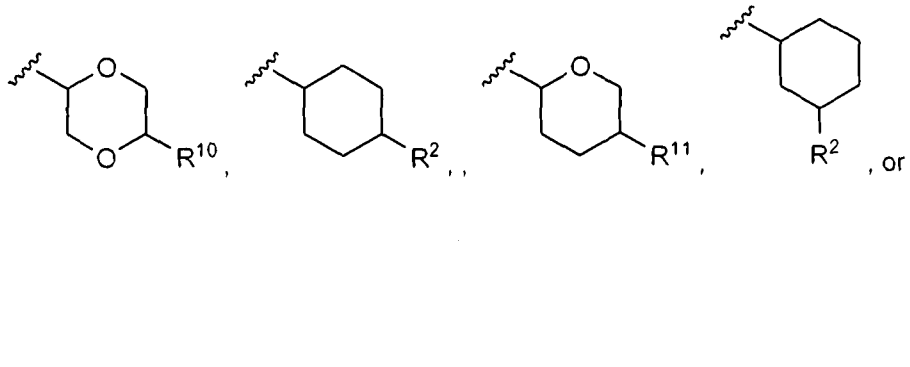
more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

Another embodiment of the invention is a compound of Formula IVA, IVA-1, IVA-2, IVA-3, or IVA-4 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

Another embodiment of the invention is a compound of Formula IVA, IVA-1, IVA-2, IVA-3, or IVA-4 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more $-OR^{34}$.

Another embodiment of the invention is a compound of Formula IVA, IVA-1, IVA-2, IVA-3, or IVA-4 wherein R^a is



Another embodiment of the invention is a compound of Formula IVA, IVA-1, IVA-2, IVA-3, or IVA-4 wherein R^a is ;

R^2 is $CH(CH_3)OH$, $C(CH_3)_2OH$, $-NR^8C(=O)(C_{1-6}$ alkylene$)R^{28}$, or $-NR^8SO_2R^{36}$;

R^{10} is $CH(CH_3)OH$, or $C(CH_3)_2OH$; and

R^{11} is $CH(CH_3)OH$, $C(CH_3)_2OH$, $-NR^8C(=O)(C_{1-6}$ alkylene$)R^{28}$, or $-NR^8SO_2R^{36}$.

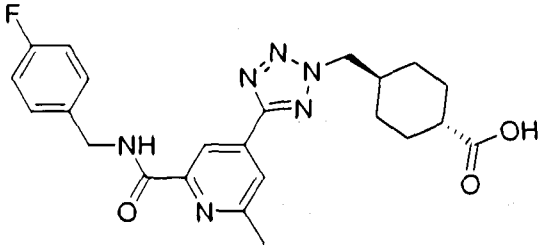
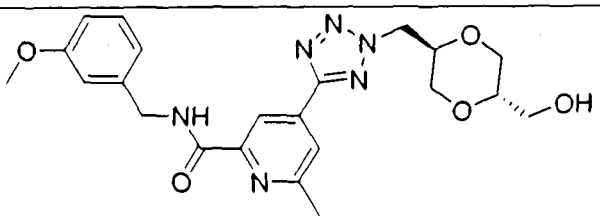
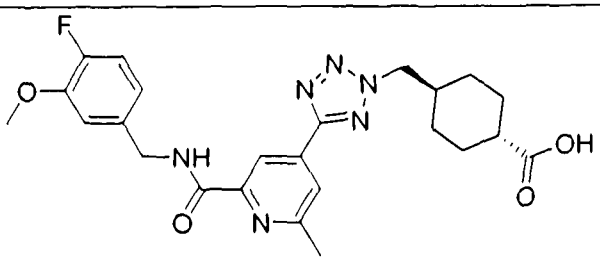
Another embodiment of the invention is a compound of Formula IVA, IVA-1, IVA-2, IVA-3, or IVA-4 wherein Y is methyl.

Another embodiment of the invention is a compound of Formula IVA, IVA-1, IVA-2, IVA-3, or IVA-4 wherein W is phenyl-(C_{1-6} alkylenyl), wherein said phenyl is substituted by one or more groups selected from R^{30} and R^{31}.

Another embodiment of the invention is a compound of Formula IVA, IVA-1, IVA-2, IVA-3, or IVA-4 wherein W is phenylmethyl, wherein said phenyl is substituted by one or more groups selected from R^{30} and R^{31}.

Another embodiment of the invention is a compound shown in Table 2.

Table 2

Compound Name	Structure
(1r,4r)-4-((5-(2-((4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2H-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid	
N-(3-methoxybenzyl)-4-(2-(((2R,5S)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2H-tetrazol-5-yl)-6-methylpicolinamide	
(1r,4r)-4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2H-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid	

Another embodiment of the invention is a compound of Formula I, II, III, or IV wherein:

G is $-CH_2R^a$, $-CH_2CH_2R^a$, $-CH(R^a)CH_3$, $-CH_2CH_2CH_2R^a$, $-CH_2CH(CH_3)R^a$, $-CH(R^a)CH_2CH_3$, or R^a, wherein said CH, CH_2, and CH_3 groups may be substituted by one or more substituents selected from OH and F;

R^a is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or indolyl-(C_{1-6} alkylenyl), wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

Y is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein Y may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

L is triazolyl, tetrazolyl, or oxadiazolyl;

R^4 is H, $-(C_{1-6}$ alkylene$)R^6$, $-C(=O)R^9$, or $-SO_2R^{12}$, wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

R^5 is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, may be substituted by one or more R^{26} substituents;

R^7 is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, $-NHR^{24}$, or $-OR^{25}$, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

R^9 is $-(C_{1-6}$ alkylene$)R^{28}$, $-NHR^{24}$, or $-OR^{25}$;

R^{12} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{12} may be substituted by one or more substituents selected

from CN, $-OR^{23}$, $-SO_2R^{37}$, $-NR^8R^{33}$, $-NR^{24}C(=O)R^{23}$, and $-NR^{24}SO_2R^{23}$, provided that any one carbon atom of R^{12} is not substituted by more than one CN or more than one $-OR^{23}$;

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl,;

R^{23} is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

R^{26} is H, OH, F, Cl, Br, NH_2, or SH;

R^{29} is H, $-C(=O)CH_3$, $-C(=O)CH_2CH_3$, $-C(=O)(CH_2)_2CH_3$, $-C(=O)CH(CH_3)_2$, $-C(=O)(CH_2)_3CH_3$, $-C(=O)CH(CH_3)CH_2CH_3$, $-C(=O)CH_2CH(CH_3)_2$, $-C(=O)(CH_2)_4CH_3$, $-C(=O)CH_2CH(CH_3)CH_2CH_3$, $-C(=O)CH_2C(CH_3)_3$, or $-C(=O)(CH_2)_5CH_3$;

R^{31} is Cl, Br, $-OR^{32}$, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, or $-OCH_2CH_2OR^{25}$;

R^{32} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{32} may be substituted with one, two, or three F;

R^{36} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl; and

R^{37} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

or a pharmaceutically-acceptable salt thereof.

Another embodiment of the invention is a compound shown in Table 3.

Table 3

Example No.	Compound Name
1.	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
2	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-((methylsulfonyl)amino)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
3.	*N*-(3-Chloro-4-fluorobenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
4	*N*-(3-Chloro-4-fluorobenzyl)-6-(2-((*trans*-4-((methylsulfonyl)amino)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine01-4-carboxamide
5.	*N*-(3-Methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

Table 3

Example No.	Compound Name
6	*N*-(3-Methoxybenzyl)-2-methyl-6-(2-(((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
7	*N*-(3-Methoxybenzyl)-6-(2-((*trans*-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
8	*N*-(3-Methoxybenzyl)-6-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
9.	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
10	*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
11	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
12	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
13.	*N*-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
14	*N*-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
15	*N*-(3-(2-Hydroxyethoxy)benzyl)-2-methyl-6-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
16	*N*-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
17	*N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
18	*N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
19	*N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
20.	*trans*-Methyl 4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate

Table 3

Example No.	Compound Name
21	*trans*-4-((5-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2H-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
22.	(*trans*)-Methyl 4-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
23	(*trans*)-4-((5-(6-((3-Methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)*cyclohexanecarboxylic acid*
24	*N*-(3-Methoxybenzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
25	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
26	*N*-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
27	*N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
28	*N*-(3-Methoxybenzyl)-6-(2-(((*trans*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
29	*N*-(3-Methoxybenzyl)-6-(2-(((*cis*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
30	*N*-(3-chloro-4-fluorobenzyl)-6-(2-((*trans*-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
31.	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
32	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((1*S**,3*R**)-3-acetamidocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
33	(+)-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((1*S**,3*R**)-3-acetamidocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
34	(-)-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((1*R**,3*S**)-3-acetamidocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
35	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-(((1*S**,3*R**)-3-(methylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
36	(+)-*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-(((1*R**,3*S**)-3-(methylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide

Table 3

Example No.	Compound Name
37	(-)-*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-(((1*S**,3*R**)-3-(methylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
38.	*N*-(3-Methoxybenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
39	*N*-(3-Methoxybenzyl)-6-(2-(((*S*)-4-acetylmorpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
40	*N*-(3-Methoxybenzyl)-2-methyl-6-(2-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
41.	*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
42	N-(4-fluoro-3-methoxybenzyl)-6-(2-(((S)-4-acetylmorpholin-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
43	*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
44.	*N*-(3-Methoxybenzyl)-2-methyl-6-(2-((*R*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
45	*N*-(3-Methoxybenzyl)-6-(2-(((*R*)-4-acetylmorpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
.46	N-(3-Methoxybenzyl)-2-methyl-6-(2-(((S)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2H-tetrazol-5-yl)pyrimidine-4-carboxamide
47.	*N*-(3-Chloro-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
48	*N*-(3-Chloro-4-fluorobenzyl)-2-methyl-6-(2-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
49.	*N*-(3-Ethyl-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide
50	N-(3-Ethyl-4-fluorobenzyl)-2-methyl-6-(2-(((R)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2H-tetrazol-5-yl)pyrimidine-4-carboxamide
51	*rac*-6-(2-((1,4-Dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide
52	*rac*-6-(2-((1,4-Dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide
53	6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide
54	6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide

Table 3

Example No.	Compound Name
55	6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-chloro-4-fluorobenzyl)-2-methylpyrimidine-4-carboxamide
56	6-(2-(((*R*)-1,4-Dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-2-methylpyrimidine-4-carboxamide
57	6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide
58	6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide
59	6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-chloro-4-fluorobenzyl)-2-methylpyrimidine-4-carboxamide
60	6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-2-methylpyrimidine-4-carboxamide
61	*rac*-*N*-(3-Methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
62	*N*-(3-Methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
63	*N*-(3-Methoxybenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
64	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
65	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
66	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
67	*rac*-*N*-(4-Fluoro-3-methylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
68	*N*-(4-Fluoro-3-methylbenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
69	*N*-(4-Fluoro-3-methylbenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
70	*rac*-*N*-(4-Fluoro-3-(trifluoromethyl)benzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
71	*rac*-*N*-(3-Ethyl-4-fluorobenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
72	*N*-(3-Ethyl-4-fluorobenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
73	*N*-(3-Ethyl-4-fluorobenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
74	*rac*-*N*-(4-Fluoro-3-isopropylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

Table 3

Example No.	Compound Name
75	*rac*-*N*-(3-Cyclopropyl-4-fluorobenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
76	*rac*-*N*-(3-Cyano-4-fluorobenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
77	*rac*-*N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
78	*rac*-*N*-(3-Chloro-4-fluorobenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
79	*N*-(3-Chloro-4-fluorobenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
80	*N*-(3-Bromo-4-fluorobenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
81	*N*-(4-Fluoro-3-hydroxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
82	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
83	*N*-(3-Chloro-4-fluorobenzyl)-6-(2-((5,5-bis(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
84	*N*-(3-Methoxybenzyl)-6-(2-((5,5-bis(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
85.	*rac*-(2*S**,5*S**)-Methyl 5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate
86	*rac*-(2*S**,5*S**)-5-((5-(6-((3-Methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid
87.	*rac*-(2*S**,5*S**)-methyl 5-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate
88	*rac*-(2*S**,5*S**)-5-((5-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid
89	(2*S*,5*S*)-5-((5-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid
90	(2*S*,5*S*)-Methyl 5-((5-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate

Table 3

Example No.	Compound Name
91	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S*,5*S*)-5-(2-hydroxypropan-2-yl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
90.	(2*S*,5*S*)-Methyl 5-((5-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate
91.	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S*,5*S*)-5-(2-hydroxypropan-2-yl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
92.	*rac*-(2*S**,5*S**)-Methyl 5-((5-(6-((3-chloro-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate
93	*rac*-(2*S**,5*S**)-5-((5-(6-((3-Chloro-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid
94.	*rac*-(2*S**,5*S**)-Methyl 5-((5-(6-((3-bromo-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate
95	*rac*-(2*S**,5*S**)-5-((5-(6-((3-Bromo-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid
96.	*rac*-*N*-(3-Methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(aminomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
97	*rac*-*N*-(3-Methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(acetamidomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
98	*rac*-*N*-(3-Methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(acetamidomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
99	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
100	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
101	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

Table 3

Example No.	Compound Name
102	*N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
103	*N*-(3-Methoxybenzyl)-6-(2-(((2*R**,5*S**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
104	*N*-(3-Methoxybenzyl)-6-(2-(((2*R**,5*S**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
105	(+)-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R**,5*S**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
106	(-)-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
107	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R**,5*S**)-5-hydroxy-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
108	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R**,5*R**)-5-hydroxy-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
109	*rac*-*N*-(3-Methoxybenzyl)-6-(1-(((2*R**,5*S**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide
110.	*N*-(3-Methoxybenzyl)-6-(1-((*trans*-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide
111	*N*-(3-Methoxybenzyl)-6-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide
112	*N*-(3-Methoxybenzyl)-2-methyl-6-(1-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide
113.	2-((*trans*)-4-((3-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
114	*N*-(3-Methoxybenzyl)-6-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide
115	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((2*R**,5*S**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide
116.	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide
117	*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(1-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide

Table 3

Example No.	Compound Name
118	*N*-(4-fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide
119	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide
120	*N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(1-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide
121	*N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(1-((*trans*-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide
122.	*N*-(4-Fluoro-3-methoxybenzyl)-6-(5-((*trans*-4-aminocyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide
123	*N*-(4-fluoro-3-methoxybenzyl)-6-(5-((*trans*-4-acetamidocyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide
124	*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(5-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)pyrimidine-4-carboxamide
125	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(3-hydroxypropyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
126	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-((*S*)-3-hydroxy-2-methylpropyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
127	*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-((*R*)-3-hydroxy-2-methylpropyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide
128	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
129	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
130.	*N*-(3-Methoxybenzyl)-2-methyl-6-(1-((*S*)-morpholin-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide
131	*N*-(3-Methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
132	*N*-(3-Methoxybenzyl)-2-methyl-6-(1-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide
133	*N*-(3-Methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
134.	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide

Table 3

Example No.	Compound Name
135	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
136	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
137.	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
138	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-acetamidocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
139	*N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-(2-hydroxyacetamido)cyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
140	*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(1-(((1*R*,3*S*)-3-(methylsulfonamido)cyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide
141.	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((1*S*,3*R*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
142	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((1*S*,3*R*)-3-acetamidocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
143	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((1*S*,3*R*)-3-(2-hydroxyacetamido)cyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
144	*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(1-(((1*S*,3*R*)-3-(methylsulfonamido)cyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide
145	6-(1-(((*S*)-1,4-Dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide
146	6-(1-(((*R*)-1,4-Dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide
147.	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-amino-tetrahydro-2*H*-pyran-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide
148	*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-acetamido-tetrahydro-2*H*-pyran-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide

Table 3

Example No.	Compound Name
149	*N*-(4-Fluoro-3-methoxybenzyl)-6-(5-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide
150	6-(5-((2*R*)-1,4-Dioxan-2-ylmethyl)-1,2,4-oxadiazol-3-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide
151	6-(5-((2*S*)-1,4-Dioxan-2-ylmethyl)-1,2,4-oxadiazol-3-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide
152	*N*-(4-Fluoro-3-methoxybenzyl)-6-(3-(((*trans*)-4-acetamidocyclohexyl)methyl)isoxazol-5-yl)-2-methylpyrimidine-4-carboxamide
153	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
154	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
155	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(ethylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
156	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(cyclopropanesulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
157	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(butylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
158	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
159	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-isobutyramidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
160	2-((*trans*)-4-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
161	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
162	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
163	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-((*S*)-2-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
164	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
165	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
166	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
167	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
168	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
169	1-((*trans*)-4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2H-tetrazol-2-yl)methyl)cyclohexyl)-3-methylurea
170	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
171	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
172	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
173	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
174	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
175	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
176	2-((*trans*)-4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
177	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
178	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
179	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
180	*N*-(3-Ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
181	*N*-(4-Fluoro-3-(hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
182	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
183	*N*-(3-(Hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide

Table 3

Example No.	Compound Name
184	*N*-(3-(2-Hydroxyethoxy)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
185	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
186	N-(4-fluoro-3-methylbenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2H-tetrazol-5-yl)picolinamide
187	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
188	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
189	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
190	2-((*trans*)-4-((5-(2-((4-Fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
191	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
192	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
193	N-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(2-aminoacetamido)cyclohexyl)methyl)-2H-tetrazol-5-yl)-6-methylpicolinamide
194	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
195	*N*-(3-Chloro-4-fluorobenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
196	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
197	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
198	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
199	2-((*trans*)-4-((5-(2-((3-Chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
200	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
201	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
202	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
203	*N*-(4-Fluoro-3-((2-hydroxyethoxy)methyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
204	4-(2-(((*trans*)-4-Acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-((6-hydroxypyridin-2-yl)methyl)-6-methylpicolinamide
205	*N*-(3-(Hydroxymethyl)benzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
206	*N*-(3-(2-Hydroxyethoxy)benzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
207	*N*-(4-Fluoro-3-(hydroxymethyl)benzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
208	*N*-(3-Ethoxybenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
209	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
210	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*cis*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
211	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
212	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
213	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
214	2-((*cis*)-4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
215	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
216	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
217	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
218	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
219	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
220	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
221	*N*-(4-Fuoro-3-methoxybenzyl)-4-(2-(((*cis*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
222	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*cis*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
223	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
224	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
225	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
226	*N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
227	*N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
228	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
229	*rac*-2-((1*R**,3*S**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
230	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
231	*N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
232	*N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
233	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
234	*rac*-2-((1*R**,3*S**)-3-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
235	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
236	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
237	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
238	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
239	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
240	*rac-N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((1*S**,3*R**)-3-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
241	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
242	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
243	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
244	*rac*-2-((1*R**,3*R**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
245	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
246	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
247	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
248	*rac-N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((1*R**,3*R**)-3-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
249	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
250	*rac-N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((1*S**,3*R**)-3-(methylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
251	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(ethylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
252	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-acetamidocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
253	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
254	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(3-hydroxypropanamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
255	(*trans*)-Methyl 4-((5-(2-((4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
256	(*trans*)-4-((5-(2-((4-Fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
257	*N*-(4-Fluorobenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
258	*N*-(4-Fluorobenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
259	(*trans*)-Methyl 4-((5-(2-((3-(hydroxymethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
260	(*trans*)-4-((5-(2-((3-(Hydroxymethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
261	(*trans*)-Methyl 4-((5-(2-((3-hydroxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
262	(*trans*)-4-((5-(2-((3-Hydroxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
263	(*trans*)-Methyl 4-((5-(2-((3-(3-methoxypropoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
264	(*trans*)-4-((5-(2-((3-(3-Methoxypropoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)-methyl)cyclohexanecarboxylic acid
265	(*trans*)-Methyl 4-((5-(2-((3,4-difluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
266	(*trans*)-4-((5-(2-((3,4-Difluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
267	(*trans*)-Methyl 4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
268	(*trans*)-4-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
269	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(piperidine-1-carbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
270	4-(2-(((*trans*)-4-((2-Methoxyethyl)carbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpicolinamide
271	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(morpholine-4-carbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
272	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(dimethylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
273	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(isopropylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
274	4-(2-(((*trans*)-4-((2-Amino-2-oxoethyl)carbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
275	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
276	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(ethylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
277	4-(2-(((*trans*)-4-((2-Hydroxyethyl)carbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-N-(3-methoxybenzyl)-6-methylpicolinamide
278	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
279	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
280	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
281	(*trans*)-Methyl 4-((5-(2-((3-(Difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
282	(*trans*)-4-((5-(2-((3-(Difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
283	*N*-(3-(Difluoromethoxy)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
284	(*trans*)-Methyl 4-((5-(2-((4-Fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
285	(*trans*)-4-((5-(2-((4-Fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
286	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
287	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
288	(*trans*)-Methyl 4-((5-(2-((3-Ethylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
289	(*trans*)-4-((5-(2-((3-Ethylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
290	*N*-(3-Ethylbenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
291	(*trans*)-Methyl 4-((5-(2-((3-Cyanobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
292	(*trans*)-4-((5-(2-((3-Cyanobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
293	(*trans*)-Methyl 4-((5-(2-((3-Ethoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
294	(*trans*)-4-((5-(2-((3-Ethoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
295	*N*-(3-Ethoxybenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
296	*N*-(3-Ethoxybenzyl)-4-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
297	(*trans*)-Methyl 4-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
298	(*trans*)-4-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
299	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
300	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
301	(*trans*)-Methyl 4-((5-(2-((3-Chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
302	(*trans*)-4-((5-(2-((3-Chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
303	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
304	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
305	(*trans*)-Methyl 4-((5-(2-((4-Fluoro-3-(trifluoromethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate
306	(*trans*)-4-((5-(2-((4-Fluoro-3-(trifluoromethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid
307	*N*-((2,3-Dihydrobenzofuran-5-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
308	*N*-(3-(Trifluoromethyl)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
309	*N*-(3-(Trifluoromethoxy)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
310	*N*-(3-Chlorobenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
311	*N*-(3-Methylbenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
312	*N*-(3-Ethylbenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
313	*N*-(3-Isopropoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
314	*N*-(3-Ethoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
315	*N*-(3,4-Difluorobenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
316	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
317	*N*-(4-Fluoro-3-(trifluoromethyl)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
318	*N*-(3-(Hydroxymethyl)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
319	*N*-(3-Hydroxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
320	*N*-(3-Fluoro-5-methoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
321	*N*-((2,3-Dihydrobenzofuran-6-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
322	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
323	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((trans)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
324	*N*-(3-Bromobenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
325	*N*-(3-(2-Hydroxyethoxy)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
326	*N*-(3-Propoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
327	*N*-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
328	4-(2-(((*trans*)-4-(Hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-((2-methoxypyridin-4-yl)methyl)-6-methylpicolinamide
329	*N*-(4-Fluorobenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
330	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
331	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxypropan-2-yl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
332	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxypropan-2-yl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
333	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
334	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
335	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
336	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*cis*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
337	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
338	*N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*cis*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
339	*N*-(3-Ethoxybenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
340	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
341	*rac-N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((3-oxocyclopentyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
342	*rac-N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-hydroxycyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
343	*rac-N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-hydroxycyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
344	*N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
345	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
346	*N*-(3-(2-Hydroxyethoxy)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
347	*N*-(3-Hydroxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
348	*N*-(3-Chloro-4-fluorobenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
349	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
350	*N*-(3-(Hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
351	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(aminomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
352	*N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(acetamidomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
353	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamidomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
354	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(aminomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
355	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-(hydroxymethyl)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
356	*rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-(aminomethyl)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
357	*rac-N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((1*R**,3*S**)-3-(methylsulfonamidomethyl)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)picolinamide
358	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((*S*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
359	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*R*)-1-(methylsulfonyl)piperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
360	*N*-(3-Methoxybenzyl)-4-(2-(((*S*)-1-acetylpiperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
361	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((*R*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
362	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*S*)-1-(methylsulfonyl)piperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
363	*N*-(3-Methoxybenzyl)-4-(2-(((*R*)-1-acetylpiperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
364	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*S*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
365	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*R*)-1-(methylsulfonyl)piperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
366	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*S*)-1-acetylpiperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
367	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
368	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*S*)-1-(methylsulfonyl)piperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
369	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*R*)-1-acetylpiperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
370	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-pyrrolidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
371	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*S*)-1-(methylsulfonyl)pyrrolidin-3-yl)methyl)-2H-tetrazol-5-yl)picolinamide
372	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*R*)-1-acetylpyrrolidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
373	2-((*R*)-3-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)pyrrolidin-1-yl)-2-oxoethyl acetate

Table 3

Example No.	Compound Name
374	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*R*)-1-(2-hydroxyacetyl)pyrrolidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
375	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-((1-benzyl-5-oxopyrrolidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
376	*N*-(3-(2-Hydroxyethoxy)benzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
377	*N*-(3-Ethoxybenzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
378	*N*-(4-Fluoro-3-methylbenzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
379	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
380	*N*-(3-Methoxybenzyl)-4-(2-((1-(2-hydroxy-2-methylpropanoyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
381	*N*-(3-Methoxybenzyl)-4-(2-((1-(3-aminopropanoyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
382	*N*-(3-Methoxybenzyl)-4-(2-((1-(2-aminoacetyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
383	*N*-(3-Methoxybenzyl)-4-(2-((1-acetylpiperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
384	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
385	*N*-(3-Methoxybenzyl)-4-(2-((1-isobutyrylpiperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
386	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((1-(methylcarbamoyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
387	*N*-(3-Chloro-4-fluorobenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
388	*N*-(3-Chloro-4-fluorobenzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
389	*N*-(4-Fluoro-3-(trifluoromethyl)benzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
390	*N*-(4-Fluoro-3-(trifluoromethyl)benzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
391	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
392	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
393	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
394	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*R*)-4-acetylmorpholin-2-yl)methyl)-2H-tetrazol-5-yl)-6-methylpicolinamide
395	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
396	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*S*)-4-acetylmorpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
397	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2H-tetrazol-5-yl)picolinamide
398	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide
399	*N*-(3-Methoxybenzyl)-4-(2-(((*S*)-4-acetylmorpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
400	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
401	*rac*-4-(2-((1,4-Dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-methoxybenzyl)-6-methylpicolinamide
402	*rac*-4-(2-((1,4-Dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-methylbenzyl)-6-methylpicolinamide
403	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
404	*N*-(3-Methoxybenzyl)-4-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
405	*N*-(3-Methoxybenzyl)-4-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
406	*rac*-(2*S**,5*S**)-Methyl 5-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate
407	*rac*-(2*S**,5*S**)-5-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid
408	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-(2-hydroxypropan-2-yl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
409	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-carbamoyl-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
410	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-cyano-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
411	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-cyano-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
412	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
413	*rac*-(2*S**,5*S**)-Methyl 5-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate
414	*rac*-(2*S**,5*S**)-5-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid
415	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-(2-hydroxypropan-2-yl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
416	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-carbamoyl-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
417	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-cyano-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
418	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-cyano-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
419	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-(2-hydroxyacetyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
420	*rac*-(2*S**,5*S**)-Methyl 5-((5-(2-((3-chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate
421	*rac*-(2*S**,5*S**)-5-((5-(2-((3-Chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid
422	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((2*R**,5*S**)-5-(aminomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
423	*rac*-*N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((2*R**,5*S**)-5-(methylsulfonamidomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
424	*rac*-*N*-(3-Methoxybenzyl)-4-(2-(((2*R**,5*S**)-5-(acetamidomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
425	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydrofuran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
426	*N*-(4-Fluoro-3-methylbenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
427	*rac*-*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
428	(-)-*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
429	(+)-*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
430	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
431	*rac*-*N*-(4-Fluoro-3-methylbenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
432	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
433	*rac*-*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide
434	*rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
435	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-((1*S**,2*S**,4*R**)-7-oxa-bicyclo[2.2.1]heptan-2-ylmethyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
436	Ethyl 4-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)bicyclo[2.2.2]octane-1-carboxylate
437	4-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)bicyclo[2.2.2]octane-1-carboxylic acid
438	*N*-(3-Methoxybenzyl)-4-(2-((4-(hydroxymethyl)bicyclo[2.2.2]octan-1-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
439	4-(2-((4-(Hydroxymethyl)pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]oct-1-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpyridine-2-carboxamide
440	4-((5-(2-(((3-Methoxybenzyl)amino)carbonyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cubane-1-carboxylic acid

Table 3

Example No.	Compound Name
441	4-(2-((4-(Aminocarbonyl)pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]oct-1-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpyridine-2-carboxamide
442	4-(2-((4-Cyanopentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]oct-1-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpyridine-2-carboxamide
443	*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((*S*)-3-methylbutan-2-yl)-2*H*-tetrazol-5-yl)picolinamide
444	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-((*R*)-3-hydroxy-2-methylpropyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
445	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-((*S*)-3-hydroxy-2-methylpropyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide
446	*N*-(4-Fluoro-3-methylbenzyl)-4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinamide
447	*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinamide
448	*N*-(3-Methoxybenzyl)-4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinamide
449	6-((4-(2-Isobutyl-2*H*-tetrazol-5-yl)-2-methylpicolinamido)methyl)-1*H*-indole-2-carboxamide
450	*N*-(3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide
451	*N*-(3-Methoxybenzyl)-6-methyl-4-(1-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)picolinamide
452	*N*-(3-Methoxybenzyl)-4-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide
453	2-((*trans*)-4-((3-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
454	*N*-(3-Methoxybenzyl)-4-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide
455	*N*-(4-Fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide
456	*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(1-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)picolinamide
457	*N*-(4-Fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide
458	2-((*trans*)-4-((3-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
459	*N*-(4-Fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide
460	*N*-(4-Fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide

Table 3

Example No.	Compound Name
461	*N*-(4-Fluoro-3-methylbenzyl)-6-methyl-4-(1-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)picolinamide
462	*N*-(4-Fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide
463	2-((*trans*)-4-((3-(2-((4-Fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate
464	N-(4-Fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamidemide
465	*N*-(3-Methoxybenzyl)-4-(1-(((trans)-4-(hydroxymethyl)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide
466	*rac-N*-(3-Methoxybenzyl)-4-(1-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide
467	*rac-N*-(4-Fluoro-3-methoxybenzyl)-4-(1-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide
468	*rac-N*-(4-Fluoro-3-methylbenzyl)-4-(1-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide

Another embodiment of the invention is a pharmaceutical composition comprising a compound as described hereinabove, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

Another embodiment of the invention is a method for inhibiting an MMP-13 enzyme in an animal, comprising administering to the animal an MMP-13 inhibiting amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating a disease mediated by an MMP-13 enzyme, comprising administering to a patient suffering from such a disease a nontoxic effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating arthritis, comprising administering to a patient suffering from an arthritis disease a nontoxic antiarthritic effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating osteoarthritis, comprising administering to a patient suffering from osteoarthritis a nontoxic effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating rheumatoid arthritis, comprising administering to a patient suffering from rheumatoid arthritis a nontoxic effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating psoriatic arthritis, comprising administering to a patient suffering from psoriatic arthritis a nontoxic effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating a cancer, comprising administering to a patient suffering from a cancer a nontoxic anti-cancer effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating inflammation, comprising administering to a patient suffering from inflammation a nontoxic effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating chronic obstructive pulmonary disease, comprising administering to a patient suffering from chronic obstructive pulmonary disease a nontoxic effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating psoriasis, comprising administering to a patient suffering from psoriasis a nontoxic effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating asthma, comprising administering to a patient suffering from asthma a nontoxic effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method for treating inflammatory bowel disease, comprising administering to a patient suffering from inflammatory bowel disease a nontoxic effective amount of a compound described hereinabove, or a pharmaceutically acceptable salt thereof.

For the purposes of this invention, the term "arthritis", which is synonymous with the phrase "arthritic condition", includes osteoarthritis, rheumatoid arthritis, degenerative joint disease, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, and psoriatic arthritis. An allosteric inhibitor of MMP-13 having an anti-arthritic effect is a compound as defined above that inhibits the progress, prevents further progress, or reverses progression, in part or in whole, of any one or more symptoms of any one of the arthritic diseases and disorders listed above.

As used herein, the term "alkyl" refers to a straight or branched chain monovalent hydrocarbon radical. For example, a C_{1-6} alkyl radical is a straight or branched chain monovalent hydrocarbon radical having 1 to 6 carbon atoms. Examples of C_{1-6} alkyl radicals include methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, and 1-hexyl.

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical. For example, a C_{1-6} alkylene radical is a straight or branched chain divalent hydrocarbon radical having 1 to 6 carbon atoms. Examples of C_{1-6} alkylene radicals include methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, and 1-hexylene.

As used herein, the term "cycloalkyl" refers to a cyclic monovalent hydrocarbon radical. For example, a C_{3-6} cycloalkyl radical is a cyclic monovalent hydrocarbon radical having 1 to 6 carbon

atoms. Examples of C_{3-6} cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "IC_{50}" means the concentration of a compound, usually expressed as μM or nM, required to inhibit an enzyme's catalytic activity by 50%.

As used herein, the phrase "cartilage damage" means a disorder of hyaline cartilage and subchondral bone characterized by hypertrophy of tissues in and around the involved joints, which may or may not be accompanied by deterioration of hyaline cartilage surface.

The phrase "treating", which is related to the terms "treat" and "treated", means administration of an invention combination as defined above that inhibits the progress, prevents further progress, or reverses progression, in part or in whole, of any one or more symptoms of any one of the diseases and disorders listed above.

The phrase "invention compound" means a compound of Formula I, or a pharmaceutically acceptable salt thereof, as fully defined above.

The term "NSAID" is an acronym for the phrase "nonsteroidal anti-inflammatory drug", which means any compound which inhibits cyclooxygenase-1 ("COX-1") and cyclooxygenase-2. Most NSAIDs fall within one of the following five structural classes: (1) propionic acid derivatives, such as ibuprofen, naproxen, naprosyn, diclofenac, and ketoprofen; (2) acetic acid derivatives, such as tolmetin and sulindac; (3) fenamic acid derivatives, such as mefenamic acid and meclofenamic acid; (4) biphenylcarboxylic acid derivatives, such as diflunisal and flufenisal; and (5) oxicams, such as piroxim, peroxicam, sudoxicam, and isoxicam. Other useful NSAIDs include aspirin, acetominophen, indomethacin, and phenylbutazone. Selective inhibitors of cyclooxygenase-2 as described above may be considered to be NSAIDs also.

A selective inhibitor of COX-2 is a compound that inhibits COX-2 selectively versus COX-1 such that a ratio of IC_{50} for a compound with COX-1 divided by a ratio of IC_{50} for the compound with COX-2 is greater than, or equal to, 5, where the ratios are determined in one or more assays. All that is required to determine whether a compound is a selective COX-2 inhibitor is to assay a compound in one of a number of well know assays in the art.

The term "drugs", which is synonymous with the phrases "active components", "active compounds", and "active ingredients", includes celecoxib, or a pharmaceutically acceptable salt thereof, valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric inhibitor of MMP-13, and may further include one or two of the other therapeutic agents described above.

An allosteric inhibitor of MMP-13 is any compound of Formula I that binds allosterically into the S1' site of the MMP-13 enzyme, including the S1' channel, and/or the S1'' site, without ligating, coordinating, or binding the catalytic zinc of the MMP-13.

Certain of the invention compounds possess one or more chiral centers, and each center may exist in the R or S configuration. The scope of the present invention encompasses any diastereomeric, enantiomeric, or epimeric form of invention compound, as well as mixtures thereof. Compounds of Formula I may be prepared as single enantiomer or as a mixture of individual enantiomers which includes racemic mixtures. Methods to obtain preferentially a single enantiomer from a mixture of individual enantiomers or a racemic mixture are well known to those ordinarily skilled in the art of

organic chemistry. Such methods include but are not limited to preferential crystallization of diastereomeric salts (e.g. tartrate or camphor sulfonate), covalent derivatization by a chiral, non-racemic reagent followed by separation of the resulting diastereomers by common methods (e.g. crystallization, chromatographic separation, or distillation) and chemical reversion to scalemic compound, Simulated Moving Bed technology, or high/medium-pressure liquid chromatography employing a chiral stationary phase These techniques may be performed on the final compounds of Formula I or on any intermediates to compounds of Formula I which bear a stereogenic center. Also, to facilitate separation by any of the methods described above, the compounds of Formula I or any intermediates to the compounds of Formula I which bear a stereogenic center may be transiently reacted with an achiral reagent, separated, and then reverted to scalemic compound by standard synthetic techniques.

Additionally, certain invention compounds may exist as geometric isomers such as the entgegen (E) and zusammen (Z) isomers of 1,2-disubstituted alkenyl groups or cis and trans isomers of disubstituted cyclic groups. Any cis, trans, syn, anti, entgegen (E), or zusammen (Z) isomer of a compound of Formula I, as well as mixtures thereof, is encompassed within the scope of the present invention.

Certain invention compounds can exist as two or more tautomeric forms. Tautomeric forms of the invention compounds may interchange, for example, via enolization/de-enolization, 1,2-hydride, 1,3-hydride, or 1,4-hydride shifts, and the like. Any tautomeric form of a compound of Formula I, as well as mixtures thereof, is encompassed within the scope of the present invention.

Some compounds of the present invention have cycloalkyl groups, which may be substituted at more than one carbon atom, in which case all geometric forms thereof, both *cis* and *trans*, and mixtures thereof, are within the scope of the present invention.

Encompassed within the scope of the present invention are isotopically-labelled compounds of Formula I, which are identical to those recited above, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as 2H, 3H, 13C, 14C, 15N, 18O, 17O, 31P, 32P, 35S, 18F and 36Cl, respectively. Compounds of the present invention and pharmaceutically acceptable salts of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labelled compounds of the present invention, for example those into which radioactive isotopes such as 3H and 14C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., 3H and carbon-14, i.e., 14C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., 2H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of those described above in this invention can generally be prepared by carrying out the procedures incorporated by reference above

or disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

Some of the invention compounds are capable of further forming nontoxic pharmaceutically acceptable salts, including, but not limited to, acid addition and/or base salts. The acid addition salts are formed from basic invention compounds, whereas the base addition salts are formed from acidic invention compounds. All of these forms are within the scope of the compounds useful in the invention.

Pharmaceutically acceptable acid addition salts of the basic invention compounds include nontoxic salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like, as well nontoxic salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, malate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate or galacturonate.

An acid addition salt of a basic invention compound is prepared by contacting the free base form of the compound with a sufficient amount of a desired acid to produce a nontoxic salt in the conventional manner. The free base form of the compound may be regenerated by contacting the acid addition salt so formed with a base, and isolating the free base form of the compound in the conventional manner. The free base forms of compounds prepared according to a process of the present invention differ from their respective acid addition salt forms somewhat in certain physical properties such as solubility, crystal structure, hygroscopicity, and the like, but otherwise free base forms of the invention compounds and their respective acid addition salt forms are equivalent for purposes of the present invention.

A nontoxic pharmaceutically acceptable base addition salt of an acidic invention compound may be prepared by contacting the free acid form of the compound with a metal cation such as an alkali or alkaline earth metal cation, or an amine, especially an organic amine. Examples of suitable metal cations include sodium cation (Na^+), potassium cation (K^+), magnesium cation (Mg^{2+}), calcium cation (Ca^{2+}), and the like. Examples of suitable amines are N,N′-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, *N*-methylglucamine, and procaine.

A base addition salt of an acidic invention compound may be prepared by contacting the free acid form of the compound with a sufficient amount of a desired base to produce the salt in the conventional manner. The free acid form of the compound may be regenerated by contacting the salt form so formed with an acid, and isolating the free acid of the compound in the conventional manner. The free acid forms of the invention compounds differ from their respective salt forms somewhat in

certain physical properties such as solubility, crystal structure, hygroscopicity, and the like, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain invention compounds can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are encompassed within the scope of the present invention.

The invention also provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, as defined above, together with a pharmaceutically acceptable carrier, diluent, or excipient.

The present invention also relates to the formulation of a compound of the present invention alone or with one or more other therapeutic agents which are to form the intended combination, including wherein said different drugs have varying half-lives, by creating controlled-release forms of said drugs with different release times which achieves relatively uniform dosing; or, in the case of non-human patients, a medicated feed dosage form in which said drugs used in the combination are present together in admixture in the feed composition. There is further provided in accordance with the present invention co-administration in which the combination of drugs is achieved by the simultaneous administration of said drugs to be given in combination; including co-administration by means of different dosage forms and routes of administration; the use of combinations in accordance with different but regular and continuous dosing schedules whereby desired plasma levels of said drugs involved are maintained in the patient being treated, even though the individual drugs making up said combination are not being administered to said patient simultaneously.

A therapeutically effective amount, or, simply, effective amount, of a compound of Formula I will generally be from about 1 to about 300 mg/kg of subject body weight of the compound of Formula I, or a pharmaceutically acceptable salt thereof. Typical doses will be from about 10 to about 5000 mg/day for an adult subject of normal weight for each component of the combination. In a clinical setting, regulatory agencies such as, for example, the Food and Drug Administration ("FDA") in the U.S. may require a particular therapeutically effective amount.

In determining what constitutes a nontoxic effective amount or a therapeutically effective amount of a compound of Formula I for treating, preventing, or reversing one or more symptoms of any one of the diseases and disorders described above that are being treated according to the invention methods, a number of factors will generally be considered by the medical practitioner or veterinarian in view of the experience of the medical practitioner or veterinarian, including the Food and Drug Administration guidelines, or guidelines from an equivalent agency, published clinical studies, the subject's (e.g., mammal's) age, sex, weight and general condition, as well as the type and extent of the disease, disorder or condition being treated, and the use of other medications, if any, by the subject. As such, the administered dose may fall within the ranges or concentrations recited above, or may vary outside them, ie, either below or above those ranges, depending upon the requirements of the individual subject, the severity of the condition being treated, and the particular therapeutic formulation being employed. Determination of a proper dose for a particular situation is within the skill of the medical or veterinary arts. Generally, treatment may be initiated using smaller dosages of the compound of Formula I that are less than optimum for a particular subject. Thereafter,

the dosage can be increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Pharmaceutical compositions, described briefly here and more fully below, of an invention combination may be produced by formulating the invention combination in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Alternatively, the compounds of Formula I may be formulated separately.

Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations.

The compositions to be employed in the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents commonly employed to treat any of the above-listed diseases and disorders.

The percentage of the active ingredients of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a total concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredients are present, for example, up to about 95%.

Preferred routes of administration of a compound of Formula I are oral or parenteral. However, another route of administration may be preferred depending upon the condition being treated. For exampled, topical administration or administration by injection may be preferred for treating conditions localized to the skin or a joint. Administration by transdermal patch may be preferred where, for example, it is desirable to effect sustained dosing.

It should be appreciated that the different routes of administration may require different dosages. For example, a useful intravenous ("IV") dose is between 5 and 50 mg, and a useful oral dosage is between 20 and 800 mg, of a compound of Formula I, or a pharmaceutically acceptable salt thereof. The dosage is within the dosing range used in treatment of the above-listed diseases, or as would be determined by the needs of the patient as described by the physician.

Compounds of Formula I may be administered in any form. Preferably, administration is in unit dosage form. A unit dosage form of the compound of Formula I to be used in this invention may also comprise other compounds useful in the therapy of diseases described above. A further description of

pharmaceutical formulations useful for administering the compounds of Formula I and invention combinations is provided below.

The invention also provides combinations, comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, together with another pharmaceutically active component as described herein.

The active components of the invention combinations, may be formulated together or separately and may be administered together or separately. The particular formulation and administration regimens used may be tailored to the particular patient and condition being treated by a practitioner of ordinary skill in the medical or pharmaceutical arts.

For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF-α inhibitors such as anti-TNF monoclonal antibodies and TNF receptor immunoglobulin molecules (such as Enbrel®), low dose methotrexate, lefunimide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as etoricoxib and rofecoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

The active ingredient of the present invention may be administered in combination with inhibitors of other mediators of inflammation, comprising one or more members selected from the group consisting essentially of the classes of such inhibitors and examples thereof which include, matrix metalloproteinase inhibitors, aggrecanase inhibitors, TACE inhibitors, leucotriene receptor antagonists, IL-1 processing and release inhibitors, ILra, H1 -receptor antagonists; kinin-B1 - and B2 - receptor antagonists; prostaglandin inhibitors such as PGD-, PGF- PGI2 - and PGE-receptor antagonists; thromboxane A2 (TXA2-) inhibitors; 5- and 12-lipoxygenase inhibitors; leukotriene LTC4 - , LTD4/LTE4 - and LTB4 -inhibitors; PAF-receptor antagonists; gold in the form of an aurothio group together with various hydrophilic groups; immunosuppressive agents, e.g., cyclosporine, azathioprine and methotrexate; anti-inflammatory glucocorticoids; penicillamine; hydroxychloroquine; anti-gout agents, e.g., colchicine, xanthine oxidase inhibitors, e.g., allopurinol and uricosuric agents, e.g., probenecid, sulfinpyrazone and benzbromarone.

The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine and antimetabolites such as methotrexate.

The compounds of the present invention may also be used in combination with anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, including hypertension, myocardial ischemia including angina, congestive heart failure and myocardial infarction, selected from vasodilators such as hydralazine, β-adrenergic receptor antagonists such as

propranolol, calcium channel blockers such as nifedipine, α2-adrenergic agonists such as clonidine, α-adrenergic receptor antagonists such as prazosin and HMG-CoA-reductase inhibitors (anti-hypercholesterolemics) such as lovastatin or atorvastatin.

The compounds of the present invention may also be administered in combination with one or more antibiotic, antifungal, antiprotozoal, antiviral or similar therapeutic agents.

The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as L-dopa, requip, mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine agonists, dopamine agonists and inhibitors of neuronal nitric oxide synthase) and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, lasofoxifene, droloxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

Compounds of Formula I may be used in combination with a COX-2 selective inhibitor, more preferably celecoxib, valdecoxib, parecoxib, lumiracoxib, or rofecoxib, or with compounds such as etanercept, infliximab, leflunomide, or methotrexate, and the like.

Compounds of Formula I may be used in combination with biological therapeutics useful for treating arthritic conditions, including CP-870, etanercept (a tumor necrosis factor alpha ("TNF-alpha") receptor immunoglobulin molecule; trade names ENBREL® and ENBREL ENTANERCEPT® by Immunex Corporation, Seattle, Washington), infliximab (an anti-TNF-alpha chimeric IgG 1K monoclonal antibody; tradename REMICADE® by Centocor, Inc., Malvern, Pennsylvania), methotrexate (tradename RHEUMATREX® by American Cyanamid Company, Wayne, New Jersey), and adalimumab (a human monoclonal anti-TNF-alpha antibody; tradename HUMIRA® by Abbott Laboratories, Abbott Park, Illinois).

The invention also provides methods of inhibiting an MMP-13 enzyme in an animal, comprising administering to the animal a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The invention also provides methods of treating a disease mediated by an MMP-13 enzyme in a patient, comprising administering to the patient a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The invention also provides methods of treating diseases such as heart disease, multiple sclerosis, osteo and rheumatoid arthritis, arthritis other than osteo- or rheumatoid arthritis, cardiac insufficiency, inflammatory bowel disease, heart failure, age-related macular degeneration, chronic obstructive pulmonary disease, asthma, periodontal diseases, psoriasis, atherosclerosis, and osteoporosis in a patient, comprising administering to the patient a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Other mammalian diseases and disorders which are treatable by administration of an invention combination alone, or contained in a pharmaceutical composition as defined below, include fever (including rheumatic fever and fever associated with influenza and other viral infections),

common cold, dysmenorrhea, menstrual cramps, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostrate cancer; hematopoietic malignancies including leukemias and lymphomas; Hodgkin's disease; aplastic anemia, skin cancer and familiar adenomatous polyposis), tissue ulceration, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent gastrointestinal lesion, gastrointestinal bleeding, coagulation, anemia, synovitis, gout, ankylosing spondylitis, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), periarteritis nodosa, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuralgia, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain (including low back and neck pain, headache and toothache), gingivitis, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, conjunctivitis, abnormal wound healing, muscle or joint sprains or strains, tendonitis, skin disorders (such as psoriasis, eczema, scleroderma and dermatitis), myasthenia gravis, polymyositis, myositis, bursitis, burns, diabetes (including types I and II diabetes, diabetic retinopathy, neuropathy and nephropathy), tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, immunodeficiency diseases (such as AIDS in humans and FLV, FIV in cats), sepsis, premature labor, hypoprothrombinemia, hemophilia, thyroiditis, sarcoidosis, Behcet's syndrome, hypersensitivity, kidney disease, Rickettsial infections (such as Lyme disease, Erlichiosis), Protozoan diseases (such as malaria, giardia, coccidia), reproductive disorders (preferably in livestock), epilepsy, convulsions, and septic shock.

One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

This invention also relates to a method of or a pharmaceutical composition for treating inflammatory processes and diseases comprising administering a compound of this invention to a mammal, including a human, cat, livestock or dog, wherein said inflammatory processes and diseases are defined as above and said inhibitory compound is used in combination with one or more other therapeutically active agents under the following conditions:

A) where a joint has become seriously inflamed as well as infected at the same time by bacteria, fungi, protozoa and/or virus, said inhibitory compound is administered in combination with one or more antibiotic, antifungal, antiprotozoal and/or antiviral therapeutic agents;

B) where a multi-fold treatment of pain and inflammation is desired, said inhibitory compound is administered in combination with inhibitors of other mediators of

inflammation, comprising one or more members independently selected from the group consisting essentially of:

1. NSAIDs;
2. H_1-receptor antagonists;
3. kinin-B_1- and B_2-receptor antagonists;
4. prostaglandin inhibitors selected from the group consisting of PGD-, PGF- PGI_2- and PGE-receptor antagonists;
5. thromboxane A_2 (TXA_2-) inhibitors;
6. 5-, 12- and 15-lipoxygenase inhibitors;
7. leukotriene LTC_4 -, LTD_4/LTE_4 - and LTB_4 -inhibitors;
8. PAF-receptor antagonists;
9. gold in the form of an aurothio group together with one or more hydrophilic groups;
10. immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine and methotrexate;
11. anti-inflammatory glucocorticoids;
12. penicillamine;
13. hydroxychloroquine;
14. anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfinpyrazone and benzbromarone;

C) where older mammals are being treated for disease conditions, syndromes and symptoms found in geriatric mammals, said inhibitory compound is administered in combination with one or more members independently selected from the group consisting essentially of:

1. cognitive therapeutics to counteract memory loss and impairment;
2. anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure and myocardial infarction, selected from the group consisting of:
   a. diuretics;
   b. vasodilators;
   c. β-adrenergic receptor antagonists;
   d. angiotensin-II converting enzyme inhibitors (ACE-inhibitors), alone or optionally together with neutral endopeptidase inhibitors;
   e. angiotensin II receptor antagonists;
   f. renin inhibitors;
   g. calcium channel blockers;
   h. sympatholytic agents;
   i. α_2-adrenergic agonists;

j. α-adrenergic receptor antagonists; and

k. HMG-CoA-reductase inhibitors (anti-hypercholesterolemics);

3. vinca alkaloids selected from:

a. vinblastine; and

b. vincristine;

4. growth hormone secretagogues;

5. strong analgesics;

6. local and systemic anesthetics; and

7. H_2 -receptor antagonists, proton pump inhibitors and other gastroprotective agents.

The invention method is useful in human and veterinary medicines for treating mammals suffering from one or more of the above-listed diseases and disorders.

An allosteric inhibitor of MMP-13 may be readily identified by one of ordinary skill in the pharmaceutical or medical arts by assaying an alkyne test compound for inhibition of MMP-13 as described, for example, in Biological Methods 1 or 2 of International Patent Application Pub. No. WO 04/014366US200400488637179822, the content of which are herein incorporated by reference. Allosteric inhibition of MMP-13 may be identified by one of ordinary skill in the pharmaceutical or medical arts by assaying the test invention compound for inhibition of MMP-13 in the presence of an inhibitor to the catalytic zinc of MMP-13 as described, for example, in Biological Methods 3 or 4 of International Patent Application Pub. No. WO 04/014366US200400488637179822, the content of which are herein incorporated by reference.

Further, a compound having an anti-inflammatory, an analgesic, anti-arthritic, or a cartilage damage inhibiting effect, or any combination of these effects, may be readily identified by one of ordinary skill in the pharmaceutical or medical arts by assaying the compound in any number of well known assays for measuring determining the compound's effects on cartilage and or other joint tissue damage, arthritis, inflammation, or pain. These assays include in vitro assays that utilize cartilage samples and in vivo assays in whole animals that measure cartilage degradation, inhibition of inflammation, or pain alleviation.

For example with regard to assaying cartilage damage in vitro, an amount of a compound or control vehicle may be administered with a cartilage-damaging agent to cartilage such as IL-1, and the cartilage damage inhibiting effects in both tests studied by gross examination or histopathologic examination of the cartilage, or by measurement of biological markers of cartilage damage such as, for example, proteoglycan content or hydroxyproline content, or by biomarkers of type II collagen degradation such as CTX-II or TIINE (Sunyer et al., *Osteo. Cartilage* 12 (2004) (Suppl. B), p. P84). Further, in vivo studies to assay cartilage damage and/or joint degeneration may be performed as follows: an amount of a compound or control vehicle may be administered with a cartilage damaging agent to an animal or may be administered in the absence of cartilage damaging agents, to animals that have surgery-induced or spontaneous OA lesions in the knee. Examples of surgery-induced animal models include the rat medial meniscus tear model or the dog anterior cruciate ligament transaction model. The effects of the compound being assayed in the animals for effects on cartilage

integrity and/or joint structure may be evaluated by gross examination or histopathologic examination of the affected joint(s), and respose to compounds further characterized by measurement of biological markers of cartilage damage such as, for example, proteoglycan content or hydroxyproline content or biomarkers of type II collagen degradation such as CTX-II or TIINE in biological fluids such as urine, plasma, serum or synovial fluids. Effect of the compounds may also be assessed by observation of the effects in an acute model on functional limitations of the affected joint.

Several methods of identifying a compound with cartilage damage inhibiting properties are described below. The amount to be administered in an assay is dependent upon the particular assay employed, but in any event is not higher than the well known maximum amount of a compound that the particular assay can effectively accommodate.

Similarly, compounds having pain-alleviating properties may be identified using any one of a number of in vivo animal models of pain.

Still similarly, compounds having anti-inflammatory properties may be identified using any one of a number of in vivo animal models of inflammation. For example, for an example of inflammation models, see United States patent number 6,329,429, which is incorporated herein by reference.

Still similarly, compounds having anti-arthritic properties may be identified using any one of a number of in vivo animal models of arthritis. For example, for an example of arthritis models, see also United States patent number 6,329,429.

Other embodiments of the present invention are compounds described herein, or a pharmaceutically acceptable salt thereof, that are ≥10, ≥20, ≥50, ≥100, or ≥1000 times more potent versus MMP-13 than versus at least two of any other MMP enzyme or TACE.

Still other aspects of the present invention are compounds of Formula I, or a pharmaceutically acceptable salt thereof, that are selective inhibitors of MMP-13 versus 2, 3, 4, 5, 6, or 7 other MMP enzymes, or versus TACE and 1, 2, 3, 4, 5, 6, or 7 other MMP enzymes.

It should be appreciated that selectivity of a compound of Formula I, or a pharmaceutically acceptable salt thereof, is a multidimensional characteristic that includes the number of other MMP enzymes and TACE over which selectivity for MMP-13 inhibition is present and the degree of selectivity of inhibition of MMP-13 over another particular MMP or TACE, as measured by, for example, the IC_{50} in μM of the compound for the inhibition of the other MMP enzyme or TACE divided by the IC_{50} in μM of the compound for the inhibition of MMP-13.

As discussed above, one aspect of the present invention is novel compounds that are selective inhibitors of the enzyme MMP-13. A selective inhibitor of MMP-13, as used in the present invention, is a compound that is ≥5X more potent *in vitro* versus MMP-13 than versus at least one other matrix metalloproteinase enzyme such as, for example, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, or MMP-14, or versus TACE. A preferred aspect of the present invention is novel compounds that are selective inhibitors of MMP-13 versus MMP-1.

The invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, which has an IC_{50} with any MMP enzyme that is less than or equal to 50 μM. Preferred are compounds of Formula I, or a pharmaceutically acceptable salt thereof, which have an IC_{50} with a human full-length MMP-13 ("hMMP-13FL") or a human MMP-13 catalytic domain ("hMMP-13CD") that

is less than or equal to 50 μM. More preferred are compounds of Formula I, or a pharmaceutically acceptable salt thereof, which have an IC_{50} with a human full-length MMP-13 ("hMMP-13FL") or a human MMP-13 catalytic domain ("hMMP-13CD") that is less than or equal to 10 μM. Examples of biological methods useful for determining IC_{50}s for compounds with an MMP are described herein.

The advantages of using an invention compound in a method of the instant invention include the nontoxic nature of the compounds at and substantially above therapeutically effective doses, their ease of preparation, the fact that the compounds are well-tolerated, and the ease of topical, IV, or oral administration of the drugs.

Another important advantage is that the present invention compounds more effectively target a particular disease that is responsive to inhibition of MMP-13 with fewer undesirable side effects than similar compounds that inhibit MMP-13 that are not invention compounds. This is so because the instant invention compounds of Formula I, or a pharmaceutically acceptable salt thereof, do not directly, or indirectly via a bridging water molecule, ligate, coordinate to, or bind to the catalytic zinc cation of MMP-13, but instead bind at a different location from where natural substrate binds to MMP-13. The binding requirements of an allosteric MMP-13 binding site are unique to MMP-13, and account for the specificity of the invention compounds for inhibiting MMP-13 over any other MMP enzyme. See *J. Chem. Biol.*, 2005(12), 181-189. Indeed, prior art inhibitors of MMP-13 bind to the catalytic zinc cations of other MMP enzymes as well as to the catalytic zinc cation of MMP-13, and are consequently significantly less selective inhibitors of MMP-13 enzyme.

The invention compounds which are invention compounds, and pharmaceutically acceptable salts thereof, are thus therapeutically superior to other inhibitors of MMP-13, or even TACE, because of fewer undesirable side effects from inhibition of the other MMP enzymes or TACE. For example, virtually all prior art MMP inhibitors tested clinically to date have exhibited an undesirable side effect known as muscoloskeletal syndrome ("MSS"). MSS is associated with administering an inhibitor of multiple MMP enzymes or an inhibitor of a particular MMP enzyme such as MMP-1. MSS will be significantly reduced in type and severity by administering the invention compound instead of any prior art MMP-13 inhibitor, or a pharmaceutically acceptable salt thereof. The invention compounds are superior to similar compounds that interact with the catalytic zinc cation of the MMP-13 enzyme as discussed above, even if similar compounds show some selectivity for the MMP-13.

General Synthetic Procedures

Intermediates for the synthesis of a compound of Formula I, or a pharmaceutically acceptable salt thereof, may be prepared by one of ordinary skill in the art of organic chemistry by adapting various synthetic procedures incorporated by reference above or that are well-known in the art of organic chemistry. These synthetic procedures may be found in the literature. Alternatively, a skilled artisan may find methods useful for preparing the intermediates in the chemical literature by searching widely available databases such as, for example, those available from the Chemical Abstracts Service, Columbus, Ohio, or MDL Information Systems GmbH (formerly Beilstein Information Systems GmbH), Frankfurt, Germany.

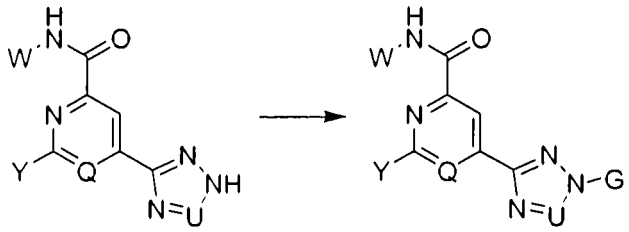
Preparations of the invention compounds may use starting materials, reagents, solvents, and catalysts that may be purchased from commercial sources or they may be readily prepared by adapting procedures in the references or resources cited above. Commercial sources of starting materials, reagents, solvents, and catalysts useful in preparing invention compounds include, for example, The Aldrich Chemical Company, and other subsidiaries of Sigma-Aldrich Corporation, St. Louis, Missouri, BACHEM, BACHEM A.G., Switzerland, or Lancaster Synthesis Ltd, United Kingdom.

Syntheses of some invention compounds may utilize starting materials, intermediates, or reaction products that contain a reactive functional group. During chemical reactions, a reactive functional group may be protected from reacting by a protecting group that renders the reactive functional group substantially inert to the reaction conditions employed. A protecting group is introduced onto a starting material prior to carrying out the reaction step for which a protecting group is needed. Once the protecting group is no longer needed, the protecting group can be removed. It is well within the ordinary skill in the art to introduce protecting groups during a synthesis of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and then later remove them. Procedures for introducing and removing protecting groups are well known. Thus, for example, protecting groups such as the following may be utilized to protect amino, hydroxyl, and other groups: carboxylic acyl groups such as, for example, formyl, acetyl, and trifluoroacetyl; alkoxycarbonyl groups such as, for example, ethoxycarbonyl, tert-butoxycarbonyl (BOC), β,β,β-trichloroethoxycarbonyl (TCEC), and β-iodoethoxycarbonyl; aralkyloxycarbonyl groups such as, for example, benzyloxycarbonyl (CBZ), para-methoxybenzyloxycarbonyl, and 9-fluorenylmethyloxycarbonyl (FMOC); trialkylsilyl groups such as, for example, trimethylsilyl (TMS) and tert-butyldimethylsilyl (TBDMS); and other groups such as, for example, triphenylmethyl (trityl), tetrahydropyranyl, vinyloxycarbonyl, ortho-nitrophenylsulfenyl, diphenylphosphinyl, para-toluenesulfonyl (Ts), mesyl, trifluoromethanesulfonyl, and benzyl. Examples of procedures for removal of protecting groups include hydrogenolysis of CBZ groups using, for example, hydrogen gas at 50 psi in the presence of a hydrogenation catalyst such as 10% palladium on carbon, acidolysis of BOC groups using, for example, hydrogen chloride in dichloromethane, trifluoroacetic acid (TFA) in dichloromethane, and the like, reaction of silyl groups with fluoride ions, and reductive cleavage of TCEC groups with zinc metal.

The following schemes are representative of the methods that can be used to prepare compounds of Formula I. Starting materials may be obtained by procedures described in the schemes, by procedures well known to one of ordinary skill in organic chemistry, and/or may be obtained commercially.

The following schemes are representative of the methods that can be used to prepare compounds of Formula I. Starting materials may be obtained by procedures described in the schemes, by procedures well known to one of ordinary skill in organic chemistry, and/or may be obtained commercially.

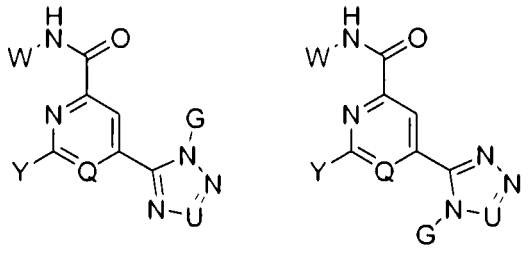
CHART A



A1 A2

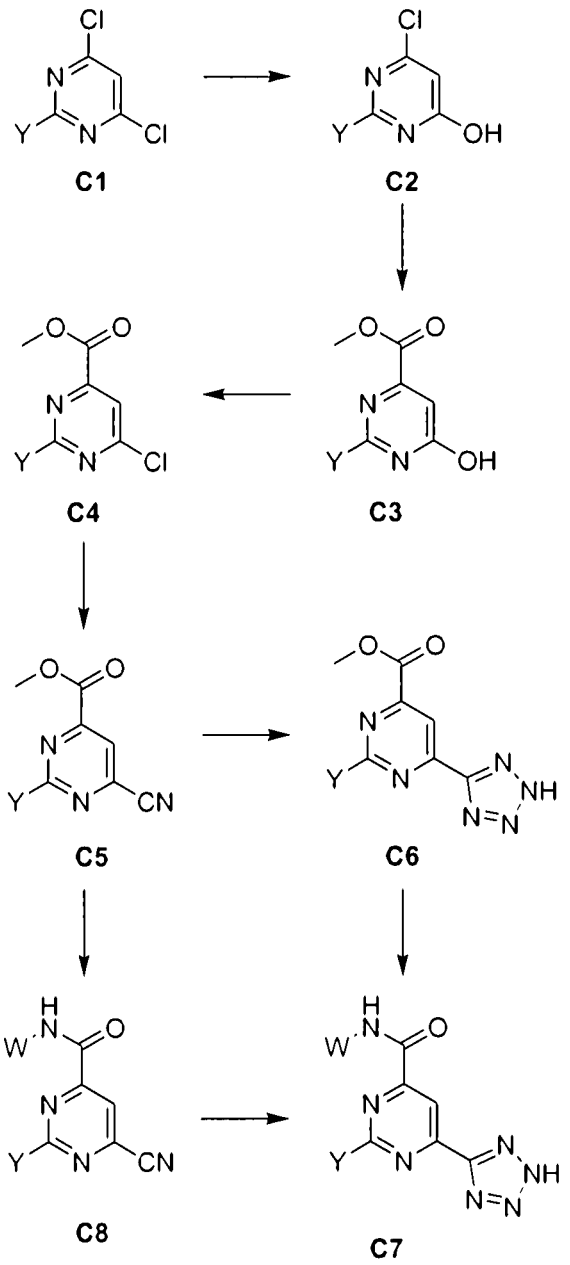
Compounds of formula (I) wherein L is a tetrazole (U = N) or triazole (U = CH) may be prepared as described in Chart A. A compound of formula A1 is reacted with an alcohol (G-OH) under Mitsunobu coupling conditions (e.g. Ph_3P, di-*tert*-butyl azodicarboxylate) wherein G is a group V-Z as described above and in which reactive functional groups may be protected. Alternatively, a compound of formula A1 may be reacted with a compound G-X in the presence of a base (e.g. tertiary amine, sodium hydride) wherein X is Cl, Br, I, alkylsulfonate ester, or arylsulfonate ester. The reagents G-OH or G-X are either commercially available or prepared as described below (Charts J – X). The above reaction conditions may afford one or more positional isomers about the five-membered heterocycle including A2 (Chart A), B1, or B2 (Chart B). Determination of the structural isomer formed is readily possible by someone skilled in the art employing NMR techniques (e.g. H1, gHSQC, gHMBC, gHMBC-N15, and 1d NOE experiments) or single crystal X-ray analysis.

CHART B



B1 B2

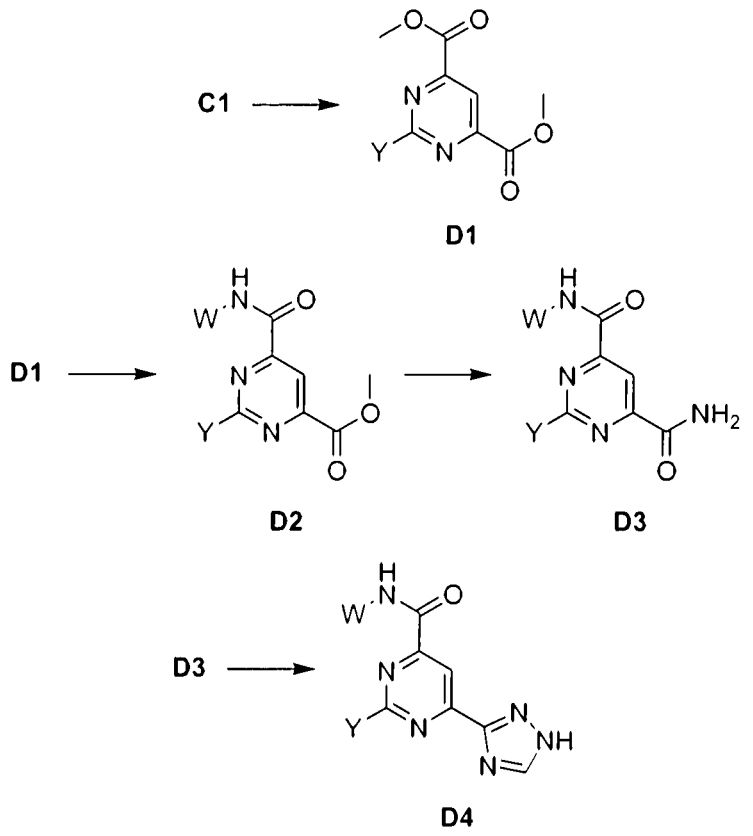
CHART C



Compounds of the formula A1 employed in Chart A are prepared as described in Charts C – H below. Hydrolysis of 4,6-dichloropyrimidines of the formula C1 under strongly acidic conditions provide compounds of the formula C2 (Henze, H. R. *J. Org. Chem.* **1952**, *17*, 1320-1326). Compounds of the formula C1 are commercially available (Y = H and CH_3) or may be prepared by literature procedures wherein Y = $(CH_2)_{1-3}CH_3$, $CH(CH_3)C_2H_5$, and $CH_2CH(CH_3)_2$ (Henze, H. R. *J. Org. Chem.* **1952**, *17*, 1320-1326); Y = $CH(CH_3)_2$ (Gershon, H. *J. Med. Chem.* **1964**, *7*, 808-811); Y = CF_3 (Inoue, S. *J. Org. Chem.* **1961**, *26*, 4504-4508); Y = CH_2F (Elvidge, J. A. *J. Chem. Soc., C*, **1968**, 2188-2198) or by analogous procedures to those described in these references. Carbonylation of compounds C2 with carbon monoxide and an alcohol solvent (e.g. methanol) in the presence of a palladium catalyst provides esters of the formula C3. Subsequent chlorination of esters C3 followed by reaction with

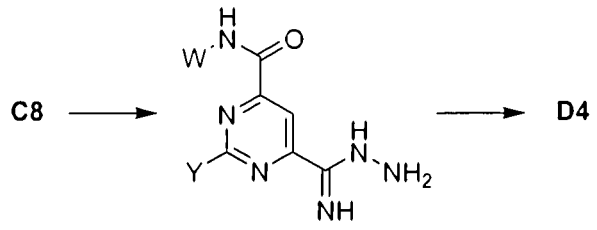
tetraethylammonium cyanide provides compounds of the formula C5. The reaction of cyano derivatives with sodium azide in the presence of zinc bromide provides the tetrazoles C6 which subsequently are reacted with a primary amine of the formula W-NH_2 to provide compounds of the formula C7. Alternatively, cyano derivatives C5 may be reacted with the amine W-NH_2 first to provide C8 which subsequently is subjected to tetrazole formation to provide C7.

CHART D



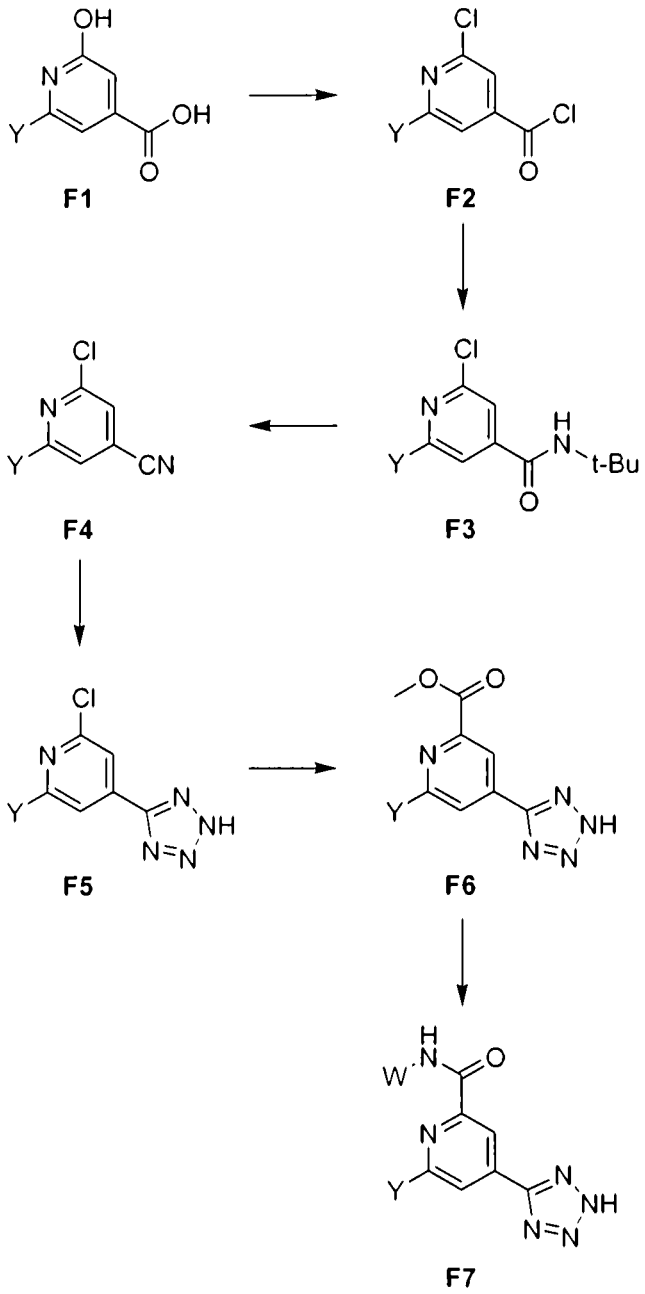
Compounds of the formula A1 employed in Chart A wherein Q is N and U is CH may be prepared as described in Chart D starting from 4,6-dichloropyrimidines of the formula C1 obtained as described above. Carbonylation of compounds C1 with carbon monoxide and an alcohol solvent (e.g. methanol) in the presence of a palladium catalyst provides esters of the formula D1. Treatment of esters D1 with less than two equivalents of a primary amine of the formula W-NH_2 affords amides D2 which are then subsequently reacted with ammonia to provide bis-amides of the formula D3. Condensation of D3 with dimethylformamide dimethylacetal followed by reaction with hydrazine (Mustazza, C. *J. Heterocyclic Chem.* **2001**, *38*, 1119-1129) affords triazoles of the formula D4. Alternatively as described in Chart E, triazoles of the formula D4 may be prepared by reacting nitriles of the formula C8 with hydrazine to provide E1 which is then heated with formic acid.

CHART E



E1

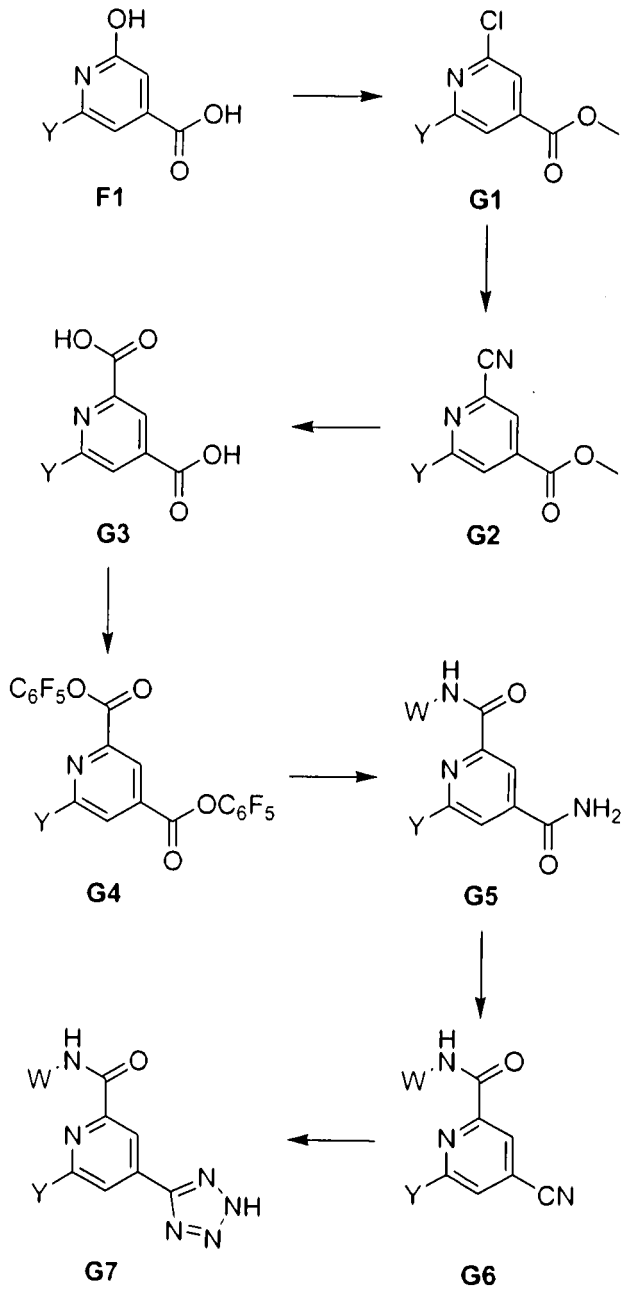
CHART F



F1 F2 F3 F4 F5 F6 F7

Compounds of the formula A1 employed in Chart A wherein Q is CH and U is N may be prepared as described in Chart F. Carboxylic acids of the formula F1 are commercially available (Y = H and CH_3) or may be prepared by literature procedures wherein Y = CH_2CH_3 (Tracy, A. H. *J. Org. Chem.* **1941**, *6*, 70-76); Y = $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$ (Libermann, D. *Bull. Soc. Chim. Fr.* **1958**, 687-694) or by analogous procedures to those described in these references. Compounds F1 may be chlorinated (e.g. $POCl_3$, PCl_5) and then reacted with tert-butylamine to provide compounds of the formula F3. Further oxidation of secondary amides F3 by treatment with $POCl_3$ affords the corresponding nitriles F4. The reaction of cyano derivatives F4 with sodium azide in the presence of zinc bromide provides the tetrazoles F5. Carbonylation of compounds F5 with carbon monoxide and an alcohol solvent (e.g. methanol) in the presence of a palladium catalyst provides esters of the formula F6 which are subsequently reacted with a primary amine of the formula W-NH_2 to provide compounds of the formula F7.

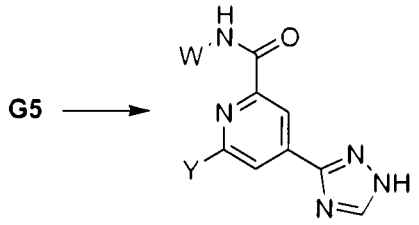
CHART G



Alternatively, compounds of the formula A1 employed in Chart A wherein Q is CH and U is N may be prepared as described in Chart G starting from compounds F1 obtained as described above. Compounds F1 may be chlorinated (e.g. $POCl_3$, PCl_5) and then reacted with an alkanol (e.g. methanol) to provide compounds of the formula G1. Cyanation of G1 in the presence of a palladium catalyst affords G2 which is subsequently hydrolyzed under basic conditions (e.g. potassium hydroxide) to provide carboxylic acids of the formula G3. Esterification of carboxylic acids G3 with pentafluorophenyl trifluoroacetate affords diesters of the formula G4. The sequential addition of a primary amine of the formula W-NH_2 followed by ammonia provides amides G5. Dehydration of the primary amide by treatment with $POCl_3$ affords the corresponding nitriles G6 which react with sodium

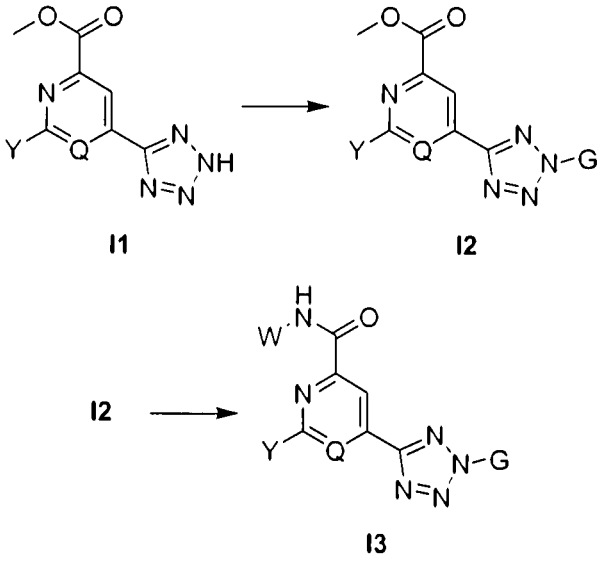
azide to provide tetrazoles of the formula G7. Intermediates of the formula G5 may also be transformed to triazole derivatives useful in Chart A wherein Q is CH and U is CH as described in Chart H. Condensation of primary carboxamides G5 with dimethylformamide dimethylacetal followed by reaction with hydrazine (Mustazza, C. *J. Heterocyclic Chem.* **2001**, *38*, 1119-1129) affords triazoles of the formula H1.

CHART H



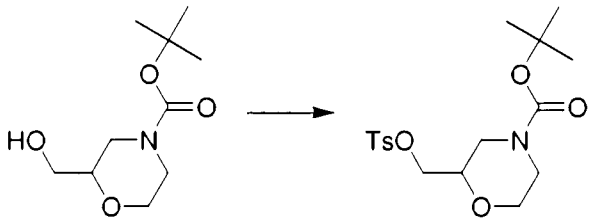
H1

CHART I



As described in Chart I, compounds of formula I3 may be prepared by reacting a compound of formula I1 (prepared as described in Chart C or Chart F) with an alcohol (G-OH) under Mitsunobu coupling conditions (e.g. Ph_3P, di-*tert*-butyl azodicarboxylate) to provide I2 wherein G is a group V-Z as described above and in which reactive functional groups may be protected. Alternatively, a compound of formula I1 may be reacted with a compound G-X in the presence of a base (e.g. tertiary amine, sodium hydride) wherein X is Cl, Br, I, alkylsulfonate ester, or arylsulfonate ester. The reagents G-OH or G-X are either commercially available or prepared as described below (Charts J – X). The resulting ester is then reacted with a primary amine of the formula W-NH_2 to provide compounds of the formula I3.

CHART J



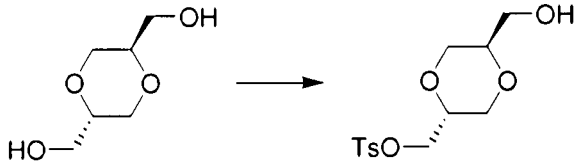
J1 **J2**

CHART K



K1 **K1**

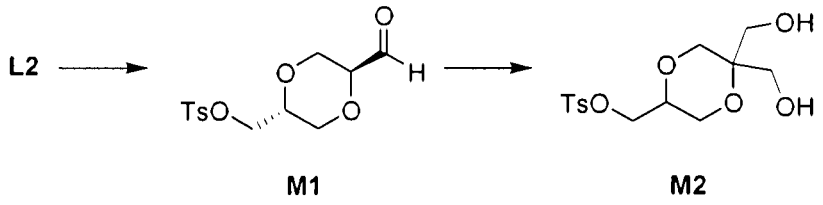
CHART L



L1 **L2**

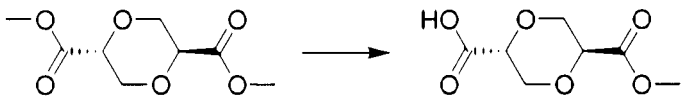
The reagents G-X employed in Chart A and Chart I above wherein X is an alkylsulfonate ester or arylsulfonate ester are prepared by reaction of an alcohol G-OH with and alkyl- or arylsulfonyl chloride in the presence of a base (e.g. triethylamine or pyridine). Representative examples are shown in Charts J - L wherein the alcohol G-OH may be prepared by literature procedures, e.g. J1, tert-butyl (*R*)-2-(hydroxymethyl)morpholine-4-carboxylate and tert-butyl (*S*)-2-(hydroxymethyl)morpholine-4-carboxylate (Yanagisawa, H. *Heterocycles*, **1993**, *35*, 105-109); K1, (*R*)-(1,4-dioxan-2-yl)methanol and (*S*)-(1,4-dioxan-2-yl)methanol (Kim, H. Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3207-3211). Tosylation of trans-2,5-bis-(hydroxymethyl)-1,4-dioxane (L1) (Summerbell, R. K. *J. Am. Chem. Soc.* **1954**, *76*, 6401-6407) affords *rac*-((2*R**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (L2) which upon resolution by chiral supercritical fluid chromatography provides the corresponding (2*R*,5*R*)- and (2*S*,5*S*)-isomers.

CHART M

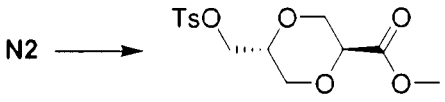


M1 M2

CHART N



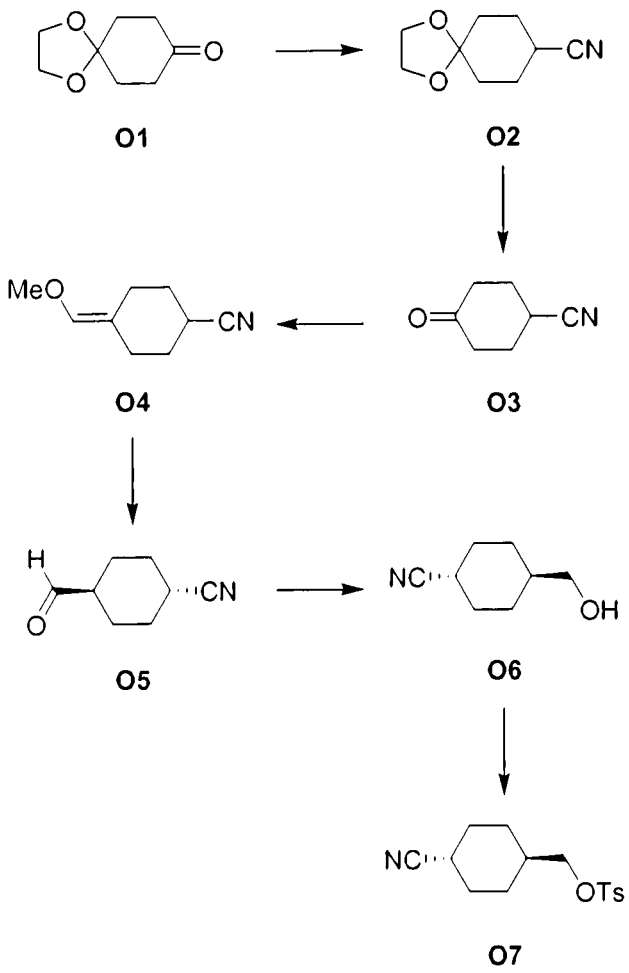
N1 N2



N3

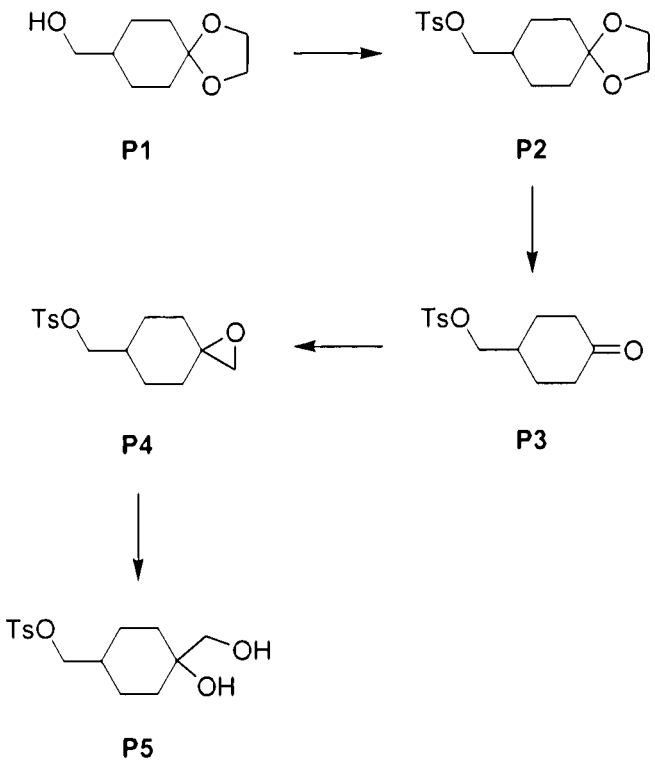
Additional examples of G-X may be prepared as described below. According to Chart M, (5,5-bis(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (M2) is prepared from *rac*-((2*R**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (L2) by oxidation under Swern conditions to afford M1 which is then reacted with formaldehyde under basic conditions. According to Chart N, *rac*-(2*S**,5*R**)-methyl 5-((tosyloxy)methyl)-1,4-dioxane-2-carboxylate (N3) is prepared from trans-dimethyl 1,4-dioxane-2,5-dicarboxylate (N1) (Summerbell, R. K. *J. Am. Chem. Soc.* **1954**, *76*, 6401-6407) by first partial saponification to provide carboxylic acid N2. Subsequent reduction of the carboxylic acid functional group with borane dimethylsulfide followed by the reaction of the resulting alcohol with p-toluenesulfonyl chloride in pyridine affords N3.

CHART O



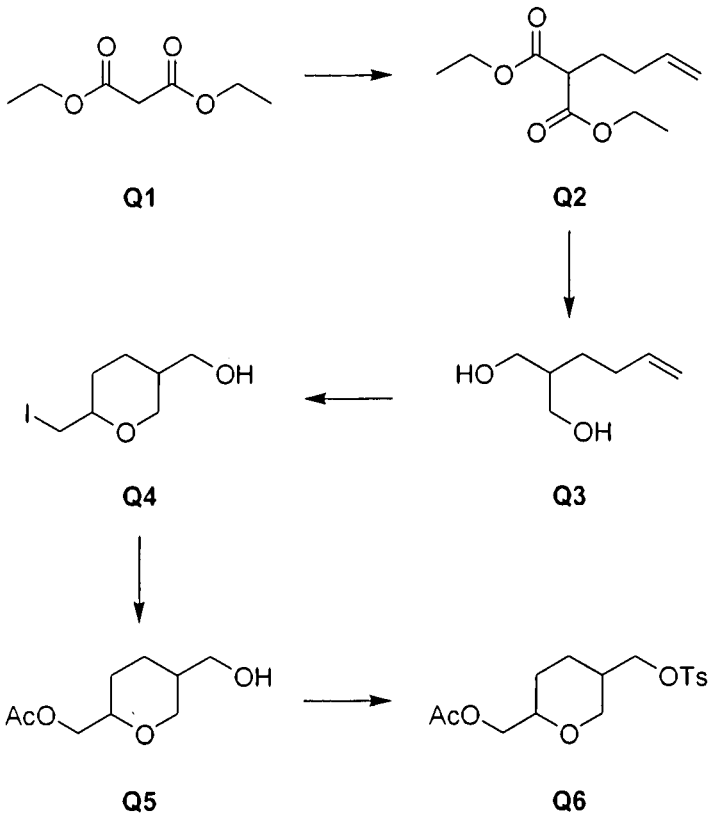
According to Chart O, (trans-4-cyanocyclohexyl)methyl 4-methylbenzenesulfonate (O7) is prepared by reacting 1,4-dioxa-spiro[4.5]decan-8-one with tosyl-methyl-isocyanide in the presence of potassium t-butoxide to afford 1,4-dioxa-spiro[4.5]decane-8-carbonitrile (O2). Acidic hydrolysis of the resulting ketal followed by Wittig olefination with methoxy methyl triphenylphosphonium ylide and acid hydrolysis provides trans-4-formylcyclohexanecarbonitrile (O5). Reduction of the aldehyde functional group with sodium borohydride and reaction of the resulting alcohol with p-toluenesulfonyl chloride in pyridine affords O7.

CHART P



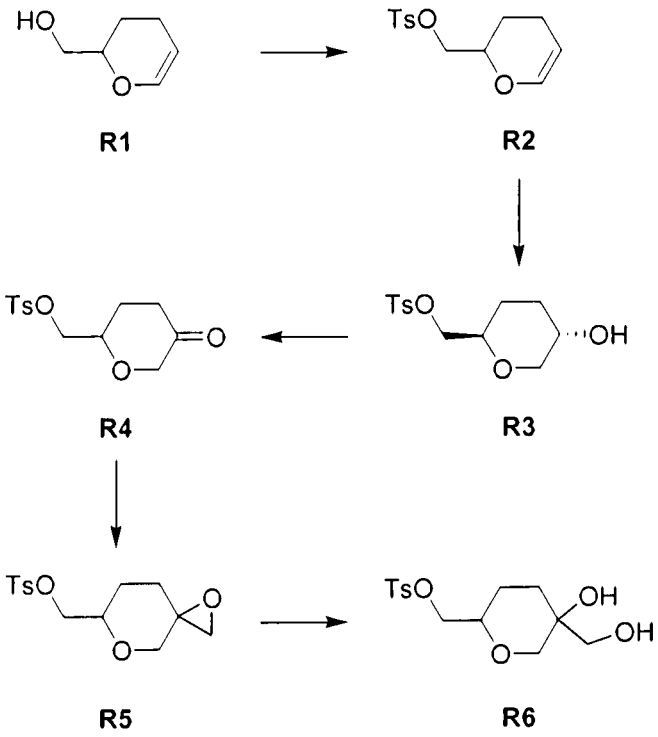
According to Chart P, cis- and trans-(4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl 4-methylbenzenesulfonate (P5) may be prepared by reacting 1,4-dioxaspiro[4.5]dec-8-ylmethanol with p-toluenesulfonyl chloride in pyridine to afford P2. The resulting ketal is subjected to acidic hydrolysis to provide (4-oxocyclohexyl)methyl 4-methylbenzenesulfonate (P3). Epoxidation of ketone P3 with trimethylsulfoxonium ylide affords P4 which upon acid promoted oxirane ring opening provides P5.

CHART Q



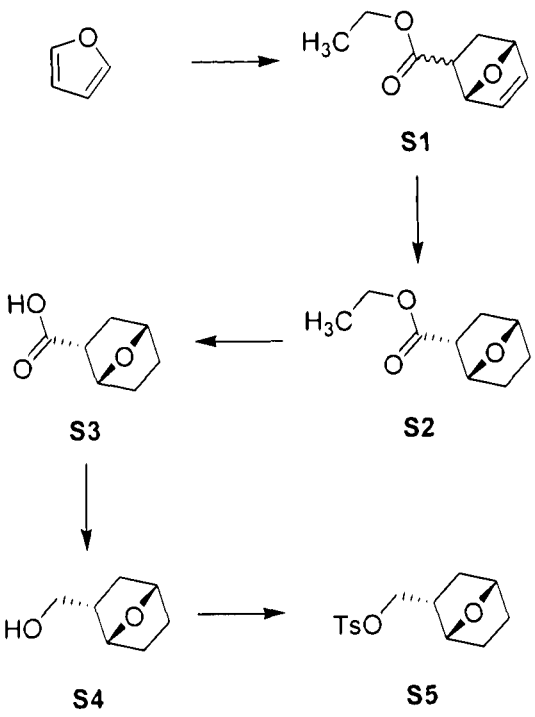
According to Chart Q, reagents of the formula G-X including 6-(iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Q4) and (5-((tosyloxy)methyl)-tetrahydro-2*H*-pyran-2-yl)methyl acetate (Q6) may be prepared starting from diethylmalonate. 6-(Iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Q4) is prepared analogous to previously described procedures in which diethylmalonate is alkylated with 1-bromo-3-butene to afford Q2 (Deleris, G. *Tetrahedron* **1988**, *44*, 4243-4258) and then subsequently Q2 is reduced with lithium aluminium hydride to afford 2-(but-3-enyl)propane-1,3-diol (Q3) (Ramos Tombo, G. M. *Tetrahedron Lett.* **1986**, *27*, 5707-5710). Cyclization of Q3 by reaction with iodine and sodium bicarbonate provides Q4 as a mixture of diastereomers (PCT Application WO2005/080317). The individual isomers of Q4 may be obtained through separation by chiral supercritical fluid chromatography. 6-(Iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Q4) may be further reacted with an acetate salt to afford Q5. The resulting alcohol is treated with p-toluenesulfonyl chloride in the presence of an amine base to provide (5-((tosyloxy)methyl)-tetrahydro-2*H*-pyran-2-yl)methyl acetate (Q6).

CHART R



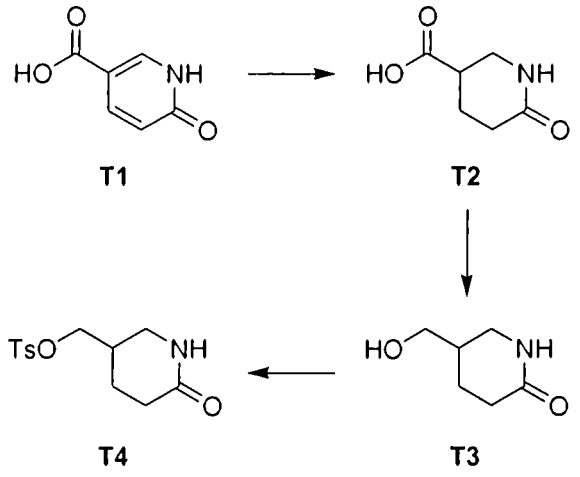
According to Chart R, reagents of the formula G-X including *rac*-((2*R**,5*S**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (R3) and (5-hydroxy-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (R6) may be prepared. (3,4-Dihydro-2*H*-pyran-2-yl)methanol (R1) is treated with p-toluenesulfonyl chloride in pyridine to afford sulfonylester R2. Analogous to literature precedent (Zhang, S. *Bioorg. Med. Chem.* **2006**, *14*, 3953-3966), reaction of R2 under hydroboration/oxidation conditions (BH_3, NaOH, H_2O_2) affords *rac*-((2*R**,5*S**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (R3). Oxidation of R3 under Swern conditions provides (5-oxo-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (R4). Epoxidation of ketone R4 with trimethylsulfoxonium ylide affords R5 which upon acid promoted oxirane ring opening provides R6.

CHART S



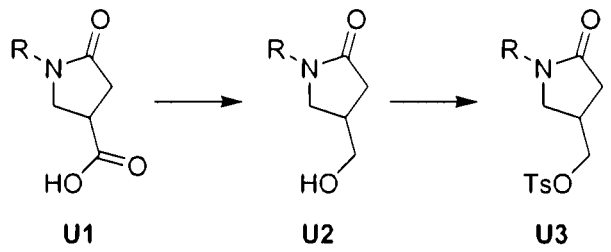
According to Chart S, *rel*-(1*R*,2*S*,4*S*)-7-oxa-bicyclo[2.2.1]heptan-2-ylmethyl 4-methylbenzenesulfonate may be prepared by initially reacting furan with ethyl acrylate in the presence of zinc iodide to afford the cycloadduct S1. Alkene S1 is then treated with hydrogen and palladium on carbon in ethanol to provide a mixture of isomers which are separated by silica gel chromatography to afford S2. Saponification of S2 with aqueous sodium hydroxide provides carboxylic acid S3 which may be reacted with 1,1'-carbonyldiimidazole and sodium borohydride to afford alcohol S4. The desired tosylate S5 is provided by reacting the resulting alcohol with p-toluenesulfonyl chloride in the presence of an amine base. By employing these same procedures and the other S2 isomer separated by chromatography, *rel*-(1*R*,2*S*,4*S*)-7-oxa-bicyclo[2.2.1]heptan-2-ylmethyl 4-methylbenzenesulfonate may be prepared.

CHART T



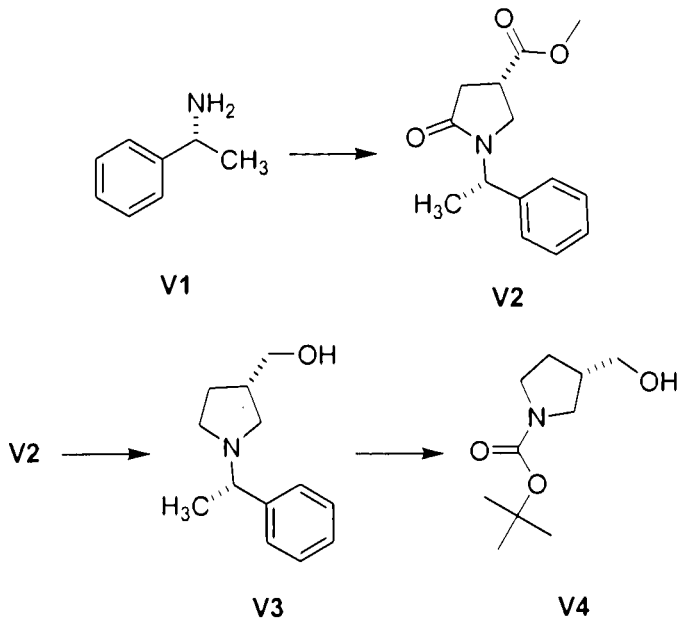
According to Chart T, (6-oxopiperidin-3-yl)methyl 4-methylbenzenesulfonate (T4) may be prepared by reacting 6-hydroxynicotinic acid (T1) with hydrogen in the presence of a palladium catalyst to afford carboxylic acid T2. The resulting acid is treated with 1,1'-carbonyldiimidazole and sodium borohydride to provide alcohol T3 which is then reacted with p-toluenesulfonyl chloride in the presence of an amine base to provide tosylate T4.

CHART U



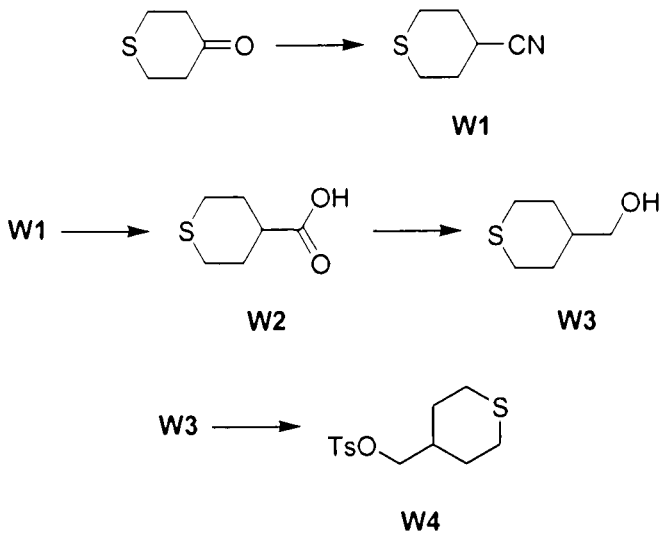
According to Chart U, reagents of the formula G-X may be prepared where lactam carboxylic acids of the formula U1 (where R may include but is not limited to hydrogen, methyl, ethyl, and iso-propyl) obtained as described by E. Valentin et. al. (*Tetrahedron Asymmetry*, **2001**, *12*, 3241-3249) are reacted with 1,1'-carbonyldiimidazole and sodium borohydride to provide alcohols of the formula U2. The resulting alcohols are reacted with p-toluenesulfonyl chloride in the presence of an amine base to provide tosylates of the formula U3.

CHART V



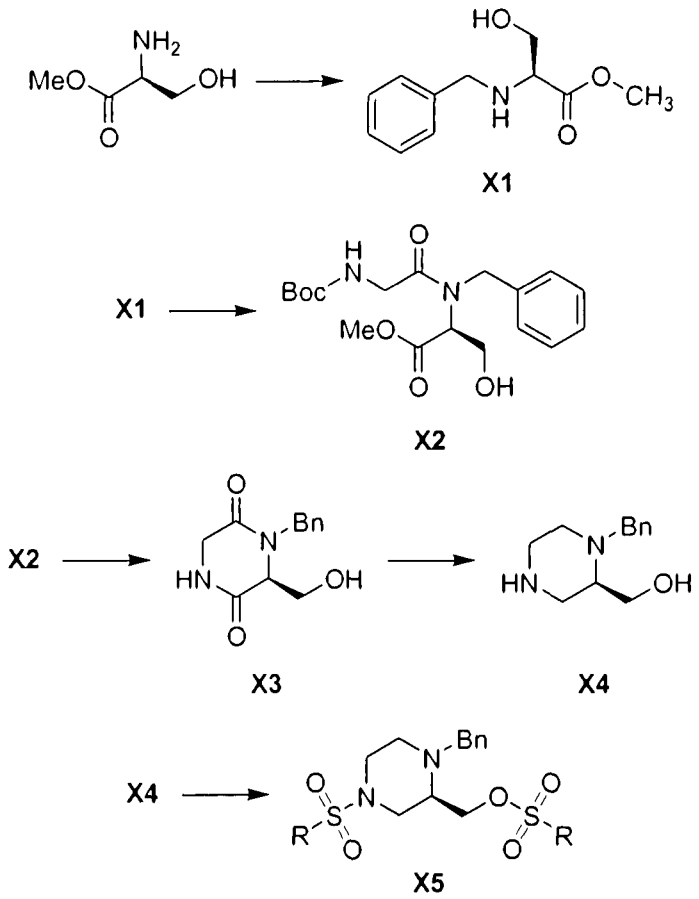
According to Chart V, (*S*)-*N*-Boc 3-(hydroxymethyl)pyrrolidine (V4) is prepared from (*R*)-1-phenylethanamine by cyclization with dimethyl 2-oxosuccinate in refluxing toluene to provide V2. Lactam V2 is then reduced with lithium aluminium hydride to provide ((*S*)-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)methanol (V3). The alcohol is reacted with hydrogen gas in the presence of $Pd(OH)_2$ on carbon, and the resulting amine is treated with di-tert-butyl dicarbonate to provide V4. In a similar manner, (*R*)-*N*-Boc 3-(hydroxymethyl)pyrrolidine is prepared from (*S*)-1-phenylethanamine.

CHART W



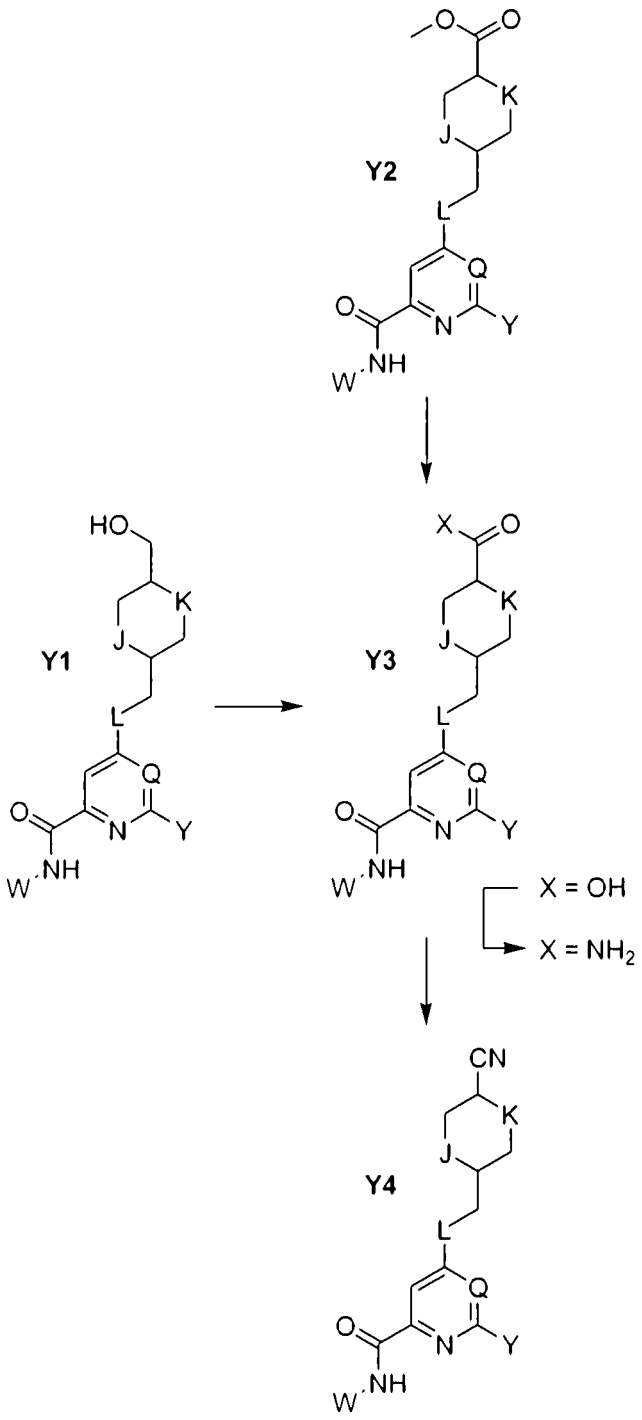
According to Chart W, reagents of the formula G-X specifically (tetrahydro-2*H*-thiopyran-4-yl)methyl 4-methylbenzenesulfonate (W4) may be prepared. Tetrahydrothiopyran-4-one is reacted with lithium chloride and samarium diiodide to afford tetrahydro-2H-thiopyran-4-carbonitrile (W1) which is then hydrolyzed under basic conditions (e.g. NaOH) to provide the corresponding carboxylic acid W2. The carboxylic acid is reacted with 1,1'-carbonyldiimidazole and sodium borohydride to provide alcohol W3. Tosylate W4 is then prepared by treating W3 with p-toluenesulfonyl chloride in the presence of an amine base.

CHART X



According to Chart X, reagents of the formula G-X as depicted in formula X5 may be prepared. L-Serine methyl ester is treated with benzaldehyde and $NaBH(OAc)_3$ to afford benzylamine X1 which is subsequently coupled (BDP, 1-HOBT, diisopropylethylamine) with *N*-(*tert*-butoxycarbonyl)glycine to provide X2. The tert-butylcarbamate is removed under acidic conditions (HCl/chloroform) and the resulting product is cyclized under basic conditions (5% aq. $NaHCO_3$) to provide piperizine-2,5-dione X3. Piperizine X4 is then prepared by reduction of X3 with a metal hydride (e.g. lithium aluminium hydride) and the product is subsequently reacted with alkyl sulfonyl chlorides in the presence of an amine base to provide compounds of the formula X5 where R may be but is not limited to methyl, ethyl, propyl, and iso-propyl.

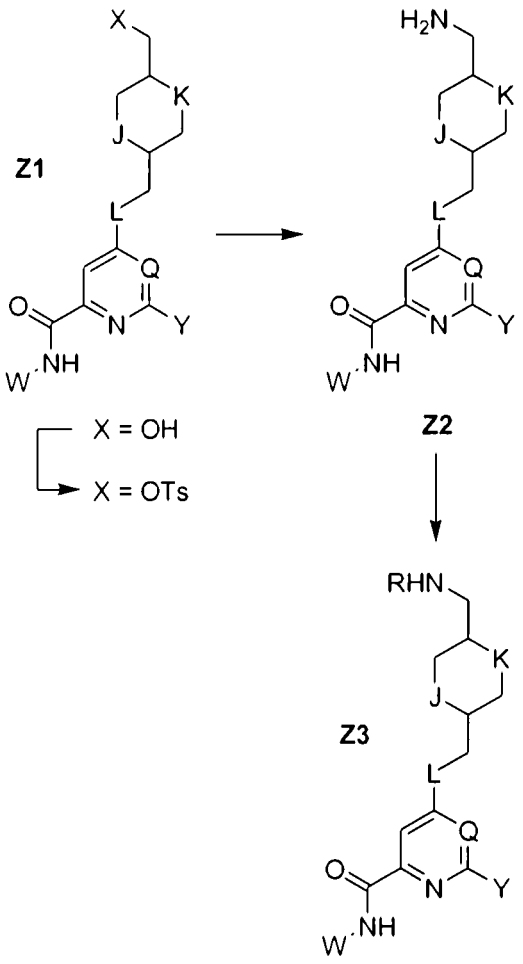
CHART Y



Compounds of the general formula Y1 and Y2 (wherein J and K are independently CH_2 or O) may be further elaborated as described in Chart Y. Compounds of the formula Y1 may be oxidized to the carboxylic acid by reaction with an appropriate oxidizing agent (e.g. pyridinium dichromate) to provide Y3 (X = OH). Similarly, saponification of compounds of the formula Y2 under basic conditions (e.g. sodium hydroxide) may provide compounds of the formula Y3 (X = OH). Treatment of the resulting carboxylic acids Y3 with oxalyl chloride followed by reaction with ammonia affords the primary amides

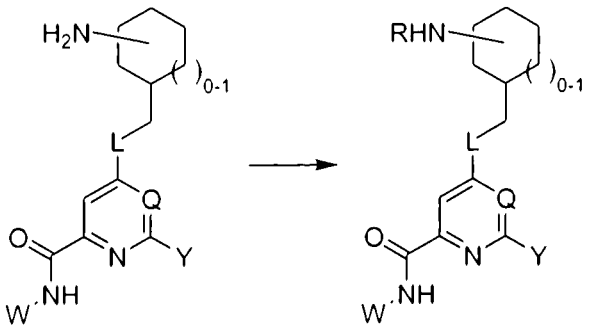
Y3 (X = NH_2). The primary amide may then be reacted with a strong dehydrating agent (e.g. $POCl_3$) to provide nitriles of the formula Y4.

CHART Z



Compounds of the general formula Z1 (wherein J and K are independently CH_2 or O) may be further elaborated as described in Chart Z. Alcohols of the formula Z1 (X = OH) may be reacted with p-toluenesulfonyl chloride in the presence of an amine base to afford compounds of the formula Z1 (Y = OTs). Subsequent reaction of Z1 (X = OTs) with ammonia in a solvent such as methanol provides amines of the formula Z2. The resulting amine may be reacted with alkyl halides or with alkanals in the presence of a reducing agent to provide compounds of the formula Z3 (R = $C_{1\text{-}6}$alkyl). Alternatively, the amine Z2 may be reacted with carboxylic acid halides to provide compounds of the formula Z3 (R = COR^{23}) or with sulfonyl chlorides to provide compounds of the formula Z3 (R = SO_2R^{37}).

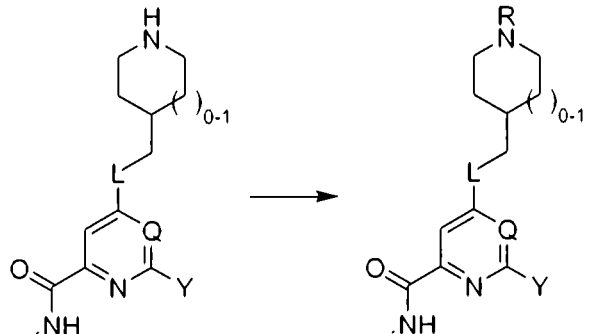
CHART AA



AA1 **AA2**

Compounds of the general formula AA1 may be further elaborated as described in Chart AA. The amine may be reacted with alkyl halides or with alkanals in the presence of a reducing agent to provide compounds of the formula AA2 (R = $C_{1\text{-}6}$alkyl). Alternatively, the amine AA1 may be reacted with carboxylic acid halides to provide compounds of the formula AA2 (R = COR^9) or with sulfonyl chlorides to provide compounds of the formula AA2 (R = SO_2R^{36}).

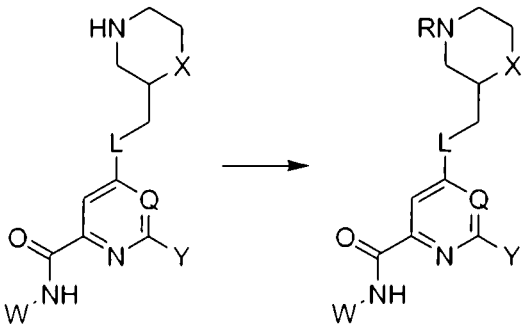
CHART BB



BB1 **BB2**

Compounds of the general formula BB1 may be further elaborated as described in Chart BB. The amine may be reacted with alkyl halides or with alkanals in the presence of a reducing agent to provide compounds of the formula BB2 (R = $C_{1\text{-}6}$alkyl). Alternatively, the amine BB1 may be reacted with carboxylic acid halides to provide compounds of the formula BB2 (R = COR^9) or with sulfonyl chlorides to provide compounds of the formula BB2 (R = SO_2R^{12}).

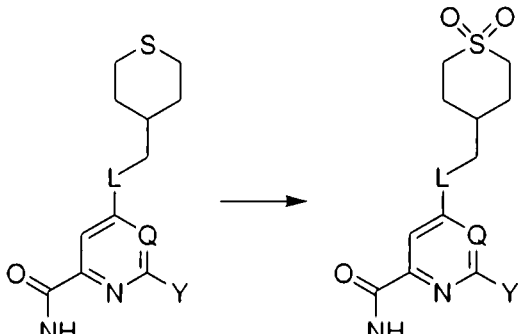
CHART CC



CC1 **CC2**

Compounds of the general formula CC1 (where X is CH_2 or O) may be further elaborated as described in Chart CC. The amine may be reacted with alkyl halides or with alkanals in the presence of a reducing agent to provide compounds of the formula CC2 (R = C_{1-6}alkyl). Alternatively, the amine CC1 may be reacted with carboxylic acid halides to provide compounds of the formula CC2 (R = R^9) or with sulfonyl chlorides to provide compounds of the formula CC2 (R = R^{12}).

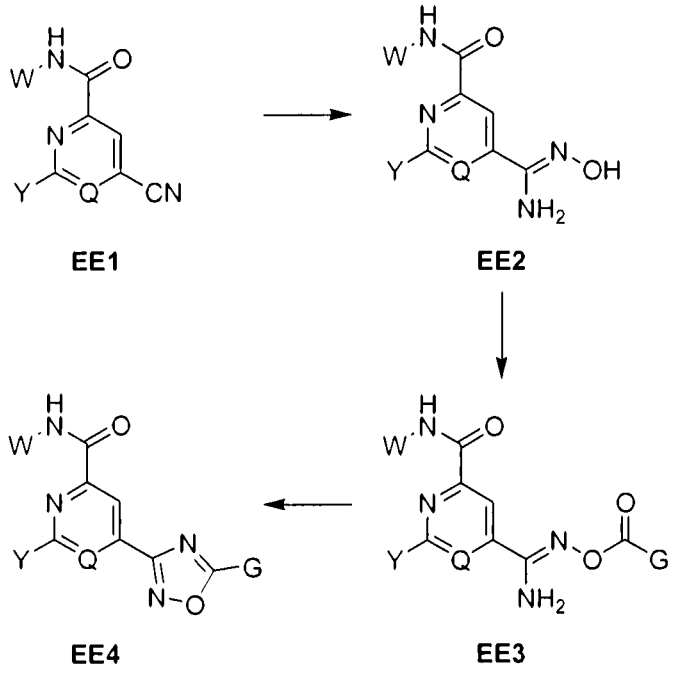
CHART DD



DD1 **DD2**

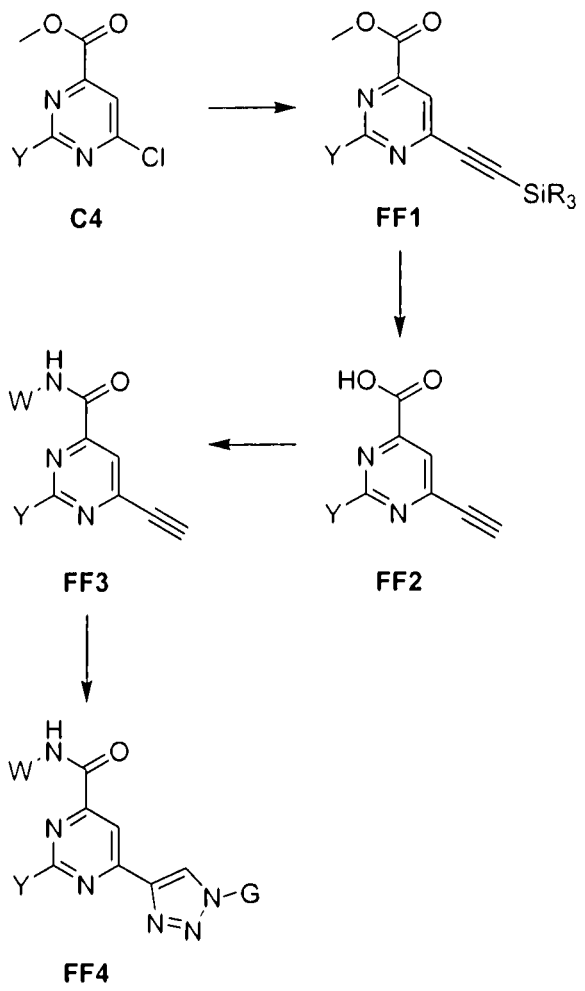
As described in Chart DD, compounds of the formula DD1 may be oxidized in the presence of oxone to provide tetrahydrothiopyran-1,1-dione derivatives of the formula DD2.

CHART EE



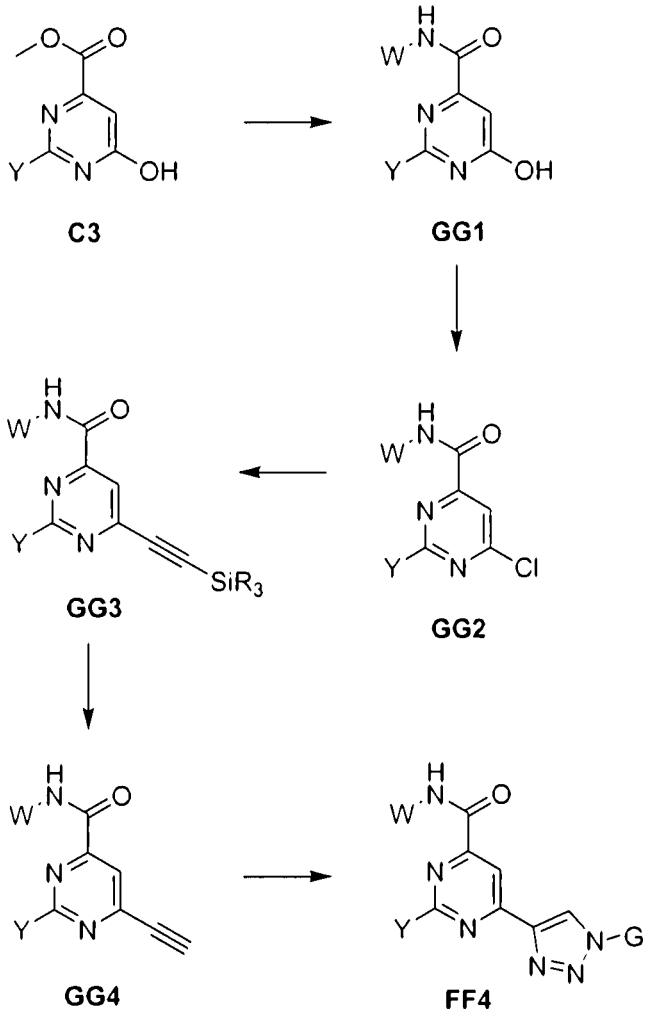
Compounds of formula (I) in which L is an oxadiazole ring may be prepared as described in Chart EE. Nitriles of the formula EE1 obtained as described in Chart C and Chart G above are treated with hydroxylamine hydrochloride under basic conditions (e.g. sodium hydroxide) to provide compounds of the formula EE2. Compounds EE2 are then reacted with compounds of the formula G-CO_2H in the presence of an activating agent (e.g. N-hydroxybenzotriazole) and a coupling reagent (e.g. polymer supported carbodiimide resin) to afford compounds of the formula EE3 which upon heating in the presence of a base provide EE4.

CHART FF



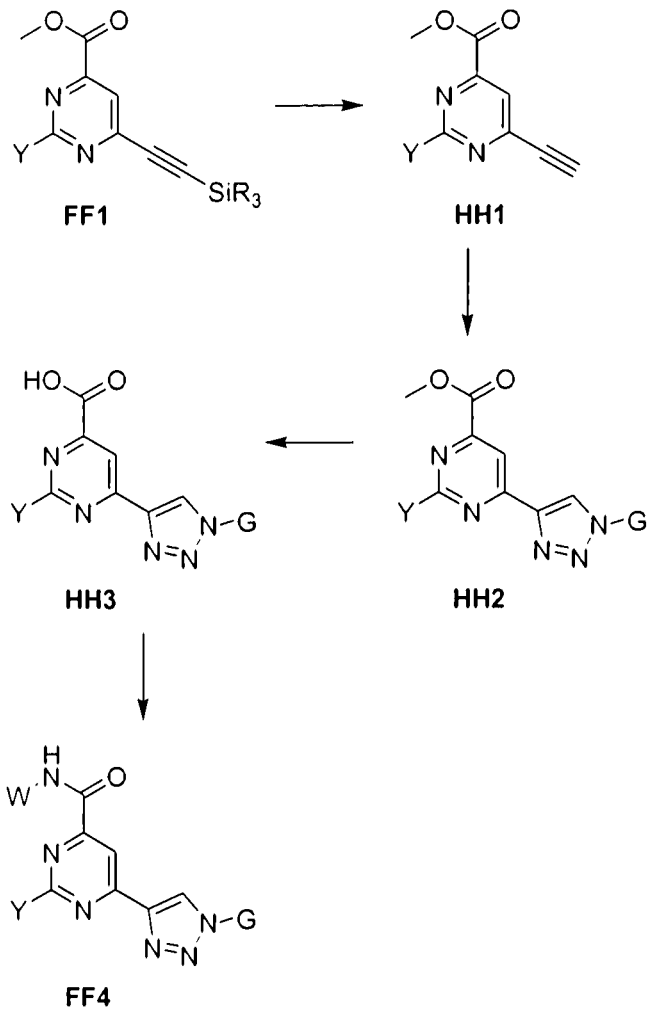
Compounds of formula (I) in which L is a 1,2,3-triazole ring, M is N, and Q is N may be prepared as described in Chart FF. Esters of the formula C4 obtained as described in Chart C are reacted with trialkylsilylacetylene (where R may be but not limited to methyl, ethyl, isopropyl) under Sonogashira coupling conditions (e.g. catalytic CuI, Ph_3P, and $(Ph_3P)_2PdCl_2$) to provide alkynes FF1 which are subsequently treated with lithium hydroxide to afford carboxylic acids of the formula FF2. Treatment of FF2 with a primary amine of the formula W-NH_2 in the presence of *O*-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate provides amides of the formula FF3. Cyclization of FF3 with azides of the formula G-N_3 in the presence of catalytic copper(II) sulfate and sodium ascorbate provide 1,2,3-triazoles of the formula FF4.

CHART GG



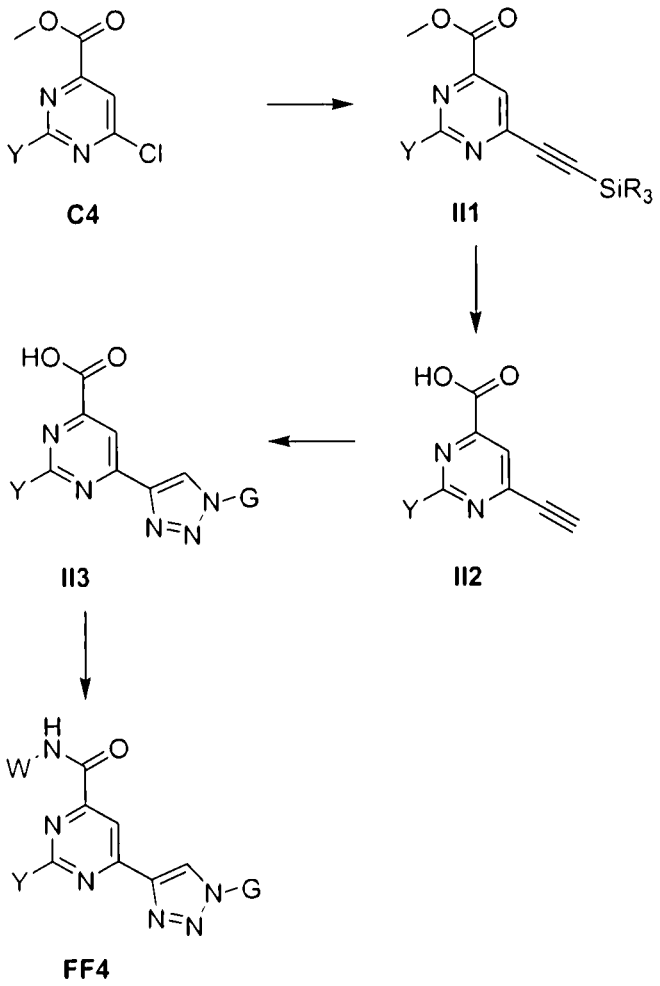
Compounds of formula (I) in which L is a 1,2,3-triazole ring, M is N, and Q is N may be prepared as described in Chart GG. Esters of the formula C3 obtained as described in Chart C are reacted with a primary amine of the formula W-NH_2 to provide amides of the formula GG1. Treatment of hydroxypyrimidines GG1 with oxalyl chloride/DMF affords chloropyrimidines of the formula GG2. Amides GG2 are reacted with trialkylsilylacetylene (where R may be but not limited to methyl, ethyl, isopropyl) under Sonogashira coupling conditions (e.g. catalytic CuI, Ph_3P, and $(Ph_3P)_2PdCl_2$) to provide alkynes GG3, which are subsequently treated with a fluoride ion source (e.g. potassium fluoride) to afford terminal alkynes of the formula GG4. Cyclization of GG4 with azides of the formula G-N_3 in the presence of catalytic copper(II) sulfate and sodium ascorbate provide 1,2,3-triazoles of the formula FF4.

CHART HH



Compounds of formula (I) in which L is a 1,2,3-triazole ring, M is N, and Q is N may be prepared as described in Chart HH. Esters of the formula FF1 obtained as described in Chart FF are reacted with a fluoride ion source (e.g. potassium fluoride) to afford terminal alkynes of the formula HH1. Cyclization of HH1 with azides of the formula G-N_3 in the presence of catalytic copper(II) sulfate and sodium ascorbate provide 1,2,3-triazoles of the formula HH2 which are subsequently treated with lithium hydroxide to afford carboxylic acids of the formula HH3. Treatment of HH3 with a primary amine of the formula W-NH_2 in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate provides amides of the formula FF4.

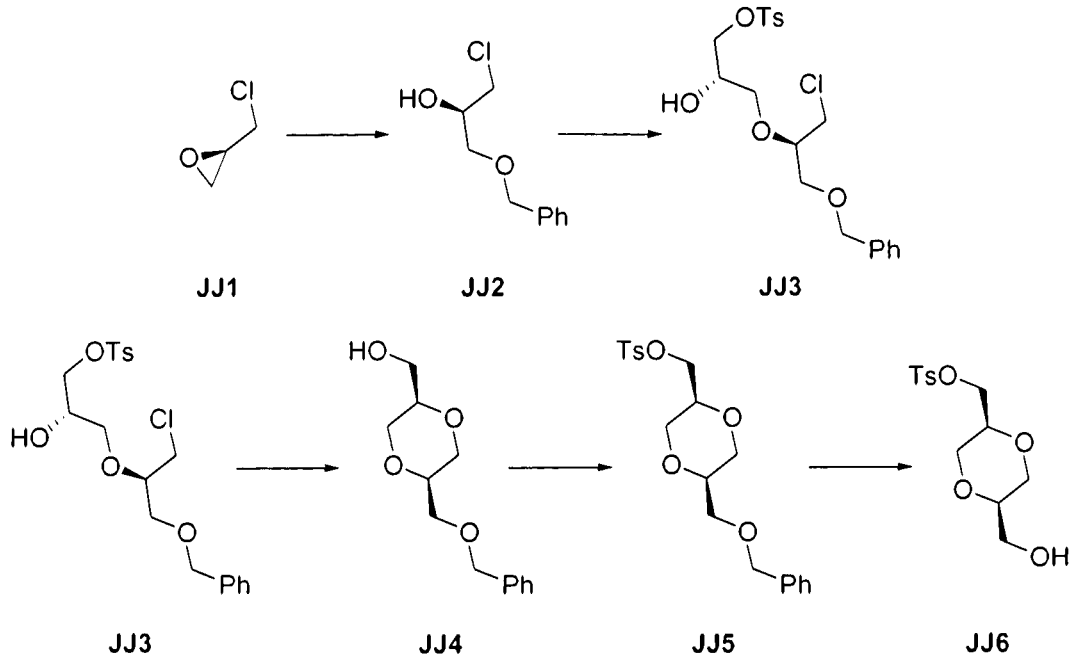
CHART II



Compounds of formula (I) in which L is a 1,2,3-triazole ring, M is N, and Q is N may be prepared as described in Chart II. Esters of the formula C4 obtained as described in Chart C are reacted with trialkylsilylacetylene (where R may be but not limited to methyl, ethyl, isopropyl) under Sonogashira coupling conditions (e.g. catalytic CuI, Ph_3P, and $(Ph_3P)_2PdCl_2$) to provide alkynes II1, which are subsequently treated with lithium hydroxide to afford carboxylic acids of the formula II2. Cyclization of II2 with azides of the formula G-N_3 in the presence of catalytic copper(II) sulfate and sodium ascorbate provide 1,2,3-triazoles of the formula II3. Treatment of II3 with a primary amine of the formula W-NH_2 in the presence of *O*-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate provides amides of the formula FF4.

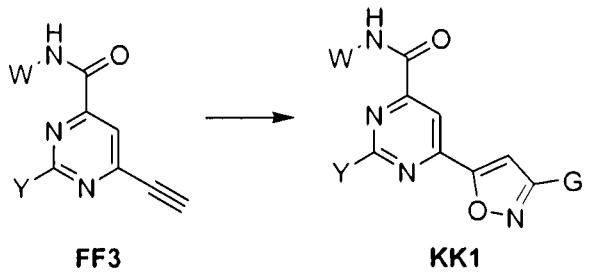
Azides of the formula G-N_3 employed in Charts FF – II may be prepared alcohols G-OH obtained commercially or prepared as described in Charts J – X. For example, the alcohol G-OH may be converted to a sulfonate ester which is then subjected to substitution by a nucleophilic azide source (e.g. sodium azide).

CHART JJ



Reagents of the formula G-X such as ((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (JJ6) may be prepared as described in Chart JJ. *R*-Epichlorohydrin, JJ1, was reacted with benzyl alcohol using boron trifluoride etherate as an acid catalyst to provide the alcohol of formula JJ2. The alcohol of formula JJ2 was reacted with the *S*-glycidol tosylate using boron trifluoride etherate as an acid catalyst to provide the alcohol of formula JJ3. The alcohol of formula JJ3 was cyclized under basic conditions (e.g., aqueous sodium hydroxide) to provide the alcohol of formula JJ4. The alcohol of formula JJ4 was reacted with p-toluenesulfonyl chloride in the presence of an amine base (e.g., pyridine) to provide the tosylate of formula JJ5. The benzyl ether of formula JJ5 was reacted with hydrogen gas in the presence of palladium on carbon to provide the alcohol of formula JJ6.

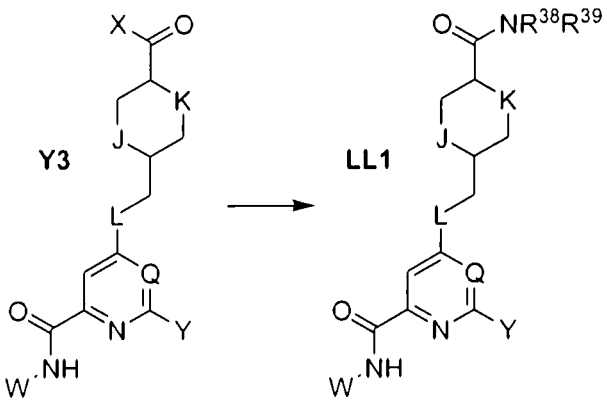
CHART KK



Compounds of formula (I) in which L is an isoxazole ring, M is N, and Q is N may be prepared as described in Chart KK. Alkynes of the formula FF3 described in Chart FF may be reacted with 2-

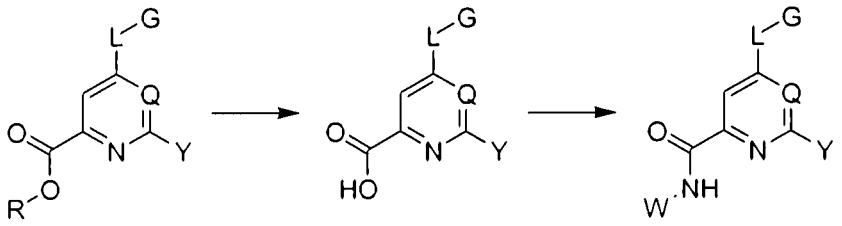
chloro-2-(hydroxyimino)-derivatives of the formula G-C(NOH)-Cl in the presence of an amine base (e.g. triethylamine) in toluene at temperatures from 20 – 110 °C. The chloro-hydroxyimines are readily prepared from the corresponding aldehydes by reaction with hydroxylamine hydrochloride and sodium acetate followed by chlorination by *N*-chlorosuccinimide.

CHART LL



Compounds of the general formula Y3 (wherein X is OH, J and K are independently CH_2 or O) may be further elaborated as described in Chart LL. Compounds of the formula Y3 (X = OH) may be reacted with an amine of the general formula $HNR^{38}R39$ in the presence of 1,1′-carbonyldiimidazole (or other suitable carboxylic acid activating agent) to afford amides of the general formula LL1.

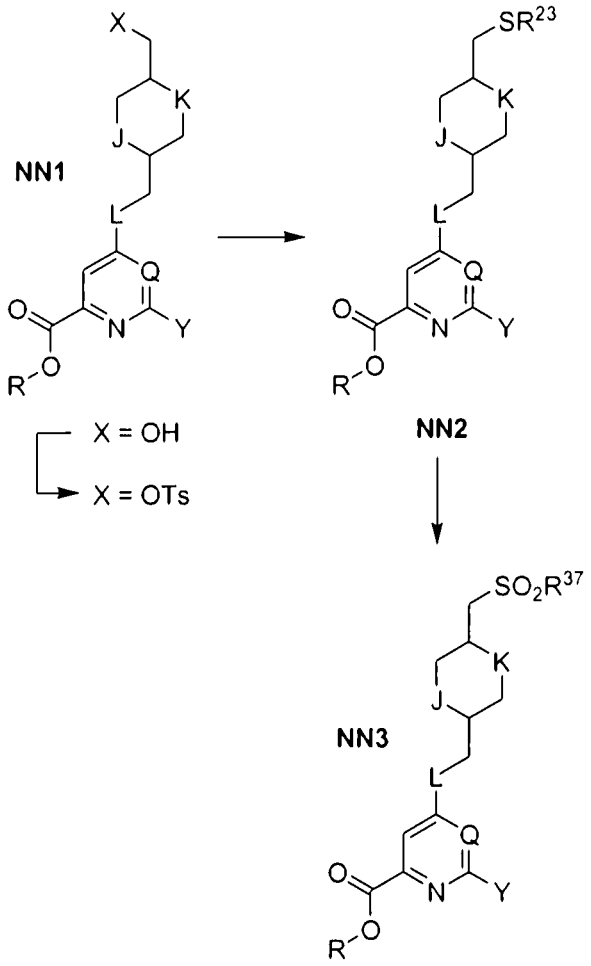
CHART MM



Compounds of the general formula MM1 (wherein R is an alkyl group) may be elaborated as described in Chart MM. Esters of the formula MM1 may be reacted with an inorganic base (e.g. sodium hydroxide, lithium hydroxide) in a mixture of water and an organic solvent (e.g. tetrahydrofuran) to afford carboxylic acids of the formula MM2. Carboxylic acids of the formula MM2 may be reacted with an amine of the formula $W\text{-}NH_2$ in the presence of a suitable carboxylic acid activating agent (e.g. 1,1′-carbonyldiimidazole, 1-hydroxybenzotriazole/1-ethyl-3-(3'-dimethylaminopropyl)carbodimide hydrochloride) to afford amides of the formula MM3. Alternatively, esters of the formula MM1 (wherein R is methyl or ethyl) may be reacted with an amine of the formula $W\text{-}NH_2$ at temperatures of 20 – 100 °C either neat or in a minimal amount of an organic solvent (e.g.

methanol, tetrahydrofuran, and *N*,*N*-dimethylformamide) to provide amides of the formula MM3 directly.

CHART NN



Compounds of the general formula NN1 (wherein R is alkyl, J and K are independently CH_2 or O) may be further elaborated as described in Chart NN. Alcohols of the formula NN1 (X = OH) may be reacted with p-toluenesulfonyl chloride in the presence of an amine base to afford compounds of the formula NN1 (Y = OTs). Subsequent reaction of NN1 (X = OTs) with the sodium salt of thioalkoxides of the formula HSR^{23} to afford compounds of the formula NN2. Sulfides of the formula NN2 may be oxidized by 3-chloroperbenzoic acid to provide sulfones of the formula NN3. Compounds of formula NN2 and NN3 may be further elaborated as described in Chart MM to afford amides of Formula (I).

The compounds of Formula (I) may be prepared as single enantiomer or as a mixture of individual enantiomers which includes racemic mixtures. Methods to obtain preferentially a single enantiomer from a mixture of individual enantiomers or a racemic mixture are well known to those ordinarily skilled in the art of organic chemistry. Such methods include but are not limited to preferential crystallization of diastereomeric salts (e.g. tartrate or camphor sulfonate), covalent derivatization by a chiral, non-racemic reagent followed by separation of the resulting diastereomers by common methods (e.g.

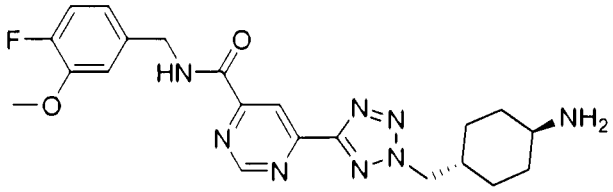
crystallization, chromatographic separation, or distillation) and chemical reversion to scalemic compound, Simulated Moving Bed technology, or high/medium-pressure liquid chromatography or supercritical fluid chromatography employing a chiral stationary phase. These techniques may be performed on the final compounds of Formula (I) or on any intermediates to compounds of Formula (I) which bear a stereogenic center. Also, to facilitate separation by any of the methods described above, the compounds of Formula (I) or any intermediates to the compounds of Formula (I) which bear a stereogenic center may be transiently reacted with an achiral reagent, separated, and then reverted to scalemic compound by standard synthetic techniques.

Detailed Preparative Methods

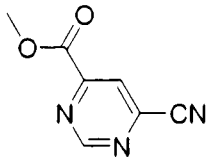
The detailed examples below illustrate preparation of compounds of this invention. Other compounds of this invention may be prepared using the methods illustrated in these examples, either alone or in combination with techniques generally known in the art. The following examples are merely illustrative, and not limiting to the remainder of this disclosure in any way.

Example 1

***N*-(4-Fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**

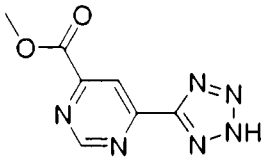


Step 1: Preparation of methyl 6-cyanopyrimidine-4-carboxylate



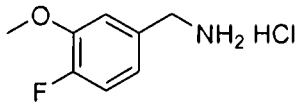
Commercially available methyl 6-chloropyrimidine-4-carboxylate (1.00 g, 5.80 mmol) was taken up in dichloromethane (20 mL) and then treated with tetraethyl ammonium cyanide (0.996 g, 6.37 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.13 g, 1.2 mmol). The reaction was allowed to stir at room temperature for 0.5 h. The reaction was diluted with diethyl ether (40 mL) then washed with water (1 x 25 mL) and brine (1 x 40 mL). The organics were poured onto a silica plug (20 g) and eluted with diethyl ether (200 mL) to afford the title compound as an orange oil (0.85 g, 90%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 0.267 min, *m/z* 164 (M+Na).

Step 2: Preparation of methyl 6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxylate



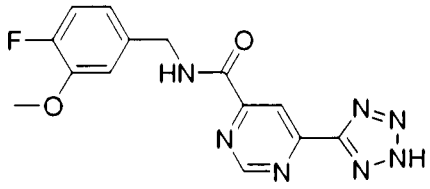
Methyl 6-cyanopyrimidine-4-carboxylate (1.43 g, 8.77 mmol) was taken up in methanol (40 mL) and treated with sodium azide (598 mg, 9.20 mmol) and zinc (II) bromide (1.97 g, 8.77 mmol). The reaction was stirred at room temperature for 15 h and then was concentrated. This residue was diluted with water (8 mL) and 1 N aqueous hydrochloric acid (40 mL) and stirred one hour. The resulting slurry was filtered with the solids washed with water (10 mL) and dried in vacuo to afford the title compound as a yellow solid (1.37 g, 76%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 0.54 min, *m/z* 207 (M+H).

Step 3. Preparation of 4-fluoro-3-methoxybenzylamine hydrochloride



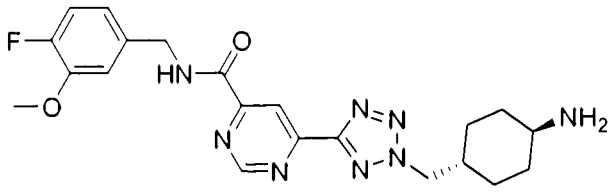
A 2G Parr reactor (4842) was charged with 4-fluoro-3-methoxy-benzonitrile (133.0 g, 0.88 mol), ethanol (3550 mL), concentrated hydrochloric acid (396 ml, 4.75 mol) and 10% Pd/C with 50% water (13.3 g). The resulting mixture was stirred with heating at 30-33 °C under hydrogen pressure (40-50 psi, first 2 hours refill hydrogen every 20 min) overnight. The reaction mixture was cooled to room temperature, filtered through Celite™ and the filtrate concentrated. The residue obtained was treated with acetonitrile (250 mL) and the white solid was filtered, washed with cold acetonitrile and vacuum dried to afford the title compound (140 g, 83%). MS (ES+) *m/z* 156 (M+H). Elemental analysis found: C, 49.97; H, 6.13; N, 7.59.

Step 4: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



Methyl 6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxylate (0.75 g, 3.64 mmol) was taken up in dimethylacetamide (5 mL) and then treated with 4-fluoro-3-methoxybenzylamine hydrochloride (1.57 g, 8.19 mmol) and triethylamine (1.5 g, 14 mmol) and left to stir for 15 hours at room temperature. The mixture was diluted with 1 N aqueous NaOH (15 mL) and then washed with diethyl ether (2 x 10 mL). The mixture was then adjusted to pH 3 with concentrated Hydrochloric acid and stirred with ethyl acetate (10 mL). After 1 h, the organic layer was separated and concentrated to an oil that solidified affording the title compound as a beige solid (1.05 g, 88%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.26 min, *m/z* 330 (M+H).

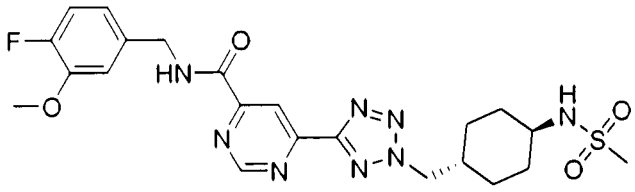
Step 5: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



N-(4-Fluoro-3-methoxybenzyl)-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (0.91 g, 2.8 mmol) and commercially available *tert*-butyl *trans*-4-(hydroxymethyl)cyclohexylcarbamate (760 mg, 3.32 mmol) were taken up in tetrahydrofuran (20 mL) and treated with polymer supported triphenylphosphine (1.54 g, 3.32 mmol). After stirring for 30 min at room temperature, di-*tert*-butyl azodicarboxylate (954 mg, 4.15 mmol) was added. After 15 h at room temperature, the reaction was filtered to remove the resin. The filtrate was concentrated to a crude oily residue. The residue was purified via normal phase chromatography (silica, 0-75% ethyl acetate/heptane with a trace 1% methanol ran through entire gradient) to afford the protected amine as a mixture of regioisomers (0.97 g, 65%, 1.80 mmol) which was subsequently dissolved in dichloromethane (5 mL) and treated with trifluoroacetic acid (2.0 mL, 15 mmol). After the reaction was stirred at ambient temperature for 3 h, the mixture was diluted with dichloromethane (5 mL) and neutralized with 2.5 N aqueous NaOH to achieve pH 7-8. The organic layer was separated and washed with water (3 mL), dried over sodium sulfate, and concentrated to afford the title compound (0.87 g, 72%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.06 min, *m/z* 441 (M+H).

Example 2

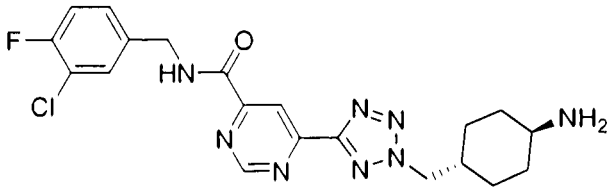
N-(4-Fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-((methylsulfonyl)amino)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



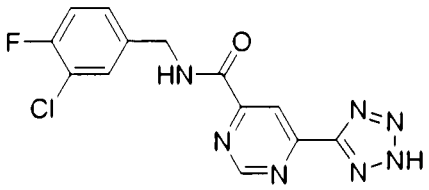
N-(4-Fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 1) (0.870 g, 1.98 mmol) was taken up in dichloromethane (5 mL) and treated with methane sulfonyl chloride (0.17 mL, 2.1 mmol) and triethylamine (0.30 mL, 2.2 mmol). After 1 h at room temperature, the reaction was concentrated. The residue was purified via reverse phase chromatography (4-60% acetonitrile/water over 45 minutes) with the first eluted compound was isolated to afford the title compound as a white solid (143 mg, 14%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.98 min, *m/z* 519 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.25 (m, 4 H), 1.61 (br. s., 2 H), 1.83 - 1.99 (m, 3 H), 2.83 (s, 3 H), 3.00 (br. s., 1 H), 3.78 (s, 3 H), 4.46 (d, *J*=6.0 Hz, 2 H), 4.66 (d, *J*=6.6 Hz, 2 H), 6.89 (d, *J*=7.3 Hz, 2 H), 7.03 - 7.21 (m, 2 H), 8.56 (s, 1 H), 9.46 (s, 1 H), 9.61 (t, *J*=6.1 Hz, 1 H).

Example 3

***N*-(3-Chloro-4-fluorobenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**

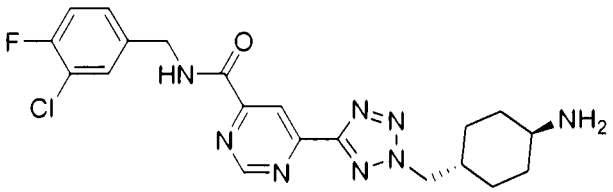


Step 1: Preparation of *N*-(3-chloro-4-fluorobenzyl)-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



Methyl 6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxylate (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (0.72 g, 3.49 mmol) was taken up in dimethylacetamide (5 mL), treated with commercially available (4-fluoro-3-chlorophenyl)methanamine (1.23 g, 7.68 mmol) and triethylamine (1.95 g, 14 mmol), and left to stir for 15 hours at room temperature. The mixture was diluted with 1 N aqueous NaOH (15 mL) and then washed with diethyl ether (2 x 10 mL). The mixture was then adjusted to pH 3 with concentrated Hydrochloric acid, stirred with ethyl acetate (10 mL), and filtered to afford the title compound as a pale yellow solid (0.71 g, 61%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.19 min, *m/z* 334 (M+H).

Step 2: Preparation of *N*-(3-chloro-4-fluorobenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide

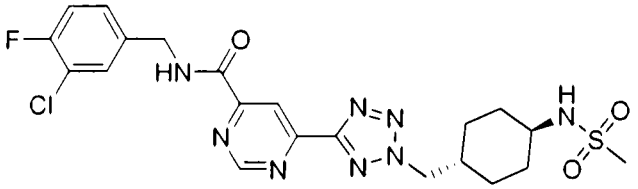


N-(4-Fluoro-3-chlorobenzyl)-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (0.71 g, 2.1 mmol) and commercially available *tert*-butyl *trans*-4-(hydroxymethyl)cyclohexylcarbamate (585 mg, 2.55 mmol) were taken up in tetrahydrofuran (20 mL) and treated with polymer supported triphenylphosphine (1.19 g, 2.55 mmol). After stirring for 30 min at room temperature, di-*tert*-butyl azodicarboxylate (735 mg, 3.19 mmol) was added. After 15 h at room temperature, the reaction was filtered to remove the resin. The filtrate was concentrated to a crude oily residue. The residue was purified via normal phase chromatography (silica, 0-75% ethyl acetate/heptane with a trace 1% methanol ran through entire gradient) to afford the protected amine (1.08 g, 93%, 1.99 mmol) which was taken up in dichloromethane (5 mL) and treated with trifluoroacetic acid (2.0 mL, 15 mmol). After the reaction was stirred at ambient temperature for 3 h, the mixture was diluted with dichloromethane (5 mL) and neutralized with 2.5 N aqueous NaOH to achieve pH 7-8. The organic layer was

separated, washed with water (3 mL), then dried over sodium sulfate, and concentrated to afford the title compound as an amber oil (0.87 g, 92%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.24 min, *m/z* 445 (M+H).

Example 4

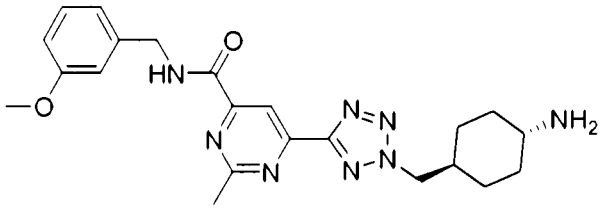
N-(3-Chloro-4-fluorobenzyl)-6-(2-((*trans*-4-((methylsulfonyl)amino)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



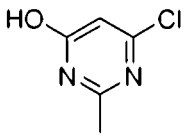
N-(3-Chloro-4-fluorobenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 3) (0.87 g, 2.0 mmol) was taken up in dichloromethane (5 mL) and treated with methane sulfonyl chloride (0.17 mL, 2.1 mmol) and triethylamine (0.30 mL, 2.2 mmol). After 1 h at room temperature, the reaction was concentrated to a crude residue. The residue was purified via reverse phase chromatography (4-60% acetonitrile/water over 45 minutes). The first eluted compound was isolated to afford the title compound as a white solid (105 mg, 10%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 4.22 min, *m/z* 523 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.27 (m, 4 H), 1.59 (d, J=10.8 Hz, 2 H), 1.80 - 1.98 (m, 3 H), 2.83 (s, 3 H), 3.01 (d, J=6.8 Hz, 1 H), 4.48 (d, J=6.2 Hz, 2 H), 4.66 (d, J=6.8 Hz, 2 H), 6.89 (d, J=7.3 Hz, 1 H), 7.25 - 7.36 (m, 2 H), 7.48 - 7.58 (m, 1 H), 8.55 (d, J=1.3 Hz, 1 H), 9.46 (d, J=1.1 Hz, 1 H), 9.71 (t, J=6.3 Hz, 1 H).

Example 5

N-(3-Methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



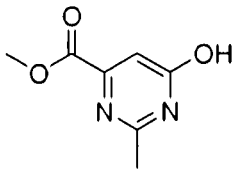
Step 1: Preparation of 6-chloro-2-methylpyrimidin-4-ol



To a 0 °C solution of 13M sulfuric acid (1.2 L, 15.6 mol) was added portion-wise solid 4,6-dichloro-2-methylpyrimidine (475 g, 2.91 mol). The resulting mixture was allowed to warm to room temperature over 1.5 hours. The solution was poured into a well stirred iced solution of 6N NaOH (3.6 L, 21.6 mol). The resulting solids were then collected by vacuum filtration and washed with warm

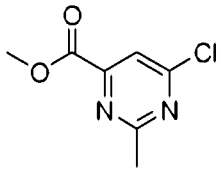
water (3 x 1 L). High vacuum drying at 35 °C provided the title compound as a white solid (393.4 g, 93%). LC/MS (5%-95% CH_3CN/H_2O, 6 min) 0.95 min, *m/z* 145 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.81 (br. s, 1 H), 6.30 (s, 1 H), 2.26 (s, 3 H).

Step 2: Preparation of methyl 6-hydroxy-2-methylpyrimidine-4-carboxylate



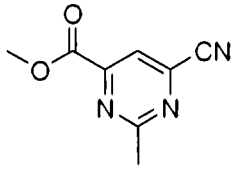
6-Chloro-2-methylpyrimidin-4-ol (36.7 g, 254 mmol), [1,1'-bis(diphenylphosphino)ferrocene]-palladium(II) dichloride (10.4 g, 12.7 mmol), and diisopropylethylamine (49.2 g, 381 mmol) were combined in methanol (254 mL). The reaction was heated to 85 °C in the presence of carbon monoxide (10.7 g, 381 mmol, 50 psi) for 24 hours. The reaction was allowed to cool to room temperature and the resulting solids collected by vacuum filtration. The solids were rinsed with methanol (100 mL) and diethyl ether (2 x 100 mL). Vacuum drying provided the title compound as a brown solid (38.7 g, 91%). LC/MS (5%-95% CH_3CN/H_2O, 3 min: 0.29 min, *m/z* 169 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.79 (br. s, 1 H), 6.68 (s, 1 H), 3.79 (s, 3 H), 2.29 (s, 3 H).

Step 3: Preparation of methyl 6-chloro-2-methylpyrimidine-4-carboxylate



Methyl 6-hydroxy-2-methylpyrimidine-4-carboxylate (30.0 g, 178 mmol) was dissolved in dichloromethane (446 mL). Oxalyl chloride (18.6 mL, 1.2 equiv) was added followed by addition of *N,N*-dimethylacetamide (3.5 mL, 0.25 equiv). The mixture was heated to reflux for 2 hours. After cooling to room temperature, the insolubles were removed by filtration and the filtrate partially concentrated. Purification by silica gel chromatography (35/65, ethyl acetate/heptane) provided the title compound as a white solid (26.6 g, 80%). LC/MS (5%-95% CH_3CN/H_2O, 4 min: 1.59 min, *m/z* 187 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.90 (s, 1 H), 3.88 (s, 3 H), 2.65 (s, 3 H).

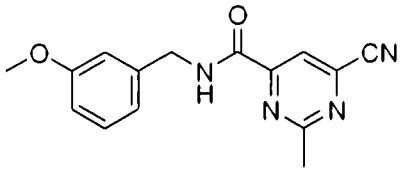
Step 4: Preparation of methyl 6-cyano-2-methylpyrimidine-4-carboxylate



Methyl 6-chloro-2-methylpyrimidine-4-carboxylate (30.0 g, 161 mmol) was dissolved in dichloromethane (460 mL). Tetraethylammonium cyanide (27.6 g, 177 mmol) was added followed by 1,4-diazabicyclo[2.2.2]octane (3.60 g, 32.0 mmol). The reaction was stirred for 30 min at room temperature. The reaction mixture was washed with 1N NaOH (3 x 100 mL), water (2 x 100 mL) and brine (200 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated to give a

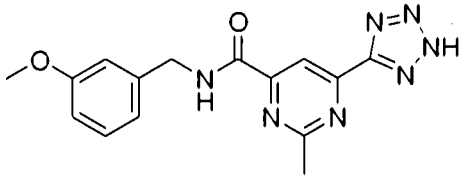
dark brown solid. Purification by silica gel chromatography (2/1, ethyl acetate/heptane) provided the title compound as a white crystalline solid (24.4 g, 86%). LC/MS (5%-95% CH_3CN/H_2O, 4 min: 0.96 min, *m/z* 178 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.38 (s, 1 H), 3.88 (s, 3 H), 2.75 (s, 3 H).

Step 5: Preparation of 6-cyano-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide



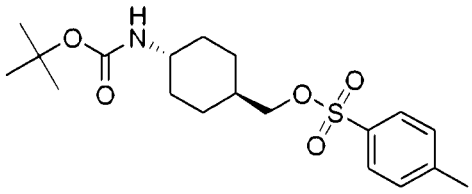
3-Methoxybenyzlamine (9.68 g, 70.6 mmol) and methyl 6-cyano-2-methylpyrimidine-4-carboxylate (10.0 g, 56.4 mmol) were dissolved in *N,N*-dimethylacetamide (113 mL). Diisopropylethylamine (25.5 g, 198 mmol) was added and the mixture heated to 100 °C for 2 hours. After cooling to room temperature, the mixture was diluted with water (250 mL) and extracted with ethyl acetate (3 x 250 mL). The combined organics were then washed with brine (250 mL) and dried over sodium sulfate, filtered, and evaporated to give a red oil. Purification by silica gel chromatography (20/80, ethyl acetate/heptane) provided the title compound as a white solid (14.6 g, 92%). LC/MS (5%-95% CH_3CN/H_2O, 4 min: 2.49 min, *m/z* 283 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.55 (t, *J*=6.2 Hz, 1 H), 8.31 (s, 1 H), 7.19 (t, J=8.1 Hz, 1 H), 6.74 - 6.89 (m, 3 H), 4.44 (d, J=6.3 Hz, 2 H), 3.69 (s, 3 H), 2.75 (s, 3 H).

Step 6: Preparation of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



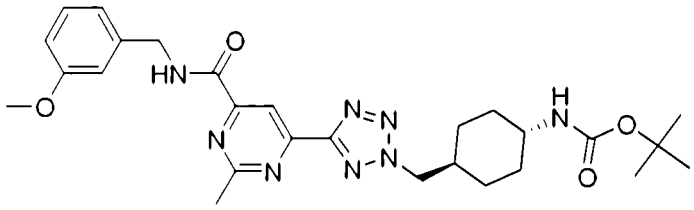
6-Cyano-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide (14.2 g, 50.3 mmol), sodium azide (3.60 g, 55.3 mmol), and zinc bromide (11.3 g, 50.3 mmol) were suspended in water (112 mL). The reaction was heated to reflux for 16 hours. After cooling to room temperature, 6N hydrochloric acid (180 mL) was added and the mixture stirred vigorously for 1 hour. The solids were collected by vacuum filtration and rinsed with 6N hydrochloric acid (3 x 100 mL) and water (2 x 100 mL). High vacuum drying at 55 °C provided the title compound as a white solid (15.0 g, 92%). LC/MS (5%-95% CH_3CN/H_2O, 4 min: 2.38 min, *m/z* 326 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.53 (t, *J*=6.4 Hz, 1 H), 8.42 (s, 1 H), 7.21 (t, *J*=8.2 Hz, 1 H), 6.86 - 6.91 (m, 2 H), 6.76 - 6.82 (m, 1 H), 4.48 (d, *J*=6.6 Hz, 2 H), 3.70 (s, 3 H), 2.82 (s, 3 H).

Step 7: Preparation of (*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)methyl 4-methylbenzenesulfonate



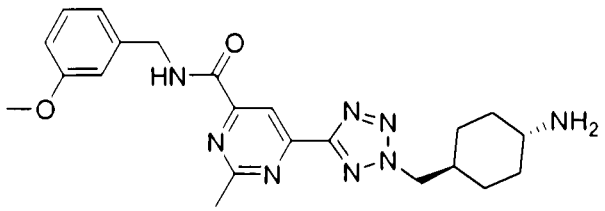
p-Toluene sulfonyl chloride (1.68 g, 8.81 mmol) was added to a solution of *tert*-butyl *trans*-(4-hydroxymethyl)cyclohexylcarbamate (1.84 g, 8.02 mmol) in pyridine (10 mL) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature. After 6 h, the mixture was cooled to 0 °C and treated with water (100 mL). The resulting precipitate was filtered, washed with cold water (2 x 20 mL), and dried in vacuo to afford the title compound as a white solid (2.91 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.78 (d, J=8.3 Hz, 2 H), 7.49 (d, J=8.2 Hz, 2 H), 6.69 (d, J=8.0 Hz, 1 H), 3.82 (d, J=6.2 Hz, 2 H), 3.04 - 3.14 (m, 1 H), 2.43 (s, 3 H), 1.69 - 1.76 (m, 2 H), 1.57 - 1.64 (m, 2 H), 1.42 - 1.53 (m, 1 H), 1.36 (s, 9 H), 1.01 - 1.12 (m, 2 H), 0.85 - 0.96 (m, 2 H).

Step 8: Preparation of *tert*-butyl *trans*-4-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate



Triethylamine (280 mg, 2.7 mmol) and (*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)methyl 4-methylbenzenesulfonate (530 mg, 1.38 mmol) was added to a solution of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (450 mg, 1.38 mmol) in anhydrous dimethylacetamide (0.5 mL). The reaction was stirred overnight at 85 °C in a capped vial. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound as a white solid (342 mg).

Step 9: Preparation of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

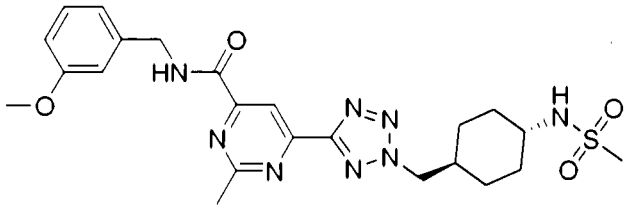


4M Hydrochloric acid in dioxane (5 mL) was added to a solution of *tert*-butyl *trans*-4-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate (342 mg) in acetonitrile (1.5 mL). The reaction was stirred overnight at room temperature. The solvent was removed under vacuum and the residue was slurried 2x in ether (ether decanted off each time) and

the resultant solid was dried under vacuum to afford the hydrochloride salt of the title compound as a white solid (418 mg).

Example 6

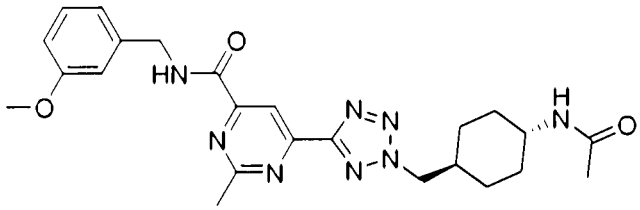
***N*-(3-Methoxybenzyl)-2-methyl-6-(2-(((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**



Triethylamine (60 mg, 0.6 mmol) and methane sulfonyl chloride (34 mg, 0.3 mmol) were added to a solution of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 5) (100 mg, 0.19 mmol) in dichloromethane (1 mL). The reaction was stirred overnight at room temperature. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound as a white solid (41 mg). MS (ES+) m/z 515 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (1 H, br. s.), 8.41 (1 H, s), 7.56 (1 H, br. s.), 7.22 - 7.30 (1 H, m), 6.93 (2 H, br. s.), 6.84 (1 H, br. s.), 4.70 (2 H, d, J=7.0 Hz), 4.51 (2 H, d, J=5.9 Hz), 3.74 (2 H, s), 3.05 (2 H, br. s.), 2.86 (6 H, d, J=19.8 Hz), 1.90 (3 H, br. s.), 1.64 (2 H, br. s.), 1.20 (5 H, d, J=11.0 Hz).

Example 7

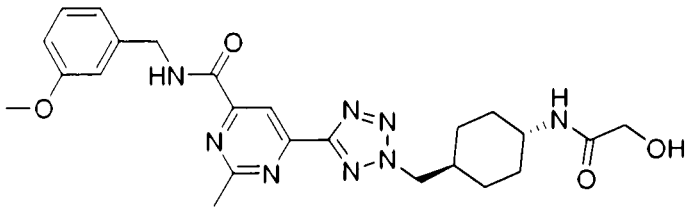
***N*-(3-Methoxybenzyl)-6-(2-((*trans*-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



Triethylamine (60 mg, 0.6 mmol) and acetic anhydride (31 mg, 0.3 mmol) were added to a solution of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 5) (100 mg, 0.19 mmol) in dichloromethane (1 mL). The reaction was stirred overnight at room temperature. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) and neutralized by passing through a small carbonate column to afford the title compound as a white solid (34 mg). MS (ES+) *m/z* 479 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (1 H, br. s.), 8.41 (1 H, s), 7.65 (1 H, d, J=7.7 Hz), 7.33 (1 H, br. s.), 7.24 (1 H, s), 6.93 (1 H, br. s.), 6.81 (1 H, br. s.), 4.70 (2 H, d, J=6.6 Hz), 4.51 (2 H, d, J=6.6 Hz), 3.74 (3 H, s), 3.46 (1 H, br. s.), 2.83 (3 H, s), 1.99 (1 H, br. s.), 1.75 (5 H, s), 1.61 (2 H, br. s.), 1.15 (5 H, d, J=10.2 Hz).

Example 8

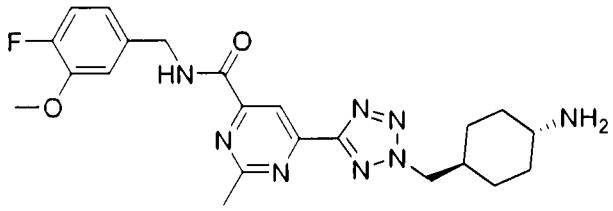
***N*-(3-Methoxybenzyl)-6-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



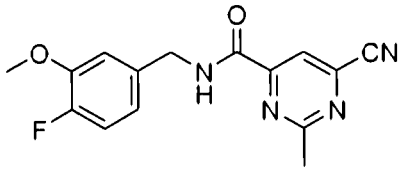
N-(3-Methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 5) (146 mg, 0.287 mmol), triethylamine (102 mg, 1.00 mmol) and acetoxy acetyl chloride (47 mg, 0.344 mmol) were combined in dichloromethane (4 mL). After stirring for 10 min, the mixture was concentrated and then treated with acetonitrile (2 mL) and 2.5 N sodium hydroxide (2 mL). After 1 h, the organics were removed under nitrogen stream and the aqueous was adjusted to pH 6 with 10% hydrogen chloride. The mixture was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford the title compound as a yellow solid (64.7 mg, 46%). LC/MS (10%-90% CH_3CN/H_2O, 6 min): 4.44 min. *m/z* 495 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (br, s, 1 H) 8.40 (s, 1 H), 7.37 (d, J = 8.05, 1 H), 7.17-7.30 (m, 1 H), 6.91 (br. s, 2 H), 6.77 - 6.84 (m, 1 H), 5.38 (s, 1 H), 4.69 (d, J = 6.6 Hz, 2 H), 4.49 (d, J = 6.6 Hz, 2 H), 3.67 - 3.79 (m, 4 H), 3.56 (br. s., 1 H), 2.81 (s, 3 H), 1.97 (br. s., 1 H), 1.72 (br. s., 2 H), 1.60 (d, J = 11.0 Hz, 2 H), 1.09 - 1.33 (m, 5 H).

Example 9

***N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



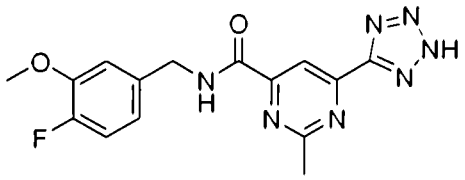
Step 1: Preparation of 6-cyano-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide



4-Fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (13.5 g, 70.6 mmol) was dissolved in methanol (56 mL). Diisopropylethylamine (29.2 g, 226 mmol) was added and the mixture stirred for 15 minutes at room temperature. Methyl 6-cyano-2-methylpyrimidine-4-carboxylate (prepared as described in step 4 of the

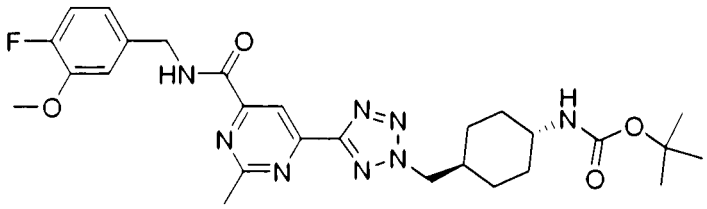
synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (10.0 g, 56.4 mmol) was added and the reaction heated to 35 °C for 1 h. The methanol was removed *in vacuo* and the crude material partitioned between ethyl acetate (500 mL) and 1N hydrochloric acid (500 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (2 x 250 mL). The combined organics were washed with saturated aqueous sodium bicarbonate (2 x 250 mL) and brine (250 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated to give a brown solid. Purification by silica gel chromatography (1/2, ethyl acetate/heptane) provided the title compound as a white solid (11.7 g, 69%). LC/MS (5%-95% CH_3CN/H_2O, 4 min: 2.67 min, *m/z* 301 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.58 (t, *J*=6.2 Hz, 1 H), 8.32 (s, 1 H), 7.04 - 7.19 (m, 2 H), 6.79 - 6.90 (m, 1 H), 4.44 (d, *J*=6.2 Hz, 2 H), 3.78 (s, 3 H), 2.76 (s, 3 H).

Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



6-Cyano-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide (4.80 g, 16.0 mmol), sodium azide (1.14 g, 17.6 mmol), and zinc bromide (3.60 g, 16.0 mmol) were suspended in water (36 mL). The reaction was heated to reflux for 16 h. After cooling to room temperature, 6N hydrochloric acid (180 mL) was added and the mixture stirred vigorously for 1 hour. The solids were collected by vacuum filtration and rinsed with 6N hydrochloric acid (3 x 100 mL) and water (2 x 100 mL). High vacuum drying at 55 °C provided the title compound as a white solid (5.45 g, 99%). LC/MS (5%-95% CH_3CN/H_2O, 4 min: 2.56 min, *m/z* 344 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.55 (t, *J*=6.4 Hz, 1 H), 8.42 (s, 1 H), 7.06 - 7.20 (m, 2 H), 6.81 - 6.94 (m, 1 H), 4.47 (d, *J*=6.4 Hz, 2 H), 3.79 (s, 3 H), 2.82 (s, 3 H).

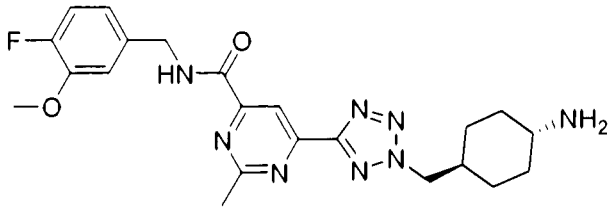
Step 3: Preparation of *tert*-butyl *trans*-4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate



Triethylamine (176 mg, 1.7 mmol) and (*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)methyl 4-methylbenzenesulfonate (prepared as described in step 7 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (335 mg, 0.87 mmol) was added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (300 mg, 0.87 mmol) in anhydrous *N*,*N*-dimethylformamide (0.6 mL). The reaction was stirred overnight at 85 °C in a capped vial. The reaction mixture was

purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound as a white solid (130 mg).

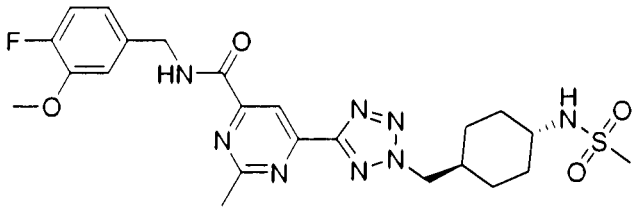
Step 4: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



A mixture of 4 M hydrochloric acid in dioxane (5 mL) and *tert*-butyl *trans*-4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate (130 mg) was stirred for 4 h at room temperature. The solvent was removed under a stream of nitrogen. The residue was slurried in ether (2x), decanting each time. The resultant solid was dried under vacuum to afford the hydrochoride salt of the title compound as a white solid (135 mg).

Example 10

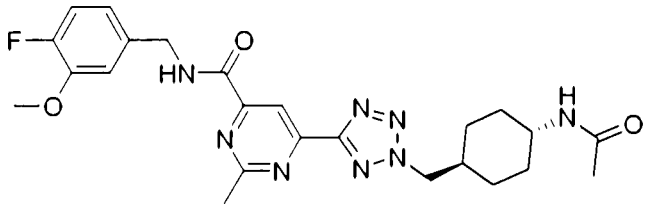
***N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**



Triethylamine (60 mg, 0.6 mmol) and methane sulfonyl chloride (34 mg, 0.3 mmol) were added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 9) (70 mg, 0.14 mmol) in dichloromethane (1 mL). The reaction was stirred overnight at room temperature. The product was isolated by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound as a white solid (37 mg). MS (ES+) *m/z* 533 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.51 (1 H, t, J=6.0 Hz), 8.42 (1 H, s), 7.11 - 7.21 (1 H, m), 7.18 (1 H, d, J=9.2 Hz), 6.94 (2 H, d, J=7.3 Hz), 4.70 (2 H, d, J=7.0 Hz), 4.50 (2 H, d, J=5.9 Hz), 3.82 (3 H, s), 3.05 (1 H, br. s.), 2.88 (3 H, s), 2.83 (3 H, s), 1.91 (3 H, d, J=10.2 Hz), 1.64 (2 H, br. s.), 1.26 (1 H, br. s.), 1.19 (3 H, d, J=10.6 Hz), 1.15 (1 H, br. s.).

Example 11

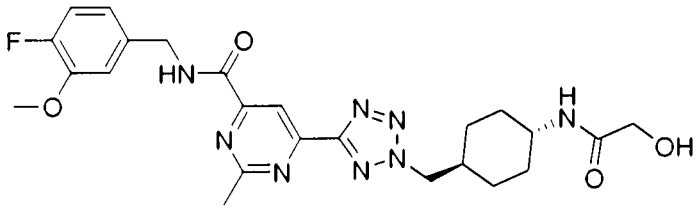
***N*-(4-Fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



Triethylamine (60 mg, 0.6 mmol) and acetic anhydride (31 mg, 0.3 mmol) were added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 9) (65 mg, 0.13 mmol) in dichloromethane (1 mL). The reaction was stirred overnight at room temperature. The product was isolated by reverse phase preparative HPLC (water/acetonitrile) and neutralized by passing through a small carbonate column to afford the title compound as a white solid (51 mg). MS (ES+) *m/z* 497 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.51 (1 H, t, J=5.7 Hz), 8.42 (1 H, s), 7.66 (1 H, d, J=7.7 Hz), 7.11 - 7.21 (1 H, m), 7.18 (1 H, d, J=8.8 Hz), 6.90 (1 H, d, J=7.3 Hz), 4.70 (2 H, d, J=7.0 Hz), 4.50 (2 H, d, J=5.9 Hz), 3.82 (3 H, s), 3.46 (1 H, br. s.), 2.83 (3 H, s), 1.99 (1 H, br. s.), 1.75 (4 H, s), 1.80 (1 H, br. s.), 1.61 (2 H, d, J=9.5 Hz), 1.25 (1 H, d, J=5.5 Hz), 1.15 (3 H, d, J=9.5 Hz), 1.10 - 1.21 (1 H, m).

Example 12

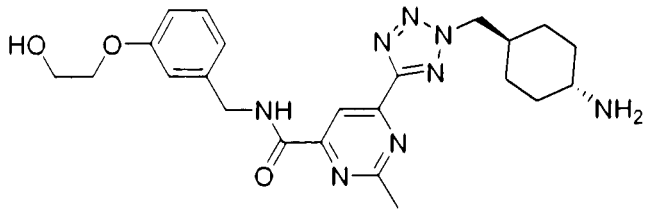
N-(4-Fluoro-3-methoxybenzyl)-6-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



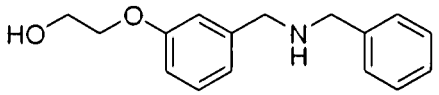
N-(4-Fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 9) (108 mg, 0.238 mmol), triethylamine (84.2 mg, 0.832 mmol) and acetoxy acetyl chloride (38.9 mg, 0.285 mmol) were combined in dichloromethane (4 mL) and stirred for 10 min. The mixture was concentrated and then treated with acetonitrile (2 mL) and 2.5 N sodium hydroxide (2 mL). After 1 hour, the organics were removed under nitrogen stream and the aqueous solution was adjusted to pH 6 with 10% hydrogen chloride. The mixture was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the title compound as an white solid (76 mg, 62%). LC/MS (10%-90% CH_3CN/H_2O, 6 min): 4.44 min, *m/z* 495 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.35 - 9.54 (m, 1 H), 8.40 (s, 1 H), 7.37 (d, J = 8.1 Hz, 1 H), 7.04-7.22 (m, 1 H), 6.89 (br. s, 1 H), 5.34 (s, 1 H), 4.68 (d, J= 6.6 Hz, 2 H), 4.48 (d, J = 5.9 Hz, 2 H), 3.77 - 3.85 (m, 3 H), 3.73 (d, J = 5.9 Hz, 2 H), 3.53 (br. s., 1 H), 2.81 (s, 3 H), 1.98 (br. s., 1 H), 1.73 (d, J = 10.3 Hz, 2 H), 1.60 (d, J = 10.3 Hz, 2 H), 1.06 - 1.36 (m, 5 H).

Example 13

N-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

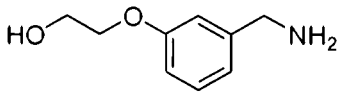


Step 1: Preparation of 2-(3-((benzylamino)methyl)phenoxy)ethanol



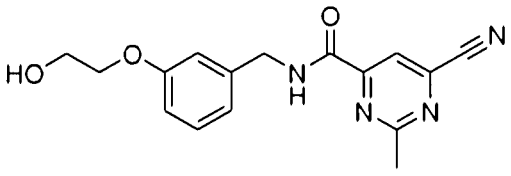
A solution of 3-(2-hydroxyethoxy) benzaldehyde (10.00 g; 60.18 mmol) in anhydrous THF (230 mL) was treated at room temperature with benzyl amine (6.90 ml, 63.19 mmol) as a bolus and the resulting yellow solution was stirred at room temperature for 1 h. Acetic acid (3.45 ml, 60.18 mmol) was added as a bolus followed by the portion-wise addition of sodium triacetoxyborohydride (19.1 g, 90.27 mmol). After 1.5 h, the reaction was quenched by the addition of 1 N NaOH (200 ml). The phases were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo to afford the title compound as an oil (13.20 g, 86.9 %).
MS (ES+) *m/z* 258 (M+H).

Step 2: Preparation of 2-(3-(aminomethyl)phenoxy)ethanol



(3-((Benzylamino)methyl)phenoxy)ethanol (13.2 g) was dissolved with heating in absolute ethanol (500 mL) and ammonium formate (40.9 g, 648 mmol) was added. The mixture was sparged with N_2 for a short period before 10% Pd/C (1.5 g, 13.9 mmol) was added. The slurry was heated to reflux (55 °C to 66 °C) and stirred for 2 h. Additional catalyst (1.5 g) was added and heating at reflux (74.7 °C) was continued for 30 min. The reaction was filtered and concentrated in vacuo. The crude material was chromatographed on a normal phase column eluting with 95/5/0.5, dichloromethane/methanol/NH_4OH to afford the title compound (3.14 g).

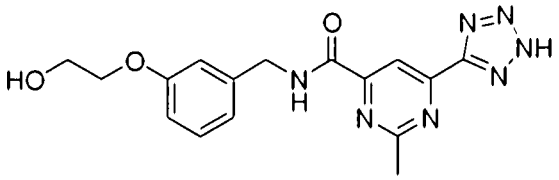
Step 3: Preparation of *N*-(3-(2-hydroxyethoxy)benzyl)-6-cyano-2-methylpyrimidine-4-carboxamide



Methyl 6-cyano-2-methylpyrimidine-4-carboxylate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (892 mg, 5.03 mmol), 2-(3-(aminomethyl)phenoxy)ethanol (894 mg, 5.35 mmol), and triethylamine (382 mg, 3.78 mmol) were combined in dimethylacetamide (6 mL). The mixture was stirred at 80 °C for 2 h. The mixture was cooled and partitioned into ethyl acetate and water. The aqueous layer was extracted with additional

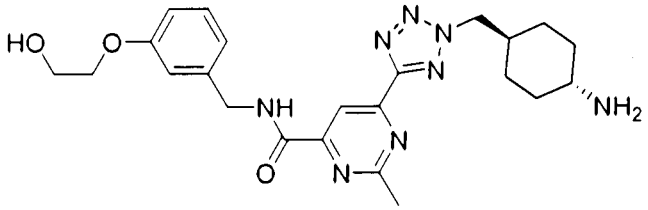
ethyl acetate (15 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated. The product was purified by silica gel chromatography (dichloromethane/methanol, 100/0 – 95/5). The pure fractions were combined and concentrated to afford the title compound as an oil (950 mg, 60%). LC/MS (10%-90% CH_3CN:H_2O, 8 min): 2.338 min, *m/z* 313 (M+H).

Step 4: Preparation of *N*-(3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



N-(3-(2-Hydroxyethoxy)benzyl)-6-cyano-2-methylpyrimidine-4-carboxamide (687 mg, 2.20 mmol), sodium azide (214 mg, 3.30 mmol), and zinc(II) bromide (248 mg, 1.10 mmol) were combined in methanol (10 mL). The resulting mixture was stirred at 60 °C until homogeneous, then cooled to 25 °C and stirred for 18 h. The methanol was removed, the solution acidified to pH 3 (3N hydrochloric acid) and extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated to afford the title compound as a yellow solid (782 mg, 100%). LC/MS (10%-90% CH_3CN/H_2O, 8 min): 3.58 min, *m/z* 356 (M+H).

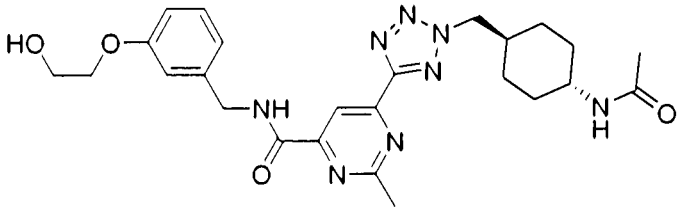
Step 5: Preparation of *N*-(3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



N-(3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (782 mg, 2.20 mmol), (*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)methyl 4-methylbenzenesulfonate (prepared as described in step 7 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (844 mg, 2.20 mmol), and triethylamine (267 mg, 2.64 mmol) were combined in dimethylacetamide (12 mL). The resulting mixture was stirred at 85 °C for 18 h. The mixture was partitioned into water/ethyl acetate and extracted with additional ethyl acetate (5 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated. Purification was accomplished by reverse phase high-pressure liquid chromatography. The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated to an oil. The intermediate was dissolved in methylene chloride (2 mL) and trifluoroacetic acid (2 mL) was added. The mixture was stirred 10 min., concentrated, and neutralized to pH 8 (NaOH). The mixture was extracted with ethyl acetate (2 x 15 mL), dried over magnesium sulfate, filtered and concentrated to afford the title compound as a clear oil (100 mg, 8%). LC/MS (10%-90% CH_3CN/H_2O, 6 min): 5.92 min, *m/z* 467 (M+H).

Example 14

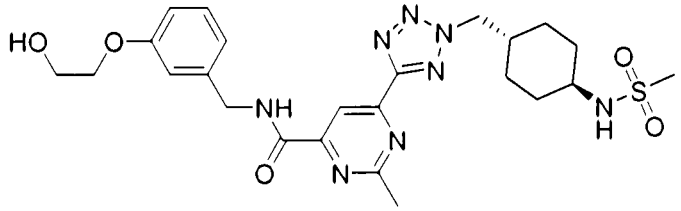
***N*-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



N-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 13) (50 mg, 0.11 mmol), triethylamine (38.0 mg, 0.375 mmol) and acetyl chloride (10.1 mg, 0.129 mmol) were combined in dichloromethane (2 mL). After stirring for 18 h, the mixture was concentrated and then treated with acetonitrile (2 mL) and 2.5 N sodium hydroxide (2 mL). After 1 h, the organics were removed under a nitrogen stream and the aqueous layer was adjusted to pH 6 with 10% hydrogen chloride. The mixture was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the title compound as a white solid (6 mg, 11%). LC/MS (10%-90% CH_3CN/H_2O, 4 min): 2.45 min, *m/z* 509 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.41-9.48 (m, 1 H), 8.39 (s, 1 H), 7.58-7.64 (m, 1 H), 7.14 - 7.24 (m, 1 H), 6.83 - 6.94 (m, 2 H), 6.77 - 6.84 (m, 1 H), 5.43 - 5.55 (m, 1 H), 4.64 - 4.71 (m, 1 H), 4.45 - 4.51 (m, 2 H), 3.97 (m, 1 H), 3.62 - 3.72 (m, 2 H), 3.37 – 3.48 (m, 1 H), 2.81 (s, 3 H), 1.88 – 2.03 (m, 2 H), 1.84 (m, 2 H), 1.72 (s, 3 H), 1.63 (m, 2 H), 0.95 - 1.26 (m, 5 H).

Example 15

***N*-(3-(2-Hydroxyethoxy)benzyl)-2-methyl-6-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**

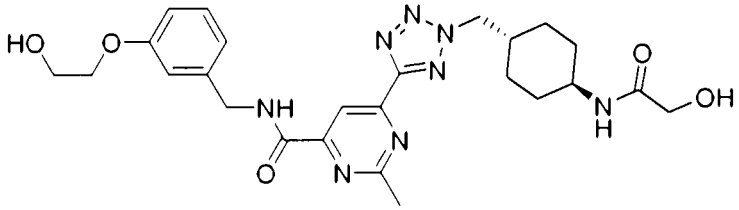


N-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 13) (184 mg, 0.409 mmol), triethylamine (200 µL) and methanesulfonyl chloride (46.9 mg, 0.409 mmol) were combined in dichloromethane (2 mL). After stirring for 18 h, the resulting mixture was stirred at 85 °C for 18 h. The mixture was concentrated under a nitrogen stream. Purification was accomplished by high-pressure liquid chromatography. Pure fractions were combined and concentrated to afford the title compound as a white solid (6.5 mg, 2.9%). LC/MS (10%-90% CH_3CN/H_2O, 8 min): 4.26 min, *m/z* 545 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (s, 1 H), 8.42 (s, 1 H), 7.23 (m, 1 H), 6.93 (m, 2 H), 6.83 (m, 1 H), 4.77 (m, 1 H), 4.70 (d, J = 6.6 Hz, 2 H), 4.51 (d, J = 6.22 Hz, 2 H), 3.96 (t, J = 4.9 Hz, 2 H), 3.69 (d,

J = 5.1 Hz, 2 H), 3.06 (m, 1 H), 2.85 (s, 3 H), 2.83 (s, 3 H), 1.90 (m, 3 H), 1.64 (m, 2 H), 1.20 (m, 4 H), 0.06 (m, 1 H).

Example 16

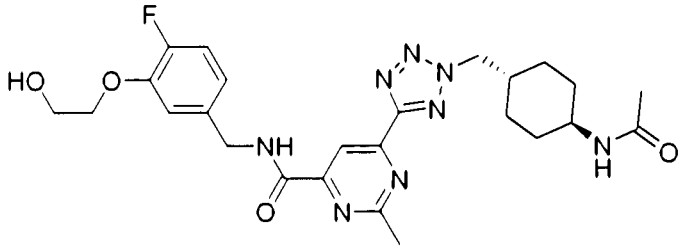
_N_-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



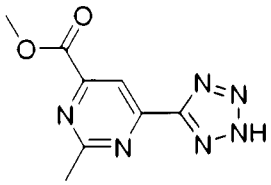
N-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 13) (184 mg, 0.409 mmol), triethylamine (200 µL) and acetoxy acetyl chloride (55.9 mg, 0.409 mmol) were combined in dichloromethane (4 mL). After stirring for 10 min., the mixture was concentrated then treated with acetonitrile (2 mL) and 2.5 N sodium hydroxide (2 mL). After 1 h, the organics were removed under a nitrogen stream and the aqueous layer was adjusted to pH 6 with 10% hydrogen chloride. The mixture was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the title compound as a white solid (79.9 mg, 37%). LC/MS (10%-90% CH_3CN/H_2O, 6 min): 4.00 min, *m/z* 525 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (s, 1 H), 8.31 (s, 1 H), 7.52 (s, 1 H), 7.38 - 6.94 (m, 4 H), 3.85 (s, 1 H), 3.72 (d, J = 11.4 Hz, 4 H), 3.47 (t, J = 11.0, 4 H), 2.60 (s, 3 H), 2.41 (d, J = 13.2, 4 H), 1.79 (m, 8 H), 0.06 (m, 1 H).

Example 17

_N_-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



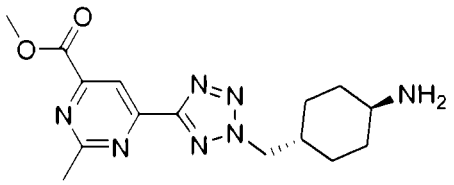
Step 1: Preparation of methyl 2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxylate



Methyl 6-cyano-2-methylpyrimidine-4-carboxylate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (5.00 g, 28.2 mmol), sodium azide (1.93 g, 29.6 mmol),

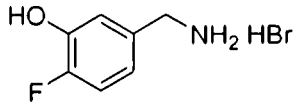
and zinc bromide (6.36 g, 28.2 mmol) were suspended in methanol (28 mL). The reaction was stirred at room temperature for 16 hours. 1 N hydrochloric acid (75 mL) was added and the mixture was stirred vigorously for 1 hour. The solids were collected by vacuum filtration and rinsed with 1 N hydrochloric acid (2 x 50 mL) and water (2 x 100 mL). High vacuum drying at 40 °C provided the title compound as a white solid (5.31 g, 85%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.24 min, *m/z* 221 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.38 (s, 1 H), 3.94 (s, 3 H), 2.80 (s, 3 H).

Step 2: Preparation of methyl 6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate



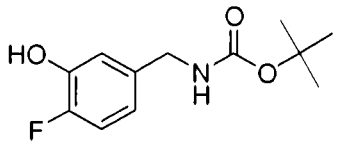
Methyl 2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxylate (2.00 g, 9.0 mmol), *tert*-butyl (*trans*)-4-(hydroxymethyl)cyclohexylcarbamate (2.29 g, 9.99 mmol), resin-bound triphenylphosphine (4.84 g, 10.9 mmol) and di-*tert*-butyl azodicarboxylate (2.3 g, 9.99 mmol) were combined in tetrahydrofuran (30 mL). The mixture was stirred at 25 °C for 18 h. The mixture was filtered and concentrated. The residue was purified by reverse phase preparative high-pressure liquid chromatography. Fractions containing methyl 6-(2-((*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated. The residue was dissolved in methylene chloride (2 mL) and trifluoroacetic acid (2 mL) was added. The mixture was stirred 10 min, concentrated, and neutralized to pH 8 (NaOH). The organic layer was extracted with ethyl acetate (2 x 15 mL), dried with magnesium sulfate, filtered and concentrated to afford the title compound as a clear oil (400 mg, 7%). LC/MS (10%-90% CH_3CN/H_2O, 4 min): 1.704 min, *m/z* 332 (M+H).

Step 3: Preparation of 5-aminomethyl-2-fluoro-phenol hydrobromide



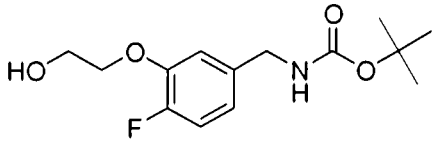
A mixture of 4-fluoro-3-methoxy-benzylamine hydrochloride (133 g, 0.642 mol), 48% aqueous HBr (1 L) and 30% HBr in acetic acid (1 L) was refluxed for 4 h and concentrated under vacuum. Ethanol was added to the residue and evaporated to remove last remaining water. The crystalline residue obtained was dissolved in a small amount of ethanol and ethyl ether was slowly added. A heavy crystalline suspension formed and was filtered, washed with ethyl ether and dried in vacuum to afford the title compound (147 g, 95.4%).

Step 4: Preparation of *tert*-butyl 4-fluoro-3-hydroxybenzylcarbamate



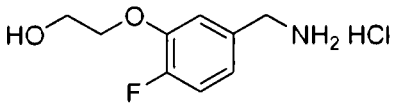
Triethylamine (13.7 g, 0.135 mol) and di-*tert*-butyl dicarbonate (29.5 g, 0.135 mol) were added to a solution of 5-aminomethyl-2-fluorophenol hydrobromide (30 g, 0.135 mol) in dichloromethane (200 mL) at ice bath temperature. The reaction mixture was stirred overnight at room temperature, diluted with water and adjusted to pH~5 with acetic acid. The organic layer was separated, washed with water and concentrated under vacuum to afford the title compound as a clear viscous oil (31.5 g, 96%).

Step 5: *tert*-butyl 4-fluoro-3-(2-hydroxyethoxy)benzylcarbamate



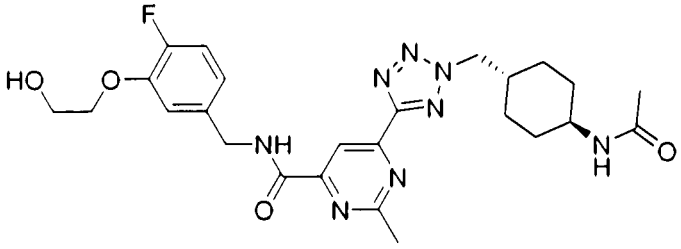
To a mixture of *tert*-butyl 4-fluoro-3-hydroxybenzylcarbamate (31.5 g, 0.13 mol) in dimethylsulfoxide (300 mL) was added KOH (15.75 g), KI (0.3 g) and bromoethanol (19.6 g, 0.157 mol). The mixture was stirred for 5 days until no starting material remained. The mixture was diluted with excess dichloromethane and washed with water. The organic solution was concentrated and the crude product purified by silica gel column chromatography (0-80% ethyl acetate in hexane) to afford the desired tert-butyl 4-fluoro-3-(2-hydroxyethoxy)benzylcarbamate as an oil (14 g, 40%).

Step 6: Preparation of 2-(5-aminomethyl-2-fluorophenoxy)ethanol hydrochloride



tert-Butyl 4-fluoro-3-(2-hydroxyethoxy)benzylcarbamate (14 g, 0.05 mol) was dissolved in excess of 4N hydrochloric acid in dioxane (125 ml) and stirred for 5 h at room temperature. The resulting solid was diluted with an additional amount of dioxane and then filtered, washed with cold dioxane and dried in vacuo to afford the title compound as the hydrochloride salt (8.5 g, 78%). MS (ES+) *m/z* 186 (M+H). Elemental analysis found: C, 48.25; H, 6.09; N, 6.45.

Step 7: Preparation of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

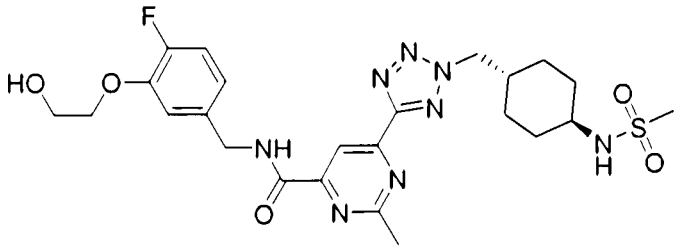


Methyl 6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate (134 mg, 0.404 mmol), acetyl chloride (104 mg, 1.33 mmol) and triethylamine (200 µL)

were combined in dichloromethane (2 mL). The resulting mixture was stirred at 25 °C for 30 min. The dichloromethane was removed under nitrogen stream. The residue was dissolved in dimethylacetamide (2 mL) and 2-(5-(aminomethyl)-2-fluorophenoxy)ethanol hydrochloride (178 mg, 0.808 mmol) and triethylamine (200 µL) were added. The mixture was stirred at 25 C for 18 h. Purification was accomplished by reverse phase preparative high-pressure liquid chromatography (acetonitrile/water, 5 – 95%, 30 min). The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried (magnesium sulfate), and concentrated to an oil that solidified under reduced pressure to afford the title compound as a white solid (48.5 mg, 23%). LC/MS (10%-90% CH_3CN/H_2O, 4 min) 2.53 min, *m/z* 527 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (s, 1 H), 8.40 (s, 1 H), 7.61 (d, J = 8.05, 1 H), 7.18 (m, 2 H), 6.90 (m, 1 H), 4.81 (t, J = 5.68, 5.86, 1 H), 4.67 (d, J = 7.32, 2 H), 4.47 (d, J = 6.59, 2 H), 4.01 (m, 2 H), 3.71 (m, 2 H), 3.45 (m, 1 H), 2.81 (s, 3 H), 1.97 (m, 1 H), 1.78 (m, 2 H), 1.73 (s, 3 H), 1.58 (m, 2 H), 1.14 (m, 4 H).

Example 18

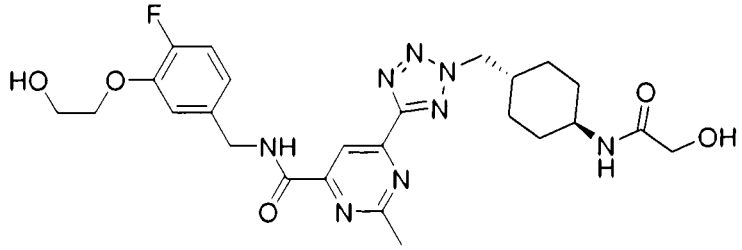
***N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**



Methyl 6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 17) (134 mg, 0.404 mmol), methanesulfonyl chloride (152 mg, 1.33 mmol) and triethylamine (200 µL) were combined in dichloromethane (2 mL). The resulting mixture was stirred at 25 °C for 30 min. The dichloromethane was removed under nitrogen stream. The residue was dissolved in dimethylacetamide (2 mL) and 2-(5-(aminomethyl)-2-fluorophenoxy)ethanol (prepared as described in steps 3 – 6 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 17) (178 mg, 0.808 mmol) and triethylamine (200 µL) were added. The mixture was stirred at 25 °C for 18 h. Purification was accomplished by reverse phase preparative high-pressure liquid chromatography (acetonitrile/water, 5 – 95%, 30 min). The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated to an oil that solidified under reduced pressure to afford the title compound as an white solid (45.3 mg, 20%). LC/MS (10%-90% CH_3CN/H_2O, 4 min) 2.64 min, *m/z* 563 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (m, 1 H), 8.40 (s, 1 H), 7.13 (m, 2 H), 6.90 (m, 2 H), 4.79 (m, 1 H), 4.68 (m, 2 H), 4.47 (m, 2 H), 4.03 (m, 2 H), 3.70 (m, 2 H), 3.05 (m, 1 H), 2.86 (s, 3 H), 2.81 (s, 3 H), 1.93 (m, 3 H), 1.61 (m, 2 H), 1.18 (m, 4 H).

Example 19

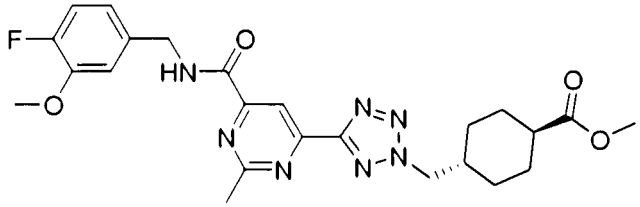
***N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



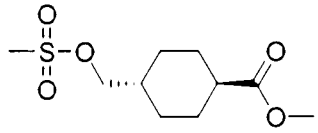
Methyl 6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 17) (134 mg, 0.404 mmol), acetoxy acetyl chloride (181 mg, 1.33 mmol) and triethylamine (200 µL) were combined in dichloromethane (2mL). The resulting mixture was stirred at 25 °C for 30 min. The dichloromethane was removed under nitrogen stream. The residue was dissolved in dimethylacetamide (2 mL) and (2-(5-(aminomethyl)-2-fluorophenoxy)ethanol (prepared as described in steps 3 – 6 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 17) (178 mg, 0.808 mmol) and triethylamine (200 µL) were added. The mixture was stirred at 25 °C for 18 h. Purification was accomplished by reverse phase preparative high-pressure liquid chromatography (acetonitrile/water, 5 – 95%, 30 min). The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated. The residue was dissolved in acetonitrile (4.5 mL) and treated with 2.5N NaOH (2.5 mL). The acetonitrile was removed in vacuo and the aqueous layer was adjusted to pH 6 with 10% hydrochloric acid. The mixture was extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated to an oil the solidified under reduced pressure to give the title compound as an white solid (52.2 mg, 24%). LC/MS (10%-90% CH_3CN/H_2O, 4 min): 2.43 min, *m/z* 543 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (s, 1 H), 8.40 (s, 1 H), 7.35 (m, 1 H), 7.09 - 7.18 (m, 2 H), 6.90 (m, 1 H), 5.30 (m, 1 H), 4.81 (m, 1 H), 4.68 (d, J = 7.32, 2 H), 4.47 (d, J = 6.59, 2 H), 4.02 (m, 2 H), 3.70 (m, 4 H), 3.53 (m, 1 H), 2.81 (s, 3 H),1.97 (m, 1 H), 1.72 (m, 2 H), 1.62 (m, 2 H), 1.15 - 1.28 (m, 4 H).

Example 20

***trans*-Methyl 4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate**

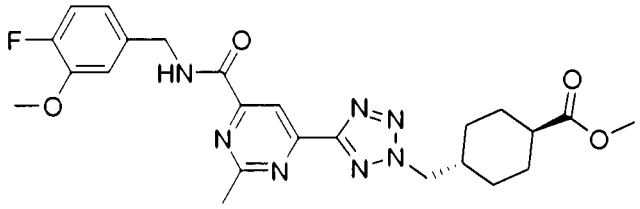


Step 1: Preparation of *trans*-methyl 4-((methylsulfonyloxy)methyl)cyclohexanecarboxylate



Triethylamine (6.46 g, 63.9 mmol) was added to a solution of *trans*-methyl 4-(hydroxymethyl)cyclohexanecarboxylate (10.0 g, 58.1 mmol) in dichloromethane (100 mL). Methane sulfonylchloride (7.98 g, 69.7 mmol) was added drop-wise and then the mixture was stirred at room temperature for 2 days. The mixture was diluted with brine. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated. The resulting oil crystallized upon addition of petroleum ether and was filtered to afford the title compound (14.0 g).

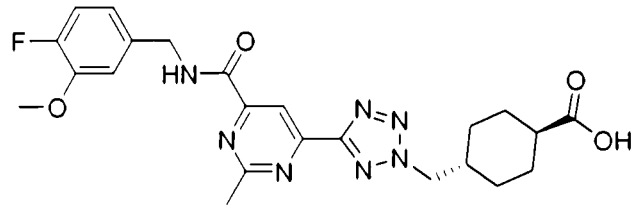
Step 2: Preparation of *trans*-methyl 4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate



trans-Methyl 4-((methylsulfonyloxy)methyl)cyclohexanecarboxylate (65 mg, 0.26 mmol) was added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (60 mg, 0.17 mmol) and triethylamine (34 mg, 0.34 mmol) in anhydrous dimethylacetamide (0.3 mL). The mixture was stirred at 80 - 90 °C in a capped vial overnight. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound (43 mg).

Example 21

trans-4-((5-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2H-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid

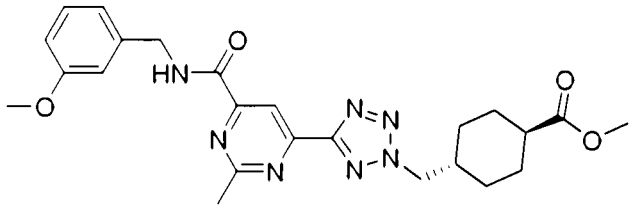


Sodium hydroxide (2 pellets) were added to a mixture of *trans*-methyl 4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (43 mg) in tetrahydrofuran (0.4 mL) and water (0.4 mL). The mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and the product was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound as a white solid (28 mg). MS (ES+) *m/z* 484 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.51 (1 H, t, *J*=6.0 Hz), 8.42 (1 H, s), 7.11 - 7.22 (1 H, m), 6.92 (1 H, br. s.), 4.70 (3 H, d, *J*=6.6 Hz), 4.51 (3 H, d, *J*=5.9 Hz), 3.82 (3 H,

s), 2.83 (3 H, s), 2.14 (1 H, br. s.), 1.99 (1 H, br. s.), 1.90 (2 H, br. s.), 1.64 (2 H, br. s.), 1.30 (3 H, d, *J*=12.8 Hz), 1.08 - 1.19 (2 H, m).

Example 22

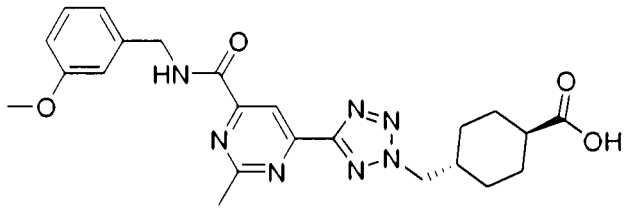
(*trans*)-Methyl 4-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate



trans-Methyl 4-((methylsulfonyloxy)methyl)cyclohexanecarboxylate (prepared as described in step 1 of the synthesis of *trans*-methyl 4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate, Example 20) (56 mg, 0.22 mmol) was added to a solution of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (50 mg, 0.15 mmol) and triethylamine (56 mg, 0.22 mmol) in anhydrous dimethylacetamide (0.3 mL). The mixture was stirred at 80 - 90 °C in a capped vial overnight. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound (37 mg).

Example 23

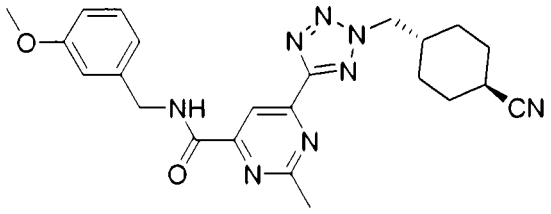
(*trans*)-4-((5-(6-((3-Methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



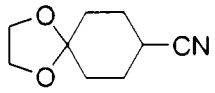
Sodium hydroxide (2 pellets) was added to mixture of (*trans*)-methyl 4-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 22) in tetrahydrofuran (0.4 mL) and water (0.4 mL). The mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse phase preparative HPLC (water/acetonitrile). The resulting residue was slurried and decanted from ethyl ether and dried in a vacuum desiccator to afford the title compound as an off-white solid (19 mg). MS (ES+) *m/z* 466 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (1 H, t, *J*=6.2 Hz), 8.41 (1H,s), 7.24 (1 H, t, *J*=8.1 Hz), 6.93 (2 H, br. s.), 6.83 (1 H, d, *J*=7.7 Hz), 4.70 (2 H, d, *J*=7.0 Hz), 4.51 (3 H, d, *J*=6.2 Hz), 3.74 (3 H, s), 2.83 (3 H, s), 2.14 (1 H, br. s.), 2.01 (1 H, br. s.), 1.91 (2 H, d, *J*=12.1 Hz), 1.64 (2 H, br. s.), 1.30 (3 H, d, *J*=12.4 Hz), 1.14 (2 H, t, *J*=11.3 Hz).

Example 24

***N*-(3-Methoxybenzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

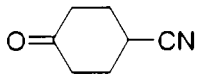


Step 1: Preparation of 1,4-dioxa-spiro[4.5]decane-8-carbonitrile



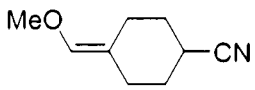
To a cold (-10 °C) suspension of 1,4-dioxa-spiro[4.5]decan-8-one (123.0 g, 0.79 mol) and tosyl-methyl-isocyanide (200.0 g, 1.024 mol) in DMF (2.2 L) and ethanol (85 mL), was added potassium *t*-butoxide (210.0 g, 1.87 mol) portion wise over a period of 2 h, and the temperature was maintained below –5 °C. After complete addition, the mixture was brought to 0 °C and stirred another 1 h at 0 °C followed by room temperature for another 2.5 h. The reaction mixture was diluted with ethyl acetate (3.5 L) and water (3.5 L). The mixture was stirred for 1 h. The organic layer was separated and washed with water (3 x 1.5 L) followed by brine solution (1.5 L), dried over anhydrous sodium sulfate, and concentrated to afford the title compound as an oil (99 g, 75 %).

Step 2: Preparation of 4-oxocyclohexanecarbonitrile



To a stirred solution of 1,4-dioxa-spiro[4.5]decane-8-carbonitrile (100 g, 0.60 mol) in tetrahydrofuran (1.0 L) was added 2N hydrochloric acid (1.0 L) at room temperature and the mixture was stirred for 24 h. The reaction mixture was diluted with ethyl acetate (1.0 L). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 700 mL). The combined organic layer was washed with water (1.5 L) followed by brine (1.0 L), dried over anhydrous sodium sulfate, and concentrated. The crude material was purified by flash column chromatography over silica gel (230-400 mesh) eluting with 20% ethyl acetate in hexane to afford the title compound (50 g, 67 %).

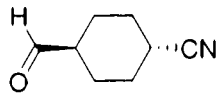
Step 3: Preparation of 4-(methoxymethylene)cyclohexanecarbonitrile



To a cold (-30 °C) suspension of methoxy methyl triphenylphosphonium chloride (84 g, 163 mmol) in dry tetrahydrofuran (300 mL) was added drop-wise 1.6 M *n*-butyllithium (153 mL, 243.6 mmol) maintaining the temperature at –25 °C to –30 °C. After complete addition, the mixture was allowed to stir for 1 h at –20 °C. A solution of 4-oxocyclohexanecarbonitrile (20 g, 162.4 mmol) in tetrahydrofuran (150 mL) was added drop-wise at –20 °C and allowed to stir for 2 h at the same temperature. Hexane (200 mL) was added, and the mixture was filtered. The filtrate was concentrated

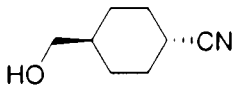
under reduced pressure and the crude material was purified by flash column chromatography over silica gel (230-400 mesh) eluting with 10% ethyl acetate in hexane to afford the title compound (9 g, 36%).

Step 4: Preparation of *trans*-4-formylcyclohexanecarbonitrile



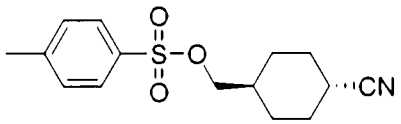
A mixture of 4-(methoxymethylene)cyclohexanecarbonitrile (9 g, 59.5 mmol) and tetrahydrofuran /2N hydrochloric acid (4:1, 400 mL v/v) was heated to reflux for 30 minutes. The reaction mixture was poured into water (300 mL) cold water and extracted with diethyl ether (3 x 300 mL). The combined organic layer was washed with water (400 mL), dried over anhydrous sodium sulfate and concentrated. Recrystallization from hexane afforded the title compound (2.1 g, 25 %).

Step 5: Preparation of *trans*-4-(hydroxymethyl)cyclohexanecarbonitrile



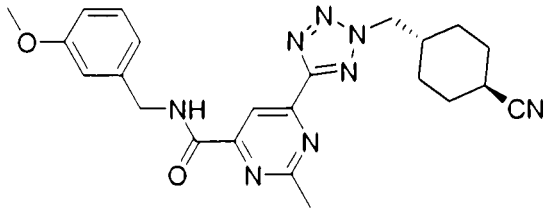
A suspension of 600 mg (189.15 mmol) of sodium borohydride in methanol/diethyl ether (9:1, 70 mL v/v) was treated drop-wise with a solution of *trans*-4-formylcyclohexanecarbonitrile (2 g, 14.6 mmol) in methanol/diethyl ether (9/1, 30 mL v/v) within 10 minutes at 0 °C. The reaction mixture was allowed to stir for 2 h at 10 °C, treated with 2N hydrochloric acid (35 mL) under ice-water cold condition, and extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to afford the title compound as an oil (1.45 g, 71 %). MS (ES+) *m/z* 162 (M+Na).

Step 6: Preparation of (*trans*-4-cyanocyclohexyl)methyl 4-methylbenzenesulfonate



p-Toluene sulfonyl chloride (2.15 g, 11.3 mmol) was added portion-wise over 30 min to a solution of *trans*-4-(hydroxymethyl)cyclohexanecarbonitrile (1.57 g, 11.3 mmol) in anhydrous pyridine (10 mL) at room temperature. The reaction mixture was stirred for 4 h and then water (40 mL) was added drop-wise with ice bath cooling. The mixture was extracted with dichloromethane. The organic layer was washed with 3 M hydrochloric acid, dried over magnesium sulfate, and concentrated under vacuum to afford the title compound as a white solid (2.4 g).

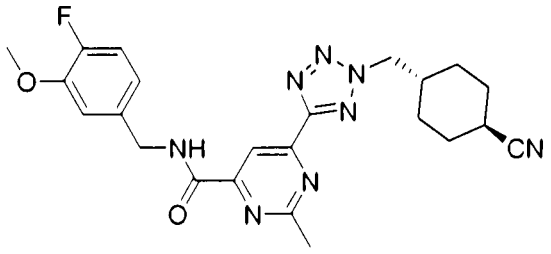
Step 7: Preparation of *N*-(3-methoxybenzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



(*trans*-4-Cyanocyclohexyl)methyl 4-methylbenzenesulfonate (232 mg, 0.79 mmol) was added to a solution of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (200 mg, 0.61 mmol) and triethylamine (186 mg, 1.8 mmol) in anhydrous dimethylacetamide (0.3 mL). The reaction was stirred overnight at 85 °C in a capped vial. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing product were neutralized by passing through a small carbonate resin column and concentrated. The residue was slurried and decanted from ethyl ether three times and dried in a vacuum desiccator to afford the title compound as a white solid (64 mg). MS (ES+) *m/z* 447 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (1 H, t, *J*=6.2 Hz), 8.41 (1 H, s), 7.24 (1 H, t, *J*=8.1 Hz), 6.93 (2 H, br. s.), 6.83 (1 H, d, *J*=8.1 Hz), 4.71 (2 H, d, *J*=7.0 Hz), 4.51 (2 H, d, *J*=6.2 Hz), 3.74 (3 H, s), 2.83 (3 H, s), 2.63 (1 H, br. s.), 2.08 (1 H, br. s.), 2.02 (2 H, d, *J*=11.3 Hz), 1.65 (3 H, d, *J*=11.0 Hz), 1.51 (2 H, d, *J*=12.8 Hz), 1.15 (2 H, t, *J*=11.3 Hz).

Example 25

N-(4-Fluoro-3-methoxybenzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

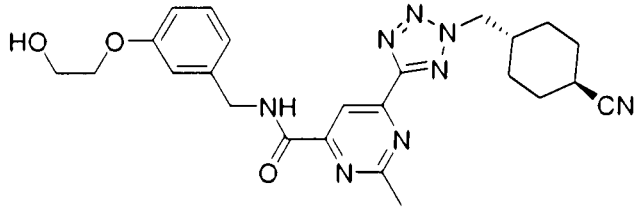


(*trans*-4-Cyanocyclohexyl)methyl 4-methylbenzenesulfonate (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 24) (214 mg, 0.73 mmol) was added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (170 mg, 0.495 mol) and triethylamine (148 mg, 1.4 mmol) in anhydrous dimethylacetamide (0.4 mL). The mixture was stirred overnight at 85 °C in a capped vial. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing product were neutralized by passing through a small carbonate resin column and concentrated. The residue was slurried and decanted from ethyl ether three times and dried in a vacuum desiccator to afford the title compound as a white

solid (65 mg). MS (ES+) *m/z* 465 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.50 (1 H, t, *J*=6.4 Hz), 8.42 (1 H, s), 7.19 (1 H, d, *J*=8.4 Hz), 7.14 (1 H, dd, *J*=11.5, 8.6 Hz), 6.91 (1 H, br. s.), 4.71 (2 H, d, *J*=7.0 Hz), 4.51 (2 H, d, *J*=6.2 Hz), 3.83 (3 H, s), 2.83 (3 H, s), 2.63 (1 H, br. s.), 2.01 (3 H, br. s.), 1.63 (3 H, br. s.), 1.50 (2 H, br. s.), 1.08 - 1.19 (2 H, m).

Example 26

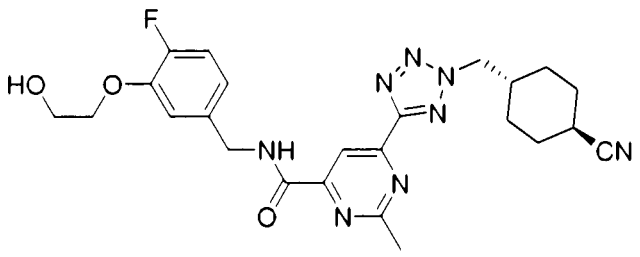
***N*-(3-(2-Hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



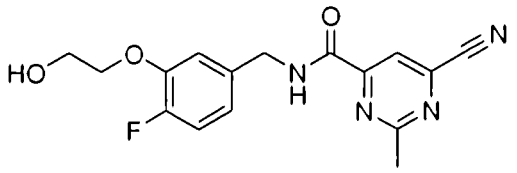
N-(3-(2-Hydroxyethoxy)benzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in steps 1 - 4 of the synthesis of *N*-(3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 13) (180 mg, 0.614 mmol), (*trans*-4-cyanocyclohexyl)methyl 4-methylbenzenesulfonate (prepared as described in steps 1 – 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 24) (150 mg, 0.423 mmol), and triethylamine (400 µL) were combined in dimethylacetamide (100 µL). The resulting mixture was stirred at 85 °C for 18 h. The mixture was concentrated under a nitrogen stream. Purification was accomplished by reverse phase preparative high-pressure liquid chromatography. Pure fractions were combined and concentrated to afford the title compound as a white solid (36.6 mg, 12%). MS (ES+) *m/z* 477 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (m, 1 H), 8.30 (s, 1 H), 7.24 (m, 1 H), 6.91 (m, 2 H), 6.79 (m, 1 H), 4.81 (m, 1 H), 4.71 (m , 2 H), 4.52 (m, 2 H), 3.96 (m, 2 H), 3.61 (m, 2 H), 2.80 (s, 3 H), 2.61 (m, 1 H), 2.40 (m, 1 H), 2.01 (m, 4 H), 1.62 (m, 2 H), 1.44 (m, 2 H), 1.05 (m, 2 H).

Example 27

***N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

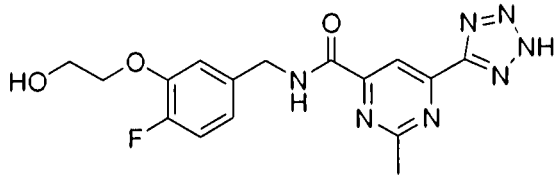


Step 1: Preparation of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-cyano-2-methylpyrimidine-4-carboxamide



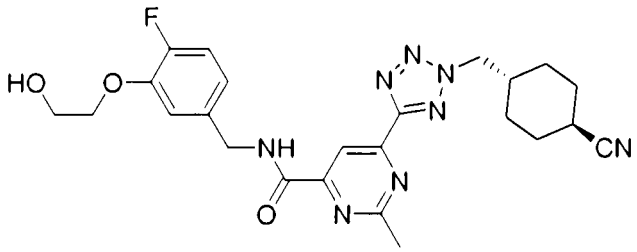
Methyl 6-cyano-2-methylpyrimidine-4-carboxylate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (5.20 g, 29.0 mmol), 2-(5-(aminomethyl)-2-fluorophenoxy)ethanol hydrochloride (prepared as described in steps 3 – 6 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 17) (8.30 g, 32.3 mmol), and triethylamine (5.94 g, 58.7 mmol) were combined in dimethylacetamide (50 mL). The mixture was stirred at 80 °C for 2 h. The mixture was cooled and poured into 1N hydrochloric acid (50 mL) and was extracted with ethyl acetate (3 x 30 mL). The combined organic layers dried over magnesium sulfate, filtered and concentrated to a crude oil. The product was triturated with ethyl acetate to afford the title compound as a solid (1.5 g, 15%). LC/MS (10%-90% CH_3CN/H_2O, 4 min): 2.437 min, *m/z* 331 (M+H).

Step 2: Preparation of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



N-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-cyano-2-methylpyrimidine-4-carboxamide (7.93 g, 24.0 mmol), sodium azide (2.34 g, 36.0 mmol), and zinc(II) bromide (2.70 g, 12.0 mmol) were combined in methanol (50 mL). The resulting mixture was stirred at 25 °C for 18 h. The methanol was removed and the residue was acidified to pH 3 (3N hydrochloric acid) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the title compound as an off-white solid (4.25g, 47%). LC/MS (10%-90% CH_3CN/H_2O, 4 min): 2.274 min, *m/z* 374 (M+H).

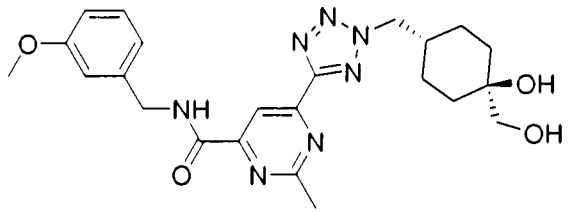
Step 3: Preparation of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



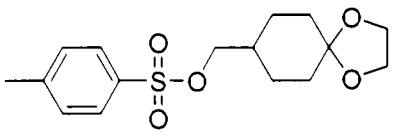
(*trans*-4-cyanocyclohexyl)methyl 4-methylbenzenesulfonate (prepared as described in steps 1 – 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 24) (114 mg, 0.389 mmol) was added to a solution of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (100 mg, 0.268 mmol) and triethylamine (162 mg, 1.6 mmol) in anhydrous dimethylacetamide (0.2 mL). The mixture was stirred overnight at 85 °C in a capped vial. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing product were neutralized by passing through a small carbonate resin column and concentrated. The residue was slurried and decanted from ethyl ether three times and dried in a vacuum desiccator to afford the title compound as a white solid (46 mg). MS (ES+) *m/z* 495 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.63 (1 H, s), 7.53 - 7.57 (1 H, m), 7.40 - 7.51 (3 H, m), 7.34 (2 H, d, *J*=6.2 Hz), 7.25 (1 H, br. s.), 7.14 (2 H, br. s.), 7.03 (1 H, br. s.), 3.96 (1 H, s), 3.85 (4 H, d, *J*=11.7 Hz), 3.58 (4 H, t, *J*=10.8 Hz), 2.55 - 2.66 (3 H, m), 1.85 - 1.96 (3 H, m).

Example 28

N-(3-Methoxybenzyl)-6-(2-(((*trans*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



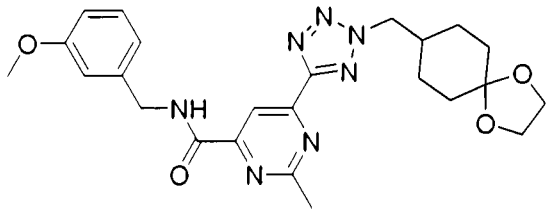
Step 1: Preparation of 1,4-dioxaspiro[4.5]dec-8-ylmethyl 4-methylbenzenesulfonate



p-Toluene sulfonylchloride (4.43 g, 23.24 mmol) was added portion-wise over 20 min to a solution of 1,4-dioxaspiro[4.5]dec-8-ylmethanol (*Bioorg. Med. Chem.* **2005**, *13*, 6309–6323) (4.0 g, 23.0 mmol) in anhydrous pyridine (30 mL). The mixture was stirred at room temperature for 2.5 hours. The reaction mixture was cooled to 0 °C and water (100 mL) was added drop-wise maintaining the temperature below 20 °C. The mixture was extracted with dichloromethane. The organic layer was

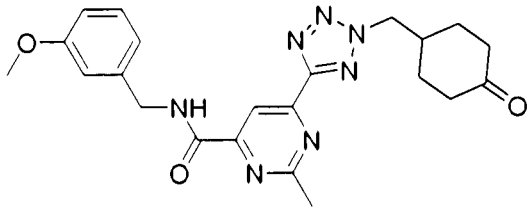
washed with water (4x), dried over magnesium sulfate, and concentrated under vacuum to afford the title compound as a clear oil (5.7 g).

Step 2: Preparation of 6-(2-(1,4-dioxaspiro[4.5]dec-8-ylmethyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide



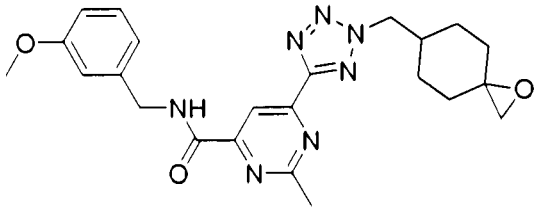
1,4-Dioxaspiro[4.5]dec-8-ylmethyl 4-methylbenzenesulfonate (552 mg, 1.69 mmol) was added to a solution of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (550 mg, 1.69 mmol) and triethylamine (171 mg, 1.7 mmol) in anhydrous dimethylacetamide (0.5 mL). The mixture was stirred overnight at 85 °C in a capped vial. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound (271 mg).

Step 3: Preparation of *N*-(3-methoxybenzyl)-2-methyl-6-(2-((4-oxocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



6-(2-(1,4-Dioxaspiro[4.5]dec-8-ylmethyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide (271 mg) was dissolved in tetrahydrofuran (3 mL) and 96% formic acid (4 mL) was added. The mixture was stirred at room temperature overnight. The solvent was removed under a stream of nitrogen and the residue was dissolved in dichloromethane. The mixture was washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated under vacuum to afford the title compound (218 mg)

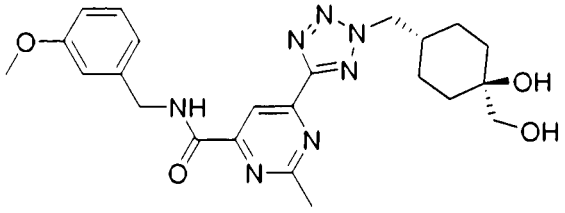
Step 4: Preparation of *N*-(3-methoxybenzyl)-2-methyl-6-(2-(1-oxaspiro[2.5]oct-6-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



A solution of *N*-(3-methoxybenzyl)-2-methyl-6-(2-((4-oxocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (218 mg) in anhydrous dimethylsulfoxide (3 mL) was added to a solid mixture of trimethylsulfoxonium iodide (223 mg, 1.0 mmol) and potassium *t*-butoxide(113 mg, 1.0

mmol). The mixture was stirred at room temperature for 40 min. Water (15 mL) was added and the resulting slurry was stirred an additional 20 min. The precipitate was filtered, washed with water, and dried under vacuum to afford the title compound (163 mg).

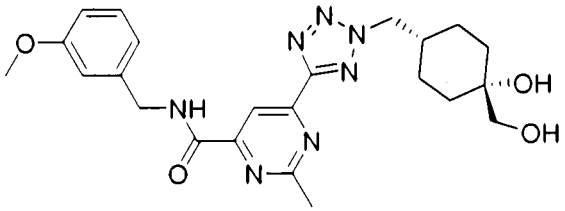
Step 5: Preparation of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



Perchloric acid (70%, 0.3 mL) was added to a solution of *N*-(3-methoxybenzyl)-2-methyl-6-(2-(1-oxaspiro[2.5]oct-6-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (163 mg) in a mixture of tetrahydrofuran (3 mL) and water (1 mL). The resulting slurry was warmed to afford a solution and the mixture was stirred at room temperature for 3.5 h. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing the first eluting product were neutralized by passing through a carbonate resin column and concentrated. The residue was slurried and decanted from ethyl ether three times and dried in a vacuum desiccator to afford the title compound as a white solid (35 mg). MS (ES+) *m/z* 468 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (1 H, t, *J*=6.2 Hz), 8.42 (1 H, s), 7.24 (1 H, t, *J*=8.1 Hz), 6.90 - 6.95 (2 H, m), 6.83 (1 H, d, *J*=8.4 Hz), 4.75 (2 H, d, *J*=7.3 Hz), 4.51 (2 H, d, *J*=6.2 Hz), 4.32 (1 H, t, *J*=5.9 Hz), 3.99 (1 H, s), 3.74 (3 H, s), 2.83 (3 H, s), 2.15 (1 H, br. s.), 1.71 (2 H, d, *J*=10.2 Hz), 1.60 (2 H, d, *J*=10.2 Hz), 1.17 (3 H, d, *J*=9.9 Hz), 1.22 (3 H, d, *J*=12.8 Hz).

Example 29

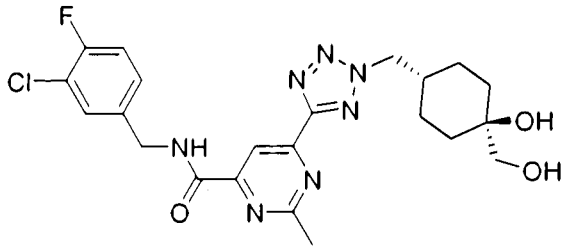
N-(3-Methoxybenzyl)-6-(2-(((*cis*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



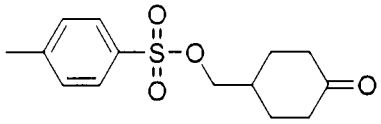
Isolation of the second eluting product by reverse phase preparative HPLC from the reaction mixture described in Example 28 afforded the title compound as a white solid (19 mg). MS (ES+) *m/z* 468 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (1 H, t, *J*=6.2 Hz), 8.41 (1 H, s), 7.24 (1 H, t, *J*=8.1 Hz), 6.90 - 6.95 (2 H, m), 6.83 (1 H, d, *J*=8.1 Hz), 4.69 (2 H, d, *J*=7.0 Hz), 4.51 (2 H, d, *J*=6.6 Hz), 4.41 (1 H, t, *J*=5.7 Hz), 3.82 (1 H, s), 3.74 (3 H, s), 3.13 (2 H, d, *J*=5.9 Hz), 2.83 (3 H, s), 1.95 (1 H, br. s.), 1.37 (3 H, d, *J*=9.2 Hz), 1.43 (5 H, t, *J*=13.0 Hz), 1.33 (1 H, br. s.).

Example 30

***N*-(3-chloro-4-fluorobenzyl)-6-(2-((*trans*-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

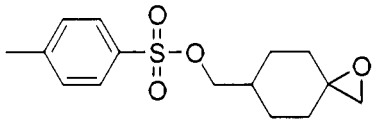


Step 1: Preparation of (4-oxocyclohexyl)methyl 4-methylbenzenesulfonate



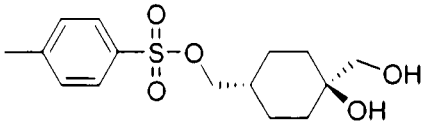
Formic acid (8 mL) was added to a solution of 1,4-dioxaspiro[4.5]dec-8-ylmethyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 28) (1.0 g, 3.0 mmol) in tetrahydrofuran (5 mL). The reaction was stirred at room temperature overnight, and then solvent was removed under a stream of nitrogen. The residue was dissolved in dichloromethane. The organic layer was washed with water (1x), dried over magnesium sulfate, and concentrated under vacuum to afford the title compound as an oil (852 mg).

Step 2: Preparation of 1-oxaspiro[2.5]oct-6-ylmethyl 4-methylbenzenesulfonate



A solution of (4-oxocyclohexyl)methyl 4-methylbenzenesulfonate (852 mg) in anhydrous dimethylsulfoxide (11 mL) was added in one portion to a mixture of trimethylsulfoxonium iodide (1.32 g, 6.0 mmol) and potassium *t*-butoxide (673 mg, 6.0 mmol). The mixture was stirred at room temperature for 1 h and then water (50 mL) was added. The reaction mixture was extracted with ethyl ether (3x). The combined organic layers were washed with water (4x), dried over magnesium sulfate, and concentrated under vacuum to afford the title compound as an oil (621 mg) consisting of cis and trans isomers.

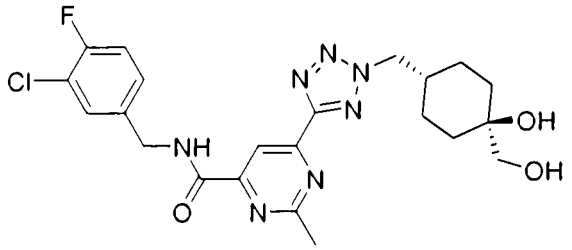
Step 3: Preparation of (*trans*-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl 4-methylbenzenesulfonate



Perchloric acid (0.5 mL) was added to a solution of 1-oxaspiro[2.5]oct-6-ylmethyl 4-methylbenzenesulfonate (621 mg) in a mixture of tetrahydrofuran (4 mL) and water (2 mL). The

mixture was stirred for 2 hours. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) afforded the title compound as a clear oil (105 mg).

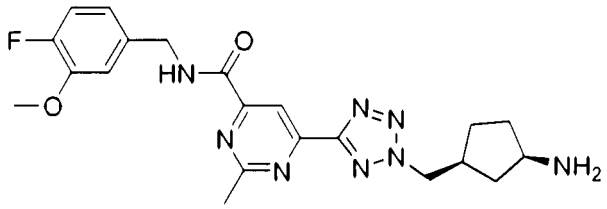
Step 4: Preparation of *N*-(3-chloro-4-fluorobenzyl)-6-(2-((*trans*-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



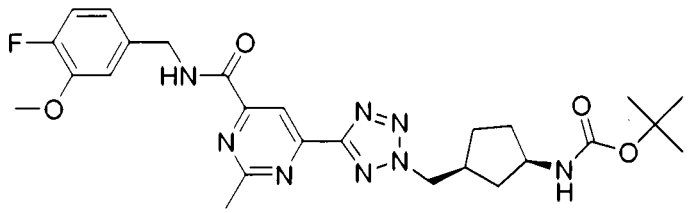
trans-(4-Hydroxy-4-(hydroxymethyl)cyclohexyl)methyl 4-methylbenzenesulfonate (100 mg, 0.318 mmol) was added to a solution of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (88 mg, 0.25 mmol) and triethylamine (140 mg, 1.38 mmol) in anhydrous dimethylacetamide (0.3 mL). The mixture was stirred overnight at 85 °C in a capped vial. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing product were neutralized by passing through a carbonate resin column and concentrated. The residue was slurried and decanted from ethyl ether three times and dried in a vacuum desiccator to afford the title compound as a white solid (35 mg). MS (ES+) *m/z* 490 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.61 (1 H, t, *J*=6.2 Hz), 8.41 (1 H, s), 7.57 (1 H, d, *J*=7.0 Hz), 7.37 (2 H, d, *J*=7.7 Hz), 4.75 (2 H, d, *J*=7.7 Hz), 4.52 (2 H, d, *J*=6.2 Hz), 4.33 (1 H, t, *J*=5.7 Hz), 4.00 (1 H, s), 3.30 (1 H, s), 2.83 (3 H, s), 2.15 (1 H, br. s.), 1.71 (2 H, d, *J*=8.4 Hz), 1.60 (2 H, d, *J*=10.2 Hz), 1.17 (2 H, d, *J*=9.5 Hz), 1.22 (3 H, d, *J*=12.8 Hz).

Example 31

rac-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((1*S,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



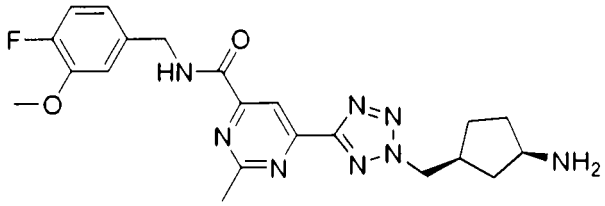
Step 1: Preparation of *tert*-butyl *rac*-(1*R**,3*S**)-3-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclopentylcarbamate



In a 20 ml scintillation vial with a magnetic stir bar at room temperature, *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step

2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (227 mg, 0.66 mmol) was combined with *tert*-butyl *rac*-(1*S**,3*R**)-3-(hydroxymethyl)cyclopentylcarbamate (193 mg, 0.90 mmol), polymer supported triphenylphosphine (247 mg, 0.531 mmol), and anhydrous tetrahydrofuran (15 ml) and stirred for 1 hour. The mixture was cooled to -10 °C. Di-*tert*-butyl azodicarboxylate (174 mg, 0.76 mmol) was added. After 2 h, the reaction mixture was allowed to warm to room temperature and continue to stir for 14 hours. The reaction mixture was concentrated, dissolved in acetonitrile and water and chromatographed by reversed phase preparative HPLC (Gilson, Delta Pak column, 30%-80% acetonitrile, 10 min hold, 45 min run, 10 min hold). The desired product fractions were collected, combine and concentrated under vacuum to afford the title compound as a white solid (80 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.17 - 1.29 (m, 1 H), 1.41 (s, 9 H), 1.44 - 1.59 (m, 1 H), 1.61 (s, 3 H), 1.70 (br. s., 1 H), 2.01 (br. s., 1 H), 2.16 (br. s., 1 H), 2.59 (d, *J*=7.52 Hz, 1 H), 2.83 (s, 1 H), 3.88 (s, 3 H), 4.50 (br. s., 1 H), 4.63 (d, *J*=6.18 Hz, 1 H), 4.97 (dd, *J*=7.52, 3.22 Hz, 2 H), 6.84 - 6.92 (m, 1 H), 6.98 (dd, *J*=8.06, 1.88 Hz, 1 H), 7.05 (dd, *J*=11.01, 8.32 Hz, 1 H), 8.18 - 8.30 (m, 1 H), 8.91 (s, 1 H). LC/MS (5%-95%, CH_3CN/H_2O,, 5 min.) 3.428 min, *m/z* 541 (M+H).

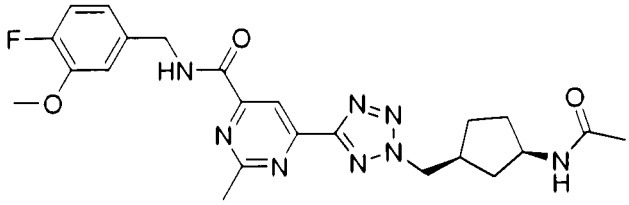
Step 2: Preparation of *rac*-*N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



Trifluoroacetic acid (21.1 mg, 0.19 mmol) was added to a solution of *tert*-butyl *rac*-(1*R**,3*S**)-3-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclopentylcarbamate (80 mg, 0.15 mmol) in dichloromethane (10 mL) and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated to afford the trifluoroacetic acid salt of the title compound (80 mg). LC/MS (5%-95%, CH_3CN/H_2O, 5 min.) 2.383 min, *m/z* 441 (M+H).

Example 32

rac-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((1*S**,3*R**)-3-acetamidocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

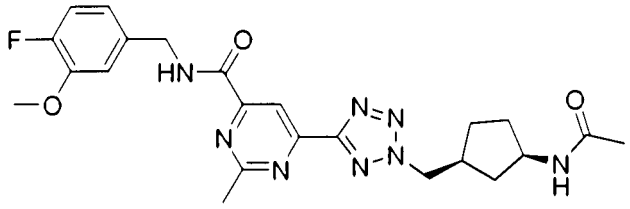


In a 2 dram vial with a magnetic stir bar at room temperature, *rac*-*N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide trifluoroacetic acid salt (prepared as described in Example 31) (40 mg, 0.7 mmol) was

dissolved in *N,N*-dimethyl formamide (2.0 ml). Acetic anhydride(9.21 mg, 0.09 mmol) and *N,N*-diisopropylethylamine (37.3 mg, 0.28 mmol) were added. The reaction mixture was concentrated, dissolved in acetonitrile and water and chromatographed by reversed phase preparative HPLC (30% - 70% acetonitrile/water, 10 min hold, 45 min run, 10 min hold). Fractions containing the desired product were collected and concentrated under vacuum to afford the title compound as a white solid (10.0 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 - 1.27 (m, 2 H), 1.43 - 1.55 (m, 2 H), 1.76 (s, 5 H), 2.01 (d, *J*=12.8 Hz, 1 H), 2.83 (s, 3 H), 3.82 (s, 3 H), 4.00 (d, *J*=7.3 Hz, 1 H), 4.51 (d, *J*=6.2 Hz, 2 H), 4.82 (br. s., 1 H), 4.83 (d, *J*=2.2 Hz, 1 H), 6.92 (d, *J*=4.4 Hz, 1 H), 7.16 (td, *J*=12.0, 8.6 Hz, 2 H), 7.84 (br. s., 1 H), 8.42 (s, 1 H), 9.48 - 9.54 (m, 1 H). LC/MS (5%-95%, CH_3CN/H_2O, 5 min.) 2.842 min, *m/z* 441 (M+H).

Example 33

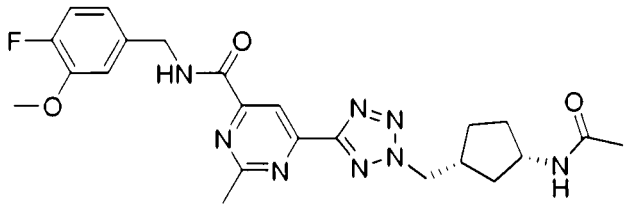
(+)-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((1*S,3*R**)-3-acetamidocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



rac-N-(4-Fluoro-3-methoxybenzyl)-6-(2-(((1*S**,3*R**)-3-acetamidocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 32) was separated by supercritical fluid chiral chromatography (Chiralcel AD-H column, 30 x 250 mm, 20% 2-propanol, 70 mL/min). Isolation of the first eluting isomer afforded the title compound (49.4 mg). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.813 min., *m/z* 483 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (br. s., 1 H), 1.47 (d, *J*=5.49 Hz, 1 H), 1.70 (br. s., 1 H), 1.76 (s, 3 H), 2.01 (br. s., 1 H), 2.61 (br. s., 1 H), 2.82 (s, 2 H), 3.37 (s, 9 H), 3.82 (s, 2 H), 4.00 (br. s., 1 H), 4.50 (d, *J*=6.22 Hz, 1 H), 4.81 (dd, *J*=7.14, 2.01 Hz, 1 H), 6.90 (br. s., 1 H), 7.16 (d, *J*=2.20 Hz, 1 H), 7.85 (br. s., 1 H), 9.51 (s, 1 H). $[\alpha]_D^{21°C}$ = +3.7° (c = 0.7, dichloromethane)

Example 34

(-)-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((1*R,3*S**)-3-acetamidocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

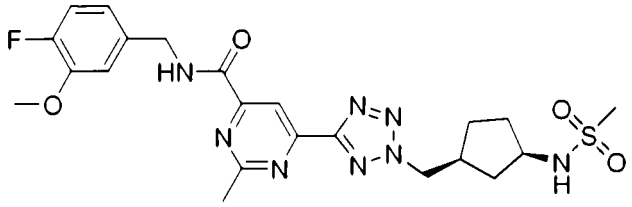


rac-N-(4-Fluoro-3-methoxybenzyl)-6-(2-(((1*S**,3*R**)-3-acetamidocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 32) was separated by supercritical fluid chiral chromatography (Chiralcel AD-H column, 30 x 250 mm, 20% 2-propanol, 70 mL/min). Isolation of the second eluting isomer afforded the title compound (44.8 mg).

LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.813 min., *m/z* 483 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (br. s., 1 H), 1.47 (d, *J*=5.89 Hz, 1 H), 1.70 (br. s., 1 H), 1.76 (s, 3 H), 2.01 (br. s., 1 H), 2.61 (br. s., 1 H), 2.83 (s, 2 H), 3.37 (s, 9 H), 3.82 (s, 2 H), 4.10 (br. s., 1 H), 4.51 (d, *J*=6.62 Hz, 1 H), 4.91 (dd, *J*=7.54, 2.01 Hz, 1 H), 6.90 (br. s., 1 H), 7.18 (d, *J*=2.50 Hz, 1 H), 7.86 (br. s., 1 H), 9.53 (s, 1 H). $[\alpha]_D^{21°C}$ = 4.6° (c = 0.7, dichloromethane)

Example 35

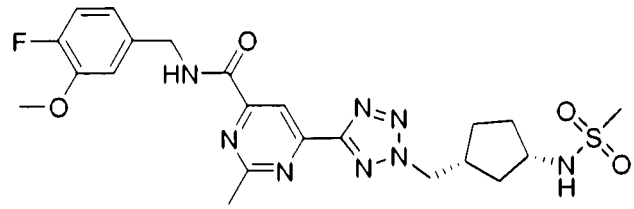
***rac-N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-(((1*S**,3*R**)-3-(methylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**



In a 2 dram vial with a magnetic stir bar at room temperature, *rac-N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide trifluoroacetic acid salt (prepared as described in Example 31) (40 mg, 0.7 mmol) was dissolved in *N,N*-dimethyl formamide (2.0 ml). *N,N*-Diisopropylethylamine (28.0 mg, 0.216 mmol) and methane sulfonyl chloride (10.3 mg, 0.09 mmol) was added and the mixture was stirred for 1 h. The reaction mixture was concentrated, dissolved in acetonitrile and water and chromatographed by reversed phase preparative HPLC (Gilson, Delta Pak column, 30%-70% acetonitrile, 10 min hold, 45 min run, 10 min hold) Fractions containing the desired product were collect and concentrated under vacuum to afford the title compound as a white solid (10.4 mg). LC/MS (5%-95%, CH_3CN/H_2O, 5 min.) 2.925 min, *m/z* 519 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (t, *J*=6.2 Hz, 1 H), 8.40 (s, 1 H), 7.06 - 7.19 (m, 3 H), 6.86 - 6.91 (m, 1 H), 4.80 (d, *J*=7.3 Hz, 2 H), 4.48 (d, *J*=6.2 Hz, 2 H), 3.80 (s, 3 H), 3.59 - 3.69 (m, 1 H), 2.85 (s, 3 H), 2.81 (s, 3 H), 2.54 - 2.63 (m, 1 H), 2.02 - 2.11 (m, 1 H), 1.83 - 1.94 (m, 1 H), 1.62 - 1.73 (m, 1 H), 1.43 - 1.60 (m, 2 H), 1.25 - 1.36 (m, 1 H).

Example 36

(+)-*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-(((1*R,3*S**)-3-(methylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**

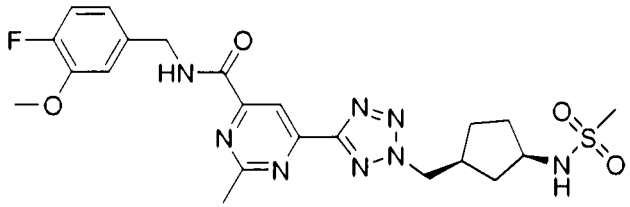


rac-N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-(((1*S**,3*R**)-3-(methylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 35) was separated by supercritical fluid chiral chromatography (Chiralcel OJ-H column, 30 x 250 mm, 25% methanol, 70 mL/min). Isolation of the first eluting isomer afforded the title compound (34.1 mg). MS (ES+) *m/z* 519 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.45 (t, *J*=6.2

Hz, 1 H), 8.37 (s, 1 H), 7.03 - 7.16 (m, 3 H), 6.83 - 6.89 (m, 1 H), 4.77 (d, *J*=7.3 Hz, 2 H), 4.46 (d, *J*=6.2 Hz, 2 H), 3.78 (s, 3 H), 3.57 - 3.65 (m, 1 H), 2.83 (s, 3 H), 2.78 (s, 3 H), 2.51 - 2.60 (m, 1 H), 2.00 - 2.09 (m, 1 H), 1.82 - 1.91 (m, 1 H), 1.59 - 1.70 (m, 1 H), 1.41 - 1.58 (m, 2 H), 1.22 - 1.33 (m, 1 H). $[\alpha]_D^{21°C}$ = +2.9° (c = 0.7, dichloromethane)

Example 37

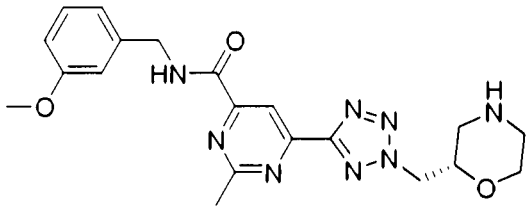
(-)-*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-(((1*S,3*R**)-3-(methylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**



rac-*N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-(((1*S**,3*R**)-3-(methylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 35) was separated by supercritical fluid chiral chromatography (Chiralcel OJ-H column, 30 x 250 mm, 25% methanol, 70 mL/min). Isolation of the second eluting isomer afforded the title compound (36.9 mg). MS (ES+) *m/z* 519 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.50 (t, *J*=6.2 Hz, 1 H), 8.42 (s, 1 H), 7.08 - 7.21 (m, 3 H), 6.88 - 6.94 (m, 1 H), 4.82 (d, *J*=7.3 Hz, 2 H), 4.51 (d, *J*=6.2 Hz, 2 H), 3.82 (s, 3 H), 3.62 - 3.70 (m, 1 H), 2.87 (s, 3 H), 2.83 (s, 3 H), 2.55 - 2.65 (m, 1 H), 2.04 - 2.13 (m, 1 H), 1.86 - 1.96 (m, 1 H), 1.65 - 1.74 (m, 1 H), 1.46 - 1.62 (m, 2 H), 1.27 - 1.37 (m, 1 H). $[\alpha]_D^{21°C}$ = -4.8° (c = 0.7, dichloromethane)

Example 38

***N*-(3-Methoxybenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**

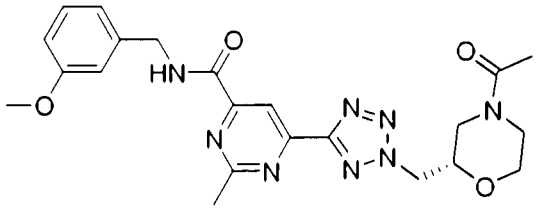


N-(3-Methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (0.656 g, 2.02 mmol) and (*S*)-*tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (438 mg, 2.02 mmol) were taken up in tetrahydrofuran (25 mL) and treated with polymer supported triphenylphosphine (1.34 g, 3.02 mmol). After stirring for 30 min at room temperature, di-*tert*-butyl azodicarboxylate (557 mg, 2.42 mmol) was added. After 36 h at room temperature, the reaction was filtered to remove the resin. The filtrate was concentrated to a crude residue as a yellow oil. The residue was purified via normal phase chromatography (silica, 0-75% ethyl acetate/heptane with a trace 1% methanol ran through entire gradient). Fractions containing (2*S*)-*tert*-butyl 2-((5-(6-((3-methoxybenzyl)carbamoyl)-2-

methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate were concentrated. The residue was taken up in dichloromethane (5 mL) and stirred with trifluoroacetic acid (1 mL). After 3 h stirring at room temperature, additional dichloromethane (5 mL) was added and the reaction was neutralized with 2.5 N aqueous NaOH to pH 7-8. The organic layer was separated and washed with water, dried over sodium sulfate, and concentrated to afford a regioisomeric mixture of products (0.28 g) containing the title compound. LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.9 min, *m/z* 525 (M+H).

Example 39

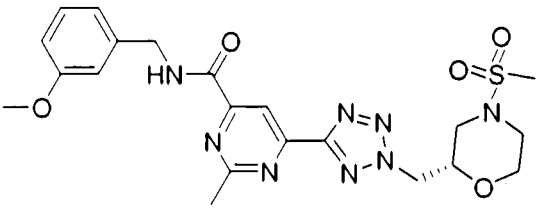
***N*-(3-Methoxybenzyl)-6-(2-(((*S*)-4-acetylmorpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



A regioisomeric mixture (0.13 g) containing *N*-(3-methoxybenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 38) was taken up in dichloromethane (2 mL) and treated with triethylamine (0.047 mL, 0.38 mmol) and a solution of acetyl chloride (0.033 mL, 0.46 mmol) in dichloromethane (1 mL). After stirring for 2 h at room temperature, the mixture was concentrated and purified via reverse phase chromatography (40-60% acetonitrile/water, 45 min). Under these conditions, isolation of the first compound to elute afforded the title compound as a white solid (31 mg, 20%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.52 min, *m/z* 467 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.01 (3 H, d, J=17.0 Hz), 2.56 - 2.74 (1 H, m), 2.81 (3 H, s), 3.40 (1 H, d, J=11.0 Hz), 3.63 (1 H, d, J=11.0 Hz), 3.71 (3 H, s), 3.79 (1 H, d, J=7.9 Hz), 3.88 - 4.13 (2 H, m), 4.37 (1 H, d, J=14.3 Hz), 4.49 (2 H, d, J=6.2 Hz), 4.85 - 5.07 (2 H, m), 6.80 (1 H, d, J=7.9 Hz), 6.91 (2 H, br. s.), 7.14 - 7.29 (1 H, m), 8.40 (1 H, s), 9.47 (1 H, s).

Example 40

***N*-(3-Methoxybenzyl)-2-methyl-6-(2-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**

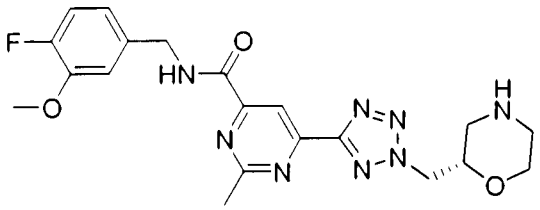


A regioisomeric mixture (0.13 g) containing *N*-(3-methoxybenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 38) was taken up in dichloromethane (2 mL) and treated with triethylamine (0.047 mL, 0.38 mmol) and a solution of methane sulfonyl chloride (0.026 mL, 0.32 mmol) in dichloromethane (1 mL). After stirring for 2 h at room temperature, the mixture was concentrated and purified via reverse phase chromatography (40-60% acetonitrile/water, 45 min). Under these conditions, isolation of the first

compound to elute afforded the title compound as a white solid (34 mg, 22%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.99 min, *m/z* 503 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.68 - 2.88 (5 H, m), 2.91 (3 H, s), 3.34 (1 H, br. s.), 3.50 (1 H, t, J=10.8 Hz), 3.67 (1 H, d, J=11.7 Hz), 3.71 (3 H, s), 3.89 (1 H, d, J=11.0 Hz), 4.13 (1 H, t, J=9.0 Hz), 4.49 (2 H, d, J=6.4 Hz), 4.89 - 5.00 (1 H, m), 5.03 - 5.13 (1 H, m), 6.80 (1 H, d, J=6.6 Hz), 6.91 (2 H, br. s.), 7.22 (1 H, t, J=8.1 Hz), 8.40 (1 H, s), 9.47 (1 H, s).

Example 41

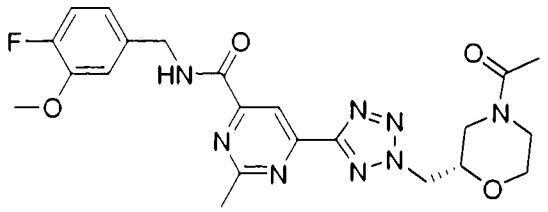
***N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**



N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (1.00 g, 2.91 mmol) and (*S*)-*tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (633 mg, 2.91 mmol) were taken up in tetrahydrofuran (50 mL) and treated with polymer supported triphenylphosphine (1.94 g, 4.37 mmol). After stirring for 30 min at room temperature, di-*tert*-butyl azodicarboxylate (895 mg, 3.50 mmol) was added. After 15 h at room temperature, the reaction was filtered to remove the resin. The filtrate was concentrated to a crude oily residue. The residue was purified via normal phase chromatography (silica, 0-75% ethyl acetate/heptane with a trace 1% methanol ran through entire gradient). Fractions containing (2*S*)-*tert*-butyl 2-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate were concentrated. The residue was taken up in dichloromethane (10 mL) and stirred with trifluoroacetic acid (3 mL). After 3 h stirring at room temperature, additional dichloromethane (5 mL) was added and the reaction was neutralized with 2.5 N aqueous NaOH to pH 7-8. The organic layer was separated and washed with water (2 mL), dried over sodium sulfate, and concentrated to afford a regioisomeric mixture of products (0.57 g) containing the title compound. LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.33 min, *m/z* 443 (M+H).

Example 42

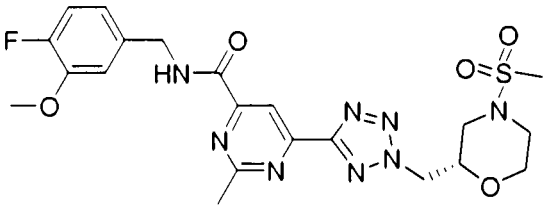
N-(4-fluoro-3-methoxybenzyl)-6-(2-(((S)-4-acetylmorpholin-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



A regioisomeric mixture (0.065 g) containing *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 41) was taken up in dichloromethane (2 mL) and treated with triethylamine (0.033 mL, 0.24 mmol) and a solution of acetyl chloride (0.016 mL, 0.23 mmol) in dichloromethane (1 mL). After stirring for 2 h at room temperature, the mixture was concentrated and the crude residue was purified via reverse phase chromatography (40-60% acetonitrile/water, 45 min). Under these conditions, isolation of the first peak to elute afforded the title compound as a white solid (35 mg, 49%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.75 min, m/z 485 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.94 - 2.02 (3 H, m), 2.58 - 2.73 (1 H, m), 2.85 (3 H, s), 3.04 - 3.20 (1 H, m), 3.60 (1 H, d, J=13.2 Hz), 3.67 - 3.76 (1 H, m), 3.80 (3 H, s), 3.83 - 3.93 (1 H, m), 3.97 - 4.06 (1 H, m), 4.40 (1 H, d, J=13.2 Hz), 4.49 (2 H, d, J=6.4 Hz), 4.93 - 5.01 (1 H, m), 5.08 (1 H, d, J=9.7 Hz), 6.83 - 6.92 (1 H, m), 7.06 - 7.20 (2 H, m), 8.46 (1 H, s), 9.54 (1 H, t, J=6.0 Hz).

Example 43

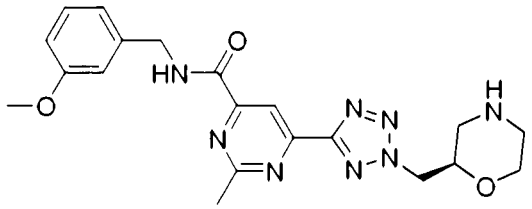
N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



A regioisomeric mixture (0.15 g) containing *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 41) was taken up in dichloromethane (3 mL) and treated with triethylamine (0.052 mL, 0.37 mmol) and a solution of methane sulfonyl chloride (0.029 mL, 0.34 mmol) in dichloromethane (1 mL). After stirring for 2 h at room temperature, the mixture was concentrated and purified via reverse phase chromatography (40-60% acetonitrile/water, 55 min). Under these conditions, isolation of the first eluted compound afforded the title compound as a white solid (68 mg, 39%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.94 min. *m/z* 521 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 - 2.88 (5 H, m), 2.91 (3 H, s), 3.32 (1 H, d, J=11.3 Hz), 3.44 - 3.55 (1 H, m), 3.65 (1 H, s), 3.80 (3 H, s), 3.89 (1 H, d, J=11.7 Hz), 4.06 - 4.16 (1 H, m), 4.48 (2 H, d, J=6.4 Hz), 4.89 - 4.99 (1 H, m), 5.01 - 5.12 (1 H, m), 6.89 (1 H, br. s.), 7.06 - 7.21 (2 H, m), 8.40 (1 H, s), 9.49 (1 H, t, J=6.4 Hz).

Example 44

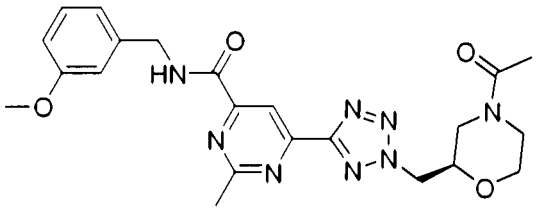
N-(3-Methoxybenzyl)-2-methyl-6-(2-((*R*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



N-(3-Methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (1.00 g, 3.07 mmol) and (*R*)-*tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (801 mg, 3.69 mmol) were taken up in tetrahydrofuran (50 mL) and treated with polymer supported triphenylphosphine (2.05 g, 4.61 mmol). After stirring for 30 min at room temperature, di-*tert*-butyl azodicarboxylate (849 mg, 3.69 mmol) was added. After 15 h at room temperature, the reaction was filtered to remove the resin. The filtrate was concentrated to a crude oily residue. The residue was purified via normal phase chromatography (silica, 0-75% ethyl acetate/heptane with a trace 1% methanol ran through entire gradient). Fractions containing (2*R*)-*tert*-butyl 2-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate were concentrated. The residue was taken up in dichloromethane (10 mL) and stirred with trifluoroacetic acid (3 mL). After 3 h stirring at room temperature, additional dichloromethane (5 mL) was added and the reaction was neutralized with 2.5 N aqueous NaOH to pH 7-8. The organic layer was separated, washed with water, dried over sodium sulfate, and concentrated to afford a regioisomeric mixture of products (0.85 g) containing the title compound. LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.69 min, *m/z* 425 (M+H).

Example 45

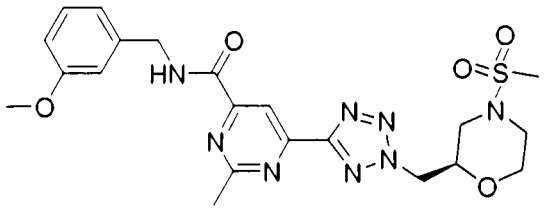
N-(3-Methoxybenzyl)-6-(2-(((*R*)-4-acetylmorpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



A regioisomeric mixture (0.42 g) containing *N*-(3-methoxybenzyl)-2-methyl-6-(2-((*R*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 44) was taken up in dichloromethane (4 mL) and treated with triethylamine (0.193 mL, 1.4 mmol) and a solution of acetyl chloride (0.077 mL, 0.1.1 mmol) in dichloromethane (1 mL). After stirring for 2 h at room temperature, the mixture was concentrated and purified via reverse phase chromatography (40-60% acetonitrile/water, 60 min). Under these conditions, isolation of the first compound to elute afforded the title compound as a white solid (67 mg, 15%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.66 min, *m/z* 467 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.01 (3 H, d, J=17.0 Hz), 2.59 - 2.73 (1 H, m), 2.81 (3 H, s), 3.42 (1 H, t, J=11.0 Hz), 3.63 (1 H, d, J=13.0 Hz), 3.71 (3 H, s), 3.80 (1 H, d, J=9.7 Hz), 3.89 - 4.13 (2 H, m), 4.37 (1 H, d, J=13.0 Hz), 4.49 (2 H, d, J=6.4 Hz), 4.86 - 5.09 (2 H, m), 6.80 (1 H, d, J=7.7 Hz), 6.91 (2 H, br. s.), 7.22 (1 H, t, J=8.1 Hz), 8.40 (1 H, s), 9.47 (1 H, t, J=6.4 Hz).

Example 46

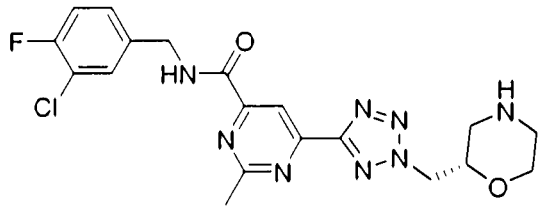
N-(3-Methoxybenzyl)-2-methyl-6-(2-(((*S*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



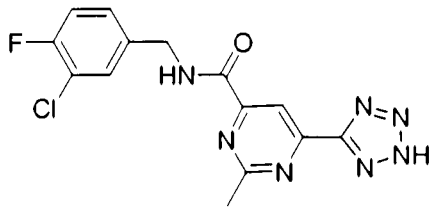
A regioisomeric mixture (0.42 g) containing *N*-(3-methoxybenzyl)-2-methyl-6-(2-((*R*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 44) was taken up in dichloromethane (5 mL) and treated with triethylamine (0.193 mL, 1.40 mmol) and a solution of methane sulfonyl chloride (0.087 mL, 1.1 mmol) in dichloromethane (1 mL). After stirring for 2 h at room temperature, the mixture was concentrated and purified via reverse phase chromatography (40-60% acetonitrile/water, 60 min). Under these conditions, isolation of the first compound to elute afforded the title compound as a white solid (43 mg, 9%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.95 min, *m/z* 503 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.71 - 2.88 (5 H, m), 2.91 (3 H, s), 3.32 (1 H, d, J=13.0 Hz), 3.42 - 3.54 (1 H, m), 3.67 (1 H, d, J=11.7 Hz), 3.71 (3 H, s), 3.89 (1 H, d, J=12.1 Hz), 4.13 (1 H, t, J=9.0 Hz), 4.49 (2 H, d, J=6.4 Hz), 4.85 - 5.01 (1 H, m), 5.01 - 5.12 (1 H, m), 6.80 (1 H, d, J=8.1 Hz), 6.91 (2 H, br. s.), 7.22 (1 H, t, J=8.1 Hz), 8.40 (1 H, s), 9.47 (1 H, t, J=6.3 Hz).

Example 47

***N*-(3-Chloro-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**



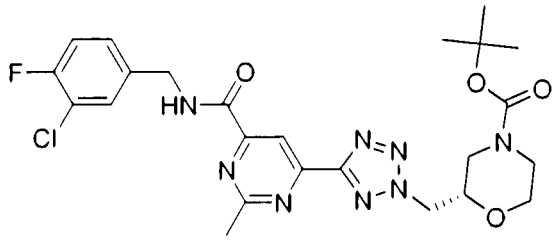
Step 1: Preparation of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



Methyl 2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxylate (prepared as described in step 1 of the synthesis of *N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 17) (3.03 g, 13.8 mmol), 3-chloro-4-fluorobenzylamine (2.31 g, 14.4 mmol) and triethylamine (2.78 g, 27.5

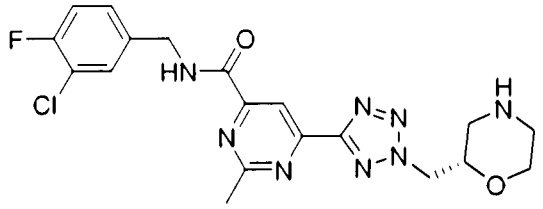
mmol) were combined in dimethylacetamide (30 mL). The resulting mixture was stirred at 25 °C for 18 h. The solvent was removed and the product was slurried with 3N hydrochloric acid (100 mL). The precipitate was collected by suction filtration, washed with water (2 x 25 mL) and dried under vacuum to afford the title compound as a tan solid (2.08 mg, 44%). LC/MS (10%-90% CH_3CN/H_2O, 4 min): 2.74 min, *m/z* 348 (M+H).

Step 2: Preparation of (2*S*)-*tert*-butyl 2-((5-(6-((3-chloro-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate



N-(3-Chloro-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (750 mg, 2.16 mmol) and (*S*)-*tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (562 mg, 2.59 mmol) were taken up in tetrahydrofuran (40 mL) and treated with polymer supported triphenylphosphine (1.44 g, 3.24 mmol). After stirring for 30 min at room temperature, di-*tert*-butyl azodicarboxylate (596 mg, 2.59 mmol) was added. After 36 h at room temperature, the reaction was filtered to remove the resin. The filtrate was concentrated and the residue was purified via normal phase chromatography (silica, 0-75% ethyl acetate/heptane with a trace 1% methanol ran through entire gradient). The resulting regioisomeric mixture was further purified by reverse phase chromatography (40-65%, acetonitrile/water, 60 minutes). Isolation of the first compound to elute afforded the title compound (0.10 g, 8%).

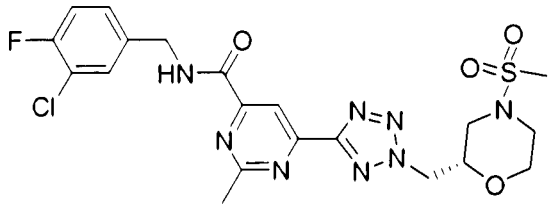
Step 3: Preparation of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



(2*S*)-*tert*-Butyl 2-((5-(6-((3-chloro-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate, (0.10 g, 0.18 mmol) was taken up in dichloromethane (1 mL) and stirred with trifluoroacetic acid (0.5 mL). After 3 h stirring at room temperature, additional dichloromethane (5 mL) was added and the reaction was neutralized with 2.5 N aqueous NaOH to pH 7-8. The organic layer was separated, washed with water, dried over sodium sulfate, and concentrated to afford the title compound as an oil (0.065 g, 7%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.30 min, *m/z* 447 (M+H).

Example 48

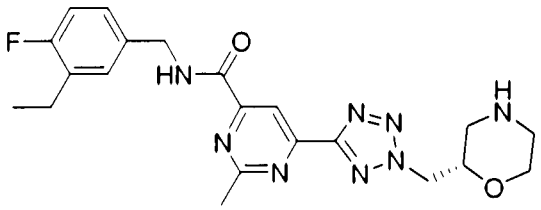
***N*-(3-Chloro-4-fluorobenzyl)-2-methyl-6-(2-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide**



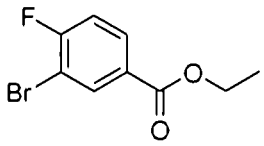
N-(3-Chloro-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 47) (0.065 g, 0.15 mmol) was taken up in dichloromethane (2 mL) and treated with triethylamine (0.018 mL, 0.11 mmol) and a solution of methane sulfonyl chloride (13.5 mg, 0.19 mmol) in dichloromethane (0.5 mL). After stirring for 2 h at room temperature, the mixture was concentrated. The resulting residue was triturated with diethyl ether to afford the title compound as a beige solid (38.5 mg, 68%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 4.23 min, 525 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.71 - 2.87 (5 H, m), 2.89 (3 H, s), 3.27 - 3.33 (1 H, m), 3.41 - 3.52 (1 H, m), 3.64 (1 H, d, J=11.5 Hz), 3.86 (1 H, d, J=9.2 Hz), 4.06 - 4.15 (1 H, m), 4.47 (2 H, d, J=6.2 Hz), 4.86 - 4.97 (1 H, m), 5.00 - 5.08 (1 H, m), 7.28 - 7.36 (2 H, m), 7.52 (1 H, d, J=7.9 Hz), 8.37 (1 H, s), 9.56 (1 H, t, J=6.2 Hz)

Example 49

N-(3-Ethyl-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide

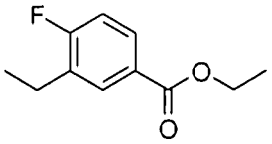


Step 1: Preparation of ethyl 3-bromo-4-fluorobenzoate



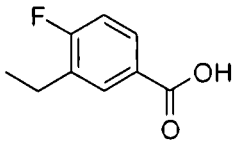
To a solution of 3-bromo-4-fluorobenzoic acid (48 g, 219.18 mmol) in ethanol (250 mL) was added conc. H_2SO_4 (15 mL) and the mixture was refluxed for 24 h. The reaction mixture was concentrated under reduced pressure and the residue was extracted with dichloromethane (2 x 300 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution followed by brine solution, dried over sodium sulfate, and concentrated under reduced pressure to afford the title compound (50.5 g, 93 %).

Step 2: Preparation of ethyl 3-ethyl-4-fluorobenzoate



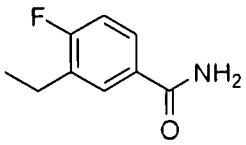
Ethylmagnesium bromide (2.0 M in ether, 137.61 mL, 275.23 mmol) was added slowly to a solution of anhydrous $ZnCl_2$ (37.43 g, 275.23 mmol) in dry tetrahydrofuran (200 mL) under argon atmosphere. The resulting white slurry was stirred at 50 °C for 3 h. In a separate flask, a solution of ethyl 3-bromo-4-fluorobenzoate (17 g, 68.80 mmol) in dry tetrahydrofuran (50 mL) was sequentially treated with $PdCl_2$(dppf) (2.8 g, 3.44 mmol) and copper(I) iodide (0.78 g, 4.12 mmol) under an argon atmosphere and the mixture was stirred at room temperature for 30 min. The alkyl zinc slurry was added to the ester mixture at room temperature. The resulting brown slurry was stirred in the dark at room temperature for 48 h. The reaction mixture was concentrated under vacuum to give a dark brown residue which was taken up in ethyl acetate (750mL) and washed sequentially with 1N hydrochloric acid (300 mL) solution, sat. $NaHCO_3$ (200 mL) solution and brine (250 mL) solution. The organic layer was concentrated in vacuo to obtain crude material which was purified by column chromatography over silica gel (100-200 mesh) using 5 % EtOAc in hexane as an eluent to afford the title compound (12.5 g, 93 %).

Step 3: Preparation of 3-ethyl-4-fluorobenzoic acid



Ethyl 3-ethyl-4-fluorobenzoate (12.5 g, 63.7 mmol) and lithium hydroxide monohydrate were taken up in dioxane (250 mL) and water (1/1) and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was acidified with 1N hydrochloric acid under ice-water cold conditions. The mixture was extracted with dichloromethane (2 x 150 mL). The combined organic layers were washed with brine solution, dried over sodium sulfate and concentrated to afford the title compound (10 g, 95 %).

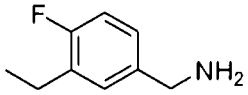
Step 4: Preparation of 3-ethyl-4-fluorobenzamide



3-Ethyl-4-fluorobenzoic acid (10.3 g, 61.3 mmol) was taken up in $SOCl_2$ (150 mL) and then refluxed for 4 h. The $SOCl_2$ was removed under reduced pressure and the residue was dissolved in dry acetonitrile (100 mL). Ammonia gas was passed through the solution at –78 °C for 10 min. and the reaction mixture was allowed to warm to room temperature very slowly and stirred overnight. The reaction mixture was concentrated to a residue which was extracted with dichloromethane (2 x 100 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution followed by brine solution,

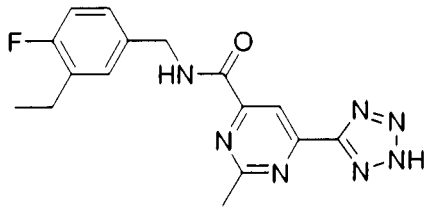
dried over sodium sulfate, and concentrated. The residue was washed with hexane to afford the title compound (9.0 g, 88 %).

Step 5: Preparation of (3-ethyl-4-fluorophenyl)methanamine



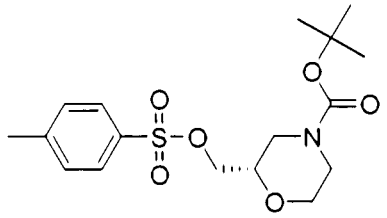
Borane dimethylsulfide complex (94%, 22 mL, 215.49 mmol) was added slowly to a solution of 3-ethyl-4-fluorobenzamide (9.0 g, 53.87 mmol) in dichloromethane (200 mL) under ice-cold condition. After the addition, the reaction mixture was stirred for 1 h at room temperature and then it was refluxed for 24 h. The reaction mixture was cooled to 0 °C and washed with $NaHCO_3$ solution followed by brine. The organic layer was concentrated to a crude material which was purified by column chromatography over silica gel (100-200 mesh) using 15 % dichloromethane in hexane as an eluent to afford (3-ethyl-4-fluorophenyl)methanamine as a solid (4.8 g, 58 %). MS (ES+) *m/z* 154 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (t, 3 H) 1.76 (br. s., 1 H) 2.67 (q, 2 H), 3.77 (br. s., 1 H), 3.88 (s, 2 H), 7.01-7.15 (m, 3 H)

Step 6: Preparation of *N*-(3-ethyl-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



A solution of methyl 2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxylate (prepared as described in step 1 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 17) (1.0 g, 4.54 mmol) in dimethylformamide (5 mL) was treated with (3-ethyl-4-fluorophenyl)methanamine (2.09 g, 13.6 mmol) and heated to 65 °C for 3 days. The mixture was cooled to room temperature. Excess 2.5 N NaOH was added to the mixture. The product mixture was washed with ethyl acetate (3 x 10 mL). Concentrated hydrochloric acid was added and the resulting precipitate was filtered, washed with water and dried in vacuo to afford the title compound (367 mg, 24%).

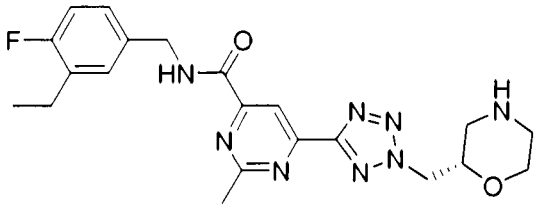
Step 7: Preparation of (*S*)-*tert*-butyl 2-((tosyloxy)methyl)morpholine-4-carboxylate



(*S*)-*tert*-Butyl 2-(hydroxymethyl)morpholine-4-carboxylate (5.00 g, 23.0 mmol) was taken up in pyridine (10 mL) and then treated with *p*-toluene sulfonyl chloride (5.70 g, 29.9 mmol). The reaction was allowed to stir at room temperature for 15 h. The mixture was poured into cold water (50 mL) and

extracted with ethyl acetate (2 × 50 mL). The organic layers were washed with water (3 × 40 mL) followed by brine (40 mL), dried over sodium sulfate, and concentrated. The residue was purified on normal phase silica (50 g, 0-75% ethyl acetate/heptane) to afford the title compound as a white solid (7.3 g, 85%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.17 min, *m/z* 394 (M+Na).

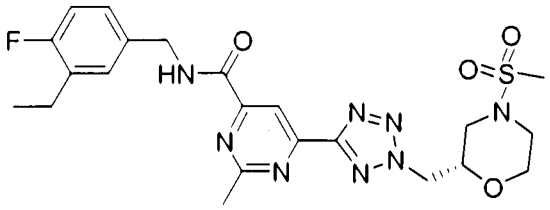
Step 8: Preparation of *N*-(3-ethyl-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



N-(3-Ethyl-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (430 mg, 1.26 mmol) and (*S*)-*tert*-butyl 2-((tosyloxy)methyl)morpholine-4-carboxylate (515 mg, 1.39 mmol) were taken up in triethylamine (7.0 mL) and dimethylformamide (0.010 mL). The reaction was stirred at 80 °C for 15 h and was then concentrated. This residue was purified on normal phase silica (20 g, 0-75% ethyl acetate/heptane with 1% methanol trace running throughout gradient). Fractions containing (2*S*)-*tert*-butyl 2-((5-(6-((3-ethyl-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate were concentrated. The residue was taken up in dichloromethane (4 mL) and stirred with trifluoroacetic acid (1 mL) for 2 h at room temperature. Additional dichloromethane (5 mL) was added and the reaction was neutralized with 2.5 N aqueous NaOH to pH 7-8. The organic layer was separated, dried over sodium sulfate, and concentrated to afford a regioisomeric mixture of products (0.41 g) containing the title compound. LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.46 min, *m/z* 441 (M+H).

Example 50

N-(3-Ethyl-4-fluorobenzyl)-2-methyl-6-(2-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide

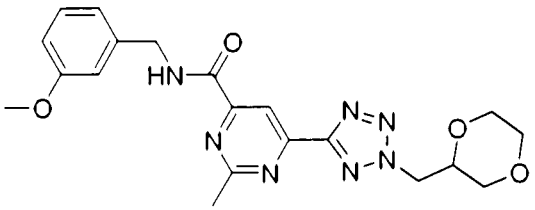


A regioisomeric mixture (0.40 g) containing *N*-(3-ethyl-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in Example 49) (0.40 g, 0.91 mmol) was taken up in dichloromethane (2 mL) and treated with triethylamine (0.512 mL, 1.09 mmol) and a solution of methane sulfonyl chloride (114 mg, 1.00 mmol) in dichloromethane (0.5 mL). After stirring for 2 h at room temperature, the mixture was concentrated and purified via reverse phase chromatography (40-65% acetonitrile/water, 60 minutes) to afford the title compound as a white solid (36 mg, 8%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 4.41 min, 519 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.16 (2 H, m), 1.21 (2 H, d, J=5.3 Hz), 2.55 (1 H, s), 2.70 - 2.83 (4 H,

m), 2.89 (3 H, s), 3.21 - 3.35 (1 H, m), 3.40 - 3.52 (1 H, m), 3.59 - 3.71 (1 H, m), 3.86 (1 H, d, J=11.0 Hz), 4.01 - 4.14 (1 H, m), 4.44 (2 H, d), 4.87 - 4.97 (1 H, m), 4.99 - 5.07 (1 H, m), 6.95 - 7.04 (2 H, m), 7.16 (1 H, d, J=5.5 Hz), 7.22 - 7.29 (1 H, m), 8.38 (1 H, s), 9.46 (1 H, t, J=6.5 Hz)

Example 51

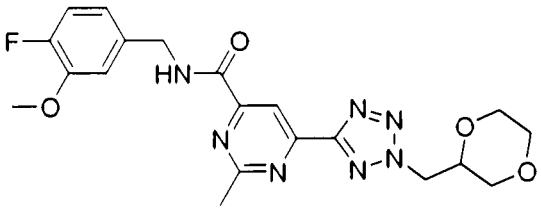
***rac*-6-(2-((1,4-Dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide**



A mixture of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (300 mg, 0.92 mmol), 2-iodomethyl-1,4-dioxane (421 mg, 1.84 mmol), triethylamine (0.51 mL, 3.69 mmol) and dimethylacetamide (0.5 mL) was stirred at 85 °C for 2 days. The mixture was purified by reverse phase preparative HPLC. Fractions containing the desired product were combined, isolated and concentrated to afford the title compound as a white solid (146 mg, 37%). LC/MS (5%-95% CH_3CN/H_2O, 4 min.; 95% CH_3CN, 1 min.): 2.75 min, *m/z* 426 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (s, 3 H), 3.38 - 3.59 (m, 3 H), 3.65 (d, *J*=10.6 Hz, 1 H), 3.73 - 3.75 (m, 4 H), 3.91 (dd, *J*=11.5, 2.38 Hz, 1 H), 4.11 - 4.20 (m, 1 H), 4.51 (d, *J*=6.2 Hz, 2 H), 4.93 (d, *J*=6.2 Hz, 2 H), 6.89 - 6.96 (m, 2 H), 7.24 (t, *J*=8.05 Hz, 1 H), 8.42 (s, 1 H), 9.49 (t, *J*=6.4 Hz, 1 H).

Example 52

***rac*-6-(2-((1,4-Dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide**

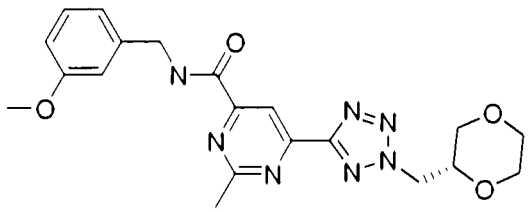


A mixture of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (300 mg, 0.87 mmol), 2-iodomethyl-1,4-dioxane (399 mg, 1.75 mmol), triethylamine (0.97 mL, 6.99 mmol) and dimethylacetamide (0.5 mL) was stirred at 85 °C for 2 days. The mixture was purified by reverse phase preparative HPLC. Fractions containing the desired product were combined, isolated and concentrated to afford the title compound as a white solid (147 mg, 38%). LC/MS (5%-95% CH_3CN/H_2O, 4 min.; 95% CH_3CN, 1 min.): 2.78 min, *m/z* 444 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ

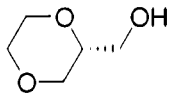
ppm 2.83 (s, 3 H), 3.38 - 3.59 (m, 3 H), 3.65 (d, *J*=10.6 Hz, 1 H), 3.73 (d, *J*=11.0 Hz, 1 H), 3.83 (s, 3 H), 3.91 (dd, *J*=11.5, 2.4 Hz, 1 H), 4.09 - 4.21 (m, 1 H), 4.51 (d, *J*=6.2 Hz, 2 H), 4.93 (d, *J*=6.2 Hz, 2 H), 6.87 - 6.95 (m, 1 H), 7.09 - 7.22 (m, 2 H), 8.42 (s, 1 H), 9.51 (t, *J*=6.2 Hz, 1 H).

Example 53

6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide

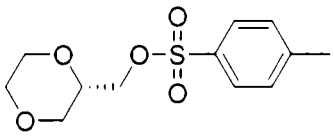


Step 1: Preparation of (R)-(1,4-dioxan-2-yl)methanol



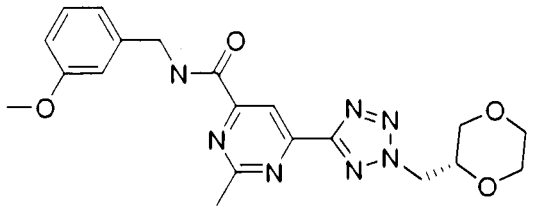
S-Epichlorohydrin (8.00 g, 86.5 mmol) was added drop wise to a stirred solution of chloro-2-ethanol (20.90 g, 259.0 mmol) and boron trifluoride diethyl etherate (0.12 mL, 1.3 mmol) at 45 °C. After 1.5 hours, the reaction mixture was allowed to cool and was diluted with ethyl ether (50 mL). The mixture was washed with water (25 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure with no heating to afford the intermediate, (*S*)-2-((2-chloroethoxy)methyl)oxirane. The oxirane was added drop wise to a stirred solution of sodium hydroxide (8.65 g, 216 mmol) in water (12 mL). The reaction mixture was stirred at room temperature for 2 hours and then was heated at 90 °C for 2 hours. The reaction mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were concentrated to afford the title compound (5.1 g).

Step 2: Preparation of (*S*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



p-Toluene sulfonyl chloride (8.75 g, 45.9 mmol) was added to a solution of (*R*)-(1,4-dioxan-2-yl)methanol (5.1 g) in pyridine (50 mL). The mixture was stirred at room temperature for 15 hours. The reaction mixture was poured into ice cold water and then extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with water (5 x 20 mL), dried over sodium sulfate and concentrated in vacuo to afford the title compound as an amber oil (6.1 g). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.50 min, *m/z* 273 (M+H).

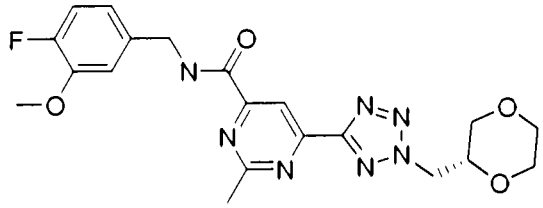
Step 3: Preparation of 6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide



A mixture of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-Methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (100 mg, 0.307 mmol), (*S*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (167 mg, 0.615 mmol), triethylamine (0.17 mL, 1.23 mmol) and dimethylacetamide (0.3 mL) was stirred at 85 °C for 18 hours. The mixture was purified by reverse phase preparative HPLC. Fractions containing the desired product were combined, isolated and concentrated to afford the title compound as a white solid (39 mg, 30%). LC/MS (5%-95% CH_3CN/H_2O, 4 min.; 95% CH_3CN, 1 min.): 2.75, *m/z* 426 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (s, 3 H), 3.38 - 3.58 (m, 3 H), 3.64 (d, *J*=10.8 Hz, 1 H), 3.70 - 3.77 (m, 4 H), 3.92 (dd, *J*=11.4, 2.4 Hz, 1 H), 4.10 - 4.19 (m, 1 H), 4.51 (d, *J*=6.5 Hz, 2 H), 4.92 (d, *J*=1.6 Hz, 2 H), 6.83 (dd, *J*=9.0, 1.6 Hz, 1 H), 6.90 - 6.95 (m, 2 H), 7.24 (t, *J*=8.1 Hz, 1 H), 8.42 (s, 1 H), 9.54 (t, *J*=6.4 Hz, 1 H).

Example 54

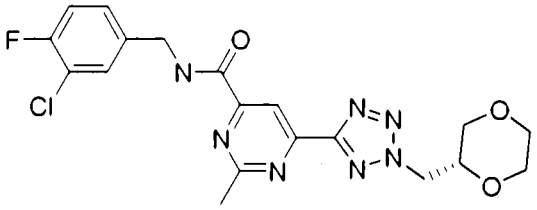
6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide



A mixture of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (100 mg, 0.291 mmol), (*S*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 2 of the synthesis of 6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide, Example 53) (159 mg, 0.583 mmol), triethylamine (0.16 mL, 1.17 mmol) and dimethylacetamide (0.3 mL) was stirred at 85 °C for 18 hours. The mixture was purified by reverse phase preparative HPLC. Fractions containing the desired product were isolated and concentrated to afford the title compound as a white solid (51 mg, 39%). LC/MS (5%-95% CH_3CN/H_2O, 4 min.; 95% CH_3CN, 1 min.): 2.78 min, *m/z* 444 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (s, 3 H), 3.38 - 3.58 (m, 3 H), 3.65 (d, *J*=10.6 Hz, 1 H), 3.73 (d, *J*=11.4 Hz, 1 H), 3.83 (s, 3 H), 3.91 (dd, *J*=11.5, 2.4 Hz, 1 H), 4.11 - 4.19 (m, 1 H), 4.51 (d, *J*=6.2 Hz, 2 H), 4.93 (d, *J*=6.2 Hz, 2 H), 6.88 - 6.94 (m, 1 H), 7.09 - 7.22 (m, 2 H), 8.42 (s, 1 H), 9.51 (t, *J*=6.4 Hz, 1 H).

Example 55

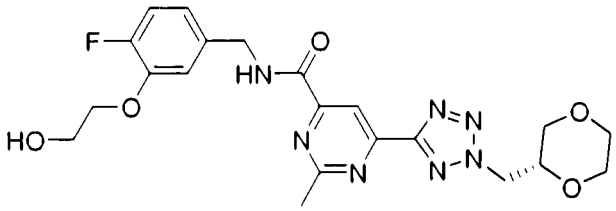
6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-chloro-4-fluorobenzyl)-2-methylpyrimidine-4-carboxamide



N-(3-Chloro-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 1 of the synthesis of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 47) (150 mg, 0.43 mmol) and (*S*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 2 of the synthesis of 6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide, Example 53) (129 mg, 0.47 mmol) were taken up in triethylamine (2.00 mL) and dimethylformamide (0.033 mL). The reaction was heated at 90 °C while shaking on a reactor block for 15 h. The mixture was concentrated and the residue was purified by reverse phase chromatography to afford the title compound as an oil (29 mg, 15%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 4.25 min, *m/z* 448 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (3 H, s), 3.35 - 3.57 (3 H, m), 3.62 (1 H, d, J=10.6 Hz), 3.71 (1 H, d, J=11.2 Hz), 3.89 (1 H, dd, J=11.53, 2.4 Hz), 4.06 - 4.20 (1 H, m), 4.49 (2 H, d, J=6.4 Hz), 4.90 (2 H, d, J=6.4 Hz), 7.35 (2 H, d, J=7.1 Hz), 7.54 (1 H, d, J=7.3 Hz), 8.39 (1 H, s), 9.59 (1 H, t, J=6.2 Hz).

Example 56

6-(2-(((*R*)-1,4-Dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-2-methylpyrimidine-4-carboxamide

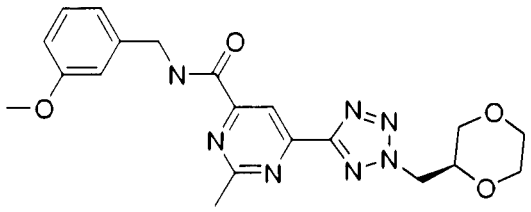


N-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 27) (45 mg, 0.20 mmol) and (*S*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 2 of the synthesis of 6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide, Example 53) (60 mg, 0.22 mmol) were taken up in triethylamine (1.00 mL) and dimethylformamide (0.12 mL). The reaction was heated at 90 °C while shaking on a reactor block for 15 h. The mixture was concentrated and the residue was purified by reverse phase chromatography to afford the title compound as an oil (17 mg, 18%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.43 min, *m/z* 474 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (3 H, s), 3.35 - 3.57 (3 H, m), 3.62 (1 H, d, J=10.8 Hz), 3.67 - 3.75 (3 H, m),

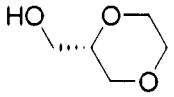
3.89 (1 H, dd, J=11.6, 2.5 Hz), 4.02 (2 H, t, J=5.0 Hz), 4.06 - 4.18 (1 H, m), 4.47 (2 H, d, J=6.2 Hz), 4.81 (1 H, t, J=5.4 Hz), 4.90 (2 H, d, J=6.6 Hz), 6.81 - 6.94 (1 H, m), 7.08 - 7.20 (2 H, m), 8.40 (1 H, s), 9.48 (1 H, t, J=6.3 Hz).

Example 57

6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide

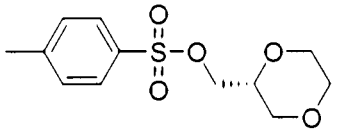


Step 1: Preparation of (*S*)-(1,4-dioxan-2-yl)methanol



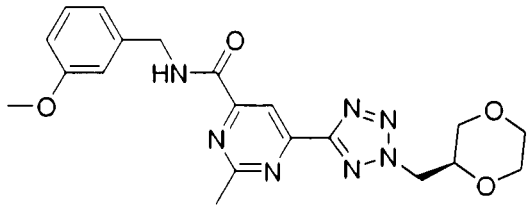
R-Epichlorohydrin (17.00 g, 180 mmol) was added drop wise to a stirred solution of chloro-2-ethanol (44.4 g, 551 mmol) and boron trifluoride diethyl etherate (1.05 g, 9.19 mmol) at 45 °C. After 18 hours, the reaction was quenched by adding diethyl ether (100 mL). The organic layer was washed with water (100 mL), dried over magnesium sulfate, filtered and evaporated. Purification was accomplished by vacuum distillation (10 torr) affording the desired intermediate as an oil (128-131 °C, 18 g, 57%). The intermediate was added drop-wise to a stirred solution of sodium hydroxide (10.4 g, 260 mmol) in water (15 mL). The reaction was stirred at room temperature for 1 h, diluted with water (15 mL) and heated at 90 °C for 2 h. The reaction mixture was extracted with dichloromethane (3 x 30 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and evaporated to afford the title compound as a clear oil (7.4 g, 35%).

Step 2: Preparation of (*R*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



(*S*)-(1,4-Dioxan-2-yl)methanol (2.52 g, 21.3 mmol) was taken up in pyridine (30 mL) and treated with p-toluene sulfonyl chloride (4.11 g, 21.5 mmol) and stirred at 25 °C for 18 hours. The reaction mixture was dripped into ice water, extracted with dichloromethane (3 x 50 mL) and washed with water (5 x 20 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated to afford the title compound as a clear oil (2.48 g, 43%). LC/MS (5%-95% CH_3CN/H_2O, 4 min): 2.60 min, *m/z* 273 (M+H).

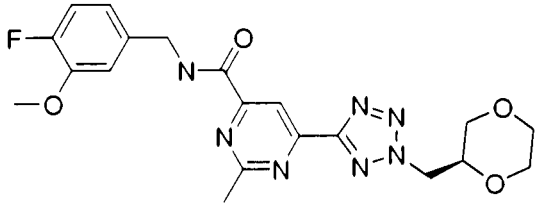
Step 3: Preparation of 6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide



A mixture of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-Methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (100 mg, 0.307 mmol), (*R*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (167 mg, 0.615 mmol), triethylamine (0.17 mL, 1.23 mmol) and dimethylacetamide (0.3 mL) was stirred at 85 °C for 18 h. The mixture was purified by reverse phase preparative HPLC. Fractions containing the desired product were isolated and concentrated to afford the title compound as a white solid (46 mg, 35%). LC/MS (5%-95% CH_3CN/H_2O, 4 min.; 95% CH_3CN, 1 min.): 2.75 min, *m/z* 426 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 (s, 3 H), 3.38 - 3.59 (m, 3 H), 3.65 (d, *J*=10.8 Hz, 1 H), 3.70 - 3.76 (m, 4 H), 3.92 (dd, *J*=11.5, 2.5 Hz, 1 H), 4.11 - 4.20 (m, 1 H), 4.51 (d, *J*=6.3 Hz, 2 H), 4.93 (d, *J*=1.8 Hz, 2 H), 6.83 (dd, *J*=8.1, 1.7 Hz, 1 H), 6.90 - 6.96 (m, 2 H), 7.25 (t, *J*=8.1 Hz, 1 H), 8.43 (s, 1 H), 9.54 (t, *J*=6.5 Hz, 1 H).

Example 58

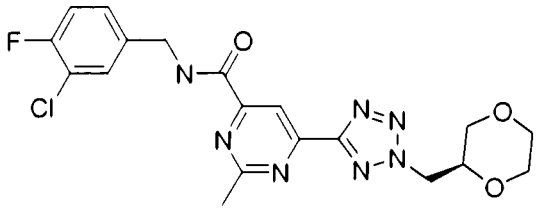
6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide



A mixture of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (100 mg, 0.291 mmol), (*R*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 2 of the synthesis of 6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide, Example 57) (159 mg, 0.583 mmol), triethylamine (0.16 mL, 1.17 mmol) and dimethylacetamide (0.3 mL) was stirred at 85 °C for 18 hours. The mixture was purified by reverse phase HPLC. Fractions containing the desired product were concentrated to afford the title compound as a white solid (41 mg, 32%). LC/MS (5%-95% CH_3CN/H_2O, 4 min.; 95% CH_3CN, 1 min.): 2.78 min, *m/z* 444 m/z (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (s, 3 H) 3.38 - 3.59 (m, 3 H) 3.65 (d, *J*=10.6 Hz, 1 H) 3.73 (d, *J*=11.4 Hz, 1 H) 3.83 (s, 3 H) 3.91 (dd, *J*=11.5, 2.38 Hz, 1 H) 4.15 (q, *J*=6.2 Hz, 1 H) 4.51 (d, *J*=6.2 Hz, 2 H) 4.93 (d, *J*=5.5 Hz, 2 H) 6.88 - 6.95 (m, 1 H) 7.09 - 7.22 (m, 2 H) 8.42 (s, 1 H) 9.50 (t, *J*=6.22 Hz, 1 H).

Example 59

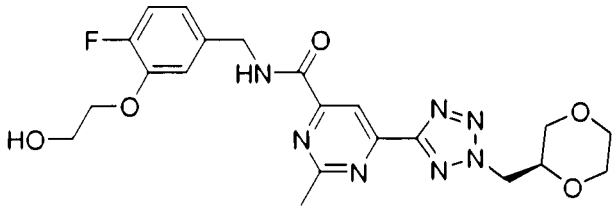
6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-chloro-4-fluorobenzyl)-2-methylpyrimidine-4-carboxamide



N-(3-Chloro-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 1 of the synthesis of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 47) (100 mg, 0.288 mmol), (*R*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 2 of the synthesis of 6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide, Example 57) (78.3 mg, 0.288 mmol), and triethylamine (400 µL) were combined in dimethylacetamide (100 µL). The resulting mixture was stirred at 90 °C for 18 h. The mixture was concentrated. The residue was purified by reverse phase high-pressure liquid chromatography. The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated to afford the title compound as a solid (8 mg, 6%). MS (ES+) *m/z* 448 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (m, 1 H), 8.40 (s, 1 H), 7.54(m, 1 H), 7.24 (m, 2 H), 4.91 (m, 2 H), 4.51 (m, 2 H), 4.18 (m, 1 H), 3.81 (m, 1 H), 3.42-3.72 (m, 5 H), 2.81 (s, 3 H).

Example 60

6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-2-methylpyrimidine-4-carboxamide

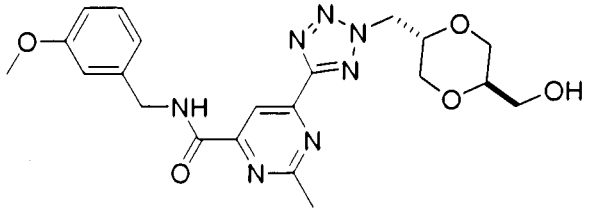


N-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 27) (56.7 mg, 0.152 mmol), (*R*)-(1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 2 of the synthesis of 6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide, Example 57) (400 µL) and triethylamine (30.7 mg, 0.304 mmol) were combined in dimethylacetamide (100 µL). After heating the reaction at 90 °C for 18 h, the mixture was concentrated. The residue was purified by reverse phase high-pressure liquid chromatography. The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated to afford the title compound as an oil (12.1 mg, 17%). MS (ES+) m/z 474 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm

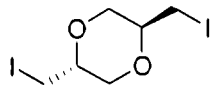
9.48 (m, 1 H), 8.41 (s, 1 H), 7.20 (m, 3 H), 6.84 (m, 1 H), 4.88 - 4.94 (m, 4 H), 4.81 (t, 1 H), 4.42 – 4.48 (m, 2 H), 4.10 - 4.16 (m, 1 H), 3.99 – 4.06 (m, 2 H), 3.84 - 3.93 (m, 2 H), 3.67 – 3.73 (m, 1 H), 3.57 – 3.65 (m, 1 H), 3.35 – 3.55 (m, 1 H), 2.81 (s, 3 H).

Example 61

***rac-N*-(3-Methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

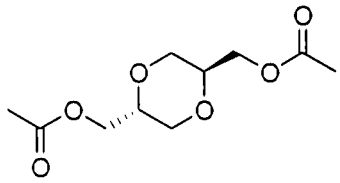


Step 1: Preparation of *trans*-2,5-bis(iodomethyl)-1,4-dioxane



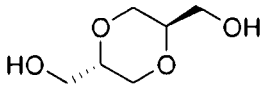
Yellow mercury oxide (700 g, 3.23 mol) was dissolved in concentrated nitric acid (70%, 443 mL, 6.53 mol) and water (295 mL). To the solution was added water (1180 mL) and it was cooled to 0 °C. Allyl alcohol (445 mL, 6.53 mol) was added in portions while the temperature was at 0-10 °C. After addition, the mixture was stirred for 6 h. The precipitate was collected by filtration and washed with water. The solid was dissolved in 10% NaOH (1.94 L, 4.85 mol) and the solution was basic. Concentrated potassium iodide (805 g, 4.85 mol) in water (560 mL) was added until precipitation of the mercury intermediate was complete. The precipitate was collected and washed with water. The wet solid was mixed with iodine (1041 g, 1.11 mol) and potassium iodide (1492 g, 8.99 mol) in water (3.7 L). The mixture was heated to reflux for 24 h. A few mL of benzene was added to wash back iodine that sublimed on the condenser. After 24 hr, the mixture was cooled to room temperature. The precipitate was filtered, washed with dilute $NaHSO_3$ and water to provide the title compound (598 g, 25%).

Step 2: Preparation of *trans*-2,5-bis-(acetoxymethyl)-1,4-dioxane



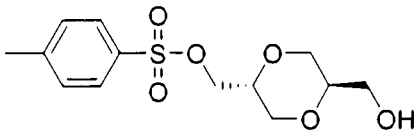
A mixture of *trans*-2,5-bis(iodomethyl)-1,4-dioxane (523 g, 1.42 mol) and potassium acetate (956 g, 9.74 mol) in acetic acid (3.35 L) was heated to reflux. The solution was seeded with 7 g of potassium iodide. The resulting mixture was heated to gently reflux for nine days. The dark mixture was cooled down and filtered to remove the solid. The filtrate was concentrated to remove half of the solvent and then diluted with ethyl acetate (5 L), and filtered. The filtrate was concentrated, and the residue was triturated with water (5 L) and cooled in an ice bath to provide the title compound as brown solid (140.5 g).

Step 3: Preparation of *trans*-2,5-bis-(hydroxymethyl)-1,4-dioxane



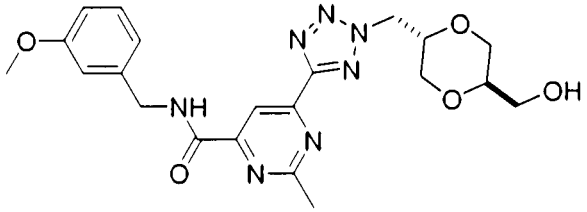
A mixture of *trans*-2,5-bis-(acetoxymethy1)-1,4-dioxane (213 g) in methanol (1065 mL) and 4N hydrochloric acid in dioxane (229 mL) was heated to reflux for 1 h. About 30 g of decolorizing charcoal was added after cooling down. The mixture was filtered through a pad of Celite™. The filtrate was concentrated, and the oily residue was dissolved in isopropyl alcohol/benzene (1/5, 600 mL). Crystals were obtained by filtration and washed with isopropyl alcohol/benzene (1/5) to provide the title compound as a solid (126.9)..

Step 4: Preparation of *rac*-((2*R**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



trans-2,5-bis-(Hydroxymethyl)-1,4-dioxane (342.9 g, 2.31 mol) and p-toluene sulfonylchloride (441.0 g, 2.31 mol), triethylamine (471.5 g, 4.66 mol) and dichloromethane (3 L) were combined in a 5 L round-bottomed flask equipped with a mechanical stirrer under nitrogen. The mixture was maintained at 35 °C for 30 min with water bath cooling and than allowed to stir at room temperature overnight. The mixture was diluted with 3 N hydrochloric acid (1 L), and the resulting solids were filtered. The organic phase of the filtrate was separated, washed with 3 N hydrochloric acid (1 L) followed by saturated ammonium chloride solution (500 mL), dried over magnesium sulfate, and concentrated to afford the title compound (338.3 g).

Step 5: Preparation of *rac*-*N*-(3-Methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

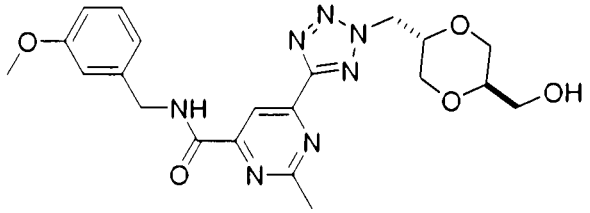


rac-((2*R**,5*R**)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (4.3 g, 14.0 mmol) was added to a solution of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (3.2 g, 9.8 mmol) and triethylamine (2.0 g, 19.7 mmol) in anhydrous dimethylacetamide (4 mL). The reaction was stirred at 85 °C in a capped vial overnight. The mixture was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing product were neutralized by passing through a carbonate resin column and concentrated. The resulting product was slurried with diethyl ether, decanted, and dried in vacuo to afford the title compound as a white solid (1.38 g). MS (ES+) *m/z* 456 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.44 - 9.52 (1 H, m), 8.42 (1 H, s), 7.24 (1 H, t, *J*=8.1

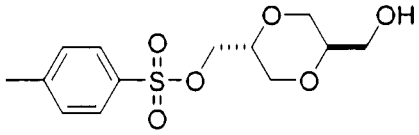
Hz), 6.89 - 6.95 (2 H, m), 6.83 (1 H, d, *J*=8.1 Hz), 4.93 (1 H, d, *J*=3.3 Hz), 4.88 (1 H, d, *J*=7.7 Hz), 4.51 (3 H, d, *J*=5.9 Hz), 4.08 (1 H, d, *J*=3.3 Hz), 3.99 (1 H, d, *J*=11.3 Hz), 3.78 (1 H, d, *J*=11.3 Hz), 3.74 (3 H, s), 3.36 - 3.48 (4 H, m), 3.31 (1 H, d, *J*=2.2 Hz), 2.83 (3 H, s)

Example 62

5 *N*-(3-Methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

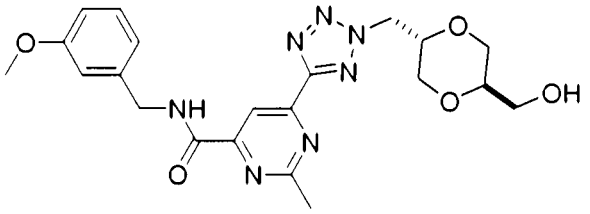


Step 1: Preparation of ((2*R*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



10 *rac*-((2*R**,5*R**)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) was chirally separated by supercritical fluid chromatography (AD-H; 30% methanol/dichloromethane, 10/1; 200 mL/min). Isolation of the first eluting isomer afforded the title compound as a white solid.

15 Step 2: Preparation of *N*-(3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



((2*R*,5*R*)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (5.2 g, 17.2 mmol) was added to a solution of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-

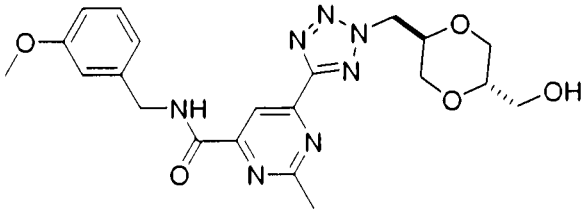
20 carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (4.0 g, 12.3 mmol) and triethylamine (3.1 g, 30.0 mmol) in anhydrous dimethylacetamide (4 mL). The reaction was stirred at 85 °C in a capped vial overnight. The mixture was purified by reverse phase preparative HPLC (water/acetonitrile), and fractions containing product were concentrated. The residue was

25 dissolved in dichloromethane and washed with dilute aqueous NaOH followed by water. The organic layer was dried over magnesium sulfate, filtered, and concentrated under vacuum. The crude product was further separated by supercritical fluid chromatography (OJ-H, 30 x 250 mm, 40% methanol, 70 mL/min). Fractions containing the desired product were concentrated and the resulting solid was

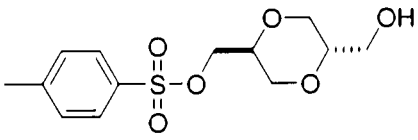
recrystallized from isopropanol to afford the title compound as a white solid (986 mg). MS (ES+) *m/z* 456 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.52 (1 H, t, *J*=6.4 Hz), 8.39 (1 H, s), 7.24 (1 H, t, *J*=8.1 Hz), 6.86-6.92 (2 H, m), 6.77-6.82 (1 H, m), 4.80-4.95 (2 H, m), 4.69 (1 H, t, *J*=5.5 Hz), 4.47 (2 H, d, *J*=6.2 Hz), 3.93-4.09 (2 H, m), 3.71-3.77 (1 H, m), 3.70 (3 H, s), 3.2-3.45 (5 H, m), 2.79 (3 H, s).

Example 63

***N*-(3-Methoxybenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

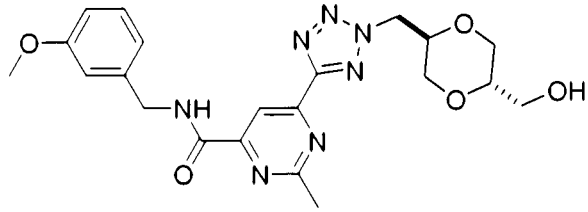


Step 1: Preparation of ((2*S*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



rac-((2*R**,5*R**)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) was chirally separated by supercritical fluid chromatography (AD-H; 30% methanol/dichloromethane, 10/1; 200 mL/min). Isolation of the second eluting isomer afforded the title compound as a white solid.

Step 2: Preparation of *N*-(3-Methoxybenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

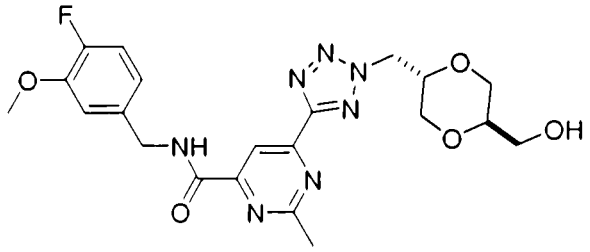


((2*S*,5*S*)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (5.2 g, 17.2 mmol) was added to a solution of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (4.0 g, 12.3 mmol) and triethylamine (3.1 g, 30.0 mmol) in anhydrous dimethylacetamide (4 mL). The reaction was stirred at 85 °C in a capped vial overnight. The mixture was purified by reverse phase preparative HPLC (water/acetonitrile), and fractions containing product were concentrated. The residue was dissolved in dichloromethane and washed with dilute aqueous NaOH followed by water. The organic layer was dried over magnesium sulfate, filtered, and concentrated under vacuum. The crude product was further separated by supercritical fluid chromatography (OJ-H, 30 x 250 mm, 40% methanol, 70

mL/min). Fractions containing the desired product were concentrated and the resulting solid was recrystallized from isopropanol to afford the title compound as a white solid (576 mg). MS (ES+) *m/z* 456 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.52 (1 H, t, *J*=6.4 Hz), 8.39 (1 H, s), 7.24 (1 H, t, *J*=8.1 Hz), 6.86-6.92 (2 H, m), 6.77-6.82 (1 H, m), 4.80-4.95 (2 H, m), 4.69 (1 H, t, *J*=5.5 Hz), 4.47 (2 H, d, *J*=6.2 Hz), 3.93-4.09 (2 H, m), 3.71-3.77 (1 H, m), 3.70 (3 H, s), 3.2-3.45 (5 H, m), 2.79 (3 H, s).

Example 64

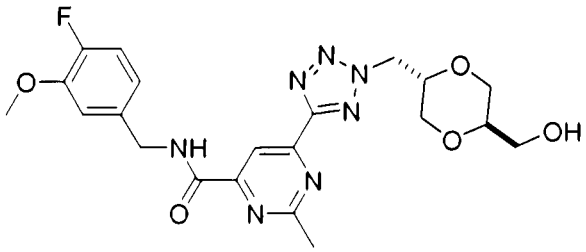
***rac-N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



rac-((2*R**,5*R**)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac-N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (2.64 g, 8.7 mmol) was added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (2.0 g, 5.8 mmol) and triethylamine (880 mg, 8.7 mmol) in anhydrous dimethylacetamide (2 mL). The reaction was stirred overnight at 85 °C in a capped vial. The mixture was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing product were neutralized by passing through a carbonate resin column and concentrated. The resulting product was slurried with diethyl ether, decanted, and dried in vacuo to afford the title compound as a white solid (1.02 g). MS (ES+) *m/z* 474 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.50 (1 H, t, *J*=6.2 Hz), 8.42 (1 H, s), 7.15 (2 H, td, *J*=12.1, 8.4 Hz), 6.92 (1 H, d, *J*=4.4 Hz), 4.93 (1 H, d, *J*=3.7 Hz), 4.88 (1 H, d, *J*=7.7 Hz), 4.65 (1 H, t, *J*=5.5 Hz), 4.51 (3 H, d, *J*=6.2 Hz), 4.08 (1 H, d, *J*=2.9 Hz), 3.99 (1 H, dd, *J*=11.5, 2.0 Hz), 3.83 (3 H, s), 3.78 (1 H, d, *J*=11.7 Hz), 3.36 - 3.48 (4 H, m), 3.31 (1 H, s), 2.83 (3 H, s).

Example 65

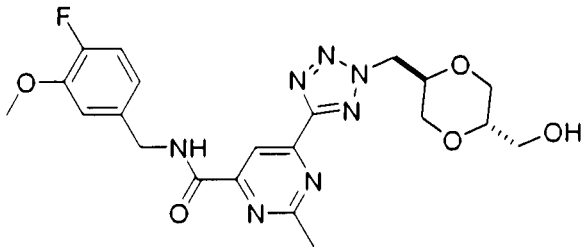
***N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (10.0 g, 29.1 mmol) was dissolved in triethylamine (7.04 g, 69.7 mmol) and *N,N*-dimethylacetamide (31 mL). ((2*R*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 62) (12.4 g, 41.0 mmol) was added and the reaction heated to 85 °C for 16 hours. After cooling to room temperature, the mixture was diluted with water (300 mL) and extracted with dichloromethane (3 x 200 mL). The combined organics were washed with 1N NaOH (2 x 100 mL), 1M hydrochloric acid (2 x 100 mL), water (100 mL), and brine (250 mL). The organic layer was dried over sodium sulfate, filtered and evaporated to give a yellow oil. Purification by silica gel chromatography using heptane, ethyl acetate and methanol provided a mixture of regioisomers as an opaque oil. The mixture was separated by supercritical fluid chromatography (OJ-H, 30 x 250 mm, 40% methanol, 70 mL/min) and the desired isomer was recrystallized from ethyl acetate (80 mL) and ethanol (1 mL) to provide the title compound as a white crystalline solid (3.5 g, 25%). LC/MS (5%-95% CH_3CN/H_2O, 4 min): 3.39 min, *m/z* 474 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.53 (t, J=6.3 Hz, 1 H), 8.39 (s, 1 H), 7.06 - 7.19 (m, 2 H), 6.83 - 6.91 (m, 1 H), 4.78 - 4.98 (m, 2 H), 4.68 (t, J=5.7 Hz, 1 H), 4.47 (d, J=6.4 Hz, 2 H), 3.99 - 4.10 (m, 1 H), 3.96 (dd, J=11.4, 2.4 Hz, 1 H), 3.79 (s, 3 H), 3.74 (dd, J=11.4, 2.2 Hz, 1 H), 3.19 - 3.47 (m, 5 H), 2.80 (s, 3 H).

Example 66

N-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

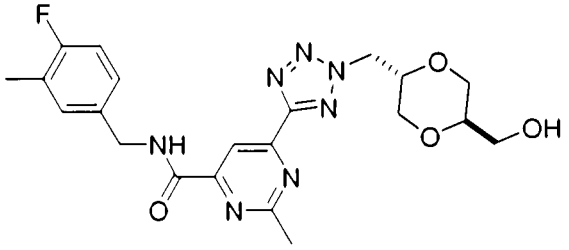


((2*S*,5*S*)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-Methoxybenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 63) (5.2 g, 17.2 mmol) was added to a solution of *N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-

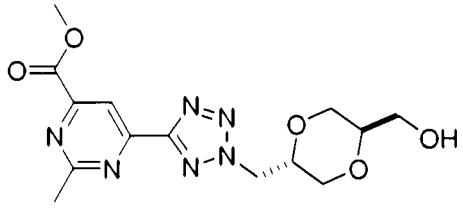
methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (4.22 g, 12.3 mmol) and triethylamine (3.1 g, 30.0 mmol) in anhydrous dimethylacetamide (4 mL). The reaction was stirred at 85 °C in a capped vial overnight. The mixture was purified by reverse phase preparative HPLC (water/acetonitrile), and fractions containing product were concentrated. The residue was dissolved in dichloromethane and washed with dilute aqueous NaOH followed by water. The organic layer was dried over magnesium sulfate, filtered, and concentrated under vacuum. The crude product was further separated by supercritical fluid chromatography (OJ-H, 30 x 250 mm, 45% acetonitrile, 70 mL/min). Fractions containing the desired product were concentrated and the resulting solid was recrystallized from ethyl acetate (80 mL) to afford the title compound as a white solid (1.5 g). MS (ES+) *m/z* 474 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.50 (1 H, t, *J*=6.2 Hz), 8.42 (1 H, s), 7.08-7.17 (2 H, m), 6.85-6.9 (1 H, m), 4.80-4.95 (2 H, m), 4.69 (1 H, t, *J*=5.5 Hz), 4.47 (2 H, d, *J*=6.2 Hz), 3.93-4.09 (2 H, m), 3.79 (3 H, s), 3.71-3.77 (1 H, m), 3.2-3.45 (5 H, m), 2.79 (3 H, s).

Example 67

***rac*-*N*-(4-Fluoro-3-methylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



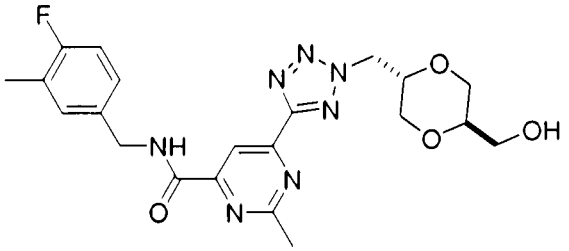
Step 1: Preparation of methyl *rac*-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate



In a 30 mL scintillation vial with a magnetic stir bar at room temperature and standard pressure, methyl 2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxylate (prepared as described in step 1 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 17) (1.57 g, 7.13 mmol) was dissolved in N,N-dimethylformamide (15ml). *N*,*N*-Diisopropylethylamine (1.86 g, 14.40 mmol) was added and the mixture was stirred at room temperature for 30 min. *rac*-((2*R**,5*R**)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (4.41 g, 14.59 mmol) was added and the reaction mixture was heated to 80 °C with stirring for 14 hours. The reaction mixture was

concentrated, dissolved in acetonitrile and water, and chromatographed by reversed phase preparative HPLC (Gilson, Delta Pak, 20%-35% acetonitrile, 20 min hold, 40 min gradient, 8 min hold). Fractions corresponding to the first eluting peak (27.34 min) were concentrated under vacuum to afford the title compound as a solid (1.4 g) LC/MS (5%-95% CH_3CN/H_2O, 6 min): 1.856 min, *m/z* 351(M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 - 1.27 (m, 2 H), 2.25 (s, 1 H), 2.79 (s, 3 H), 3.11 (dd, *J*=7.4, 4.2 Hz, 1 H), 3.18 - 3.29 (m, 2 H), 3.29 - 3.46 (m, 2 H), 3.59 (d, *J*=3.8 Hz, 1 H), 3.74 (dd, *J*=11.6, 2.4 Hz, 1 H), 4.80 - 4.88 (m, 1 H), 4.89 - 4.97 (m, 1 H), 7.08 (d, *J*=7.8 Hz, 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 8.36 (s, 1 H).

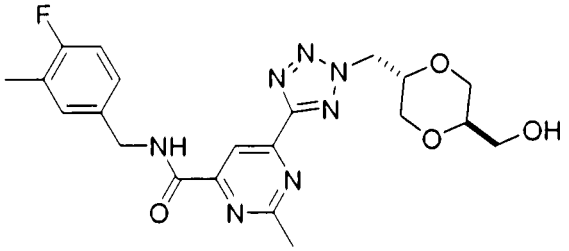
Step 2: Preparation of *rac-N*-(4-fluoro-3-methylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



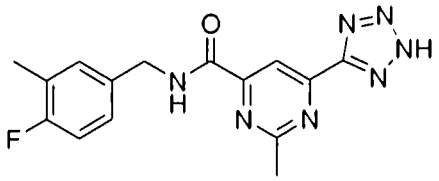
A mixture of *rac*-methyl 6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate (100 mg, 0.285 mmol), 4-fluoro-3-methylbenzylamine (119 mg, 0.856 mmol), and dimethylacetamide (1 mL) was heated to 85 °C for 18 hours. The title compound was isolated as a solid by reverse phase preparative HPLC (73 mg, 56%). MS (ES+) *m/z* 458 m/z (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H), 2.83 (s, 3 H), 3.34 - 3.55 (m, 5 H), 3.78 (dd, *J*=11.5, 2.0 Hz, 1 H), 3.99 (dd, *J*=11.5, 2.0 Hz, 1 H), 4.04 - 4.16 (m, 1 H), 4.48 (d, *J*=6.2 Hz, 2 H), 4.65 (t, *J*=5.7 Hz, 1 H), 4.80 - 5.00 (m, 2 H), 7.07 (t, *J*=9.2 Hz, 1 H), 7.16 - 7.24 (m, 1 H), 7.26 (d, *J*=7.3 Hz, 1 H), 8.42 (s, 1 H), 9.50 (t, *J*=6.2 Hz, 1 H).

Example 68

***N*-(4-Fluoro-3-methylbenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

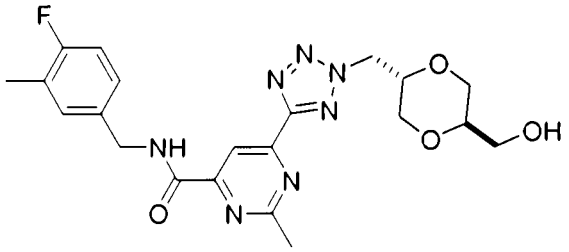


Step 1: Preparation of *N*-(4-fluoro-3-methylbenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



A solution of methyl 2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxylate (prepared as described in step 1 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 17) (1.0 g, 4.54 mmol) in dimethylformamide (5 mL) was treated with 4-fluoro-3-methylbenzylamine (1.9 g, 13.6 mmol) and heated to 65 °C for 3 days. The mixture was cooled to room temperature. Excess 2.5 N NaOH was added to the mixture. The product mixture was washed with ethyl acetate (3 x 10 mL). Concentrated hydrochloric acid was added and the resulting precipitate was filtered, washed with water and dried in vacuo to afford the title compound (1.21 g, 75%).

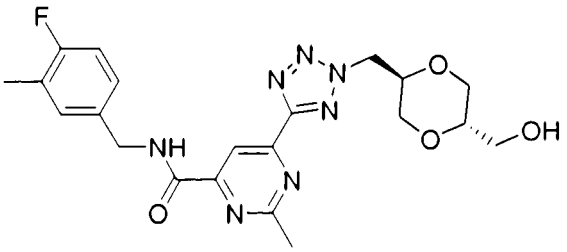
Step 2: Preparation of *N*-(4-fluoro-3-methylbenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



A mixture of *N*-(4-fluoro-3-methylbenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (96 mg, 0.293 mmol), ((2*R*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 62) (106 mg, 0.352 mmol), and triethylamine (0.16 mL, 1.17 mmol) was heated in dimethylformamide at 85 °C overnight. The mixture was chromatographed by reverse phase preparative HPLC. Fractions containing the desired product were passed through a carbonate cartridge and concentrated to afford the title compound (39 mg, 28%). MS (ES+) *m/z* 458 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.83 (t, *J*=5.9 Hz, 1 H), 2.28 (d, *J*=2.0 Hz, 3 H), 2.89 (s, 3 H), 3.47 - 3.62 (m, 3 H), 3.62 - 3.71 (m, 2 H), 3.82 (dd, *J*=11.6, 2.3 Hz, 1 H), 3.99 (dd, *J*=11.6, 2.4 Hz, 1 H), 4.17 - 4.26 (m, 1 H), 4.64 (d, *J*=6.1 Hz, 2 H), 4.68 - 4.88 (m, 2 H), 6.96 - 7.03 (m, 1 H), 7.14 - 7.23 (m, 2 H), 8.27 - 8.34 (m, 1 H), 8.80 (s, 1 H).

Example 69

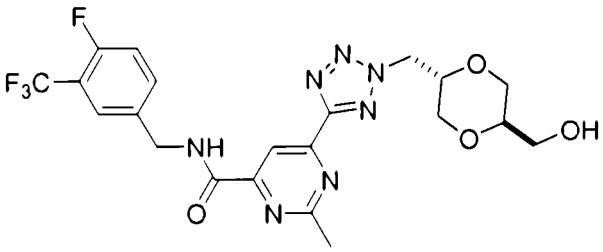
N-(4-Fluoro-3-methylbenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



A mixture of *N*-(4-fluoro-3-methylbenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 1 in the synthesis of *N*-(4-fluoro-3-methylbenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 68) (96 mg, 0.293 mmol), ((2*S*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-Methoxybenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 63) (106 mg, 0.352 mmol), and triethylamine (0.16 mL, 1.17 mmol) was heated in dimethylformamide at 85 °C overnight. The mixture was chromatographed by reverse phase preparative HPLC. Fractions containing the desired product were passed through a carbonate cartridge and concentrated to afford the title compound (21mg, 16%).
MS (ES+) *m/z* 458 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.26 (d, *J*=1.4 Hz, 3 H), 2.87 (s, 3 H), 3.43 - 3.70 (m, 6 H), 3.79 (dd, *J*=11.6, 2.1 Hz, 1 H), 3.96 (dd, *J*=11.5, 2.5 Hz, 1 H), 4.14 - 4.25 (m, 1 H), 4.61 (d, *J*=6.3 Hz, 2 H), 4.66 - 4.86 (m, 2 H), 6.97 (t, *J*=8.9 Hz, 1 H), 7.10 - 7.21 (m, 2 H), 8.29 (t, *J*=5.8 Hz, 1 H), 8.77 (s, 1 H).

Example 70

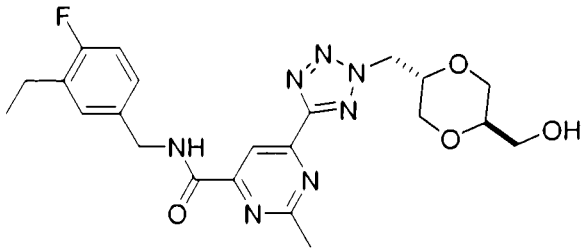
***rac-N*-(4-Fluoro-3-(trifluoromethyl)benzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



A mixture of *rac*-methyl 6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate (prepared as described in step 1 of the synthesis of *rac-N*-(4-fluoro-3-methylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 67) (100 mg, 0.285 mmol), 4-fluoro-3-trifluoromethylbenzylamine (165 mg, 0.856 mmol), and dimethylacetamide (1 mL) was heated to 85 °C for 18 hours. The title compound was isolated as a solid by reverse phase preparative HPLC (52 mg, 36%). MS (ES+) *m/z* 512 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 (s, 3 H), 3.31 - 3.52 (m, 5 H), 3.78 (dd, *J*=11.4, 1.8 Hz, 1 H), 3.99 (dd, *J*=11.4, 2.2 Hz, 1 H), 4.03 - 4.14 (m, 1 H), 4.59 (d, *J*=6.2 Hz, 2 H), 4.65 (t, *J*=5.7 Hz, 1 H), 4.81 - 5.00 (m, 2 H), 7.41 - 7.53 (m, 1 H), 7.69 - 7.83 (m, 2 H), 8.41 (s, 1 H), 9.66 (t, *J*=6.04 Hz, 1 H).

Example 71

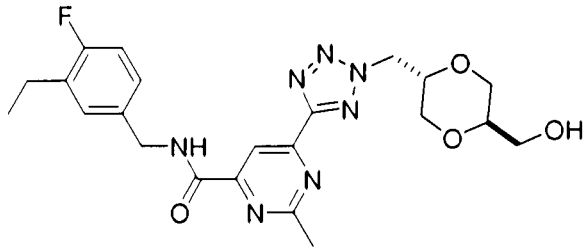
***rac-N*-(3-Ethyl-4-fluorobenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



A mixture of methyl *rac*-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate (prepared as described in step 1 of the synthesis of *rac-N*-(4-fluoro-3-methylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 67) (100 mg, 0.285 mmol), (3-ethyl-4-fluorophenyl)methanamine (prepared as described in steps 1 – 5 of the synthesis of *N*-(3-ethyl-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 49) (131 mg, 0.856 mmol), and dimethylacetamide (1 mL) was heated to 85 °C for 18 hours. The title compound was isolated as a solid by reverse phase preparative HPLC (57 mg, 42%). MS (ES+) *m/z* 472 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, *J*=7.7 Hz, 3 H), 2.57 (q, *J*=7.3 Hz, 2 H), 2.79 (s, 3 H), 3.26 - 3.47 (m, 5 H), 3.74 (dd, *J*=11.0, 2.2 Hz, 1 H), 3.95 (dd, *J*=11.0, 2.2 Hz, 1 H), 4.00 - 4.10 (m, 1 H), 4.46 (d, *J*=6.6 Hz, 2 H), 4.62 (t, *J*=5.9 Hz, 1 H), 4.77 - 4.96 (m, 2 H), 6.97 - 7.09 (m, 1 H), 7.13 - 7.21 (m, 1 H), 7.25 (d, *J*=9.5 Hz, 1 H), 8.38 (s, 1 H), 9.46 (t, *J*=6.2 Hz, 1 H).

Example 72

***N*-(3-Ethyl-4-fluorobenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

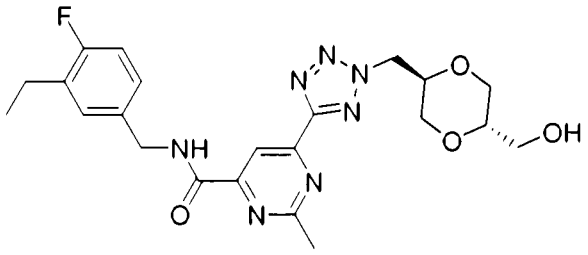


A mixture of *N*-(3-ethyl-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in steps 1 – 6 of the synthesis of *N*-(3-ethyl-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 49) (100 mg, 0.293 mmol), ((2*R*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 62) (106 mg, 0.352 mmol), and triethylamine (0.16 mL, 1.17 mmol) was heated in dimethylformamide at 85 °C overnight. The mixture was chromatographed by reverse phase preparative HPLC. Fractions containing the desired product were passed through a carbonate cartridge and concentrated to afford the title compound (28 mg, 20%). MS (ES+) *m/z* 472 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (t, J=7.5 Hz, 3 H), 1.80

(br. s., 1 H), 2.67 (q, J=7.6 Hz, 2 H), 2.89 (s, 3 H), 3.41 - 3.73 (m, 5 H), 3.82 (dd, J=11.6, 2.3 Hz, 1 H), 3.99 (dd, J=11.5, 2.5 Hz, 1 H), 4.15 - 4.26 (m, 1 H), 4.65 (d, J=6.3 Hz, 2 H), 4.68 - 4.89 (m, 2 H), 7.00 (dd, J=9.7, 8.3 Hz, 1 H), 7.13 - 7.24 (m, 2 H), 8.32 (t, J=6.0 Hz, 1 H), 8.79 (s, 1 H).

Example 73

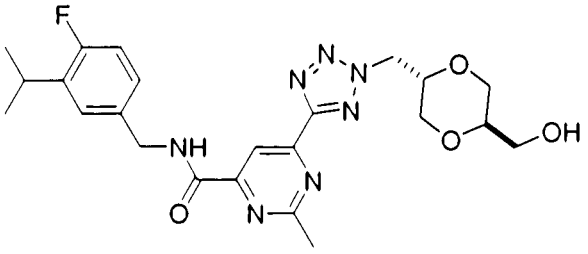
***N*-(3-Ethyl-4-fluorobenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



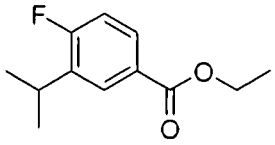
A mixture of *N*-(3-ethyl-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in steps 1 – 6 of the synthesis of *N*-(3-ethyl-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 49) (100 mg, 0.293 mmol), ((2*S*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-Methoxybenzyl)-6-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 63) (106 mg, 0.352 mmol), and triethylamine (0.16 mL, 1.17 mmol) was heated in dimethylformamide at 85 °C overnight. The mixture was chromatographed by reverse phase preparative HPLC. Fractions containing the desired product were passed through a carbonate cartridge and concentrated to afford the title compound (39 mg, 28%). MS (ES+) *m/z* 472 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (t, *J*=7.5 Hz, 3 H), 1.72 (br. s., 1 H), 2.67 (q, *J*=7.5 Hz, 2 H), 2.89 (s, 3 H), 3.46 - 3.70 (m, 5 H), 3.82 (dd, *J*=11.6, 2.3 Hz, 1 H), 3.98 (dd, *J*=11.5, 2.5 Hz, 1 H), 4.16 - 4.27 (m, 1 H), 4.65 (d, *J*=6.1 Hz, 2 H), 4.68 - 4.88 (m, 2 H), 7.00 (dd, *J*=9.6, 8.4 Hz, 1 H), 7.14 - 7.24 (m, 2 H), 8.32 (t, *J*=6.0 Hz, 1 H), 8.79 (s, 1 H).

Example 74

***rac*-*N*-(4-Fluoro-3-isopropylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

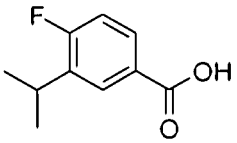


Step 1: Preparation of ethyl 4-fluoro-3-isopropylbenzoate



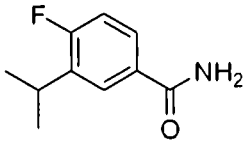
Isopropylmagnesium chloride (2.0 M in ether, 137.61 mL, 275.23 mmol) was added slowly to a solution of anhydrous $ZnCl_2$ (37.43 g, 275.23 mmol) in dry tetrahydrofuran (200 mL) under an argon atmosphere. The resulting white slurry was stirred at 50 °C for 3 h. In a separate flask, a solution of ethyl 3-bromo-4-fluorobenzoate (prepared as described in step 1 of the synthesis of *N*-(3-ethyl-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 49) (17 g, 68.80 mmol) in dry tetrahydrofuran (150 mL) was sequentially treated with $PdCl_2$(dppf) (2.8 g, 3.44 mmol) and copper(I) iodide (0.78 g, 4.12 mmol) under an argon atmosphere. The alkyl zinc slurry was added to the ester mixture at room temperature. The resulting brown slurry was stirred in the dark at room temperature for 48 h. The reaction mixture was concentrated under vacuum to give a dark brown residue, which was taken up in ethyl acetate (750 mL) and washed sequentially with 1N hydrochloric acid (300 mL) solution, sat. $NaHCO_3$ solution, and brine. The ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography over silica gel (100-200 mesh) using 5 % ethyl acetate in hexane as an eluent to afford the title compound (12.5 g, 89%).

Step 2: Preparation of 4-fluoro-3-isopropylbenzoic acid



Ethyl 4-fluoro-3-isopropylbenzoate (12.5 g, 59.46 mmol) and lithium hydroxide monohydrate (7.49 g, 178.40 mmol) were taken up in a mixture of dioxane/water (1/1, 250 mL) and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was acidified with 1N hydrochloric acid under ice-water cold condition. The mixture was extracted with dichloromethane (2 x 150 mL). The combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford the title compound (10 g, 92 %).

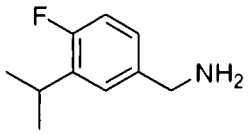
Step 3: Preparation of 4-fluoro-3-isopropylbenzamide



4-Fluoro-3-isopropylbenzoic acid (10.3g, 54.94 mmol) was taken up in $SOCl_2$ (150 mL) and then refluxed for 4 h. The $SOCl_2$ was removed under reduced pressure and the resulting residue was dissolved in dry acetonitrile (125 mL). Ammonia gas was passed through the solution at –78 °C for 10 min. The reaction mixture was allowed to warm to room temperature very slowly and stirred for overnight. The reaction mixture was concentrated to a residue which was extracted with

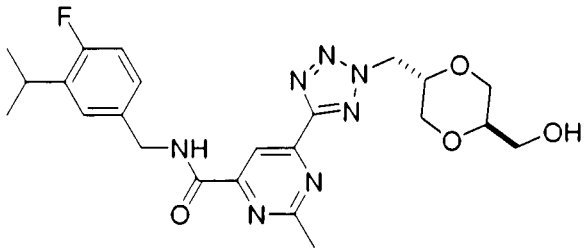
dichloromethane (2 x 100 mL). The combined dichloromethane layers were washed with sat. $NaHCO_3$ solution followed by brine, dried over sodium sulfate, and concentrated. The resulting solid was washed with hexane (2 x 25 mL) to afford the title compound (9 g, 90%).

Step 4: Preparation of (4-fluoro-3-isopropylphenyl)methanamine



Borane dimethylsulfide complex (94 %, 20.33 mL, 198.67 mmol) was added slowly to a solution of 4-fluoro-3-isopropylbenzamide (9 g, 49.66 mmol) in dichloromethane (200 mL) at ice cold condition. After the addition, the reaction mixture was stirred for 1 h at room temperature and then it was refluxed for 24 h. The reaction mixture was cooled to 0 °C, washed with $NaHCO_3$ solution followed by brine, and dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (100-200 mesh) using 15 % CH_2Cl_2 in hexane as an eluent to afford the title compound (4.8 g, 54%). MS (ES+) *m/z* 168 (M+H).

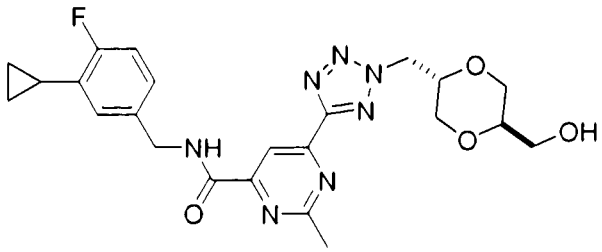
Step 5: Preparation of *rac-N*-(4-fluoro-3-isopropylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



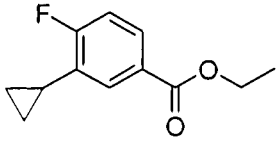
A mixture of *rac*-methyl 6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate (prepared as described in step 1 of the synthesis of *rac-N*-(4-fluoro-3-methylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 67) (100 mg, 0.285 mmol), (4-fluoro-3-isopropylphenyl)methanamine (143 mg, 0.856 mmol), and dimethylacetamide (1 mL) was heated to 85 °C for 18 hours. The title compound was isolated as a solid by reverse phase preparative HPLC (49 mg, 35%). MS (ES+) *m/z* 486 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (d, *J*=7.0 Hz, 6 H), 2.83 (s, 3 H), 3.07 - 3.20 (m, 1 H), 3.31 - 3.52 (m, 5 H), 3.78 (dd, *J*=11.4, 1.8 Hz, 1 H), 3.99 (dd, *J*=11.4, 2.2 Hz, 1 H), 4.04 - 4.14 (m, 1 H), 4.51 (d, *J*=6.2 Hz, 2 H), 4.66 (t, *J*=5.7 Hz, 1 H), 4.79 - 5.02 (m, 2 H), 7.07 (dd, *J*=10.4, 8.6 Hz, 1 H), 7.15 - 7.25 (m, 1 H), 7.28 - 7.37 (m, 1 H), 8.42 (s, 1 H), 9.50 (t, *J*=6.2 Hz, 1 H).

Example 75

rac-N-(3-Cyclopropyl-4-fluorobenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

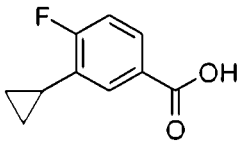


Step 1: Preparation of ethyl 3-cyclopropyl-4-fluorobenzoate



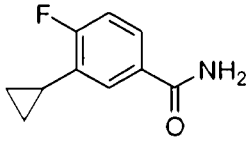
Cyclopropylmagnesium bromide (2.0 M in ether, 137.61 mL, 275.23 mmol) was added slowly to a solution of anhydrous $ZnCl_2$ (37.43 g, 275.23 mmol) in dry tetrahydrofuran (200 mL) under an argon atmosphere. The resulting white slurry was stirred at 50 °C for 3 h. In a separate flask a solution of ethyl 3-bromo-4-fluorobenzoate (prepared as described in step 1 of the synthesis of *N*-(3-ethyl-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 49) (17 g, 68.80 mmol) in dry tetrahydrofuran (150 mL) was sequentially treated with $PdCl_2$(dppf) (2.8 g, 3.44 mmol) and copper(I) iodide (0.78 g, 4.12 mmol) under an argon atmosphere. The alkyl zinc slurry was added to the ester mixture at room temperature. The resulting brown slurry was stirred in the dark at room temperature for 48 h. The reaction mixture was concentrated under vacuum to give a dark brown residue, which was taken up in ethyl acetate (750 mL) and washed sequentially with 1N hydrochloric acid (300 mL) solution, sat. $NaHCO_3$ solution and brine. The ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated in vacuo to obtain a mixture of the desired product and bromo starting material (9.8 g of ~ 40/60 product/starting material). The mixture was carried on to the next step without further purification.

Step 2: Preparation of 3-cyclopropyl-4-fluorobenzoic acid



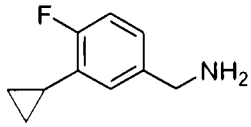
A mixture containing ethyl 3-cyclopropyl-4-fluorobenzoate from step 1 (16 g) and lithium hydroxide monohydrate (9.68 g, 230.54 mmol) were taken up in a mixture of dioxane/water (1/1, 300 mL) and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was acidified with 1N hydrochloric acid under ice-water cold condition. The mixture was extracted with dichloromethane (2 x 150 mL). The combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford the title compound contaminated by 3-bromo-4-fluorobenzoic acid (12.0 g).

Step 3: Preparation of 3-cyclopropyl-4-fluorobenzamide



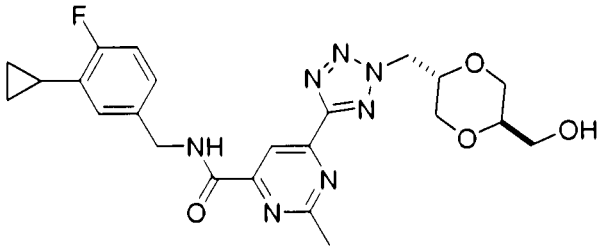
A mixture containing 3-cyclopropyl-4-fluorobenzoic acid from step 2 (10.5 g) was taken up in $SOCl_2$ (150 mL) and then refluxed for 4 h. The $SOCl_2$ was removed under reduced pressure and the residue was dissolved in dry acetonitrile (125 mL). Ammonia gas was passed through solution at –78 °C for 10 min. The reaction mixture was allowed to warm at room temperature very slowly and stirred overnight. The reaction mixture was concentrated to a residue and extracted with dichloromethane (2 x 100 mL). The combined dichloromethane layers were washed with sat. $NaHCO_3$ solution followed by brine, dried over sodium sulfate and concentrated. The crude product was washed with hexane (2 x 25 mL) to afford a mixture of the title compound and 3-bromo-4-fluorobenzamide and bromo impurity (9.5 g).

Step 4: Preparation of (3-cyclopropyl-4-fluorophenyl)methanamine



Borane dimethylsulfide complex (94%, 21.70 mL, 212.05 mmol) was added slowly to a solution of the mixture containing 3-cyclopropyl-4-fluorobenzamide from step 3 (9.5 g) in dichloromethane (200 mL) under ice-cold condition. After the addition, the reaction mixture was stirred for 1 h at room temperature and then it was refluxed for 24 h. The reaction mixture was cooled to 0 °C, washed with $NaHCO_3$ solution followed by brine, and dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (100-200 mesh) using 25 % CH_2Cl_2 in hexane as an eluent to afford the title compound (1.8 g). MS (ES+) *m/z* 166 (M+H).

Step 5: Preparation of *rac-N*-(3-cyclopropyl-4-fluorobenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

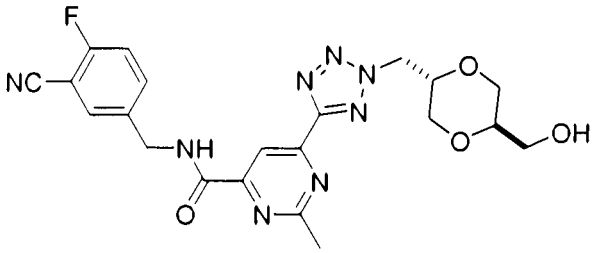


A mixture of *rac*-methyl 6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate (prepared as described in step 1 of the synthesis of *rac-N*-(4-fluoro-3-methylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 67) (100 mg, 0.285 mmol), (3-cyclopropyl-4-fluorophenyl)methanamine (141 mg, 0.856 mmol), and dimethylacetamide (1 mL) was heated to 85 °C for 18 hours. The title compound was isolated as a solid by reverse phase preparative HPLC (58

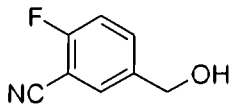
mg, 42%). MS (ES+) *m/z* 484 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.60 - 0.75 (m, 2 H), 0.95 (d, J=10.3 Hz, 2 H), 1.91 - 2.07 (m, 1 H), 2.81 (s, 3 H), 3.18 - 3.46 (m, 5 H), 3.76 (d, J=11.4 Hz, 1 H), 3.97 (d, J=11.4 Hz, 1 H), 4.03 - 4.14 (m, 1 H), 4.45 (d, J=6.2 Hz, 2 H), 4.70 - 4.79 (m, 1 H), 4.78 - 4.97 (m, 2 H), 6.94 - 7.10 (m, 2 H), 7.10 - 7.20 (m, 1 H), 8.39 (s, 1 H), 9.47 (t, J=6.0 Hz, 1 H).

Example 76

***rac-N*-(3-Cyano-4-fluorobenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

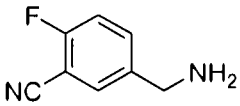


Step 1: Preparation of 2-fluoro-5-(hydroxymethyl)benzonitrile



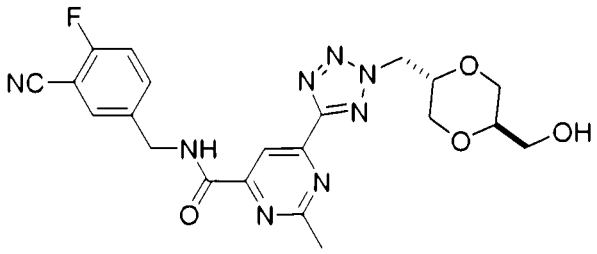
2-fluoro-5-formylbenzonitrile (7.0 g, 46.93 mmol) was dissolved in a mixture of methanol (30 mL) and dichloromethane (20 mL). Solid $NaBH_4$ (1.8 g, 46.93 mmol) was added portion-wise, and the mixture was stirred at room temperature overnight. The organic volatile was removed and the residue was dissolved in water (50 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic layer was washed with saturated sodium bicarbonate solution followed by brine solution, dried over anhydrous sodium sulfate, and concentrated to afford the title compound (6.6 g, 93 %).

Step 2: Preparation of 5-(aminomethyl)-2-fluorobenzonitrile



2-fluoro-5-(hydroxymethyl)benzonitrile (6.6 g, 43.66 mmol) was dissolved in dichloromethane (75 mL), and triethylamine (12 mL) was added. Mesityl chloride (4.4 mL, 56.76 mmol) was added drop-wise under ice-cold condition and the reaction mixture was stirred for 2 h at room temperature. The mixture was poured into cold water (50 mL). The organic layer was separated and was washed with saturated aqueous sodium bicarbonate solution, 1% aqueous hydrochloric acid solution and brine solution. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in acetonitrile (50 mL), and aqueous NH_4OH (30 mL) was added to it. The reaction mixture was stirred at room temperature for 3 h and was then concentrated under reduced pressure. The crude product was purified by washing with hexane and then with ethyl acetate to afford the title compound as a solid (6.8 g, quantitative).

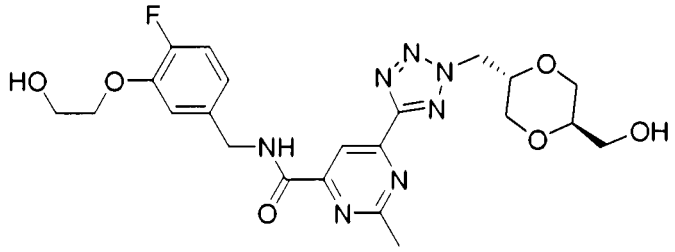
Step 3: Preparation of *rac-N*-(3-cyano-4-fluorobenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



A mixture of *rac*-methyl 6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxylate (prepared as described in step 1 of the synthesis of *rac-N*-(4-fluoro-3-methylbenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 67) (100 mg, 0.285 mmol), 5-(aminomethyl)-2-fluorobenzonitrile (129 mg, 0.856 mmol), and dimethylacetamide (1 mL) was heated to 85 °C for 18 hours. The title compound was isolated as a solid by reverse phase preparative HPLC 51 mg, 38%). MS (ES+) *m/z* 469 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.54 (s, 1 H), 2.84 (s, 3 H), 3.29 - 3.51 (m, 4 H), 3.78 (dd, *J*=11.7, 2.2 Hz, 1 H), 3.99 (dd, *J*=11.35, 2.56 Hz, 1 H), 4.03 - 4.14 (m, 1 H), 4.56 (d, *J*=6.6 Hz, 2 H), 4.65 (t, *J*=5.5 Hz, 1 H), 4.80 - 5.01 (m, 2 H), 7.49 (t, *J*=9.2 Hz, 1 H), 7.72 - 7.83 (m, 1 H), 7.88 (dd, *J*=5.9, 2.2 Hz, 1 H), 8.41 (s, 1 H), 9.63 (t, *J*=6.2 Hz, 1 H).

Example 77

***rac-N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

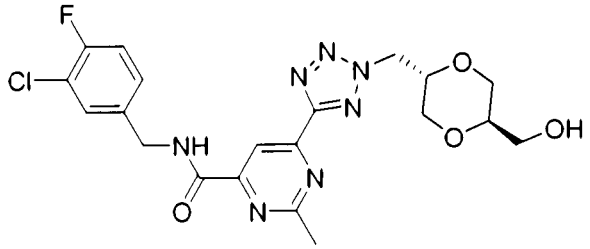


N-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 27) (491 mg, 1.32 mmol), *rac*-((2*R**,5*R**)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac-N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (398 mg, 1.32 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (240 mg, 1.58 mmol) were combined in dimethylacetamide (5 mL). After heating the reaction at 90 °C for 18 h, the reaction mixture was purified by reverse phase preparative high-pressure liquid chromatography. The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated to an oil which solidified under reduced pressure to give the title compound as an white solid (70 mg, 11%). MS (ES+) *m/z* 504. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (s, 1 H), 8.40 (s, 1 H), 7.14 (m, 2 H), 6.89 (m, 1 H), 4.74 (m, 2 H), 4.62 (m ,1 H), 4.41 (m ,

2 H), 4.15 (m, 1 H), 4.02 (m. 2 H), 3.91 (m, 1 H), 3.78 - 3.95 (m, 2 H), 3.59 - 3.72 (m, 1 H), 3.72 (m, 1 H), 3.61 (m, 2 H), 3.65-3.79 (m, 4 H), 2.81 (s, 3 H).

Example 78

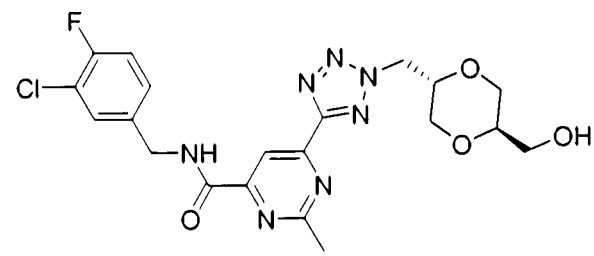
***rac-N*-(3-Chloro-4-fluorobenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



rac-((2*R**,5*R**)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac-N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (224 mg, 0.741 mmol) was added to a mixture of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 1 of the synthesis of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 47) (200 mg, 0.575 mmol) and triethylamine (349 mg, 3.4 mmol) in anhydrous dimethylacetamide (0.3 mL). The reaction was stirred overnight at 85 °C in a capped vial. The mixture was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing product were neutralized by passing through a carbonate resin column and concentrated. The resulting product was slurried with diethyl ether, decanted, and dried in vacuo to afford the title compound as a white solid (95 mg). MS (ES+) *m/z* 478 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.60 (1 H, t, *J*=6.2 Hz), 8.41 (1H,s), 7.57 (1 H, d, *J*=7.0 Hz), 7.37 (2 H, d, *J*=7.7 Hz), 4.93 (1 H, d, *J*=3.7 Hz), 4.88 (1 H, d, *J*=8.1 Hz), 4.66 (1 H, br. s.), 4.52 (2 H, d, *J*=6.2 Hz), 4.08 (1 H, d, *J*=2.9 Hz), 3.99 (1 H, d, *J*=11.3 Hz), 3.78 (1 H, d, *J*=9.9 Hz), 3.36 - 3.48 (2 H, m), 3.45 (3 H, t, *J*=10.8 Hz), 3.30 - 3.34 (1 H, m), 2.84 (3 H, s).

Example 79

***N*-(3-Chloro-4-fluorobenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

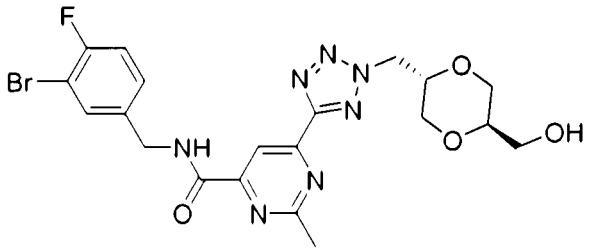


((2*R*,5*R*)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 62) (136 mg, 0.45

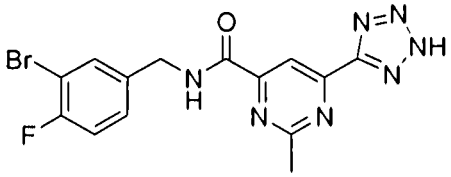
mmol) was added to a mixture of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 1 of the synthesis of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 47) (125 mg, 0.359 mmol) and triethylamine (153 mg, 1.5 mmol) in anhydrous dimethylacetamide (0.3 mL). The reaction was stirred overnight at 85 °C in a capped vial. The mixture was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing product were neutralized by passing through a carbonate resin column and concentrated. The resulting product was slurried with diethyl ether, decanted, and dried in vacuo to afford the title compound as a white solid (49 mg). MS (ES+) *m/z* 478 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.60 (1 H, t, *J*=6.2 Hz), 8.41 (1H,s), 7.57 (1 H, d, *J*=7.0 Hz), 7.37 (2 H, d, *J*=7.7 Hz), 4.93 (1 H, d, *J*=3.7 Hz), 4.88 (1 H, d, *J*=8.1 Hz), 4.66 (1 H, br. s.), 4.52 (2 H, d, *J*=6.2 Hz), 4.08 (1 H, d, *J*=2.9 Hz), 3.99 (1 H, d, *J*=11.3 Hz), 3.78 (1 H, d, *J*=9.9 Hz), 3.36 - 3.48 (2 H, m), 3.45 (3 H, t, *J*=10.8 Hz), 3.30 - 3.34 (1 H, m), 2.84 (3 H, s).

Example 80

_N_-(3-Bromo-4-fluorobenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

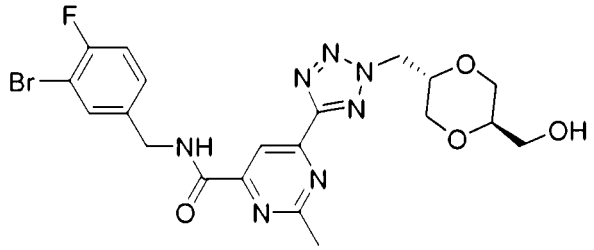


Step 1: Preparation of *N*-(3-bromo-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide



3-Bromo-4-fluorobenzylamine (865 mg, 3.6 mmol) was added to a solution of methyl 2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxylate (229 mg, 1.04 mmol) (prepared as described in step 1 of the synthesis of *N*-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 17) and triethylamine (316 mg, 3.1 mmol) in anhydrous dimethylacetamide (2.0 mL). The mixture was stirred at 65 °C for 2.5 days. After cooling to room temperature, the reaction mixture was diluted with excess 2.5 N NaOH solution and washed with ethyl acetate (2x). The aqueous layer was acidified with concentrated hydrochloric acid. The resulting precipitate was filtered, washed with water, and dried to afford the title compound as a light yellow solid (300 mg).

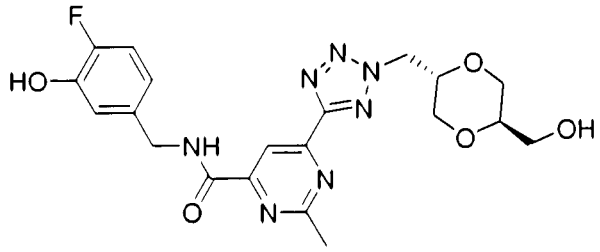
Step 2: Preparation of *N*-(3-bromo-4-fluorobenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



((2*R*,5*R*)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 62) (136 mg, 0.45 mmol) was added to a mixture of *N*-(3-bromo-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (125 mg, 0.359 mmol) and triethylamine (153 mg, 1.5 mmol) in anhydrous dimethylacetamide (0.3 mL). The reaction was stirred overnight at 85 °C in a capped vial. The mixture was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing product were neutralized by passing through a carbonate resin column and concentrated. The resulting product was slurried with diethyl ether, decanted, and dried in vacuo to afford the title compound as a white solid (61 mg). MS (ES+) *m/z* 522 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.60 (1 H, t, *J*=6.0 Hz), 8.41 (1 H, s), 7.69 (1 H, d, *J*=5.5 Hz), 7.41 (1 H, d, *J*=1.8 Hz), 7.33 (1 H, t, *J*=8.8 Hz), 4.93 (1 H, d, *J*=3.7 Hz), 4.88 (1 H, d, *J*=8.1 Hz), 4.66 (1 H, br. s.), 4.52 (2 H, d, *J*=6.2 Hz), 4.08 (1 H, d, *J*=2.9 Hz), 3.99 (1 H, d, *J*=11.3 Hz), 3.78 (1 H, d, *J*=9.9 Hz), 3.36 - 3.48 (2 H, m), 3.45 (2 H, t, *J*=10.8 Hz), 3.31 (1 H, br. s.), 2.84 (3 H, s).

Example 81

N-(4-Fluoro-3-hydroxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

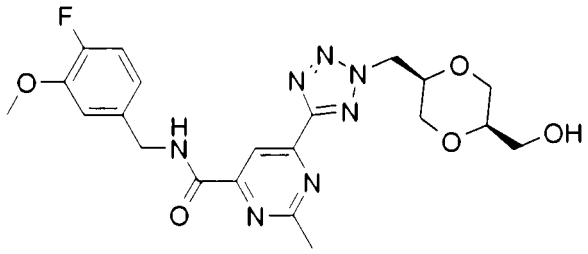


N-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 65) (476 mg, 1.0 mmol) was dissolved in dichloromethane (20 mL) and the solution was cooled to -70 °C. A solution of boron tribromide (4.0 mL, 1.0 M in dichloromethane, 4.0 mmol) was added. After 30 min, the mixture was allowed to warm to room temperature and was stirred for 2 hours. The reaction mixture was poured into a mixture of ice and saturated aq. sodium bicarbonate. The mixture was extracted with dichloromethane (2 x 50 mL). The aqueous layer was acidified to pH 2 with 1N hydrochloric acid and extracted with dichloromethane (50 mL). The combined organic layers were dried (sodium sulfate) and concentrated. The residue was purified by silica gel column chromatography

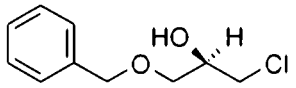
(dichloromethane/methanol, 100/2; 100/3; 100/4) to afford the title compound as a foaming white solid (114 mg, 25%). MS (ES+) *m/z* 460 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.72 (s, 1 H), 9.50 (t, *J*=6.4 Hz, 1 H), 8.37 (s, 1 H), 7.00 (dd, *J*=11.3, 8.4 Hz, 1 H), 6.89 (dd, *J*=8.6, 2.1 Hz, 1 H), 6.72 - 6.68 (m, 1 H), 4.89 (dd, *J*=14.3, 3.7 Hz, 1 H), 4.84 - 4.77 (m, *J*=14.3, 8.0 Hz, 1 H), 4.65 (t, *J*=5.7 Hz, 1 H), 4.37 (d, *J*=6.4 Hz, 2 H), 4.06 - 3.98 (m, 1 H), 3.93 (dd, *J*=11.5, 2.3 Hz, 1 H), 3.72 (dd, *J*=11.5, 2.5 Hz, 1 H), 3.42 - 3.18 (m, 5 H), 2.78 (s, 3 H).

Example 82

N-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

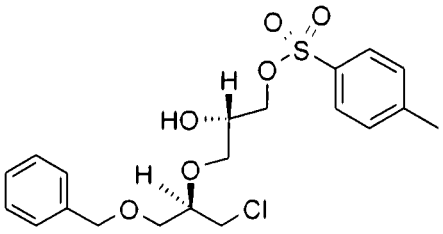


Step 1: Preparation of (2*R*)-1-(benzyloxy)-3-chloropropan-2-ol



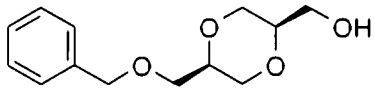
To a flame-dried, three neck round bottomed flask was added dry 1,2-dichloroethane (50 mL) and charged with *R*-(-)-epichlorohydrin (3.8 mL, 49 mmol) and benzyl alcohol (10 mL, 100 mmol). The solution was cooled to 0 °C under nitrogen. The stirring solution was then treated with boron trifluoride etherate (0.27 mL, 2.2 mmol) dropwise and allowed to warm to room temperature overnight. The reaction mixture was then heated to reflux. After about 2 hours, the mixture was cooled to room temperature. The mixture was partitioned against 10% aqueous saturated sodium bicarbonate (25 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (2 x 25 mL). The organic layers were combined and washed with brine (2 x 10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a viscous oil. The oil was adsorbed onto silica and purified by silica column chromatography eluting with 20-30% ethyl acetate in heptanes to provide the title compound as a viscous oil (5.6 g, 57%). LCMS (5%-100% CH_3CN/H_2O, 5 min) 2.7 min, m/z 223 (M+Na). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 - 7.41 (m, 5 H), 4.58 (s, 2 H), 3.98 - 4.07 (m, 1 H), 3.58 - 3.71 (m, 4 H), 2.49 (d, *J*=5.8 Hz, 1 H).

Step 2: Preparation of (2*S*)-3-((1*R*)-2-(benzyloxy)-1-(chloromethyl)ethoxy)-2-hydroxypropyl 4-methylbenzenesulfonate



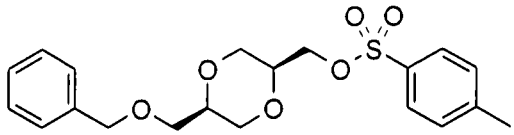
To a flask containing (2*R*)-1-(benzyloxy)-3-chloropropan-2-ol (2.5 g, 12.5 mmol) was added *S*-glycidol tosylate (0.95 g, 0.33 mmol) and back-filled with nitrogen. The flask was charged with dry 1,2-dichloroethane (50 mL) and the resulting stirring solution cooled to 0 °C. The mixture was treated with boron trifluoride etherate (0.10 mL, 0.81 mmol) dropwise and the reaction mixture was allowed to slowly warm to room temperature overnight. The mixture was diluted with dichloromethane (50 mL) and partitioned against 10% aqueous saturated sodium bicarbonate (100 mL). The layers were separated and the aqueous phase extracted with dichloromethane (2 x 50 mL). The organic layers were combined and washed with water (25 mL) and brine (25 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a viscous oil. The oil was adsorbed onto silica and purified by silica column chromatography eluting with 30-50% ethyl acetate in heptanes to provide the title compound as a viscous oil (0.80 gm, 45%). LCMS (5%-100% CH_3CN/H_2O, 5 min) 4.0 min, *m/z* 429 (M+H). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (d, *J*=8.2 Hz, 2 H), 7.28 - 7.41 (m, 7 H), 4.54 (s, 2 H), 4.02 - 4.13 (m, 2 H), 3.69 - 3.76 (m, 2 H), 3.50 - 3.65 (m, 6 H), 2.95 (d, *J*=4.3 Hz, 1 H), 2.45 (s, 3 H).

Step 3: Preparation of ((2*R*,5*R*)-5-((benzyloxy)methyl)-1,4-dioxan-2-yl)methanol



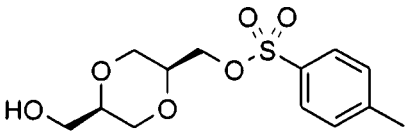
To a flask containing (2*S*)-3-((1*R*)-2-(benzyloxy)-1-(chloromethyl)ethoxy)-2-hydroxypropyl 4-methylbenzenesulfonate (0.80 g, 1.9 mmol) was added 2.5 N aqueous sodium hydroxide solution (2.6 mL, 6.5 mmol). The resulting bi-phasic reaction mixture was vigorously stirred at room temperature. After about 2.5 hours, the reaction mixture was heated to 90 °C. After about 4 hours, the reaction mixture was cooled to room temperature and stirred overnight. The mixture was then re-heated to 90 °C for about 2 hours and finally cooled to room temperature. The reaction was neutralized with 1 N hydrochloric acid and solid sodium chloride was added to saturation. The reaction mixture was partitioned against dichloromethane (10 mL). The aqueous layer was extracted with additional portions of dichloromethane (3 x 10 mL). The organic layers were combined and washed with saturated aqueous sodium bicarbonate, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a viscous oil. The oil was purified by silica column chromatography eluting with 1-4% methanol in dichloromethane to provide the title compound as a viscous oil (0.20 gm, 45%). LCMS (5%-100% CH_3CN/H_2O, 5 min) 2.6 min, *m/z* 239 (M+H). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.25 - 7.45 (m, 5 H), 4.59 (s, 2 H), 3.5 - 3.9 (m, 10 H), 2.3 (br. S., 1 H).

Step 4: Preparation of ((2*S*,5*R*)-5-((benzyloxy)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



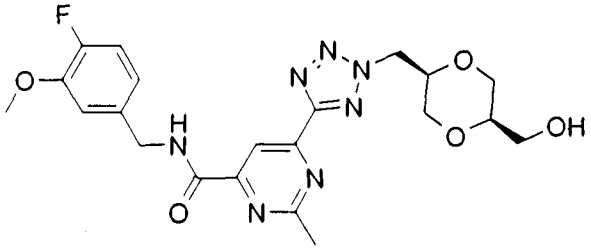
To a solution of ((2*R*,5*R*)-5-((benzyloxy)methyl)-1,4-dioxan-2-yl)methanol (0.20 g, 0.59 mmol) in pyridine (3 mL) was added p-toluenesulfonyl chloride (0.38 g, 3.4 mmol) and a small crystal of 4-dimethylaminopyridine. The reaction mixture was left to stir at room temperature overnight. The mixture was then treated with additional p-toluenesulfonyl chloride (0.10 gm) and left to stir for about 8 hours. The reaction mixture was treated with toluene (10 mL) and concentrated under reduced pressure using a cold bath. The addition of toluene and concentration under reduced pressure was repeated (3x). The resulting residue was partitioned between water (20 mL) and ethyl acetate (20 mL). The layers were separated and the aqueous phase extracted with ethyl acetate (2 x 20 mL). The organic phases were combined and washed with saturated aqueous sodium bicarbonate solution, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a viscous oil. This oil was adsorbed onto silica and purified by silica column chromatography eluting with 30-40% ethyl acetate in heptanes to provide the title compound as a viscous oil (0.19 gm, 82%). LCMS (50%-100% CH_3CN/H_2O, 5 min) 2.6 min, *m/z* 393 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.81 (d, *J*=8.2 Hz, 2 H), 7.28 - 7.41 (m, 7 H), 4.54 (s, 2 H), 4.30 (dd, *J*=10.4, 7.0 Hz, 1 H), 4.12 (dd, *J*=10.4, 5.6 Hz, 1 H), 3.52 - 3.86 (m, 7 H), 3.42 - 3.50 (m, 1 H), 2.45 (s, 3 H).

Step 5: Preparation of ((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



To a solution of ((2*S*,5*R*)-5-((benzyloxy)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (0.19 g, 0.48 mmol) in ethanol (5 mL) under nitrogen was added palladium on carbon and back-filled with hydrogen gas. The mixture was allowed to stir at room temperature overnight under a balloon of hydrogen gas. The reaction mixture was filtered through Celite™ with ethanol washes. The combined filtrates were concentrated under reduced pressure to give the title compound as a viscous oil (0.13 gm, 89%). LCMS (5%-100% CH_3CN/H_2O, 5 min) 2.8 min, *m/z* 303 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (d, *J*=8.2 Hz, 2 H), 7.35 (d, *J*=8.2 Hz, 2 H), 4.21 - 4.30 (m, 1 H), 4.11 - 4.19 (m, 1 H), 3.76 - 3.85 (m, 1 H), 3.52 - 3.75 (m, 7 H), 2.45 (s, 3 H).

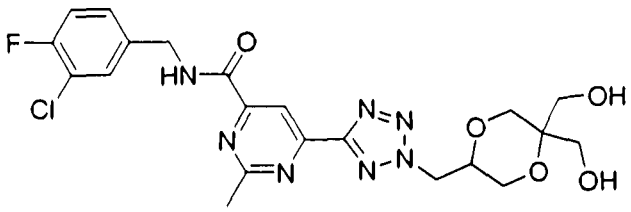
Step 6: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((2*R*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



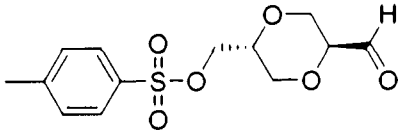
To a vial containing *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (101 mg, 0.29 mmol) and ((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (115 mg, 0.38 mmol) was added *N*,*N*-dimethylformamide (0.3 mL) followed by triethylamine (1.0 mL). The vial was flushed with nitrogen, tightly capped and heated to 85 °C with stirring. After about 2 days, the mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was diluted with dichloromethane (10 mL) and partitioned with water (10 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The organic layers were combined and washed with 1 N hydrochloric acid solution (10 mL), water (10 mL), 1 N sodium hydroxide solution (10 mL), water (10 mL), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica column chromatography eluting with 1-3% methanol in ethyl acetate. The crude product was further purified by reverse phase preparative HPLC (acetonitrile/water) to provide the title compound as a white solid (39 mg, 28%). LCMS (5%-100% CH_3CN/H_2O, 5 min) 3.05 min, *m/z* 474 (M+H). ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 9.58 (t, *J*=6.4 Hz, 1 H), 8.42 (s, 1 H), 7.09 - 7.24 (m, 2 H), 6.83 - 6.96 (m, 1 H), 5.35 (dd, *J*=14.2, 9.9 Hz, 1 H), 4.98 (dd, *J*=14.3, 4.0 Hz, 1 H), 4.70 - 4.82 (m, 1 H), 4.50 (d, *J*=6.3 Hz, 2 H), 4.16 - 4.28 (m, 1 H), 3.82 (s, 3 H), 3.73 - 3.81 (m, 3 H), 3.43 - 3.58 (m, 4 H), 2.83 (s, 3 H).

Example 83

***N*-(3-Chloro-4-fluorobenzyl)-6-(2-((5,5-bis(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

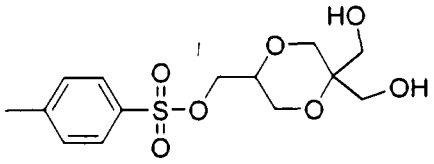


Step 1: Preparation of *trans*-(5-formyl-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



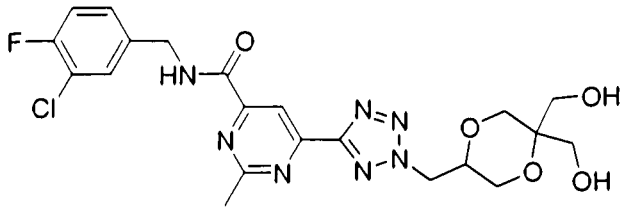
To a -78 °C solution of oxalyl chloride (6.43 g, 49.6 mmol) in dichloromethane (30 mL) was slowly added dimethyl sulfoxide (7.29 g, 93.3 mmol). The reaction was stirred at -78 °C for 20 min at which time a solution of *rac*-((2*R**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (6.0 g, 20 mmol) in dichloromethane (12 mL) was added drop-wise. The resulting solution was stirred at -78 °C for 1h and then quenched with triethylamine (11.0 g, 109 mmol) forming a thick white precipitate. The ice bath was removed and the reaction was slowly warmed to room temperature. The mixture was diluted in dichloromethane (100 mL) and washed successively with 1N hydrochloric acid (75 mL), sat. sodium bicarbonate (75 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated to afford the title compound as a yellow oil (6.4 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.43 (s, 1 H), 7.75 (m, 2 H), 7.47 (m, 2 H), 3.63 - 4.08 (m, 5 H), 3.17 – 3.38 (m, 3 H), 2.39 (s, 3 H).

Step 2: Preparation of (5,5-bis(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



2.5 N Sodium hydroxide (17.0 mL, 1.70 g, 42.6 mmol) was added to a solution of *trans*-((5-formyl-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (6.4 g, 21.0 mmol) in 2:1 tetrahydrofuran/water (30 mL). To this reaction was added a 37% solution of formaldehyde (3.69 mL, 3.80 g, 46.9 mmol) and the mixture was stirred at 25 °C for 18 hours. The reaction mixture was neutralized with formic acid (2 mL). The reaction was concentrated, washed with ethyl acetate (150 mL) and filtered. The filtrate was concentrated to afford the title compound as a yellow oil that solidified upon standing (5.4 g, 76%). LC/MS (5%-95% CH_3CN:H_2O, 6 min): 3.69 min, *m/z* 333 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (m, 2 H), 7.33 (m, 2 H), 4.75 (m, 2 H), 3.95 - 3.49 (m, 3 H), 3.45 - 3.75 (m, 9 H), 2.43 (s, 3 H).

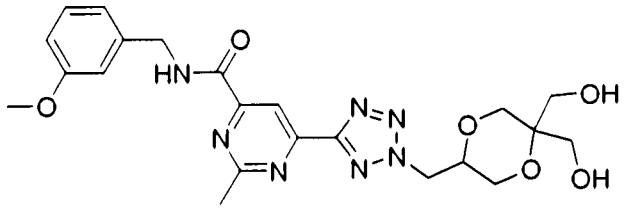
Step 3: *N*-(3-chloro-4-fluorobenzyl)-6-(2-((5,5-bis(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



N-(3-Chloro-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 1 of the synthesis of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 47) (50 mg, 0.144 mmol), (5,5-bis(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (47.8 mg, 0.144 mmol), and triethylamine (400 µL) were combined in dimethylacetamide (100 µL). The resulting mixture was stirred at 90 °C for 18 h. The mixture was concentrated. The residue was purified by reverse phase high-pressure liquid chromatography. The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated to afford the title compound as a solid (12 mg, 16%). MS (ES+) *m/z* 508 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.61 (t, J = 6.2 Hz, 1 H), 7.57 d, J = 7.0 Hz, 1 H), 7.37 (d, J = 7.7 Hz, 2 H), 4.97 (s, 1 H), 4.95 (d, J = 3.3 Hz, 1 H), 4.44 - 4.54 (m, 1 H), 4.52 (d, J = 6.2 Hz, 3 H), 3.73 (d, J = 3.3 Hz, 1 H), 3.60 (t, J = 5.5 Hz, 1 H), 3.66 (m, 2 H), 3.39 (d, J = 4.4 Hz, 1 H), 3.35 - 3.44 (m, 1 H), 3.23 (s, 1 H), 3.25 (d, J = 5.5 Hz, 2 H), 2.84 (s, 3 H), 2.74 (s, 1H).

Example 84

N-(3-Methoxybenzyl)-6-(2-((5,5-bis(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

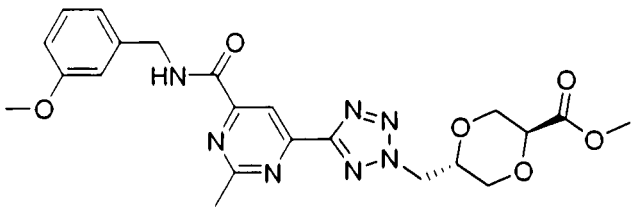


N-(3-Methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (47 mg, 0.144 mmol), (5,5-bis(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 2 of the synthesis of *N*-(3-chloro-4-fluorobenzyl)-6-(2-((5,5-bis(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 83) (48 mg, 0.144 mmol), and triethylamine (400 µL) were combined in dimethylacetamide (100 µL). The resulting mixture was stirred at 90 °C for 18 h. The mixture was concentrated and the residue was purified by reverse phase high-pressure liquid chromatography. The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated to afford the title compound as a solid (12 mg, 16%). MS (ES+) *m/z* 486 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (m, 1 H), 8.42 (s,

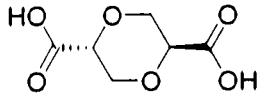
1 H), 7.24 (m, 1 H), 6.93 (m, 2 H), 6.81 (m, 2 H), 4.96 (m, 2 H), 4.53 (m, 3 H), 4.18 (m, 2 H), 3.74 (s, 3 H), 3.48 – 3.62 (m, 4 H), 3.42 (m, 2 H), 2.86 (s, 3 H).

Example 85

***rac*-(2*S**,5*S**)-Methyl 5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate**

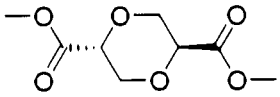


Step 1: Preparation of *trans*-1,4-dioxane-2,5-dicarboxylic acid



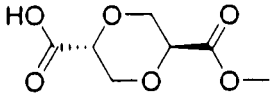
A solution of *trans*-2,5-bis-(hydroxymethyl)-1,4-dioxane (prepared as described in step 3 of the synthesis of *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (88.17 g) in water (458 mL) and HNO_3 (1238 mL) was heated to reflux for 100 min and then cooled to 5 °C. The resulting precipitate was collected by filtration, washed with cold water (500 mL), and dried in vacuo at 50 °C overnight to provide the title compound (100.75 g).

Step 2: Preparation of *trans*-dimethyl 1,4-dioxane-2,5-dicarboxylate



trans-1,4-Dioxane-2,5-dicarboxylic acid (90 g) was dissolved in hot methanol (1380 mL). The solution was cooled to 15 °C and HCl gas (approximately 45 g) was bubbled through the solution until saturated. The reaction mixture was stirred at room temperature for 24 hours, and then cooled to 5 °C. The resulting precipitate was collected by filtration, washed methanol and cold saturated sodium bicarbonate solution (500 mL). The solid was further washed with cold water (500 mL) until the wash was neutral. The product was dried in a vacuo at 50 °C overnight to afford the title compound (97 g).

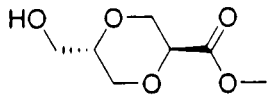
Step 3: Preparation of *rac*-(2*R**,5*S**)-5-(methoxycarbonyl)-1,4-dioxane-2-carboxylic acid



A solution of *trans*-dimethyl 1,4-dioxane-2,5-dicarboxylate (68.54 g, 336 mmol) in methanol (3.2 L) and water (0.8 L) was slowly added to a solution of lithium hydroxide monohydrate (10.56 g, 252 mmol) in water (0.6 L). The reaction mixture was maintained at 20 °C during the addition by applying a water bath. The resulting solution was stirred for 24 h and concentrated to remove most of the methanol in vacuo. The remaining aqueous mixture was extracted with ethyl acetate (2 L). The aqueous layer was then acidified to pH 2 with 6 N hydrochloric acid and concentrated to a small

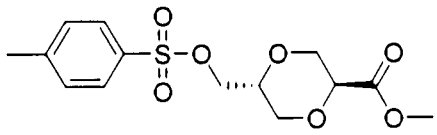
volume (ca. 400 mL). The mixture was cooled to 0-5 °C and filtered. The solids were washed with cold water and dried in a vacuum oven at 50 °C for 24 h to afford the title compound (33.34 g).

Step 4: Preparation of *rac*-(2*S**,5*S**)-methyl 5-(hydroxymethyl)-1,4-dioxane-2-carboxylate



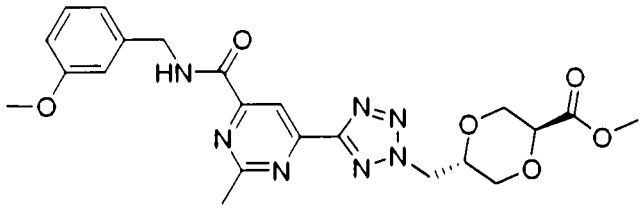
rac-(2*R**,5*S**)-5-(Methoxycarbonyl)-1,4-dioxane-2-carboxylic acid (19.34 g, 102 mmol) was dissolved in tetrahydrofuran (800 mL). A solution of borane dimethylsulfide (10 M, 12.2 mL) was slowly added to the solution. The mixture was stirred at room temperature for 3 h and then quenched with water (50 mL). The mixture was concentrated under vacuum. The residue was suspended in ethyl acetate and filtered. The filtrate was concentrated. The residue was again suspended in chloroform, filtered, and the filtrate concentrated. The crude product was purified by silica gel chromatography (dichloromethane/methanol, 99.5/0.5 – 98/2) to afford the title compound.

Step 5: Preparation of *rac*-(2*S**,5*R**)-methyl 5-((tosyloxy)methyl)-1,4-dioxane-2-carboxylate



p-Toluene sulfonylchloride (3.46 g, 18.15 mmol) was added portion-wise over 30 min to a solution of *rac*-(2*S**,5*S**)-methyl 5-(hydroxymethyl)-1,4-dioxane-2-carboxylate (3.2 g, 18.0 mmol) in anhydrous pyridine (24 mL). The mixture was stirred at room temperature for 3.5 h. Water (100 mL) was added drop-wise at ice bath temperatures. The resulting precipitate was filtered, washed with water, and dried to afford the title compound as a white solid (4.31 g).

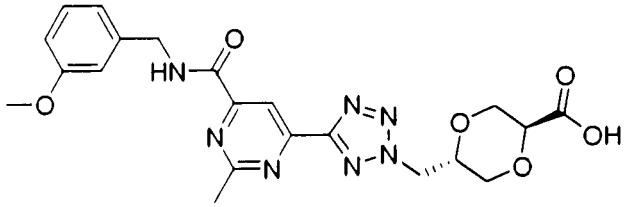
Step 6: Preparation of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate



rac-(2*S**,5*R**)-Methyl 5-((tosyloxy)methyl)-1,4-dioxane-2-carboxylate (2.19 g, 6.6 mmol) was added to a solution of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (2.16 g, 6.6 mmol) and triethylamine (1.33 g, 13.2 mmol) in anhydrous dimethylacetamide (4 mL). The mixture was stirred at 85 °C in a capped vial overnight. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound (54 mg).

Example 86

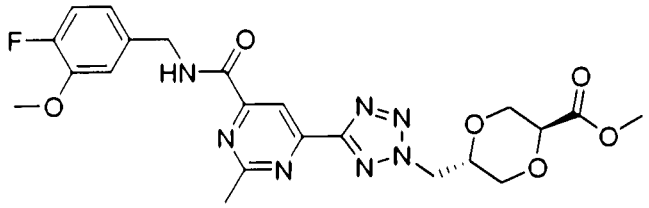
***rac*-(2*S**,5*S**)-5-((5-(6-((3-Methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid**



Sodium hydroxide (10 pellets) was added to a mixture of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (54 mg) in tetrahydrofuran (3 mL) and water (3 mL). The mixture was stirred overnight at room temperature. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing the product were concentrated. The residue was slurried and decanted from ethyl ether and dried in a vacuum desiccator to afford the title compound as a white solid (736 mg). MS (ES+) *m/z* 470 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (1 H, t, *J*=6.2 Hz), 8.42 (1 H, s), 7.24 (1 H, t, *J*=8.1 Hz), 6.93 (2 H, br. s.), 6.83 (1 H, d, *J*=7.3 Hz), 4.96 (1 H, d, *J*=3.3 Hz), 4.92 (1 H, d, *J*=7.7 Hz), 4.51 (2 H, d, *J*=6.2 Hz), 4.09 (2 H, t, *J*=10.4 Hz), 4.12 (1 H, d, *J*=12.8 Hz), 3.95 (1 H, dd, *J*=11.7, 2.6 Hz), 3.74 (3 H, s), 3.49 (2 H, dt, *J*=16.4, 10.8 Hz), 2.83 (3 H, s), 2.43 (1 H, s).

Example 87

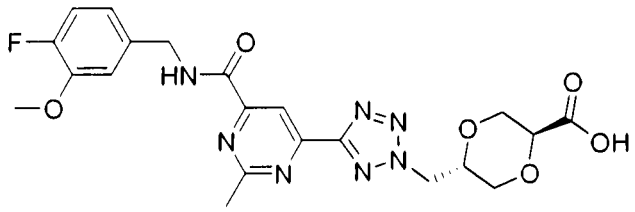
***rac*-(2*S**,5*S**)-methyl 5-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate**



rac-(2*S**,5*R**)-Methyl 5-((tosyloxy)methyl)-1,4-dioxane-2-carboxylate (prepared as described in step 1 of the synthesis of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate, Example 85) (562 mg, 1.7 mmol) was added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (400 mg, 1.17 mmol) and triethylamine (233 mg, 2.3 mmol) in anhydrous dimethylacetamide (1.0 mL). The mixture was stirred at 85 °C in a capped vial overnight. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound (210 mg).

Example 88

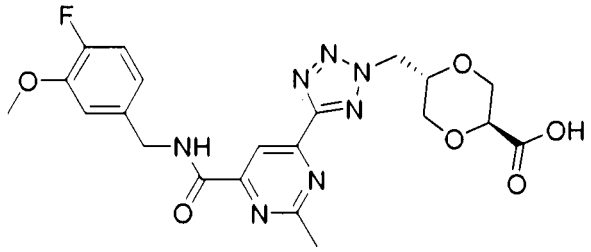
***rac*-(2*S**,5*S**)-5-((5-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid**



Sodium hydroxide (2 pellets) was added to a mixture of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as described in Example 87) (34 mg, 0.068 mmol) in tetrahydrofuran (0.4 mL) and water (0.4 mL). The mixture was stirred overnight at room temperature. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing the product were concentrated. The residue was slurried and decanted from ethyl ether and dried in a vacuum desiccator to afford the title compound as a white solid (31 mg). MS (ES+) *m/z* 488 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.46 - 9.56 (1 H, m), 8.42 (1 H, s), 7.17 (1 H, dd, *J*=12.8, 8.8 Hz), 6.92 (1 H, br. s.), 4.89 - 5.00 (2 H, m), 4.50 (2 H, d, *J*=5.9 Hz), 4.06 (3 H, br. s.), 3.95 (1 H, d, *J*=11.7 Hz), 3.82 (3 H, s), 3.48 (2 H, dd, *J*=10.4, 7.5 Hz), 3.22 (2 H, br. s.), 2.83 (2 H, s), 1.25 (2 H, d, *J*=5.1 Hz)

Example 89

(2*S*,5*S*)-5-((5-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid

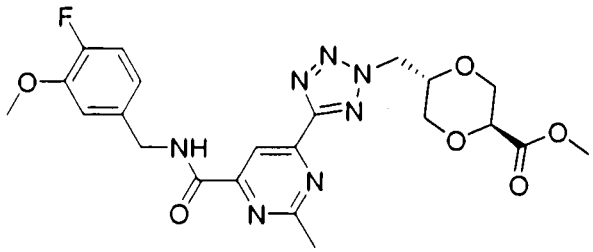


A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 65) (238 mg, 0.5 mmol) and pyridinium dichromate (1.15 g, 3.0 mmol) in DMF (5.0 mL) was shaken for 24 hours at room temperature. The reaction mixture was diluted with dichloromethane (50 mL) and washed with 1 N hydrochloric acid solution (2 x 50 mL). The organic layer was extracted with 1 N sodium hydroxide solution (2 x 40 mL). The combined aqueous layers were acidified with concentrated hydrochloric acid and extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried (sodium sulfate) and concentrated. The residue was triturated with diethyl ether and filtered to afford the title compound as a white solid (79 mg, 32%). MS (ES+) *m/z* 488 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.58 (t, *J*=6.6 Hz, 1 H), 8.41 (s, 1 H), 7.17 (dd, *J*=8.4, 2.2 Hz, 1 H), 7.13 (dd, *J*=11.7, 8.4 Hz, 1 H), 6.89 (ddd, *J*=8.3, 4.5, 2.2 Hz, 1 H), 4.97 (dd, *J*=14.3, 3.7

Hz, 1 H), 4.89 (dd, *J*=14.3, 7.7 Hz, 1 H), 4.49 (d, *J*=6.2 Hz, 2 H), 4.15 - 4.03 (m, 3 H), 3.93 (dd, *J*=11.5, 3.1 Hz, 1 H), 3.81 (s, 3 H), 3.53 - 3.41 (m, 2 H), 2.82 (s, 3 H).

Example 90

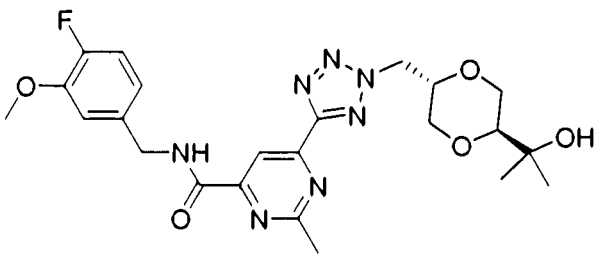
(2*S*,5*S*)-Methyl 5-((5-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate



A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 65) (952 mg, 2.0 mmol) and pyridinium dichromate (4.61 g, 12.0 mmol) in DMF (20.0 mL) was shaken for 36 h at room temperature. The reaction mixture was poured into 1 N hydrochloric acid solution (100 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were dried (sodium sulfate) and concentrated. The residue was dissolved in methanol (50 mL) and a solution of hydrochloric acid (4M in dioxane, 25 mL) was added. The mixture was allowed to stand for 18 h and was then concentrated. The residue was mixed with dichloromethane (50 mL) and water (100 mL). The aqueous layer was further extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried (sodium sulfate), and concentrated. The crude product was purified by silica gel column chromatography (dichloromethane/methanol, 100/1; 100/2) to afford the title compound (711 mg, 71%). MS (ES+) *m/z* 502 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.58 (t, *J*=6.2 Hz, 1 H), 8.41 (s, 1 H), 7.17 (dd, *J*=8.1, 2.2 Hz, 1 H), 7.13 (dd, *J*=11.3, 8.1 Hz, 1 H), 6.89 (ddd, *J*=8.3, 4.5, 1.8 Hz, 1 H), 4.98 (dd, *J*=14.3, 3.7 Hz, 1 H), 4.90 (dd, *J*=14.3, 7.7 Hz, 1 H), 4.48 (d, *J*=6.6 Hz, 2 H), 4.24 (dd, *J*=10.2, 2.9 Hz, 1 H), 4.17 - 4.10 (m, 1 H), 4.08 (dd, *J*=11.5, 2.7 Hz, 1 H), 3.99 - 3.91 (m, 1 H), 3.81 (s, 3 H), 3.63 (s, 3 H), 3.56 - 3.44 (m, 2 H), 2.82 (s, 3 H).

Example 91

***N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S*,5*S*)-5-(2-hydroxypropan-2-yl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

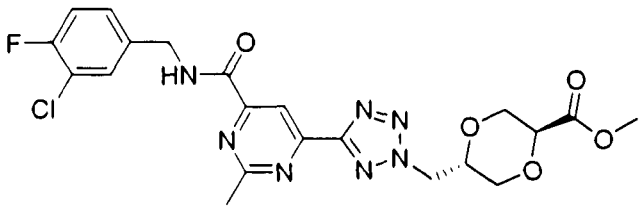


(2*S*,5*S*)-Methyl 5-((5-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as in Example 90) (251 mg, 0.5 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL) and the solution was cooled to -70 °C. A solution of

methylmagnesium bromide (3 M in ethyl ether, 666 μL, 2.0 mmol) was added and the mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was quenched with 1 N hydrochloric acid (5 mL). The mixture was poured into water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried (sodium sulfate) and concentrated. The crude product was purified by silica gel column chromatography (dichloromethane/methanol, 100/1; 100/2) to afford the title compound (51.7 mg, 21%). MS (ES+) *m/z* 502 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.57 (t, *J*=6.6 Hz, 1 H), 8.41 (s, 1 H), 7.20 - 7.10 (m, 2 H), 6.89 (ddd, *J*=8.4, 4.4, 2.2 Hz, 1 H), 4.93 (dd, *J*=13.9, 3.7 Hz, 1 H), 4.88 - 4.82 (m, *J*=14.3, 7.7 Hz, 1 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.46 (s, 1 H), 4.07 - 3.98 (m, 2 H), 3.85 - 3.77 (m, 4 H), 3.39 (dt, *J*=16.8, 11.3 Hz, 2 H), 3.19 - 3.13 (m, *J*=10.2, 2.2 Hz, 1 H), 2.82 (s, 3 H), 1.06 (s, 3 H), 0.99 (s, 3 H).

Example 92

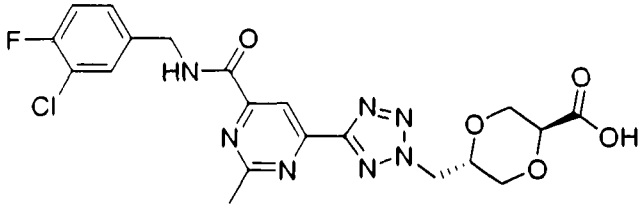
***rac*-(2*S**,5*S**)-Methyl 5-((5-(6-((3-chloro-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate**



rac-(2*S**,5*R**)-Methyl 5-((tosyloxy)methyl)-1,4-dioxane-2-carboxylate (prepared as described in step 1 of the synthesis of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate, Example 85) (244 mg, 0.74 mmol) was added to a solution of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 1 of the synthesis of *N*-(3-chloro-4-fluorobenzyl)-2-methyl-6-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 47) (200 mg, 0.575 mmol) and triethylamine (349 mg, 3.4 mmol) in anhydrous dimethylacetamide (0.3 mL). The mixture was stirred at 85 °C in a capped vial overnight. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound (103 mg).

Example 93

***rac*-(2*S**,5*S**)-5-((5-(6-((3-Chloro-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid**

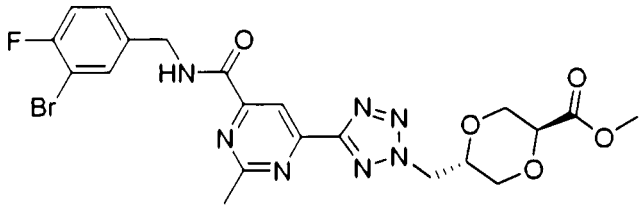


Sodium hydroxide (3 pellets) was added to a mixture of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((3-chloro-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as described in Example 92) (103 mg) in tetrahydrofuran (0.4 mL) and water (0.4 mL). The mixture was stirred overnight at room temperature. The reaction mixture was acidified

with trifluoroacetic acid with ice bath cooling and purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing the product were concentrated. The residue was slurried and decanted from ethyl ether and dried in a vacuum desiccator to afford the title compound as a white solid (88 mg). MS (ES+) *m/z* 492 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.55 - 9.64 (1 H, m), 8.42 (1 H, s), 7.57 (1 H, d, *J*=7.3 Hz), 7.37 (2 H, d, *J*=7.0 Hz), 4.91 (1 H, br. s.), 4.95 (1 H, d, *J*=12.8 Hz), 4.52 (2 H, d, *J*=5.9 Hz), 4.11 (3 H, d, *J*=12.8 Hz), 4.06 (1 H, br. s.), 3.95 (1 H, d, *J*=11.7 Hz), 3.48 (1 H, t, *J*=11.0 Hz), 3.44 - 3.55 (1 H, m), 2.84 (3 H, s).

Example 94

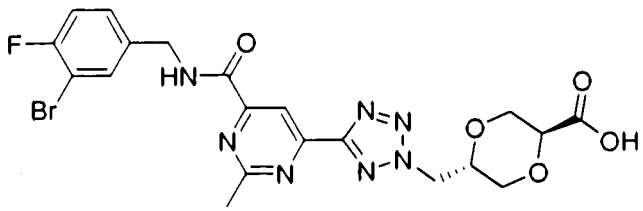
***rac*-(2*S**,5*S**)-Methyl 5-((5-(6-((3-bromo-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate**



rac-(2*S**,5*R**)-Methyl 5-((tosyloxy)methyl)-1,4-dioxane-2-carboxylate (prepared as described in step 1 of the synthesis of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate, Example 85) (150 mg, 0.454 mmol) was added to a solution of *N*-(3-bromo-4-fluorobenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 1 of the synthesis of *N*-(3-bromo-4-fluorobenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 80) (150 mg, 0.382 mmol) and triethylamine (153 mg, 1.5 mmol) in anhydrous dimethylacetamide (0.3 mL). The mixture was stirred at 85 °C in a capped vial overnight. The reaction mixture was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound (70 mg).

Example 95

***rac*-(2*S**,5*S**)-5-((5-(6-((3-Bromo-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid**

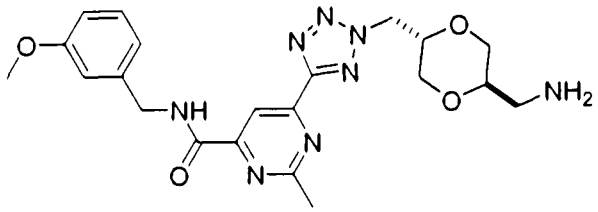


Sodium hydroxide (3 pellets) was added to a mixture of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((3-bromo-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as described in Example 94) (70 mg) in tetrahydrofuran (0.4 mL) and water (0.4 mL). The mixture was stirred overnight at room temperature. The reaction mixture was acidified with trifluoroacetic acid with ice bath cooling and purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing the product were concentrated. The residue was slurried and

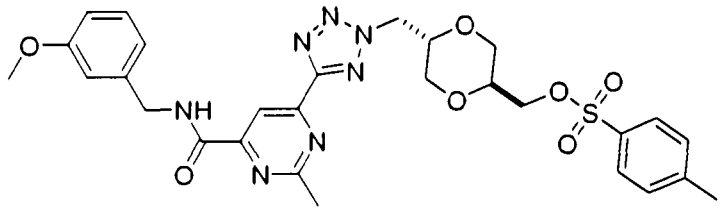
decanted from ethyl ether and dried in a vacuum desiccator to afford the title compound as a white solid (18 mg). MS (ES+) *m/z* 536 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.61 (1 H, t, *J*=6.2 Hz), 8.42 (1 H, s), 7.69 (1 H, d, *J*=7.0 Hz), 7.41 (1 H, t, *J*=5.7 Hz), 7.33 (1 H, t, *J*=8.6 Hz), 4.90 - 5.00 (2 H, m), 4.52 (3 H, d, *J*=6.2 Hz), 4.05 - 4.17 (3 H, m), 3.95 (1 H, dd, *J*=11.9, 2.7 Hz), 3.50 (2 H, dt, *J*=16.3, 11.1 Hz), 2.84 (3 H, s).

Example 96

rac-*N*-(3-Methoxybenzyl)-6-(2-(((2*S,5*R**)-5-(aminomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

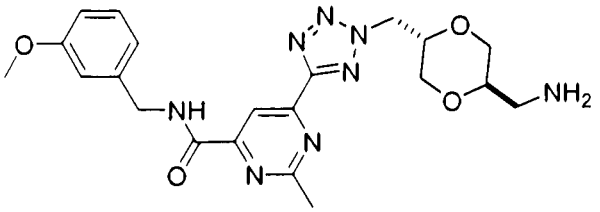


Step 1: Preparation of *rac*-((2*S**,5*S**)-5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



In a 40 mL scintillation vial with a magnetic stir bar at room temperature and standard pressure, *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (520 mg, 1.60 mmol) was combined with *rac*-((2*R**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (604 mg, 2.00 mmol), polymer supported triphenylphosphine (1490 mg, 3.20 mmol), and anhydrous tetrahydrofuran (15 ml). The reaction mixture was cooled to 0 °C and di-*tert*-butyl azodicarboxylate (736 mg, 3.20 mmol) was added. The mixture was stirred at 0 °C for 2 hours and then was allowed to warm to room temperature for 12 hours. The reaction mixture was filtered and concentrated to oil. The oil was dissolved in acetonitrile and water and chromatographed by reversed phased preparative HPLC (Gilson prep, Delta Pak column, 30 to 40% acetonitrile, 10 min hold, 40 min run, 10 min hold). Fractions containing the desired were combined and concentrated under vacuum to afford the title compound as a white solid (136.5 mg). ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 2.84 - 2.86 (m, 3 H), 3.03 (dd, *J*=13.3, 2.8 Hz, 1 H), 3.37 (dd, *J*=11.6, 10.2 Hz, 1 H), 3.60 (dd, *J*=11.6, 10.5 Hz, 1 H), 3.74 - 3.77 (m, 3 H), 4.12 (dd, *J*=11.7, 2.6 Hz, 1 H), 4.20 - 4.28 (m, 1 H), 4.57 - 4.62 (m, 2 H), 4.87 - 4.90 (m, 2 H), 6.81 (dd, *J*=7.9, 2.0 Hz, 1 H), 6.90 - 6.95 (m, 2 H), 7.22 (t, 1 H), 8.57 (s, 1 H), 9.50 (t, 1 H). LC/MS (5%-95% CH_3CN/H_2O, 8 min): 6.47 min, *m/z* 610 (M+H).

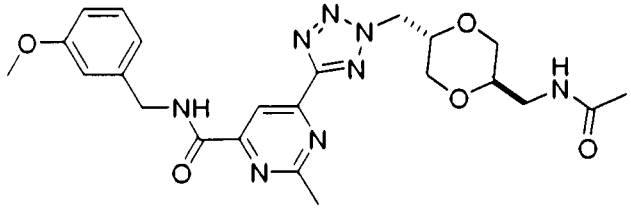
Step 2: Preparation of *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(aminomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



In a 20 ml scintillation vial with a magnetic stir bar at room temperature and standard pressure, *rac*-((2*S**,5*S**)-5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (130 mg) was dissolved in dimethyl sulfoxide (5 mL) and ammonium hydroxide (31.5 mg, 0.898 mmol) was added. The mixture was stirred at room temperature for 2 hours and then heated to 80 °C for 12 hours. The reaction mixture was concentrated, dissolved in acetonitrile and water, acidified with acetic acid, and chromatographed by reversed phase preparative HPLC (Gilson, Delta Pak column, 30-60% acetonitrile, 5 min hold, 30 min run, 5 min hold). Fractions containing the desired product were collected and concentrated under vacuum to afford the trifluoroacetic acid salt of the title compound as a clear oil (81.6 mg). ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 2.85 (s, 3 H), 3.03 (dd, *J*=13.3, 2.8 Hz, 1 H), 3.37 (dd, *J*=11.4, 10.3 Hz, 1 H), 3.60 (dd, *J*=11.6, 10.5 Hz, 1 H), 3.76 (s, 3 H), 3.81 (dd, *J*=11.6, 2.4 Hz, 1 H), 4.12 (dd, *J*=11.7, 2.6 Hz, 1 H), 4.20 - 4.28 (m, 1 H), 4.58 - 4.61 (m, 2 H), 4.87 - 4.90 (m, 2 H), 6.79 - 6.83 (m, 1 H), 6.91 - 6.95 (m, 2 H), 7.22 (t, *J*=8.1 Hz, 1 H), 8.57 (s, 1 H), 9.50 (t, *J*=6.58 Hz, 1 H). LC/MS (5%-95% CH_3CN/H_2O, 5 min): 2.241 min, *m/z* 455 (M+H).

Example 97

rac-*N*-(3-Methoxybenzyl)-6-(2-(((2*S,5*R**)-5-(acetamidomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

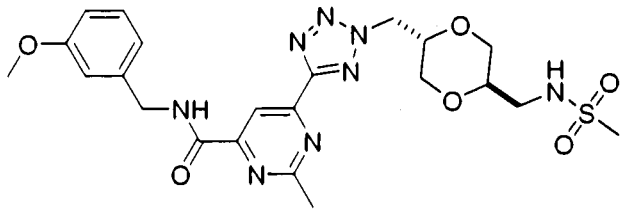


In a 20 mL scintillation vial with a magnetic stir bar at room temperature and standard pressure, *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(aminomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide trifluoroacetate (prepared as described in Example 96) (40 mg, 0.70 mmol) was combined with *N*,*N*-dimethylformamide (5 mL) and *N*,*N*-diisopropylethylamine (59.2 mg, 0.458 mmol). Acetic anhydride (19.1 mg, 0.187 mmol) was added and the mixture was stirred overnight. The reaction mixture was concentrated, re-dissolved in acetonitrile and water, and chromatographed by reversed phase preparative HPLC (Gilson, Delta Pak column, 20-60% acetonitrile, 10 min hold, 20 min run, 10 min hold). Fractions containing the desired product were collected and concentrated to afford the title compound as a white solid (21.3 mg). ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.32 - 1.37 (m, 2 H), 1.91 (s, 3 H), 2.85 (s, 3 H), 3.09 - 3.16 (m, 1 H), 3.18 - 3.24

(m, 1 H), 3.49 - 3.60 (m, 1 H), 3.76 (s, 3 H), 4.01 (dd, *J*=11.6, 2.4 Hz, 1 H), 4.14 - 4.22 (m, 1 H), 4.58 - 4.62 (m, 1 H), 6.81 (dd, *J*=8.1, 1.9 Hz, 1 H), 6.92 - 6.95 (m, 2 H), 7.23 (t, *J*=8.1 Hz, 1 H), 8.58 (s, 1 H), 9.49 (t, *J*=6.6 Hz, 1 H). LC/MS (5%-95% CH_3CN/H_2O, 5 min) 2.59 min, *m/z* 497 (M+H).

Example 98

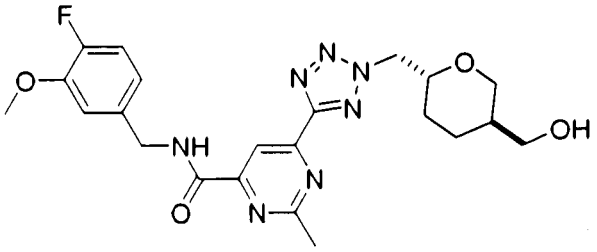
rac-*N*-(3-Methoxybenzyl)-6-(2-(((2*S,5*R**)-5-(acetamidomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



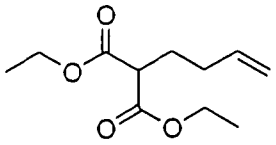
In a 20 mL scintillation vial with a magnetic stir bar at room temperature and standard pressure, *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(aminomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide trifluoroacetate (prepared as described in Example 96) (115 mg, 0.253 mmol) was combined with *N*,*N*-dimethylformamide (5 mL) and *N*,*N*-diisopropylethylamine (98.1 mg, 0.759 mmol) at room temperature. After 30 min, methane sulfonyl chloride was added and the reaction mixture was stirred for 12 hours. The reaction mixture was concentrated, dissolved in acetonitrile and water, and chromatographed by reversed phased preparative HPLC (Gilson, Delta Pak column, 30-60% acetonitrile, 10 min hold, 30 min run, 5 min hold). Fractions containing the desired product were collected and concentrated to afford the title compound as a white solid (10 mg). ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 2.68 (s, 3 H), 2.84 (dd, *J*=13.2, 9.4 Hz, 1 H), 3.03 (dd, *J*=13.3, 2.6 Hz, 1 H), 3.37 (dd, *J*=11.6, 10.5 Hz, 1 H), 3.56 - 3.63 (m, 1 H), 3.76 (s, 3 H), 3.82 (dd, *J*=11.4, 2.6 Hz, 1 H), 4.11 (dd, *J*=11.6, 2.4 Hz, 1 H), 4.18 - 4.26 (m, 1 H), 4.60 (s, 2 H), 6.81 (dd, *J*=9.0, 2.3 Hz, 1 H), 6.91 - 6.96 (m, 2 H), 7.23 (t, *J*=8.1 Hz, 1 H), 8.11 (d, *J*=1.1 Hz, 1 H), 8.57 (s, 1 H). LC/MS (5%-95% CH_3CN/H_2O, 5 min) 2.695 min, *m/z* 533 (M+H).

Example 99

(-)-*N*-(4-Fuoro-3-methoxybenzyl)-6-(2-(((2*R,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

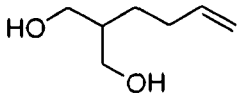


Step 1: Preparation of diethyl 2-(but-3-enyl)malonate



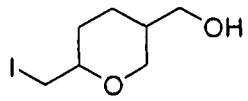
Small pieces of sodium (13 g, 565 mmol) were added to absolute ethanol (300 mL) slowly. After complete consumption, diethylmalonate (100 g, 625 mmol) was added drop wise. The reaction mixture was heated to 50 °C for 30 min and then cooled to room temperature. 1-Bromo-3-butene (76 g, 565 mmol) was added and the mixture was refluxed overnight. The ethanol was evaporated and the residue was diluted with water (500 mL). The mixture was extracted with ethyl acetate (3 x 500 mL). The combined ethyl acetate extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified by vacuum (0.1mm) distillation (bath temp. 125-135 °C and vapor temp. 82-85 °C) to afford the title compound (110 g, 82%).

Step 2: Preparation of 2-(but-3-enyl)propane-1,3-diol



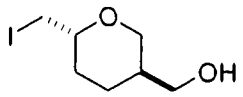
To a suspension of lithium aluminum hydride (56 g, 1.47 mol) in tetrahydrofuran (800 mL) was added diethyl 2-(but-3-enyl)malonate (80.0 g, 0.373 mol) dissolved in tetrahydrofuran (400 mL) drop-wise under ice-water cold condition. Lithium bromide (3.2 g, 37.3 mmol) was added and the mixture was stirred at room temperature overnight under nitrogen atmosphere. The mixture was cooled in an ice water bath and the reaction was cautiously quenched by the drop-wise addition of water (56 mL), then with 15% aqueous NaOH solution (168 mL) and finally with water (56 mL). The mixture was stirred for another 1 h and filtered. The solid residue was thoroughly washed with tetrahydrofuran (3 x 500 mL). The combined filtrate was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the title compound (41.5 g, 85 %).

Step 3: Preparation of (6-(iodomethyl)-tetrahydro-2H-pyran-3-yl)methanol



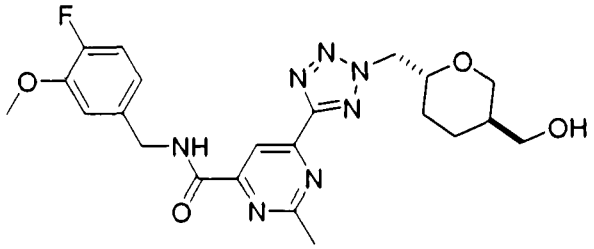
To a suspension of iodine (98 g, 386 mmol) and $NaHCO_3$ (32.6 g, 388.56 mmol) in ether (430 mL) and water (205 mL) was added a solution of 2-(but-3-enyl)propane-1,3-diol (33.5 g, 257.33 mmol) in ether (250 mL) at 0 °C. The mixture was stirred at room temperature for 8-10 h and then was quenched by the addition of saturated aqueous $Na_2S_2O_3$ at 0 °C. The organic layer was separated and the aqueous layer was extracted with ether (2 x 350 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The crude material was purified by flash column chromatography over silica gel (230-400 mesh) using 40% ethyl acetate in hexane as an eluent to afford the title compound as an oil consisting of a mixture of cis/trans isomers (53.0 g, 80.5%). MS (ES+) *m/z* 256 (M+H).

Step 4: Preparation of *(-)*-((3*R**,6*R**)-6-(iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Peak 1)



An isomeric mixture of (6-(iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (4.0 g) in ethanol (50 mL) was separated by supercritical-fluid chromatography (AD-H 30 x 250 mm, 15% ethanol, 70 mL/min, 0.5 mL/injection). The first eluting isomer was isolation and concentrated under vacuum to afford the title compound as a colorless oil (920 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.07 - 1.28 (m, 2 H), 1.50 - 1.64 (m, 1 H), 1.67 - 1.80 (m, 2 H), 2.99 - 3.36 (m, 6 H), 3.89 - 4.00 (m, 1 H), 4.42 (t, *J*=5.1 Hz, 1 H). SFC (AD-H, 20% ethanol) 3.01 min. LC/MS (5% to 95%, CH_3CN/H_2O, 12 min) 4.197 min, *m/z* 257 (M+H). $[\alpha]^{22.4\,C}_D$ = -0.380 (acetonitrile, 6.76)

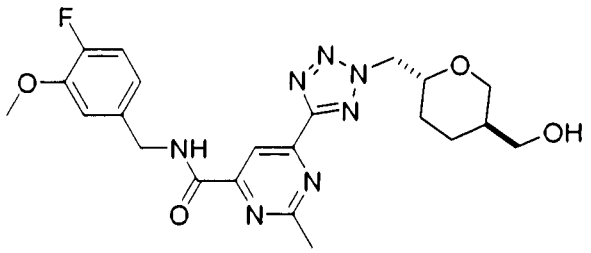
Step 5: Preparation of *(-)*-*N*-(4-Fuoro-3-methoxybenzyl)-6-(2-(((2*R**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



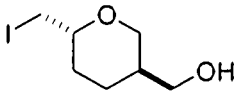
In a 20 ml scintillation vial with a magnetic stir bar at room temperature and standard pressure, *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (600 mg, 1.75 mmol) was dissolved in *N*,*N*-dimethyl acetamide (3 mL). *N*,*N*-Diisopropylethylamine (226 mg, 1.75 mmol) was added, and the mixture was stirred at room temperature for 30 min. A solution of *(-)*-((3*R**,6*R**)-6-(iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Peak 1) (895 mg, 3.50 mmol) in *N*,*N*-dimethyl acetamide (2 mL) was added, and the mixture was warmed to 80 °C for 14 hours. After cooling, the reaction mixture was concentrated, dissolved in acetonitrile and water, and chromatographed by reversed phase preparative HPLC (Gilson, Delta Pak column, 20-60% acetonitrile, 10 minute hold, 60 minutes run, 5 minute hold). The first eluting peak (49 min) was isolated and concentrated under vacuum to afford the title compound as a clear, colorless oil (373 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.14 - 1.25 (m, 1 H), 1.29 - 1.40 (m, 1 H), 1.54 - 1.65 (m, 1 H), 1.78 (d, *J*=9.9 Hz, 2 H), 2.06 (s, 3 H), 2.82 (s, 3 H), 3.00 (t, *J*=11.1 Hz, 1 H), 3.14 (dd, *J*=10.8, 7.20 Hz, 1 H), 3.23 (dd, *J*=10.7, 5.6 Hz, 1 H), 3.81 (s, 3 H), 3.86 (dd, *J*=11.1, 3.9 Hz, 2 H), 4.49 (d, *J*=6.3 Hz, 2 H), 4.80 - 4.92 (m, 2 H), 6.87 - 6.92 (m, 1 H), 7.10 - 7.20 (m, 2 H), 8.41 (s, 1 H), 9.53 (t, *J*=6.5 Hz, 1 H). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.748 min, *m/z* 472 (M+H). HPLC (5%-95% CH_3CN/H_2O, 40 min) 19.509 min. $[\alpha]^{22.4\,C}_D$ = -0.193 (acetonitrile, 0.27)

Example 100

***(+)-N*-(4-Fuoro-3-methoxybenzyl)-6-(2-(((2*R**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

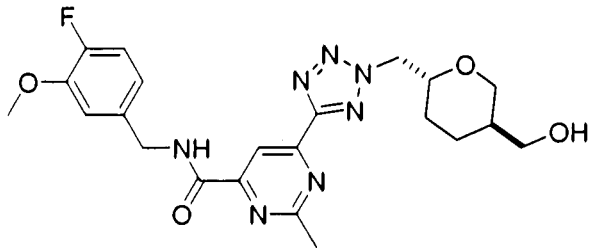


Step 1: Preparation of *(+)*-((3*R**,6*R**)-6-(iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Peak 2)



The second eluting isomer from the separation described in step 3 of Example 99 was isolated and concentrated under vacuum to afford the title compound as a clear, colorless oil (1.0 g). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.07 - 1.28 (m, 2 H), 1.50 - 1.64 (m, 1 H), 1.67 - 1.80 (m, 2 H), 2.99 - 3.36 (m, 6 H), 3.89 - 4.00 (m, 1 H), 4.42 (t, *J*=5.1 Hz, 1 H). SFC (AD-H, 20% ethanol) 3.18 min. LC/MS (5% -95%, CH_3CN/H_2O, 12 min.) 4.210 min, *m/z* 257(M+H). $[\alpha]^{22.4\,C}_{D}$ = 0.289 (acetonitrile, 2.56)

Step 2: Preparation of *(+)-N*-(4-Fuoro-3-methoxybenzyl)-6-(2-(((2*R**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

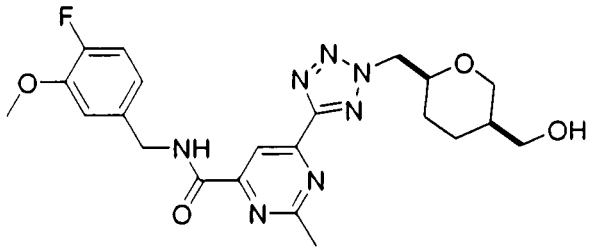


In a 20 ml scintillation vial with a magnetic stir bar at room temperature and standard pressure, *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (680 mg, 1.98 mmol) was dissolved in *N*,*N*-dimethyl acetamide (3 mL). *N*,*N*-Diisopropylethylamine (256 mg, 1.98 mmol) was added, and the mixture was stirred at room temperature for 30 min. A solution of *(+)*-((3*R**,6*R**)-6-(iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Peak 2) (1010 mg, 3.96 mmol) in *N*,*N*-dimethyl acetamide (2 mL) was added, and the mixture was warmed to 80 °C for 14 hours. After cooling, the reaction mixture was concentrated, dissolved in acetonitrile and water, and chromatographed by reversed phase preparative HPLC (Gilson, Delta Pak column, 20-60% acetonitrile, 10 minute hold, 60 minutes run, 5 minute hold). The first eluting peak (49 min) was isolated and concentrated under vacuum to afford the title compound as a clear, colorless oil (344 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.14 - 1.25 (m, 1 H), 1.29 - 1.40 (m, 1 H), 1.54 - 1.65 (m, 1

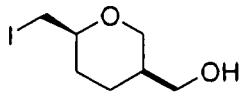
H), 1.78 (d, *J*=9.9 Hz, 2 H), 2.06 (s, 3 H), 2.82 (s, 3 H), 3.00 (t, *J*=11.1 Hz, 1 H), 3.14 (dd, *J*=10.8, 7.2 Hz, 1 H), 3.23 (dd, *J*=10.7, 5.3 Hz, 1 H), 3.81 (s, 3 H), 3.86 (dd, *J*=11.1, 3.9 Hz, 2 H), 4.49 (d, *J*=6.3 Hz, 2 H), 4.80 - 4.92 (m, 2 H), 6.87 - 6.92 (m, 1 H), 7.10 - 7.20 (m, 2 H), 8.41 (s, 1 H), 9.53 (t, *J*=6.5 Hz, 1 H). LC/MS (5%-95% CH_3CN/H_2O, 5 min) 2.752 min, *m/z* 472 (M+H). HPLC (5%-95% CH_3CN/H_2O, 40 min) 19.501 min. $[\alpha]^{22.4\,C}_{D}$ = 0.200 (acetonitrile, 0.09)

Example 101

***(-)-N*-(4-Fuoro-3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

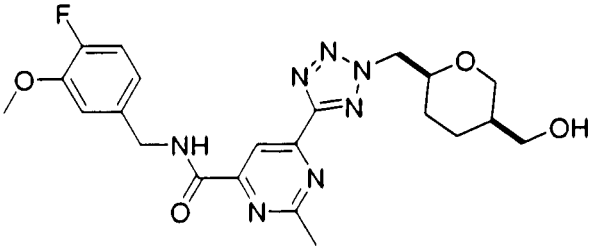


Step 1: Preparation of *(-)*-((3*R**,6*S**)-6-(iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Peak 3)



The third eluting isomer from the separation described in step 3 of Example 99 was isolated and concentrated under vacuum to afford the title compound as a clear, colorless oil (440 mg). ^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.07 - 1.27 (m, 2 H), 1.50 - 1.62 (m, 1 H), 1.66 - 1.80 (m, 2 H), 3.02 - 3.35 (m, 6 H), 3.89 - 4.00 (m, 1 H), 4.42 (t, *J*=5.1 Hz, 1 H). SFC (AD-H, 20% ethanol) 3.48 min. LC/MS (5% -95%, CH_3CN/H_2O, 12 min.) 4.154 min, *m/z* 257 (M+H). $[\alpha]^{22.4\,C}_{D}$ = -1.469 (acetonitrile, 2.37)

Step 2: Preparation of *(-)-N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

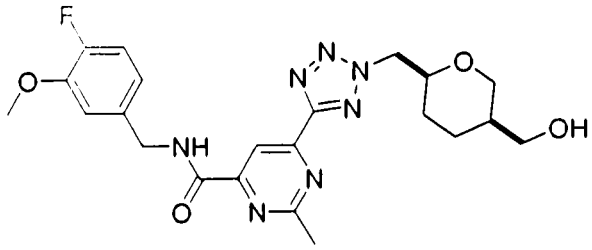


In a 20 ml scintillation vial with a magnetic stir bar at room temperature and standard pressure, *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (296 mg, 0.862 mmol) was dissolved in *N*,*N*-dimethyl acetamide (3 mL). *N*,*N*-Diisopropylethylamine (111 mg,

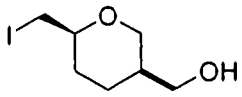
0.862 mmol) was added, and the mixture was stirred at room temperature for 30 min. A solution of *(-)*-((3*R**,6*S**)-6-(iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Peak 3) (442 mg, 1.72 mmol) in *N,N*-dimethyl acetamide (2 mL) was added, and the mixture was warmed to 80 °C for 14 hours. After cooling, the reaction mixture was concentrated, dissolved in acetonitrile and water, and chromatographed by reversed phase preparative HPLC (Gilson, Delta Pak column, 20-50% acetonitrile, 10 minute hold, 60 minutes run, 5 minute hold). The first eluting peak (47 min) was isolated and concentrated under vacuum to afford the title compound as a clear, colorless oil (206 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.41 - 1.71 (m, 3 H), 1.71 - 1.85 (m, 1 H), 2.47 - 2.52 (m, 1 H), 2.81 (s, 3 H), 3.34 - 3.43 (m, 1 H), 3.45 - 3.53 (m, 1 H), 3.69 - 3.77 (m, 1 H), 3.81 (s, 3 H), 3.92 - 4.06 (m, 1 H), 4.43 - 4.54 (m, 2 H), 4.77 - 4.97 (m, 2 H), 6.86 - 6.93 (m, 1 H), 7.13 (dd, *J*=11.4, 8.4 Hz, 1 H), 7.17 (dd, *J*=8.5, 1.8 Hz, 1 H), 8.41 (s, 1 H), 9.52 (t, *J*=6.4 Hz, 1 H). LC/MS (5%-95% CH_3CN/H_2O, 5 min) 2.753 min *m/z* 472 (M+H). HPLC (5%-95% CH_3CN/H_2O, 40 min) 19.582 min. $[\alpha]^{22.4\,C}_D$ = -0.154 (acetonitrile, 0.39)

Example 102

***(+)-N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

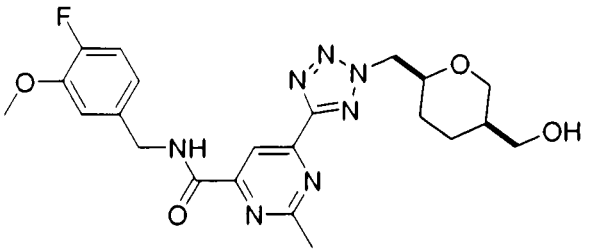


Step 1: Preparation of *(+)*-((3*R**,6*S**)-6-(iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Peak 4)



The fourth eluting isomer from the separation described in step 3 of Example 99 was isolated and concentrated under vacuum to afford the title compound as a clear, colorless oil (390 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.07 - 1.27 (m, 2 H), 1.50 - 1.62 (m, 1 H), 1.66 - 1.80 (m, 2 H), 3.02 - 3.35 (m, 6 H), 3.89 - 4.00 (m, 1 H), 4.42 (t, *J*=5.12 Hz, 1 H). SFC (AD-H, 20% ethanol) 3.402 min. LC/MS (5%-95%, CH_3CN/H_2O, 12 min.) 4.153 min, *m/z* 257 (M+H). $[\alpha]^{22.4\,C}_D$ = 0.194 (acetonitrile, 1.99)

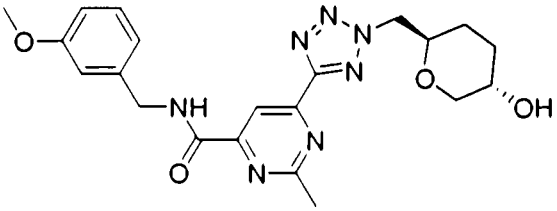
Step 2: Preparation of *(+)-N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



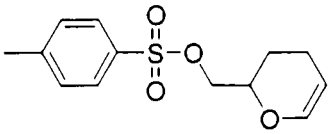
In a 20 ml scintillation vial with a magnetic stir bar at room temperature and standard pressure, *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (275 mg, 0.801 mmol) was dissolved in *N*,*N*-dimethyl acetamide (3 mL). *N*,*N*-Diisopropylethylamine (104 mg, 0.801 mmol) was added, and the mixture was stirred at room temperature for 30 min. A solution of *(+)*-((3*R**,6*S**)-6-(iodomethyl)-tetrahydro-2*H*-pyran-3-yl)methanol (Peak 4) (410 mg, 1.60 mmol) in *N*,*N*-dimethyl acetamide (2 mL) was added, and the mixture was warmed to 80 °C for 14 hours. After cooling, the reaction mixture was concentrated, dissolved in acetonitrile and water, and chromatographed by reversed phase preparative HPLC (Gilson, Delta Pak column, 30-50% acetonitrile, 10 minute hold, 60 minutes run, 5 minute hold). The first eluting peak (39 min) was isolated and concentrated under vacuum to afford the title compound as a clear, colorless oil (130 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.41 - 1.71 (m, 3 H), 1.71 - 1.85 (m, 1 H), 2.47 - 2.52 (m, 1 H), 2.81 (s, 3 H), 3.34 - 3.43 (m, 1 H), 3.45 - 3.53 (m, 1 H), 3.69 - 3.77 (m, 1 H), 3.81 (s, 3 H), 3.92 - 4.06 (m, 1 H), 4.43 - 4.54 (m, 2 H), 4.77 - 4.97 (m, 2 H), 6.86 - 6.93 (m, 1 H), 7.13 (dd, *J*=11.4, 8.4 Hz, 1 H), 7.17 (dd, *J*=8.5, 1.8 Hz, 1 H), 8.41 (s, 1 H), 9.52 (t, *J*=6.4 Hz, 1 H). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.751 min, *m/z* 472 (M+H). HPLC (5%-95% CH_3CN/H_2O, 40 min.) 19.586 min. $[\alpha]^{22.4\ C}_D$ = 0.267 (acetonitrile, 0.45)

Example 103

N-(3-Methoxybenzyl)-6-(2-(((2R*,5S*)-5-hydroxy-tetrahydro-2H-pyran-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

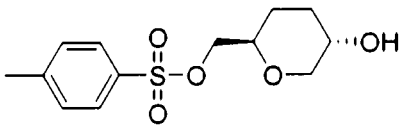


Step 1: Preparation of *rac*-(3,4-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate



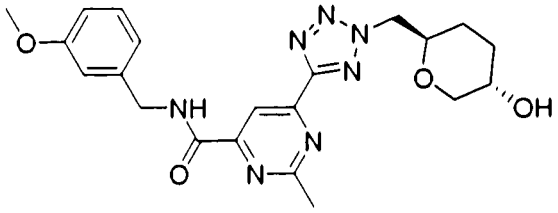
A mixture of (3,4-dihydro-2*H*-pyran-2-yl)methanol (10 g, 87.6 mmol), p-toluenesulfonyl chloride (16.7 g, 87.6 mmol), and pyridine (20 mL) was stirred at room temperature overnight. The reaction was cooled in an ice bath and water (50 mL) was added slowly while keeping the mixture cold. The mixture was then extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with 3N hydrochloric acid, dried over magnesium sulfate, and concentrated to afford the title compound as an oil (20.2 g, 86%).

Step 2: Preparation of *rac*-((2*R**,5*S**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate



To a solution of *rac*-(3,4-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (1.5 g, 5.6 mmol) in dry tetrahydrofuran (10 mL) cooled to 0 °C was added a 1M BH_3/THF solution (16.8 mL, 16.8 mmol) drop-wise. After complete addition, the reaction was brought to room temperature and stirred overnight. The reaction was treated with 2.5 N NaOH (13.4 mL) by careful drop-wise addition followed by H_2O_2 (4.6 mL), and then the mixture was heated to 55 °C for 1 h. The mixture was cooled in an ice bath and K_2CO_3 was added until the aqueous layer was saturated (~7 g). The resulting mixture was stirred for 30 min and then was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to an oil. The crude product mixture was purified by reverse phase preparative HPLC to afford the title compound as an oil (3.69 g, 97%). LC/MS (5%-95% CH_3CN/H_2O, 4 min.; 95% CH_3CN, 1 min.): 2.37 min, *m/z* 287 (M+H).

Step 3: Preparation of *N*-(3-methoxybenzyl)-6-(2-(((2*R**,5*S**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

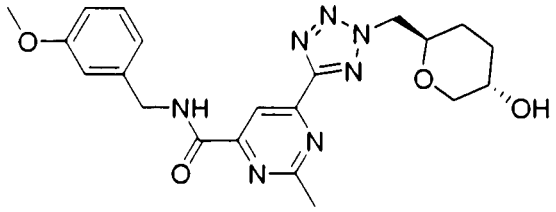


A mixture of *N*-(3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 6 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (400 mg, 1.23 mmol), *rac*-((2*R**,5*S**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (704 mg, 2.46 mmol), triethylamine (1.37 mL, 9.84 mmol), and dimethylacetamide (2 mL) was stirred at 85 °C for 3 days. The reaction mixture was purified by reverse phase preparative HPLC and the peak containing the desired regioisomer was isolated. Further separation by supercritical fluid

chromatography (Chiralcel AS-H, 30 x 250 mm, 12% methanol, 70 mL/min) and isolation of the first eluting enantiomer afforded the title compound (40 mg). MS (ES+) *m/z* 439 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.39 (d, *J*=10.3 Hz, 1 H), 1.78 - 1.90 (m, 1 H), 1.99 (d, *J*=8.4 Hz, 1 H), 2.83 (s, 3 H), 2.91 (t, *J*=10.4 Hz, 1 H), 3.34 - 3.49 (m, 1 H), 3.68 - 3.78 (m, 4 H), 3.80 - 3.93 (m, 2 H), 4.51 (d, *J*=6.6 Hz, 2 H), 4.77 (d, *J*=4.8 Hz, 1 H), 4.81 - 4.95 (m, 2 H), 6.83 (d, *J*=8.1 Hz, 1 H), 6.88 - 6.97 (m, 2 H), 7.24 (t, *J*=8.1 Hz, 1 H), 8.42 (s, 1 H), 9.48 (t, *J*=6.4 Hz, 1 H).

Example 104

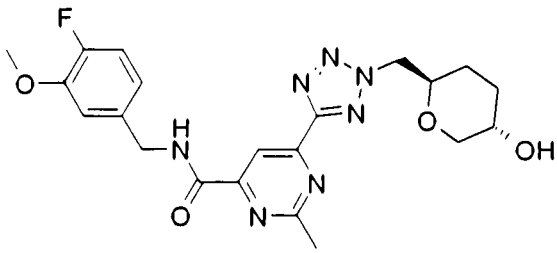
N-(3-Methoxybenzyl)-6-(2-(((2R*,5S*)-5-hydroxy-tetrahydro-2H-pyran-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



Isolation of the second eluting enantiomer from the product mixture described in Example 103 afforded the title compound (40 mg). MS (ES+) *m/z* 439 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 - 1.52 (m, 2 H), 1.76 - 1.90 (m, 1 H), 1.99 (d, *J*=11.0 Hz, 1 H), 2.83 (s, 3 H), 2.85 - 2.96 (m, 1 H), 3.36 - 3.49 (m, 1 H), 3.68 - 3.79 (m, 4 H), 3.84 - 3.95 (m, 1 H), 4.52 (d, *J*=6.6 Hz, 2 H), 4.72 - 4.95 (m, 3 H), 6.84 (d, *J*=1.5 Hz, 1 H), 6.89 - 6.97 (m, 2 H), 7.24 (t, *J*=8.1 Hz, 1 H), 8.42 (s, 1 H), 9.48 (t, *J*=6.2 Hz, 1 H).

Example 105

(+)-N-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2R*,5S*)-5-hydroxy-tetrahydro-2H-pyran-2-yl)methyl)-2H-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide

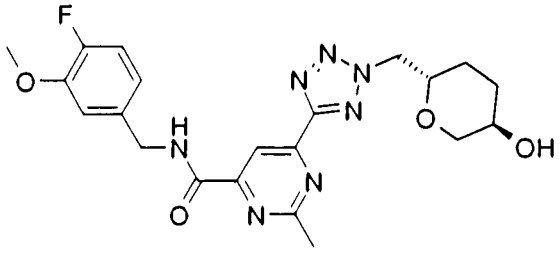


A mixture of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (461 mg, 1.34 mmol), *rac*-((2R*,5S*)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 2 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((2R*,5S*)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 103) (500 mg, 1.75 mmol), and triethylamine (1.50 mL, 10.7 mmol) was heated in *N*,*N*-dimethylacetamide (15 mL) at 85 °C for 18 hours. The mixture was purified by reverse phase preparative HPLC. The racemate was further separated by supercritical fluid chiral chromatography

(Chiralcel AD-H column, 30 x 250 mm, 50% 2-propanol, 70 mL/min) and the first eluting isomer was isolated to afford the title compound (25 mg, 4%). MS (ES+) *m/z* 458 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 - 1.48 (m, 2 H), 1.77 - 1.88 (m, 1 H), 1.91 - 2.03 (m, 1 H), 2.74 - 2.95 (m, 4 H), 3.38 - 3.46 (m, 1 H), 3.64 - 3.75 (m, 1 H), 3.76 - 3.92 (m, 4 H), 4.49 (d, *J*=6.59 Hz, 2 H), 4.74 - 4.98 (m, 3 H), 6.81 - 6.96 (m, 1 H), 7.06 - 7.23 (m, 2 H), 8.40 (s, 1 H), 9.50 - 9.64 (m, 1 H). $[\alpha]_D^{21°C}$ = +9.1° (c = 0.7, dichloromethane)

Example 106

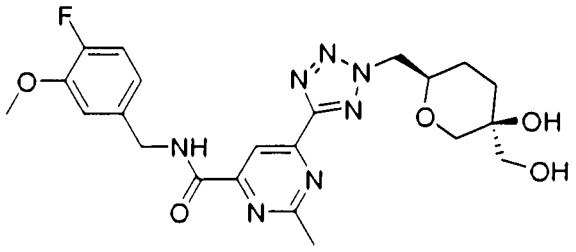
(-)-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*S,5*R**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



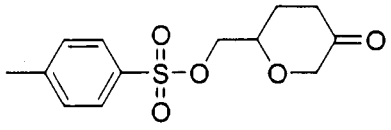
Isolation of the second eluting isomer by supercritical fluid chiral chromatography (Chiralcel AD-H column, 30 x 250 mm, 50% 2-propanol, 70 mL/min) of the racemic mixture provided in Example 105 afforded the title compound (21 mg, 3%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 - 1.48 (m, 2 H), 1.78 - 1.89 (m, 1 H), 1.92 - 2.03 (m, 1 H), 2.77 - 2.93 (m, 4 H), 3.38 - 3.48 (m, 1 H), 3.67 - 3.75 (m, 1 H), 3.77 - 3.93 (m, 4 H), 4.49 (d, *J*=6.59 Hz, 2 H), 4.74 - 4.96 (m, 3 H), 6.83 - 6.95 (m, 1 H), 7.08 - 7.23 (m, 2 H), 8.40 (s, 1 H), 9.50 - 9.64 (m, 1 H).

Example 107

***rac*-*N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R**,5*S**)-5-hydroxy-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



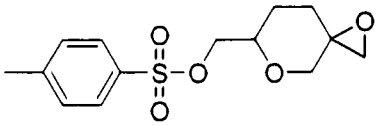
Step 1: Preparation of (5-oxo-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate



A solution of dichloromethane (40 mL) and dimethylsulfoxide (1.37 mL, 19.3 mmol) was cooled to -78 °C and oxalyl chloride (0.84 mL, 9.64 mmol) was added drop-wise. *rac*-((2*R**,5*S**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 2 of the synthesis of *rac*-*N*-(3-Methoxybenzyl)-6-(2-(((2*R**,5*S**)-5-hydroxy-tetrahydro-2*H*-pyran-2-

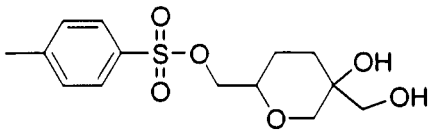
yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 103) (2.51 g, 8.77 mmol) in dichloromethane (20 mL) was then added via pipette. The mixture was stirred at -78 °C for 15 min and then triethylamine (6.11 mL, 43.8 mmol) was added drop-wise. After 5 min, the dry ice bath was removed and the mixture allowed to warm to room temperature over 30 minutes. The mixture was washed with sat. $NaHCO_3$ (2 x 20 mL), brine (2 x 20 mL), and water (20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to an oil. The crude product was purified by reverse phase preparative HPLC to afford the title compound as an oil. (2.43 g, 97%). MS (ES+) *m/z* 285 (M+H).

Step 2: Preparation of 1,5-dioxaspiro[2.5]oct-6-ylmethyl 4-methylbenzenesulfonate



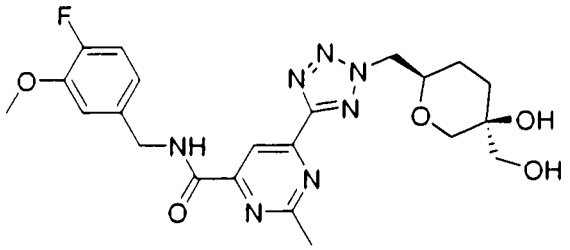
5-Oxo-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (2.4 g, 8.4 mmol) in dimethylsulfoxide (25 mL) was added to a dry mixture of trimethylsulfoxonium iodide (3.72 g, 16.9 mmol) and potassium *t*-butoxide (1.89 g, 16.9 mmol). The resulting mixture was stirred at room temperature for 3 hours. The solution was poured into water (200 mL) and stirred for 30 min. Ethyl acetate and brine were added and the mixture extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, dried over magnesium sulfate and concentrated to afford the title compound as an oil (1.32 g). LC/MS (5%-95% CH_3CN/H_2O, 4 min.; 95% CH_3CN, 1 min.): 2.72 min, *m/z* 321 (M+Na).

Step 3: Preparation of (5-hydroxy-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate



1,5-dioxaspiro[2.5]oct-6-ylmethyl 4-methylbenzenesulfonate (1.3 g, 4.4 mmol) was taken up in tetrahydrofuran (6 mL) and water (3 mL). The resulting solution was treated with perchloric acid (1 mL) and the reaction stirred at room temperature for 3 hours. The product mixture was purified by reverse phase preparative HPLC to afford the title compound. LC/MS (5%-95% CH_3CN/H_2O, 4 min.; 95% CH_3CN, 1 min.): 2.23 min, *m/z* 317 (M+H).

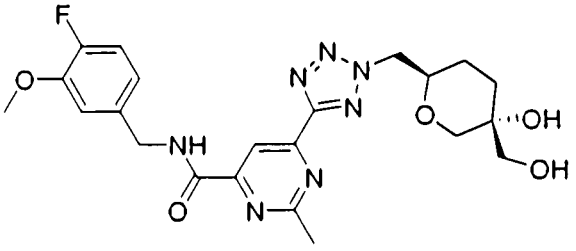
Step 4: Preparation of *rac-N*-(4-fluoro-3-methoxybenzyl)-6-(2-(((2*R**,5*S**)-5-hydroxy-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide



A mixture of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (116 mg, 0.337 mmol), (5-hydroxy-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (160 mg, 0.506 mmol), triethylamine (0.38 mL, 2.70 mmol), and dimethylacetamide (1 mL) was stirred at 85 °C overnight. The reaction mixture was purified by reverse phase preparative HPLC to provide a mixture of isomers which was further separated by supercritical fluid chromatography (Pegasus, 30 x 250 mm, 20% n-butanol, 70 mL/min) / (Diol, 30 x 250 mm, 25% n-butanol, 70 mL/min) to afford the title compound (20 mg, 12%). LC/MS (5%-95% CH_3CN/H_2O, 6 min) 2.545 min, *m/z* 488 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.40 - 1.50 (m, 2 H), 1.74 (d, *J*=9.2 Hz, 1 H), 1.84 - 1.98 (m, 1 H), 2.83 (s, 3 H), 2.97 (d, *J*=11.0 Hz, 1 H), 3.33 – 3.38 (m, 1 H), 3.40 - 3.46 (m, 1 H), 3.56 (d, *J*=11.0 Hz, 1 H), 3.82 (s, 3 H), 3.93 (d, *J*=5.9 Hz, 1 H), 4.51 (d, *J*=6.2 Hz, 3 H), 4.89 (d, *J*=5.5 Hz, 2 H), 6.87 - 6.94 (m, 1 H), 7.15 (td, *J*=12.2, 8.2 Hz, 2 H), 8.14 (s, 1 H), 8.42 (s, 1 H), 9.50 (t, *J*=6.4 Hz, 1 H).

Example 108

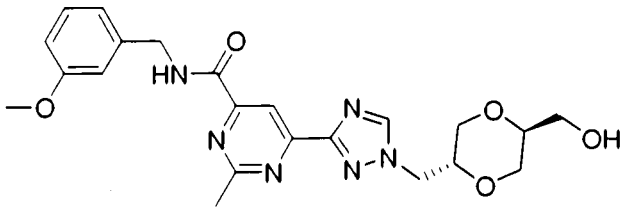
***rac-N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(((2*R**,5*R**)-5-hydroxy-5-(hydroxymethyl)-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



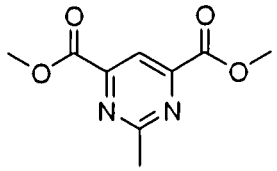
Isolation of a second eluting isomer from the product mixture described in Example 107 afforded the title compound (30 mg, 18%). LC/MS (5%-95% CH_3CN/H_2O, 6 min) 2.531 min, *m/z* 488 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (br. s., 1 H), 1.44 - 1.84 (m, 6 H), 2.83 (s, 3 H), 3.14 (d, *J*=1.8 Hz, 2 H), 3.41 - 3.53 (m, 1 H), 3.84 (s, 3 H), 3.85 - 3.94 (m, 1 H), 4.51 (d, *J*=6.2 Hz, 2 H), 4.82 - 4.93 (m, 2 H), 6.84 - 6.95 (m, 1 H), 7.15 (td, *J*=12.0, 8.2 Hz, 2 H), 8.42 (s, 1 H), 9.50 (t, *J*=6.2 Hz, 1 H).

Example 109

***rac-N*-(3-Methoxybenzyl)-6-(1-(((2*R**,5*S**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide**

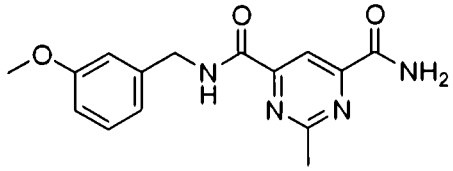


Step 1: Preparation of dimethyl 2-methylpyrimidine-4,6-dicarboxylate



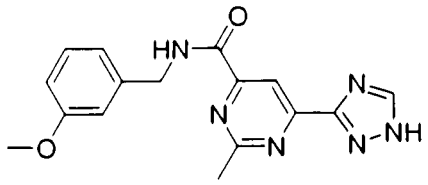
4,6-Dichloro-2-methylpyrimidine (24 g, 147 mmol), $Pd(Ph_3P)_2Cl_2$ (1.03 g, 1.47 mmol), triethylamine (45.1 mL, 324 mmol), and methanol (400 mL) were added to a 1 L high-pressure vessel. The vessel was pressurized to 500 psi with carbon monoxide and heated to 100 °C for 10 h. The mixture was filtered and the filtrate concentrated. The residue was suspended in a mixture of ethyl acetate/tetrahydrofuran (2/1) and the mixture was refluxed for 30 min. After cooling to below 40 °C, the mixture was filtered and the filtrate was concentrated. The crude product was purified by silica gel chromatography eluting with ethyl acetate. Fractions containing product were concentrated. The residue was slurried in a mixture of acetone/hexanes (2/1), filtered and dried in vacuo at 45 °C to afford the title compound as a light yellow solid.

Step 2: Preparation of *N*-(3-methoxybenzyl)-2-methylpyrimidine-4,6-dicarboxamide



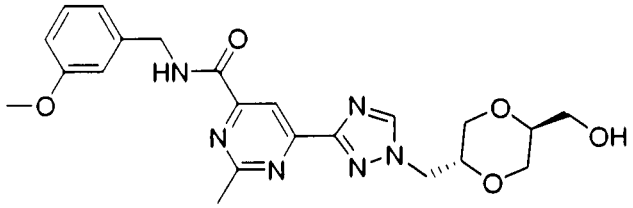
Dimethyl 2-methylpyrimidine-4,6-dicarboxylate (5.0 g, 23.8 mmol), 3-methoxybenzylamine (3.59 g, 26.2 mmol), and 2-methyltetrahydrofuran (31.7 mL) were combined in an 50 mL microwave reaction tube and heated to 90 °C for 15 min. The reaction mixture was filtered through a plug of silica gel, and the filtrate was concentrated. The residue was suspended in methanol (25 mL) and a solution of ammonia in methanol (7 N, 3.0 mL) was added. The mixture was stirred at room temperature overnight and then concentrated. The crude product was purified by silica gel chromatography (ethyl acetate/heptane/methanol, 65/34/1) to afford the title compound as a white solid (2.2 g). MS (ES+) *m/z* 301 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 9.46 (t, *J*=6.3 Hz, 1 H), 8.27 (br. s., 1 H), 8.22 (s, 1 H), 7.98 (br. s., 1 H), 7.20 (t, *J*=8.1 Hz, 1 H), 6.85 - 6.90 (m, 2 H), 6.79 (dd, *J*=8.3, 2.1 Hz, 1 H), 4.45 (d, *J*=6.2 Hz, 2 H), 3.70 (s, 3 H), 2.77 (s, 3 H).

Step 3: Preparation of *N*-(3-methoxybenzyl)-2-methyl-6-(1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide



N-(3-Methoxybenzyl)-2-methylpyrimidine-4,6-dicarboxamide (1.49 g, 4.96 mmol) was treated with dimethylformamide dimethylacetal (50 mL, 380 mmol) followed by heating at 101 °C for 2h. A short path distillation was utilized to collect the generated methanol. The solvent was then removed in vacuo to afford a crude residue. The residue was dissolved in glacial acetic acid (20 ml) and treated with monohydrazine hydrate (0.75 mL, 14.9 mmol). The mixture was heated at 90 °C for 2 hours and then allowed to cool to room temperature. The mixture was poured into H_2O (75 mL) and left to stand at room temperature overnight. The resulting solids were filtered and dried to afford the title compound (1.11 g, 69 %). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.95 min, *m/z* 325 (M+H).

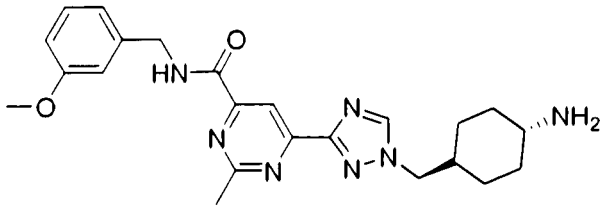
Step 4: Preparation of *rac-N*-(3-methoxybenzyl)-6-(1-(((2*R**,5*S**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide.



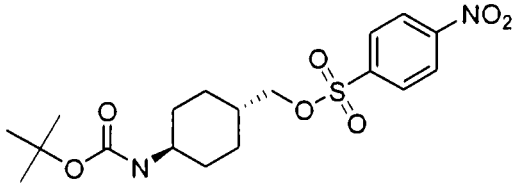
N-(3-Methoxybenzyl)-2-methyl-6-(1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide (0.070 g, 0.22 mmol) was treated with *rac*-((2*R**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac-N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (0.085 g, 0.28 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.082 g, 0.54 mmol) in acetonitrile (5 mL). After the reaction was stirred for 12 h at 75 °C, the mixture was concentrated to a crude residue that was purified via reverse phase chromatography (40-60% acetonitrile/water, 55 min) to afford the title compound as a white solid (30 mg, 31%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.83 min, *m/z* 455 (M+H). 1H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 (3 H, s), 3.30 - 3.38 (4 H, m), 3.42 (1 H, d, J=5.9 Hz), 3.74 (3 H, s), 3.79 (1 H, br. s.), 3.90 (2 H, d, J=9.2 Hz), 4.29 - 4.36 (1 H, m), 4.38 - 4.46 (1 H, m), 4.50 (2 H, d, J=6.2 Hz), 4.60 - 4.69 (1 H, m), 6.82 (1 H, d, J=7.7 Hz), 6.93 (2 H, br. s.), 7.24 (1 H, t, J=8.1 Hz), 8.36 (1 H, s), 8.69 (1 H, s), 9.39 (1 H, t, J=6.2 Hz).

Example 110

N-(3-Methoxybenzyl)-6-(1-((*trans*-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide

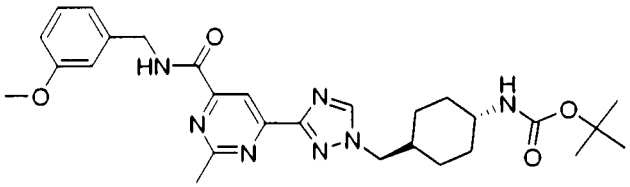


Step 1: Preparation of (*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)methyl 4-nitrobenzenesulfonate



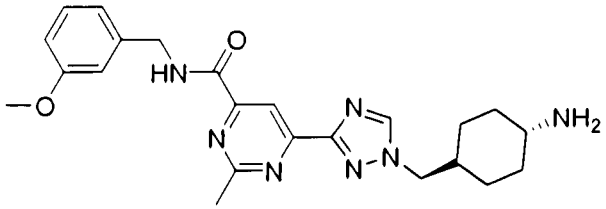
The commercially available tert-butyl (*trans*)-4-(hydroxymethyl)cyclohexylcarbamate (0.30 g, 1.3 mmol) was taken up in dichloromethane (7 mL) and treated with pyridine (0.16 mL, 2.0 mmol) before dripping in a solution of 4-nitrobenzene-1-sulfonyl chloride (0.43 g, 1.96 mmol) in dichloromethane (3.0 mL). The reaction was allowed to stir at room temperature for 15 h. The mixture was washed with water (5 mL), 5% aqueous hydrochloric acid (3 mL), followed by water (5 mL) before drying over sodium sulfate. The organic layer was concentrated to a crude oily residue that crystallized to afford the title compound as a beige solid (0.44 g, 81%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 5.48 min, *m/z* 439 (M+Na).

Step 2: Preparation of *tert*-butyl (*trans*)-4-((3-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate



(*trans*-4-((*tert*-Butoxycarbonyl)amino)cyclohexyl)methyl 4-nitrobenzenesulfonate (0.096 g, 0.23 mmol) and *N*-(3-methoxybenzyl)-2-methyl-6-(1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *rac*-*N*-(3-methoxybenzyl)-6-(1-(((2*R**,5*S**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide, Example 109) (0.050 g, 0.15 mmol) were treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.022 mL, 0.15 mmol) in acetonitrile (5mL) at 75 °C for 12 h. The mixture was concentrated and the residue was purified via reverse phase chromatography (10-90% acetonitrile/water, 30 min) to afford the title compound as a tan oil (0.057 mg, 69%). LC/MS (5%-95% CH_3CN/H_2O, 5 min): 3.10 min, *m/z* 536 (M+H).

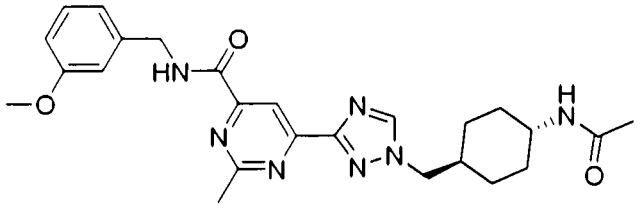
Step 3: Preparation of *N*-(3-methoxybenzyl)-6-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide.



tert-Butyl (*trans*)-4-((3-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate (0.057 g, 0.11 mmol) was taken up in dichloromethane (2 mL) and treated with trifluoroacetic acid (1.0 mL, 7.7 mmol). The reaction was stirred at ambient temperature for 3 h, diluted with dichloromethane (5 mL), and then neutralized with 2.5 N aqueous NaOH to achieve pH 7-8. The organic layer was separated, washed with water (3 mL), dried over sodium sulfate, and concentrated to afford the title compound (0.037 g, 51%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.78 min, *m/z* 436 (M+H).

Example 111

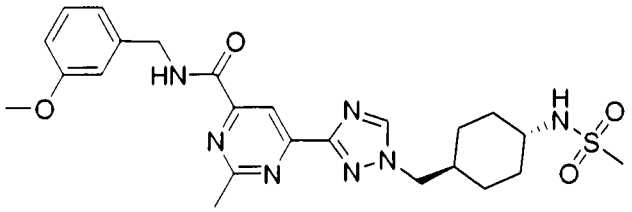
N-(3-Methoxybenzyl)-6-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide



N-(3-Methoxybenzyl)-6-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 110) (0.034 g, 0.078 mmol) was taken up in dichloromethane (2 mL) and treated with acetyl chloride (0.006 mL, 0.086 mmol) and triethylamine (0.012 mL, 0.086 mmol). After 1 h, the reaction was concentrated, and the residue was purified via reverse phase chromatography (10-95% acetonitrile/water over 30 minutes) to afford the title compound as a clear oil (11.7 mg, 31%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 4.07 min, *m/z* 477 m/e. 1H NMR (400 MHz, DMSO-d6) d ppm 1.09 (4 H, br. s.) 1.22 - 1.33 (1 H, m) 1.60 (2 H, br. s.) 1.73 - 1.84 (2 H, m) 1.75 (3 H, s) 2.78 (3 H, s) 3.46 (1 H, br. s.) 3.74 (3 H, s) 4.16 (2 H, d, J=6.95 Hz) 4.50 (2 H, d, J=6.22 Hz) 6.82 (1 H, d, J=8.05 Hz) 6.92 (2 H, br. s.) 7.24 (1 H, t, J=8.05 Hz) 7.64 (1 H, d, J=7.69 Hz) 8.36 (1 H, s) 8.72 (1 H, s) 9.39 (1 H, t, J=6.04 Hz)

Example 112

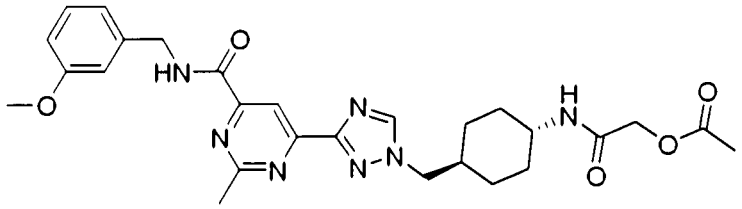
N-(3-Methoxybenzyl)-2-methyl-6-(1-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide



N-(3-Methoxybenzyl)-6-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 110) (0.050 g, 0.115 mmol) was taken up in dichloromethane (1 mL) and treated with methane sulfonyl chloride (0.009 mL, 0.115 mmol) and triethylamine (0.018 mL, 0.126 mmol). After 1 h, the reaction was concentrated to a crude residue. The residue was purified via reverse phase chromatography (10-95% acetonitrile/water over 25 minutes) to afford the title compound as a clear oil (38.1 mg, 64%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 2.57 min, *m/z* 514 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.26 (5 H, m), 1.58 (2 H, d), 1.79 (1 H, br. s.), 1.88 (2 H, d, J=9.9 Hz), 2.76 (3 H, s), 2.86 (3 H, s), 3.02 (1 H, br. s.), 3.71 (3 H, s), 4.14 (2 H, d, J=7.0 Hz), 4.48 (2 H, d, J=6.2 Hz), 6.80 (1 H, d, J=7.9 Hz), 6.90 (2 H, br. s.), 7.15 - 7.29 (1 H, m), 8.33 (1 H, s), 8.70 (1 H, s), 9.37 (1 H, br. s.)

Example 113

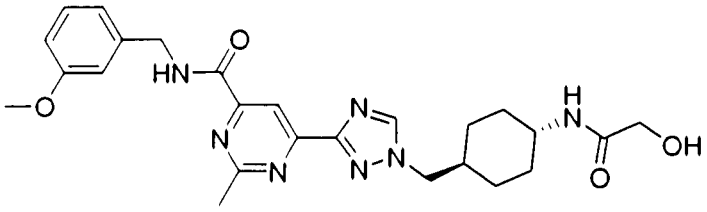
2-((*trans*)-4-((3-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate



N-(3-Methoxybenzyl)-6-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 110) (0.085 g, 0.195 mmol) was taken up in dichloromethane (2 mL) and treated with acetoxy acetyl chloride (0.025 mL, 0.234 mmol) and triethylamine (0.041 mL, 0.293 mmol). After stirring 2 hours at room temperature, the reaction was concentrated and the residue was purified via reverse phase chromatography (10-95% acetonitrile/water over 25 minutes) to afford the title compound (0.095 g, 91%).

Example 114

***N*-(3-Methoxybenzyl)-6-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide**

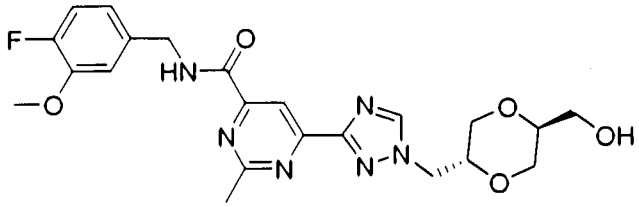


2-((*trans*)-4-((3-(6-((3-Methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate (prepared as described in Example 113) (0.095g, 0.18

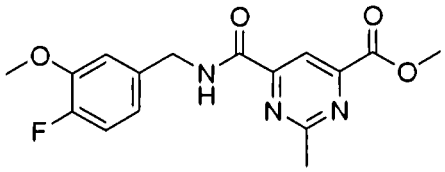
mmol) was taken up in acetonitrile (3 mL) and stirred with 2.5 N aqueous NaOH (2.0 mL) for 2 hours at room temperature. The acetonitrile was removed in vacuo and the aqueous solution was acidified to pH 5 via 10% aqueous hydrochloric acid to afford a solid. The solid was filtered, washed with water (2 x 3 mL), and dried to afford the title compound as a beige solid (11.1 mg, 11.3%). LC/MS (5%-95% CH_3CN/H_2O, 6 min): 3.45 min, *m/z* 494 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.16 (2 H, m), 1.16 - 1.30 (2 H, m), 1.58 (2 H, d, J=13.2 Hz), 1.73 (2 H, d, J=9.5 Hz), 2.52 (2 H, s), 2.76 (3 H, s), 3.42 - 3.59 (1 H, m), 3.66 - 3.78 (4 H, m), 4.15 (2 H, d, J=6.6 Hz), 4.48 (2 H, d, J=6.2 Hz), 5.30 (1 H, t, J=5.5 Hz), 6.80 (1 H, d, J=10.6 Hz), 6.86 - 6.95 (2 H, m), 7.16 - 7.26 (1 H, m), 7.35 (1 H, d, J=8.4 Hz), 8.34 (1 H, s), 8.71 (1 H, s), 9.29 - 9.40 (1 H, m).

Example 115

rac-*N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((2*R,5*S**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide**

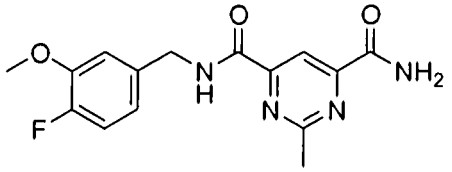


Step 1: Preparation of methyl 6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidine-4-carboxylate



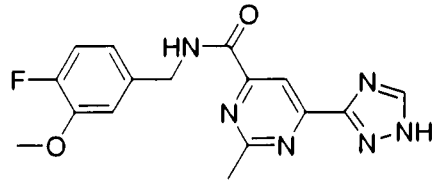
Dimethyl 2-methylpyrimidine-4,6-dicarboxylate (prepared as described in step 1 of the synthesis of *rac-N*-(3-Methoxybenzyl)-6-(1-(((2*R**,5*S**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide, Example 109) (4.50 g, 21.4 mmol), 4-fluoro-3-methoxybenzylamine (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (3.65 g, 23.6 mmol), and 2-methyltetrahydrofuran (21.4 mL) were combined in an 80 mL microwave reaction tube and heated to 110 °C for 30 min. The reaction mixture was filtered through a plug of silica gel eluting with 65/35, ethyl acetate/heptane. The filtrate was concentrated and purified by silica gel chromatography (heptane/acetone, 4/1) to afford the title compound as a white solid (1.95 g). MS (ES+) *m/z* 334 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) 9.53 (t, *J*=6.3 Hz, 1 H), 8.20 (s, 1 H), 7.14 (dd, *J*=7.8, 1.9 Hz, 1 H), 7.07 - 7.13 (m, *J*=11.5, 8.2 Hz, 1 H), 6.85 (ddd, *J*=8.3, 4.4, 1.9 Hz, 1 H), 4.45 (d, *J*=6.4 Hz, 2 H), 3.91 (s, 3 H), 3.78 (s, 3 H), 2.77 (s, 3 H).

Step 2: Preparation of *N*-4-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4,6-dicarboxamide



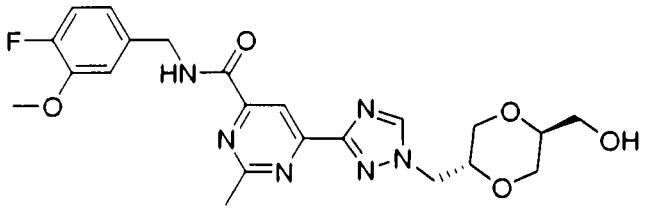
Methyl 6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidine-4-carboxylate (1.945 g, 5.84 mmol) was dissolved in a mixture of methanol (80 mL) and dichloromethane (15 mL). A solution of ammonia in methanol (7 N, 16.7 mL, 117 mmol) was added and the mixture was stirred at room temperature for 18 h. The mixture was concentrated to minimal volume. The resulting precipitate was filtered and washed with ethyl ether to afford the title compound as a white solid (1.785 g). MS (ES+) *m/z* 319 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) 9.48 (t, *J*=6.4 Hz, 1 H), 8.27 (s, 1 H), 8.22 (s, 1 H), 7.98 (s, 1 H), 7.14 (dd, *J*=7.9, 1.7 Hz, 1 H), 7.11 (dd, *J*=11.5, 8.3 Hz, 1 H), 6.86 (ddd, *J*=8.2, 4.4, 1.9 Hz, 1 H), 4.45 (d, *J*=6.3 Hz, 2 H), 3.78 (s, 3 H), 2.77 (s, 3 H).

Step 3: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide.



N-4-(4-Fluoro-3-methoxybenzyl)-2-methylpyrimidine-4,6-dicarboxamide (1.0 g, 3.1 mmol) was dissolved in dimethylformamide dimethylacetal (25 mL), and the reaction was refluxed for approximately 2 h. The reaction was concentrated under reduced pressure, and the residue was dissolved in acetic acid (20 mL). Hydrazine hydrate (1.0 mL) was added and the reaction mixture was heated at 90 °C for 1 h. The reaction mixture was poured into water and left to sit overnight. The resulting precipitate was collected by suction filtration and washed with water and diethyl ether to afford the title compound (702 mg, 65%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 4.60 min, *m/z* 343 (M+H).

Step 4: Preparation of *rac-N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*R**,5*S**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide

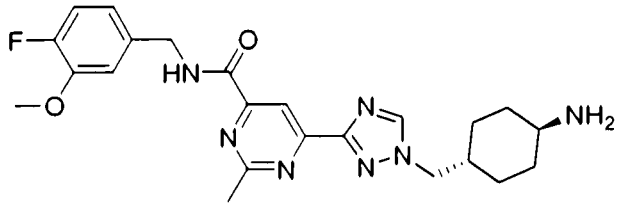


N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide (110 mg, 0.321 mmol) and *rac*-((2*R**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac-N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (126 mg, 0.418 mmol) were stirred in acetonitrile (5

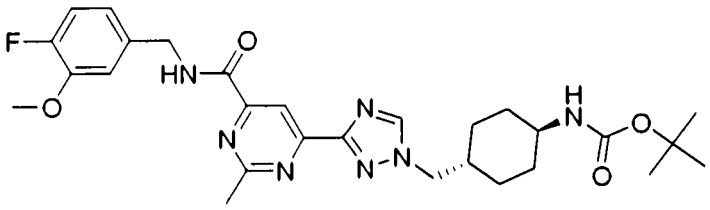
mL), and 1,8-diazobicyclo[5.4.0]undec-7ene (73.4 mg, 0.482 mmol) was subsequently added. The reaction was heated at 75 °C overnight before cooling to room temperature and concentrating under reduced pressure. The residue was dissolved in acetonitrile (2 mL)/water (1 mL) and was purified by reverse phase HPLC (20-minute hold at 20% B followed by a 30 minute gradient from 20% B to 80% B (A = 0.1% TFA / water and B = 0.1% TFA / acetonitrile)). The combined fractions were lyophilized to afford the title compound (4.5 mg, 2.4%) as the TFA salt. LC/MS: (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.) 4.73 min, *m/z* 473 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.48 (t, 1 H), 8.71 (s, 1 H), 8.33 (s, 1 H), 7.04 – 7.23 (m, 2 H), 6.87 (s, 1 H) 4.19 – 4.53 (m, 5 H), 3.56 - 4.05 (m, 6 H), 3.78 (s, 3 H), 3.19 – 3.49 (m, 2 H), 2.75 (s, 3 H).

Example 116

***N*-(4-Fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide**

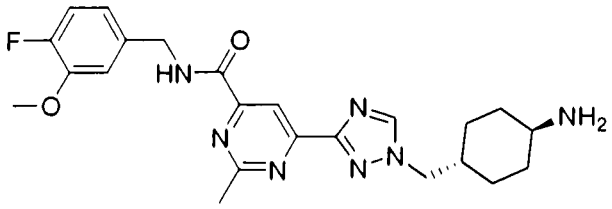


Step 1: Preparation of *tert*-butyl *trans*-4-((3-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate



N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *rac*-*N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*R**,5*S**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide, Example 115) (702 mg, 2.05 mmol) and (*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)methyl 4-methylbenzenesulfonate (prepared as described in step 7 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (786 mg, 2.05 mmol) were stirred in acetonitrile (40 mL), and 1,8-diazobicyclo[5.4.0]undec-7ene (480 mg, 3.15 mmol) was subsequently added. The reaction was heated at 75 °C overnight before cooling to room temperature and concentrating under reduced pressure. The residue was purified by reverse phase HPLC using a 40% B to 60% B, 30 minutes (A = 0.1% TFA / water and B = 0.1% TFA / acetonitrile) to afford the title compound (230 mg, 20%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 6.28 min, *m/z* 554 (M+H).

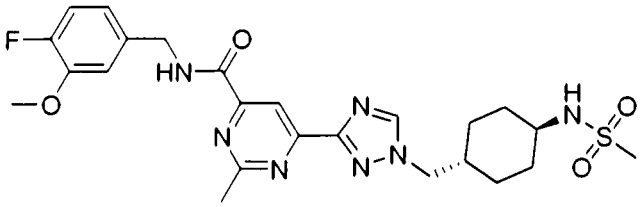
Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide



tert-Butyl *trans*-4-((3-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate (230 mg, 0.415 mmol) was dissolved in 1:1 TFA / dichloromethane (2 mL each), and the reaction was stirred at room temperature for an hour. The reaction was then concentrated under reduced pressure, and the residue was dissolved in water. The pH was adjusted to 8, and the product was extracted into ethyl acetate. The organic layer was washed with water and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound (120 mg, 64% yield). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.) 4.28 min, *m/z* 454 (M+H).

Example 117

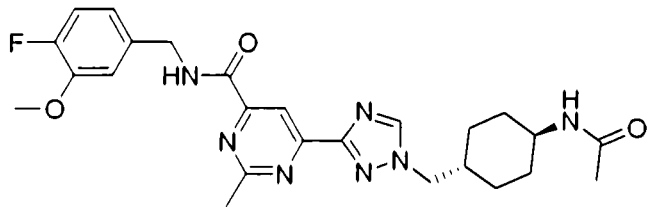
N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(1-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide



N-(4-Fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 116) (60 mg, 0.13 mmol) was dissolved in dichloromethane (2 mL). Triethylamine (26.8 mg, 0.265 mmol) and methanesulfonyl chloride (18.2 mg, 0.159 mmol) were subsequently added, and the reaction was continued overnight at room temperature. The solvent was then removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with water (3x), 1 N hydrochloric acid (2x), and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as an off-white solid (60 mg, 85% yield). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 5.19 min, *m/z* 532 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.38 (t, 1 H), 8.69 (s, 1 H), 8.31 (s, 1 H), 7.03 – 7.20 (m, 2 H), 6.83 – 7.00 (m, 2 H), 4.40 – 4.52 (m, 2 H), 4.09 - 4.23 (m, 2 H), 3.80 (s, 3 H), 2.94 – 3.12 (m, 1 H), 2.86 (s, 3 H), 2.75 (s, 3 H), 1.68 – 1.99 (m, 3 H), 1.50 – 1.66 (m, 2 H), 0.90 – 1.29 (m, 4 H).

Example 118

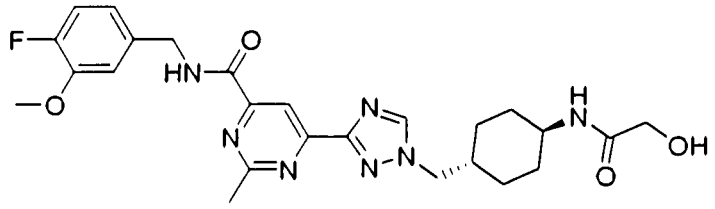
N-(4-fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide



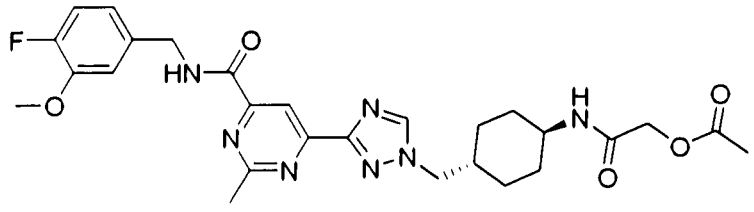
N-(4-Fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 116) (60 mg, 0.13 mmol) was dissolved in dichloromethane (2 mL). Triethylamine (26.8 mg, 0.265 mmol) and acetyl chloride (12.5 mg, 0.159 mmol) were subsequently added, and the reaction was continued overnight at room temperature. The solvent was then removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with water (3x), 1 N hydrochloric acid (2x), and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded a crude solid which was dissolved in acetonitrile (1 mL), water (0.5 mL), and DMF (0.5 mL) and purified by reverse phase HPLC using a 30 - 60% B, 30 minutes (A = 0.1% TFA / water and B = 0.1% TFA / acetonitrile). The product-containing fractions were combined and concentrated under reduced pressure to afford the title compound as a white solid (14 mg, 17% yield). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 5.16 min, 496 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.37 (t, 1 H), 8.66 (s, 1 H), 8.33 (s, 1 H), 7.54 – 7.68 (m, 1 H), 7.04 – 7.22 (m, 2 H), 6.76 – 6.97 (m, 1 H), 4.41 – 4.53 (m, 2 H), 4.04 - 4.18 (m, 2 H), 3.78 (s, 3 H), 3.38 – 3.53 (m, 1 H), 2.76 (s, 3 H), 1.73 – 1.89 (m, 3 H), 1.73 (s, 3 H), 1.40 – 1.63 (m, 2 H), 0.95 – 1.17 (m, 4 H).

Example 119

N-(4-Fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide



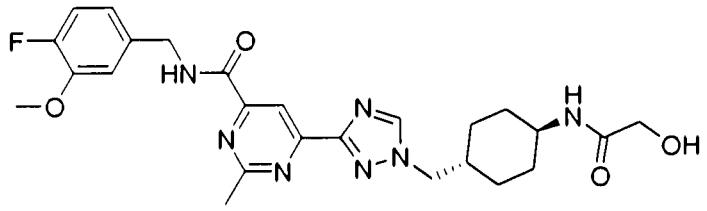
Step 1: Preparation of 2-(*trans*-4-((3-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate



N-(4-Fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 116) (60 mg, 0.13 mmol) was dissolved in dichloromethane (2 mL). Triethylamine (26.8 mg, 0.265 mmol) and acetoxyacetyl chloride

(21.7 mg, 0.159 mmol) were subsequently added, and the reaction was continued overnight at room temperature. The solvent was then removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with water (3x), 1 N hydrochloric acid (2x), and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound (56 mg, 76%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.) 5.26 min, *m/z* 554 (M+H).

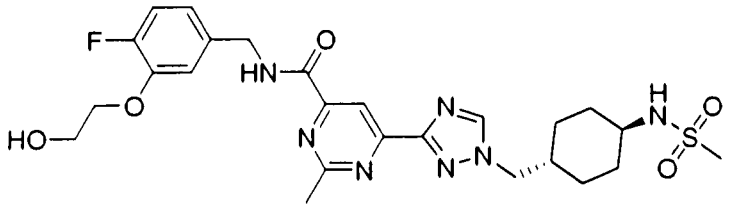
Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-((*trans*-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide



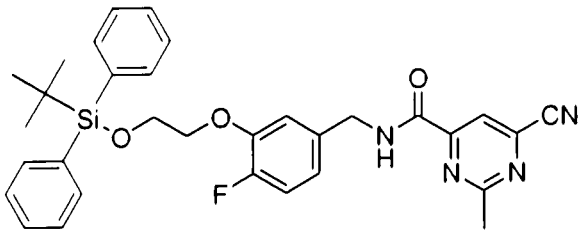
2-(*trans*-4-((3-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate (56 mg, 0.10 mmol) was dissolved in acetonitrile (3 mL), and 2.5 N NaOH (1.5 mL) was added. The reaction was continued overnight at room temperature. The pH was adjusted with concentrated hydrochloric acid, and the product was extracted into ethyl acetate (2x). The organic layer was washed with water and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as a solid (26 mg, 50% yield). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 4.82 min, *m/z* 512 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.36 (t, 1 H), 8.72 (s, 1 H), 8.31 (s, 1 H), 7.29 – 7.41 (m, 1 H), 6.97 – 7.25 (m, 2 H), 6.79 – 7.00 (m, 1 H), 5.21 – 5.40 (m, 1 H), 4.40 – 4.55 (m, 2 H), 4.06 - 4.23 (m, 2 H), 3.80 (s, 3 H), 3.65 – 3.75 (m, 2 H), 3.40 – 3.60 (m, 1 H), 2.77 (s, 3 H), 1.66 – 1.85 (m, 3 H), 1.52 – 1.63 (m, 2 H), 0.99 – 1.31 (m, 4 H).

Example 120

N-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(1-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide

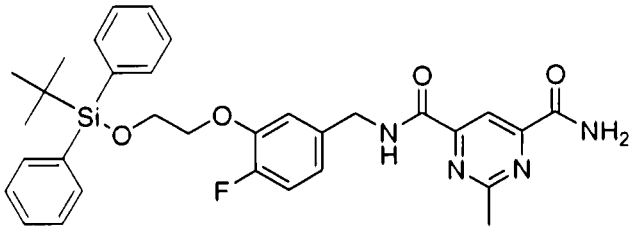


Step 1: Preparation of *N*-(3-(2-(*tert*-butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)-6-cyano-2-methylpyrimidine-4-carboxamide



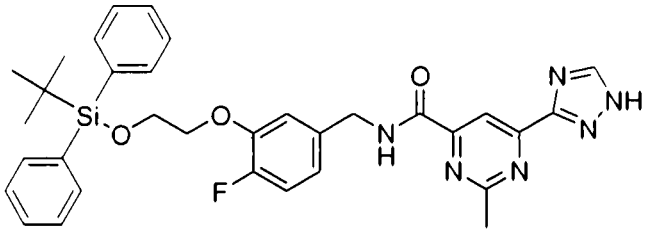
N-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-cyano-2-methylpyrimidine-4-carboxamide (prepared as described in step 1 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 27) (2.2 g, 6.7 mmol) and imidazole (453 mg, 6.7 mmol) were dissolved in dry DMF (36 mL). After cooling to 0 °C, *tert*-butyldiphenylsilyl chloride (2.2 g, 8.0 mmol) was added. The reaction was permitted to warm to room temperature with stirring for 2 days. The reaction was then diluted with ethyl acetate and washed with water (3x) and saturated sodium chloride (1X) before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as an oil (3 g, 79%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 8.48 min, 591 (M+Na).

Step 2: Preparation of *N*-(3-(2-(*tert*-butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)-2-methylpyrimidine-4,6-dicarboxamide.



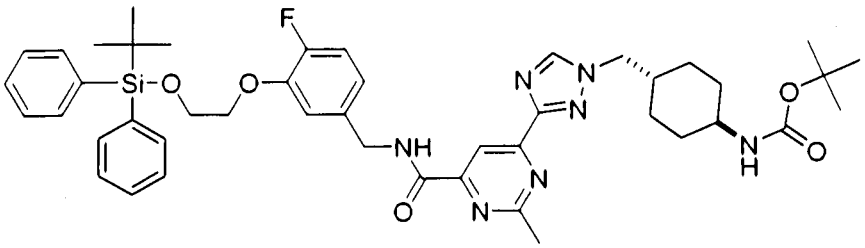
To a solution of *N*-(3-(2-(*tert*-butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)-6-cyano-2-methylpyrimidine-4-carboxamide (3 g, 5 mmol) in acetone (21 mL) was added 2.5 N sodium hydroxide (11 mL) followed by 30% hydrogen peroxide (3.15 mL). The reaction was stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as an oil (2.95 g, 100%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 8.00 min, *m/z* 609 (M+Na).

Step 3: Preparation of *N*-(3-(2-(*tert*-butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)-2-methyl-6-(1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide.



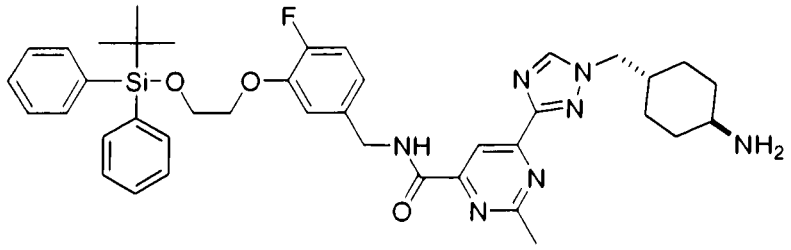
N-(3-(2-(*tert*-butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)-2-methylpyrimidine-4,6-dicarboxamide (2.95 g, 5.0 mmol) was dissolved in dimethylformamide dimethylacetal (45 mL), and the mixture was refluxed for approximately 2 h. The reaction was concentrated under reduced pressure, and the residue was dissolved in acetic acid (30 mL). Hydrazine hydrate (1.5 mL) was then added and the mixture was heated at 90 °C for 1 h. After cooling to room temperature, the reaction was poured into water. The pH was adjusted to 7, and the product was extracted into ethyl acetate. The organic layer was washed with water and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound (1.7 g). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.) 7.88 min, *m/z* 611 (M+H).

Step 4: Preparation of *tert*-butyl *trans*-4-((3-(6-((3-(2-(*tert*-butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate



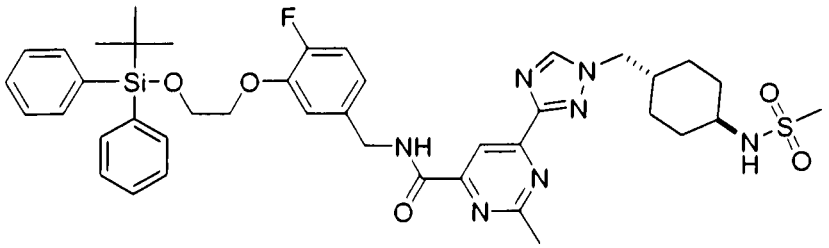
N-(3-(2-(*tert*-Butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)-2-methyl-6-(1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide (1.73 g, 2.83 mmol) and (*trans*-4-((*tert*-butoxycarbonyl)amino)cyclohexyl)methyl 4-methylbenzenesulfonate (prepared as described in step 7 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (1.19 g, 3.12 mmol) were stirred in acetonitrile (50 mL), and 1,8-diazobicyclo[5.4.0]undec-7ene (647 mg, 4.25 mmol) was subsequently added. The reaction was heated at 75 °C overnight before cooling to room temperature and concentrating under reduced pressure. The residue was purified by reverse phase HPLC using a 40% B to 60% B, 30 minutes (A = 0.1% TFA / water and B = 0.1% TFA / acetonitrile) to afford the title compound (300 mg, 13%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 9.04 min, 822 (M+H).

Step 5: Preparation of *N*-(3-(2-(*tert*-butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)-6-(1-((*trans*-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide



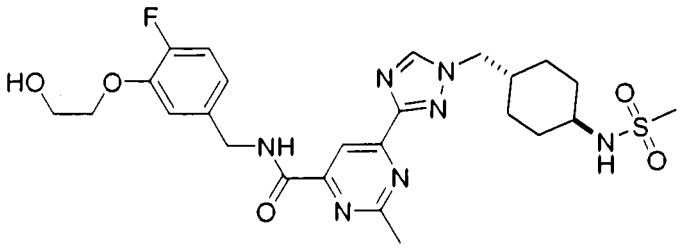
tert-Butyl *trans*-4-((3-(6-((3-(2-(*tert*-butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate (300 mg, 0.365 mmol) was dissolved in 1:1 TFA / dichloromethane (3 mL each), and the reaction was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the residue was dissolved in water. The pH was adjusted to 8, and the product was extracted into ethyl acetate. The organic layer was washed with water followed by saturated sodium chloride and concentrated to afford title compound (60 mg, 23%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.) 7.07 min, 722 (M+H).

Step 6: Preparation of *N*-(3-(2-(*tert*-butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)-2-methyl-6-(1-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide



N-(3-(2-(tert-Butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)-6-(1-((*trans*-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide (60 mg, 0.0.83 mmol) was dissolved in dichloromethane (3 mL). Triethylamine (16.8 mg, 0.166 mmol) and methanesulfonyl chloride (11.4 mg, 0.0997 mmol) were subsequently added, and the reaction was continued overnight at room temperature. The solvent was then removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with water (3X) and saturated sodium chloride (1X) before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as a solid (60 mg, 90%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 7.97 min, 800 (M+H).

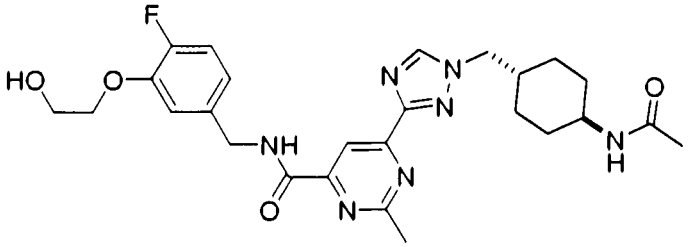
Step 7: Preparation of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(1-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide



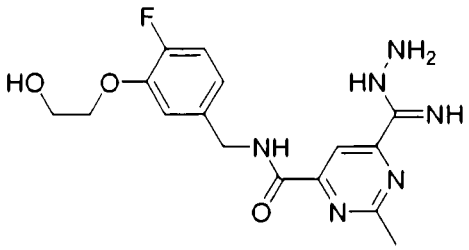
N-(3-(2-(*tert*-Butyldiphenylsilyloxy)ethoxy)-4-fluorobenzyl)-2-methyl-6-(1-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide (60 mg, .075 mmol) was dissolved in THF (2 mL). Tetrabutylammonium fluoride in THF (1 M) (19.6 mg, 0.075 mmol) was subsequently added and the mixture stirred for a couple of hours. The reaction mixture was purified by reverse phase chromatography using an acetonitrile gradient in water (10% - 85% over 30 minutes). The product-containing fractions were combined and neutralized with 2.5 N sodium hydroxide. The product was extracted into ethyl acetate, and the organic layer was washed with saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure. The residue was redissolved in ethyl acetate and washed with saturated ammonium chloride and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as a solid (5 mg, 10%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 4.57 min, 562 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.40 (t, 1 H), 8.70 (s, 1 H), 8.33 (s, 1 H), 7.58 – 7.76 (m,1 H), 7.05 – 7.23 (m, 2 H), 6.83 – 6.98 (m, 1 H), 4.82 (t, 1 H), 4.41 – 4.53 (m, 2 H), 4.08 - 4.21 (m, 2 H), 3.98 – 4.08 (m, 2 H), 3.61 - 3.78 (m, 2 H), 3.02 – 3.12 (m, 1 H), 2.87 (s, 3 H), 2.76 (s, 3 H), 1.77 – 1.92 (m, 3 H), 1.51 – 1.65 (m, 2 H), 0.98 – 1.33 (m, 4 H).

Example 121

N-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(1-((*trans*-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide

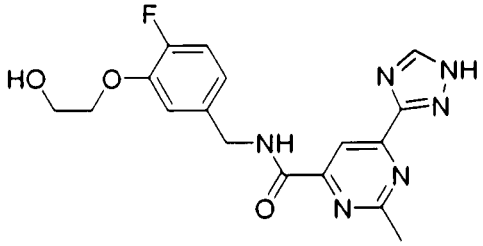


Step 1: Preparation of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(carbamimidoyl)-2-methylpyrimidine-4-carboxamide



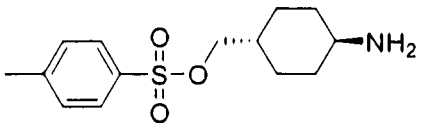
N-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-cyano-2-methylpyrimidine-4-carboxamide (prepared as described in step 1 of the synthesis of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 27) (700 mg, 2.12 mmol) was dissolved in absolute ethanol (20 mL). Hydrazine hydrate (2.33 g, 46.6 mmol) was added, and the reaction was refluxed for 3 h. The reaction mixture was allowed to cool to room temperature. The reaction was diluted with ethyl acetate and washed with water (3X) and saturated sodium chloride (1X) before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as an oil (300 mg, 39%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 3.19 min., *m/z* 363 (M+H).

Step 2: Preparation of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide



N-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-6-(carbamimidoyl)-2-methylpyrimidine-4-carboxamide (300 mg, 0.83 mmol) was dissolved in formic acid (3 mL), and the reaction was refluxed overnight. The reaction was then cooled and concentrated under reduced pressure. The residue was partitioned between saturated sodium bicarbonate and ethyl acetate. The layers were separated, and the organic layer was washed with saturated sodium bicarbonate and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as an oil (80 mg, 26%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 4.77 min, *m/z* 373 (M+H).

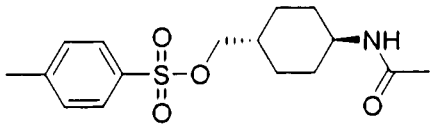
Step 3: Preparation of (*trans*-4-aminocyclohexyl)methyl 4-methylbenzenesulfonate



(*trans*-4-((*tert*-Butoxycarbonyl)amino)cyclohexyl)methyl 4-methylbenzenesulfonate (prepared as described in step 7 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (1.0 g, 2.6

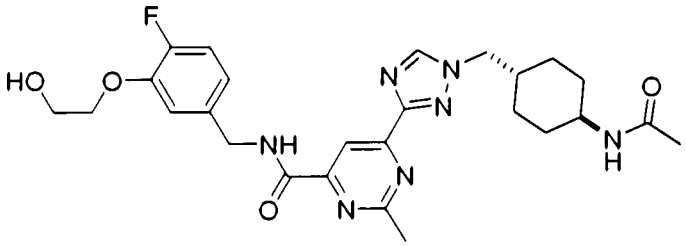
mmol) was dissolved in 1:1 TFA / dichloromethane (5 mL each), and the reaction was stirred at room temperature for an hour. The reaction was then concentrated under reduced pressure, and the residue was dissolved in water. The pH was adjusted to 8, and the product was extracted into ethyl acetate. The organic layer was washed with water followed by saturated sodium chloride, dried over anhydrous sodium sulfate, filtration and concentrated to afforded the title compound (450 mg, 61% yield). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 3.99 min., *m/z* 284 (M+H).

Step 4: Preparation of (*trans*-4-acetamidocyclohexyl)methyl 4-methylbenzenesulfonate



(*trans*-4-Aminocyclohexyl)methyl 4-methylbenzenesulfonate (450 mg, 1.59 mmol) was dissolved in dichloromethane (10 mL). Triethylamine (321 mg, 3.18 mmol) and acetyl chloride (150 mg, 1.91 mmol) were subsequently added, and the reaction was continued overnight at room temperature. The solvent was then removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with water (3x), 1 N hydrochloric acid (2x), and saturated sodium chloride solution before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as an oil (450 mg). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.) 5.23 min, *m/z* 326 (M+H).

Step 5: Preparation of *N*-(4-fluoro-3-(2-hydroxyethoxy)benzyl)-6-(1-((*trans*-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-2-methylpyrimidine-4-carboxamide

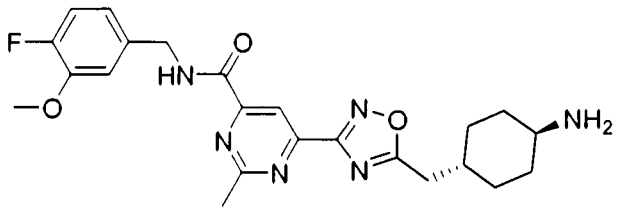


N-(4-Fluoro-3-(2-hydroxyethoxy)benzyl)-2-methyl-6-(1*H*-1,2,4-triazol-3-yl)pyrimidine-4-carboxamide (80 mg, 0.21 mmol) and ((*trans*-4-acetamidocyclohexyl)methyl 4-methylbenzenesulfonate (76.9 mg, 0.236 mmol) were stirred in acetonitrile (5 mL), and 1,8-diazobicyclo[5.4.0]undec-7ene (DBU) (49.1 mg, 0.322 mmol) was subsequently added. The reaction was heated at 75 °C overnight before cooling to room temperature and diluting with ethyl acetate. The organic layer was washed with water (3X) and saturated sodium chloride (1X) before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded an oil which was purified by reverse phase HPLC using a 20% B to 60% B, 40 minutes (A = 0.1% TFA / water and B = 0.1% TFA / acetonitrile). The product-containing fractions were combined, and the pH was made basic with 2.5 N sodium hydroxide. The product was extracted into ethyl acetate, and the combined organic layer was washed with saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound (3.9 mg, 3.5%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 4.56 min, *m/z*

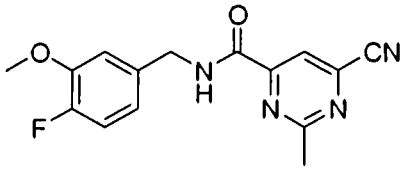
326 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.39 (t, 1 H), 8.73 (s, 1 H), 8.32 (s, 1 H), 7.54 – 7.72 (m,1 H), 7.04 – 7.26 (m, 2 H), 6.84 – 6.96 (m, 1 H), 4.80 (t, 1 H), 4.41 – 4.54 (m, 2 H), 4.11 - 4.22 (m, 2 H), 3.96 – 4.09 (m, 2 H), 3.63 - 3.80 (m, 2 H), 3.33 – 3.52 (m, 1 H), 2.76 (s, 3 H), 1.78 – 2.05 (m, 3 H), 1.71 (s, 3 H), 1.48 – 1.65 (m, 2 H), 1.09 – 1.34 (m, 4 H).

Example 122

***N*-(4-Fluoro-3-methoxybenzyl)-6-(5-((*trans*-4-aminocyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide**

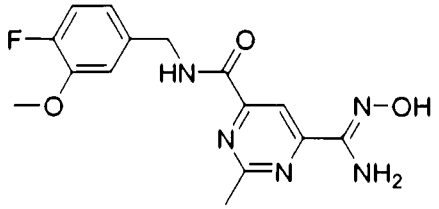


Step 1: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-cyano-2-methylpyrimidine-4-carboxamide



A mixture of methyl 6-cyano-2-methylpyrimidine-4-carboxylate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (10.0 g, 56.4 mmol), 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (13.5 g, 70.6 mmol), *N*,*N*-diisopropylethylamine (39.3 mL, 226 mmol), and methanol (56.4 mL) was heated to 35 °C for 1 h. The mixture was concentrated and the residue was partitioned between ethyl acetate (500 mL) and 1 N hydrochloric acid (500 mL). The aqueous layer was extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (2 x 250 mL) followed by brine, dried over sodium sulfate, and concentrated.. The crude product was purified by silica gel chromatography (2/1, heptane/ethyl acetate) to afford the title compound as a white solid (11.7 g). MS (ES+) *m/z* 301 (M+H).

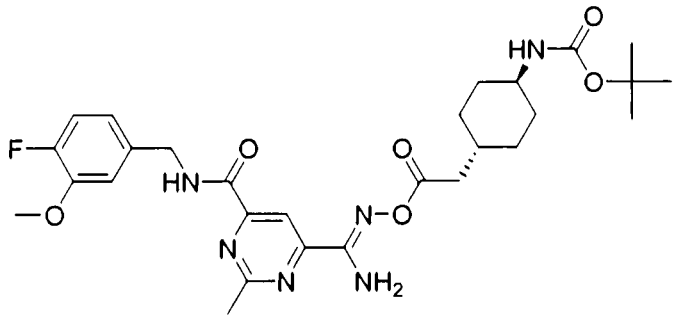
Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(carbamimidoyl)-2-methylpyrimidine-4-carboxamide



N-(4-Fluoro-3-methoxybenzyl)-6-cyano-2-methylpyrimidine-4-carboxamide (1.0 g, 3.3 mmol) was dissolved in ethanol / water (20 mL / 5 mL). Hydroxylamine hydrochloride (255 mg, 3.66 mmol)

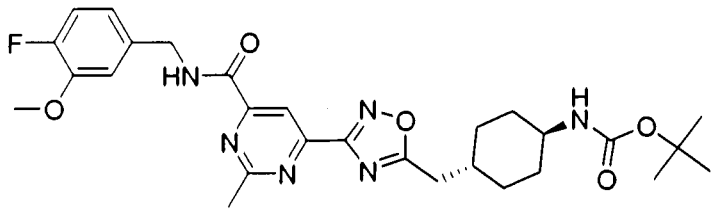
and sodium hydroxide (213 mg, 3.66 mmol) were subsequently added, and the reaction was heated at 75 °C for 2 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate and washed with water and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as an off-white solid (1.0 g, 90% yield). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 4.65 min, *m/z* 334 (M+H).

Step 3: Preparation of *tert*-butyl (4-(2-((((1*Z*)-amino(6-(((4-fluoro-3-methoxybenzyl)amino)carbonyl)-2-methylpyrimidin-4-yl)methylene)amino}oxy)-2-oxoethyl)cyclohexyl)carbamate



N-(4-fluoro-3-methoxybenzyl)-6-(carbamimidoyl)-2-methylpyrimidine-4-carboxamide (500 mg, 1.50 mmol), 2-(*trans*-4-(*tert*-butoxycarbonyl)cyclohexyl)acetic acid (386 mg, 1.50 mmol), *N*-hydroxybenzotriazole (230 mg, 1.50 mmol), and diisopropyethylamine (582 mg, 4.50 mmol) were dissolved in acetonitrile (20 mL) and dimethylacetamide (2 mL). PS-carbodiimide resin (3.49 g, 4.50 mmol) was subsequently added, and the reaction was agitated at 40 °C overnight. The reaction was filtered to remove the resin, and the resin was washed with dimethylformamide. The filtrate was diluted with ethyl acetate, and the organic layer was washed with water and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound as a white solid (700 mg, 82%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.) 6.23 min, *m/z* 517 (M+H-*t*-butyl).

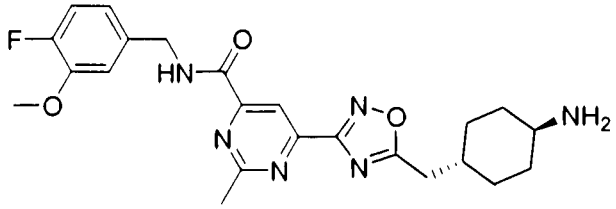
Step 4: Preparation of *tert*-butyl (*trans*)-4-((3-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1,2,4-oxadiazol-5-yl)methyl)cyclohexylcarbamate



tert-Butyl (4-(2-((((1*Z*)-amino(6-(((4-fluoro-3-methoxybenzyl)amino)carbonyl)-2-methylpyrimidin-4-yl)methylene)amino}oxy)-2-oxoethyl)cyclohexyl)carbamate (400 mg, 0.70 mmol) was dissolved in acetonitrile (8 mL) and dimethylacetamide (4 mL). MP-carbonate resin (732 mg, 2.1 mmol) was added, and the reaction was microwaved for 15 min at 120 °C at 200W. The reaction was filtered to remove the resin, and the filtrate was diluted with ethyl acetate. The organic layer was washed with water (3X) and saturated sodium chloride (1X) before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound

as a solid (388 mg, 95%). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.): 6.76 min, *m/z* 577 (M+Na).

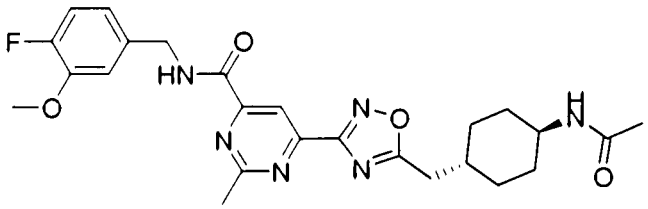
Step 5: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(5-((*trans*-4-aminocyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide



tert-Butyl (*trans*)-4-((3-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1,2,4-oxadiazol-5-yl)methyl)cyclohexylcarbamate (370 mg, 0.67 mmol) was dissolved in a mixture of trifluoroacetic acid (5 mL) and dichloromethane (5 mL). The reaction mixture was stirred at room temperature for several hours before being concentrated under reduced pressure. The residue was treated with saturated sodium bicarbonate, and the product was extracted into ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and saturated sodium chloride before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound. LC/MS (5%-95% CH_3CN/H_2O, 8 min, 2 min): 4.53 min, *m/z* 455 (M+H).

Example 123

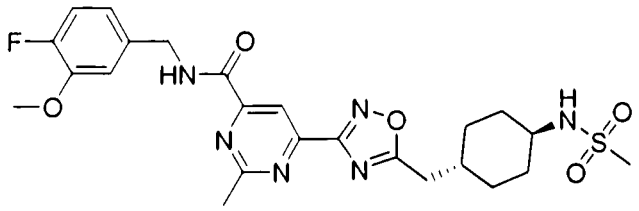
N-(4-fluoro-3-methoxybenzyl)-6-(5-((*trans*-4-acetamidocyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide



N-(4-Fluoro-3-methoxybenzyl)-6-(5-((*trans*-4-aminocyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 122) (10 mg, 0.022 mmol) was dissolved in dichloromethane (2 mL). Triethylamine (4.45 mg, 0.0440 mmol) and acetyl chloride (1.90 mg, 0.0242 mmol) were subsequently added, and the reaction was continued overnight at room temperature. The solvent was then removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with water (3x), 1 N hydrochloric acid (3x), and saturated sodium chloride solution before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound (9 mg, 83% yield). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.) 5.61 min, *m/z* 497 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.46 (t, 1 H), 8.28 (s, 1 H), 8.08 (s, 1 H), 7.49 – 7.67 (m,1 H), 7.02 – 7.19 (m, 1 H), 6.81 – 6.94 (m, 1 H), 4.39 – 4.52 (m, 2 H), 3.76 (s, 3 H), 3.31 – 3.50 (m, 1 H), 2.89 – 2.99 (m, 2 H), 2.78 (s, 3 H), 1.70 – 1.91 (m, 2 H), 1.71 (s, 3 H), 1.10– 1.28 (m, 7 H).

Example 124

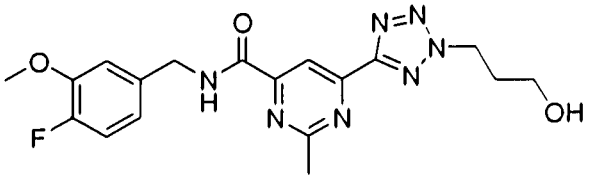
***N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(5-((*trans*-4-(methylsulfonamido)cyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)pyrimidine-4-carboxamide**



N-(4-Fluoro-3-methoxybenzyl)-6-(5-((*trans*-4-aminocyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 122) (15 mg, 0.033 mmol) was dissolved in dichloromethane (2 mL). Triethylamine (6.69 mg, 0.0661 mmol) and methanesulfonyl chloride (4.55 mg, 0.0397 mmol) were subsequently added, and the reaction was continued overnight at room temperature. The solvent was then removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with water (3x), 1 N hydrochloric acid (3x), and saturated sodium chloride solution before drying over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded the title compound (6.5 mg, 37% yield). LC/MS (5%-95% CH_3CN/H_2O, 8 min.; 95% CH_3CN, 2 min.) 5.70 min, *m/z* 534 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (t, 1 H), 8.28 (s, 1 H), 7.55 – 7.72 (m,1 H), 7.02 – 7.21 (m, 2 H), 6.81 – 6.97 (m, 1 H), 4.40 – 4.52 (m, 2 H), 3.76 (s, 3 H), 2.99 – 3.08 (m, 1 H), 2.89 – 2.99 (m, 2 H), 2.85 (s, 3 H), 2.75 (s, 3 H), 1.62 – 2.02 (m, 2 H),1.11 – 1.31 (m, 7 H).

Example 125

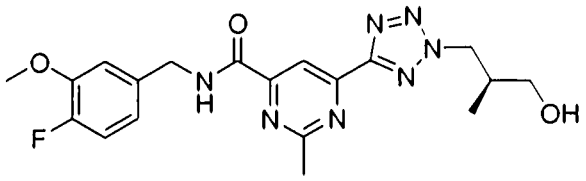
***N*-(4-Fluoro-3-methoxybenzyl)-6-(2-(3-hydroxypropyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (355 mg, 1.03 mmol), 2-bromoethanol (194 mg, 1.55 mmol), triethylamine (400 µL) and dimethylacetamide (400 µL) were combined. The resulting mixture was stirred at 130 °C for 2 h. The mixture was cooled and purification was accomplished by reverse phase preparative high-pressure liquid chromatography. The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrate to afford a residue that upon methanol trituration provided the title compound as a white solid (25 mg, 6.2%). LC/MS (10%-90% CH_3CN/H_2O, 8 min): 4.94 min, *m/z* 388 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.54 (m, 1 H), 8.42 (s, 1 H), 7.15 (td, J = 12.3, 8.4 Hz, 2 H), 6.92 (br. s, 1 H), 4.87 (t, J = 6.8 Hz, 2 H), 4.69 (br. s., 1 H), 4.51 (d, J = 5.9 Hz, 2 H), 3.82 (s, 3 H), 3.49 (d, J = 5.1 Hz, 2 H), 2.83 (s, 3 H), 2.11 (m, 2 H).

Example 126

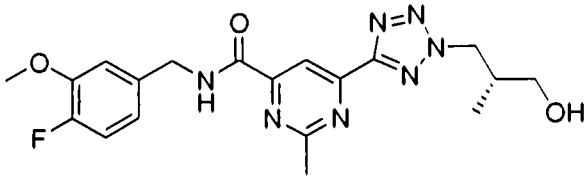
***N*-(4-Fluoro-3-methoxybenzyl)-6-(2-((*S*)-3-hydroxy-2-methylpropyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**



N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (104 mg, 0.303 mmol), (*R*)-3-bromo-2-methylpropan-1-ol (46.4 mg, 0.303 mmol), triethylamine (400 µL) and dimethylacetamide (100 µL) were combined. The resulting mixture was stirred at 130 °C for 2 h. The mixture was cooled and purification was accomplished by reverse phase preparative high-pressure liquid chromatography. The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated to afford a residue that upon methanol trituration provided the title compound as a white solid (10 mg, 7.9%). MS (ES+) *m/z* 416 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.50 (s, 1 H), 8.42 (s, 1 H), 7.18 (dd, J = 8.4, 1.8 Hz, 1 H), 7.14 (dd, J = 11.7, 8.4 Hz, 1 H), 6.91 (br. s, 1 H), 4.87 (dd, J = 13.5, 5.9 Hz, 1 H), 4.77 (t, J = 5.1 Hz, 1 H), 4.65 (dd, J = 13.5, 8.1, 1 H), 4.50 (d, J = 6.2 Hz, 2 H), 3.82 (s, 3 H), 3.38 (dt, J = 10.0, 5.1 Hz, 2 H), 2.83 (s, 3 H), 2.33 (s, 1 H), 0.86 (d, J = 7.0 Hz, 3H).

Example 127

***N*-(4-Fluoro-3-methoxybenzyl)-6-(2-((*R*)-3-hydroxy-2-methylpropyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide**

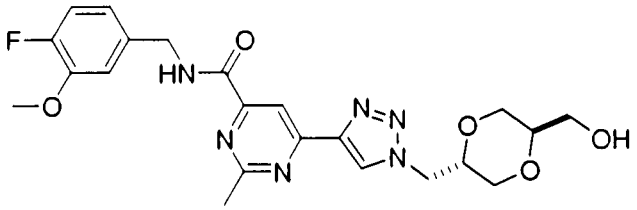


N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-(*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 9) (104 mg, 0.303 mmol), (*S*)-3-bromo-2-methylpropan-1-ol (46.4 mg, 0.303 mmol), triethylamine (400 µL) and dimethylacetamide (100 µL) were combined. The resulting mixture was stirred at 130 °C for 2 h. The mixture was cooled and purification was accomplished by reverse phase preparative high-pressure liquid chromatography. The pure fractions were combined, extracted with ethyl acetate (2 x 20 mL), dried over magnesium sulfate, and concentrated to afford a residue that upon methanol trituration provided the title compound as a white solid (10 mg, 7.9%). MS (ES+) *m/z* 416 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.51 (s, 1 H), 8.42 (s, 1 H), 7.15 (td, J = 11.7, 8.4, Hz, 2 H), 6.91 (br. s, 1 H), 4.87 (dd, J = 13.5, 5.9 Hz, 1 H), 4.77 (t, J = 5.1 Hz, 1 H), 4.65 (dd, J = 13.5, 8.1, 1 H), 4.50 (d, J = 6.2

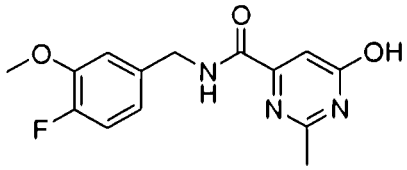
Hz, 2 H), 3.82 (s, 3 H), 3.38 (dt, J = 10.0, 5.1 Hz, 2 H), 2.83 (s, 3 H), 2.33 (s, 1 H), 0.86 (d, J = 7.0 Hz, 3H).

Example 128

N-(4-Fluoro-3-methoxybenzyl)-6-(1-(((2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1H-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide

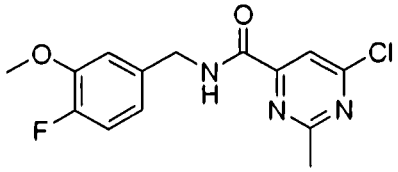


Step 1: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-hydroxy-2-methylpyrimidine-4-carboxamide.



Methyl 6-hydroxy-2-methylpyrimidine-4-carboxylate (prepared as described in step 2 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 5) (10.0 g, 59.5 mmol), 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3- methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (13.7 g, 71.4 mmol, 1.20 equiv.), and *N,N*-diisopropylethylamine (26 mL, 149 mmol, 2.50 equiv.) were combined in methanol (120 mL). After stirring for 2 hours at reflux, the mixture was cooled to room temperature, and diluted with 1.0 N aqueous hydrochloric acid (150 mL) and water (100 mL). The resulting solid was collected by suction filtration, and the filter cake was washed with water (2 x 100 mL) and air dried for 1 h. The solid was dried under vacuum at 40 °C to provide the title compound as a tan solid (13.9 g, 80%). MS (ES+) *m/z* 292 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.75 (1 H, br. s.), 9.09 (1 H, t, *J*=6.2 Hz), 7.04 - 7.21 (2 H, m), 6.78 - 6.90 (1 H, m), 6.67 (1 H, s), 4.40 (2 H, d, *J*=6.2 Hz), 3.81 (3 H, s), 2.35 (3 H, s).

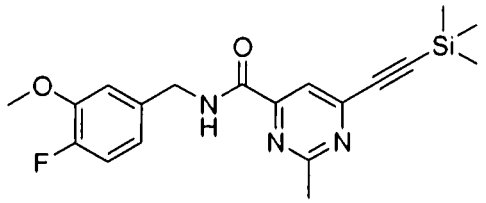
Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-chloro-2-methylpyrimidine-4-carboxamide.



N-(4-Fluoro-3-methoxybenzyl)-6-hydroxy-2-methylpyrimidine-4-carboxamide (10.0 g, 34.3 mmol) and *N,N*-dimethylformamide (0.66 mL, 8.58 mmol, 0.25 equiv.) were combined in tetrahydrofuran (137 mL) and the mixture was heated to 60 °C. To the mixture was added dropwise oxalyl chloride (5.1 mL, 58.4 mmol, 1.70 equiv.). After stirring for 1 hour at 60 °C, the mixture was cooled to room temperature, water (25 mL) was added dropwise, the mixture was filtered through

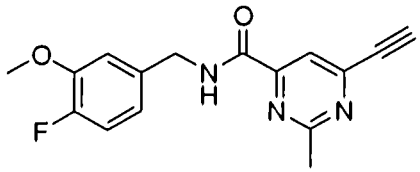
Celite™, the filter cake was washed with tetrahydrofuran (100 mL), and the filtrate was evaporated to one-third the original volume. Water (150 mL) was added and the mixture was concentrated under reduced pressure to induce precipitation of the product. The solid was collected by suction filtration, the filter cake was washed with water (3 x 100 mL), and the solid was air dried for 15 hours to provide the title compound as a red solid (9.50 g, 89%). MS (ES+) *m/z* 310 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.50 (1 H, t, *J*=6.2 Hz), 7.88 (1 H, s), 7.07 - 7.19 (2 H, m), 6.82 - 6.92 (1 H, m), 4.45 (2 H, d, *J*=6.4 Hz), 3.81 (3 H, s), 2.71 (3 H, s).

Step 3: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2-(trimethylsilyl)ethynyl)pyrimidine-4-carboxamide.



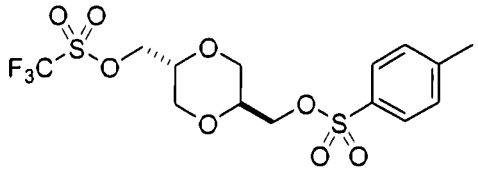
A solution of tetrahydrofuran (10.0 mL) and triethylamine (15.0 mL) was sparged with nitrogen gas for 5 minutes. To this solution was added sequentially *N*-(4-fluoro-3-methoxybenzyl)-6-chloro-2-methylpyrimidine-4-carboxamide (3.00 g, 9.69 mmol), dichlorobis(triphenylphosphine)palladium(II) (68 mg, 97 μmol, 0.01 equiv.), triphenylphosphine (51 mg, 0.19 mmol, 0.02 equiv.), copper (I) iodide (37 mg, 0.19 mmol, 0.02 equiv.), and trimethylsilylacetylene (2.2 mL, 15.5 mmol, 1.60 equiv.). After stirring for 3 hours at 50 °C, the mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), filtered, and concentrated under reduced pressure to give a red oil. Purification by silica gel chromatography (gradient 5:1 heptane/EtOAc to 2:1 heptane/EtOAc) provided the title compound as a viscous, yellow oil (2.60 g, 72%). LC/MS (5%-100% CH_3CN/H_2O, 5 min): 4.12 min, *m/z* 372 (M+H).

Step 4: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-ethynyl-2-methylpyrimidine-4-carboxamide.



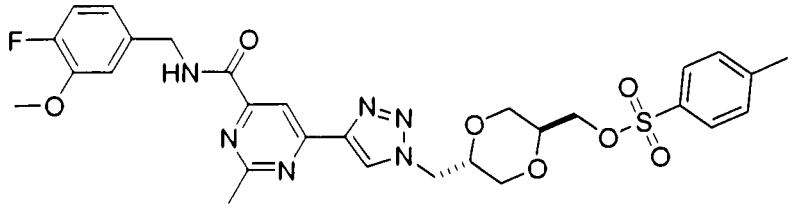
To a solution of *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2-(trimethylsilyl)ethynyl)pyrimidine-4-carboxamide (2.60 g, 7.00 mmol) in tetrahydrofuran (20 mL) and water (10 mL) was added potassium fluoride (447 mg, 7.70 mmol, 1.10 equiv.). After stirring for 2 hours at room temperature, the mixture was concentrated under reduced pressure to remove the tetrahydrofuran, diluted with ethyl acetate (50 mL), and washed with pH 7.0 aqueous phosphate buffer. The layers were separated and the aqueous layer was washed with ethyl acetate (1x). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound as a brown solid (2.06 g, >95%). LC/MS (5%-100% CH_3CN/H_2O, 5 min): 3.24 min, *m/z* 300 (M+H).

Step 5: Preparation of ((2*S*,5*R*)-5-((trifluoromethylsulfonyloxy)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate.



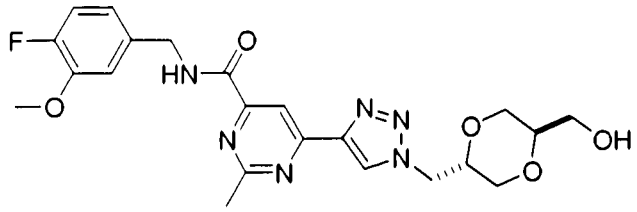
((2*S*,5*S*)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 62) (5.0 g, 16.5 mmol) and pyridine (1.4 mL, 17.3, 1.05 equiv.) were combined in 70 mL dichloromethane, the resulting solution was cooled in a methanol/ice bath, and a solution of trifluoromethanesulfonic anhydride (2.9 mL, 17.3 mmol, 1.05 equiv.) in dichloromethane (10 mL) was added dropwise via cannula. After warming to room temperature, the mixture was diluted with dichloromethane (150 mL) and treated with 1.0 N aqueous hydrochloric acid (40 mL). The layers were separated and the aqueous layer was washed with dichloromethane (3 x 10 mL). The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound as a light yellow solid (6.89 g, >95%).

Step 6: Preparation of ((2*S*,5*S*)-5-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate.



((2*S*,5*R*)-5-((Trifluoromethylsulfonyloxy)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (100 mg, 0.23 mmol) and sodium azide (16 mg, 0.24 mmol, 1.05 equiv.) were combined in tetrahydrofuran (0.8 mL), *tert*-butanol (0.4 mL), and water (0.4 mL). After stirring for 1 hour at room temperature, the reaction vessel was charged sequentially with *N*-(4-fluoro-3-methoxybenzyl)-6-ethynyl-2-methylpyrimidine-4-carboxamide (69 mg, 0.23 mmol, 1.00 equiv.), 1.0 M aqueous sodium ascorbate (23 μL, 0.023 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (17 μL, 0.005 mmol, 0.02 equiv.). After stirring for 15 hours at room temperature, the mixture was diluted with ethyl acetate and washed with 50% aqueous sodium chloride. The layers were separated and the aqueous layer was washed with ethyl acetate (3x). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a dark, orange oil. Purification by silica gel chromatography (gradient 1:1 heptane/EtOAc to 100% EtOAc) provided the title compound as a white solid (142 mg, >95%). LC/MS (10%-90% CH_3CN/H_2O, 5 min): 3.07 min, *m/z* 627 (M+H).

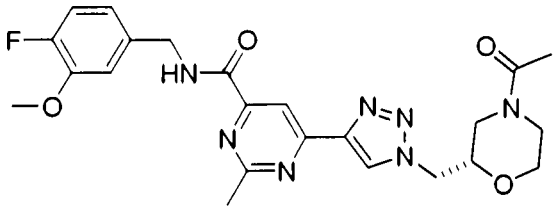
Step 7: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide.



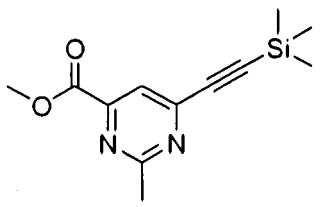
((2*S*,5*S*)-5-((4-(6-((4-Fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (75 mg, 0.12 mmol) and tetrabutylammonium acetate (40 mg, 0.13 mmol, 1.10 equiv.) were combined in dimethylformamide (1.0 mL). After stirring for 1 hour at 65 °C, the mixture was cooled to room temperature, and the reaction vessel was charged sequentially with water (250 μL) and 1.0 N aqueous sodium hydroxide (144 μL, 0.144 mmol, 1.20 equiv.). After stirring for 20 minutes at room temperature, the mixture was diluted with ethyl acetate (10 mL) and washed with 50% aqueous sodium chloride (2 x 3 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give an orange oil. Purification by silica gel chromatography (gradient 100% EtOAc to 5% MeOH/EtOAc) provided the title compound as a white solid (40 mg, 71%). LC/MS (10%-90% CH_3CN/H_2O, 5 min): 2.01 min, *m/z* 473 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.65 (1 H, s), 8.47 (1 H, s), 7.13 (1 H, dd, *J*=8.3, 1.8 Hz), 7.03 (1 H, dd, *J*=11.4, 8.3 Hz), 6.86 - 6.97 (1 H, m), 4.60 - 4.70 (1 H, m), 4.58 (3 H, s), 4.45 - 4.55 (1 H, m), 3.92 - 4.01 (2 H, m), 3.88 (1 H, d, *J*=11.1 Hz), 3.86 (3 H, s), 3.51 - 3.59 (1 H, m), 3.47 - 3.51 (2 H, m), 3.41 - 3.48 (1 H, m), 3.33 - 3.41 (1 H, m), 2.77 (3 H, s).

Example 129

N-(4-Fluoro-3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide



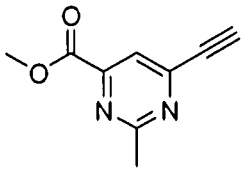
Step 1: Preparation of methyl 2-methyl-6-(2-(trimethylsilyl)ethynyl)pyrimidine-4-carboxylate.



The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-2-methyl-6-(2-(trimethylsilyl)ethynyl)pyrimidine-4-carboxamide (step 3, Example 128) by reaction of methyl 6-chloro-2-methylpyrimidine-4-carboxylate (prepared as described in step 3 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-

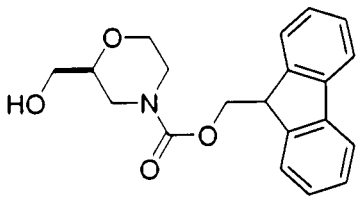
4-carboxamide, Example 5) (1.00 g, 5.36 mmol), dichlorobis(triphenylphosphine)palladium(II) (38 mg, 54 μmol, 0.01 equiv.), triphenylphosphine (28 mg, 0.11 mmol, 0.02 equiv.), copper (I) iodide (20 mg, 0.11 mmol, 0.02 equiv.), and trimethylsilylacetylene (1.2 mL, 8.50 mmol, 1.60 equiv.). Purification by silica gel chromatography (gradient 3:1 heptane/EtOAc to 2:1 heptane/EtOAc) provided the title compound as a tan solid (1.15 g, 86%). LC/MS (10%-90% CH_3CN/H_2O, 5 min): 2.91 min, *m/z* 249 (M+H).

Step 2: Preparation of methyl 6-ethynyl-2-methylpyrimidine-4-carboxylate.



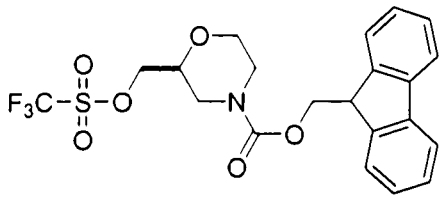
The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-6-ethynyl-2-methylpyrimidine-4-carboxamide (step 4, Example 128) by reaction of methyl 2-methyl-6-(2-(trimethylsilyl)ethynyl)pyrimidine-4-carboxylate (100 mg, 0.40 mmol) and potassium fluoride (26 mg, 0.44 mmol, 1.10 equiv.) to afford the title compound as an orangish-brown solid (70 mg, >95%). LC/MS (10%-90% CH_3CN/H_2O, 5 min): 1.20 min, *m/z* 177 (M+H).

Step 3: Preparation of (9*H*-fluoren-9-yl)methyl (*S*)-2-(hydroxymethyl)morpholine-4-carboxylate.



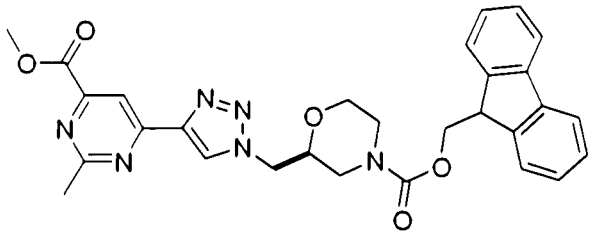
tert-Butyl (*S*)-2-(hydroxymethyl)morpholine-4-carboxylate (1.0 g, 4.60 mmol) and 4.0 M hydrochloric acid in 1,4-dioxane (5.0 mL, 20.0 mmol, 4.35 equiv.) were combined and the solution was stirred at room temperature for 30 minutes. The solvent was evaporated and to the crude residue was added sequentially tetrahydrofuran (10 mL), water (5.0 mL), sodium bicarbonate (1.16 g, 13.8 mmol, 3.0 equiv.), and 9-fluorenylmethyl chloroformate (1.19 g, 4.60 mmol, 1.00 equiv.). After stirring for 15 h at room temperature, the tetrahydrofuran was evaporated under reduced pressure and the mixture was diluted with ethyl acetate (25 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (3x). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound as a white solid (1.56 g, >95%).

Step 4: Preparation of (9*H*-fluoren-9-yl)methyl (*S*)-2-((trifluoromethylsulfonyloxy)methyl)morpholine-4-carboxylate.



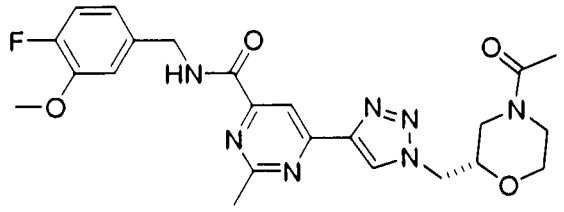
The title compound was prepared in a similar manner to ((2*S*,5*R*)-5-((trifluoromethylsulfonyloxy)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (step 5, Example 128) by reaction of (9*H*-fluoren-9-yl)methyl (*S*)-2-(hydroxymethyl)morpholine-4-carboxylate (1.25 g, 3.68 mmol), pyridine (313 μL, 3.87 mmol, 1.05 equiv.), and trifluoromethanesulfonic anhydride (0.65 mL, 3.87 mmol, 1.05 equiv.) to afford the title compound as a light tan solid (1.68 g, >95%).

Step 5: Preparation of methyl 6-(1-(((*S*)-4-(((9*H*-fluoren-9-yl)methoxy)carbonyl)morpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxylate.



The title compound was prepared in a similar manner to ((2*S*,5*S*)-5-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (step 6, Example 128) by reaction of (9*H*-fluoren-9-yl)methyl (*S*)-2-((trifluoromethylsulfonyloxy)methyl)morpholine-4-carboxylate (140 mg, 0.30 mmol), sodium azide (20 mg, 0.31 mmol, 1.05 equiv.), methyl 6-ethynyl-2-methylpyrimidine-4-carboxylate (52 mg, 0.30 mmol, 1.00 equiv.), 1.0 M aqueous sodium ascorbate (30 μL, 0.030 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (20 μL, 0.006 mmol, 0.02 equiv.). Purification by silica gel chromatography (gradient 1:1 heptane/EtOAc to 100% EtOAc) provided the title compound as a tan solid (113 mg, 71%). LC/MS (10%-90% CH_3CN/H_2O, 5 min): 2.99 min, *m/z* 541 (M+H).

Step 6: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide.

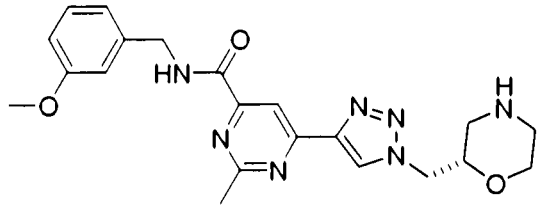


Methyl 6-(1-(((*S*)-4-(((9*H*-fluoren-9-yl)methoxy)carbonyl)morpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxylate (49 mg, 91 μmol), 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3- methoxybenzy1)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-y1)pyrimidine-4-carboxamide, Example 1) (52 mg,

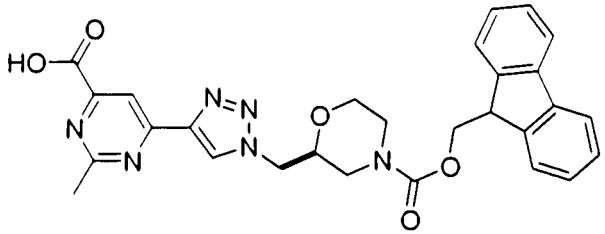
0.27 mmol, 3.00 equiv.), and triethylamine (51 μL, 0.36 mmol, 4.00 equiv.) were combined in *N,N*-dimethylacetamide (1.0 mL). After stirring for 1 hour at 65 °C, the mixture was cooled to room temperature, and to the mixture was added sequentially dichloromethane (1.0 mL), triethylamine (76 μL, 0.54 mmol, 6.00 equiv.), and acetyl chloride (32 μL, 0.45 mmol, 5.00 equiv.). After stirring for 1 hour at room temperature, the mixture was concentrated under reduced pressure, diluted with ethyl acetate (5 mL), and washed with pH 7.0 aqueous phosphate buffer (2 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (3 x 1 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. Partial purification by silica gel chromatography (gradient 1:2 heptane/EtOAc to 100% EtOAc to 5% MeOH/EtOAc) provided an oily residue, which was further purified by reverse-phase HPLC to afford the title compound as a white solid (7 mg, 16%). MS (ES+) *m/z* 484 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (1 H, t, *J*=5.9 Hz), 8.80 (1 H, d, *J*=11.9 Hz), 8.34 (1 H, s), 7.17 - 7.21 (1 H, m), 7.14 (1 H, dd, *J*=11.7, 8.6 Hz), 6.81 - 6.98 (1 H, m), 4.63 - 4.77 (1 H, m), 4.54 - 4.63 (1 H, m), 4.49 (2 H, d, *J*=6.2 Hz), 4.21 (1 H, dd, *J*=86.2, 13.0 Hz), 3.85 - 3.98 (2 H, m), 3.82 (3 H, s), 3.39 - 3.71 (1 H, m), 2.92 - 3.23 (1 H, m), 2.75 (3 H, s), 2.52 - 2.73 (1 H, m), 2.02 (3 H, d, *J*=11.3 Hz).

Example 130

***N*-(3-Methoxybenzyl)-2-methyl-6-(1-((*S*)-morpholin-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide**



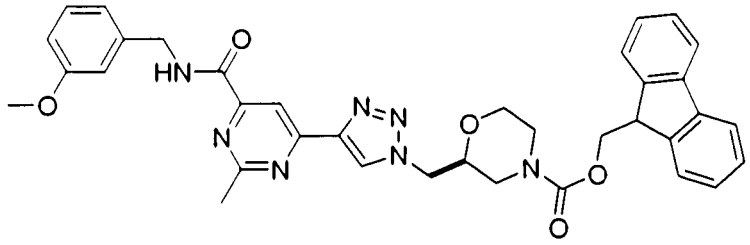
Step 1: Preparation of 6-(1-(((*S*)-4-(((9*H*-fluoren-9-yl)methoxy)carbonyl)morpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxylic acid.



Methyl 2-methyl-6-(2-(trimethylsilyl)ethynyl)pyrimidine-4-carboxylate (prepared as described in step 4 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 129) (200 mg, 0.81 mmol) was dissolved in tetrahydrofuran (0.90 mL), *tert*-butanol (0.90 mL), and water (0.90 mL), and to this mixture was added 2.0 N aqueous lithium hydroxide (423 μL, 0.85 mmol, 1.05 equiv.). In a separate reaction vessel, (9*H*-fluoren-9-yl)methyl (*S*)-2-((trifluoromethylsulfonyloxy)methyl)morpholine-4-carboxylate (prepared as described in step 4 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 129)

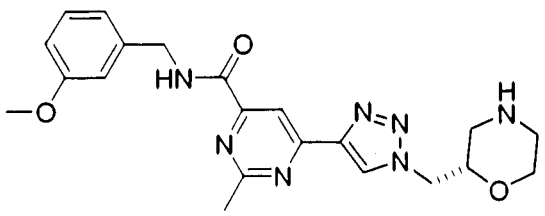
(380 mg, 0.81 mmol, 1.00 equiv.) and sodium azide (55 mg, 0.85 mmol, 1.05 equiv.) were combined in tetrahydrofuran (0.90 mL), *tert*-butanol (0.90 mL), and water (0.90 mL). After stirring for 2 hours at room temperature, both crude reaction mixtures were combined into a single reaction vessel. To this mixture was added sequentially 1.0 M aqueous sodium ascorbate (81 μL, 0.081 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (54 μL, 0.016 mmol, 0.02 equiv.). After stirring for 15 hours at room temperature, the mixture was diluted with ethyl acetate (4 mL) and washed with 2.0 N aqueous sodium hydroxide (0.5 mL). The layers were separated, the aqueous layer was acidified with 1.0 N aqueous hydrochloric acid (1.2 mL), and extracted with ethyl acetate (3 x 2 mL) and dichloromethane (3 x 2 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the crude title compound as a purple solid (424 mg) that was used in subsequent reactions without further purification. LC/MS (10%-90% CH_3CN/H_2O, 5 min): 2.60 min, *m/z* 527 (M+H).

Step 2: Preparation of (2*S*)-(9*H*-fluoren-9-yl)methyl 2-((4-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)morpholine-4-carboxylate.



6-(1-(((*S*)-4-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)morpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxylic acid (200 mg, 0.38 mmol), 3-methoxybenzylamine (54 μL, 0.42 mmol, 1.10 equiv.), *N,N*-diisopropylethylamine (79 μL, 0.42 mmol, 1.20 equiv.), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (188 mg, 0.49 mmol, 1.30 equiv.) were combined in *N,N*-dimethylformamide (2.5 mL). After stirring for 15 hours at room temperature, the mixture was diluted with ethyl acetate (10 mL), and washed with pH 7.0 aqueous phosphate buffer (3 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (3 x 2 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give an oily residue. Purification by silica gel chromatography (gradient 1:1 heptane/EtOAc to 100% EtOAc) provided the title compound as a white solid (192 mg, 78%). LC/MS (10%-90% CH_3CN/H_2O, 5 min): 3.43 min, *m/z* 646 (M+H).

Step 3: Preparation of *N*-(3-methoxybenzyl)-2-methyl-6-(1-((*S*)-morpholin-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide.

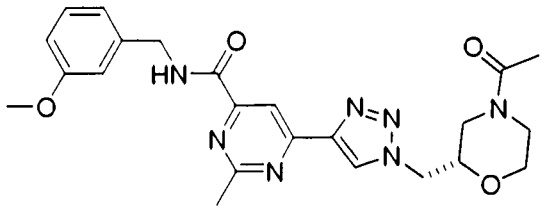


(2*S*)-(9*H*-Fluoren-9-yl)methyl 2-((4-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)morpholine-4-carboxylate (192 mg, 0.30 mmol) and piperidine (60 μL,

0.60 mmol, 2.0 equiv.) were combined in *N,N*-dimethylformamide (1.2 mL). After stirring for 5 minutes at room temperature, the mixture was concentrated under reduced pressure to afford the crude title compound as an oil that was used in subsequent reactions without further purification. LC/MS (10%-90% CH_3CN/H_2O, 5 min): 1.62 min, *m/z* 424 (M+H).

Example 131

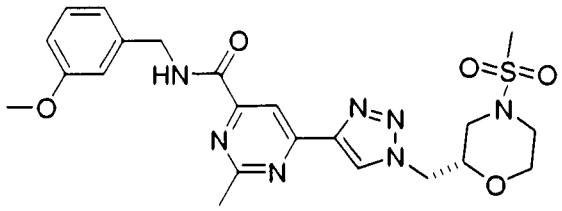
N-(3-Methoxybenzyl)-6-(1-(((S)-4-acetylmorpholin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide



N-(3-Methoxybenzyl)-2-methyl-6-(1-((*S*)-morpholin-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide (prepared as described in Example 130) (63 mg, 0.15 mmol), triethylamine (83 μL, 0.60 mmol, 4.00 equiv.), and acetyl chloride (32 μL, 0.45 mmol, 3.00 equiv.) were combined in dichloromethane (1.5 mL). After stirring for 1 hour at room temperature, methanol (0.5 mL) was added and the mixture was concentrated under reduced pressure to give a salty slurry. Purification by silica gel chromatography (gradient 100% EtOAc to 10% MeOH/EtOAc) provided the title compound as an off-white foam (41 mg, 60%). MS (ES+) *m/z* 466 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (1 H, t, *J*=6.3 Hz), 8.80 (1 H, d, *J*=12.3 Hz), 8.34 (1 H, s), 7.24 (1 H, t, *J*=8.1 Hz), 6.89 - 6.98 (2 H, m), 6.82 (1 H, dd, *J*=8.3, 1.9 Hz), 4.65 - 4.79 (1 H, m), 4.52 - 4.64 (1 H, m), 4.50 (2 H, d, *J*=6.2 Hz), 4.21 (1 H, dd, *J*=86.1, 12.7 Hz), 3.77 - 3.99 (3 H, m), 3.74 (3 H, s), 3.65 (1 H, d, *J*=14.3 Hz), 3.33 - 3.51 (1 H, m), 2.94 - 3.21 (1 H, m), 2.75 (3 H, s), 2.02 (3 H, d, *J*=11.5 Hz).

Example 132

N-(3-Methoxybenzyl)-2-methyl-6-(1-(((R)-4-(methylsulfonyl)morpholin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide

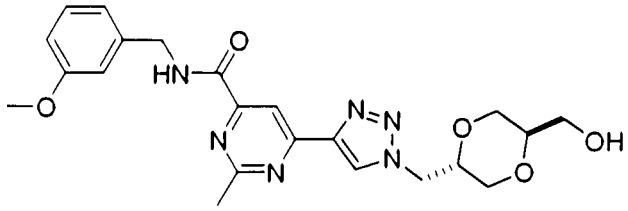


The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (Example 131) by reaction of *N*-(3-methoxybenzyl)-2-methyl-6-(1-((*S*)-morpholin-2-ylmethyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide (prepared as described in Example 130) (63 mg, 0.15 mmol), triethylamine (83 μL, 0.60 mmol, 4.00 equiv.), and methanesulfonyl chloride (34 μL, 0.45 mmol, 3.00 equiv.) to afford the title compound as an off-white foam (48 mg, 65%). MS (ES+) *m/z* 502 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (1 H, t, *J*=6.4 Hz), 8.84 (1 H, s), 8.34 (1 H, s), 7.24 (1 H, t, *J*=8.1 Hz), 6.88 - 6.98 (2 H, m), 6.82 (1 H, dd, *J*=8.2, 2.0 Hz), 4.68 - 4.76 (1 H, m), 4.55 - 4.65 (1 H, m), 4.50

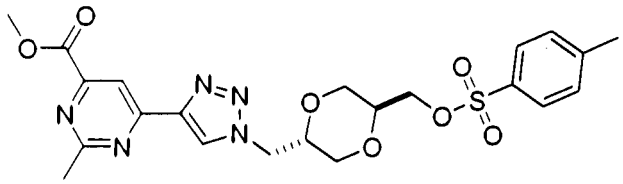
(2 H, d, *J*=6.2 Hz), 3.98 - 4.08 (1 H, m), 3.95 (1 H, d, *J*=11.0 Hz), 3.74 (3 H, s), 3.48 - 3.63 (2 H, m), 3.32 - 3.40 (1 H, m), 2.92 (3 H, s), 2.80 - 2.90 (1 H, m), 2.75 (3 H, s), 2.68 (1 H, dd, *J*=11.4, 10.2 Hz).

Example 133

N-(3-Methoxybenzyl)-6-(1-(((2S,5R)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1H-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide

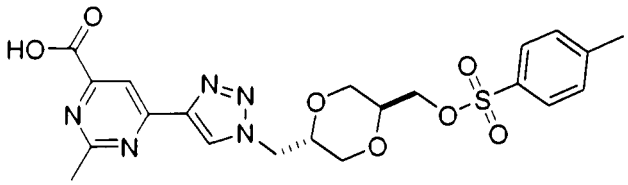


Step 1: Preparation of methyl 2-methyl-6-(1-(((2*S*,5*S*)-5-((tosyloxy)methyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxylate.



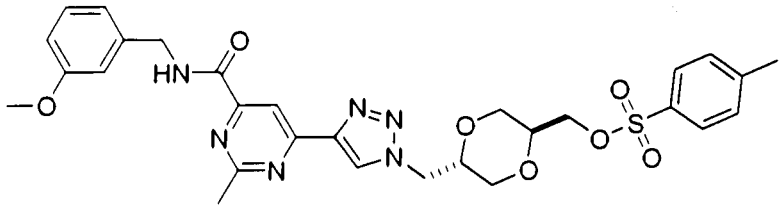
Methyl 2-methyl-6-(2-(trimethylsilyl)ethynyl)pyrimidine-4-carboxylate (prepared as described in step 4 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 129) (30 mg, 0.12 mmol) was dissolved in tetrahydrofuran (0.20 mL), *tert*-butanol (0.20 mL), and water (0.20 mL), and to this mixture was added potassium fluoride (7 mg, 0.12 mmol, 1.00 equiv.). In a separate reaction vessel, ((2*S*,5*R*)-5-((trifluoromethylsulfonyloxy)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 5 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 128) (50 mg, 0.12 mmol, 1.00 equiv.) and sodium azide (8 mg, 0.12 mmol, 1.00 equiv.) were combined in tetrahydrofuran (0.2 mL), *tert*-butanol (0.2 mL), and water (0.2 mL).. After stirring for 1 hour at room temperature, both crude reaction mixtures were combined into a single reaction vessel. To this mixture was added sequentially 1.0 M aqueous sodium ascorbate (12 μL, 0.012 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (8 μL, 0.002 mmol, 0.02 equiv.). After stirring for 15 hours at room temperature, the mixture was diluted with ethyl acetate (4 mL) and washed with saturated aqueous sodium chloride (1 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (2 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide an orange oil. Purification by silica gel chromatography (gradient 1:1 heptane/EtOAc to 100% EtOAc) provided the title compound as a yellow solid (59 mg, >95%). LC/MS (10%-90% CH_3CN/H_2O, 5 min): 2.50 min, *m/z* 504 (M+H).

Step 2: Preparation of 2-methyl-6-(1-(((2*S*,5*S*)-5-((tosyloxy)methyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxylic acid.



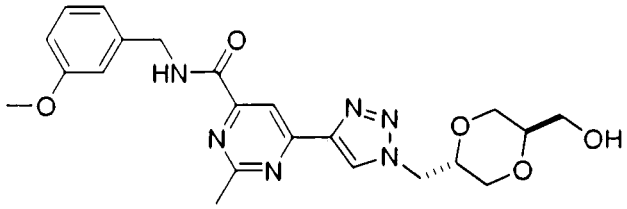
Methyl 2-methyl-6-(1-(((2*S*,5*S*)-5-((tosyloxy)methyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxylate (59 mg, 0.12 mmol) was dissolved in tetrahydrofuran (0.80 mL), and water (0.40 mL), and to this mixture was added 2.0 N aqueous lithium hydroxide (65 μL, 0.13 mmol, 1.08 equiv.). After stirring for 5 minutes at room temperature, the solution was neutralized with 1.0 N aqueous hydrochloric acid (130 μL, 0.13 mmol, 1.08 equiv.). The mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate (4 mL) and methanol (2 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the crude title compound as an orange solid (57 mg) that was used in subsequent reactions without further purification. LC/MS (10%-90% CH_3CN/H_2O, 5 min): 2.13 min, *m/z* 490 (M+H).

Step 3: Preparation of ((2*S*,5*S*)-5-((4-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate.



2-Methyl-6-(1-(((2*S*,5*S*)-5-((tosyloxy)methyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxylic acid (108 mg, 0.22 mmol), 3-methoxybenzylamine (30 μL, 0.23 mmol, 1.05 equiv.), *N,N*-diisopropylethylamine (40 μL, 0.23 mmol, 1.05 equiv.), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (88 mg, 0.23 mmol, 1.05 equiv.) were combined in *N,N*-dimethylformamide (1.5 mL). After stirring for 15 hours at room temperature, the mixture was diluted with ethyl acetate (10 mL) and washed with 10% aqueous sodium bisulfate (3 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (3 x 2 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give an oily residue. Purification by silica gel chromatography (gradient 1:2 heptane/EtOAc to 100% EtOAc to 10% MeOH/EtOAc) provided the title compound as a white solid (131 mg, >95%). LC/MS (10%-90% CH_3CN/H_2O, 5 min): 3.02 min, *m/z* 609 (M+H).

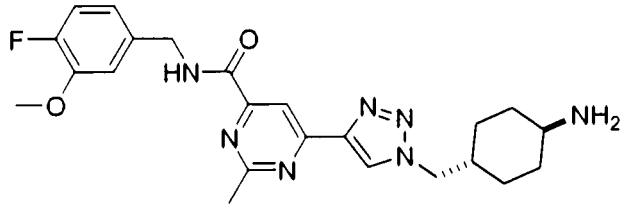
Step 4: Preparation of *N*-(3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide.



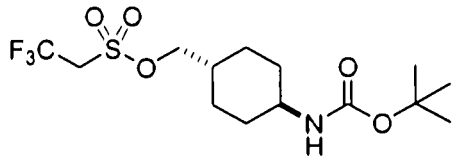
The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (step 7, Example 128) by reaction of ((2*S*,5*S*)-5-((4-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (131 g, 0.22 mmol), tetrabutylammonium acetate (71 mg, 0.24 mmol, 1.10 equiv.), and 1.0 N aqueous sodium hydroxide (260 μL, 0.26 mmol, 1.20 equiv.). Purification by silica gel chromatography (gradient 100% EtOAc to 10% MeOH/EtOAc) provided the title compound as a white solid (50 mg, 51%). MS (ES+) *m/z* 455 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (1 H, t, *J*=6.4 Hz), 8.80 (1 H, s), 8.33 (1 H, s), 7.24 (1 H, t, *J*=8.1 Hz), 6.88 - 6.99 (2 H, m), 6.82 (1 H, dd, *J*=8.1, 2.0 Hz), 4.67 (1 H, t, *J*=5.6 Hz), 4.55 - 4.63 (1 H, m), 4.43 - 4.54 (3 H, m), 3.87 - 4.01 (2 H, m), 3.77 - 3.85 (1 H, m), 3.74 (3 H, s), 3.32 - 3.47 (4 H, m), 2.75 (3 H, s).

Example 134

N-(4-Fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide



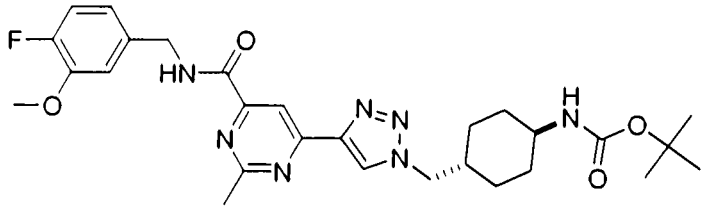
Step 1: Preparation of ((*trans*)-4-(*tert*-butoxycarbonyl)cyclohexyl)methyl 2,2,2-trifluoroethanesulfonate.



Commercially available *tert*-butyl *trans*-4-(hydroxymethyl)cyclohexylcarbamate (2.00 g, 8.72 mmol), 2,2,2-trifluoroethanesulfonyl chloride (1.2 mL, 11.0 mmol, 1.20 equiv.), and *N,N*-diisopropylethylamine (2.0 mL, 11.0 mmol, 1.20 equiv.) were combined in dichloromethane (35 mL). After stirring for 1 hour at 0 °C, the mixture was concentrated under reduced pressure, and the salty residue was partitioned between ethyl acetate (100 mL) and 1.0 N aqueous hydrochloric acid (20 mL). The layers were separated and the organic layer was washed with 1.0 N aqueous hydrochloric acid (10 mL), saturated aqueous sodium bicarbonate (20 mL), and brine (20 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by

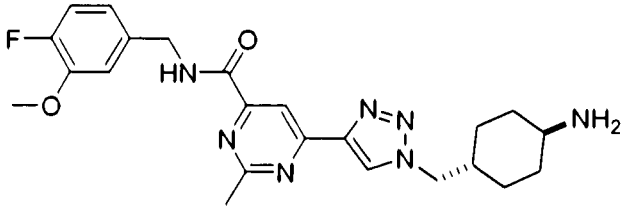
recrystallization (1:2 heptane/EtOAc) provided the title compound as a white needles (2.29 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (1 H, br. s.), 4.15 (2 H, d, J=6.5 Hz), 3.89 (2 H, q, J=8.7 Hz), 3.40 (1 H, br. s.), 1.98 - 2.16 (2 H, m), 1.80 - 1.93 (2 H, m), 1.66 - 1.79 (1 H, m), 1.44 (9 H, s), 1.05 - 1.20 (4 H, m).

Step 2: Preparation of *tert*-butyl (*trans*)-4-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)cyclohexylcarbamate.



((*trans*)-4-(*tert*-Butoxycarbonyl)cyclohexyl)methyl 2,2,2-trifluoroethanesulfonate (450 mg, 1.20 mmol) and sodium azide (80 mg, 1.22 mmol, 1.02 equiv.) were combined in *N,N*-dimethylformamide (1.0 mL). After stirring for 18 hours at room temperature, the reaction vessel was charged sequentially with *N,N*-dimethylformamide (3.0 mL), water (1.0 mL), *N*-(4-fluoro-3-methoxybenzyl)-6-ethynyl-2-methylpyrimidine-4-carboxamide (prepared as described in step 4 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 128) (305 mg, 1.20 mmol, 1.00 equiv.), 1.0 M aqueous sodium ascorbate (120 μL, 0.12 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (80 μL, 0.024 mmol, 0.02 equiv.). After stirring for 23 hours at room temperature, to the reaction mixture was added sequentially *N,N*-dimethylformamide (2.0 mL), 1.0 M aqueous sodium ascorbate (120 μL, 0.12 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (80 μL, 0.024 mmol, 0.02 equiv.). After stirring for 6 hours at room temperature, the mixture was poured with vigorous stirring into ice-cold water (150 mL). The precipitate was collected by suction filtration, washed with water (3x), dissolved in ethyl acetate, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The reddish-orange amorphous solid was dissolved in 5% methanol/ethyl acetate, filtered through a short pad of silica, and concentrated under reduced pressure. Purification by recrystallization (2:3 heptane/EtOAc) provided the title compound as a pale orange solid (504 mg, 76%). LC/MS (5%-100% CH_3CN/H_2O, 5 min): 3.71 min, *m/z* 554 (M+H).

Step 3: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide.

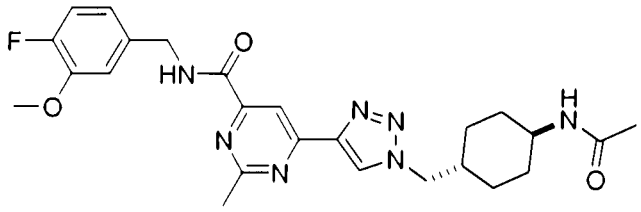


tert-Butyl (*trans*)-4-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)cyclohexylcarbamate (497 mg, 0.90 mmol) and 4.0 N hydrochloric acid in 1,4-dioxane (3.6 mL, 14.4 mmol, 16.0 equiv.) were combined in 1,4-dioxane (4.0 mL). After stirring for 18 hours at room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in methanol, concentrated under reduced pressure, and dried under high vacuum to afford

the hydrochloride salt form of title compound as a white solid (440 mg, >95%) that was used in subsequent reactions without further purification. LC/MS (5%-100% CH_3CN/H_2O, 5 min): 2.74 min, *m/z* 454 (M+H).

Example 135

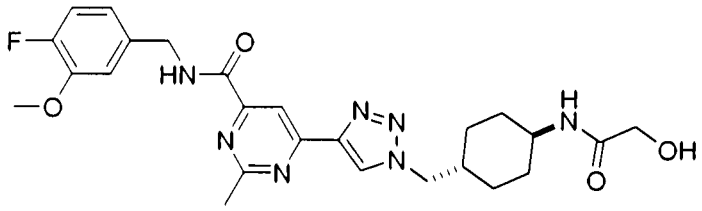
N-(4-Fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide



The hydrochloride salt form of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-aminocyclohexyl)-methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 134) (440 mg, 0.90 mmol), triethylamine (376 μL, 2.70 mmol, 3.00 equiv.), and acetyl chloride (77 μL, 1.08 mmol, 1.20 equiv.) were combined in dichloromethane (5.0 mL). After stirring for 1 hour at room temperature, methanol (2 mL) was added and the mixture was diluted with dichloromethane (20 mL) and water (5 mL). The layers were separated and the organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (gradient 100% EtOAc to 20% MeOH/EtOAc) provided the title compound as a white solid (353 mg, 79%). LC/MS (5%-100% CH_3CN/H_2O, 5 min): 3.17 min, *m/z* 496 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (1 H, t, *J*=6.4 Hz), 8.90 (1 H, s), 8.33 (1 H, s), 7.71 (1 H, d, *J*=7.9 Hz), 7.10 - 7.23 (2 H, m), 6.84 - 6.95 (1 H, m), 4.49 (2 H, d, *J*=6.3 Hz), 4.33 (2 H, d, *J*=7.2 Hz), 3.82 (3 H, s), 2.75 (3 H, s), 1.82 - 1.94 (1 H, m), 1.75 - 1.82 (2 H, m), 1.75 (3 H, s), 1.47 - 1.63 (2 H, m), 1.00 - 1.18 (4 H, m).

Example 136

N-(4-Fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide

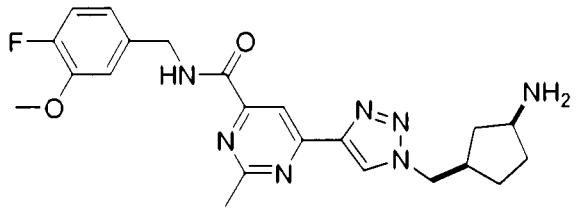


The hydrochloride salt form of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-aminocyclohexyl)-methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (prepared as described Example 134) (224 mg, 0.46 mmol), triethylamine (160 μL, 1.14 mmol, 2.50 equiv.), and 2-acetoxyacetyl chloride (59 μL, 0.55 mmol, 1.20 equiv.) were combined in dichloromethane (10 mL). After stirring for 1 hour at room temperature, the mixture was concentrated under reduced pressure. To the salty residue were added sequentially tetrahydrofuran (4.0 mL) and 2.0 N aqueous lithium hydroxide (2.0 mL, 4.00 mmol, 8.70 equiv.). After stirring for 1 hour at room temperature, the mixture was diluted with ethyl acetate (20 mL) and water (5 mL). The layers were separated and the organic layer was dried

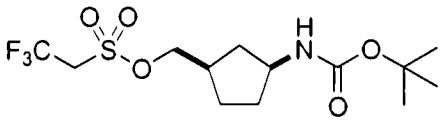
over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (gradient 100% EtOAc to 10% MeOH/EtOAc) provided the title compound as a white solid (185 mg, 81%). MS (ES+) *m/z* 512 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (1 H, t, *J*=6.3 Hz), 8.90 (1 H, s), 8.33 (1 H, s), 7.47 (1 H, d, *J*=8.2 Hz), 7.11 - 7.21 (2 H, m), 6.90 (1 H, ddd), 5.41 (1 H, t, *J*=5.8 Hz), 4.49 (2 H, d, *J*=6.4 Hz), 4.34 (2 H, d, *J*=7.1 Hz), 3.82 (3 H, s), 3.75 (2 H, d, *J*=5.7 Hz), 3.48 - 3.64 (1 H, m), 2.74 (3 H, s), 1.80 - 1.98 (1 H, m), 1.73 (2 H, d, *J*=11.2 Hz), 1.56 (2 H, d, *J*=11.9 Hz), 1.19 - 1.36 (2 H, m), 1.00 - 1.19 (2 H, m).

Example 137

***N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide**

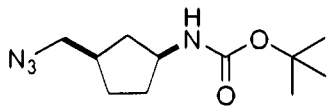


Step 1: Preparation of ((1*R*,3*S*)-3-(*tert*-butoxycarbonyl)cyclopentyl)methyl 2,2,2-trifluoroethanesulfonate.



tert-Butyl (1*S*,3*R*)-3-(hydroxymethyl)cyclopentylcarbamate (prepared from commercially available 1-(*R*)-(—)-2-azabicyclo[2.2.1]hept-5-en-3-one according to the method described by Shuto and coworkers, see Kudoh, T. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8846-8855) (150 mg, 0.70 mmol), 2,2,2-trifluoroethanesulfonyl chloride (82 μL, 0.73 mmol, 1.05 equiv.), and *N,N*-diisopropylethylamine (140 μL, 0.80 mmol, 1.15 equiv.) were combined in dichloromethane (3.0 mL). After stirring for 30 minutes at 0 °C, the mixture was diluted with dichloromethane (15 mL) and 10% aqueous sodium bisulfate (5 mL). The layers were separated and the aqueous layer was washed with dichloromethane (1x). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (gradient 4:1 heptane/EtOAc to 2:1 heptane/EtOAc) provided the title compound as a white solid (206 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (1 H, br. s.), 4.28 (2 H, d, *J*=6.4 Hz), 3.97 (1 H, br. s.), 3.90 (2 H, q, *J*=8.8 Hz), 2.33 - 2.46 (1 H, m), 2.20 - 2.32 (1 H, m), 1.95 - 2.09 (1 H, m), 1.77 - 1.91 (1 H, m), 1.46 - 1.58 (2 H, m), 1.45 (9 H, s), 1.10 - 1.23 (1 H, m).

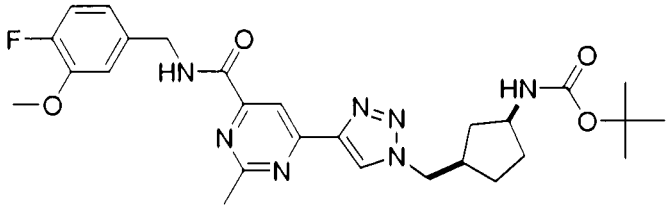
Step 2: Preparation of *tert*-butyl (1*S*,3*R*)-3-(azidomethyl)cyclopentylcarbamate.



((1*R*,3*S*)-3-(*tert*-Butoxycarbonyl)cyclopentyl)methyl 2,2,2-trifluoroethanesulfonate (125 mg, 0.35 mmol) and sodium azide (35 mg, 0.54 mmol, 1.54 equiv.) were combined in *N,N*-

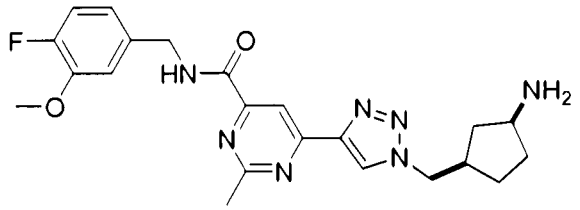
dimethylformamide (0.90 mL). After stirring for 1 hour at 60 °C, the mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and 50% aqueous sodium chloride (2 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (3 x 1 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (gradient 4:1 heptane/EtOAc to 2:1 heptane/EtOAc) provided the title compound as a colorless oil (83 mg, >95%).

Step 3: Preparation of *tert*-butyl (1*S*,3*R*)-3-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)cyclopentylcarbamate.



tert-Butyl (1*S*,3*R*)-3-(azidomethyl)cyclopentylcarbamate (75 mg, 0.31 mmol), *N*-(4-fluoro-3-methoxybenzyl)-6-ethynyl-2-methylpyrimidine-4-carboxamide (prepared as described in step 4 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 128) (93 mg, 0.31 mmol, 1.00 equiv.), 1.0 M aqueous sodium ascorbate (31 μL, 0.031 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (20 μL, 0.006 mmol, 0.02 equiv.) were combined in tetrahydrofuran (0.50 mL), *tert*-butanol (0.50 mL), and water (0.50 mL). After stirring for 15 hours at room temperature, the mixture was diluted with ethyl acetate (10 mL) and saturated aqueous sodium chloride (2 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (3 x 1 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (gradient 4:1 heptane/EtOAc to 100% EtOAc) provided the title compound as an off-white solid (136 mg, 81%). LC/MS (5%-100% CH_3CN/H_2O, 5 min): 3.78 min, *m/z* 484 (M – 2-Me-propene + H).

Step 4: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide.

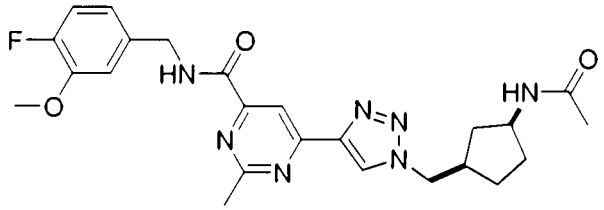


tert-Butyl (1*S*,3*R*)-3-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)cyclopentylcarbamate (136 mg, 0.25 mmol) was dissolved in 4.0 N hydrochloric acid in methanol (1.5 mL, 6.00 mmol, 24.2 equiv.). After stirring for 18 hours at room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in methanol, concentrated under reduced pressure, and dried under high vacuum to afford the hydrochloride salt form of title compound as a white solid (118 mg, >95%) that was used in

subsequent reactions without further purification. LC/MS (5%-100% CH_3CN/H_2O, 5 min): 2.73 min, *m/z* 440 (M+H).

Example 138

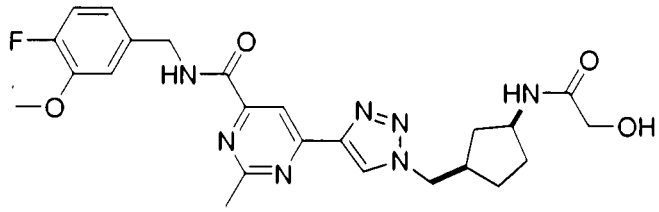
N-(4-Fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-acetamidocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (Example 131) by reaction of the hydrochloride salt form of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 137) (39 mg, 0.089 mmol), triethylamine (35 μL, 0.25 mmol, 2.80 equiv.), and acetyl chloride (15 μL, 0.21 mmol, 2.40 equiv.). Purification by silica gel chromatography (gradient 100% EtOAc to 10% MeOH/EtOAc) provided the title compound as a light yellow foam (27 mg, 63%). MS (ES+) *m/z* 482 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (1 H, t, *J*=6.2 Hz), 8.89 (1 H, s), 8.34 (1 H, s), 7.81 (1 H, d, *J*=7.3 Hz), 7.18 (1 H, dd, *J*=8.6, 1.6 Hz), 7.14 (1 H, dd, *J*=12.0, 8.5 Hz), 6.85 - 6.96 (1 H, m), 4.50 (2 H, d, *J*=6.2 Hz), 4.46 (2 H, d, *J*=7.3 Hz), 3.92 - 4.05 (1 H, m), 3.83 (3 H, s), 2.75 (3 H, s), 1.91 - 2.01 (1 H, m), 1.78 - 1.88 (1 H, m), 1.76 (3 H, s), 1.57 - 1.70 (1 H, m), 1.37 - 1.54 (2 H, m), 1.07 - 1.22 (1 H, m).

Example 139

N-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-(2-hydroxyacetamido)cyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide

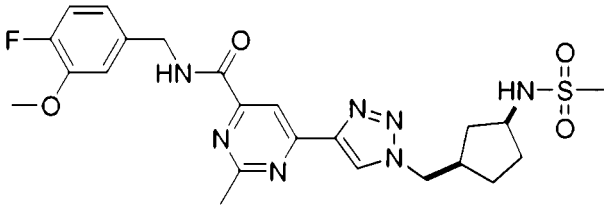


The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (Example 136) by reaction of the hydrochloride salt form of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 137) (39 mg, 0.089 mmol), triethylamine (35 μL, 0.25 mmol, 2.80 equiv.), 2-acetoxyacetyl chloride (20 μL, 0.19 mmol, 2.10 equiv.), and 2.0 N aqueous lithium hydroxide (0.45 mL, 0.89 mmol, 10.0 equiv.). Purification by silica gel chromatography (gradient 100% EtOAc to 10% MeOH/EtOAc) provided the title compound as a light yellow foam (25 mg, 56%). MS (ES+) *m/z* 498 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (1 H, t, *J*=6.2 Hz), 8.89 (1

H, s), 8.34 (1 H, s), 7.61 (1 H, d, *J*=7.5 Hz), 7.18 (1 H, dd, *J*=8.6, 1.5 Hz), 7.14 (1 H, dd, *J*=11.6, 8.3 Hz), 6.82 - 6.96 (1 H, m), 5.31 (1 H, t, *J*=5.9 Hz), 4.50 (2 H, d, *J*=6.4 Hz), 4.46 (2 H, dd, *J*=7.0, 2.1 Hz), 4.02 - 4.16 (1 H, m), 3.82 (3 H, s), 3.77 (2 H, d, *J*=5.9 Hz), 2.75 (3 H, s), 1.90 - 2.01 (1 H, m), 1.75 - 1.90 (1 H, m), 1.42 - 1.70 (4 H, m), 1.21 - 1.35 (1 H, m).

Example 140

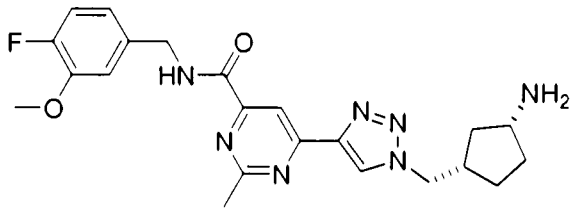
***N*-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(1-(((1*R*,3*S*)-3-(methylsulfonamido)cyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide**



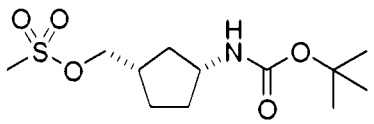
The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (Example 131) by reaction of the hydrochloride salt form of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 137) (39 mg, 0.089 mmol), triethylamine (35 μL, 0.25 mmol, 2.80 equiv.), and methanesulfonyl chloride (15 μL, 0.19 mmol, 2.10 equiv.). Purification by silica gel chromatography (gradient 100% EtOAc to 10% MeOH/EtOAc) provided the title compound as a light yellow foam (33 mg, 72%). MS (ES+) *m/z* 518 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (1 H, t, *J*=6.5 Hz), 8.89 (1 H, s), 8.34 (1 H, s), 7.18 (1 H, dd, *J*=8.6, 1.6 Hz), 7.11 - 7.17 (1 H, m), 7.09 (1 H, d, *J*=7.3 Hz), 6.83 - 6.96 (1 H, m), 4.50 (2 H, d, *J*=6.2 Hz), 4.45 (2 H, d, *J*=7.3 Hz), 3.82 (3 H, s), 3.51 - 3.71 (1 H, m), 2.88 (3 H, s), 2.75 (3 H, s), 1.97 - 2.09 (1 H, m), 1.82 - 1.96 (1 H, m), 1.35 - 1.72 (4 H, m), 1.19 - 1.34 (1 H, m).

Example 141

***N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((1*S*,3*R*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide**



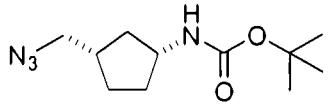
Step 1: Preparation of ((1*S*,3*R*)-3-(*tert*-butoxycarbonyl)cyclopentyl)methyl methanesulfonate.



tert-Butyl (1*R*,3*S*)-3-(hydroxymethyl)cyclopentylcarbamate (prepared from commercially available 1-(*S*)-(+)-2-azabicyclo[2.2.1]hept-5-en-3-one according to the method described by Shuto

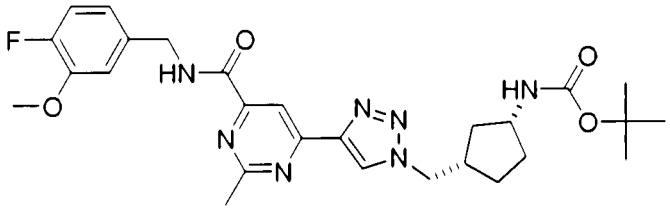
and coworkers, see Kudoh, T. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8846-8855) (250 mg, 1.16 mmol), methanesulfonyl chloride (108 μL, 1.39 mmol, 1.20 equiv.), and *N,N*-diisopropylethylamine (263 μL, 1.51 mmol, 1.30 equiv.) were combined in dichloromethane (5.0 mL). After stirring for 30 minutes at 0 °C, the mixture was diluted with dichloromethane (15 mL) and 10% aqueous sodium bisulfate (5 mL). The layers were separated and the aqueous layer was washed with dichloromethane (3 x 2 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the title compound as an off-white solid (341 mg, >95%).

Step 2: Preparation of *tert*-butyl (1*R*,3*S*)-3-(azidomethyl)cyclopentylcarbamate.



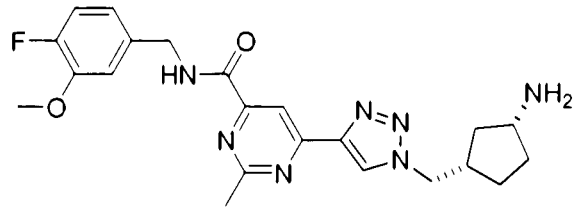
((1*S*,3*R*)-3-(*tert*-Butoxycarbonyl)cyclopentyl)methyl methanesulfonate (100 mg, 0.34 mmol) and sodium azide (69 mg, 1.07 mmol, 3.15 equiv.) were combined in *N,N*-dimethylformamide (0.60 mL). After stirring for 15 hours at 50 °C, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and washed with water (3 x 2 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (gradient 4:1 heptane/EtOAc to 2:1 heptane/EtOAc) provided the crude title compound as a pale orange oil (82 mg, >95%) that was used in subsequent reactions without further purification.

Step 3: Preparation of *tert*-butyl (1*R*,3*S*)-3-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)cyclopentylcarbamate.



The title compound was prepared in a similar manner to *tert*-butyl (1*S*,3*R*)-3-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)cyclopentylcarbamate (step 3, Example 137) by the reaction of *tert*-butyl (1*R*,3*S*)-3-(azidomethyl)cyclopentylcarbamate (82 mg, 0.34 mmol), *N*-(4-fluoro-3-methoxybenzyl)-6-ethynyl-2-methylpyrimidine-4-carboxamide (prepared as described in step 4 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 128) (102 mg, 0.34 mmol, 1.00 equiv.), 1.0 M aqueous sodium ascorbate (34 μL, 0.034 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (23 μL, 0.007 mmol, 0.02 equiv.) to afford title compound as a light yellow foam (128 mg, 70%). LC/MS (5%-100% CH_3CN/H_2O, 5 min): 3.78 min, *m/z* 484 (M – 2-Me-propene + H).

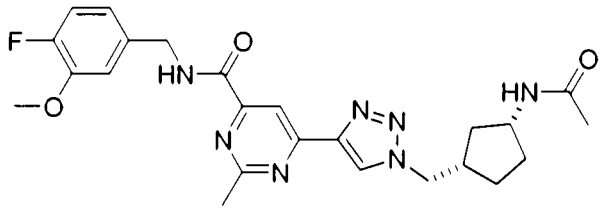
Step 4: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*S*,3*R*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide.



The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*R*,3*S*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (step 4, Example 137) by the reaction of *tert*-butyl (1*R*,3*S*)-3-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)cyclopentylcarbamate (128 mg, 0.24 mmol) and 4.0 N hydrochloric acid in methanol (1.5 mL, 6.00 mmol, 25.0equiv.) to afford the hydrochloride salt form of title compound as a white solid (114 mg, >95%) that was used in subsequent reactions without further purification. LC/MS (5%-100% CH_3CN/H_2O, 5 min): 2.73 min, *m/z* 440 (M+H).

Example 142

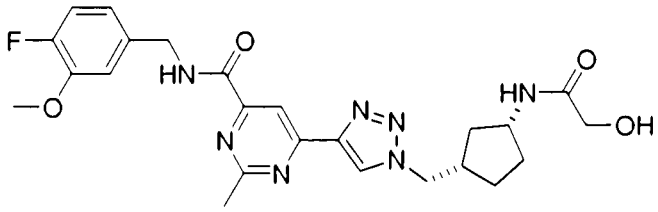
N-(4-Fluoro-3-methoxybenzyl)-6-(1-(((1S,3R)-3-acetamidocyclopentyl)methyl)-1H-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (Example 131) by reaction of the hydrochloride salt form of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*S*,3*R*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 141) (38 mg, 0.079 mmol), triethylamine (35 μL, 0.25 mmol, 3.16 equiv.), and acetyl chloride (11 μL, 0.16 mmol, 2.02 equiv.). Purification by reverse phase HPLC provided the title compound as a white solid (15 mg, 39%). MS (ES+) *m/z* 482 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (1 H, t, *J*=6.2 Hz), 8.89 (1 H, s), 8.34 (1 H, s), 7.81 (1 H, d, *J*=7.0 Hz), 7.18 (1 H, dd, *J*=8.5, 1.6 Hz), 7.14 (1 H, dd, *J*=11.6, 8.3 Hz), 6.84 - 6.95 (1 H, m), 4.50 (2 H, d, *J*=6.4 Hz), 4.45 (2 H, d, *J*=7.1 Hz), 3.91 - 4.05 (1 H, m), 3.82 (3 H, s), 2.75 (3 H, s), 1.90 - 2.02 (1 H, m), 1.78 - 1.88 (1 H, m), 1.76 (3 H, s), 1.57 - 1.70 (1 H, m), 1.37 - 1.53 (2 H, m), 1.09 - 1.21 (1 H, m).

Example 143

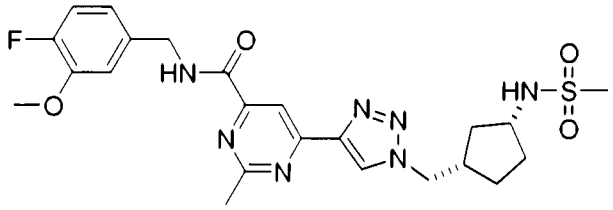
N-(4-Fluoro-3-methoxybenzyl)-6-(1-(((1S,3R)-3-(2-hydroxyacetamido)cyclopentyl)methyl)-1H-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide



The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (Example 136) by reaction of the hydrochloride salt form of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*S*,3*R*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 141) (38 mg, 0.079 mmol), triethylamine (35 μL, 0.25 mmol, 3.16 equiv.), 2-acetoxyacetyl chloride (17 μL, 0.16 mmol, 2.02 equiv.), and 2.0 N aqueous lithium hydroxide (0.40 mL, 0.80 mmol, 10.1 equiv.). Purification by reverse phase HPLC provided the title compound as a white solid (16 mg, 41%). MS (ES+) *m/z* 498 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (1 H, t, *J*=6.4 Hz), 8.89 (1 H, s), 8.34 (1 H, s), 7.61 (1 H, d, *J*=7.7 Hz), 7.18 (1 H, dd, *J*=8.5, 1.9 Hz), 7.14 (1 H, dd, *J*=11.6, 8.3 Hz), 6.87 - 6.96 (1 H, m), 5.32 (1 H, t, *J*=5.7 Hz), 4.50 (2 H, d, *J*=6.2 Hz), 4.39 - 4.48 (2 H, m), 4.04 - 4.16 (1 H, m), 3.82 (3 H, s), 3.77 (2 H, d, *J*=5.9 Hz), 2.75 (3 H, s), 1.90 - 2.03 (1 H, m), 1.77 - 1.90 (1 H, m), 1.41 - 1.70 (4 H, m), 1.21 - 1.35 (1 H, m).

Example 144

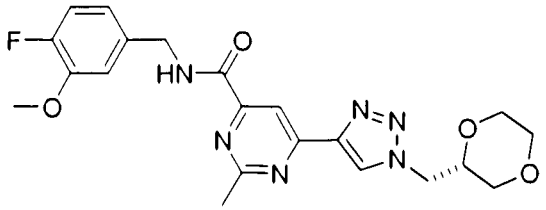
N-(4-Fluoro-3-methoxybenzyl)-2-methyl-6-(1-(((1*S*,3*R*)-3-(methylsulfonamido)cyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)pyrimidine-4-carboxamide



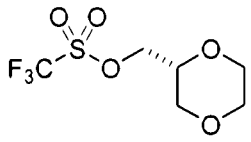
The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-(1-(((*S*)-4-acetylmorpholin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (Example 131) by reaction of the hydrochloride salt form of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((1*S*,3*R*)-3-aminocyclopentyl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 141) (38 mg, 0.079 mmol), triethylamine (35 μL, 0.25 mmol, 3.16 equiv.), and methanesulfonyl chloride (12 μL, 0.16 mmol, 2.02 equiv.). Purification by reverse phase HPLC provided the title compound as a white solid (12 mg, 29%). MS (ES+) *m/z* 518 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (1 H, t, *J*=6.3 Hz), 8.89 (1 H, s), 8.33 (1 H, s), 7.18 (1 H, dd, *J*=8.4, 1.8 Hz), 7.13 (1 H, dd, *J*=11.7, 8.4 Hz), 7.09 (1 H, d, *J*=7.1 Hz), 6.86 - 6.95 (1 H, m), 4.49 (2 H, d, *J*=6.2 Hz), 4.45 (2 H, d, *J*=7.3 Hz), 3.82 (3 H, s), 3.56 - 3.70 (1 H, m), 2.87 (3 H, s), 2.74 (3 H, s), 1.97 - 2.09 (1 H, m), 1.83 - 1.95 (1 H, m), 1.39 - 1.69 (3 H, m), 1.20 - 1.33 (1 H, m).

Example 145

6-(1-(((*S*)-1,4-Dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide

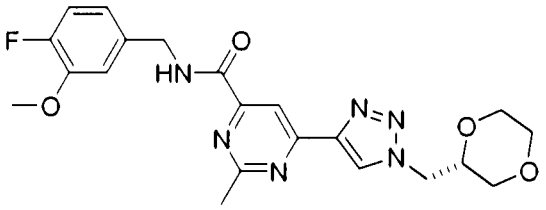


Step 1: Preparation of (*R*)-(1,4-dioxan-2-yl)methyl trifluoromethanesulfonate.



The title compound was prepared in a similar manner to ((2*S*,5*R*)-5-((trifluoromethylsulfonyloxy)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (step 5, Example 128) by reaction of (*S*)-(1,4-dioxan-2-yl)methanol (prepared as described in step 1 of the synthesis of 6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide, Example 57) (100 mg, 0.85 mmol), pyridine (72 μL, 0.89 mmol, 1.05 equiv.), and trifluoromethanesulfonic anhydride (150 μL, 0.89 mmol, 1.05 equiv.) to afford the title compound as a tan oil (185 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 - 4.54 (2 H, m), 3.90 - 3.97 (1 H, m), 3.72 - 3.90 (4 H, m), 3.59 - 3.70 (1 H, m), 3.48 (1 H, dd, *J*=11.4, 10.0 Hz).

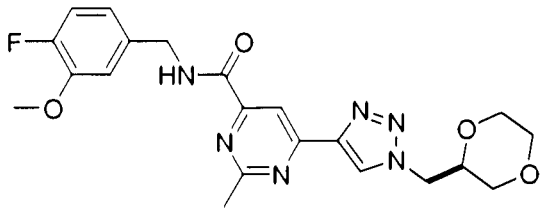
Step 2: Preparation of 6-(1-(((*S*)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide.



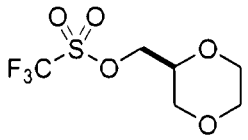
The title compound was prepared in a similar manner to ((2*S*,5*S*)-5-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (step 6, Example 128) by reaction of (*R*)-(1,4-dioxan-2-yl)methyl trifluoromethanesulfonate (175 mg, 0.70 mmol, 1.20 equiv.), sodium azide (38 mg, 0.58 mmol, 1.00 equiv.), *N*-(4-fluoro-3-methoxybenzyl)-6-ethynyl-2-methylpyrimidine-4-carboxamide (prepared as described in step 4 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 128) (174 mg, 0.58 mmol), 1.0 M aqueous sodium ascorbate (58 μL, 0.058 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (40 μL, 0.012 mmol, 0.02 equiv.). Purification by silica gel chromatography (gradient 1:2 heptane/EtOAc to 100% EtOAc) provided the title compound as a white solid (258 mg, >95%). MS (ES+) *m/z* 443 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (1 H, t, *J*=6.4 Hz), 8.82 (1 H, s), 8.33 (1 H, s), 7.10 - 7.24 (2 H, m), 6.90 (1 H, ddd, *J*=8.1, 4.3, 1.8 Hz), 4.50 - 4.65 (2 H, m), 4.49 (2 H, d, *J*=6.8 Hz), 3.94 - 4.06 (1 H, m), 3.80 - 3.87 (4 H, m), 3.75 (1 H, d, *J*=11.3 Hz), 3.64 (1 H, d, *J*=11.0 Hz), 3.51 - 3.59 (1 H, m), 3.40 - 3.50 (1 H, m), 3.24 - 3.33 (1 H, m), 2.75 (3 H, s).

Example 146

6-(1-(((*R*)-1,4-Dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide

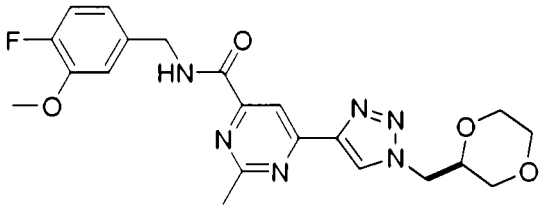


Step 1: Preparation of (*S*)-(1,4-dioxan-2-yl)methyl trifluoromethanesulfonate.



The title compound was prepared in a similar manner to ((2*S*,5*R*)-5-((trifluoromethylsulfonyloxy)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (step 5, Example 128) by reaction of (*R*)-(1,4-dioxan-2-yl)methanol (prepared as described in step 1 of the synthesis of 6-(2-(((*R*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-y1)-*N*-(3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide, Example 53) (54 mg, 0.46 mmol), pyridine (41 μL, 0.50 mmol, 1.10 equiv.), and trifluoromethanesulfonic anhydride (85 μL, 0.50 mmol, 1.10 equiv.) to afford the title compound as a tan oil (96 mg, 84%).

Step 2: Preparation of 6-(1-(((*R*)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide.

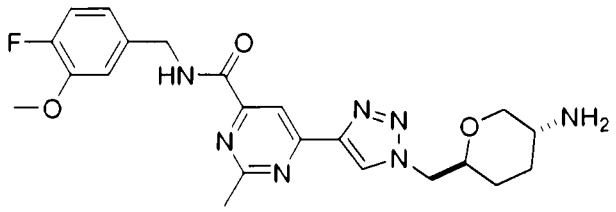


The title compound was prepared in a similar manner to ((2*S*,5*S*)-5-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (step 6, Example 128) by reaction of (*S*)-(1,4-dioxan-2-yl)methyl trifluoromethanesulfonate (96 mg, 0.38 mmol, 1.30 equiv.), sodium azide (20 mg, 0.31 mmol, 1.05 equiv.), *N*-(4-fluoro-3-methoxybenzyl)-6-ethynyl-2-methylpyrimidine-4-carboxamide (prepared as described in step 4 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 128) (88 mg, 0.30 mmol), 1.0 M aqueous sodium ascorbate (30 μL, 0.030 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (20 μL, 0.006 mmol, 0.02 equiv.). Purification by silica gel chromatography (gradient 1:2 heptane/EtOAc to 100% EtOAc) provided the title compound as a white solid (95 mg, 73%). MS (ES+) *m/z* 443 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (1 H, t, *J*=6.2 Hz), 8.82 (1 H, s), 8.33 (1 H, s), 7.11 - 7.22 (2 H, m), 6.85 - 6.94 (1 H, m), 4.51 - 4.63 (2 H, m), 4.49 (2 H, d, *J*=6.6

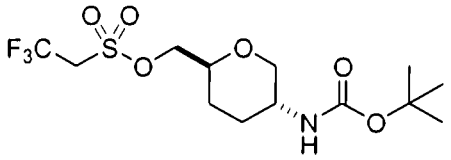
Hz), 3.96 - 4.05 (1 H, m), 3.79 - 3.87 (4 H, m), 3.75 (1 H, d, *J*=11.5 Hz), 3.64 (1 H, d, *J*=11.2 Hz), 3.51 - 3.59 (1 H, m), 3.41 - 3.49 (1 H, m), 3.25 - 3.32 (1 H, m), 2.75 (3 H, s).

Example 147

***N*-(4-Fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-amino-tetrahydro-2*H*-pyran-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide**

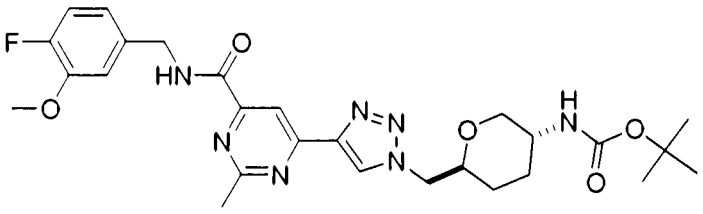


Step 1: Preparation of ((2*S*,5*R*)-5-(*tert*-butoxycarbonyl)-tetrahydro-2*H*-pyran-2-yl)methyl 2,2,2-trifluoroethanesulfonate.



tert-Butyl (3*R*,6*S*)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3-ylcarbamate (prepared from commercially available tri-*O*-acetyl-D-glucal according to the method described by Overkleeft and coworkers, see Kriek, N. M. A. J. et al. *Eur. J. Org. Chem.* **2003**, 2418-2427) (75 mg, 0.32 mmol), 2,2,2-trifluoroethanesulfonyl chloride (43 μL, 0.39 mmol, 1.20 equiv.), and triethylamine (59 μL, 0.42 mmol, 1.30 equiv.) were combined in dichloromethane (2.0 mL). After stirring for 2 hours at 0 °C, the mixture was diluted with dichloromethane (10 mL) and 10% aqueous sodium bisulfate (3 mL). The layers were separated and the aqueous layer was washed with dichloromethane (3 x 1 mL). The organics were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a faint yellow residue. Purification by silica gel chromatography (gradient 2:1 heptane/EtOAc to 100% EtOAc) provided the title compound as a white solid (111 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (2 H, d, *J*=4.8 Hz), 4.27 (1 H, br. s.), 3.88 - 4.19 (3 H, m), 3.48 - 3.70 (2 H, m), 3.03 (1 H, t, *J*=10.8 Hz), 2.06 - 2.25 (1 H, m), 1.65 - 1.79 (1 H, m), 1.46 - 1.58 (1 H, m), 1.45 (9 H, s), 1.24 - 1.40 (1 H, m).

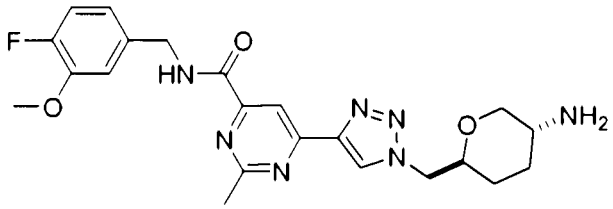
Step 2: Preparation of *tert*-butyl (3*R*,6*S*)-6-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)-tetrahydro-2*H*-pyran-3-ylcarbamate.



((2*S*,5*R*)-5-(*tert*-Butoxycarbonyl)-tetrahydro-2*H*-pyran-2-yl)methyl 2,2,2-trifluoroethanesulfonate (97 mg, 0.26 mmol) and sodium azide (18 mg, 0.28 mmol, 1.10 equiv.) were combined in *N*,*N*-dimethylformamide (0.50 mL). After stirring for 18 hours at room temperature, the

reaction vessel was charged sequentially with *N,N*-dimethylformamide (1.0 mL), water (0.50 mL), *N*-(4-fluoro-3-methoxybenzyl)-6-ethynyl-2-methylpyrimidine-4-carboxamide (prepared as described in step 4 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 128) (77 mg, 0.26 mmol, 1.00 equiv.), 1.0 M aqueous sodium ascorbate (26 μL, 0.026 mmol, 0.10 equiv.), and 0.30 M aqueous copper (II) sulfate (17 μL, 0.005 mmol, 0.02 equiv.). After stirring for 15 hours at room temperature, water (15 mL) was added, the precipitate was collected by suction filtration, and the filter cake was washed with water (3x). The solid was dissolved in ethyl acetate, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a solid residue. Purification by silica gel chromatography (gradient 1:1 heptane/EtOAc to 100% EtOAc) provided the title compound as a pale yellow solid (95 mg, 66%). LC/MS (5%-100% CH_3CN:H_2O, 5 min): 3.61 min, *m/z* 556 (M+H).

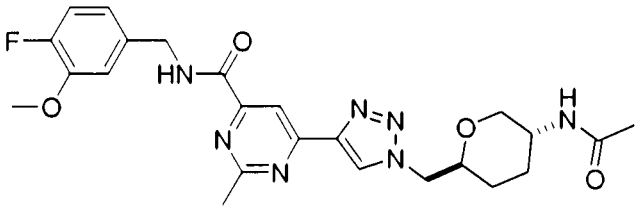
Step 3: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-amino-tetrahydro-2*H*-pyran-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide



tert-Butyl (3*R*,6*S*)-6-((4-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-1*H*-1,2,3-triazol-1-yl)methyl)-tetrahydro-2*H*-pyran-3-ylcarbamate (95 mg, 0.17 mmol) was dissolved in 4.0 N hydrochloric acid in 1,4-dioxane (1.0 mL, 4.00 mmol, 23.5 equiv.). After stirring for 2 hours at room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in methanol, concentrated under reduced pressure, and dried under high vacuum to afford the title compound as the hydrochloride salt (84 mg, >95%)

Example 148

N-(4-Fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-acetamido-tetrahydro-2*H*-pyran-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide

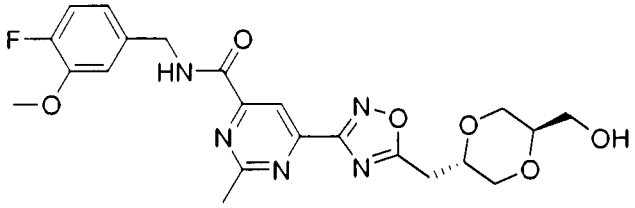


The hydrochloride salt of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-amino-tetrahydro-2*H*-pyran-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide (prepared as described in Example 147) (84 mg), triethylamine (71 μL, 0.51 mmol, 3.00 equiv.), and acetyl chloride (24 μL, 0.34 mmol, 2.00 equiv.) were combined in dichloromethane (1.2 mL). After stirring for 15 hours at room temperature, methanol (2 mL) was added and the mixture concentrated under reduced pressure to give a salty residue. Purification by silica gel chromatography (gradient 100% EtOAc to 10% MeOH/EtOAc) provided the title compound as a white solid (60 mg, 71%). MS (ES+) *m/z* 498 (M+H).

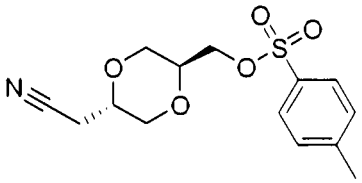
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (1 H, t, J=6.3 Hz), 8.77 (1 H, s), 8.33 (1 H, s), 7.74 (1 H, d, J=7.7 Hz), 7.08 - 7.24 (2 H, m), 6.82 - 6.96 (1 H, m), 4.55 - 4.64 (1 H, m), 4.43 - 4.54 (3 H, m), 3.70 - 3.86 (5 H, m), 3.52 - 3.67 (1 H, m), 2.92 (1 H, t, J=10.6 Hz), 2.75 (3 H, s), 1.83 - 1.95 (1 H, m), 1.68 - 1.82 (4 H, m), 1.20 - 1.50 (2 H, m).

Example 149

***N*-(4-Fluoro-3-methoxybenzyl)-6-(5-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide**

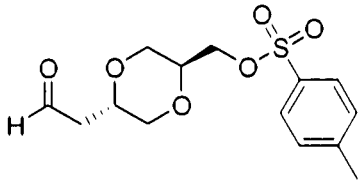


Step 1:Preparation of ((2*S*,5*S*)-5-(cyanomethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



Potassium cyanide (580 mg, 8.91 mmol) was added to a solution of ((2*S*,5*R*)-5-((trifluoromethylsulfonyloxy)methyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 5 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 128) (3.87 g, 8.91 mmol) in acetonitrile (30 mL) and water (3 ml). The mixture was stirred for 2 hours at room temperature and then was concentrated. The residue washed with water and dried to afford the title compound as a solid (2.17 g, 78%).

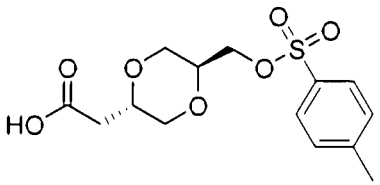
Step 2: Preparation of ((2*S*,5*S*)-5-(2-oxoethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



A diisobutylaluminum hydride solution (1 M in dichloromethane, 17.4 mL, 17.4 mmol) was added to a solution of ((2*S*,5*S*)-5-(cyanomethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (2.17 g, 6.97 mmol) in dichloromethane (60 mL) cooled in a dry ice/acetone bath. The mixture was stirred at -78 °C for 1 hour. 1 N Hydrochloric acid solution (25 mL) was added and the mixture was allowed to warm to room temperature. The mixture was poured into water (100 mL) and extracted with ethyl acetate (3x). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound (553 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.32 - 2.42 (m, 1 H), 2.44 (s, 3 H), 2.47 - 2.58 (m, 1 H), 3.25

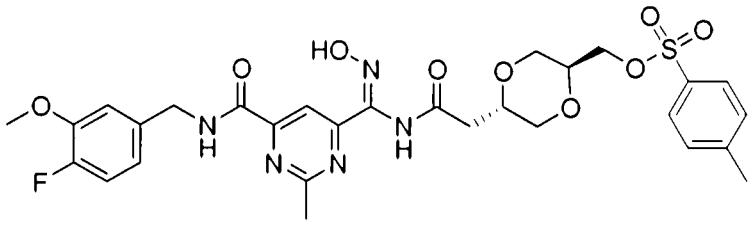
- 3.48 (m, 2 H), 3.67 - 3.83 (m, 3 H), 3.89 - 4.03 (m, 3 H), 7.34 (d, *J*=8.01 Hz, 2 H), 7.77 (d, *J*=8.40 Hz, 2 H), 9.57 - 9.80 (m, 1 H).

Step 3: Preparation of ((2*S*,5*S*)-5-((((4-methylphenyl)sulfonyl)oxy)methyl)-1,4-dioxan-2-yl)acetic acid



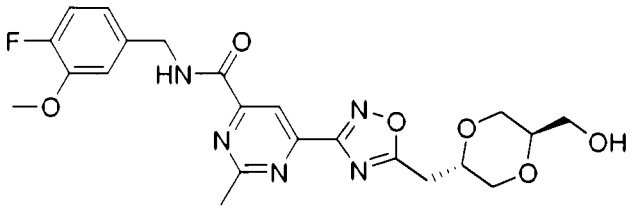
((2*S*,5*S*)-5-(2-oxoethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (390 mg, 1.24 mmol) was dissolved in *t*-butanol (20 mL). A 2M solution of 2-methyl-2-butene (12.4 mL, 24.8 mmol) was added to the stirring mixture followed by a solution of sodium chlorite (1.12 g, 10 mmol) and mono-sodium phosphate (monobasic) monohydrate (2.23 g, 13.0 mmol) in water (10 mL). The mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane and saturated aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted with dichloromethane (3x). The combined organic layers were dried over magnesium sulfate and concentrated to afford the title compound as an oil which crystallized upon standing (515 mg). MS (ES+) *m/z* 331 (M+H).

Step 5: Preparation of ((2*S*,5*S*)-5-(2-(((6-(((4-fluoro-3-methoxybenzyl)amino)carbonyl)-2-methylpyrimidin-4-yl)(hydroxyimino)methyl)amino)-2-oxoethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate



A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-(carbamimidoyl)-2-methylpyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(5-((*trans*-4-aminocyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide, Example 122) (353 mg, 1.06 mmol), ((2*S*,5*S*)-5-((((4-methylphenyl)sulfonyl)oxy)methyl)-1,4-dioxan-2-yl)acetic acid (350 mg, 1.06 mmol), 1-hydroxybenzotriazole (143 mg, 1.06 mmol), diisopropylethylamine (0.55 mL, 3.18 mmol), and polymer supported-carbodiimide resin (2.86 g, 3.18 mmol) in acetonitrile (10 mL) was stirred at 40 °C for 42 hours. The reaction mixture was filtered and the resin was washed with acetonitrile. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound as a solid (155 mg, 23%).

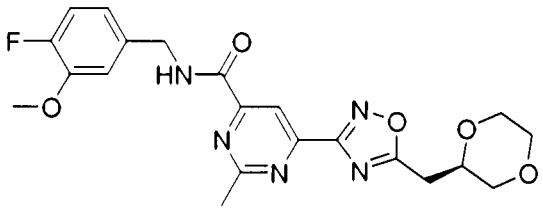
Step 6: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(5-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide



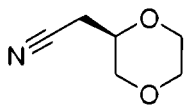
A solution of ((2*S*,5*S*)-5-(2-(((6-(((4-fluoro-3-methoxybenzyl)amino)carbonyl)-2-methylpyrimidin-4-yl)(hydroxyimino)methyl)amino)-2-oxoethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (134 mg, 0.209 mmol) in acetonitrile (5 mL) was treated with MP-carbonate resin and heated to 65 °C for 18 hours. The resin was filtered and washed with acetonitrile. The filtrate was concentrated to a volume of 5 mL. Tetrabutyl ammonium acetate (126 mg, 0.418 mmol) was added and the mixture was heated to 65 °C for 5 hours. The mixture was then treated with a 2.5 M sodium hydroxide solution (1 mL) and the solution was stirred at room temperature for 18 hours. After reaction mixture was purified by reverse phase preparative HPLC. The crude product was dissolved in ethyl acetate and washed several times with a saturated solution of ammonium chloride. The organic layer was dried over magnesium sulfate and concentrated to afford the title compound as an oil (22 mg, 11%). MS (ES+) *m/z* 474 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (d, *J*=5.49 Hz, 2 H), 2.83 (s, 3 H), 3.07 - 3.22 (m, 2 H), 3.31 - 3.54 (m, 4 H), 3.74 - 3.87 (m, 4 H), 4.50 (d, *J*=6.22 Hz, 2 H), 4.60 - 4.72 (m, 1 H), 5.28 (dd, 1 H), 6.80 - 6.98 (m, 1 H), 7.06 - 7.25 (m, 2 H), 8.33 (s, 1 H), 9.43 - 9.60 (m, 1 H).

Example 150

6-(5-((2*R*)-1,4-Dioxan-2-ylmethyl)-1,2,4-oxadiazol-3-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide



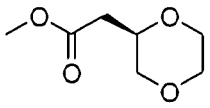
Step 1: Preparation of (2*R*)-1,4-dioxan-2-ylacetonitrile



Potassium cyanide (2.27 g) was added to (*S*)-(1,4-dioxan-2-yl)methyl trifluoromethanesulfonate (prepared as describe in step 1 of the synthesis of 6-(1-(((*R*)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide, Example 146) (7.3 g, 29.0 mmol) in a mixture of acetonitrile (60 mL) and water (6 mL). The mixture was stirred at room temperature for 18 hours and was then concentrated. The residue was taken up

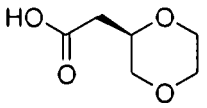
in ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate to afford the title compound as an oil (3.23 g, 87%). MS (ES+) *m/z* 128 (M+H).

Step 2: Preparation of methyl (2*R*)-1,4-dioxan-2-ylacetate



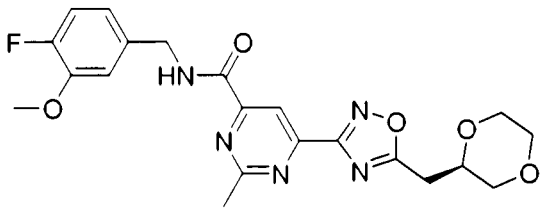
(2*R*)-1,4-dioxan-2-ylacetonitrile (3.2 g, 25.0 mmol) was dissolved in methanol (10 mL) and HCl gas was bubbled through the mixture for several minutes. The resulting solution was stirred at room temperature for 1 hour. Water (2 mL) was added and most of the solvent was removed in vacuo. The residue was taken up in ethyl acetate and washed with a saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, and concentrated to afford the title compound as an oil. MS (ES+) *m/z* 161 (M+H).

Step 3: Preparation of (2*R*)-1,4-dioxan-2-ylacetic acid



A mixture of methyl (2*R*)-1,4-dioxan-2-ylacetate (300 mg, 1.87 mmol), tetrahydrofuran (5 mL), water (1 mL), and lithium hydroxide (359 mg, 15.0 mmol) was stirred at room temperature for 18 hours. The mixture was acidified with the addition of 3N hydrochloric acid and then passed through a Chem Elute extraction column eluting with ethyl acetate. The eluant was concentrated to afford the title compound as a solid (262 mg, 96%). MS (ES+) *m/z* 147 (M+H).

Step 4: Preparation of 6-(5-((2*R*)-1,4-dioxan-2-ylmethyl)-1,2,4-oxadiazol-3-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide

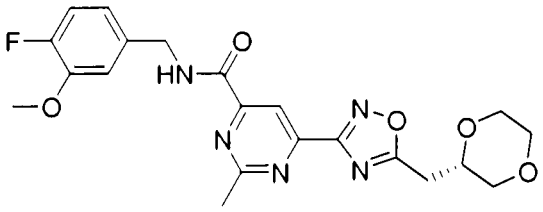


A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-(carbamimidoyl)-2-methylpyrimidine-4-carboxamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(5-((*trans*-4-aminocyclohexyl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylpyrimidine-4-carboxamide, Example 122) (100 mg, 0.30 mmol), (2*R*)-1,4-dioxan-2-ylmethanol (87 mg, 0.60 mmol), 1-hydroxybenzotriazole (61 mg, 0.45 mmol), polymer supported-carbodiimide resin (811 mg, 0.90 mmol), and diisopropylamine (0.16 mL, 0.90 mmol) in acetonitrile (5 mL) was heated to 40 °C for 3 days. The reaction mixture was filtered and the resin was washed with a minimal amount of acetonitrile. The filtrate was then treated with MP-carbonate resin (523 mg, 1.5 mmol) and heated to 65 °C for 18 hours. The mixture was filtered and the resin was washed with acetonitrile. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound as a solid (16 mg, 12%). MS (ES+) *m/z* 444 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.82 (s, 3 H), 3.13 - 3.20 (m, 1 H), 3.22 - 3.31 (m, 2 H), 3.42 - 3.50 (m, 1 H), 3.54 - 3.66 (m, 2 H), 3.68

- 3.73 (m, 1 H), 3.77 - 3.89 (m, 4 H), 4.00 - 4.08 (m, 1 H), 4.48 (d, *J*=6.22 Hz, 2 H), 6.88 (ddd, *J*=8.33, 4.30, 2.01 Hz, 1 H), 7.09 - 7.19 (m, 2 H), 8.32 (s, 1 H), 9.55 - 9.62 (m, 1 H).

Example 151

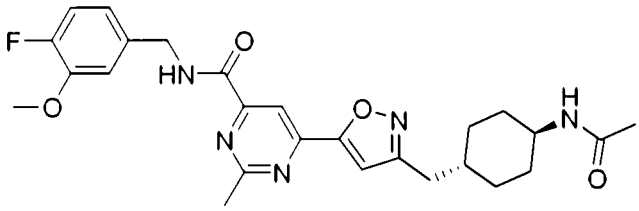
6-(5-((2*S*)-1,4-Dioxan-2-ylmethyl)-1,2,4-oxadiazol-3-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide



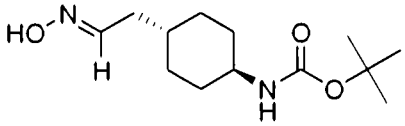
The title compound was prepared in a similar manner to 6-(5-((2*R*)-1,4-dioxan-2-ylmethyl)-1,2,4-oxadiazol-3-yl)-*N*-(4-fluoro-3-methoxybenzyl)-2-methylpyrimidine-4-carboxamide (Example 150) starting from (S)-1,4-dioxan-2-ylmethanol (prepared as described in step 1 of the synthesis of 6-(2-(((*S*)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol5-yl)-*N*-(3-methyoxybenzyl)-2-methylpyrimidine-4-carboxamide, Example 57) to afford 75 mg (56%). MS (ES+) *m/z* 444 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.82 (s, 3 H), 3.12 - 3.21 (m, 1 H), 3.22 - 3.30 (m, 1 H), 3.42 - 3.50 (m, 1 H), 3.55 (d, *J*=2.56 Hz, 1 H), 3.57 - 3.66 (m, 2 H), 3.68 - 3.73 (m, 1 H), 3.77 - 3.90 (m, 4 H), 4.00 - 4.08 (m, 1 H), 4.48 (d, *J*=6.22 Hz, 2 H), 6.88 (ddd, *J*=8.33, 4.30, 2.01 Hz, 1 H), 7.09 - 7.19 (m, 2 H), 8.32 (s, 1 H), 9.55 - 9.62 (m, 1 H).

Example 152

***N*-(4-Fluoro-3-methoxybenzyl)-6-(3-(((*trans*)-4-acetamidocyclohexyl)methyl)isoxazol-5-yl)-2-methylpyrimidine-4-carboxamide**

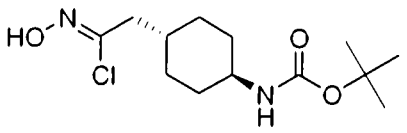


Step 1: Preparation of *tert*-butyl (*trans*)-4-((*E*)-2-(hydroxyimino)ethyl)cyclohexylcarbamate



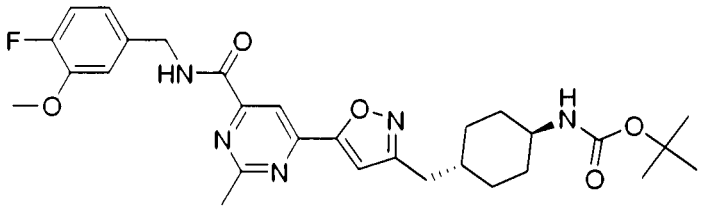
tert-Butyl (*trans*)-4-(2-oxoethyl)cyclohexylcarbamate (403 mg, 1.67 mmol) was dissolved in a mixture of ethanol (12 ml) and water (8 mL). Sodium acetate (407 mg, 4.96 mmol) was added and the mixture was stirred for 30 min at room temperature. Hydroxylamine hydrochloride (363 mg, 5.01 mmol) was added and the mixture was heated to 60 °C for 1.5 hours. The reaction mixture was concentrated to obtain the title compound as a white solid (70 mg).

Step 2: Preparation of *tert*-butyl (*trans*)-4-((*Z*)-2-chloro-2-(hydroxyimino)ethyl)cyclohexylcarbamate



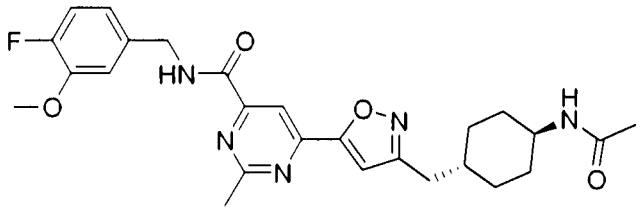
N-Chlorosuccinimide (51.5 mg, 0.38 mmol) was added to a solution of *tert*-butyl (*trans*)-4-((*E*)-2-(hydroxyimino)ethyl)cyclohexylcarbamate (99 mg, 0.38 mmol) in acetonitrile(5 mL) and the mixture was stirred at room temperature for 18 hours. Additional *N*-chlorosuccinimide was added (25.7 mg, 0.19 mmol). After 4 hours, the reaction mixture was concentrated. The residue was suspended in dichloromethane and filtered. The filtrate was concentrated to afford the title compound as a white solid (177 mg). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.621 min., *m/z* 338 (M+H). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.09 (d, *J*=10.16 Hz, 2 H), 1.43 (s, 9 H), 1.77 (d, *J*=10.94 Hz, 2 H), 2.77 (s, 5 H), 2.92 (s, 1 H), 5.30 (s, 1 H).

Step 3: Preparation of *tert*-butyl (*trans*)-4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)isoxazol-3-yl)methyl)cyclohexylcarbamate



tert-Butyl (*trans*)-4-((*Z*)-2-chloro-2-(hydroxyimino)ethyl)cyclohexylcarbamate (48.6 mg, 0.16 mmol) was added to a mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-ethynyl-2-methylpyrimidine-4-carboxamide (prepared as described in step 4 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(1-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpyrimidine-4-carboxamide, Example 128) (50.1 mg, 0.16 mmol) and triethylamine (0.023 mL, 0.16 mmol) in toluene (5 mL). The mixture was stirred at room temperature for 2 hours, then heated to 110 °C for 2 hours, and finally allowed to stir at room temperature for 18 hours. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound as an orange solid (51.7 mg, 46%). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.72 min., *m/z* 498 (M-C_4H_9). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.02 - 1.20 (m, 4 H), 1.22 - 1.27 (m, 1 H), 1.36 - 1.51 (m, 9 H), 1.58 - 1.72 (m, 1 H), 1.80 (d, *J*=10.55 Hz, 2 H), 1.94 - 2.06 (m, 2 H), 2.64 (d, *J*=7.04 Hz, 2 H), 2.74 - 2.82 (m, 3 H), 3.36 (br. s., 1 H), 3.84 - 3.91 (m, 3 H), 4.62 (d, *J*=5.86 Hz, 2 H), 5.28 (s, 1 H), 6.83 - 6.91 (m, 1 H), 6.92 - 6.99 (m, 2 H), 6.99 - 7.07 (m, 1 H), 8.29 - 8.37 (m, 1 H), 8.38 (s, 1 H).

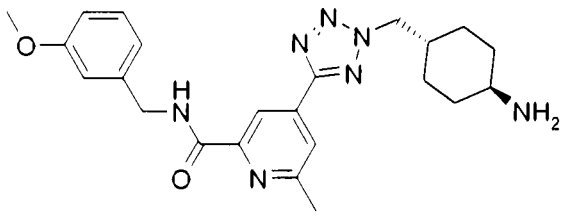
Step 4: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-(3-(((*trans*)-4-acetamidocyclohexyl)methyl)isoxazol-5-yl)-2-methylpyrimidine-4-carboxamide



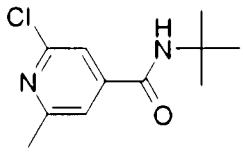
Trifluoroacetic acid (1 mL) was added to a solution of *tert*-butyl (*trans*)-4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)isoxazol-3-yl)methyl)cyclohexylcarbamate (51 mg, 0.076 mmol) in dichloromethane (40 mL) and the mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated and the residue was dissolved in *N*,*N*-dimethylformamide (10 mL). Diisopropylethylamine (0.05 mL, 0.30 mmol) and acetic anhydride (0.015 mL, 0.152 mmol) were added and the mixture was stirred at room temperature under nitrogen for 16 hours. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound as a white solid (32.3 mg). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.062 min., *m/z* 496 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 - 1.15 (m, 4 H), 1.17 (d, *J*=0.73 Hz, 1 H), 1.69 (d, *J*=11.71 Hz, 3 H), 1.73 - 1.79 (m, 5 H), 2.61 (d, *J*=6.95 Hz, 2 H), 2.79 (s, 3 H), 3.31 (br. s., 1 H), 3.44 (dt, *J*=7.05, 3.61 Hz, 1 H), 3.81 (s, 3 H), 4.48 (d, *J*=6.59 Hz, 2 H), 6.89 (ddd, *J*=8.33, 4.30, 2.01 Hz, 1 H), 7.09 - 7.20 (m, 2 H), 7.41 (s, 1 H), 7.71 (d, *J*=7.69 Hz, 1 H), 8.20 (s, 1 H), 9.50 - 9.57 (m, 1 H).

Example 153

N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



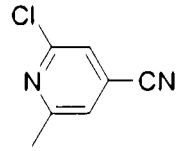
Step 1: Preparation of *N*-*tert*-butyl-2-chloro-6-methylisonicotinamide



Oxalyl chloride (95 mL, 1.10 mol) was added to 2-chloro-6-methylisonicotinic acid (95 g, 0.55 mol) in dichloromethane (950 mL, anhydrous) The mixture was cooled in an ice/water bath and DMF (2.0 mL) was slowly added. When gas evolution subsided, the ice/water bath was removed and the mixture was allowed to reach ambient temp and stir for 15 hours. The solution was then concentrated in vacuo and azeotroped with toluene (2 x 200 mL). The residue was taken into dichloromethane (800 mL, anhydrous), cooled in an ice/water bath, and a solution of *tert*-butylamine (175 mL, 1.7 mol) in

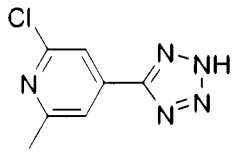
dichloromethane (300 mL, anhydrous) was added drop wise. The mixture was allowed to reach ambient temp and stir for 15 hours. Water (250 mL) was added. The organic layer was washed with water (200 mL) followed by brine (200 mL), dried over magnesium sulfate, filtered, and concentrated to afford the title compound as a beige solid (120 g, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.39 (s, 1 H), 7.38 (s, 1 H), 6.05 (s, 1 H), 2.59 (s, 3 H), 1.5 (s, 9 H).

Step 2: Preparation of 2-chloro-6-methylisonicotinonitrile



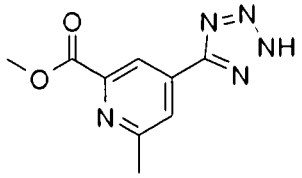
To *N-tert*-butyl-2-chloro-6-methylisonicotinamide (120 g, 0.53 mol) in toluene (2.5 L, anhydrous) was added $POCl_3$ (572 mL, 6.26 mol). The resulting mixture was refluxed 15 h, cooled to ambient temperature, and concentrated in vacuo. The residue was dissolved in dichloromethane (1.0 L) and aqueous saturated sodium bicarbonate (500 mL) was carefully added. Solid sodium bicarbonate was then added portion wise until the aqueous layer was basic. The organic layer was washed with brine (300 mL), dried (magnesium sulfate), filtered, and concentrated to afford the title compound as a pale tan solid (76 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.41 (s, 1 H), 7.37 (s, 1 H), 2.61 (s, 3 H).

Step 3: Preparation of 2-chloro-6-methyl-4-(2*H*-tetrazol-5-yl)pyridine hydrochloride



Triethylamine hydrochloride (72 g, 0.52 mol) and sodium azide (34 g, 0.52 mol) were added to a solution of 2-chloro-6-methylisonicotinonitrile (76 g, 0.50 mol) in toluene (1.2 L, anhydrous). The mixture was refluxed for 4 hours behind a blast shield. After cooling to ambient temperature, water (1.5 L) was added and the layers were separated. The toluene layer was washed with water (500 mL) and the combined aqueous layers were acidified with 6N hydrochloric acid (100 mL). The resulting precipitate was filtered and dried in vacuo (60 °C) to afford the title compound (105 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.92 (s, 1 H), 7.89 (s, 1 H), 2.79 (s, 3 H).

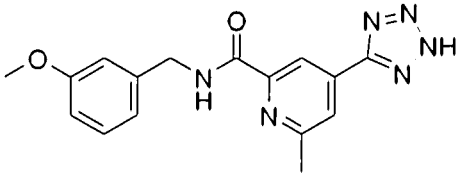
Step 4: Preparation of methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate



Triethylamine (120 mL), 1,1'-bis(diphenylphosphino)ferrocene (8.0 g, 14 mmol), and $Pd(OAc)_2$ (9.2 g, 40 mmol) were added to a solution of 2-chloro-6-methyl-4-(2*H*-tetrazol-5-yl)pyridine hydrochloride (88 g, 380 mmol) in methanol (1.5 L, anhydrous) in a pressure reactor. The reactor was evacuated and purged with carbon monoxide gas twice and finally pressurized to 120 PSI and heated

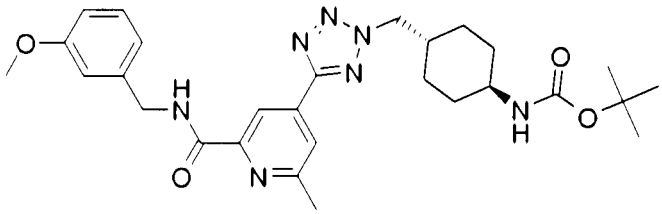
to 100 °C for 24 hr (190 PSI reached). An aliquot was taken and analyzed by HPLC revealing consumption of the starting material. After cooling to ambient temp, the mixture was filtered through Celite™ and concentrated in vacuo. Water (700 mL) and aq. saturated $NaHCO_3$ (200 mL) were added to provide an almost clear solution. 3N hydrochloric acid was added until a pH of 2 was reached. The resulting solid was filtered and dried in vacuo (50 °C) until constant weight (78 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.48 (s, 1 H), 8.15 (s, 1 H), 3.95 (s, 3 H), 2.67 (s, 3 H).

Step 5. Preparation of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide



A mixture of methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (3.29 g, 15.0 mmol) and 3-methoxybenzylamine (6.17 g, 45.0 mmol) was heated at 100 °C with removal of methanol in a stream of nitrogen for 1 hour. A solution of 1 N hydrochloric acid (50 mL) was added. The resulting precipitate was filtered and washed with ethyl ether. The solid was suspended in a solution of 2.5 N sodium hydroxide (30 mL)/water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The aqueous layer was cooled in an ice bath and acidified to pH 1 with concentrated hydrochloric acid. The resulting precipitate was filtered and dried to afford the title compound as a white solid (4.69 g, 96%). MS (ES+) *m/z* 325 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.28 (t, *J*=6.3 Hz, 1 H), 8.49 (d, *J*= 0.8 Hz, 1 H), 8.13 (d, *J*=1.2 Hz, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.94-6.90 (m, 2 H), 6.82 (dd, *J*=8.0, 2.1 Hz, 1 H), 4.51 (d, *J*=6.3 Hz, 2 H), 3.73 (s, 3 H), 2.68 (s, 3 H).

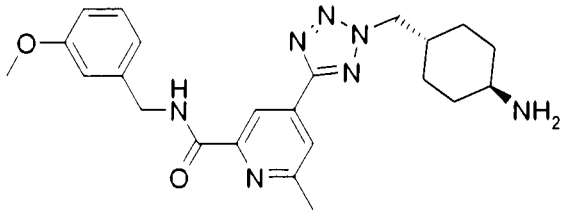
Step 6. Preparation of *tert*-butyl (*trans*)-4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate



N-(3-Methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (1.62 g, 5.0 mmol), polymer supported triphenylphosphine (3.49 g, 7.5 mmol), and *tert*-butyl *trans*-(4-hydroxymethyl)cyclohexylcarbamate (1.38 g, 6.0 mmol) were suspended in tetrahydrofuran (100 mL). Di-*tert*-butyl azodicarboxylate (1.73 g, 7.5 mmol) was added. The mixture was allowed to stir for 18 hours. The reaction mixture was filtered and the resin washed with THF (100 mL). The filtrate was concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2). Combined fractions were concentrated onto silica and repurified by silica column chromatography (heptane/EtOAc, 2/1; 1/1). Combined fractions were concentrated. The resulting solid was slurried in heptane and filtered to afford the title compound as a white solid (1.824 g, 68%). MS (ES+) *m/z* 536 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (t, *J*=6.3 Hz, 1 H), 8.40 (d, *J*=0.8 Hz,

1 H), 8.05 (d, *J*=1.1 Hz, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.86 - 6.90 (m, 2 H), 6.79 (dd, *J*=8.2, 1.9 Hz, 1 H), 6.68 (d, *J*=7.8 Hz, 1 H), 4.63 (d, *J*=7.0 Hz, 2 H), 4.48 (d, *J*=6.3 Hz, 2 H), 3.70 (s, 3 H), 3.13 (br. s., 1 H), 2.64 (s, 3 H), 1.90 (br. s., 1 H), 1.71 - 1.77 (m, 2 H), 1.53 - 1.59 (m, 2 H), 1.33 (s, 9 H), 1.06 - 1.14 (m, 4 H).

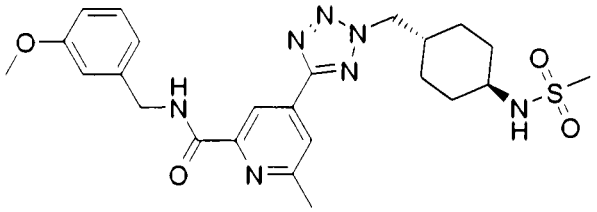
Step 7. Preparation of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



tert-Butyl (*trans*)-4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate (1.82 g, 3.40 mmol) was dissolved in dichloromethane (20 mL) and trifluoroacetic acid (5.05 mL, 68.0 mmol) was added. The mixture was allowed to stand for 2 hours and was then concentrated. The residue was dissolved in dichloromethane (150 mL) and washed with 1N NaOH solution (2 x 40 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was triturated with heptane and filtered to afford the title compound as a white solid (1.407 g, 95%). MS (ES+) *m/z* 436 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (t, *J*=6.3 Hz, 1 H), 8.39 (d, *J*=0.8 Hz, 1 H), 8.05 (d, *J*=1.2 Hz, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.90 - 6.86 (m, 2 H), 6.79 (dd, *J*=8.2, 1.9 Hz, 1 H), 4.62 (d, *J*=7.1 Hz, 2 H), 4.48 (d, *J*=6.3 Hz, 2 H), 3.70 (s, 3 H), 2.64 (s, 3 H), 2.45 - 2.37 (m, 1 H), 1.96 - 1.84 (m, 1 H), 1.71 (d, *J*=12.0 Hz, 2 H), 1.53 (d, *J*=12.2 Hz, 2 H), 1.37 (br. s., 2 H), 1.07 (q, *J*=12.8 Hz, 2 H), 1.01 - 0.88 (m, *J*=10.6, 10.6, 10.6 Hz, 2 H).

Example 154

N-(3-Methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide

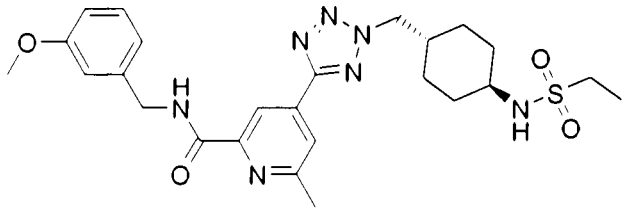


Triethylamine (0.096 mL, 0.690 mmol) and methane sulfonyl chloride (0.021 mL, 0.276 mmol) were added to a solution of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 153) (100.0 mg, 0.230 mmol) in dichloromethane (2 mL). The mixture was stirred for 2 hours at room temperature. Volatiles were removed under a nitrogen stream. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (28.2 mg, 24%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.148 min., *m/z* 514 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 - 1.32 (m, 4 H), 1.49 - 1.69 (m, 2 H), 1.78 - 2.04 (m, 3 H), 2.65 (s, 3 H), 2.86 (s, 3 H),

3.71 (s, 3 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.64 (d, *J*=7.3 Hz, 2 H), 6.77 - 6.82 (m, 1 H), 6.90 (m, 2 H), 6.93 (s, 1 H), 7.12 - 7.29 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.04 - 9.31 (m, 1 H).

Example 155

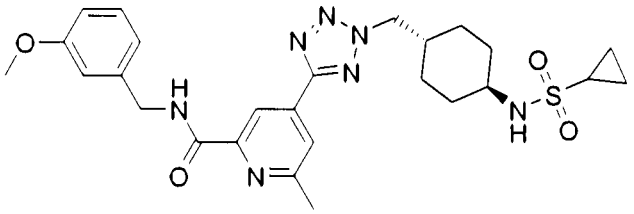
***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(ethylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Triethylamine (0.096 mL, 0.690 mmol) and ethane sulfonyl chloride (44.3 mg, 0.344 mmol) were added to a solution of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 153) (100.0 mg, 0.230 mmol) in tetrahydrofuran (2 mL). The mixture was stirred overnight at room temperature. Volatiles were removed under a nitrogen stream. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (9.9 mg, 8%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.252 min., *m/z* 528 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 - 1.36 (m, 7 H), 1.52 - 1.70 (m, 2 H), 1.78 - 1.90 (m, 2 H), 1.89 - 2.10 (m, 1 H), 2.65 (s, 3 H), 2.94 - 3.09 (m, 1 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.63 (d, *J*=6.6 Hz, 2 H), 6.73 - 6.84 (m, 1 H), 6.86 - 6.92 (m, 2 H), 6.92 - 7.01 (m, 1 H), 7.15 - 7.27 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.10 - 9.25 (m, 1 H).

Example 156

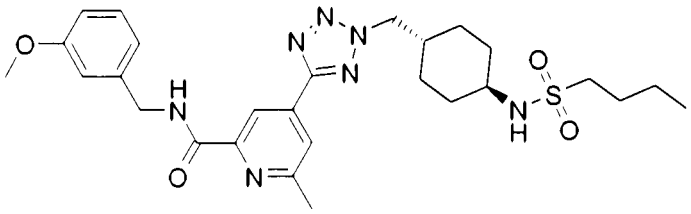
***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(cyclopropanesulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(ethylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 155) by reaction with cyclopropane sulfonyl chloride and afforded 22.3 mg (18%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.310 min., *m/z* 540 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 - 0.95 (m, 4 H), 1.04 - 1.33 (m, 4 H), 1.51 - 1.68 (m, 2 H), 1.83 - 2.01 (m, 2 H), 2.41 - 2.55 (m, 1 H), 2.65 (s, 3 H), 2.96 - 3.14 (m, 1 H), 3.71 (s, 3 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.64 (d, *J*=6.6 Hz, 2 H), 6.73 - 6.84 (m, 1 H), 6.86 - 6.93 (m, 2 H), 6.93 - 7.02 (m, 1 H), 7.13 - 7.29 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.11 - 9.27 (m, 1 H).

Example 157

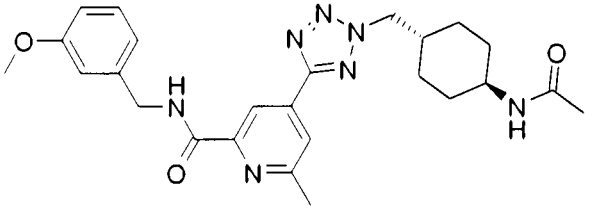
***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(butylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(ethylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 155) by reaction with butane sulfonyl chloride and afforded 45.6 mg (36%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min, 95% CH_3CN, 1.5 min.): 3.574 min., 556 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.91 (m) 1.07 - 1.47 (m) 1.48 - 1.91 (m) 1.91 - 2.05 (m, 1 H), 2.65 (s, 3 H), 2.83 - 3.01 (m) 3.48 - 3.65 (m, 1 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.59 Hz, 2 H), 4.66 (d, *J*=7.32 Hz, 2 H), 6.76 - 6.82 (m, 1 H), 6.87 - 6.97 (m) 7.17 - 7.26 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.15 - 9.25 (m).

Example 158

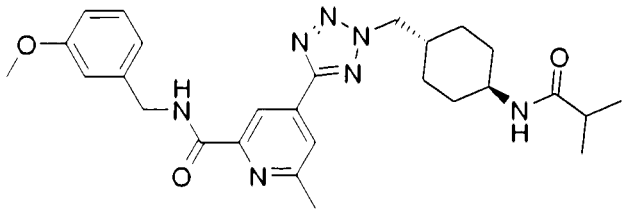
***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Acetic anhydride (0.033 mL, 0.344 mmol) and silica-bound 4-(dimethylamino)pyridine (833.0 mg, 0.575 mmol, 0.69 mmol/g loading) were added to a solution of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 153) (50.1 mg, 0.115 mmol) in dichloromethane (2 mL). The reaction mixture was agitated overnight at room temperature, filtered, and washed with *N*,*N*-dimethylformamide. The filtrate was concentrated under a stream of nitrogen. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound (22.4 mg, 41%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.994 min., *m/z* 478 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.28 (m, 4 H), 1.60 (m, 2 H), 1.73 (s, 3 H), 1.74 - 1.81 (m, 3 H), 1.89 - 2.06 (m, 1 H), 2.65 (s, 3 H), 3.71 (s, 3 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.64 (d, *J*=7.3 Hz, 2 H), 6.75 - 6.83 (m, 1 H), 6.86 - 6.98 (m, 2 H), 7.13 - 7.30 (m, 1 H), 7.63 (s, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.06 - 9.25 (m, 1 H).

Example 159

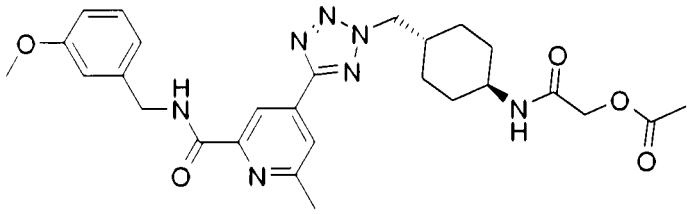
***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-isobutyramidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 158) by reaction with isobutyric anhydride and afforded 22.6 mg (39%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.325 min., *m/z* 506 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.02 - 1.26 (m, 4 H), 1.54 - 1.66 (m, 2 H), 1.69 - 1.81 (m, 2 H), 1.86 - 2.04 (m, 1 H), 2.18 - 2.36 (m, 1 H), 2.65 (s, 3 H), 3.71 (s, 3 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.65 (d, *J*=7.3 Hz, 1 H), 6.71 - 6.83 (m, 1 H), 6.86 - 6.98 (m, 2 H), 7.13 - 7.30 (m, 1 H), 7.38 - 7.55 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.12 - 9.26 (m, 1 H).

Example 160

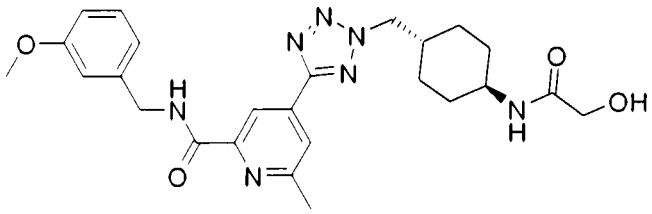
2-((*trans*)-4-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-cyclohexylamino)-2-oxoethyl acetate



Triethylamine (651 μL, 6.43 mmol), 4-(dimethylamino)pyridine (78.5 mg, 0.64 mmol), and acetoxyacetyl chloride (415 μL, 3.86 mmol) were added to a solution of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 153) (1.400 g, 3.21 mmol) in dichloromethane (60 mL).. The mixture was allowed to stir at room temperature for 1 hour. The reaction mixture was diluted with dichloromethane (150 mL) and washed with saturated aq. sodium bicarbonate solution (2 x 40 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2). Fractions were concentrated and the oily residue was partially concentrated from a mixture of dichloromethane/heptane/ethyl ether. The resulting slurry was filtered to afford the title compound as a white solid (1.513 g, 88%). MS (ES+) *m/z* 536 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.4 Hz, 1 H), 8.40 (d, *J*=0.8 Hz, 1 H), 8.06 (d, *J*=1.2 Hz, 1 H), 7.82 (d, *J*=7.9 Hz, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.90 - 6.86 (m, 2 H), 6.79 (dd, *J*=7.9, 2.0 Hz, 1 H), 4.65 (d, *J*=7.0 Hz, 2 H), 4.48 (d, *J*=6.4 Hz, 2 H), 4.35 (s, 2 H), 3.70 (s, 3 H), 3.49 (br. s., 1 H), 2.65 (s, 3 H), 2.03 (s, 3 H), 1.95 (br. s., 1 H), 1.78 - 1.71 (m, 2 H), 1.63 - 1.56 (m, 2 H), 1.21 - 1.11 (m, 4 H).

Example 161

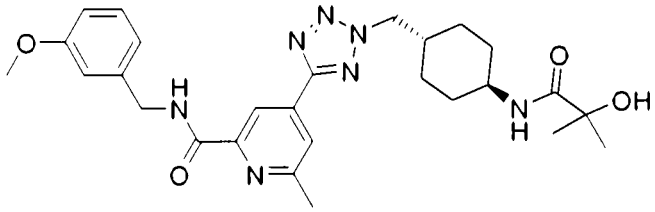
***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



2-((*trans*)-4-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate (prepared as described in Example 160) (1.50 g, 2.80 mmol) was dissolved in tetrahydrofuran (100 mL). Lithium hydroxide (201 mg, 8.40 mmol) followed by water (35 mL) were added. The mixture was stirred for 1 hour and then the tetrahydrofuran was removed in vacuo. The residue was added to dichloromethane (100 mL) and washed with water (2 x 20 mL). The organic layer was dried over sodium sulfate and concentrated to afford a foaming solid. The residue was dissolved in methanol (10 mL) and seeded. The resulting slurry was filtered to afford the title compound as a white crystalline solid (1.233 g, 89%). MS (ES+) *m/z* 494 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (t, *J*=6.4 Hz, 1 H), 8.40 (s, 1 H), 8.06 (d, *J*=1.2 Hz, 1 H), 7.41 (d, *J*=8.3 Hz, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.90 - 6.86 (m, 2 H), 6.79 (dd, *J*=8.2, 1.9 Hz, 1 H), 5.36 (t, *J*=5.8 Hz, 1 H), 4.65 (d, *J*=7.0 Hz, 2 H), 4.48 (d, *J*=6.4 Hz, 2 H), 3.72 (d, *J*=5.8 Hz, 2 H), 3.70 (s, 3 H), 3.59 - 3.48 (m, 1 H), 2.65 (s, 3 H), 2.00 - 1.89 (m, 1 H), 1.71 (d, *J*=10.6 Hz, 2 H), 1.59 (d, *J*=13.6 Hz, 2 H), 1.32 - 1.09 (m, 4 H).

Example 162

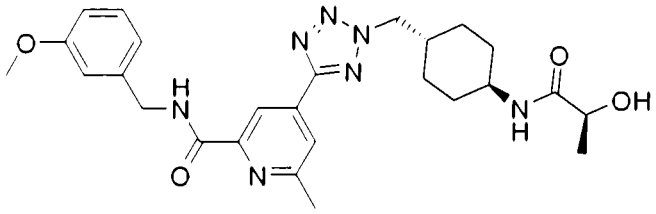
***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



A mixture of 2-hydroxy isobutyric acid (10 mg, 0.10 mmol) and 1-hydroxybenzatriazole (15 mg, 0.11 mmol) in 2- methyl tetrahydrofuran (2 mL) for was stirred for 5 minutes. *N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 153) (0.050 g, 0.09 mmol), triethylamine (0.015 mL, 0.11 mmol), and polymer supported carbodiimide (0.11 g, 0.14 mmol) were added. The mixture was stirred for 18 hours at room temperature and was then filtered. The filtrate was washed with water (3 x 5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound (21 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.2 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 2 H), 6.90 (br. s., 2 H), 6.80 (d, *J*=8.8 Hz, 1 H), 4.65 (d, *J*=6.6 Hz, 2 H), 4.49 (d, *J*=5.9 Hz, 2 H), 3.71 (s, 3 H), 3.21 - 3.35 (m, 1 H), 2.65 (s, 3 H), 1.91 - 2.05 (m, 1 H), 1.72 (d, *J*=11.7 Hz, 2 H), 1.60 (d, *J*=11.7 Hz, 2 H), 1.06 - 1.33 (m, 10 H).

Example 163

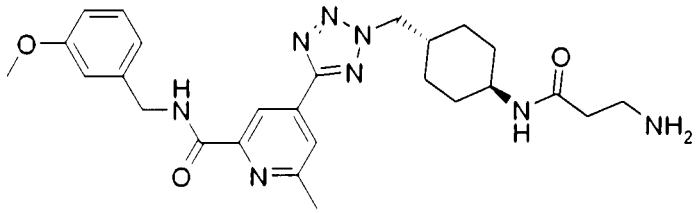
***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-((*S*)-2-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



A mixture of (*S*)-2-acetoxypropanoic acid (13 mg, 0.10 mmol) and 1-hydroxybenzatriazole (16 mg, 0.12 mmol) in 2-methyl tetrahydrofuran (2 mL) was stirred for 5 minutes. *N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 153) (0.055 g, 0.10 mmol), triethylamine (0.017 mL, 0.12 mmol), and polymer supported carbodiimide (0.12 g, 0.15 mmol) were added. The mixture was stirred for 18 hours at room temperature and was then filtered. The filtrate was concentrated, and the residue was dissolved in acetonitrile (5 mL). Aqueous sodium hydroxide solution (2.5 N, 1.0 mL) was added and the mixture was stirred for 18 hours at room temperature. The acetonitrile was removed in vacuo and the aqueous phase was acidified to pH 6 with an aqueous 10% solution of hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with water (2 x 5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound (23 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, J=6.2 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.31 (d, J=8.1 Hz, 1 H), 7.22 (t, J=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, J=7.3 Hz, 1 H), 5.32 (d, J=5.1 Hz, 1 H), 4.65 (d, J=6.6 Hz, 2 H), 4.49 (d, J=6.6 Hz, 2 H), 3.83 - 3.96 (m, 1 H), 3.71 (s, 3 H), 3.42 - 3.55 (m, 1 H), 2.65 (s, 3 H), 1.97 (d, J=2.9 Hz, 1 H), 1.72 (d, J=6.6 Hz, 2 H), 1.61 (d, J=12.4 Hz, 2 H), 0.97 - 1.34 (m, 7 H).

Example 164

***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

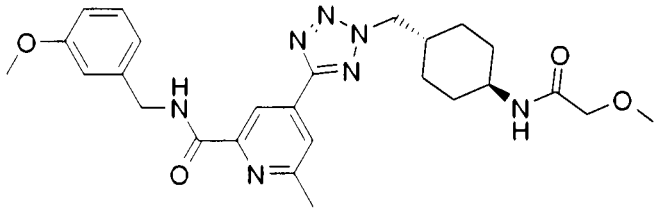


A solution of 1-hydroxybenzotriazole (3.2 mg, 0.024 mmol) in *N*,*N*-dimethylformamide (2 mL) was added to 3-(tert-butoxycarbonyl)propanoic acid (27.2 mg, 0.144 mmol). Carbodiimide resin (138 mg, 0.18 mmol, 1.30 mmol/g loading), dichloromethane (2 mL), *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 153) (52.3 mg, 0.120 mmol), and *N*-methylmorpholine (0.066 mL, 0.60 mmol) were added. The mixture was agitated at room temperature overnight. The reaction mixture was filtered washing with

N,*N*-dimethylformamide followed by dichloromethane, and volatiles were removed under a stream of nitrogen. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min). After concentration, the resulting intermediate was dissolved in a mixture of trifluoroacetic acid/dichloromethane (1/1) and stirred for 1 hour. The reaction mixture was filtered and concentrated. The residue was suspended in dichloromethane and neutralized using MP-carbonate resin to afford the title compound (10 mg, 16%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.642 min., *m/z* 507 (M+H).

Example 165

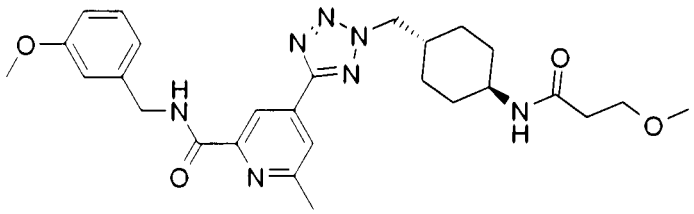
N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 164) by reaction with 2-methoxyacetic acid to afford 25.6 mg (42%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.162 min., *m/z* 508 (M+H).

Example 166

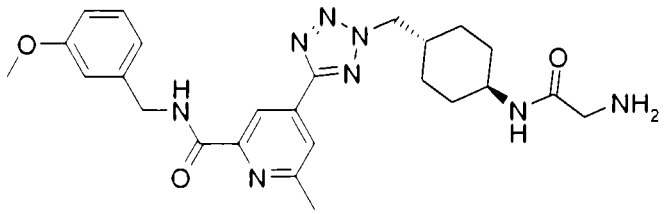
N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 164) by reaction with 3-methoxypropanoic acid to afford 24.3 mg (39%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.087 min., *m/z* 522 (M+H).

Example 167

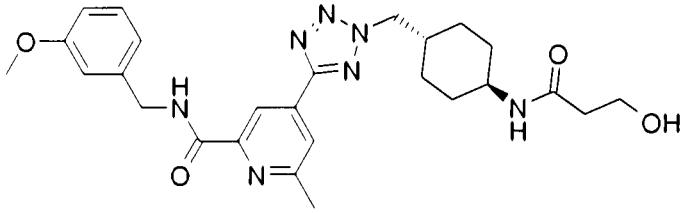
N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



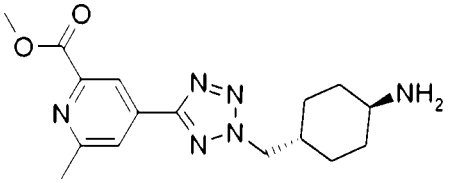
The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 164) by reaction with 2-(tert-butoxycarbonyl)acetic acid to afford 10.0 mg (17%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.631 min., *m/z* 493 (M+H).

Example 168

N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

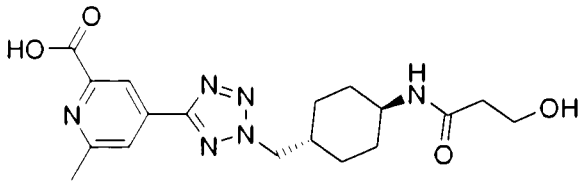


Step 1: Preparation of methyl 4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate



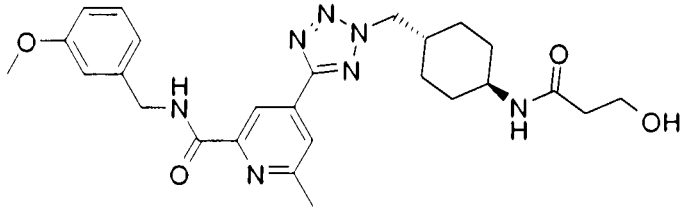
A mixture of methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (1.5 g, 6.8 mmol), *tert*-butyl *trans*-(4-hydroxymethyl)cyclohexylcarbamate (3.14 g, 13.7 mmol), and polymer supported triphenylphosphine resin (6.37 g, 13.7 mmol, 2.15 mmol/g loading) in tetrahydrofuran (75 mL) was cooled in an ice bath. Di-*tert*-butylazodicarboxylate (3.15 g, 13.7 mmol) was added and the mixture was stirred with cooling for 30 minutes. The mixture was then allowed to warm to room temperature and stir for 18 hours. The reaction mixture was filtered and the resin was washed with tetrahydrofuran and methanol. The filtrate was concentrated. The residue was dissolved in methanol (25 mL) and treated with 4N hydrochloric acid in dioxane (10.2 mL, 40.8 mmol) for 18 hours at room temperature. The reaction mixture was concentrated and the residue washed with ethanol to afford the hydrochloride salt of the product as a solid (2.09 g, 84%). MS (ES+) *m/z* 331 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (s, 2 H), 1.26 - 1.42 (m, 2 H), 1.65 (d, *J*=11.28 Hz, 2 H), 1.97 (s, *J*=9.94 Hz, 3 H), 2.64 (s, 3 H), 2.89 (br. s., 1 H), 3.91 (s, 3 H), 4.67 (d, *J*=6.71 Hz, 2 H), 8.11 (s, *J*=1.34 Hz, 1 H), 8.25 (br. s., 2 H), 8.39 (s, 1 H).

Step 2: Preparation of 4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid



2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (775 mg, 2.04 mmol) was added to a solution of methyl 4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (500 mg, 1.36 mmol), 3-hydroxypropanoic acid (147 mg, 1.63 mmol), and triethylamine (0.23 mL, 1.63 mmol) in *N*,*N*-dimethylformamide (20 mL). The reaction mixture was allowed to stir at room temperature for 2 days and was then treated with lithium hydroxide (326 mg, 13.6 mmol). The mixture was stirred for 18 hours. The reaction mixture was acidified with the addition of 3 N hydrochloric acid and then extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to afford the title compound as a solid

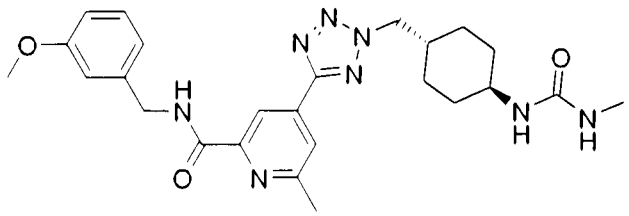
Step 3: Preparation of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (109 mg, 0.289 mmol) was added to a solution of 4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (50 mg, 0.13 mmol), 3-methoxyphenylmethanamine (50 mg, 0.36 mmol), and triethylamine (0.07 mL, 0.48 mmol) in *N*,*N*-dimethylformamide (1 mL), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC. Fractions containing the product were passed through a carbonate cartridge eluting with methanol and then concentrated to afford the title compound as a white solid (16 mg, 24%). MS (ES+) *m/z* 508 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.23 (m, 4 H), 1.53 - 1.64 (m, 2 H), 1.68 - 1.81 (m, 2 H), 1.86 - 2.03 (m, 2 H), 2.15 (t, *J*=6.59 Hz, 2 H), 2.44 - 2.48 (m, 1 H), 2.64 (s, 3 H), 3.54 (t, *J*=6.22 Hz, 2 H), 3.70 (s, 3 H), 4.48 (d, *J*=6.59 Hz, 2 H), 4.63 (d, *J*=6.59 Hz, 2 H), 6.78 (d, *J*=8.05 Hz, 1 H), 6.85 - 6.91 (m, 1 H), 7.12 - 7.25 (m, 2 H), 7.58 (d, *J*=8.05 Hz, 1 H), 8.04 (s, 1 H), 8.39 (s, 1 H), 9.18 (t, *J*=6.22 Hz, 1 H).

Example 169

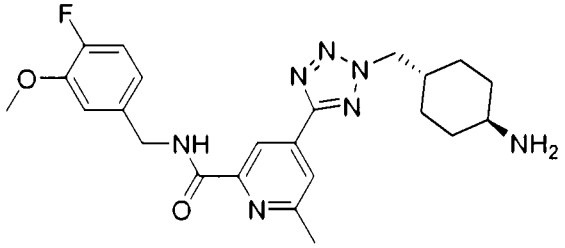
1-((*trans*)-4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2H-tetrazol-2-yl)methyl)cyclohexyl)-3-methylurea



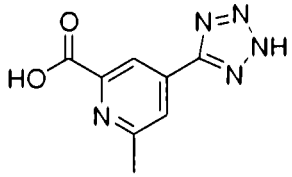
Methyl isocyanate (1 mL, 4M solution in dichloromethane) and silica-bound 4-(dimethylamino)pyridine (833.0 mg, 0.575 mmol, 0.69 mmol/g loading) were added to a solution of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 153) (50.0 mg, 0.115 mmol) in dichloromethane (1 mL). The mixture was agitated overnight at room temperature and was then filtered washing with *N*,*N*-dimethylformamide. The filtrate was concentrated under a stream of nitrogen. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (22.8 mg, 40%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.963 min., *m/z* 493 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 - 1.30 (m, 4 H), 1.48 - 1.68 (m, 2 H), 1.71 - 1.85 (m, 2 H), 1.95 (s, 1 H), 2.38 - 2.53 (m, 3 H), 2.65 (s, 3 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.64 (d, *J*=7.3 Hz, 2 H), 5.42 - 5.55 (m, 1 H), 5.58 - 5.72 (m, 1 H), 6.71 - 6.84 (m, 1 H), 6.86 - 6.95 (m, 2 H), 7.14 - 7.32 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.19 (s, 1 H).

Example 170

N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



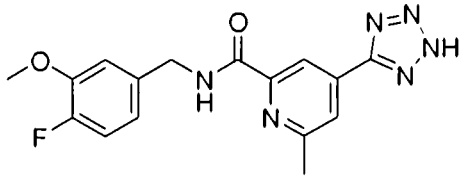
Step 1: Preparation of 6-methyl-4-(2*H*-tetrazol-5-yl)picolinic acid



A solution of lithium hydroxide monohydrate (4.1 g, 100 mmol) in water (100 mL) was added to a suspension of methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) in tetrahydrofuran (300 mL). The mixture was heated to reflux overnight, concentrated in vacuo, and dissolved in water. The mixture was cooled in an ice/water bath and acidified with 1 N hydrochloric acid. The resulting precipitate was filtered, washed with water, and air dried to afford the title compound as an odd-white solid (10.35 g, 100%). MS (ES+) *m/z* 206

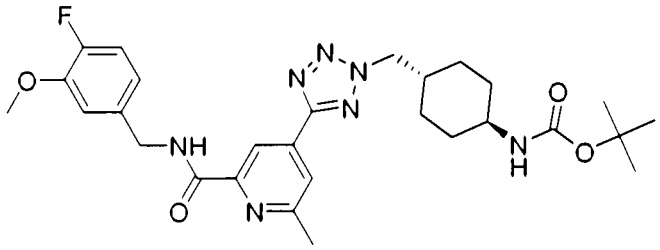
(M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.41 (d, J=0.8 Hz, 1 H), 8.06 (d, J=1.1 Hz, 1 H), 2.62 (s, 3 H).

Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide



A mixture of 6-methyl-4-(2*H*-tetrazol-5-yl)picolinic acid (27 g, 0.132 mol), 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (26.5 g, 0.138 mol), tetrahydrofuran (445 mL), and 1-hydroxybenzotriazole (18.6 g, 0.138 mmol) was cooled in an ice bath. *N*-Methylmorpholine (43.5 mL, 0.396 mmol) followed by dimethylsulfoxide (335 mL) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (26.5 g, 0.138 mmol) were added. The mixture was allowed to warm to room temperature overnight. Dimethylsulfoxide (100 mL) was added followed by 1N hydrochloric acid (400 mL) with ice bath cooling. After stirring for 45 min, the precipitate was filtered. The resulting solid was slurried in ethyl acetate, filtered, and dried in vacuo to afford the title compound (31.98 g). MS (ES+) *m/z* 343 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (t, J=6.4 Hz, 1 H), 8.47 (d, J=1.1 Hz, 1 H), 8.09 (d, J=1.2 Hz, 1 H), 7.18 (dd, J=8.5, 1.9 Hz, 1 H), 7.14 (dd, J=11.7, 8.3 Hz, 1 H), 6.90 (ddd, J=8.2, 4.4, 2.0 Hz, 1 H), 4.50 (d, J=6.3 Hz, 2 H), 3.82 (s, 3 H), 2.68 (s, 3 H)

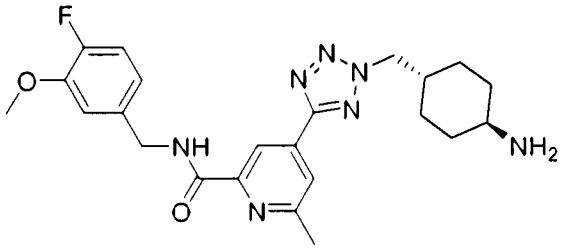
Step 3: Preparation of *tert*-butyl (*trans*)-4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate



N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (1.71 g, 5.0 mmol), polymer supported triphenylphosphine (3.49 g, 7.5 mmol), and *tert*-butyl *trans*-(4-hydroxymethyl)cyclohexylcarbamate (1.38 g, 6.0 mmol) were suspended in tetrahydrofuran (100 mL). Di-*tert*-butyl azodicarboxylate (1.73 g, 7.5 mmol) was added. The mixture was allowed to stir for 18 hours. The reaction mixture was filtered and the resin washed with tetrahydrofuran (100 mL). The filtrate was concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2). Combined fractions were concentrated onto silica and repurified by silica column chromatography (heptane/EtOAc, 2/1; 1/1). Combined fractions were concentrated and triturated with heptane to afford the title compound as a white solid (1.903 g, 69%). MS (ES+) *m/z* 554 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (t, J=6.4 Hz, 1 H), 8.40 (d, J=0.8 Hz, 1 H), 8.05 (d, J=1.2 Hz, 1 H), 7.15 (dd, J=8.7, 1.9 Hz, 1 H), 7.11 (dd, J=11.7, 8.3 Hz, 1 H), 6.87 (ddd, J=8.3, 4.3, 2.0

Hz, 1 H), 6.68 (d, *J*=7.7 Hz, 1 H), 4.63 (d, *J*=7.0 Hz, 2 H), 4.47 (d, *J*=6.4 Hz, 2 H), 3.79 (s, 3 H), 3.14 (br. s., 1 H), 2.64 (s, 3 H), 1.89 (br. s., 1 H), 1.78 - 1.70 (m, 2 H), 1.59 - 1.53 (m, 2 H), 1.33 (s, 9 H), 1.16 - 1.04 (m, 4 H).

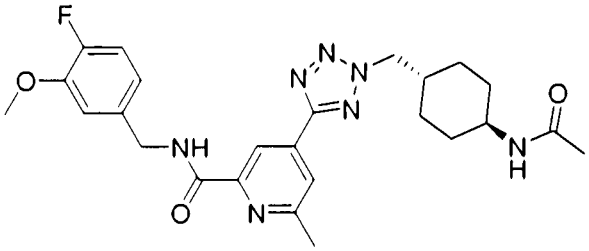
Step 3: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



tert-Butyl (*trans*)-4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate (1.90 g, 3.43 mmol) was dissolved in dichloromethane (20 mL) and trifluoroacetic acid (5.1 mL, 68.6 mmol) was added. The mixture was allowed to stand for 2 hours and was then concentrated. The residue was dissolved in dichloromethane (150 mL) and washed with 1N NaOH solution (2 x 40 mL). The organic layer was dried over sodium sulfate and concentrated to afford the title compound as a glass (1.541 g, 98%). MS (ES+) *m/z* 454 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.25 (t, *J*=6.4 Hz, 1 H), 8.39 (s, 1 H), 8.05 (d, *J*=1.1 Hz, 1 H), 7.15 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.11 (dd, *J*=11.7, 8.3 Hz, 1 H), 6.87 (ddd, *J*=8.3, 4.4, 2.0 Hz, 1 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.47 (d, *J*=6.4 Hz, 2 H), 3.79 (s, 3 H), 2.64 (s, 3 H), 2.42 (tt, *J*=10.9, 3.4 Hz, 1 H), 1.95 - 1.84 (m, 1 H), 1.71 (d, *J*=11.1 Hz, 2 H), 1.53 (d, *J*=12.5 Hz, 2 H), 1.37 (br. s., 2 H), 1.07 (q, *J*=12.1 Hz, 2 H), 0.94 (q, *J*=11.5 Hz, 2 H).

Example 171

N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

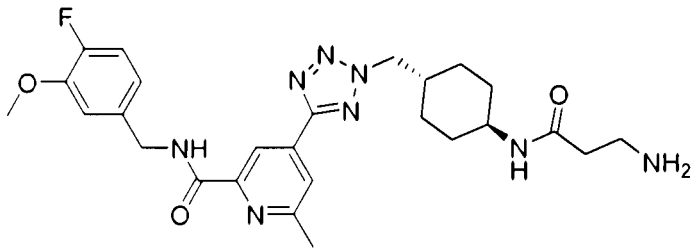


Triethylamine (944 μL, 6.77 mmol), 4-(dimethylamino)pyridine (83 mg, 0.68 mmol), and acetyl chloride (289 μL, 4.06 mmol) was added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 170) (1.535 g, 3.39 mmol) in dichloromethane (60 mL).. The mixture was allowed to stir at room temperature for 1 hour. The reaction mixture was diluted with dichloromethane (150 mL) and washed with saturated aq. sodium bicarbonate solution (2 x 40 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2; 100/4). Fractions were concentrated. The resulting solid was

triturated with ethyl ether and filtered to afford the title compound as a white solid (1.370 g, 82%). MS (ES+) *m/z* 496 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (t, *J*=6.4 Hz, 1 H), 8.40 (d, *J*=0.8 Hz, 1 H), 8.05 (d, *J*=1.2 Hz, 1 H), 7.67 (d, *J*=7.8 Hz, 1 H), 7.15 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.11 (dd, *J*=11.6, 8.4 Hz, 1 H), 6.87 (ddd, *J*=8.3, 4.4, 2.0 Hz, 1 H), 4.64 (d, *J*=7.1 Hz, 2 H), 4.47 (d, *J*=6.3 Hz, 2 H), 3.79 (s, 3 H), 3.47 - 3.38 (m, 1 H), 2.65 (s, 3 H), 1.98 - 1.90 (m, 1 H), 1.78 - 1.72 (m, 2 H), 1.72 (s, 3 H), 1.62 - 1.55 (m, 2 H), 1.19 - 1.03 (m, 4 H).

Example 172

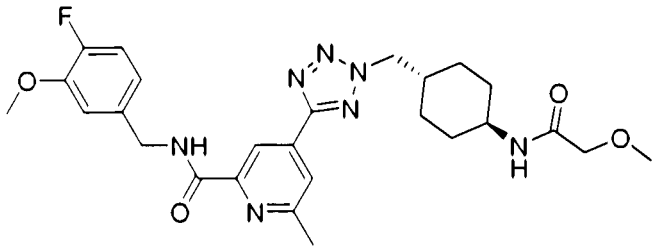
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



O-(7-Azabenzotriazole-1-yl)-*N*,*N*,*N*'*N*'-tetramethyluronium hexafluorophosphate (75.0 mg, 0.198 mmol), 3-(tert-butoxycarbonyl)propanoic acid (31.2 mg, 0.165 mmol), and diisopropylethylamine (0.057 mL, 0.330 mmol) were added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 170) (74.8 mg, 0.165 mmol) in *N*,*N*-dimethylformamide (2 mL). The mixture was stirred overnight at room temperature. Volatiles were removed under a stream of nitrogen. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound (30.5mg, 35%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 3.69 min., *m/z* 525 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 - 1.28 (m), 1.50 - 1.84 (m), 1.88 - 2.05 (m), 2.10 (t, *J*=6.6 Hz, 2 H), 2.65 (s, 3 H), 2.69 (t, *J*=6.6 Hz, 2 H), 3.27 (br. s.), 3.46 (br. s.), 3.80 (s, 3 H), 4.48 (d, *J*=5.9 Hz, 2 H), 4.65 (d, *J*=6.6 Hz, 2 H), 6.78 - 6.95 (m), 7.04 - 7.21 (m), 7.66 - 7.75 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.14 - 9.27 (m, 1 H).

Example 173

***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

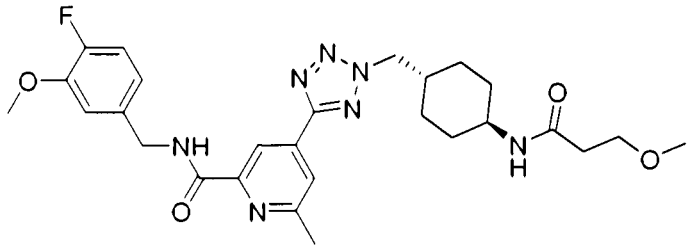


The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 172) by reaction with 2-methoxyacetic acid to afford 41.5 mg (48%). LC/MS (5%-100% CH_3CN/H_2O,

10.0 min.): 4.71 min., *m/z* 526 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.35 (m, 4 H), 1.55 - 1.80 (m, 4 H), 1.87 - 2.03 (m, 1 H), 2.65 (s, 3 H), 3.44 - 3.63 (m, 1 H), 3.72 (s, 3 H), 3.80 (s, 3 H), 4.48 (d, *J*=6.6 Hz, 2 H), 4.65 (d, *J*=6.6 Hz, 2 H), 6.84 - 6.92 (m, 1 H), 7.06 - 7.20 (m, 2 H), 7.42 - 7.50 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.11 - 9.27 (m, 1 H).

Example 174

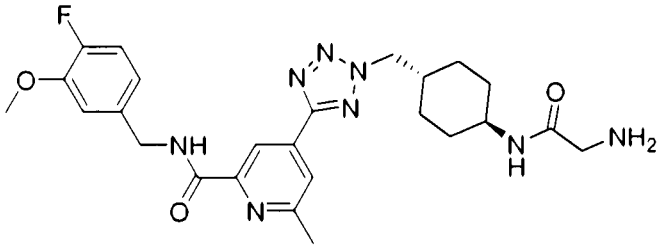
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 172) by reaction with 3-methoxypropanoic acid to afford 52.7 mg (59%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 4.61 min., *m/z* 540 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 - 1.25 (m, 4 H), 1.56 - 1.83 (m, 4 H), 1.90 - 2.02 (m, 1 H), 2.23 (t, *J*=6.2 Hz, 2 H), 2.65 (s, 3 H), 3.28 (s), 3.47 (t, *J*=6.6 Hz, 2 H), 3.80 (s, 3 H), 4.48 (d, *J*=6.6 Hz, 2 H), 4.65 (d, *J*=6.6 Hz, 2 H), 6.84 - 6.92 (m, 1 H), 7.05 - 7.20 (m, 2 H), 7.61 - 7.68 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.18 - 9.26 (m, 1 H).

Example 175

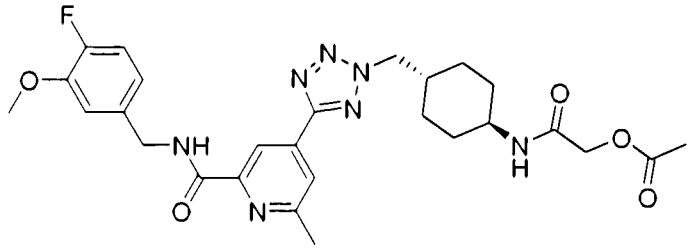
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 172) by reaction with 2-(tert-butoxycarbonyl)acetic acid to afford 34.5 mg (41%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 3.66 min., *m/z* 511 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.27 (m, 4 H), 1.53 - 1.84 (m, 4 H), 1.91 - 2.03 (m, 1 H), 2.65 (s, 3 H), 3.01 (s, 2 H), 3.28 (br. s.), 3.41 - 3.58 (m, 1 H), 3.80 (s, 3 H), 4.48 (d, *J*=6.6 Hz, 2 H), 4.65 (d, *J*=6.6 Hz, 2 H), 6.85 - 6.91 (m, 1 H), 7.06 - 7.20 (m, 2 H), 7.53 - 7.61 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.16 - 9.27 (m, 1 H).

Example 176

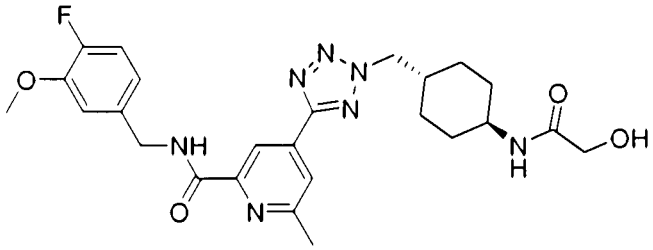
2-((*trans*)-4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate



The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 172) by reaction with 2-acetoxyacetic acid to afford 48.0 mg (53%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 4.76 min., *m/z* 554 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.26 (m, 4 H), 1.56 - 1.81 (m, 4 H), 1.90 - 2.02 (m, 1 H), 2.04 (s, 3 H), 2.65 (s, 3 H), 3.42 - 3.56 (m, 1 H), 3.80 (s, 3 H), 4.36 (s, 2 H), 4.48 (d, *J*=5.9 Hz, 2 H), 4.65 (d, *J*=6.6 Hz, 2 H), 6.84 - 6.93 (m, 1 H), 7.06 - 7.20 (m, 2 H), 7.74 - 7.82 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.17 - 9.25 (m, 1 H).

Example 177

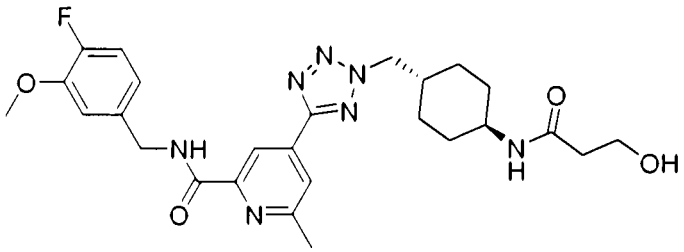
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 172) by reaction with 2-hydroxyacetic acid to afford 41.0 mg (49%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 4.41 min., *m/z* 512 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.39 (m, 4 H), 1.53 - 1.79 (m, 4 H), 1.88 - 2.05 (m, 1 H), 2.65 (s, 3 H), 3.48 - 3.61 (m, 1 H), 3.73 (s, 3 H), 3.80 (s, 2 H), 4.48 (d, *J*=6.6 Hz, 2 H), 4.65 (d, *J*=7.3 Hz, 2 H), 6.85 - 6.92 (m, 1 H), 7.06 - 7.19 (m, 2 H), 7.33 - 7.40 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.17 - 9.26 (m, 1 H).

Example 178

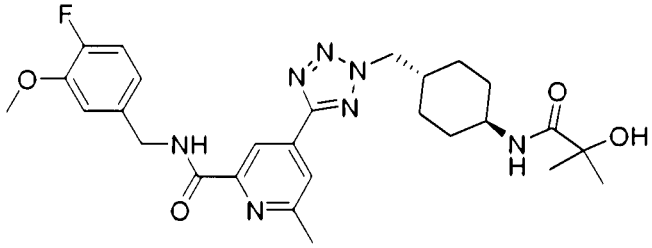
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



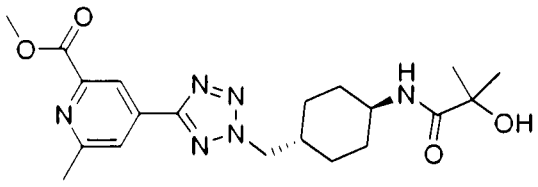
The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 168) by reaction with 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) to afford 25 mg (37%) of a white solid. MS (ES+) *m/z* 526 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.25 (m, 4 H), 1.57 - 1.68 (m, 2 H), 1.73 - 1.84 (m, 2 H), 1.92 - 2.04 (m, 1 H), 2.19 (t, *J*=6.59 Hz, 2 H), 2.54 (s, 2 H), 2.67 (s, 3 H), 3.53 - 3.62 (m, 2 H), 3.82 (s, 3 H), 4.51 (d, *J*=5.86 Hz, 2 H), 4.67 (d, *J*=7.32 Hz, 2 H), 6.86 - 6.95 (m, 1 H), 7.06 - 7.25 (m, 2 H), 7.62 (d, *J*=7.32 Hz, 1 H), 8.07 (s, 1 H), 8.43 (s, 1 H), 9.24 (t, *J*=6.22 Hz, 1 H).

Example 179

N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



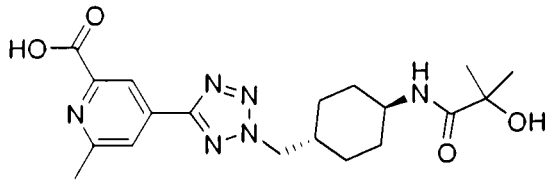
Step 1: Preparation of methyl 4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate



A mixture of 2-hydroxy isobutyric acid (25 mg, 0.24 mmol) and 1-hydroxybenzatriazole (37 mg, 0.27 mmol) in 2- methyl tetrahydrofuran (2 mL) was stirred for 5 minutes. 4-(2-(((*trans*)-4-Aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 168) (0.10 g, 0.23 mmol), triethylamine (0.038 mL, 0.27 mmol), and polymer supported carbodiimide (0.27 g, 0.34 mmol) were added. The mixture was stirred for 18 hours at room temperature. The reaction mixture was filtered. The filtrate was washed with water (3 x 5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated.

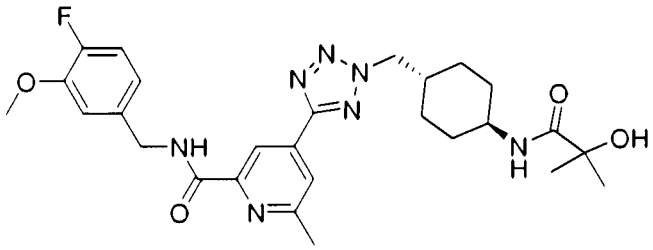
The residue was purified by silica column chromatography (0-50% ethyl acetate/heptane) to afford the title compound (65 mg, 69%).

Step 2: Preparation of 4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid



Aqueous sodium hydroxide (2.5 N, 1.0 mL) was added to a solution of methyl 4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (65 mg, 0.16 mmol) in acetonitrile (2 mL), and the mixture was stirred for 1 hour at room temperature. The acetonitrile was removed in a stream of nitrogen. Water (1 mL) was added to the residue and the mixture was acidified to pH 6 with 10% aqueous hydrochloric acid. The resulting solid was collected by filtration, washed with water (2 x 2 mL), and dried to afford the title compound (53 mg, 84%). MS (ES+) *m/z* 403 (M+H).

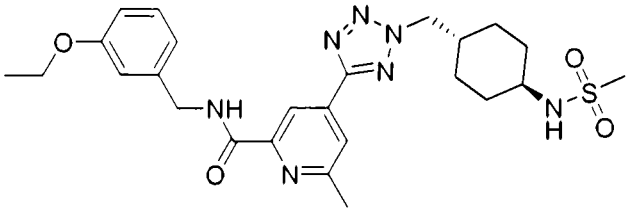
Step 3: Preparation of *N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



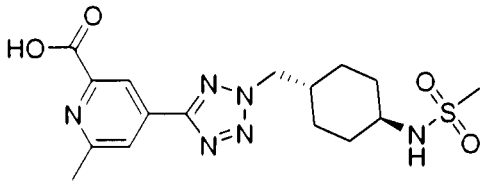
A mixture of 4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (0.040 g, 0.10 mmol) and 1-hydroxybenzatriazole (21 mg, 0.12 mmol) in *N*,*N*-dimethylformamide was stirred for 15 minutes. 4-Fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (27 mg, 0.16 mmol) was then added followed by polymer supported carbodiimide (0.135 g, 0.15 mmol). The mixture was stirred for 18 hours at room temperature. The reaction mixture was filtered, and the filtrate was extracted by ethyl acetate (3 x 5 mL). The combined organic layers were washed with water (2 x 5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound (8.3 mg, 15%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (s, 1 H), 8.41 (br. s., 1 H), 8.06 (br. s., 1 H), 7.06 - 7.28 (m, 2 H), 6.88 (d, *J*=8.8 Hz, 1 H), 6.43 (br. s., 1 H), 5.25 (br. s., 1 H), 4.67 (d, *J*=3.7 Hz, 2 H), 4.48 (d, *J*=5.9 Hz, 2 H), 3.80 (s, 3 H), 3.60 (d, *J*=9.5 Hz, 1 H), 2.66 (s, 3 H), 2.05 (s, 1 H), 1.72 (d, *J*=11.7 Hz, 2 H), 1.60 (d, *J*=7.3 Hz, 2 H), 1.10 - 1.34 (m, 9 H).

Example 180

***N*-(3-Ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**

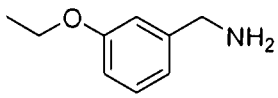


Step 1: Preparation of 6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinic acid



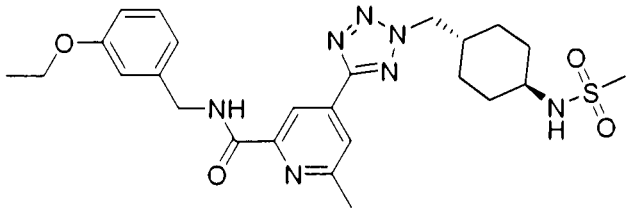
Diisopropylethylamine (0.59 mL, 3.4 mmol) and methanesulfonyl chloride (0.16 mL, 2.1 mmol) were added to a solution of methyl 4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 168) (125 mg, 0.34 mmol) in *N*,*N*-dimethylformamide (1 mL). The mixture was allowed to stir at room temperature overnight. The reaction mixture was concentrated and the residue was dissolved in tetrahydrofuran (8 mL). A 4N aqueous solution of lithium hydroxide (2 mL) was added and the mixture was allowed to stir for 4 hours. The reaction mixture was concentrated and purified by reverse phase preparative HPLC (20-60% acetonitrile/water) to afford the title compound (42 mg, 25%).

Step 2: Preparation of (3-ethoxyphenyl)methanamine



Lithium aluminum hydride (59.5 g) was added to anhydrous ethyl ether (900 mL) cooled to 10 °C. A solution of 3-ethoxybenzonitrile (35.5 g) in anhydrous ethyl ether (100 mL) was added over 1.25 hours, and the mixture was stirred for 4.5 hours. The reaction mixture was quenched with water (60 mL) and was stirred for 1.25 hours. A 15% aqueous solution of sodium hydroxide (60 mL) was added followed by ether (500 mL) and water (180 mL). The slurry was filtered. The filtrate was dried over sodium sulfate and concentrated to afford the title compound as an oil (35.3 g). MS (ES+) *m/z* 152 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.20 (t *J*=8.1, 1 H), 6.87-6.72 (m, 3 H), 4.00 (q, *J*=6.9, 2 H), 3.78 (s, 2 H), 1.38 (t, *J*=7.2, 3 H)

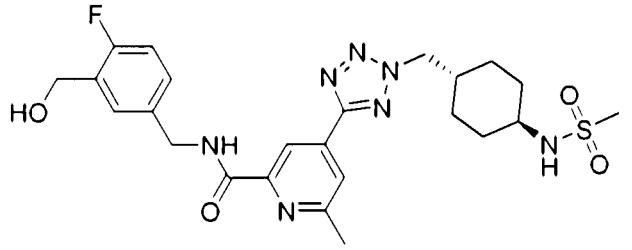
Step 3: Preparation of *N*-(3-ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



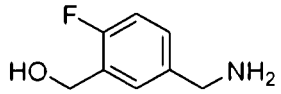
In a 2 dram vial with a magnetic stir bar, 6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinic acid (70 mg, 0.177 mmol) was dissolved in *N*,*N*-dimethylformamide (2 mL). Diisopropylethylamine (0.19 mL, 1.06 mmol) and (3-ethoxyphenyl)methanamine (33.4 mg, 0.221 mmol) were added and the mixture was stirred for 30 minutes. *O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (128 mg, 0.398 mmol) was added and stirring continued at room temperature overnight. The reaction mixture was purified by reverse phase preparative HPLC to afford the title compound (27.2 mg). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.54 min, *m/z* 514 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.33 (m, 8 H), 1.54 - 1.65 (m, 3 H), 1.82 - 1.98 (m, 3 H), 2.45 - 2.50 (m, 1 H), 2.50 - 2.53 (m, 1 H), 2.61 - 2.68 (m, 3 H), 2.80 - 2.88 (m, 3 H), 2.97 - 3.08 (m, 1 H), 3.94 - 3.98 (m, 2 H), 4.43 - 4.52 (m, 2 H), 4.58 - 4.69 (m, 2 H), 6.73 - 6.80 (m, 1 H), 6.83 - 6.97 (m, 2 H), 7.15 - 7.26 (m, 1 H), 8.02 - 8.07 (m, 1 H), 8.38 - 8.43 (m, 1 H), 9.14 - 9.23 (m, 1 H).

Example 181

N-(4-Fluoro-3-(hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide

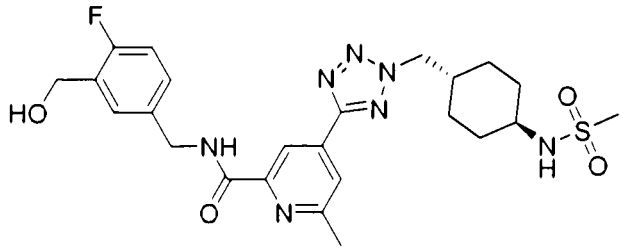


Step 1: Preparation of (5-(aminomethyl)-2-fluorophenyl)methanol



In a 250 round bottomed flask with a magnetic stir bar, 4-fluoro-3-formylbenzonitrile (1.50 g, 10.06 mmol) was dissolved in tetrahydrofuran (30 mL). The mixture was cooled in an ice bath to 0 °C and lithium aluminum hydride (573 mg, 15.1 mmol) was added. The reaction mixture was stirred at 0 °C for 3 hours and then was allowed to warm to room temperature and stir overnight. The mixture was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound as a white solid (478 mg, 30%). MS (ES+) *m/z* 156 (M+H). ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 4.09 (s, 2 H), 4.68 (s, 2 H), 7.13 (dd, *J*=9.67, 8.59 Hz, 1 H), 7.31 - 7.44 (m, 1 H), 7.56 (dd, *J*=6.85, 2.28 Hz, 1 H).

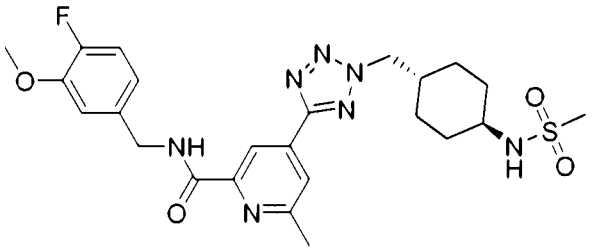
Step 2: Preparation of *N*-(4-fluoro-3-(hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



The title compound was prepared in a similar manner to *N*-(3-ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 180) by reaction with (5-(aminomethyl)-2-fluorophenyl)methanol to afford 14.1 mg. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.28 (d, *J*=11.6 Hz, 4 H), 1.34 (d, 1 H), 1.73 (s, 2 H), 2.67 (s, 3 H), 3.12 - 3.22 (m, 1 H), 4.59 - 4.64 (m, 6 H), 7.02 (s, 1 H), 7.26 - 7.34 (m, 1 H), 7.45 - 7.51 (m, 1 H), 8.09 (d, *J*=1.1 Hz, 1 H).

Example 182

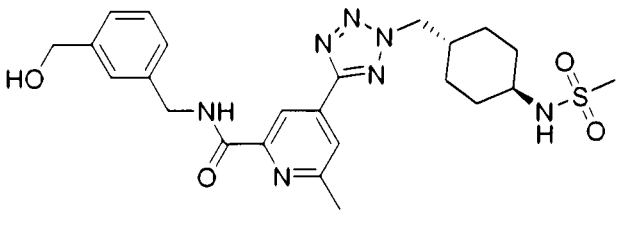
N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



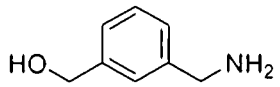
The title compound was prepared in a similar manner to *N*-(3-ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 180) by reaction with 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) to afford 15.9 mg. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.27 (m, 5 H), 1.61 (d, *J*=10.3 Hz, 2 H), 1.89 (d, *J*=10.3 Hz, 2 H), 2.51 (s, 1 H), 2.65 (s, 3 H), 2.86 (s, 3 H), 2.96 - 3.11 (m, 2 H), 3.27 (s, 1 H), 3.80 (s, 3 H), 4.48 (d, *J*=5.9 Hz, 2 H), 4.64 (d, *J*=6.6 Hz, 2 H), 6.85 - 6.95 (m, 2 H), 7.05 - 7.19 (m, 2 H), 8.03 - 8.07 (m, 1 H), 8.37 - 8.43 (m, 1 H), 9.15 - 9.25 (m, 1 H).

Example 183

N-(3-(Hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide

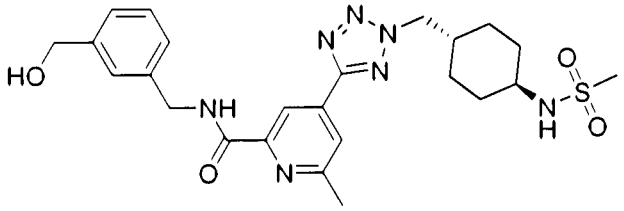


Step 1: Preparation of (3-(aminomethyl)phenyl)methanol



To a refluxing (33.8 °C) suspension of lithium aluminum hydride (20.0 g) in anhydrous ethyl ether (300 mL) under nitrogen was added portionwise of 3-cyanobenzaldehyde (10.51 g) over a 2 min period. The resulting slurry was heated at reflux for 10 hours. The reaction mixture was cooled in an ice bath and water (20 mL) was added in 1 mL increments while keeping the temperature < 20 °C. A 15 % sodium hydroxide solution (20 mL) was added in a similar fashion, followed by water (60 mL). The resulting solids were filtered off and washed. The filtrate was concentrated in vacuo. The residue was dissolved in a mixture of dichloromethane/methanol/ammonium hydroxide (95/5/0.5, 10 mL), filtered, and purified by silica column chromatography eluting with the same to afford the title compound as a light yellow oil (4.25 g).

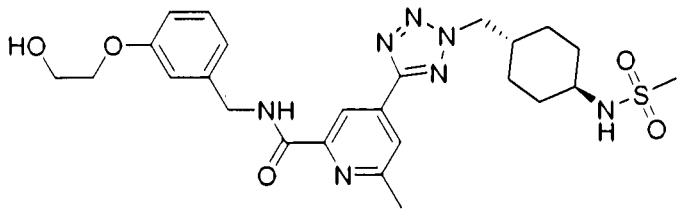
Step 2: Preparation of *N*-(3-(hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



The title compound was prepared in a similar manner to *N*-(3-ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 180) by reaction with (3-(aminomethyl)phenyl)methanol to afford 27.2 mg. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.28 (m, 5 H), 1.61 (d, *J*=10.3 Hz, 3 H), 1.89 (d, *J*=11.0 Hz, 2 H), 2.65 (s, 3 H), 2.85 (s, 3 H), 2.97 - 3.08 (m, 1 H), 3.32 (s, 1 H), 4.45 (d, *J*=5.1 Hz, 2 H), 4.51 (d, *J*=6.6 Hz, 2 H), 4.64 (d, *J*=7.3 Hz, 2 H), 6.92 (d, *J*=7.3 Hz, 1 H), 7.13 - 7.21 (m, 1 H), 7.22 - 7.30 (m, 2 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.20 (t, *J*=6.2 Hz, 1 H).

Example 184

N-(3-(2-Hydroxyethoxy)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide

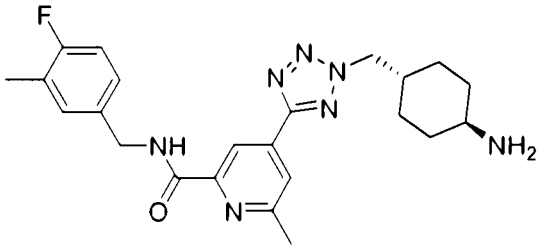


The title compound was prepared in a similar manner to *N*-(3-ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 180) by reaction with 2-(3-(aminomethyl)phenoxy)ethanol (prepared as described in step 2 of the synthesis of *N*-(3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-

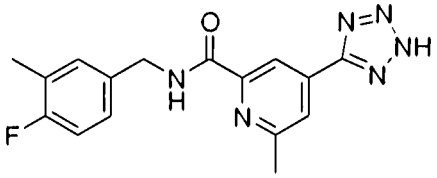
methylpyrimidine-4-carboxamide, Example 13) to afford 10.6 mg. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 - 1.27 (m, 5 H), 1.61 (d, J=10.3 Hz, 2 H), 1.89 (d, J=9.5 Hz, 2 H), 2.51 (s, 1 H), 2.65 (s, 3 H), 2.86 (s, 3 H), 3.03 (s, 1 H), 3.67 (t, J=4.8 Hz, 2 H), 3.93 (t, J=5.1 Hz, 2 H), 4.49 (d, J=6.6 Hz, 2 H), 4.64 (d, J=7.3 Hz, 2 H), 6.79 (d, J=7.3 Hz, 1 H), 6.86 - 6.95 (m, 3 H), 7.20 (t, J=8.1 Hz, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.19 (t, J=6.2 Hz, 1 H).

Example 185

***N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

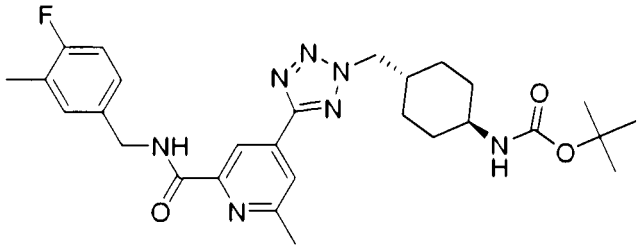


Step 1: Preparation of *N*-(4-fluoro-3-methylbenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide



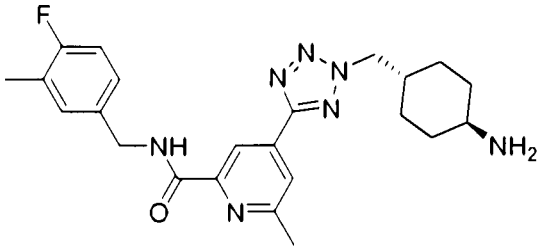
Tetrahydrofuran (2 mL) and 4-fluoro-3-methylbenzylamine (3.5 g) was added to methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (2.69 g). The resultant slurry was treated with *N*,*N*-dimethylacetamide (2 mL) and heated to 90 °C. After 3 h, the mixture was allowed to cool to room temperature, treated with 1N hydrochloric acid, diluted with water and filtered. The crude product was triturated with methanol, (50 mL) to provided the title compound as a solid (2.06 g, 51%): MS(ES+) m/z 327 (M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (d, J=1.6 Hz, 3 H), 2.65 (s, 3 H), 4.45 (d, J=6.2 Hz, 2 H), 7.05 (t, 1 H), 7.13 - 7.20 (m, 1 H), 7.22 (d, J=7.5 Hz, 1 H), 8.06 (d, J=1.3 Hz, 1 H), 8.45 (d, J=1.1 Hz, 1 H), 9.27 (t, J=6.3 Hz, 1 H).

Step 2: Preparation of *tert*-butyl (*trans*)-4-((5-(2-((4-fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate



To *N*-(4-fluoro-3-methylbenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (1.95 g) was added *tert*-butyl-*trans*-(4-hydroxymethyl)cyclohexylcarbamate (1.65 g), polymer supported triphenylphosphine (7.00 g, Argonaut, 2.15 mmol/g) and anhydrous THF (60 mL). The stirred mixture was cooled in an ice-water bath and treated with di-tert-butyl azodicarboxylate (2.76 g). The mixture was concentrated in vacuo and the residue was purified by silica column chromatography (40% ethyl acetate/hexanes) to afford the title compound as a white, crystalline solid (2.00 g, 62%): MS(ES+) 538 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.02 - 1.30 (m, 4 H), 1.42 (s, 9 H), 1.56 - 1.65 (m, 1 H), 1.71 (d, *J*=13.2 Hz, 2 H), 2.00 - 2.12 (m, 3 H), 2.26 (d, *J*=1.9 Hz, 3 H), 2.63 (s, 3 H), 4.37 (s, 1 H), 4.52 (d, *J*=7.3 Hz, 2 H), 4.61 (d, *J*=6.2 Hz, 2 H), 6.96 (t, 1 H), 7.11 - 7.23 (m, 2 H), 8.04 (d, *J*=1.1 Hz, 1 H), 8.40 (t, 1 H), 8.71 (s, 1 H).

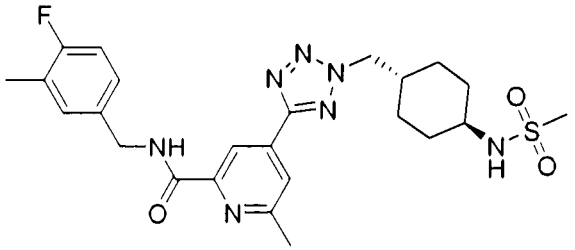
Step 3: Preparation of *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Trifluoroacetic acid (5 mL) was added to a solution of tert-butyl (*trans*)-4-((5-(2-((4-fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate (849.5 mg, 1.58 mmol) in dichloromethane (5 mL), and the mixture was stirred for 30 minutes. The reaction mixture was concentrated under a stream of nitrogen. The residue was dissolved in dichloromethane and neutralized with MP-carbonate resin. The mixture was filtered, washed with dichloromethane followed by methanol, and concentrated under a stream of nitrogen to afford the title compound (781 mg). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.625 min., *m/z* 438 (M+H).

Example 186

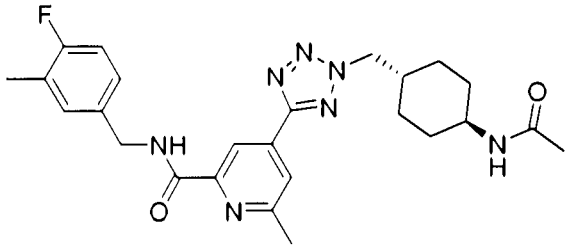
N-(4-fluoro-3-methylbenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2H-tetrazol-5-yl)picolinamide



Triethylamine (0.071 mL, 0.513 mmol) and methane sulfonyl chloride (0.020 mL, 0.257 mmol) was added to a solution of *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 185) (75.0 mg, 0.171 mmol) in tetrahydrofuran (2 mL). The mixture was stirred for approximately 30 min at room temperature and was then concentrated under a stream of nitrogen. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (29 mg, 33%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.365 min., *m/z* 516 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.91 - 1.35 (m, 4 H), 1.49 - 1.68 (m, 2 H), 1.75 - 2.02 (m, 3 H), 2.19 (s, 3 H), 2.65 (s, 3 H), 2.85 (s, 3 H), 2.94 - 3.13 (m, 1 H), 4.45 (d, *J*=6.6 Hz, 2 H), 4.64 (d, *J*=7.3 Hz, 2 H), 6.88 - 6.97 (m, 1 H), 6.99 - 7.09 (m, 1 H), 7.12 - 7.21 (m, 1 H), 7.21 - 7.27 (m, 1 H), 8.00 - 8.08 (m, 1 H), 8.35 - 8.45 (m, 1 H), 9.14 - 9.25 (m, 1 H).

Example 187

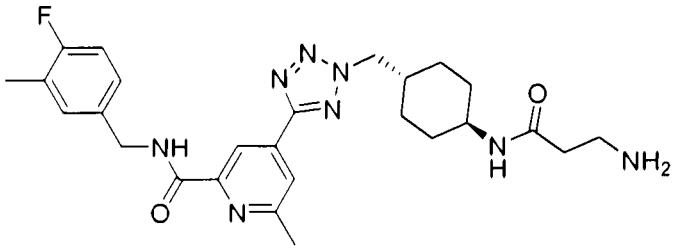
N-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Acetic anhydride (0.065 mL, 0.687 mmol) and 4-(dimethylamino)pyridine Si bound (1.659 g, 1.145 mmol, 0.69 mmol/g loading) was added to a solution of *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 185) (100.0 mg, 0.229 mmol) in dichloromethane (2 mL). The mixture was agitated overnight at room temperature, filtered, and *N*,*N*-dimethylformamide. The filtrate was concentrated under a stream of nitrogen. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (33 mg, 30%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 4.82 min., *m/z* 480 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 - 1.29 (m), 1.53 - 1.82 (m), 1.90 - 2.04 (m, 1 H), 2.19 (s, 3 H), 3.35 - 3.52 (m, 1 H), 4.46 (d, *J*=5.9 Hz, 2 H), 4.64 (d, *J*=6.6 Hz, 2 H), 6.99 - 7.08 (m, 1 H), 7.13 - 7.21 (m, 1 H), 7.21 - 7.28 (m, 1 H), 7.59 - 7.67 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.16 - 9.24 (m, 1 H).

Example 188

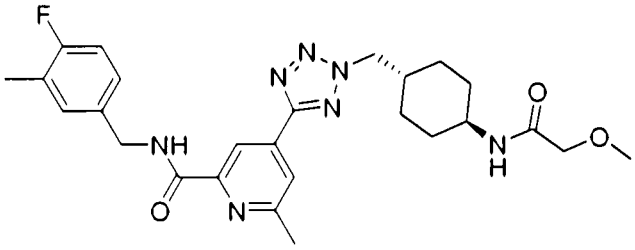
***N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



O-(7-Azabenzotriazole-1-yl)-*N*,*N*,*N*'*N*'-tetramethyluronium hexafluorophosphate (78.0 mg, 0.205 mmol), 3-(tert-butoxycarbonyl)propanoic acid (32.4 mg, 0.171 mmol), and diisopropylethylamine (0.060 mL, 0.342 mmol) was added to a solution of *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 185) (100.0 mg, 0.229 mmol) (75.0 mg, 0.171 mmol) in *N*,*N*-dimethylformamide (2 mL). The mixture was stirred overnight at room temperature and was then concentrated under a stream of nitrogen. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min). The resulting intermediate was dissolved in dichloromethane and trifluoroacetic acid was added. The mixture was stirred for approximately 30 min and then concentrated under a stream of nitrogen. The residue was dissolved in dichloromethane and stirred with MP-carbonate resin for approximately 30 minutes. The mixture was filtered and washed with dichloromethane followed by methanol. The filtrate was concentrated under a stream of nitrogen to afford the title compound as a solid (15 mg, 17%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.833 min., *m/z* 509 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.98 - 1.20 (m, 4 H), 1.49 - 1.65 (m, 2 H), 1.67 - 1.82 (m, 2 H), 1.94 (s, 3 H), 2.06 - 2.14 (m, 2 H), 2.17 (s, 3 H), 2.49 - 2.56 (m, 2 H), 2.60 (s, 3 H), 4.43 (d, *J*=6.6, Hz, 2 H), 4.59 (d, *J*=6.6 Hz, 2 H), 6.95 - 7.07 (m, 1 H), 7.10 - 7.19 (m), 7.21 (m, 1 H), 7.70 (m, 1 H), 7.96 (s, 1 H), 8.34 (s, 1 H), 9.08 - 9.18 (m, 1 H).

Example 189

***N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

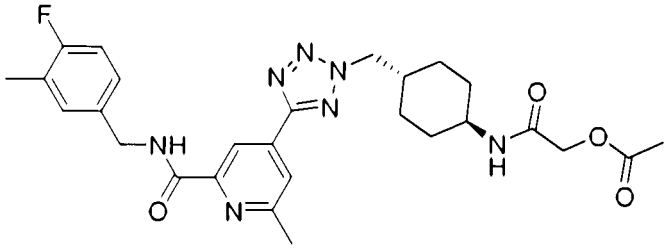


The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 188) by reaction with 2-methoxyacetic acid to afford 42.2 mg (48%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min, 95% CH_3CN, 1.5 min.): 3.356 min., *m/z* 510 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.39 (m, 4 H), 1.51 - 1.81 (m, 4 H), 1.83 - 2.07 (m, 2 H), 2.19 (s, 3 H), 2.65 (s, 3 H),

3.43 - 3.63 (m, 2 H), 3.72 (s, 3 H), 4.45 (d, *J*=6.6 Hz, 2 H), 4.65 (d, *J*=7.3 Hz, 2 H), 6.96 - 7.10 (m, 1 H), 7.12 - 7.21 (m, 1 H), 7.20 - 7.29 (m, 1 H), 7.39 - 7.50 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.13 - 9.26 (m, 1 H).

Example 190

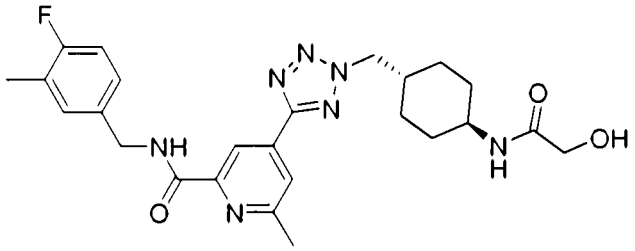
2-((*trans*)-4-((5-(2-((4-Fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate



The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 188) by reaction with 2-acetoxyacetic acid to afford 49.2 mg (54%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min, 95% CH_3CN, 1.5 min.): 3.353 min. 538 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.31 (m, 4 H), 1.49 - 1.84 (m, 4 H), 1.87 - 2.01 (m, 1 H), 2.03 (s, 3 H), 2.19 (s, 3 H), 2.65 (s, 3 H), 3.39 - 3.61 (m, 1 H), 4.36 (s, 2 H), 4.45 (d, *J*=5.9 Hz, 2 H), 4.65 (d, *J*=7.3 Hz, 2 H), 6.96 - 7.10 (m, 1 H), 7.12 - 7.21 (m, 1 H), 7.21 - 7.28 (m, 1 H), 7.71 - 7.84 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.16 - 9.25 (m, 1 H).

Example 191

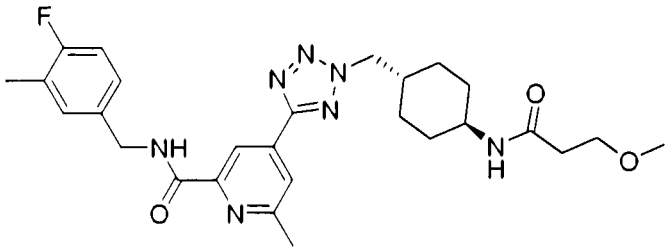
***N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 188) by reaction with 2-hydroxyacetic acid to afford 37.5 mg (44%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.080 min., *m/z* 496 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.42 (m, 4 H), 1.50 - 1.83 (m, 4 H), 1.85 - 2.07 (m, 1 H), 2.19 (s, 3 H), 2.65 (s, 3 H), 3.41 - 3.64 (m, 1 H), 3.73 (s, 2 H), 4.45 (d, *J*=6.6 Hz, 2 H), 4.65 (d, *J*=7.3 Hz, 2 H), 6.97 - 7.11 (m, 1 H), 7.13 - 7.21 (m, 1 H), 7.21 - 7.27 (m, 1 H), 7.32 - 7.43 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.13 - 9.26 (m, 1 H).

Example 192

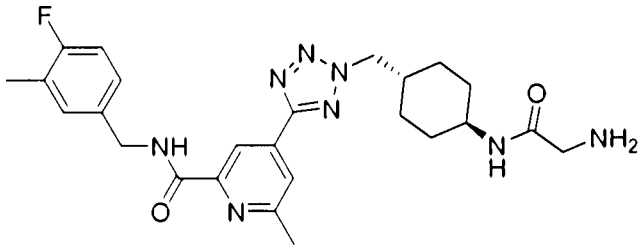
***N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 188) by reaction with 3-methoxypropanoic acid to afford 39.7 mg (44%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.298 min., *m/z* 524 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.22 (m, 4 H), 1.52 - 1.82 (m, 4 H), 1.87 - 2.03 (m, 1 H), 2.19 (s, 3 H), 2.23 (t, *J*=6.6 Hz, 2 H), 2.65 (br. s., 6 H), 3.35 - 3.54 (m, 3 H), 4.45 (d, *J*=6.6 Hz, 2 H), 4.64 (d, *J*=7.3 Hz, 2 H), 6.96 - 7.09 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.20 - 7.27 (m, 1 H), 7.55 - 7.75 (m, 1 H), 7.97 - 8.09 (m, 1 H), 8.35 - 8.46 (m, 1 H), 9.15 - 9.27 (m, 1 H).

Example 193

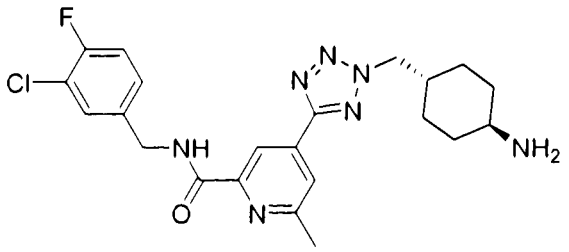
N-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(2-aminoacetamido)cyclohexyl)methyl)-2H-tetrazol-5-yl)-6-methylpicolinamide



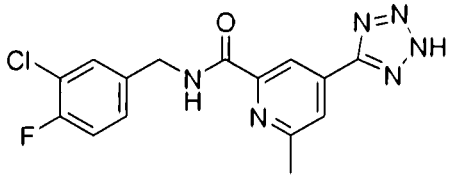
The title compound was prepared in a similar manner to *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 188) by reaction with 2-(tert-butoxycarbonyl)acetic acid to afford 33.7 mg (40%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.790 min., *m/z* 495 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 - 1.28 (m, 4 H), 1.52 - 1.83 (m, 4 H), 1.89 - 2.04 (m, 1 H), 2.19 (s, 3 H), 2.65 (s, 3 H), 3.01 (s, 2 H), 3.38 - 3.57 (m, 1 H), 4.45 (d, *J*=5.9 Hz, 1 H), 4.65 (d, *J*=7.3 Hz, 1 H), 7.00 - 7.09 (m, 1 H), 7.11 - 7.19 (m, 1 H), 7.21 - 7.28 (m, 1 H), 7.51 - 7.62 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.17 - 9.26 (m, 1 H).

Example 194

***N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

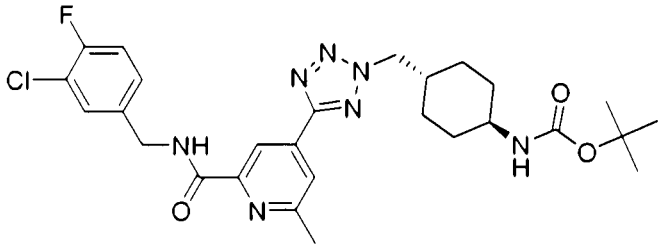


Step 1: Preparation of *N*-(3-chloro-4-fluorobenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide



4-Fluoro-3-chlorobenzylamine (3.52 g) was added to a solution of methyl 6-methyl-4-(2H-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (2.20 g) in *N*,*N*-dimethylacetamide (4 mL). The mixture was heated to 90 °C for 2 hours. The reaction mixture was allowed to cool, treated with water and filtered. The solids were triturated with methanol (50 mL) overnight to afford the title compound as an off-white solid (2.00 g, 47%). MS(ES+) *m/z* 347 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.66 (s, 3 H), 4.49 (d, *J*=6.4 Hz, 2 H), 7.30 - 7.39 (m, 1 H), 7.53 (d, *J*=7.8 Hz, 1 H), 8.07 (d, *J*=1.1 Hz, 1 H), 8.44 (s, 1 H), 9.40 (t, *J*=6.4 Hz, 1 H). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -119.66 (q).

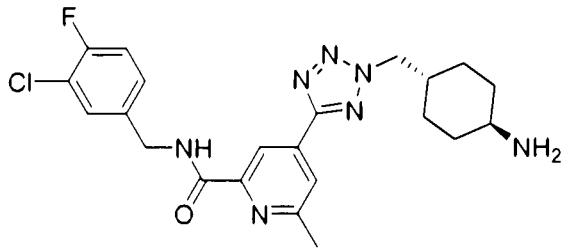
Step 2: Preparation of tert-butyl (*trans*)-4-((5-(2-((3-chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate.



tert-Butyl-trans-(4-hydroxymethyl)cyclohexylcarbamate (1.46 g), polymer supported triphenylphosphine (Argonaut, 2.15 mmol/g, 6.17 g), and anhydrous tetrahydrofuran (55 mL) were added to *N*-(3-chloro-4-fluorobenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (1.84 g). The stirred mixture was cooled in an ice-water bath and treated with di-tert-butyl azodicarboxylate (2.45 g). After 30 min, the ice bath was removed and the mixture allowed to stir overnight at room temperature. The mixture was concentrated in vacuo and the residue was purified by silica column chromatography (40% ethyl acetate/hexanes) to afford the title compound as a yellow, crystalline solid (0.83 g, 28%). MS(ES+) *m/z* 558 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.02 - 1.29 (m, 4 H), 1.42 (s, 9 H), 1.71 (d, *J*=12.6 Hz, 2 H), 2.00 - 2.14 (m, 3 H), 2.62 - 2.68 (m, 3 H), 3.31 - 3.50 (m, 1 H), 4.34 - 4.45 (m, 1 H), 4.52 (d, *J*=7.3 Hz, 2 H), 4.63 (d, *J*=6.4 Hz, 2 H), 7.10 (t, *J*=8.6 Hz, 1 H), 7.21 - 7.29 (m, 1 H), 7.42

(dd, *J*=7.0, 2.2 Hz, 1 H), 8.06 (d, *J*=1.1 Hz, 1 H), 8.51 (t, *J*=6.2 Hz, 1 H), 8.71 (d, *J*=1.1 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -117.85 (br s).

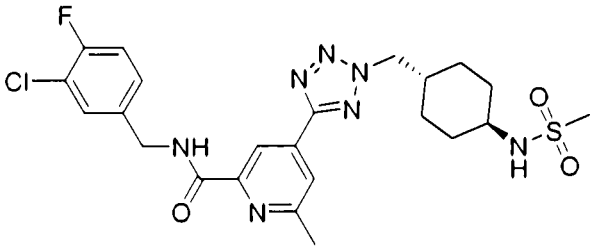
Step 3: Preparation of *N*-(3-chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Trifluoroacetic acid (5 mL) was added to a solution of tert-butyl (*trans*)-4-((5-(2-((3-chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2H-tetrazol-2-yl)methyl)cyclohexylcarbamate (199.8 mg, 0.358 mmol) in dichloromethane (5 mL), and the mixture was stirred for 30 min at room temperature. The reaction mixture was concentrated under a stream of nitrogen. The residue was dissolved in dichloromethane and neutralized for approximately 30 min with MP-carbonate resin. The mixture was filtered and washed with dichloromethane and methanol. The filtrate was concentrated under a stream of nitrogen for a quantitative yield. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.687 min., *m/z* 458 (M+H).

Example 195

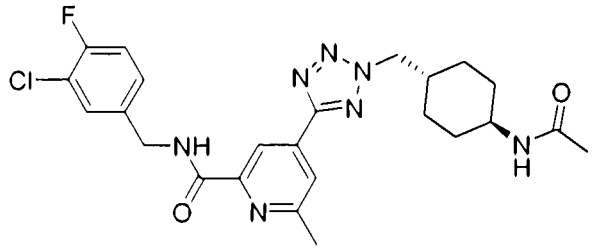
***N*-(3-Chloro-4-fluorobenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



Triethylamine (0.068 mL, 0.492 mmol) and methane sulfonyl chloride (0.019 mL, 0.246 mmol) were added to a solution of *N*-(3-chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 194) (75.1 mg, 0.164 mmol) in tetrahydrofuran (5 mL), and the mixture was stirred for 30 min at room temperature. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (45.6 mg, 52%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.384 min., *m/z* 536 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.98 - 1.31 (m, 4 H), 1.53 - 1.67 (m, 2 H), 1.78 - 2.03 (m, 3 H), 2.66 (s, 3 H), 2.85 (s, 3 H), 2.95 - 3.12 (m, 1 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.64 (d, *J*=6.6 Hz, 2 H), 6.86 - 6.96 (m, 1 H), 7.26 - 7.39 (m, 2 H), 7.49 - 7.56 (m, 1 H), 8.02 - 8.10 (m, 1 H), 8.36 - 8.42 (m, 1 H), 9.29 - 9.38 (m, 1 H).

Example 196

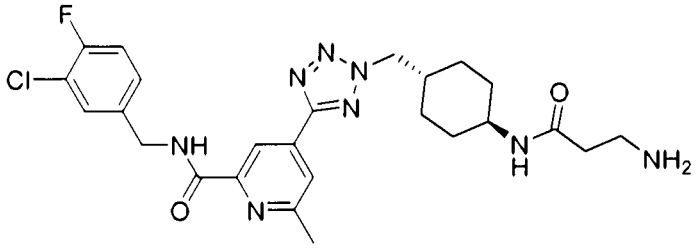
***N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Acetic anhydride (0.037 mL, 0.393 mmol) and 4-(dimethylamino)pyridine Si bound (949.0 mg, 0.655 mmol, 0.69 mmol/g loading) were added to a solution of *N*-(3-chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 194) (60.0 mg, 0.131 mmol) in dichloromethane (2 mL), and the mixture was agitated overnight at room temperature. The reaction mixture was filtered and washed with *N*,*N*-dimethylformamide. The filtrate was concentrated under a stream of nitrogen and purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (23 mg, 35%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 4.93 min., *m/z* 500 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.94 - 1.27 (m), 1.54 - 1.83 (m), 1.89 - 2.04 (m, 1 H), 2.66 (s, 3 H), 3.28 (s), 3.35 - 3.52 (m, 1 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.64 (d, *J*=7.3 Hz, 2 H), 7.26 - 7.38 (m, 2 H), 7.46 - 7.57 (m, 1 H), 7.59 - 7.67 (m, 1 H), 8.06 (s, 1 H), 8.40 (s, 1 H), 9.30 - 9.39 (m, 1 H).

Example 197

***N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

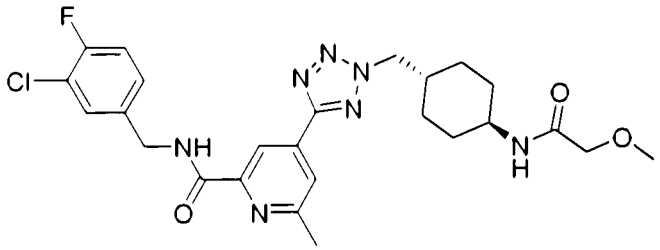


O-(7-Azabenzotriazole-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (65.0 mg, 0.170 mmol), 3-(tert-butoxycarbonyl)propanoic acid (26.9 mg, 0.142 mmol), and diisopropylethylamine (0.049 mL, 0.284 mmol) were added to a solution of *N*-(3-chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 194) (65.0 mg, 0.142 mmol) in *N*,*N*-dimethylformamide (2 mL), and the mixture was overnight at room temperature. The reaction mixture was concentrated, treated with trifluoroacetic acid, and purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (24.0 mg, 32%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 3.86 min., *m/z* 529 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.23 (m, 4 H), 1.53 - 1.81 (m, 4 H), 1.90 - 2.03 (m, 1 H), 2.10 (t, *J*=6.6 Hz, 2 H), 2.66 (s, 3 H), 2.69 (t, *J*=6.6 Hz, 2 H), 3.28 (br. s.), 3.40 - 3.53 (m, 1 H), 4.49 (d, *J*=5.9 Hz, 2

H), 4.65 (d, *J*=6.6 Hz, 2 H), 7.23 - 7.38 (m, 2 H), 7.48 - 7.57 (m, 1 H), 7.66 - 7.75 (m, 1 H), 8.06 (s, 1 H), 8.40 (s, 1 H), 9.30 - 9.39 (m, 1 H).

Example 198

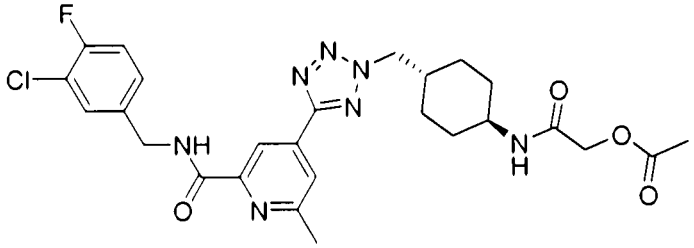
N-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound was prepared in a similar manner to *N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 197) by reaction with 2-methoxyacetic acid to afford 35 mg (46%) as a solid. LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 5.13 min., *m/z* 530 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.34 (m, 4 H), 1.54 - 1.78 (m, 4 H), 1.86 - 2.05 (m, 1 H), 2.66 (s), 3.23 - 3.33 (m), 3.45 - 3.62 (m, 1 H), 3.72 (s, 3 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.65 (d, *J*=7.3 Hz, 2 H), 7.29 - 7.39 (m, 2 H), 7.43 - 7.49 (m, 1 H), 7.50 - 7.58 (m, 1 H), 8.06 (s, 1 H), 8.40 (s, 1 H), 9.30 - 9.37 (m, 1 H).

Example 199

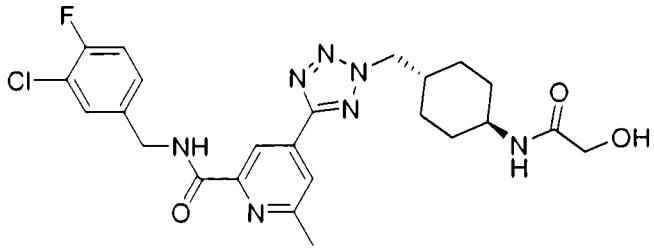
2-(((*trans*)-4-((5-(2-((3-Chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate



The title compound was prepared in a similar manner to *N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 197) by reaction with 2-acetoxyacetic acid to afford 31.2 mg (39%) as a solid. LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 5.06 min., *m/z* 558 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.29 (m, 4 H), 1.55 - 1.84 (m, 4 H), 1.89 - 2.01 (m, 1 H), 2.04 (s, 3 H), 2.66 (s, 3 H), 3.41 - 3.59 (m, 1 H), 4.36 (s, 2 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.65 (d, *J*=7.3 Hz, 2 H), 7.30 - 7.38 (m, 2 H), 7.50 - 7.55 (m, 1 H), 7.75 - 7.82 (m, 1 H), 8.06 (s, 1 H), 8.40 (s, 1 H), 9.30 - 9.38 (m, 1 H).

Example 200

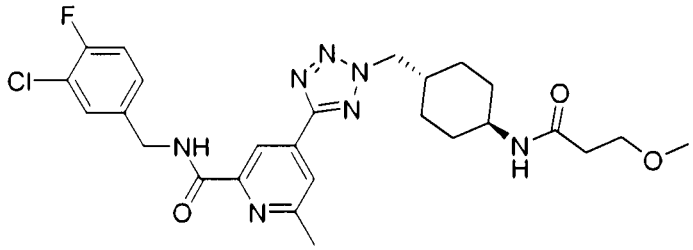
N-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound was prepared in a similar manner to *N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 197) by reaction with 2-hydroxyacetic acid to afford 48.2 mg (66%) as a solid. LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 4.74 min., *m/z* 516 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.35 (m, 4 H), 1.55 - 1.79 (m, 4 H), 1.88 - 2.03 (m, 1 H), 2.66 (s, 3 H), 3.28 (br. s.), 3.47 - 3.61 (m, 1 H), 3.73 (s, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.65 (d, *J*=6.6 Hz, 2 H), 7.24 - 7.44 (m, 3 H), 7.48 - 7.58 (m, 1 H), 8.06 (s, 1 H), 8.40 (s, 1 H), 9.27 - 9.41 (m, 1 H).

Example 201

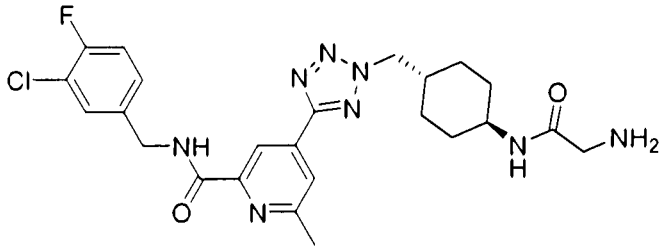
N-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound was prepared in a similar manner to *N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 197) by reaction with 3-methoxypropanoic acid to afford 49.1 mg (64%) as a solid. LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 5.01 min., *m/z* 544 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.01 - 1.25 (m, 4 H), 1.50 - 1.81 (m, 4 H), 1.86 - 2.05 (m, 1 H), 2.23 (t, *J*=6.6 Hz, 2 H), 2.66 (s, 3 H), 3.24 - 3.32 (m), 3.47 (t, *J*=6.2 Hz, 2 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.64 (d, *J*=6.6 Hz, 2 H), 7.29 - 7.39 (m, 2 H), 7.49 - 7.55 (m, 1 H), 7.60 - 7.68 (m, 1 H), 8.06 (s, 1 H), 8.40 (s, 1 H), 9.30 - 9.38 (m, 1 H).

Example 202

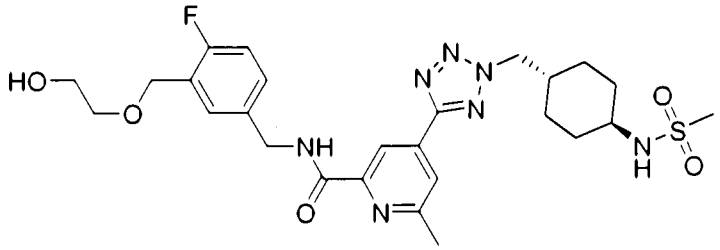
N-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound was prepared in a similar manner to *N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 197) by reaction with 2-(tert-butoxycarbonyl)acetic acid to afford 45.6 mg (62%) as a solid. LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 3.81 min., *m/z* 515 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 - 1.27 (m, 4 H), 1.50 - 1.84 (m, 4 H), 1.89 - 2.05 (m, 1 H), 2.66 (s, 3 H), 3.04 (s), 3.27 (br. s.), 3.41 - 3.57 (m, 1 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.65 (d, *J*=7.3 Hz, 2 H), 7.26 - 7.39 (m, 2 H), 7.50 - 7.55 (m, 1 H), 7.58 - 7.65 (m, 1 H), 8.06 (s, 1 H), 8.40 (s, 1 H), 9.30 - 9.38 (m, 1 H).

Example 203

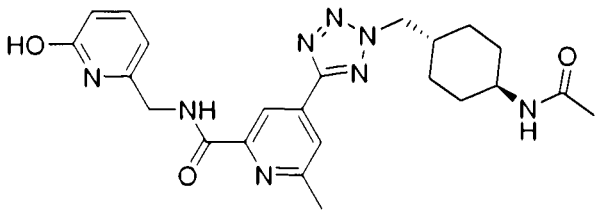
N-(4-Fluoro-3-((2-hydroxyethoxy)methyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)-cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



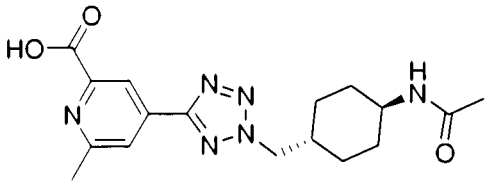
N-(4-Fluoro-3-(hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 181) (38 mg, 0.059 mmol), potassium carbonate (8.13 mg, 0.59 mmol), and ethanol (5 mL) were combined in a 20 mL scintillation vial with a magnetic stir bar and reflux for 2 hours. The reaction mixture was cooled in an ice bath and ethylene oxide (7.13 mg, 0.162 mmol) was added. The mixture was slowly warmed to room temperature and stirred for 36 hours. The reaction mixture was concentrated and purified by preparative reverse phase preparative HPLC to afford the title compound as a white solid (30.8 mg, 76%). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.71 min., *m/z* 576 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.25 (t, *J*=6.22 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.44 (d, J=7.32 Hz, 1 H), 7.19 - 7.28 (m, J=6.59 Hz, 1 H), 7.06 (t, 1 H), 6.92 (d, J=7.32 Hz, 1 H), 5.20 (t, J=5.49 Hz, 1 H), 4.64 (d, J=6.59 Hz, 2 H), 4.50 (d, J=5.12 Hz, 3 H), 3.28 (d, J=5.12 Hz, 1 H), 2.97 - 3.11 (m, J=6.59 Hz, 1 H), 2.79 - 2.91 (m, 2 H), 2.65 (s, 2 H), 2.43 - 2.53 (m, 1 H), 1.75 (dd, J=111.63, 10.61 Hz, 4 H), 1.05 - 1.28 (m, 3 H).

Example 204

4-(2-(((*trans*)-4-Acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-((6-hydroxypyridin-2-yl)methyl)-6-methylpicolinamide

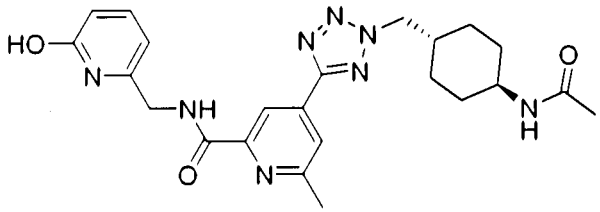


Step 1: Preparation of 4-(2-((4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid



Triethylamine (0.95 mL, 6.81 mmol) and acetic anhydride (0.52 mL, 5.45 mmol) were added to a solution of methyl 4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(3-hydroxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 168) (500 mg, 1.36 mmol) in dichloromethane (20 mL) and the mixture was stirred at room temperature for two days. The reaction mixture was filtered and washed with dichloromethane. The filtrate was concentrated and the residue was dissolved in a mixture of tetrahydrofuran/water (12 mL, 5/1). Lithium hydroxide (131 mg, 5.45 mmol) was added and the mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound as a white solid (165 mg, 34%). MS (ES+) *m/z* 359 (M+H).

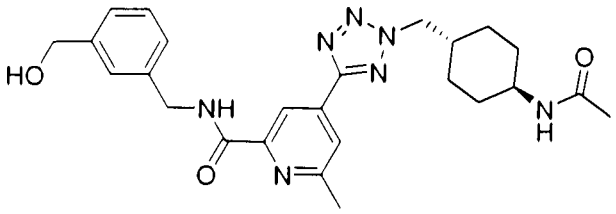
Step 2: Preparation 4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-((6-hydroxypyridin-2-yl)methyl)-6-methylpicolinamide



N,N,N',N'-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (254 mg, 0.67 mmol) was added to a mixture of 4-(2-((4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (160 mg, 0.446 mmol), 6-(aminomethyl)pyridin-2(1*H*)-one (Bronn, W. R. US 4,555,573, 1985) (191 mg, 0.67 mmol), and triethylamine (0.22 mL, 1.56 mmol) in *N,N*-dimethylformamide (2 mL). The mixture was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC to afford the title compound as a solid (106 mg, 51%). MS (ES+) *m/z* 465 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.21, (m, 4 H), 1.58 (s, *J*=9.52 Hz, 2 H), 1.67 - 1.81 (m, 5 H), 1.87 - 2.00 (m, 2 H), 2.66 (s, 3 H), 3.36 - 3.48 (m, 1 H), 4.33 (d, *J*=5.86 Hz, 2 H), 4.63 (d, *J*=7.32 Hz, 2 H), 5.98 - 6.10 (m, 1 H), 6.17 (d, *J*=9.52 Hz, 1 H), 7.24 - 7.37 (m, 1 H), 7.61 (d, *J*=8.05 Hz, 1 H), 8.07 (s, 1 H), 8.38 (s, 1 H), 9.24 (t, *J*=6.95 Hz, 1 H).

Example 205

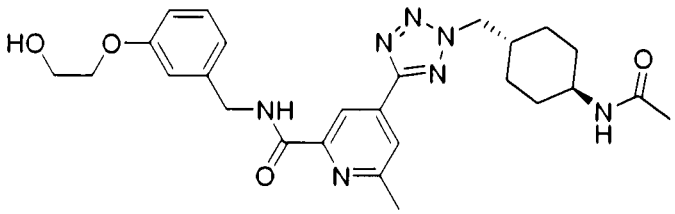
***N*-(3-(Hydroxymethyl)benzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



N,N,N',N'-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (159 mg, 0.42 mmol) was added to a mixture of 4-(2-((4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 1 of the synthesis of 4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-((6-hydroxypyridin-2-yl)methyl)-6-methylpicolinamide, Example 204) (50 mg, 0.14 mmol), (3-(aminomethyl)phenyl)methanol (prepared as described in step 1 of the synthesis of *N*-(3-(hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide, Example 183) (29 mg, 0.21 mmol), and triethylamine (0.03 mL, 0.21 mmol) in *N,N*-dimethylformamide (2 mL). The mixture was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC. Fractions containing desired product were combined and concentrated. The resulting residue was taken up in methanol and passed through a carbonate cartridge. The filtrate was concentrated to afford the title compound as a solid (22 mg, 33%). MS (ES+) *m/z* 478 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.26 (m, 6 H), 1.56 - 1.67 (m, 2 H), 1.71 - 1.85 (m, 5 H), 1.91 - 2.03 (m, 1 H), 2.67 (s, 3 H), 3.25 - 3.35 (m, 1 H), 4.48 (s, 2 H), 4.54 (d, *J*=6.59 Hz, 2 H), 4.67 (d, *J*=7.32 Hz, 2 H), 7.14 - 7.34 (m, 3 H), 7.66 (d, *J*=7.32 Hz, 1 H), 8.08 (s, 1 H), 8.44 (s, 1 H), 9.22 (t, *J*=5.86 Hz, 1 H).

Example 206

***N*-(3-(2-Hydroxyethoxy)benzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

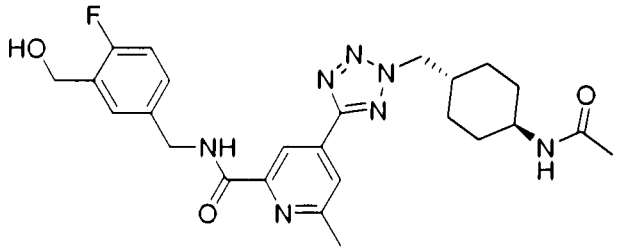


N,N,N',N'-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (159 mg, 0.42 mmol) was added to a mixture of 4-(2-((4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 1 of the synthesis of 4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-((6-hydroxypyridin-2-yl)methyl)-6-methylpicolinamide, Example 204) (50 mg, 0.14 mmol), 2-(3-(aminomethyl)phenoxy)ethanol (prepared as described in step 2 of the synthesis of *N*-(3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 13) (35 mg, 0.21 mmol), and triethylamine

(0.03 mL, 0.21 mmol) in *N*,*N*-dimethylformamide (2 mL). The mixture was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC. Fractions containing desired product were combined and concentrated. The resulting residue was taken up in methanol and passed through a carbonate cartridge. The filtrate was concentrated to afford the title compound as a solid (26 mg, 37%). MS (ES+) *m/z* 508 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.24 (m, 5 H), 1.58 - 1.68 (m, 2 H), 1.72 - 1.84 (m, 5 H), 1.92 - 2.05 (m, 2 H), 2.68 (s, 3 H), 3.69 (t, *J*=5.12 Hz, 2 H), 3.96 (t, *J*=5.12 Hz, 2 H), 4.51 (d, *J*=5.86 Hz, 2 H), 4.67 (d, *J*=7.32 Hz, 2 H), 6.82 (d, *J*=7.32 Hz, 1 H), 6.88 - 6.96 (m, 1 H), 7.23 (t, *J*=8.05 Hz, 1 H), 7.66 (d, *J*=7.32 Hz, 1 H), 8.08 (s, 1 H), 8.43 (s, 1 H), 9.22 (t, *J*=6.59 Hz, 1 H).

Example 207

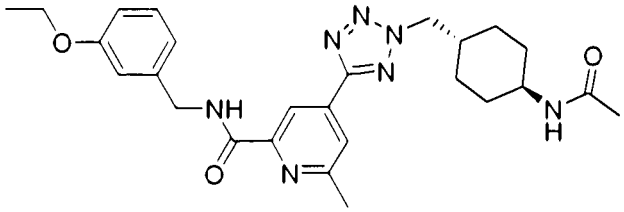
***N*-(4-Fluoro-3-(hydroxymethyl)benzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



N,*N*,*N*',*N*'-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (476 mg, 1.26 mmol) was added to a mixture of 4-(2-((4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 1 of the synthesis of 4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-((6-hydroxypyridin-2-yl)methyl)-6-methylpicolinamide, Example 204) (150 mg, 0.42 mmol), (5-(aminomethyl)-2-fluorophenyl)methanol (prepared as described in step 1 of the synthesis of *N*-(4-fluoro-3-(hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide, Example 181) (120 mg, 0.63 mmol), and triethylamine (0.15 mL, 1.05 mmol) in *N*,*N*-dimethylformamide (6 mL). The mixture was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC. Fractions containing desired product were combined and concentrated. The resulting residue was taken up in methanol and passed through a carbonate cartridge. The filtrate was concentrated to afford the title compound as a solid (112 mg, 54%). MS (ES+) *m/z* 496 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.27 (m, 4 H), 1.55 - 1.68 (m, Hz, 2 H), 1.71 - 1.84 (m, 5 H), 1.91 - 2.06 (m, 2 H), 2.67 (s, 3 H), 3.82 (s, 3 H), 4.51 (d, *J*=5.86 Hz, 2 H), 4.67 (d, *J*=7.32 Hz, 2 H), 6.82 - 6.96 (m, 1 H), 7.05 - 7.26 (m, 2 H), 7.65 (d, *J*=7.32 Hz, 1 H), 8.07 (s, 1 H), 8.43 (s, 1 H), 9.24 (t, *J*=6.22 Hz, 1 H).

Example 208

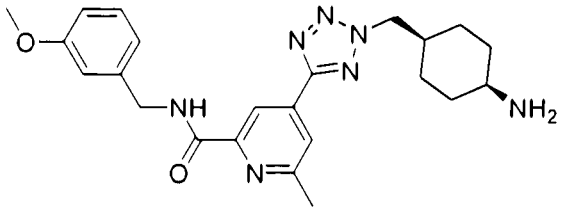
***N*-(3-Ethoxybenzyl)-4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



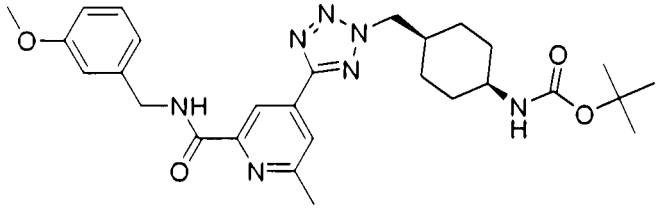
N,N,N',N'-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (159 mg, 0.42 mmol) was added to a mixture of 4-(2-((4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 1 of the synthesis of 4-(2-(((*trans*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-((6-hydroxypyridin-2-yl)methyl)-6-methylpicolinamide, Example 204) (50 mg, 0.14 mmol), (3-ethoxyphenyl)methanamine (prepared as described in step 2 of the synthesis of *N*-(3-ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide, Example 180) (31 mg, 0.21 mmol), and triethylamine (0.03 mL, 0.21 mmol) in *N,N*-dimethylformamide (2 mL). The mixture was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC. Fractions containing desired product were combined and concentrated. The resulting residue was taken up in methanol and passed through a carbonate cartridge. The filtrate was concentrated to afford the title compound as a solid (39 mg, 57%). MS (ES+) *m/z* 492 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 - 1.25 (m, 4 H), 1.30 (t, *J*=6.95 Hz, 3 H), 1.53-1.68(m, 2H), 1.72 - 1.85 (m, 5 H), 1.98 (m, 2 H), 2.68 (s, 3 H), 4.00 (q, *J*=6.83 Hz, 2 H), 4.50 (d, *J*=6.59 Hz, 2 H), 4.67 (d, *J*=6.59 Hz, 2 H), 6.77 - 6.83 (m, 1 H), 6.87 - 6.94 (m, 2 H), 7.17 - 7.26 (m, 8.05 Hz, 1 H), 7.60 - 7.70 (m, 1 H), 8.08 (s, 1 H), 8.43 (s, 1 H), 9.21 (t, *J*=6.22 Hz, 1 H).

Example 209

N-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



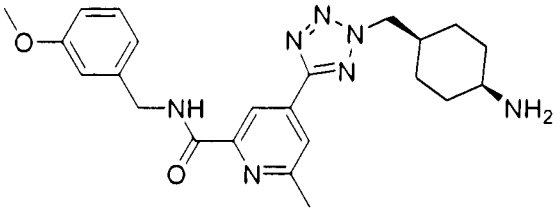
Step 1: Preparation of tert-butyl (*cis*)-4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate



A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (1.0 g, 3.08 mmol), tert-butyl *cis*-(4-

hydroxymethyl)cyclohexyl carbamate (1.41 g, 6.17 mmol), and polymer supported-triphenylphosphine (3.580 g, 7.07 mmol) in anhydrous tetrahydrofuran (60 mL) was cooled to 0 °C in an ice bath and then di-tert-butyl azodicarboxylate (1.42 g, 3.08 mmol) was added. The reaction was allowed to warm to room temperature while stirring over 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O) to afford the title compound.

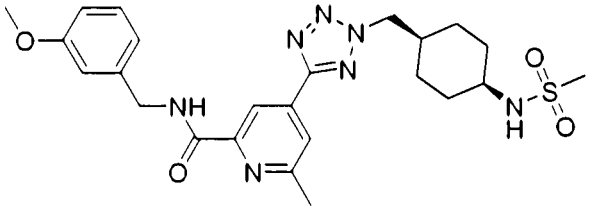
Step 2: Preparation of *N*-(3-methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Trifluoroacetic acid was added to a solution of tert-butyl (*cis*)-4-((5-(2-((3-methoxybenzyl)-carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate in dichloromethane and the mixture was allowed to stir for 30 min at room temperature. The reaction mixture was concentrated. The residue was dissolved in dichloromethane and MP-carbonate resin was added. The mixture was agitated for 1 h, filtered, and washed with dichloromethane and methanol. The filtrate was concentrated to afford the title compound as a solid (1.091 g, 81%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.479 min., *m/z* 436 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 - 1.86 (m, 8 H), 2.17 - 2.31 (m, 1 H), 2.65 (s, 3 H), 3.18 - 3.28 (m, 1 H), 3.70 (s, 3 H), 4.48 (d, *J*=6.4 Hz, 2 H), 4.72 (d, *J*=7.3 Hz, 2 H), 6.76 - 6.84 (m, 1 H), 6.85 - 6.93 (m, 2 H), 7.17 - 7.27 (m, 1 H), 7.93 (br. s., 2 H), 8.03 - 8.09 (m, 1 H), 8.41 (s, 1 H), 9.19 - 9.28 (m, 1 H).

Example 210

N-(3-Methoxybenzyl)-6-methyl-4-(2-(((*cis*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide

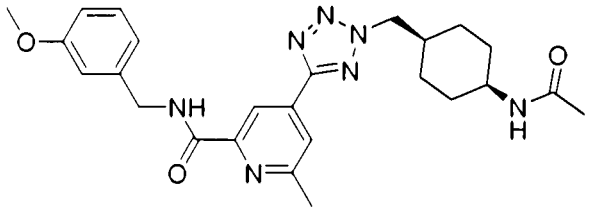


Triethylamine (0.048 mL, 0.345 mmol) and methane sulfonyl chloride (0.013 mL, 0.173 mmol) were added to a solution of *N*-(3-methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in (Example 209) (50.1 mg, 0.115 mmol) in tetrahydrofuran (1.5 mL) and the mixture was stirred 2 hours at room temperature. The reaction mixture was concentrated and purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O) to afford the title compound as a solid (33.7 mg, 57%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.188 min., *m/z* 514 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 - 1.79 (m), 1.99 - 2.22 (m), 2.65 (s, 3 H), 2.87 (s, 3 H), 3.36 - 3.48 (m), 3.71 (s, 3 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.67

(d, *J*=6.6 Hz, 2 H), 6.73 - 6.84 (m, 1 H), 6.84 - 6.97 (m, 3 H), 7.13 - 7.28 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.12 - 9.25 (m, 1 H).

Example 211

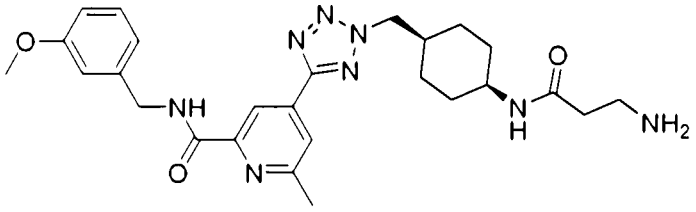
***N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Acetic anhydride (0.033 mL, 0.345 mmol) and 4-(dimethylamino)pyridine Si bound (833.0 mg, 0.575 mmol, 0.69 mmol/g loading) were added to a solution of *N*-(3-methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 209) (50.0 mg, 0.115 mmol) in dichloromethane (2 mL) and the mixture was agitated overnight at room temperature. The reaction mixture was filtered, washed with *N*,*N*-dimethylformamide, and concentrated. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O) to afford the title compound as a solid (27.1 mg, 49%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 4.64 min., *m/z* 478 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 - 1.66 (m), 1.80 (s, 3 H), 2.07 - 2.21 (m, 1 H), 2.62 - 2.69 (m, 3 H), 3.23 - 3.31 (m), 3.71 (s, 3 H), 3.74 - 3.82 (m, 1 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.68 (d, *J*=7.3 Hz, 2 H), 6.76 - 6.82 (m, 1 H), 6.86 - 6.94 (m, 2 H), 7.17 - 7.25 (m, 1 H), 7.60 - 7.68 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.14 - 9.23 (m, 1 H).

Example 212

***N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

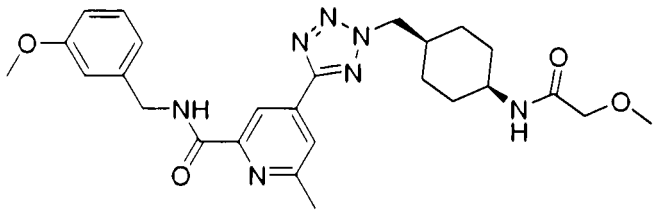


O-(7-Azabenzotriazole-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (52.0 mg, 0.138 mmol), 3-(tert-butoxycarbonyl)propanoic acid (21.6 mg, 0.115 mmol), and diisopropylethylamine (0.040 mL, 0.230 mmol) were added to a solution of *N*-(3-methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 209) (50.1 mg, 0.115 mmol) in *N*,*N*-dimethylformamide (2 mL) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated, treated with trifluoroacetic acid, and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O) to afford the title compound as a solid (16.3 mg, 28%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.665 min., *m/z* 507 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 - 1.69 (m), 2.14 (t, *J*=6.6 Hz, 2

H), 2.18 - 2.27 (m, 1 H), 2.65 (s, 3 H), 2.70 (t, *J*=6.6 Hz, 2 H), 3.71 (s, 3 H), 3.80 (br. s), 4.49 (d, *J*=6.6 Hz, 2 H), 4.68 (d, *J*=7.3 Hz, 2 H), 6.74 - 6.82 (m, 1 H), 6.84 - 6.93 (m, 2 H), 7.14 - 7.25 (m, 1 H), 7.80 - 7.87 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.13 - 9.23 (m, 1 H).

Example 213

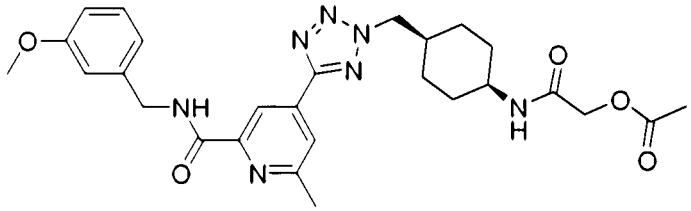
N-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*cis*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 212) by reaction with 2-methoxyacetic acid and afforded 26.8 mg (46%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.151 min., *m/z* 508 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.22 - 1.75 (m), 2.13 - 2.28 (m), 2.52 (s), 2.65 (s, 3 H), 3.71 (s, 3 H), 3.77 (s), 3.78 - 3.86 (m), 4.49 (d, *J*=6.6 Hz, 2 H), 4.76 (d, *J*=7.3 Hz, 2 H), 6.75 - 6.83 (m, 1 H), 6.86 - 6.94 (m, 2 H), 7.17 - 7.25 (m, 1 H), 7.38 - 7.45 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.15 - 9.24 (m, 1 H).

Example 214

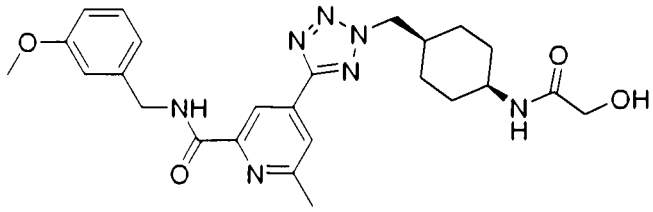
2-((*cis*)-4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-cyclohexylamino)-2-oxoethyl acetate



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*cis*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 212) by reaction with 2-acetoxyacetic acid and afforded 20.9 mg (34%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.163 min., *m/z* 536 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 - 1.71 (m), 2.04 (s, 3 H), 2.11 - 2.26 (m, 1 H), 2.65 (s, 3 H), 3.71 (s, 3 H), 3.74 - 3.84 (m, 1 H), 4.43 (s, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.70 (d, *J*=7.3 Hz, 2 H), 6.74 - 6.83 (m, 1 H), 6.85 - 6.98 (m, 2 H), 7.15 - 7.27 (m, 1 H), 7.70 - 7.82 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.12 - 9.24 (m, 1 H).

Example 215

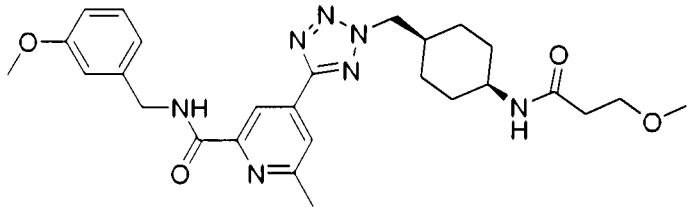
N-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*cis*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 212) by reaction with 2-hydroxyacetic acid and afforded 27.4 mg (48%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.897 min., *m/z* 494 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 - 1.76 (m), 2.14 - 2.29 (m), 2.65 (s, 3 H), 3.71 (s, 3 H), 3.78 (s), 3.80 - 3.90 (m, 1 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.76 (d, *J*=7.3 Hz, 2 H), 6.74 - 6.84 (m, 1 H), 6.84 - 6.97 (m, 2 H), 7.16 - 7.28 (m, 1 H), 7.34 - 7.46 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.12 - 9.25 (m, 1 H).

Example 216

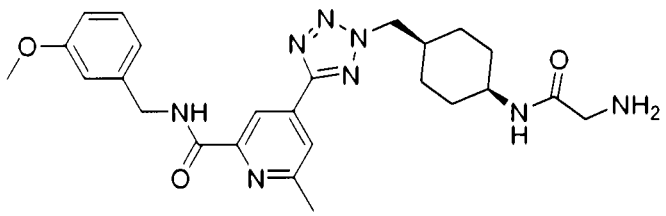
N-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*cis*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 212) by reaction with 3-methoxypropanoic acid and afforded 23.7 mg (40%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.111 min., *m/z* 522 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 - 1.71 (m), 2.06 - 2.21 (m, 1 H), 2.31 (t, *J*=6.2 Hz, 2 H), 2.65 (s), 3.49 (t, *J*=6.6 Hz, 2 H), 3.71 (s), 3.75 - 3.83 (m, 1 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.68 (d, *J*=7.3 Hz, 2 H), 6.74 - 6.84 (m, 1 H), 6.84 - 6.96 (m, 2 H), 7.13 - 7.30 (m, 1 H), 7.56 - 7.68 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.12 - 9.25 (m, 1 H).

Example 217

N-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

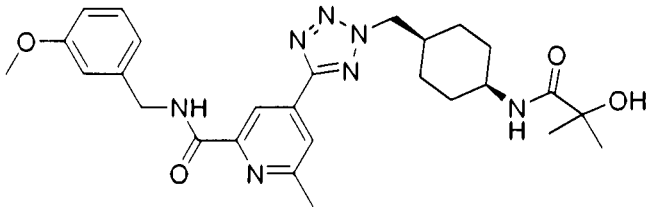


The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*cis*)-4-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 212) by

reaction with 2-(tert-butoxycarbonyl)acetic acid and afforded 13.6 mg (24%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.628 min., *m/z* 493 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.19 - 1.73 (m), 2.10 - 2.25 (m, 1 H), 2.60 - 2.66 (m), 2.65 (s, 3 H), 3.05 (s), 3.28 (s), 3.71 (s, 3 H), 3.76 - 3.88 (m, 1 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.72 (d, *J*=7.3 Hz, 2 H), 6.73 - 6.84 (m, 1 H), 6.85 - 6.95 (m, 2 H), 7.14 - 7.26 (m, 1 H), 7.62 - 7.70 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.13 - 9.23 (m, 1 H).

Example 218

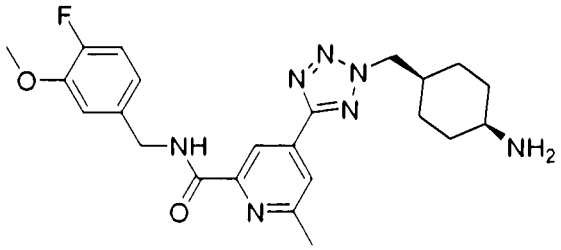
***N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



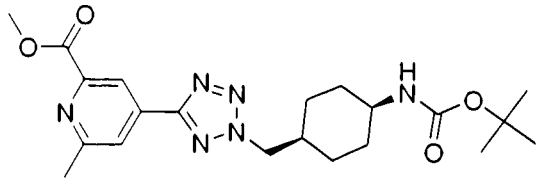
A mixture of 2-hydroxy isobutyric acid (19 mg, 0.19 mmol) and 1-hydroxybenzatriazole (25 mg, 0.19 mmol) in 2- methyl tetrahydrofuran (2 mL) was stirred for 5 minutes. *N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 209) (0.085 g, 0.15 mmol), triethylamine (0.026 mL, 0.19 mmol),and polymer supported carbodiimide (0.18 g, 0.23 mmol) were then added. The mixture was allowed to stir for 18 hours at room temperature and then filtered. The filtrate was washed with water (3 x 5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound (20 mg, 25%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.6 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.29 (d, *J*=8.05 Hz, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, *J*=8.1 Hz, 1 H), 5.35 (s, 1 H), 4.77 (d, *J*=7.3 Hz, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 3.71 (s, 3 H), 2.65 (s, 3 H), 2.17 - 2.30 (m, 1 H), 1.61 - 1.74 (m, 2 H), 1.42 - 1.55 (m, 4 H), 1.30 - 1.41 (m, 2 H), 1.22 (s, 6 H).

Example 219

***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

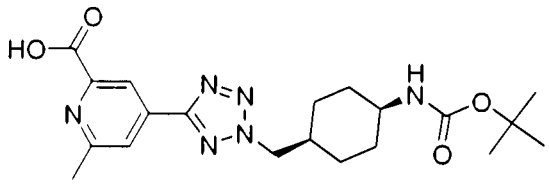


Step 1: Preparation of methyl 4-(2-(((*cis*)-4-(tert-butoxycarbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate



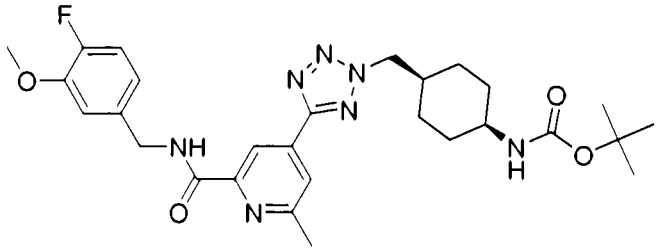
A mixture of methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (0.23 g, 1.1 mmol), tert-butyl *cis*-(4-hydroxymethyl)cyclohexyl carbamate (0.24 g, 1.1 mmol), and polymer supported-triphenylphosphine (0.70 g, 1.6 mmol) in anhydrous tetrahydrofuran (15 mL) was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (0.29 g, 1.3 mmol) was added. The reaction was allowed to warm to room temperature while stirring over 15 hours. The reaction mixture was filtered and the filtrate was concentrated to afford the title compound.

Step 2: Preparation of 4-(2-(((*cis*)-4-(tert-butoxycarbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid



An aqueous solution of sodium hydroxide (2.5 N, 1.0 mL) was added to a mixture of 4-(2-(((*cis*)-4-(tert-butoxycarbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate in acetonitrile (3 mL), and the mixture was stirred 2 hours. The acetonitrile was removed in vacuo and the aqueous residue was acidified to pH 6 with a 10% aqueous solution of hydrochloric acid. This mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with water (2 x 5mL) followed by brine (5 mL), dried over sodium sulfate, and concentrated to afford the title compound.

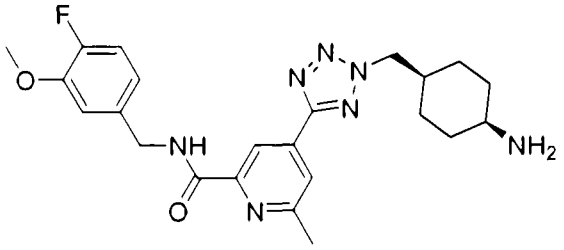
Step 3: Preparation of tert-butyl (*cis*)-4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate



A mixture of 4-(2-(((*cis*)-4-(tert-butoxycarbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid and 1-hydroxybenzatriazole (97 mg, 0.72 mmol) in *N*,*N*-dimethylformamide (2 mL) was stirred for 5 minutes. 4-Fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-

tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (0.13g, 0.66 mmol), triethylamine (0.10 mL, 0.72 mmol), and polymer supported carbodiimide (0.88 g, 0.98 mmol) were added. The mixture was stirred for 18 hours at room temperature and then was filtered. The filtrate was washed with water (3 x 5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica column chromatography (0-50%, ethyl acetate/heptane) to afford the title compound as a beige oil.

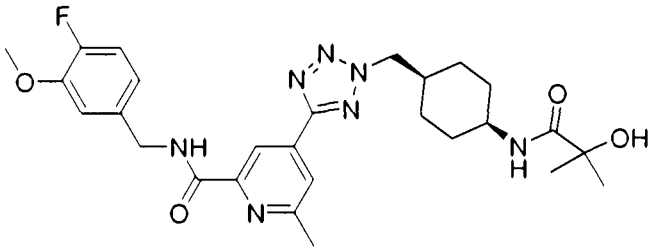
Step 4: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Trifluoroacetic acid (1.0 mL) was added to a solution of tert-butyl (*cis*)-4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate in dichloromethane (5 mL), and the mixture was stirred for 3 hours at room temperature. The reaction mixture was concentrated and then triturated with diethyl ether to afford the title compound as a trifluoroacetate salt (0.12 g). LC/MS (5-100% CH_3CN/H_2O, 6 min) 5.33 min, *m/z* 454 (M+H).

Example 220

N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxy-2-methylpropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

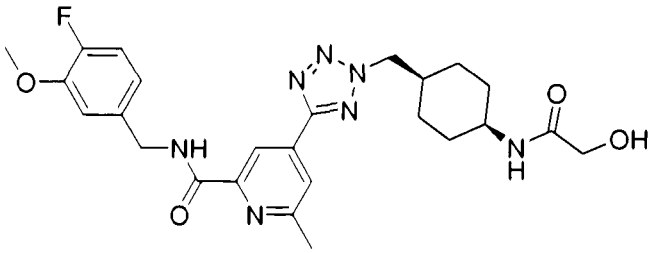


A mixture of 2-hydroxy isobutyric acid (10 mg, 0.09 mmol) and 1-hydroxybenzatriazole (11 mg, 0.08 mmol) in 2- methyl tetrahydrofuran (2 mL) was stirred for 5 minutes. *N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 219) (0.040 g, 0.07 mmol), triethylamine (0.012 mL, 0.085 mmol), and polymer supported carbodiimide (0.082 g, 0.11 mmol) were added. The mixture was stirred for 18 hours at room temperature and was then filtered. The filtrate was washed with water (3 x 5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound (10 mg, 29%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, *J*=6.2 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.29 (d, *J*=7.3 Hz, 1 H), 7.05 - 7.20 (m, 2 H), 6.89 (d, *J*=3.7 Hz, 1 H), 5.35 (s, 1 H), 4.77 (d, *J*=8.1 Hz, 2 H), 4.48 (d, *J*=5.9 Hz, 2

H), 3.80 (s, 3 H), 3.71 (br. s., 1 H), 2.61 - 2.70 (m, 3 H), 2.21 (d, *J*=3.7 Hz, 1 H), 1.61 - 1.74 (m, 2 H), 1.48 (dd, *J*=10.3, 3.7 Hz, 3 H), 1.27 - 1.40 (m, 2 H), 1.14 - 1.28 (m, 6 H).

Example 221

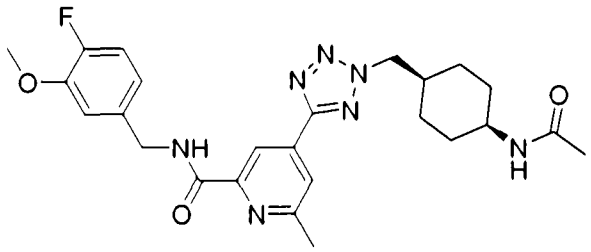
N-(4-Fuoro-3-methoxybenzyl)-4-(2-(((*cis*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



A mixture of 2-acetoxyacetic acid (11 mg, 0.092 mmol) and 1-hydroxybenzatriazole (11 mg, 0.08 mmol) in 2- methyl tetrahydrofuran (2 mL) was stirred for 5 minutes. *N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*cis*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 219) (0.040 g, 0.07 mmol), triethylamine (0.012 mL, 0.085 mmol), and polymer supported carbodiimide (0.082 g, 0.11 mmol) were added. The mixture was stirred for 18 hours at room temperature and was then filtered. The filtrate was washed with water (3 x 5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was dissolved in tetrahydrofuran (2 mL) and stirred with an aqueous solution of sodium hydroxide (2.5 N, 0.5 mL) for 2 hours at room temperature. The tetrahydrofuran was removed in vacuo and the aqueous residue was acidified with a 10% aqueous solution of hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with water (5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated. The residue that was purified by reverse phase preparative HPLC to afford the title compound (7.3 mg, 20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=6.22 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.39 (d, *J*=8.8 Hz, 1 H), 7.04 - 7.23 (m, 2 H), 6.89 (d, *J*=6.6 Hz, 1 H), 5.35 (t, *J*=5.9 Hz, 1 H), 4.76 (d, *J*=7.3 Hz, 2 H), 4.48 (d, *J*=5.9 Hz, 2 H), 3.69 - 3.93 (m, 5 H), 2.65 (s, 3 H), 2.21 (br. s., 1 H), 1.65 (br. s., 2 H), 1.41 - 1.55 (m, 4 H), 1.36 (d, *J*=8.8 Hz, 2 H).

Example 222

N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*cis*)-4-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

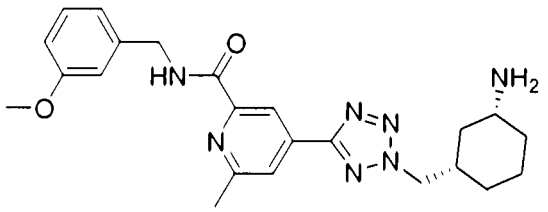


Triethylamine (0.012 mL, 0.085 mmol) and a solution of acetyl chloride (6.3 mg in 0.5 mL dichloromethane) were added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*cis*)-4-

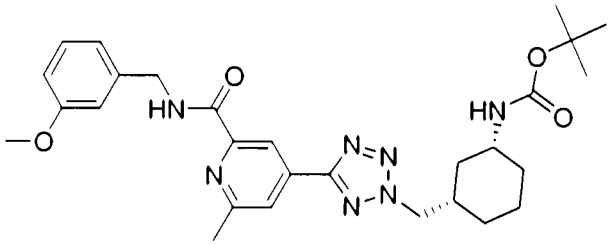
aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 219) (0.040 g, 0.07 mmol) in 2-methyltetrahydrofuran (2 mL). The reaction mixture was stirred for 1 hour at room temperature and was then concentrated. The residue was purified by reverse phase preparative HPLC (10-90 % acetonitrile/water) to afford the title compound (11 mg, 31%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=6.2 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.63 (d, *J*=7.3 Hz, 1 H), 7.03 – 7.25 (m, 2 H), 6.75 – 6.95 (m, 1 H), 4.68 (d, *J*=7.3 Hz, 2 H), 4.48 (d, *J*=5.9 Hz, 2 H), 3.80 (s, 4 H), 2.65 (s, 3 H), 2.06 – 2.24 (m, 1 H), 1.79 (s, 3 H), 1.52 – 1.62 (m, 2 H), 1.31 – 1.52 (m, 6 H).

Example 223

***rac*-*N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

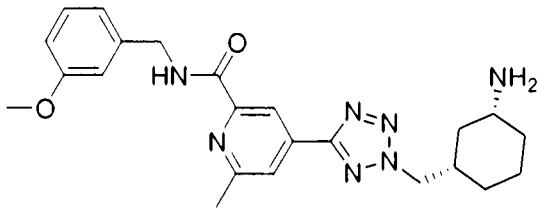


Step 1: Preparation of *rac-tert*-butyl (1*R**,3*S**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate



A solution of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (500.0 mg, 1.54 mmol) in anhydrous tetrahydrofuran (30 mL) and triphenylphosphine resin (1.790 g, 3.85 mmol, 2.15 mmol/g loading) was added to a vial containing *rac-tert*-butyl (1*R**,3*S**)-3-(hydroxymethyl)cyclohexylcarbamate (707.0 mg, 3.08 mmol). The mixture was cooled in an ice bath and di-tert-butylazodicarboxylate (710.0 mg, 3.08 mmol) was added. The reaction mixture was agitated overnight at room temperature and then concentrated. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound.

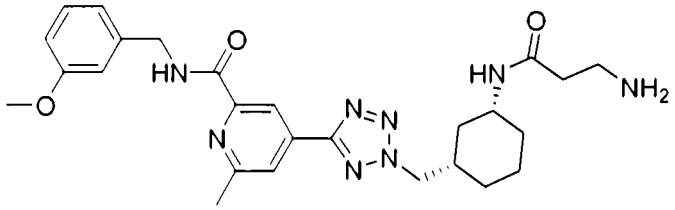
Step 2: Preparation of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



rac-tert-butyl (1*R**,3*S**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate obtained in step 1 was dissolved in dichloromethane and trifluoroacetic acid and stirred for approximately 30 minutes. The mixture was concentrated and the residue was dissolved in dichloromethane. MP-carbonate resin was added to the solution and the mixture was agitated for approximately 1 hour. The mixture was filtered and the resin was washed with dichloromethane and methanol. The filtrate was concentrated under a stream of nitrogen and dried under high vacuum overnight to afford the title compound as a solid (456 mg, 68%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.531 min., *m/z* 436 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.86 - 1.99 (m, 8 H), 2.04 - 2.24 (m, 1 H), 2.66 (s, 3 H), 2.91 - 3.11 (m, 1 H), 3.71 (s, 3 H), 4.48 (d, *J*=6.44 Hz, 2 H), 4.65 - 4.88 (m, 2 H), 6.74 - 6.83 (m, 1 H), 6.86 - 6.93 (m, 2 H), 7.17 - 7.26 (m, 1 H), 7.86 (br. s., 2 H), 8.00 - 8.11 (m, 1 H), 8.41 (s, 1 H), 9.19 - 9.30 (m, 1 H).

Example 224

rac-*N*-(3-Methoxybenzyl)-4-(2-(((1*S,3*R**)-3-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

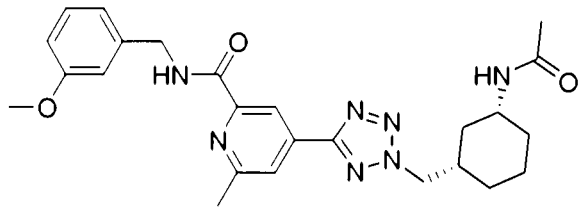


O-(7-Azabenzotriazole-1-yl)-*N*,*N*,*N*,*N*'-tetramethyluronium hexafluorophosphate (52.0 mg, 0.138 mmol), 3-(*tert*-butoxycarbonyl)propanoic acid (21.6 mg, 0.115 mmol), and diisopropylethylamine (0.040 mL, 0.230 mmol) were added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 223) (50.1 mg, 0.115 mmol) in dimethylformamide (2 mL). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min). The resulting intermediate was added to a mixture of dichloromethane and trifluoroacetic acid and stirred approximately 30 minutes. The mixture was concentrated and the residue was dissolved in dichloromethane. MP-carbonate resin was added and the mixture was agitated for approximately 30 minutes. The mixture was filtered and the resin was washed with dichloromethane and methanol. The filtrate was concentrated and dried overnight under high vacuum to afford the title compound as a solid (19.1 mg, 33%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.669 min., *m/z* 507 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 - 1.79 (m), 2.01 - 2.19 (m), 2.65 (s, 3 H), 3.51 (s), 3.71 (s, 3 H), 4.49 (d, *J*=6.59 Hz, 2 H), 4.68 (m,

2 H), 6.76 - 6.83 (m, 1 H), 6.86 - 6.94 (m, 2 H), 7.18 - 7.26 (m, 1 H), 7.69 - 7.77 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.13 - 9.24 (m, 1 H).

Example 225

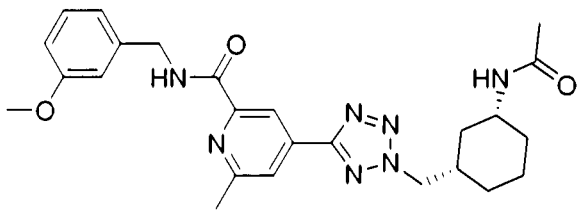
***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Acetic anhydride (0.033 mL, 0.345 mmol) and 4-(dimethylamino)pyridine Si bound (833.0 mg, 0.575 mmol, 0.69 mmol/g loading) were added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 223) (50.0 mg, 0.115 mmol) in dichloromethane (2 mL). The mixture was agitated overnight at room temperature. The reaction mixture was filtered, and the resin was washed with dimethylformamide. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (28.0 mg, 51%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 4.61 min., *m/z* 478 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.83 - 1.82 (m), 2.01 - 2.18 (m, 1 H), 3.40 - 3.61 (m, 1 H), 3.71 (s, 3 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.61 - 4.75 (m), 6.76 - 6.83 (m, 1 H), 6.86 - 6.93 (m, 2 H), 7.17 - 7.26 (m, 1 H), 7.63 - 7.71 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.14 - 9.23 (m, 1 H).

Example 226

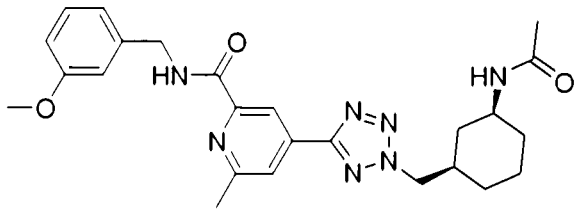
***N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



rac-N-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 225) was resolved by chiral supercritical-fluid chromatography (OJ-H, 30 x 250 mm, 15% methanol, 70 mL/min). The first eluting enantiomer was isolated to provide 22 mg (8%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.6 Hz, 1 H), 8.42 (s, 1 H), 8.07 (s, 1 H), 7.68 (d, *J*=7.3 Hz, 1 H), 7.23 (t, *J*=8.1 Hz, 1 H), 6.92 (br. s., 2 H), 6.81 (d, *J*=8.8 Hz, 1 H), 4.62 - 4.78 (m, 2 H), 4.51 (d, *J*=5.9 Hz, 2 H), 3.73 (s, 3 H), 3.42 - 3.57 (m, 1 H), 2.67 (s, 3 H), 2.53 (s, 1 H), 2.11 (br. s., 1 H), 1.64 - 1.80 (m, 5 H), 1.59 (d, *J*=11.7 Hz, 1 H), 1.20 - 1.34 (m, 1 H), 0.82 - 1.09 (m, 3 H).

Example 227

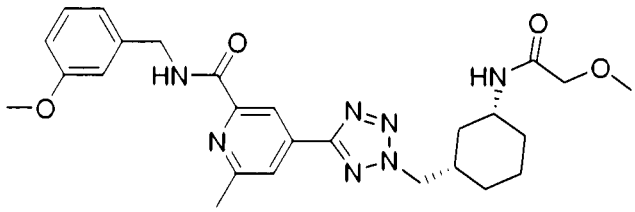
***N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



rac-N-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 225) was resolved by chiral supercritical-fluid chromatography (OJ-H, 30 x 250 mm, 15% methanol, 70 mL/min). The second eluting enantiomer was isolated to provide 23 mg (9%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.6 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.66 (d, *J*=7.3 Hz, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, *J*=7.3 Hz, 1 H), 4.62 - 4.77 (m, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 3.71 (s, 3 H), 3.41 - 3.55 (m, 1 H), 2.60 - 2.73 (m, 3 H), 2.51 (s, 1 H), 2.07 (d, *J*=19.76 Hz, 1 H), 1.64 - 1.81 (m, 5 H), 1.55 (br. s., 1 H), 1.19 - 1.36 (m, 2 H), 0.80 - 1.08 (m, 2 H).

Example 228

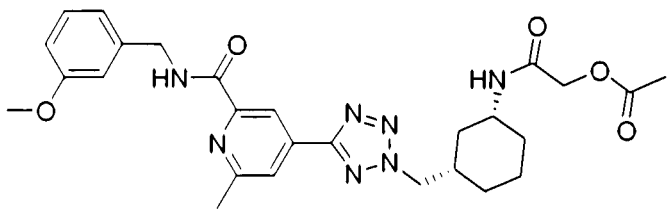
***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 224) by reaction with 2-methoxyacetic acid and afforded 33.9 mg (58%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.169 min., *m/z* 508 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 - 1.80 (m), 2.03 - 2.20 (m), 2.65 (s, 3 H), 3.50 - 3.66 (m, 1 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.59 - 4.77 (m, 2 H), 6.74 - 6.83 (m, 1 H), 6.86 - 6.94 (m, 2 H), 7.17 - 7.25 (m, 1 H), 7.51 - 7.58 (m, 1 H), 8.06 (s, 1 H), 8.41 (s, 1 H), 9.13 - 9.26 (m, 1 H).

Example 229

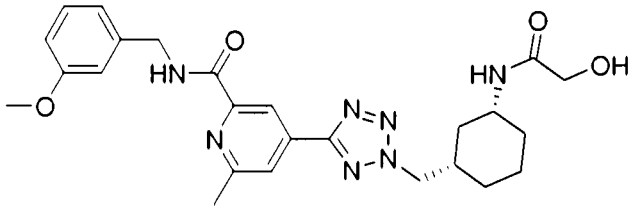
***rac*-2-((1*R**,3*S**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate**



The title compound was prepared in a similar manner to *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 224) by reaction with 2-acetoxyacetic acid and afforded 32.7 mg (53%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.174 min., *m/z* 536 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.85 - 1.80 (m), 2.03 (s, 3 H), 2.06 - 2.24 (m, 1 H), 2.65 (s, 3 H), 3.46 - 3.64 (m, 1 H), 3.71 (s, 3 H), 4.34 (s, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.69 (d, *J*=5.9 Hz, 2 H), 6.74 - 6.84 (m, 1 H), 6.86 - 6.93 (m, 2 H), 7.17 - 7.26 (m, 1 H), 7.76 - 7.85 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.14 - 9.25 (m, 1 H).

Example 230

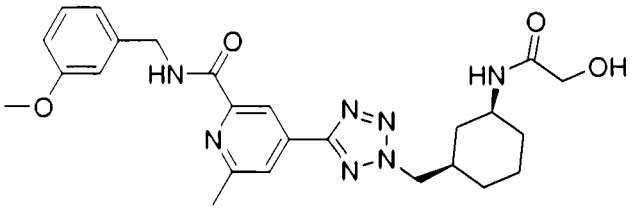
rac-*N*-(3-Methoxybenzyl)-4-(2-(((1*S,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 224) by reaction with 2-hydroxyacetic acid and afforded 32.1 mg (57%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.902 min., *m/z* 493 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 - 1.77 (m), 1.99 - 2.20 (m, 1 H), 2.52 (s), 2.65 (s, 3 H), 3.27 - 3.39 (m), 3.71 (s, 3 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.57 - 4.77 (m, 2 H), 5.23 - 5.37 (m), 6.74 - 6.82 (m, 1 H), 6.86 - 6.94 (m, 2 H), 7.17 - 7.25 (m, 1 H), 7.39 - 7.48 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.11 - 9.24 (m, 1 H).

Example 231

***N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

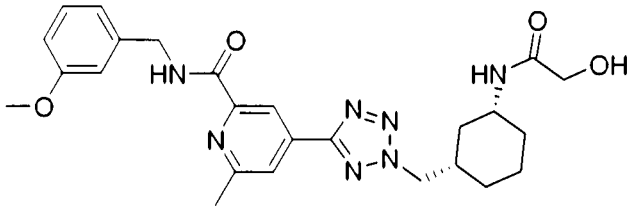


rac-N-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 230) was resolved by chiral supercritical-fluid chromatography (OJ-H, 30 x 250 mm, 15% methanol, 70 mL/min). The first eluting enantiomer was isolated to provide 23 mg (10%) of the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.2 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.43 (d, *J*=8.1 Hz, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, *J*=7.3 Hz, 1 H), 5.28 (t, *J*=5.5 Hz, 1 H), 4.68 (dd, *J*=6.2, 3.3 Hz, 2 H),

4.49 (d, *J*=6.6 Hz, 2 H), 3.71 (s, 3 H), 3.59 (d, *J*=13.9 Hz, 1 H), 2.65 (s, 3 H), 2.51 (s, 1 H), 2.11 (br. s., 1 H), 1.63 (dd, *J*=34.8, 20.1 Hz, 4 H), 0.90 - 1.35 (m, 5 H).

Example 232

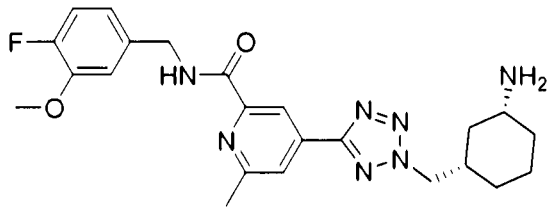
***N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



rac-N-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 230) was resolved by chiral supercritical-fluid chromatography (OJ-H, 30 x 250 mm, 15% methanol, 70 mL/min). The second eluting enantiomer was isolated to provide 21 mg (10%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.6 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.43 (d, *J*=8.1 Hz, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, *J*=8.1 Hz, 1 H), 5.28 (t, *J*=5.9 Hz, 1 H), 4.63 - 4.76 (m, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 3.71 (s, 3 H), 3.60 (d, *J*=11.0 Hz, 1 H), 2.65 (s, 3 H), 2.51 (s, 1 H), 2.11 (br. s., 1 H), 1.54 - 1.78 (m, 4 H), 0.84 - 1.37 (m, 5 H).

Example 233

***rac-N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

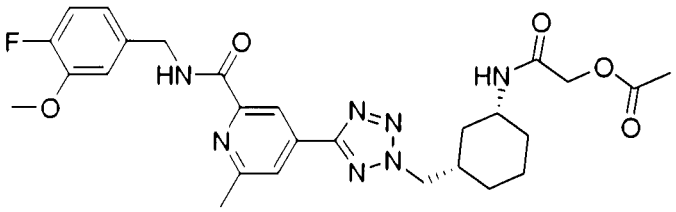


N-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (1.00 g, 2.64 mmol), t-butyl cis-(3-hydroxymethyl)cyclohexylcarbamate (0.73 g, 3.2 mmol), and polymer supported-triphenylphosphine (1.76 g, 4.0 mmol) were suspended in anhydrous tetrahydrofuran (50 mL). The mixture was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (0.73 g, 3.2 mmol) was added. The reaction mixture was allowed to warm to room temperature while stirring over 15 hours. The mixture was filtered and the filtrate was concentrated. The crude residue was purified on silica (20 g, 0-2% methanol/dichloromethane) to afford the protected amine. The intermediate was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (2 mL) was added. After 2 hours at room temperature, the reaction mixture was diluted with dichloromethane (10 mL) and neutralized with an aqueous solution of sodium hydroxide (2.5 N) for pH 7. The organic layer was

separated, dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound as a beige oil (689 mg, 58%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 3.90-4.15 min, *m/z* 454 (M+H).

Example 234

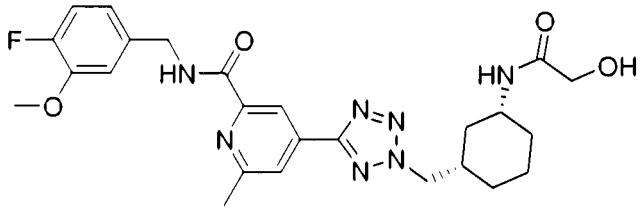
***rac*-2-((1*R**,3*S**)-3-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate**



rac-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 233) (1.00 g, 2.20 mmol) was dissolved in dichloromethane (10 mL). Triethylamine (0.19 mL, 2.6 mmol) and a solution of acetoxy acetyl chloride (336 mg) in dichloromethane (1.0 mL) was added. The mixture was stirred for 4 hours at room temperature and was then concentrated. The residue was purified by reverse phase preparative HPLC (10-90 % acetonitrile/water) to afford the title compound (190 mg).

Example 235

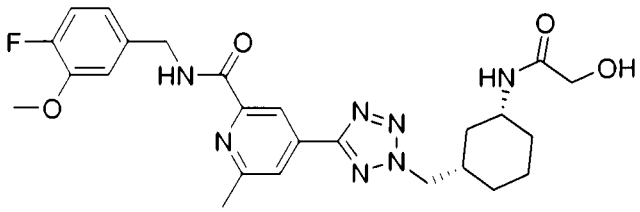
***rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



rac-2-((1*R**,3*S**)-3-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate (190 mg) was dissolved in acetonitrile (10 mL). An aqueous solution of sodium hydroxide (2.5 N, 4.0 mL) was added and the mixture was stirred for 2 hours. The reaction mixture was concentrated and the aqueous residue was acidified to pH 7 with a 10% solution of hydrochloric acid in water. The neutralized mixture was extracted with ethyl acetate (3 x 10mL). The combined organics were washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, and filtered, and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound (150 mg). MS (ES+) *m/z* 512 (M+H).

Example 236

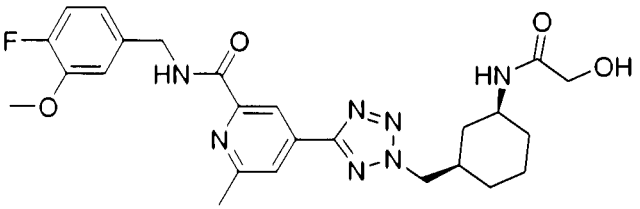
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



rac-N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 235) was resolved by chiral supercritical-fluid chromatography (OJ-H, 30 x 250 mm, 15% methanol, 70 mL/min). The first eluting enantiomer was isolated to provide 120 mg (21%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.6 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.42 (d, *J*=8.1 Hz, 1 H), 7.05 - 7.20 (m, 2 H), 6.88 (d, *J*=8.1 Hz, 1 H), 5.27 (t, *J*=5.9 Hz, 1 H), 4.59 - 4.72 (m, 2 H), 4.48 (d, *J*=5.9 Hz, 2 H), 3.77 - 3.84 (m, 3 H), 3.71 (d, *J*=5.1 Hz, 2 H), 3.53 - 3.64 (m, 1 H), 2.65 (s, 3 H), 2.51 (s, 1 H), 2.06 - 2.19 (m, 1 H), 1.49 - 1.75 (m, 3 H), 0.88 - 1.33 (m, 4 H).

Example 237

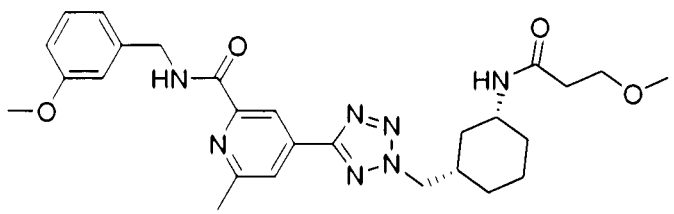
N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*R,3*S**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



rac-N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 235) was resolved by chiral supercritical-fluid chromatography (OJ-H, 30 x 250 mm, 15% methanol, 70 mL/min). The second eluting enantiomer was isolated to provide 107 mg (19%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=5.9 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.42 (d, *J*=8.8 Hz, 1 H), 7.05 - 7.22 (m, 2 H), 6.89 (br. s., 1 H), 5.27 (t, *J*=5.9 Hz, 1 H), 4.68 (d, *J*=2.9 Hz, 2 H), 4.48 (d, *J*=5.9 Hz, 2 H), 3.80 (s, 3 H), 3.71 (d, *J*=5.1 Hz, 2 H), 3.60 (d, *J*=11.7 Hz, 1 H), 2.65 (s, 3 H), 2.51 (s, 1 H), 2.11 (br. s., 1 H), 1.59 (d, *J*=20.5 Hz, 3 H), 0.84 - 1.36 (m, 4 H).

Example 238

***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

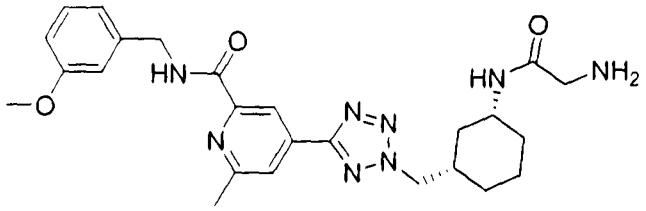


The title compound was prepared in a similar manner to *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

(Example 224) by reaction with 3-methoxypropanoic acid and afforded 35.2 mg (59%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.115 min., *m/z* 522 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 - 1.79 (m), 2.01 - 2.17 (m, 1 H), 2.22 (t, *J*=6.6 Hz, 2 H), 2.65 (s, 3 H), 3.37 - 3.60 (m), 3.71 (s, 3 H), 4.49 (d, *J*=5.9 Hz, 2 H), 4.61 - 4.77 (m, 2 H), 6.76 - 6.83 (m, 1 H), 6.87 - 6.93 (m, 2 H), 7.18 - 7.25 (m, 1 H), 7.64 - 7.72 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.14 - 9.22 (m, 1 H).

Example 239

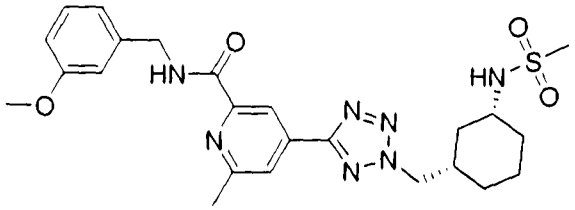
***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(3-aminopropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 224) by reaction with 2-(tert-butoxycarbonyl)acetic acid and afforded 23.0 mg (41%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.634min., *m/z* 493 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 - 1.83 (m), 2.02 - 2.21 (m), 2.65 (s, 3 H), 2.98 (s, 1 H), 3.45 - 3.61 (m, 1 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.61 - 4.73 (m, 2 H), 6.75 - 6.83 (m, 1 H), 6.86 - 6.94 (m, 2 H), 7.17 - 7.26 (m, 1 H), 7.54 - 7.62 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.13 - 9.25 (m, 1 H).

Example 240

***rac-N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((1*S**,3*R**)-3-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**

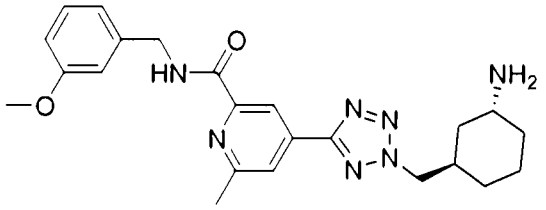


Triethylamine (0.048 mL, 0.345 mmol) and methane sulfonyl chloride (0.013 mL, 0.173 mmol) were added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 223) (50.1 mg, 0.115 mmol) in tetrahydrofuran (1.5 mL). The mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (26.0 mg, 44%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.188 min., *m/z* 514 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 - 9.24 (m, 1 H), 8.41 (s, 1 H),8.05 (s, 1 H), 7.16 - 7.26 (m, 1 H), 6.95 - 7.03 (m, 1 H), 6.86 - 6.93 (m, 2 H), 6.75 - 6.83 (m, 1 H), 4.68 (d, *J*=6.6 Hz, 2 H), 4.49 (d, *J*=5.9 Hz, 2 H), 3.71

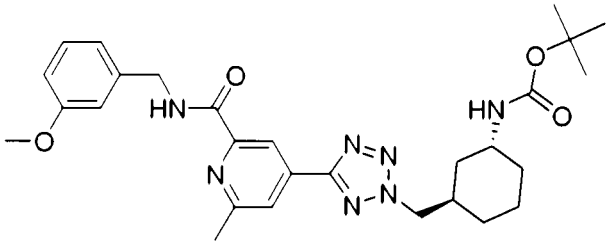
(s, 3 H), 2.85 (s, 3 H), 2.65 (s, 3 H), 2.03 - 2.20 (m), 1.81 - 1.92 (m), 1.63 - 1.74 (m), 1.43 - 1.58 (m), 0.82 - 1.37 (m).

Example 241

***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

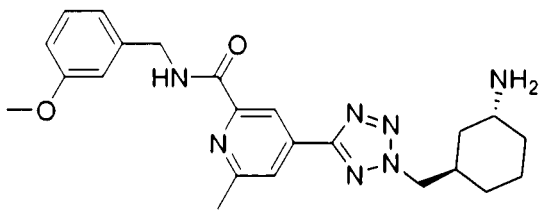


Step 1: Preparation of *rac-tert*-butyl (1*R**,3*R**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate



A solution of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (500.0 mg, 1.54 mmol) in anhydrous tetrahydrofuran (30 mL) and triphenylphosphine resin (1.790 g, 3.85 mmol, 2.15 mmol/g loading) was added to a vial containing *rac-tert*-butyl (1*R**,3*R**)-3-(hydroxymethyl)cyclohexylcarbamate (707.0 mg, 3.08 mmol). The mixture was cooled in an ice bath and di-tert-butylazodicarboxylate (710.0 mg, 3.08 mmol) was added. The reaction mixture was agitated overnight at room temperature and then concentrated. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound.

Step 2: Preparation of rac-*N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

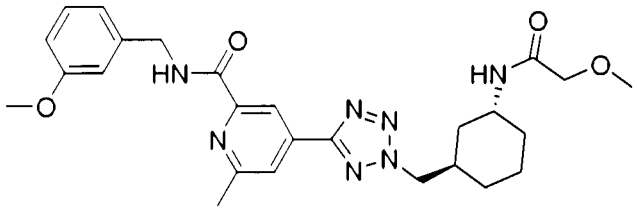


rac-tert-butyl (1*R**,3*R**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylcarbamate obtained in step 1 was dissolved in dichloromethane and trifluoroacetic acid and stirred for approximately 30 minutes. The mixture was concentrated and the residue was dissolved in dichloromethane. MP-carbonate resin was added to the solution and the mixture was agitated for approximately 1 hour. The mixture was filtered and the resin was washed

with dichloromethane and methanol. The filtrate was concentrated under a stream of nitrogen and dried under high vacuum overnight to afford the title compound as a solid (460 mg, 68%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.514 min., *m/z* 436 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 - 9.29 (m, 1 H), 8.41 (s, 1 H), 8.05 - 8.08 (m, 1 H), 7.93 (br. s., 2 H), 7.17 - 7.26 (m, 1 H), 6.85 - 6.94 (m, 2 H), 6.75 - 6.83 (m, 1 H), 4.68 - 4.86 (m, 2 H), 4.48 (d, *J*=6.4 Hz, 2 H), 3.70 (s, 3 H), 3.37 - 3.49 (m, 1 H), 2.66 (s, 3 H), 2.45 - 2.56 (m, 1 H), 1.12 - 1.78 (m).

Example 242

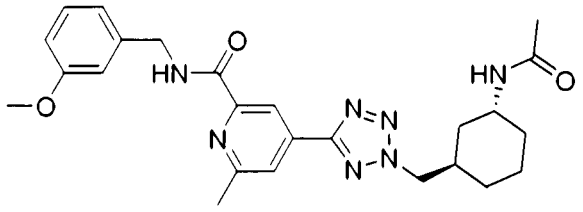
rac-*N*-(3-Methoxybenzyl)-4-(2-(((1*R,3*R**)-3-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



O-(7-Azabenzotriazole-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (52.0 mg, 0.138 mmol), 2-methoxyacetic acid (10.4 mg, 0.115 mmol), and diisopropylethylamine (0.040 mL, 0.230 mmol) were added to a solution of rac-*N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 241) (50.1 mg, 0.115 mmol) in *N*,*N*-dimethylformamide (2 mL). The mixture was allowed to stir at room temperature overnight and was then concentrated. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (31.9 mg, 55%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.196 min., *m/z* 508 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.05 - 9.24 (m, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.41 - 7.50 (m, 1 H), 7.16 - 7.26 (m, 1 H), 6.86 - 6.93 (m, 2 H), 6.76 - 6.84 (m, 1 H), 4.70 (d, *J*=7.32 Hz, 2 H), 4.49 (d, *J*=5.86 Hz, 2 H), 4.01 (br. s.), 3.76 (s, 3 H), 3.71 (s, 3 H), 2.62 - 2.70 (s, 3 H), 2.32 - 2.45 (m, 1 H), 1.04 - 1.74 (m).

Example 243

rac-*N*-(3-Methoxybenzyl)-4-(2-(((1*R,3*R**)-3-acetamidocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

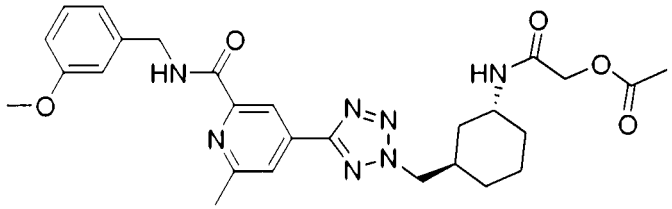


Acetic anhydride (0.033 mL, 0.345 mmol) and 4-(dimethylamino)pyridine Si bound (833.0 mg, 0.575 mmol, 0.69 mmol/g loading) were added to a solution of rac-*N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 241) (50.0 mg, 0.115 mmol) in dichloromethane (2 mL). The mixture was agitated overnight and then filtered. The filtrate was concentrated and the residue was purified by reverse

phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound (30.0 mg, 55%). LC/MS (5%-100% CH_3CN/H_2O, 10.0 min.): 4.57 min., *m/z* 478 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.14 - 9.23 (m, 1 H), 8.41 (s, 1 H), 8.06 (s, 1 H), 7.65 - 7.73 (m, 1 H), 7.18 - 7.26 (m, 1 H), 6.86 - 6.94 (m, 2 H), 6.75 - 6.83 (m, 1 H), 4.66 (d, *J*=7.32 Hz, 2 H), 4.49 (d, *J*=5.86 Hz, 2 H), 3.92 - 4.02 (m, 1 H), 3.71 (s, 3 H), 2.65 (s, 3 H), 3.28 (s), 2.32 - 2.45 (m, 1 H), 1.78 (s, 3 H), 0.95 - 1.70 (m).

Example 244

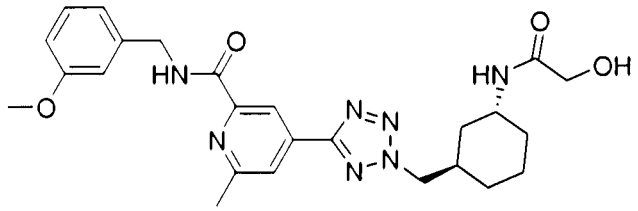
***rac*-2-((1*R**,3*R**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexylamino)-2-oxoethyl acetate**



The title compound was prepared in a similar manner to *rac-N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 242) by reaction with 2-acetoxyacetic acid to afford 23.7 mg (38%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.188 min., *m/z* 536 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.73 (m) 2.01 (s, 3 H), 2.26 - 2.46 (m, 1 H), 2.65 (s, 3 H), 3.71 (s, 3 H), 3.99 (br. s.) 4.41 (s, 2 H), 4.49 (d, *J*=6.59 Hz, 1 H), 4.68 (d, *J*=7.32 Hz, 2 H), 6.74 - 6.83 (m, 1 H), 6.86 - 6.95 (m, 2 H), 7.16 - 7.25 (m, 1 H), 7.79 - 7.87 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.14 - 9.23 (m, 1 H).

Example 245

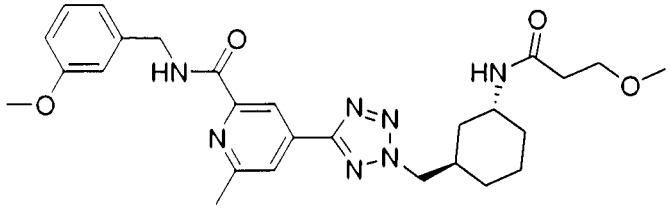
***rac*-*N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(2-hydroxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *rac-N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 242) by reaction with 2-hydroxyacetic acid to afford 26.1 mg (46%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.927 min., *m/z* 494 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 - 1.75 (m) 2.27 - 2.43 (m, 1 H), 2.52 (s, 3 H), 2.65 (s, 3 H), 3.71 (s, 3 H), 3.77 (br. s.) 4.01 (br. s.) 4.49 (d, *J*=5.86 Hz, 2 H), 4.70 (d, *J*=7.32 Hz, 2 H), 6.72 - 6.83 (m, 1 H), 6.86 - 6.93 (m, 2 H), 7.17 - 7.26 (m, 1 H), 7.32 - 7.39 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.15 - 9.24 (m, 1 H).

Example 246

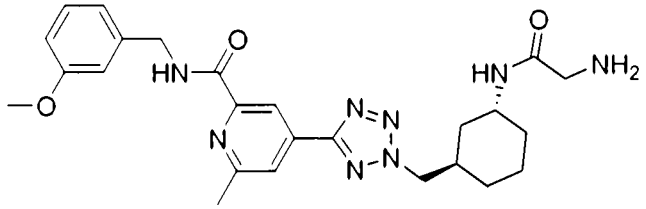
***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(3-methoxypropanamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *rac-N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 242) by reaction with 3-methoxypropanoic acid to afford 33.0 mg (55%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.152 min., *m/z* 522 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.98 - 1.70 (m) 2.30 (t, *J*=6.22 Hz, 2 H), 2.39 (br. s.) 2.65 (s, 3 H), 3.46 (t, *J*=6.59 Hz, 2 H), 3.71 (s, 3 H), 3.97 (br. s.) 4.49 (d, *J*=6.59 Hz, 2 H), 4.66 (d, *J*=7.32 Hz, 2 H), 6.76 - 6.83 (m, 1 H), 6.85 - 6.93 (m, 2 H), 7.18 - 7.26 (m, 1 H), 7.65 - 7.73 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.14 - 9.24 (m, 1 H).

Example 247

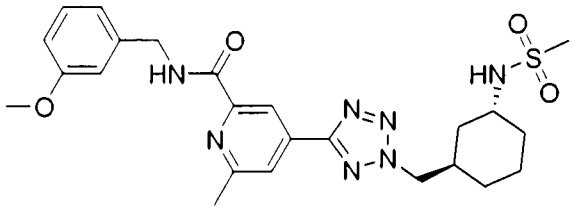
***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(2-aminoacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *rac-N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-(2-methoxyacetamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 242) by reaction with 2-(tert-butoxycarbonyl)acetic acid to afford 19.8 mg (41%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.653 min., *m/z* 493 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.97 - 1.69 (m) 2.34 (br. s.) 2.65 (s, 3 H), 3.27 (br. s.) 3.71 (s, 3 H), 3.99 (br. s.) 4.49 (d, *J*=5.86 Hz, 2 H), 4.57 - 4.77 (m, 2 H), 6.72 - 6.84 (m, 1 H), 6.85 - 6.94 (m, 2 H), 7.13 - 7.27 (m, 1 H), 7.63 - 7.72 (m, 1 H), 8.04 - 8.08 (m, 1 H), 8.39 - 8.47 (m, 1 H), 9.13 - 9.23 (m, 1 H).

Example 248

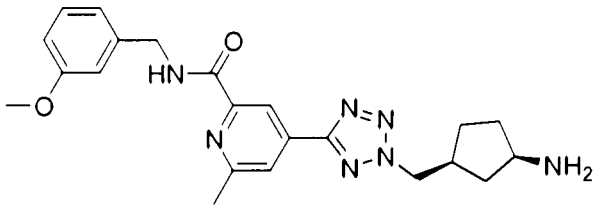
***rac-N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((1*R**,3*R**)-3-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



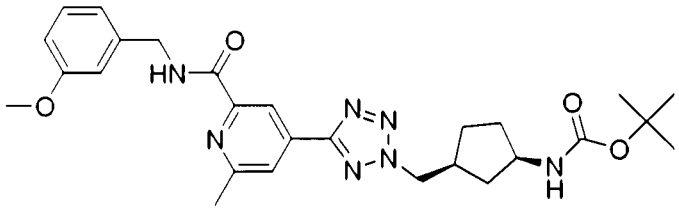
Triethylamine (0.048 mL, 0.345 mmol) and methane sulfonyl chloride (0.013 mL, 0.173 mmol) were added to a solution of rac-*N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 241) (50.1 mg, 0.115 mmol) in tetrahydrofuran (1.5 mL). The mixture was stirred for 2 hours at room temperature and was then concentrated. The residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min) to afford the title compound as a solid (29.2 mg, 49%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.198 min., *m/z* 514 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.09 - 9.25 (m, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.15 - 7.28 (m, 1 H), 6.92 - 6.99 (m, 1 H), 6.86 - 6.93 (m, 2 H), 6.73 - 6.83 (m), 4.68 (d, *J*=7.3 Hz, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 3.71 (s, 3 H), 3.52 - 3.63 (m), 2.84 (s, 3 H), 2.65 (s, 3 H), 2.32 - 2.46 (m), 1.30 - 1.75 (m), 0.86 - 1.21 (m).

Example 249

rac-*N*-(3-Methoxybenzyl)-4-(2-(((1*S,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



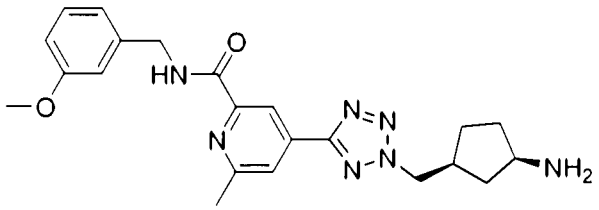
Step 1: Preparation of *tert*-butyl rac-(1*R**,3*S**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclopentylcarbamate



tert-Butyl (*cis*)-3-(hydroxymethyl)cyclopentylcarbamate (1.66 g, 6.166 mmol) and polymer supported-triphenylphosphine (5.74 g, 12.3 mmol) was added to a solution of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) in THF (25 mL) cooled to -20 °C. Di-tert-butylazodicarboxylate (2.84 g, 12.3 mmol) was added and the mixture was stirred at -20 °C for 2 hours. The reaction mixture was allowed to warm and stir overnight. The mixture was filtered and the resin was washed with tetrahydrofuran. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound (1.759 g). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.647 min., *m/z* 522 (M+H). ^{1}H NMR

(400 MHz, $CDCl_3$) δ ppm 1.17 - 1.29 (m, 1 H), 1.37 - 1.46 (m, 9 H), 1.46 - 1.62 (m, 1 H), 1.75 - 1.86 (m, 1 H), 1.86 - 1.96 (m, 1 H), 1.97 - 2.09 (m, 1 H), 2.17 - 2.30 (m, 1 H), 2.57 - 2.73 (m, 3 H), 3.75 - 3.84 (m, 3 H), 3.96 (br. s., 1 H), 4.54 (d, *J*=5.6 Hz, 1 H), 4.65 (t, *J*=7.3 Hz, 3 H), 6.82 (dd, *J*=8.2, 2.3 Hz, 1 H), 6.88 - 7.01 (m, 1 H), 7.20 - 7.34 (m, 1 H), 8.03 (s, 1 H), 8.42 (t, *J*=5.8 Hz, 1 H), 8.70 (s, 1 H).

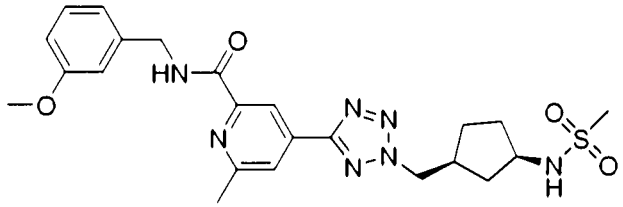
Step 2: Preparation of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Trifluoroacetic acid (0.73 mL, 9.84 mmol) was added to a solution of *tert*-butyl *rac*-(1*R**,3*S**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclopentylcarbamate (1.475 g, 1.968 mmol) in dichloromethane (25 mL). The mixture was allowed to stir at room temperature overnight and was then concentrated to afford the title compound as a clear, yellow oil (1.59 g, 100% yield). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.484 min., *m/z* 422 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.62 - 1.75 (m, 2 H), 1.79 - 1.95 (m, 2 H), 2.02 - 2.13 (m, 1 H), 2.21 - 2.32 (m, 1 H), 2.70 (s, 3 H), 3.50 (br. s., 1 H), 3.76 (s, 3 H), 4.62 (d, *J*=5.9 Hz, 2 H), 4.64 - 4.81 (m, 2 H), 5.28 (s, 2 H), 6.78 - 6.92 (m, 2 H), 6.95 (br. s., 2 H), 7.23 - 7.27 (m, 1 H), 7.72 (br. s., 1 H), 8.15 (s, 1 H), 8.63 (s, 1 H).

Example 250

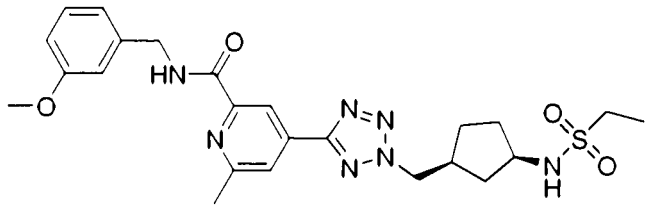
***rac-N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((1*S**,3*R**)-3-(methylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



Diisopropylethylamine (0.64 ml, 13.4 mmol) was added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 249) (116 mg, 0.275 mmol) in DMF (5.0 mL). After 20 minutes, methanesulfonyl chloride (158 mg, 1.38 mmol) was added and the mixture was allowed to stir overnight. The reaction mixture was concentrated and the residue was purified by preparative reverse phase preparative HPLC to afford the title compound as an oil (62.8 mg, 49%). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.156 min., *m/z* 500 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm9.19 (t, *J*=6.22 Hz, 1 H), 8.41 (br. s., 1 H), 8.06 (s, 1 H), 7.22 (t, *J*=8.05 Hz, 1 H), 7.09 (d, *J*=7.32 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, *J*=8.05 Hz, 1 H), 4.77 (d, *J*=7.32 Hz, 2 H), 4.49 (d, *J*=5.86 Hz, 2 H), 3.71 (s, 3 H), 2.85 (s, 3 H), 2.65 (s, 3 H), 2.01 - 2.13 (m, 2 H), 1.82 - 1.96 (m, 2 H), 1.69 (br. s., 2 H), 1.44 - 1.60 (m, 2 H), 1.23 - 1.37 (m, 2 H).

Example 251

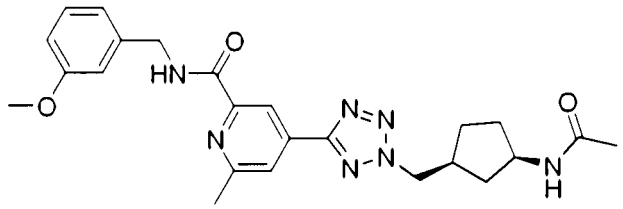
***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(ethylsulfonamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Diisopropylethylamine (0.23 mL, 1.31 mmol) was added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 249) (100 mg, 0.131 mmol) in DMF (5.0 mL). After 20 minutes, ethanesulfonyl chloride (101 mg, 0.786 mmol) was added and the mixture was allowed to stir overnight. The reaction mixture was concentrated and the residue was purified by preparative reverse phase preparative HPLC to afford the title compound as an oil (25.3 mg, 26%). MS (ES+) *m/z* 514 (M+H). ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.28 (t, *J*=7.38 Hz, 3 H), 1.34 - 1.45 (m, 1 H), 1.55 - 1.69 (m, 1 H), 1.79 (d, *J*=6.71 Hz, 1 H), 1.96 - 2.07 (m, 1 H), 2.14 - 2.24 (m, 1 H), 2.67 (s, 3 H), 3.01 (q, *J*=7.25 Hz, 2 H), 3.76 (s, 3 H), 4.59 (s, 2 H), 4.74 (d, *J*=7.52 Hz, 2 H), 6.80 (dd, *J*=8.06, 2.42 Hz, 1 H), 6.90 - 6.96 (m, 1 H), 7.22 (t, *J*=8.19 Hz, 1 H), 8.10 (d, *J*=1.07 Hz, 1 H), 8.57 (s, 1 H).

Example 252

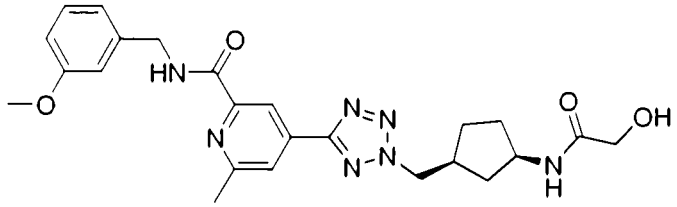
***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-acetamidocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Diisopropylethylamine (128 mg, 1.00 mmol) was added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 249) (100 mg, 0.131 mmol) in dichloromethane (5 mL). After 20 minutes, acetic anhydride (40 mg, 0.40 mmol) was added. The mixture was allowed to stir at room temperature overnight. The reaction mixture was concentrated and the residue was purified by preparative reverse phase preparative HPLC to afford the title compound (58.3 mg, 43%). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.071 min., *m/z* 464 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.22 Hz, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.82 (d, *J*=5.86 Hz, 1 H), 7.21 (t, *J*=8.05 Hz, 1 H), 6.90 (br. s., 1 H), 6.79 (d, *J*=7.32 Hz, 2 H), 4.76 (d, *J*=6.59 Hz, 2 H), 4.49 (d, *J*=5.86 Hz, 2 H), 3.98 (dd, *J*=14.64, 7.32 Hz, 1 H), 3.71 (s, 3 H), 2.65 (s, 3 H), 2.50 - 2.60 (m, 1 H), 2.48 (br. s., 1 H), 1.94 - 2.07 (m, 1 H)1.61 - 1.87 (m, 4 H), 1.37 - 1.56 (m, 2 H), 1.13 - 1.26 (m, 1 H).

Example 253

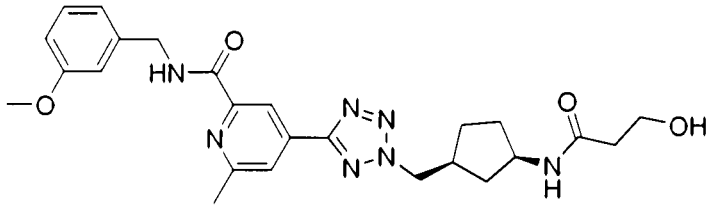
***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(2-hydroxyacetamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Diisopropylethylamine (118 mg, 0.917 mmol) and glycolic acid (19.9 mg, 0.262 mmol) were added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 249) (100 mg, 0.131 mmol) in *N*,*N*-dimethylformamide (5 mL). After 20 min, O-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (116 mg, 0.360 mmol) was added and the mixture was allowed to stir for 72 hours. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound (30.5 mg, 33%). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.958 min., *m/z* 480 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.22 Hz, 1 H), 8.41 (br. s., 1 H), 8.06 (s, 1 H), 7.22 (t, *J*=8.05 Hz, 1 H), 6.90 (br. s., 1 H), 6.80 (d, *J*=8.05 Hz, 1 H), 5.29 (br. s., 1 H), 4.49 (d, *J*=5.86 Hz, 2 H), 4.03 - 4.18 (m, 1 H), 3.67 - 3.80 (m, 3 H), 2.65 (s, 3 H), 2.50 - 2.62 (m, 1 H), 2.48 (br. s., 1 H), 1.76 - 1.88 (m, 1 H), 1.61 - 1.73 (m, 1 H), 1.53 (d, *J*=6.59 Hz, 2 H), 1.22 - 1.39 (m, 1 H).

Example 254

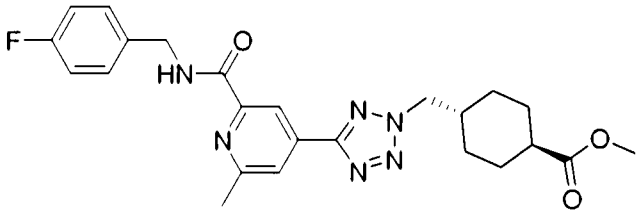
***rac-N*-(3-Methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-(3-hydroxypropanamido)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



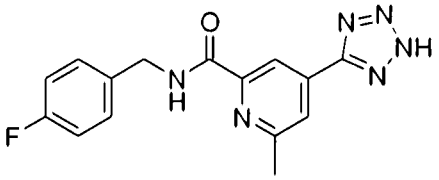
Diisopropylethylamine (130 mg, 1.01 mmol) and 3-hydroxypropionic acid (26 mg, 0.288 mmol) were added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*S**,3*R**)-3-aminocyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 249) (110 mg, 0.144 mmol) in *N*,*N*-dimethylformamide (5 mL). After 20 min, O-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (127 mg, 0.396 mmol) was added and the mixture was allowed to stir for 72 hours. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound (16.1 mg, 15%). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.936 min., *m/z* 494 (M+H). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.20 (s, 1 H), 8.55 (s, 1 H), 8.10 (s, 1 H), 7.23 (t, *J*=8.19 Hz, 1 H), 6.91 - 6.96 (m, 2 H), 6.78 - 6.83 (m, 1 H), 4.73 - 4.81 (m, 2 H), 4.59 (s, 2 H), 3.74 - 3.79 (m, 3 H), 2.66 - 2.70 (m, 3 H), 2.35 (t, *J*=6.31 Hz, 1 H), 2.13 - 2.22 (m, 1 H), 1.99 (d, *J*=6.18 Hz, 1 H), 1.81 (s, 1 H), 1.51 - 1.67 (m, 2 H), 1.28 - 1.38 (m, 1 H).

Example 255

(*trans*)-Methyl 4-((5-(2-((4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate

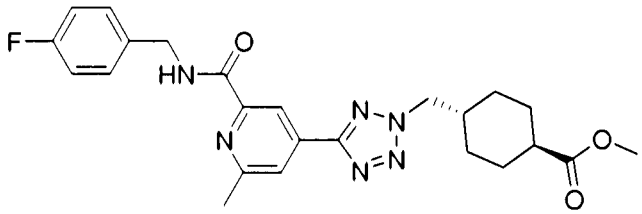


Step 1: Preparation of *N*-(4-fluorobenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide



A solution of trimethyl aluminum (2M in toluene, 91.25 mL, 0.183 mol) was added to a solution of 4-fluorobenzylamine (22.84 g, 0.183 mol) in anhydrous tetrahydrofuran (400 mL). The reaction mixture was stirred at room temperature for 4 h, at which time the solution was cannulated into a suspension of methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (20.0 g, 0.0913 mol) in anhydrous tetrahydrofuran (400 mL). The reaction mixture was then stirred overnight. The mixture was quenched slowly with methanol and was poured into a 2 L Erlenmeyer containing methanol (500 mL). The mixture was filtered through Celite™ and concentrated in vacuo. The crude product was purified by silica column chromatography (CH_2Cl_2/tetrahydrofuran, 9/1). The desired fractions were combined and concentrated to afford the title compound (25.4 g, 89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.33 (t, J= 6.34, 1 H), 8.43 (s, 1 H), 8.05 (s, 1 H), 7.34 (dd, J= 8.5, 2 H), 7.11 (dd, J= 8.9, 2 H), 4.48 (d, J= 6.6, 2 H), 2.64 (s, 3 H).

Step 2: Preparation of (*trans*)-methyl 4-((5-(2-((4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate

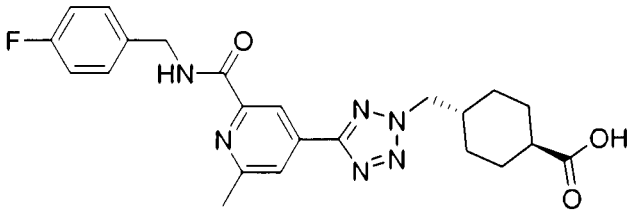


Triethylamine (9.12 g, 0.09 mol)was added to a suspension of the *N*-(4-fluorobenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (12.8 g, 0.04 mol) in acetonitrile (400 mL, anhydrous). *trans*-methyl 4-((methylsulfonyloxy)methyl)cyclohexanecarboxylate (prepared as described in step 1 of the synthesis of *trans*-methyl 4-((5-(6-((4-fluoro-3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate, Example 20) (10.77 g, 0.04 mol) was then added and the reaction mixture was stirred over night at 60 °C. The mixture was concentrated under reduced pressure and the crude product was purified by silica column chromatography

(CH_2Cl_2/tetrahydrofuran, 9/1). The desired fractions were combined and concentrated to afford the title compound (11 g, 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.29 (t, J= 6.34, 1H), 8.39 (s, 1H), 8.04 (s, 1 H), 7.36 (m, 2H), 7.11 (m, 2H), 4.64 (d, J= 7.1, 2H), 4.49 (d, J= 6.6, 2H), 3.30 (s, 3H), 2.64 (s, 3H), 2.1 (m, 1H), 1.96 (m, 1H), 1.89 (m, 2H), 1.64 (m, 2H), 1.26 (m, 2H), 1.09 (m, 2H).

Example 256

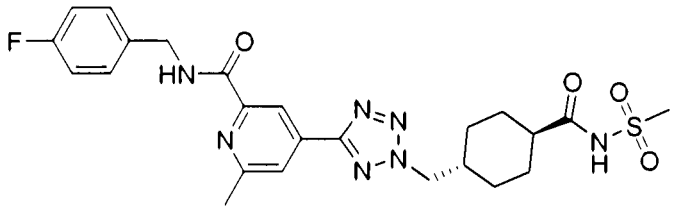
(*trans*)-4-((5-(2-((4-Fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



To a solution of (*trans*)-methyl 4-((5-(2-((4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 255) (10 g, 0.021 mol) in tetrahydrofuran (300 mL) was added water (300 mL) and then sodium hydroxide (4.3 g, 0.107 mol). The mixture was stirred vigorously overnight. The tetrahydrofuran was removed under reduced pressure and the resulting alkaline solution was acidified drop wise with 1 M hydrochloric acid until the solution reached pH 5. The mixture was left sitting in a refrigerator overnight. The resulting precipitate was isolated by filtration and washed with water (pH 5). The solid was dried in a vacuum oven overnight to afford the title compound (7.5 g, 77%). Mp 122-124 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.96 (s, 1H), 9.27 (t, J= 6.4, 1H), 8.36 (s, 1H), 8.02 (s, 1 H), 7.33 (dd, J= 8.5, 2H), 7.09 (dd, J= 9.0, 2H), 4.61 (d, J= 6.8, 2H), 4.45 (d, J= 6.3, 2H), 2.61 (s, 3H), 2.07 (m, 1H), 1.93 (m, 1H), 1.85 (d, J= 11, 2H), 1.58 (d, J= 10.8, 2H), 1.25 (m, 2H), 1.07 (m, 2H).

Example 257

***N*-(4-Fluorobenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**

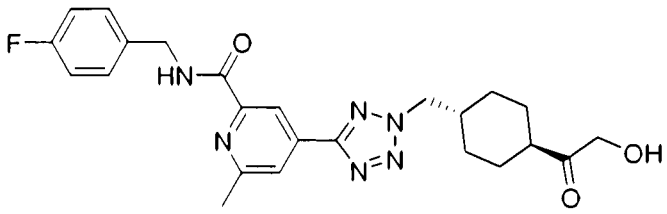


4-(Dimethylamino)pyridine (5.4mg, 0.041mmol) was added to a mixture of (*trans*)-4-((5-(2-((4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid (prepared as described in Example 256) (0.20 g, 0.442 mmol), di-(*N*,*N*'-succinimidyl)carbonate (0.14g, 0.53 mmol), and triethylamine (0.092 mL, 0.66 mmol) in *N*,*N*-dimethylacetamide (2 mL). After 5 minutes, methanesulfonamide (51 mg, 0.53 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 hours and then purified by reverse phase preparative HPLC to afford the title compound as a solid (0.040 g, 17%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.29 (t, J=6.31 Hz,

1 H), 8.39 (s, 1 H), 8.05 (s, 1 H), 7.26 - 7.44 (m, 2 H), 7.02 - 7.18 (m, 2 H), 4.66 (d, *J*=6.99 Hz, 2 H), 4.48 (d, *J*=6.45 Hz, 2 H), 3.31 (br. s., 1 H), 2.76 (s, 3 H), 2.61 - 2.69 (m, 4 H), 1.92 - 2.13 (m, 3 H), 1.68 (d, *J*=12.90 Hz, 2 H), 1.33 - 1.50 (m, 2 H), 1.10 - 1.29 (m, 2 H).

Example 258

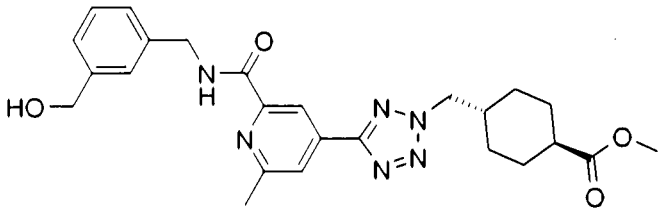
***N*-(4-Fluorobenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



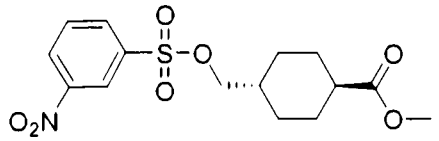
Oxalyl chloride (3 mL) was added to a solution of (*trans*)-4-((5-(2-((4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid (prepared as described in Example 256) (380 mg, 0.84 mmol) in dichloromethane (2 mL) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated and the residue was treated with tris(trimethylsiloxy)ethylene (541 mg, 1.85 mmol). The mixture was heated to 90 °C for 3 hours and then was stirred at room temperature for 2 days. The mixture was treated with several drops of 4 N hydrochloric acid until gas stopped evolving. The reaction mixture was purified by reverse phase preparative HPLC. The crude product was taken up in methanol and passed through a carbonate cartridge. The filtrate was concentrated to afford the title compound as a white solid (79 mg, 20%). LCMS (ES+) *m/z* 467(M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 - 1.40 (m, 4 H), 1.61 - 1.73 (m, *J*=10.98 Hz, 2 H), 1.91 (s, *J*=10.98 Hz, 2 H), 1.96 - 2.08 (m, 1 H), 2.20 - 2.32 (m, 1 H), 2.67 (s, 3 H), 3.26 - 3.33 (m, *J*=2.20 Hz, 1 H), 3.57 (s, 2 H), 4.52 (d, *J*=5.86 Hz, 2 H), 4.58 - 4.72 (m, 3 H), 7.14 (s, *J*=8.78, 8.78 Hz, 1 H), 7.39 (dd, *J*=8.05, 5.86 Hz, 2 H), 8.07 (s, 1 H), 8.42 (s, 1 H), 9.28 (t, *J*=6.59 Hz, 1 H).

Example 259

(*trans*)-Methyl 4-((5-(2-((3-(hydroxymethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate

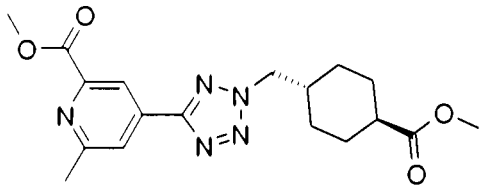


Step 1: Preparation of (*trans*)-methyl 4-((3-nitrophenylsulfonyloxy)methyl)cyclohexanecarboxylate



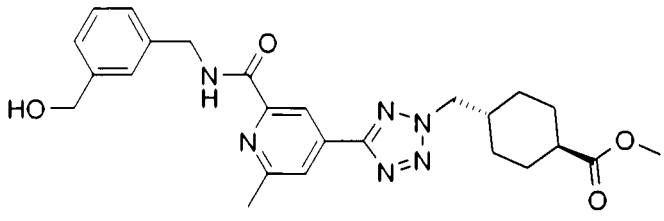
A mixture of *trans*-methyl 4-(hydroxymethyl)cyclohexanecarboxylate (22.0 g, 128 mmol) and 3-nitrobenzene-1-sulfonyl chloride (35.7 g, 161 mmol) in dichloromethane (130 mL) was cooled in an ice bath and triethylamine (23.7 mL, 170 mmol) was added by addition funnel maintaining the temperature below 7°C. The mixture was stirred at this temperature for 1 hour and then quenched with water (1 mL). The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was slurried in methanol, filtered, and dried in a vacuum oven to afford the title compound as a white solid (40.66 g, 89%).

Step 2: Preparation of methyl 4-(2-(((*trans*)-4-(methoxycarbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate



Diisopropylethylamine (20.7 mL, 118.6 mmol) was added by addition funnel to a mixture of (*trans*)-methyl 4-((3-nitrophenylsulfonyloxy)methyl)cyclohexanecarboxylate (35.9 g, 100.4 mmol) and methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (20 g, 91.2 mmol) in acetonitrile (120 mL). The mixture was heated at reflux for 7 hours and then was concentrated in vacuo. The residue was suspended in dichloromethane and washed with 1N aqueous sodium hydroxide solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography (heptane/ethyl acetate, 65/35; 50/50) to afford the title compound as a white solid (27 g, 79%).

Step 3: Preparation of (*trans*)-methyl 4-((5-(2-((3-(hydroxymethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate

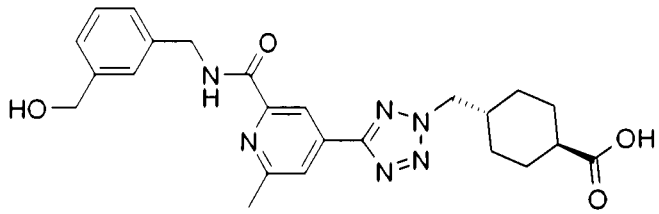


(3-(Aminomethyl)phenyl)methanol (prepared as described in step 1 of the synthesis of *N*-(3-(hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide, Example 183) (115 mg, 0.838 mmol) was added to a solution of methyl 4-(2-(((*trans*)-4-(methoxycarbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (75 mg, 0.201

mmol) in *N*,*N*-dimethylformamide (6 mL) and the mixture was heated at 60 °C for 3 days. The reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound as a solid (50 mg, 65%). LC/MS (0%-25% CH_3CN/H_2O, 5 min.) 3.010 min., *m/z* 479 (M+H). ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.10 - 1.24 (m, 2 H), 1.34 - 1.49 (m, 2 H), 1.74 (dd, *J*=13.7, 3.0 Hz, 2 H), 1.99 (dd, *J*=13.8, 3.1 Hz, 2 H), 2.03 - 2.16 (m, 1 H), 2.23 - 2.35 (m, 1 H), 2.65 - 2.71 (m, 3 H), 3.62 (s, 3 H), 3.96 (s, 1 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.74 (s, 2 H), 7.77 (d, *J*=8.1 Hz, 1 H), 8.03 (dd, *J*=8.2, 1.5 Hz, 1 H), 8.09 (d, *J*=1.1 Hz, 1 H), 8.54 (s, 1 H), 8.72 (d, *J*=1.6 Hz, 1 H).

Example 260

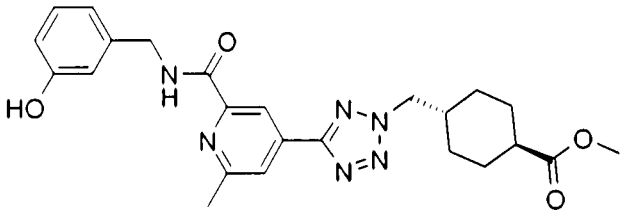
(*trans*)-4-((5-(2-((3-(Hydroxymethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



(*trans*)-Methyl 4-((5-(2-((3-(hydroxymethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (50 mg, 0.13 mmol) was dissolved in tetrahydrofuran (1.0 mL) and a 4 N aqueous solution of lithium hydroxide (1.0 mL) was added. The mixture was allowed to stir at room temperature overnight. The reaction mixture was concentrated to afford the title compound (16.7 mg, 18%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.12 - 1.25 (m, 2 H), 1.35 - 1.48 (m, 2 H), 1.70 - 1.78 (m, 2 H), 1.95 - 2.03 (m, 2 H), 2.05 - 2.14 (m, 1 H), 2.25 - 2.35 (m, 1 H), 2.67 (s, 3 H), 3.33 (s, 1 H), 3.62 (s, 3 H), 3.85 (s, 3 H), 4.62 (d, *J*=7.25 Hz, 2 H), 4.67 (s, 2 H), 6.90 - 6.97 (m, 1 H), 6.97 - 7.08 (m, 2 H), 8.09 (s, 1 H), 8.55 (s, 1 H).

Example 261

(*trans*)-Methyl 4-((5-(2-((3-hydroxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate

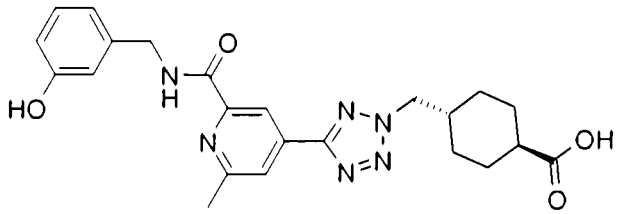


A mixture of 3-(aminomethyl)phenol (1.01 g, 8.21 mmol) and methyl 4-(2-(((*trans*)-4-(methoxycarbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (prepared as described in step 2 of the synthesis of (*trans*)-methyl 4-((5-(2-((3-(hydroxymethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate, Example 260) (1.0 g, 2.05 mmol) in methanol (25 mL) was heated at 60 °C for 4 days. The reaction mixture was allowed to cool to room temperature and filtered. The resulting solids were washed with methanol to afford the title compound (770 mg, 80%). MS (ES+) *m/z* 465 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 -

1.22 (m, 2 H), 1.24 - 1.41 (m, 2 H), 1.58 - 1.71 (m, 2 H), 1.85 - 1.95 (m, 2 H), 1.96 - 2.08 (m, 1 H), 2.20 - 2.32 (m, 1 H), 2.67 (s, 3 H), 3.57 (s, 3 H), 4.45 (d, *J*=6.44 Hz, 2 H), 4.67 (d, *J*=6.98 Hz, 2 H), 6.62 (d, 1 H), 6.72 - 6.80 (m, 2 H), 7.10 (t, *J*=7.92 Hz, 1 H), 8.08 (d, *J*=1.34 Hz, 1 H), 8.43 (s, 1 H), 9.22 (t, *J*=6.31 Hz, 1 H), 9.32 (s, 1 H).

Example 262

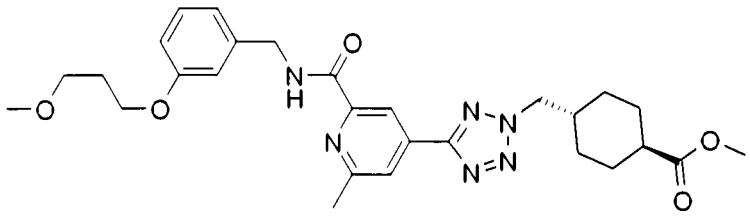
(*trans*)-4-((5-(2-((3-Hydroxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-cyclohexanecarboxylic acid



A mixture of (*trans*)-methyl 4-((5-(2-((3-hydroxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 261) (50 mg, 0.11 mmol) and lithium hydroxide (15 mg, 0.65 mmol) in a mixture of tetrahydrofuran/water (5/1, 3 mL) was stirred at room temperature for 3 days. The reaction mixture was concentrated and the aqueous residue was treated dropwise with 3N hydrochloric acid until a precipitate formed. The precipitate was taken up in a mixture of dichloromethane and methanol and then passed through an Isolute SPE 103 cartridge eluting with dichloromethane/methanol (9/1). The filtrate was concentrated. The residue was washed with water and dried to afford the title compound as a white solid (38 mg, 76%). MS (ES+) *m/z* 451 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.20 (m, 2 H), 1.21 - 1.38 (m, 2 H), 1.65 (d, *J*=10.74 Hz, 2 H), 1.90 (d, *J*=11.01 Hz, 2 H), 1.99 (s, *J*=7.12, 3.89 Hz, 1 H), 2.08 - 2.20 (m, 1 H), 2.68 (s, 3 H), 4.46 (d, *J*=6.18 Hz, 2 H), 4.67 (d, *J*=6.98 Hz, 2 H), 6.58 - 6.66 (m, 1 H), 6.71 - 6.79 (m, 1 H), 7.10 (t, *J*=8.06 Hz, 1 H), 8.08 (d, *J*=1.34 Hz, 1 H), 8.43 (s, 1 H), 9.15 - 9.27 (m, 1 H), 9.30 (s, 1 H), 12.03 (s, 1 H).

Example 263

(*trans*)-Methyl 4-((5-(2-((3-(3-methoxypropoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate

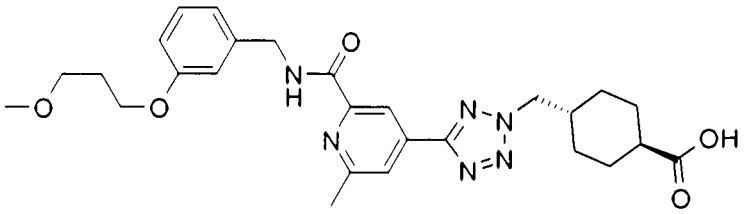


A mixture of (*trans*)-methyl 4-((5-(2-((3-hydroxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 261) (50 mg, 0.11 mmol), 1-bromo-3-methoxypropane (33 mg, 0.22 mmol), potassium carbonate (37 mg, 0.27 mmol), and tetrabutylammonium iodide (4 mg, 0.01 mmol) in *N*,*N*-dimethylformamide (2 mL) was heated at 60 °C for 18 hours. Additional potassium carbonate (30 mg) was added and heating was continued for

18 hours. The reaction mixture was purified by reverse phase preparative HPLC to afford the title compound as an oil (26 mg, 45%). MS (ES+) *m/z* 537 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.08 - 1.24 (m, 2 H), 1.37 - 1.55 (m, 2 H), 1.74 - 1.85 (m, 2 H), 1.96 - 2.21 (m, 5 H), 2.22 - 2.35 (m, 1 H), 2.67 (s, 3 H), 3.35 (d, *J*=1.61 Hz, 3 H), 3.55 (t, *J*=5.91 Hz, 2 H), 3.67 (s, 3 H), 4.06 (t, *J*=6.31 Hz, 2 H), 4.56 (d, *J*=6.71 Hz, 2 H), 4.68 (d, *J*=6.18 Hz, 2 H), 6.77 - 6.89 (m, *J*=8.32 Hz, 1 H), 6.91 - 7.03 (m, 2 H), 7.21 - 7.33 (m, 1 H), 8.08 (s, 1 H), 8.46 - 8.60 (m, 1 H), 8.76 (s, 1 H)

Example 264

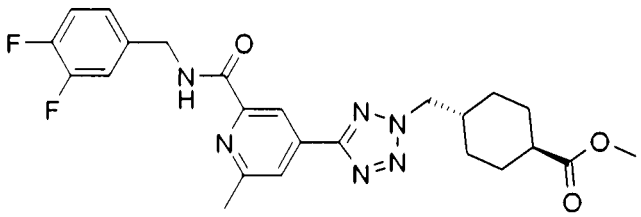
(*trans*)-4-((5-(2-((3-(3-Methoxypropoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



A mixture of (*trans*)-methyl 4-((5-(2-((3-(3-methoxypropoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 263) (25 mg, 0.05 mmol) and lithium hydroxide (5 mg, 0.2 mmol) in a mixture of tetrahydrofuran/water (5/1, 3 mL) was stirred at room temperature for 18 hours. The reaction mixture was acidified with a few drops of 4N hydrochloric acid and purified by reverse phase preparative HPLC to afford the title compound (17 mg, 57%). MS (ES+) *m/z* 523 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.11 - 1.25 (m, 2 H), 1.41 - 1.55 (m, 2 H), 1.77-1.86 (m, 2 H), 2.00 - 2.19 (m, 6 H), 2.26 - 2.37 (m, 1 H), 2.65 (s, 3 H), 3.35 (s, 3 H), 3.46-3.56 (m, 1 H), 3.56 (t, *J*=6.18 Hz, 2 H), 4.06 (t, *J*=6.18 Hz, 2 H), 4.56 (d, *J*=6.98 Hz, 2 H), 4.68 (d, *J*=5.91 Hz, 2 H), 6.85 (t, *J*=8.19, 2.28 Hz, 1 H), 6.91 - 7.00 (m, 2 H), 8.06 (d, *J*=1.07 Hz, 1 H), 8.46 (t, *J*=6.04 Hz, 1 H), 8.74 (s, 1 H).

Example 265

(*trans*)-Methyl 4-((5-(2-((3,4-difluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate

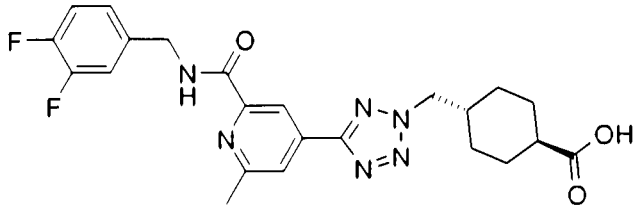


A mixture of (3,4-difluorophenyl)methanamine (153 mg, 1.07 mmol) and 4-(2-(((*trans*)-4-(methoxycarbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (prepared as described in step 2 of the synthesis of (*trans*)-methyl 4-((5-(2-((3-(hydroxymethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate, Example 260) (100 mg, 0.27 mmol) in tetrahydrofuran (0.5 mL) was heated at 60 °C for 3 days. The reaction mixture was purified by reverse phase preparative HPLC. The fractions containing the desired product were combined and

concentrated. The residue was taken up in methanol and passed through a carbonate cartridge. The filtrate was concentrated to afford the title compound as a white solid (87 mg, 61%). MS (ES+) *m/z* 485 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.08 - 1.25 (m, 2 H), 1.38 - 1.53 (m, 2 H), 1.79 (dd, *J*=13.70, 2.95 Hz, 2 H), 1.99 - 2.19 (m, 3 H), 2.22 - 2.35 (m, 1 H), 2.66 (s, 3 H), 3.67 (s, 3 H), 4.56 (d, *J*=6.98 Hz, 2 H), 4.66 (d, *J*=6.44 Hz, 2 H), 7.07 - 7.26 (m, 3 H), 8.08 (d, *J*=1.07 Hz, 1 H), 8.43 - 8.54 (m, 1 H), 8.73 (s, 1 H)

Example 266

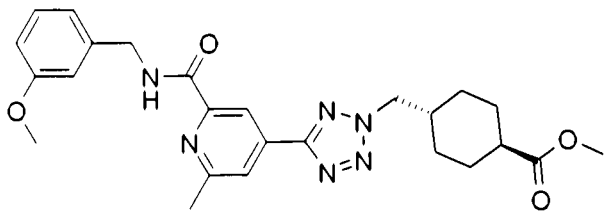
(*trans*)-4-((5-(2-((3,4-Difluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-cyclohexanecarboxylic acid



A mixture of (*trans*)-methyl 4-((5-(2-((3,4-difluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 265) (50 mg, 0.11 mmol) and lithium hydroxide (8 mg, 0.33 mmol) in a mixture of tetrahydrofuran/water (5/1, 6 mL) was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC. The fractions containing the desired product were combined and concentrated. The residue was taken up in dichloromethane and saturated sodium chloride solution (2 mL) and passed through a Varian ChemElute column eluting with dichloromethane. The filtrate was concentrated to afford the title compound as a white solid (35 mg, 72%). MS (ES+) *m/z* 471 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.11 - 1.29 (m, 2 H), 1.40 - 1.56 (m, 2 H), 1.74 - 1.86 (m, 2 H), 2.02 - 2.22 (m, 3 H), 2.25 - 2.38 (m, 2 H), 2.67 (s, 3 H), 4.56 (d, *J*=6.98 Hz, 2 H), 4.66 (d, *J*=6.18 Hz, 2 H), 7.07 - 7.26 (m, 3 H), 8.09 (s, 1 H), 8.44 - 8.63 (m, 1 H), 8.73 (s, 1 H).

Example 267

(*trans*)-Methyl 4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate

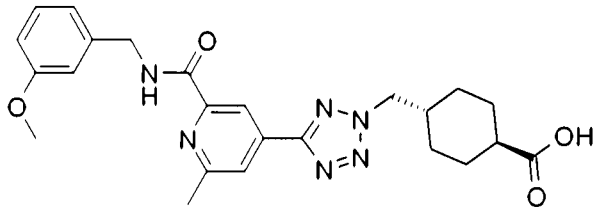


A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (2.0 g, 6.17 mmol), (*trans*)-methyl 4-(hydroxymethyl)cyclohexanecarboxylate (2.12 g, 12.33 mmol), and polymer supported triphenylphosphine resin (7.18 g, 15.43 mmol, 2.15 mmol/g loading) in tetrahydrofuran (100 mL) was

cooled in an ice bath and di-*tert*-butylazodicarbxylate (2.84 g, 12.33 mmol) was added. The mixture was stirred for 10 minutes in the ice bath, allowed to warm to room temperature, and stirred an additional 2 hours. The reaction mixture was filtered and the resin was washed with tetrahydrofuran and methanol. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound as a white solid (1.58 g, 54%). MS (ES+) *m/z* 479 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.21 (m, 2 H), 1.25 - 1.39 (m, 2 H), 1.58 - 1.70 (m, 2 H), 1.84 - 1.95 (m, 2 H), 1.95 - 2.08 (m, 1 H), 2.19 - 2.31 (m, 1 H), 2.67 (s, 3 H), 3.57 (s, 3 H), 3.73 (s, 3 H), 4.51 (d, *J*=6.18 Hz, 2 H), 4.67 (d, *J*=6.98 Hz, 2 H), 6.77 - 6.86 (m, 1 H), 6.88 - 6.97 (m, 2 H), 7.24 (t, *J*=8.19 Hz, 1 H), 8.07 (s, 1 H), 8.42 (s, 1 H), 9.26 (t, *J*=6.44 Hz, 1 H)

Example 268

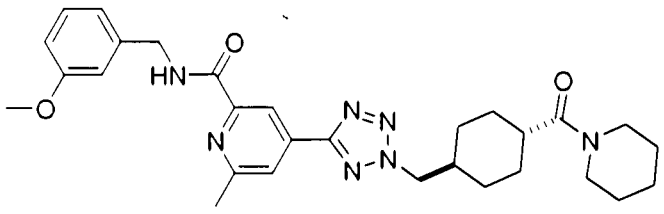
(*trans*)-4-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-cyclohexanecarboxylic acid



A mixture of (*trans*)-methyl 4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 267) (2.729 g, 5.697 mmol), aqueous 2.5 N sodium hydroxide solution (28.515 mmol, 5 equiv.), water (114 mL), and tetrahydrofuran (114 mL) was stirred overnight at room temperature. The reaction mixture was concentrated and the aqueous residue was acidified. The precipitate was filtered, washed with water, and dried under high vacuum to afford the title compound as a solid (2.598 g, 98%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.217 min., *m/z* 465 (M+H). ^{1}H NMR (400 MHz, acetone-d_6) δ ppm 1.15 - 1.32 (m, 2 H), 1.33 - 1.50 (m, 2 H), 1.72 - 1.83 (m, 2 H), 1.99 - 2.02 (m, *J*=3.22 Hz, 2 H), 2.07 - 2.18 (m, 1 H), 2.20 - 2.33 (m, 1 H), 2.64 (s, 3 H), 3.77 (s, 3 H), 4.64 (d, *J*=6.44 Hz, 2 H), 4.68 (d, *J*=6.98 Hz, 2 H), 6.82 (dd, *J*=8.32, 1.61 Hz, 1 H), 6.93 - 7.02 (m, 2 H), 7.24 (t, *J*=7.92 Hz, 1 H), 8.06 (d, *J*=1.07 Hz, 1 H), 8.61 (s, 1 H), 8.88 (s, 1 H).

Example 269

***N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(piperidine-1-carbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**

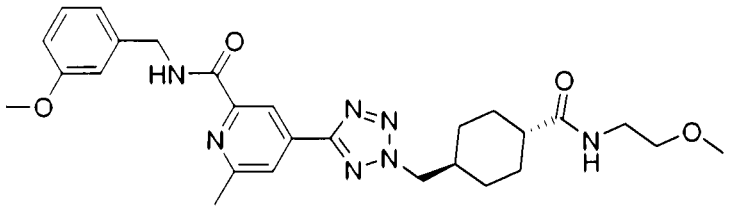


To a vial containing piperidine, (13.79 mg, 0.162 mmol) added a solution of (*trans*)-4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid

(prepared as described in Example 268) (51.0 mg, 0.108 mmol) and 1-hydroxybenzotriazole (2.9 mg, 0.022 mmol) in *N*,*N*-dimethylformamide (2 mL), followed by carbodiimide resin (125 mg, 0.162 mmol, 1.30 mmol/g loading), dichloromethane (2 mL), and *N*-methylmorpholine (54.54 mg, 0.54 mmol). The mixture was agitated on an orbital shaker overnight at room temperature. The mixture was filtered and the resin was washed with *N*,*N*-dimethylformamide and dichloromethane. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min.) to afford the title compound (34.5 mg, 60%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.705 min., *m/z* 532 (M+H).

Example 270

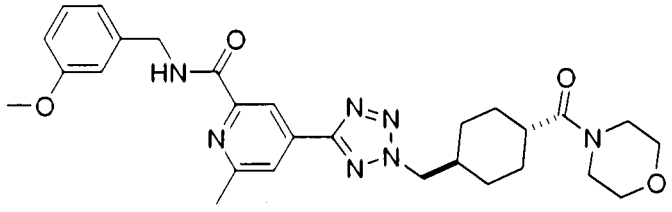
4-(2-(((*trans*)-4-((2-Methoxyethyl)carbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpicolinamide



The title compound (34.1 mg, 61%) was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(piperidine-1-carbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 269) by reaction with 2-methoxyethanamine. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.183 min., *m/z* 522 (M+H).

Example 271

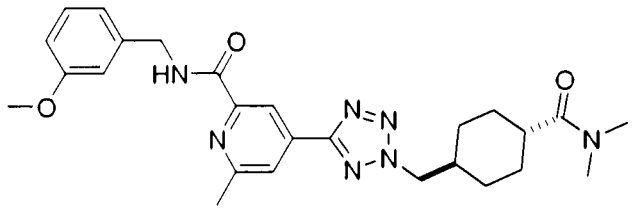
***N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(morpholine-4-carbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



The title compound (32.9 mg, 57%) was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(piperidine-1-carbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 269) by reaction with morpholine. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.259 min., *m/z* 534 (M+H).

Example 272

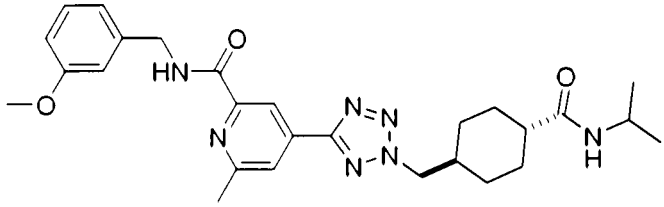
***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(dimethylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound (37.0 mg, 70%) was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(piperidine-1-carbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 269) by reaction with dimethylamine. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.295 min., *m/z* 492 (M+H).

Example 273

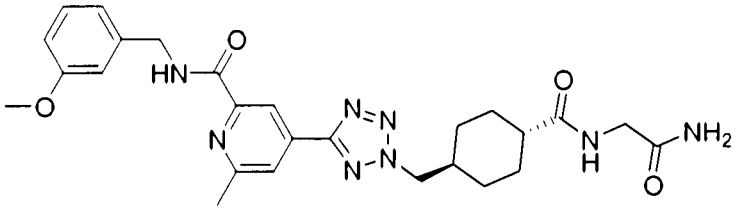
N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(isopropylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound (16.6 mg, 30%) was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(piperidine-1-carbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 269) by reaction with propan-2-amine. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.422 min., *m/z* 506 (M+H).

Example 274

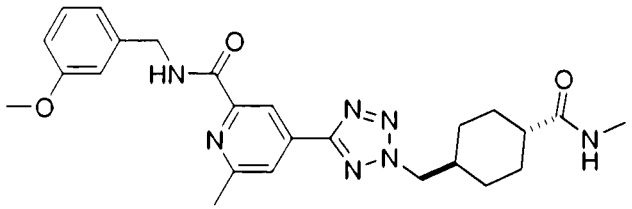
4-(2-(((*trans*)-4-((2-Amino-2-oxoethyl)carbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpicolinamide



The title compound (29.9 mg, 53%) was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(piperidine-1-carbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 269) by reaction with 2-aminoacetamide. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.861 min., *m/z* 521 (M+H).

Example 275

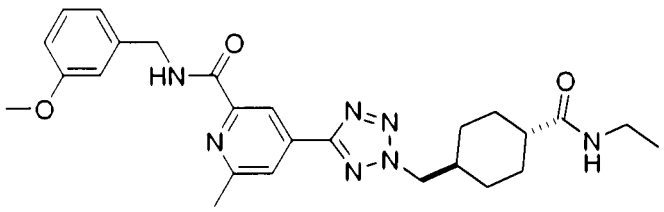
N-(3-Methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



O-(7-Azabenzotriazole-1-yl)-*N*,*N*,*N*'*N*'-tetramethyluronium hexafluorophosphate (49.0 mg, 0.130 mmol), methylamine (0.054 mL of a 2M solution in tetrahydrofuran, 0.108 mmol), and diisopropylethylamine (0.038 mL, 0.216 mmol) was added to a solution of (*trans*)-4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid (prepared as described in Example 268) (50.0 mg, 0.108 mmol) in *N*,*N*-dimethylformamide (1 mL), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min.) to afford the title compound as a solid (47.4 mg, 92%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.996 min., *m/z* 478 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 - 1.18 (m, 2 H), 1.21 - 1.43 (m, 2 H), 1.53 - 1.80 (m, 4 H), 1.87 - 2.13 (m, 1 H), 2.51 (d, *J*=4.39 Hz, 3 H), 2.65 (s, 3 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.59 Hz, 2 H), 4.65 (d, *J*=7.32 Hz, 2 H), 6.74 - 6.83 (m, 1 H), 6.90 (m, 2 H), 7.15 - 7.29 (m, 1 H), 7.48 - 7.64 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.11 - 9.29 (m, 1 H).

Example 276

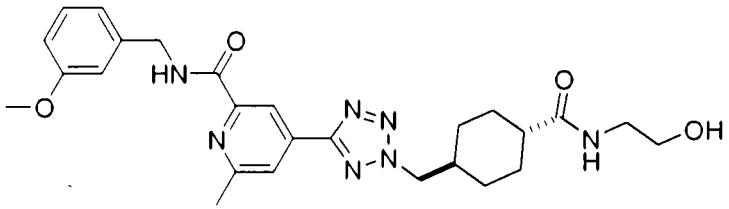
N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(ethylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound (45.2 mg, 85%) was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 275) by reaction with ethylamine. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.163 min., *m/z* 492 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 (t, *J*=7.32 Hz, 3 H), 1.00 - 1.15 (m, 2 H), 1.22 - 1.41 (m, 2 H), 1.52 - 1.82 (m, 4 H), 1.87 - 2.13 (m, 1 H), 2.65 (s, 3 H), 2.89 - 3.09 (m, 2 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.59 Hz, 2 H), 4.65 (d, *J*=6.59 Hz, 2 H), 6.74 - 6.85 (m, 1 H), 6.90 (m, 2 H), 7.13 - 7.29 (m, 1 H), 7.51 - 7.68 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.08 - 9.26 (m, 1 H).

Example 277

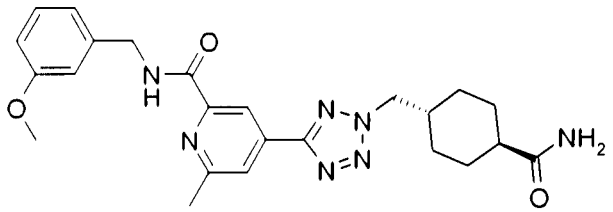
4-(2-(((*trans*)-4-((2-Hydroxyethyl)carbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-N-(3-methoxybenzyl)-6-methylpicolinamide



The title compound (45.2 mg, 85%) was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylcarbamoyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 275) by reaction with 2-aminoethanol. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.835 min. 508 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 - 1.19 (m, 2 H), 1.21 - 1.44 (m, 2 H), 1.54 - 1.80 (m, 4 H), 1.88 - 2.16 (m, 3 H), 2.65 (s, 3 H), 2.96 - 3.14 (m, 2 H), 3.71 (s, 3 H), 4.49 (d, *J*=5.86 Hz, 2 H), 4.65 (d, *J*=6.59 Hz, 2 H), 6.73 - 6.85 (m, 1 H), 6.90 (m, 2 H), 7.10 - 7.33 (m, 1 H), 7.50 - 7.68 (m, 1 H), 8.06 (s, 1 H), 8.41 (s, 1 H).

Example 278

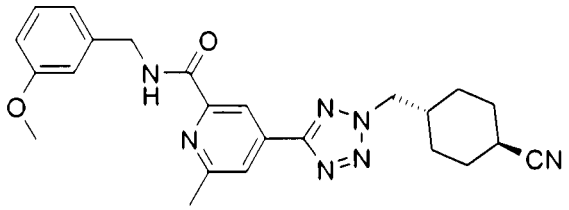
N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Formamide (120 mg) was added to a solution of (*trans*)-methyl 4-((5-(2-((3-methoxybenzyl)-carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 267) (100 mg, 0.2 mmol) in anhydrous tetrahydrofuran (1 mL) and the mixture was heated to reflux. A 25% sodium methoxide solution in methanol (120 mg) was added and the reaction was stirred at reflux for 2 hours. The reaction mixture was allowed to cool to room temperature and then diluted with methanol (2 mL). The resulting precipitate was filtered, washed with a small amount of methanol and the solid was dried in a vacuum desiccator to afford the title compound as a white solid (77.5 mg). MS (ES+) *m/z* 464 (M+H).

Example 279

N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

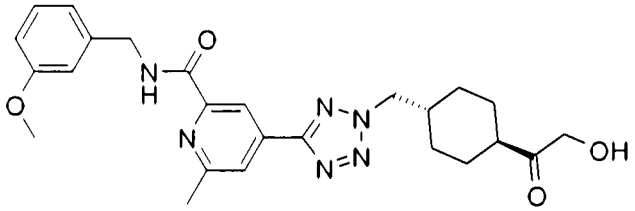


Polymer supported triphenylphosphine (Argonaut; 2.15 mmol/g, 500 mg) was added to *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

(Example 278) (77.5 mg, 0.16 mmol) in a mixture of carbon tetrachloride (0.5 mL) and dichloroethane (4.5 mL) and the mixture was heated at 80 °C for 2 hours. The reaction mixture was filtered and the resin was washed with dichloroethane. The filtrate was concentrated and the residue was recrystallized from methanol to afford the title compound as a white solid (33.6 mg). MS (ES+) *m/z* 446 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.29 (t, *J*=6.6 Hz, 1 H), 8.43 (s, 1 H), 8.09 (s, 1 H), 7.25 (t, *J*=8.0 Hz, 1 H), 6.90 - 6.94 (m, 2 H), 6.83 (dd, *J*=8.1, 2.3 Hz, 1 H), 4.69 (d, *J*=6.8 Hz, 2 H), 4.51 (d, *J*=6.5 Hz, 2 H), 3.74 (s, 3 H), 2.68 (s, 3 H), 2.59 - 2.67 (m, 1 H), 1.98 - 2.13 (m, 3 H), 1.65 (d, *J*=13.1 Hz, 2 H), 1.45 - 1.56 (m, 2 H), 1.07 - 1.19 (m, 2 H).

Example 280

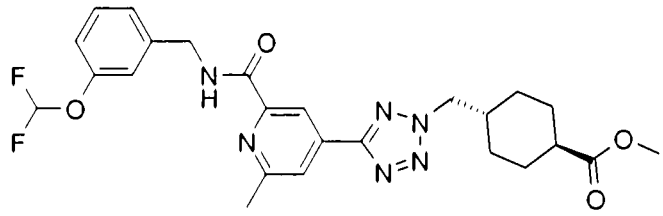
N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxyacetyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Oxalyl chloride (10 mL) was added to a solution of (*trans*)-4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid (prepared as described in Example 268) (1.4 g, 3.0 mmol) in dichloromethane (10 mL) and the mixture was stirred at room temperate for 3 hours. The reaction mixture was concentrated. The residue was taken up in dioxane (15 mL) and treated with tris(trimethylsiloxy)ethylene (1.94 g, 6.63 mmol). The mixture was heated to 90 °C for 3 hours and then stirred at room temperate for 18 hours. The mixture was treated with several drops of 4 N hydrochloric acid until gas stopped evolving. The reaction mixture was purified by reverse phase preparative HPLC. The crude product was taken up in methanol and passed through a carbonate cartridge. The filtrate was concentrated to afford the title compound as a white solid (24 mg, 2%). LCMS (ES+) *m/z* 479 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.41 (m, 4 H), 1.60 - 1.71 (m, *J*=10.98 Hz, 2 H), 1.85 - 1.96 (m, *J*=10.98 Hz, 2 H), 1.96 - 2.07 (m, 1 H), 2.20 - 2.31 (m, *J*=12.08, 12.08 Hz, 1 H), 2.67 (s, 3 H), 3.28 - 3.34 (m, 1 H), 3.57 (s, 2 H), 3.73 (s, 3 H), 4.51 (d, *J*=5.86 Hz, 2 H), 4.67 (d, *J*=6.59 Hz, 2 H), 6.82 (d, *J*=8.05 Hz, 1 H), 6.88 - 6.98 (m, 2 H), 7.24 (t, *J*=8.05 Hz, 1 H), 8.07 (s, 1 H), 8.43 (s, 1 H), 9.21 (t, *J*=6.22 Hz, 1 H).

Example 281

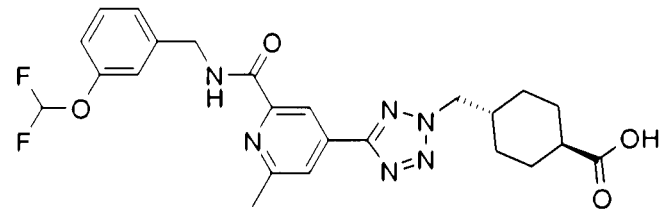
(*trans*)-Methyl 4-((5-(2-((3-(Difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate



A mixture of (3-(difluoromethoxy)phenyl)methanamine (380 mg, 2.2 mmol) and 4-(2-(((*trans*)-4-(methoxycarbonyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (prepared as described in step 2 of the synthesis of (*trans*)-methyl 4-((5-(2-((3-(hydroxymethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate, Example 260) (205 mg, 0.54 mmol) in *N*,*N*-dimethylacetamide (0.5 mL) was allowed to stir at room temperature for 3 days. The reaction mixture was purified by reverse phase preparative HPLC. The product containing fractions were passed through a carbonate resin column and concentrated. The residue was slurried with ethyl ether, decanted, and the solid was dried to afford the title compound (135 mg). MS (ES+) *m/z* 515 (M+H).

Example 282

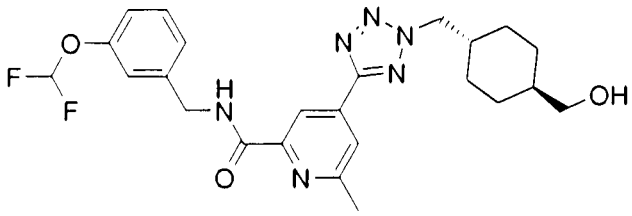
(*trans*)-4-((5-(2-((3-(Difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



Sodium hydroxide (1 pellet) was added to a solution of (*trans*)-methyl 4-((5-(2-((3-(difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 281) (40 mg, 0.077 mmol) in a mixture of tetrahydrofuran/water (0.6 mL, 1/1) and the mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse phase preparative HPLC. The crude product was slurried in ethyl ether, decanted, and the solid was dried to afford the title compound as a white solid (29 mg). MS (ES+) *m/z* 502 (M+H).

Example 283

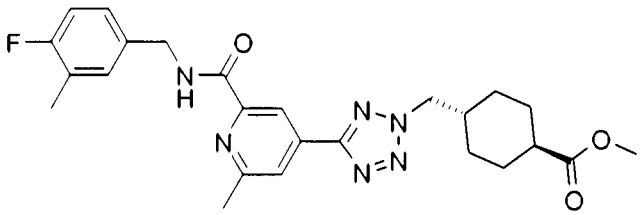
***N*-(3-(Difluoromethoxy)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Lithium aluminum hydride (50 mg) was added to a solution of (*trans*)-methyl 4-((5-(2-((3-(difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 281) (53 mg, 0.1 mmol) in anhydrous tetrahydrofuran (1 mL) cooled in an ice bath. The mixture was stirred at room temperature for 1 hour. Water (1 mL) was slowly added followed by acetonitrile (1 mL). The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by reverse phase preparative HPLC. Fractions containing the product were passed through a carbonate resin column. The crude product was slurried and decanted from ethyl ether several times, and dried in a vacuum desiccator to afford the title compound as a white solid (28 mg). MS (ES+) *m/z* 487 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.39 (t, *J*=6.4 Hz, 1 H), 8.43 (s, 1 H), 8.10 (s, 1 H), 7.36 - 7.41 (m, 1 H), 7.21 - 7.24 (m, 1 H), 7.16 (s, 1 H), 7.03 - 7.09 (m, 2 H), 4.67 (d, *J*=7.0 Hz, 2 H), 4.55 (d, *J*=6.3 Hz, 2 H), 4.37 (t, *J*=5.2 Hz, 1 H), 3.19 (t, *J*=5.8 Hz, 2 H), 2.69 (s, 3 H), 1.91 - 2.03 (m, 1 H), 1.74 (d, *J*=11.4 Hz, 2 H), 1.62 (d, *J*=10.9 Hz, 2 H), 1.25 - 1.36 (m, 1 H), 1.02 - 1.15 (m, 2 H), 0.81 - 0.94 (m, 2 H).

Example 284

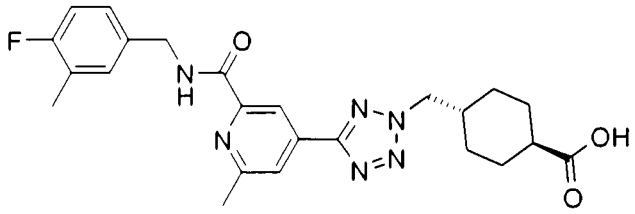
(*trans*)-Methyl 4-((5-(2-((4-Fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate



The title compound was prepared in a similar manner to (*trans*)-methyl 4-((5-(2-((3-(difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (Example 281) by reaction with 4-fluoro-3-methylbenzylamine to afford 172 mg as a solid. MS (ES+) *m/z* 481 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (t, *J*=6.4 Hz, 1 H), 8.43 (s, 1 H), 8.09 (d, *J*=0.9 Hz, 1 H), 7.26 (d, *J*=7.9 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.05 - 7.11 (m, 1 H), 4.68 (d, *J*=6.8 Hz, 2 H), 4.48 (d, *J*=6.5 Hz, 2 H), 3.58 (s, 3 H), 2.68 (s, 3 H), 2.22 - 2.31 (m, 1 H), 2.21 (d, *J*=1.5 Hz, 3 H), 1.95 - 2.07 (m, 1 H), 1.91 (d, *J*=11.1 Hz, 2 H), 1.66 (d, *J*=13.0 Hz, 2 H), 1.26 - 1.39 (m, 2 H), 1.07 - 1.21 (m, 2 H).

Example 285

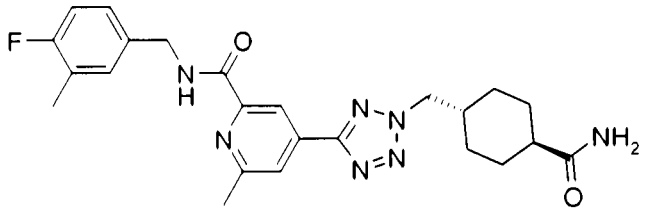
(*trans*)-4-((5-(2-((4-Fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



Sodium hydroxide (1 pellet) was added to a solution of (*trans*)-methyl 4-((5-(2-((4-fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 284) (81 mg, 0.168 mmol) in a mixture of tetrahydrofuran/water (0.6 mL, 1/1) and the mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse phase preparative HPLC. The crude product was slurried in ethyl ether, decanted, and the solid was dried to afford the title compound as a white solid (71 mg). MS (ES+) *m/z* 467 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.12 (br. s., 1 H), 9.30 (t, *J*=6.4 Hz, 1 H), 8.43 (s, 1 H), 8.09 (s, 1 H), 7.26 (d, *J*=7.7 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.08 (t, *J*=9.6 Hz, 1 H), 4.68 (d, *J*=7.0 Hz, 2 H), 4.48 (d, *J*=6.3 Hz, 2 H), 2.68 (s, 3 H), 2.21 (d, *J*=1.4 Hz, 3 H), 2.08 - 2.17 (m, 1 H), 1.94 - 2.05 (m, 1 H), 1.90 (d, *J*=10.8 Hz, 2 H), 1.65 (d, *J*=12.5 Hz, 2 H), 1.22 - 1.36 (m, 2 H), 1.06 - 1.18 (m, 2 H).

Example 286

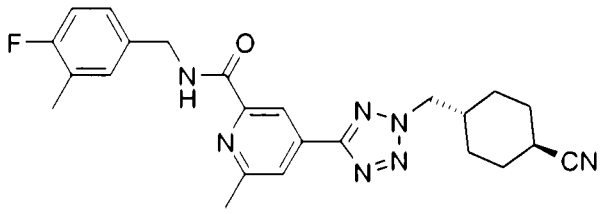
N-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Formamide (60 mg) was added to a solution of (*trans*)-methyl 4-((5-(2-((4-fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 284) (50 mg, 0.1 mmol) in anhydrous tetrahydrofuran (0.6 mL) and the mixture was heated to reflux. A 25% sodium methoxide solution in methanol (60 mg) was added and the reaction was stirred at reflux for 2 hours. The reaction mixture was allowed to cool to room temperature, diluted with excess methanol, and then concentrated. Methanol (2 mL) was added to the residue. The resulting precipitate was filtered, washed with a small amount of methanol and the solid was dried in a vacuum desiccator to afford the title compound as a white solid (25.4 mg). MS (ES+) *m/z* 466 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (t, *J*=6.4 Hz, 1 H), 8.43 (s, 1 H), 8.09 (s, 1 H), 7.26 (d, *J*=7.7 Hz, 1 H), 7.16 - 7.22 (m, 2 H), 7.08 (t, *J*=9.1 Hz, 1 H), 6.67 (br. s., 1 H), 4.68 (d, *J*=6.8 Hz, 2 H), 4.48 (d, *J*=6.3 Hz, 2 H), 2.68 (s, 3 H), 2.22 (d, *J*=1.0 Hz, 3 H), 2.02 (t, *J*=12.0 Hz, 2 H), 1.76 (d, *J*=10.9 Hz, 2 H), 1.65 (d, *J*=11.8 Hz, 2 H), 1.25 - 1.37 (m, 2 H), 1.03 - 1.15 (m, 2 H).

Example 287

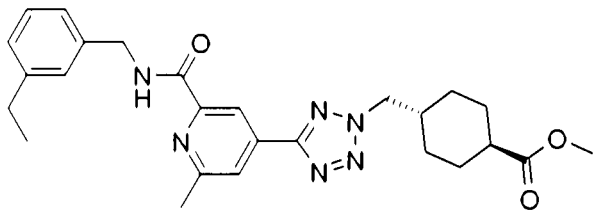
***N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Polymer supported triphenylphosphine (Argonaut; 2.15 mmol/g) was added to *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 286) (20 mg, 0.043 mmol) in a mixture of carbon tetrachloride (0.16 mL) and dichloroethane (1.5 mL) and the mixture was heated at 80 °C for 2 hours. The reaction mixture was filtered and the resin was washed with dichloroethane. The filtrate was concentrated to afford the title compound as a white solid (9.7 mg). MS (ES+) *m/z* 448 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (t, *J*=6.3 Hz, 1 H), 8.43 (s, 1 H), 8.09 (d, *J*=0.9 Hz, 1 H), 7.26 (d, *J*=7.3 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.08 (t, *J*=9.1 Hz, 1 H), 4.69 (d, *J*=7.0 Hz, 2 H), 4.48 (d, *J*=6.3 Hz, 2 H), 2.68 (s, 3 H), 2.59 - 2.67 (m, 1 H), 2.22 (d, *J*=1.4 Hz, 3 H), 1.98 - 2.11 (m, 3 H), 1.65 (d, *J*=13.3 Hz, 2 H), 1.44 - 1.58 (m, 2 H), 1.05 - 1.19 (m, 2 H).

Example 288

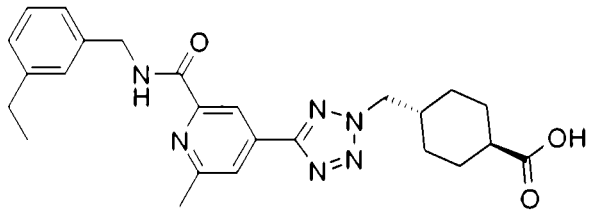
(*trans*)-Methyl 4-((5-(2-((3-Ethylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate



The title compound was prepared in a similar manner to (*trans*)-methyl 4-((5-(2-((3-(difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (Example 281) by reaction with 3-ethylbenzylamine to afford 155 mg. MS (ES+) *m/z* 477 (M+H).

Example 289

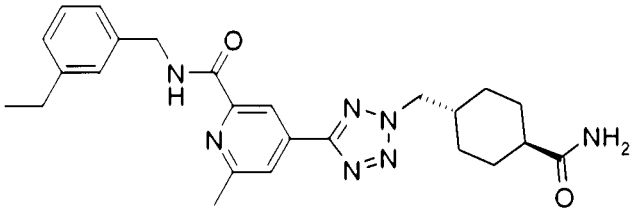
(*trans*)-4-((5-(2-((3-Ethylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



The title compound was prepared in a similar manner to (*trans*)-4-((5-(2-((3-(difluoromethoxy)-benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid (Example 282) by reaction with(*trans*)-methyl 4-((5-(2-((3-ethylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (Example 288) to afford 45 mg as a white solid. MS (ES+) *m/z* 463 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.11 (br. s., 1 H), 9.27 (t, *J*=6.5 Hz, 1 H), 8.44 (s, 1 H), 8.09 (s, 1 H), 7.08 - 7.26 (m, 4 H), 4.68 (d, *J*=6.8 Hz, 2 H), 4.52 (d, *J*=6.3 Hz, 2 H), 2.68 (s, 3 H), 2.59 (q, *J*=7.6 Hz, 2 H), 2.09 - 2.17 (m, 1 H), 1.95 - 2.05 (m, 1 H), 1.90 (d, *J*=11.1 Hz, 2 H), 1.65 (d, *J*=10.6 Hz, 2 H), 1.23 - 1.36 (m, 2 H), 1.06 - 1.19 (m, 5 H).

Example 290

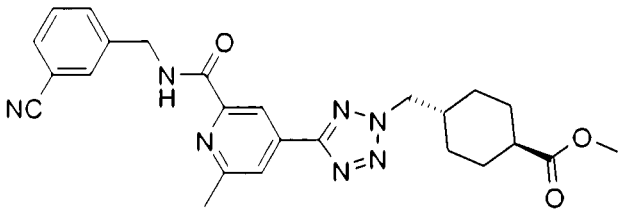
N-(3-Ethylbenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Formamide (120 mg) was added to a solution of (*trans*)-methyl 4-((5-(2-((3-ethylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 288) (80 mg, 0.16 mmol) in anhydrous tetrahydrofuran (1 mL) and the mixture was heated to reflux. A 25% sodium methoxide solution in methanol (120 mg) was added and the reaction was stirred at reflux for 2 hours. The reaction mixture was allowed to cool to room temperature and was diluted with methanol (2 mL). The mixture was stirred for 15 minutes and then the resulting precipitate was filtered, washed with a small amount of methanol and dried in a vacuum desiccator to afford the title compound as a white solid (41 mg). MS (ES+) *m/z* 462 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.17 (t, *J*=6.2 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.03 - 7.25 (m, 5 H), 6.58 (br. s., 1 H), 4.65 (d, *J*=7.0 Hz, 2 H), 4.50 (d, *J*=6.2 Hz, 2 H), 2.65 (s, 3 H), 2.56 (q, *J*=7.4 Hz, 2 H), 1.90 - 2.05 (m, 2 H), 1.74 (d, *J*=11.3 Hz, 2 H), 1.63 (d, *J*=11.0 Hz, 2 H), 1.22 - 1.36 (m, 2 H), 1.01 - 1.18 (m, 5 H).

Example 291

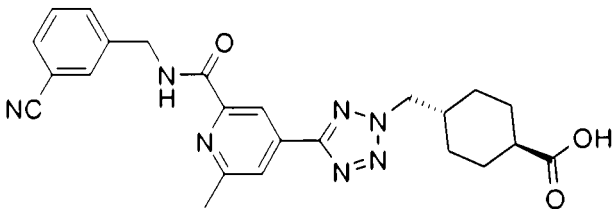
(*trans*)-Methyl 4-((5-(2-((3-Cyanobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate



The title compound was prepared in a similar manner to (*trans*)-methyl 4-((5-(2-((3-(difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (Example 281) by reaction with 3-(aminomethyl)benzonitrile to afford 157 mg as a white solid. MS (ES+) *m/z* 474 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.47 (t, *J*=6.3 Hz, 1 H), 8.43 (s, 1 H), 8.10 (s, 1 H), 7.79 (s, 1 H), 7.74 (d, *J*=7.7 Hz, 1 H), 7.70 (d, *J*=7.9 Hz, 1 H), 7.56 (t, *J*=7.8 Hz, 1 H), 4.68 (d, *J*=6.8 Hz, 2 H), 4.58 (d, *J*=6.1 Hz, 2 H), 3.58 (s, 3 H), 2.69 (s, 3 H), 2.22 - 2.31 (m, 1 H), 1.96 - 2.06 (m, 1 H), 1.91 (d, *J*=11.1 Hz, 2 H), 1.65 (d, *J*=10.8 Hz, 2 H), 1.33 (q, *J*=12.6 Hz, 2 H), 1.07 - 1.21 (m, 2 H).

Example 292

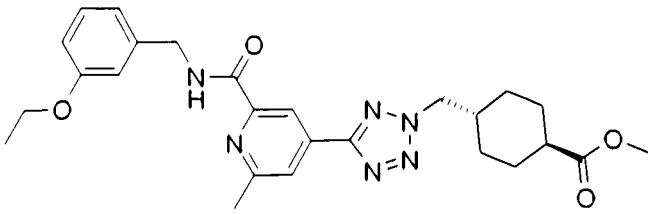
(*trans*)-4-((5-(2-((3-Cyanobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



Sodium hydroxide (1 pellet) was added to a solution of (*trans*)-methyl 4-((5-(2-((3-cyanobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 291) (81 mg, 0.17 mmol) in a mixture of tetrahydrofuran/water (0.6 mL, 1/1) and the mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse phase preparative HPLC. The crude product was slurried in ethyl ether, decanted, and the solid was dried to afford the title compound as a white solid (45 mg). MS (ES+) *m/z* 460 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.46 (t, *J*=6.4 Hz, 1 H), 8.43 (s, 1 H), 8.10 (d, *J*=0.9 Hz, 1 H), 7.79 (s, 1 H), 7.67 - 7.76 (m, 2 H), 7.56 (t, *J*=7.7 Hz, 1 H), 4.66 (d, *J*=7.0 Hz, 2 H), 4.58 (d, *J*=6.5 Hz, 2 H), 2.69 (s, 3 H), 1.92 - 2.02 (m, 2 H), 1.87 (d, *J*=10.9 Hz, 2 H), 1.61 (d, *J*=10.8 Hz, 2 H), 1.18 - 1.31 (m, 2 H), 1.01 - 1.15 (m, 2 H).

Example 293

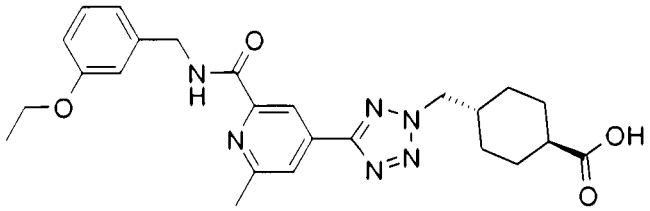
(*trans*)-Methyl 4-((5-(2-((3-Ethoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate



The title compound was prepared in a similar manner to (*trans*)-methyl 4-((5-(2-((3-(difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (Example 281) by reaction with (3-ethoxyphenyl)methanamine (prepared as described in step 2 of the synthesis of *N*-(3-ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide, Example 180) to afford 182 mg as a white solid. MS (ES+) *m/z* 493 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.28 (t, *J*=6.4 Hz, 1 H), 8.43 (s, 1 H), 8.09 (d, *J*=0.9 Hz, 1 H), 7.23 (t, *J*=8.0 Hz, 1 H), 6.89 - 6.92 (m, 2 H), 6.80 (dd, *J*=8.0, 1.9 Hz, 1 H), 4.68 (d, *J*=7.0 Hz, 2 H), 4.50 (d, *J*=6.5 Hz, 2 H), 4.00 (q, *J*=6.9 Hz, 2 H), 3.58 (s, 3 H), 2.68 (s, 3 H), 2.21 - 2.31 (m, 1 H), 1.97 - 2.07 (m, 1 H), 1.91 (d, *J*=10.6 Hz, 2 H), 1.66 (d, *J*=10.6 Hz, 2 H), 1.27 - 1.39 (m, 5 H), 1.09 - 1.21 (m, 2 H).

Example 294

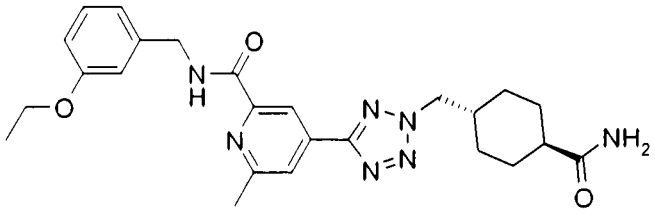
(*trans*)-4-((5-(2-((3-Ethoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



Sodium hydroxide (1 pellet) was added to a solution of (*trans*)-methyl 4-((5-(2-((3-ethoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 293) (78 mg, 0.15 mmol) in a mixture of tetrahydrofuran/water (0.6 mL, 1/1) and the mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse phase preparative HPLC. The crude product was slurried in ethyl ether, decanted, and the solid was dried to afford the title compound as a white solid (7 mg). MS (ES+) *m/z* 479 (M+H).

Example 295

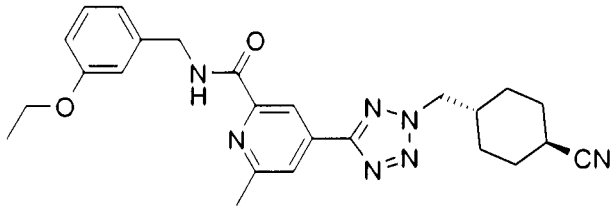
***N*-(3-Ethoxybenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Formamide (120 mg) was added to a solution of (*trans*)-methyl 4-((5-(2-((3-ethoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 293) (85 mg, 0.17 mmol) in anhydrous tetrahydrofuran (1 mL) and the mixture was heated to reflux. A 25% sodium methoxide solution in methanol (120 mg) was added and the reaction was stirred at reflux for 2 hours. The reaction mixture was allowed to cool to room temperature, diluted with excess methanol, and was concentrated. Methanol (2 mL) was added to the residue. The resulting precipitate was filtered, washed with a small amount of methanol and the solid was dried in a vacuum desiccator to afford the title compound as a white solid (33 mg). MS (ES+) *m/z* 478 (M+H).

Example 296

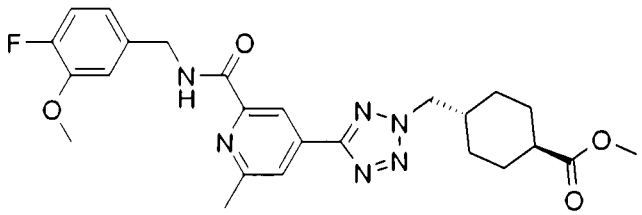
N-(3-Ethoxybenzyl)-4-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Polymer supported triphenylphosphine (Argonaut; 2.15 mmol/g, 200 mg) was added to *N*-(3-ethoxybenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 295) (30 mg, 0.062 mmol) in a mixture of carbon tetrachloride (0.25 mL) and dichloroethane (2.25 mL) and the mixture was heated at 80 °C for 2 hours. The reaction mixture was filtered and the resin was washed with dichloroethane. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC. Fractions containing product were passed through a carbonate resin column and were concentrated. The product was slurried and decanted several times from ether and the solid was dried in a vacuum desiccator to afford the title compound as a white solid (18.3 mg). MS (ES+) *m/z* 460 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.2 Hz, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.20 (t, *J*=8.1 Hz, 1 H), 6.85 - 6.90 (m, 2 H), 6.78 (d, *J*=8.8 Hz, 1 H), 4.65 (d, *J*=7.3 Hz, 2 H), 4.48 (d, *J*=5.9 Hz, 2 H), 3.97 (q, *J*=7.3 Hz, 2 H), 2.65 (s, 3 H), 2.56 - 2.64 (m, 1 H), 1.95 - 2.11 (m, 3 H), 1.63 (d, *J*=11.0 Hz, 2 H), 1.49 (q, *J*=12.7 Hz, 2 H), 1.28 (t, *J*=7.0 Hz, 3 H), 1.05 - 1.17 (m, 2 H).

Example 297

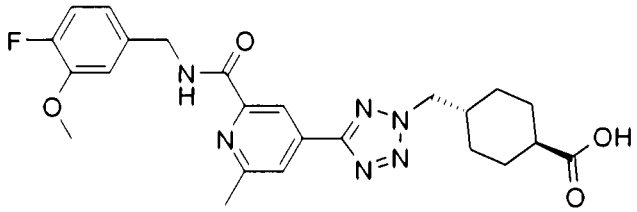
(*trans*)-Methyl 4-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate



The title compound was prepared in a similar manner to (*trans*)-methyl 4-((5-(2-((3-(difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (Example 281) by reaction with 4-fluoro-3-methoxybenzylamine (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) to afford 121 mg as a white solid. MS (ES+) *m/z* 497 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.31 (t, *J*=6.3 Hz, 1 H), 8.43 (s, 1 H), 8.09 (d, *J*=0.9 Hz, 1 H), 7.19 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.15 (dd, *J*=11.6, 8.4 Hz, 1 H), 6.87 - 6.93 (m, 1 H), 4.68 (d, *J*=7.0 Hz, 2 H), 4.50 (d, *J*=6.5 Hz, 2 H), 3.82 (s, 3 H), 3.58 (s, 3 H), 2.68 (s, 3 H), 2.21 - 2.31 (m, 1 H), 1.98 (br. s., 1 H), 1.92 (d, *J*=13.3 Hz, 2 H), 1.65 (d, *J*=10.6 Hz, 2 H), 1.26 - 1.39 (m, 2 H), 1.09 - 1.20 (m, 2 H).

Example 298

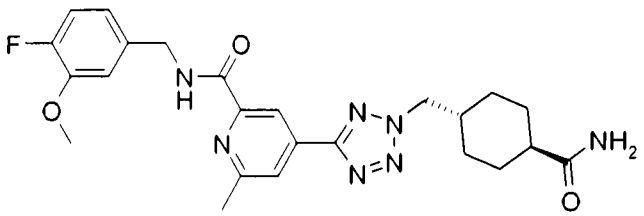
(*trans*)-4-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



Sodium hydroxide (1 pellet) was added to a solution of (*trans*)-methyl 4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 297) (63 mg, 0.13 mmol) in a mixture of tetrahydrofuran/water (0.6 mL, 1/1) and the mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse phase preparative HPLC. The crude product was slurried in ethyl ether, decanted, and the solid was dried to afford the title compound as a white solid (30 mg). MS (ES+) *m/z* 483 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (t, *J*=6.3 Hz, 1 H), 8.43 (s, 1 H), 8.09 (s, 1 H), 7.19 (dd, *J*=9.0, 2.1 Hz, 1 H), 7.15 (dd, *J*=11.6, 8.4 Hz, 1 H), 6.88 - 6.93 (m, 1 H), 4.67 (d, *J*=6.8 Hz, 2 H), 4.50 (d, *J*=6.3 Hz, 2 H), 3.82 (s, 3 H), 2.68 (s, 3 H), 1.93 - 2.12 (m, 2 H), 1.89 (d, *J*=10.9 Hz, 2 H), 1.63 (d, *J*=10.9 Hz, 2 H), 1.28 (q, *J*=12.5 Hz, 2 H), 1.05 - 1.18 (m, 2 H)

Example 299

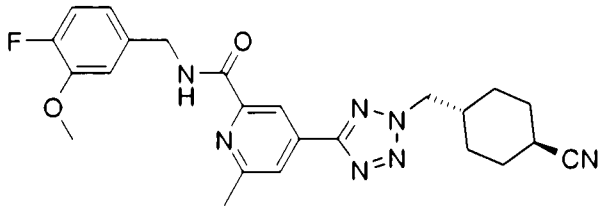
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Formamide (720 mg) was added to a solution of (*trans*)-methyl 4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 297) (476 mg (0.95 mmol) in anhydrous tetrahydrofuran (6 mL) and the mixture was heated to reflux. A 25% sodium methoxide solution in methanol (720 mg) was added and the reaction was stirred at reflux for 2 hours. The reaction mixture was allowed to cool to room temperature, diluted with methanol (6 mL), and then concentrated. Methanol (3 mL) was added to the residue. The resulting precipitate was filtered, washed with methanol and the solid was dried in a vacuum desiccator to afford the title compound as a white solid (262 mg). MS (ES+) *m/z* 482 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.31 (t, *J*=6.4 Hz, 1 H), 8.43 (s, 1 H), 8.09 (s, 1 H), 7.12 - 7.23 (m, 3 H), 6.91 (dd, *J*=6.1, 3.9 Hz, 1 H), 6.67 (br. s., 1 H), 4.68 (d, *J*=7.0 Hz, 2 H), 4.51 (d, *J*=6.1 Hz, 2 H), 3.83 (s, 3 H), 2.68 (s, 3 H), 1.94 - 2.07 (m, 2 H), 1.76 (d, *J*=12.1 Hz, 2 H), 1.65 (d, *J*=12.1 Hz, 2 H), 1.24 - 1.38 (m, 2 H), 1.03 - 1.16 (m, 2 H).

Example 300

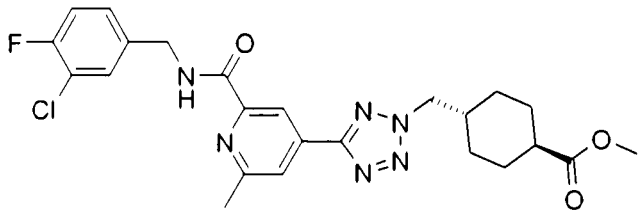
N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Polymer supported triphenylphosphine (Argonaut; 2.15 mmol/g, 1 g) was added to *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 299) (223 mg, 0.46 mmol) in a mixture of carbon tetrachloride (1.5 mL) and dichloroethane (13.5 mL) and the mixture was heated at 80 °C for 2 hours. The reaction mixture was filtered and the resin was washed with dichloroethane. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC. The product was slurried and decanted several times from ether and the solid was dried in a vacuum desiccator to afford the title compound as a white solid (139 mg). MS (ES+) *m/z* 464 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.31 (t, *J*=6.4 Hz, 1 H), 8.43 (s, 1 H), 8.09 (d, *J*=0.9 Hz, 1 H), 7.19 (dd, *J*=8.5, 1.7 Hz, 1 H), 7.15 (dd, *J*=11.6, 8.2 Hz, 1 H), 6.87 - 6.93 (m, 1 H), 4.69 (d, *J*=6.8 Hz, 2 H), 4.50 (d, *J*=6.3 Hz, 2 H), 3.83 (s, 3 H), 2.68 (s, 3 H), 2.58 - 2.67 (m, 1 H), 1.98 - 2.12 (m, 3 H), 1.65 (dd, *J*=13.2, 2.6 Hz, 2 H), 1.44 - 1.57 (m, 2 H), 1.07 - 1.19 (m, 2 H).

Example 301

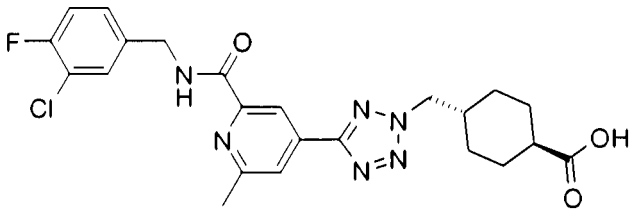
(*trans*)-Methyl 4-((5-(2-((3-Chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate



The title compound was prepared in a similar manner to (*trans*)-methyl 4-((5-(2-((3-(difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (Example 281) by reaction with 3-chloro-4-fluorobenzylamine to afford 123 mg as a white solid. MS (ES+) *m/z* 501 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.43 (t, *J*=6.4 Hz, 1 H), 8.42 (s, 1 H), 8.10 (d, *J*=0.7 Hz, 1 H), 7.56 (d, *J*=7.9 Hz, 1 H), 7.35 - 7.40 (m, 2 H), 4.68 (d, *J*=7.0 Hz, 2 H), 4.51 (d, *J*=6.3 Hz, 2 H), 3.58 (s, 3 H), 2.69 (s, 3 H), 2.21 - 2.31 (m, 1 H), 1.96 - 2.07 (m, 1 H), 1.91 (d, *J*=11.1 Hz, 2 H), 1.65 (d, *J*=10.8 Hz, 2 H), 1.27 - 1.38 (m, 2 H), 1.09 - 1.21 (m, 2 H).

Example 302

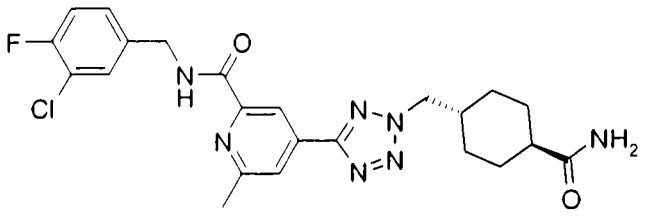
(*trans*)-4-((5-(2-((3-Chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



Sodium hydroxide (1 pellet) was added to a solution of (*trans*)-methyl 4-((5-(2-((3-chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 301) (65 mg, 0.13 mmol) in a mixture of tetrahydrofuran/water (0.6 mL, 1/1) and the mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse phase preparative HPLC. The crude product was slurried in ethyl ether, decanted, and the solid was dried to afford the title compound as a white solid (41 mg). MS (ES+) *m/z* 487 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (t, *J*=6.2 Hz, 1 H), 8.42 (s, 1 H), 8.10 (s, 1 H), 7.78 (d, *J*=7.0 Hz, 1 H), 7.71 - 7.75 (m, 1 H), 7.45 - 7.52 (m, 1 H), 4.68 (d, *J*=6.8 Hz, 2 H), 4.58 (d, *J*=6.3 Hz, 2 H), 3.58 (s, 3 H), 2.69 (s, 3 H), 2.20 - 2.30 (m, 1 H), 1.96 - 2.04 (m, 1 H), 1.91 (d, *J*=13.0 Hz, 2 H), 1.66 (d, *J*=12.8 Hz, 2 H), 1.26 - 1.39 (m, 2 H), 1.08 - 1.20 (m, 2 H).

Example 303

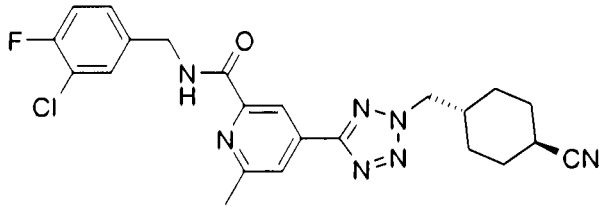
***N*-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Formamide (720 mg) was added to a solution of (*trans*)-methyl 4-((5-(2-((3-chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 301) (268 mg, 0.53 mmol) in anhydrous tetrahydrofuran (6 mL) and the mixture was heated to reflux. A 25% sodium methoxide solution in methanol (720 mg) was added and the reaction was stirred at reflux for 2 hours. The reaction mixture was allowed to cool to room temperature, diluted with methanol (6 mL), and then concentrated. Methanol (3 mL) was added to the residue. The resulting precipitate was filtered, washed with a small amount of methanol and the solid was dried in a vacuum desiccator to afford the title compound as a white solid (135 mg). MS (ES+) *m/z* 486 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.43 (t, *J*=6.4 Hz, 1 H), 8.42 (s, 1 H), 8.10 (s, 1 H), 7.56 (d, *J*=7.0 Hz, 1 H), 7.37 (d, *J*=7.9 Hz, 2 H), 7.17 (br. s., 1 H), 6.67 (br. s., 1 H), 4.68 (d, *J*=6.8 Hz, 2 H), 4.51 (d, *J*=6.5 Hz, 2 H), 2.69 (s, 3 H), 1.92 - 2.07 (m, 2 H), 1.76 (d, *J*=11.1 Hz, 2 H), 1.64 (d, *J*=10.8 Hz, 2 H), 1.25 - 1.38 (m, 2 H), 1.03 - 1.15 (m, 2 H).

Example 304

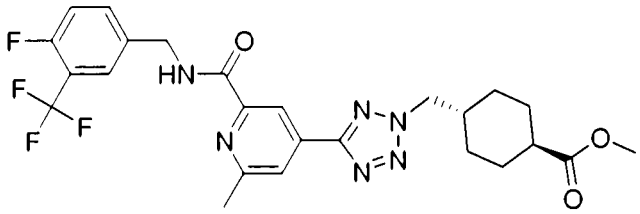
N-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-cyanocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Polymer supported triphenylphosphine (Argonaut; 2.15 mmol/g, 1 g) was added to *N*-(3-chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-carbamoylcyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 303) (100 mg, 0.2 mmol) in a mixture of carbon tetrachloride (1.5 mL) and dichloroethane (13.5 mL) and the mixture was heated at 80 °C for 2 hours. The reaction mixture was filtered and the resin was washed with methanol. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC. Fractions containing product were passed through a carbonate resin column and then concentrated. The product was slurried and decanted several times from ether and the solid was dried in a vacuum desiccator to afford the title compound as a white solid (33.9 mg). MS (ES+) *m/z* 468 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.43 (t, *J*=6.4 Hz, 1 H), 8.42 (s, 1 H), 8.09 (d, *J*=1.0 Hz, 1 H), 7.53 - 7.59 (m, 1 H), 7.35 - 7.41 (m, 2 H), 4.69 (d, *J*=6.8 Hz, 2 H), 4.51 (d, *J*=6.3 Hz, 2 H), 2.69 (s, 3 H), 2.58 - 2.67 (m, 1 H), 1.98 - 2.13 (m, 3 H), 1.60 - 1.69 (m, 2 H), 1.45 - 1.57 (m, 2 H), 1.07 - 1.19 (m, 2 H).

Example 305

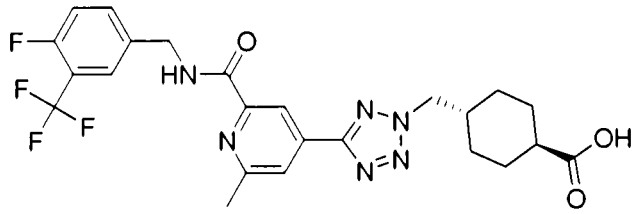
(*trans*)-Methyl 4-((5-(2-((4-Fluoro-3-(trifluoromethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate



The title compound was prepared in a similar manner to (*trans*)-methyl 4-((5-(2-((3-(difluoromethoxy)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (Example 281) by reaction with (4-fluoro-3-(trifluoromethyl)phenyl)methanamine to afford 143 mg as a white solid. MS (ES+) *m/z* 535 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (t, *J*=6.2 Hz, 1 H), 8.42 (s, 1 H), 8.10 (s, 1 H), 7.76 - 7.79 (m, 1 H), 7.71 - 7.76 (m, 1 H), 7.48 (dd, *J*=10.5, 8.5 Hz, 1 H), 4.68 (d, *J*=6.8 Hz, 2 H), 4.58 (d, *J*=6.3 Hz, 2 H), 3.58 (s, 3 H), 2.69 (s, 3 H), 2.20 - 2.31 (m, 1 H), 1.91 (d, *J*=11.9 Hz, 2 H), 1.65 (d, *J*=14.7 Hz, 2 H), 1.26 - 1.39 (m, 2 H), 1.08 - 1.21 (m, 2 H)

Example 306

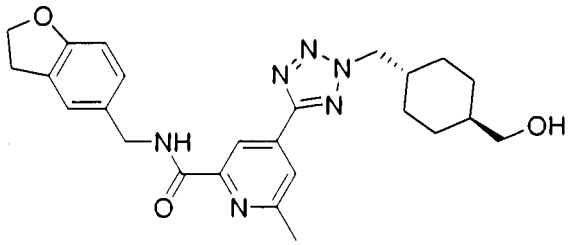
(*trans*)-4-((5-(2-((4-Fluoro-3-(trifluoromethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylic acid



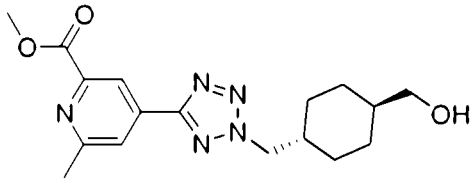
Sodium hydroxide (1 pellet) was added to a solution of *trans*)-methyl 4-((5-(2-((4-fluoro-3-(trifluoromethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate (prepared as described in Example 305) (68 mg, 0.13 mmol) in a mixture of tetrahydrofuran/water (0.6 mL, 1/1) and the mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse phase preparative HPLC. The crude product was slurried in ethyl ether, decanted, and the solid was dried to afford the title compound as a white solid (46 mg). MS (ES+) *m/z* 521 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (t, *J*=6.3 Hz, 1 H), 8.42 (s, 1 H), 8.10 (s, 1 H), 7.76 - 7.80 (m, 1 H), 7.71 - 7.75 (m, 1 H), 7.48 (dd, *J*=10.7, 8.8 Hz, 1 H), 4.67 (d, *J*=6.8 Hz, 2 H), 4.58 (d, *J*=6.3 Hz, 2 H), 2.69 (s, 3 H), 2.06 - 2.15 (m, 1 H), 1.94 - 2.03 (m, 1 H), 1.86 - 1.93 (m, 2 H), 1.64 (d, *J*=12.5 Hz, 2 H), 1.22 - 1.35 (m, 2 H), 1.05 - 1.18 (m, 2 H).

Example 307

***N*-((2,3-Dihydrobenzofuran-5-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

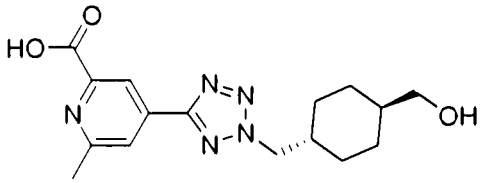


Step 1: Preparation of methyl 4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate



Methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (2.19 g, 10.0 mmol), polymer supported triphenylphosphine (9.3 g, 20.0 mmol), and trans-cyclohexane-1,4-dimethanol (2.88 g, 20.0 mmol) were suspended in tetrahydrofuran (200 mL). The mixture was cooled to 0 °C. Di-*tert*-butyl azodicarboxylate (4.6 g, 20.0 mmol) was added. The mixture was allowed to warm to room temperature and stir for 18 hours. The reaction mixture was filtered and the resin washed with tetrahydrofuran (100 mL). The filtrate was concentrated. The residue was dissolved in ethyl acetate (200 mL) and washed with water (50 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2; 100/4) to afford the title compound as an oil (2.3 g, 67%). MS (ES+) *m/z* 346 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.40 (d, *J*=0.8 Hz, 1 H), 8.12 (d, *J*=1.1 Hz, 1 H), 4.67 (d, *J*=7.0 Hz, 2 H), 4.35 (t, *J*=5.3 Hz, 1 H), 3.93 (s, 3 H), 3.19 (t, *J*=5.8 Hz, 2 H), 2.66 (s, 3 H), 2.04 - 1.90 (m, 1 H), 1.74 (d, *J*=10.6 Hz, 2 H), 1.61 (d, *J*=10.6 Hz, 2 H), 1.37 - 1.23 (m, 1 H), 1.08 (dq, *J*=12.6, 2.7 Hz, 2 H), 0.87 (dq, *J*=12.8, 3.1 Hz, 2 H).

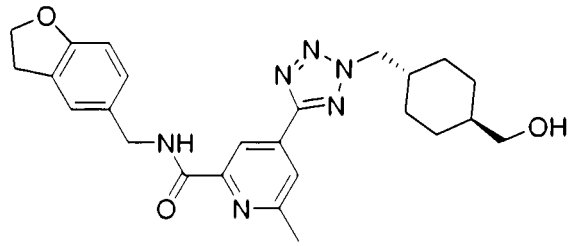
Step 2: Preparation of 4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid



Methyl 4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (2.3 g, 6.68 mmol) was dissolved in a mixture of tetrahydrofuran/water (40 mL, 1/1). Lithium hydroxide (479 mg, 20.0 mmol) was added and the mixture was stirred at room temperature for 3 hours. The solvent was removed in vacuo and the residue was diluted with water (20 mL). The solution was made acidic with 1N hydrochloric acid solution (20 mL) and the resulting precipitate was filtered to afford the title compound as a white solid (1.03 g, 47%). MS (ES+) m/z 332 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.36 (br, 1 H), 8.40 (d, *J*=0.8 Hz, 1 H), 8.09 (d, *J*=1.1 Hz, 1 H), 4.66 (d, *J*=7.1

Hz, 2 H), 4.35 (br, 1 H), 3.19 (d, *J*=6.2 Hz, 2 H), 2.65 (s, 3 H), 2.03 – 1.90 (m, 1 H), 1.74 (d, *J*=10.5 Hz, 2 H), 1.61 (d, *J*=10.9, 2 H), 1.35 – 1.25 (m, 1 H), 1.08 (dg, *J*=12.6, 2.8 Hz, 2 H), 0.87 (dg, *J*=12.8, 3.2 Hz, 2 H).

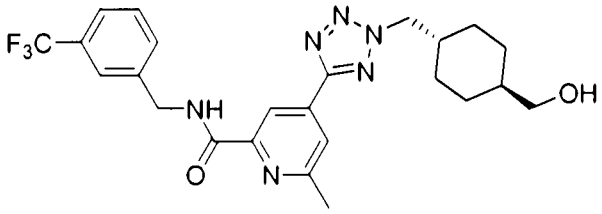
Step 3: Preparation of *N*-((2,3-dihydrobenzofuran-5-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



A mixture of 4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (33 mg, 0.10 mmol) and 1-hydroxybenzotriazole (18.9 mg, 0.14 mmol) in *N*,*N*-dimethylformamide (0.5 mL) was shaken for 15 minutes. *N*-Methylmorpholine (44 μL, 0.40 mmol) was added followed by (2,3-dihydrobenzofuran-5-yl)methanamine (17.9 mg, 0.12 mmol) in *N*,*N*-dimethylformamide (0.5 mL). 1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (26.8 mg, 0.14 mmol) was then added and the mixture was shaken for 18 hours. The reaction mixtures were purified by preparative reverse phase preparative HPLC to afford the title compound (33 mg). MS (ES+) *m/z* 463 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.48 (s, 0.5 H), 9.11 (t, *J*=6.2 Hz, 1 H), 8.37 (s, 1 H), 8.02 (s, 1 H), 7.18 (s, 1 H), 7.03 (d, *J*=7.7 Hz, 1 H), 6.64 (d, *J*=8.1 Hz, 1 H), 4.61 (d, *J*=7.0 Hz, 2 H), 4.44 (t, *J*=8.8 Hz, 2 H), 4.39 (d, *J*=6.6 Hz, 2 H), 4.32 (t, *J*=5.1 Hz, 1 H), 3.14 (t, *J*=5.5 Hz, 2 H), 3.09 (t, *J*=8.8 Hz, 2 H), 2.61 (s, 3 H), 1.99 - 1.84 (m, 1 H), 1.69 (d, *J*=12.8 Hz, 2 H), 1.56 (d, *J*=11.7 Hz, 2 H), 1.30 - 1.19 (m, 1 H), 1.03 (q, *J*=11.7 Hz, 2 H), 0.82 (q, *J*=12.2 Hz, 2 H).

Example 308

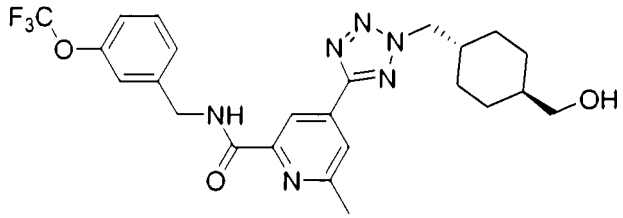
N-(3-(Trifluoromethyl)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



3-Trifluoromethylbenzylamine was reacted according to procedures described in Example 307 to afford the title compound (37 mg). MS (ES+) *m/z* 489 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.43 (t, *J*=6.2 Hz, 1 H), 8.37 (s, 1 H), 8.04 (s, 1 H), 7.69 - 7.48 (m, 4 H), 4.61 (d, *J*=7.0 Hz, 2 H), 4.56 (d, *J*=6.2 Hz, 2 H), 4.31 (t, *J*=5.1 Hz, 1 H), 3.13 (t, *J*=5.7 Hz, 2 H), 2.63 (s, 3 H), 1.98 - 1.85 (m, 1 H), 1.68 (d, *J*=11.7 Hz, 2 H), 1.56 (d, *J*=11.3 Hz, 2 H), 1.31 - 1.19 (m, 1 H), 1.02 (q, *J*=12.8 Hz, 2 H), 0.82 (q, *J*=12.4 Hz, 2 H).

Example 309

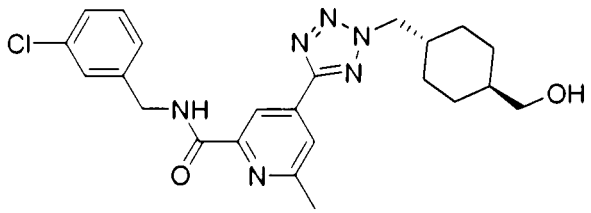
***N*-(3-(Trifluoromethoxy)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



3-Trifluoromethoxybenzylamine was reacted according to procedures described in Example 307 to afford the title compound (31 mg). MS (ES+) *m/z* 527 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.40 (t, *J*=6.4 Hz, 1 H), 8.38 (s, 1 H), 8.05 (s, 1 H), 7.43 (t, *J*=7.9 Hz, 1 H), 7.34 (d, *J*=7.7 Hz, 1 H), 7.29 (s, 1 H), 7.21 (d, *J*=8.1 Hz, 1 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.53 (d, *J*=6.2 Hz, 2 H), 4.32 (t, *J*=5.3 Hz, 1 H), 3.14 (t, *J*=5.7 Hz, 2 H), 2.64 (s, 3 H), 1.97 - 1.87 (m, 1 H), 1.70 (d, *J*=12.4 Hz, 2 H), 1.57 (d, *J*=11.7 Hz, 2 H), 1.31 - 1.20 (m, 1 H), 1.03 (q, *J*=13.2 Hz, 2 H), 0.83 (q, *J*=12.8 Hz, 2 H).

Example 310

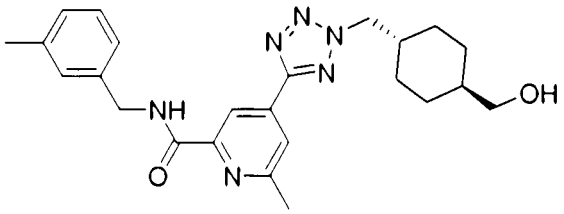
***N*-(3-Chlorobenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



3-Chlorobenzylamine was reacted according to procedures described in Example 307 to afford the title compound (16 mg). MS (ES+) *m/z* 455 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.37 (t, *J*=6.4 Hz, 1 H), 8.38 (s, 1 H), 8.05 (s, 1 H), 7.26 - 7.37 (m, 4 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.33 (t, *J*=5.3 Hz, 1 H), 3.14 (t, *J*=5.7 Hz, 2 H), 2.64 (s, 3 H), 1.97 - 1.87 (m, 1 H), 1.70 (d, *J*=10.6 Hz, 2 H), 1.57 (d, *J*=11.3 Hz, 2 H), 1.31 - 1.21 (m, 1 H), 1.03 (q, *J*=12.4 Hz, 2 H), 0.83 (q, *J*=12.4 Hz, 2 H).

Example 311

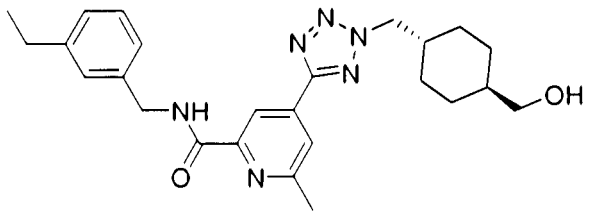
***N*-(3-Methylbenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



3-Methylbenzylamine was reacted according to procedures described in Example 307 to afford the title compound (33 mg). MS (ES+) *m/z* 435 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, *J*=6.4 Hz, 1 H), 8.39 (s, 1 H), 8.04 (s, 1 H), 7.17 (t, *J*=7.5 Hz, 1 H), 7.07 - 7.13 (m, 2 H), 7.02 (d, *J*=7.3 Hz, 1 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.46 (d, *J*=6.2 Hz, 2 H), 4.32 (t, *J*=5.1 Hz, 1 H), 3.14 (t, *J*=5.9 Hz, 2 H), 2.63 (s, 3 H), 2.24 (s, 3 H), 1.97 - 1.87 (m, 1 H), 1.70 (d, *J*=11.0 Hz, 2 H), 1.57 (d, *J*=11.3 Hz, 2 H), 1.30 - 1.20 (m, 1 H), 1.04 (q, *J*=13.2 Hz, 2 H), 0.83 (q, *J*=12.2 Hz, 2 H).

Example 312

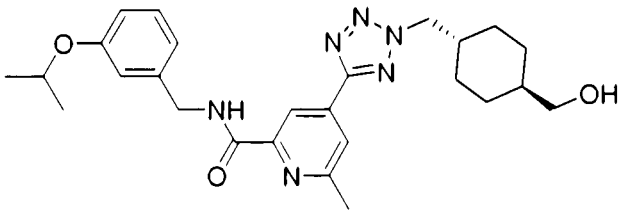
***N*-(3-Ethylbenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



3-Ethylbenzylamine was reacted according to procedures described in Example 307 to afford the title compound (32 mg). MS (ES+) *m/z* 449 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, *J*=6.2 Hz, 1 H), 8.38 (s, 1 H), 8.03 (s, 1 H), 7.21 - 7.02 (m, 4 H), 4.61 (d, *J*=7.0 Hz, 2 H), 4.46 (d, *J*=6.6 Hz, 2 H), 4.32 (t, *J*=5.3 Hz, 1 H), 3.14 (t, *J*=5.7 Hz, 2 H), 2.62 (s, 3 H), 2.53 (q, *J*=7.6 Hz, 2 H), 1.97 - 1.87 (m, 1 H), 1.69 (d, *J*=11.0 Hz, 2 H), 1.56 (d, *J*=10.2 Hz, 2 H), 1.30 - 1.20 (m, 1 H), 1.11 (t, *J*=7.7 Hz, 3 H), 1.03 (q, *J*=12.4 Hz, 2 H), 0.82 (q, *J*=12.1 Hz, 2 H).

Example 313

***N*-(3-Isopropoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

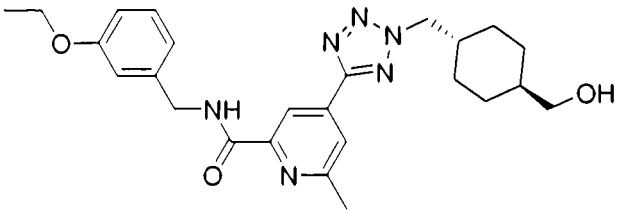


3-Isopropoxybenzylamine was reacted according to procedures described in Example 307 to afford the title compound (37 mg). MS (ES+) *m/z* 479 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=6.2 Hz, 1 H), 8.38 (s, 1 H), 8.04 (s, 1 H), 7.16 (t, *J*=8.1 Hz, 1 H), 6.87 - 6.72 (m, 3 H), 4.61 (d, *J*=7.0 Hz, 2 H), 4.52 (qq, *J*=5.9 Hz, 1 H), 4.44 (d, *J*=6.2 Hz, 2 H), 4.31 (t, *J*=5.1 Hz, 1 H), 3.14 (t,

J=5.7 Hz, 2 H), 2.63 (s, 3 H), 1.98 - 1.86 (m, 1 H), 1.69 (d, *J*=11.3 Hz, 2 H), 1.56 (d, *J*=11.0 Hz, 2 H), 1.30 - 1.19 (m, 1 H), 1.19 (d, *J*=5.9 Hz, 6 H), 1.03 (q, *J*=12.8 Hz, 2 H), 0.82 (q, *J*=12.4 Hz, 2 H).

Example 314

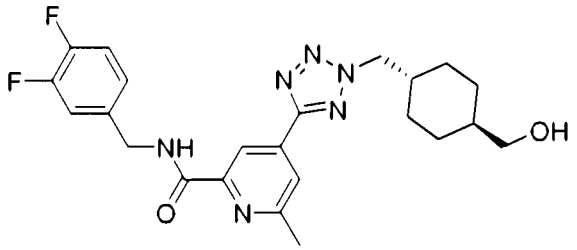
***N*-(3-Ethoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



(3-Ethoxyphenyl)methanamine (prepared as described in step 2 of the synthesis of *N*-(3-ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide, Example 180) was reacted according to procedures described in Example 307 to afford the title compound (36 mg). MS (ES+) *m/z* 465 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=6.2 Hz, 1 H), 8.38 (s, 1 H), 8.04 (s, 1 H), 7.18 (t, *J*=8.1 Hz, 1 H), 6.88 - 6.83 (m, 2 H), 6.76 (d, *J*=8.4 Hz, 1 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.46 (d, *J*=6.2 Hz, 2 H), 4.33 (t, *J*=5.3 Hz, 1 H), 3.95 (q, *J*=7.0 Hz, 2 H), 3.14 (t, *J*=5.7 Hz, 2 H), 2.63 (s, 3 H), 1.97 - 1.87 (m, 1 H), 1.69 (d, *J*=12.4 Hz, 2 H), 1.57 (d, *J*=12.4 Hz, 2 H), 1.26 (t, *J*=7.0 Hz, 3 H), 1.28 - 1.20 (m, 1 H), 1.04 (q, *J*=12.4 Hz, 2 H), 0.83 (q, *J*=11.3 Hz, 2 H).

Example 315

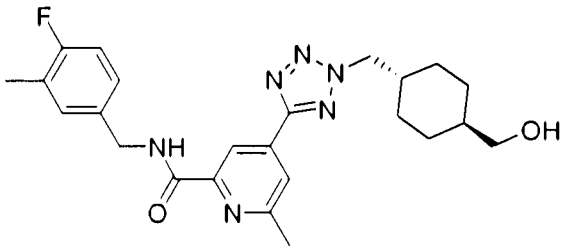
***N*-(3,4-Difluorobenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



3,4-Difluorobenzylamine was reacted according to procedures described in Example 307 to afford the title compound (33 mg). MS (ES+) *m/z* 457 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.36 (t, *J*=6.4 Hz, 1 H), 8.38 (s, 1 H), 8.05 (s, 1 H), 7.39 - 7.30 (m, *J*=8.5, 8.5, 8.5 Hz, 2 H), 7.13 - 7.18 (m, 1 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.47 (d, *J*=6.6 Hz, 2 H), 4.32 (t, *J*=5.3 Hz, 1 H), 3.14 (t, *J*=5.9 Hz, 2 H), 2.64 (s, 3 H), 1.97 - 1.87 (m, 1 H), 1.70 (d, *J*=11.0 Hz, 2 H), 1.57 (d, *J*=12.1 Hz, 2 H), 1.30 - 1.18 (m, 1 H), 1.03 (q, *J*=12.8 Hz, 2 H), 0.83 (q, *J*=11.3 Hz, 2 H).

Example 316

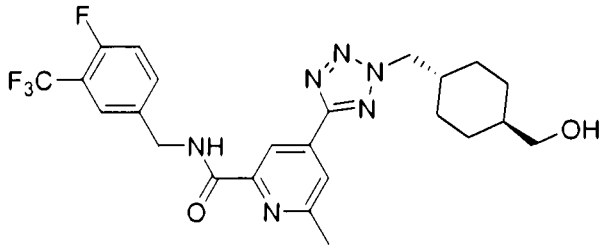
***N*-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



4-Fluoro-3-methylbenzylamine was reacted according to procedures described in Example 307 to afford the title compound (35 mg). MS (ES+) *m/z* 453 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.25 (t, *J*=6.2 Hz, 1 H), 8.38 (s, 1 H), 8.04 (s, 1 H), 7.21 (d, *J*=7.3 Hz, 1 H), 7.17 - 7.13 (m, 1 H), 7.03 (t, *J*=9.2 Hz, 1 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.43 (d, *J*=6.2 Hz, 2 H), 4.32 (t, *J*=5.1 Hz, 1 H), 3.14 (t, *J*=5.7 Hz, 2 H), 2.63 (s, 3 H), 2.17 (s, 3 H), 1.97 - 1.87 (m, 1 H), 1.70 (d, *J*=11.0 Hz, 2 H), 1.57 (d, *J*=13.2 Hz, 2 H), 1.30 - 1.20 (m, 1 H), 1.03 (q, *J*=10.6 Hz, 2 H), 0.83 (q, *J*=12.4 Hz, 2 H).

Example 317

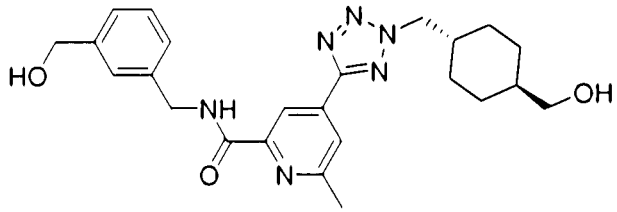
***N*-(4-Fluoro-3-(trifluoromethyl)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



4-Fluoro-3-trifluorobenzylamine was reacted according to procedures described in Example 307 to afford the title compound (30 mg). MS (ES+) *m/z* 507 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.43 (t, *J*=6.2 Hz, 1 H), 8.37 (s, 1 H), 8.05 (s, 1 H), 7.73 (d, *J*=6.2 Hz, 1 H), 7.71 - 7.66 (m, 1 H), 7.47 - 7.40 (m, 1 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.53 (d, *J*=6.2 Hz, 2 H), 4.32 (t, *J*=5.3 Hz, 1 H), 3.14 (t, *J*=5.5 Hz, 2 H), 2.64 (s, 3 H), 1.97 - 1.87 (m, 1 H), 1.69 (d, *J*=10.6 Hz, 2 H), 1.57 (d, *J*=11.3 Hz, 2 H), 1.30 - 1.20 (m, 1 H), 1.03 (q, *J*=12.8 Hz, 2 H), 0.83 (q, *J*=12.4 Hz, 2 H).

Example 318

***N*-(3-(Hydroxymethyl)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

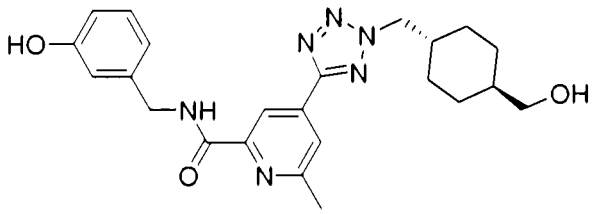


(3-(Aminomethyl)phenyl)methanol was reacted according to procedures described in Example 307 to afford the title compound (34 mg). MS (ES+) *m/z* 451 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.4 Hz, 1 H), 8.39 (s, 1 H), 8.04 (s, 1 H), 7.12 - 7.29 (m, 4 H), 5.13 (t, *J*=5.7 Hz, 1 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.49 (d, *J*=6.2 Hz, 2 H), 4.43 (d, *J*=5.5 Hz, 2 H), 4.33 (t, *J*=5.1 Hz, 1 H), 3.14

(t, *J*=5.7 Hz, 2 H), 2.63 (s, 3 H), 1.97 - 1.87 (m, 1 H), 1.70 (d, *J*=11.0 Hz, 2 H), 1.57 (d, *J*=11.0 Hz, 2 H), 1.30 - 1.20 (m, 1 H), 1.03 (q, *J*=12.1 Hz, 2 H), 0.83 (q, *J*=12.1 Hz, 2 H).

Example 319

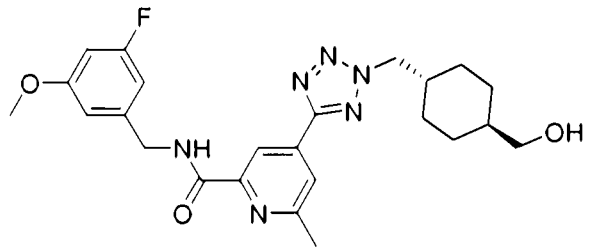
N-(3-Hydroxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



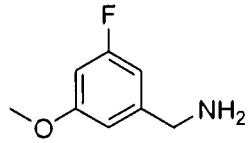
3-Hydroxybenzylamine was reacted according to procedures described in Example 307 to afford the title compound (34 mg). MS (ES+) *m/z* 437 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.27 (s, 1 H), 9.18 (t, *J*=6.0 Hz, 1 H), 8.38 (s, 1 H), 8.04 (s, 1 H), 7.06 (t, *J*=7.9 Hz, 1 H), 6.73 - 6.67 (m, 2 H), 6.57 (d, *J*=8.8 Hz, 1 H), 4.62 (d, *J*=7.0 Hz, 2 H), 4.40 (d, *J*=6.2 Hz, 2 H), 4.32 (t, *J*=5.1 Hz, 1 H), 3.14 (t, *J*=5.5 Hz, 2 H), 2.63 (s, 3 H), 1.98 - 1.86 (m, 1 H), 1.69 (d, *J*=11.3 Hz, 2 H), 1.56 (d, *J*=11.0 Hz, 2 H), 1.31 - 1.20 (m, 1 H), 1.03 (q, *J*=12.8 Hz, 2 H), 0.82 (q, *J*=12.8 Hz, 2 H).

Example 320

N-(3-Fluoro-5-methoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

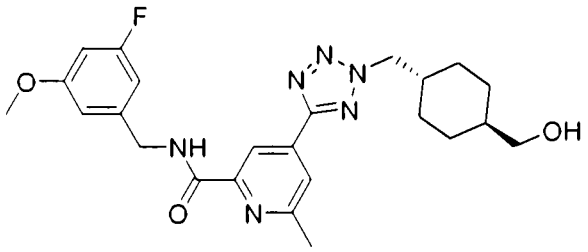


Step 1: Preparation of (3-fluoro-5-methoxyphenyl)methanamine



To a suspension of lithium aluminum hydride (3.3 mL, 2.0 M in tetrahydrofuran) was added dropwise a solution of 3-fluoro-5-methoxybenzonitrile (0.20 g, 1.34 mmol) in tetrahydrofuran (5.0 mL) at 0 °C. After 2 h, a saturated solution of sodium sulfate (2-3 mL) was added dropwise until hydrogen gas evolution ceased. The precipitate was filtered off and the filtrate was diluted with ethyl acetate (10 mL). The organic layer was separated, washed with water (2 x 5 mL), brine (5 mL), dried over sodium sulfate, and concentrated to afford the title compound (0.14 g, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.68 - 6.74 (m, 2 H), 6.54 - 6.61 (m, 1 H), 3.72 (s, 3 H), 3.64 (s, 2 H), 1.68 - 1.87 (m, 2 H).

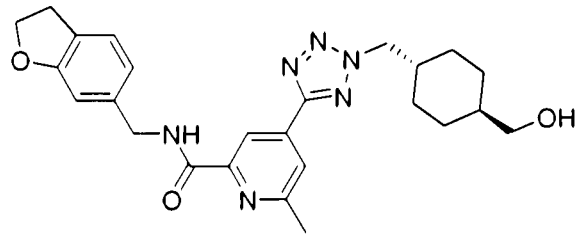
Step 2 : Preparation of *N*-(3-fluoro-5-methoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



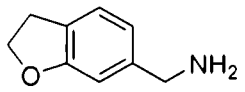
(3-Fluoro-5-methoxyphenyl)methanamine was reacted according to procedures described in Example 307 to afford the title compound (22 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.27 (t, J=6.2 Hz, 1 H), 8.40 (s, 1 H), 8.06 (s, 1 H), 6.55 - 6.84 (m, 3 H), 4.63 (d, J=7.3 Hz, 2 H), 4.48 (d, J=6.6 Hz, 2 H), 4.29 (t, J=5.1 Hz, 1 H), 3.60 - 3.80 (m, 3 H), 2.66 (s, 3 H), 2.40 - 2.54 (m, 1 H), 1.88 - 2.06 (m, 1 H), 1.72 (d, J=11.0 Hz, 2 H), 1.60 (d, J=11.0 Hz, 2 H), 1.27 (d, J=11.7 Hz, 1 H), 0.96 - 1.14 (m, 2 H), 0.74 - 0.98 (m, 2 H).

Example 321

N-((2,3-Dihydrobenzofuran-6-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

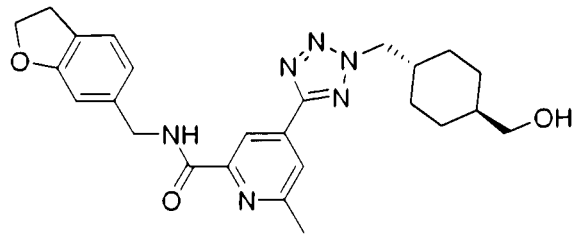


Step 1: Preparation of (2,3-dihydrobenzofuran-5-yl)methanamine



To a suspension of lithium aluminum hydride (0.38 mL, 2.0 M in tetrahydrofuran) was added dropwise a solution of 2,3-dihydrobenzofuran-6-carbonitrile (0.10 g, 0.61 mmol) in tetrahydrofuran (2.0 mL) at 0 °C. The reaction was allowed to warm to room temperature and then was heated at 70 °C for 3 hours. A saturated solution of sodium sulfate (1-2 mL) was added dropwise until hydrogen gas evolution ceased. The precipitate was filtered off and the filtrate was diluted with ethyl acetate (10 mL). The organic layer was separated, washed with water (2 x 5 mL) followed by brine (5 mL), dried over sodium sulfate, and concentrated. The residue was taken up in acetonitrile and filtered through a Celite™ pad. The filtrate was concentrated to afford the title compound as an oil (65 mg, 61%). LC/MS (5-100% CH_3CN/H_2O, 5 min) 0.73 min, *m/z* 150 (M+H).

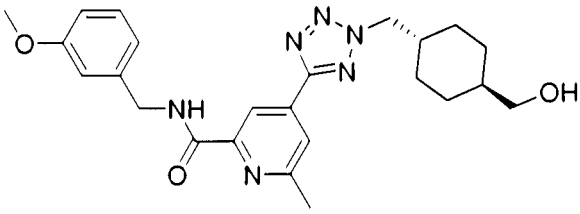
Step 2 : Preparation of *N*-((2,3-dihydrobenzofuran-6-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



(2,3-Dihydrobenzofuran-5-yl)methanamine was reacted according to procedures described in Example 307 to afford the title compound (33 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (t, J=6.6 Hz, 1 H), 8.39 (s, 1 H), 8.04 (s, 1 H), 7.13 (d, J=7.3 Hz, 1 H), 6.61 - 6.84 (m, 3 H), 4.63 (d, J=7.3 Hz, 2 H), 4.37 - 4.56 (m, 4 H), 4.29 (t, J=5.1 Hz, 1 H), 3.00 - 3.19 (m, 1 H), 2.64 (s, 3 H), 2.46 - 2.58 (m, 2 H), 1.84 - 2.04 (m, 1 H), 1.72 (d, J=10.3 Hz, 2 H), 1.60 (d, J=11.0 Hz, 2 H), 1.29 (d, J=5.9 Hz, 1 H), 0.93 - 1.18 (m, 2 H), 0.72 - 0.97 (m, 2 H).

Example 322

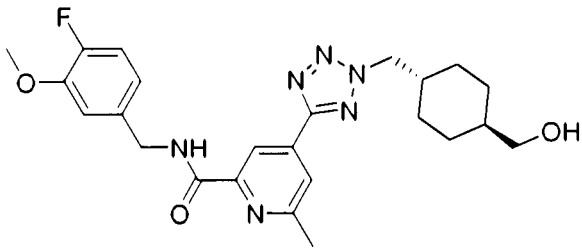
***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



(3-Methoxyphenyl)methanamine was reacted according to procedures described in Example 307 to afford the title compound (46 mg). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.261 min., *m/z* 451 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (m, 1 H), 8.39 (s, 1 H), 8.05 (s, 1 H), 7.12 - 7.28 (m, 1 H), 6.94 - 6.84 (m, 2 H), 6.82 - 6.72 (m, 1 H), 4.63 (d, *J*=7.0 Hz, 2 H), 4.47 (d, *J*=6.4 Hz, 2 H), 3.70 (s, 3 H), 3.21 - 3.08 (m, 2 H), 2.64 (s, 3 H), 2.04 - 1.81 (m, 1 H), 1.78 - 1.50 (m, 4 H), 1.43 - 1.16 (m), 1.15 - 0.71 (m, 4 H).

Example 323

***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((trans)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

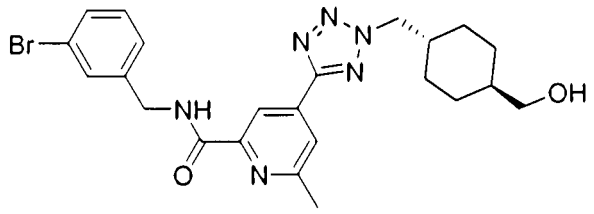


4-Fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-

yl)pyrimidine-4-carboxamide, Example 1) (133 mg, 0.857 mmol) and diisopropylethylamine (0.5 mL, 0.308 mmol) was added to a solution of 4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 2 of the synthesis of *N*-((2,3-dihydrobenzofuran-5-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 307) (102 mg, 0.308 mmol) in DMF (10 mL), and the mixture was stirred at room temperature for 10 minutes. (Benzotriazol-1-yloxy)-dimethylaminomethylene]dimethylammonium tetrafluoroborate (254 mg, 0.79 mmol) was added and stirring continued for 30 minutes. The reaction mixture was concentrated and purified by reverse phase preparative HPLC followed by neutralization using a carbonate column to afford the title compound (50 mg, 28%). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.331 min., *m/z* 469 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 - 1.04 (m, 2 H), 1.05 - 1.19 (m, 2 H), 1.39 - 1.54 (m, 1 H), 1.66 - 1.90 (m, 4 H), 2.00 - 2.14 (m, 1 H), 2.61 (s, 3 H), 3.38 - 3.48 (m, 3 H), 3.86 (s, 3 H), 4.52 (d, *J*=7.0 Hz, 2 H), 4.62 (d, *J*=6.4 Hz, 2 H), 6.85 - 6.92 (m, 1 H), 6.94 - 7.06 (m, 2 H), 8.03 (d, *J*=1.3 Hz, 1 H), 8.42 (t, *J*=6.2 Hz, 1 H), 8.70 (s, 1 H).

Example 324

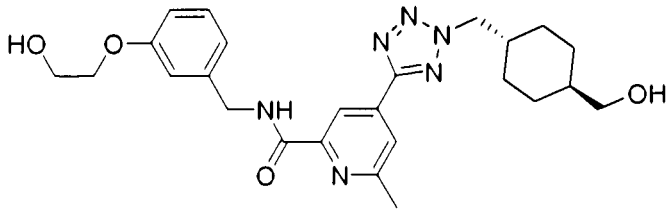
N-(3-Bromobenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Triethylamine (0.16 mL, 1.18 mmol) and 3-bromobenzylamine hydrochloride (55 mg, 0.245 mmol) were added to a solution of 4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 2 of the synthesis of *N*-((2,3-dihydrobenzofuran-5-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 307) (65 mg, 0.196 mmol) in *N*,*N*-dimethylformamide (2 mL), and the mixture was stirred for 30 minutes. *O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (186 mg, 0.49 mmol) was added and stirring continued overnight. The reaction mixture was purified by reverse phase preparative HPLC to afford the title compound (1.5 mg, 1.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.13 - 1.31 (m, 4 H), 1.74 - 1.98 (m, 3 H), 2.01 - 2.23 (m, 3 H), 2.64 (s, 2 H), 4.35 (d, *J*=6.7 Hz, 2 H,) 4.56 (d, *J*=7.0 Hz, 2 H), 4.66 (d, *J*=6.2 Hz, 2 H), 7.14 - 7.27 (m, 1 H), 7.30 (d, *J*=7.8 Hz, 1 H), 7.34 - 7.44 (m, 2 H), 7.44 - 7.57 (m, 2 H), 8.02 (d, *J*=8.6 Hz, 1 H), 8.07 (d, *J*=1.1 Hz, 1 H), 8.52 (t, *J*=6.2 Hz, 1 H), 8.71 (s, 1 H).

Example 325

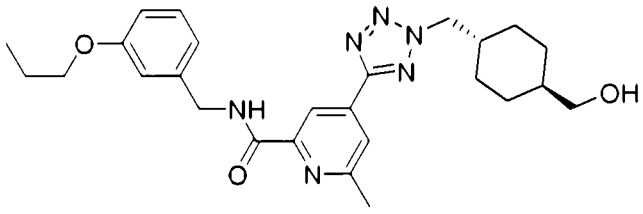
N-(3-(2-Hydroxyethoxy)benzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



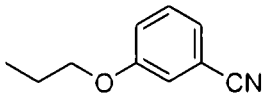
2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (137 mg, 0.362 mmol) was added to a mixture of 4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 2 of the synthesis of *N*-((2,3-dihydrobenzofuran-5-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 307) (100 mg, 0.302 mmol), 2-(3-(aminomethyl)phenoxy)ethanol (prepared as described in step 2 of the synthesis of *N*-(3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 13) (60.55 mg, 0.362 mmol), and triethylamine (0.09 mL, 0.664 mmol) in tetrahydrofuran (1 mL). The mixture was stirred at room temperature for 18 hours and then purified by reverse phase preparative HPLC. Fractions containing the desired product were combined, passed through a carbonate cartridge to neutralize, and concentrated to afford the title compound as a white solid (32 mg, 22%). MS (ES+) *m/z* 481 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.89 - 1.32 (m, 4 H), 1.40 - 1.58 (m, 1 H), 1.65 - 2.01 (m, 6 H), 1.99 - 2.19 (m, 1 H), 2.64 (s, 3 H), 3.47 (d, *J*=6.18 Hz, 2 H), 3.89 - 4.01 (m, 2 H), 4.03 - 4.15 (m, 2 H), 4.54 (d, *J*=6.98 Hz, 2 H), 4.67 (d, *J*=6.18 Hz, 2 H), 6.79 - 6.89 (m, 1 H), 6.91 - 7.04 (m, 2 H), 7.21 - 7.34 (m, 1 H), 8.06 (s, 1 H), 8.48 (t, *J*=5.77 Hz, 1 H), 8.73 (s, 1 H).

Example 326

N-(3-Propoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

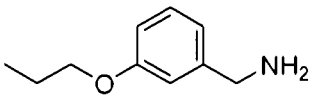


Step 1: Preparation of 3-propoxybenzonitrile



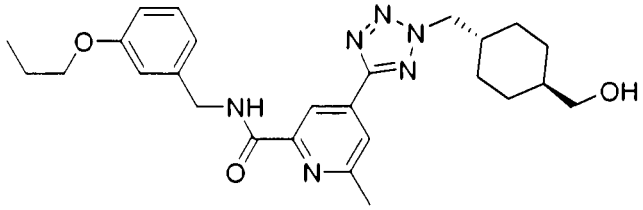
A mixture of potassium hydroxide (18.8 g, 85 %, crushed) in dimethylsulfoxide (80 mL) was stirred for 5 minutes at ambient temperature. To this white slurry was added 3-cyanophenol (10.0 g) and iodopropane (28.5 g). The mixture was stirred for 2.5 hours at room temperature. The reaction mixture was poured into 1 L of ice water and then extracted with dichloromethane (5 x 300 mL). The combined organic layers were washed with water (5 x 500 mL) and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo afforded the title compound (13.23 g, 97.8%).

Step 2: Preparation of (3-propoxyphenyl)methanamine



3-Propoxybenzonitrile (13.2 g) was dissolved in absolute ethanol (100 mL) and the solution was sparged with nitrogen gas. Palladium on carbon catalyst (4.0 g) was added and the mixture was shaken under hydrogen gas for 2 hours. The mixture was sparged, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (dichloromethane/methanol/NH_4OH, 97/3/0.3; 94/6/0.6; 90/10/1) to afford the title compound (8.47 g).

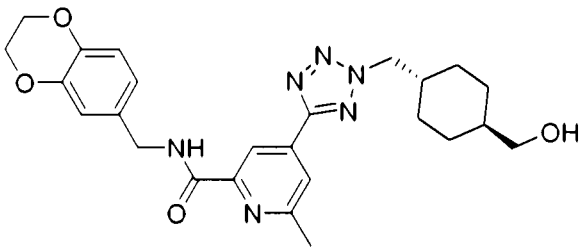
Step 3: Preparation of *N*-(3-propoxybenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



(3-Propoxyphenyl)methanamine (59.8 mg, 0.362 mmol) was reacted according to procedures described in Example 325 to afford the title compound as a solid (44mg, 30%). MS (ES+) *m/z* 479 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 - 1.06 (m, 5 H), 1.08 - 1.25 (m, 3 H), 1.43 - 1.56 (m, 1 H), 1.71 - 1.91 (m, 6 H), 2.04 - 2.18 (m, 1 H), 2.66 (s, 3 H), 3.43 - 3.50 (m, 2 H), 3.93 (t, *J*=6.58 Hz, 2 H), 4.55 (d, *J*=7.25 Hz, 2 H), 4.68 (d, *J*=6.18 Hz, 2 H), 6.84 (dd, *J*=8.19, 2.28 Hz, 1 H), 6.91 - 7.01 (m, 2 H), 7.22 - 7.32 (m, 1 H), 8.07 (d, *J*=1.34 Hz, 1 H), 8.49 (t, *J*=5.91 Hz, 1 H), 8.75 (s, 1 H).

Example 327

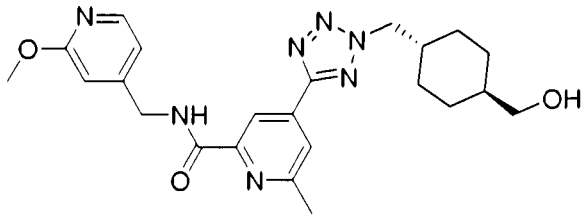
N-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methanamine (37.4 mg, 0.226 mmol) was reacted according to procedures described in Example 325 to afford the title compound as a solid (3.2 mg, 9%). MS (ES+) *m/z* 479 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 - 1.32 (m, 8 H), 1.71 - 1.93 (m, 4 H), 2.02 - 2.17 (m, 1 H), 2.70 (s, 2 H), 3.48 (d, *J*=6.18 Hz, 2 H), 4.26 (s, 3 H), 4.58 (dd, *J*=17.19, 6.44 Hz, 4 H), 6.80 - 6.95 (m, 3 H), 8.10 (d, *J*=1.34 Hz, 1 H), 8.62 (br. s., 1 H), 8.77 (s, 1 H).

Example 328

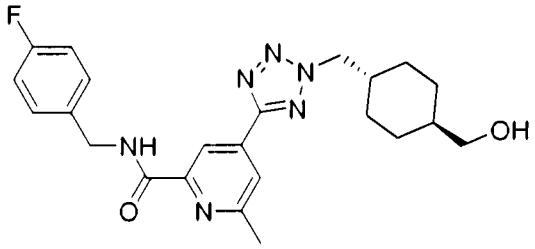
4-(2-(((*trans*)-4-(Hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-*N*-((2-methoxypyridin-4-yl)methyl)-6-methylpicolinamide



(2-Methoxypyridin-4-yl)methanamine (39.5 mg, 0.226 mmol) was reacted according to procedures described in Example 325 to afford the title compound as a solid (5.4 mg, 7%). MS (ES+) *m/z* 452 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.93 - 1.30 (m, 5 H), 1.41 - 1.56 (m, 1 H), 1.76 (d, *J*=12.89 Hz, 2 H), 1.87 (d, *J*=10.47 Hz, 2 H), 2.04 - 2.17 (m, 1 H), 2.68 (s, 3 H), 3.48 (d, *J*=6.18 Hz, 2 H), 3.96 (s, 3 H), 4.55 (d, *J*=6.98 Hz, 2 H), 4.69 (d, *J*=6.18 Hz, 2 H), 6.77 (s, 1 H), 6.92 (d, *J*=5.10 Hz, 1 H), 8.10 (s, 1 H), 8.15 (d, *J*=5.37 Hz, 1 H), 8.54 (t, *J*=6.31 Hz, 1 H), 8.73 (s, 1 H).

Example 329

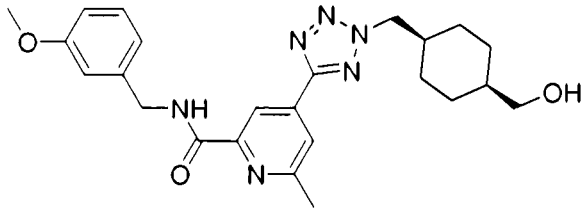
***N*-(4-Fluorobenzyl)-4-(2-(((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



A mixture of *N*-(4-fluorobenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 1 of the synthesis of (*trans*)-Methyl 4-((5-(2-((4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexanecarboxylate, Example 255) (50 mg, 0.16 mmol), polymer supported triphenylphosphine (186 mg, 0.4 mmol), and *trans*-cyclohexane-1,4-dimethanol (46 mg, 0.32 mmol) in tetrahydrofuran (3 mL) was cooled in an ice bath and di-*tert*-butyl azodicarboxylate (74 mg, 0.32 mmol) was added. The mixture was allowed to warm to room temperature and stir for 2 hours. The reaction mixture was acidified with trifluoroacetic acid and filtered. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC. The product was dissolved in dichloromethane and passed through a carbonate resin column. The filtrate was concentrated to afford the title compound as a white solid (36.7 mg). MS (ES+) *m/z* 439 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.35 (t, *J*=6.4 Hz, 1 H), 8.43 (s, 1 H), 8.09 (s, 1 H), 7.39 (dd, *J*=8.4, 5.7 Hz, 2 H), 7.16 (t, *J*=8.9 Hz, 2 H), 4.67 (d, *J*=7.0 Hz, 2 H), 4.52 (d, *J*=6.3 Hz, 2 H), 4.37 (t, *J*=5.3 Hz, 1 H), 3.19 (t, *J*=5.7 Hz, 2 H), 2.68 (s, 3 H), 1.91 - 2.02 (m, 1 H), 1.71 - 1.78 (m, 2 H), 1.58 - 1.64 (m, 2 H), 1.24 - 1.37 (m, 1 H), 1.02 - 1.14 (m, 2 H), 0.81 - 0.94 (m, 2 H).

Example 330

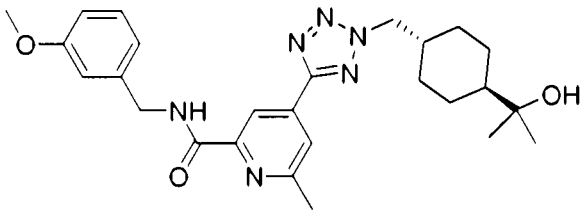
***N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



N-(3-Methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (100 mg, 0.31 mmol), polymer supported triphenylphosphine (287 mg, 0.62mmol), and cis-cyclohexane-1,4-dimethanol (89 mg, 0.62 mmol) (Kuroda, C.; Murase, A.; Suzuki, hours.; Endo, T.; Anzai, S. Bull Chem. Soc. Jpn. 1998, 71, 1639-1647.) were suspended in tetrahydrofuran (10 mL). The mixture was cooled to 0 °C. Di-*tert*-butyl azodicarboxylate (142 mg, 0.62 mmol) was added. The mixture was allowed to warm to room temperature and stir for 36 hours. The reaction mixture was filtered and the resin washed with tetrahydrofuran (20 mL). The filtrate was concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2) to afford the title compound as an oil (62 mg, 45%). MS (ES+) *m/z* 351 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (t, *J*=6.4 Hz, 1 H), 8.42 (d, *J*=0.9 Hz, 1 H), 8.08 (d, *J*=1.1 Hz, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 - 6.90 (m, 2 H), 6.82 (ddd, *J*=8.2, 2.5, 0.9 Hz, 1 H), 4.76 (d, *J*=7.7 Hz, 2 H), 4.51 (d, *J*=6.4 Hz, 2 H), 4.37 (t, *J*=5.4 Hz, 1 H), 3.73 (s, 3 H), 3.33 (dd, *J*=6.4, 5.5 Hz, 2 H), 2.68 (s, 3 H), 2.31 - 2.21 (m, 1 H), 1.65 - 1.27 (m, 9 H).

Example 331

***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxypropan-2-yl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

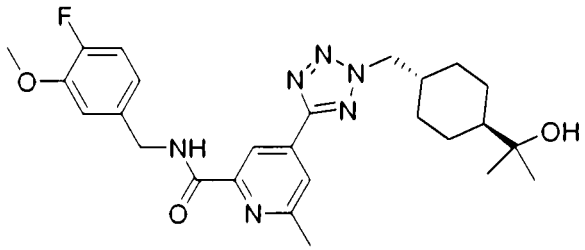


A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (105 mg), 2-((*trans*)-4-(hydroxymethyl)cyclohexyl)propan-2-ol (*Aust. J. Chem.* **1993**, *46*, 1869-1879) (98.7 mg), and polymer supported triphenylphosphine (740 mg) in anhydrous tetrahydrofuran (10 mL) was cooled in an ice bath. Di-*tert*-butyl azodicarboxylate (126 mg) was added and the mixture was placed in an ultrasonic bath for 30 minutes. The reaction mixture was filtered and the resin was washed with tetrahydrofuran and methanol. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC (acetonitrile/water, 50/50 - 80/20). The fractions containing product were

concentrated. The aqueous residue was made basic with 5% aqueous sodium bicarbonate (3 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the title compound (118 mg). MS (ES+) *m/z* 479 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, *J*=6.2 Hz, 1 H), 8.42 (s, 1 H), 8.07 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.90 - 6.94 (m, 2 H), 6.82 (d, *J*=7.7 Hz, 1 H), 4.65 (d, *J*=7.0 Hz, 2 H), 4.51 (d, *J*=6.6 Hz, 2 H), 3.94 (s, 1 H), 3.73 (s, 3 H), 2.67 (s, 3 H), 1.95 (s, 1 H), 1.80 (d, *J*=12.1 Hz, 2 H), 1.65 (d, *J*=11.3 Hz, 2 H), 1.13 (d, *J*=8.1 Hz, 1 H), 0.97 - 1.07 (m, 10 H)

Example 332

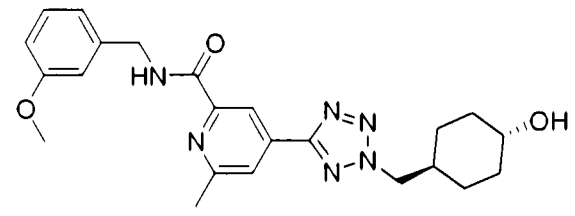
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxypropan-2-yl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



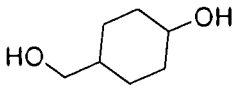
The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(2-hydroxypropan-2-yl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 331) by reaction with *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) and afforded 53.8 mg as an oil. MS (ES+) *m/z* 497 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, *J*=6.2 Hz, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.16 (d, *J*=8.4 Hz, 1 H), 7.11 (dd, *J*=11.5, 8.2 Hz, 1 H), 6.85 - 6.92 (m, 1 H), 4.62 (d, *J*=6.6 Hz, 2 H), 4.48 (d, *J*=6.2 Hz, 2 H), 3.92 (s, 1 H), 3.80 (s, 3 H), 2.65 (s, 3 H), 1.87 - 1.98 (m, 1 H), 1.78 (d, *J*=11.7 Hz, 2 H), 1.63 (d, *J*=11.3 Hz, 2 H), 0.90 - 1.23 (m, 11 H).

Example 333

***N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

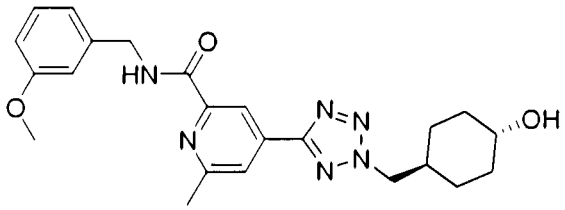


Step 1: Preparation of 4-(hydroxymethyl)cyclohexanol



A solution of 2M lithium aluminum hydride in tetrahydrofuran (70 mL) was added to diethyl ether (100 mL) in a mechanically stirred 2L flask. A solution of ethyl 4-hydroxycyclohexanecarboxylate (24.92 g) in diethyl ether (100 mL) was added dropwise over 50 minutes. The mixture was heated at reflux for 1 hour and then stirred overnight at room temperature. Ethyl acetate (5 mL) was carefully added and the mixture was acidified with 12 N hydrochloric acid (50 mL) with ice bath cooling. The organic layer was decanted and the aqueous layer was extracted with a mixture of tetrahydrofuran (150 mL) and ether (100 mL). The aqueous layer was neutralized with sodium bicarbonate (75 g) and extracted with ethyl acetate (4 x 400 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The resulting oil was distilled under reduced pressure to afford the title compound as a colorless oil (15.07 g).

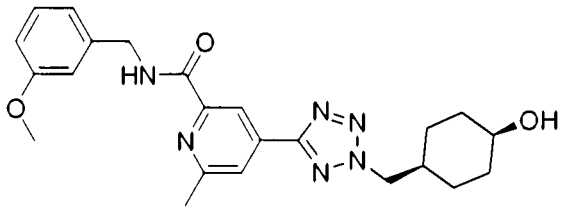
Step 2: Preparation of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (986 mg), 4-(hydroxymethyl)cyclohexanol (614 mg), and polymer supported triphenylphosphine (3.55 g, 7.5 mmol) in tetrahydrofuran (60 mL) was cooled in an ice bath. Di-*tert*-butylazodicarboxylate (1.046 g) was added and the mixture was placed in an ultrasonic bath for 50 minutes. The mixture was filtered and the resin was washed with tetrahydrofuran. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC (acetonitrile/water, 35/65 – 55/45). Fractions containing the first eluting isomer were combined and concentrated. The residue was dissolved in dichloromethane and washed with 5% aqueous sodium bicarbonate (3 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford the title compound (298 mg). MS (ES+) *m/z* 437 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.4 Hz, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.87 - 6.92 (m, 2 H), 6.77 - 6.82 (m, 1 H), 4.63 (d, *J*=7.0 Hz, 2 H), 4.49 (d, *J*=6.2 Hz, 2 H), 3.71 (s, 3 H), 2.65 (s, 3 H), 2.52 (s, 1 H), 1.89 - 1.98 (m, 1 H), 1.77 - 1.85 (m, 2 H), 1.53 - 1.61 (m, 2 H), 1.37 (d, *J*=7.3 Hz, 2 H), 1.03 - 1.17 (m, 2 H).

Example 334

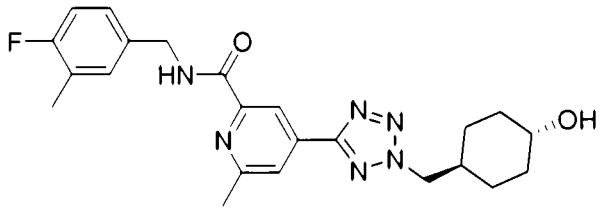
N-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



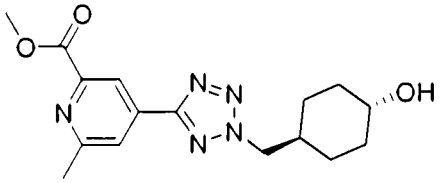
Isolation of the second eluting isomer by reverse phase preparative HPLC from the reaction mixture described in Example 333 afforded the title compound (520 mg). MS (ES+) *m/z* 437 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.4 Hz, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.87 - 6.92 (m, 2 H), 6.79 (dd, *J*=8.4, 1.5 Hz, 1 H), 4.65 (d, *J*=7.0 Hz, 2 H), 4.48 (d, *J*=6.6 Hz, 2 H), 4.30 (br. s., 1 H), 3.73 (br. s., 1 H), 3.71 (s, 3 H), 2.65 (s, 3 H), 2.52 (s, 1 H), 2.04 (br. s., 1 H), 1.54 - 1.63 (m, 2 H), 1.27 - 1.48 (m, 5 H).

Example 335

N-(4-Fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



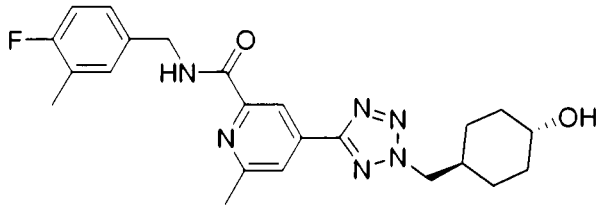
Step 1: Preparation of methyl 4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate



A mixture of methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (5.0 g, 28.8 mmol), 4-(hydroxymethyl)cyclohexanol (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 333) (3.71 g, 28.5 mmol), and polymer supported-triphenylphosphine (21.2 g, 45.6 mmol) in tetrahydrofuran (100 mL) was cool to 0 °C in an ice bath. Di-*tert*-butyl azodicarboxylate (10.5 g, 45.6 mmol) was added and stirring was continued for 60 minutes in an ice bath. The mixture was allowed to warm to room temperature and stir overnight. The reaction mixture was filtered and the resin was washed with tetrahydrofuran. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC. Isolation of the first eluting isomer afforded the title compound as a clear, light yellow colored oil (1.48 g). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.22 min., *m/z* 332 (M+H). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.04 - 1.16 (m, 3 H), 1.57 (d, *J*=7.07 Hz, 2 H), 1.78 - 1.84 (m, 2 H), 1.89 - 1.97 (m, 1 H), 2.63 (s, 3

H), 3.29 - 3.36 (m, 1 H), 3.91 (s, 3 H), 4.63 (d, *J*=7.07 Hz, 2 H), 4.70 (d, *J*=7.07 Hz, 1 H), 8.08 (d, *J*=1.63 Hz, 1 H), 8.36 (d, *J*=1.36 Hz, 1 H).

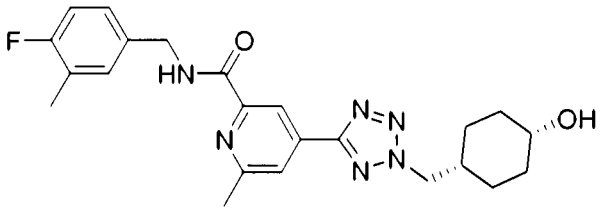
Step 2: Preparation of *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



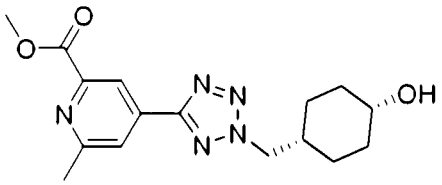
Diisopropylethylamine (77.9 mg, 0.603 mmol) and (4-fluoro-3-methylphenyl)methanamine (125.9 mg, 0.905 mmol) were added to a solution of methyl 4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (100 mg, 0.301 mmol) in *N*,*N*-dimethylformamide (2 mL). The mixture was stirred for 30 minutes and then heated to 60 °C overnight. The reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound (18.5 mg, 12%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (t, *J*=10.25 Hz, 3 H), 1.57 (s, 2 H), 1.79 (s, 2 H), 1.93 (s, 1 H), 2.19 (s, 2 H), 2.65 (s, 2 H), 4.46 (d, *J*=6.59 Hz, 2 H), 4.63 (d, *J*=6.59 Hz, 2 H), 6.99 - 7.09 (m, 1 H), 7.12 - 7.28 (m, 2 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.21 (t, *J*=6.59 Hz, 1 H).

Example 336

N-(4-Fluoro-3-methylbenzyl)-4-(2-(((*cis*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

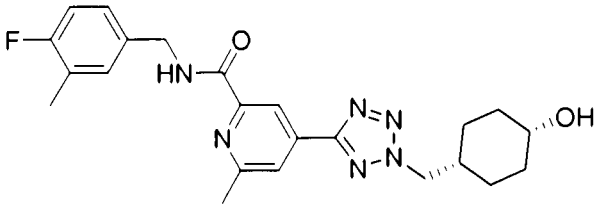


Step 1: Preparation of methyl 4-(2-(((*cis*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate



Isolation of the second eluting isomer from reverse phase preparative HPLC of the reaction mixture obtained in step 1 of the synthesis of *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 335) afforded the title compound as a clear, light yellow colored oil (2.41 g). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.34 min., *m/z* 332 (M+H). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.29 - 1.35 (m, 2 H), 1.37 - 1.47 (m, 3 H), 1.60 (dd, *J*=9.65, 3.67 Hz, 2 H), 1.89 - 2.10 (m, 1 H), 2.64 (s, 3 H), 3.75 (br. s., 1 H), 3.91 (s, 3 H), 4.67 (d, *J*=7.07 Hz, 2 H), 4.74 (d, *J*=7.07 Hz, 1 H), 8.11 (s, 1 H), 8.39 (s, 1 H).

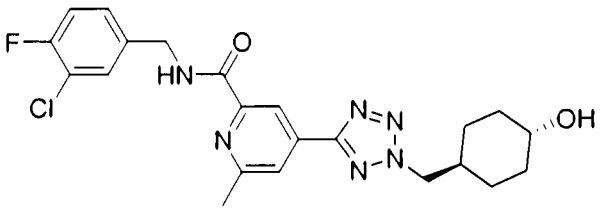
Step 2: Preparation of *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*cis*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Diisopropylethylamine (0.5 mL, 0.287 mmol) and (4-fluoro-3-methylphenyl)methanamine (41.7 mg, 0.30 mmol) were added to a solution of methyl 4-(2-(((*cis*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (25 mg, 0.075 mmol) in *N*,*N*-dimethylacetamide (2 mL). The mixture was stirred for 30 minutes and then heated to 60 °C overnight. The reaction mixture was purified by reverse-phase preparative HPLC to afford the title compound (21.5 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (t, *J*=10.25 Hz, 4 H), 1.57 (s, 2 H), 1.79 (s, 2 H), 1.93 (s, 2 H), 2.19 (s, 3 H), 2.65 (s, 3 H), 3.27 (s, 1 H), 4.43 - 4.49 (m, 2 H), 7.01 - 7.08 (m, 1 H), 7.14 - 7.21 (m, 1 H), 7.23 (d, *J*=6.59 Hz, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.21 (t, *J*=6.22 Hz, 1 H)

Example 337

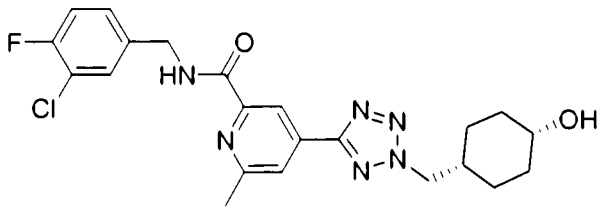
N-(3-Chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound (18.7 mg, 13%) was prepared in a similar manner to *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 335) by reaction with (3-chloro-4-fluorophenyl)methanamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (t, *J*=9.88 Hz, 5 H), 1.57 (s, 2 H), 1.79 (s, 2 H), 1.91 (d, *J*=13.91 Hz, 2 H), 2.66 (s, 3 H), 4.43 - 4.53 (m, 3 H), 4.63 (d, *J*=6.59 Hz, 2 H), 7.34 (d, *J*=7.32 Hz, 2 H), 7.53 (d, *J*=7.32 Hz, 1 H), 8.05 (s, 1 H), 8.39 (s, 1 H), 9.34 (t, *J*=6.22 Hz, 1 H).

Example 338

N-(3-Chloro-4-fluorobenzyl)-4-(2-(((*cis*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

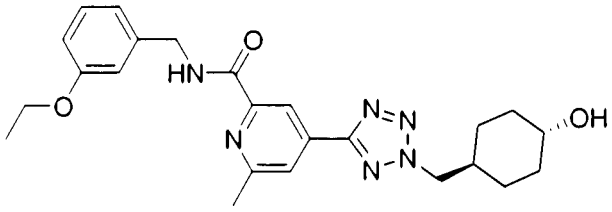


The title compound (18.8 mg, 55%) was prepared in a similar manner to *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*cis*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

(Example 336) by reaction with (3-chloro-4-fluorophenyl)methanamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.01 - 1.18 (m, 4 H), 1.57 (s, 3 H), 1.79 (s, 2 H), 1.91 (d, J=13.91 Hz, 1 H), 2.66 (s, 3 H), 4.43 - 4.54 (m, 3 H), 4.63 (d, J=6.59 Hz, 2 H), 7.34 (d, J=7.32 Hz, 2 H), 7.53 (d, J=8.05 Hz, 1 H), 8.05 (s, 1 H), 8.39 (s, 1 H), 9.34 (t, J=6.22 Hz, 1 H)

Example 339

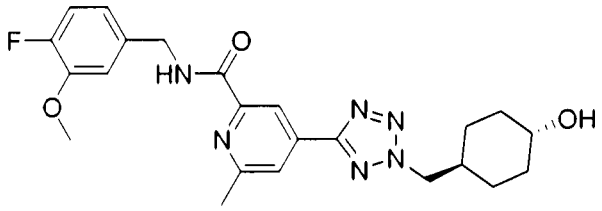
***N*-(3-Ethoxybenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound (18.5 mg, 13%) was prepared in a similar manner to *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 335) by reaction with (3-ethoxyphenyl)methanamine (prepared as described in step 2 of the synthesis of *N*-(3-ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide, Example 180). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (t, J=9.88 Hz, 5 H), 1.28 (t, J=6.95 Hz, 3 H), 1.57 (s, 2 H), 1.79 (s, 2 H), 1.93 (s, 1 H), 2.65 (s, 3 H), 3.27 (s, 1 H), 3.97 (q, J=6.59 Hz, 2 H), 4.41 - 4.53 (m, 2 H), 4.63 (d, J=6.59 Hz, 2 H), 6.78 (d, J=8.05 Hz, 1 H), 6.87 (s, 2 H), 7.20 (t, J=8.05 Hz, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.18 (t, J=6.59 Hz, 1 H)

Example 340

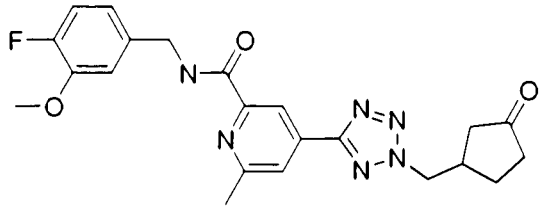
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



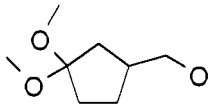
The title compound (20.9 mg, 15%) was prepared in a similar manner to *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-hydroxycyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 335) by reaction with 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (d, J=8.78 Hz, 2 H), 1.43 (t, J=10.25 Hz, 3 H), 1.59 (dd, J=10.25, 4.39 Hz, 2 H), 2.05 (s, 1 H), 2.51 (s, 1 H), 2.65 (s, 3 H), 3.72 (d, J=10.25 Hz, 1 H), 3.80 (s, 3 H), 4.27 (d, J=2.93 Hz, 1 H), 4.48 (d, J=6.59 Hz, 2 H), 4.65 (d, J=7.32 Hz, 2 H), 6.89 (s, 1 H), 7.07 - 7.13 (m, 1 H), 7.13 - 7.19 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.17 - 9.25 (m, 1 H).

Example 341

***rac-N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((3-oxocyclopentyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**

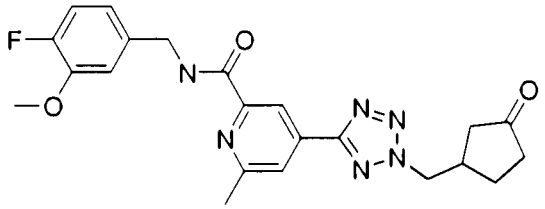


Step 1: Preparation of (3,3-dimethoxycyclopentyl)methanol



A solution of methyl 3,3-dimethoxycyclopentanecarboxylate (*Tetrahedron* **1977**, *33*, 1113) (6.22 g) in anhydrous tetrahydrofuran (60 mL) was added dropwise to a solution of 2 M lithium aluminum hydride (20 mL) in anhydrous tetrahydrofuran (240 mL) and the mixture was heated at 40 °C for 18 hours. The reaction mixture was cooled in an ice bath and water (7 mL) was added slowly, followed by 10% aqueous sodium hydroxide (2.0 mL). The mixture was heated to 40 °C for an hour. The mixture was filtered through a pad of neutral alumina and rinsed with tetrahydrofuran. The filtrate was concentrated to afford the title compound as an oil (4.77 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.47 - 3.56 (m, 2 H), 3.18 (s, 3 H), 3.18 (s, 3 H), 2.19 - 2.29 (m, 1 H), 1.97 (dd, *J*=13.2, 8.9 Hz, 1 H), 1.92 (s, 1 H), 1.72 - 1.84 (m, 3 H), 1.51 - 1.58 (m, 1 H), 1.36 - 1.47 (m, 1 H).

Step 2: Preparation of *rac-N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((3-oxocyclopentyl)methyl)-2*H*-tetrazol-5-yl)picolinamide

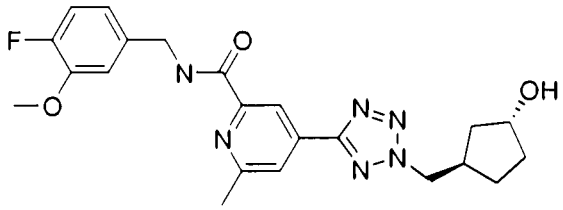


A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (500 mg), (3,3-dimethoxycyclopentyl)methanol (350 mg), polymer support triphenylphosphine (1.388 g, 3.0 mmol) in anhydrous tetrahydrofuran (50 mL) was cooled in an ice bath. Di-tert-butylazodicarboxylate (403 mg) was added and the mixture was placed in an ultrasonic bath for one hour. After standing overnight, the mixture was filtered and the resin was washed with tetrahydrofuran and methanol. The filtrate was acidified with trifluoroacetic acid and concentrated. The residue was purified by reverse phase preparative HPLC (acetonitrile/water, 50/50 – 75/25). The product containing fractions were concentrated. The aqueous residue was made basic with 5% aqueous sodium bicarbonate and extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over magnesium

sulfate, filtered and concentrated to afford the title compound (435 mg). MS (ES+) *m/z* 439 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.09 - 7.21 (m, 2 H), 6.90 (s, 1 H), 4.91 (d, *J*=7.3 Hz, 2 H), 4.50 (d, *J*=6.2 Hz, 2 H), 3.82 (s, 3 H), 2.88 - 2.97 (m, 1 H), 2.68 (s, 3 H), 2.27 - 2.37 (m, 1 H), 2.18 - 2.24 (m, 2 H), 1.99 - 2.17 (m, 2 H), 1.67 - 1.77 (m, 1 H).

Example 342

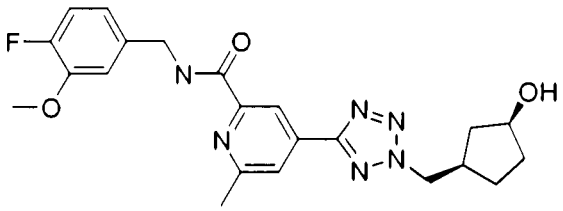
***rac-N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*R**,3*R**)-3-hydroxycyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



A 2 M solution of lithium aluminum hydride in tetrahydrofuran (0.20 mL) was added to a cooled solution (ice/acetone bath) of *rac-N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((3-oxocyclopentyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 341) (272 mg) in anhydrous tetrahydrofuran (5.0 mL) under nitrogen. The mixture was allowed to stir for 5 minutes and was then quenched with methanol (1 mL). The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC (acetonitrile/water, 40/60 – 60/40). Fractions containing the first eluting isomer were combined and concentrated. The aqueous residue was extracted with dichloromethane (3 x 5 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford the title compound (83 mg). MS (ES+) *m/z* 441 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (t, *J*=5.9 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.15 - 7.20 (m, 1 H), 7.09 - 7.15 (m, 1 H), 6.86 - 6.93 (m, 1 H), 4.73 (d, *J*=7.3 Hz, 2 H), 4.50 (d, *J*=6.2 Hz, 2 H), 4.43 (s, 1 H), 4.16 (s, 1 H), 3.82 (s, 3 H), 2.75 - 2.83 (m, 1 H), 2.67 (s, 3 H), 1.77 - 1.86 (m, 2 H), 1.62 (d, *J*=6.6 Hz, 1 H), 1.43 - 1.52 (m, 2 H), 1.28 - 1.38 (m, 1 H).

Example 343

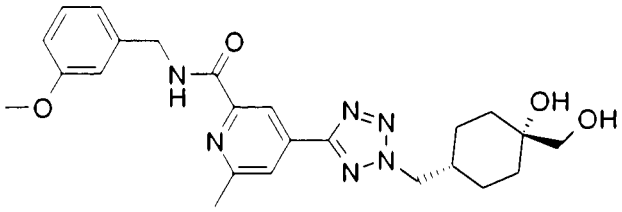
***rac-N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-hydroxycyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



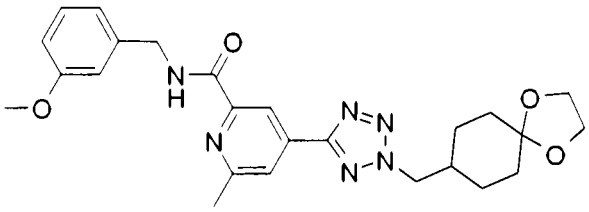
Isolation of the second eluting isomer by reverse phase preparative HPLC from the reaction mixture described in Example 342 afforded the title compound as a white solid (122 mg). MS(ES+) *m/z* 441 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.07 (s, 1 H), 7.15 - 7.20 (m, 1 H), 7.10 - 7.15 (m, 1 H), 6.87 - 6.93 (m, 1 H), 4.78 (d, *J*=7.3 Hz, 2 H), 4.56 (d, *J*=3.7 Hz, 1 H), 4.50 (d, *J*=6.2 Hz, 2 H), 4.10 - 4.16 (m, 1 H), 3.82 (s, 3 H), 2.67 (s, 3 H), 2.55 - 2.62 (m, 1 H), 1.86 - 1.94 (m, 1 H), 1.62 - 1.70 (m, 2 H), 1.52 - 1.62 (m, 2 H), 1.31 - 1.38 (m, 1 H).

Example 344

***N*-(3-Methoxybenzyl)-4-(2-(((*cis*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

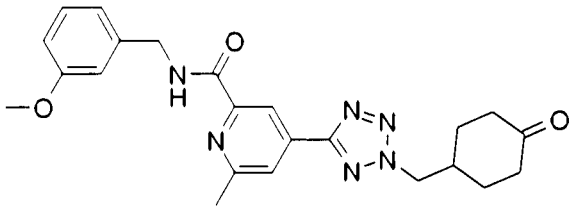


Step 1: Preparation of 4-(2-(1,4-dioxaspiro[4.5]dec-8-ylmethyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpyridine-2-carboxamide



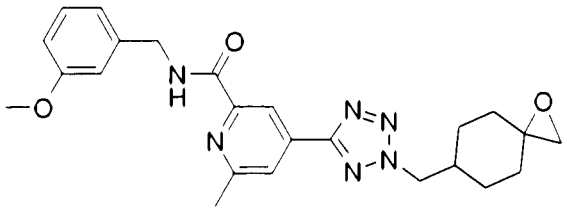
1,4-Dioxaspiro[4.5]dec-8-ylmethyl 4-methylbenzenesulfonate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-6-(2-(((*trans*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 28) (1.4 g, 4.3 mmol) is added to a mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (1.39 g, 4.3 mmol) and triethylamine (434 mg) in anhydrous *N*,*N*-dimethylacetamide (2 mL). The mixture was stirred at 85 °C for 64 hours. The reaction mixture is purified by reverse phase preparative HPLC to afford the title compound as an oil (1.7 g).

Step 2: Preparation of *N*-(3-methoxybenzyl)-6-methyl-4-(2-((4-oxocyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



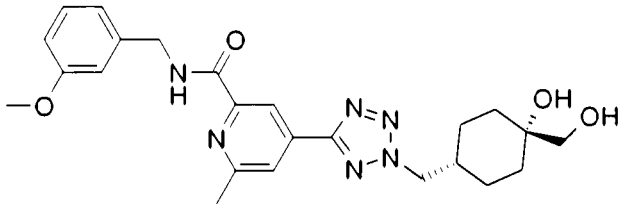
Formic acid (96%, 20 mL) was added to a solution of 4-(2-(1,4-dioxaspiro[4.5]dec-8-ylmethyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpyridine-2-carboxamide (1.6 g, 3.3 mmol) in tetrahydrofuran (13 mL) and the mixture is stirred overnight at room temperature. The reaction mixture is concentrated and the residue is dissolved in dichloromethane. The mixture was washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and concentrated to afford the title compound as a white solid (1.6 g).

Step 3: Preparation of *N*-(3-methoxybenzyl)-6-methyl-4-(2-(1-oxaspiro[2.5]oct-6-ylmethyl)-2*H*-tetrazol-5-yl)pyridine-2-carboxamide



A solution of *N*-(3-methoxybenzyl)-6-methyl-4-(2-((4-oxocyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (445 mg, 1.0 mmol) in anhydrous dimethylsulfoxide (4 mL) was added to a solid mixture of trimethylsulfoxonium iodide (445 mg, 2.0 mmol) and potassium t-butoxide (225 mg, 2.0 mmol). The mixture was allowed to stir at room temperature for 30 minutes. Water (25 mL) was then added and the slurry was stirred at room temperature for 20 minutes. The resulting precipitate was filtered, washed with water and dried under vacuum to afford the title compound (266 mg)

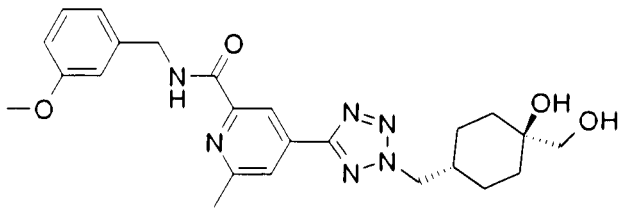
Step 4: Preparation of *N*-(3-methoxybenzyl)-4-(2-(((*cis*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Perchloric acid (70%, 0.4 mL) was added to *N*-(3-methoxybenzyl)-6-methyl-4-(2-(1-oxaspiro[2.5]oct-6-ylmethyl)-2*H*-tetrazol-5-yl)pyridine-2-carboxamide (260 mg, 0.58 mmol) in a mixture of tetrahydrofuran (4 ml) and water (1.2 mL). The mixture was allowed to stir at room temperature for 3.5 hours. The reaction mixture was purified by reverse phase preparative HPLC followed by elution through a carbonate resin column. The resulting mixture of isomers were separated by supercritical fluid chiral chromatography (OJ-H column, 30 x 250 mm, 20% 2-propanol, 70 mL/min) and the first eluting isomer was isolated to afford the title compound as a white solid (32 mg). MS (ES+) *m/z* 467 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.4 Hz, 1 H), 8.41 (s, 1 H), 8.06 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.88 - 6.92 (m, 2 H), 6.80 (d, *J*=8.8 Hz, 1 H), 4.64 (d, *J*=7.0 Hz, 2 H), 4.49 (d, *J*=6.2 Hz, 2 H), 4.39 (t, *J*=5.3 Hz, 1 H), 3.80 (s, 1 H), 3.71 (s, 3 H), 3.10 (d, *J*=5.5 Hz, 2 H), 2.65 (s, 3 H), 1.87 - 1.97 (m, 1 H), 1.25 - 1.49 (m, 8 H).

Example 345

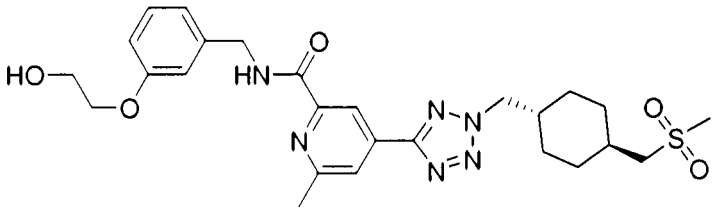
N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-hydroxy-4-(hydroxymethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



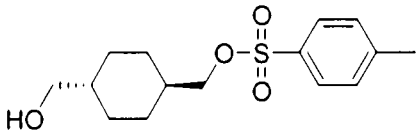
Isolation of the second eluting isomer by supercritical fluid chiral chromatography (OJ-H column, 30 x 250 mm, 20% 2-propanol, 70 mL/min) from the reaction mixture described in Example 344 afforded the title compound as a white solid (54 mg). MS (ES+) *m/z* 467 (M+H).

Example 346

***N*-(3-(2-Hydroxyethoxy)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**

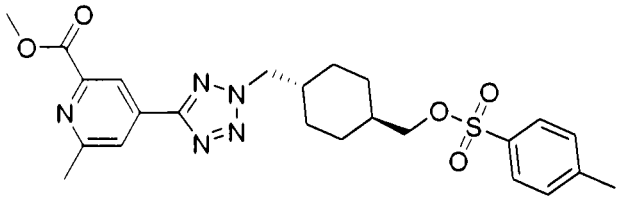


Step 1: Preparation of ((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl 4-methylbenzenesulfonate



4-Methylbenzenesulfonyl chloride (19.0 g, 100 mmol) was added to a solution of *trans*-1,4-cyclohexane dimethanol (14.4 g, 100 mmol) in anhydrous pyridine (50 mL) cooled in an ice bath. The mixture was allowed to warm to room temperature and was stirred for 18 hours. The reaction mixture was diluted with ether (300 mL), poured into water (400 mL), and filtered. The separated aqueous layer was further extracted with ether (2 x 200 mL). The combined organic layers were washed with water (200 mL), 1N hydrochloric acid (2 x 200 mL), water (200 mL), and saturated aqueous sodium bicarbonate solution (200 mL). The organic layer was dried over magnesium sulfate and concentrated to afford the title compound as an oil (14.8 g).

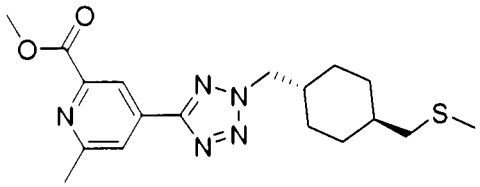
Step 2: Preparation of methyl 6-methyl-4-(2-(((*trans*)-4-((tosyloxy)methyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinate



In a 100 ml round-bottomed flask under nitrogen at room temperature, methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (0.835 mg,

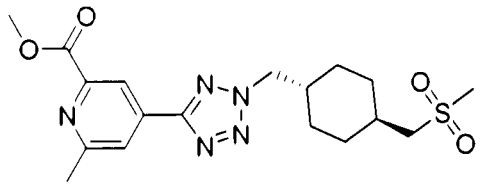
3.81 mmol) was combined with ((*trans*)-4-(hydroxymethyl)cyclohexyl)methyl 4-methylbenzenesulfonate (1.25 g, 4.19 mmol), polymer supported-triphenylphosphine (4.87 g, 10.5 mmol) and tetrahydrofuran (30 mL). The mixture was cool to 0 °C in a dry ice bath for 20 minutes and di-*tert*-butyl azodicarboxylate (1.75 g, 7.62 mmol) was added. The mixture was stirred in a dry ice bath for 1 hour and then allowed to warm to room temperature and stir overnight. The reaction mixture was filtered and the resin was washed with tetrahydrofuran. The residue was purified by reverse phase preparative HPLC to afford the title compound (1.295 g). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.565 min., *m/z* 500 (M+H). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.88 - 1.18 (m, 3 H), 1.55 - 1.82 (m, 4 H), 1.95 - 2.12 (m, 1 H), 2.38 - 2.46 (m, 3 H), 2.91 (s, 3 H), 3.79 (d, *J*=6.18 Hz, 2 H), 4.04 (s, 3 H), 4.56 (d, *J*=7.25 Hz, 2 H), 7.31 (d, *J*=8.06 Hz, 2 H), 7.67 - 7.79 (m, 2 H), 8.44 (s, 1 H), 8.85 (s, 1 H), 13.80 (s, 2 H).

Step 3: Preparation of methyl 6-methyl-4-(2-(((*trans*)-4-(methylthiomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinate



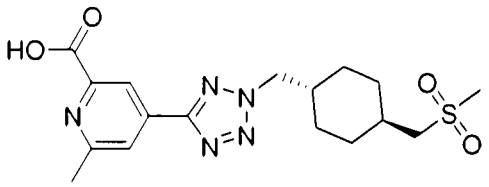
Sodium thiomethoxide (0.363 g, 5.18 mmol) was added to a solution of methyl 6-methyl-4-(2-(((*trans*)-4-((tosyloxy)methyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinate (1.295 g, 2.592 mmol) in dimethylsulfoxide (20 mL) and the mixture was heated at 50 °C for 2 hours. The reaction mixture was passed through a silica plug, eluted with ethyl acetate, and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound as a clear, light yellow colored oil (0.973 g). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.536 min., *m/z* 376 (M+H).

Step 4: Preparation of methyl 6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinate



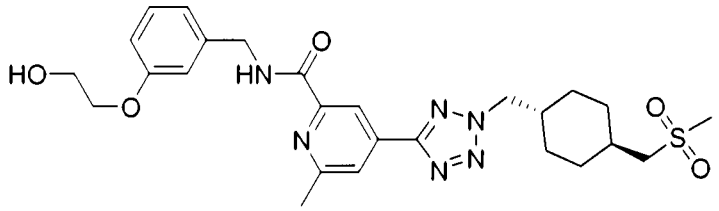
3-Chloroperoxybenzoic acid (772 mg, 4.47 mmol) was added to a solution of methyl 6-methyl-4-(2-(((*trans*)-4-(methylthiomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinate (381.4 mg, 1.016 mmol) in dichloromethane (10 mL) and the mixture was allowed to stir overnight. A saturated aqueous sodium bicarbonate solution (5 mL) was added. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated to afford the title compound as a clear, colorless oil (415 mg). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.626 min., *m/z* 408 (M+H).

Step 5: Preparation of 6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinic acid



A solution of lithium hydroxide (1 M, 1 ml, 1.0 mmol) was added to a solution of methyl 6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinate (414 mg, 1.02 mmol) in tetrahydrofuran (10 mL). The mixture was allowed to stir at room temperature overnight and was then concentrated to afford the title compound. LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 2.090 min., *m/z* 394 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.08 - 1.29 (m, 4 H), 1.99 (s, 1 H), 2.00 - 2.17 (m, 4 H), 2.86 - 3.00 (m, 8 H), 4.60 (d, *J*=6.98 Hz, 2 H), 8.48 (s, 1 H), 8.87 (s, 1 H), 12.53 (br. s., 2 H).

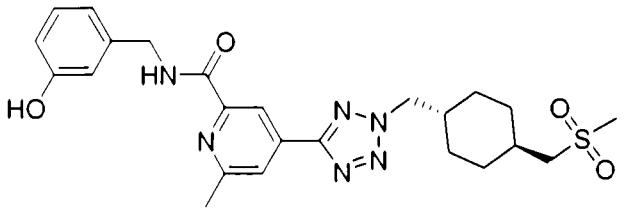
Step 6: Preparation of *N*-(3-(2-hydroxyethoxy)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)-cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



A mixture of 6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinic acid (50.0 mg, 0.130 mmol), diisopropylethylamine (150 mg, 1.10 mmol), and 2-(3-(aminomethyl)phenoxy)ethanol (prepared as described in step 2 of the synthesis of *N*-(3-(2-hydroxyethoxy)benzyl)-6-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 13) (42.0 mg, 0.250 mmol) in *N*,*N*-dimethylformamide (2.0 mL) was stirred for 20 minutes. O-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (102 mg, 0.318 mmol) was added and the mixture was stirred for 3 hours. The reaction mixture was purified by reverse phase preparative HPLC to afford the title compound as the trifluoroacetate salt (38.0 mg, 55% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.16 (m, 14 H), 1.61 (d, *J*=10.25 Hz, 9 H), 1.90 (d, *J*=10.98 Hz, 11 H), 2.65 (s, 9 H), 2.90 - 2.96 (m, 10 H), 2.99 (d, *J*=6.59 Hz, 7 H), 3.67 (d, *J*=4.39 Hz, 7 H), 3.93 (t, *J*=5.12 Hz, 8 H), 4.49 (d, *J*=6.59 Hz, 9 H), 4.64 (d, *J*=7.32 Hz, 8 H), 6.85 - 6.93 (m, 6 H).

Example 347

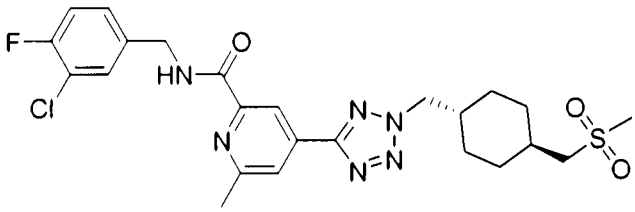
N-(3-Hydroxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



The title compound (49.0 mg, 77%) was prepared in a similar manner to *N*-(3-(2-hydroxyethoxy)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 346) by reaction with 3-(aminomethyl)phenol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.16 (m, 17 H), 1.61 (d, *J*=10.98 Hz, 11 H), 1.82 - 1.93 (m, 14 H), 2.65 (s, 12 H), 2.90 - 2.97 (m, 12 H), 2.99 (d, *J*=5.86 Hz, 8 H), 4.44 (d, *J*=6.59 Hz, 10 H), 4.64 (d, *J*=6.59 Hz, 9 H), 6.70 - 6.77 (m, 7 H)

Example 348

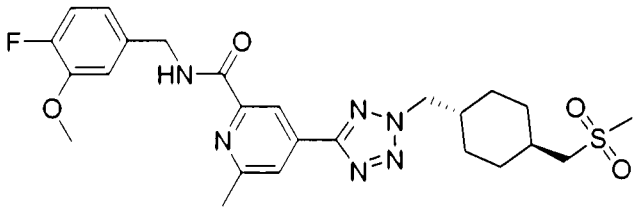
N-(3-Chloro-4-fluorobenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



The title compound (48.0 mg, 58%) was prepared in a similar manner to *N*-(3-(2-hydroxyethoxy)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 346) by reaction with (3-chloro-4-fluorophenyl)methanamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.15 (m, 18 H), 1.61 (d, *J*=11.71 Hz, 12 H), 1.81 - 1.93 (m, 16 H), 2.66 (s, 13 H), 2.89 - 2.95 (m, 12 H), 2.99 (d, *J*=5.86 Hz, 9 H), 4.49 (d, *J*=5.86 Hz, 10 H), 4.64 (d, *J*=6.59 Hz, 10 H).

Example 349

N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide

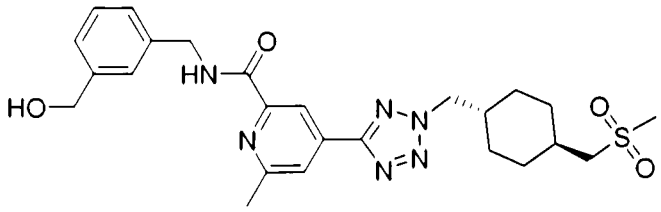


The title compound (76.5.0 mg, 56%) was prepared in a similar manner to *N*-(3-(2-hydroxyethoxy)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 346) by reaction with 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 - 1.16 (m, 12 H), 1.61 (d, *J*=10.26 Hz, 10 H), 1.82 - 1.93 (m, 12 H), 1.97 (s, 7

H), 2.65 (s, 9 H), 2.92 (s, 9 H), 2.99 (d, *J*=5.86 Hz, 8 H), 3.80 (s, 8 H), 4.48 (d, *J*=5.86 Hz, 9 H), 4.64 (d, *J*=5.86 Hz, 8 H), 7.06 - 7.18 (m, 7 H).

Example 350

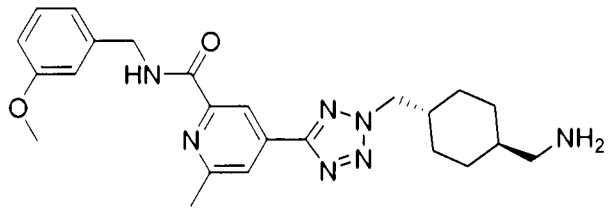
N-(3-(Hydroxymethyl)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide



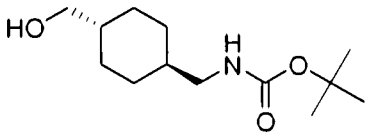
The title compound (45.0 mg, 69%) was prepared in a similar manner to *N*-(3-(2-hydroxyethoxy)benzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonylmethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 346) by reaction with (3-(aminomethyl)phenyl)methanol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.16 (m, 17 H), 1.61 (d, *J*=11.71 Hz, 11 H), 1.81 - 1.93 (m, 14 H), 2.65 (s, 12 H), 2.89 - 2.95 (m, 12 H), 2.99 (d, *J*=5.86 Hz, 8 H), 4.45 (s, 7 H), 4.48 - 4.56 (m, 10 H), 4.64 (d, *J*=7.32 Hz, 9 H)

Example 351

N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(aminomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

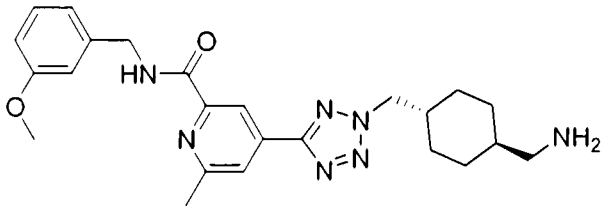


Step 1: Preparation of *tert*-butyl ((*trans*)-4-(hydroxymethyl)cyclohexyl)methylcarbamate



A solution of trans 4-(*tert*-butyloxycarbonylamino)methylcyclohexanecarboxylic acid (5.0 g, 19 mmol) in a mixture of 1,4-dioxane/tetrahydrofuran (1/1, 20 mL) was added drop wise to a cooled suspension of lithium aluminum hydride (2.1 g, 57 mmol) and the resulting mixture was stirred at room temperature for 15 hours. The excess of lithium aluminum hydride was destroyed by drop wise addition of water (2 mL). The suspension was filtered and the filter cake was washed with tetrahydrofuran (10 mL) and methanol (2 x 10 mL). The filtrate was concentrated in vacuo and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried with sodium sulfate and concentrated to afford the title compound as a light amber oil which solidified on standing (3.7 g, 80%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 4.79 min, *m/z* 266 (M+Na).

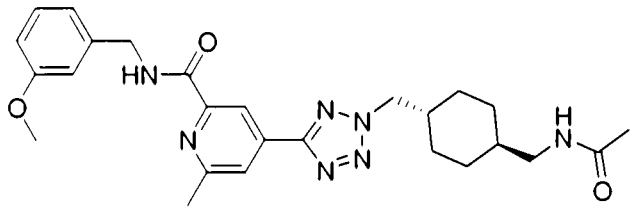
Step 2: Preparation of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(aminomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



A mixture of *tert*-butyl ((*trans*)-4-(hydroxymethyl)cyclohexyl)methylcarbamate (0.75 g, 3.1 mmol), *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (0.50 g, 1.5 mmol), and polymer supported-triphenylphosphine (1.85 g, 2.65 mmol) in tetrahydrofuran (25.0 mL) was cooled to 0 °C in an ice bath for 15 minutes. Di-*tert*-butyl azodicarboxylate (755 mg, 3.08 mmol) was added and the mixture was allowed to warm to room temperature and stir for 48 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in dichloromethane (4 mL) and trifluoroacetic acid (2 mL) was added. The mixture was stirred for 30 minutes at room temperature and then concentrated in vacuo. The residue was triturated with diethyl ether and further purified by reverse phase preparative HPLC (10-90% acetonitrile/water) to afford the title compound as a white solid (0.24 g, 52%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 4.59 min, *m/z* 450 (M+H).

Example 352

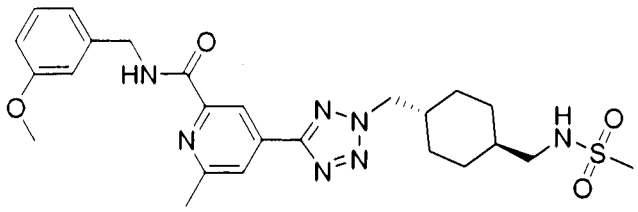
N-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-(acetamidomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Triethylamine (0.031 ml) and acetyl chloride (0.010 mL) was added to a solution of *N*-(3-methoxybenzyl)- 4-(2-(((*trans*)-4-(aminomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 351) (0.050 g, 0.010 mmol) in *N,N*-dimethylformamide (1 mL) and the mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (2 x 5 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound as a solid (19 mg, 39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 - 9.25 (m, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.69 (s, 1 H), 7.17 - 7.26 (m, 1 H), 6.90 (s, 2 H), 6.80 (d, *J*=8.05 Hz, 1 H), 4.64 (d, *J*=6.59 Hz, 2 H), 4.49 (d, *J*=6.59 Hz, 2 H), 3.71 (s, 3 H), 2.84 (t, *J*=5.86 Hz, 2 H), 2.65 (s, 3 H), 1.96 (d, *J*=2.93 Hz, 1 H), 1.76 (s, 3 H), 1.68 (d, *J*=11.71 Hz, 2 H), 1.60 (d, *J*=12.45 Hz, 2 H), 1.30 (s, 1 H), 0.98 - 1.12 (m, 2 H), 0.79 - 0.94 (m, 2 H).

Example 353

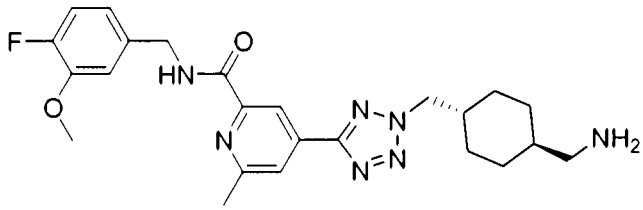
***N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamidomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



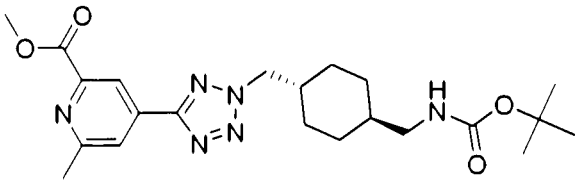
Triethylamine (0.031 ml) and methane sulfonylchloride (0.010 mL) was added to a solution of *N*-(3-methoxybenzyl)- 4-(2-(((*trans*)-4-(aminomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 351) (0.050 g, 0.010 mmol) in *N,N*-dimethylformamide (1 mL) and the mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (2 x 5 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound as a solid (15 mg, 28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.14 - 9.25 (m, 1 H), 8.41 (s, 1 H), 8.06 (s, 2 H), 7.16 - 7.27 (m, 1 H), 6.87 - 6.96 (m, 2 H), 6.80 (d, *J*=7.32 Hz, 1 H), 4.64 (d, *J*=7.32 Hz, 2 H), 4.49 (d, *J*=6.59 Hz, 2 H), 3.71 (s, 3 H), 2.82 (s, 3 H), 2.74 (t, *J*=6.59 Hz, 2 H), 2.65 (s, 3 H), 1.97 (s, 1 H), 1.75 (d, *J*=13.18 Hz, 2 H), 1.61 (d, *J*=11.71 Hz, 2 H), 1.34 (s, 1 H), 0.98 - 1.17 (m, 2 H), 0.79 - 0.95 (m, 2 H).

Example 354

***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(aminomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



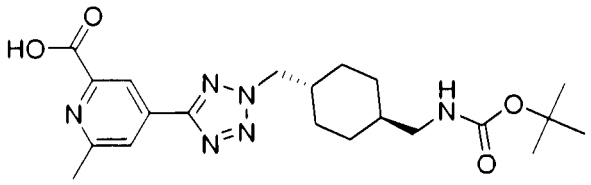
Step 1: Preparation of methyl 4-(2-(((*trans*)-4-((*tert*-butoxycarbonyl)methyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate



A mixture of methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (1.50g, 6.85 mmol), *tert*-butyl ((*trans*)-4-(hydroxymethyl)cyclohexyl)methylcarbamate (prepared as described in step 1 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-(aminomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-

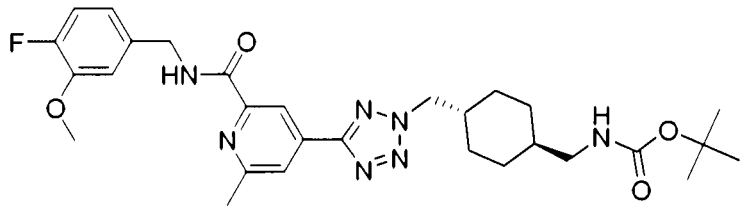
methylpicolinamide, Example 351) (3.00 g, 12.3 mmol), and polymer supported-triphenylphosphine (7.78 g, 17.1 mmol) in tetrahydrofuran (150 mL) was cooled to 0 °C in an ice bath for 15 minutes. Di-*tert*-butyl azodicarboxylate (3.15 g, 13.7 mmol) was added and the mixture was allowed to warm to room temperature and stir for 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography (0-50% ethyl acetate/heptane) to afford the title compound as an beige solid (2.15 g, 71%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 5.84 min, *m/z* 445 (M+H).

Step 2: Preparation of 4-(2-(((*trans*)-4-((*tert*-butoxycarbonyl)methyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid



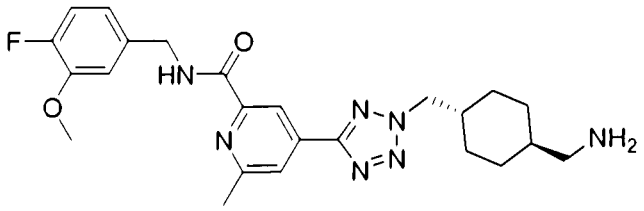
An aqueous solution of sodium hydroxide (2.5 N, 5.0 mL) was added to a solution of methyl 4-(2-(((*trans*)-4-((*tert*-butoxycarbonyl)methyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinate (0.50 g, 1.1 mmol) in tetrahydrofuran (5 mL) and water (2 mL) and the mixture was stirred at room temperature for 15 hours. The tetrahydrofuran was removed in vacuo and the aqueous residue was acidified with aqueous hydrochloric acid to pH 7. The resulting white solid was filtered and dried to afford the title compound (0.45g, 92%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 5.10 min, *m/z* 431 (M+H).

Step 3: Preparation of *tert*-butyl ((*trans*)-4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexyl)methylcarbamate



A mixture of 4-(2-(((*trans*)-4-((*tert*-butoxycarbonyl)methyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (0.080 g, 0.19 mmol) and 1-hydroxybenzatriazole (30 mg, 0.22 mmol) in *N,N*-dimethylacetamide (2 mL) was stirred for 5 minutes. Triethylamine (0.028 g, 0.28 mmol), 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (35 mg, 0.22 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (53 mg, 0.28 mmol) were added, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC to afford the title compound as solid (100 mg, 95%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 5.72 min, *m/z* 568 (M+H).

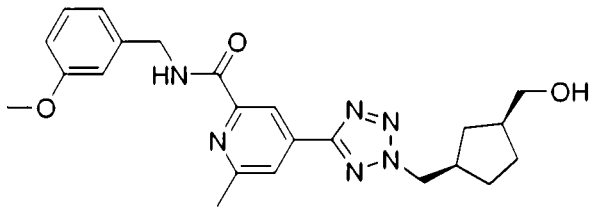
Step 4: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-(aminomethyl)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide hydrochloride



A solution of hydrochloric acid in dioxane (4 N, 6.0 mL) was added to a solution of *tert*-butyl ((*trans*)-4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclohexyl)methylcarbamate (105 mg, 0.185 mmol) in dichloromethane (2 mL) and the mixture was stirred for 1.5 hours. The reaction mixture was concentrated and the residue was triturated with diethyl ether to afford the title compound as the hydrochloride salt (41 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (br. s., 1 H), 8.40 (br. s., 1 H), 8.05 (br. s., 1 H), 7.97 (br. s., 1 H), 7.04 - 7.19 (m, 1 H), 6.87 (br. s., 1 H), 4.65 (br. s., 2 H), 4.47 (br. s., 2 H), 3.79 (br. s., 2 H), 3.54 (s, 3 H), 3.35 (br. s., 1 H), 2.65 (br. s., 3 H), 2.59 (br. s., 1 H), 1.98 (br. s., 1 H), 1.77 (d, *J*=9.94 Hz, 2 H), 1.61 (d, *J*=10.47 Hz, 2 H), 1.50 (br. s., 1 H), 1.06 (br. s., 2 H), 0.92 (d, *J*=8.32 Hz, 2 H).

Example 355

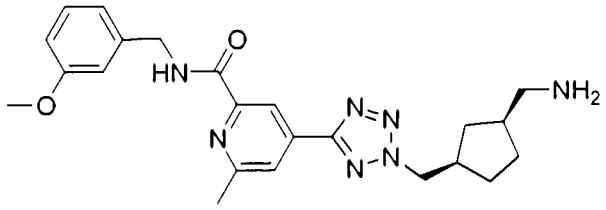
***rac*-*N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-(hydroxymethyl)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



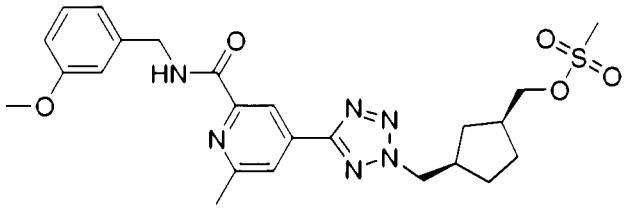
A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (325 mg), *cis*-cyclopentane-1,3-dimethanol (*Bioorg. Med. Chem. Lett.* **2005**, *15*, 2685-2688) (203 mg), and polymer supported triphenylphosphine (1.27 g) in anhydrous tetrahydrofuran (15 mL) was cooled in an ice bath. . Di-*tert*-butyl azodicarboxylate (345 mg) was added and the mixture was placed in an ultrasonic bath for 30 minutes. The mixture was filtered and the resin was washed with tetrahydrofuran. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC (acetonitrile/water, 40/60 - 70/30). The product was dissolved in dichloromethane (20 mL) and stirred with Argonaut MP-CO_3H resin (2.62 mmol/g, 0.9 g) and eluting through a Stratosphere MP-CO_3H SPE column. The eluent was concentrated to afford the title compound as an oil (245 mg). MS (ES+) *m/z* 437 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.2 Hz, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.22 (t, *J*=8.2 Hz, 1 H), 6.87 - 6.92 (m, 2 H), 6.79 (dd, *J*=8.1, 1.5 Hz, 1 H), 4.67 - 4.77 (m, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.41 (t, *J*=5.1 Hz, 1 H), 3.71 (s, 3 H), 3.23 - 3.32 (m, 2 H), 2.65 (s, 3 H), 2.50 - 2.59 (m, 1 H), 1.96 - 2.07 (m, 1 H), 1.74 - 1.84 (m, 1 H), 1.57 - 1.71 (m, 2 H), 1.31 - 1.42 (m, 2 H), 0.96 - 1.06 (m, 1 H).

Example 356

***rac*-*N*-(3-Methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-(aminomethyl)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

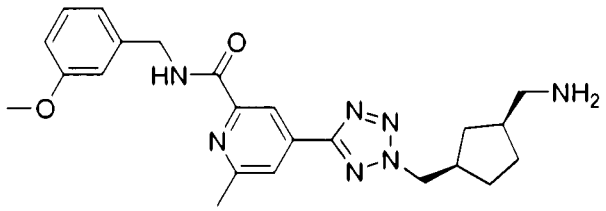


Step 1: Preparation of *rac*-((1*S**,3*R**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclopentyl)methyl methanesulfonate



Methanesulfonyl chloride (0.160 mL) was added to a solution of *rac*-*N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-(hydroxymethyl)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 355) (742 mg) in pyridine (15 mL) cooled in an ice bath. The mixture was allowed to warm to room temperature and was stirred for 3 hours. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC (acetonitrile/water, 50/50 - 80/20). The combined fractions were made basic with 5% aqueous sodium bicarbonate (3 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford the title compound (752 mg). MS (ES+) *m/z* 515 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.4 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.87 - 6.92 (m, 2 H), 6.80 (d, *J*=8.1 Hz, 1 H), 4.76 (d, *J*=7.3 Hz, 2 H), 4.49 (d, *J*=6.2 Hz, 2 H), 4.05 - 4.14 (m, 2 H), 3.71 (s, 3 H), 2.65 (s, 3 H), 2.56 - 2.64 (m, 1 H), 2.52 (s, 3 H), 2.25 - 2.36 (m, 1 H), 1.85 - 1.94 (m, 1 H), 1.67 - 1.77 (m, 2 H), 1.38 - 1.48 (m, 2 H), 1.04 - 1.15 (m, 1 H).

Step 2: Preparation of *rac*-*N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-(aminomethyl)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

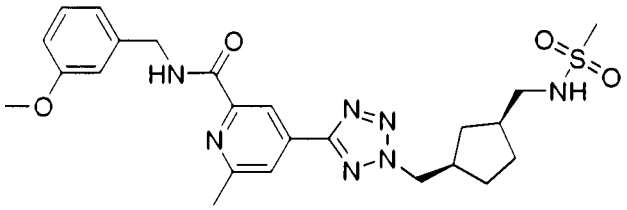


Ammonium hydroxide (2 mL) was added to a solution of *rac*-((1*S**,3*R**)-3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cyclopentyl)methyl methanesulfonate (227 mg) in DMSO (2 mL) and the mixture was heated to 70 °C overnight. The mixture was poured into water (10 mL) and extracted with dichloromethane (2 x 5 mL). The combined organic layers were washed with water (5 mL), dried over magnesium sulfate, filtered and

concentrated. The residue was purified by reverse phase preparative HPLC (acetonitrile/water, 30/70 – 60/40). The product containing fractions were concentrated. The aqueous residue was made basic with 5% aqueous sodium bicarbonate and extracted with dichloromethane (5 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the title compound as an oil (110 mg). MS (ES+) m/z 436 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, J=6.2 Hz, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.22 (t, J=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, J=8.1 Hz, 1 H), 4.72 (d, J=7.3 Hz, 2 H), 4.49 (d, J=6.2 Hz, 2 H), 3.71 (s, 3 H), 2.65 (s, 3 H), 2.50 - 2.59 (m, 1 H), 1.78 - 1.94 (m, 2 H), 1.62 - 1.72 (m, 2 H), 1.23 - 1.44 (m, 2 H), 0.90 - 1.02 (m, 1 H).

Example 357

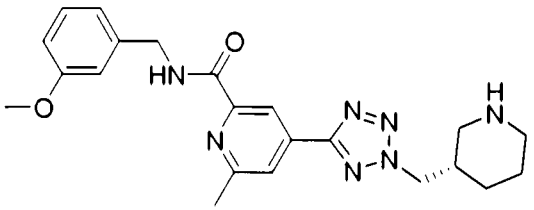
***rac-N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((1*R**,3*S**)-3-(methylsulfonamidomethyl)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



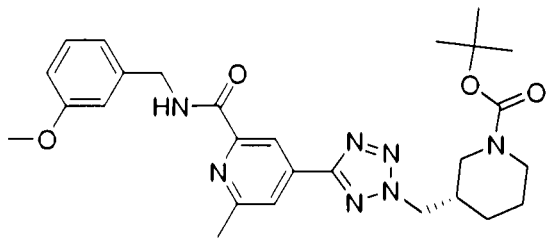
Methanesulfonyl chloride (11.4 µL) was added to a mixture of *rac-N*-(3-methoxybenzyl)-4-(2-(((1*R**,3*S**)-3-(aminomethyl)cyclopentyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 356) (53 mg) and diisopropylethylamine (30 µL) in anhydrous tetrahydrofuran (3 mL). The mixture was stirred at room temperature for 1 hour and was then concentrated. The residue was purified by reverse phase preparative HPLC (acetonitrile/water, 50/50 – 75/25). The product containing fractions were concentrated. The aqueous residue was made basic with 5% aqueous sodium bicarbonate and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the title compound as an oil (63 mg). MS (ES+) *m/z* 514 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, J=6.2 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.22 (t, J=8.1 Hz, 1 H), 6.87 - 6.95 (m, 3 H), 6.80 (d, J=8.1 Hz, 1 H), 4.74 (d, J=7.3 Hz, 2 H), 4.49 (d, J=6.2 Hz, 2 H), 3.71 (s, 3 H), 2.87 (t, J=6.6 Hz, 2 H), 2.83 (s, 3 H), 2.65 (s, 3 H), 2.52 - 2.62 (m, 1 H), 2.00 - 2.11 (m, 1 H), 1.82 - 1.92 (m, 1 H), 1.65 - 1.74 (m, 2 H), 1.28 - 1.47 (m, 2 H), 0.95 - 1.06 (m, 1 H).

Example 358

***N*-(3-Methoxybenzyl)-6-methyl-4-(2-((*S*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide**

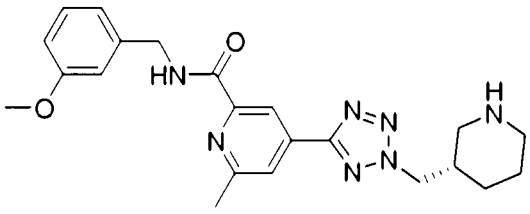


Step 1: Preparation of (3*S*)-*tert*-butyl 3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate



N-(3-Methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (324 mg, 1.0 mmol), polymer supported triphenylphosphine (698 mg, 1.5 mmol), and (*S*)-1-Boc-3-(hydroxymethyl)piperidine (258 mg, 1.2 mmol) were suspended in tetrahydrofuran (16 mL). Di-*tert*-butyl azodicarboxylate (345 mg, 1.5 mmol) was added. The mixture was allowed to stir for 18 hours. The reaction mixture was filtered and the resin washed with tetrahydrofuran (20 mL). The filtrate was concentrated. The crude product was purified by silica column chromatography (heptane/EtOAc, 2/1; 1/1). Fractions containing the product were concentrated to afford the title compound as an oil (461 mg, 88%). MS (ES+) *m/z* 522 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) ppm 9.24 (t, *J*=6.4 Hz, 1 H), 8.41 (d, *J*=0.8 Hz, 1 H), 8.07 (d, *J*=1.1 Hz, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.90 - 6.87 (m, 2 H), 6.79 (dd, *J*=8.0, 2.1 Hz, 1 H), 4.77 - 4.66 (m, 2 H), 4.48 (d, *J*=6.6 Hz, 2 H), 3.70 (s, 3 H), 3.78 - 3.62 (m, 2 H), 2.82 (br. s., 1 H), 2.65 (s, 3 H), 2.12 (br. s., 1 H), 1.75 - 1.56 (m, 2 H), 1.37 - 1.17 (m, 12 H).

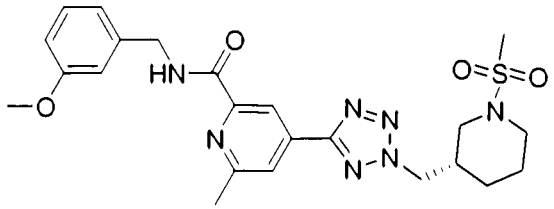
Step 2: Preparation of *N*-(3-methoxybenzyl)-6-methyl-4-(2-((*S*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



(3*S*)-*tert*-Butyl 3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate (455 mg, 0.72 mmol) was dissolved in dichloromethane (5.0 mL). Trifluoroacetic acid (1.0 mL, 13.0 mmol) was added and the solution was shaken for 2 hours at room temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (100 mL). The mixture was washed with 1N NaOH solution (2 x 10 mL). The organic layer was dried over sodium sulfate and concentrated to afford the title compound as an oil (349 mg, 94%). MS (ES+) m/z 422 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.4 Hz, 1 H), 8.40 (d, *J*=0.8 Hz, 1 H), 8.05 (d, *J*=1.1 Hz, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.90 - 6.86 (m, 2 H), 6.79 (dd, *J*=7.9, 2.1 Hz, 1 H), 4.74 - 4.62 (m, 2 H), 4.47 (d, *J*=6.4 Hz, 2 H), 3.70 (s, 3 H), 2.83 - 2.74 (m, 2 H), 2.65 (s, 3 H), 2.47 - 2.40 (m, 1 H), 2.35 (dd, *J*=12.1, 9.5 Hz, 1 H), 2.18 - 2.07 (m, 1 H), 1.68 - 1.52 (m, 2 H), 1.40 - 1.27 (m, 1 H), 1.16 (qd, *J*=11.1, 3.2 Hz, 1 H).

Example 359

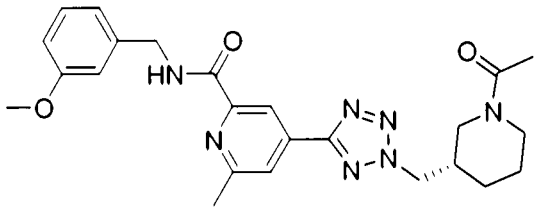
***N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((*R*)-1-(methylsulfonyl)piperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



N-(3-Methoxybenzyl)-6-methyl-4-(2-((*S*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 358) (165 mg, 0.35 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (98 μL, 0.71 mmol) and methanesulfonyl chloride (41 μL, 0.53 mmol) were added. The reaction mixture was shaken at room temperature for 1 hour and then diluted with dichloromethane (50 mL). The mixture was washed with saturated aq. sodium bicarbonate (10 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (heptane/EtOAc, 1/1; 1/2; 1/4) to afford the title compound as a foaming solid (116 mg, 66%). MS (ES+) *m/z* 500 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 - 9.20 (m, 1 H), 8.43 (s, 1 H), 8.07 (s, 1 H), 7.24 (t, *J*=7.9 Hz, 1 H), 6.94 - 6.89 (m, 2 H), 6.81 (d, *J*=7.7 Hz, 1 H), 4.86 - 4.73 (m, 2 H), 4.51 (d, *J*=5.9 Hz, 2 H), 3.73 (s, 3 H), 3.48 - 3.36 (m, 2 H), 2.84 (s, 3 H), 2.83 - 2.75 (m, 1 H), 2.72 (t, *J*=9.9 Hz, 1 H), 2.67 (s, 3 H), 2.35 (br. s., 1 H), 1.80 - 1.68 (m, 2 H), 1.57 - 1.46 (m, 1 H), 1.29 - 1.18 (m, 1 H).

Example 360

***N*-(3-Methoxybenzyl)-4-(2-(((*S*)-1-acetylpiperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

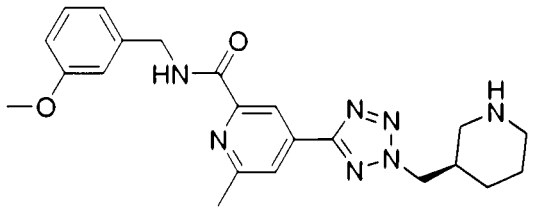


N-(3-Methoxybenzyl)-6-methyl-4-(2-((*S*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 358) (165 mg, 0.35 mmol) was dissolved in dichloromethane (5.0 mL). Triethylamine (98 μL, 0.71 mmol), 4-(dimethylamino)pyridine (8.6 mg, 0.07 mmol), and acetyl chloride (30 μL, 0.42 mmol) was added. The mixture was allowed to stir at room temperature for 20 hours. The reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aq. sodium bicarbonate solution (20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2) to afford the title compound as an oil (160 mg, 100%). MS (ES+) *m/z* 464 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.4 Hz, 1 H), 8.40 (s, 1 H), 8.06 (d, *J*=1.2 Hz, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.91 - 6.86 (m, 2 H), 6.79 (dd, *J*=8.2, 2.1 Hz, 1 H), 4.85 - 4.66 (m, 2 H), 4.48 (d, *J*=6.4 Hz, 2 H), 4.12 (dd, *J*=12.6, 3.4 Hz, 0.5 H), 4.01 (d, *J*=13.0 Hz, 0.5 H), 3.70 (s, 3 H), 3.64 (d, *J*=13.2 Hz, 0.5 H), 3.52 - 3.43 (m, 0.5 H), 3.00 (dd, *J*=13.4, 10.3 Hz, 1 H), 2.75 - 2.68 (m, 0.5 H), 2.65

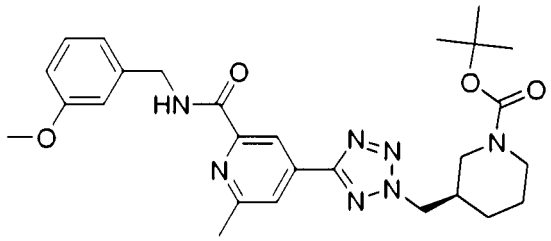
(s, 3 H), 2.59 (dd, *J*=12.7, 10.3 Hz, 0.5 H), 2.26 - 2.18 (m, 0.5 H), 2.13 - 2.06 (m, 0.5 H), 1.95 (s, 1.5 H), 1.93 (s, 1.5 H), 1.74 - 1.53 (m, 2 H), 1.44 - 1.19 (m, 2 H).

Example 361

***N*-(3-Methoxybenzyl)-6-methyl-4-(2-((*R*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide**

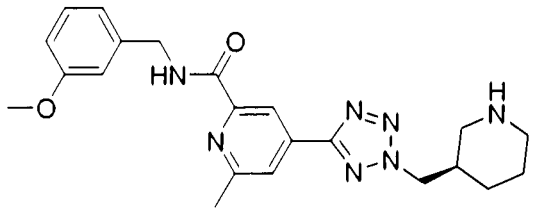


Step 1: Preparation of (3*R*)-*tert*-butyl 3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate



N-(3-Methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-Methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (324 mg, 1.0 mmol), polymer supported triphenylphosphine (698 mg, 1.5 mmol), and (*R*)-1-Boc-3-(hydroxymethyl)piperidine (258 mg, 1.2 mmol) were suspended in tetrahydrofuran (16 mL). Di-*tert*-butyl azodicarboxylate (345 mg, 1.5 mmol) was added. The mixture was allowed to stir for 18 hours. The reaction mixture was filtered and the resin washed with tetrahydrofuran (20 mL). The filtrate was concentrated. The crude product was purified by silica column chromatography (heptane/EtOAc, 2/1; 1/1). Fractions containing product were concentrated and repurified by silica column chromatography (CH_2Cl_2/methanol, 100/1) to afford the title compound as a foaming solid (352 mg, 67%). MS (ES+) *m/z* 522 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.4 Hz, 1 H), 8.41 (d, *J*=0.8 Hz, 1 H), 8.07 (d, *J*=1.2 Hz, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.90 - 6.87 (m, 2 H), 6.79 (dd, *J*=8.1, 1.8 Hz, 1 H), 4.78 - 4.66 (m, 2 H), 4.48 (d, *J*=6.4 Hz, 2 H), 3.70 (s, 3 H), 3.66 (br. s., 2 H), 2.82 (br. s., 1 H), 2.65 (s, 3 H), 2.13 (br. s., 1 H), 1.74 - 1.67 (m, 1 H), 1.64 - 1.57 (m, 1 H), 1.35 - 1.21 (m, 12 H).

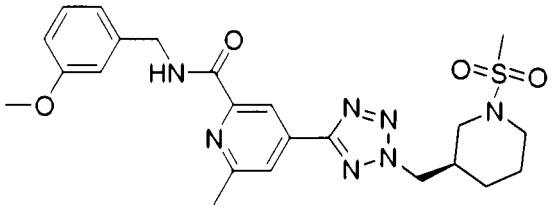
Step 2: Preparation of *N*-(3-methoxybenzyl)-6-methyl-4-(2-((*R*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



(3*R*)-*tert*-Butyl 3-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate (348 mg, 0.65 mmol) was dissolved in dichloromethane (5.0 mL). Trifluoroacetic acid (1.0 mL, 13.0 mmol) was added and the solution was shaken for 2 hours at room temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (100 mL). The mixture was washed with 1N NaOH solution (2 x 10 mL). The organic layer was dried over sodium sulfate and concentrated to afford the title compound as an oil (283 mg, 96%). MS (ES+) m/z 422 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.4 Hz, 1 H), 8.40 (d, *J*=0.8 Hz, 1 H), 8.05 (d, *J*=1.2 Hz, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.90 - 6.86 (m, 2 H), 6.79 (dd, *J*=7.9, 2.1 Hz, 1 H), 4.74 - 4.62 (m, 2 H), 4.47 (d, *J*=6.4 Hz, 2 H), 3.70 (s, 3 H), 2.81 - 2.74 (m, 2 H), 2.65 (s, 3 H), 2.46 - 2.39 (m, 1 H), 2.34 (dd, *J*=11.9, 9.5 Hz, 1 H), 2.15 - 2.07 (m, 1 H), 1.66 - 1.52 (m, 2 H), 1.38 - 1.26 (m, 1 H), 1.16 (qd, *J*=10.5, 3.8 Hz, 1 H).

Example 362

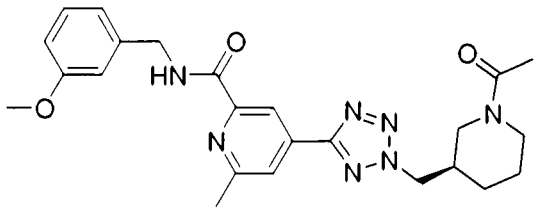
N-(3-Methoxybenzyl)-6-methyl-4-(2-(((*S*)-1-(methylsulfonyl)piperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



N-(3-Methoxybenzyl)-6-methyl-4-(2-((*R*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 361) (135 mg, 0.35 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (83 μL, 0.60 mmol) and methanesulfonyl chloride (35 μL, 0.48 mmol) were added. The reaction mixture was shaken at room temperature for 1 hour and then diluted with dichloromethane (50 mL). The mixture was washed with saturated aq. sodium bicarbonate (10 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (heptane/EtOAc, 1/1; 1/2; 1/4) to afford the title compound as a foaming solid (99 mg, 66%). MS (ES+) *m/z* 500 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.95 - 6.89 (m, 2 H), 6.82 (d, *J*=8.1 Hz, 1 H), 4.87 - 4.74 (m, 2 H), 4.51 (d, *J*=6.2 Hz, 2 H), 3.73 (s, 3 H), 3.48 - 3.36 (m, 2 H), 2.85 (s, 3 H), 2.79 (t, *J*=10.4 Hz, 1 H), 2.72 (t, *J*=10.2 Hz, 1 H), 2.67 (s, 3 H), 2.36 (br. s., 1 H), 1.80 - 1.68 (m, 2 H), 1.58 - 1.47 (m, 1 H), 1.29 - 1.19 (m, 1 H).

Example 363

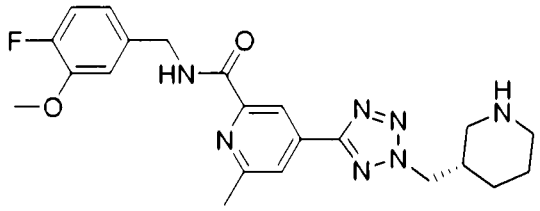
***N*-(3-Methoxybenzyl)-4-(2-(((*R*)-1-acetylpiperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



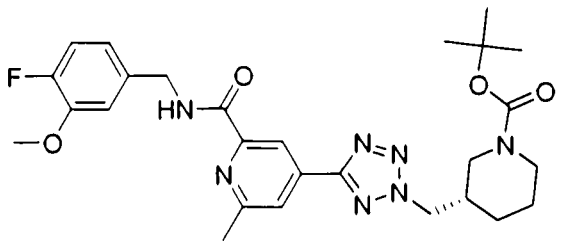
N-(3-Methoxybenzyl)-6-methyl-4-(2-((*R*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 361) (135 mg, 0.30 mmol) was dissolved in dichloromethane (5.0 mL). Triethylamine (83 μL, 0.60 mmol), 4-(dimethylamino)pyridine (7.3 mg, 0.06 mmol), and acetyl chloride (25 μL, 0.36 mmol) was added. The mixture was allowed to stir at room temperature for 20 hours. The reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aq. sodium bicarbonate solution (20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2). Fractions were concentrated to afford the title compound as an oil (123 mg, 88%). MS (ES+) *m/z* 464 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, *J*=6.2 Hz, 1 H), 8.44 (s, 1 H), 8.09 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.95 - 6.89 (m, 2 H), 6.82 (d, *J*=8.1 Hz, 1 H), 4.88 - 4.68 (m, 2 H), 4.51 (d, *J*=6.2 Hz, 2 H), 4.17 - 4.12 (m, 0.5 H), 4.06 - 4.00 (m, 0.5 H), 3.79 - 3.73 (m, 0.5 H), 3.73 (s, 3 H), 3.71 - 3.64 (m, 0.5 H), 3.08 - 3.00 (m, 1 H), 2.80 - 2.72 (m, 0.5 H), 2.68 (s, 3 H), 2.65 - 2.60 (m, 0.5 H), 2.29 - 2.23 (m, 0.5 H), 2.17 - 2.10 (m, 0.5 H), 1.98 (s, 1.5 H), 1.96 (s, 1.5 H), 1.77 - 1.59 (m, 2 H), 1.46 - 1.25 (m, 2 H).

Example 364

***N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*S*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide**

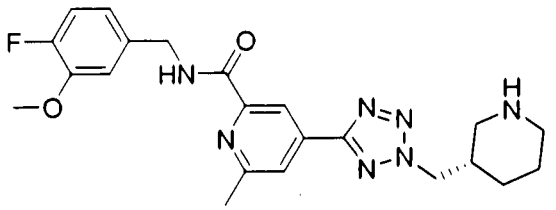


Step 1: Preparation of (3*S*)-*tert*-butyl 3-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate



N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (342 mg, 1.0 mmol), polymer supported triphenylphosphine (698 mg, 1.5 mmol), and (*S*)-1-Boc-3-(hydroxymethyl)piperidine (258 mg, 1.2 mmol) were suspended in tetrahydrofuran (16 mL). Di-*tert*-butyl azodicarboxylate (345 mg, 1.5 mmol) was added. The mixture was allowed to stir for 18 hours. The reaction mixture was filtered and the resin washed with tetrahydrofuran (20 mL). The filtrate was concentrated. The crude product was purified by column chromatography (heptane/EtOAc, 2/1; 1/1). Fractions containing the product were concentrated to afford the title compound as an oil (455 mg, 84%). MS (ES+) *m/z* 540 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (t, *J*=6.4 Hz, 1 H), 8.40 (d, *J*=0.8 Hz, 1 H), 8.07 (d, *J*=1.1 Hz, 1 H), 7.15 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.11 (dd, *J*=11.7, 8.3 Hz, 1 H), 6.87 (ddd, *J*=8.3, 4.4, 1.9 Hz, 1 H), 4.77 - 4.66 (m, 2 H), 4.47 (d, *J*=5.9 Hz, 2 H), 3.79 (s, 3 H), 3.72 - 3.62 (m, 2 H), 2.85 - 2.79 (m, 1 H), 2.65 (s, 3 H), 2.17 - 2.09 (m, 1 H), 1.76 - 1.50 (m, 2 H), 1.36 - 1.21 (m, 12 H).

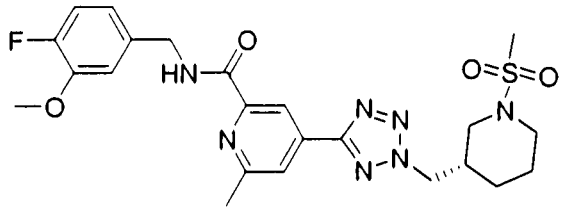
Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*S*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



(3*S*)-*tert*-Butyl 3-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate (450 mg, 0.63 mmol) was dissolved in dichloromethane (5.0 mL). Trifluoroacetic acid (1.0 mL, 13.0 mmol) was added and the solution was shaken for 2 hours at room temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (100 mL). The mixture was washed with 1N NaOH solution (2 x 10 mL). The organic layer was dried over sodium sulfate and concentrated to afford the title compound as an oil (331 mg, 97%). MS (ES+) m/z 440 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (t, *J*=6.4 Hz, 1 H), 8.39 (d, *J*=0.9 Hz, 1 H), 8.05 (d, *J*=1.2 Hz, 1 H), 7.15 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.11 (dd, *J*=11.6, 8.4 Hz, 1 H), 6.87 (ddd, *J*=8.2, 4.4, 1.9 Hz, 1 H), 4.73 - 4.62 (m, 2 H), 4.47 (d, *J*=6.4 Hz, 2 H), 3.79 (s, 3 H), 2.81 - 2.74 (m, 2 H), 2.65 (s, 3 H), 2.46 - 2.39 (m, 1 H), 2.34 (dd, *J*=12.0, 9.5 Hz, 1 H), 2.15 - 2.07 (m, 1 H), 1.67 - 1.52 (m, 2 H), 1.38 - 1.26 (m, 1 H), 1.16 (qd, *J*=10.7, 3.5 Hz, 1 H).

Example 365

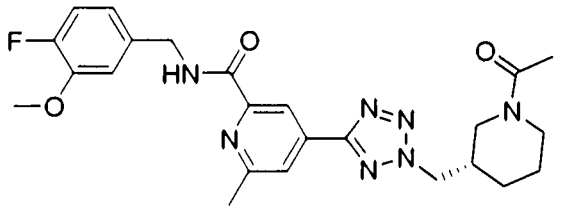
***N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*R*)-1-(methylsulfonyl)piperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*S*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 364) (160 mg, 0.34 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (95 μL, 0.68 mmol) and methanesulfonyl chloride (40 μL, 0.51 mmol) were added. The reaction mixture was shaken at room temperature for 1 hour and then diluted with dichloromethane (50 mL). The mixture was washed with saturated aq. sodium bicarbonate (10 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (heptane/EtOAc, 1/1; 1/2; 1/4) to afford the title compound as a foaming solid (111 mg, 63%). MS (ES+) *m/z* 518 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.4 Hz, 1 H), 8.44 (s, 1 H), 8.09 (s, 1 H), 7.19 (d, *J*=8.4 Hz, 1 H), 7.14 (dd, *J*=11.5, 8.2 Hz, 1 H), 6.91 (d, *J*=2.2 Hz, 1 H), 4.88 - 4.75 (m, 2 H), 4.51 (d, *J*=6.2 Hz, 2 H), 3.82 (s, 3 H), 3.49 - 3.37 (m, 2 H), 2.85 (s, 3 H), 2.83 - 2.77 (m, 1 H), 2.72 (t, *J*=9.9 Hz, 1 H), 2.68 (s, 3 H), 2.42 - 2.31 (m, 1 H), 1.80 - 1.69 (m, 2 H), 1.59 - 1.47 (m, 1 H), 1.30 - 1.19 (m, 1 H).

Example 366

***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*S*)-1-acetylpiperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

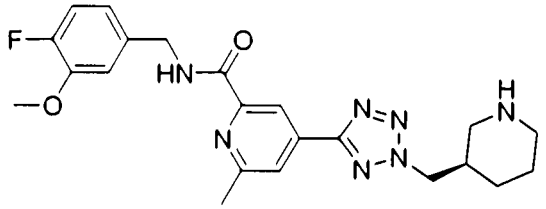


N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*S*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 364) (160 mg, 0.34 mmol) was dissolved in dichloromethane (5.0 mL). Triethylamine (95 μL, 0.68 mmol), 4-(dimethylamino)pyridine (8.4 mg, 0.07 mmol), and acetyl chloride (29 μL, 0.41 mmol) was added. The mixture was allowed to stir at room temperature for 20 hours. The reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aq. sodium bicarbonate solution (20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2). Fractions were concentrated to afford the title compound as a foaming solid (123 mg, 77%). MS (ES+) *m/z* 482 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (t, *J*=6.4 Hz, 1 H), 8.40 (s, 1 H), 8.06 (d, *J*=1.2 Hz, 1 H), 7.15 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.11 (dd, *J*=11.6, 8.4 Hz, 1 H), 6.87 (ddd, *J*=8.2, 4.3, 1.9 Hz, 1 H), 4.85 - 4.66 (m, 2 H), 4.47 (d, *J*=6.4 Hz, 2 H), 4.11 (dd, *J*=12.6, 3.5 Hz, 0.5 H), 4.01 (d, *J*=13.4 Hz, 0.5 H), 3.79 (s, 3 H), 3.73 (d, *J*=14.0 Hz, 0.5 H), 3.64 (d,

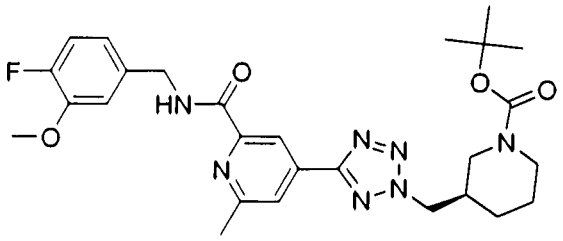
J=12.8 Hz, 0.5 H), 3.00 (dd, *J*=13.2, 10.1 Hz, 1 H), 2.76 - 2.67 (m, 0.5 H), 2.65 (s, 3 H), 2.59 (dd, *J*=12.7, 10.4 Hz, 0.5 H), 2.26 - 2.19 (m, 0.5 H), 2.13 - 2.05 (m, 0.5 H), 1.95 (s, 1.5 H), 1.93 (s, 1.5 H), 1.75 - 1.54 (m, 2 H), 1.46 - 1.19 (m, 2 H).

Example 367

5 *N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



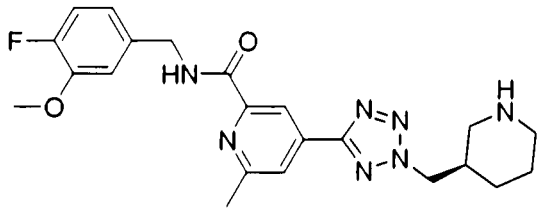
Step 1: Preparation of (3*R*)-*tert*-butyl 3-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate



10

N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (342 mg, 1.0 mmol), polymer supported triphenylphosphine (698 mg, 1.5 mmol), and (*R*)-1-Boc-3-**15** (hydroxymethyl)piperidine (258 mg, 1.2 mmol) were suspended in tetrahydrofuran (16 mL). Di-*tert*-butyl azodicarboxylate (345 mg, 1.5 mmol) was added. The mixture was allowed to stir for 18 hours. The reaction mixture was filtered and the resin washed with tetrahydrofuran (20 mL). The filtrate was concentrated. The crude product was purified by silica column chromatography (heptane/EtOAc, 2/1; 1/1). Fractions containing the product were concentrated to afford the title compound as a foaming **20** solid (472 mg, 87%). MS (ES+) *m/z* 540 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (t, *J*=6.4 Hz, 1 H), 8.40 (d, *J*=0.8 Hz, 1 H), 8.07 (d, *J*=1.1 Hz, 1 H), 7.15 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.11 (dd, *J*=11.5, 8.3 Hz, 1 H), 6.87 (ddd, *J*=8.3, 4.4, 1.9 Hz, 1 H), 4.77 - 4.66 (m, 2 H), 4.47 (d, *J*=6.0 Hz, 2 H), 3.79 (s, 3 H), 3.70 - 3.62 (m, 2 H), 2.81 (br. s., 1 H), 2.65 (s, 3 H), 2.12 (br. s., 1 H), 1.74 - 1.56 (m, 2 H), 1.27 (br. s., 12 H).

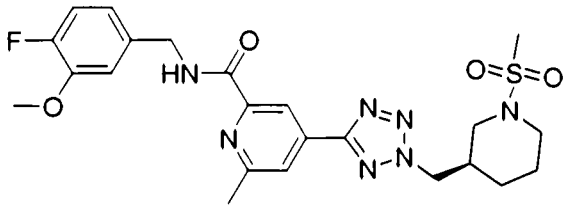
Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



(3*R*)-*tert*-Butyl 3-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate (465 mg, 0.67 mmol) was dissolved in dichloromethane (5.0 mL). Trifluoroacetic acid (1.0 mL, 13.0 mmol) was added and the solution was shaken for 2 hours at room temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (100 mL). The mixture was washed with 1N NaOH solution (2 x 10 mL). The organic layer was dried over sodium sulfate and concentrated to afford the title compound as an oil (362 mg, 96%). MS (ES+) m/z 440 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (t, *J*=6.4 Hz, 1 H), 8.40 (d, *J*=0.8 Hz, 1 H), 8.05 (d, *J*=1.1 Hz, 1 H), 7.15 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.11 (dd, *J*=11.7, 8.3 Hz, 1 H), 6.87 (ddd, *J*=8.2, 4.4, 2.0 Hz, 1 H), 4.73 - 4.62 (m, 2 H), 4.47 (d, *J*=6.4 Hz, 2 H), 3.79 (s, 3 H), 2.80 - 2.74 (m, 2 H), 2.65 (s, 3 H), 2.46 - 2.39 (m, 1 H), 2.33 (dd, *J*=11.9, 9.5 Hz, 1 H), 2.10 (br. s., 1 H), 1.66 - 1.51 (m, 2 H), 1.39 - 1.26 (m, 1 H), 1.15 (qd, *J*=10.6, 3.5 Hz, 1 H).

Example 368

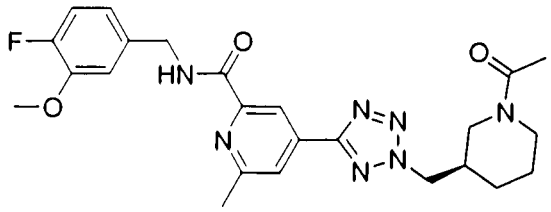
N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*S*)-1-(methylsulfonyl)piperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 367) (175 mg, 0.36 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (101 μL, 0.73 mmol) and methanesulfonyl chloride (42 μL, 0.54 mmol) were added. The reaction mixture was shaken at room temperature for 1 hour and then diluted with dichloromethane (50 mL). The mixture was washed with saturated aq. sodium bicarbonate (10 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2; 100/4). The resulting impure product was further purified by silica column chromatography (heptane/EtOAc, 1/1; 1/2; 1/4) to afford the title compound as a foaming solid (99 mg, 53%). MS (ES+) *m/z* 518 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.2 Hz, 1 H), 8. 44 (s, 1 H), 8.08 (s, 1 H), 7.18 (d, *J*=8.4 Hz, 1 H), 7.13 (dd, *J*=11.5, 8.2 Hz, 1 H), 6.94 - 6.88 (m, 1 H), 4.87 - 4.74 (m, 2 H), 4.51 (d, *J*=6.2 Hz, 2 H), 3.82 (s, 3 H), 3.49 - 3.37 (m, 2 H), 2.85 (s, 3 H), 2.84 - 2.76 (m, 1 H), 2.75 - 2.69 (m, 1 H), 2.68 (s, 3 H), 2.36 (br. s., 1 H), 1.81 - 1.68 (m, 2 H), 1.58 - 1.47 (m, 1 H), 1.30 - 1.18 (m, 1 H).

Example 369

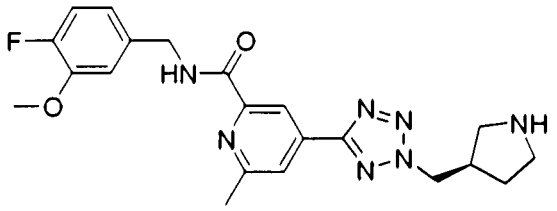
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*R*)-1-acetylpiperidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



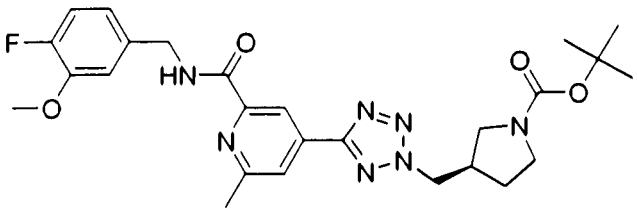
N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-piperidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 367) (175 mg, 0.36 mmol) was dissolved in dichloromethane (5.0 mL). Triethylamine (73 μL, 0.73 mmol), 4-(dimethylamino)pyridine (8.9 mg, 0.06 mmol), and acetyl chloride (31 μL, 0.36 mmol) was added. The mixture was allowed to stir at room temperature for 20 hours. The reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aq. sodium bicarbonate solution (20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2) to afford the title compound as a foaming solid (134 mg, 79%). MS (ES+) *m/z* 482 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.18 (d, *J*=8.4 Hz, 1 H), 7.13 (dd, *J*=11.7, 8.4 Hz, 1 H), 6.93 - 6.88 (m, 1 H), 4.88 - 4.69 (m, 2 H), 4.50 (d, *J*=6.2 Hz, 2 H), 4.17 - 4.12 (m, 0.5 H), 4.06 - 4.00 (m, 0.5 H), 3.82 (s, 3 H), 3.79 - 3.73 (m, 0.5 H), 3.70 - 3.64 (m, 0.5 H), 3.04 (t, *J*=12.8 Hz, 1 H), 2.80 - 2.72 (m, 0.5 H), 2.68 (s, 3 H), 2.67 - 2.60 (m, 0.5 H), 2.30 - 2.22 (m, 0.5 H), 2.18 - 2.09 (m, 0.5 H), 1.98 (s, 1.5 H), 1.96 (s, 1.5 H), 1.77 - 1.59 (m, 2 H), 1.47 - 1.24 (m, 2 H).

Example 370

***N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-pyrrolidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide**



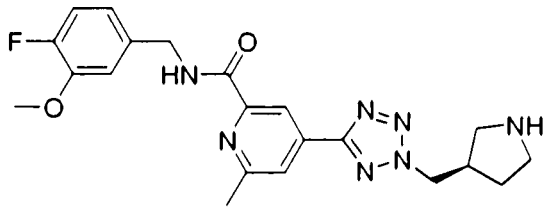
Step 1: Preparation of (3*R*)-tert-butyl 3-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)pyrrolidine-1-carboxylate



A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-

aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (0.45 g, 1.3 mmol), (*R*)-tert-butyl 3-(hydroxymethyl) pyrrolidine-1-carboxylate (0.27 g, 1.3 mmol), and polymer supported-triphenylphosphine (0.73 g, 1.6 mmol) in anhydrous tetrahydrofuran (15 mL) was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (0.45 g, 2.0 mmol) was added. The mixture was allowed to warm to room temperature while stirring over 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica column chromatography (0-50%, ethyl acetate/heptane) to afford the title compound.

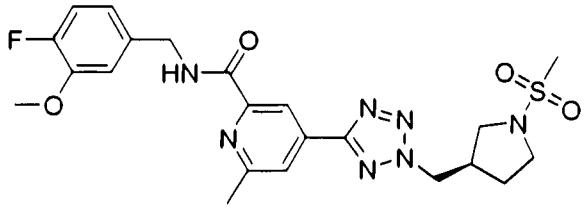
Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-pyrrolidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



Trifluoroacetic acid (3 mL) was added to a solution of (3*R*)-tert-butyl 3-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)pyrrolidine-1-carboxylate in dichloromethane (5 mL). After 30 min at ambient temperature, the reaction mixture was neutralized to pH 7 with 2.5 N aqueous sodium hydroxide. The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL) followed by brine (10 mL), dried over sodium sulfate, and concentrated to afford the title compound (0.35g, 63%). LC/MS (5-100% CH_3CN/H_2O, 5 min) 2.05 min, *m/z* 426 (M+H).

Example 371

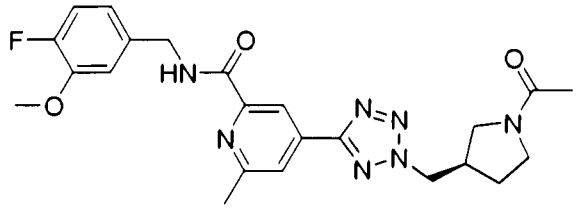
N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*S*)-1-(methylsulfonyl)pyrrolidin-3-yl)methyl)-2H-tetrazol-5-yl)picolinamide



Triethylamine (0.037 mL) and methane sulfonyl chloride (0.028 mg, 0.21 mmol) were added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-pyrrolidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 370) (0.075 g, 0.18 mmol) in dichloromethane (3 mL). The mixture was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated in vacuo and the residue was purified via reverse phase preparative HPLC to afford the title compound as an oil (15 mg, 17%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (br. s., 1 H), 8.44 (s, 1 H), 8.08 (s, 1 H), 7.10 - 7.21 (m, 2 H), 6.91 (br. s., 1 H), 4.90 (d, *J*=7.0 Hz, 2 H), 4.51 (d, *J*=5.9 Hz, 2 H), 3.82 (s, 3 H), 3.46 (br. s., 1 H), 3.07 - 3.17 (m, 1 H), 2.91 (s, 5 H), 2.68 (s, 4 H), 2.05 (br. s., 1 H), 1.81 (d, *J*=7.7 Hz, 1 H).

Example 372

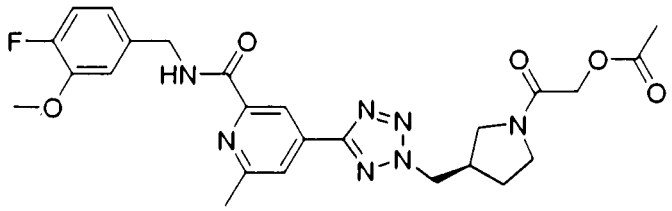
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*R*)-1-acetylpyrrolidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Triethylamine (0.037 mL) and acetyl chloride (0.017 mg, 0.21 mmol) were added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-pyrrolidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 370) (0.075 g, 0.18 mmol) in dichloromethane (3 mL). The mixture was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated in vacuo and the residue was purified via reverse phase preparative HPLC to afford the title compound as an oil (15 mg, 18%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (br. s., 1 H), 8.44 (s, 1 H), 8.08 (s, 1 H), 7.14 (d, *J*=2.9 Hz, 1 H), 7.10 - 7.21 (m, 1 H), 6.91 (br. s., 1 H), 4.88 (t, 2 H), 4.51 (d, *J*=6.2 Hz, 2 H), 3.82 (s, 3 H), 3.42 - 3.51 (m, 3 H), 3.12 - 3.18 (m, 1 H), 2.83 - 2.99 (m, 1 H), 2.68 (s, 3 H), 1.97 - 2.13 (m, 1 H), 1.92 (br. s., 3 H), 1.64 - 1.86 (m, 1 H).

Example 373

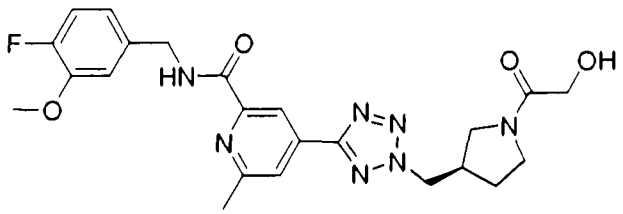
2-((*R*)-3-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)pyrrolidin-1-yl)-2-oxoethyl acetate



Triethylamine (0.037 mL) and acetoxy acetyl chloride (0.029 mg, 0.21 mmol) were added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-pyrrolidin-3-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 370) (0.075 g, 0.18 mmol) in dichloromethane (3 mL). The mixture was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated in vacuo and the residue was purified by reverse phase preparative HPLC to afford the title compound.

Example 374

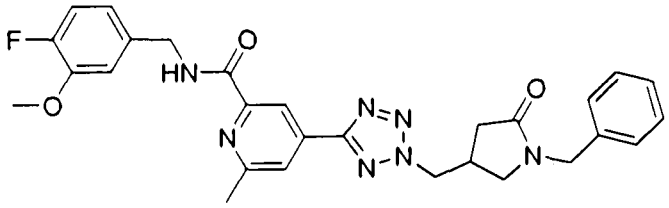
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*R*)-1-(2-hydroxyacetyl)pyrrolidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



A mixture of 2-((*R*)-3-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)pyrrolidin-1-yl)-2-oxoethyl acetate (prepared as described in Example 373) and 2.5 N aqueous sodium hydroxide (1 mL) in acetonitrile (3 mL) was stirred for 2 hours at room temperature. The acetonitrile was removed in vacuo and the aqueous residue was acidified to pH 5 with 10% aqueous hydrochloric acid. The resulting solid was filtered and dried to afford .9 mg (10%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (br. s., 1 H), 8.44 (s, 1 H), 8.08 (s, 1 H), 7.17 (br. s., 1 H), 7.11 (s, 1 H), 6.91 (br. s., 1 H), 4.89 (d, *J*=6.2 Hz, 2 H), 4.51 (d, *J*=6.2 Hz, 3 H), 3.97 (br. s., 2 H), 3.82 (s, 3 H), 3.57 (br. s., 2 H), 3.37 (br. s., 2 H), 2.82 - 3.07 (m, 1 H), 2.68 (s, 3 H), 1.98 - 2.12 (m, 1 H).

Example 375

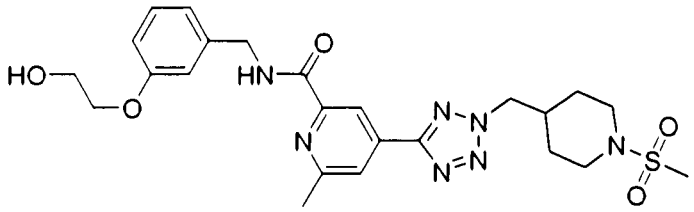
***rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-((1-benzyl-5-oxopyrrolidin-3-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



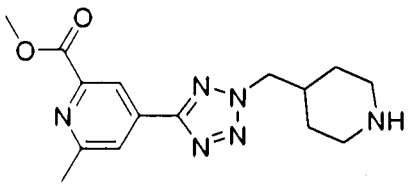
A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (0.17 g, 0.48 mmol), 1-benzyl-4-(hydroxymethyl)pyrrolidin-2-one (0.99 g, 0.48 mmol) (*Org. Lett.* **1999**, *1*, 799-801), and polymer supported-triphenylphosphine (0.32 g, 0.72 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to 0°C in an ice bath for 15 minutes. Di-tert-butyl azodicarboxylate (0.13 g, 0.58 mmol) was added and the reaction was allowed to warm to room temperature over 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by reverse phase preparative HPLC (5-95% acetonitrile/water) to afford the title compound as a beige oil (0.18 g, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 - 9.29 (m, 1 H), 8.41 (s, 1 H), 8.04 (s, 1 H), 7.32 (t, *J*=7.69 Hz, 2 H), 7.20 (d, *J*=6.95 Hz, 2 H), 7.17 - 7.27 (m, 1 H), 7.14 (dd, *J*=11.71, 8.42 Hz, 1 H), 6.91 (d, *J*=6.22 Hz, 1 H), 4.89 (d, *J*=6.95 Hz, 2 H), 4.51 (d, *J*=6.22 Hz, 2 H), 4.35 (s, 2 H), 3.82 (s, 3 H), 3.40 (t, *J*=8.97 Hz, 1 H), 3.13 - 3.19 (m, 1 H), 2.67 (s, 3 H), 2.57 (d, *J*=7.69 Hz, 1 H), 2.35 (dd, *J*=16.65, 6.77 Hz, 1 H), 1.37 (d, *J*=15.37 Hz, 1 H), 1.24 (dd, *J*=12.63, 5.67 Hz, 1 H).

Example 376

***N*-(3-(2-Hydroxyethoxy)benzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide**

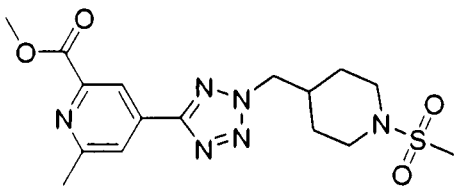


Step 1: Preparation of methyl 6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinate trifluoroacetate



Methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (1.99 g, 9.08mmol) and *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (1.95 g, 9.08 mmol) were suspended in anhydrous tetrahydrofuran (50 mL) along with polymer supported-triphenylphosphine (6.05 g, 13.6 mmol). The mixture was cooled to 0 °C in an ice bath for 15 minutes and then di-*tert*-butyl azodicarboxylate (2.51 g, 10.9 mmol) was added. The mixture was allowed to warm to room temperature while stirring over 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified on silica (70 g, 0-50 % ethyl acetate/heptane). The resulting intermediate was dissolved in dichloromethane (15 mL) and stirred with trifluoroacetic acid (5.0 mL) for 1 hour at room temperature. The reaction mixture was concentrate to 1/3 volume and *tert*-butyl methyl ether (5 mL) was slowly added to cause precipitation. The resulting solids were collected by filtration, washed with diethyl ether (3 x 5 mL) and dried to afford the title compound as a beige solid (3.3 g, 84%). MS (ES+) *m/z* 317 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.72 (br. s., 1 H), 8.37 (s, 1 H), 8.09 (s, 1 H), 4.78 (d, *J*=6.7 Hz, 2 H), 3.90 (s, 3 H), 3.27 (d, *J*=12.4 Hz, 2 H), 2.87 (d, *J*=10.8 Hz, 2 H), 2.63 (s, 3 H), 2.22 - 2.41 (m, 1 H), 1.66 - 1.82 (m, 2 H), 1.30 - 1.57 (m, 2 H).

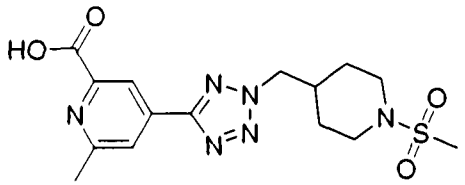
Step 2: Preparation of methyl 6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinate



Triethylamine (0.34 mL, 2.4 mmol) was added to a solution of methyl 6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinate trifluoroacetate (0.50 g, 1.2 mmol) in 2-methyltetrahydrofuran (5 mL). A solution of methane sulfonyl chloride (0.16 mL) in 2-methyltetrahydrofuran (2 mL) was added

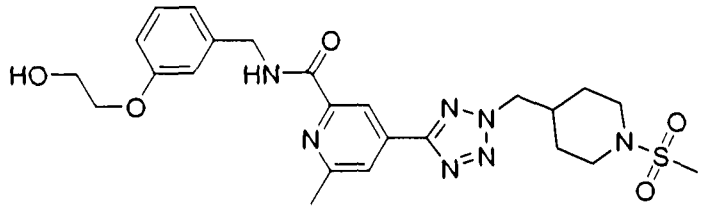
and the mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was concentrated and the residue was purified by silica gel chromatography (0-50 % ethyl acetate/heptane) to afford the title compound (0.46 g, 100%). MS (ES+) *m/z* 395 (M+H).

Step 3: Preparation of 6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinic acid



An aqueous sodium hydroxide solution (2.5 N, 2.5 mL) was added to a solution of methyl 6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinate (0.46g, 1.2 mmol) in tetrahydrofuran (5 mL). The mixture was stirred at room temperature for 3 hours. The tetrahydrofuran was removed *in vacuo* and the aqueous residue was acidified with concentrated hydrochloric acid to pH 6. The resulting precipitate was filtered, washed with water (3 x 10 mL), and then dried to afford the title compound (0.41 g, 93%). MS (ES+) *m/z* 381 (M+H).

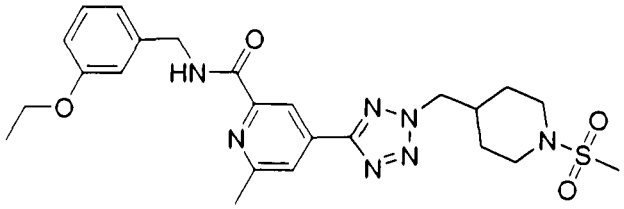
Step 4: Preparation of *N*-(3-(2-hydroxyethoxy)benzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



1-Hydroxybenzatriazole (22 mg, 0.16 mmol) was added to a solution of 6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinic acid (0.050 g, 0.13 mmol) in 2-methyl tetrahydrofuran (5 mL). After 15 minutes, 2-(3-(aminomethyl)phenoxy) ethanol (27 mg, 0.16 mmol) and polymer supported carbodiimide (0.16 g, 0.20 mmol) were added. The mixture was stirred for 18 hours at room temperature. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified via reverse phase preparative HPLC to afford the title compound (25 mg, 36%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.6 Hz, 1 H), 8.41 (s, 1 H), 8.06 (s, 1 H), 7.20 (t, *J*=8.1 Hz, 1 H), 6.85 - 6.96 (m, 2 H), 6.79 (d, *J*=7.3 Hz, 1 H), 4.76 (d, *J*=7.3 Hz, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 3.93 (t, *J*=5.1 Hz, 2 H), 3.67 (q, *J*=5.1 Hz, 2 H), 3.55 (d, *J*=11.7 Hz, 2 H), 2.81 (s, 3 H), 2.59 - 2.77 (m, 5 H), 2.07 - 2.27 (m, 1 H), 1.67 (d, *J*=12.4 Hz, 2 H), 1.25 - 1.46 (m, 2 H).

Example 377

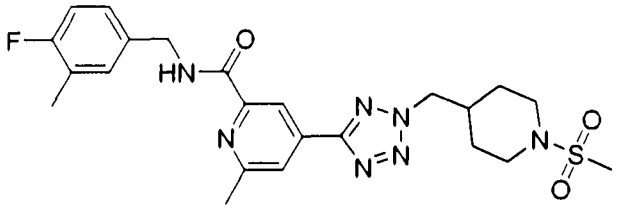
N-(3-Ethoxybenzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



The title compound was prepared in a similar manner to *N*-(3-(2-hydroxyethoxy)benzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 376, step 4) by reaction with (3-ethoxyphenyl)methanamine (prepared as described in step 2 of the synthesis of *N*-(3-ethoxybenzyl)-6-methyl-4-(2-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-2*H*-tetrazol-5-yl)picolinamide, Example 180) to afford 28 mg (42%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, J=6.2 Hz, 1 H), 8.41 (s, 1 H), 8.06 (s, 1 H), 7.20 (t, J=8.1 Hz, 1 H), 6.88 (d, J=5.9 Hz, 2 H), 6.78 (d, J=8.8 Hz, 1 H), 4.76 (d, J=7.3 Hz, 2 H), 4.48 (d, J=6.6 Hz, 2 H), 3.97 (q, J=6.8 Hz, 2 H), 3.55 (d, J=11.7 Hz, 2 H), 2.81 (s, 3 H), 2.58 - 2.77 (m, 5 H), 2.10 - 2.28 (m, 1 H), 1.67 (d, J=11.7 Hz, 2 H), 1.31 - 1.44 (m, 2 H), 1.28 (t, J=7.0 Hz, 3 H).

Example 378

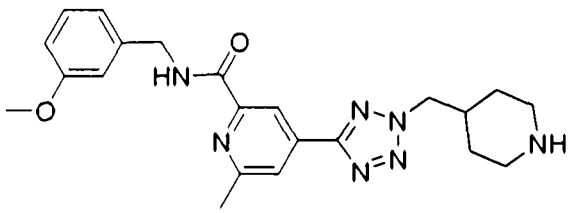
***N*-(4-Fluoro-3-methylbenzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



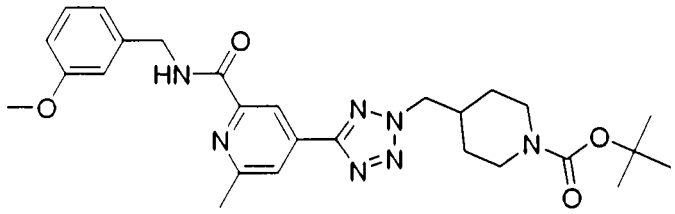
The title compound was prepared in a similar manner to *N*-(3-(2-hydroxyethoxy)benzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 376, step 4) by reaction with (4-fluoro-3-methylphenyl)methanamine to afford 25 mg (39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, J=6.2 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.23 (d, J=6.6 Hz, 1 H), 7.12 - 7.20 (m, 1 H), 6.99 - 7.10 (m, 1 H), 4.76 (d, J=6.6 Hz, 2 H), 4.46 (d, J=6.6 Hz, 2 H), 3.55 (d, J=11.7 Hz, 2 H), 2.81 (s, 3 H), 2.59 - 2.75 (m, 5 H), 2.07 - 2.27 (m, 4 H), 1.67 (d, J=13.2 Hz, 2 H), 1.26 - 1.45 (m, 2 H).

Example 379

***N*-(3-Methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide**

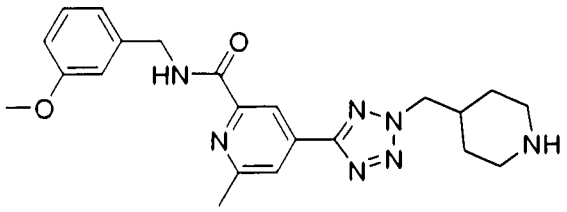


Step 1: Preparation of *tert*-butyl 4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate



A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (1.00 g, 3.10 mmol), *tert*-butyl 4-(hydroxymethyl) piperidine-1-carboxylate (0.81 g, 3.8 mmol), and polymer supported-triphenylphosphine (2.90 g, 6.21 mmol) were suspended in anhydrous tetrahydrofuran (32 mL). The mixture was cooled to 0 °C in an ice bath for 15 minutes and then di-*tert*-butyl azodicarboxylate (1.11 g, 4.82 mmol) was added. The mixture was allowed to warm to room temperature while stirring over 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography (20 g, 0-50% gradient ethyl acetate/heptane) to afford the title compound as a white solid (1.52 g, 94%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 6.24 min, *m/z* 544 (M+Na).

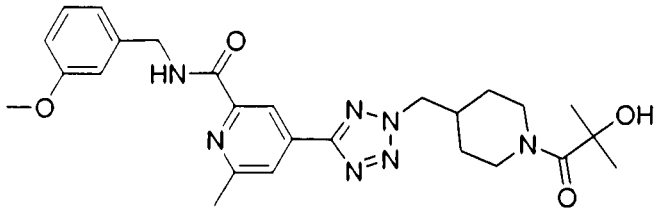
Step 2: Preparation of *N*-(3-methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



Trifluoroacetic acid (6 mL) was added to a solution of *tert*-butyl 4-((5-(2-((3-methoxybenzyl)-carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate (1.51 g, 2.89 mmol) in dichloromethane (20 mL). The reaction mixture was stirred for 1 hour at room temperature and was then concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound as the trifluoroacetate salt (0.83 g, 56%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 5.33 min, *m/z* 422 (M+H).

Example 380

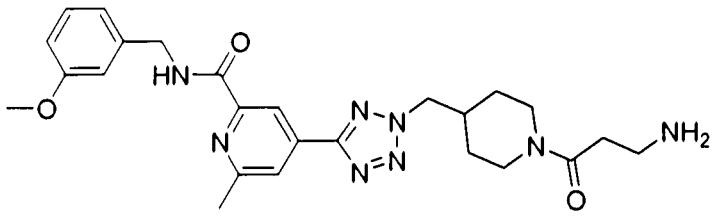
N-(3-Methoxybenzyl)-4-(2-((1-(2-hydroxy-2-methylpropanoyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Triethylamine (31 mg, 0.31 mmol) and 1-chloro-2-methyl-1-oxopropan-2-yl acetate (0.023 g, 0.14 mmol) were added to a solution of *N*-(3-methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 379) (75 mg, 0.14 mmol) in *N*,*N*-dimethylacetamide (2 mL), and the mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (3 x-5 mL). The organic layer was washed with water (3 x 5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography (10 g, 0-50% ethyl acetate/heptane). The intermediate was dissolved in a mixture of methanol/water (4 mL, 3/1)and potassium carbonate (41 mg, 0.30 mmol) was added. The mixture was stirred for 10 hours at 60°C. The methanol was removed in vacuo and the aqueous residue was acidified with a 10% aqueous solution of hydrochloric acid. This mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with water (5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate, and concentrated. The residue that was purified by reverse phase preparative HPLC to afford the title compound (21 mg, 30%). MS (ES+) *m/z* 508 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.2 Hz, 1 H), 8.41 (s, 1 H), 8.06 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, *J*=8.1 Hz, 1 H), 5.26 (s, 1 H), 4.71 (d, *J*=7.3 Hz, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 3.71 (s, 3 H), 2.65 (s, 3 H), 2.30 (d, *J*=2.9 Hz, 1 H), 1.58 (d, *J*=13.2 Hz, 4 H), 1.22 - 1.33 (m, 6 H), 1.19 (br. s., 4 H).

Example 381

N-(3-Methoxybenzyl)-4-(2-((1-(3-aminopropanoyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

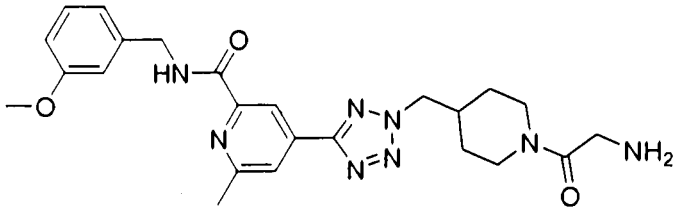


1-Hydroxybenzotriazole (3.2 mg, 0.024 mmol) was added to a solution of 3-(tert-butoxycarbonyl)propanoic acid (27.2 mg, 0.144 mmol) in *N*,*N*-dimethylformamide (2 mL). Carbodiimide resin (138 mg, 0.18 mmol, 1.30 mmol/g loading), *N*-(3-methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 379) (50.6 mg, 0.120 mmol), and *N*-methylmorpholine (0.066 mL, 0.60 mmol) were added with dichloromethane (2 mL), and the mixture was agitated overnight at room temperature. The reaction mixture was filtered and the resin was washed with *N*,*N*-dimethylformamide followed by dichloromethane. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min.). The intermediate was added to a 1:1 mixture of trifluoroacetic acid and dichloromethane and

stirred for 1 hour. The reaction mixture was concentrated. The residue was dissolved in dichloromethane, neutralized with MP-carbonate resin, and concentrated to afford the title compound (10 mg, 17%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.572 min., *m/z* 493 (M+H).

Example 382

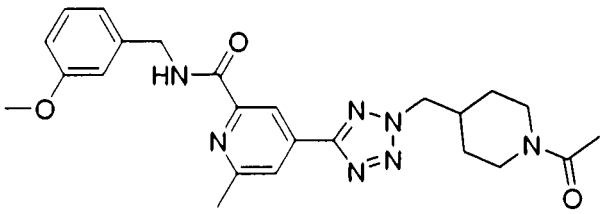
***N*-(3-Methoxybenzyl)-4-(2-((1-(2-aminoacetyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-((1-(3-aminopropanoyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 381) by reaction with 2-(tert-butoxycarbonyl)acetic acid to afford 10 mg (17%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.543 min., *m/z* 479 (M+H).

Example 383

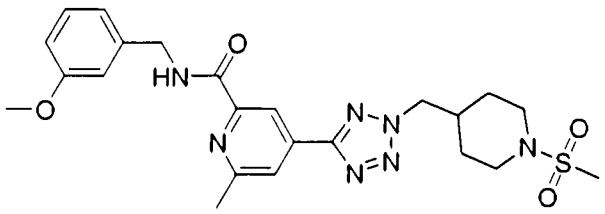
***N*-(3-Methoxybenzyl)-4-(2-((1-acetylpiperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Acetic anhydride (0.034 mL, 0.356 mmol) and 4-(dimethylamino)pyridine Si bound (862.0 mg, 0.595 mmol, 0.69 mmol/g loading) were added to a solution of *N*-(3-methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 379) (50.2 mg, 0.119 mmol) in dichloromethane (2 mL), and the mixture was agitated overnight at room temperature. The reaction mixture was filtered and the resin was washed with *N*,*N*-dimethylformamide. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min.) to afford the title compound as a solid (24.5 mg, 44%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 2.959 min., *m/z* 464 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.98 - 1.35 (m, 4 H), 1.57 (m, 2 H), 1.94 (s, 3 H), 2.16 - 2.37 (m, 1 H), 2.44 - 2.57 (m, 2 H), 2.65 (s, 3 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.71 (d, *J*=7.3 Hz, 2 H), 6.80 (m, 1 H), 6.86 - 6.95 (m, 2 H), 7.14 - 7.28 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.11 - 9.27 (m, 1 H).

Example 384

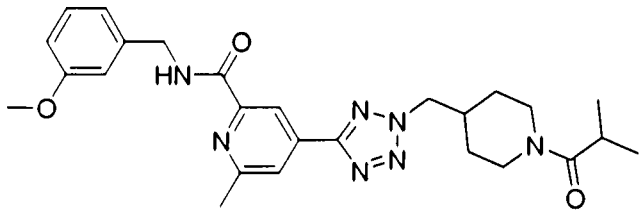
***N*-(3-Methoxybenzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-((1-acetylpiperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 383) by reaction with methane sulfonylchloride to afford 32.5 mg (55%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.154 min., *m/z* 500 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 - 1.48 (m, 4 H), 1.61 - 1.72 (m, 2 H), 2.07 - 2.27 (m, 1 H), 2.65 (s, 3 H), 2.81 (s, 3 H), 3.47 - 3.60 (m, 2 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.76 (d, *J*=7.3 Hz, 2 H), 6.73 - 6.83 (m, 1 H), 6.86 - 6.95 (m, 2 H), 7.15 - 7.27 (m, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.19 (s, 1 H).

Example 385

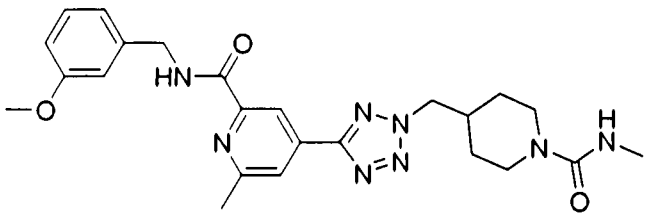
N-(3-Methoxybenzyl)-4-(2-((1-isobutyrylpiperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-4-(2-((1-acetylpiperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 383) by reaction with isobutyryl chloride to afford 37.2 mg (63%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.296 min., *m/z* 492 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.37 (m, 6 H), 1.47 - 1.72 (m, 2 H), 2.28 (s, 1 H), 2.65 (s, 3 H), 2.74 - 2.90 (m, 1 H), 2.90 - 3.10 (m, 2 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.72 (d, *J*=7.3 Hz, 2 H), 6.80 (s, 1 H), 6.86 - 6.97 (m, 2 H), 7.22 (s, 1 H), 8.05 (s, 1 H), 8.41 (s, 1 H), 9.19 (s, 1 H).

Example 386

N-(3-Methoxybenzyl)-6-methyl-4-(2-((1-(methylcarbamoyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide

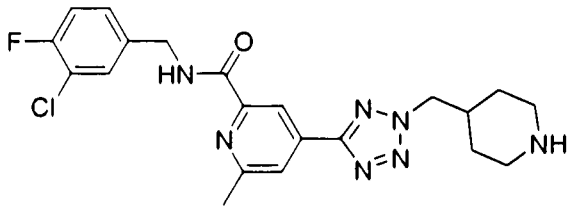


Methylisocyanate (4M solution in dichloromethane, 1 mL) and 4-(dimethylamino)pyridine Si bound (862.0 mg, 0.595 mmol, 0.69 mmol/g loading) were added to a solution of *N*-(3-methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example

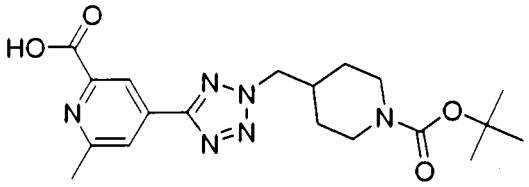
379) in dichloromethane (1 mL), and the mixture was agitated overnight at room temperature. The reaction mixture was filtered and the resin was washed with *N*,*N*-dimethylformamide. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min.) to afford the title compound (35.5 mg, 62%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN , 1.5 min.): 2.887 min., *m/z* 479 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.01 - 1.24 (m, 4 H), 1.44 - 1.55 (m, 2 H), 2.20 (s, 1 H), 2.50 - 2.54 (m, 3 H), 2.56 - 2.63 (m, 2 H), 2.65 (s, 3 H), 3.71 (s, 3 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.70 (d, *J*=6.6 Hz, 2 H), 6.30 (s, 1 H), 6.80 (m, 1 H), 6.85 - 6.95 (m, 2 H), 7.22 (s, Hz, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.09 - 9.26 (m, 1 H).

Example 387

***N*-(3-Chloro-4-fluorobenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide**

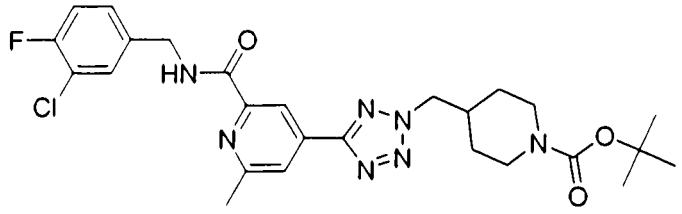


Step 1: Preparation of 4-(2-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid



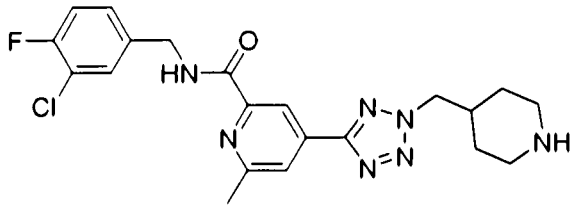
A flask was charged with methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (1.0 g, 4.6 mmol), *tert*-butyl 4-(hydroxymethyl) piperidine-1-carboxylate (2.0 g, 9.1 mmol), polymer supported triphenylphosphine resin (4.2 g, 9.1 mmol, 2.15 mmol/g loading) and tetrahydrofuran (60 mL). The mixture was cooled in an ice bath and di-*tert*-butylazodicarbxylate (2.1 g, 9.1 mmol) was added. The mixture was stirred for 30 minutes and then allowed to warm to room temperature over 18 hours. The reaction mixture was filtered and the resin was washed with methanol. The filtrate was concentrated and the residue was dissolved in a mixture of tetrahydrofuran/water (25 mL/5 mL). LiOH (660 mg, 28.0 mmol) was added and the resulting mixture was stirred at room temperature over 3 days. The tetrahydrofuran was removed in vacuo and the aqueous residue was treated with 4N hydrochloric acid carefully until pH 5-6. The mixture was extracted with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by reverse phase preparative HPLC and then recrystallized from methanol/water to afford the title compound as a white solid (1.21 g, 65%). MS (ES+) *m/z* 508 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 - 1.24 (m, 2 H), 1.34 - 1.43 (m, 11 H), 1.55 (m, 2 H), 2.14 - 2.28 (m, 1 H), 2.65 (s, 3 H), 3.89 - 3.98 (m, 2 H), 4.73 (d, *J*=6.98 Hz, 2 H), 8.09 (d, *J*=1.07 Hz, 1 H), 8.39 (s, 1 H), 8.55 - 8.64 (m, 1 H).

Step 2: Preparation of *tert*-butyl 4-((5-(2-((3-chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate



2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (141 mg, 0.37 mmol) was added to a mixture of 4-(2-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (100 mg, 0.25 mmol), (3-chloro-4-fluorophenyl)methanamine (47 mg, 0.30 mmol), and triethylamine (0.05 mL, 0.37 mmol) in *N*,*N*-dimethylformamide (2 mL), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC. The product was dissolved in methanol, passed through a carbonate cartridge, and concentrated to afford the title compound as a solid (59 mg, 43%). LCMS (ES+) *m/z* 544 (M+H).

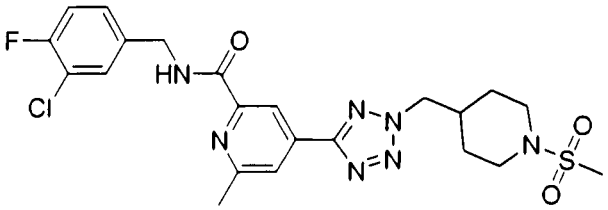
Step 3: Preparation of *N*-(3-chloro-4-fluorobenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



A vial was charged with *tert*-butyl 4-((5-(2-((3-chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate (59 mg, 0.12 mmol), methanol (1 mL), and a 4N solution of hydrochloric acid in dioxane (0.5 mL). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was then passed through a carbonate cartridge eluting with methanol and concentrated to afford the title compound as a solid (49 mg, 95%). MS (ES+) *m/z* 444 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.38 - 1.53 (m, 2 H), 1.69 (s, *J*=12.08 Hz, 2 H), 2.20 - 2.34 (m, 1 H), 2.60 - 2.72 (m, 5 H), 3.17 - 3.25 (m, 2 H), 4.57 (d, *J*=6.98 Hz, 2 H), 4.63 (d, *J*=6.44 Hz, 2 H), 7.10 (t, *J*=8.59 Hz, 1 H), 7.21 - 7.28 (m, 1 H), 7.41 (dd, *J*=6.98, 2.15 Hz, 1 H), 8.05 (d, *J*=1.34 Hz, 1 H), 8.46 (t, *J*=6.31 Hz, 1 H), 8.70 (s, 1 H).

Example 388

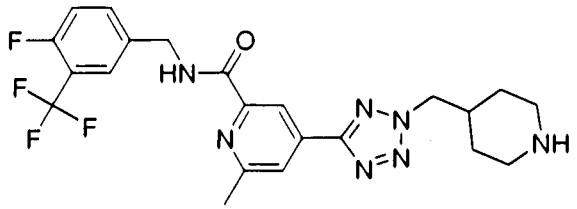
_N_-(3-Chloro-4-fluorobenzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



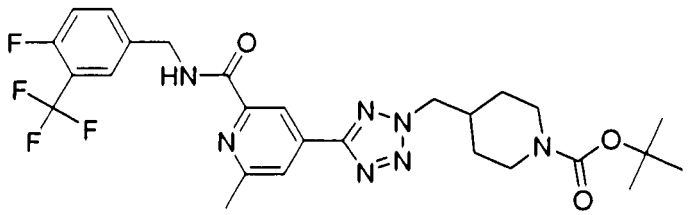
Methane sulfonylchloride (0.007 mL, 0.08 mmol) was added to a mixture of *N*-(3-chloro-4-fluorobenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 387) (25 mg, 0.06 mmol) and triethylamine (0.016 mL, 0.11 mmol) in dichloromethane (1 mL), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was purified by reverse phase preparative HPLC. Fractions containing desired product were combined and concentrated. The residue was dissolved in methanol and passed through a carbonate cartridge. Concentration of the resulting solution afforded the title compound as a solid (16 mg, 55%). MS (ES+) *m/z* 522 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.01 - 1.27 (m, 3 H), 1.51 (d, *J*=11.71 Hz, 2 H), 1.93 - 2.10 (m, 2 H), 2.51 - 2.60 (m, 1 H), 2.65 (s, 3 H), 3.05 - 3.16 (m, 1 H), 3.38 (d, *J*=11.71 Hz, 3 H), 4.33 (d, *J*=5.86 Hz, 2 H), 4.60 (d, *J*=7.32 Hz, 2 H), 7.18 (d, *J*=7.32 Hz, 2 H), 7.31 - 7.44 (m, *J*=8.05 Hz, 1 H), 7.90 (s, 1 H), 8.24 (s, 1 H), 9.18 (t, *J*=6.59 Hz, 1 H).

Example 389

N-(4-Fluoro-3-(trifluoromethyl)benzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



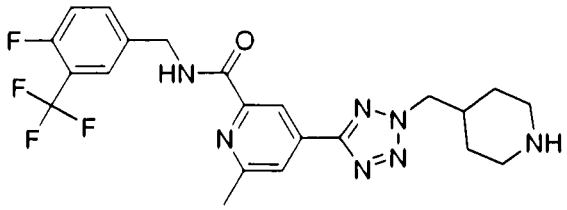
Step 1: Preparation of *tert*-butyl 4-((5-(2-((4-fluoro-3-(trifluoromethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate



2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (141 mg, 0.37 mmol) was added to a mixture of 4-(2-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 1 of the synthesis of *N*-(3-chloro-4-fluorobenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide, Example 387) (100 mg, 0.25 mmol), (4-fluoro-3-(trifluoromethyl)phenyl)methanamine (58 mg, 0.30 mmol), and triethylamine (0.05 mL, 0.37 mmol) in *N*,*N*-dimethylformamide (2 mL), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC. The product was

dissolved in methanol, passed through a carbonate cartridge, and concentrated to afford the title compound as a solid (61 mg, 43%). LCMS (ES+) *m/z* 578 (M+H).

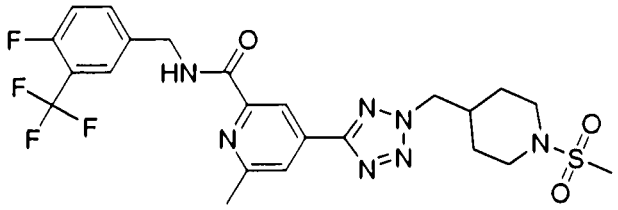
Step 2: Preparation of *N*-(4-fluoro-3-(trifluoromethyl)benzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



A vial was charged with *tert*-butyl 4-((5-(2-((4-fluoro-3-(trifluoromethyl)benzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate (63 mg, 0.12 mmol), methanol (1 mL), and a 4N solution of hydrochloric acid in dioxane (0.5 mL). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was then passed through a carbonate cartridge eluting with methanol and concentrated to afford the title compound as a solid (49 mg, 100%). MS (ES+) *m/z* 478 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.11 - 1.24 (m, 3 H), 1.50 (d, *J*=11.72 Hz, 2 H), 2.04 - 2.17 (m, 1 H), 2.42 - 2.50 (m, 2 H), 2.64 (s, 3 H), 2.95 (d, *J*=11.72 Hz, 2 H), 4.54 (d, *J*=7.33 Hz, 2 H), 4.66 (d, *J*=5.86 Hz, 2 H), 7.34 - 7.49 (m, 1 H), 7.63 - 7.79 (m, *J*=19.78, 6.59 Hz, 2 H), 8.05 (s, 1 H), 8.38 (s, 1 H), 9.39 (t, *J*=6.59 Hz, 1 H).

Example 390

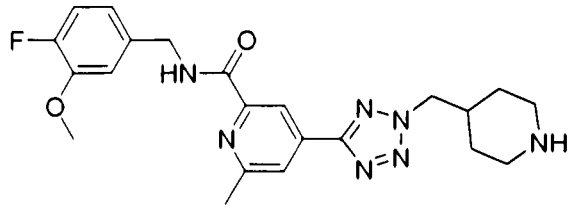
N-(4-Fluoro-3-(trifluoromethyl)benzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



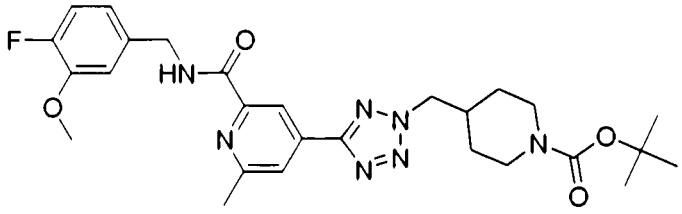
Methane sulfonylchloride 0.006 mL, 0.07 mmol) was added to a mixture of *N*-(4-fluoro-3-(trifluoromethyl)benzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 389) (23 mg, 0.05 mmol) and triethylamine (0.013 mL, 0.10 mmol) in dichloromethane (1 mL), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was purified by reverse phase preparative HPLC. Fractions containing desired product were combined and concentrated. The residue was dissolved in methanol and passed through a carbonate cartridge. Concentration of the resulting solution afforded the title compound as a solid (16 mg, 58%). MS (ES+) *m/z* 556 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.19 - 1.43 (m, 3 H), 1.67 (d, *J*=11.71 Hz, 2 H), 2.08 - 2.24 (m, 2 H), 2.66 - 2.75 (m, 2 H), 2.81 (s, 3 H), 3.54 (d, *J*=11.71 Hz, 3 H), 4.55 (d, *J*=5.86 Hz, 2 H), 4.75 (d, *J*=7.32 Hz, 2 H), 7.38 - 7.51 (m, 1 H), 7.64 - 7.81 (m, 2 H), 8.06 (s, 1 H), 8.40 (s, 1 H), 9.40 (t, *J*=6.22 Hz, 1 H).

Example 391

***N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide**

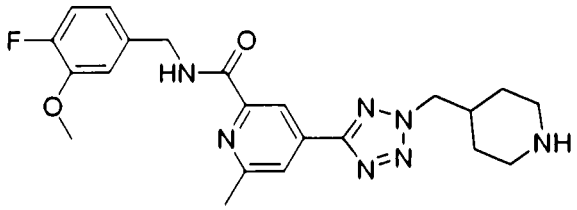


Step 1: Preparation of *tert*-butyl 4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate



2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (141 mg, 0.37 mmol) was added to a mixture of 4-(2-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 1 of the synthesis of *N*-(3-chloro-4-fluorobenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide, Example 387) (100 mg, 0.25 mmol), 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (46 mg, 0.30 mmol), and triethylamine (0.05 mL, 0.37 mmol) in *N*,*N*-dimethylformamide (2 mL), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was purified by reverse phase preparative HPLC. The product was dissolved in methanol, passed through a carbonate cartridge, and concentrated to afford the title compound as a solid (63 mg, 47%). MS (ES+) *m/z* 540(M+H).

Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide

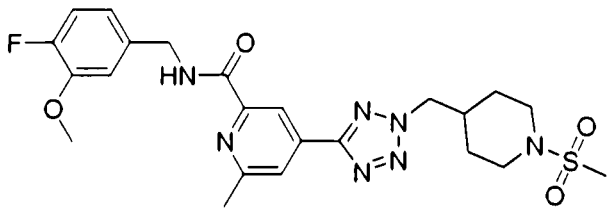


A vial was charged with *tert*-butyl 4-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)piperidine-1-carboxylate (53 mg, 0.10 mmol), methanol (1 mL), and a 4N solution of hydrochloric acid in dioxane (0.5 mL). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was then passed through a carbonate cartridge eluting with methanol and concentrated to afford the title compound as a solid (43 mg, 100%). MS (ES+) *m/z* 440 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.26 (m, 3 H), 1.49 (d, *J*=11.72 Hz, 2 H), 2.03 - 2.18 (m, 2 H), 2.44 - 2.52 (m, 2 H), 2.65 (s, 3 H), 2.94 (d, *J*=11.72 Hz, 2 H), 3.80 (s, 3 H),

4.48 (d, *J*=7.33 Hz, 2 H), 4.67 (d, *J*=5.86 Hz, 2 H), 6.85 - 6.93 (m, 1 H), 7.04 - 7.22 (m, 2 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.21 (t, *J*=5.86 Hz, 1 H).

Example 392

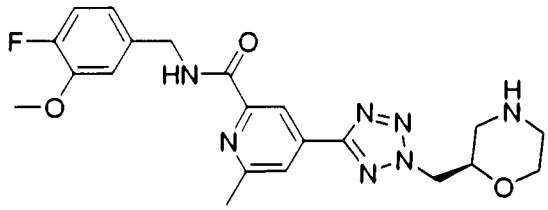
N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((1-(methylsulfonyl)piperidin-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



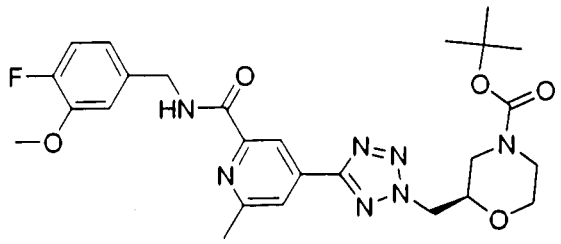
Methane sulfonylchloride 0.006 mL, 0.07 mmol) was added to a mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-(piperidin-4-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 391) (20 mg, 0.05 mmol) and triethylamine (0.013 mL, 0.10 mmol) in dichloromethane (1 mL), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was purified by reverse phase preparative HPLC. Fractions containing desired product were combined and concentrated. The residue was dissolved in methanol and passed through a carbonate cartridge. Concentration of the resulting solution afforded the title compound as a solid (15 mg, 61%). MS (ES+) *m/z* 518 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 - 1.43 (m, 3 H), 1.67 (d, *J*=11.71 Hz, 2 H), 2.09 - 2.24 (m, 2 H), 2.62 - 2.76 (m, 2 H), 2.81 (s, 3 H), 3.54 (d, *J*=12.45 Hz, 3 H), 3.80 (s, 3 H), 4.48 (d, *J*=5.86 Hz, 2 H), 4.76 (d, *J*=6.59 Hz, 2 H), 6.82 - 6.92 (m, 1 H), 7.05 - 7.20 (m, 2 H), 8.06 (s, 1 H), 8.41 (s, 1 H), 9.22 (t, *J*=6.22 Hz, 1 H).

Example 393

N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide

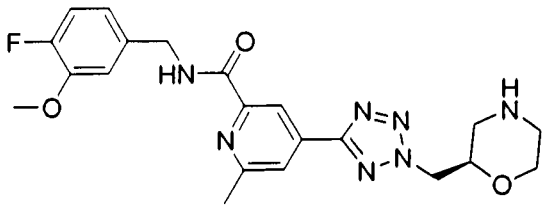


Step 1: Preparation of (2*R*)-tert-butyl 2-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate



A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (0.070 g, 0.19 mmol), (*R*)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (0.050 g, 0.23 mmol), and polymer supported-triphenylphosphine (0.60 g, 0.29 mmol) in anhydrous tetrahydrofuran (5 mL) was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (0.053 g, 0.23 mmol) was added. The mixture was allowed to warm to room temperature while stirring over 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica column chromatography (0-2% methanol/dichloromethane) to afford the title compound as a beige oil (65 mg, 62%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 5.58 min, *m/z* 564 (M+Na).

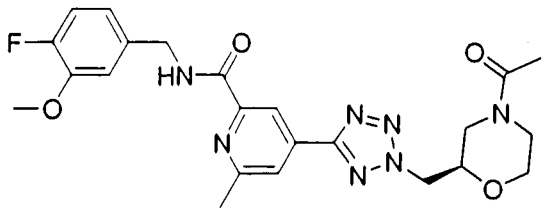
Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



Trifluoroacetic acid (0.5 mL) was added to a solution of (2*R*)-tert-butyl 2-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate in dichloromethane (2 mL), and the mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated, and the residue was triturated with diethyl ether (4 x 5 mL) to afford the title compound.

Example 394

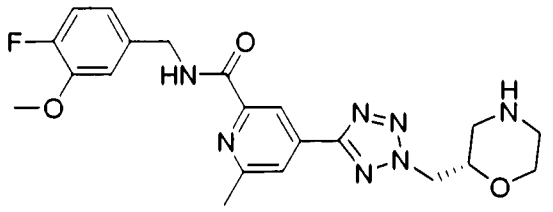
N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*R*)-4-acetylmorpholin-2-yl)methyl)-2H-tetrazol-5-yl)-6-methylpicolinamide



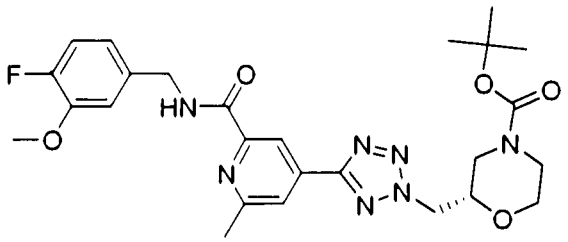
Triethylamine (0.037 mL, 0.26 mmol) and a solution of acetyl chloride (13 mg in 0.5 mL dichloromethane) were added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*R*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 393) (0.065 g, 0.12 mmol) in dichloromethane (2 mL). The mixture was stirred for 1 hour at room temperature and then was concentrated. The residue was purified by reverse phase preparative HPLC (10-90 % acetonitrile/water) to afford the title compound (26 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (br. s., 1 H), 8.41 (br. s., 1 H), 8.06 (br. s., 1 H), 7.13 (dd, *J*=23.4, 10.3 Hz, 1 H), 6.89 (d, *J*=5.1 Hz, 1 H), 4.82 - 5.04 (m, 2 H), 4.48 (d, *J*=6.6 Hz, 2 H), 4.37 (d, *J*=11.7 Hz, 1 H), 3.97 (br. s., 2 H), 3.80 (s, 3 H), 3.61 (br. s., 1 H), 3.39 (br. s., 1 H), 3.11 (br. s., 1 H), 2.66 (s, 5 H), 2.01 (d, *J*=16.1 Hz, 3 H).

Example 395

N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



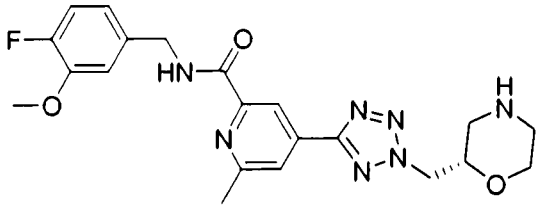
Step 1: Preparation of (2*S*)-tert-butyl 2-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate



A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (0.070 g, 0.19 mmol), (*S*)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (0.050 g, 0.23 mmol), and polymer supported-triphenylphosphine (0.60 g, 0.29 mmol) in anhydrous tetrahydrofuran (5 mL) was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (0.053 g, 0.23 mmol) was added. The mixture was allowed to warm to room temperature while stirring over 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica column

chromatography (0-2% methanol/dichloromethane) to afford the title compound as a beige oil (63 mg, 61%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 5.57 min, *m/z* 564 (M+Na).

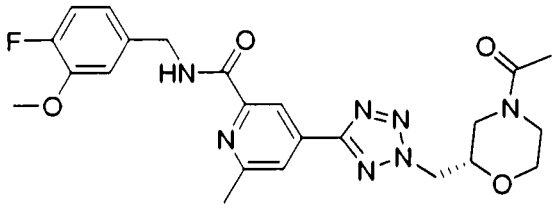
Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



Trifluoroacetic acid (0.5 mL) was added to a solution of (2*S*)-tert-butyl 2-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate in dichloromethane (2 mL), and the mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated, and the residue was triturated with diethyl ether (4 x 5 mL) to afford the title compound.

Example 396

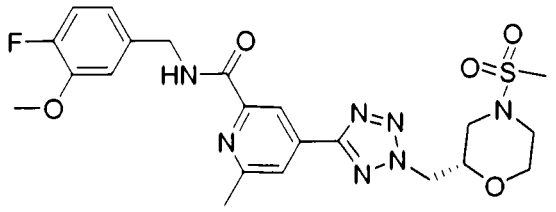
N-(4-Fluoro-3-methoxybenzyl)-4-(2-(((*S*)-4-acetylmorpholin-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Triethylamine (0.037 mL, 0.26 mmol) and a solution of acetyl chloride (13 mg in 0.5 mL dichloromethane) was added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 395) (0.063 g, 0.12 mmol) in dichloromethane (2 mL). The mixture was stirred for 1 hour at room temperature and then was concentrated. The residue was purified by reverse phase preparative HPLC (10-90 % acetonitrile/water) to afford the title compound (29 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (d, *J*=5.9 Hz, 1 H), 8.41 (br. s., 1 H), 8.06 (br. s., 1 H), 7.05 - 7.22 (m, 2 H), 6.80 - 6.95 (m, 1 H), 4.80 - 5.08 (m, 2 H), 4.48 (d, *J*=6.6 Hz, 3 H), 4.37 (d, *J*=13.9 Hz, 1 H), 3.90 - 4.15 (m, 2 H), 3.80 (s, 3 H), 3.63 (d, *J*=13.2 Hz, 1 H), 3.33 - 3.47 (m, 1 H), 3.02 - 3.20 (m, 1 H), 2.66 (s, 3 H), 2.02 (d, *J*=16.8 Hz, 3 H).

Example 397

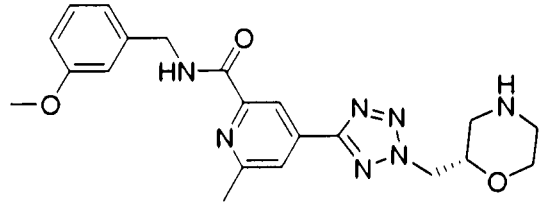
N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-(((*R*)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2H-tetrazol-5-yl)picolinamide



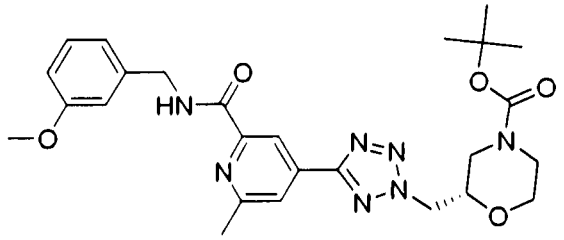
Triethylamine (0.037 mL, 0.26 mmol) and a solution of methanesulfonyl chloride (18 mg in 0.5 mL dichloromethane) was added to a solution of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 395) (0.075 g, 0.18 mmol) in dichloromethane (2 mL). The mixture was stirred for 1 hour at room temperature and then was concentrated. The residue was purified by reverse phase preparative HPLC (10-90 % acetonitrile/water) to afford the title compound (18 mg, 20%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=6.2 Hz, 1 H), 8.42 (s, 1 H), 8.07 (s, 1 H), 7.06 - 7.22 (m, 2 H), 6.89 (br. s., 1 H), 5.04 (dd, *J*=14.3, 3.3 Hz, 1 H), 4.91 (dd, *J*=13.9, 8.1 Hz, 1 H), 4.48 (d, *J*=6.6 Hz, 2 H), 4.06 - 4.17 (m, 1 H), 3.89 (d, *J*=12.4 Hz, 1 H), 3.80 (s, 3 H), 3.67 (d, *J*=11.7 Hz, 1 H), 3.44 - 3.55 (m, 1 H), 3.32 (d, *J*=11.0 Hz, 1 H), 2.91 (s, 3 H), 2.73 - 2.88 (m, 2 H), 2.66 (s, 3 H).

Example 398

***N*-(3-Methoxybenzyl)-6-methyl-4-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide**

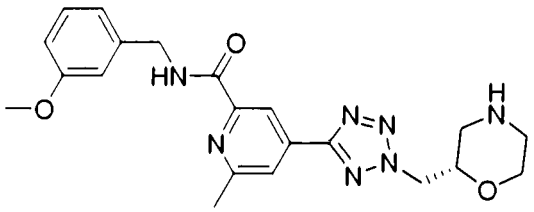


Step 1: Preparation of (2*S*)-tert-butyl 2-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate



A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (0.75 g, 2.3 mmol), (*S*)-tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (0.53 g, 2.4 mmol), and polymer supported-triphenylphosphine (1.29 g, 2.77 mmol) in anhydrous tetrahydrofuran (20 mL) was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (0.80 g, 3.5 mmol) was added. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica column chromatography (0-2% methanol/dichloromethane) to afford the protected amine as a beige oil.

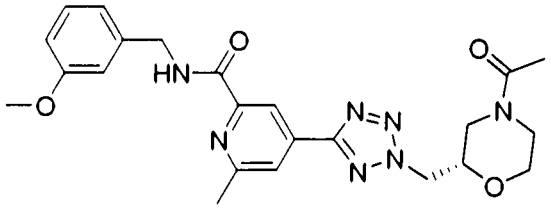
Step 2: Preparation of *N*-(3-methoxybenzyl)-6-methyl-4-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide



Trifluoroacetic acid (1.0 mL) was added to a solution of (2*S*)-tert-butyl 2-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)morpholine-4-carboxylate in dichloromethane (5 mL), and the mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated, and the residue was triturated with diethyl ether (4 x 5 mL) to afford the title compound. The reaction mixture was diluted with dichloromethane (10 mL) and neutralized to pH 7 with a 2.5 N aqueous solution of sodium hydroxide. The organic phase was separated and washed with water (10 mL) followed by brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to afford the title compound (0.43 g, 44%).

Example 399

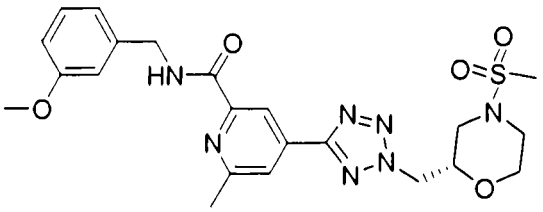
N-(3-Methoxybenzyl)-4-(2-(((S)-4-acetylmorpholin-2-yl)methyl)-2H-tetrazol-5-yl)-6-methylpicolinamide



Triethylamine (0.037 mL, 0.26 mmol) and a solution of acetyl chloride (17 mg in 0.5 mL dichloromethane) was added to a solution of *N*-(3-methoxybenzyl)-6-methyl-4-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 398) (0.075 g, 0.18 mmol) in dichloromethane (2 mL). The mixture was stirred for 1 hour at room temperature and then was concentrated. The residue was purified by reverse phase preparative HPLC (10-90 % acetonitrile/water) to afford the title compound (44 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=5.9 Hz, 1 H), 8.41 (s, 1 H), 8.06 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, *J*=8.1 Hz, 1 H), 4.95 - 5.04 (m, 1 H), 4.85 - 4.95 (m, 1 H), 4.49 (d, *J*=6.6 Hz, 2 H), 3.90 - 4.13 (m, 2 H), 3.79 (d, *J*=10.3 Hz, 1 H), 3.71 (s, 3 H), 3.43 (d, *J*=9.5 Hz, 1 H), 3.05 - 3.20 (m, 2 H), 2.62 - 2.73 (m, 4 H), 2.01 (d, *J*=16.8 Hz, 3 H).

Example 400

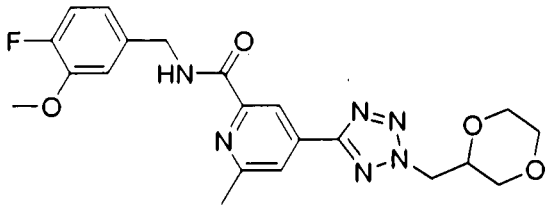
N-(3-Methoxybenzyl)-6-methyl-4-(2-(((R)-4-(methylsulfonyl)morpholin-2-yl)methyl)-2H-tetrazol-5-yl)picolinamide



Triethylamine (0.022 mL, 0.16 mmol) and a solution of methanesulfonyl chloride (15 mg in 0.5 mL dichloromethane) was added to a solution of *N*-(3-methoxybenzyl)-6-methyl-4-(2-((*S*)-morpholin-2-ylmethyl)-2*H*-tetrazol-5-yl)picolinamide (prepared as described in Example 398) (0.045 g, 0.11 mmol) in dichloromethane (2 mL). The mixture was stirred for 1 hour at room temperature and then was concentrated. The residue was purified by silica column chromatography (0-75%ethyl acetate/heptane) to afford the title compound (20 mg, 37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.2 Hz, 1 H), 8.42 (s, 1 H), 8.07 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, *J*=7.3 Hz, 1 H), 4.98 - 5.09 (m, 1 H), 4.91 (dd, *J*=14.6, 8.1 Hz, 1 H), 4.49 (d, *J*=6.6 Hz, 2 H), 4.11 (d, *J*=9.5 Hz, 1 H), 3.89 (d, *J*=11.7 Hz, 1 H), 3.71 (s, 3 H), 3.67 (d, *J*=11.0 Hz, 1 H), 3.50 (t, *J*=10.3 Hz, 1 H), 3.32 (d, *J*=11.7 Hz, 1 H), 2.91 (s, 3 H), 2.75 - 2.88 (m, 2 H), 2.66 (s, 3 H).

Example 401

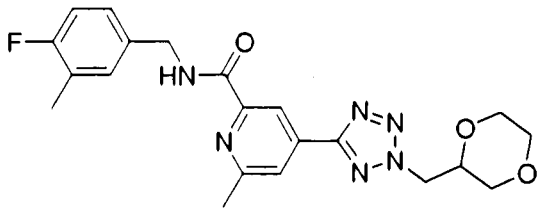
***rac*-4-(2-((1,4-Dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-methoxybenzyl)-6-methylpicolinamide**



rac-2-(Iodomethyl)-1,4-dioxane (57 mg, 0.25 mmol) was added to a mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (79 mg, 0.23 mmol) and triethylamine (23 mg, 0.23 mole) in anhydrous acetonitrile (1 mL). The mixture was stirred at reflux temperature in a capped vial for two days and then was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing the product were passed through a carbonate resin column and the filtrate was concentrated. The residue was slurried with ether, decanted, and dried in a vacuum desiccator to afford the title compound as a white solid (39 mg). MS (ES+) *m/z* 443 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.0 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.10-7.24 (m, 2 H), 6.91 (br s, 1 H), 4.85-4.95 (m, 2 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.20 (m, 1 H), 3.85-3-95 (m, 1 H), 3.82 (s, 3 H), 3.30-3-80 (m, 5 H), 2.68 (s, 3 H).

Example 402

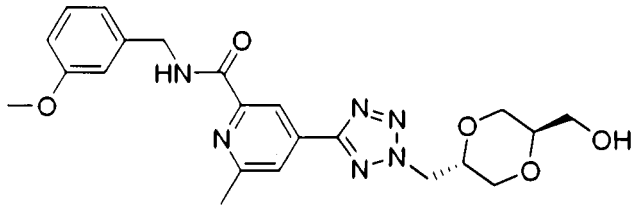
***rac*-4-(2-((1,4-Dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(4-fluoro-3-methylbenzyl)-6-methylpicolinamide**



rac-2-(Iodomethyl)-1,4-dioxane (114 mg, 0.5 mmol) was added to a mixture of *N*-(4-fluoro-3-methylbenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as describe in step 1 of the synthesis of *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 185) (150 mg, 0.46 mmol) and triethylamine (46 mg, 0.46 mmol) in anhydrous acetonitrile (2 mL). The mixture was stirred at reflux temperature in a capped vial for two days and then was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing the product were passed through a carbonate resin column and the filtrate was concentrated. The residue was slurried with ether, decanted, and dried in a vacuum desiccator to afford the title compound as a white solid (61 mg). MS (ES+) *m/z* 427 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.0 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.00-7.30 (m, 3 H), 4.85-4.95 (m, 2 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.20 (m, 1 H), 3.85-3-95 (m, 1 H), 3.30-3-80 (m, 5 H), 2.68 (s, 3 H), 2.20 (s, 3 H).

Example 403

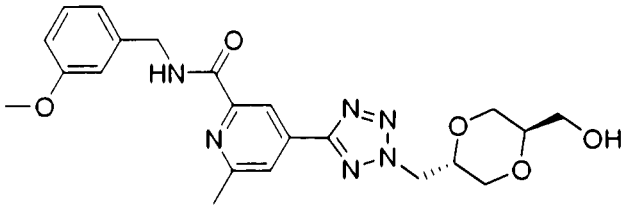
***rac*-*N*-(3-Methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



rac-((2*R**,5*R**)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (1.4 g, 4.3 mmol) was added to a mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (1.0 g, 3.1 mmol) and triethylamine (0.4 g, 4.0 mmole) in anhydrous *N*,*N*-dimethylacetamide (1 mL). The mixture was stirred at 85°C in a capped vial overnight and then was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing the product were passed through a carbonate resin column and the filtrate was concentrated. The residue was slurried with ether, decanted, and dried in a vacuum desiccator to afford the title compound as a white solid (1.04 g). MS (ES+) *m/z* 455 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 (br. s., 2 H), 6.83 (d, *J*=1.5 Hz, 1 H), 4.80-4.95 (m, 2 H), 4.65 (t, *J*=5.7 Hz, 1 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.15 (m, 1 H), 3.99 (dd, *J*=11.3, 1.8 Hz, 1 H), 3.77 (d, J=11.3Hz, 1 H), 3.73 (s, 3 H), 3.30-3.50 (m, 4 H), 2.68 (s, 3 H).

Example 404

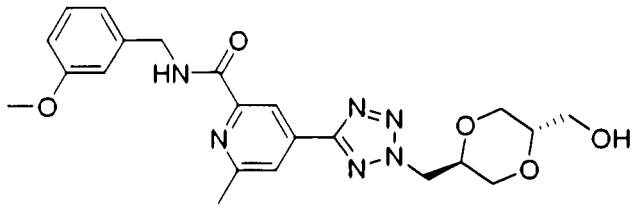
***N*-(3-Methoxybenzyl)-4-(2-(((2*S*,5*R*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



rac-N-(3-Methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 403) was separated by chiral supercritical-fluid chromatography (AS-H, 30 x 250 mm, 20% methanol, 70 mL/min) and the first eluting isomer was isolated to afford the title compound (50 mg). MS (ES+) *m/z* 455 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 (br. s., 2 H), 6.83 (d, *J*=1.5 Hz, 1 H), 4.80-4.95 (m, 2 H), 4.65 (t, *J*=5.7 Hz, 1 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.15 (m, 1 H), 3.99 (dd, *J*=11.3, 1.8 Hz, 1 H), 3.77 (d, J=11.3 Hz, 1 H), 3.73 (s, 3 H), 3.30-3-50 (m, 4 H), 2.68 (s, 3 H).

Example 405

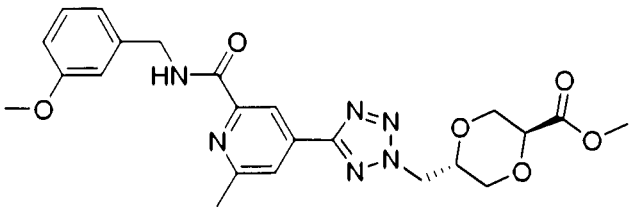
***N*-(3-Methoxybenzyl)-4-(2-(((2*R*,5*S*)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



rac-N-(3-Methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 403) was separated by chiral supercritical-fluid chromatography (AS-H, 30 x 250 mm, 20% methanol, 70 mL/min) and the second eluting isomer was isolated to afford the title compound (50 mg). MS (ES+) *m/z* 455 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 (br. s., 2 H), 6.83 (d, *J*=1.5 Hz, 1 H), 4.80-4.95 (m, 2 H), 4.65 (t, *J*=5.7 Hz, 1 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.15 (m, 1 H), 3.99 (dd, *J*=11.3, 1.8 Hz, 1 H), 3.77 (d, J=11.3 Hz, 1 H), 3.73 (s, 3 H), 3.30-3-50 (m, 4 H), 2.68 (s, 3 H).

Example 406

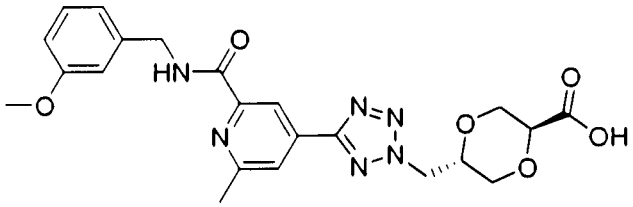
***rac*-(2*S**,5*S**)-Methyl 5-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate**



rac-(2*S**,5*R**)-Methyl 5-((tosyloxy)methyl)-1,4-dioxane-2-carboxylate (prepared as described in step 1 of the synthesis of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate, Example 85) (1.22 g, 3.7 mmol) was added to a mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (1.2 g, 3.7 mmol) and triethylamine (749 mg, 7.4 mmol) in anhydrous N,N-dimethylacetamide (2.3 mL). The mixture was stirred at 85°C in a capped vial overnight and then was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound as a white solid (1.7 g).

Example 407

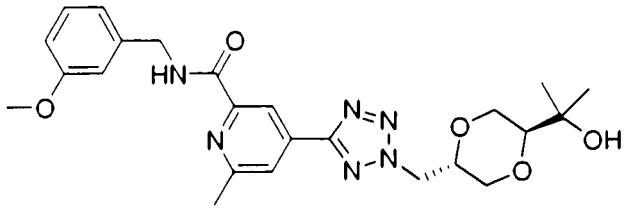
rac-(2*S,5*S**)-5-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid**



Sodium hydroxide (10 pellets) was added to *rac*-(2*S**,5*S**)-methyl 5-((5-(2-((3-methoxybenzyl)-carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as described in Example 406) (1.35 g, 2.8 mmol) in a mixture of tetrahydrofuran/water (6 mL, 1/1) and the mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse-phase preparative HPLC (water/ acetonitrile). The resulting product was slurried and decanted from ether several times and dried in a vacuum desiccator to afford the title compound as a white solid (1.09 g). MS (ES+) *m/z* 469 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 (br. s., 2 H), 6.83 (d, *J*=1.5 Hz, 1 H), 4.85-4.99 (m, 2 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.20 (s, 3 H), 3.90-3.99 (m, 1 H), 3.73 (s, 3 H), 3.45-3-60 (m, 2 H), 2.68 (s, 3 H).

Example 408

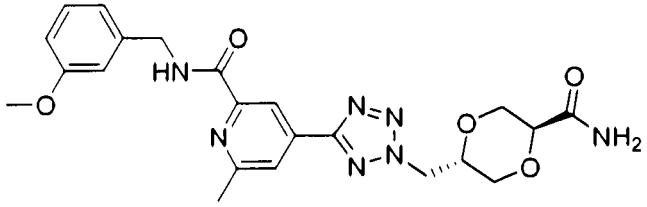
rac-*N*-(3-Methoxybenzyl)-4-(2-(((2*S,5*S**)-5-(2-hydroxypropan-2-yl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



A solution of methyl magnesium iodide (3M in ether, 0.16 mL, 0.48 mmol) was added dropwise at room temperature to a solution of *rac*-(2*S**,5*S**)-methyl 5-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as described in Example 406) (75 mg, 0.15 mmol) in anhydrous tetrahydrofuran (1 mL). Additional tetrahydrofuran (0.5 mL) was added and the mixture was stirred at room temperature for 2 hours. The reaction mixture was cooled to ice bath temperature and saturated aqueous ammonium chloride solution (0.5 mL) was added dropwise. The product was purified by reverse phase preparative HPLC (water/ acetonitrile). Fractions containing the product were passed through a carbonate resin column and the filtrate was concentrated. The residue was slurried and decanted from ether several times and then dried in a vacuum desiccator to afford the title compound as a white solid (25 mg). MS (ES+) *m/z* 483 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 (br. s., 2 H), 6.83 (d, *J*=1.5 Hz, 1 H), 4.80-4.99 (m, 2 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.00-4.15 (m, 2 H), 3.90-3.99 (m, 1 H), 3.73 (s, 3 H), 3.33-3.45 (m, 2 H), 3.12-3.19 (m, 1 H), 2.68 (s, 3 H), 1.07 (s, 3 H), 1.01 (s, 3 H).

Example 409

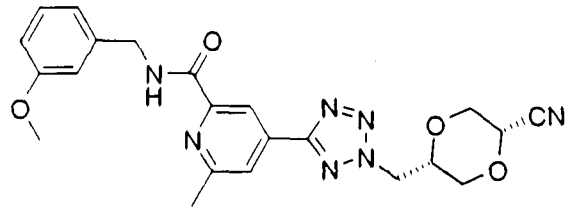
***rac*-*N*-(3-Methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-carbamoyl-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Formamide (300 mg) was added to a solution of *rac*-(2*S**,5*S**)-methyl 5-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as described in Example 406) (149 mg, 0.3 mmol) in anhydrous tetrahydrofuran (3 mL) at reflux temperature. A solution of sodium methoxide (25% in methanol, 300 mg) was added and the mixture was stirred at reflux for 1.5 hours. The reaction mixture was purified by reverse phase preparative HPLC (water/ acetonitrile). Fractions containing the product were passed through a carbonate resin column and the filtrate was concentrated. The residue was slurried and decanted from ether several times and then dried in a vacuum desiccator to afford the title compound as a white solid (106 mg). MS (ES+) *m/z* 468 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 (br. s., 2 H), 6.83 (d, *J*=1.5 Hz, 1 H), 4.85-4.99 (m, 2 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.20 (m, 3 H), 3.90-3.99 (m, 1 H), 3.73 (s, 3 H), 3.45-3-60 (m, 2 H), 2.68 (s, 3 H).

Example 410

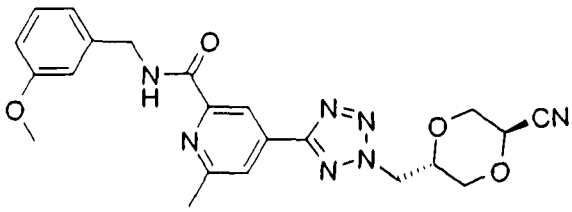
***rac-N*-(3-Methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-cyano-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Polymer supported triphenylphosphine (Argonaut; 2.15 mmol/g, 300 mg) was added to *rac-N*-(3-methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-carbamoyl-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 409) (85 mg, 0.18 mmol) in a mixture of carbon tetrachloride (0.5 mL) and dichloroethane (4.5 mL) and the mixture was heated at 80 °C for 3 hours. The reaction mixture was filtered and the resin was washed with dichloroethane. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC. Fractions containing the first eluting isomer were passed through a carbonate resin column and were concentrated. The product was slurried and decanted several times from ether and the solid was dried in a vacuum desiccator to afford the title compound as a white solid (23 mg). MS (ES+) *m/z* 450 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.29 (t, *J*=6.4 Hz, 1 H), 8.44 (s, 1 H), 8.11 (s, 1 H), 7.25 (t, *J*=8.1 Hz, 1 H), 6.90 - 6.94 (m, 2 H), 6.83 (dd, *J*=8.1, 2.0 Hz, 1 H), 5.04 (d, *J*=2.7 Hz, 1 H), 4.99 (br. s., 1 H), 4.97 (d, *J*=3.6 Hz, 1 H), 4.51 (d, *J*=6.3 Hz, 2 H), 4.24 - 4.31 (m, 1 H), 4.08 (dd, *J*=11.9, 2.6 Hz, 1 H), 3.95 (d, *J*=12.5 Hz, 1 H), 3.81 (dd, *J*=12.5, 3.2 Hz, 1 H), 3.74 (s, 3 H), 3.71 - 3.75 (m, 1 H), 2.69 (s, 3 H).

Example 411

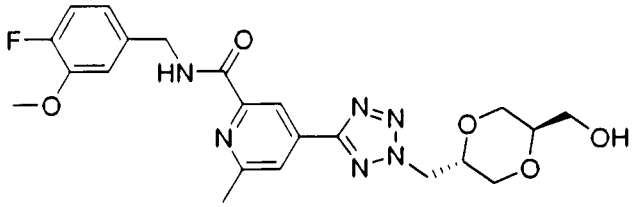
***rac-N*-(3-Methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-cyano-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Isolation of the second eluting isomer by reverse phase preparative HPLC from the reaction mixture described in Example 410 afforded the title compound as a white solid (24 mg). MS (ES+) *m/z* 450 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.4 Hz, 1 H), 8.41 (s, 1 H), 8.06 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.87 - 6.93 (m, 2 H), 6.80 (d, *J*=8.1 Hz, 1 H), 4.92 - 5.02 (m, 2 H), 4.77 (dd, *J*=8.4, 2.9 Hz, 1 H), 4.49 (d, *J*=6.2 Hz, 2 H), 4.21 - 4.30 (m, 1 H), 4.05 - 4.13 (m, 2 H), 3.71 (s, 3 H), 3.64 (ddd, *J*=22.0, 12.0, 8.4 Hz, 2 H), 2.66 (s, 3 H).

Example 412

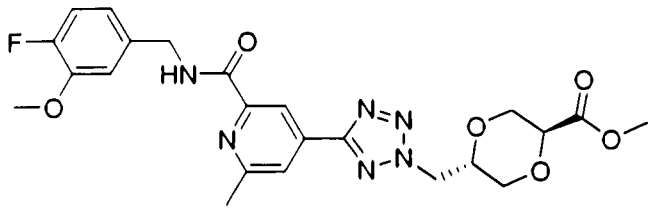
***rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



rac-((2*R**,5*R**)-5-(Hydroxymethyl)-1,4-dioxan-2-yl)methyl 4-methylbenzenesulfonate (prepared as described in step 4 of the synthesis of *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (3.03 g, 10.0 mmol) was added to a mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (1.9 g, 5.0 mmol) and triethylamine (2.8 g, 27.0 mmol) in anhydrous DMA (3 mL). The mixture was stirred at 90°C in a capped vial overnight. The reaction mixture is allowed to cool, diluted with excess dichloromethane, and washed with 2N aqueous sodium hydroxide solution (2x) and water (4x). The organic layer was concentrated and the residue was crystallized from a mixture of methanol/ethyl acetate (70/30) over 48 hours in a refrigerator to afford the title compound as a white solid (1.03 g). MS (ES+) *m/z* 473 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.0 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.10-7.24 (m, 2 H), 6.91 (br. s. 1 H), 4.80-4.95 (m, 2 H), 4.65 (t, *J*=5.7 Hz, 1 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.15 (m, 1 H), 3.99 (dd, *J*=11.3, 1.8 Hz, 1 H), 3.77 (d, J=11.3 Hz, 1 H), 3.82 (s, 3 H), 3.30-3-50 (m, 4 H), 2.68 (s, 3 H).

Example 413

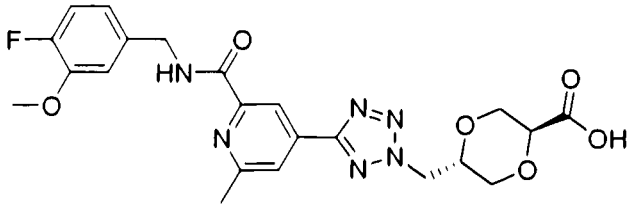
***rac*-(2*S**,5*S**)-Methyl 5-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate**



rac-(2*S**,5*R**)-Methyl 5-((tosyloxy)methyl)-1,4-dioxane-2-carboxylate (prepared as described in step 1 of the synthesis of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate, Example 85) (77 mg, 0.23 mmol) was added to a mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (80 mg, 0.23 mmol) and triethylamine (24 mg, 0.23 mmol) in anhydrous acetonitrile (2 mL). The mixture was stirred at 80°C in a capped vial overnight and then was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound as a white solid (65 mg).

Example 414

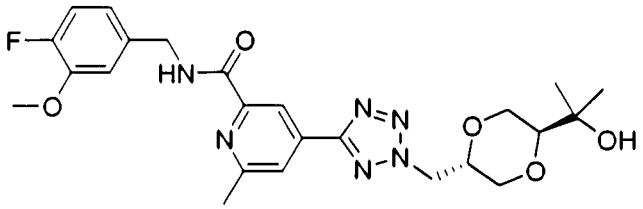
***rac*-(2*S**,5*S**)-5-((5-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid**



Sodium hydroxide (2 pellets) was added to *rac*-(2*S**,5*S**)-methyl 5-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as described in Example 413) (65 mg, 0.13 mmol) in a mixture of tetrahydrofuran/water (1 mL, 1/1) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse-phase preparative HPLC (water/ acetonitrile). The resulting product was slurried and decanted from ether several times and then dried in a vacuum desiccator to afford the title compound as a white solid (50 mg). MS (ES+) *m/z* 487 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.0 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.10-7.24 (m, 2 H), 6.91 (br. S., 1 H), 4.85-4.99 (m, 2 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.20 (m, 3 H), 3.90-3.99 (m, 1 H), 3.82 (s, 3 H), 3.45-3-60 (m, 2 H), 2.68 (s, 3 H).

Example 415

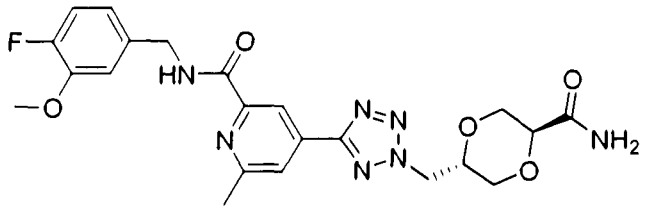
***rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-(2-hydroxypropan-2-yl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



A solution of methyl magnesium iodide (3M in ether, 0.1 mL, 0.3 mmol) was added dropwise at room temperature to a solution of *rac*-(2*S**,5*S**)-methyl 5-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as described in Example 413) (35 mg, 0.07 mmol) in anhydrous tetrahydrofuran (1 mL). Additional tetrahydrofuran (0.5 mL) was added and the mixture was stirred at room temperature for 2 hours. The reaction mixture was cooled to ice bath temperature and saturated aqueous ammonium chloride solution (0.5 mL) was added dropwise. The product was purified by reverse phase preparative HPLC (water/ acetonitrile). Fractions containing the product were passed through a carbonate resin column and the filtrate was concentrated. The residue was slurried and decanted from ether several times and then dried in a vacuum desiccator to afford the title compound as a white solid (21 mg). MS (ES+) m/z 501 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.1-7.25 (m, 2 H), 6.91 (br. s., 1 H), 4.80-4.99 (m, 2 H, m), 4.52 (d, *J*=6.2 Hz, 2 H), 4.00-4.15 (m, 2 H), 3.90-3.99 (m, 1 H), 3.82 (s, 3 H), 3.33-3.45 (m, 2 H), 3.12-3.19 (m, 1H), 2.68 (s, 3 H), 1.07 (s, 3H), 1.01 (s, 3H).

Example 416

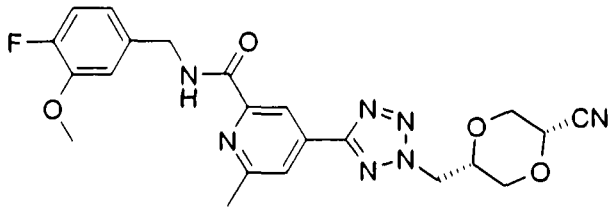
***rac-N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-carbamoyl-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Formamide (200 mg) was added to a solution of *rac*-(2*S**,5*S**)-methyl 5-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as described in Example 413) (123 mg, 0.3 mmol) in anhydrous tetrahydrofuran (1.5 mL) at reflux temperature. A solution of sodium methoxide (25% in methanol, 200 mg) was added and the mixture was stirred at reflux for 1.5 hours. The reaction mixture was purified by reverse phase preparative HPLC (water/ acetonitrile). Fractions containing the product were passed through a carbonate resin column and the filtrate was concentrated. The residue was slurried and decanted from ether several times and then dried in a vacuum desiccator to afford the title compound as a white solid (78 mg). MS (ES+) *m/z* 486 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.0 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.10-7.24 (m, 2 H), 6.91 (br. S., 1 H), 4.85-4.99 (m, 2 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.20 (m, 3 H), 3.90-3.99 (m, 1 H), 3.82 (s, 3 H), 3.45-3-60 (m, 2 H), 2.68 (s, 3 H).

Example 417

***rac-N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-cyano-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

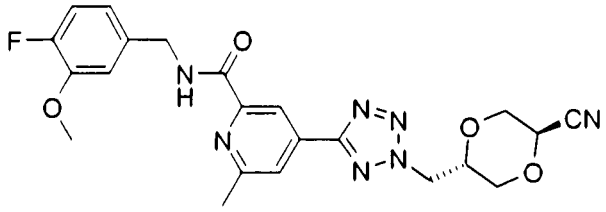


Polymer supported triphenylphosphine (Argonaut; 2.15 mmol/g, 200 mg) was added to *rac-N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-carbamoyl-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (Example 416) (65.2 mg, 0.13 mmol) in a mixture of carbon tetrachloride (0.25 mL) and dichloroethane (2.25 mL) and the mixture was heated at 80 °C for 3 hours. The reaction mixture was filtered and the resin was washed with dichloroethane. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC. Fractions containing the first eluting isomer were passed through a carbonate resin column and were concentrated. The product was slurried and decanted several times from ether and the solid was dried in a vacuum desiccator to afford the title compound as a white solid (23 mg). MS (ES+) *m/z* 468 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.31 (t, *J*=6.3 Hz, 1 H), 8.44 (s, 1 H), 8.11 (d, *J*=1.0 Hz, 1 H), 7.19 (dd, *J*=9.1, 2.5 Hz, 1 H), 7.15 (dd, *J*=11.7, 8.4 Hz, 1 H), 6.87 - 6.94 (m, 1 H), 5.04 (d, *J*=2.7 Hz, 1 H), 4.99 (br. s., 1 H), 4.97 (d, *J*=4.1 Hz,

1 H), 4.51 (d, *J*=6.3 Hz, 2 H), 4.23 - 4.31 (m, 1 H), 4.08 (dd, *J*=11.9, 2.6 Hz, 1 H), 3.95 (d, *J*=12.5 Hz, 1 H), 3.83 (s, 3 H), 3.71 - 3.82 (m, 2 H), 2.69 (s, 3 H).

Example 418

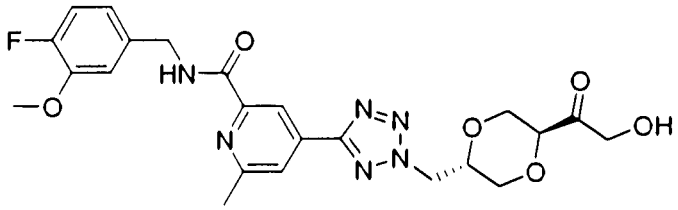
***rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-cyano-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Isolation of the second eluting isomer by reverse phase preparative HPLC from the reaction mixture described in Example 417 afforded the title compound as a white solid (18 mg). MS (ES+) *m/z* 468 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=6.0 Hz, 1 H), 8.41 (s, 1 H), 8.06 (s, 1 H), 7.87 (s, 1 H), 7.16 (d, *J*=8.1 Hz, 1 H), 7.11 (dd, *J*=11.5, 8.2 Hz, 1 H), 6.85 - 6.91 (m, 1 H), 4.74 - 5.00 (m, 2 H), 4.48 (d, *J*=6.2 Hz, 2 H), 4.05 - 4.17 (m, 2 H), 4.02 (d, *J*=8.1 Hz, 1 H), 3.89 (dd, *J*=11.5, 2.7 Hz, 1 H), 3.80 (s, 3 H), 3.62 - 3.72 (m, 1 H), 2.65 (s, 3 H).

Example 419

***rac*-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*S**)-5-(2-hydroxyacetyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

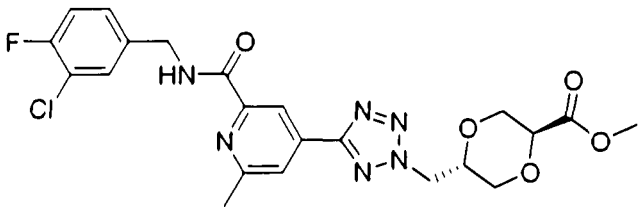


Oxalyl chloride (10 mL) was added to a stirred solution of *rac*-(2*S**,5*S**)-5-((5-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid (prepared as described in Example 414) (820 mg, 1.69 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 18 hours and then concentrated. The residue was repeatedly taken up in dichloromethane and concentrated to remove excess oxalyl chloride. The resulting residue was then taken up in dioxane (5 mL) and treated with tris(trimethylsiloxy)ethylene (5.0 g, 17.0 mmol). The mixture was heated to 95°C for 18 hours. Additional tris(trimethylsiloxy)ethylene (5.0 g, 17.0 mmol) was added and heating at 95°C was continued for 1 week. The mixture was treated with several drops of 3 N hydrochloric acid until gas evolution stopped. The reaction mixture was purified by reverse phase preparative HPLC. Fractions containing desired product were combined and concentrated. The residue was dissolved in methanol and passed through a carbonate cartridge. The filtrate was concentrated to afford the title compound as a solid (29 mg, 3%). MS (ES+) *m/z* 501 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.66 (s, 3 H), 3.43 - 3.58 (m, 2 H), 3.63 (s, 2 H), 3.80 (s, 3 H), 3.90 - 4.00 (m, 1 H), 4.02 - 4.19 (m, 2 H), 4.19 - 4.27 (m, 1

H), 4.48 (d, *J*=5.86 Hz, 2 H), 4.79 - 4.99 (m, 3 H), 6.83 - 6.94 (m, 1 H), 7.06 - 7.20 (m, 2 H), 8.06 (br. s., 1 H), 8.41 (br. s., 1 H), 9.16 - 9.26 (m, 1 H).

Example 420

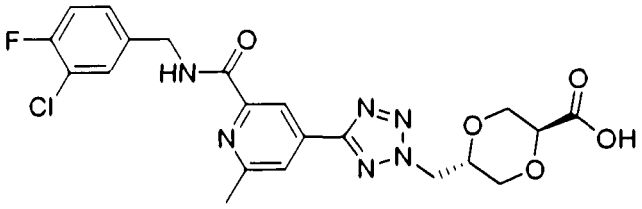
***rac*-(2*S**,5*S**)-Methyl 5-((5-(2-((3-chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate**



rac-(2*S**,5*R**)-Methyl 5-((tosyloxy)methyl)-1,4-dioxane-2-carboxylate (prepared as described in step 1 of the synthesis of *rac*-(2*S**,5*S**)-methyl 5-((5-(6-((3-methoxybenzyl)carbamoyl)-2-methylpyrimidin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate, Example 85) (83 mg, 0.25 mmol) was added to a mixture of *N*-(3-chloro-4-fluorobenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 1 of the synthesis of *N*-(3-chloro-4-fluorobenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 194) (75 mg, 0.22 mmol) and triethylamine (109 mg, 1.0 mmol) in anhydrous *N*,*N*-dimethylacetamide (0.3 mL). The mixture was stirred at 85°C in a capped vial overnight and then was purified by reverse phase preparative HPLC (water/acetonitrile) to afford the title compound as a white solid (99 mg).

Example 421

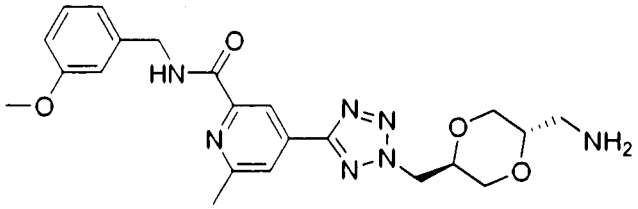
***rac*-(2*S**,5*S**)-5-((5-(2-((3-Chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylic acid**



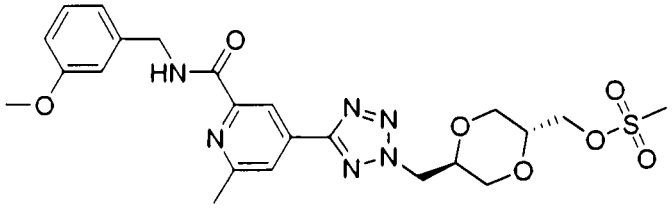
Sodium hydroxide (3 pellets) was added to *rac*-(2*S**,5*S**)-methyl 5-((5-(2-((3-chloro-4-fluorobenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxane-2-carboxylate (prepared as described in Example 420) (99 mg, 0.2 mmol) in a mixture of tetrahydrofuran/water (0.8 mL, 1/1) and the mixture was stirred at room temperature overnight. The reaction mixture was acidified with trifluoroacetic acid and purified by reverse-phase preparative HPLC (water/acetonitrile). The resulting product was slurried and decanted from ether several times and then dried in a vacuum desiccator to afford the title compound as a white solid (68 mg). MS (ES+) *m/z* 491 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.36 (t, *J*=6.0 Hz, 1 H), 8.42 (s, 1 H), 8.09 (s, 1 H), 7.55-7.6 (m, 1 H), 7.35-7.45 (m, 2 H), 4.85-4.99 (m, 2 H), 4.52 (d, *J*=6.2 Hz, 2 H), 4.05-4.20 (m, 3 H), 3.90-3.99 (m, 1 H), 3.45-3-60 (m, 2 H), 2.68 (s, 3 H).

Example 422

***rac-N*-(3-Methoxybenzyl)-4-(2-(((2*R**,5*S**)-5-(aminomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

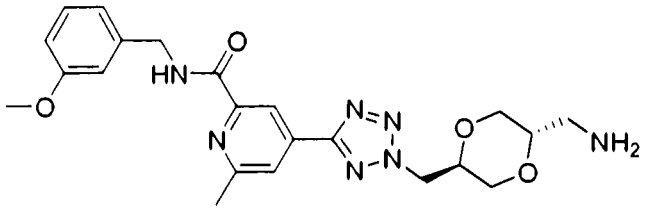


Step 1: Preparation of *rac*-((2*R**,5*R**)-5-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxan-2-yl)methyl methanesulfonate



Methane sulfonyl chloride (172 mg, 1.5 mmol) was added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 403) (620 mg, 1.36 mmol) in anhydrous pyridine (2 ml) at 0 °C. The mixture was allowed to stir at room temperature overnight. The reaction mixture was cooled to 0 °C, diluted with water, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated to afford the title compound (546 mg).

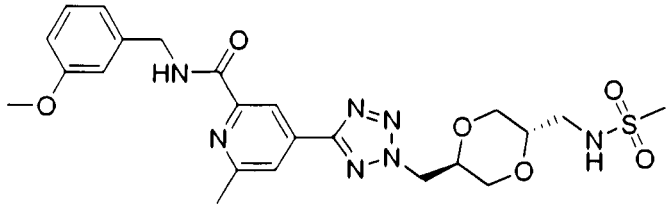
Step 2: Preparation of *rac-N*-(3-methoxybenzyl)-4-(2-(((2*R**,5*S**)-5-(aminomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



Concentrated ammonium hydroxide (50 mg, 1.40 mmol) was added to a solution of *rac*-((2*R**,5*R**)-5-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)-1,4-dioxan-2-yl)methyl methanesulfonate (140 mg, 0.263 mmol) in tetrahydrofuran (5 mL) and the mixture was heated to 100 °C overnight. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound as a white solid (25 mg, 16%). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.690 min., *m/z* 568 (M+H). ^1H NMR (400 MHz, methanol-d_4) δ ppm 2.65 - 2.69 (m, 2 H), 2.78 - 2.90 (m, 2 H), 2.94 - 3.10 (m, 2 H), 3.32 - 3.46 (m, 1 H), 3.55 - 3.68 (m, 1 H), 3.74 - 3.77 (m, 3 H), 3.78 - 3.84 (m, 1 H), 4.07 - 4.14 (m, 1 H), 4.17 - 4.27 (m, 1 H), 4.56 - 4.63 (m, 2 H), 6.81 (dd, *J*=7.79, 2.15 Hz, 1 H), 6.77 - 6.83 (m, 1 H), 6.90 - 6.96 (m, 2 H), 7.22 (t, *J*=8.19 Hz, 1 H), 8.09 (s, 1 H), 8.56 (s, 1 H).

Example 423

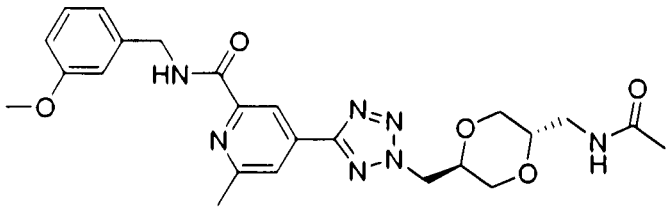
***rac-N*-(3-Methoxybenzyl)-6-methyl-4-(2-(((2*R**,5*S**)-5-(methylsulfonamidomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



Diisopropylethylamine (157 mg, 1.21 mmol) was added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((2*R**,5*S**)-5-(aminomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 422) (55 mg, 0.12 mmol) in *N,N*-dimethylformamide (5.0 mL). After 20 minutes, methanesulfonyl chloride (69.5 mg, 0.606 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated, and the residue was purified by reverse phase preparative HPLC to afford the title compound as a solid (36.4 mg, 46%). LCMS (5%-95% CH_3CN/H_2O, 5 min.) 4.923 min., *m/z* 532 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.66 (s, 3 H), 2.87 (s, 3 H), 2.94 (t, *J*=5.86 Hz, 3 H), 3.46 (d, *J*=10.98 Hz, 4 H), 3.42 (br. s., 1 H), 3.71 (s, 3 H), 3.76 (d, *J*=11.71 Hz, 3 H), 4.49 (d, *J*=6.59 Hz, 4 H), 4.78 - 4.94 (m, 5 H).

Example 424

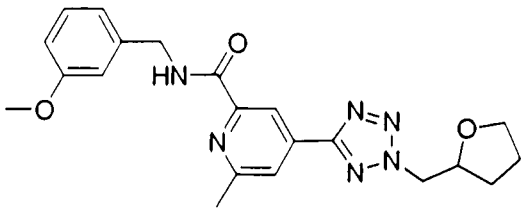
***rac-N*-(3-Methoxybenzyl)-4-(2-(((2*R**,5*S**)-5-(acetamidomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



Diisopropylethylamine (0.45 mL, 0.97 mmol) was added to a solution of *rac-N*-(3-methoxybenzyl)-4-(2-(((2*R**,5*S**)-5-(aminomethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide (prepared as described in Example 422) (55 mg, 0.12 mmol) in *N,N*-dimethylformamide (5.0 mL). After 20 minutes, acetic anhydride (0.34 mL, 0.364 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated, and the residue was purified by reverse phase preparative HPLC to afford the title compound as a solid (36.7 mg, 50%). LC/MS (5%-95% CH_3CN/H_2O, 5 min.) 3.17 min., *m/z* 496 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.78 (s, 3 H), 2.49 (s, 1 H), 2.67 (s, 1 H), 2.97 - 3.08 (m, 1 H), 3.38 - 3.51 (m, 3 H), 3.65 - 3.75 (m, 4 H), 3.92 - 4.02 (m, 2 H), 4.02 - 4.09 (m, 2 H), 4.44 - 4.53 (m, 3 H), 4.75 - 4.95 (m, 4 H), 6.76 - 6.82 (m, 1 H), 6.85 - 6.93 (m, 1 H), 7.16 - 7.26 (m, 1 H), 7.78 - 7.89 (m, 1 H), 8.05 (s, 1 H), 8.40 (s, 1 H), 9.12 - 9.25 (m, 1 H).

Example 425

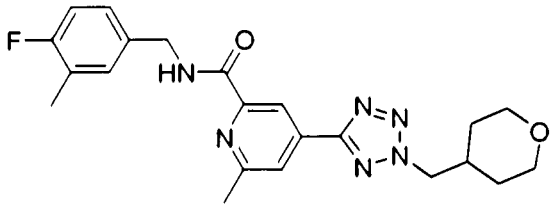
***N*-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydrofuran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide**



Di-*tert*-butylazodicarboxylate (74.0 mg, 0.320 mmol) was added to a cooled (ice bath) mixture of (tetrahydrofuran-2-yl)methanol (32.68 mg, 0.320 mmol), N-(3-methoxybenzyl)-6-methyl-4-(2H-tetrazol-5-yl)picolinamide (52.0 mg, 0.160 mmol) (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153), and triphenylphosphine resin (186.0 mg, 0.400 mmol, 2.15 mmol/g loading) in anhydrous tetrahydrofuran (3 mL). The mixture was allowed to warm to room temperature and agitated overnight. Trifluoroacetic acid (2 mL) was added and the mixture was agitated for 1 hour. The reaction mixture was filtered and the resin was washed with trifluoroacetic acid (1 mL). The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC (5%-95% CH_3CN/H_2O, 8 min.) to afford the title compound as a solid (30.8 mg, 47%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.198 min., *m/z* 409 (M+H).

Example 426

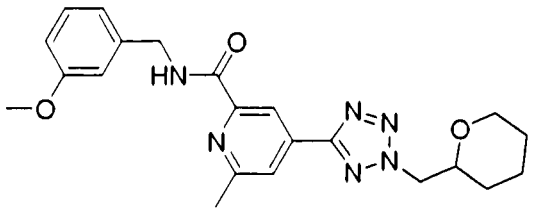
N-(4-Fluoro-3-methylbenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-4-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



4-(Bromomethyl)-tetrahydro-2H-pyran (90 mg, 0.5 mmol) was added to a mixture of *N*-(4-fluoro-3-methylbenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as describe in step 1 of the synthesis of *N*-(4-fluoro-3-methylbenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 185) (150 mg, 0.46 mmol) and triethylamine (46 mg, 0.46 mmol) in anhydrous acetonitrile (2 mL). The mixture was stirred at reflux temperature in a capped vial for two days and then was purified by reverse phase preparative HPLC (water/acetonitrile). Fractions containing the product were passed through a carbonate resin column and the filtrate was concentrated. The residue was slurried with ether, decanted, and dried in a vacuum desiccator to afford the title compound as a white solid (135 mg). MS (ES+) *m/z* 425 (M+H).

Example 427

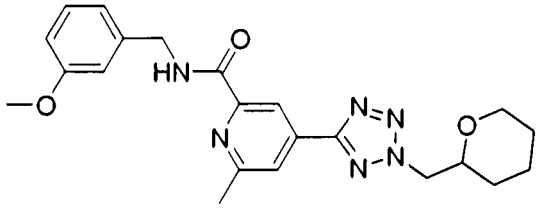
rac-N-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



To a vial containing tetrahydropyran-2-methanol (0.348 mL, 3.08 mmol), a solution of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (500.0 mg, 1.54 mmol) in anhydrous tetrahydrofuran (25 mL) and triphenylphosphine resin (1.791 g, 3.85 mmol, 2.15 mmol/g loading) was added. The reaction mixture was chilled in an ice bath, and di-tert-butylazodicarboxylate (709.0 mg, 3.08 mmol) was added. The ice bath was removed and the reaction mixture was agitated (orbital) overnight at room temperature. Volatiles were removed under a nitrogen stream. The residue was purified by silica gel chromatography to afford the title compound as a solid (350 mg, 54%). LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN,1.5 min.): 3.506 min., *m/z* 423 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (m, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.23 - 7.19 (m, 1 H), 6.89 - 6.87 (m, 2 H), 6.80 - 6.77 (m, 1 H), 4.79 - 4.74 (m, 2 H), 4.48 (d, *J*=6.0 Hz, 2 H), 3.93 - 3.75 (m), 3.70 (s, 3 H), 2.65 (s, 3 H), 1.80 - 1.25 (m).

Example 428

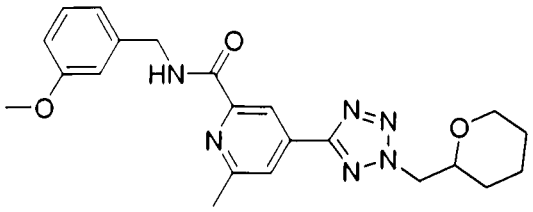
(-)-*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



rac-*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide was resolved by supercritical fluid chromatography (Chiralcel OD-H, 30 x 250 mm, 25/75 ethanol/CO_2, 70 mL/min) to afford the title compound as an oil (0.25 g). Chiralcel OD-H analytical column (4.6 x 250 mm; 20/80, ethanol/CO_2), 8.06 min, > 99% ee; $[\alpha]_D^{21°C}$ = 22.7° (c = 8.3, DMF).

Example 429

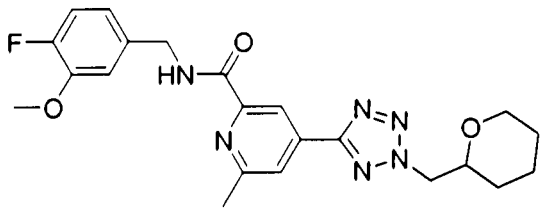
(+)-*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



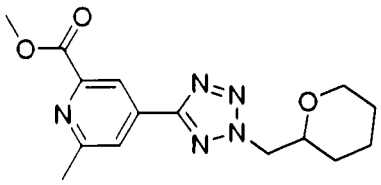
rac-N-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide was resolved by supercritical fluid chromatography (Chiralcel OD-H, 30 x 250 mm, 25/75 ethanol/CO_2, 70 mL/min) to afford the title compound as an oil (0.26 g). Chiralcel OD-H analytical column (4.6 x 250 mm; 20/80, ethanol/CO_2), 9.99 min, > 99% ee; $[\alpha]_D^{21°C}$ = 19.0°.(c = 9.8, DMF).

Example 430

rac-*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide

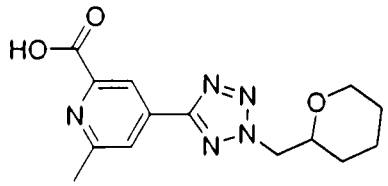


Step 1: Preparation of methyl 6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinate



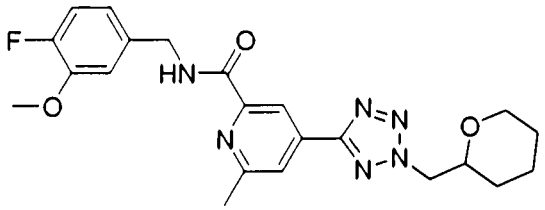
Methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (0.50 g, 2.0 mmol), tetrahydropyran-2- methanol (0.27 g, 2.28 mmol), and polymer supported-triphenylphosphine (2.65 g, 5.70 mmol) were suspended in tetrahydrofuran (100 mL). The mixture was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (1.05 g, 4.56 mmol) was added. The reaction was allowed to warm to room temperature and was stirred for 15 hours. The mixture was filtered through a Celite™ pad and washed with tetrahydrofuran (15 mL). The filtrate was concentrated and purified by silica gel column chromatography (0-50 % ethyl acetate/hexanes) to afford the title compound as an oil (0.58 g, 81%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 4.88 min, *m/z* 318 (M+H).

Step 2: Preparation of 6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinic acid



6-Methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinate (0.54 g, 1.84 mmol) was dissolved in tetrahydrofuran (5 mL) and then treated with an aqueous sodium hydroxide solution (2.5 N). The mixture was stirred at ambient temperature for 2 hours and then the tetrahydrofuran was removed in a stream of nitrogen. The aqueous residue was acidified to pH 3 with concentrated hydrochloric acid and extracted with ethyl acetate (2 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to afford the title compound (0.48 g, 86%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 3.88 min, *m/z* 304 (M+H).

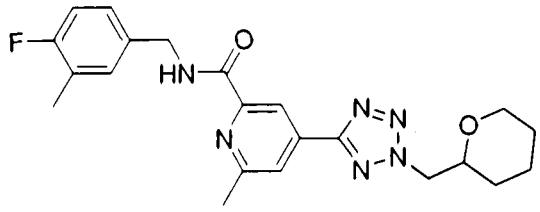
Step 3: Preparation of *rac-N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



1-Hydroxybenzatriazole (22 mg, 0.16 mmol) was added to a solution of 6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinic acid (0.035g, 0.12 mmol) in *N,N*-dimethylformamide (0.5 mL). After being stirred for 5 min, *N*-methylmorpholine (0.051 mL, 0.46 mmol) was then added followed by a solution of 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (18 mg, 0.12 mmol) in *N,N*-dimethylformamide (0.5 mL). 1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (31 mg, 0.16 mmol) was then added. The mixture was stirred at room temperature for 18 hours and then purified by reverse phase preparative HPLC to afford the title compound as an oil (6.5 mg, 13%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, *J*=6.2 Hz, 1 H), 8.40 (s, 1 H), 8.06 (s, 1 H), 7.21 - 7.06 (m, 2 H), 6.89 (s, 1 H), 4.72 - 4.86 (m, 2 H), 4.48 (d, *J*=5.9 Hz, 2 H), 3.92 (dd, *J*=11.0, 5.1 Hz, 1 H), 3.84 - 3.74 (m, 3 H), 2.66 (s, 3 H), 1.80 (d, *J*=12.5 Hz, 2 H), 1.71 (d, *J*=11.7 Hz, 2 H), 1.58 - 1.16 (m, 4 H).

Example 431

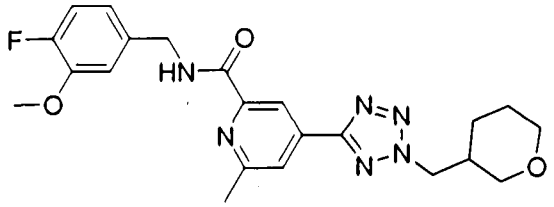
rac-N-(4-Fluoro-3-methylbenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



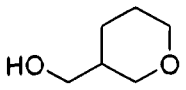
1-Hydroxybenzatriazole (22 mg, 0.16 mmol) was added to a solution of 6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinic acid (prepared as described in step 2 of the synthesis of *rac*-*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide, Example 430) (0.035g, 0.12 mmol) in *N*,*N*-dimethylformamide (0.5 mL). After being stirred for 5 min, *N*-methylmorpholine (0.051 mL, 0.46 mmol) was then added followed by a solution of (4-fluoro-3-methylphenyl)methanamine (16 mg, 0.12 mmol) in *N*,*N*-dimethylformamide (0.5 mL). 1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (31 mg, 0.16 mmol) was then added. The mixture was stirred at room temperature for 18 hours and then purified by reverse phase preparative HPLC to afford the title compound as an oil (5.1 mg, 10%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.2 Hz, 1 H), 8.40 (s, 1 H), 8.06 (s, 1 H), 7.20 (t, *J*=8.1 Hz, 1 H), 6.87 (s, 2 H), 6.77 (d, *J*=8.8 Hz, 1 H), 4.68 - 4.90 (m, 2 H), 4.48 (d, *J*=6.6 Hz, 2 H), 3.86 - 4.06 (m, 4 H), 3.78 (d, *J*=11.0 Hz, 1 H), 2.65 (s, 3 H), 1.75 (dd, *J*=34.8, 12.8 Hz, 2 H), 1.13 - 1.58 (m, 4 H).

Example 432

rac-*N*-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide

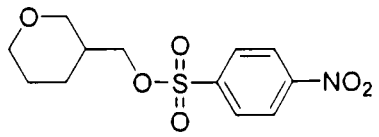


Step 1: Preparation of *rac*-(tetrahydro-2*H*-pyran-3-yl)methanol



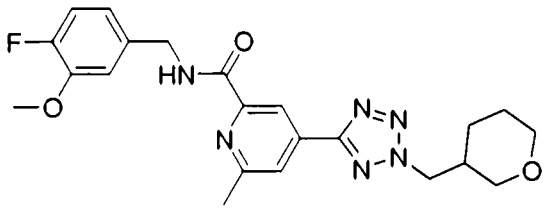
Tetrahydro-2*H*-pyran-3-carbaldehyde (0.40 g, 3.5 mmol) was dissolved in anhydrous methanol (7 mL) and cooled to -10 °C. Sodium borohydride (0.53 g, 14 mmol) was added in three portions. The reaction was stirred 1 hour at 0 °C and was then quenched with a saturated aqueous solution of ammonium chloride (5 mL). The mixture was filtered and the filtrate was concentrated to aqueous in vacuo without heat. The residue was then diluted with water (5 mL) and ethyl acetate (15 mL), and the mixture was again filtered. The filtrate was transferred to a separatory funnel and the phases separated. The aqueous layer was re-extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with water (4 x 10 mL) followed by brine (10 mL), dried over sodium sulfate, and concentrated at 30 °C under vacuum to afford the title compound as an oil (0.31 g, 76%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 0.85 min, *m/z* 117 (M+H).

Step 2: Preparation of *rac*-(tetrahydro-2*H*-pyran-3-yl)methyl 4-nitrobenzenesulfonate



4-Nitrobenzene-1-sulfonyl chloride (0.62 g, 2.8 mmol) and pyridine (253 mg, 3.20 mmol) were added to a solution of *rac*-(tetrahydro-2*H*-pyran-3-yl)methanol (0.31 g, 2.67 mmol) in dichloromethane (5 mL), and the mixture was stirred at room temperature for 15 hours. The reaction mixture was diluted with dichloromethane (10 mL) and washed with water (2 x 10 mL), brine (10 mL), dried over sodium sulfate, and concentrating. The residue was purified on silica gel column chromatography (0-50% ethyl acetate/heptane) to afford the title compound as an oil (0.65 g, 81%). LC/MS (5-100% CH_3CN/H_2O, 5 min) 2.56 min, *m/z* 302 (M+H).

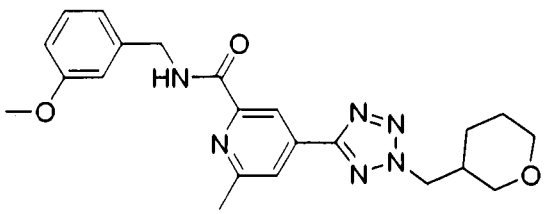
Step 3: Preparation of *rac*-*N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide



A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (79 mg, 0.23 mmol), *rac*-(tetrahydro-2*H*-pyran-3-yl)methyl 4-nitrobenzenesulfonate (77 mg, 0.25 mmol), and triethylamine (0.40 mL) in *N*,*N*-dimethylacetamide (0.1 mL) was stirred at 85 °C for 15 hours. The reaction mixture was purified by reverse phase preparative HPLC to afford the title compound as a beige solid (68 mg, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=6.2 Hz, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 7.12 (d, *J*=8.4 Hz, 1 H), 7.16 (dd, *J*=13.4, 8.2 Hz, 2 H), 6.91 (d, *J*=4.0 Hz, 1 H), 4.74 (dd, *J*=12.6, 7.1 Hz, 2 H), 4.51 (d, *J*=6.2 Hz, 2 H), 3.82 (s, 3 H), 3.72 (t, *J*=12.4 Hz, 2 H), 3.39 (t, *J*=9.0 Hz, 1 H), 2.68 (s, 3 H), 2.28 (br. s., 1 H), 1.74 (d, *J*=12.4 Hz, 1 H), 1.63 (d, *J*=4.0 Hz, 1 H), 1.49 (dd, *J*=9.5, 4.0 Hz, 1 H), 1.35 (d, *J*=9.5 Hz, 1 H).

Example 433

rac-*N*-(3-Methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide

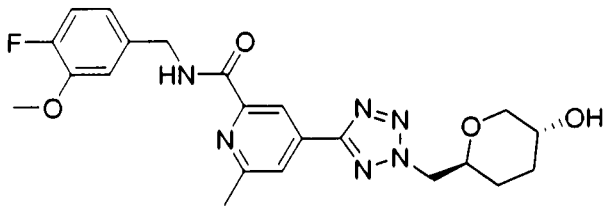


A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-

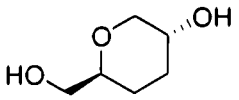
2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (79 mg, 0.23 mmol), *rac*-(tetrahydro-2*H*-pyran-3-yl)methyl 4-nitrobenzenesulfonate (prepared as described in step 2 of the synthesis of *rac*-*N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2-((tetrahydro-2*H*-pyran-3-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide, Example 432) (77 mg, 0.25 mmol), and triethylamine (0.40 mL) in *N*,*N*-dimethylacetamide (0.1 mL) was stirred at 85 °C for 15 hours. The reaction mixture was purified by reverse phase preparative HPLC to afford the title compound as a beige solid (62 mg, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (br. s., 1 H), 8.08 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 (br. s., 2 H), 6.82 (d, *J*=7.7 Hz, 1 H), 4.75 (dq, *J*=13.0, 6.8 Hz, 2 H), 4.51 (d, *J*=6.2 Hz, 2 H), 3.73 (s, 5 H), 3.68 (br. s., 1 H), 3.41 (br. s., 1 H), 3.37 (d, *J*=2.2 Hz, 1 H), 2.68 (s, 3 H), 2.28 (br. s., 1 H), 1.74 (br. s., 1 H), 1.62 (br. s., 1 H), 1.50 (d, *J*=8.8 Hz, 1 H), 1.35 (d, *J*=9.5 Hz, 1 H).

Example 434

rac-*N*-(4-Fluoro-3-methoxybenzyl)-4-(2-(((2*S,5*R**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

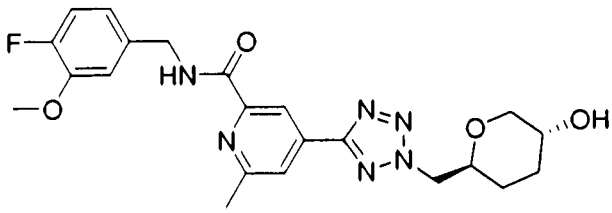


Step 1: Preparation of *rac*-(3*R**,6*S**)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3-ol



Tetrabutylammonium fluoride (23.0 g, 88.0 mmol) was added to a suspension of *rac*-(3*R**,6*S**)-6-((*tert*-butyldiphenylsilyloxy)methyl)-tetrahydro-2*H*-pyran-3-ol (*Bioorg. Med. Chem.* **2006**, *14*, 3953–3966) (16.3 g, 44.0 mmol) in tetrahydrofuran (700 mL). The mixture was allowed to stir at room temperature for 6 hours and was then concentrated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 2/1; ethyl acetate/ethanol, 40/1). The crude product was further purified by silica gel chromatography (ethyl acetate) to afford a waxy solid which was repeatedly triturated with chloroform and then filtered to provide the title compound as a white solid (2.44 g, 42%).

Step 2: Preparation of *rac*-*N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((2*S**,5*R**)-5-hydroxy-tetrahydro-2*H*-pyran-2-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide

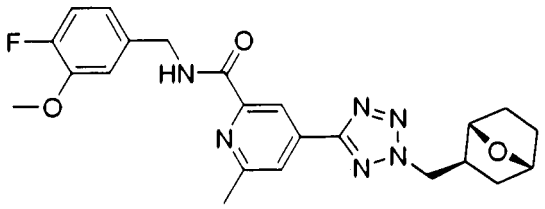


A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-

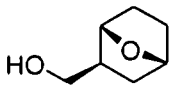
aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (1.50 g, 3.96 mmol), *rac*-(3*R**,6*S**)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3-ol (1.05 g, 7.92 mmol), and polymer supported triphenylphosphine resin (3.68 g, 7.92 mmol) in tetrahydrofuran (20 mL) was cooled in an ice bath. Di-*tert*-butyl-azodicarboxylate (1.82 g, 7.92 mmol) was added and the resulting mixture was stirred in the ice bath for 30 min. The ice bath was removed and the mixture stirred at room temperature for 18 hours. Trifluoroacetic acid (5 mL) was added and the reaction mixture was filtered. The resin washed with tetrahydrofuran, methanol, and acetonitrile. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound as a white solid (251 mg, 11%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 - 1.47 (m, 2 H), 1.78 - 1.88 (m, 1 H), 1.93 - 2.04 (m, 1 H), 2.68 (s, 3 H), 2.90 (t, *J*=10.25 Hz, 1 H), 3.37 - 3.47 (m, 1 H), 3.68 - 3.77 (m, 1 H), 3.78 - 3.92 (m, 4 H), 4.51 (d, *J*=6.59 Hz, 2 H), 4.74 - 4.93 (m, 3 H), 6.85 - 6.95 (m, 1 H), 7.08 - 7.24 (m, 2 H), 8.08 (s, 1 H), 8.43 (s, 1 H), 9.24 (t, *J*=6.22 Hz, 1 H).

Example 435

N-(4-Fluoro-3-methoxybenzyl)-4-(2-((1*S,2*S**,4*R**)-7-oxa-bicyclo[2.2.1]heptan-2-ylmethyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

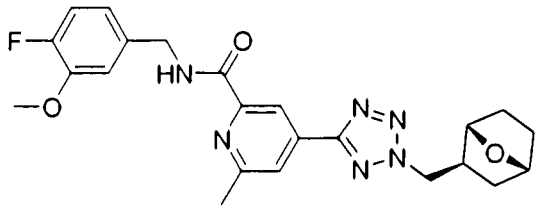


Step 1: Preparation of (1*S**,2*S**,4*R**)-7-oxa-bicyclo[2.2.1]heptan-2-ylmethanol



A mixture of (1*S**,2*R**,4*R**)-7-oxa-bicyclo[2.2.1]heptane-2-carboxylic acid (*J. Med. Chem.* **1971**, *14*, 698-702) (0.25 g, 1.8 mmol) and carbodiimidazole (0.29 g, 1.8 mmol) in tetrahydrofuran (5 mL) was stirred for 15 minutes. A solution of sodium borohydride (0.11 g, 2.8 mmol) in water (1 mL) was slowly added and the mixture was allowed to stir at room temperature for 15 hours. The reaction mixture was diluted with an aqueous 10% hydrochloric acid solution (2 mL) and brine (2 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over sodium sulfate and concentrated to afford the title compound as an oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.29 (br. s., 1 H), 2.94 - 3.13 (m, 2 H), 1.68 - 1.82 (m, 2 H), 1.40 - 1.60 (m, 4 H), 1.28 - 1.40 (m, 2 H), 0.89 - 1.01 (m, 1 H).

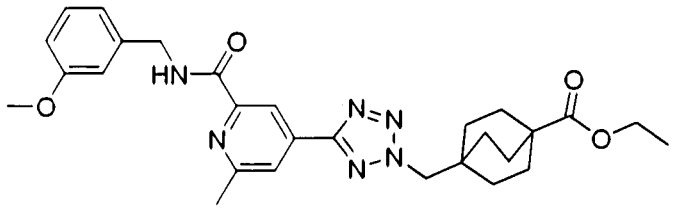
Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-((1*S**,2*S**,4*R**)-7-oxa-bicyclo[2.2.1]heptan-2-ylmethyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide



A mixture of (1*S**,2*S**,4*R**)-7-oxa-bicyclo[2.2.1]heptan-2-ylmethanol (0.13 g, 0.98 mmol), *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (0.31 g, 0.81 mmol), and polymer supported-triphenylphosphine (0.58 g, 1.22 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to 0°C in an ice bath for 15 minutes. Di-tert-butyl azodicarboxylate (0.23 g, 0.98 mmol) was added and the mixture was allowed to warm to room temperature and stir for 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by reverse phase preparative HPLC (5-95% acetonitrile/water) to afford the title compound as a beige oil (66 mg, 18%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.08 - 9.26 (m, 1 H), 8.40 (br. s., 1 H), 8.05 (br. s., 1 H), 7.05 - 7.21 (m, 2 H), 6.88 (br. s., 1 H), 4.64 (dd, *J*=13.18, 8.05 Hz, 1 H), 4.42 - 4.56 (m, 4 H), 4.33 (d, *J*=5.12 Hz, 1 H), 3.79 (s, 3 H), 3.22 (br. s., 1 H), 2.64 (s, 3 H), 1.63 (dd, *J*=11.35, 8.42 Hz, 1 H), 1.49 - 1.57 (m, 2 H), 1.38 - 1.48 (m, 2 H), 1.34 (d, *J*=13.18 Hz, 1 H).

Example 436

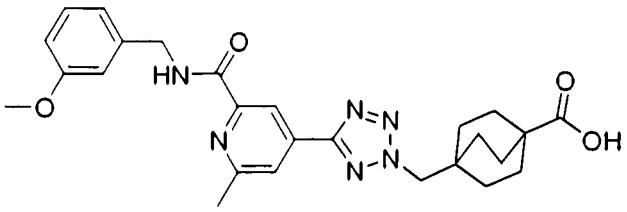
Ethyl 4-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)bicyclo[2.2.2]octane-1-carboxylate



A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (130 mg), ethyl 4-((tosyloxy)methyl)bicyclo[2.2.2]octane-1-carboxylate (*J. Amer. Chem. Soc.* **1965**, *87*, 2404) (147 mg), and diisopropylethylamine (0.090 mL) in dimethylsulfoxide (2.0 mL) was heated to 115 °C for 5 days. The reaction mixture was purified by reverse phase preparative HPLC (acetonitrile/water, 70/30 – 90/10). Fractions containing the product were concentrated and extracted with dichloromethane (3 x 8 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford the title compound (118 mg). MS (ES+) *m/z* 519 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.4 Hz, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.88 - 6.92 (m, 2 H), 6.80 (d, *J*=8.4 Hz, 1 H), 4.54 (s, 2 H), 4.49 (d, *J*=6.2 Hz, 2 H), 3.98 (q, *J*=7.0 Hz, 2 H), 3.71 (s, 3 H), 2.65 (s, 3 H), 1.63 - 1.71 (m, 6 H), 1.43 - 1.50 (m, 6 H), 1.11 (t, *J*=7.0 Hz, 3 H).

Example 437

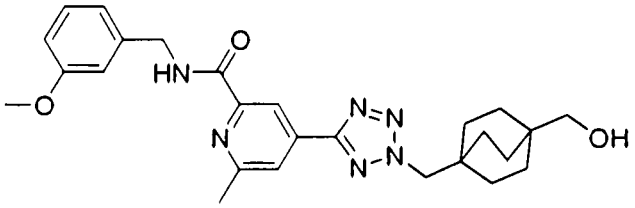
4-((5-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)bicyclo[2.2.2]octane-1-carboxylic acid



Water (0.5 mL) and lithium hydroxide-monohydrate (21.4 mg) was added to a solution of ethyl 4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)bicyclo[2.2.2]octane-1-carboxylate (prepared as described in Example 436) (75 mg) in tetrahydrofuran (1.0 mL). The mixture was heated at reflux for 3 days and then allowed to cool to room temperature. The reaction mixture was filtered and the pH was adjusted to 4 with 1N aqueous hydrochloric acid. The resulting slurry was filtered, washed with water, and dried to afford the title compound as a white solid (54 mg). MS (ES+) *m/z* 491 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.4 Hz, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.87 - 6.92 (m, 2 H), 6.80 (d, *J*=8.1 Hz, 1 H), 4.54 (s, 2 H), 4.49 (d, *J*=6.6 Hz, 2 H), 3.71 (s, 3 H), 2.65 (s, 3 H), 1.61 - 1.70 (m, 6 H), 1.41 - 1.50 (m, 6 H).

Example 438

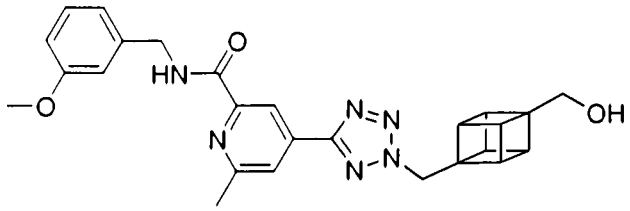
***N*-(3-Methoxybenzyl)-4-(2-((4-(hydroxymethyl)bicyclo[2.2.2]octan-1-yl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



A solution of 4-((5-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)bicyclo[2.2.2]octane-1-carboxylic acid (prepared as described in Example 437) (102 mg) in 2-methyltetrahydrofuran (5 mL) was cooled in an ice bath and a solution of lithium aluminum hydride (1 M in tetrahydrofuran, 0.30 mL) was added. After 5 minutes the reaction was quenched with water. The layers were separated and the aqueous layer was extracted with 2-methyltetrahydrofuran (2 x 3 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was purified by reverse phase preparative HPLC to afford the title compound (30.7 mg). MS (ES+) *m/z* 477 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.2 Hz, 1 H), 8.40 (s, 1 H), 8.05 (s, 1 H), 7.22 (t, *J*=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (dd, *J*=7.7, 1.5 Hz, 1 H), 4.47 - 4.53 (m, 4 H), 4.24 (t, *J*=5.5 Hz, 1 H), 3.71 (s, 3 H), 2.99 (d, *J*=5.1 Hz, 2 H), 2.65 (s, 3 H), 1.26 - 1.45 (m, 12 H).

Example 439

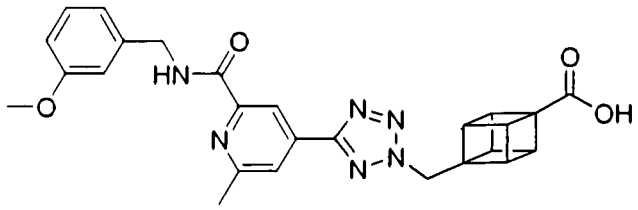
4-(2-((4-(Hydroxymethyl)pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]oct-1-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpyridine-2-carboxamide



A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (52 mg, 0.16 mmol), 1,4-bis(hydroxymethyl)cubane (*J. Amer. Chem. Soc.* **1991**, *113*, 7692) (52 mg, 0.32 mmol), and polymer supported triphenylphosphine (190 mg, 0.4 mmol) in anhydrous tetrahydrofuran (3 mL) was cooled in an ice bath and di-*tert*-butyl azodicarboxylate (74 mg, 0.32 mmol) was added. The mixture was placed in an ultrasonic bath for 10 min and then filtered. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound (14.6 mg). MS (ES+) *m/z* 471 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, *J*=6.4 Hz, 1 H), 8.38 (s, 1 H), 8.04 (s, 1 H), 7.2 (t, *J*= 8.1 Hz, 1 H), 6.88 (s, 2 H), 6.78 (d, *J*=8.1 Hz, 1 H), 5.01 (s, 2 H), 4.46 (d, *J*=6.2 Hz, 3 H), 3.79 - 3.74 (m, 3 H), 3.71 - 3.64 (m, 6 H), 3.46 (d, *J*=5.5 Hz, 2 H), 2.63 (s, 3 H).

Example 440

4-((5-(2-(((3-Methoxybenzyl)amino)carbonyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cubane-1-carboxylic acid

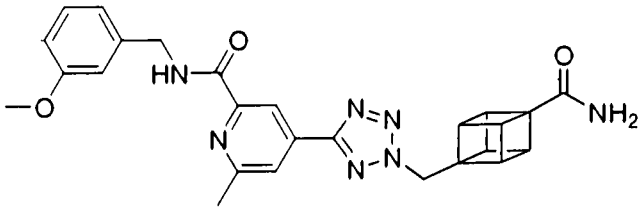


A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (155 mg), methyl 4-hydroxymethylcubanecarboxylate (136 mg), and polymer supported triphenylphosphine (453 mg) in anhydrous tetrahydrofuran (10 mL) was cooled in an ice bath and di-*tert*-butyl azodicarboxylate (165 mg) was added. The mixture was placed in an ultrasonic bath for 30 min and then filtered. The filtrate was acidified with trifluoroacetic acid (0.5 mL) and then concentrated. The residue was purified by reverse phase preparative HPLC (acetonitrile/water, 50/50 – 80/20). The fractions containing product were concentrated and extracted with methylene chloride (3 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the title compound as a white solid (146 mg). MS (ES+) *m/z* 485 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.26 (S, 1 H), 9.24 (t, *J*=6.4 Hz, 1 H), 8.39 (s, 1 H), 8.05 (d, *J*=1.3 Hz, 1 H), 7.21 (t, *J*=8.1 Hz, 1 H), 6.87 - 6.90 (m, 2 H),

6.79 (dd, *J*=8.1, 2.1 Hz, 1 H), 5.06 (s, 2 H), 4.47 (d, *J*=6.4 Hz, 2 H), 4.01 - 4.05 (m, 3 H), 3.88 - 3.92 (m, 3 H), 3.70 (s, 3 H), 2.65 (s, 3 H).

Example 441

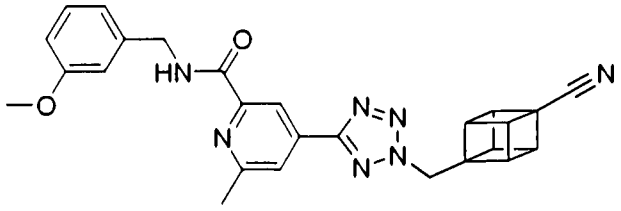
4-(2-((4-(Aminocarbonyl)pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]oct-1-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpyridine-2-carboxamide



4-((5-(2-(((3-Methoxybenzyl)amino)carbonyl)-6-methylpyridin-4-yl)-2*H*-tetrazol-2-yl)methyl)cubane-1-carboxylic acid (prepared as described in Example 440) (92 mg) was dissolved in anhydrous tetrahydrofuran (5 mL) under nitrogen and oxalyl chloride (0.100 mL) was added followed by *N*,*N*-dimethylformamide (one drop). The mixture was stirred at room temperature for 30 minutes and then concentrated. The residue was dissolved in anhydrous tetrahydrofuran (4.0 mL) and a solution of 7N ammonia in methanol (0.30 mL) was added in one portion. The mixture was diluted with water (5 mL), acidified with trifluoroacetic acid, and concentrated. The residue was purified by reverse phase preparative HPLC (acetonitrile/water, 40/60 – 65/35) to afford the title compound as a white solid (52 mg). MS (ES+) *m/z* 484 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=6.0 Hz, 1 H), 8.43 (s, 1 H), 8.07 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 7.17 (br. s., 1 H), 6.93 (br. s., 2 H), 6.87 (br. s., 1 H), 6.82 (d, *J*=6.2 Hz, 1 H), 5.07 (s, 2 H), 4.51 (d, *J*=6.2 Hz, 2 H), 4.00 - 4.05 (m, 3 H), 3.86 - 3.91 (m, 3 H), 3.73 (s, 3 H), 2.68 (s, 3 H).

Example 442

4-(2-((4-Cyanopentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]oct-1-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpyridine-2-carboxamide

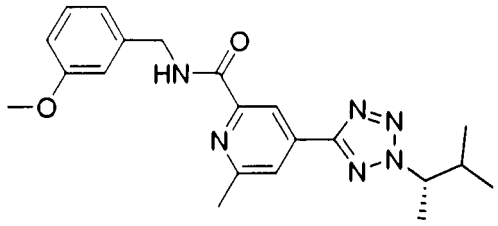


Phosphorus oxychloride (0.030 mL) was added to a solution of 4-(2-((4-(aminocarbonyl)-pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]oct-1-yl)methyl)-2*H*-tetrazol-5-yl)-*N*-(3-methoxybenzyl)-6-methylpyridine-2-carboxamide (prepared as described in Example 441) (32 mg) in DMF (0.8 mL). The mixture was stirred for 2 minutes and then a solution of 5% aqueous sodium bicarbonate (2 mL) was slowly added. The liquid was decanted and the solid was stirred with water (2 mL) and placed in an ultrasonic bath for 1 hour. The resulting slurry was filtered, washed with water, and dried to afford the title compound as a white solid (26 mg). MS (ES+) *m/z* 466 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (t, *J*=5.5 Hz, 1 H), 8.42 (s, 1 H), 8.06 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 (br. s., 2 H), 6.82 (d, *J*=8.4 Hz,

1 H), 5.09 (s, 2 H), 4.51 (d, *J*=6.2 Hz, 2 H), 4.25 - 4.29 (m, 3 H), 4.01 - 4.06 (m, 3 H), 3.73 (s, 3 H), 2.68 (s, 3 H).

Example 443

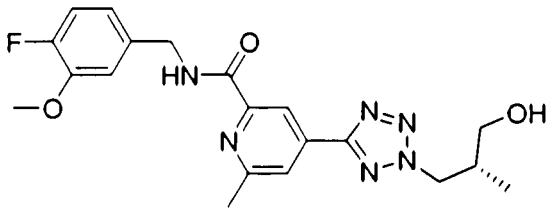
***N*-(3-Methoxybenzyl)-6-methyl-4-(2-((*S*)-3-methylbutan-2-yl)-2*H*-tetrazol-5-yl)picolinamide**



A mixture of *N*-(3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 5 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 153) (100 mg, 0.31 mmol), polymer supported triphenylphosphine (287 mg, 0.62 mmol), and (*R*)-(-)-3-methyl-2-butanol(54 mg, 0.62 mmol) in tetrahydrofuran (100 mL) was cooled to 0 °C and di-tert-butyl azodicarboxylate (142 mg, 0.62 mmol) was added. The mixture was allowed to warm to room temperature and stir for 18 hours. The reaction mixture was filtered and the resin washed with tetrahydrofuran (20 mL). The filtrate was concentrated. The crude product was purified by silica column chromatography (hexane/EtOAc, 8/1; 4/1). Fractions containing product were concentrated and further purified by reverse phase preparative HPLC (acetonitrile/water, 0.05% TFA, 15/85 - 85/15). Combined fractions were neutralized with 2.5 N NaOH solution and acetonitrile was removed in vacuo. The remaining aqueous solution was extracted with EtOAc (50 mL). The organic layer was dried over sodium sulfate and concentrated to afford the title compound as an oil (16 mg, 13%). MS (ES+) *m/z* 395 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (t, *J*=6.4 Hz, 1 H), 8.43 (d, *J*=0.9 Hz, 1 H), 8.09 (d, *J*=1.1 Hz, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.90 - 6.93 (m, 2 H), 6.82 (ddd, *J*=8.2, 2.5, 0.8 Hz, 1 H), 4.95 (qd, *J*=6.9, 6.8 Hz, 1 H), 4.51 (d, *J*=6.4 Hz, 2 H), 3.73 (s, 3 H), 2.68 (s, 3 H), 2.31 - 2.18 (m, 1 H), 1.62 (d, *J*=6.9 Hz, 3 H), 0.97 (d, *J*=6.9 Hz, 3 H), 0.78 (d, *J*=6.7 Hz, 3 H).

Example 444

***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-((*R*)-3-hydroxy-2-methylpropyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**

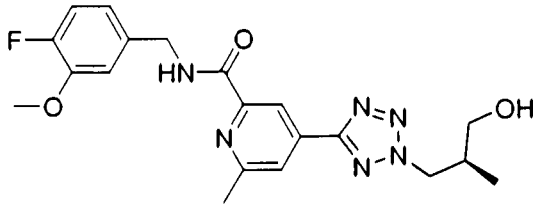


A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (45 mg, 0.13 mmol), (*S*)-(+)-3-bromo-2-methyl-1-propanol (33 mL, 0.20 mmol), and triethylamine (33 mL, 0.24 mmol) in

acetonitrile (3 mL) was stirred at 80 °C for 15 hours. The reaction mixture was concentrated and the residue was purified by reverse-phase preparative HPLC to afford the title compound as a beige solid (35 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 - 9.34 (m, 1 H), 8.45 (s, 1 H), 8.19 (s, 1 H), 8.05 (s, 1 H), 7.90 (s, 1 H), 7.06 - 7.21 (m, 2 H), 6.88 (d, J=7.3 Hz, 1 H), 4.59 (dd, J=14.3, 6.2 Hz, 1 H), 4.49 (d, J=5.9 Hz, 2 H), 4.31 (dd, J=13.9, 8.1 Hz, 1 H), 3.80 (s, 3 H), 3.32 (s, 1 H), 2.65 (d, J=3.7 Hz, 3 H), 2.02 - 2.22 (m, 1 H), 0.75 (d, J=6.6 Hz, 3 H).

Example 445

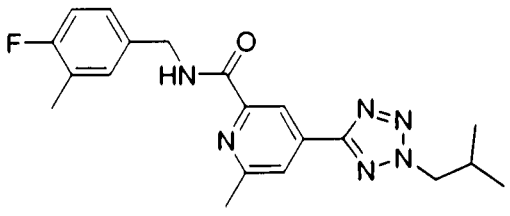
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-((*S*)-3-hydroxy-2-methylpropyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



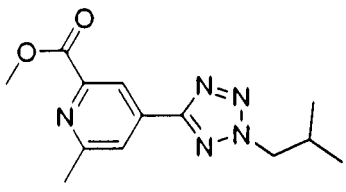
A mixture of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(2*H*-tetrazol-5-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 170) (45 mg, 0.13 mmol), (*R*)-(-)-3-bromo-2-methyl-1-propanol (33 mL, 0.20 mmol), and triethylamine (33 mL, 0.24 mmol) in acetonitrile (3 mL) was stirred at 80 °C for 15 hours. The reaction mixture was concentrated and the residue was purified by reverse-phase preparative HPLC to afford the title compound as a beige solid (38 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 - 9.33 (m, 1 H), 8.19 (s, 1 H), 7.90 (s, 1 H), 7.02 - 7.24 (m, 2 H), 6.89 (d, J=5.86 Hz, 1 H), 4.59 (dd, J=14.3, 6.2 Hz, 1 H), 4.48 (d, J=5.9 Hz, 2 H), 4.31 (dd, J=14.3, 7.7 Hz, 1 H), 3.80 (s, 3 H), 3.29 (s, 1 H), 2.62 - 2.74 (m, 3 H), 2.52 (s, 2 H), 2.11 (dd, J=13.5, 6.2 Hz, 1 H), 0.75 (d, J=6.6 Hz, 3 H).

Example 446

***N*-(4-Fluoro-3-methylbenzyl)-4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



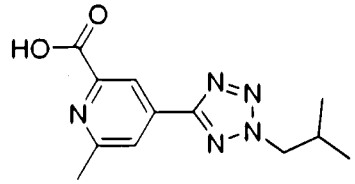
Step 1: preparation methyl 4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinate



A suspension of methyl 6-methyl-4-(2*H*-tetrazol-5-yl)picolinate (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(2-(((*trans*)-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)-6-

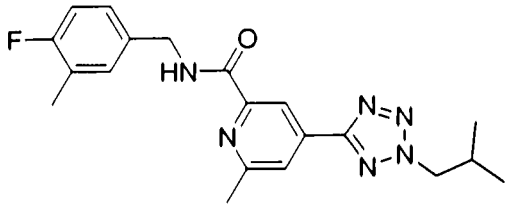
methylpicolinamide, Example 153) (1.00 g, 4.56 mmol), 2-methylpropan-1-ol (0.34 g, 4.6 mmol), and polymer supported-triphenylphosphine (3.04 g, 6.84 mmol) in anhydrous tetrahydrofuran (25 mL) was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (1.26 g, 5.47 mmol) was added. The mixture was allowed to warm to room temperature while stirring over 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica chromatography (0-50% ethyl acetate:/heptane) to afford the title compound as a beige oil.

Step 2: Preparation of 4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinic acid



A mixture of methyl 4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinate and an aqueous solution of sodium hydroxide (2.5N, 4.0 mL) in tetrahydrofuran (10 mL) was stirred for 2 hours at room temperature. Tetrahydrofuran was removed in vacuo and the aqueous residue was acidified to pH 6 with concentrated hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water (2 x 10 mL) followed by brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to afford the title compound (1.05 g, 88%). LC/MS (5-100% CH_3CN/H_2O, 8 min) 4.03 min, *m/z* 262 (M+H).

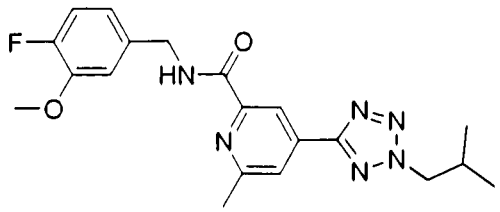
Step 3: Preparation of *N*-(4-fluoro-3-methylbenzyl)-4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinamide



A mixture of 4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (0.050 g, 0.19 mmol) and 1-hydroxybenzatriazole (31 mg, 0.23 mmol) in tetrahydrofuran (5 mL) was stirred for 5 min. (4-Fluoro-3-methylphenyl)methanamine (27 mg, 0.19 mmol) and polymer supported carbodiimide (0.23 g, 0.29 mmol) were then added. The mixture was stirred for 18 hours at room temperature and was then filtered. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound (23 mg, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.6 Hz, 1 H), 8.41 (s, 1 H), 8.05 (s, 1 H), 7.23 (d, *J*=7.3 Hz, 1 H), 7.12 - 7.20 (m, 1 H), 6.93 - 7.10 (m, 1 H), 4.61 (d, *J*=6.6 Hz, 2 H), 4.46 (d, *J*=5.9 Hz, 2 H), 2.65 (s, 3 H), 2.27 - 2.40 (m, 1 H), 2.19 (s, 3 H), 0.92 (d, *J*=6.6 Hz, 6 H).

Example 447

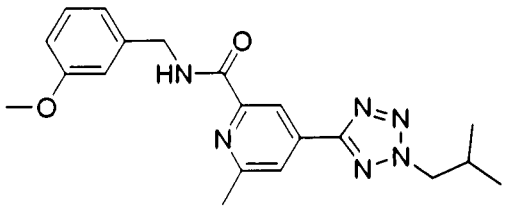
***N*-(4-Fluoro-3-methoxybenzyl)-4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinamide**



A mixture of 4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methylbenzyl)-4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 446) (0.050 g, 0.19 mmol) and 1-hydroxybenzatriazole (31 mg, 0.23 mmol) in tetrahydrofuran (5 mL) was stirred for 5 minutes. 4-Fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-yl)pyrimidine-4-carboxamide, Example 1) (31 mg, 0.19 mmol) and polymer supported carbodiimide (0.23 g, 0.29 mmol) were added. The mixture was stirred for 18 hours at room temperature and was then filtered. The filtrate was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound (18 mg, 24%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, *J*=6.22 Hz, 1 H), 8.41 (s, 1 H), 8.06 (s, 1 H), 7.05 - 7.21 (m, 2 H), 6.89 (d, *J*=2.9 Hz, 1 H), 4.61 (d, *J*=6.6 Hz, 2 H), 4.48 (d, *J*=5.9 Hz, 2 H), 3.80 (s, 3 H), 2.65 (s, 3 H), 2.19 - 2.40 (m, 1 H), 0.92 (d, *J*=7.3 Hz, 6 H).

Example 448

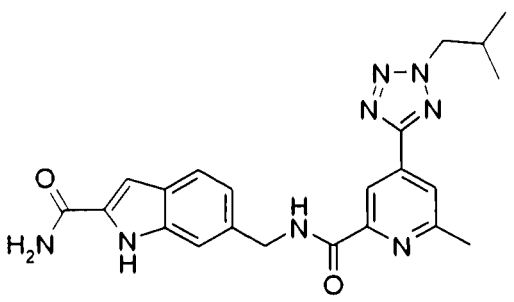
N-(3-Methoxybenzyl)-4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinamide



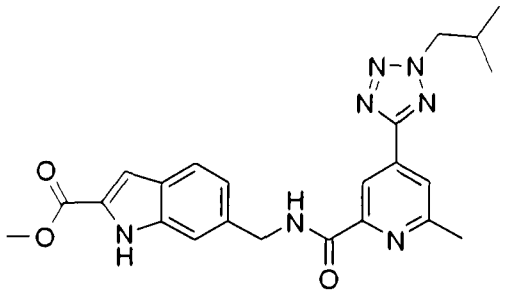
The title compound was prepared in a similar manner to *N*-(3-methoxybenzyl)-6-methyl-4-(2-((tetrahydrofuran-2-yl)methyl)-2*H*-tetrazol-5-yl)picolinamide (Example 425) by reaction with 2-methylpropan-1-ol and afforded 20.9 mg (34%) as a solid. LC/MS (5%-95% CH_3CN/H_2O, 4.5 min.; 95% CH_3CN, 1.5 min.): 3.638 min., *m/z* 381 (M+H).

Example 449

6-((4-(2-Isobutyl-2*H*-tetrazol-5-yl)-2-methylpicolinamido)methyl)-1*H*-indole-2-carboxamide

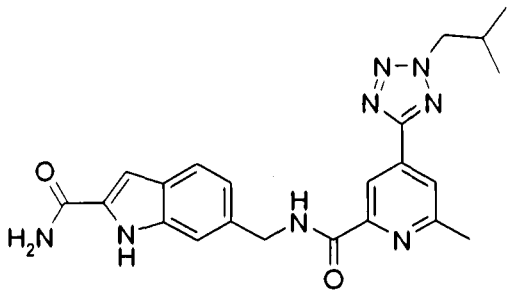


Step 1: Preparation of methyl 6-((4-(2-isobutyl-2*H*-tetrazol-5-yl)-2-methylpicolinamido)methyl)-1*H*-indole-2-carboxylate



A mixture of 4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinic acid (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methylbenzyl)-4-(2-isobutyl-2*H*-tetrazol-5-yl)-6-methylpicolinamide, Example 446) (0.090 g, 0.34 mmol) and 1-hydroxybenzatriazole (56 mg, 0.41 mmol) in *N*,*N*-dimethylacetamide (3 mL) was stirred for 5 minutes. Methyl 6-(aminomethyl)-1*H*-indole-2-carboxylate (71 mg, 0.34 mmol) was then added followed by triethylamine (0.106 mL, 0.758 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (99 mg, 0.52 mmol). The mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with water (3 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with water (2 x 5 mL) followed by brine (5 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica column chromatography (0-50% ethyl acetate/heptane) to afford the title compound (140 mg, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.25 (t, *J*=6.22 Hz, 1 H), 8.52 (br. s., 2 H), 8.43 (s, 1 H), 8.06 (s, 1 H), 7.58 (d, *J*=8.78 Hz, 1 H), 7.41 (s, 1 H), 6.97 - 7.16 (m, 1 H), 4.62 (d, *J*=7.32 Hz, 4 H), 3.83 (s, 3 H), 2.65 (s, 3 H), 2.26 - 2.38 (m, 1 H), 0.92 (d, *J*=6.59 Hz, 6 H).

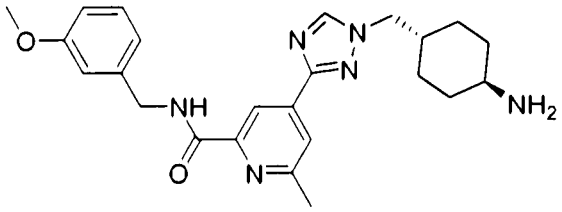
Step 2: Preparation of methyl 6-((4-(2-isobutyl-2*H*-tetrazol-5-yl)-2-methylpicolinamido)methyl)-1*H*-indole-2-carboxylate



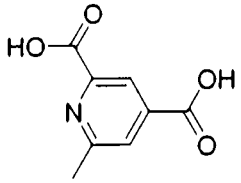
A solution of ammonia in methanol (7 N, 15 mL) was added to methyl 6-((4-(2-isobutyl-2*H*-tetrazol-5-yl)-2-methylpicolinamido)methyl)-1*H*-indole-2-carboxylate (0.13 g, 0.29 mmol) and the mixture was heated to 60 °C in a sealed vial for 30 hours. The reaction mixture was concentrated and the residue was purified by reverse phase preparative HPLC to afford the title compound (15 mg, 10%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.40 (s, 1 H), 9.19 (t, *J*=6.59 Hz, 1 H), 8.42 (s, 1 H), 8.11 (s, 1 H), 8.06 (s, 1 H), 7.84 (br. s., 1 H), 7.52 (d, *J*=8.05 Hz, 1 H), 7.39 (s, 1 H), 7.23 (br. s., 1 H), 6.93 - 7.10 (m, 1 H), 4.61 (t, *J*=7.69 Hz, 4 H), 2.64 (s, 3 H), 2.22 - 2.42 (m, 1 H), 0.92 (d, *J*=6.59 Hz, 6 H).

Example 450

***N*-(3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide**

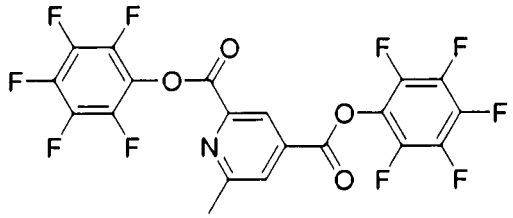


Step 1: Preparation of 6-methylpyridine-2,4-dicarboxylic acid



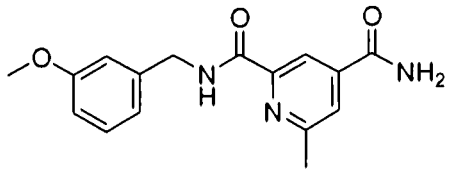
A solution of ammonia in ethanol (2 M, 400 mL) was cooled to 0 °C. Pyruvic acid (29.6 mL, 425 mmol) was added dropwise maintaining the temperature below 5 °C. After complete addition, the mixture was stirred for 30 min and then filtered. The resulting solid was washed with cold ethanol and immediately transferred to a 2 L Erlenmeyer. The above procedures are repeated and the resulting solids were combined and dissolved in water (100 mL). The mixture was heated to reflux for 30 min and then diluted with 1 N hydrochloric acid (200 mL). The mixture was cooled in an ice bath and further acidified until acidic. The resulting precipitate was filtered and washed with ethyl ether to afford the title compound as a solid (10.97 g, 27%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.52 (br, 2 H), 8.20 (d, J=0.7 Hz, 1 H), 7.90 (d, J=1.0 Hz, 1 H), 2.62 (s, 3H).

Step 2: Preparation of bis(perfluorophenyl) 6-methylpyridine-2,4-dicarboxylate



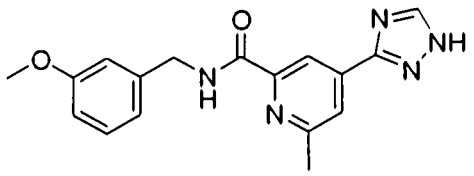
6-Methylpyridine-2,4-dicarboxylic acid (10.87 g, 60.0 mmol) and 1,3-dicyclohexylcarbodiimide (27.24 g, 132.0 mmol) were dissolved in *N*,*N*-dimethylformamide (400 mL). Pentafluorophenol (33.13 g, 180 mmol) was added in *N*,*N*-dimethylformamide (25 mL). The mixture was allowed to stir at room temperature for 18 hours and then the solvent was removed in vacuo. The residue was diluted with dioxane (500 mL) and filtered. The filtrate was concentrated, dissolved in dichloromethane/hexane (2/1, 100 mL), and filtered through a silica plug (5 cm x 8 cm) eluting with dichloromethane/hexane (2/1). The filtrate was concentrated, dissolved in ethyl acetate (500 mL), and washed with saturated aqueous sodium bicarbonate (2 x 50 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was purified by silica column chromatography (CH_2Cl_2/hexane, 1/2; 1/1). After concentration, the residue was triturated with hexanes and filtered to afford the title compound as a solid (8.45 g, 27%). MS (ES+) *m/z* 514 (M+H).

Step 3: Preparation of *N*-(3-methoxybenzyl)-6-methylpyridine-2,4-dicarboxamide



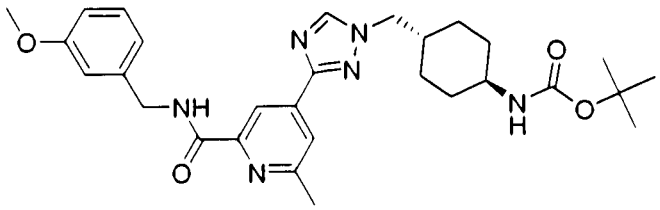
A solution of bis(perfluorophenyl) 6-methylpyridine-2,4-dicarboxylate (4.23 g, 8.24 mmol) in dichloromethane (150 mL) was cooled to -78 °C. A solution of 3-methoxybenzylamine (1.24 g, 9.07 mmol) and diisopropylethylamine (1.12 mL, 9.07 mL) in dichloromethane (10 mL) was added. The mixture was allowed to slowly warm to room temperature over 20 hours. The solvent was removed in vacuo and the residue was dissolved in tetrahydrofuran (50 mL). A solution of ammonia (0.5 M in dioxane, 18.1 mL, 9.07 mmol) was added followed by diisopropylethylamine (1.12 mL, 9.07 mmol). The mixture was stirred at room temperature for 2 h, and then the solvent was removed in vacuo. The resulting residue was suspended in ethyl acetate and filtered to afford the title compound as a white solid (2.36 g, 96%). MS (ES+) *m/z* 300 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.16 (t, *J*=6.4 Hz, 1 H), 8.31 (s, 1 H), 8.22 (d, *J*=0.8 Hz, 1 H), 7.81 (d *J*=1.1 Hz, 1 H), 7.70 (s, 1 H), 7.20 (t, *J*=8.1 Hz, 1 H), 6.89-6.85 (m, 2 H), 6.78 (dd, *J*=8.2, 1.9 Hz, 1 H), 4.46 (d, *J*=6.4, 2 H), 3.69 (s, 3 H), 2.59 (s, 3 H).

Step 4: Preparation of *N*-(3-methoxybenzyl)-6-methyl-4-(1*H*-1,2,4-triazol-3-yl)picolinamide



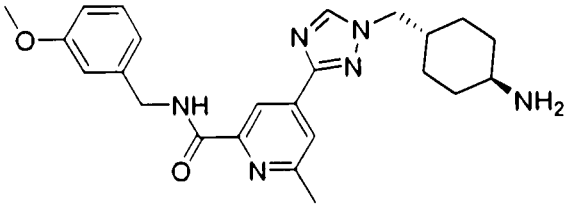
N-(3-Methoxybenzyl)-6-methylpyridine-2,4-dicarboxamide (599 mg, 2.0 mmol) and *N*,*N*-dimethylformamide dimethylacetal (26.5 mL) was heated at 110 °C such that any methanol formed is collected through a short path condenser. After 2 h, the remaining ,*N*-dimethylformamide dimethylacetal was removed in vacuo. The residue was dissolved in glacial acetic acid (20 mL) and hydrazine hydrate (344 μL, 6.0 mmol) was added. The mixture was heated at 90 °C for 2 hours and then allowed to cool to room temperature. The reaction mixture was poured into water (20 mL), cooled in an ice bath, and adjusted to pH 7 with 2.5 N sodium hydroxide solution. The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate, and concentrated. The residue was crystallized from ethyl acetate/ether ether/hexane to afford the title compound as a white solid (486 mg, 75%). MS (APCI+) *m/z* 324 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 14.48 (s, 1 H), 9.19 (t, *J*=6.1 Hz, 1 H), 8.74 (s, 1 H), 8.44 (s, 1 H), 8.02 (s, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.94-6.89 (m, 2 H), 6.82 (dd, *J*=8.1, 1.9 Hz, 1 H), 4.50 (d, *J*=6.4 Hz, 2 H), 3.73 (s, 3 H), 2.64 (s, 3 H).

Step 5: Preparation of *tert*-butyl (*trans*)-4-((3-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate



N-(3-Methoxybenzyl)-6-methyl-4-(1*H*-1,2,4-triazol-3-yl)picolinamide (323 mg, 1.00 mmol), polymer supported triphenylphosphine (698 mg, 1.50 mmol), and *tert*-butyl *trans*-(4-hydroxymethyl)cyclohexylcarbamate (275 mg, 1.20 mmol) were suspended in THF (16 mL). Di-*tert*-butyl azodicarboxylate (345 mg, 1.50 mmol) was added. The mixture was allowed to warm to room temperature and stir for 18 hours. The reaction mixture was filtered and the resin washed with THF (20 mL). The filtrate was concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2; 100/4). Combined fractions were concentrated to afford the title compound as a foaming white solid (491 mg, 92%). MS (ES+) *m/z* 535 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.4 Hz, 1 H), 8.69 (s, 1 H), 8.39 (s, 1 H), 7.97 (d, *J*=1.1 Hz, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 - 6.89 (m, 2 H), 6.82 (dd, *J*=8.1, 1.9 Hz, 1 H), 6.70 (d, *J*=7.8 Hz, 1 H), 4.50 (d, *J*=6.4 Hz, 2 H), 4.12 (d, *J*=7.0 Hz, 2 H), 3.73 (s, 3 H), 3.21 - 3.11 (m, 1 H), 2.63 (s, 3 H), 1.82 - 1.71 (m, 3 H), 1.59 - 1.53 (m, 2 H), 1.36 (s, 9 H), 1.15 - 1.01 (m, 4 H).

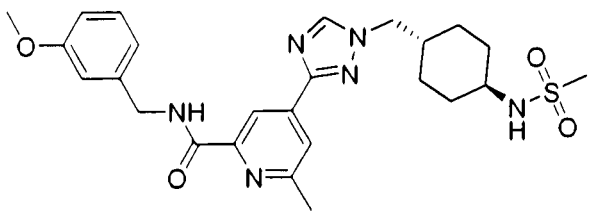
Step 6: Preparation of *N*-(3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide



tert-Butyl (*trans*)-4-((3-(2-((3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate (380 mg, 0.71 mmol) was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (1.06 mL, 14.2 mmol) was added. The mixture was allowed to stand for 2 hours and was then concentrated. The residue was dissolved in dichloromethane (100 mL) and washed with 1N NaOH solution (2 x 10 mL). The organic layer was dried over sodium sulfate and concentrated to afford the title compound as a glass which slowly solidified (276 mg, 89%). MS (ES+) *m/z* 435 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.17 (t, *J*=6.4 Hz, 1 H), 8.68 (s, 1 H), 8.39 (d, *J*=0.9 Hz, 1 H), 7.97 (d, *J*=1.2 Hz, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.93 - 6.89 (m, 2 H), 6.82 (ddd, *J*=8.2, 2.5, 0.8 Hz, 1 H), 4.50 (d, *J*=6.4 Hz, 2 H), 4.11 (d, *J*=7.1 Hz, 2 H), 3.73 (s, 3 H), 2.63 (s, 3 H), 2.48 - 2.40 (m, 1 H), 1.84 - 1.71 (m, 3 H), 1.57 - 1.51 (m, 2 H), 1.40 (br. s., 1 H), 1.09 – 0.90 (m, 4 H).

Example 451

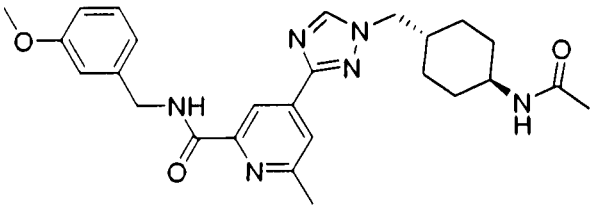
N-(3-Methoxybenzyl)-6-methyl-4-(1-(((trans)-4-(methylsulfonamido)cyclohexyl)methyl)-1H-1,2,4-triazol-3-yl)picolinamide



N-(3-Methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide (prepared as described in Example 450) (135 mg, 0.31 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (86.6 μL, 0.62 mmol) and methanesulfonyl chloride (28.9 μL, 0.37 mmol) were added. The reaction mixture was shaken at room temperature for 1 hour and then diluted with dichloromethane (50 mL). The mixture was washed with saturated aq. sodium bicarbonate (10 mL). The organic layer was dried over sodium sulfate and concentrated on to silica. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2; 100/4) to afford the title compound as a white solid (115 mg, 72%). MS (ES+) *m/z* 513 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.17 (t, *J*=6.4 Hz, 1 H), 8.69 (s, 1 H), 8.39 (s, 1 H), 7.97 (d, *J*=1.1 Hz, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.98 (d, *J*=7.4 Hz, 1 H), 6.93 - 6.89 (m, 2 H), 6.82 (dd, *J*=8.2, 1.7 Hz, 1 H), 4.50 (d, *J*=6.4 Hz, 2 H), 4.13 (d, *J*=7.0 Hz, 2 H), 3.73 (s, 3 H), 3.09 - 3.00 (m, 1 H), 2.88 (s, 3 H), 2.63 (s, 3 H), 1.90 (d, *J*=12.1 Hz, 2 H), 1.85 - 1.76 (m, 1 H), 1.59 (d, *J*=12.0 Hz, 2 H), 1.26 - 1.02 (m, 4 H).

Example 452

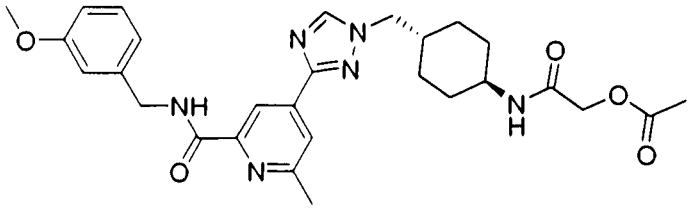
N-(3-Methoxybenzyl)-4-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide



N-(3-Methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide (prepared as described in Example 450) (135 mg, 0.31 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (86.6 μL, 0.62 mmol), DMAP (7.6 mg, 0.062 mmol), and acetyl chloride (26.5 μL, 0.37 mmol) was added. The reaction mixture was shaken at room temperature for 1 hour and then diluted with dichloromethane (50 mL). The mixture was washed with saturated aq. sodium bicarbonate (10 mL). The organic layer was dried over sodium sulfate and concentrated onto silica. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2; 100/4; 100/5) to afford the title compound as a white foaming solid (105 mg, 71%). MS (ES+) *m/z* 477 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.4 Hz, 1 H), 8.69 (s, 1 H), 8.40 (s, 1 H), 7.97 (s, 1 H), 7.69 (d, *J*=7.7 Hz, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.94 - 6.90 (m, 2 H), 6.82 (dd, *J*=8.1, 2.1 Hz, 1 H), 4.50 (d, *J*=6.3 Hz, 2 H), 4.13 (d, *J*=7.0 Hz, 2 H), 3.73 (s, 3 H), 3.46 (br. s., 1 H), 2.63 (s, 3 H), 1.88 - 1.72 (m, 6 H), 1.62 - 1.55 (m, 2 H), 1.15 - 1.02 (m, 4 H).

Example 453

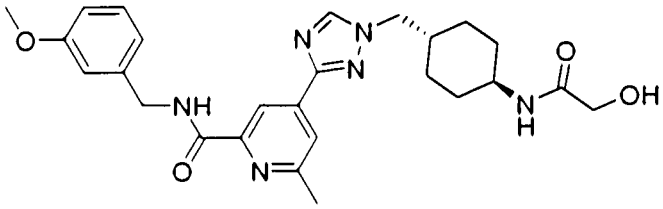
2-((*trans*)-4-((3-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate



N-(3-Methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide (prepared as described in Example 450) (335 mg, 0.77 mmol) was dissolved in dichloromethane (20 mL). Triethylamine (215 μL, 1.54 mmol), DMAP (18.8 mg, 0.15 mmol), and acetoxyacetyl chloride (99.5 μL, 0.93 mmol) were added. The mixture was allowed to stir at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (80 mL) and washed with saturated aq. sodium bicarbonate solution (2 x 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2; 100/4). Fractions were concentrated, and upon addition of EtOAc, the product crystallized. The resulting slurry was filter to afford the title compound as a white crystalline solid (288 mg, 70%). MS (ES+) *m/z* 535 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.4 Hz, 1 H), 8.70 (s, 1 H), 8.40 (s, 1 H), 7.97 (d, *J*=1.1 Hz, 1 H), 7.85 (d, *J*=7.9 Hz, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.94 - 6.88 (m, 2 H), 6.82 (dd, *J*=8.1, 2.1 Hz, 1 H), 4.50 (d, *J*=6.4 Hz, 2 H), 4.38 (s, 2 H), 4.14 (d, *J*=7.0 Hz, 2 H), 3.73 (s, 3 H), 3.55 - 3.46 (m, 1 H), 2.63 (s, 3 H), 2.06 (s, 3 H), 1.89 - 1.73 (m, 3 H), 1.63 - 1.57 (m, 2 H), 1.24 - 1.04 (m, 4 H).

Example 454

N-(3-Methoxybenzyl)-4-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide

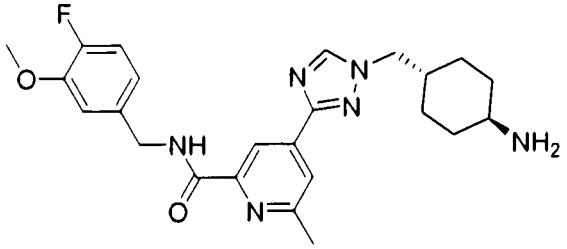


2-((*trans*)-4-((3-(2-((3-Methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate (prepared as described in Example 453) (200 mg, 0.375 mmol) was dissolved in THF (15 mL). Lithium hydroxide (26.9 mg, 1.12 mmol) followed by water (5.0 mL) were added. The mixture was stirred for 1 hour and then the THF was removed in vacuo. The residue was added to dichloromethane (100 mL) and washed with water (2 x 20 mL). The organic layer was dried over sodium sulfate and concentrated to afford an oil. The residue was dissolved in ethyl acetate/methanol (4/1) and partially concentrated until solids formed. The suspension was filtered to afford the title compound as a white solid (165 mg, 89%). MS (ES+) *m/z* 493 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.4 Hz, 1 H), 8.70 (s, 1 H), 8.40 (d, *J*=0.8 Hz, 1 H), 7.97 (d, *J*=1.2 Hz, 1 H), 7.44 (d, *J*=8.3 Hz, 1 H), 7.24 (t, *J*=8.1 Hz, 1 H), 6.89 - 6.93 (m, 2 H), 6.82 (dd,

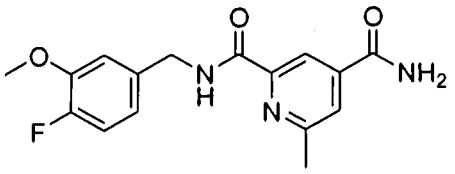
J=8.1, 1.8 Hz, 1 H), 5.39 (t, *J*=5.6 Hz, 1 H), 4.50 (d, *J*=6.3 Hz, 2 H), 4.14 (d, *J*=7.0 Hz, 2 H), 3.75 (d, *J*=5.6 Hz, 2 H), 3.73 (s, 3 H), 3.61 - 3.51 (m, 1 H), 2.63 (s, 3 H), 1.88 - 1.77 (m, 1 H), 1.74 (d, *J*=12.5 Hz, 2 H), 1.59 (d, *J*=12.5 Hz, 2 H), 1.27 (qd, *J*=12.4, 2.6 Hz, 2 H), 1.10 (qd, *J*=12.7, 2.4 Hz, 2 H).

Example 455

5 *N*-(4-Fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide

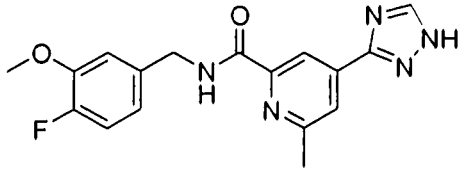


Step 1: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-methylpyridine-2,4-dicarboxamide



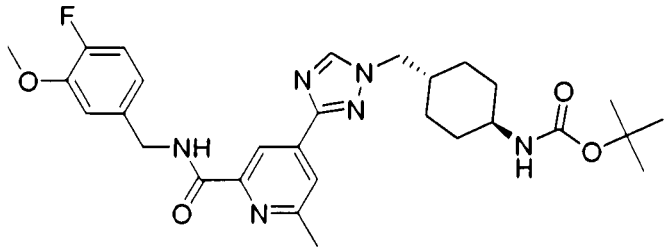
10 A solution of bis(perfluorophenyl) 6-methylpyridine-2,4-dicarboxylate (prepared as described in step 2 of the synthesis of *N*-(3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide, Example 450) (104 g) in dichloromethane (945 mL) was cooled to -70 °C. A solution of 4-fluoro-3-methoxybenzylamine hydrochloride (prepared as described in step 3 of the synthesis of *N*-(4-fluoro-3-methoxybenzyl)-6-(2-((*trans*-4-aminocyclohexyl)methyl)-2*H*-tetrazol-5-
15 yl)pyrimidine-4-carboxamide, Example 1) (23.5 g, 123 mmol) and triethylamine (33.4 mL, 240 mmol) in dichloromethane (140 mL) was added. The mixture was allowed to slowly warm to room temperature over 20 hours. The solvent was removed in vacuo and the residue was dissolved in tetrahydrofuran (575 mL). Triethylamine (18.4 mL, 132 mmol) was added followed by a solution of ammonia (0.5 M in dioxane, 260 mL, 130 mmol). The mixture was stirred at room temperature for 20 h, and then the
20 solvent was removed in vacuo. The resulting residue was suspended in ethyl acetate and filtered. The resulting solid was again suspended in methanol and filtered to afford the title compound as a white solid (27.7 g, 75%). MS (ES+) *m/z* 318 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (t, *J*=6.4 Hz, 1 H), 8.32 (br. s., 1 H), 8.22 (d, *J*=0.8 Hz, 1 H), 7.81 (d, *J*=1.2 Hz, 1 H), 7.71 (br. s., 1 H), 7.14 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.10 (dd, *J*=11.5, 8.3 Hz, 1 H), 6.82 - 6.87 (m, 1 H), 4.45 (d, *J*=6.4 Hz, 2
25 H), 3.78 (s, 3 H), 2.59 (s, 3 H).

Step 2: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-6-methyl-4-(1*H*-1,2,4-triazol-3-yl)picolinamide



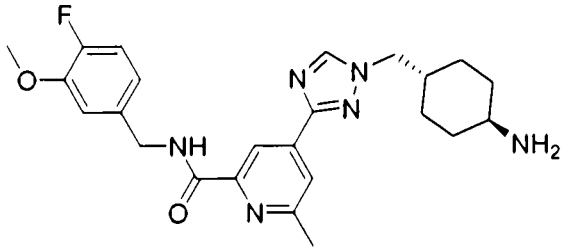
N-(4-Fluoro-3-methoxybenzyl)-6-methylpyridine-2,4-dicarboxamide (27.67 g, 87 mmol) and *N*,*N*-dimethylformamide dimethylacetal (290 mL) was heated at 110 °C such that any methanol formed is collected through a short path condenser. After 2 h, the remaining ,*N*-dimethylformamide dimethylacetal was removed in vacuo. The residue was dissolved in glacial acetic acid (293 mL) and hydrazine hydrate (15.6 mL, 323 mmol) was added. The mixture was heated at 90 °C for 2 hours and then allowed to cool to room temperature. The reaction mixture was poured into water (250 mL) and filtered to afford the title compound as a solid (24.1 g, 81%). MS (ES+) *m/z* 342 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 14.47 (br. s., 1 H), 9.19 (t, *J*=6.4 Hz, 1 H), 8.67 (br. s., 1 H), 8.41 (s, 1 H), 7.98 (d, *J*=1.2 Hz, 1 H), 7.15 (dd, *J*=8.3, 1.9 Hz, 1 H), 7.11 (dd, *J*=11.7, 8.5 Hz, 1 H), 6.89 - 6.84 (m, 1 H), 4.46 (d, *J*=6.4 Hz, 2 H), 3.79 (s, 3 H), 2.60 (s, 3 H)

Step 3: Preparation of *tert*-butyl (*trans*)-4-((3-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate



N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(1*H*-1,2,4-triazol-3-yl)picolinamide (683 mg, 2.00 mmol), polymer supported triphenylphosphine (1.40 g, 3.00 mmol), and *tert*-butyl *trans*-(4-hydroxymethyl)cyclohexylcarbamate (550 mg, 2.40 mmol) were suspended in tetrahydrofuran (32 mL). Di-*tert*-butyl azodicarboxylate (691 mg, 3.00 mmol) was added. The mixture was allowed to warm to room temperature and stir for 18 hours. The reaction mixture was filtered and the resin washed with tetrahydrofuran (40 mL). The filtrate was concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2; 100/4). Combined fractions were concentrated to afford the title compound as a foaming white solid (955 mg, 86%). MS (ES+) *m/z* 533 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.4 Hz, 1 H), 8.66 (s, 1 H), 8.36 (d, *J*=0.8 Hz, 1 H), 7.94 (d, *J*=1.1 Hz, 1 H), 7.15 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.11 (dd, *J*=11.7, 8.3 Hz, 1 H), 6.86 (ddd, *J*=8.3, 4.4, 1.9 Hz, 1 H), 6.67 (d, *J*=7.9 Hz, 1 H), 4.46 (d, *J*=6.4 Hz, 2 H), 4.09 (d, *J*=7.0 Hz, 2 H), 3.79 (s, 3 H), 3.12 (br. s., 1 H), 2.60 (s, 3 H), 1.74 (br. s., 3 H), 1.57 - 1.50 (m, 2 H), 1.33 (s, 9 H), 1.12 - 0.98 (m, 4 H).

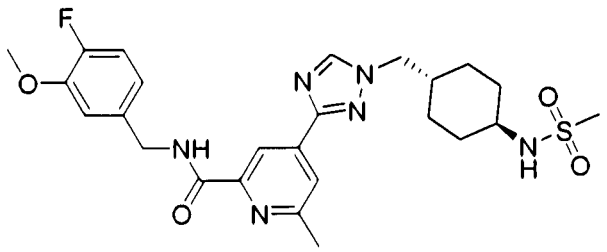
Step 4: Preparation of *N*-(4-fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide



tert-Butyl (*trans*)-4-((3-(2-((4-fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate (950 mg, 1.72 mmol) was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (2.55 mL, 34.4 mmol) was added. The mixture was allowed to stand for 2 hours and was then concentrated. The residue was dissolved in dichloromethane (100 mL) and washed with 1N NaOH solution (2 x 20 mL). The organic layer was dried over sodium sulfate and concentrated to afford the title compound as a foaming solid (730 mg, 94%). MS (ES+) *m/z* 453 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.4 Hz, 1 H), 8.65 (s, 1 H), 8.36 (d, *J*=0.8 Hz, 1 H), 7.94 (d, *J*=1.1 Hz, 1 H), 7.15 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.11 (dd, *J*=11.7, 8.3 Hz, 1 H), 6.86 (ddd, *J*=8.3, 4.4, 2.0 Hz, 1 H), 4.46 (d, *J*=6.4 Hz, 2 H), 4.08 (d, *J*=7.0 Hz, 2 H), 3.79 (s, 3 H), 2.60 (s, 3 H), 2.44 - 2.38 (m, 1 H), 1.81 - 1.61 (m, 3 H), 1.55 - 1.34 (m, 4 H), 1.06 - 0.82 (m, 4 H).

Example 456

N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(1-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)picolinamide

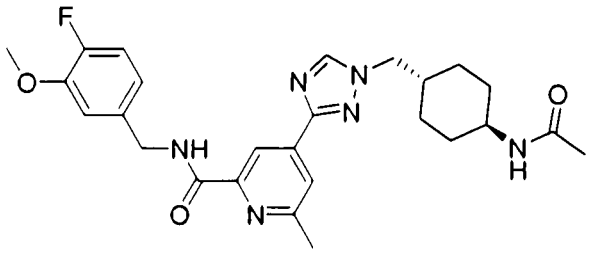


N-(4-Fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide (prepared as described in Example 455) (725 mg, 1.6 mmol) was dissolved in dichloromethane (30 mL). Triethylamine (447 μL, 3.2 mmol) and methanesulfonyl chloride (149 μL, 1.92 mmol) were added. The reaction mixture was stirred at room temperature for 1 hour and then diluted with dichloromethane (100 mL). The mixture was washed with saturated aq. sodium bicarbonate (20 mL). The organic layer was dried over sodium sulfate and concentrated onto silica. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2; 100/4). Fractions were concentrated and the resulting oil crystallized from ethyl acetate to afford the title compound as a white solid (623 mg, 73%). MS (ES+) *m/z* 531 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.4 Hz, 1 H), 8.66 (s, 1 H), 8.36 (d, *J*=0.8 Hz, 1 H), 7.94 (d, *J*=1.1 Hz, 1 H), 7.15 (dd, *J*=8.5, 1.7 Hz, 1 H), 7.11 (dd, *J*=11.5, 8.3 Hz, 1 H), 6.95 (d, *J*=7.4 Hz, 1 H), 6.86 (ddd, *J*=8.4, 4.3, 1.9 Hz, 1 H), 4.46 (d, *J*=6.3 Hz, 2 H), 4.10 (d, *J*=6.8 Hz, 2 H), 3.79 (s, 3 H), 3.05 - 2.97 (m, 1 H), 2.85

(s, 3 H), 2.60 (s, 3 H), 1.87 (d, *J*=10.5 Hz, 2 H), 1.82 - 1.71 (m, 1 H), 1.56 (d, *J*=12.4 Hz, 2 H), 1.22 - 1.00 (m, 4 H).

Example 457

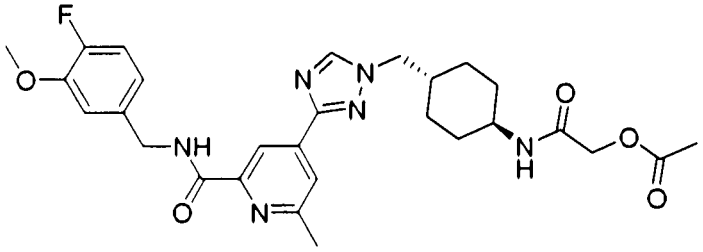
N-(4-Fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide



N-(4-Fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide (prepared as described in Example 455) (115 mg, 0.25 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (70.8 μL, 0.51 mmol), DMAP (6.2 mg, 0.051 mmol), and acetyl chloride (21.7 μL, 0.31 mmol) was added. The reaction mixture was shaken at room temperature for 1 hour and then diluted with dichloromethane (50 mL). The mixture was washed with saturated aq. sodium bicarbonate (10 mL). The organic layer was dried over sodium sulfate and concentrated on to silica. The crude product was purified by silica column chromatography (Biotage 40S, CH_2Cl_2/methanol, 100/2 x 0.75 L; 100/4 x 0.75 L; 100/5 x 0.75 L) to afford the title compound as a white foaming solid (109 mg, 87%). MS (ES+) *m/z* 495 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.20 (t, *J*=6.4 Hz, 1 H), 8.69 (s, 1 H), 8.40 (s, 1 H), 7.97 (s, 1 H), 7.69 (d, *J*=7.8 Hz, 1 H), 7.18 (dd, *J*=8.5, 1.7 Hz, 1 H), 7.17 - 7.11 (m, *J*=11.6, 8.3 Hz, 1 H), 6.89 (ddd, *J*=8.2, 4.3, 1.9 Hz, 1 H), 4.49 (d, *J*=6.3 Hz, 2 H), 4.13 (d, *J*=7.0 Hz, 2 H), 3.82 (s, 3 H), 3.45 (br. s., 1 H), 2.63 (s, 3 H), 1.88 - 1.73 (m, 6 H), 1.62 - 1.56 (m, 2 H), 1.17 - 1.02 (m, 4 H).

Example 458

2-((*trans*)-4-((3-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate

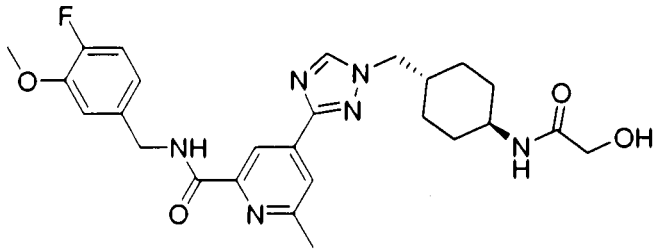


N-(4-Fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide (prepared as described in Example 455) (349 mg, 0.77 mmol) was dissolved in dichloromethane (20 mL). Triethylamine (215 μL, 1.54 mmol), DMAP (18.8 mg, 0.15 mmol), and acetoxyacetyl chloride (99.5 μL, 0.93 mmol) were added. The mixture was allowed to stir at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (80 mL) and washed with saturated aq. sodium bicarbonate solution (2 x 20 mL). The organic layer was dried over sodium

sulfate and concentrated. The crude product was purified by silica column chromatography (CH_2Cl_2/methanol, 100/1; 100/2; 100/4). Fractions were concentrated, and upon addition of EtOAc, the product crystallized. The resulting slurry was filter to afford the title compound as a white solid (290 mg, 68%). MS (ES+) *m/z* 553 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, *J*=6.4 Hz, 1 H), 8.70 (s, 1 H), 8.40 (s, 1 H), 7.97 (s, 1 H), 7.85 (d, *J*=7.9 Hz, 1 H), 7.18 (dd, *J*=8.1, 1.7 Hz, 1 H), 7.14 (dd, *J*=11.5, 8.3 Hz, 1 H), 6.89 (ddd, *J*=8.1, 4.6, 1.9 Hz, 1 H), 4.49 (d, *J*=6.3 Hz, 2 H), 4.38 (s, 2 H), 4.14 (d, *J*=7.0 Hz, 2 H), 3.82 (s, 3 H), 3.55 - 3.46 (m, 1 H), 2.63 (s, 3 H), 2.06 (s, 3 H), 1.88 - 1.74 (m, 3 H), 1.63 - 1.56 (m, 2 H), 1.24 - 1.03 (m, 4 H).

Example 459

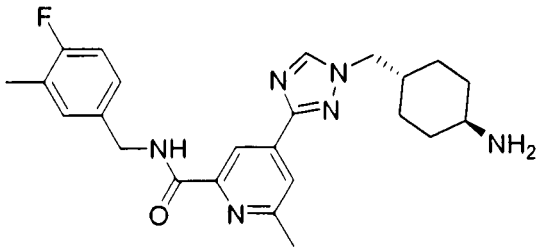
N-(4-Fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide



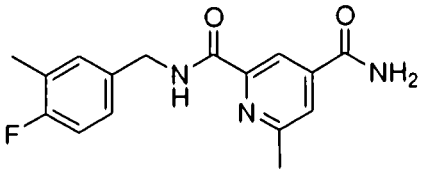
2-((*trans*)-4-((3-(2-((4-Fluoro-3-methoxybenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate (prepared as described in Example 458) (207 mg, 0.375 mmol) was dissolved in THF (15 mL). Lithium hydroxide (26.9 mg, 1.12 mmol) followed by water (5.0 mL) were added. The mixture was stirred for 1 hour and then the tetrahydrofuran was removed in vacuo. The residue was added to dichloromethane (100 mL) and washed with water (2 x 20 mL). The organic layer was dried over sodium sulfate and concentrated to afford an oil. The residue was dissolved in acetonitrile and partially concentrated, and upon standing, the product crystallizes. The slurry was filtered to afford 63 mg of a white solid. The filtrate was concentrated, dissolved in a minimum amount of acetonitrile, and seeded to afford a second crop of 79 mg. The two crops were combined to afford the title compound as a white solid (142 mg, 74%). MS (ES+) *m/z* 511 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, *J*=6.4 Hz, 1 H), 8.70 (s, 1 H), 8.40 (s, 1 H), 7.97 (d, *J*=0.9 Hz, 1 H), 7.44 (d, *J*=8.3 Hz, 1 H), 7.18 (dd, *J*=8.5, 1.7 Hz, 1 H), 7.14 (dd, *J*=11.7, 8.3 Hz, 1 H), 6.89 (ddd, *J*=8.3, 4.5, 1.9 Hz, 1 H), 5.40 (t, *J*=5.7 Hz, 1 H), 4.49 (d, *J*=6.3 Hz, 2 H), 4.14 (d, *J*=7.0 Hz, 2 H), 3.82 (s, 3 H), 3.75 (d, *J*=5.6 Hz, 2 H), 3.60 - 3.52 (m, 1 H), 2.63 (s, 3 H), 1.88 - 1.77 (m, 1 H), 1.74 (d, *J*=10.1 Hz, 2 H), 1.59 (d, *J*=12.8 Hz, 2 H), 1.27 (dq, *J*=12.4, 2.3 Hz, 2 H), 1.10 (qd, *J*=12.5, 2.0 Hz, 2 H).

Example 460

N-(4-Fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide

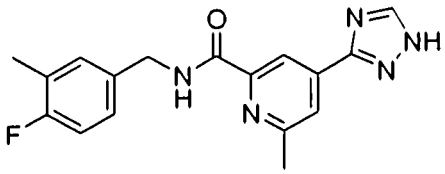


Step 1: Preparation of *N*-(4-fluoro-3-methylbenzyl)-6-methylpyridine-2,4-dicarboxamide



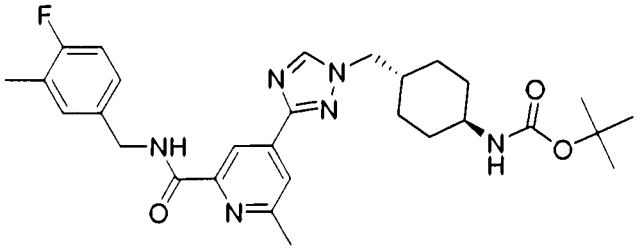
A solution of bis(perfluorophenyl) 6-methylpyridine-2,4-dicarboxylate (prepared as described in step 2 of the synthesis of *N*-(3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide, Example 450) (104 g) in dichloromethane (945 mL) was cooled to -70 °C. A solution of 4-fluoro-3-methylbenzylamine (16.92 g, 122 mmol) and triethylamine (17.0 mL, 122 mmol) in dichloromethane (140 mL) was added. The mixture was allowed to slowly warm to room temperature over 20 hours. The solvent was removed in vacuo and the residue was dissolved in tetrahydrofuran (575 mL). Triethylamine (19.2 mL, 138 mmol) was added followed by a solution of ammonia (0.5 M in dioxane, 271 mL, 135 mmol). The mixture was stirred at room temperature for 20 h, and then the solvent was removed in vacuo. The resulting residue was suspended in ethyl acetate and filtered to afford the title compound as a white solid (35.4 g, 62%). MS (ES+) *m/z* 302 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, *J*=6.3 Hz, 1 H), 8.32 (br. s., 1 H), 8.22 (d, *J*=0.9 Hz, 1 H), 7.81 (d, *J*=1.2 Hz, 1 H), 7.71 (br. s., 1 H), 7.20 (d, *J*=7.7 Hz, 1 H), 7.12 - 7.17 (m, 1 H), 7.04 (t, *J*=9.7 Hz, 1 H), 4.42 (d, *J*=6.4 Hz, 2 H), 2.58 (s, 3 H), 2.17 (d, *J*=1.6 Hz, 3 H).

Step 2: Preparation of *N*-(4-fluoro-3-methylbenzyl)-6-methyl-4-(1*H*-1,2,4-triazol-3-yl)picolinamide



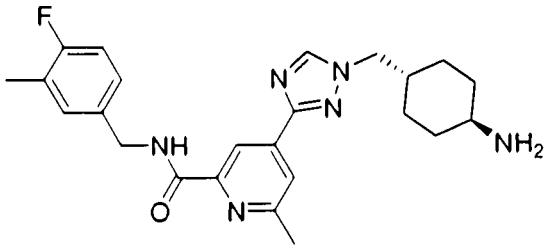
N-(4-Fluoro-3-methylbenzyl)-6-methylpyridine-2,4-dicarboxamide (35.0 g, 116 mmol) and *N*,*N*-dimethylformamide dimethylacetal (387 mL) was heated at 110 °C such that any methanol formed is collected through a short path condenser. After 2 h, the remaining ,*N*-dimethylformamide dimethylacetal was removed in vacuo. The residue was dissolved in glacial acetic acid (370 mL) and hydrazine hydrate (21.5 mL, 430 mmol) was added. The mixture was heated at 90 °C for 2 hours and then allowed to cool to room temperature. The reaction mixture was poured into water (375 mL) and filtered to afford the title compound as a white solid (20.7 g, 55%). MS (ES+) *m/z* 326 (M+H).

Step 3: Preparation of *tert*-butyl (*trans*)-4-((3-(2-((4-fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate



N-(4-Fluoro-3-methylbenzyl)-6-methyl-4-(1*H*-1,2,4-triazol-3-yl)picolinamide (2.50 g, 7.68 mmol), tert-butyl *trans*-(4-hydroxymethyl)cyclohexyl carbamate (2.29 g, 10.0 mmol), and polymer supported-triphenylphosphine (5.12g, 11.5 mmol) were suspended in anhydrous tetrahydrofuran (100 mL). The mixture was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (2.12 g, 9.22 mmol) was added. The reaction was allowed to warm to room temperature while stirring over 15 hours. The reaction was filtered and the filtrate was concentrated. The crude residue was purified by silica gel column chromatography (50 g, 0-2% methanol/dichloromethane) to afford the title compound as a beige oil.

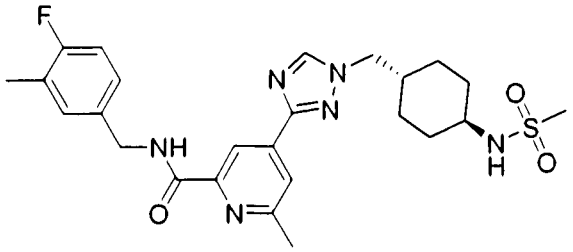
Step 4: Preparation of *N*-(4-fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide



tert-Butyl (*trans*)-4-((3-(2-((4-fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylcarbamate was dissolved in dichloromethane (15 mL) and stirred with trifluoroacetic acid (4 mL) for 1 hour at room temperature. The reaction was concentrated and then triturated with diethyl ether to afford the title compound (2.76 g, 65%). LC/MS (5-95% CH_3CN/H_2O, 6 min) 3.99 min, *m/z* 437 (M+H).

Example 461

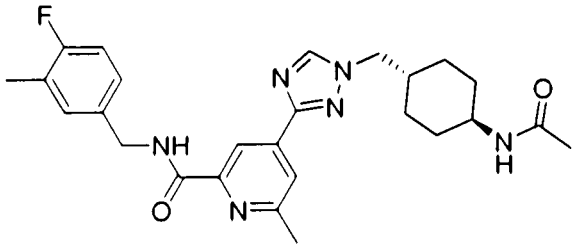
N-(4-Fluoro-3-methylbenzyl)-6-methyl-4-(1-(((*trans*)-4-(methylsulfonamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)picolinamide



Triethylamine (0.11 mL, 0.77 mmol) was added to a solution of *N*-(4-fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide (prepared as described in Example 460) (96 mg, 0.22 mmol) in dichloromethane (2 mL). A solution of methane sulfonyl chloride (30 mg) in dichloromethane (0.5 mL) was then added. The reaction mixture was stirred for 1 hour at room temperature and then was concentrated. The residue was purified by reverse phase preparative HPLC (10-90 % acetonitrile/water) to afford the title compound (17 mg, 15%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.01 - 9.20 (m, 1 H), 8.65 (s, 1 H), 8.37 (s, 1 H), 7.94 (br. s., 1 H), 6.99 - 7.30 (m, 3 H), 6.92 (d, *J*=7.3 Hz, 1 H), 4.45 (d, *J*=5.9 Hz, 2 H), 4.11 (d, *J*=7.3 Hz, 2 H), 3.03 (s, 1 H), 2.86 (s, 3 H), 2.60 (s, 3 H), 2.19 (s, 3 H), 1.88 (d, *J*=10.3 Hz, 2 H), 1.79 (s, 1 H), 1.58 (d, *J*=13.2 Hz, 2 H), 0.96 - 1.29 (m, 4 H).

Example 462

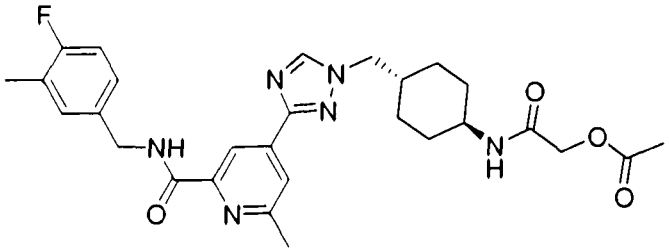
N-(4-Fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-acetamidocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide



Triethylamine (0.22 mL, 1.5 mmol) was added to a solution of *N*-(4-fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide (prepared as described in Example 460) (96 mg, 0.22 mmol) in dichloromethane (2 mL). A solution of acetyl chloride (21 mg) in dichloromethane (0.5 mL) was then added. The mixture was stirred for 1 hour at room temperature and was then concentrated. The residue was purified by reverse phase preparative HPLC (10-90 % acetonitrile/water) to afford the title compound (18 mg, 17%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (t, *J*=5.9 Hz, 1 H), 8.65 (s, 1 H), 8.37 (br. s., 1 H), 7.94 (s, 1 H), 7.63 (d, *J*=8.1 Hz, 1 H), 7.19 (dd, *J*=26.7, 6.2 Hz, 2 H), 6.92 - 7.11 (m, 1 H), 4.45 (d, *J*=5.9 Hz, 2 H), 4.11 (d, *J*=6.6 Hz, 2 H), 3.43 (br. s., 1 H), 2.60 (s, 3 H), 2.19 (s, 3 H), 1.69 - 1.88 (m, 5 H), 1.58 (br. s., 2 H), 0.95 - 1.20 (m, 5 H).

Example 463

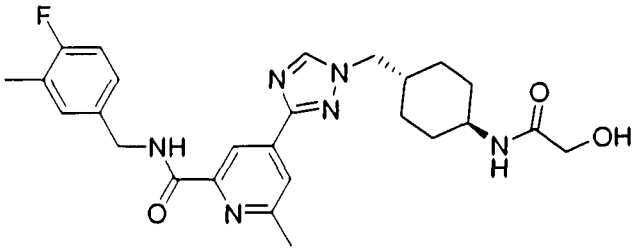
2-((*trans*)-4-((3-(2-((4-Fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate



Triethylamine (0.22 mL, 1.5 mmol) was added to a solution of *N*-(4-fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide (prepared as described in Example 460) (96 mg, 0.22 mmol) in dichloromethane (2 mL). A solution of acetoxy acetyl chloride (36 mg) in dichloromethane (0.5 mL) was added. The mixture was stirred for 1 hour at room temperature and was then concentrated. The residue was purified by reverse phase preparative HPLC (10-90 % acetonitrile/water) to afford the title compound (26 mg).

Example 464

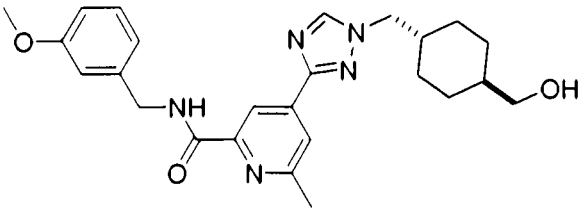
N-(4-Fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-(2-hydroxyacetamido)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamidemide



2-((*trans*)-4-((3-(2-((4-Fluoro-3-methylbenzyl)carbamoyl)-6-methylpyridin-4-yl)-1*H*-1,2,4-triazol-1-yl)methyl)cyclohexylamino)-2-oxoethyl acetate (prepared as described in Example 464) (26 mg) was dissolved in acetonitrile (amount). A 2.5N sodium hydroxide solution (amount) was added and the mixture was stirred for 2 hours. The mixture was acidified to ph 6-7 and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to 18 mg of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (t, *J*=6.2 Hz, 1 H), 8.66 (s, 1 H), 8.37 (br. s., 1 H), 7.94 (s, 1 H), 7.36 (d, *J*=8.8 Hz, 1 H), 6.94 - 7.26 (m, 3 H), 5.32 (d, *J*=5.1 Hz, 1 H), 4.45 (d, *J*=6.6 Hz, 2 H), 4.11 (d, *J*=7.3 Hz, 2 H), 3.73 (d, *J*=5.1 Hz, 3 H), 3.53 (d, *J*=8.8 Hz, 1 H), 2.60 (s, 3 H), 2.19 (s, 2 H), 1.81 (br. s., 1 H), 1.73 (d, *J*=11.0 Hz, 2 H), 1.58 (d, *J*=11.7 Hz, 2 H), 1.17 - 1.34 (m, 2 H), 0.99 - 1.17 (m, 2 H).

Example 465

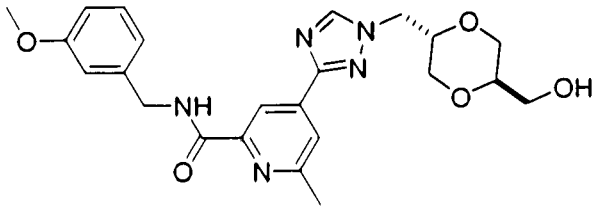
***N*-(3-Methoxybenzyl)-4-(1-(((trans)-4-(hydroxymethyl)cyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide**



N-(3-Methoxybenzyl)-6-methyl-4-(1*H*-1,2,4-triazol-3-yl)picolinamide (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide, Example 450) (0.20 g, 0.6 mmol), *trans*-1,4 cyclohexylenedimethanol (0.18 g, 1.24 mmol), and polymer supported-triphenylphosphine (0.72 g, 1.6 mmol) were suspended in anhydrous tetrahydrofuran (5 mL). The mixture was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (0.29 g, 1.2 mmol) was added. The reaction was allowed to warm to room temperature while stirring over 15 hours. The reaction was filtered and the filtrate was concentrated. The crude residue was purified by reverse phase preparative HPLC (5-95% gradient acetonitrile/water) to afford the title compound as a white solid (97 mg, 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.11 (t, J=6.2 Hz, 1 H), 8.65 (s, 1 H), 8.37 (s, 1 H), 7.94 (s, 1 H), 7.22 (t, J=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, J=8.1 Hz, 1 H), 4.48 (d, J=5.9 Hz, 2 H), 4.24 - 4.32 (m, 1 H), 4.19 (d, J=5.9 Hz, 1 H), 4.01 - 4.15 (m, 2 H), 3.71 (s, 3 H), 2.60 (s, 3 H), 1.81 (dd, J=11.4, 4.0 Hz, 1 H), 1.71 (d, J=11.7 Hz, 2 H), 1.58 (d, J=13.2 Hz, 2 H), 1.20 - 1.35 (m, 1 H), 0.91 - 1.06 (m, 2 H), 0.74 - 0.91 (m, 2 H).

Example 466

***rac*-*N*-(3-Methoxybenzyl)-4-(1-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide**

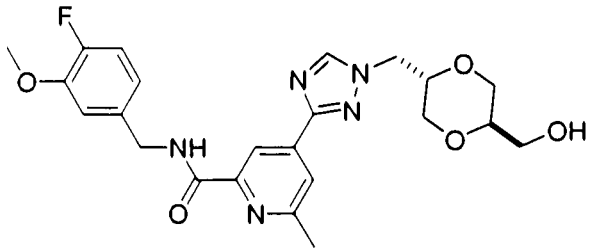


N-(3-Methoxybenzyl)-6-methyl-4-(1*H*-1,2,4-triazol-3-yl)picolinamide (prepared as described in step 4 of the synthesis of *N*-(3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide, Example 450) (32 mg, 0.10 mmol), *trans*-2,5-bis-(hydroxymethyl)-1,4-dioxane (prepared as described in step 3 of the synthesis of *rac*-*N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (22 mg, 0.15 mmol), and polymer supported-triphenylphosphine (0.071 g, 0.15 mmol) were suspended in anhydrous tetrahydrofuran (2 mL). The mixture was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (28 mg, 0.12 mmol) was added. The reaction was allowed to warm to room temperature while stirring over 15 hours. The reaction was filtered and the filtrate was concentrated. The crude residue was purified by reverse phase preparative HPLC (5-95% gradient acetonitrile/water) to afford the title compound as a white solid (15 mg, 33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 (t, J=6.2 Hz, 1 H), 8.63 (s, 1 H), 8.37 (s, 1 H), 7.95 (s, 1 H),

7.22 (t, *J*=8.1 Hz, 1 H), 6.90 (br. s., 2 H), 6.80 (d, *J*=8.8 Hz, 1 H), 4.60 - 4.70 (m, 1 H), 4.48 (d, *J*=6.6 Hz, 2 H), 4.18 - 4.39 (m, 5 H), 3.88 (d, *J*=9.5 Hz, 2 H), 3.78 (d, *J*=11.0 Hz, 1 H), 3.71 (s, 3 H), 2.56 - 2.71 (m, 4 H), 1.32 - 1.44 (m, 1 H).

Example 467

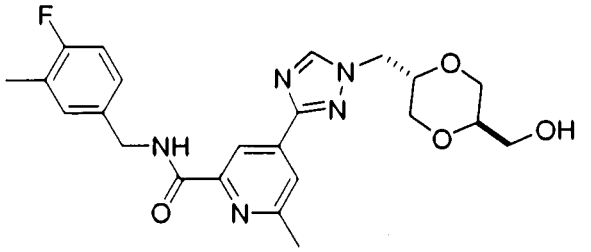
***rac-N*-(4-Fluoro-3-methoxybenzyl)-4-(1-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide**



N-(4-Fluoro-3-methoxybenzyl)-6-methyl-4-(1*H*-1,2,4-triazol-3-yl)picolinamide (prepared as described in step 1 of the preparation of *N*-(4-fluoro-3-methoxybenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide, Example 455) (34 mg, 0.10 mmol), *trans*-2,5-bis-(hydroxymethyl)-1,4-dioxane (prepared as described in step 3 of the synthesis of *rac-N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (22 mg, 0.15 mmol), and polymer supported-triphenylphosphine (0.071 g, 0.15 mmol) were suspended in anhydrous tetrahydrofuran (2 mL). The mixture was cooled to 0 °C in an ice bath for 15 min then di-tert-butyl azodicarboxylate (28 mg, 0.12 mmol) was added. The reaction was allowed to warm to room temperature while stirring over 15 hours. The reaction was filtered and the filtrate was concentrated. The crude residue was purified by reverse phase preparative HPLC (5-95% gradient acetonitrile/water) to afford the title compound as a white solid (22 mg, 47%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.14 (t, *J*=6.6 Hz, 1 H), 8.63 (s, 1 H), 8.37 (s, 1 H), 7.95 (s, 1 H), 7.05 - 7.22 (m, 2 H), 6.88 (br. s., 1 H), 4.64 (t, *J*=5.1 Hz, 1 H), 4.47 (d, *J*=6.6 Hz, 2 H), 4.18 - 4.40 (m, 5 H), 3.88 (d, *J*=9.5 Hz, 2 H), 3.67 - 3.83 (m, 5 H), 2.61 (s, 3 H), 1.30 - 1.45 (m, 1 H).

Example 468

***rac-N*-(4-Fluoro-3-methylbenzyl)-4-(1-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide**



N-(4-Fluoro-3-methylbenzyl)-6-methyl-4-(1*H*-1,2,4-triazol-3-yl)picolinamide (prepared as described in step 2 of the synthesis of *N*-(4-fluoro-3-methylbenzyl)-4-(1-(((*trans*)-4-aminocyclohexyl)methyl)-1*H*-1,2,4-triazol-3-yl)-6-methylpicolinamide, Example 460) (33 mg, 0.10

mmol), *trans*-2,5-bis-(hydroxymethyl)-1,4-dioxane (prepared as described in step 3 of the synthesis of *rac-N*-(3-methoxybenzyl)-6-(2-(((2*S**,5*R**)-5-(hydroxymethyl)-1,4-dioxan-2-yl)methyl)-2*H*-tetrazol-5-yl)-2-methylpyrimidine-4-carboxamide, Example 61) (22 mg, 0.15 mmol), and polymer supported-triphenylphosphine (0.071 g, 0.15 mmol) were suspended in anhydrous tetrahydrofuran (2 mL). The mixture was cooled to 0 °C in an ice bath for 15 min and then di-tert-butyl azodicarboxylate (28 mg, 0.12 mmol) was added. The reaction was allowed to warm to room temperature while stirring over 15 hours. The reaction mixture was filtered and the filtrate was concentrated. The crude residue was purified by reverse phase preparative HPLC (5-95% gradient acetonitrile/water) to afford the title compound as a white solid (20 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (t, *J*=6.2 Hz, 1 H), 8.63 (s, 1 H), 8.37 (s, 1 H), 7.94 (s, 1 H), 7.19 (dd, *J*=27.1, 6.6 Hz, 2 H), 7.04 (t, *J*=9.2 Hz, 1 H), 4.64 (t, *J*=5.1 Hz, 1 H), 4.45 (d, *J*=6.6 Hz, 2 H), 4.18 - 4.40 (m, 5 H), 3.88 (d, *J*=9.5 Hz, 2 H), 3.78 (d, *J*=11.7 Hz, 2 H), 2.60 (s, 3 H), 2.19 (s, 3 H), 1.37 (br. s., 1 H).

In Vitro MMP Inhibition Analysis

Matrix Metalloproteinase inhibitor compounds were analyzed in *in vitro* MMP Inhibition assays to determine their ability to inhibit the MMP cleavage of peptide substrates. Inhibition constants (K_i) were calculated from the assayed compound-MMP interactions.

Human recombinant MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12, MMP-13, MMP-14 and MMP-15 were used in these assays. The enzymes are prepared following known laboratory procedures. Protocols for the preparation and use of these enzymes are available in the scientific literature. See, for example, Frije et al., *J. Biol. Chem.*, 269(24), 16766-73 (1994).

In addition, many MMPs may be purchased from suppliers. For example, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-24, MMP-25, and MMP-26 are commercially available from R&D Systems in their 2006 catalog. Available in the 2006 Millipore Chemicon catalog are MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17 and MMP-24.

The MMP-1 proenzyme may be purified from spent media of MMP-1-transfected HT-1080 cells and the protein purified on a zinc chelating column. The MMP-2 proenzyme may be purified by gelatin Sepharose chromatography from MMP-2-transfected p2AHT2 cells. The MMP-9 proenzyme may be purified by gelatin Sepharose chromatography from spent media of MMP-9-transfected HT1080 cells.

The catalytic domain MMP-3 cDNA may be used to express the catalytic domain enzyme in E. coli inclusion bodies. Then the enzyme is solubilized in urea, purified on a preparative C-14 reverse phase HPLC column, and refolded in the presence of zinc acetate and purified for use.

The MMP-7 cDNA may be used to express the enzyme in E. coli inclusion bodies. Then the enzyme is solubilized in urea, purified on a preparative C-14 reverse phase HPLC column, and refolded in the presence of zinc acetate and purified for use.

The MMP-13 may be obtained as a proenzyme from a full-length cDNA clone using baculovirus expression. The expressed proenzyme was first purified over a heparin agarose column,

and then over a chelating zinc chloride column. Further details on baculovirus expression systems may be found in, for example, Luckow et al., *J. Virol.*, 67, 4566-79 (1993).

The MMP-14 cDNA may be used to express the catalytic domain enzyme in E. coli inclusion bodies. Then the enzyme is solubilized in urea, purified on a preparative C-14 reverse phase HPLC column, and refolded in the presence of zinc acetate and purified for use.

The catalytic domain of MMP-12 and MMP-15 enzymes were purchased commercially for these assays.

All full length MMPs were activated using 4-aminophenylmercuric acetate ("APMA", Sigma Chemical, St. Louis, Mo.) or trypsin. MMP-9 also was activated using human recombinant MMP-3 following standard cloning and purification techniques.

The fluorogenic, methoxycoumarin-containing polypeptide substrate MCA-ArgProLeuGlyLeuDpaAlaArgGluArgNH_2 was used as the MMP substrate in the MMP inhibition assays for human recombinant MMP-1, MMP-2, MMP-7, MMP-9, MMP-12, MMP-13, MMP-14 and MMP-15. Here, "MCA" is 7-methoxycoumarin-4-yl acetyl and "Dpa" is 3-(2,4-dinitrophenyl)-L-2,3-di-aminopropionyl group. In the absence of MMP inhibitory activity, the substrate is cleaved at the Gly-Leu peptide bond. The cleavage separates the highly fluorogenic peptide from the 2,4-dinitrophenyl quencher, resulting in an increase of fluorescent intensity.

For the human MMP-1, MMP-2, MMP-7, MMP-9, MMP-12, MMP-13, MMP-14 and MMP-15 assays, dilutions of the inhibitors (or salts thereof) were prepared in 100% dimethyl sulfoxide (DMSO). The stock solutions were diluted in Buffer A (100 mM Tris-HCl, 100 mM NaCl, 10 mM $CaCl_2$, 0.005% polyoxyethylene 23 lauryl ether, pH 7.5) to obtain solutions with different compound concentrations, i.e., assay solutions with different concentrations of the assayed MMP inhibitory compound in 1% DMSO. The experiment controls contained the same amount of Buffer A /DMSO as the assayed sample, but contained no inhibitor.

The fluorogenic, methoxycoumarin-containing polypeptide substrate Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH_2 (Bachem catalog number M-2110) was used as the MMP substrate in the MMP inhibition assays for catalytic domain of human recombinant MMP-3 (which refers to the catalytic domain of stromelysin). Here, "MCA" is 7-methoxycoumarin-4-yl acetyl and "Dpa" is 3-(2,4-dinitrophenyl)-L-2,3-di- aminopropionyl group. In the absence of MMP inhibitory activity, the substrate is cleaved at the Gly-Leu peptide bond. The cleavage separates the highly fluorogenic peptide from the 2,4-dinitrophenyl quencher, resulting in an increase of fluorescent intensity.

For the human MMP-3 assay, dilutions of the inhibitors (or salts thereof) were prepared in 100% DMSO. The stock solutions were diluted in Buffer B (50 mM *N*-morpholinoethane sulfonate ("MES"), 100 mM NaCl, 10 mM $CaCl_2$, 0.005% polyoxyethylene 23 lauryl ether, pH 6.0)) to obtain solutions with different compound concentrations, i.e., assay solutions with different concentrations of the assayed MMP inhibitory compound in 1% DMSO. The experiment controls contained the same amount of Buffer B /DMSO as the assayed sample, but contained no inhibitor.

To determine K_i, the inhibitor samples are incubated at room temperature for 1 hr in the presence of enzyme and then 4 μM of appropriate MMP substrate was added, and samples were

analyzed on a Tecan SpectraFlour Plus plate reader. The excitation wavelength is 330 nm, and the emission (fluorescence) wavelength is 420 nm. In the absence of MMP inhibitory activity, the substrate is cleaved at the Gly-Leu bond resulting in an increase of relative fluorescence. Inhibition is observed as a reduced rate of increase in relative fluorescence.

The inhibitors are analyzed using a single low enzyme concentration with a single substrate concentration fixed at or below the K_m. This protocol is a modification of method by Knight et al., *FEBS Lett.*, 296(3), 263-266 (1992). Apparent inhibitory constants are determined by non-linear regression of reaction velocity as a function of inhibitor and enzyme concentration using Morrison's equation, as described by Kuzmic, *Anal. Biochem.* 286, 45-50 (2000). Modifications were made in the non-linear regression method to allow a common control reaction rate and effective enzyme concentration to be shared between all dose-response relationships on a given assay plate. Since the substrate concentration was chosen to be at or below the K_m, the apparent K_i's from this analysis were reported as K_i's without correction for the influence of substrate.

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
1							NT		
2			>10000				8.91		
3							NT		
4							34.5		
5							NT		
6	>10000	>10000	7870	>10000	>10000	>10000	0.41	>10000	>10000
7			>10000				0.96		
8			>10000				0.98		
9							NT		
10			3260			>10000	0.13		
11	>10000	>10000	8960	>10000	>10000	>10000	0.63	>10000	>10000
12			>10000			>10000	2.97	>10000	>10000
13							NT		
14			>10000				6.76		
15			>10000				2.4		
16							11		
17			>10000				2.21		
18			>10000				1.15		
19			>10000				1.67		
20							NT		
21			2620				0.09		
22							NT		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
23	>10000	5030	3500	>10000	>10000	>10000	0.08	>10000	>10000
24			5520				1.37		
25	>10000	>10000	2170	>10000	>10000	>10000	0.77	>10000	>10000
26	>10000	>10000	9470	>10000	>10000	>10000	6.87	>10000	>10000
27			7030				2.23		
28	>10000	>10000	9340	>10000	>10000	>10000	0.81	>10000	>10000
29			9070				1.1		
30			>10000				2.15		
31							NT		
32			>10000				2.85		
33			>10000				2.54		
34			>10000				5.68		
35			>10000				2		
36			>10000				2.78		
37			>10000				5.91		
38							NT		
39	>10000	>10000	>10000	>10000	>10000	>10000	6.05	>10000	>10000
40	>10000	>10000	8880	>10000	>10000	>10000	0.69	>10000	>10000
41							NT		
42	>10000	>10000	8910	>10000	>10000	>10000	4.97	>10000	>10000
43			5130				0.58		
44							NT		
45	>10000	>10000	>10000	>10000	>10000	>10000	2.69	>10000	>10000
46			>10000				3.12		
47							NT		
48			8460				1.7		
49							NT		
50			>10000				2.91		
51			>10000				6.94		
52			>10000				3.26		
53			>10000				7.08		
54	>10000	>10000	8410	>10000	>10000	>10000	6.17	>10000	>10000
55							27.4		
56							22.5		
57			>10000				6.85		
58	>10000	>10000	>10000	>10000	>10000	>10000	3.94	>10000	>10000

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
59							8.85		
60							16.9		
61	>10000	>10000	>10000	>10000	>10000	>10000	5.84	>10000	>10000
62	>10000	>10000	>10000	>10000	>10000	>10000	3.67	>10000	>10000
63	>10000	>10000	>10000	>10000	>10000	>10000	7.81	>10000	>10000
64	>10000	>10000	>10000	>10000	>10000	>10000	3	>10000	>10000
65	9990	6290	>10000	6290	9380	4240	1.58	>10000	>10000
66	>10000	>10000	>10000	>10000	>10000	>10000	4.19	>10000	>10000
67			>10000				6.39		
68	>10000	>10000	9940	>10000	>10000	>10000	3.46	>10000	>10000
69			6670				7.65		
70							9.6		
71			>10000				1.69		
72	>10000	>10000	8290	>10000	>10000	>10000	1.75	>10000	>10000
73	>10000	>10000	>10000	>10000	>10000	>10000	4.12	>10000	>10000
74							32.8		
75							10.5		
76							21.6		
77							18.4		
78			>10000				4.77		
79	5230	4380	>10000	>10000	5790	4550	6.5	>10000	>10000
80			>10000				2.34		
81			>10000				25.9		
82							22.5		
83							16.2		
84							16.1		
85							NT		
86	>10000	>10000	>10000	>10000	>10000	>10000	0.51	>10000	>10000
87							NT		
88	>10000	>10000	>10000	>10000	>10000	>10000	0.2	>10000	>10000
89			>10000				0.29		
90							3.11		
91			>10000				3.65		
92							NT		
93			>10000				1.09		
94							NT		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
95	>10000	>10000	>10000	>10000	>10000	>10000	0.16	>10000	>10000
96							NT		
97			>10000				5.94		
98			>10000				1.36		
99	>10000	>10000	9970	>10000	>10000	>10000	1.67	>10000	>10000
100			>10000				4.01		
101			>10000				3.66		
102			9890				4.26		
103			>10000				3.73		
104	>10000	>10000	>10000	>10000	>10000	>10000	2.86	>10000	>10000
105			>10000				7.86		
106			>10000				1.8		
107			>10000				6.6		
108			>10000				2.85		
109							26.9		
110							NT		
111			>10000			3820	3.01	>10000	>10000
112			>10000				2		
113							NT		
114			>10000			7640	2.66	>10000	>10000
115			>10000			>10000	10.8		
116							NT		
117			6330			1080	0.63	>10000	>10000
118	>10000	>10000	>10000	>10000	>10000	3900	2.94	>10000	>10000
119			6860			2140	2.23		
120			>10000				4.6		
121							6.51		
122							NT		
123	>10000	>10000	>10000	>10000	>10000	>10000	3.01	>10000	>10000
124			>10000				5		
125							21		
126	5340	3910	>10000	>10000	6270	3360	27.1	>10000	>10000
127							16.2		
128	>10000	>10000	>10000	>10000	>10000	>10000	6.81	>10000	>10000
129							121		
130							NT		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
131							123		
132							40.2		
133							26.2		
134							NT		
135	>10000	>10000	>10000	>10000	>10000	>10000	1.88	>10000	>10000
136	>10000	>10000	>10000	>10000	>10000	>10000	3.37	>10000	>10000
137							NT		
138							46.6		
139							41.2		
140							21.7		
141							NT		
142							17.8		
143							18.5		
144							22.8		
145			>10000				12.1		
146			>10000				31.4		
147							NT		
148			>10000				15.9		
149	>10000	>10000	>10000	>10000	>10000	>10000	6.47	>10000	>10000
150			>10000				27.4		
151			>10000				11.1		
152	10400	4710	1590	>10000	>10000	6060	1.37	>10000	>10000
153	>10000	>10000	>10000	>10000	>10000	>10000	15.6	>10000	>10000
154	>10000	>10000	>10000	>10000	>10000	>10000	0.25	>10000	>10000
155			>10000				0.45		
156			>10000				0.50		
157			>10000				1.03		
158			>10000				1.98		
159							3.57		
160							1.33		
161	>10000	>10000	>10000	>10000	>10000	>10000	2.27	>10000	>10000
162			>10000				0.68		
163			>10000				2.26		
164			>10000				10		
165			>10000				4.54		
166			>10000				2.68		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
167	>10000	>10000	>10000	>10000	>10000	>10000	3.64	>10000	>10000
168			9030				1.4		
169			>10000				2.99		
170							NT		
171	>10000	>10000	>10000	>10000	>10000	>10000	0.66	>10000	>10000
172			>10000				1.23		
173			>10000				0.59		
174			>10000				0.88		
175			>10000				0.39		
176							0.54		
177			>10000				0.74		
178			>10000				1.18		
179							25.3		
180			>10000				0.59		
181			>10000				1.5		
182			>10000			>10000	0.17		
183			>10000				4.19		
184	>10000	>10000	>10000	>10000	>10000	>10000	3.18	>10000	>10000
185							NT		
186			>10000				0.57		
187			>10000				2.67		
188			>10000				17.8		
189			9420				4.21		
190							1.32		
191			>10000				2.3		
192			>10000				4.01		
193			>10000				3.26		
194							NT		
195			>10000				0.87		
196			>10000				4.69		
197							23.8		
198							8.46		
199							2.69		
200							7.6		
201							10.6		
202							7.57		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
203			>10000				4.07		
204			>10000				7.53		
205			>10000				17.8		
206			>10000				9.63		
207			>10000				8.82		
208			>10000				4.15		
209							NT		
210							5.31		
211			>10000				1.36		
212							7.06		
213			>10000				1.96		
214							2.98		
215	>10000	>10000	>10000	>10000	>10000	>10000	1.55	>10000	>10000
216			>10000				2.66		
217							8.48		
218							6.34		
219							NT		
220			8300				2.9		
221			4420				0.49		
222			6220				0.57		
223							NT		
224							7.92		
225	>10000	>10000	>10000	>10000	>10000	>10000	3.71	>10000	>10000
226							13.6		
227			>10000				3.16		
228							7.01		
229							4.7		
230			>10000				5		
231							32.3		
232			>10000				3.06		
233							NT		
234							NT		
235			>10000				1.74		
236							8.18		
237			8360				1.08		
238							9.16		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
239			>10000				3.8		
240							8.67		
241							NT		
242							24.8		
243							5.03		
244							24.5		
245							19.9		
246							21		
247							35.7		
248							14.8		
249							NT		
250			>10000				9.58		
251							8.48		
252			>10000				7.47		
253	>10000	>10000	>10000	>10000	>10000	>10000	3.76	>10000	>10000
254							9.88		
255							NT		
256	>10000	>10000	>10000	>10000	>10000	>10000	4.39	>10000	>10000
257							9.51		
258			>10000				37.2		
259							NT		
260							2.5		
261							5.06		
262							1.54		
263							NT		
264							0.56		
265							53.8		
266			>10000				7.54		
267							0.75		
268			11000				0.16		
269							2.21		
270			>10000				4.19		
271							1.8		
272							2.35		
273							2.71		
274							0.78		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
275			>10000				1.8		
276							1.8		
277			>10000				1.85		
278							NT		
279	>10000	>10000	7210	>10000	>10000	>10000	2.66	>10000	>10000
280			7130				0.97		
281							NT		
282							3.53		
283			>10000				14.2		
284							8.79		
285							0.24		
286							1.76		
287	>10000	>10000	6340	>10000	>10000	>10000	4.06	>10000	>10000
288							NT		
289			>10000				1.17		
290							13.6		
291							22.5		
292							6.74		
293							4.34		
294							NT		
295							NT		
296			>10000				2.79		
297							0.92		
298							0.30		
299			6750				0.67		
300			3850				0.90		
301							15.6		
302							0.28		
303			>10000				1.69		
304			>10000				4.62		
305							7.62		
306							0.62		
307							4.05		
308							23.8		
309							46.7		
310							38.5		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
311							47.2		
312							19.5		
313							17.1		
314							3.19		
315							29.3		
316							3.78		
317							6.31		
318			8260				14.7		
319			5970				7.3		
320							18.8		
321							19.6		
322			10100				2.06		
323			6630				1.18		
324							15.4		
325			>10000				7.47		
326							15.6		
327							9.19		
328							15.9		
329							32.9		
330			8730				4.1		
331			>10000				2.99		
332			4340				1.87		
333	>10000	>10000	>10000	>10000	>10000	>10000	4.46	>10000	>10000
334			>10000				10.9		
335							14.5		
336							9.84		
337							6.94		
338							10.5		
339							12.9		
340							8.08		
341							33.3		
342			>10000				3.54		
343			>10000				5.2		
344	>10000	>10000	>10000	>10000	>10000	>10000	4.02	>10000	>10000
345	>10000	>10000	>10000	>10000	>10000	>10000	3.25	>10000	>10000
346			>10000				2.69		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
347			>10000				3.61		
348			>10000				1.35		
349			5630				0.27		
350			>10000				4.3		
351							2.95		
352							3.46		
353							0.53		
354							3.99		
355			>10000				7.24		
356							17.3		
357			>10000				2.65		
358							682		
359			>10000				4.47		
360							18		
361							288		
362							42.5		
363							28.9		
364							274		
365			8620				1.59		
366							7.9		
367							199		
368							17.6		
369							11		
370							260		
371							20.1		
372							63.5		
373							NT		
374							56		
375							46.4		
376							17.3		
377			>10000				4		
378			>10000				5.18		
379							NT		
380							11.1		
381			>10000				37.6		
382			>10000				29.5		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
383	>10000	>10000	>10000	>10000	>10000	>10000	16.6	>10000	>10000
384							5.77		
385							18.3		
386							17.3		
387							100		
388			>10000				8.85		
389							171		
390			>10000				14.2		
391							47.8		
392	>10000	>10000	>10000	>10000	>10000	>10000	4.3	>10000	>10000
393							NT		
394	>10000	>10000	>10000	>10000	>10000	>10000	4.47	>10000	>10000
395							NT		
396			>10000				3.86		
397			6800				0.88		
398							NT		
399			>10000				17.9		
400			>10000				2.56		
401			>10000				10.3		
402			>10000				14.7		
403	>10000	>10000	>10000	>10000	>10000	>10000	11.7	>10000	>10000
404			>10000			>10000	14.9	>10000	>10000
405			>10000			>10000	11.2	>10000	>10000
406							NT		
407			>10000				0.83		
408							21.7		
409			>10000				5.06		
410			>10000				12.3		
411			>10000				10.6		
412	>10000	>10000	>10000	>10000	>10000	>10000	7.58	>10000	>10000
413							NT		
414	>10000	>10000	>10000	>10000	>10000	>10000	0.43	>10000	>10000
415							15.2		
416			>10000				2.52		
417			>10000				5.82		
418			9780				2.27		

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
419			>10000				3.1		
420							NT		
421			>10000				2.23		
422							NT		
423			>10000				3.34		
424							14.8		
425							61.8		
426			>10000				11.8		
427							NT		
428							7.65		
429							20.6		
430			>10000				8.58		
431							15.4		
432							11.8		
433							16.5		
434							10.9		
435			>10000				5.02		
436							25		
437			2960				2.63		
438							10.6		
439			3460				0.57		
440			4480				0.13		
441			8170				1.69		
442			3580				2.57		
443			>10000				15.7		
444							25		
445							46.7		
446			>10000				19.8		
447			>10000				6.9		
448							30.6		
449	>10000	>10000	>10000	>10000	>10000	>10000	13	>10000	>10000
450							NT		
451			>10000			8500	2.32		
452			>10000			>10000	5.6		
453			>10000				1.62		
454	>10000	>10000	>10000	>10000	>10000	>10000	3.15	>10000	>10000

Example No.	hMMP K_i (nM)								
	01/FL	02/FL	03/CD	07/CD	09/FL	12/CD	13/FL	14/CD	15/CD
455							NT		
456			5780			2550	0.62		
457			>10000			4850	1.66		
458			9740				0.81		
459	>10000	>10000	>10000	>10000	>10000	7200	2.02	>10000	>10000
460							NT		
461			7240				4.62		
462							7.18		
463							NT		
464							14.6		
465	>10000	>10000	8130	>10000	>10000	>10000	5.13	>10000	>10000
466							66.9		
467							39.2		
468							63.6		

Cartilage damage in vitro assay

Human articular cartilage (HAC) was dissected from knees obtained from Asterand from patients undergoing knee replacement. Apparently normal (not fibrillated) cartilage was cut in small pieces (~ 2 mm) and cultured in 96 well plates with 200 µl of DMEM media (Gibco BRL high glucose, 25 mM Hepes, containing 2 mM L-glutamine and 1 mM Sodium Pyruvate) freshly supplemented with 1x HL-1 (Bio Whitaker) and 5 µg/ml ascorbic acid (Sigma), and with or without 0.1 ng/ml IL-1β (R &D Systems, Minneapolis, MN) + 50 µg/ml Oncostatin M (R & D Systems). Some cartilage wells were incubated in the presence of serially diluted MMP inhibitors, tested in quadruplicate at 6 concentrations. Media were replaced every 3 to 5 days and cartilage was cultured for a total of 18-22 days. Conditioned media were frozen and analyzed later for hydroxyproline content (or type II collagen degradation biomarker TIINE).

TIINE sandwich immunoassay for culture media.

A chemiluminescent sandwich immunoassay was developed with the neoepitope 9A4 antibody (recognizing the conserved sequence at the C-terminus of the ¾ type II collagen fragment GPPGPQG following collagenase cleavage) and the capture 5109 antibody (recognizing the type II collagen specific epitope GEPGDDGPS) as detailed elsewhere (Nemirovskiy et al., *Anal. Biochem.* 2007;361(1):93-101) utilizing the proprietary, chemiluminescent Bioveris technology (Bioveris Corporation, Gaithersburg, MD). This immunoassay utilizes a sandwich format on a paramagnetic bead support phase in which the sandwich complex is bound to the bead in suspension, passed through a flow cell, and captured by a magnet. The process effectively separates the analyte from the

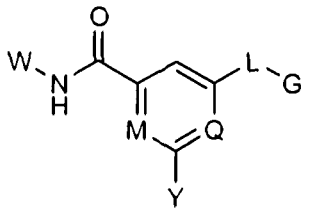
sample, decreasing background interference and eliminating wash steps required in other formats. Briefly, serially diluted culture supernatant samples were assayed in a 96-well plate. In this one step assay, 25 μL of sample, 25 μL of streptavidin beads (0.4 mg/mL), 25 μL of each antibody at 1μg/mL (Biotin conjugated mouse 5109 anti-capture and BVTAG labeled 9A4 anti-neoepitope) and 100 μL of assay buffer (DPBS, 0.1% BSA, 0.05% Tween 20, pH 7.4) were incubated for 2 hours at room temperature before reading on the Bioveris M384 Analyzer. Values were calculated from a standard curve prepared from either human 45-mer or bovine 30-mer (0.14-100 ng/ml) neoepitope peptide.

Cartilage damage and/or joint degeneration in vivo assay: surgical-induce medial meniscus tear rat OA model

Adult male Sprague Dawley rats (Charles River, Wilmington, MA) weighing 275-300 g were allowed to acclimate for 1 week prior to surgery. OA was surgically induced as described (Bendele, "Animal models of osteoarthritis," *J. Musculoskelet. Neuronal. Interact.* **1** (2001) (4), pp. 363–376). Briefly, animals were anesthetized with isoflurane and the right knee joint prepped for surgery. The medial collateral ligament (MCL) was exposed by blunt dissection and transected to reflect the meniscus toward the femur. The joint space was visualized and the meniscus was cut through the full thickness at its narrowest point to simulate a complete tear. The skin was closed with stainless steel staples. Compound or vehicle treatment started the day of surgery and continued for 3 to 4 weeks. The animals are then sacrificed, the femoro-tibial joint space lavaged with 100ul sterile saline to collect synovial fluid, and the total joint removed and fixed in 10% formalin for histology. Scoring was performed by hispopathology quantification.

Claims

1. A compound of Formula I:



I

wherein

G is (C_{1-3} alkylenyl)-R^a or R^a, wherein said C_{1-3} alkylenyl may be substituted by one or more substituents selected from OH and F;

R^a is C_{1-6} alkyl, 3- to 7-membered heterocycloalkyl, or 3- to 8-membered cycloalkyl, wherein said C_{1-6} alkyl may be substituted by one or more substituents selected from F, $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said heterocycloalkyl and cycloalkyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

M is N or C-R^b;

Q is N or C-R^c, provided that if Q is C-R^c, then M is N;

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or 9-membered heteroaryl-(C_{1-6} alkylenyl), wherein said phenyl, pyridyl, or 9-membered heteroaryl is substituted by one or more groups selected from R^{30} and R^{31};

Y is C_{1-6} alkyl, C_{1-6} haloalkyl; or C_{1-6} hydroxyalkyl;

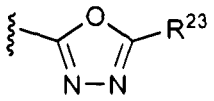
L is 5-membered heteroaryl;

R^2 is H, F, CN, $-OR^5$, R^{12}, $-C(=O)R^7$, $-NR^8R^{33}$, $-NR^8C(=O)R^9$, $-NR^8SO_2R^{36}$, or $-SO_2R^{12}$;

R^3 is H, F, CN, or $-OR^{22}$;

R^4 is H, -(C_{1-6} alkylene)R^6, $-C(=O)R^9$, or $-SO_2R^{12}$;

R^5 is H or -(C_{1-6} alkyl), wherein said C_{1-6} alkyl may be substituted by one or more R^{26} substituents;

R^6 is H, CN, $-OR^{23}$, $-SO_2R^{37}$, $-NR^{24}C(=O)R^{23}$, $-NR^{24}SO_2R^{37}$, or ;

R^7 is -(C_{1-6} alkyl), -(C_{1-6} haloalkyl), -(C_{1-6} alkylene)OH, $-NR^{38}R^{39}$, $-NHSO_2CH_3$, or $-OR^{25}$;

R^9 is -(C_{1-6} alkylene)R^{28}, $-NHR^{24}$, or $-OR^{25}$;

R^{10} is H, F, CN, R^{12}, or $-C(=O)R^7$;

R^{11} is H, F, CN, $-OR^5$, R^{12}, $-C(=O)R^7$, $-NR^8R^{33}$, $-NR^8C(=O)R^9$, $-NR^8SO_2R^{36}$, or $-SO_2R^{12}$;

R^{12} is -(C_{1-6} alkyl), wherein said C_{1-6} alkyl may be substituted by one or more substituents selected from CN, $-OR^{23}$, $-SR^{23}$, $-SO_2R^{37}$, $-NR^8R^{33}$, $-NR^{24}C(=O)R^{23}$, and $-NR^{24}SO_2R^{23}$, provided that any one carbon atom of said C_{1-6} alkyl is not substituted by more than one CN or more than one $-OR^{23}$;

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H or -(C_{1-6} alkyl);

R^{21} is H, F, or R^{12};

R^{23} is H, -(C_{1-6} alkyl), or -(C_{1-6} alkylene)OH;

R^{26} is H, OH, halo, NH_2, or SH;

R^{28} is H, NH_2, or $-OR^{29}$;

R^{29} is H, (C_{1-6} alkyl), or $-C(=O)(C_{1-6}$ alkyl);

R^{30} is H or F;

R^{31} is F, Cl, Br, -CN, $-C(=O)NH_2$, -OH, $-OR^{32}$, $-OCH_2CH_2OR^{25}$, R^{32}, ,or (C_{1-6} alkyl) optionally substituted by $-OR^{25}$ or $-OCH_2CH_2OR^{25}$

where R^{30} and R^{31} when adjacent may be taken together to constitute a group of the formula $-O-(CH_2)_n-$ or $-O-(CH_2)_n-O-$;

n is 1 or 2;

R^{32} is $-(C_{1-6}$ alkyl) optionally substituted with one, two, or three F;

R^{36} is $-(C_{1-6}$ alkyl) or $-(C_{3-6}$ cycloalkyl); and

R^{37} is $-(C_{1-6}$ alkyl), $-(C_{3-6}$ cycloalkyl), or $-(C_{1-6}$ alkylene)OH;

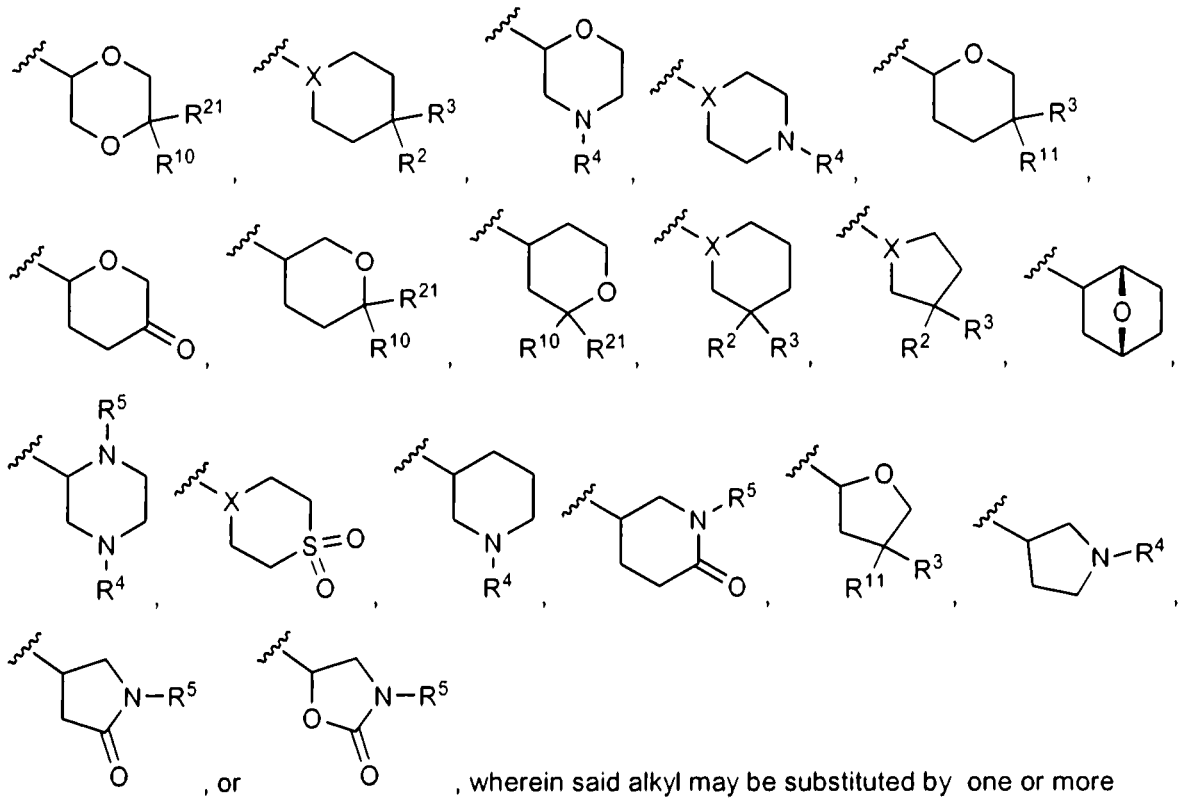
R^{38} and R^{39} are independently H, $-(C_{1-6}$ alkyl), or R^{38} and R^{39} taken together form a 5- or 6-membered heterocycloalkyl;

or a pharmaceutically-acceptable salt thereof.

2. A compound according to claim 1 wherein R^a is C_{1-6} alkyl, 1,4-dioxanyl, piperidinyl, cyclohexyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydropyranonyl, pyrrolidinyl, cyclopentyl, 7-oxa-bicyclo[2.2.1]heptanyl, piperazinyl, 1,1'-dioxothiomorpholinyl, tetrahydro-1,1'-dioxothiopyranyl, tetrahydrothiopyranyl, piperidinonyl, tetrahydrofuryl, pyrrolidinonyl, or oxazolidinonyl, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$, and wherein said 1,4-dioxyl, piperidinyl, cyclohexyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydropyranonyl, pyrrolidinyl, cyclopentyl, 7-oxa-bicyclo[2.2.1]heptanyl, piperazinyl, 1,1'-dioxothiomorpholinyl, tetrahydro-1,1'-dioxothiopyranyl, tetrahydrothiopyranyl, piperidinonyl, tetrahydrofuryl, pyrrolidinonyl, or oxazolidinonyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21}.

3. A compound according to claim 1 wherein R^a is C_{1-6} alkyl, 1,4-dioxanyl substituted by R^{10} and R^{21}, piperidinyl substituted by R^2 and R^3 or by R^4, cyclohexyl substituted by R^2 and R^3 or by R^4, morpholinyl substituted by R^4, thiomorpholinyl substituted by R^{10} and R^{21}, tetrahydropyranyl substituted by R^3 and R^{11} or by R^{10} and R^{21}, tetrahydropyranonyl, pyrrolidinyl substituted by R^2 and R^3 or by R^4, cyclopentyl substituted by R^2 and R^3, 7-oxa-bicyclo[2.2.1]heptanyl, piperazinyl substituted by R^4 and R^5, 1,1'-dioxothiomorpholinyl, tetrahydro-1,1'-dioxothiopyranyl, tetrahydrothiopyranyl, piperidinonyl substituted by R^5, tetrahydrofuryl substituted by R^3 and R^{11}, pyrrolidinonyl substituted by R^5, oxazolidinonyl substituted by R^5, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

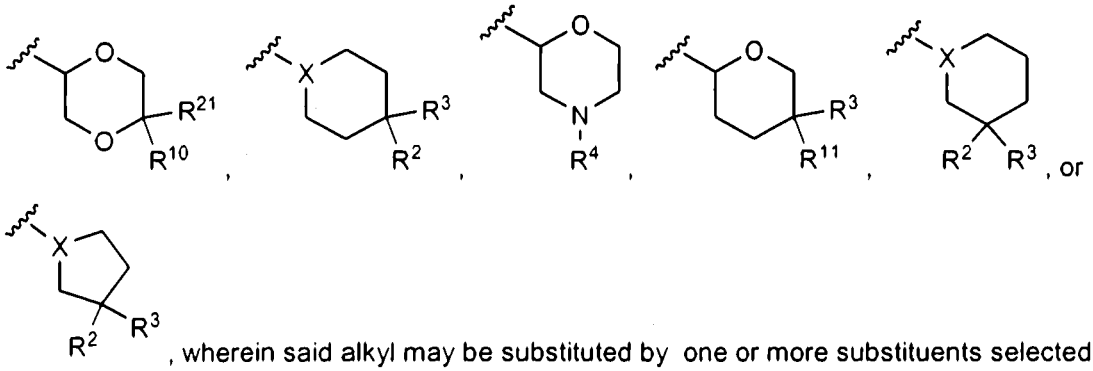
4. A compound according to claim 3 wherein R^a is C_{1-6} alkyl,



, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$; and

X is N or CH, provided that when X is N, G is (C_{2-3} alkylenyl)-R^a, wherein said C_{1-3} alkylenyl may be substituted by one or more substituents selected from OH and F.

5. A compound according to claim 4 wherein R^a is C_{1-6} alkyl,

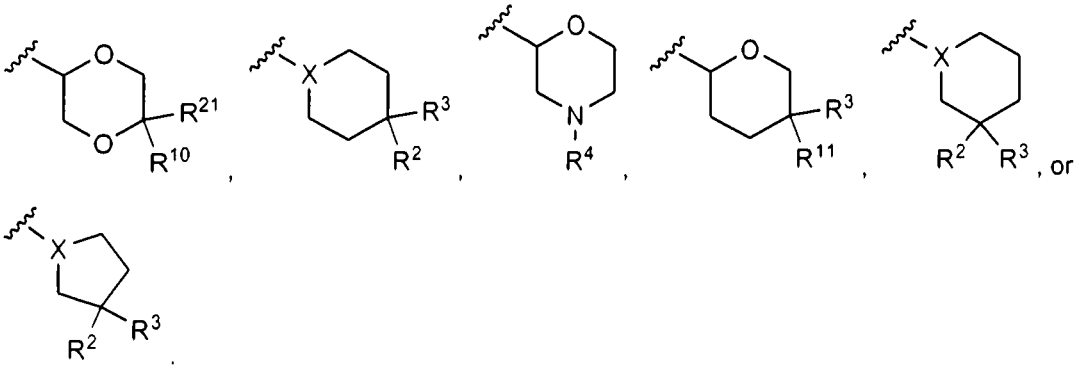


, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

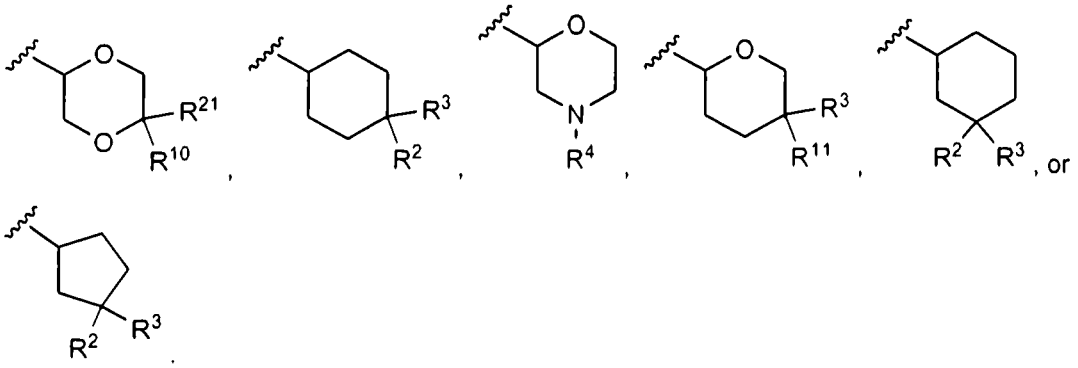
6. A compound according to claim 5 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

7. A compound according to claim 6 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more $-OR^{34}$.

8. A compound according to claim 5 wherein R^a is



9. A compound according to claim 8 wherein R^a is



10. A compound according to claim 1 wherein:

G is $-CH_2R^a$, $-CH_2CH_2R^a$, $-CH(R^a)CH_3$, $-CH_2CH_2CH_2R^a$, $-CH_2CH(CH_3)R^a$, $-CH(R^a)CH_2CH_3$, or R^a, wherein said CH, CH_2, and CH_3 groups may be substituted by one or more substituents selected from OH and F;

R^a is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or indolyl-(C_{1-6} alkylenyl), wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

Y is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein Y may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

L is triazolyl, tetrazolyl, or oxadiazolyl;

R^4 is H, -(C_{1-6} alkylene)R^6, -C(=O)R^9, or -SO_2R^{12}, wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

R^5 is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, may be substituted by one or more R^{26} substituents;

R^7 is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, -NHR^{24}, or -OR^{25}, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

R^9 is -(C_{1-6} alkylene)R^{28}, -NHR^{24}, or -OR^{25};

R^{12} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{12} may be substituted by one or more substituents selected from CN, -OR^{23}, -SO_2R^{37}, -NR^8R^{33}, -$NR^{24}C(=O)R^{23}$, and -$NR^{24}SO_2R^{23}$, provided that any one carbon atom of R^{12} is not substituted by more than one CN or more than one -OR^{23};

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl,;

R^{23} is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

R^{26} is H, OH, F, Cl, Br, NH_2, or SH;

R^{29} is H, -C(=O)CH_3, -C(=O)CH_2CH_3, -C(=O)$(CH_2)_2CH_3$, -C(=O)$CH(CH_3)_2$, -C(=O)$(CH_2)_3CH_3$, -C(=O)$CH(CH_3)CH_2CH_3$, -C(=O)$CH_2CH(CH_3)_2$, -C(=O)$(CH_2)_4CH_3$, -C(=O)$CH_2CH(CH_3)CH_2CH_3$, -C(=O)$CH_2C(CH_3)_3$, or -C(=O)$(CH_2)_5CH_3$;

R^{31} is Cl, Br, -OR^{32}, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, or -$OCH_2CH_2OR^{25}$;

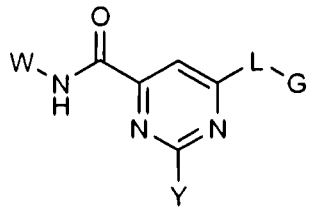
R^{32} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{32} may be substituted with one, two, or three F;

R^{36} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl; and

R^{37} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

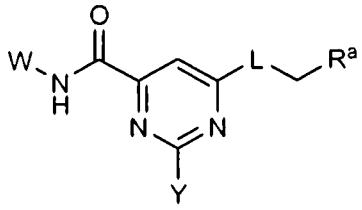
or a pharmaceutically-acceptable salt thereof.

11. A compound according to claim 1 having Formula II:



II.

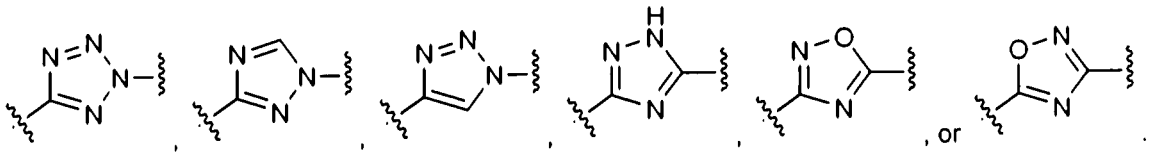
12. A compound according to claim 11 having Formula IIA:



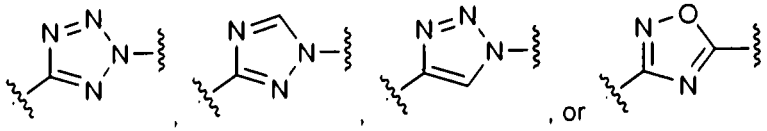
IIA.

13. A compound according to claim 12 wherein L is triazolyl, tetrazolyl, or oxadiazolyl.

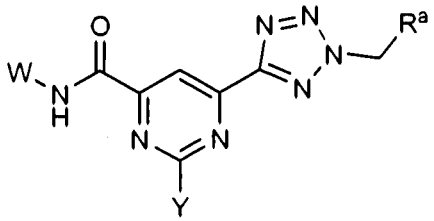
14. A compound according to claim 13 wherein L is



15. A compound according to claim 14 wherein L is

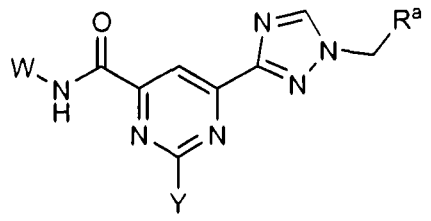


16. A compound according to claim 14 of Formula IIA-1



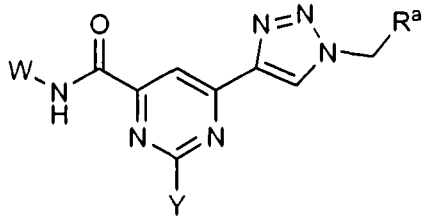
IIA-1.

17. A compound according to claim 14 of Formula IIA-2



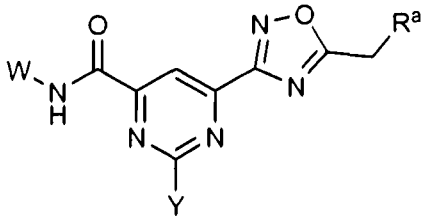
IIA-2.

18. A compound according to claim 14 of Formula IIA-3



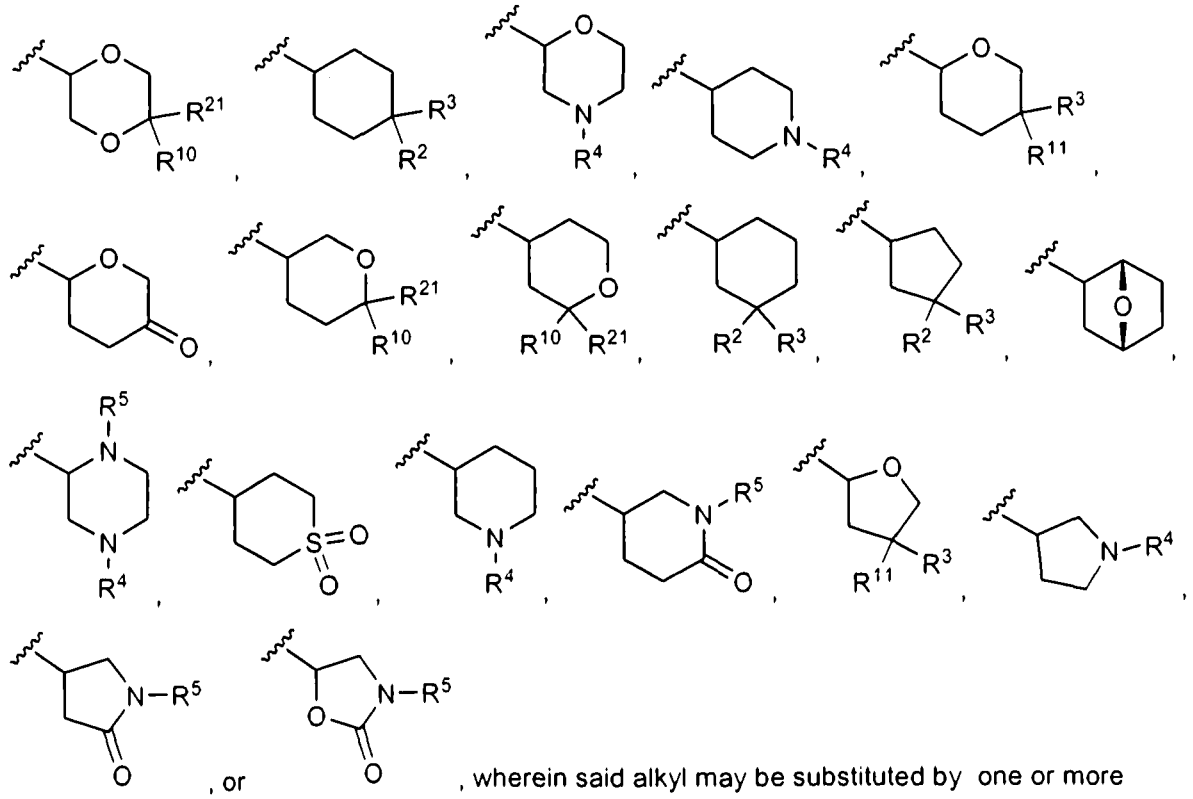
IIA-3.

19. A compound according to claim 14 of Formula IIA-4



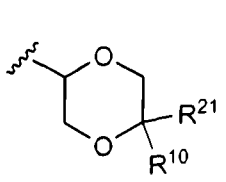
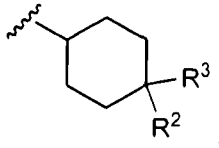
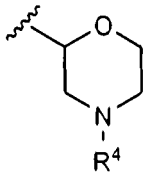
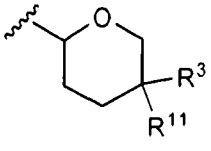
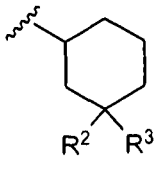
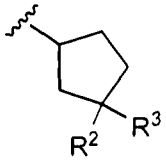
IIA-4.

20. A compound according to any one of claims 13 through 19 wherein R^a is C_{1-6} alkyl,



, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

21. A compound according to claim 20 wherein R^a is C_{1-6} alkyl,

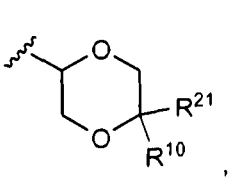
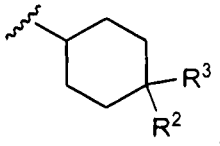
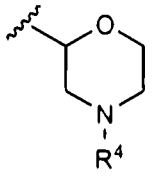
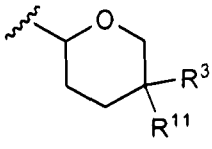
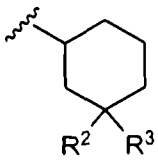
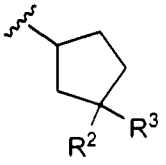







, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

22. A compound according to claim 20 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

23. A compound according to claim 22 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more $-OR^{34}$.

24. A compound according to claim 21 wherein R^a is

.

25. A compound according to any one of claims 15 through 19 wherein:

R^a is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl,

cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or indolyl-(C_{1-6} alkylenyl), wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

Y is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein Y may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

L is triazolyl, tetrazolyl, or oxadiazolyl;

R^4 is H, -(C_{1-6} alkylene)R^6, -C(=O)R^9, or -SO_2R^{12}, wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

R^5 is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, may be substituted by one or more R^{26} substituents;

R^7 is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, -NHR^{24}, or -OR^{25}, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

R^9 is -(C_{1-6} alkylene)R^{28}, -NHR^{24}, or -OR^{25};

R^{12} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{12} may be substituted by one or more substituents selected from CN, -OR^{23}, -SO_2R^{37}, -NR^8R^{33}, -$NR^{24}C(=O)R^{23}$, and -$NR^{24}SO_2R^{23}$, provided that any one carbon atom of R^{12} is not substituted by more than one CN or more than one -OR^{23};

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl,;

R^{23} is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

R^{26} is H, OH, F, Cl, Br, NH_2, or SH;

R^{29} is H, -C(=O)CH_3, -C(=O)CH_2CH_3, -C(=O)$(CH_2)_2CH_3$, -C(=O)$CH(CH_3)_2$, -C(=O)$(CH_2)_3CH_3$, -C(=O)$CH(CH_3)CH_2CH_3$, -C(=O)$CH_2CH(CH_3)_2$, -C(=O)$(CH_2)_4CH_3$, -C(=O)$CH_2CH(CH_3)CH_2CH_3$, -C(=O)$CH_2C(CH_3)_3$, or -C(=O)$(CH_2)_5CH_3$;

R^{31} is Cl, Br, -OR^{32}, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, or -$OCH_2CH_2OR^{25}$;

R^{32} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{32} may be substituted with one, two, or three F;

R^{36} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl; and

R^{37} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

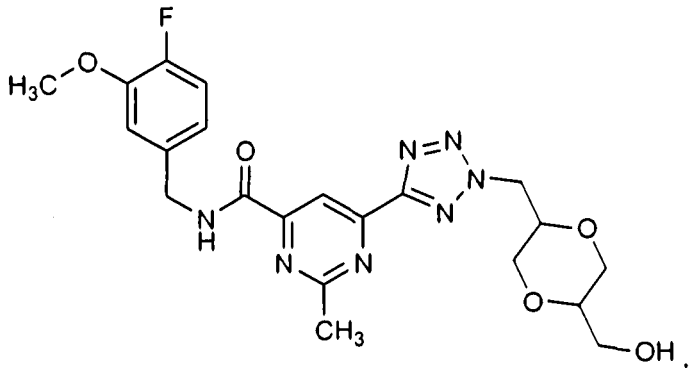
or a pharmaceutically-acceptable salt thereof.

26. A compound according to any one of claims 11 through 25 wherein Y is methyl.

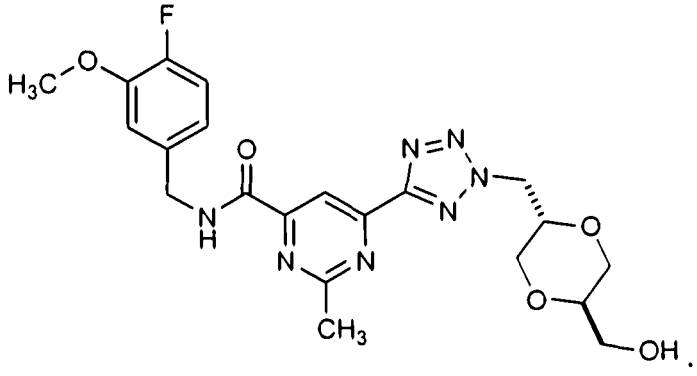
27. A compound according to any one of claims 11 through 26 wherein W is phenyl-(C_{1-6} alkylenyl), wherein said phenyl is substituted by one or more groups selected from R^{30} and R^{31}.

28. A compound according to claim 27 wherein W is phenylmethyl, wherein said phenyl is substituted by one or more groups selected from R^{30} and R^{31}.

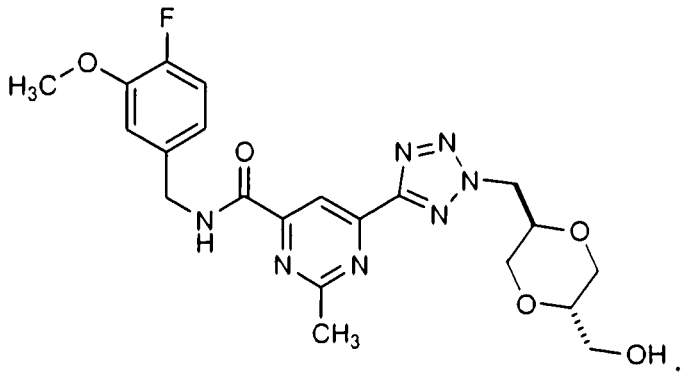
29. A compound having the structure:



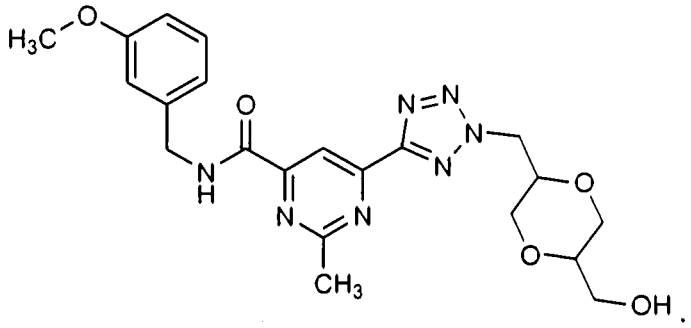
30. A compound having the structure:



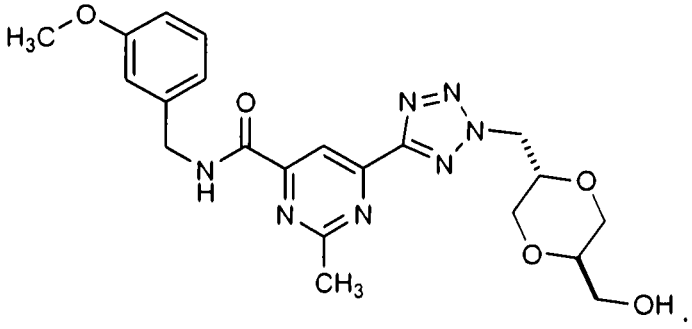
31. A compound having the structure:



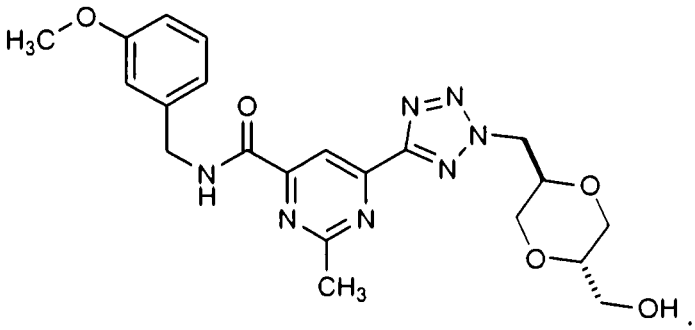
32. A compound having the structure:



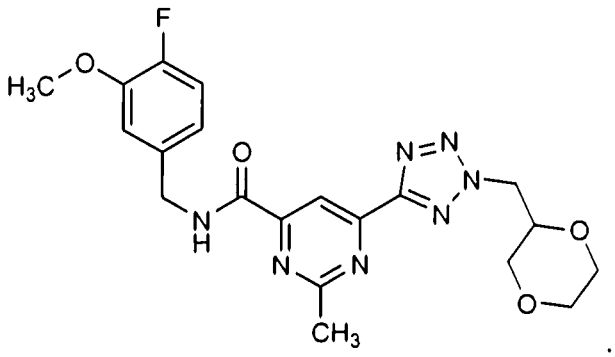
33. A compound having the structure:



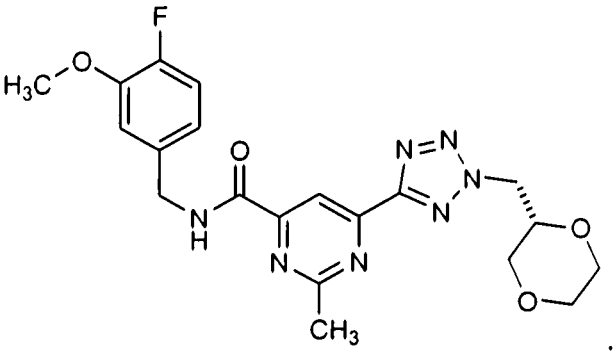
34. A compound having the structure:



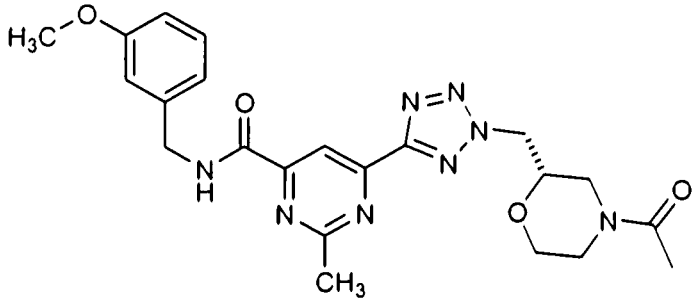
35. A compound having the structure:



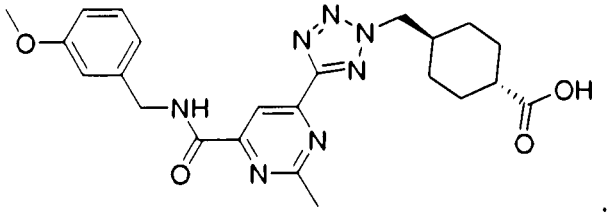
36. A compound having the structure:



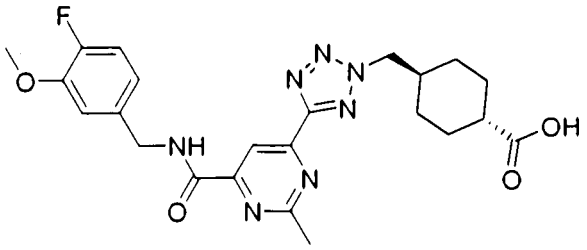
37. A compound having the structure:



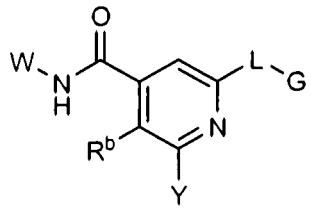
38. A compound having the structure:



39. A compound having the structure:

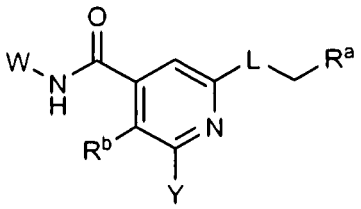


40. A compound according to claim 1 having Formula III:



III.

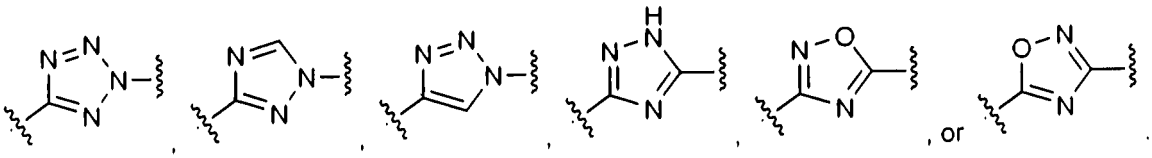
41. A compound according to claim 40 having Formula IIIA:



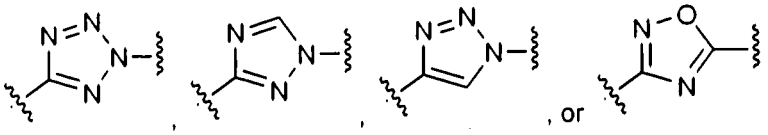
IIIA.

42. A compound according to claim 41 wherein L is triazolyl, tetrazolyl, or oxadiazolyl.

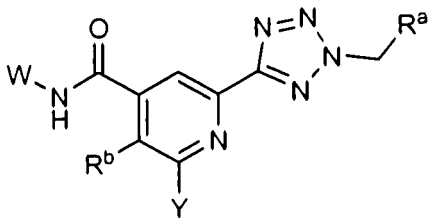
43. A compound according to claim 42 wherein L is



44. A compound according to claim 43 wherein L is

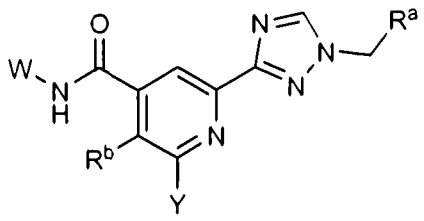


45. A compound according to claim 41 of Formula IIIA-1



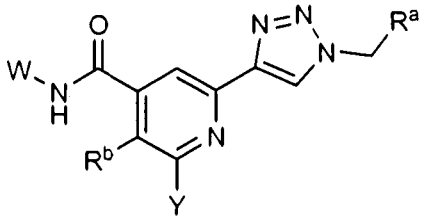
IIIA-1.

46. A compound according to claim 41 of Formula IIIA-2



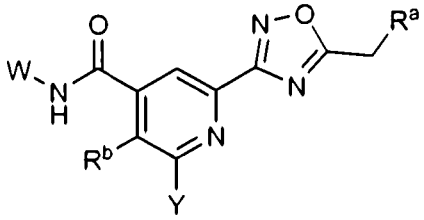
IIIA-2.

47. A compound according to claim 41 of Formula IIIA-3



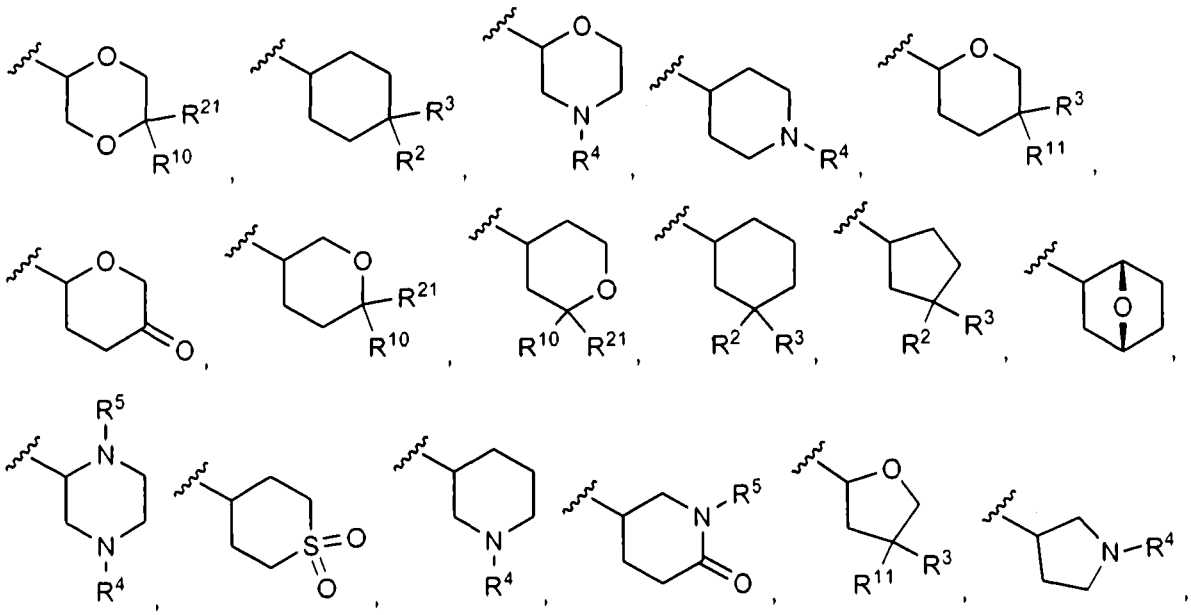
IIIA-3.

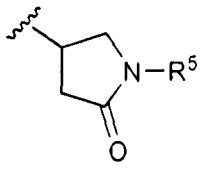
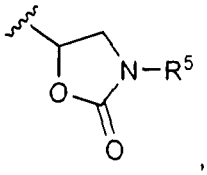
48. A compound according to claim 41 of Formula IIIA-4



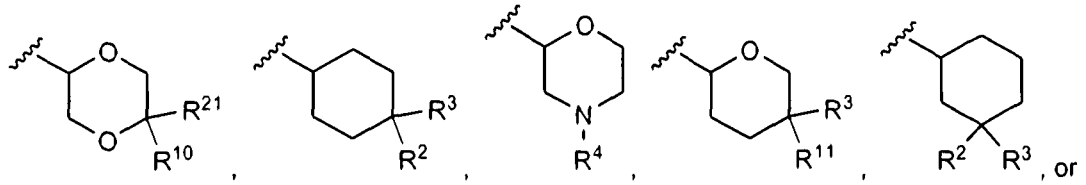
IIIA-4.

49. A compound according to any one of claims 42 through 48 wherein R^a is C_{1-6} alkyl,




, or 
, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

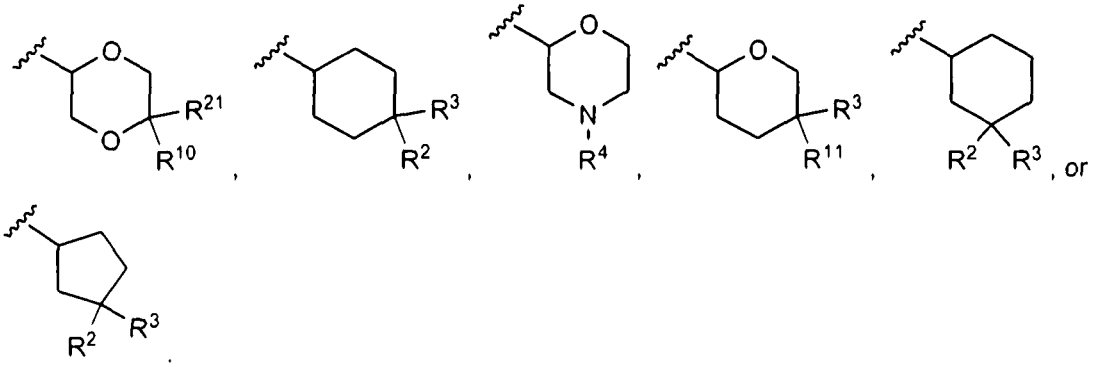
50. A compound according to claim 49 wherein R^a is C_{1-6} alkyl,


, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

51. A compound according to claim 49 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

52. A compound according to claim 51 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more $-OR^{34}$;

53. A compound according to claim 50 wherein R^a is


.

54. A compound according to any one of claims 44 through 48 wherein:

R^a is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by one or more substituents selected

from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or indolyl-(C_{1-6} alkylenyl), wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

Y is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein Y may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

L is triazolyl, tetrazolyl, or oxadiazolyl;

R^4 is H, $-(C_{1-6}$ alkylene)R^6, $-C(=O)R^9$, or $-SO_2R^{12}$, wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

R^5 is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, may be substituted by one or more R^{26} substituents;

R^7 is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, $-NHR^{24}$, or $-OR^{25}$, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

R^9 is $-(C_{1-6}$ alkylene)R^{28}, $-NHR^{24}$, or $-OR^{25}$;

R^{12} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{12} may be substituted by one or more substituents selected from CN, $-OR^{23}$, $-SO_2R^{37}$, $-NR^8R^{33}$, $-NR^{24}C(=O)R^{23}$, and $-NR^{24}SO_2R^{23}$, provided that any one carbon atom of R^{12} is not substituted by more than one CN or more than one $-OR^{23}$;

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl,;

R^{23} is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

R^{26} is H, OH, F, Cl, Br, NH_2, or SH;

R^{29} is H, $-C(=O)CH_3$, $-C(=O)CH_2CH_3$, $-C(=O)(CH_2)_2CH_3$, $-C(=O)CH(CH_3)_2$, $-C(=O)(CH_2)_3CH_3$, $-C(=O)CH(CH_3)CH_2CH_3$, $-C(=O)CH_2CH(CH_3)_2$, $-C(=O)(CH_2)_4CH_3$, $-C(=O)CH_2CH(CH_3)CH_2CH_3$, $-C(=O)CH_2C(CH_3)_3$, or $-C(=O)(CH_2)_5CH_3$;

R^{31} is Cl, Br, -OR^{32}, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, or -$OCH_2CH_2OR^{25}$;

R^{32} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{32} may be substituted with one, two, or three F;

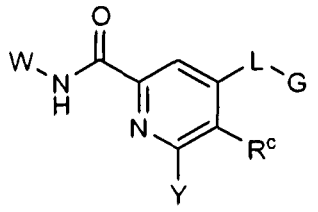
R^{36} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl; and

R^{37} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

or a pharmaceutically-acceptable salt thereof.

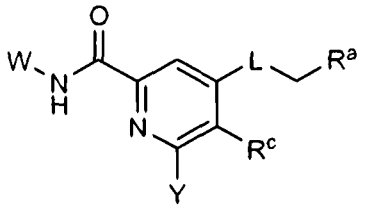
55. A compound according to any one of claims 40 through 54 wherein Y is methyl.

56. A compound according to claim 1 having Formula IV:



IV.

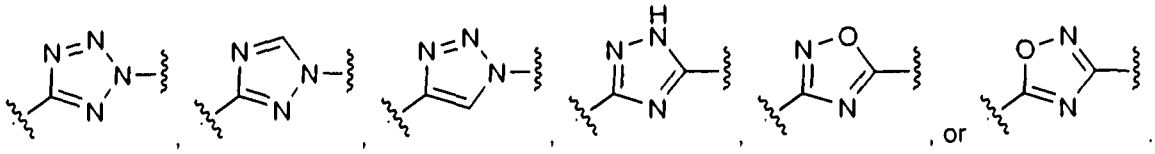
57. A compound according to claim 56 having Formula IVA:



IVA.

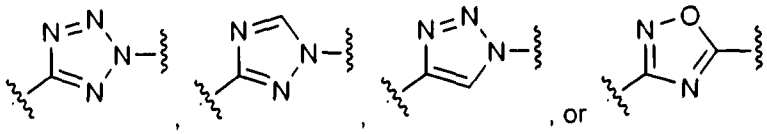
58. A compound according to claim 57 wherein L is triazolyl, tetrazolyl, or oxadiazolyl.

59. A compound according to claim 58 wherein L is



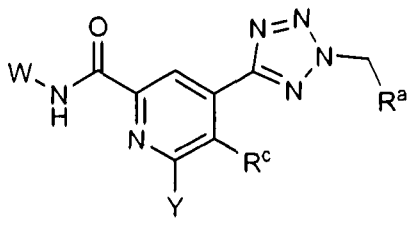
, or .

60. A compound according to claim 59 wherein L is



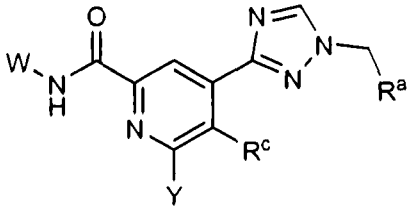
, or .

61. A compound according to claim 59 of Formula IVA-1



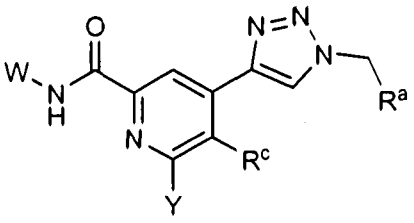
IVA-1.

62. A compound according to claim 59 of Formula IVA-2



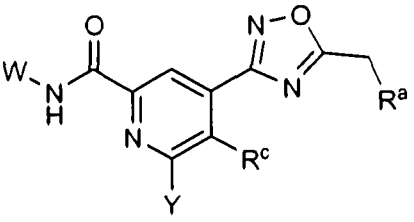
IVA-2.

63. A compound according to claim 59 of Formula IVA-3



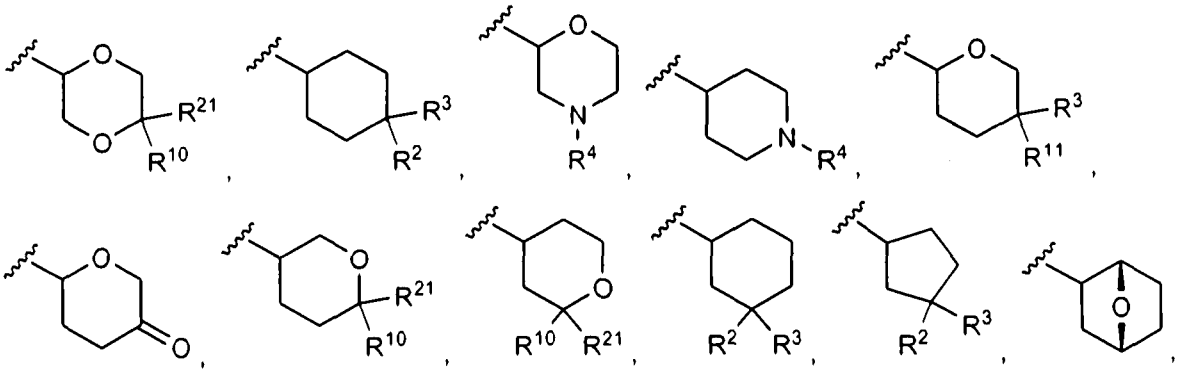
IVA-3.

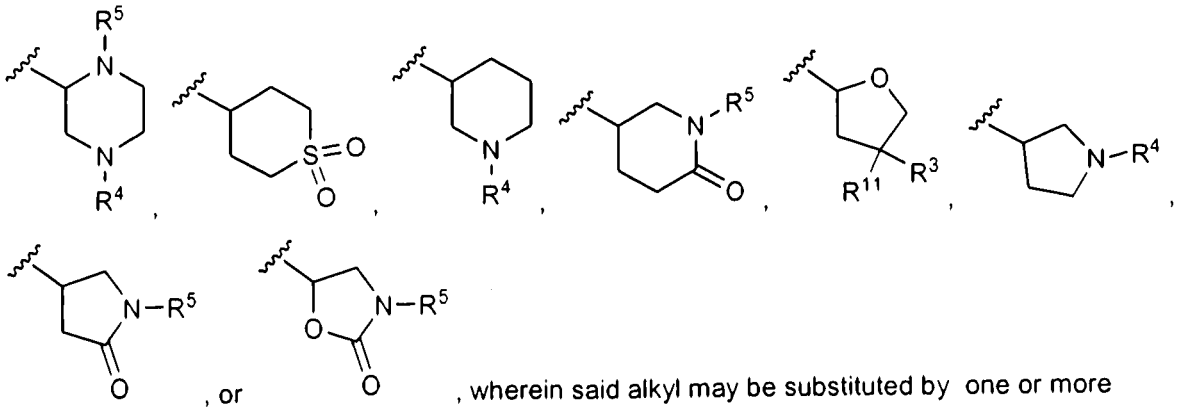
64. A compound according to claim 59 of Formula IVA-4



IVA-4.

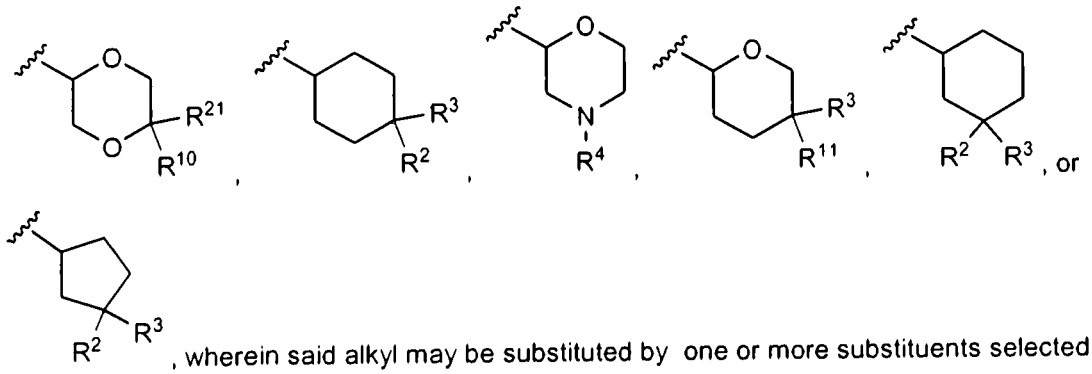
65. A compound according to any one of claims 58 through 64 wherein R^a is C_{1-6} alkyl,





substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

66. A compound according to claim 65 wherein R^a is C_{1-6} alkyl,

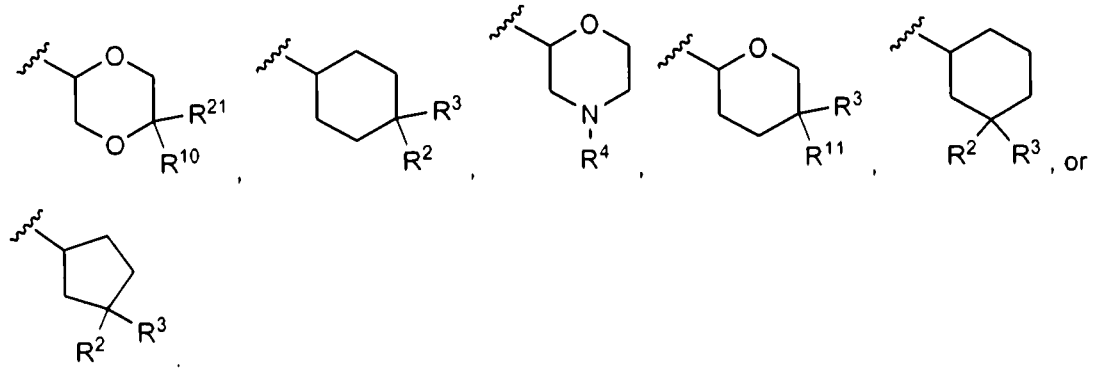


from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

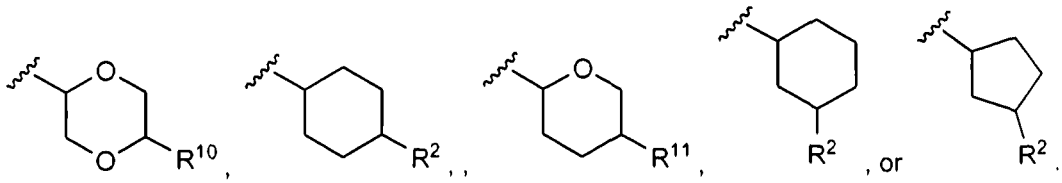
67. A compound according to claim 65 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more substituents selected
from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{35}$.

68. A compound according to claim 67 wherein R^a is C_{1-6} alkyl, wherein said alkyl may be substituted by one or more $-OR^{34}$;

69. A compound according to claim 66 wherein R^a is



70. A compound according to claim 69 wherein R^a is



R^2 is $CH(CH_3)OH$, $C(CH_3)_2OH$, $-NR^8C(=O)(C_{1-6}$ alkylene$)R^{28}$, or $-NR^8SO_2R^{36}$;

R^{10} is $CH(CH_3)OH$, or $C(CH_3)_2OH$; and

R^{11} is $CH(CH_3)OH$, $C(CH_3)_2OH$, $-NR^8C(=O)(C_{1-6}$ alkylene$)R^{28}$, or $-NR^8SO_2R^{36}$.

71. A compound according to any one of claims 60 through 64 wherein:

R^a is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by one or more substituents selected from $-OR^{34}$, $-SR^{34}$, $-C(=O)NR^{34}R^{35}$, $-NR^{34}R^{35}$, $-NR^{34}C(=O)R^{35}$, or $-NR^{34}SO_2R^{36}$, and wherein said aziridinyl, azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, oxiranyl, oxetanyl, tetrahydrofuryl, dioxolyl, tetrahydropyranyl, dioxanyl, oxazetidinyl, isoxazolidinyl, oxazolidinyl, morpholinyl, oxazinanyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl may be substituted by one or more substituents selected from R^2, R^3, R^4, R^5, R^{10}, R^{11}, and R^{21};

W is phenyl-(C_{1-6} alkylenyl), pyridyl-(C_{1-6} alkylenyl), or indolyl-(C_{1-6} alkylenyl), wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

Y is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein Y may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

L is triazolyl, tetrazolyl, or oxadiazolyl;

R^4 is H, $-(C_{1-6}$ alkylene$)R^6$, $-C(=O)R^9$, or $-SO_2R^{12}$, wherein said C_{1-6} alkylene is methylene, ethylene, 1-propylene, 2-propylene, 1-butylene, 2-butylene, 2,2-dimethylethylene, 1-pentylene, 2-pentylene, 2,2-dimethylpropylene, or 1-hexylene, and wherein said phenyl, pyridyl, or indolyl is substituted by one or more groups selected from R^{30} and R^{31};

R^5 is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, may be substituted by one or more R^{26} substituents;

R^7 is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, $-NHR^{24}$, or $-OR^{25}$, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl,

2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl may be substituted by OH or by one or more substituents selected from F, Cl, and Br;

R^9 is -(C_{1-6} alkylene)R^{28}, -NHR^{24}, or -OR^{25};

R^{12} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{12} may be substituted by one or more substituents selected from CN, -OR^{23}, -SO_2R^{37}, -NR^8R^{33}, -$NR^{24}C(=O)R^{23}$, and -$NR^{24}SO_2R^{23}$, provided that any one carbon atom of R^{12} is not substituted by more than one CN or more than one -OR^{23};

R^b, R^c, R^8, R^{20}, R^{22}, R^{24}, R^{25}, R^{33}, R^{34}, and R^{35} are independently H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl,;

R^{23} is H, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

R^{26} is H, OH, F, Cl, Br, NH_2, or SH;

R^{29} is H, -$C(=O)CH_3$, -$C(=O)CH_2CH_3$, -$C(=O)(CH_2)_2CH_3$, -$C(=O)CH(CH_3)_2$, -$C(=O)(CH_2)_3CH_3$, -$C(=O)CH(CH_3)CH_2CH_3$, -$C(=O)CH_2CH(CH_3)_2$, -$C(=O)(CH_2)_4CH_3$, -$C(=O)CH_2CH(CH_3)CH_2CH_3$, -$C(=O)CH_2C(CH_3)_3$, or -$C(=O)(CH_2)_5CH_3$;

R^{31} is Cl, Br, -OR^{32}, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, or -$OCH_2CH_2OR^{25}$;

R^{32} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein R^{32} may be substituted with one, two, or three F;

R^{36} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl; and

R^{37} is methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, or 1-hexyl, wherein said methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2,2-dimethylethyl, 1-pentyl, 2-pentyl, 2,2-dimethylpropyl, 1-hexyl, may be substituted by OH;

or a pharmaceutically-acceptable salt thereof.

72. A compound according to any one of claims 56 through 71 wherein Y is methyl.

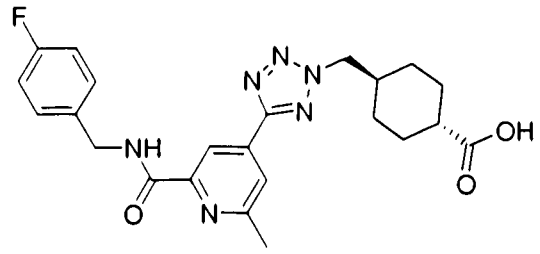
73. A compound according to any one of claims 56 through 71 wherein W is phenyl-(C_{1-6} alkylenyl), wherein said phenyl is substituted by one or more groups selected from R^{30} and R^{31}.

74. A compound according to claim 73 wherein W is phenylmethyl, wherein said phenyl is substituted by one or more groups selected from R^{30} and R^{31}.

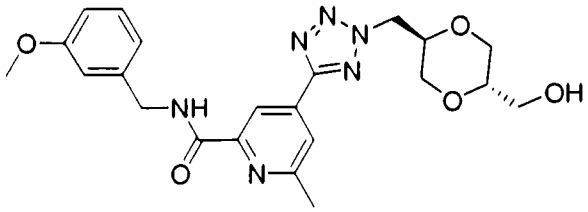
75. A compound which is: [pyridine triazole names – update or remove]

76. A compound which is: [pyridine tetrazole names – update or remove]

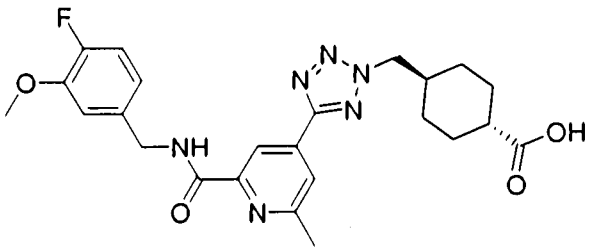
77. A compound having the structure:



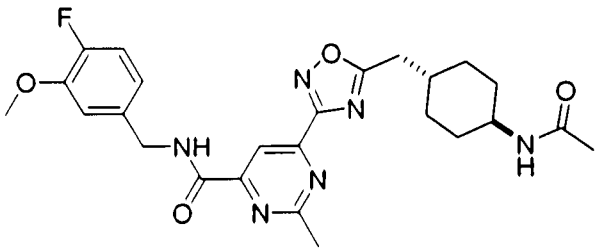
78. A compound having the structure:



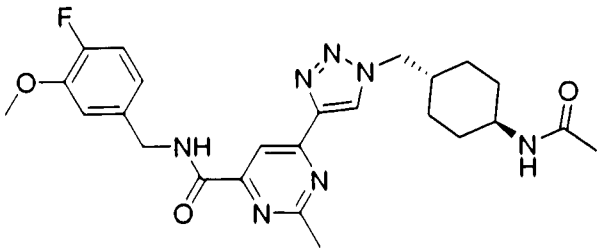
79. A compound having the structure:



80. A compound having the structure:



81. A compound having the structure:



82. A pharmaceutical composition, comprising a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

83. A method for inhibiting an MMP-13 enzyme in an animal, comprising administering to the animal an MMP-13 inhibiting amount of a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof.

84. A method for treating a disease mediated by an MMP-13 enzyme, comprising administering to a patient suffering from such a disease a nontoxic effective amount of a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof.

85. A method for treating arthritis, comprising administering to a patient suffering from an arthritis disease a nontoxic antiarthritic effective amount of a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof.

86. A method for treating osteoarthritis, comprising administering to a patient suffering from osteoarthritis a nontoxic effective amount of a compound according to any one of claims 1 through 79, or a pharmaceutically acceptable salt thereof.

87. A method for treating rheumatoid arthritis, comprising administering to a patient suffering from rheumatoid arthritis a nontoxic effective amount of a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof.

88. A method for treating psoriatic arthritis, comprising administering to a patient suffering from psoriatic arthritis a nontoxic effective amount of a compound according to any one of claims 1 through 79, or a pharmaceutically acceptable salt thereof.

89. A method for treating a cancer, comprising administering to a patient suffering from a cancer a nontoxic anti-cancer effective amount of a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof.

90. A method for treating inflammation, comprising administering to a patient suffering from inflammation a nontoxic effective amount of a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof.

91. A method for treating chronic obstructive pulmonary disease, comprising administering to a patient suffering from chronic obstructive pulmonary disease a nontoxic effective amount of a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof.

92. A method for treating psoriasis, comprising administering to a patient suffering from psoriasis a nontoxic effective amount of a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof.

93. A method for treating asthma, comprising administering to a patient suffering from asthma a nontoxic effective amount of a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof.

94. A method for treating inflammatory bowel disease, comprising administering to a patient suffering from inflammatory bowel disease a nontoxic effective amount of a compound according to any one of claims 1 through 81, or a pharmaceutically acceptable salt thereof.