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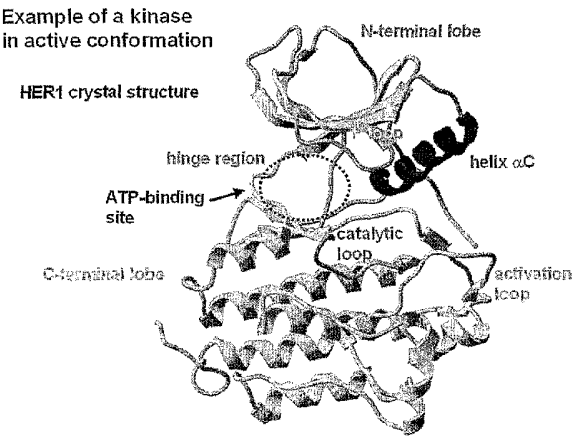
X-ray structure of HER1, color-coded by key elements of a typical kinase.



(57) Abstract: The present invention provides compounds of formula (I); and pharmaceutically acceptable salts thereof. The formula (I) compounds inhibit tyrosine kinase activity of growth factor receptors such as HER1, HER2 and HER4 thereby making them useful as antiproliferative agents. The formula (I) compounds are also useful for the treatment of other diseases associated with signal transduction pathways operating through growth factor receptors.

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PYRROLOTRIAZINE COMPOUNDS AS KINASE INHIBITORS

This application claims priority from U.S. Provisional Application No. 60/533,335 filed December 29, 2003, the disclosures of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to compounds that inhibit the tyrosine kinase activity of growth factor receptors such as HER1, HER2, and HER4 thereby making them useful as anti-cancer agents. The compounds are also useful in the treatment of diseases, other than cancer, which are associated with signal transduction pathways operating through growth factor receptors such as HER1, HER2 and HER4.

BACKGROUND OF THE INVENTION

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain.

The human epidermal growth factor receptor (HER) family consists of four distinct receptor tyrosine kinases referred to HER1, HER2, HER3, and HER4. These kinases are also referred to as erbB1, erbB2, etc. HER1 is also commonly referred to as the epidermal growth factor (EGF) receptor. With the exception of HER3, these receptors have intrinsic protein kinase activity that is specific for tyrosine residues of phosphoacceptor proteins. The HER kinases are expressed in most epithelial cells as well as tumor cells of epithelial origin. They are also often expressed in tumor cells of mesenchymal origin such as sarcomas or rhabdomyosarcomas. RTKs such as HER1 and HER2 are involved in cell proliferation and are associated with diseases such as psoriasis and cancer. Disruption of signal transduction by inhibition of these kinases would have an antiproliferative and therapeutic effect.

The enzymatic activity of receptor tyrosine kinases can be stimulated by either overexpression, or by ligand-mediated dimerization. The formation of homodimers as well as heterodimers has been demonstrated for the HER receptor family. An

example of homodimerization is the dimerization of HER1 (EGF receptor) by one of the EGF family of ligands (which includes EGF, transforming growth factor alpha, betacellulin, heparin-binding EGF, and epiregulin). Heterodimerization among the four HER receptor kinases can be promoted by binding to members of the heregulin (also referred to neuregulin) family of ligands. Such heterodimerization as involving HER2 and HER3, or a HER3/HER4 combination, results in a significant stimulation of the tyrosine kinase activity of the receptor dimers even though one of the receptors (HER3) is enzymatically inert. The kinase activity of HER2 has been shown to be activated also by virtue of overexpression of the receptor alone in a variety of cell types. Activation of receptor homodimers and heterodimers results in phosphorylation of tyrosine residues on the receptors and on other intracellular proteins. This is followed by the activation of intracellular signaling pathways such as those involving the microtubule associated protein kinase (MAP kinase) and the phosphatidylinositol 3-kinase (PI3 kinase). Activation of these pathways have been shown to lead to cell proliferation and the inhibition of apoptosis. Inhibition of HER kinase signaling has been shown to inhibit cell proliferation and survival.

All protein kinases contain a structurally conserved catalytic domain of approximately 250-300 amino acid residues[1]. Figure 1 shows an X-ray structure of HER1[2] which encompasses the highly conserved features of all members of the protein kinase family. The protein kinase fold is separated into two subdomains, or lobes. The smaller N-terminal lobe, or N lobe, is composed of a five-stranded β sheet and one prominent α helix, called helix αC. The C lobe is larger and is predominantly helical. The two lobes are connected through a single polypeptide strand (the linker/hinge region), which acts as a hinge about which the two domains can rotate with respect to one other upon binding of ATP and/or substrate. ATP is bound in the deep cleft between the two lobes and sits beneath a highly conserved loop connecting strands β1 and β2. This phosphate binding loop, or P loop, contains a conserved glycine-rich sequence motif (GXGXφG) where φ is usually tyrosine or phenylalanine. The glycine residues allow the loop to approach the phosphates of ATP very closely and to coordinate them via backbone interactions. The conserved aromatic side chain caps the site of phosphate transfer. ATP is anchored to the enzyme via hydrogen

bonds between its adenine moiety and the backbone atoms of the linker region, and the ribose ring to residues at the start of the C-terminal domain.

Optimal phosphotransfer requires the precise spatial arrangement of several catalytic residues that are absolutely conserved among all known kinases. Asp813 and Asn818 (HER1 numbering as given in reference 2 or numbered as Asp837 and Asn842 as found in REFSEQ: accession NM_005228) emanate from a highly conserved loop structure at the base of the active site, called the catalytic loop. Asp813 interacts with the attacking hydroxyl side chain of the substrate, while Asn818 engages in hydrogen bonding interactions that orient Asp813. Asn818 and another absolutely conserved catalytic residue, Asp831 (numbered as Asp855 as found in REFSEQ: accession NM_005228), are also required for the binding of two divalent metal cations involved in coordination of the triphosphate group.

Numerous structures of complexes with ATP, its analogs, or small-molecule inhibitors bound to different protein kinases have provided a clear description of the organization of the catalytic domain and the ATP-binding cleft and of the similarities and differences that exist within the binding region[3]. It is now clear that there are regions within the binding cleft that are not occupied by ATP, and that these show structural diversity between members of the kinase family. Figure 2 shows the interactions of ATP with the hinge region of human cyclin-dependent kinase 2 (CDK2)[4]. The generic regions of all known kinase ATP binding sites are delineated in the figure as: (1) the adenine binding region; (2) the ribose pocket; (3) the phosphate binding pocket; (4) a mostly hydrophobic region 1, behind the adenine ring, and (5) region 2, a cleft or a tunnel adjacent to the ribose pocket and the N3 nitrogen of adenine which points towards a surface-exposed area of the kinase domain. The available structures of kinase/inhibitor complexes indicate that one can take advantage of the regions not occupied by ATP, e.g. regions 1 and 2, for increasing binding interactions and hence binding potency and potentially because of sequence differences between kinases in these regions also modulate selectivity.

A combination of crystallography, modeling, screening and medicinal chemistry efforts has led to the understanding of the binding mode of the pyrrolotriazine chemotype in the ATP binding site. Based on an X-ray crystal structure of the pyrrolotriazine chemotype inhibitor in VEGFR-2, it has been shown

that the pyrrolotriazine ring binds in the adenine pocket and makes several key interactions with the hinge region similarly to ATP. In this binding mode, the C5 group is directed into the highly conserved ribose-phosphate pockets. The C4 group, depending on its chemical constituency, can be directed into the specificity region 1 and the C6 group is directed into the specificity region 2. Modeling of enumerated examples of this chemotype in HER1 shows that the C5 group claimed in this invention can at the least occupy the ribose-phosphate pocket and interact with at least one or more of the absolutely conserved residues involved in phosphate binding, e.g., Asn818 and Asp831 (HER1 numbering).

The conserved nature of the kinase catalytic core structure makes it an excellent target for the generic kinase inhibitor template afforded by the pyrrolotriazine ring and the C5 group. This template can be successfully derivatized to make specific and potent kinase ATP-competitive inhibitors by targeting the poorly conserved areas of the ATP-binding site.

It has surprisingly been found that compounds of the invention and other compounds such as those disclosed in U.S. Patents U.S. 5,457,105, 5,616,582 and 5,770,599, which contain a small aniline derivative as the substituent off of the C4 position of the bicyclic ring, exhibit both HER1 and HER2 activity.

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(4) PDB ID: 1HCK

Schulze-Gahmen, U., De Bondt, H. L., Kim, S. H.: High-resolution crystal structures of human cyclin-dependent kinase 2 with and without ATP: bound waters and natural ligand as guides for inhibitor design. J Med Chem 39 pp. 4540 (1996).

BRIEF DESCRIPTION OF THE DRAWINGS

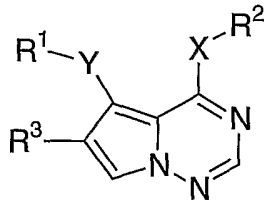
Figure 1 depicts the X-ray structure of HER1, color-coded by key elements of a typical kinase.

Figure 2 depicts an X-ray structure of CDK2 complexed with ATP. Different regions of a typical ATP-binding site are delineated.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds.

In accordance with the present invention, there are disclosed compounds of formula I



(I)

wherein the symbols have the following meanings and are, for each occurrence, independently selected:

R^1 is cycloalkyl or substituted cycloalkyl, aryl or substituted aryl, heterocyclyl or substituted heterocyclyl;

R^2 is aryl, substituted aryl, heteroaryl or substituted heteroaryl, heterocyclyl or substituted heterocyclyl;

R^3 is hydrogen, alkyl or substituted alkyl;

X is a direct bond, $-NR^3-$ or -O- ;

Y is a direct bond, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl;

or a pharmaceutically acceptable salt or stereoisomer thereof,

with the proviso that R^2 is not indazolyl or substituted indazolyl.

These compounds inhibit the tyrosine kinase activity of growth factor receptors such as HER2.

In another embodiment, the invention comprises a compound of formula I wherein

R^1 is heterocyclyl or substituted heterocyclyl;

R^2 is aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R^3 is hydrogen;

X is $-NR^3-$ or -O- ;

Y is alkyl or substituted alkyl;

or a pharmaceutically acceptable salt or stereoisomer thereof.

Preferred R^2 substituents include

oxazolyl, thienyl, pyridinyl, thiazolyl, pyrazinyl, and phenyl, all of which may be suitably substituted with one or more substitutents.

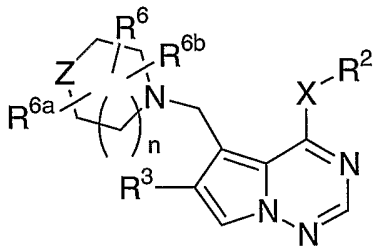
Preferred R^1 substituents include

benzyl, imidazolyl-ethyl, (methyl-imidazolyl)-ethyl, piperidinyl-ethyl, pyridinyl-propyl, pyridinyl-methyl, morpholinyl-ethyl, (methyl-imidazolyl)-methyl, pyridinyl-ethyl, amino- piperidinyl-methyl, 4-amino-1-methyl-piperidin-3-ol, (methyl-piperazinyl)-ethyl, pyridinyl-ethyl, (methyl-piperidinyl)-ethyl, (methyl-imidazolyl)-propyl, (methyl-piperidinyl)-methyl, (methyl-piperazinyl)-propyl, diisopropylamino-ethyl, piperidinyl-propyl, dimethylamino-ethyl, dimethylamino-propyl, [(trifluoro-acetyl)-piperidinyl]-propyl, piperidinyl-ethyl, piperazinyl-ethyl, piperazinyl-propyl, pyrrolidinyl-ethyl, triazolyl-ethyl, triazolyl-propyl, (dimethylamino-ethoxy)-ethyl, imidazolyl-propyl, [(trifluoro-acetyl)-piperidinyl]-propyl, (piperazinyl-ethoxy)-ethyl, [(trifluoro-acetyl)-piperazinyl]-propyl, [(trifluoro-acetyl)-piperazinyl]-ethyl, piperidinyl-methyl, pyrazolyl-ethyl, (amino-ethoxy)-ethyl, (methoxy-ethoxy)-ethyl, pyrazolyl-propyl, [(methoxy-ethyl)-methyl-amino]-ethyl, morpholinyl-propyl,

(cyanomethyl-piperazinyl)-ethyl, [(cyano-ethyl)-methyl-amino]-ethyl, [(methoxy-ethyl)-piperidinyl]-methyl, [(methoxy-ethyl)-piperidinyl]-ethyl, [(fluoro-ethyl)-methyl-amino]-ethyl, [(fluoro-ethyl)-methyl-amino]-propyl, (methyl-piperidinyl)-propyl, [(methanesulfonyl-ethyl)-piperazinyl]-ethyl, [(cyano-ethyl)-piperazinyl]-ethyl, [(methoxy-ethyl)-piperazinyl]-ethyl, [(methoxy-ethyl)-methyl-amino]-propyl, (cyanomethyl-methyl-amino)-propyl, (cyanomethyl-methyl-amino)-ethyl, [(methanesulfonyl-ethyl)-methyl-amino]-propyl, (difluoro-piperidinyl)-propyl, (difluoro-piperidinyl)-ethyl, [(cyano-ethyl)-methyl-amino]-propyl, [(methanesulfonyl-ethyl)-methyl-amino]-ethyl, [(trifluoro-ethyl)-piperazinyl]-ethyl, [cyanomethyl-(methanesulfonyl-ethyl)-amino]-propyl, [cyanomethyl-(methanesulfonyl-ethyl)-amino]-ethyl, (cyanomethyl-piperazinyl)-propyl, [(methanesulfonyl-ethyl)-piperazinyl]-propyl, [(cyano-ethyl)-piperazinyl]-propyl, [(trifluoro-ethyl)-piperazinyl]-propyl, (methanesulfonyl-ethyl-amino)-ethyl, [(cyano-ethyl)-piperidinyl]-methyl, (cyanomethyl-piperidinyl)-methyl, (hydroxy-piperidinyl)-propyl, [(methanesulfonyl-ethyl)-piperidinyl]-methyl, piperidinyl-methyl, piperidinyl, imidazolyl-propyl, 1-methyl-[1,4]-diazepan-6-ol, methanesulfonyl-propyl, (methanesulfonyl-ethyl-amino)-propyl, pyrrolidinyl-methyl, methanesulfonyl-ethyl, (cyanomethyl-amino)-ethyl, (cyanomethyl-amino)-propyl, (dioxo-thiomorpholinyl)-propyl, (oxo-piperidinyl)-propyl, [(difluoro-ethyl)-methyl-amino]-ethyl, morpholinyl-methyl, (hydroxy-pyrrolidinyl)-propyl, (hydroxy-piperidinyl)-propyl, pyrrolidinyl-methyl, (hydroxy-pyrrolidinyl)-propyl, methyl-piperidinyl, (methyl-pyrrolidinyl)-methyl, morpholinyl-methyl, pyrrolidinyl-methyl, (methyl-tetrahydro-pyridinyl)-methyl, (cyano-ethyl)-piperidinyl, azetidinyl, (methanesulfonyl-ethyl)-piperidinyl, (cyano-methyl)-piperidinyl, isopropyl-piperidinyl, propyl-piperidinyl, acetyl-piperidinyl, ethyl-piperidinyl, allyl-piperidinyl, tetrahydro-pyranyl, (hydroxy-ethyl)-piperidinyl, (methyl-pyrrolidinyl)-methyl, (methoxyethyl)-piperidinyl, piperidinyl, (methoxy-ethyl)-azetidinyl, (methoxy-methoxymethyl-ethyl)-piperidinyl, (methoxy-acetyl)-piperidinyl, methoxycarbonyl-piperidnyl, (hydroxy-acetyl)-piperidinyl, piperidine-carboxylic acid-acetoxy-ethyl, piperidine-carboxylic acid-acetoxy-methyl-ethyl, hydroxy-piperidinyl, amino-cyclohexyl, piperidinyl, piperidine-carboxylic acid-methyl-oxo-dioxolylmethyl, hydroxymethyl-piperidinyl, (aminomethyl)-cyclohexyl, amino-methyl-cyclohexyl, hydroxy-piperidinyl-methyl, morpholinyl, amino-cyclohexyl,

hydroxymethyl-piperidinyl, tetrahydro-pyranyl, methanesulfonyl-propyl, amino-methyl-propyl, amino-cyclohexyl, amino-methyl-cyclohexyl, (hydroxy-piperidinyl)-propyl, piperidinyl, amino-propyl, morpholinyl-methyl, piperidinyl, (tert-butoxycarbonyl-morpholinyl)-methyl, benzyl, imidazolyl-ethyl, piperidinyl-ethyl, methoxyethyl, (diethylamino)-(methoxyethyl), pyrrolidinyl-ethyl, acetamide and methyl.

In another embodiment, the invention comprises a compound of formula II,



(II)

wherein

X is a direct bond, $-NR^3-$ or -O- ;

Z is $-\overset{R^6}{\underset{|}{C}}H-$ or $-NR^7-$;

R^2 is aryl or substituted aryl, heteroaryl or substituted heteroaryl,

R^3, R^4 and R^5 are independently selected from hydrogen, alkyl and substituted alkyl;

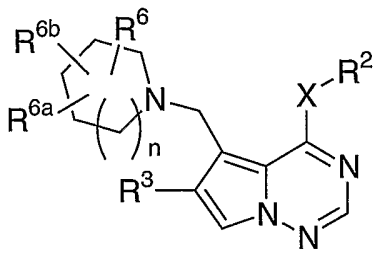
R^6, R^{6a} and R^{6b} are independently selected from the group consisting of one or more hydrogen, halogen, alkyl, alkoxy, aryloxy, -CN, $-NH_2$, -OH, -COOH, $-CH_2OR^5$, $-CONHSO_2R^5$, $-CONR^4R^5$, -NHalkyl, -NHCOalkyl, $-NR^4SO_2$alkyl, $-NR^4SO_2NR^4R^5$, $-OCONR^4R^5$, $-CF_3$ and $-OCF_3$, two of which may be attached to the same ring carbon atom provided that the resultant compound is chemically stable;

R^7 is hydrogen, alkyl or $-NH_2$, and

n is 0, 1, 2 or 3;

or a pharmaceutically acceptable salt or stereoisomer thereof.

In another embodiment, the invention comprises a compound of formula III,



(III)

wherein

X is a direct bond, $-NR^3-$ or -O- ;

R^2 is aryl or substituted aryl, heteroaryl or substituted heteroaryl,

R^3, R^4 and R^5 are independently selected from hydrogen, alkyl and substituted alkyl;

R^6, R^{6a} and R^{6b} are independently selected from the group consisting of one or more hydrogen, halogen, alkyl, alkoxy, aryloxy, -CN, $-NH_2$, -OH, -COOH, $-CH_2OR^5$, $-CONHSO_2R^5$, $-CONR^4R^5$, -NHalkyl, -NHCOalkyl, $-NR^4SO_2$alkyl, $-NR^4SO_2NR^4R^5$, $-OCONR^4R^5$,$-CF_3$ and $-OCF_3$, two of which may be attached to the same ring carbon atom provided that the resultant compound is chemically stable; and

n is 0, 1, 2 or 3;

or a pharmaceutically acceptable salt or stereoisomer thereof.

In another embodiment, the invention comprises a compound of formula III, wherein

R^2 is phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, oxazole, substituted oxazole, thiazole, substituted thiazole, pyrazinyl or substituted pyrazinyl;

R^6, R^{6a} and R^{6b} are independently selected from the group consisting of one or more hydrogen, $-NH_2$, OH, alkoxy, $-CONR^4R^5$, $-NR^4SO_2$alkyl, $-NR^4SO_2NR^4R^5$, $-OCONR^4R^5$, -NHalkyl and -NHCOalkyl;

X is –NH-;and

n is 1 or 2.

Preferred compounds of the invention include the following

5-[(4-Amino-1-piperidinyl)methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-amine,

5-[(4-Amino-1-piperidinyl)methyl]-N-2-naphthalenylpyrrolo[2,1-f][1,2,4]triazin-4-amine,

5-[(4-Amino-1-piperidinyl)methyl]-N-phenylpyrrolo[2,1-f][1,2,4]triazin-4-amine,

5-[(4-Amino-1-piperidinyl)methyl]-N-(3-methoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine,

5-[(4-Amino-1-piperidinyl)methyl]-N-(3-ethynylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine,

5-[(4-aminopiperidin-1-yl)methyl]-*N*-(4-fluoro-3-methoxyphenyl)pyrro-lo[2,1-*f*][1,2,4]triazin-4-amine,

(3R,4R)-4-amino-1-[[4-[(3-chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol,

(3S,4S)-4-amino-1-[[4-[(3-chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol,

(3R,4R)-4-amino-1-[[4-[(3-methoxyphenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol,

(3S,4S)-4-amino-1-[[4-[(3-methoxyphenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol,

(3R,4R)-4-amino-1-[[4-[(3-methoxy-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*]-[1,2,4]-triazin-5-yl}-methyl)piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-ethoxyphenyl)-amino]-pyrrolo[2,1-*f*]-[1,2,4]triazin-5-yl}-methyl)piperidin-3-ol

(3*R*,4*R*)-4-amino-1-{[4-(2-naphthylamino)-pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl]methyl}piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxy-4-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-bromophenyl)amino]pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-fluoro-5-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol,

(3*S*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol,

(3*R*,4*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol

(3*S*,4*R*)-4-amino-1-({4-[(3-chlorophenyl)amino]-pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-ol,

(3*S*,4*R*)-4-amino-1-({4-[(3-chloro-4-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol,

(3*S*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl) amino]pyrrolo[2,1-*f*][1, 2,4]triazin-5-yl}methyl) piperidin-3-ol,

(3*R*,4*S*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1, 2,4]triazin-5-yl}methyl)piperidin-3-ol,

(3*R*,4*S*)-4-amino-1-({4-[(3-chlorophenyl)amino]pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl carbamate,

(3*R*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1, 2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate,

(3*R*,4*R*)-4-amino-1-({4-[(3-chloro-4-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate,

(3*S*,4*R*)-4-amino-1-({4-[(3-chloro-4-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate,

(3*S*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1, 2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate,

(3*S*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-3-methylpiperidin-3-ol,

(3R/*S*,5R/*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3,5-diol,

(3*S*,5*S*)-4-amino-1-({4-[(4-fluoro-3-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidine-3,5-diol,

(3*R*,5*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1, 2,4]triazin-5-yl}methyl)piperidine-3,5-diol,

5-{[(3*R*,4*R*)-4-amino-3-methoxypiperidin-1-yl]methyl}-*N*-(3-methoxyphenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine,

5-(((4aR,8aR)-*rel*-hexahydro-1H-pyrido[3,4-b][1,4]oxazin-6(7H)-yl)methyl)-N-(3-methoxyphenyl)pyrrolo[1,2-f][1,2,4]triazin-4-amine,

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-(methylsulfonyl)piperidine-3-carboxamide,

(3*R*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-methylpiperidine-3-carboxamide,

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-methylpiperidine-3-carboxamide,

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3-carboxamide,

((3R,4R)-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-f][1,2,4]-triazin-5-yl)methyl)-4-((R)-1-phenylethylamino)piperidin-3-yl)methanol,

N-[(3R,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]urea,

N-[(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]methanesulfonamide, and

N-[(3S,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]methanesulfonamide,

or a pharmaceutically acceptable salt thereof.

The following are definitions of terms that may be used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated.

The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group substituted by, for example, one to four substituents, such as, halo, hydroxy, alkoxy, oxo, alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, e.g. SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, e.g. $CONH_2$, substituted carbamyl e.g. CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino, heterocyclyl, e.g., indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, homopiperazinyl and the like, and substituted heterocyclyl. Where noted above where the substituent is further substituted it will be with alkyl, alkoxy, aryl or aralkyl.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, biphenyl and diphenyl groups, each of which may be substituted.

The term "aralkyl" refers to an aryl or a substituted aryl group bonded directly through an alkyl group, such as benzyl.

The term "aryloxy" refers to an aryl or a substituted aryl group bonded directly through an alkoxy group, such as methoxy or ethoxy.

The term "substituted aryl" refers to an aryl group substituted by, for example, one to four substituents such as alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aralkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, aryloxy, aralkyloxy, amino, alkylamino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio,

ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and the like. The substituent may be further substituted by hydroxy, halo, alkyl, alkoxy, alkenyl, alkynyl, aryl or aralkyl.

The term "heteroaryl" refers to an optionally substituted, aromatic group for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom and at least one carbon atom-containing ring, for example, pyridine, tetrazole, indazole.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 20 carbon atoms, preferably 2 to 15 carbon atoms, and most preferably 2 to 8 carbon atoms, having one to four double bonds.

The term "substituted alkenyl" refers to an alkenyl group substituted by, for example, one to two substituents, such as, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 20 carbon atoms, preferably 2 to 15 carbon atoms, and most preferably 2 to 8 carbon atoms, having one to four triple bonds.

The term "substituted alkynyl" refers to an alkynyl group substituted by, for example, a substituent, such as, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino and heterocyclyl, e.g. imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocylic ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cycloctyl, cyclodecyl, cyclododecyl, and adamantyl. Exemplary

substituents include one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

The terms "heterocycle", "heterocyclic" and "heterocyclyl" refer to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, homopiperazinyl, 2-oxohomopiperazinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1, 1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic heterocyclic groups include 2,3-dihydro-2-oxo-1H-indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, indazolyl, isochromanyl, isoindolinyl, naphthyridinyl,

phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

Exemplary substituents include one or more alkyl or aralkyl groups as described above or one or more groups described above as alkyl substituents. Also included are smaller heterocyclyls, such as, epoxides and aziridines.

The term "carbocyclic ring" refers to stable, saturated or partially unsaturated monocyclic hydrocarbon rings of 3 to 7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "optionally substituted" as it refers to "carbocyclic ring" herein indicates that the carbocyclic ring may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups.

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

The compounds of formula I may form salts which are also within the scope of this invention. Pharmaceutically acceptable (i.e. non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, e.g., in isolating or purifying the compounds of this invention.

The compounds of formula I may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclohexylamine, tributylamine, pyridine and amino acids such as arginine, lysine and the like. Such salts can be formed as known to those skilled in the art.

The compounds for formula I may form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrogen chloride, hydrogen bromide, methanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, oxalic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid and various others (e.g.,

nitrates, phosphates, borates, tartrates, citrates, succinates, benzoates, ascorbates, salicylates and the like). Such salts can be formed as known to those skilled in the art.

In addition, zwitterions ("inner salts") may be formed.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

Compounds of the formula I may also have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (i.e., the compound for formulas I) is a prodrug within the scope and spirit of the invention.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol.42, p. 309-396, edited by K. Widder, et al. (Acamedic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, p. 113-191 (1991); and

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992).

It should further be understood that solvates (e.g., hydrates) of the compounds of formula I are also with the scope of the present invention. Methods of solvation are generally known in the art.

UTILITY

The present invention is based on the discovery that certain pyrrolotriazines are inhibitors of protein kinases. More specifically, pyrrolotriazines such as those described in this invention inhibit the protein tyrosine kinase activity of members of the HER family of receptors. These inhibitors will be useful in the treatment of proliferative diseases that are dependent on signaling by one or more of these receptors. Such diseases include psoriasis, rheumatoid arthritis, and solid tumors of the lung, head and neck, breast, colon, ovary, and prostate. The invention relates to a pharmaceutical composition of compound of formula I, or pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier in the treatment of hyperproliferative disorder in mammal. In particular, the said pharmaceutical composition is expected to inhibit the growth of those primary and recurrent solid tumors which are associated with HER1 (EGF receptor) and HER2, especially those tumors which are significantly dependent on HER1 or HER2 for their growth and spread, including for example, cancers of the bladder, squamous cell, head, colorectal, oesophageal, gynecological (such as ovarian), pancreas, breast, prostate, vulva, skin, brain, genitourinary tract, lymphatic system (such as thyroid), stomach, larynx and lung. In another embodiment, the compounds of the present invention are also useful in the treatment of noncancerous disorders such as psoriasis and rheumatoid arthritis.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiproliferative effect in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for producing an antiproliferative effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined herein before.

By virtue of their ability to inhibit HER1, HER2, and HER4 kinases, compounds of the present invention can be used for the treatment of proliferative diseases, including psoriasis and cancer. The HER1 receptor kinase has been shown

to be expressed and activated in many solid tumors including head and neck, prostate, non-small cell lung, colorectal, and breast cancer. Similarly, the HER2 receptor kinase has been shown to be overexpressed in breast, ovarian, lung and gastric cancer. Monoclonal antibodies that downregulate the abundance of the HER2 receptor or inhibit signaling by the HER1 receptor have shown anti-tumor efficacy in preclincal and clinical studies. It is therefore expected that inhibitors of the HER1 and HER2 kinases will have efficacy in the treatment of tumors that depend on signaling from either of the two receptors. In addition, these compounds will have efficacy in inhibiting tumors that rely on HER receptor heterodimer signaling. These compounds are expected to have efficacy either as single agent or in combination (simultaneous or sequentially) with other chemotherapeutic agents such as Taxol®, adriamycin, and cisplatin. Since HER1 and HER2 signaling has been shown to regulate expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and interleukin 8 (IL8), these compounds are expected to have anti-tumor efficacy resulting from the inhibition of angiogenesis in addition to the inhibition of tumor cell proliferation and survival. The HER2 receptor has been shown to be involved in the hyperproliferation of synovial cells in rheumatoid arthritis, and may contribute to the angiogenic component of that inflammatory disease state. The inhibitors described in this invention are therefore expected to have efficacy in the treatment of rheumatoid arthritis. The ability of these compounds to inhibit HER1 further adds to their use as anti-angiogenic agents. See the following documents and references cited therein: Schlessinger J. , "Cell signaling by receptor tyrosine kinases", *Cell* 103(2), p. 211-225 (2000); Cobleigh, M. A., Vogel, C. L., Tripathy, D., Robert, N. J., Scholl, S., Fehrenbacher, L., Wolter, J. M., Paton, V., Shak, S., Lieberman, G., and Slamon, D. J., "Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease", *J. of Clin. Oncol.* 17(9), p. 2639-2648 (1999); Baselga, J., Pfister, D., Cooper, M. R., Cohen, R., Burtness, B., Bos, M., D'Andrea, G., Seidman, A., Norton, L., Gunnett, K., Falcey, J., Anderson, V., Waksal, H., and Mendelsohn, J., "Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin", *J. Clin. Oncol.* 18(4), p. 904-914 (2000); Satoh, K., Kikuchi, S., Sekimata,

M., Kabuyama, Y., Homma, M. K., and Homma Y., "Involvement of ErbB-2 in rheumatoid synovial cell growth", *Arthritis Rheum.* 44(2), p. 260-265 (2001).

The antiproliferative treatment defined herein before may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. The compounds of this invention may also be useful in combination with known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. Compounds of formula I may be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate.

In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiproliferative treatment defined herein before may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example, linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, razoxane);

(ii) cytostatic agents such as antiestrogens (for example, tamoxifen, toremifene, raloxifene, droloxifene, iodoxifene), progestogens (for example, megestrol acetate), aromatase inhibitors (for example, anastrozole, letrozole, borazole, exemestane), antihormones, antiprogestogens, antiandrogens (for example, flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example, gosereline acetate, leuprolide), inhibitors of testosterone 5α-dihydroreductase (for example, finasteride), farnesyltransferase inhibitors, anti-invasion agents (for example, metalloproteinase inhibitors such as marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function,

(such growth factors include for example, EGF, FGF, platelet derived growth factor and hepatocyte growth factor, such inhibitors include growth factor antibodies, growth factor receptor antibodies such as Avastin® (bevacizumab) and Erbitux® (cetuximab); tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example, antifolates such as methotrexate, fluoropyrimidines such as 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); Intercalating antitumour antibiotics (for example, anthracyclines such as doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example, cisplatin, carboplatin); alkylating agents (for example, nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide nitrosoureas, thiotepa; antimitotic agents (for example, vinca alkaloids like vincristine, vinorelbine, vinblastine and vinflunine, and taxoids such as Taxol® (paclitaxel), Taxotere® (docetaxel) and newer microbtubule agents such as epothilone analogs, discodermolide analogs, and eleutherobin analogs); topoisomerase inhibitors (for example, epipodophyllotoxins such as etoposide and teniposide, amsacrine, topotecan, irinotecan); cell cycle inhibitors (for example, flavopyridols); biological response modifiers and proteasome inhibitors such as Velcade® (bortezomib).

As stated above, the formula I compounds of the present invention are of interest for their antiproliferative effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, psoriasis, and rheumatoid arthritis.

More specifically, the compounds of formula I are useful in the treatment of a variety of cancers, including (but not limited to) the following:

-carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder,

ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

-tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and

-other tumors, including melanoma, seminoma, teratocarcinoma, and osteosarcoma.

Due to the key role of kinases in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation and inflammatory bowel disease

The compounds of formula I are especially useful in treatment of tumors having a high incidence of tyrosine kinase activity, such as colon, lung, and pancreatic tumors. By the administration of a composition (or a combination) of the compounds of this invention, development of tumors in a mammalian host is reduced.

Compounds of formula I may also be useful in the treatment of diseases other than cancer that may be associated with signal transduction pathways operating through growth factor receptors such as HER1 (EGF receptor), HER2, or HER4.

The pharmaceutical compositions of the present invention containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of

tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropyl-cellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and

lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS.TM. model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those

of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent or treatment within its approved dosage range. Compounds of formula I may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of formula I may be administered either prior to or after administration of the known anticancer or cytotoxic agent(s).

The compounds may be administered in a dosage range of about 0.05 to 200 mg/kg/day, preferably less than 100 mg/kg/day, in a single dose or in 2 to 4 divided doses.

Biological assays

HER1, HER2 or HER4 Kinase Assays

Compounds of interest were assayed in a kinase buffer that contained 20 mM Tris.HCl, pH 7.5, 10 mM $MnCl_2$, 0.5 mM dithiothreitol, bovine serum albumin at 0.1 mg/ml, poly(glu/tyr, 4:1) at 0.1 mg/ml, 1 μM ATP, and 4 μCi/ml [γ-^{33}P]ATP. Poly(glu/tyr, 4:1) is a synthetic polymer that serves as a phosphoryl acceptor and is purchased from Sigma Chemicals. The kinase reaction is initiated by the addition of enzyme and the reaction mixtures were incubated at 26 °C for 1 h. The reaction is terminated by the addition of EDTA to 50 mM and proteins are precipitated by the addition of trichloroacetic acid to 5%. The precipitated proteins are recovered by

filtration onto Packard Unifilter plates and the amount of radioactivity incorporated is measured in a Topcount scintillation counter.

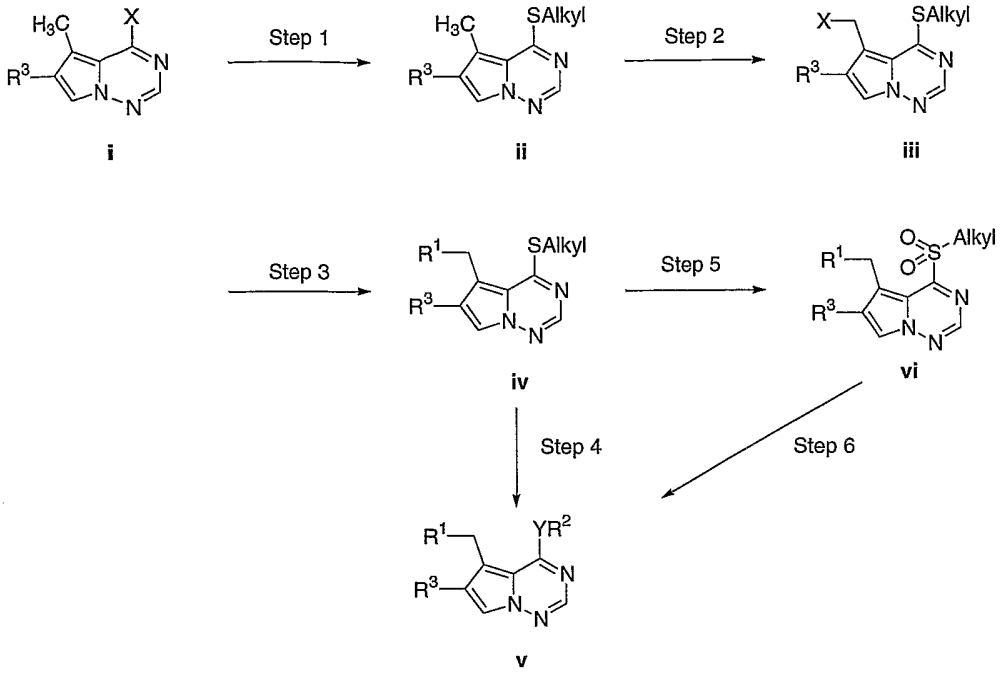
For the preparation of recombinant HER1 and HER4, the cytoplasmic sequences of the receptors were expressed in insect cells as GST fusion proteins, which were purified by affinity chromatography. The cytoplasmic sequence of HER2 was subcloned into the baculovirus expression vector pBlueBac4 (Invitrogen) and was expressed as an untagged protein in insect cells. The recombinant protein was partially purified by ion-exchange chromatography.

The instant compounds inhibit HER1, HER2, and HER4 kinases with IC50 values between 0.001 to 25 μM. Preferred compounds have IC_{50} values between 0.001 – 5.0 μM. More preferred compounds have IC_{50} values between 0.001 – 1.0 μM. Most preferred compounds have IC_{50} values between 0.001 – 0.1 μM.

Methods of Preparation

Certain compounds of formula I may generally be prepared according to the following schemes and the knowledge of one skilled in the art. Supplemental preparation information may also be found in co-pending US patent application serial number 09/573,829 filed May 18, 2000 and International Publication Number WO 00/71129, both herein incorporated by reference.

Scheme 1



Step 1

The first step of **Scheme 1** is accomplished by treating Compound **i** (Ref. WO 03/042172 A2) with a thiol such as methanethiol or butanethiol or their sodium salts in an anhydrous solvent such as THF under an inert atmosphere such as N_2 to give Compound **ii**.

Step 2

Halogenation of the 5-methyl group of Compound **ii** is affected by treatment with a halogenating reagent such as N-bromosuccinimide. The reaction is preformed under an inert atmosphere such Ar in the presence of a catalyst such as dibenzoyl peroxide or 2,2'-azobisisobutyronitrile and gives the 5-halomethyl-pyrrolotrazine Compound **iii**.

Step 3

Treatment of Compound **iii** with a primary or secondary amine or alcohol in the presence of a base such as $NaHCO_3$ or triethylamine or diisopropylethylamine in a

solvent such as acetonitrile or N,N-dimehylformamide affords intermediate Compound **iv**.

Step 4

Treatment of intermediate Compound **iv** with an aniline in the presence of $HgCl_2$ in a solvent such as toluene affords the 4-substituted pyrrolotriazines Compound **v**.

Step 5

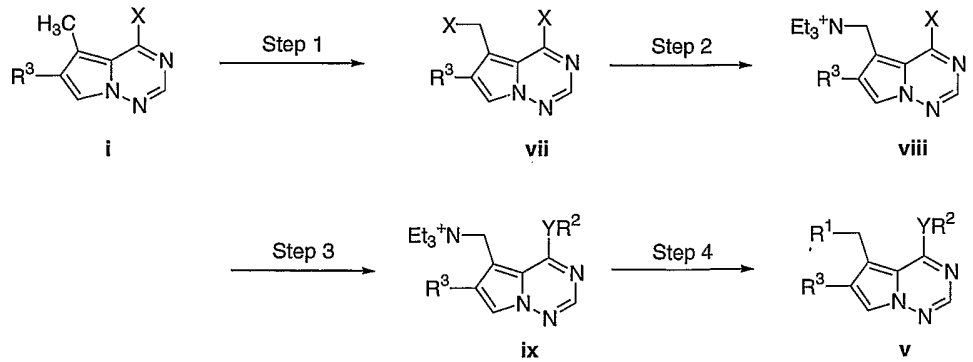
Alternatively compounds of formula **iv** may be treated with an appropriate oxidizing agent such as m-chloroperbenzoic acid in a solvent such as CH_2Cl_2 to afford sulfones **vi**.

Step 6

Sulfones **vi** may be converted to compound **v** by treatment with a primary or secondary amine or alcohol in an inert solvent such as CH_2Cl_2

Alternatively, compounds of general formula I may be prepared as shown in Scheme 2.

Scheme 2



Where X = Halogen, Y = N or O

Step 1

The first step of **Scheme 2** is accomplished by treating Compound **i** (Ref. WO 03/042172 A2) with a halogenating reagent such as N-bromosuccinimide under an inert atmosphere such as Ar. The reaction is performed in an appropriate solvent such as CCl_4 in the presence of a catalyst such as dibenzoyl peroxide or 2,2'-azobisisobutyronitrile to afford the dihalopyrrolotrazine Compound **vii**.

Step 2

Compound **vii** may be converted to ammonium salt Compound **viii** by treatment with a tertiary base such as triethylamine in an anhydrous solvent such as THF.

Step 3

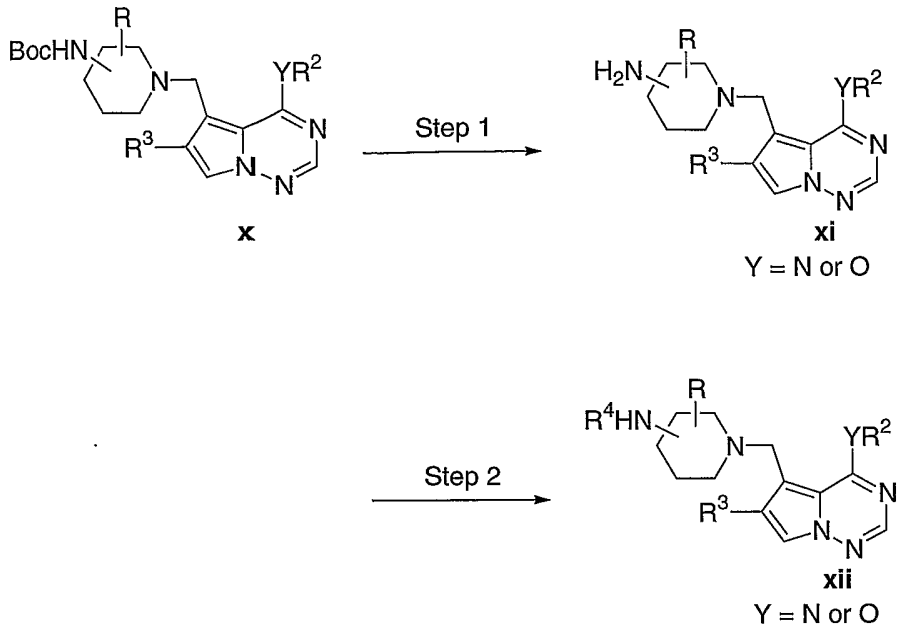
Treatment of Compound **viii** with an amine or its anion in an anhydrous solvent such as acetonitrile, chloroform or THF affords ammonium salt Compound **ix**.

Step 4

Conversion of Compound **ix** to pyrrolotriazine Compound **v** may be accomplished by treatment of Compound **ix** with a primary or secondary amine or alcohol in the presence of a base such as diisopropylethylamine in a solvent such as acetonitrile.

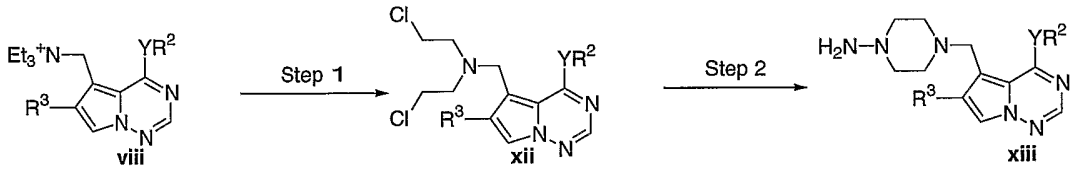
Compounds prepared by the above methods having general formula **x** in **Scheme 3** in which the 5-methylsubstituent contains a protecting group such as t-butoxycarbonyl may further be modified by removal of the protecting group in **Step 1** by treatment with anhydrous HCl in diethyl ether or 1,4-dioxane or by treatment of a solution of the compound in CH_2Cl_2 with trifluoroacetic acid to prepare the free amines **xi**. Further modification may be accomplished in **Step 2** by treating Compound **xi** with a carbonyl compound such as propanal in the presence of a reducing agent such as sodium triacetoxyborohydride in a solvent such as CH_2Cl_2 to afford substituted amines **xii**.

Scheme 3



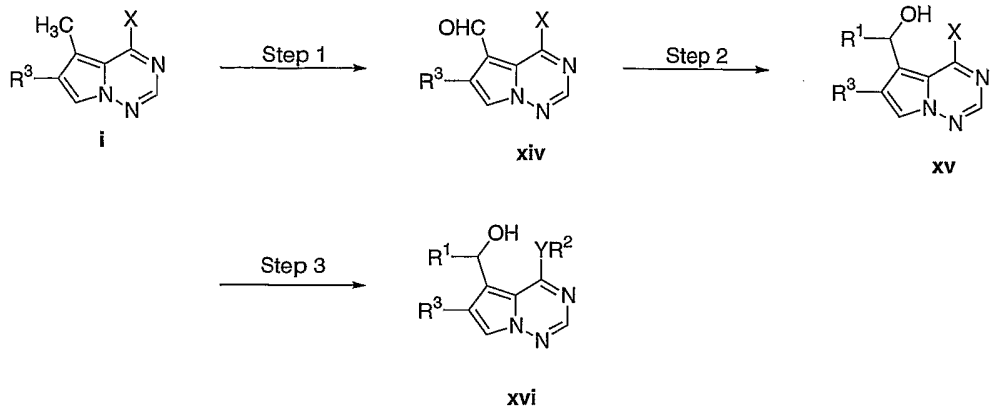
Further compounds may be prepared as shown in **Scheme 4**. In **Step 1**, compound **ix** may be treated with a secondary amine such as bis-(2-chloroethyl)amine in an appropriate solvent such as acetonitrile in the presence of a base such as diisopropylethylamine to afford Compound **xii**. Compound **xii** may further be treated with a nucleophile such as hydrazine in **Step 2** to afford Compund **xiii**.

Scheme 4



Further 5-substituted pyrrolotriazines may be prepared according to **Scheme 5**.

Scheme 5



Step 1

Compound **i** may be treated with two equivalents of a brominating reagent such as N-bromosuccinimide in a solvent such as CCl_4 at elevated temperature. The resulting 5-dibromopyrrolotriazine may be converted to the corresponding dimethylacetal using methanol in the presence of a base such as $NaHCO_3$ and then to the aldehyde Compound **xiv** by treating the intermediate acetal with an acid such as trifluoroacetic acid in the presence of water.

Step 2

Treatment of aldehyde Compound **xiv** with an organometallic reagent such as a Grignard reagent in an anhydrous solvent such as THF affords alcohol **xv**.

Step 3

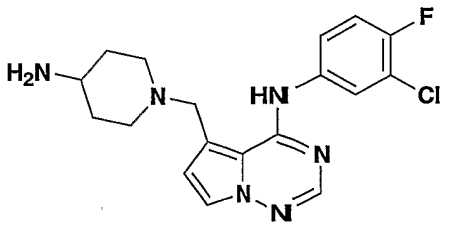
Alcohol **xv** may be treated with a primary or secondary amine or alcohol in the presence of a base such as $NaHCO_3$ in an appropriate solvent such as acetonitrile to afford compounds of formula **xvi**.

In addition, other compounds of formula I may be prepared using procedures generally known to those skilled in the art. In particular, the following examples provide additional methods for the preparation of the compounds of this invention.

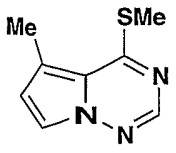
The invention will now be further described by the following working examples(s), which are preferred embodiments of the invention. All temperatures are in degrees Celsius (^{o}C) unless otherwise indicated. "HPLC Ret Time" is the HPLC retention time that was obtained under the following conditions: column type and length, gradient time [unless otherwise indicated, all gradients started with 100% solvent A (10% MeOH, 90% H_2O, ***0.1% TFA***) and ended with 100% solvent B (90% MeOH, 10% H_2O, ***0.1% TFA***)], flow rate (mL/min). UV detection was always conducted at 220 nM. These examples are illustrative rather than limiting and it is to be understood that there may be other embodiments that fall within the spirit and scope of the invention as defined by the claims appended hereto.

EXAMPLE 1

5-[(4-Amino-1-piperidinyl)methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



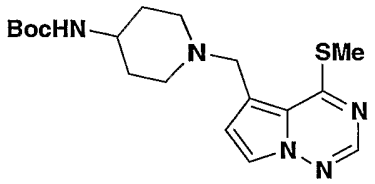
1A. Preparation of 5-methyl-4-methylsulfanyl-pyrrolo[2,1f] [1,2,4]triazine



To a solution of 4-chloro-5-methyl-pyrrolo[2,1f][1,2,4] triazine (4.02 g, 24.0 mmol)(Ref. WO 03/042172 A2) in dry THF (200 ml) sparged with N_2 at 0°C was added NaSMe (1.85 g, 26.3 mmol). The sparging was continued for 5 min. The reaction mixture was then stirred at rt overnight, concentrated *in vacuo* to about 50 ml

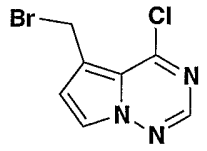
volumn left. Diluted with H_2O (280 ml) and stirred at 0 °C. The solid was filtered, washed with cold water, dried to give **1A** (3.91 g, 91%). It had an analytical HPLC retention time = 3.38 min. (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 180.

1B. Preparation of [1-(4-methylsulfanyl-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl)-piperidin-4-yl]-carbamic acid tert-butyl ester



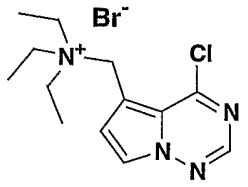
A mixture of **1A** (1.94 g, 10.8 mmol), benzoyl peroxide (0.262 g, 1.08 mmol), NBS (2.12 g, 11.90 mmol) in CCl_4 (100 ml) was sparged with N_2, then immediately heated to 85 °C for 1.5 h. The mixture was cooled to rt and the precipitate was filtered off. The filtrate was concentrated *in vacuo*, diluted with dichloroethane (35 ml), and DIEA (2.24 ml, 12.96 mmol) and piperidin-4-yl-carbamic acid tert-butyl ester (2.38 g, 11.90 mmol) were added. The reaction mixture was stirred at rt for 1 h. The mixture was diluted with saturated $NaHCO_3$ (70 ml) and extracted with EtOAc (3 x 100 ml). The combined EtOAc extracts were washed with brine (1 x 100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column to give **1B** (2.87 g, 70%)(0.1%-2% MeOH-CH_2Cl_2). It had an analytical HPLC retention time = 2.12 min. (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 378.

1C. Preparation of 5-bromomethyl-4-chloro-pyrrolo[2,1-f] [1,2,4]triazine



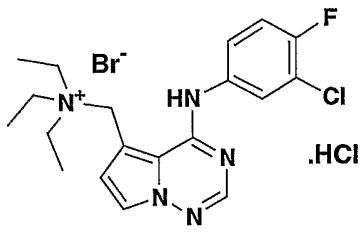
A mixture of 4-chloro-5-methyl-pyrrolo[2,1f][1,2,4] triazine (2.0 g, 11.93 mmol) (Ref. WO 03/042172 A2) and AIBN (195 mg, 1.19 mmol) in CCl_4 (80 ml) under N_2 was heated to 100 °C for 5 min, NBS (2.55 g, 14.3 mmol) was added. The reaction mixture was stirred for 10 min, then cooled to rt, filtered. The CCl_4 layer was washed with dilute $NaHCO_3$ aqueous solution, dried ($MgSO_4$), filtered and concentrated to give **1C**(2.70 g, 92%).

1D. Preparation of (4-chloro-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl)-triethyl-ammonium bromide



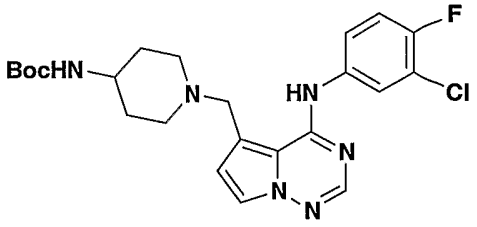
A mixture of **1C** (2.7 g, 11 mmol), Et_3N (5 ml, 36 mmol) in THF (20 ml) was stirred at rt for 12h. The solid was filtered and rinsed with THF and Et_2O, dried to give **1D** (3.38 g, 89%). It had an analytical HPLC retention time = 0.776 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS $M^+ = 267$.

1E. Preparation of [4-(3-chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl]-triethyl-ammonium bromide hydrochloride



A mixture of **1C** (1.0 g, 2.2 mmol) and 3-chloro-4-fluoro-phenylamine (418 mg, 2.87 mmol) in $CHCl_3$ (10 ml) was heated at 50 °C for 2 h. The solid was filtered and rinsed with $CHCl_3$, dried to give **1E** (1.24 g, 87.4%). It had an analytical HPLC retention time = 2.19 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS $M^+ = 376$.

1F. Preparation of {1-[4-(3-chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester



Method one:

A mixture of **1B** (30 mg, 0.08 mmol), 3-chloro-4-fluoro-phenylamine (11 mg, 0.08 mmol) and $HgCl_2$ (24 mg, 0.088 mmol) in toluene (2 ml) was heated to reflux for 8 h. Cooled to rt, diluted with EtOAc (5 ml) and filtered. The filtrate was concentrated, and the residue was purified by prep HPLC to give **1F** as an oil.

Method two:

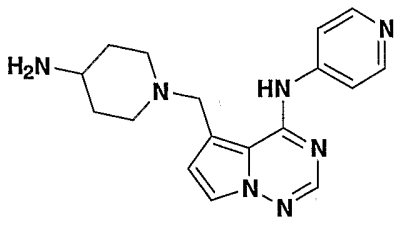
To a suspension of piperidin-4-yl-carbamic acid tert-butyl ester (4.1 g, 20.3 mmol) in CH_3CN (55 ml) at 70 °C was added a mixture of 1E (9.1 g, 18.4 mmol) and DIPEA (3.2 ml, 18.4 mmol) in CH_3CN (40 ml) dropwise in a period of 40 min. The reaction mixture was stirred at 70 °C for 1 h, then cooled to rt, after which H_2O (155 ml) was added slowly. The solid was filtered and rinsed with 15% CH_3CN/ H_2O, then H_2O, and ried under vacuum to give **1F** (7.84 g, 90%). It had an analytical HPLC retention time = 2.73 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 475.

1G. Preparation of 5-[(4-amino-1-piperidinyl)methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

Compound **1F** (from *Method one*) was treated 20% TFA/CH_2Cl_2 (3 ml) at 0 °C, then stirred at rt for 2 h. The reaction mixture was concentrated and purified by prep HPLC to give the product as the TFA salt, which was treated with saturated $NaHCO_3$ to give the ree base 1G (4 mg, 13% for two steps). It had an analytical HPLC retention time = 1.49 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 375.

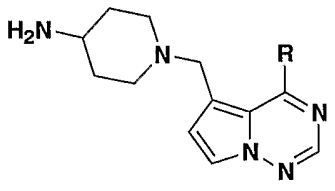
EXAMPLE 2

5-[(4-Amino-1-piperidinyl)methyl]-N-4-pyridinylpyrrolo[2,1-f][1,2,4]triazin-4-amine

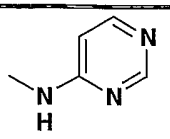
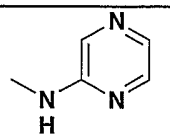
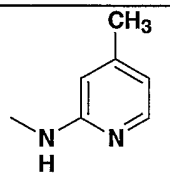
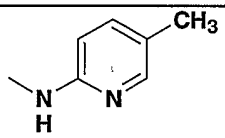
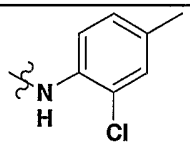
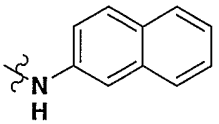
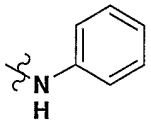
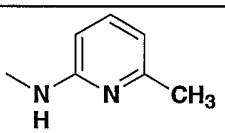
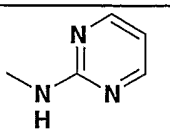


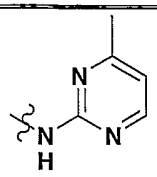
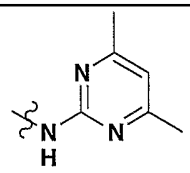
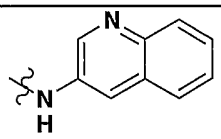
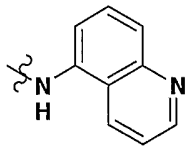
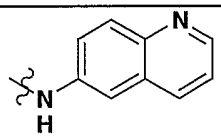
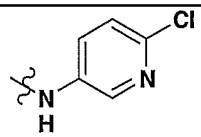
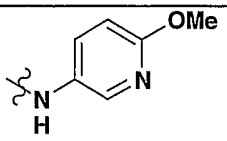
To a mixture of pyridin-4-ylamine (34 mg, 0.361 mmol) in THF (500 µl) was added 1N NaHMDS in THF (722 µl, 0.722 mmol). The mixture was cooled to 0 °C and a suspension of **1D** (125 mg, 0.27 mmol) in DMF (800 µl) was added. The mixture was stirred at this temperature for 0.5 h. and piperidin-4-yl-carbamic acid tert-butyl ester (144 mg, 0.72 mmol) was added to the cold mixture. The reaction mixture was heated to 50 °C for 10 min and concentrated to remove THF. TFA (1 ml) was added, the mixture was stirred until the protecting group was removed (2h) (progress was monitored by HPLC). TFA was removed *in vacuo* and saturated $NaHCO_3$ was added. The mixture was extracted with EtOAc and the combined extracts were dried, concentrated and triturated first with Et2O to give the title compound (46 mg, 53%). Analytical HPLC retention time = 0.51 min (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 324.

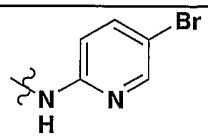
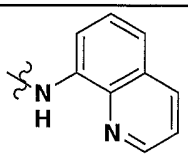
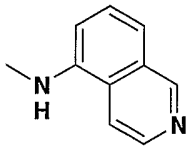
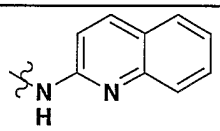
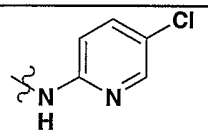
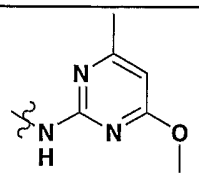
EXAMPLES 3-37

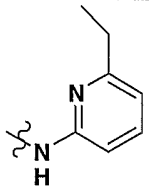
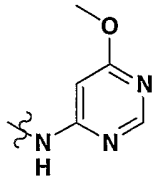
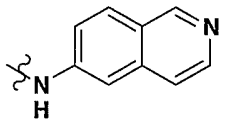
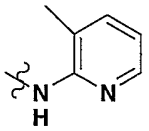
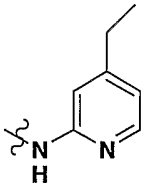
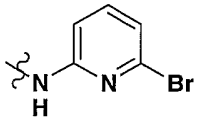


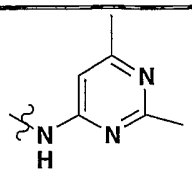
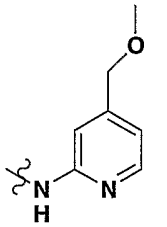
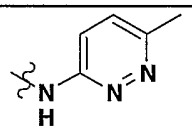
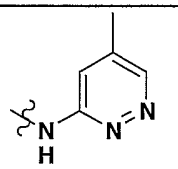
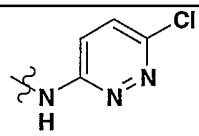
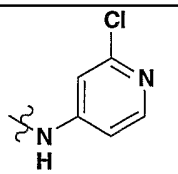
Compounds **3-37** were prepared using a similar process as the compound in Example 2 utilizing the corresponding amines.

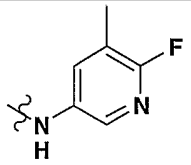
	Ex. #	R	Compound Name	[M+H]	HPLC Ret Time (min)
	3		5-[(4-Amino-1-piperidinyl)methyl]-N-4-pyrimidinylpyrrolo[2,1-f][1,2,4]triazin-4-amine	325	0.65 (b)
	4		5-[(4-Amino-1-piperidinyl)methyl]-N-pyrazinylpyrrolo[2,1-f][1,2,4]triazin-4-amine	325	1.02 (b)
	5		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-methyl-2-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	338	0.71 (b)
	6		5-[(4-Amino-1-piperidinyl)methyl]-N-(5-methyl-2-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	338	0.80 (b)
	7		5-[(4-Amino-1-piperidinyl)methyl]-N-(2-chloro-4-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine.	371	1.61(b)
	8		5-[(4-Amino-1-piperidinyl)methyl]-N-2-naphthalenylpyrrolo[2,1-f][1,2,4]triazin-4-amine.	373	1.81(b)
	9		5-[(4-Amino-1-piperidinyl)methyl]-N-phenylpyrrolo[2,1-f][1,2,4]triazin-4-amine.	323	1.06(b)
	10		5-[(4-Amino-1-piperidinyl)methyl]-N-(6-methyl-2-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	338	0.60 (b)
	11		5-[(4-Amino-1-piperidinyl)methyl]-N-2-pyrimidinylpyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1)	325	1.00 (b)

	Ex. #	R	Compound Name	[M+H]	HPLC Ret Time (min)
	12		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-methyl-2-pyrimidinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	339	1.03 (b)
	13		5-[(4-Amino-1-piperidinyl)methyl]-N-(4,6-dimethyl-2-pyrimidinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	353	1.08 (b)
	14		N-[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]-3-quinolinamine, trifluoroacetic acid salt (1:1).	374	1.03 (b)
	15		N-[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]-5-quinolinamine, trifluoroacetic acid salt (1:1).	374	0.64 (b)
	16		N-[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-quinolinamine, trifluoroacetic acid salt (1:1).	374	0.80 (b)
	17		5-[(4-Amino-1-piperidinyl)methyl]-N-(6-chloro-3-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	358	1.03 (b)
	18		5-[(4-Amino-1-piperidinyl)methyl]-N-(6-methoxy-3-pyridinyl)pyrrolo[2,1-	354	0.98 (b)

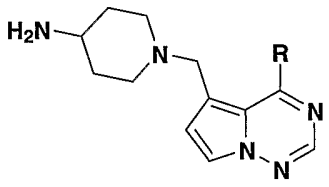
	Ex. #	R	Compound Name	[M+H]	HPLC Ret Time (min)
			f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).		
	19		5-[(4-Amino-1-piperidinyl)methyl]-N-(5-bromo-2-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	402	1.63 (b)
	20		N-[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]-8-quinolinamine, trifluoroacetic acid salt (1:1).	374	0.92 (b)
	21		N-[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]-5-isoquinolinamine, trifluoroacetic acid salt (1:1).	374	0.59 (b)
	22		N-[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2-quinolinamine, trifluoroacetic acid salt (1:1).	374	1.49(b)
	23		5-[(4-Amino-1-piperidinyl)methyl]-N-(5-chloro-2-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	374	1.55(b)
	24		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-methoxy-6-methyl-2-pyrimidinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	369	1.03(b)

	Ex. #	R	Compound Name	[M+H]	HPLC Ret Time (min)
	25		5-[(4-Amino-1-piperidinyl)methyl]-N-(6-ethyl-2-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	352	1.91(b)
	26		5-[(4-Amino-1-piperidinyl)methyl]-N-(6-methoxy-4-pyrimidinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	355	1.25(b)
	27		N-[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]-6-isoquinolinamine, trifluoroacetic acid salt (1:1).	374	1.85(b)
	28		5-[(4-Amino-1-piperidinyl)methyl]-N-(3-methyl-2-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	338	1.67(b)
	29		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-ethyl-2-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	352	1.00 (b)
	30		5-[(4-Amino-1-piperidinyl)methyl]-N-(6-bromo-2-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	402	1.62 (b)

	Ex. #	R	Compound Name	[M+H]	HPLC Ret Time (min)
	31		5-[(4-Amino-1-piperidinyl)methyl]-N-(2,6-dimethyl-4-pyrimidinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	353	0.89 (b)
	32		5-[(4-Amino-1-piperidinyl)methyl]-N-[6-(methoxymethyl)-4-pyrimidinyl]- pyrrolo[2,1-f][1,2,4]triazin-4-amine	369	1.12 (b)
	33		5-[(4-Amino-1-piperidinyl)methyl]-N-(6-methyl-3-pyridazinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	339	0.88 (b)
	34		5-[(4-Amino-1-piperidinyl)methyl]-N-(5-methyl-3-pyridazinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	339	0.97 (b)
	35		5-[(4-Amino-1-piperidinyl)methyl]-N-(6-chloro-3-pyridazinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	359	1.29 (b)
	36		5-[(4-Amino-1-piperidinyl)methyl]-N-(2-chloro-4-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	358	1.11 (b)

	Ex. #	R	Compound Name	[M+H]	HPLC Ret Time (min)
	37		5-[(4-Amino-1-piperidinyl)methyl]-N-(6-fluoro-5-methyl-3-pyridinyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	35	1.05 (b)

EXAMPLES 38-121



Method one:

Compounds (with HPLC note (a)) were prepared by the following standard method.

In a 1 dram vial was added 1D (55.0 mg, 0.16 mmol), aniline (0.16 mmol, 1.0 eq) and CH_3CN (1 ml). The mixture was shaken at 65 °C overnight. To this mixture was added piperidin-4-yl-carbamic acid tert-butyl ester (34.9 mg, 0.17 mmol) followed by addition of DIEA (28 µl, 0.16 mmol). The reaction was continued at 65 °C for 3 h. The mixture was concentrated; the residue was purified by Prep HPLC, and the desired fraction was collected and concentrated. The obtained residue was dried under high vacuum overnight.

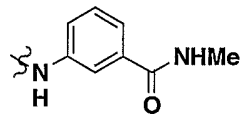
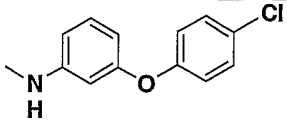
To the above residue was added CH_2Cl_2 (1.5 ml) and TFA (0.2 ml), and the reaction mixture was shaken at rt for 2 h. The mixture was concentrated, and dried in

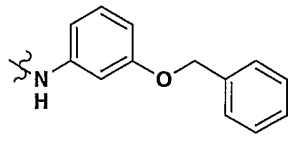
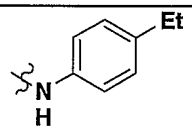
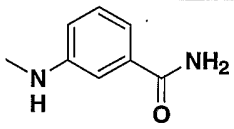
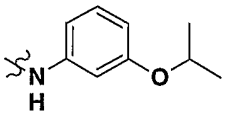
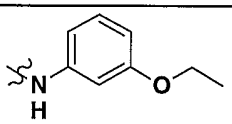
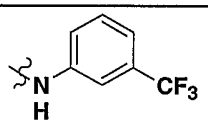
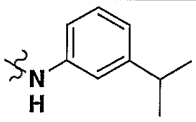
speed vacuum overnight to give the solid product. Further Prep HPLC was used only when the solid was impure.

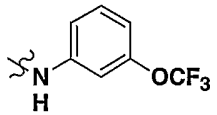
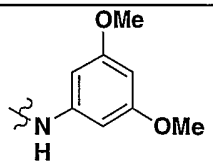
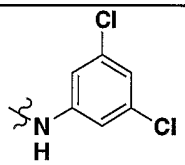
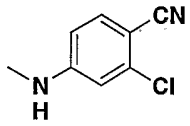
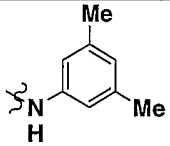
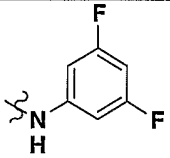
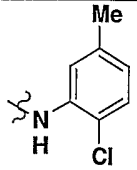
Method two:

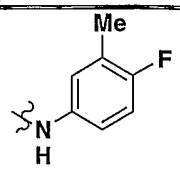
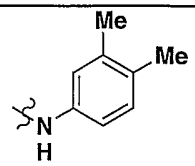
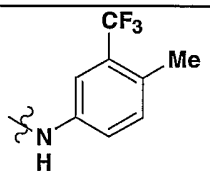
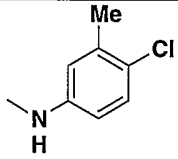
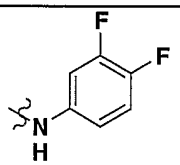
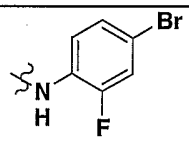
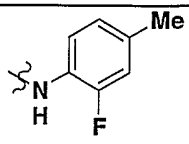
Compounds (with HPLC note (b)) were prepared by the following standard method.

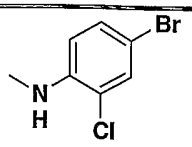
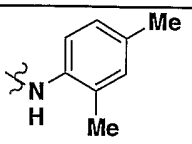
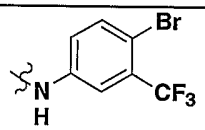
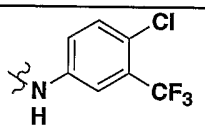
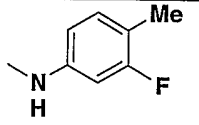
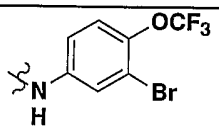
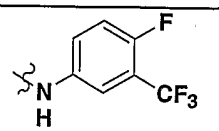
A mixture of 1D (75 mg, 0.216 mmol) and anilines (1.0 eq, 0.216 mmol) in N,N-dimethyl acetamide (0.5 ml) in a small vial was heated at 70 °C for 3-5 hrs until a clear solution obtained. HPLC was used to follow the progress of the reaction. The reaction mixture was cooled to rt and piperidin-4-yl-carbamic acid tert-butyl ester (43 mg, 0.216 mmol) was added, followed by N,N-diisopropylethylamine (75 µl). The reaction mixture again was heated to 70 °C overnight. Upon cooling, the reaction mixture was diluted with CH_2Cl_2 (0.5 ml) and cooled to 0 °C. TFA (1.0 ml) was added and the mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure (speedVac) and the residue was taken into methanol and purified by Prep HPLC to give the desired product.

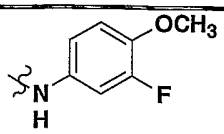
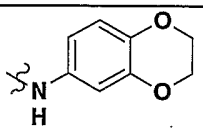
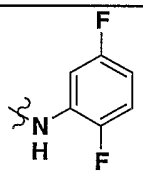
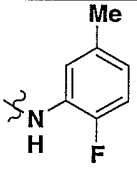
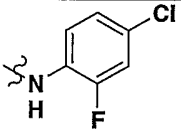
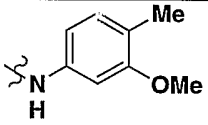
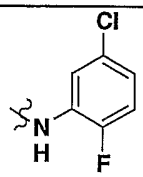
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	38		3-[[5-[(4-Amino-1-piperidinyl)methyl] pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]-N-methyl benzamide	380.25	0.91 (a)
	39		5-[(4-Amino-1-piperidinyl)methyl]-N-[3-(4-chlorophenoxy)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	449.20	2.59 (a)

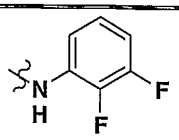
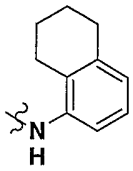
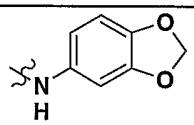
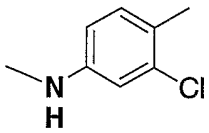
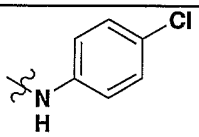
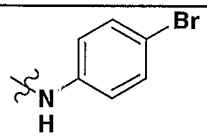
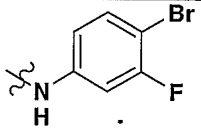
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	40		5-[(4-Amino-1-piperidinyl)methyl]-N-[3-(phenylmethoxy)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	429.26	2.183 (a)
	41		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-ethylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	351.28	1.64 (a)
	42		3-[[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide	366.25	0.76 (a)
	43		5-[(4-Amino-1-piperidinyl)methyl]-N-[3-(1-methylethoxy)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	381.27	1.66 (a)
	44		5-[(4-Amino-1-piperidinyl)methyl]-N-(3-ethoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	367.26	1.44 (a)
	45		5-[(4-Amino-1-piperidinyl)methyl]-N-[3-(trifluoromethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	391.18	1.71 (a)
	46		5-[(4-Amino-1-piperidinyl)methyl]-N-[3-(1-methylethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	365.29	1.89 (a)

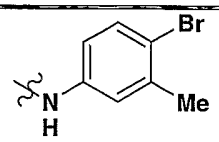
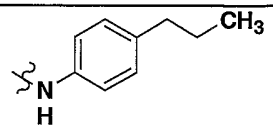
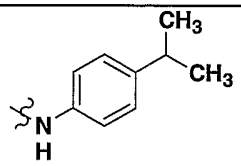
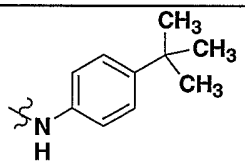
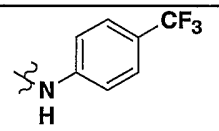
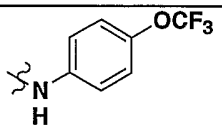
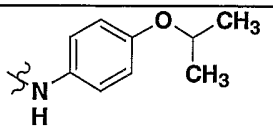
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	47		5-[(4-Amino-1-piperidinyl)methyl]-N-[3-(trifluoromethoxy)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	407.19	1.90 (a)
	48		5-[(4-Amino-1-piperidinyl)methyl]-N-(3,5-dimethoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	383.24	1.32 (a)
	49		5-[(4-Amino-1-piperidinyl)methyl]-N-(3,5-dichlorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	391.13	1.85 (a)
	50		4-[[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]-2-chlorobenzonitrile	382.19	1.63 (a)
	51		5-[(4-Amino-1-piperidinyl)methyl]-N-(3,5-dimethylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	351.28	1.56 (a)
	52		5-[(4-Amino-1-piperidinyl)methyl]-N-(3,5-difluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	359.24	1.14 (a)
	53		5-[(4-Amino-1-piperidinyl)methyl]-N-(2-chloro-5-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	371.21	1.38 (a)

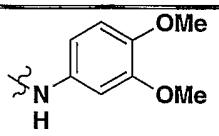
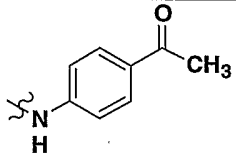
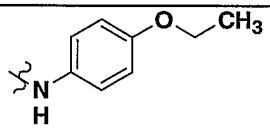
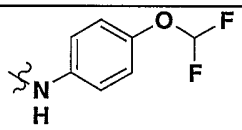
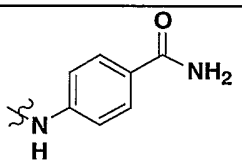
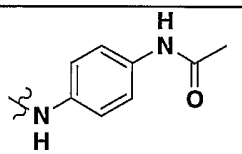
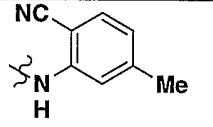
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	54		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-fluoro-3-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	355.27	1.33 (a)
	55		5-[(4-Amino-1-piperidinyl)methyl]-N-(3,4-dimethylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	351.28	1.58 (a)
	56		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	405.21	2.10 (a)
	57		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-chloro-3-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	371.21	1.74 (a)
	58		5-[(4-Amino-1-piperidinyl)methyl]-N-(3,4-difluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	359.23	1.16 (a)
	59		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-bromo-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	419.08	1.55 (a)
	60		5-[(4-Amino-1-piperidinyl)methyl]-N-(2-fluoro-4-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	355.22	1.42 (a)

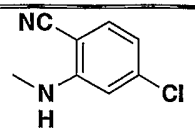
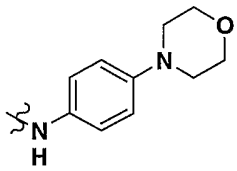
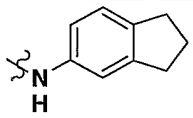
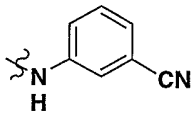
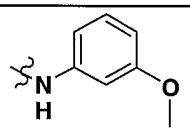
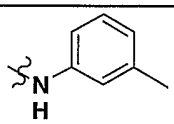
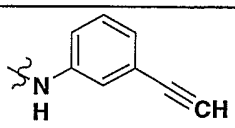
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	61		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-bromo-2-chlorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	435.08	1.68 (a)
	62		5-[(4-Amino-1-piperidinyl)methyl]-N-(2,4-dimethylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	351.24	1.36 (a)
	63		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-bromo-3-(trifluoromethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	469.12	2.35 (a)
	64		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-chloro-3-(trifluoromethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	425.13	2.26 (a)
	65		5-[(4-Amino-1-piperidinyl)methyl]-N-(3-fluoro-4-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	355.22	1.51 (a)
	66		5-[(4-Amino-1-piperidinyl)methyl]-N-[3-bromo-4-(trifluoromethoxy)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	485.11	2.43 (a)
	67		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-fluoro-3-(trifluoromethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	409.17	1.88 (a)

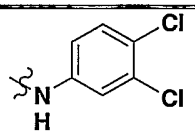
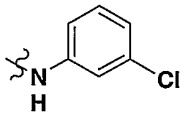
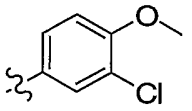
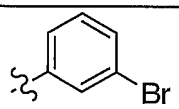
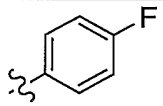
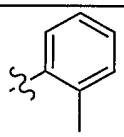
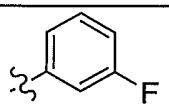
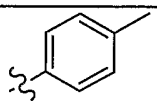
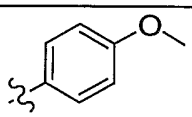
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	68		5-[(4-Amino-1-piperidinyl)methyl]-N-(3-fluoro-4-methoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	371.23	0.76 (a)
	69		5-[(4-Amino-1-piperidinyl)methyl]-N-(2,3-dihydro-1,4-benzodioxin-6-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	381.23	1.24 (a)
	70		5-[(4-Amino-1-piperidinyl)methyl]-N-(2,5-difluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	359.20	1.13 (a)
	71		5-[(4-Amino-1-piperidinyl)methyl]-N-(2-fluoro-5-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	355.22	1.35 (a)
	72		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-chloro-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	375.19	1.45 (a)
	73		5-[(4-Amino-1-piperidinyl)methyl]-N-(3-methoxy-4-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	367.25	1.48 (a)
	74		5-[(4-Amino-1-piperidinyl)methyl]-N-(5-chloro-2-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	375.18	1.44 (a)

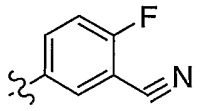
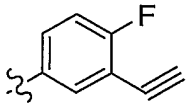
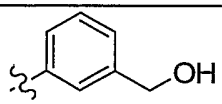
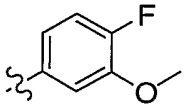
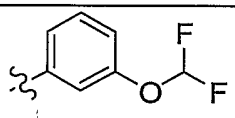
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	75		5-[(4-Amino-1-piperidinyl)methyl]-N-(2,3-difluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	359.21	1.16 (a)
	76		5-[(4-Amino-1-piperidinyl)methyl]-N-(5,6,7,8-tetrahydro-1-naphthalenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	377	1.79 (b)
	77		5-[(4-Amino-1-piperidinyl)methyl]-N-1,3-benzodioxol-5-ylpyrrolo[2,1-f][1,2,4]triazin-4-amine	367	1.17 (b)
	78		5-[(4-aminopiperidin-1-yl)methyl]-N-(3-chloro-4-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	371	1.793
	79		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-chlorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	357	1.44 (b)
	80		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-bromophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	401	1.56 (b)
	81		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-bromo-3-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	419	1.68 (b)

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	82		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-bromo-3-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	415	1.85 (b)
	83		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-propylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	365	1.98 (b)
	84		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-(1-methylethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	365	1.93 (b)
	85		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-(1,1-dimethylethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	379	2.21 (b)
	86		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-(trifluoromethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	391	1.83 (b)
	87		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-(trifluoromethoxy)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	407	1.88 (b)
	88		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-(1-methylethoxy)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	381	1.68 (b)

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	89		5-[(4-Amino-1-piperidinyl)methyl]-N-(3,4-dimethoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	383	1.09 (b)
	90		1-[4-[[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]phenyl]ethanone	365	1.44 (b)
	91		5-[(4-Amino-1-piperidinyl)methyl]-N-(4-ethoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	367	1.44 (b)
	92		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-(difluoromethoxy)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine	389	1.45 (b)
	93		4-[[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide	366	0.82 (b)
	94		N-[4-[[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino] phenyl]acetamide.	380	1.04 (b)
	95		2-[[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]-4-methylbenzonitrile.	362	2.40 (b)

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	96		2-[[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]-4-chlorobenzonitrile.	382	2.55 (b)
	100		5-[(4-Amino-1-piperidinyl)methyl]-N-[4-(4-morpholinyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine.	408	1.12 (b)
	102		5-[(4-Amino-1-piperidinyl)methyl]-N-(2,3-dihydro-1H-inden-5-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine.	363	1.78 (b)
	103		3-[[5-[(4-Amino-1-piperidinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzonitrile, trifluoroacetic acid salt (1:1).	348	1.05(a)
	105		5-[(4-Amino-1-piperidinyl)methyl]-N-(3-methoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1)	353	1.17(a)
	106		5-[(4-Amino-1-piperidinyl)methyl]-N-(3-methylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1)	337	1.25(a)
	107		5-[(4-Amino-1-piperidinyl)methyl]-N-(3-ethynylphenyl) pyrrolo[2,1-f][1,2,4]triazin-4-amine	347	1.35(a)

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	108		5-[(4-Amino-1-piperidinyl)methyl]-N-(3,4-dichloro phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine.	391	1.91(a)
	109		5-[(4-Amino-1-piperidinyl)methyl]-N-(3-chlorophenyl) pyrrolo[2,1-f][1,2,4]triazin-4-amine.	357	0.75(a)
	110		5-[(4-aminopiperidin-1-yl)methyl]-*N*-(3-chloro-4-methoxyphenyl)pyrro-lo[2,1-*f*][1,2,4]triazin-4-amine	387	1.530
	111		5-[(4-aminopiperidin-1-yl)methyl]-N-(3-bromo-phenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	401	1.560
	112		5-[(4-aminopiperidin-1-yl)methyl]-*N*-(4-fluoro-phenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine	341	1.020
	113		5-[(4-aminopiperidin-1-yl)methyl]-*N*-(2-methylphenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine	337	1.030
	114		5-[(4-aminopiperidin-1-yl)methyl]-*N*-(3-fluoro-phenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine	341	1.110
	115		5-[(4-aminopiperidin-1-yl)methyl]-*N*-(4-methyl-phenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine	337	1.310
	116		5-[(4-aminopiperidin-1-yl)methyl]-*N*-(4-meth-oxyphenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine	353	1.170

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	117		5-({5-[(4-aminopiperidin-1-yl)methyl]pyrrolo[2,1-*f*][1,2,4]triazin-4-yl}amino)-2-fluorobenzonitrile	366	1.103
	118		5-[(4-aminopiperidin-1-yl)methyl]-*N*-(3-ethynyl-4-fluorophenyl)-pyrrolo[2,1-*f*][1,2,4]triazin-4-amine	365	1.350
	119		[3-({5-[(4-aminopiperidin-1-yl)methyl]pyrrolo[2,1-*f*][1,2,4]triazin-4-yl}amino)phenyl]methanol	353	0.837
	120		5-[(4-aminopiperidin-1-yl)methyl]-*N*-(4-fluoro-3-methoxyphenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine	371	1.162
	121		5-[(4-aminopiperidin-1-yl)methyl]-*N*-[3-(difluoromethoxy)phenyl]pyrrolo[2,1-*f*][1,2,4]triazin-4-amine	389	1.370

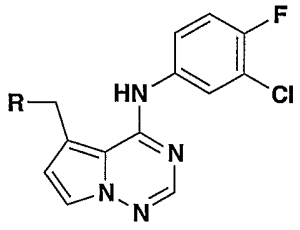
HPLC conditions:

(a): (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 3 ml/min, monitoring at 220 nm)

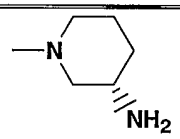
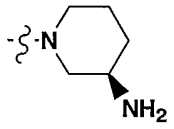
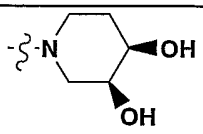
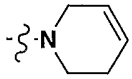
(b): (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm)

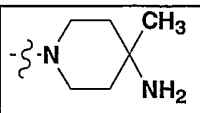
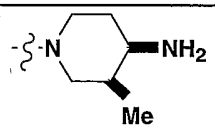
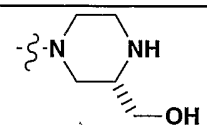
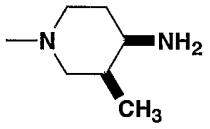
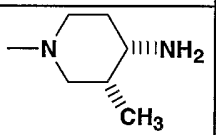
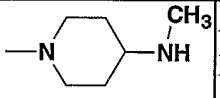
Note: Examples 97-99, 101 and 104 have been deleted from the table as duplicates.

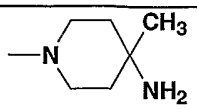
EXAMPLES 122-132



Compounds **122-132** were prepared from Compound **1D**, 3-chloro-4-fluoro-phenylamine and corresponding amines or Boc protected amines by a route analogous to that used for the preparation of Compounds **38-121.**

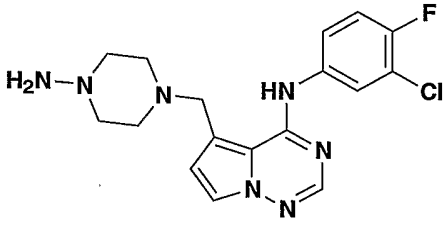
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	122		5-[[(3S)-3-Amino-1-piperidinyl]methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine.	375	1.82 (b)
	123		5-[[(3R)-3-Amino-1-piperidinyl]methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine.	375	1.83 (b)
	124		1-[[4-[(3-Chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]-(3R,4S)-rel-3,4-piperidinediol.	392	1.74 (b)
	125		N-(3-Chloro-4-fluorophenyl)-5-[(3,6-dihydro-1(2H)-pyridinyl)methyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine.	358	2.12 (b)

	126		5-[[(3R,4R)-rel-4-Amino-3-methyl-1-piperidinyl]methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	389	1.71(b)
	127		5-[[(3R,4S)-rel-4-Amino-3-methyl-1-piperidinyl]methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	389	1.557(b)
	128		4-[[4-[(3-Chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]-(2S)-2-piperazinemethanol, trifluoroacetic acid salt (1:1).	391	1.97(b)
	129		5-[[(3R,4S)-4-Amino-3-methyl-1-piperidinyl]methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	389	1.557(b)
	130		5-[[(3S,4R)-rel-4-Amino-3-methyl-1-piperidinyl]methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine, trifluoroacetic acid salt (1:1).	389	1.557(b)
	131		*N*-(3-chloro-4-fluoro-phenyl)-5-{[4-(methyl-amino)piperidin-1-yl]-methyl}pyrrolo[2,1-*f*]-[1,2,4]triazin-4-amine	389	1.000[a]

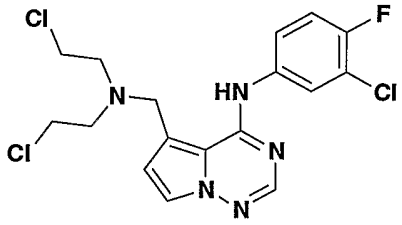
	132		5-[(4-amino-4-methyl-piperidin-1-yl)methyl]-*N*-(3-chloro-4-fluoro-phenyl)pyrrolo[2,1-*f*]-[1,2,4]triazin-4-amine	389	1.030[a]

EXAMPLE 133

5-[(4-Amino-1-piperazinyl)methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



133A Preparation of (5-{[bis-(2-chloro-ethyl)-amino]-methyl}-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-(3-chloro-4-fluoro-phenyl)-amine

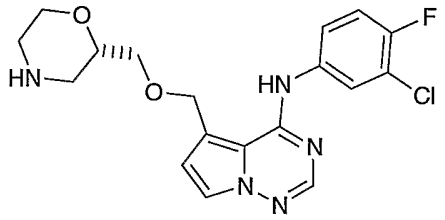


A mixture of Compound **1E** (50 mg, 0.1 mmol), bis-(2-chloroethyl)amine hydrochloride (18 mg, 0.1 mmol), DIEA (36 µl, 0.2 mmol) in CH_3CN (0.5 ml) was heated to 60 °C for 3 h. The mixture was cooled to rt and concentrated to give Compound **133A** which was used directly in next step. **133A** had an analytical HPLC retention time = 2.986 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS $M^+ + 1 = 416$.

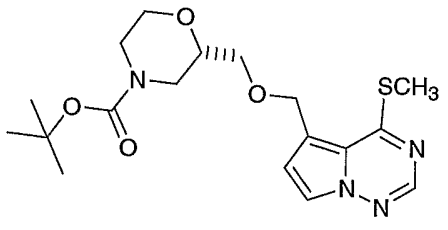
The crude **133A** from the last step was taken into neat anhydrous N_2H_4 (0.5 ml) and heated at 100 °C for several hours. The mixture was cooled to rt, diluted with H_2O and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep HPLC to give, after neutralization and extraction (with CH_2Cl_2), Compound **133** (38.8 mg, 100% for two steps). Analytical HPLC retention time = 1.709 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS $M^+ + 1 = 376$.

EXAMPLE 134

(3-Chloro-4-fluoro-phenyl)-[5-(morpholin-2-ylmethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine



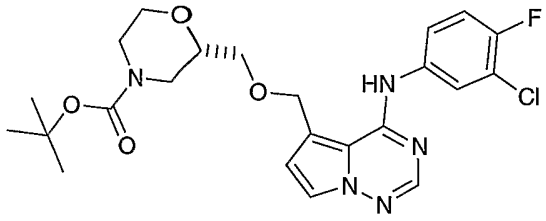
134A Preparation of 2-(4-Methylsulfanyl-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxymethyl)-morpholine-4-carboxylic acid tert-butyl ester



A solution of Compound **1A** (1.0 g, 5.6 mmol) in CCl_4 (50 mL) was purged with nitrogen for one hour. Benzoyl peroxide (270 mg, 1.12 mmol) was added and the reaction mixture was heated to 86 °C. N-bromosuccinimide (1.04 g, 5.88 mmol) was added in one portion. After 30 minutes, the reaction was cooled to room

temperature and filtered. The filtrate was concentrated, re-dissolved in toluene (10 mL) and treated with 2-hydroxymethyl-morpholine-4-carboxylic acid tert-butyl ester (1.5 g, 6.9 mmol). The solution was heated to 110 °C for eight hours, cooled to room temperature and concentrated. Flash chromatography on silica (20% EtOAc/Hexanes) afforded the product as a light yellow oil that crystallized upon standing (770 mg, 32%). HPLC t_R = 3.783 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol, 4 min gradient, monitored at 220 nm). LC/MS (M+H) = 178.

134B Preparation of 2-[4-(3-Chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxymethyl]-morpholine-4-carboxylic acid tert-butyl ester



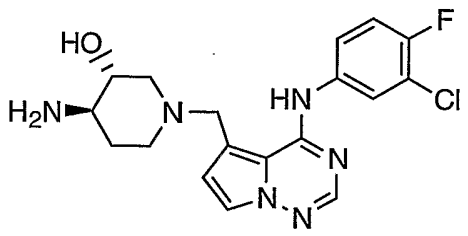
A solution of 2-(4-methylsulfanyl-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxymethyl)-morpholine-4-carboxylic acid tert-butyl ester (60 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 C and treated with a solution of mCPBA (56 mg, 0.32 mmol) in CH_2Cl_2 (2 mL). The reaction was stirred for 15 minutes at 0 C then warmed to room temperature. To this solution was added 3-chloro-4-fluoroaniline and stirred at room temperature for one hour. The resulting orange solution was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$, then saturated aqueous NaCl. The organic layer was dried (Na_2SO_4), filtered and concentrated. Preparative reverse-phase HPLC afforded the desired compound (30 mg, 41%). HPLC t_R = 4.383 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol, 4 min gradient, monitored at 220 nm). LC/MS (M+H) = 492.

A solution of **134B** (30 mg, 0.06 mmol) in CH_2Cl_2 (3 mL) at 0 °C was treated with trifluoroacetic acid (0.3 mL) dropwise. The reaction was stirred for two hours then diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic

layer was separated, dried (Na_2SO_4), filtered and concentrated. The crude compound was purified by radial chromatography (1mm plate, 15% MeOH/CH_2Cl_2 to 30% MeOH/CH_2Cl_2) to afford Compound **134** (17 mg, 67%). HPLC t_R = 2.83 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol, 4 min gradient, monitored at 220 nm). LC/MS (M+H) = 392.

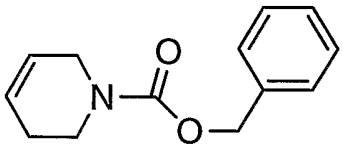
EXAMPLE 135

4-Amino-1-[[4-[(3-chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]-(3R,4R)-rel-3-piperidinol



135

Compound **135A**:

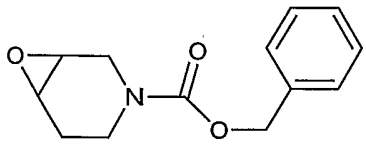


135A

To a solution of 1,2,3,6-tetrabydropyridine (1.66 g, 20.0 mmol) in dry CH_2Cl_2 (10 mL) was added triethyl amine (3.35 mL, 24.0 mmol), followed by a solution of N-(benzyloxycarbonyloxy)succinimide (5.23 g, 21.0 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 10% citric acid, sat'd $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure afforded

4.34 g of Compound **135A**: (100%) as an oil. Analytical HPLC retention time = 2.996 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm). ^{1}H-NMR (CDCl3): 7.20-7.35 (m, 5H), 5.88 (bs, 1H), 5.60-5.78 (m, 1H), 5.18 (s, 2H), 3.99 (t, J = 2.64, 2H), 3.59 (t, J = 5.69, 2H), 2.18 (m, 2H).

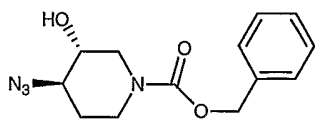
Compound **135B**



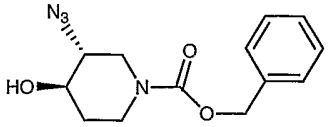
135B

To a solution of Compound **135A** (1.1 g, 5.0 mmol) in dry CH_2Cl_2 (10 mL) cooled at 0°C was added a solution of 75% m-CPBA (1.38 g, 6.0 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred at 0°C for 15 min, then at room temperature for 3 hrs. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with sat'd Na_2S2O_3, sat'd $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave 1.14 g (98%) of Compound **135B** as an oil. Analytical HPLC retention time = 2.279 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm). ^{1}H-NMR ($CDCl_3$): 7.20-7.36 (m, 5H), 5.05 (s, 2H), 3.80-3.96 (m, 1H), 3.70 (m, 1H), 3.47 (m, 1H), 3.22 (bs, 1H), 3.07-3.20 (m, 2H)2.00 (m, 1H), 1.87 (m, 1H).

Compounds **135C** and **135D**:



135C



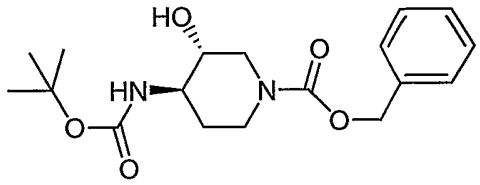
135D

To a solution of Compound **135B** (233 mg, 1.0 mmol) in dry DMF (2 mL) was added a solution of sodium azide (100 mg, 1.5 mmol) in a 2:1 mixture of acetone-water (2 mL). The reaction mixture was heated at 80°C overnight. The solvents were removed under reduced pressure and the residue was taken into EtOAc (20 mL), washed with water, 10% LiCl and brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave an oil. Flash chromatography (hexane-ethyl acetate: 8:2 to 7:3) on silica gel afforded 180 mg of Compound **135C** (early eluent, a major isomer) as an oil and 98 mg of Compound **135D** (late eluent, minor isomer) as an oil.

Compound **135C:** ^{1}H-NMR ($CDCl_3$): 7.28-7.40 (m, 5H), 5.10 (s, 2H), 4.14 (dd, J1 = 4.03, J2 = 13.44, 1H), 4.02 (m, 1H), 3.50 (m, 1H), 3.38 (m, 1H), 3.00 (m, 1H), 2.88 (m, 1H), 2.70 and 2.40 (partial m, 1H), 2.00 (m, 1H), 1.50 (m, 1H).

Compound **135D**: ^{1}H-NMR ($CDCl_3$): 7.20-7.35 (m, 5H), 5.06 (s, 2H), 4.25 and 4.10 (partial m, 1H), 3.99 (d, J = 13.44, 1H), 3.50 (m, 1H), 3.22 (m, 1H), 2.85 (t, J = 2.69, 1H), 2.73 (m, 1H), 2.40 (m, 1H), 1.90 (m, 1H), 1.45 (m, 1H).

Compound **135E**



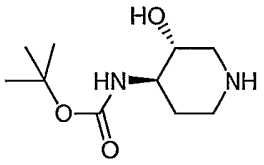
135E

To a solution of Compound **135C** (180 mg, 0.65 mmol) in THF (5 mL) was added water (0.05 mL) and triphenylphosphine (340 mg, 1.3 mmol) and the reaction mixture was heated to reflux for 6 hrs. After cooling to room temperature, EtOAc (20 mL) was added to the reaction mixture. The organic layers were extracted with 1.0 N HCl (10 mL x 2) and combined aqueous layers were back washed once with EtOAc (5 mL). 1.0 N NaOH was added to the aqueous layers to make it pH 10.0 and the mixture was extracted with EtOAc (20 mL x 2). The combined organic layers were

dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave 165 mg of amine intermediate as a colorless oil.

To a solution of 165 mg of amine intermediate in dry CH_2Cl_2 (4 mL) was added triethylamine (0.11 mL, 0.78 mmol), followed by Boc2O (156 mg, 0.72 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with sat'd $NaHCO_3$ and dried over anhydrous Na_2SO_4. Purification by flash chromatography (hexane-EtOAc: 9:1 to 8:2) on silica gel afforded 170 mg of Compound **135E** as a white solid. Analytical HPLC retention time = 2.859 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 351^+$. ^{1}H-NMR ($CDCl_3$): 7.29-7.40 (m, 5H), 5.10 (s, 2H), 4.61 (bs, 1H), 4.32 (bs, 1H), 3.90-4.30 (m, 1H), 3.30-3.60 (m, 2H), 2.80 (m, 1H), 2.66 (m, 1H), 1.90 (m, 1H), 1.45 (s, 9H), 1.40 (m, 1H).

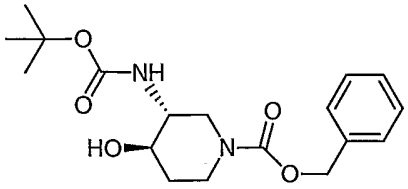
Compound **135F**



135F

A solution of Compound **135E** (170 mg) in 5 mL of MeOH containing 10 mg of Pd(OH)2 was stirred under hydrogen atmosphere (balloon) overnight. The catalyst was removed by filtration and rinsed with MeOH. The combined filtrates were concentrated under reduced pressure to give 138 mg of Compound **135F** as an oil. Analytical HPLC retention time = 1.270 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 220 nm) and a LC/MS $M^+ + 1 = 217^+$.

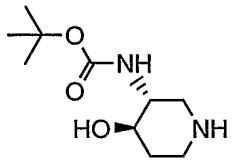
Compound **135G**



135G

Compound **135G** was prepared from Compound **135D** in a similar procedure as Compound **135E**. Analytical HPLC retention time = 2.849 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm). ^{1}H-NMR ($CDCl_3$): 7.40-7.52 (m, 5H), 5.20 (s, 2H), 4.30 (m, 2H), 3.40 (m, 1H), 2.95 (m, 1H), 2.67 (m, 2H), 2.08 (m, 1H), 1.45-1.96 (m, 3H), 1.45 (s, 9H).

Compound **135H**



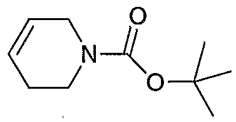
135H

Compound **135H** was prepared from Compound **135G** in a similar procedure as Compound **135F**. Analytical HPLC retention time = 1.380 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 220 nm).

Compound **135** was prepared in a similar manner as Example 1 using Compound **135F** and **1E** . Compound 135 is a solid with an analytical HPLC retention time = 1.666 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 391^+$. ^{1}H-NMR ($CDCl_3$): 11.62 (s, 1H), 7.94 (s, 1H), 7.89 (dd, $J_1 = 2.60$, $J_2 = 6.61$, 1H), 7.48 (d, J = 2.60, 1H), 7.45 (m, 1H), 7.15 (t, J = 8.72, 1H), 6.51 (d, J = 2.60, 1H), 3.82 (AB, J = 13.60, $\Delta\nu = 26.94$, 2H), 3.33 (m, 1H), 3.25 (m, 1H), 3.08 (d, J = 12.09, 1H), 2.57 (m, 1H), 2.22 (t, J = 12.03, 1H), 2.05 (m, 1H), 1.97 (m, 1H), 1.43 (m, 1H).

Alternatively, Compound **135** can be prepared as shown below.

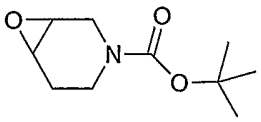
Preparation of Compound **135J**



135J

Compound **135J** was prepared according to a published literature procedure: Jacob Szmuszkovicz et al., *Heterocycles*, **1994**, *39* (1), 163-170.

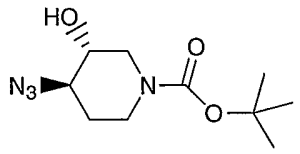
Preparation of Compound **135K**:



135K

Compound **135K** was prepared according to a published literature procedure: Jacob Szmuszkovicz et al., *Heterocycles*, **1994**, *39* (1), 163-170.

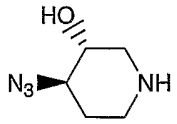
Preparation of Compound **135L**:



135L

Compound **135L** was prepared from Compound **135K** in a similar way as Compound **1C**. Analytical HPLC retention time = 2.323 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 220 nm). ^{1}H-NMR (CDCl3): 4.11 (dd, J1 = 3.09, J2 = 13.29, 1H), 3.95 (m, 1H), 3.50 (m, 1H), 3.38 (m, 1H), 2.90 (m, 1H), 2.79 (dd, J1 = 9.27, J2 = 13.29, 1H), 2.45 (m, 1H), 2.00 (m, 1H), 1.55 (m, 1H), 1.46 (s, 9H).

Preparation of Compound **135M**:

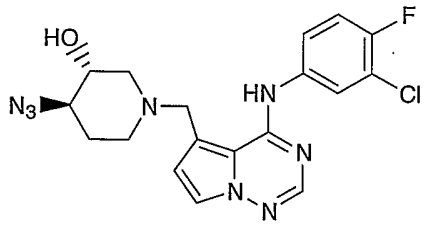


135M

To a solution of Compound **135L** (0.6 g, 2.48 mmol) in dry CH_2Cl_2 cooled at 0°C, was added trifluoroacetic acid (5 mL). The reaction mixture was stirred at 0°C for 15 min, then warmed to room temperature and stirred for 3 hrs. The solvent and TFA were removed under reduced pressure and the residue was taken into CH_2Cl_2 (20

mL). The organic layer was washed with sat'd $NaHCO_3$ and the aqueous layer was supersaturated with solid NaCl, and back extracted with EtOAc (15 mL x 10). The combined organic extracts were dried over anhydrous Na2SO4. Concentration *in vacuo* gave 350 mg of Compound **135M** as an oil. ^{1}H-NMR ($CDCl_3$ + CD_3OD): 3.55 (m, 1H), 3.43 (m, 1H), 3.18 (dd, J1 = 3.95, J2 = 12.63, 1H), 3.07 (d of t, J1 = 12.90, J2 = 4.78, 1H), 2.74 (m, 1H), 2.63 (dd, J1 = 8.28, J2 = 12.58, 1H), 2.10 (m, 1H), 1.57 (m, 1H).

Preparation of Compound **135N**:



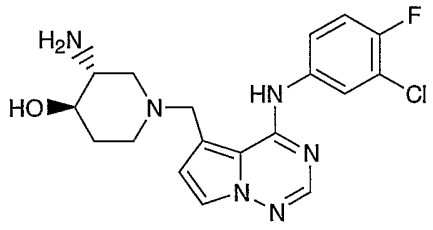
135N

Compound **135N** was prepared in a similar way as Compound **1F** (using Method Two) in Example 1 starting from Compound **135M** and **1E** of Example **1** . Compound **135N** is a solid and has an analytical HPLC retention time = 2.099 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 417^+$.

To a solution of above prepared Compound **135N** (0.5 mmol) in a mixture of THF (5 mL) and water (0.05 mL) was added triphenylphosphine (262 mg, 1.0 mmol). The reaction mixture was heated to reflux for 8 hrs. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was directly purified by flash chromatography (CH_2Cl_2-MeOH-NH_4OH: 95:5:0.5) on silica gel to give 166 mg of Compound **135** as a solid.

EXAMPLE 136

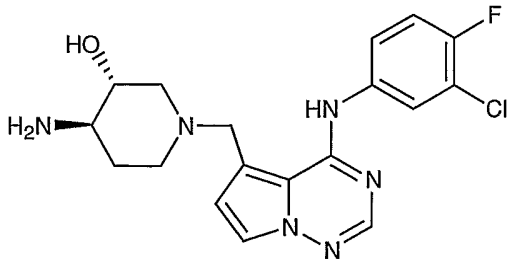
3-Amino-1-[[4-[(3-chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]-(3R,4R)-rel-4-piperidinol



Compound **136** was prepared in a similar manner as Example 1 using Compound **135H** and **1E** . Compound **136** is a solid, with an analytical HPLC retention time = 1.953 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 391^+$.

EXAMPLE 137

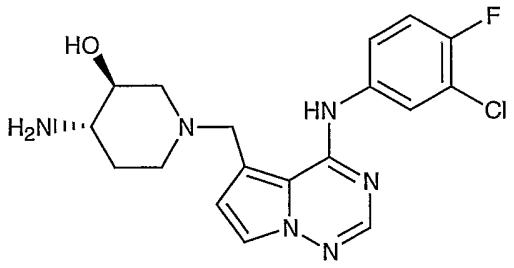
4-Amino-1-[[4-[(3-chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]-(3R,4R)-(+)-rel-3-piperidinol



and

EXAMPLE 138

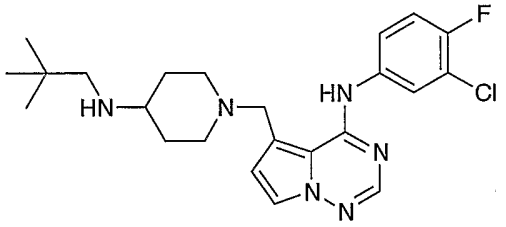
4-Amino-1-[[4-[(3-chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]-(3R,4R)-(-)-rel-3-piperidinol



The racemic Compound **135** was resolved using a normal phase chiral preparative HPLC (Chiralpak AD) using hexane-isopropyl alcohol-diethylamine (80:20:0.05) as mobil phase. Compound **137** (Eanatiomer A) and Compound **138** (Enantiomer B) were obtained as single enantiomers with >99% ee.

EXAMPLE 139

N-(3-Chloro-4-fluorophenyl)-5-[[4-[(2,2-dimethylpropyl)amino]-1-piperidinyl]methyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine

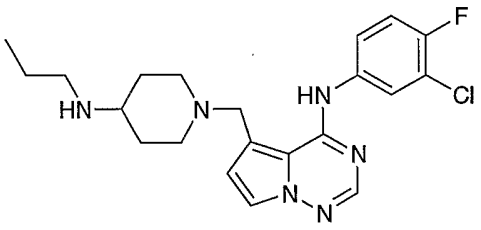


To a solution of the compound of Example 1 (19 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added glacial acidic acid (0.05 mL), followed by 3,3-dimethylbutyraldehyde (0.008 mL, 0.073 mmol) and sodium triacetoxyborohydride (25 mg, 0.12 mol). The mixture was stirred at room temperature for 30 hrs. The reaction mixture was diluted with CH_2Cl_2, washed with water, sat'd $NaHCO_3$, brine

and dried over anhydrous Na_2SO_4. Concentration *in vacuo* followed by flash chromatography (CH_2Cl_2-MeOH-NH_4OH: 98:2:0.2 to 98:5:0.5) on silica gel gave Compound **139** as an oil. Analytical HPLC retention time = 1.976 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 445^+$.

EXAMPLE 140

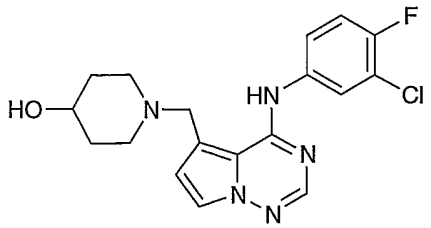
N-(3-Chloro-4-fluorophenyl)-5-[[4-(propylamino)-1-piperidinyl]methyl]-pyrrolo[2,1-f][1,2,4]triazin-4-amine



Compound **140** was prepared in a similar way as Compound **139** from Compound 1. Compound **140** is a solid and has an analytical HPLC retention time = 1.689 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 417^+$.

EXAMPLE 141

1-[[4-[(3-Chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]-4-piperidinol

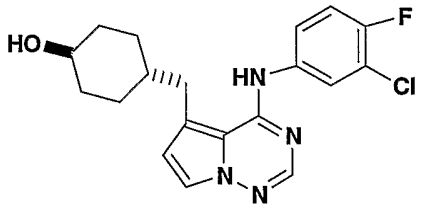


Compound **141** was prepared in a similar way as Compound **1** from **1E** of Example **1**. Compound **141** is a solid and had an analytical HPLC retention time =

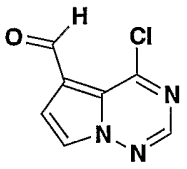
1.803 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 376^+$.

EXAMPLE 142

trans-4-[4-(3-Chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl]-cyclohexanol



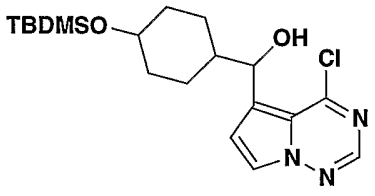
A. Preparation of 4-Chloro-pyrrolo[2,1-f][1,2,4]triazine-5-carbaldehyde



A solution of 4-chloro-5-methyl-pyrrolo[2,1-f][1,2,4]triazine (1.68 g, 10 m mole) in CCl_4 was sparged with N_2 for 20 min and then NBS (3.74 g, 21 mmole) followed by benzoyl peroxide (242 mg, 1 mmole) were added. The reaction mixture was put into a 100 °C oil bath and refluxed for 3 h. After cooling to RT, this was filtered and the solvent removed. The residue was suspended in CH_3OH (100 ml) and solid $NaHCO_3$ (5 g) was added. The reaction mixture was stirred vigorously for 1 h, filtered, and the solvent removed. The residue oil was resuspended in DCM, filtered, and concentrated to afford the crude dimethyl acetal which was treated with DCM (20 ml) / H_2O (20 ml) / TFA (1 ml). After stirring vigorously for 1.5 hours, this was neutralized with aqueous saturated $NaHCO_3$ and extracted with DCM. The combined extracts were dried (Na_2SO_4), concentrated and chromatographed (3 x 15 cm silica gel column eluted with DCM) to afford the title compound (1.02 g, 56%) as a solid. MS:

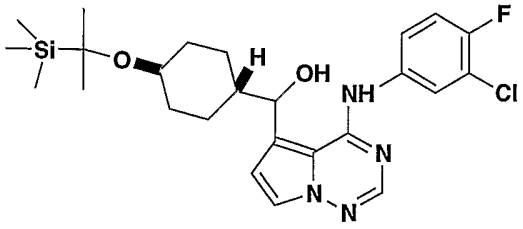
182 $(M+H)^+$; HPLC Ret Time: 0.79 min (Xterra 3.0 x 50 mm S7 column, 2 min gradient, 5 mL/min);

B. Preparation of [4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclohexyl]-(4-chloro-pyrrolo[2,1-f][1,2,4]triazin-5-yl)-methanol



A solution of *trans*-4-tertbutyldimethylsilyoxy-cyclohexylmagnesium bromide (Bioorg. and Med. Chem., 1996, 6, 201) in THF (4 equiv) was added slowly to an ice-cooled solution of 4-chloro-pyrrolo[2,1-f][1,2,4]triazine-5-carbaldehyde (1.05g, 5.8 mmole) in THF (15 mL). After 1 h, a saturated aqueous solution of NH_4Cl (15 mL) was added and the aqueous layer was extracted with EtOAc/hexane (1:1) (50 mL x 2). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified via radial chromatography (4 mm silica gel plate, gradient elution with 0 to 15 % EtOAc in DCM) to afford the title compound: 189 mg of *cis*-isomer, 496 mg of *tran*-isomer and 415 mg of mixture (total yield 48%, the ratio of *cis : trans* is about 1:4). *cis*-isomer: MS: 396 $(M+H)^+$; HPLC Ret Time: 2.10 min (Xterra 3.0 x 50 mm S7 column, 2 min gradient, 5 mL/min); *trans*-isomer: MS: 396 (M+H)+; HPLC Ret Time 2.08 min (Xterra 3.0 x 50 mm S7 column, 2 min gradient, 5 mL/min).

C. Preparation of [4-(3-Chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-yl]-[4-(1-methyl-1-trimethylsilanyl-ethoxy)-cyclohexyl]-methanol



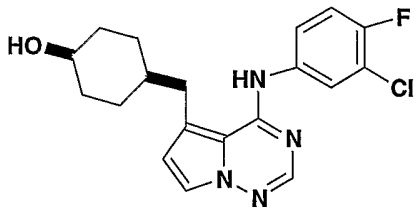
A mixture of *trans*-[4-(*tert*-butyldimethylsilanyloxy)-cyclohexyl]-(4-chloro-pyrrolo[2,1-f][1,2,4]triazin-5-yl)-methanol (840 mg, 2.13 mmole), 3-chloro-4-fluoro-phenylamine (309 mg, 2.13 mmole) and $NaHCO_3$ (536 mg, 6.39 mmole) in CH_3CN (10 mL) was heated at 70 °C overnight. The solvent was removed and the residue was suspended in DCM, washed with water, and dried over Na_2SO_4. Removal of the solvent followed by radial chromatography (4 mm silica gel plate, gradient elution with 0 to 2 % NH_3 in MeOH (2N) in DCM) afforded the title compound (612 mg, 57%) as a solid: MS: 506 $(M+H)^+$; HPLC Ret Time: 2.29 min (Xterra 3.0 x 50 mm S7 column, 2 min gradient, 5 mL/min).

D. Preparation of *trans*-4-[4-(3-Chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl]-cyclohexanol

A mixture of [4-(3-chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-yl]-[4-(1-methyl-1-trimethylsilanyl-ethoxy)-cyclohexyl]-methanol (448mg, 0.887 mmole) triethylsilane (1.03g, 8.87 mmole) in TFA (8 mL) under N_2 in a pressure flask was heated at 75 °C overnight. The solvents were removed and the residue was dissolved in CH_3OH (10ml) and solid Na_2CO_3 (2.0 g) was added. After stirring vigorously for 1 h, the solvent was removed and the residue was partitioned between DCM (200 ml) and H_2O (50ml). The organic phase was separated, dried over Na_2SO_4, and the solvent was removed. Purification via radial chromatography (2 mm silica gel plate, gradient elution with 0 to 4 % NH_3 in MeOH (2N) in DCM) afforded the title compound (209 mg, 63%) as a solid: MS: 375 $(M+H)^+$; HPLC Ret Time: 1.49 min (Xterra 3.0 x 50 mm S7 column, 2 min gradient, 5 mL/min).

EXAMPLE 143

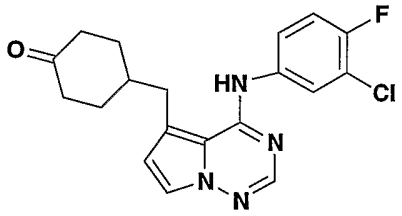
cis-4-[4-(3-Chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl]-cyclohexanol



Similarly, the title compound was prepared from *cis*-[4-(*tert*-butyldimethylsilanyloxy)-cyclohexyl]-(4-chloro-pyrrolo[2,1-f][1,2,4]triazin-5-yl)-methanol: 375 $(M+H)^+$; HPLC Ret Time: 1.56 min (Xterra 3.0 x 50 mm S7 column, 2 min gradient, 5 mL/min).

EXAMPLE 144

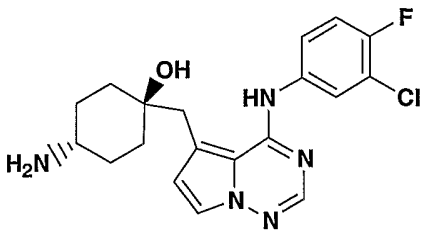
4-[4-(3-Chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl]-cyclohexanone



A solution of *cis*-[4-(*tert*-butyldimethylsilanyloxy)-cyclohexyl]-(4-chloro-pyrrolo[2,1-f][1,2,4]triazin-5-yl)-methanol: (53 mg, 0.14 m mole), 4-methylmorpholine *N*-oxide (25 mg, 0.21 mmole), TPAP (5 mg, 0.1 eq) and powered 4A molecular sieves (100 mg) in DCM (3 ml) under N_2 was stirred at RT. After 5 h, this was filtered and the solvent removed. Radial chromatography (1 mm silica gel plate, gradient elution with 0 to 5 % NH_3 in MeOH (2 N) in DCM) afforded the title compound (25 mg, 47%) as a solid: MS: 373 $(M+H)^+$; HPLC Ret Time: 1.50 min (Xterra 3.0 x 50 mm S7 column, 2 min gradient, 5 mL/min).

EXAMPLE 145

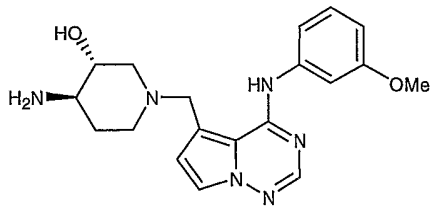
4-Amino-1-[4-(3-chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl]-cyclohexanol



To a solution of 4-[4-(3-chloro-4-fluoro-phenylamino)-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl]-4-hydroxy- cyclohexanone (24 mg, 0.06 mmole) in dry MeOH (0.5 mL) was added powdered 3A molecular sieves (24 mg), (10 eq) NH_4OAc (48 mg, 0.06 mmole), and $NaCNBH_3$ (4 mg, 0.06 mmole); the reaction stirred under nitrogen for 12 hr. The reaction mixture was filtered and a 15% NaOH solution was added. After 10 min, the mixture was diluted with DCM (50 mL) and washed with water. The organic phase was dried (Na_2SO_4) and the solvent was removed. The material was purified and separated by preparative HPLC to afford the title compound (3.5 mg, 15%) and the cis isomer (7.9 mg, 32%). The title compound: MS: 390 $(M+H)^+$; HPLC Ret Time: 2.070 min (XTERRA 4.6 x 50 mm S5 column, 3 min gradient, 4 mL/min). The cis isomer: MS: 390 $(M+H)^+$; HPLC Ret Time: 2.190 min (XTERRA 4.6 x 50 mm S5 column, 3 min gradient, 4 mL/min).

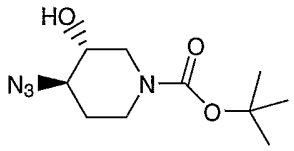
EXAMPLE 146

(3R,4R)-4-amino-1-[[4-[(3-methoxyphenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol



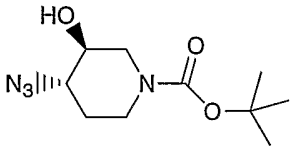
Preparation of Compounds **146A** and **146B**:

(3R,4R)-4-Azido-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (**146A**):



146A

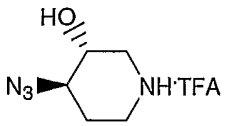
(3S,4S)-4-Azido-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (**146B**):



146B

Compounds **146A** and **146B** were obtained from Compound **135L** by optical resolution using a normal phase chiral preparative HPLC (Chiralpak AD) using MeOH-EtOH (50:50) as mobil phase. Compound **146A** (first eluent) and Compound **146B** (second eluent) were obtained as single enantiomers with >99% ee. The absolute stereochemistry of Compound **146A** (3R, 4R) was determined by a single X-ray crystallographic analysis.

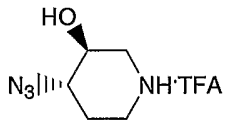
Preparation of Compound **146C**:



146C

To a solution of Compound **146A** (1.76 g, 7.26 mmol) in dry CH_2Cl_2 (15 mL) cooled at 0°C, was added trifluoroacetic acid (10 mL). The reaction mixture was stirred at 0°C for 15 min, then warmed to room temperature and stirred for 3 hrs. The solvent and TFA were removed under reduced pressure and the residue was azeotropically evaporated several times with CH_2Cl_2 to give Compound **146C** as a TFA salt.

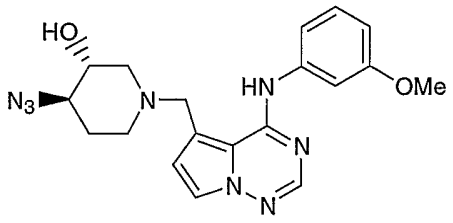
Preparation of Compound **146D**:



146D

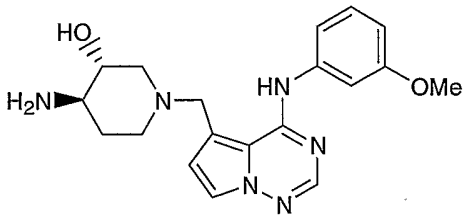
Compound **146D** was prepared, as a TFA salt, in a similar manner as Compound **146C** using Compound **146B**.

Preparation of Compound **146E**:



146E

Compound **146E** was prepared in a similar way as Example **105** (using Method One) replacing Compound **146C** for piperidin-4-yl-carbamic acid tert-butyl ester. Compound **146E** is a solid and has an analytical HPLC retention time = 2.019 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 395^+$.

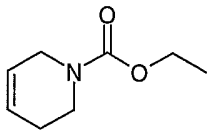


146

Compound **146** was prepared from Compound **146E** in a similar way as Compound **135**. Compound **146** is a solid, with an analytical HPLC retention time = 1.213 min (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 369^+$. The enantiomeric excess (ee) of Compound **146** is >99% (Chiralpak AD, 250 x 4.6 mm 10 micron, EtOH-MeOH-Et2NH: 50:50:0.1).

Alternate preparation of Compuond **146**

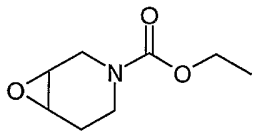
Preparation of Compound **146F**:



146F

To a solution of 1-methyl-1,2,3,6-tetrahydropiperidine HCl salt (227 g) in 570 mL of water was added solid K_2CO_3 (235 g) and the mixture was stirred at room temperature for 30 min. The mixture was extracted with toluene (500 mL x 3) and combined extracts were dried over anhydrous $MgSO_4$. Filtration to remove $MgSO_4$ and the filtrate was placed in a 3-L three-necked RB flask. K_2CO_3 (22.7 g) was added to the filtrate and the mixture was heated to gentle reflux (bath temperature 110°C). Ethyl chloroformate (318 mL) was added slowly over 2.5 hrs via an additional funnel (the reaction is extremely exothermic so slow addition with magnetic stirring is highly recommended). Upon completion of addition, the mixture was refluxed for an additional 2.0 hrs and cooled to room temperature. The reaction mixture was washed with water, brine and dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* afforded 188.6 g (72%) of Compound **146F** as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$):

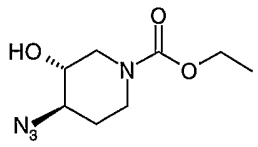
Preparation of Compound **146G (racemic)**:



146G

To a solution of Compound **146F** (178.2 g, 1.15 mol) in 2 L of dry CH_2Cl_2 at 0°C was added solid *m*-CPBA (386 g, 1.72 mol, 77% max) in small portions. The reaction mixture was stirred for 1.0 hr at 0°C and then overnight at room temperature. The precipitate was removed by filtration and the filtration cake was rinsed with CH_2Cl_2. The combined filtrate and washes were washed with 20% $Na_2S_2O_3$ (3 L x 3), saturated $NaHCO_3$ (3 L x 3) and dried over anhydrous Na_2SO_4. Filtration followed by concentration *in vacuo* afforded 170 g of Compound **146G** as an oil. This material was used directly in the next reaction step without further purification.

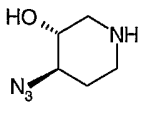
Preparation of Compound **146H (chiral)**:



146H

The mixture of Compound **146G** (140 g, 0.818 mol), NaN_3 (68.9 g, 1.06 mol) and NH_4Cl (56.7 g, 1.06 mol) in ethanol (600 mL) and water (150 mL) was heated at 70°C overnight. Upon cooling to room temperature, the solid was removed by filtration and rinsed with ethanol. The combined filtrates were concentrated *in vacuo* to small volume (ca. 80 mL), then diluted with water (500 mL) and extracted with EtOAc (500 mL x 4). The combined extracts were dried over anhydrous Na_2SO_4. Filtration followed by concentration *in vacuo* and purification by flash chromatography (hexane-EtOAc 7:3 to 6:4) on silica gel afforded Compound **146G** in following fractions: 80.7 g of first fraction (AP: >98%), 22.7 g of second fraction (AP: 92-95%) and 15.8 g of third fraction (AP: <60%) as an oil. This material was used directly in next step reaction without further purification. The first and second fractions were combined and subjected to optical resolution using chiral preparatory HPLC with following conditions: Chiralpak AD column, eluted with MeOH-EtOH (1:1). The first eluted peak (Rt = 5.605 min) was collected to give 47.52 g of Compound **146H**, with >99% ee.

Preparation of Compound **146I (Chiral)**:



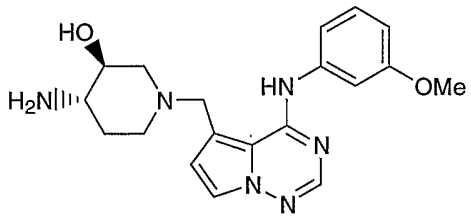
146I

To a solution of Compound **146H** (36.42 g, 0.17 mol) in 480 mL of EtOH was added a solution of KOH (112 g, 1.7 mol, 85%) in 240 mL of water. The mixture was heated to reflux for 9.0 hrs and the reaction progress was monitored by TLC. Upon cooling to room temperature, the mixture was concentrated *in vacuo* to give a paste. Solid NaCl was added and the mixture was extracted with EtOAc (500 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4. Filtration followed by removal of solvent under reduced pressure afforded 23 g (77%) of crude Compound **146I** as a solid. Trituration with ether (250 mL) gave 18.53 g of Compound **146I** as a solid (AP: 99%). The mother liquid was concentrated *in vacuo*, solid NaCl was added and further extracted with more EtOAc (250 mL x 4) to provide an additional 4.2 g of crude Compound **146I** (AP: <85%).

Compound **146** was prepared from Compound **146I** following the procedure used for the preparation of Compound **146E**.

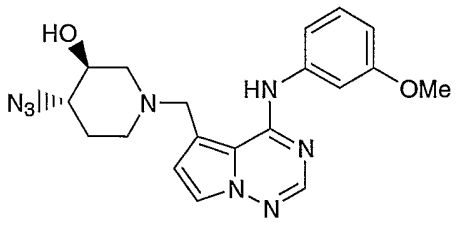
EXAMPLE 147

(3S,4S)-4-amino-1-[[4-[(3-methoxyphenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]3-piperidin-3-ol.



147

Preparation of Compound **147A**:



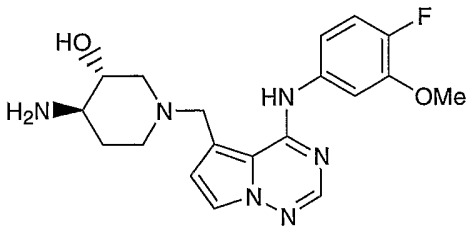
147A

\Compound **147A** was prepared in a similar way as Example **105** (using Method One) replacing Compound **130D** for piperidin-4-yl-carbamic acid tert-butyl ester. Compound **147A** is a solid and had an analytical HPLC retention time = ? min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 395^+$.

Compound **147** was prepared from Compound **147A** in a similar way as Compound **135**. Compound **147** is a solid, with an analytical HPLC retention time = 1.213 min (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 369^+$. The enantiomeric excess (ee) of Compound **147** is >99% (Chiralpak AD, 250 x 4.6 mm 10 micron, EtOH-MeOH-Et2NH: 50:50:0.1).

EXAMPLE 148

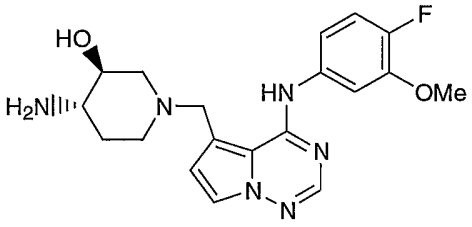
(3R,4R)-4-amino-1-[[4-[(3-methoxy-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol



Compound **148** was prepared from Compound **146C** in a similar way as Compound **135**. Compound **148** is a solid, with an analytical HPLC retention time = 1.187 min (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 387^+$. The enantiomeric excess (ee) of Compound **148** is >99%.(Chiralpak AD, 250 x 4.6 mm 10 micron, EtOH-MeOH-Et2NH: 50:50:0.1).

EXAMPLE 149

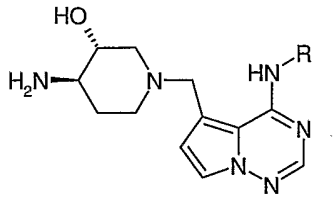
(3S,4S)-4-amino-1-[[4-[(3-methoxy-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]-piperidin-3-ol.



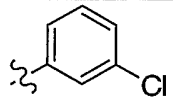
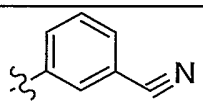
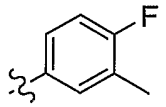
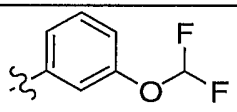
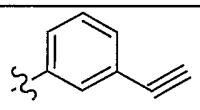
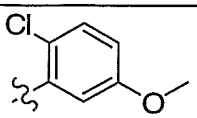
Compound **149** was prepared from Compound **146D** in a similar way as Compound **135**. Compound **149** is a solid, with an analytical HPLC retention time = 1.187 min (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 387^+$. The enantiomeric excess (ee) of Compound **149** is >99% (Chiralpak AD, 250 x 4.6 mm 10 micron, EtOH-MeOH-Et2NH: 50:50:0.1).

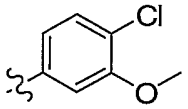
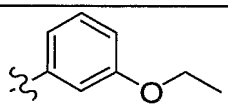
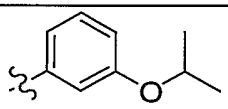
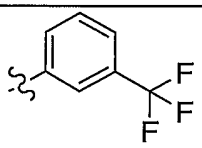
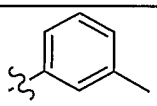
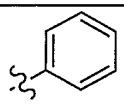
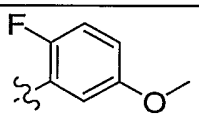
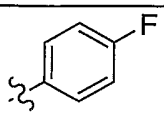
EXAMPLES 150-200

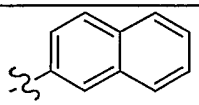
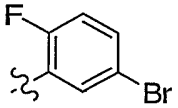
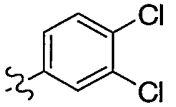
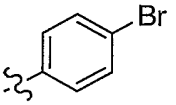
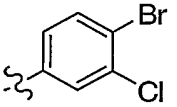
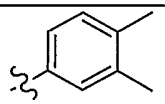
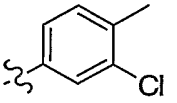
Compounds **150-200** (with HPLC note (b)) were similarly prepared from **146I** as Compound **146**.

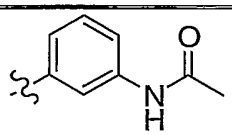
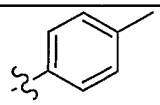
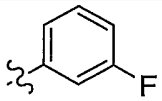
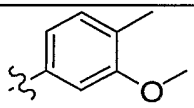
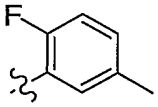
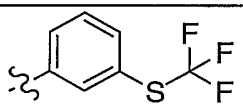
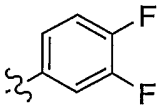
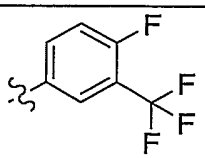


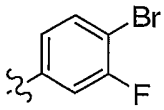
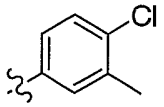
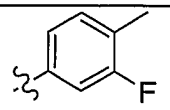
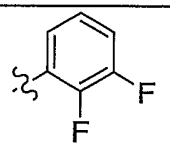
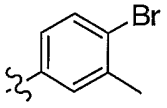
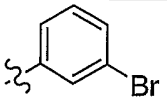
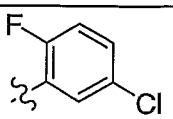
5

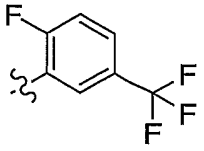
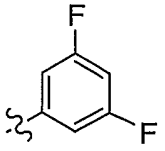
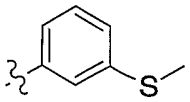
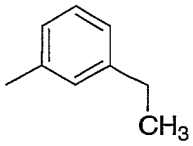
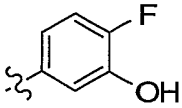
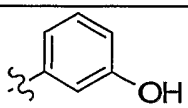
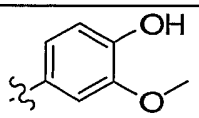
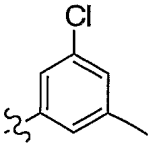
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	150		(3*R*,4*R*)-4-amino-1-({4-[(3-chlorophenyl) amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol	373	1.508
	151		3-[(5-{[(3*R*,4*R*)-4-amino-3-hydroxy piperidin-1-yl]methyl}pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino]benzonitrile	364	1.348
	152		(3*R*,4*R*)-4-amino-1-({4-[(4-fluoro-3-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	371	1.542
	153		(3*R*,4*R*)-4-amino-1-[(4-{[3-(difluoromethoxy)-phenyl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)-methyl]piperidin-3-ol	405	1.610
	154		(3*R*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*]-[1,2,4]-triazin-5-yl}-methyl)piperidin-3-ol	363	1.730
	155		(3*R*,4*R*)-4-amino-1-({4-[(2-chloro-5-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-	403	1.300

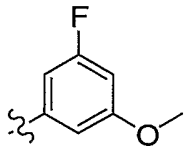
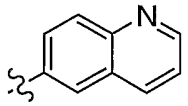
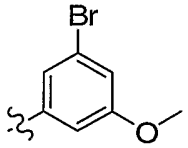
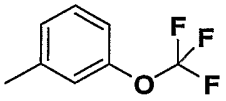
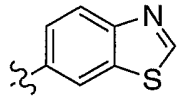
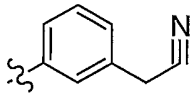
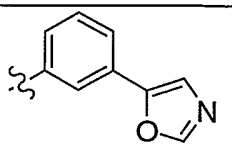
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
			methyl)piperidin-3-ol		
	156		(3*R*,4*R*)-4-amino-1-({4-[(4-chloro-3-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	403	1.620
	157		(3*R*,4*R*)-4-amino-1-({4-[(3-ethoxyphenyl)-amino]-pyrrolo[2,1-*f*]-[1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	383	1.540
	158		(3*R*,4*R*)-4-amino-1-({4-[(3-isopropoxyphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl-)-piperidin-3-ol	397	1.820
	159		(3*R*,4*R*)-4-amino-1-[(4-{[3-(trifluoromethyl)-phenyl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)-methyl]piperidin-3-ol	407	1.110[b]
	160		(3*R*,4*R*)-4-amino-1-({4-[(3-methylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	353	1.410
	161		(3*R*,4*R*)-4-amino-1-[(4-anilinopyrrolo[2,1-*f*]-[1,2,4]triazin-5-yl)-methyl]piperidin-3-ol	339	0.580[b]
	162		(3*R*,4*R*)-4-amino-1-({4-[(2-fluoro-5-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	387	1.283
	163		(3*R*,4*R*)-4-amino-1-({4-[(4-fluorophenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-	357	0.820[a]

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
			methyl)piperidin-3-ol		
	164		(3*R*,4*R*)-4-amino-1-{[4-(2-naphthylamino)-pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl]methyl}-piperidin-3-ol	389	1.130[a]
	165		(3*R*,4*R*)-4-amino-1-({4-[(5-bromo-2-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	435	2.100
	166		(3*R*,4*R*)-4-amino-1-({4-[(3,4-dichlorophenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	407	1.260[a]
	167		(3*R*,4*R*)-4-amino-1-({4-[(4-bromophenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	419	1.310[a]
	168		(3*R*,4*R*)-4-amino-1-({4-[(4-bromo-3-chloro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	453	1.670[a]
	169		(3*R*,4*R*)-4-amino-1-({4-[(3,4-dimethylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	367	1.200[a]
	170		(3*R*,4*R*)-4-amino-1-({4-[(3-chloro-4-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	387	1.460[a]

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	171		*N*-{3-[(5-{[(3*R*,4*R*)-4-amino-3-hydroxy-piperidin-1-yl]methyl}-pyrrolo[2,1-*f*][1,2,4]-triazin-4-yl)amino]-phenyl}acetamide	396	0.900[a]
	172		(3*R*,4*R*)-4-amino-1-({4-[(4-methylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	353	1.040[a]
	173		(3*R*,4*R*)-4-amino-1-({4-[(3-fluorophenyl)amino]pyrrolo[2,1-*f*][1, 2, 4] triazin-5-yl}methyl)-piperidin-3-ol	357	0.870[a]
	174		(3*R*,4*R*)-4-amino-1-({4-[(3-methoxy-4-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	383	1.160[a]
	175		(3*R*,4*R*)-4-amino-1-({4-[(2-fluoro-5-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	371	1.120[a]
	176		(3*R*,4*R*)-4-amino-1-{[4-({3-[(trifluoromethyl)-thio]phenyl}amino)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl]methyl}piperidin-3-ol	439	1.770[a]
	177		(3*R*,4*R*)-4-amino-1-({4-[(3,4-difluorophenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl-methyl)-piperidin-3-ol	375	1.080[a]
	178		(3*R*,4*R*)-4-amino-1-[(4-{[4-fluoro-3-(trifluoro-methyl)phenyl]amino}pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl)methyl]piperi-	425	1.230[a]

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
			din-3-ol		
	179		(3*R*,4*R*)-4-amino-1-({4-[(4-bromo-3-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	435	1.480[a]
	180		(3*R*,4*R*)-4-amino-1-({4-[(4-chloro-3-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	387	1.430[a]
	181		(3*R*,4*R*)-4-amino-1-({4-[(3-fluoro-4-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	371	1.240[a]
	182		(3*R*,4*R*)-4-amino-1-({4-[(2,3-difluorophenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)-piperidin-3-ol	375	0.880[a]
	183		(3*R*,4*R*)-4-amino-1-({4-[(4-bromo-3-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	431	1.520[a]
	184		(3*R*,4*R*)-4-amino-1-({4-[(3-bromophenyl)amino]pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-ol	419	1.260[a]
	185		(3*R*,4*R*)-4-amino-1-({4-[(5-chloro-2-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	391	1.060[a]

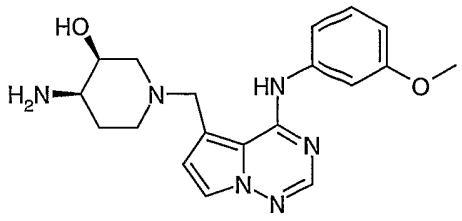
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	186		(3*R*,4*R*)-4-amino-1-[(4-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)methyl]piperidin-3-ol	425	1.200[a]
	187		(3*R*,4*R*)-4-amino-1-({4-[(3,5-difluorophenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)-piperidin-3-ol	375	1.120[a]
	188		(3*R*,4*R*)-4-amino-1-[(4-{[3-(methylthio)phenyl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)-methyl]piperidin-3-ol	385	1.200[a]
	189		(3*R*,4*R*)-4-amino-1-({4-[(3-ethylphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol	367	1.870[a]
	190		(3*R*,4*R*)-4-amino-1-({4-[(4-fluoro-3-hydroxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	373	0.876
	191		(3*R*,4*R*)-4-amino-1-({4-[(3-hydroxyphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol	355	0.915
	192		(3*R*,4*R*)-4-amino-1-({4-[(4-hydroxy-3-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	385	0.850
	193		(3*R*,4*R*)-4-amino-1-({4-[(3-chloro-5-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	387	1.717

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	194		(3*R*,4*R*)-4-amino-1-({4-[(3-fluoro-5-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	387	1.346
	195		(3*R*,4*R*)-4-amino-1-{[4-(quinolin-6-ylamino)-pyrrolo[2,1-*f*][1,2,4]triazin-5-yl]methyl}piperidin-3-ol	390	0.870
	196		(3*R*,4*R*)-4-amino-1-({4-[(3-bromo-5-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	447	1.709
	197		(3*R*,4*R*)-4-amino-1-[(4-{[3-(trifluoromethoxy)-phenyl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)-methyl]piperidin-3-ol	423	1.200[b]
	198		(3*R*,4*R*)-4-amino-1-{[4-(1,3-benzothiazol-6-yl-amino)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl]methyl}piperidin-3-ol	396	0.840[a]
	199		{3-[(5-{[(3*R*,4*R*)-4-amino-3-hydroxypiperidin-1-yl]methyl}pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino]phenyl}acetonitrile	378	0.790[a]
	200		(3*R*,4*R*)-4-amino-1-[(4-{[3-(1,3-oxazol-5-yl)-phenyl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)-methyl]piperidin-3-ol	406	0.910[a]

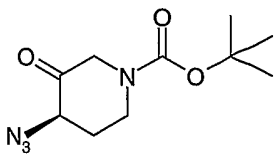
[a]2 min gradient time for HPLC. [b]2 min gradient time for HPLC (Phenom-prime S5 C18 4.6 x 30 mm column.

EXAMPLE 201

rac-(3*S*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol



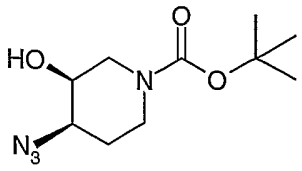
201A. Preparation of (±)-*tert*-butyl 4-azido-3-oxopiperidine-1-carboxylate



201A

Anhydrous DMSO (0.28 mL, 3.79 mmol) was added to a stirred solution of oxalyl chloride (0.172 mL, 1.96 mmol) in 6 mL of dry CH_2Cl_2 at -78°C under argon. After 10 min, a solution of Compound **135L** (396 mg, 1.63 mmol) in 4.5 mL of dry CH_2Cl_2 was added dropwise, and the reaction mixture was stirred at -78°C for 30 min. Triethylamine (1.38 mL, 10.0 mmol) was added and the reaction mixture was allowed to warm to room temperature. 2.0 mL of pH 7.0 buffer solution was added and the mixture was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration *in vacuo* afforded crude **201A** as an oil which was used immediately in the next reaction step. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.30 (d, J = 17.84, 1H), 4.05 (m, 1H), 3.90-4.00 (m 1H), 3.45 (m, 1H), 2.85 (m, 1H), 2.33 (m, 1H), 1.86 (m, 1H), 1.47 (s, 9H).

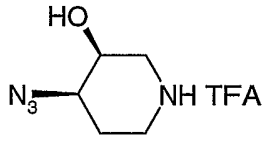
201B. Preparation of (±)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate



201B

To a solution of Compound **201A** prepared above in dry THF (2 mL) cooled at -78°C was added L-Selectride (1.0 M in THF, 0.98 mL, 0.98 mmol). The mixture was stirred at -78°C for 2.0 hrs. Saturated NH_4Cl (2 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was diluted with water and extracted with EtOAc (3x). The combined organic layers were washed once with brine and dried over anhydrous Na_2SO_4. Concentration *in vacuo* followed by flash chromatography (hexane-EtOAc 4:1) on silica gel gave 44 mg of Compound **201B** as an oil. ^{1}H-NMR (400 mHz, $CDCl_3$): 3.84 (m, 1H), 3.69 (m, 1H), 3.58 (m, 2H), 3.40 (m, 1H), 3.30 (m, 1H), 1.96 (m, 1H), 1.73 (m, 1H), 1.46 (s, 9H).

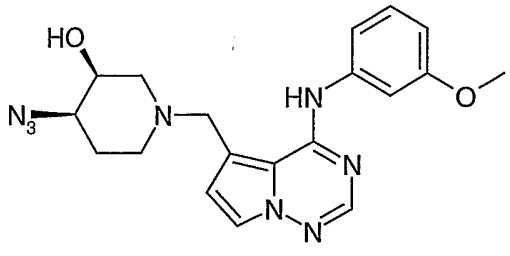
201C. Preparation of (±)-4-azidopiperidin-3-ol



201C

Compound **201B** (44 mg, 0.18 mmol) was treated with a mixture of CH_2Cl_2 and TFA (1:1, 2 mL) for 30 min. The volatiles were removed under reduced pressure and the residue was azeotropically evaporated with heptane-CH_2Cl_2 three times to give a TFA salt of Compound **201C**, which was used immediately in the next reaction without step further purification.

Preparation of **201D**:



201D

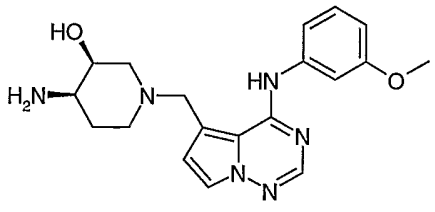
Compounds **201D** was prepared as a solid from Compound **201C** in a similar way as Compound **146E**. It had an analytical HPLC retention time = 1.795 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^+ = 395.

Compound **201** was prepared from Compound **201D** in a similar way as Compound **146**. It had an analytical HPLC retention time = 1.169 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^+ = 369.

EXAMPLE 202A AND 202B

(3*S*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol

(Enantiomer A, chiral)

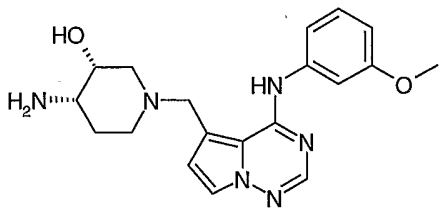


202A

and

(3*R*,4*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol

(Enantiomer B, chiral)



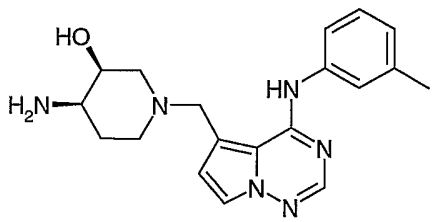
202B

Compound **202A** (15 mg) and compound **202B** (15 mg) were obtained by optical resolution of Compound **201** (30 mg) using the following method: Chiralpak AD chiral preparatory column eluted with hexane-isopropyl alcohol-diethylamine (50:50:0.1) using gradient of 6.0 ml/min flow rate and detected at 220 nm. The first eluted peak corresponds to Compound **202A** (retention time = 4.337 min) with ee% ≥ 98%; the second eluted peak corresponds to Compound **202B** (retention time = 6.050 min) with ee% ≥ 98%.

EXAMPLE 203

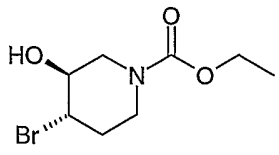
(3*S*,4*R*)-4-amino-1-({4-[(3-methylphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol

(chiral)



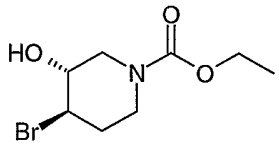
203

Preparation of Compound **203A** and **203B (Chiral)**:



203A

and



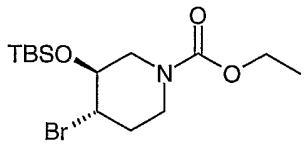
203B

To a solution of Compound **146G** (100 g, 0.585 mol) in 2 L of chloroform cooled at -60°C was added, dropwise via an additional funnel, 196.5 mL of 48% HBr while the internal temperature was kept below -60°C. Upon completion of addition, the reaction mixture was stirred for another 1.0 hr at -60°C. The reaction mixture was warmed to room temperature and washed with water (1 L x 2), brine (1 L) and dried over anhydrous MgSO4. Filtration followed by concentration *in vacuo* afforded 134.2 g (91%) of crude compound (racemic mixture of **203A** and **203B**) as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.25 (m, 1H), 4.15 (q, J = 7.10, 2H), 4.00 (m, 1H), 3.90 (bs, 1H), 3.75 (m, 1H), 2.85-3.15 (m, 2H), 2.32 (m, 1H), 2.00 (m, 1H), 1.28 (t, J = 7.10, 3H).

Compounds **203A** and **203B** were obtained from optical resolution of the above racemic mixture by a normal phase chiral preparative HPLC (Chirlapak AD) using CH_3CN as a mobil phase. 54.77 g of Compound **203B** (first eluent, Rt = 5.861 min) and 53.71 g of Compound **203A** (second eluent, Rt = 8.719 min) were obtained as single enantiomers with >99% ee. The absolute stereochemistry of Compound

203B (3R, 4S) was assigned based on the a single x-ray crystallographic analysis of Compound **203**.

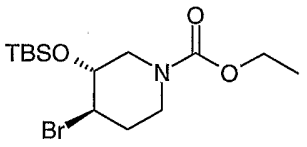
Preparation of Compound **203C (Chiral)**:



203C

To a solution of Compound **203A** (53.7 g, 0.213 mol) in 250 mL of DMF, was added imidazole (21.8 g, 0.32 mol), followed by t-butyldimethylsilyl chloride (38.5 g, 0.258 mol) at 0°C. The reaction mixture was stirred at ambient temperature overnight. Ether (1 L) was added to the reaction mixture, followed by water (1 L) at 0°C. The organic layer was separated. The aqueous layer was extracted with ether (1 L x 2) and combined organic layers were washed with 10% LiCl (750 mL x 3), dried over anhydrous $MgSO_4$. Filtration followed by concentration *in vacuo* afforded crude Compound **203C** as an oil, which was used immediately without further purification.

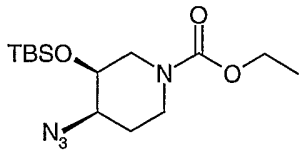
Preparation of Compound **203D (Chiral)**:



203D

Compound **203D** was prepared from Compound **203B** in a similar way as Compound **203C**.

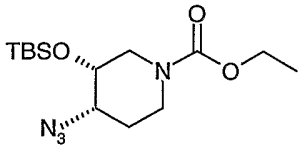
Preparation of Compound **203E (Chiral)**:



203E

To a solution of Compound **203C** (0.213 mol) in 300 mL of DMSO was added NaN_3 (15.3 g, 0.234 mol) and the mixture was heated at 85°C for 12 hrs. Additional NaN_3 (15.0 g, 0.230 mol) was added and the reaction mixture was heated overnight. Upon cooling to room temperature, ice water was added to the reaction mixture and extracted with ether (1 L x 3). The combined organic layers were washed once with brine (1 L) and dried over anhydrous $MgSO_4$. Filtration followed by concentration *in vacuo* afforded 69.5 g of crude Compound **203E** as an oil, which was used immediately without further purification.

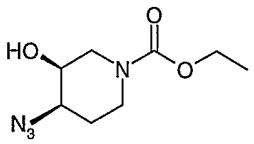
Preparation of Compound **203F (Chiral)**:



203F

Compound **203F** was prepared from Compound **203D** in a similar way as Compound **203E**.

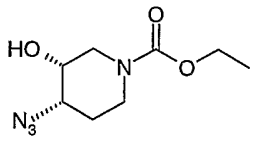
Preparation of Compound **203G (Chiral)**:



203G

The mixture of Compound **203E** (0.213 mol) prepared above and TBAF·xH_2O (67 g, 0.255 mol) in 200 mL of THF was stirred at room temperature for 3.0 hrs. Ether (1L) was added and the mixture was washed with water (1L). The aqueous phase was extracted with ether (1L x 2). The combined organic layers were washed once with water (1L) and dried over anhydrous $MgSO_4$. Concentration *in vacuo* followed by flash chromatography (CH_2Cl_2-EtOAc: 4:1) on silica gel afforded 29.8 g of Compound **203G** as an oil. Second flash chromatography (hexane-EtOAc: 6.5:3.5) on silica gel gave 20 g (44%) of Compound **203G** as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.15 (q, J = 7.10, 2H), 3.86 (bs, 1H), 3.70 (bs, 1H), 3.65 (m, 1H), 3.47 (dd, J = 3.20, J = 13.62, 1H), 3.35 (m, 1H), 2.02 (m, 1H), 1.79 (bs, 1H), 1.28 (t, J = 7.10, 3H).

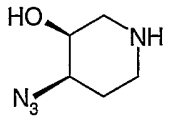
Preparation of Compound **203H (Chiral)**:



203H

Compound **203H** was prepared from Compound **203F** in a similar way as Compound **203G**.

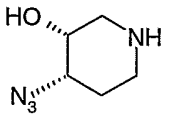
Preparation of Compound **203I (Chiral)**:



203I

Compound **203I** was prepared from Compound **203G** in a similar way as Compound **146I**. Compound **203I** is a solid with ≥ 99ee%. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.80 (m, 1H), 3.44 (m, 1H), 3.04 (m, 2H), 2.72 (m, 1H), 2.69 (m, 1H), 1.90 (m, 1H), 1.75 (m, 1H).

Preparation of Compound **203J (Chiral)**:



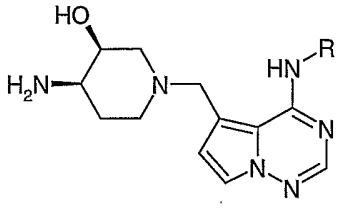
203J

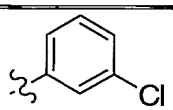
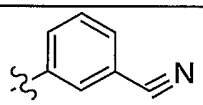
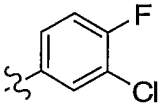
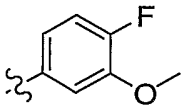
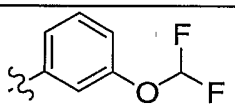
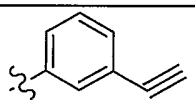
Compound **203J** was prepared from Compound **203H** in a similar way as Compound **146I**. Compound **203J** is a solid with ≥ 99ee%.

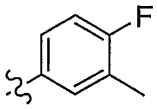
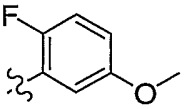
Compound **203** was prepared from Compound **1B**, *meta*-methylaniline and Compound **203I** in a similar way as Compound **146**. It had an analytical HPLC retention time = 1.278 min. (Chromolith SpeedROD 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 353.

EXAMPLES 204-211

Compounds **204-211** (with HPLC note (b)) were similarly prepared from Compound **1B**, the corresponding anilines and Compound **203I**, as used for Compound **146**.

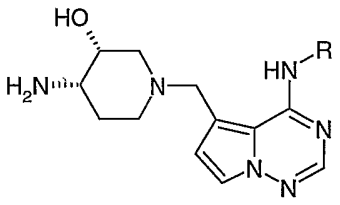


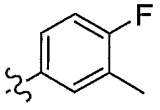
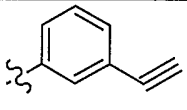
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	204		(3*S*,4*R*)-4-amino-1-({4-[(3-chlorophenyl)amino]-pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-ol	373	1.356
	205		3-[(5-{[(3*S*,4*R*)-4-amino-3-hydroxypiperi-din-1-yl]methyl}pyrro-lo[2,1-*f*][1,2,4]triazin-4-yl)amino]benzonitrile	364	0.948
	206		(3*S*,4*R*)-4-amino-1-({4-[(3-chloro-4-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	391	1.394
	207		(3*S*,4*R*)-4-amino-1-({4-[(4-fluoro-3-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	387	1.092
	208		(3*S*,4*R*)-4-amino-1-[(4-{[3-(difluoromethoxy)-phenyl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)-methyl]piperidin-3-ol	405	1.312
	209		(3*S*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl) amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl) piperidin-3-ol	363	1.224

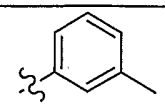
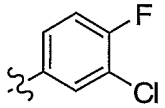
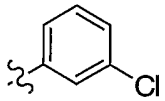
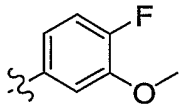
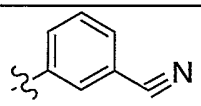
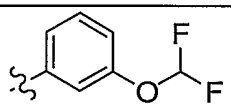
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	210		(3*S*,4*R*)-4-amino-1-({4-[(4-fluoro-3-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	371	1.346
	211		(3*S*,4*R*)-4-amino-1-({4-[(2-fluoro-5-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl-methyl)piperidin-3-ol	387	1.182

EXAMPLES 212-219

Compounds **212-219** (with HPLC note (b)) were similarly prepared from Compound **1B**, the corresponding anilines and Compound **203J**, as used for Compound **146**.

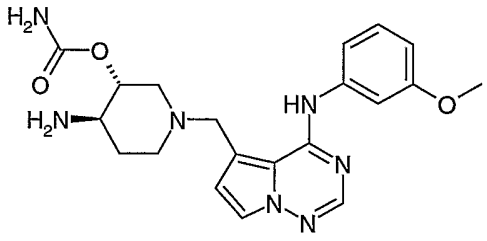


BMS#	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	212		(3*R*,4*S*)-4-amino-1-({4-[(4-fluoro-3-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	371	1.298
	213		(3*R*,4*S*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol	363	1.218

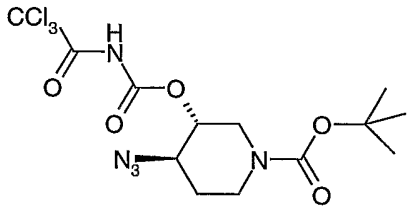
	214		(3*R*,4*S*)-4-amino-1-({4-[(3-methylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol	353	1.253
	215		(3*R*,4*S*)-4-amino-1-({4-[(3-chloro-4-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	391	1.354
	216		(3*R*,4*S*)-4-amino-1-({4-[(3-chlorophenyl)amino]pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-ol	373	1.304
	217		(3*R*,4*S*)-4-amino-1-({4-[(4-fluoro-3-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol	387	1.086
	218		3-[(5-{[(3*R*,4*S*)-4-amino-3-hydroxypiperidin-1-yl]methyl}pyrro-lo[2,1-*f*][1,2,4]triazin-4-yl)amino]benzonitrile	364	0.932
	219		(3*R*,4*S*)-4-amino-1-[(4-{[3-(difluoromethoxy)-phenyl]amino}pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)-methyl]piperidin-3-ol	405	1.318

EXAMPLE 220

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl carbamate



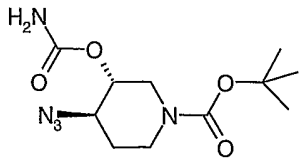
Preparation of Compound **220A** (Chiral):



220A

To a solution of Compound **146A** (121 mg, 0.5 mmol) in 1 mL of dry CH_2Cl_2 cooled at 0°C, was added trichloroacetylisocyanate (0.075 mL, 0.6 mmol). The reaction mixture was stirred at 0°C for 1.0 hr. MeOH (0.5 mL) was added and the reaction mixture was concentrated *in vacuo* to give crude Compound **220A** as a foam. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.35 (bs, 1H), 4.67 (bs, 1H), 3.90 (m, 1H), 3.65 (m, 2H), 3.25 (m, 2H), 2.02 (m, 1H), 1.60 (m, 1H), 1.38 (s, 9H).

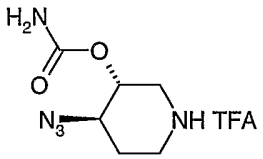
Preparation of Compound **220B**(Chiral):



220B

To a solution of **220A** (0.5 mmol) in 3 mL of dry MeOH was added a solution of 20% aq. K_2CO_3 (2 mL) and the reaction mixture was stirred at room temperature for 2.0 hrs. Water (15 mL) was added and the MeOH was removed by rotary evaporation. The mixture was extracted with EtOAc (x2) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* afforded crude **220B** as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.70 (bs, 2H), 4.50 (m, 1H), 3.90 (bs, 1H), 3.68 (m, 1H), 3.50 (m, 1H), 3.03 (m, 1H), 1.90 (m, 1H), 1.50 (m, 1H), 1.38 (s, 9H).

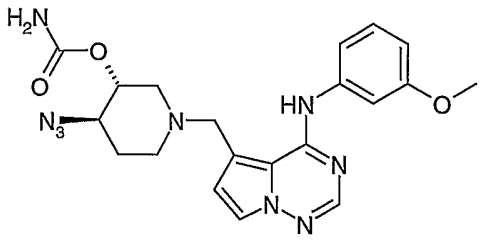
Preparation of Compound **220C**(Chiral):



220C

A mixture of **220B** (0.5 mmol) in 5 mL of dry CH_2Cl_2 and 5 mL of TFA was stirred at 0°C for 1.0 hr. The mixture was concentrated *in vacuo*, azeotropically evaporated several times with CH_2Cl_2-MeOH-hexane and dried under high vacuum to afforded crude **220C** as an oil.

Preparation of Compound **220D**(Chiral):



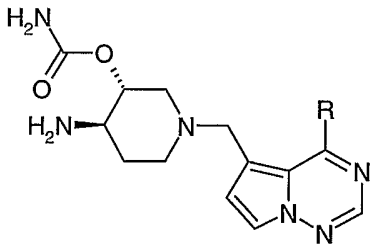
220D

Compound **220D** was prepared from Compound **220C** in a similar way as Compound **146E**. It had an analytical HPLC retention time = 1.793 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^+ = 438.

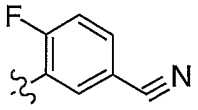
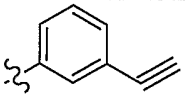
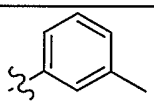
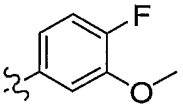
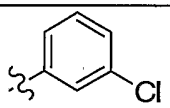
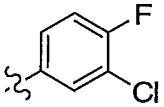
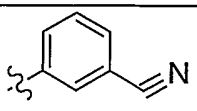
Compound **220** was prepared from Compound **220D** in a similar way as Compound **146**. It had an analytical HPLC retention time = 1.310 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^+ = 412.

EXAMPLES 221-227

Compounds **221-227** (with HPLC note (b)) were similarly prepared from Compound **1B**, corresponding anilines and Compound **220C** as Compound **146**.

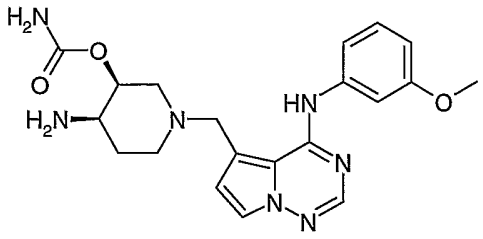


	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	221		(3*R*,4*R*)-4-amino-1-({4-[(5-cyano-2-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate	425	1.545
	222		(3*R*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate	406	1.562
	223		(3*R*,4*R*)-4-amino-1-({4-[(3-methylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate	396	1.381
	224		(3*R*,4*R*)-4-amino-1-({4-[(4-fluoro-3-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl carbamate	430	1.236
	225		(3*R*,4*R*)-4-amino-1-({4-[(3-chlorophenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl) piperidin-3-ylcarbamate	416	1.782
	226		(3*R*,4*R*)-4-amino-1-({4-[(3-chloro-4-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate	434	1.849
	227		(3*R*,4*R*)-4-amino-1-({4-[(3-cyanophenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl carba-mate	407	1.486

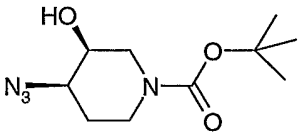
EXAMPLE 229

(3*R*,4*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl carbamate



229

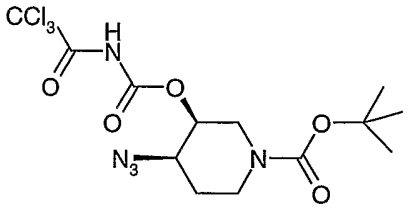
229A. Preparation of Compound **229A** (Chiral):



229A

Compound **229A** was prepared from Compound **203I** in a similar way as Compound **135E**, step 2.

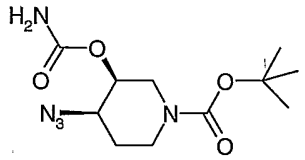
229B. Preparation of Compound 229B (Chiral):



229B

Compound **229B** was prepared from Compound **229A** in a similar way as Compound **220A**.

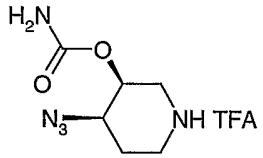
229C. Preparation of Compound **229C** (Chiral):



229C

Compound **229C** was prepared from Compound **229B** in a similar way as Compound **220B**.

229D. Preparation of Compound **229D**:

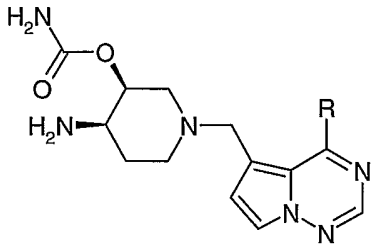


229D

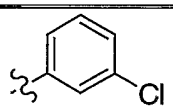
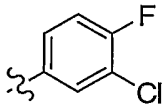
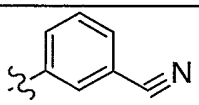
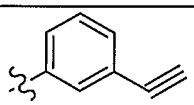
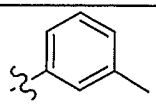
Compound **229D** was prepared from Compound **229C** in a similar way as Compound **220C**.

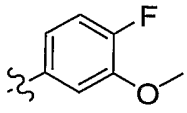
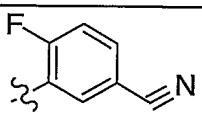
Compound **229** was prepared from Compound **229D** in a similar way as Compound **146**. It had an analytical HPLC retention time = 1.229 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS $M^+ = 412$.

EXAMPLES 230-236



Compounds **230-236** (with HPLC note (b)) were similarly prepared from Compound **1B**, corresponding anilines and Compound **229D** as Compound **146**.

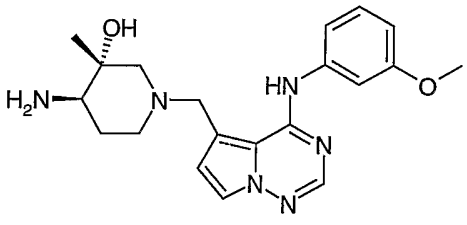
	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	230		(3*S*,4*R*)-4-amino-1-({4-[(3-chlorophenyl)amino]pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-yl carbamate	416	1.506
	231		(3*S*,4*R*)-4-amino-1-({4-[(3-chloro-4-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate	434	1.573
	232		(3*S*,4*R*)-4-amino-1-({4-[(3-cyanophenyl)amino]pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-yl carbamate	407	1.211
	233		(3*S*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate	406	1.396
	234		(3*S*,4*R*)-4-amino-1-({4-[(3-methylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-	396	1.273

	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
			methyl)piperidin-3-yl carbamate		
	235		(3*S*,4*R*)-4-amino-1-({4-[(4-fluoro-3-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate	430	1.173
	236		(3*S*,4*R*)-4-amino-1-({4-[(5-cyano-2-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate	425	1.230

EXAMPLE 237

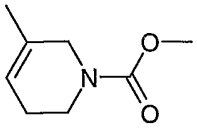
(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-3-methylpiperidin-3-ol

(Chiral, Enantiomer A)



237

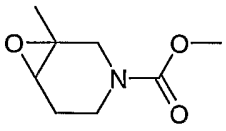
Preparation of Compound **237A** (racemic):



237A

To a solution of N-benzyltetrahydropyridine (100 mmol) in 150 mL of benzene was added solid $NaHCO_3$ (4.2 g, 49 mmol), followed by methyl chloroformate (9.3 mL, 120 mmol) dropwise via a syringe at room temperature. The reaction mixture was heated to reflux for 3 hrs. After cooling to room temperature, the volatiles were removed by evaporation under reduced pressure and the residue was dissolved in EtOAc (100 mL) and washed with water (20 ml x 2), 0.5 M HCl (20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. The reaction mixture was concentrated *in vacuo* and the residual benzyl chloride was further removed under high vacuum (bp. 42-50°C/2 mmHg, bath temperature: 75-80°C) to give Compound **237A** as a viscous syrup. Flash chromatography (hexane-EtOAc: 9.5:0.5 to 9:1) on silica gel afforded 11.77 g (Yield: 76%) of Compound **237A** as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.52 (bs, 1H), 3.78 (m, 2H), 3.70 (s, 3H), 3.46 (m, 2H), 2.08 (m, 2H), 1.68 (s, 3H).

Preparation of Compound **237B** (racemic):

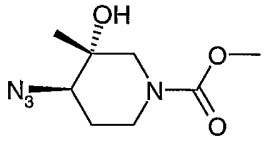


237B

The mixture of Compound **237A** (775 mg, 5.0 mmol) and *m*-CPBA (1.21 g, 7.0 mmol, 77% max) in 10 mL of dry CH_2Cl_2 was stirred overnight at room temperature. The precipitate was removed by filtration and the filtrate was washed by 10% $Na_2S_2O_3$, sat'd $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$.

Concentration *in vacuo* afforded crude Compound **237B** as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.65-3.75 (m, 2H), 3.68 (s, 3H), 3.60 (m, 1H), 3.33 (m, 2H), 3.12 (m, 1H), 2.07 (m, 1H), 1.92 (m, 1H), 1.35 (s, 3H).

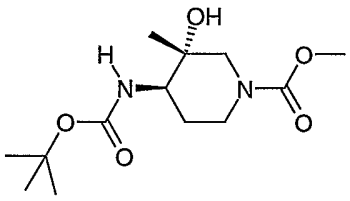
Preparation of Compound **237C** (racemic):



237C

To a solution of Compound **237B** (5.0 mmol) in 10 mL of DMF was added NaN_3 (810 mg, 12.4 mmol) in a 2:1 mixture of 10 mL of acetone-H2O and the mixture was heated at 80°C overnight. After cooling to room temperature, EtOAc was added and the mixture was washed by water, 10% LiCl aq. solution and dried over anhydrous Na_2SO_4. Concentration *in vacuo* afforded 1.09 g of Compound **237C** as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.70 (s, 3H), 3.72 (m, 1H), 3.50 (m, 2H), 3.35 (m, 1H), 3.20 (bs, 1H), 2.03 (m, 1H), 1.63 (m, 1H), 1.20 (s, 3H).

Preparation of Compound **237D** (racemic):



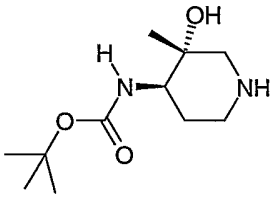
237D

The mixture of Compound **237C** (428 mg, 2.0 mmol) and 150 mg of Pd(OH)2 in 10 mL of MeOH was stirred under hydrogen atmosphere (balloon) for 4.0 hrs. The

catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give a crude residue.

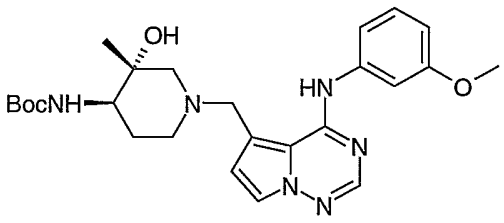
The residue was taken into 5 mL of dry CH_2Cl_2 and to this was added Boc_2O (460 mg, 2.10 mmol) and triethylamine (0.334 mL, 2.40 mmol). After stirring at room temperature overnight, the reaction mixture was diluted with was CH_2Cl_2 and washed with 10% citric acid, sat'd $NaHCO_3$ and dried (Na_2SO_4). Concentration *in vacuo* followed by flash chromatography (hexane-EtOAc: 7:3 to 1:1) on silica gel gave 330 mg of **237D** as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.78 (m, 1H), 3.90-4.40 (m, 3H), 3.70 (s, 3H), 3.60 (m, 1H), 2.70-3.00 (m, 2H), 1.80 (m, 1H), 1.45 (s, 9H), 1.40 (m, 1H), 1.10 (s, 3H).

Preparation of Compound **237E** (racemic):



Compound **237E** was prepared from Compound **237D** in a similar way as Compound **146I**.

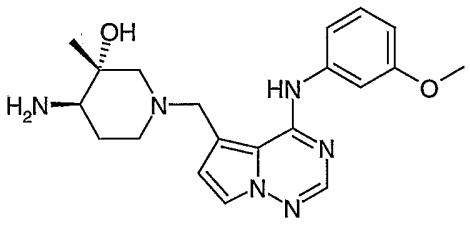
Preparation of Compound **237F** (racemic):



237F

Compound **237F** was prepared from Compound **237E** in a similar way as Compound **1D**.

Preparation of Compound **237G** (racemic):



237G

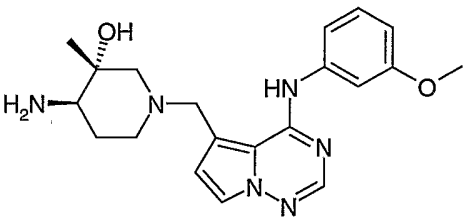
Compound **237G** was prepared from Compound **237F** in a similar way as Compound **1E**. It had an analytical HPLC retention time = 1.262 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 383.

Compound **237** was obtained from **237G** by chiral preparative HPLC separation (Chiralpak AD, 250 x 4.6 mm, 10 micron, eluted by EtOH/MeOH/DEA 50:50:0.1) as the first peak (Rt = 5.390 min) with ee% ≥99%. It had an analytical HPLC retention time = 1.51 min. (Chromolith SpeedROD 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 383.

EXAMPLE 238

(3*S*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-3-methylpiperidin-3-ol

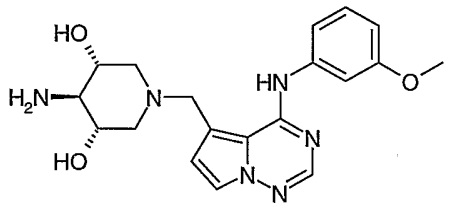
(Chiral, Enantiomer B)



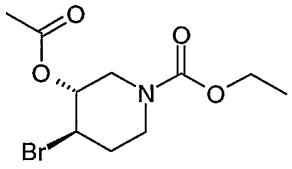
Compound **238** was obtained from **237G** by chiral preparative HPLC separation (Chiralpak AD, 250 x 4.6 mm, 10 micron, eluted by EtOH/MeOH/DEA 50:50:0.1) as the second peak (Rt = 8.523 min) with ee% ≥99%. It had an analytical HPLC retention time = 1.51 min. (Chromolith SpeedROD 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 383.

EXAMPLE 239

(3*R*,4*r*,5*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3,5-diol



239A. Preparation of (±)-ethyl 3-acetoxy-4-bromopiperidine-1-carboxylate

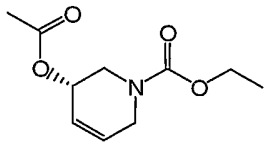


239A

A mixture of Compound **203A/B** (racemic mixture) (107 g, 371 mmol) and acetic anhydride (101 mL) in 165 mL of dry pyridine was stirred at room temperature for 2.0 hrs. The solvent was removed under reduced pressure and the residue was diluted with water and made basic with K_2CO_3. The mixture was extracted with chloroform (250 mL x 3) and the combined extracts were washed with water and dried over anhydrous $MgSO_4$. Concentration *in vacuo* afforded crude **239A** as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.90 (bs, 1H), 4.13 (q, J = 7.08, 2H), 4.10 (m, 1H),

3.89 (m, 1H), 3.60 (m, 1H), 3.50 (m, 2H), 2.34 (m, 1H), 2.08 (s 3H), 1.93 (m, 1H), 1.27 (t, J = 7.80, 3H).

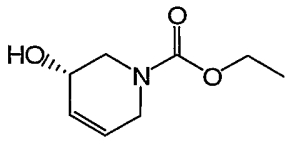
239B. Preparation of (±)-ethyl 5-acetoxy-5,6-dihydropyridine-1(2H)-carboxylate



239B

A mixture of Compound **239A** (371 mmol) and DBU (92 g, 604 mmol) was heated to 90 - 110°C for 30 min. After cooling to room temperature, the mixture was diluted with toluene and stirred for an additional 30 min. The precipitate was removed by filtration and rinsed with toluene. Combined filtrates were washed with 1.0 N HCl, water and dried over anhydrous anhydrous $MgSO_4$. Concentration *in vacuo* afforded 67.56 g (yield: 85.4%) of **239B** as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.00 (bs, 1H), 5.90 (bs, 1H), 5.20 (m, 1H), 4.20 (q, J = 7.08, 2H), 4.19 (m, 1H), 3.85 (m, 1H), 3.80 (m, 1H), 3.55 (m, 1H), 2.08 (s, 3H), 1.28 (t, J = 7.08, 3H).

239C. Preparation of (±)-ethyl 5-hydroxy-5,6-dihydropyridine-1(2H)-carboxylate

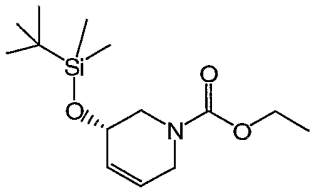


239C

To a solution of Compound **239B** (10.5 g, 49.2 mmol) in 30 mL of EtOH was added a solution of 0.2N NaOH in EtOH (65 mL) and the mixture was stirred at 0°C for 30 min. After warming to room temperature, the reaction mixture was neutralized with glacial acetic acid. Concentration *in vacuo* afforded 8.5 g of **239C** as an oil. ^{1}H-

NMR (400 MHz, $CDCl_3$): 5.90 (m, 1H), 5.82 (bs, 1H), 4.20 (bs, 1H), 4.18 (q, J = 7.08, 2H), 4.04 (m, 1H), 3.85 (m, 1H), 3.55 (m, 2H), 1.28 (t, J = 7.08, 3H).

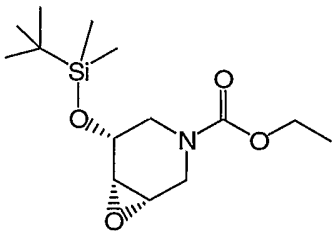
239D. Preparation of (±)-ethyl 5-(tert-butyldimethylsilyloxy)-5,6-dihydropyridine-1(2H)-carboxylate



239D

To a solution of Compound **239C** (16 g, 93.5 mmol) in 150 mL of dry CH_2Cl_2 at 0°C was added imidazole (9.5 g, 140.0 mmol) and *t*-butyldimethylsilylchloride (15.5 g, 102.8 mmol) and the mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with ether (500 mL) and water (1 L) at 0°C. The organic phase was separated and washed with 10% LiCl (150 mL x 3), dried over anhydrous MgSO4. Concentration *in vacuo* followed by flash chromatography (hexane-EtOAc: 15:1 to 10:1) afforded 25.2 g (Yield: 94.4%) of **239D** as an oil.

239E. Preparation of (±)-ethyl 5-hydroxy-7-oxa-3-aza-bicyclo[4.1.0] heptane-3-carboxylate

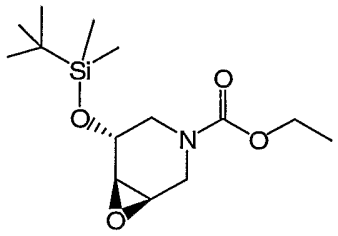


239E

To a solution of Compound **239D** (25.2 g, 88.3 mmol) in 250 mL of CH_2Cl_2 at 0°C was added solid *m*-CPBA (39.6 g, 176.6 mmol, 77% max) in small portions

while the internal temperature was kept below 0°C during the addition. The mixture was stirred at 0°C for 30 min and then room temperature for 4.0 hrs. More solid *m*-CPBA (39.6 g, 176.6 mmol, 77% max) was added in small portions and the mixture was stirred at room temperature for three days. The precipitate was removed by filtration and the filtrate was washed with 20% $Na_2S_2O_3$ (500 mL x 3), sat'd $NaHCO_3$ (500 mL x 3) and brine (250 mL), dried over anhydrous Na_2SO_4. Purification by flash chromatography (hexane-EtOAc: 9.5:0.5 to 9:1) on silica gel afforded 4.33 g of **239E** (lower Rf) as an oil.

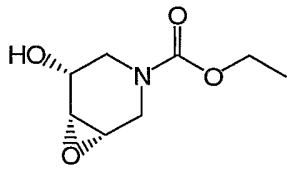
239F. Preparation of (±)-ethyl 5-(tert-butyldimethylsilyloxy)-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylate



239F

Compound **239F** was prepared from **239D** in a same reaction as Compound **239E** as an oil.

239G. Preparation of (±)-ethyl 5-hydroxy-7-oxa-3-aza-bicyclo[4.1.0] heptane-3-carboxylate



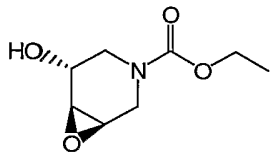
239G

To a solution of Compound **239E** (4.33 g, 14.4 mmol) in 10 mL of dry THF was added a solution of TBAF (17.2 mL, 17.2 mmol) in THF. The mixture was

stirred overnight at room temperature. Water was added and the reaction mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration *in vacuo* followed by flash chromatography (hexane-EtOAc: 1:1 to 1:2) on silica gel afforded 2.01 g (Yield: 74.5%) of **239G** as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 4.13 (q, J = 7.08, 2H), 4.05 (m, 1H), 3.80 (m, 1H), 3.70 (d, J = 10.15, 1H), 3.62 (m, 1H), 3.45 (m, 2H), 3.13 (dd, J = 10.15, J = 7.63, 1H), 2.40 and 2.25 (partial, 1H), 1.27 (t, J = 7.08, 3H).

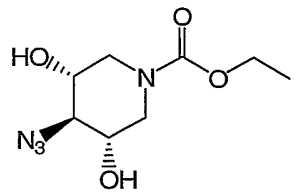
239H. Preparation of (±)-ethyl 5-hydroxy-7-oxa-3-aza-bicyclo [4.1.0]heptane-3-carboxylate



239H

To a solution of Compound **239F** (13.6 g, 45.1 mmol) in 10 mL of dry THF was added a solution of TBAF (67.6 mL, 67.6 mmol) in THF. The mixture was stirred overnight at room temperature. Water was added and the reaction mixture was extracted with EtOAc (250 mL x 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration *in vacuo* followed by flash chromatography (hexane-EtOAc: 1:1 to 1:2) on silica gel afforded 6.03 g (Yield: 75%) of **239H** as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.15 (m, 1H), 4.13 (q, J = 7.08, 2H), 3.95 (m, 1H), 3.75 (m, 1H), 3.52 (m, 1H), 3.32 (m, 1H), 3.25 (m, 2H), 3.10 and 2.55 (partial, 1H), 1.27 (t, J = 7.08, 3H).

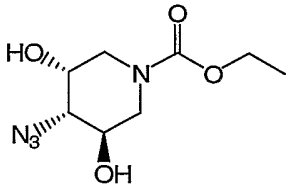
239I. Preparation of (±)-ethyl 4-azido-3,5-dihydroxypiperidine-1-carboxylate



239I

To a solution of Compound **239G** (2.0 g, 10.7 mmol) in 2-methoxyethanol (40 mL) was added NaN_3 (3.5 g, 53.4 mmol) and NH_4Cl (2.3 g, 42.72 mmol). The reaction mixture was heated at 125°C overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was taken into EtOAc (50 mL), washed with water (10 mL x 2) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* followed by flash chromatography (hexane-EtOAc: 1:1 to 1:2) on silica gel afforded 0.64 g of **239I** (higher Rf) as a crystalline material. The stereochemistry was confirmed by a single x-ray crystallographic determination.

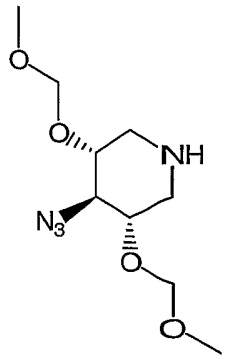
239J. Preparation of (±)-ethyl 4-azido-3,5-dihydroxypiperidine-1-carboxylate



239J

Compound **239J** was prepared from **239H** in a similar reaction as Compound **239I** as a crystalline material.

239K. Preparation of (*meso*)-4-azido-3,5-bis(methoxymethoxy) piperidine



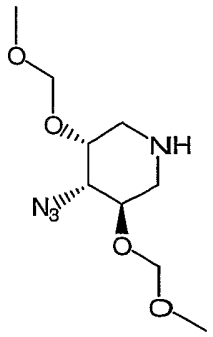
239K

To a solution of Compound **239I** (640 mg, 2.78 mmol) in dry CH_2Cl_2 (5 mL) was added *i*-Pr_2NEt (5.9 mL, 33.4 mmol), followed by MOMCl (1.69 mL, 22.2 mmol). The reaction mixture was heated at 60°C overnight. After cooling to room temperature, the reaction was diluted with CH_2Cl_2, washed with 10% citric acid, sat'd $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave the crude intermediate as an oil, which was used immediately in the next reaction step without further purification.

The mixture of the above prepared intermediate and KOH (1.84 g, 85%) in 8 mL of EtOH and 4 mL of water was heated to reflux overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was diluted with water and extracted with CH_2Cl_2 (x2). The combined organic layers were dried over anhydrous Na_2SO_4. Concentration *in vacuo* afforded 662 mg of **239K** as an oil. This material was used directly in the next reaction step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): 4.73 (q, J = 6.82 Hz, 4H), 3.41 (s, 6H), 3.20-3.40 (m 5H), 2.46 (m, 2H).

239L. Preparation of (±)-(3R,5R)-*rel*-4-azido-3,5-bis(methoxymethoxy)-piperidine



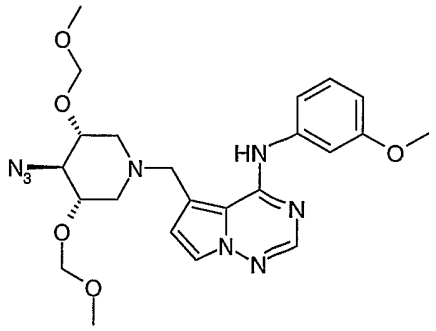
239L

Compound **239L** was prepared from **239J** in a similar reaction as Compound **239K** as a crystalline material.

^{1}H-NMR (400 MHz, $CDCl_3$): 4.72 (q, J = 6.82 Hz, 4H), 3.92 (m, 1H), 3.79 (m, 1H), 3.49 (m, 1H), 3.42 (s, 3H), 3.41 (s, 1H), 3.25 (m, 1H), 3.03 (m, 1H), 2.70 (m, 1H), 2.53 (m, 1H).

.

239M. Preparation of (±)-(3S,4r,5R)-*rel*-4-azido-1-((4-(3-methoxyphenylamino)-pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)-3,5-bis(methoxymethoxy)piperidine

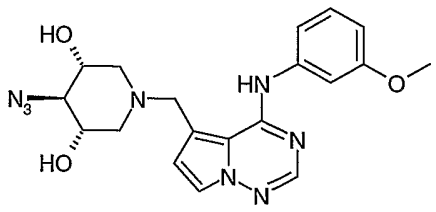


239M

Compound **239M** was prepared from **239K** in a same reaction as Compound **146E** as a foam. Compound **239M** had an analytical HPLC retention time = 2.582 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol

containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 502^+$.

239N. Preparation of (3S,4r,5R)-*rel*-4-azido-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)piperidine-3,5-diol



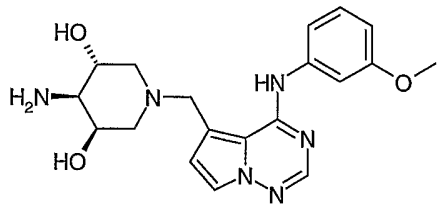
239N

The mixture of Compound **239M** (0.65 mmol) and 6N HCl (2 mL) in 3 mL of THF was heated at 50°C for 2 hrs. After cooling to room temperature, the mixture was made basic with NaOH, extracted with EtOAc and dried over anhydrous Na_2SO_4. Concentration *in vacuo* afforded 260 mg of **239N** as a solid. Compound **239N** had an analytical HPLC retention time = 2.063 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 411^+$.

The mixture of Compound **239N** (260 mg, 0.633 mmol) and Ph_3P (332 mg, 1.27 mmol) in THF (3 mL) and water (0.3 mL) was heated at 70°C overnight. After cooling to room temperature, the mixture was diluted with water, acidified with 2N HCl and washed with EtOAc (2x). The aqueous layer was basified with 2N NaOH and extracted with EtOAc (2x). The combined organic layers were washed once with water and dried over anhydrous Na_2SO_4. Concentration *in vacuo* followed by trituration with ether afforded 180 mg of **239** as a solid. Compound **239** had an analytical HPLC retention time = 1.211 min (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 385^+$.

EXAMPLE 240

(3R/*S*,5R/*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3,5-diol



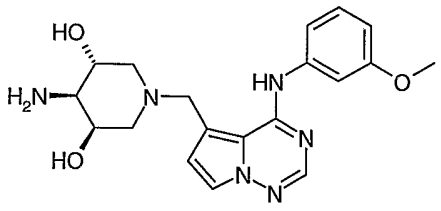
Compound **240** was prepared from **239L** in a similar way as Compound **239**.

Compound **240** is a solid and had an analytical HPLC retention time = 1.045 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 384^+$.

EXAMPLE 241A

(3*S*,5*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3,5-diol

(Enantiomer A, chiral)



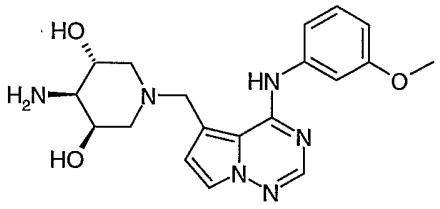
Compound **241A** (Enantiomer A) was prepared from **240** by chiral preparative HPLC separation (using Chiralpak AD, eluted with EtOH/DEA: 100/0.1), as the first peak (Rt = 5.827 min) with ee ≥ 99%.

Compound **241A** is a solid and had an analytical HPLC retention time = 1.044 min. (Chromolith SpeedROD column 4.6 x 50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 minutes, 4 mL/min, monitoring at 254 nm) and a LC/MS $M^+ + 1 = 384^+$.

EXAMPLE 241B

(3*R*,5*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3,5-diol

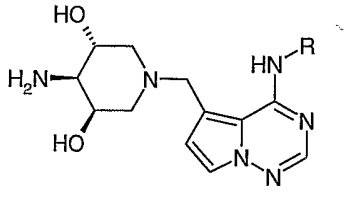
(Enantiomer B, chiral)

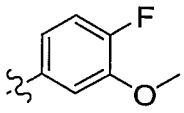
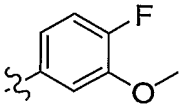
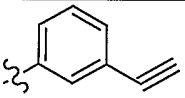
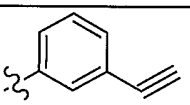
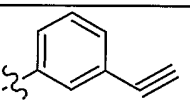


Compound **241B** (Enantiomer B) was obtained from **240** by chiral preparative HPLC separation (using Chiralpak AD, eluted with EtOH/DEA: 100/0.1), as the second peak (Rt = 8.430 min) with ee ≥ 96%.

EXAMPLES 242-246

Compounds **242-246** (with HPLC note (b)) were prepared from either **239L** in a similar process as Compound **239**.

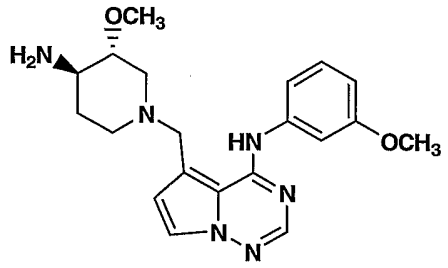


	Ex.	R	Compound Name	[M+H]	HPLC Ret Time (min)
	242	 Enantiomer A	(3*S*,5*S*)-4-amino-1-({4-[(4-fluoro-3-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidine-3,5-diol	403	0.958 (4.565[a])
	243	 Enantiomer B	(3*R*,5*R*)-4-amino-1-({4-[(4-fluoro-3-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidine-3,5-diol	403	0.958 (5.395[a])
	244	 racemic	*rac*-(3*R*,5*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3,5-diol	379	1.122
	245	 Enantiomer A	(3*R*,5*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3,5-diol	379	1.122 (8.496[a])
	246	 Enantiomer B	(3*S*,5*S*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3,5-diol	379	1.122 (12.704[a])

[a]Chiral normal phase HPLC conditions: Chiralpak AD, isocratic, eluted with EtOH-DEA: 100/0.1.

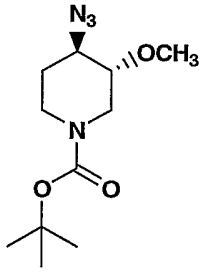
EXAMPLE 247

rac-5-{[(3*R*,4*R*)-4-amino-3-methoxypiperidin-1-yl]methyl}-*N*-(3-methoxyphenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine



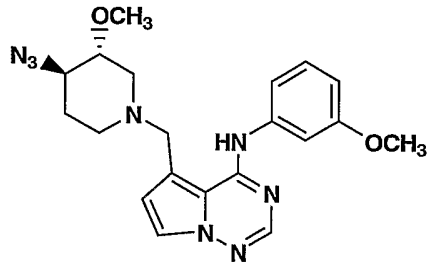
247

247A. Preparation of (3R,4R)-rel-*tert*-butyl 4-azido-3-methoxypiperidine-1-carboxylate



To a stirred mixture of **146A** (320 mg, 1.32 mmol) and iodomethane (O.25 mL, 3.96 mmol) in 4 mL of dry THF at room temperature under nitrogen was added 95% NaH (40.0 mg. 1.58 mmol). This mixture was stirred at room temperature for 15 h and then quenched by addition of 30 mL of water. The aqueous solution was extracted with EtOAc (2 x 40 mL). The combined EtOAc extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 310 mg (Yield: 92%) of **247A**. It had an analytical HPLC retention time = 2.86 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++ Na = 279.

247B. Preparation of 5-(((3R,4R)-*rel*-4-azido-3-methoxypiperidin-1-yl)methyl)-N-(3-methoxyphenyl)pyrrolo[1,2-f][1,2,4]triazin-4-amine

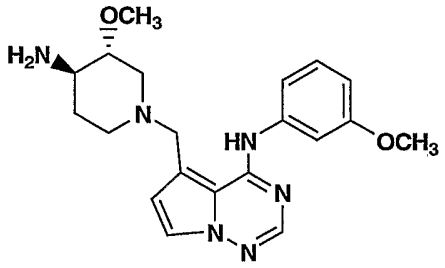


To a stirred solution of **247A** (310 mg, 1.21 mmol) in 2 mL of CH_2Cl_2 at room temperature was added TFA (2.00 mL, 26.0 mmoL). This mixture was stirred at room temperature for 15 min and concentrated *in vacuo* to give 390 mg of (3R,4R)-*rel*-4-azido-3-methoxypiperidine as the TFA salt. Compound **247B** was prepared from this TFA salt (52.0 mg, 0.19 mmoL) in a similar process as described for **146E**. It had an analytical HPLC retention time = 1.97 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 409.

247C. Preparation of 5-(((3R,4R)-4-amino-3-methoxypiperidin-1-yl)methyl)-N-(3-methoxyphenyl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (racemic)

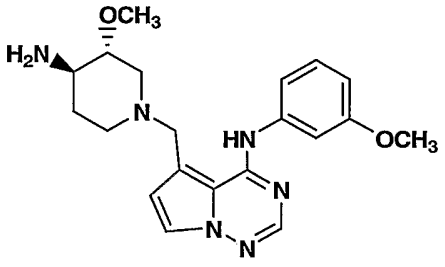
Compound **247C** (racemic) was prepared from **247B** in a similar process as described for **146**. Compound **247C** was purified by passing a 1 g SCX cartridge, eluted with MeOH (16 mL), followed by the elution of 2M NH_3 in MeOH (16 mL). The eluant was concentrated *in vacuo* and further purified by prep HPLC to give 26 mg of 247C (Yield: 42%) as a solid. It had an analytical HPLC retention time = 1.51 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 383.

247D. Preparation of 5-(((3R,4R)-4-amino-3-methoxypiperidin-1-yl)methyl)-N-(3-methoxyphenyl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (Enantiomer A).



Compound **247D** was obtained from Compound **247C** by a chiral preparative HPLC separation (Chiralpak AD, 10 micro, 2x5 cm column, 220 nm, 20 mL/min, EtOH/MeOH/DEA, 50/50/0.1). Compound **247D** is a solid and has an >99% ee with the HPLC retention time = 6.5 min (Chiralpak AD, 250x4.6 mm, 10 micron; EtOH/MeOH/DEA: 50/50/0.1, 0.8 mL/min, 220 nM).

247E. Preparation of 5-(((3S,4S)-4-amino-3-methoxypiperidin-1-yl)methyl)-N-(3-methoxyphenyl)pyrrolo[1,2-f][1,2,4]triazin-4-amine (Enantiomer B).

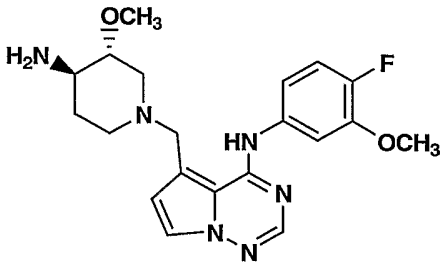


247E

Compound **247E** was obtained from Compound **247C** by a chiral preparative HPLC separation (Chiralpak AD, 10 micro, 2x5 cm column, 220 nm, 20 mL/min, EtOH/MeOH/DEA, 50/50/0.1). Compound **247E** is a solid and has an >99% ee with the HPLC retention time = 8.9 min (Chiralpak AD, 250x4.6 mm, 10 micron; EtOH/MeOH/DEA: 50/50/0.1, 0.8 mL/min, 220 nM).

EXAMPLE 248

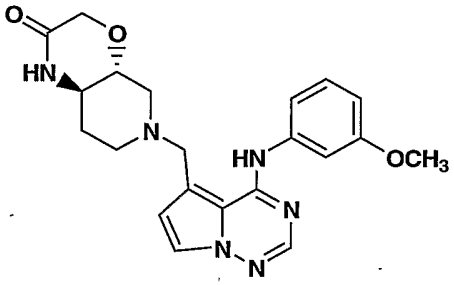
rac-5-{[(3*R*,4*R*)-4-amino-3-methoxypiperidin-1-yl]methyl}-*N*-(4-fluoro-3-methoxyphenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine



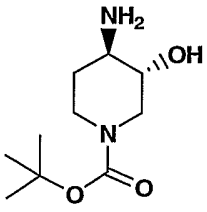
Compound **248** was prepared from **247A** in a similar process as Compound **247** and had an analytical HPLC retention time = 1.18 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 401.

EXAMPLE 249

(4aR,8aR)-*rel*-6-((4-(3-methoxyphenylamino)pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)-hexahydro-1H-pyrido[3,4-b][1,4]oxazin-2(3H)-one

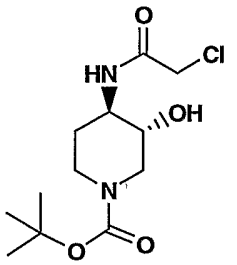


249A. Preparation of (3R,4R)-*rel*-tert-butyl 4-amino-3-hydroxypiperidine-1-carboxylate



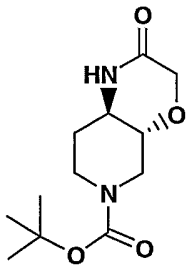
To a stirred solution of **15A** (540 mg, 2.23 mmol) in 10 mL of MeOH under N_2 was added 20%$Pd(OH)_2/C$ (108 mg). The reaction flask was purged with H_2 several times and stirred under hydrogen atmosphere for 18 hrs. The catalyst was removed by filtration through a 4μM polycarbonate film and rinsed with MeOH (6x30 mL). The filtrate was concentrated *in vacuo* to give 453 mg (Yield: 94%) of **249A**. It had an analytical HPLC retention time = 0.73 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 217.

249B. Preparation (3R,4R)-*rel-tert*-butyl 4-(2-chloroacetamido)-3-hydroxypiperidine-1-carboxylate



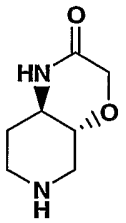
To a stirred mixture of **249A** (428 mg, 1.98 mmol) and NaOAc (325 mg, 3.96 mmol) in 2.5 mL of acetone and 0.8 mL of water under N_2 at 0°C was added dropwise chloroacetyl chloride (0.17 mL, 2.08 mmol) over 5 min. This mixture was stirred at 0°C for 10 min and at room temperature for 25 min. The mixture was diluted with 160 mL of EtOAc and washed with water (2x40 mL), saturated $NaHCO_3$ solution (1x30 mL) and brine (1x30 mL). The EtOAc layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 415 mg (yield: 72%) of **249B**. It had an analytical HPLC retention time = 1.96 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm) and a flow injection MS M^-= 291 .

249C. Preparation (4aR,8aR)-*rel-tert*-butyl 2-oxo-hexahydro-1H-pyrido[3,4-b] [1,4]oxazine-6(7H)-carboxylate



To a stirred mixture of **249B** (410 mg, 14.0 mmol) in 10 mL of dry THF under N_2 at room temperature was added 60% NaH (84.0 mg, 2.10 mmol). This mixture was stirred at room temperature for 45 min and quenched with 3 mL of saturated NH_4Cl solution. The mixture was concentrated *in vacuo* and diluted with 40 mL of saturated $NaHCO_3$ solution. The aqueous solution was extracted with EtOAc (3x 60 mL). The combined EtOAc extracts were washed with brine (1x 30 mL). The EtOAc layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 344 mg (yield: 96%) of **249C**. It had an analytical HPLC retention time = 2.01 min. (Chromolith SpeedROD 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 ml/min, monitoring at 220 nm) and a LC/MS M^+ = 257.

249D. Preparation (4aR,8aR)-*rel*-hexahydro-1H-pyrido[3,4-b][1,4]oxazin-2(3H)-one



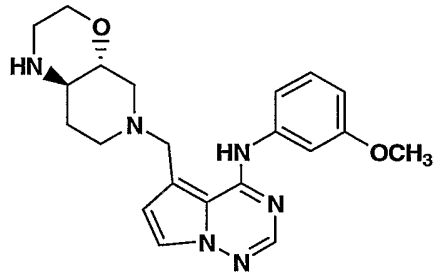
To a stirred mixture of **249C** (70.0 mg, 0.0.27 mmol) in 1 mL of CH_2Cl_2 at room temperature was added TFA (2.00 mL, 25.9 mmol). The mixture was stirred at room temperature for 1 hr and concentrated *in vacuo* to give crude **249D**. This material was mixed with DMA to make a 2 mL stock solution and was used as is in next step reaction.

Compound **249** was prepared from **249D** in a similar process as Compound **146**. It had an analytical HPLC retention time = 1.85 min. (Phenomenox S5 C18-HC

4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 409.

EXAMPLE 250

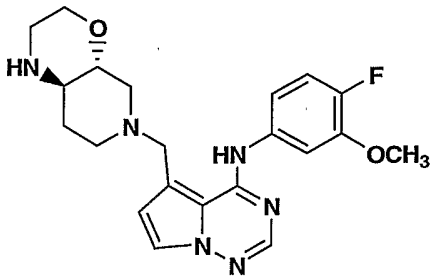
5-(((4aR,8aR)-*rel*-hexahydro-1H-pyrido[3,4-b][1,4]oxazin-6(7H)-yl)methyl)-N-(3-methoxyphenyl)pyrrolo[1,2-f][1,2,4]triazin-4-amine



To a stirred mixture of Compound **249** (100 mg, 0.24 mmoL) at room temperature in 4 mL of dry THF was added dropwise 1M $LiAlH_4$/ether solution (0.70 mL, 0.70 mmoL). This mixture was stirred at room temperature for 70 min and quenched by the addition of 200 mg of Celite and 200 mg of sodium sulfate decahydrate. The mixture was stirred at room temperature for 50 min. The insoluble was filtered off and rinsed with MeOH (3x 15 mL). The filtrate was concentrated *in vacuo* and purified by a prep HPLC to give 78 mg (yield: 81%) of Compound **250**. It had an analytical HPLC retention time = 1.68 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 395.

EXAMPLE 251

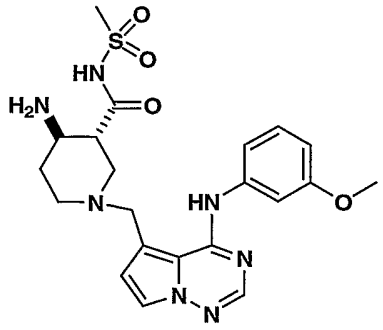
N-(4-fluoro-3-methoxyphenyl)-5-(((4aR,8aR)-*rel*-hexahydro-1H-pyrido[3,4-b][1,4]oxazin-6(7H)-yl)methyl)pyrrolo[1,2-f][1,2,4]triazin-4-amine



Compound **251** was prepared from **249D** in a similar process as Compound **250**. It had an analytical HPLC retention time = 1.64 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 413.

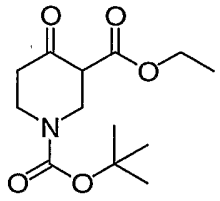
EXAMPLE 252

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-(methylsulfonyl)piperidine-3-carboxamide



252

252A. Preparation of 1-tert-butyl 3-ethyl 4-oxopiperidine-1,3-dicarboxylate

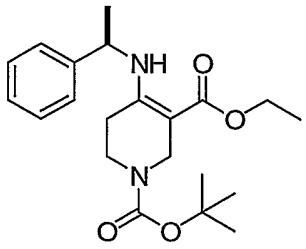


252A

A solution of ethyl 4-oxopiperidine-3-carboxylate (16.2 g, 95 mmol) in $CHCl_3$ (160 mL) was treated with a solution of $NaHCO_3$ (9.6 g, 114 mmol) in water (170 mL). This biphasic reaction was treated with a solution of Boc_2O (20.7 g, 95 mmol) in $CHCl_3$ (60 mL). The resulting reaction was heated to reflux for 18 hours, cooled to room temperature and the layers were separated. The aqueous layer was extracted

with $CHCl_3$ (2 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give 22g (yield: 86%) of Compound **252A** as an oil.

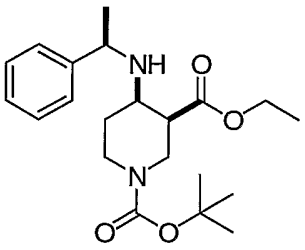
252B. Preparation of (R)-1-tert-butyl 3-ethyl 4-(1-phenylethylamino)-5,6-dihydro-pyridine-1,3(2H)-dicarboxylate



252B

A solution of **252A** (22g, 81 mmol) and toluene (400 mL) was treated with (*R*)-1-phenylethanamine (12.5 mL, 97 mmol) and *p*-TsOH (1.5 g). The reaction mixture was heated to reflux with a Dean-Stark trap for 23 hours. The mixture was cooled to room temperature, washed with saturated aqueos $NaHCO_3$ (2 × 200 mL) and brine (2 × 200 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was filtered through a pad of silica (100% CH_2Cl_2) and concentrated to provide 14.7 g (yield: 49%) of Compound **252B** as an oil.

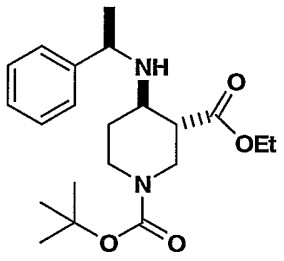
252C. Preparation of (3*S*,4*R*)-1-tert-butyl 3-ethyl 4-((*R*)-1-phenylethylamino)-piperidine-1,3-dicarboxylate



252C

A 1L 3-neck round bottom flask equipped with a mechanical stirrer and addition funnel was charged with **252B** (14.7 g, 39 mmol) and acetonitrile (200 mL) and acetic acid (100 mL). The solution was cooled to 0 °C and $Na(OAc)_3BH$ (33.3 g, 157 mmol) was added in three portions over 2 hours. The reaction was stirred for two hours at this temperature after the final addition. The mixture was then cooled to -10 °C and slowly quenched by addition of 1 N NaOH (100 mL), 4 N NaOH (100 mL), 6 N NaOH (100 mL)followed by 50% NaOH (50 mL). The reaction was warmed to room temperature and the layers were separated. The aqueous layer was extracted with CH_2Cl2_2 (2 × 250 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (10% to 30% EtOAc/hexane gradient) on silica gel afforded 6.0 g (yield: 41%) of Compound **252C**.

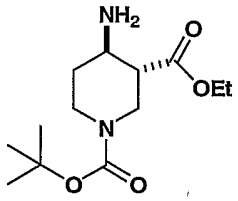
252D. Preparation of (3*R*,4*R*)-1-tert-butyl 3-ethyl 4-((*R*)-1-phenylethylamino)-piperidine-1,3-dicarboxylate



252D

A solution of **252C** (2.90 g, 7.71 mmol) in ethanol (70 mL) was treated with 21% NaOEt in ethanol (7.5 mL). The reaction mixture was heated to 50 °C for three hours, cooled to room temperature, and then concentrated. The resulting oil was taken up in dichloromethane (150 mL), washed with 20% NH_4Cl (2 × 50 mL). The organic layer was dried (Na_2SO_4) and concentrated to an oil. Purification by flash chromatography (10 to 25% EtOAc/Hexane gradient) on silica gel afforded 1.20 g (yield: 41%) of Compound **252D** as an oil.

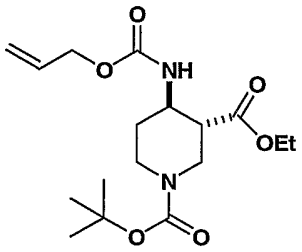
252E. Preparation of (3*R*,4*R*)-1-*tert*-butyl 3-ethyl 4-aminopiperidine-1,3-dicarboxylate.



252E

A solution of **252D** (1.18 g, 3.13 mmol) in MeOH (31 mL) was treated with ammonium formate (1.58 g, 25.1 mmol) and 10% Pd/C. The reaction mixture was heated to reflux for 14 hours then cooled to room temperature. The resulting solid was removed by filtration and washed with MeOH. The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure to give 0.82 g (yield: 96%) of Compound **252E** as an oil.

252F. Preparation of (3*R*,4*R*)-1-tert-butyl 3-ethyl 4-aminopiperidine-1,3-dicarboxylate

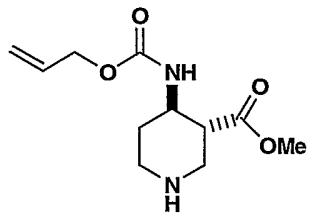


252F

A solution of **252E** (0.80 g, 2.94 mmol) in dichloromethane (29 mL) at 0 °C was treated with diisopropylethylamine (0.41 g, 3.23 mmol). A solution of allylchloroformate (0.46 g, 3.83 mmol) in dichloromethane (29 mL) was slowly added over 30 minutes. The reaction mixture was stirred at 0°C for 16 hours, then slowly warmed to room temperature. The resulting solution was diluted with dichloromethane and washed with saturated $NaHCO_3$ (2 × 50 mL). The organic layer

was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (20 to 25% EtOAc/Hexane) on silica gel to give 0.88 g (yield: 84%) of Compound **252F** as an oil .

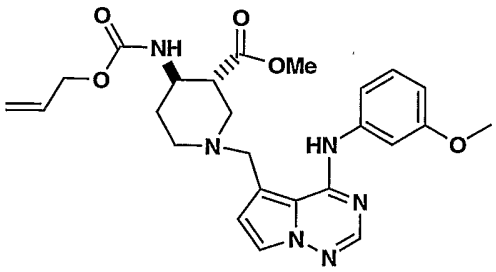
252G. Preparation of (3*R*,4*R*)-methyl 4-(allyloxycarbonyl)piperidine-3-carboxylate



252G

A solution of **252F** (0.87 g, 2.44 mmol) in dichloromethane (12 mL) was treated with TFA (2.4 mL) at 0 °C. The reaction mixture was stirred at 0 °C for one hour then allowed to slowly warm to room temperature. Stirring was continued at this temperature for five hours, concentrated, and azeotropically evaporated with MeOH and toluene. The resulting oil was purified by flash chromatography (0 to 2% $MeOH/CH_2Cl_2$) on silica gel to give 0.47 g (yield: 79%) of Compound **252G** as an oil.

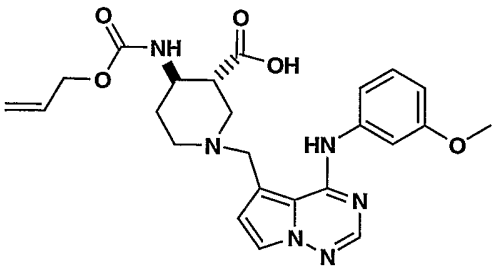
252H. Preparation of (3*R*,4*R*)-methyl 4-(allyloxycarbonyl)-1-((4-(3-methoxyphenyl-amino)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylate



252H

A suspension of **252G** (0.21 g, 0.87 mmol), 4-(3-methoxyphenylamino)-pyrrolo[1,2,4]trizin-5-ylmethyl triethylammonium bromide (0.40 g, 0.87 mmol), and diisopropylethylamine (0.11 g, 0.87 mmol) in MeCN (15 mL) was heated to 60 °C for one hour then concentrated *in vacuo*. The resulting oil was purified by flsh chromatography (2 to 5% MeOH/CH_2Cl_2) on silic gel to give 0.33 g (yield: 77%) of Compound **252H** as a solid.

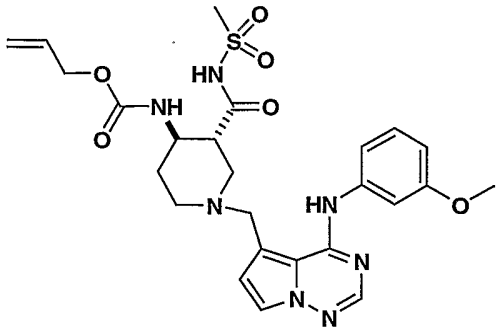
252I. Preparation of (3*R*,4*R*)-4-(allyloxycarbonyl)-1-((4-(3-methoxyphenylamino)-pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylic acid



252I

A solution of **252H** (0.33 g, 0.67 mmol) in MeOH/THF/water (3/3/1/ mL) was treated with LiOH monohydrate (0.25 g, 6.7 mmol). The reaction mixture was stirred for 14 hours, neutralized to *p*H = 7 with saturated aqueous $NaHCO_3$, then concentrated to a volume of 1 mL. The resulting slurry was dissolved in MeOH and purified by preparative HPLC (YMC ODS-A 5um, 20 × 100 mm, solvent A 10% MeOH-90% H_2O-0.1% TFA, solvent B 90% MeOH-10% H_2O-0.1% TFA, gradient 0-100%B, 12 mintues). The desired fractions were combined and concentrated under reduced pressure to remove most of the MeOH, neutralized with saturated aqueous $NaHCO_3$ to *p*H =7, and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 0.30 g (yield: 94%) of Compound **252I** as a solid.

252J. Preparation of allyl (3*R*,4*R*)-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-*f*][1,2,4]-triazin-5-yl)methyl)-3-(methylsulfonylcarbamoyl)piperidin-4-ylcarbamate



252J

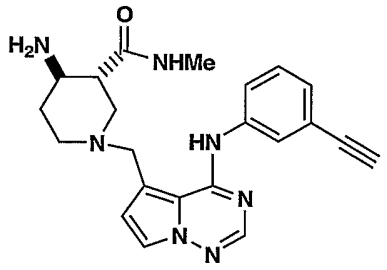
A solution of **252I** (0.30 g, 0.63 mmol) in MeCN (6.2 mL) was treated with dimethylaminopiperidine (77 mg, 0.63 mmol), DECI (0.18 g, 0.94 mmol), followed by methanesulfonamide (0.18 g, 1.88 mmol). The reaction mixture was stirred for two hours, quenched with water, and concentrated. The resulting slurry was dissolved in MeOH and purified by preparative HPLC (YMC ODS-A 5um, 20 × 100 mm, solvent A 10% MeOH-90% H_2O-0.1% TFA, solvent B 90% MeOH-10% H_2O-0.1% TFA, gradient 0-100%B, 12 minutes). The desired fractions were combined and concentrated *in vacuo*, neutralized with saturated aqueous $NaHCO_3$ to *p*H =10, and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 0.22 g (yield: 62%) of Compound **252J** as a- solid.

A solution of **252J** (100 mg, 0.18 mmol) in THF (4 mL, degassed with argon) was treated with $Pd(PPh_3)_4$ (21 mg, 0.018 mmol) and Et_2NH (33 mg, 0.45 mmol). The reaction mixture was stirred for 90 minutes then concentrated. The resulting solid was dissolved in MeOH, purified by preparative HPLC (YMC ODS-A 5um, 20 × 100 mm, solvent A 10% MeOH-90% H_2O-0.1% TFA, solvent B 90% MeOH-10% H_2O-0.1% TFA, gradient 0-100%B, 12 minutes). The desired fractions were concentrated to, neutralized with saturated aqueous $NaHCO_3$ to *p*H =10, and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 36 mg (yield: 42%) of Compound **252** as a solid. It had an analytic HPLC retention time = 1.62 min (Phenomenex Su C18 4.6 x 50 mm column

10-90% aqueous methanol containing 0.2% H_3PO_4, 4 min grad. monitored at 220 nm), $[M+H]^+ = 474$.

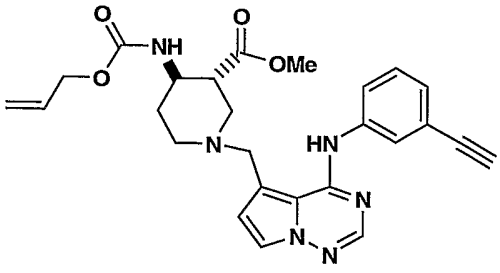
EXAMPLE 253

(3*R*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-methylpiperidine-3-carboxamide



253

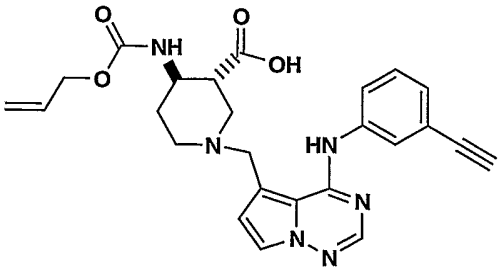
253A. Preparation of (3*R*,4*R*)-methyl 4-(allyloxycarbonyl)-1-((4-(3-ethynylphenylamino)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylate



253A

A suspension of **252G** (0.24 g, 1.0 mmol), 4-(3-ethylnylphenylamino)-pyrrolo[1,2,4]trizin-5-ylmethyl triethylammonium bromide (0.43 g, 1.0 mmol), and diisopropylethyl amine (0.13 g, 1.0 mmol) in MeCN (15 mL) was heated to 60 °C for one hour, then concentrated *in vacuo*. The residue was purified by flash chromatography (2 to 5% MeOH/CH_2Cl_2) on silica gel gave 0.24 g (yield: 50%) of Compound **253A** as a solid.

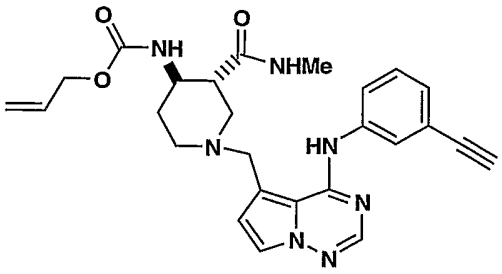
253B. Preparation of (3*R*,4*R*)-4-(allyloxycarbonyl)-1-((4-(3-ethynylphenylamino)-pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylic acid



253B

A solution of **253A** (0.24 g, 0.50 mmol) in MeOH/THF/water (3/3/1/ mL) was treated with LiOH monohydrate (0.21 g, 5.0 mmol) at room temperature. The reaction mixture was stirred for 14 hours, neutralized to pH = 7 with saturated aqueous $NaHCO_3$, then concentrated. The resulting slurry was dissolved in MeOH and purified by preparative HPLC (YMC ODS-A 5um, 20 x 100 mm, solvent A 10% MeOH-90% H_2O-0.1% TFA, solvent B 90% MeOH-10% H_2O-0.1% TFA, gradient 0-100%B, 12 minutes). The desired fractions were concentrated, neutralized with saturated $NaHCO_3$ to pH =7, and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give 0.22 g (yield: 93%) of Compound **253B** as a solid.

253C. Preparation of allyl (3*R*,4*R*)-1-((4-(3-ethynylphenylamino)pyrrolo[1,2-*f*][1,2,4]-triazin-5-yl)methyl)-3-(methylcarbamoyl)piperidin-4-ylcarbamate



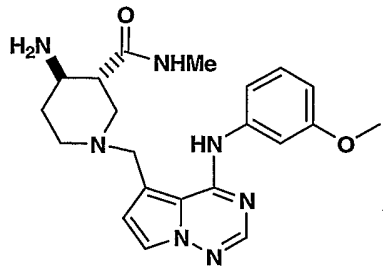
253C

A solution of **253B** (0.22 g, 0.46 mmol) in MeCN (4.6 mL) was treated with diisopropylethylamine (59 mg, 0.46 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (hereinafter referred to as the "Bop Reagent") (0.36 g, 0.69 mmol), and 2 N methylamine in THF (0.70 mL, 1.38 mmol). The reaction mixture was stirred for two hours, quenched with water, and concentrated. The resulting slurry was dissolved in MeOH and purified by preparative HPLC (YMC ODS-A 5um, 20 × 100 mm, solvent A 10% MeOH-90% H_2O-0.1% TFA, solvent B 90% MeOH-10% H_2O-0.1% TFA, gradient 0-100%B, 12 minutes). The desired fractions were concentrated, neutralized by saturated aqueous $NaHCO_3$ to pH =10, and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give 0.21 g (yield: 92%) of Compound **253C** as a solid.

A solution of **253C** (100mg, 0.20 mmol) in THF (5 mL, degassed with argon) was treated with $Pd(PPh_3)_4$ (23 mg, 0.020 mmol) and Et_2NH (37 mg, 0.51 mmol). The reaction mixture was stirred for 90 minutes, and then concentrated. The resulting solid was dissolved in MeOH and purified by preparative HPLC (YMC ODS-A 5um, 20 × 100 mm, solvent A 10% MeOH-90% H_2O-0.1% TFA, solvent B 90% MeOH-10% H_2O-0.1% TFA, gradient 0-100%B, 12 minutes). The desired fractions were concentrated, neutralized with saturated aqueous $NaHCO_3$ to pH =10, and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give 36 mg (yield: 42%) of Compound **253** as a solid. It had an analytic HPLC retention time = 1.96 min (Phenomenex Su C18 4.6 x 50 mm column 10-90% aqueous methanol containing 0.2% H_3PO_4, 4min grad. monitored at 220 nm), $[M+H]^+ = 404$.

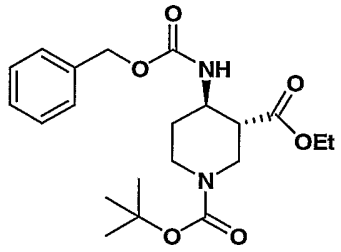
EXAMPLE 254

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-methylpiperidine-3-carboxamide



254

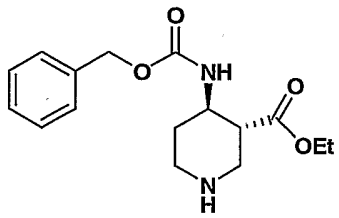
254A. Preparation of (3*R*,4*R*)-1-*tert*-butyl 3-ethyl 4-(benzyloxycarbonyl)piperidine-1,3-dicarboxylate



254A

A solution of **252E** (180 mg, 0.66 mmol) in CH_2Cl_2 (5 mL) was treated with benzyloxychloroformate (0.1 mL, 0.73 mmol) and triethylamine (0.12 mL, 0.86 mmol). The reaction was stirred at room temperature for 18 hours, diluted with CH_2Cl_2 (10 mL) and washed with water (2 × 10 mL), 0.1 N HCl (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to give 243 mg (yield: 91%) of Compound **254A** as an oil.

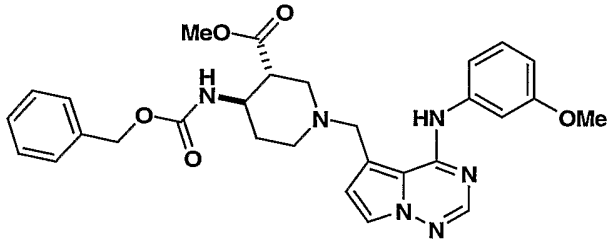
254B. Preparation of (3*R*,4*R*)-ethyl 4-(benzyloxycarbonyl)piperidine-3-carboxylate



254B

A solution of **254A** (243 mg, 0.60 mmol) in CH_2Cl_2 (3 mL) at 0 °C was treated with trifluoroacetic acid (0.3 mL). The reaction was stirred at room temperature for one hour, then concentrated to an oil. The crude amine was dissolved in EtOAc (10 mL), washed with saturated aqueous $NaHCO_3$ and dried (Na_2SO_4), filtered and concentrated *in vacuo*. The product was purified by flash chromatography (10% MeOH/CH_2Cl_2) on silica gel to afford 95 mg (yield: 52%) of Compound **254B**.

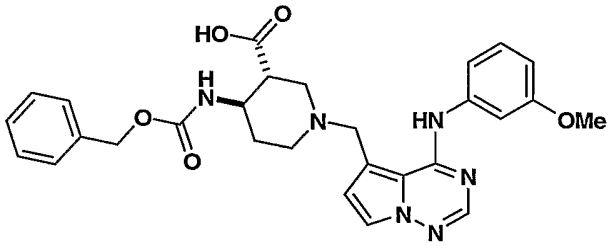
254C. Preparation of (3*R*,4*R*)-methyl 4-(benzyloxycarbonyl)-1-((4-(3-methoxyphenyl-amino)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylate



254C

A suspension of N,N-diethyl-N-((4-(3-methoxyphenylamino)pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)ethanaminium bromide (1.7 g, 3.62 mmol) and **254B** (1.06g, 3.6 mmol) in acetonitrile (75 mL) was treated with DIEA (0.63 mL, 3.6 mmol) and warmed to 55 °C for 12 hours. The reaction was concentrated, dissolved in EtOAc (100 mL) and washed with water (2 × 100 mL). The crude material was dried (Na_2SO_4), filtered and concentrated to afford 1.7 g (yield: 89%) of Compound **254C**.

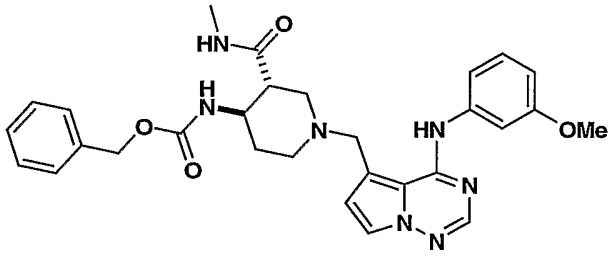
254D. Preparation of (3*R*,4*R*)-4-(benzyloxycarbonyl)-1-((4-(3-methoxyphenylamino)-pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylic acid



254D

Compound **254D** (1.67 g, yield: 100%) was prepared from **254C** (1.7 g, 3.13 mmol) in a similar process as used for Compound **252I.**

254E. Preparation of Benzyl (3*R*,4*R*)-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)-3-(methylcarbamoyl)piperidin-4-ylcarbamate



254E

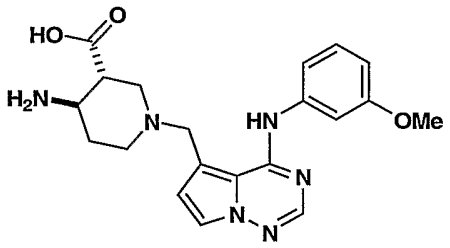
Compound **254E** (790 mg, yield: 54%) was prepared from **254D** (1.44 g, 2.71 mmol) in a similar process as used for Compound **253C.**

A solution of **254E** (1.66 g, 3.13 mmol) in MeOH (50 mL) was purged with argon for 30 minutes. 5% Pd/C (300 mg) was added. The reacton mixture was stirred under a hydrogen atmosphere for three hours, then filtered through a pad of celite. The filtrate was concentrated in vitro to provide 1.21 g (yield: 94%) of Compound

254 as a solid. It had an analytical HPLC retention time = 1.57 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol containing 0.2% H3PO4, 4 min gradient, monitored at 220 nm), $[M+H]^+ = 410$.

EXAMPLE 255

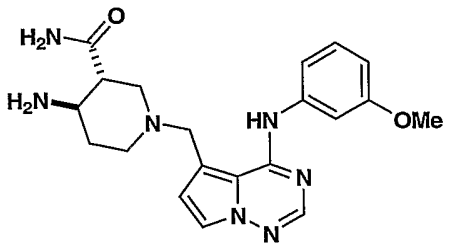
(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3-carboxylic acid



Compound **255** (33 mg, yield: 89%) was prepared from **254D** (50 mg, 0.094 mmol) in a similar process as used for **254**. It had an analytical HPLC retention time = 1.54 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol containing 0.2% H_3PO_4, 4 min gradient, monitored at 220 nm). $[M+H]^+ = 397$.

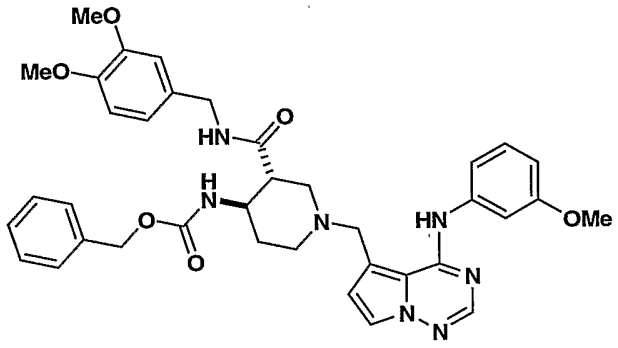
EXAMPLE 256

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3-carboxamide



256

256A. Preparation of Benzyl (3*R*,4*R*)-3-((3,4-dimethoxybenzyl)carbamoyl)-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidin-4-ylcarbamate



256A

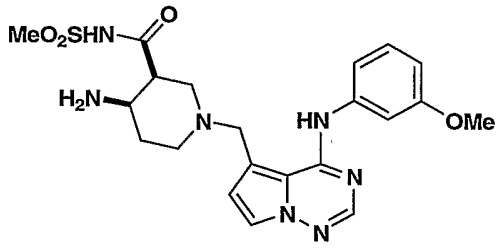
A solution of **254D** (150 mg, 0.23 mmol) in DMF (5 mL) was treated with 3,4-dimethoxybenzylamine (77 mg, 0.46 mmol), DIEA (80 µL, 0.46 mmol) and Bop Reagent (132 mg, 0.25 mmol). The reaction was stirred at room temperature for four hours, then poured into EtOAc (25 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (3 × 25 mL) and dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (3% MeOH/CH_2Cl_2) on silica gel to afford 174 mg (yield: 95%) of Compound **256A**.

A solution of **256A** (50 mg, 0.06 mmol) in TFA (3 mL) was stirred at room temperature for 5 days. The reaction was concentrated and purified by preparative HPLC to afford 7 mg (yield: 30%) of Compound **256** as a solid. It had an analytical HPLC retention time = 1.62 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous

methanol containing 0.2% H_3PO_4, 4 min gradient, monitored at 220 nm), $[M+H]^+$ = 396.

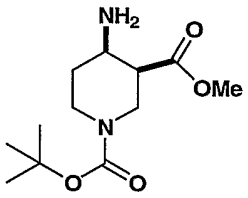
EXAMPLE 257

(3*S*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-(methylsulfonyl)piperidine-3-carboxamide



257

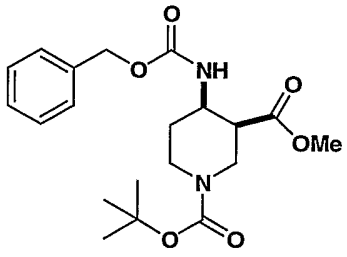
257A. Preparation of (3*S*,4*R*)-1-*tert*-butyl 3-methyl 4-aminopiperidine-1,3-dicarboxylate



257A

Compound **257A** (447 mg, 63%) was prepared in a similar process as used for **252E**.

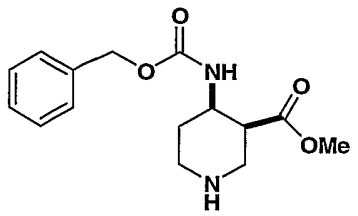
257B. Preparation of (3*S*,4*R*)-1-tert-butyl 3-methyl 4-(benzyloxycarbonyl)piperidine-1,3-dicarboxylate



257B

A solution of **257A** (447 mg, 1.7 mmol) in CH_2Cl_2 (20 mL) was treated with triethylamine (0.3 mL, 2.2 mmol) followed by benzyl chloroformate (0.27 mL, 1.9 mmol) at room temperature. The reaction mixture was stirred for 18 hours, then washed with water (25 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL) and the combine organics were washed with saturated aqueous $NaHCO_3$, 0.1N HCl, and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to an oil. The crude material was purified by flash chromatography (30% EtOAc/hexanes) on silica gel to afford 411 mg (yield: 75%) of Compound **257B** as an oil.

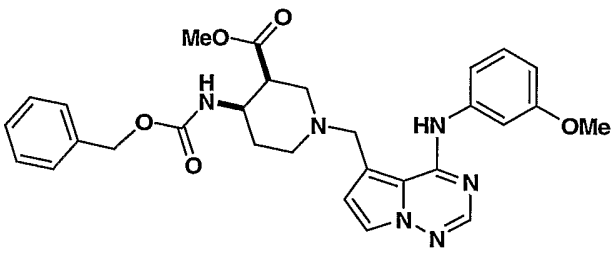
257C. Preparation of (3*S*,4*R*)-methyl 4-(benzyloxycarbonyl)piperidine-3-carboxylate



257C

A solution of **257B** (411 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (0.5 mL) at room temperature. The reaction mixture was stirred for 5.0 hours, then concentrated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$. The organics were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 365 mg of **257C** as a solid.

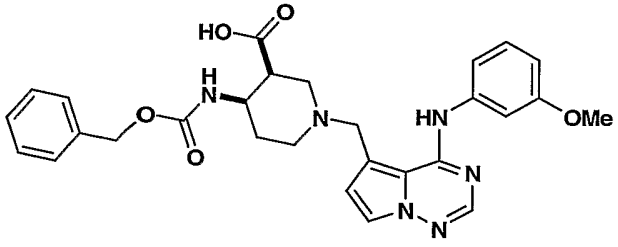
257D. Preparation of (3*S*,4*R*)-methyl 4-(benzyloxycarbonyl)-1-((4-(3-methoxyphenyl-amino)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylate



257D

A suspension of **257C** (292 mg, 0.62 mmol) and N,N-diethyl-N-((4-(3-methoxyphenylamino)pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)ethanaminium bromide (292 mg, 0.62 mmol) in acetonitrle (10 mL) were treated with DIEA (0.2 mL, 1.24 mmol) at room temperature. The reaction mixture was warmed to 55 °C for 3.0 hours, then concentrated *in vacuo* to dryness. The crude residue was purified by flash chromatography (30% EtOAc/hexanes) on silica gel to afford 269 mg (yield: 80%) of **257D**.

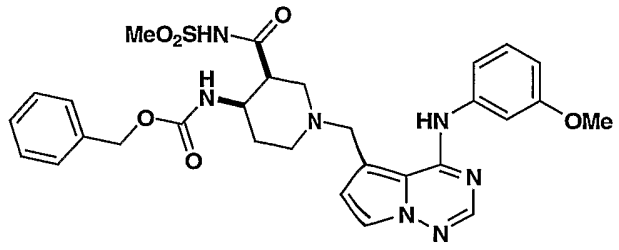
257E. Preparation of (3*S*,4*R*)-4-(benzyloxycarbonyl)-1-((4-(3-methoxyphenylamino)-pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylic acid



257E

A solution of **257D** (200 mg, 0.37 mmol) in THF/MeOH (1:1, 4 mL) was treated with LiOH monohydrate (30 mg, 0.74 mmol) in water (1 mL) at room temperature. The reaction mixture was stirred for eight hours, then concentrated to 1 mL. The residue was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organics were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 200 mg (yield: 100%) of Compound **257E** as a solid.

257F. Preparation of (3*S*,4*R*)-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)-3-(methylsulfonylcarbamoyl)piperidin-4-ylcarbamate acid.



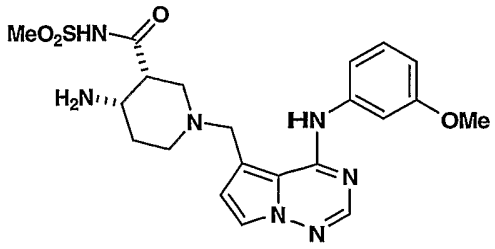
257F

A solution of **257E** (30 mg, 0.06 mmol) in DMF (2 mL) was treated with methansulfonamide (11 mg, 0.11 mmol), DMAP (7 mg, 0.06 mmol) and EDAC (13 mg, 0.07 mmol). The reaction mixture was stirred at room temperature for 48 hours. The resulting suspension was diluted with EtOAc (10 mL), washed with brine (3 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 35 mg of **257E** which was used without further purification.

A solution of **257F** (35 mg) in MeOH (3 mL) was treated with 10% Pd/C (15 mg) and stirred under a hydrogen atmosphere for three hours at room temperature. The slurry was filtered through a nylon filter and the filtrate was concentrated. The crude material was purified by preparative HPLC to afford 12 mg of Compound **257** as a solid. It had an analytical HPLC retention time = 1.77 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol containing 0.2% H_3PO_4, 4 min gradient, monitored at 220 nm) $[M+H]^+ = 474$.

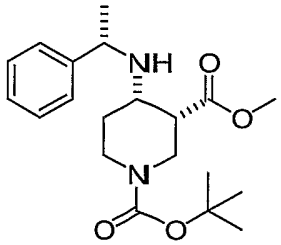
EXAMPLE 258

(3*R*,4*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-(methylsulfonyl)piperidine-3-carboxamide



258

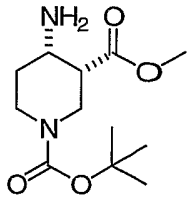
258A. Preparation of (3*R*,4*S*)-1-tert-butyl 3-methyl 4-((*S*)-1-phenylethylamino)-piperidine-1,3-dicarboxylate



258A

Compound **258A** was prepared in the same manner as **252C** using the appropriate starting materials.

258B. Preparation of (3*R*,4*S*)-1-tert-butyl 3-methyl 4-aminopiperidine-1,3-dicarboxylate



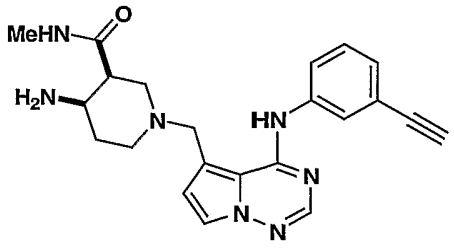
258B

Compound **258B** was prepared according to the procedures described in **Example 257** using the appropriate starting materials.

Compound **258** was prepared from **258B** in the same manner as described for **257.** Compound **258** had an analytical HPLC retention time = 1.77 min (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol containing 0.2% H_3PO_4, 4 min gradient, monitored at 220 nm) $[M+H]^+ = 474$.

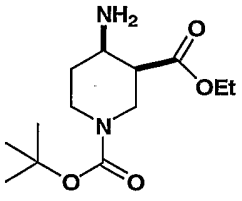
EXAMPLE 259

(3*S*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-methylpiperidine-3-carboxamide



259

259A. Preparation of (3*S*,4*R*)-1-*tert*-butyl 3-ethyl 4-aminopiperidine-1,3-dicarboxylate

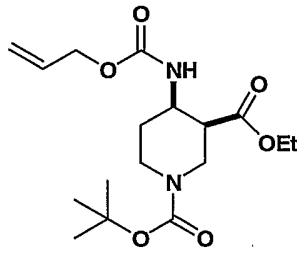


259A

A solution of **252C** (2.6 g, 6.9 mmol) in EtOH (100 mL) was treated with ammonium formate (3.5 g, 55.3 mmol)and 10% Pd/C (390 mg). The reaction mixture was heated to reflux under a nitrogen atmosphere for three hours. The resulting

suspension was filtered through a pad of celite and concentrated *in vacuo* to afford 1.8 g (yield: 96%) Compound **259A** as a solid.

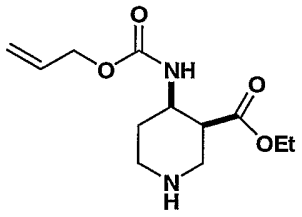
259B. Preparation of ((3*S*,4*R*)-1-tert-butyl 3-ethyl 4-(allyloxycarbonyl)piperidine-1,3-dicarboxylate



259B

A solution of **259A** (900 mg, 3.3 mmol) in CH_2Cl_2 (20 mL) was treated with triethylamine (0.64 mL, 4.62 mmol) and allylchloroformate (0.35 mL, 3.96 mmol) at room temperature. The mixture was stirred for four hours, then washed with 0.1 N HCl (2 × 10 mL), 1N NaOH (2 × 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 680 mg (yield: 58%) of Compound **259B** as an oil.

259C. Preparation of (3*S*,4*R*)-ethyl 4-(allyloxycarbonyl)piperidine-3-carboxylate

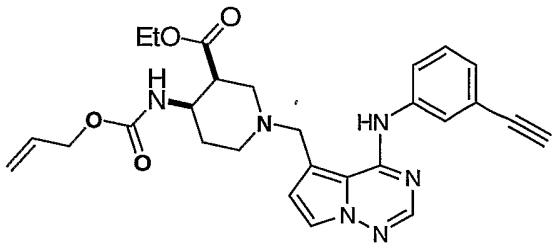


259C

A solution of **259B** (680 mg, 1.9 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (1 mL) at room temperature. The reaction mixture was stirred for 16 hours, then

concentrated. The residues was dissolved in EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 170 mg of Compound **259C**.

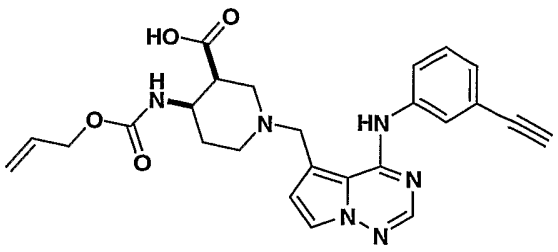
259D. Preparation of (3*S*,4*R*)-methyl 4-(allyloxycarbonyl)-1-((4-(3-ethynylphenylamino)-pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylate



259D

A suspension of **259C** (50 mg, 0.2 mmol) and N,N-diethyl-N-((4-(3-ethynylphenyl-amino)pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)ethanaminium bromide (82 mg, 0.18 mmol) in acetonitrile (2 mL) were treated with DIEA (31 µL, 0.18 mmol). The mixture was heated to 65 °C for 6.0 hours, cooled to room temperature and concentrated. The crude material was purified by radial chromatography (SiO_2, 2 mm plate, 100% CH_2Cl_2 to 1% MeOH/CH_2Cl_2 gradient) to afford 63 mg (yield: 70%) of Compound **259D**.

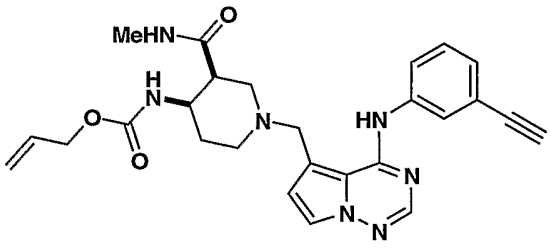
259E. Preparation of (3*S*,4*R*)-4-(allyloxycarbonyl)-1-((4-(3-ethynylphenylamino)-pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylic acid



259E

A solution of **259D** (63 mg, 0.13 mmol) in THF/MeOH (1:1, 4 mL) was treated with a solution of LiOH monohydrate (17 mg, 0.39 mmol) at room temperature. The reaction mixture was stirred for 18 hours, then concentrated to 0.5 mL volume. The residues was diluted with water (5 mL) and brought to pH 6 with saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (2 × 10 mL), the organic layers were dried (Na_2SO_4) filtered and concentrated *in vacuo* to afford 56 mg (yield: 92%) of Compound **259E**.

259F. Preparatio of allyl (3*S*,4*R*)-1-((4-(3-ethynylphenylamino)pyrrolo[1,2-*f*][1,2,4]-triazin-5-yl)methyl)-3-(methylcarbamoyl)piperidin-4-ylcarbamate



259F

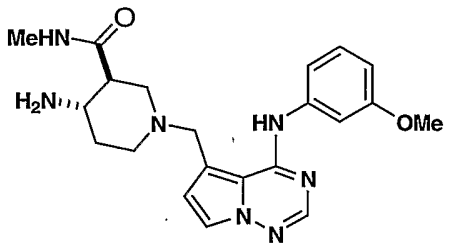
A solution of **259E** (56 mg, 0.12 mmol) in DMF (3 mL) was treated sequentially with methylamine (2M in THF, 0.12 mL, 0.24 mmol), DIEA (0.02 mL, 0.12 mmol) and Bop Reagent (68 mg, 0.13 mmol). The reaction mixture was stirred for 18 hours at room temperature. The resulting mixture was diluted with EtOAc (25 mL), washed with brine (3 × 15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude **259E** (71 mg) was used without further purification.

A solution of **259F** (71 mg, 0.15 mmol) in THF(3 mL) was degassed with argon and treated with diethylamine (28 mg, 0.38 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.02 mmol). The reaction was stirred under an argon atmosphere for 2.0 hours, then concentrated *in vacuo* and purified by preparative HPLC to afford 14 mg of Compound **259**. It had an analytical HPLC retention time = 2.10 min (YMC S5 ODS

4.6 x 50 mm, 10-90% aqueous methanol containing 0.2% H_3PO_4, 4 min gradient, monitored at 220 nm) $[M+H]^+ = 404$.

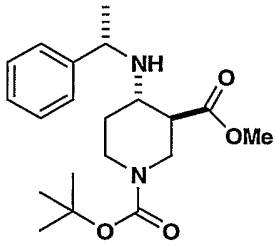
EXAMPLE 260

(3*S*,4*S*)-4-amino-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)-N-methylpiperidine-3-carboxamide



260

260A. Preparation of (3*S*,4*S*)-1-tert-butyl 3-methyl 4-((*S*)-1-phenylethylamino)-piperidine-1,3-dicarboxylate

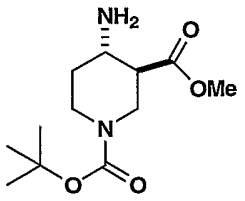


260A

A solution of **258A** (4.50 g, 12.4 mmol) in methanol (124 mL) at room temperature was treated with 25% NaOMe in methanol (8.04 mL). This reaction mixture was heated to 50 °C for 3.0 hours, cooled to room temperature, and then concentrated *in vacuo*. The oily residue was dissolved in dichloromethane (200 mL), and washed with 20% NH_4Cl (2 × 75 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (10 to

25% EtOAc/hexanes) on silica gel to give 1.50 g (yield: 30%) of Compound **260A** as an oil.

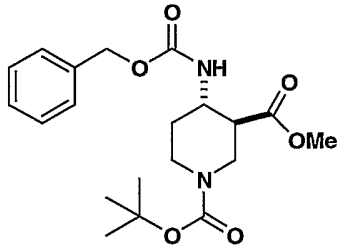
260B. Preparation of (3*S*,4*S*)-1-tert-butyl 3-methyl 4-aminopiperidine-1,3-dicarboxylate



260B

A solution of **260A** (1.10 g, 3.03 mmol) in MeOH (31 mL) at room temperature was treated with ammonium formate (1.51 g, 24.3 mmol) and 10% Pd/C (110 mg). The reaction mixture was heated to reflux for 14 hours then cooled to room temperature. The solid material was removed by filtration and washed with MeOH. The filtrate was concentrated *in vacuo* to give 0.75 g (yield: 96%) of Compound **260B** as an oil.

260C. Preparation of (3*S*,4*S*)-1-tert-butyl 3-methyl 4-(benzyloxycarbonyl)piperidine-1,3-dicarboxylate

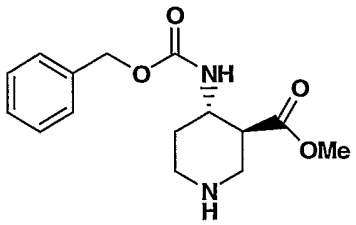


260C

A solution of **260B** (0.75 g, 2.90 mmol) in dichloromethane (30 mL) at 0°C was treated with triethylamine (0.35 g, 3.48 mmol) and N-(benzyloxycarbonyoxy) succinimide (0.72 g, 2.90 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The reaction mixture was diluted with

dichloromethane, washed with 10% citric acid (2 × 50 mL), then saturated $NaHCO_3$ (2 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 1.01 g (yield: 89%) of Compound **260C** as an oil. It was used in the next step without further purification.

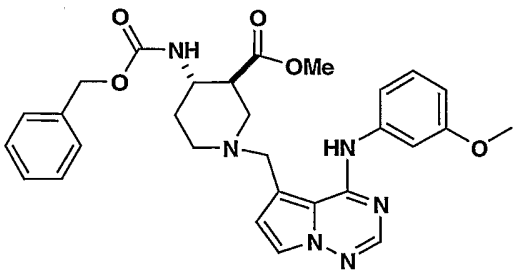
260D. Preparation of (3*S*,4*S*)-methyl 4-(benzyloxycarbonyl)piperidine-3-carboxylate



260D

A solution of **260C** (1.01 g, 2.58 mmol) in dichloromethane (50 mL) at 0°C was treated with TFA (5 mL). The reaction mixture was stirred at 0°C for 1.0 hour then allowed to slowly warm to room temperature and stirred for an additional 2.0 hours. The mixture was concentrated, and then azeotropically evaporated with MeOH and toluene. The residue was dissolved in dichloromethane and washed with saturated $NaHCO_3$ (2 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 0.61 g (yield: 81%) of Compound **260D** as an oil. It was used in the next step without further purification.

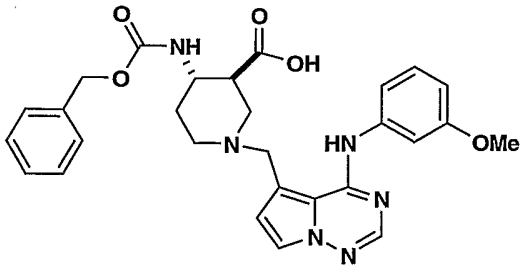
260E. Preparation of (3*S*,4*S*)-methyl 4-(benzyloxycarbonyl)-1-((4-(3-methoxyphenyl-amino)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylate



260E

A reaction mixture of **260D** (0.18 g, 0.61 mmol), 4-(3-methoxyphenylamino)-pyrrolo[1,2,4]trizin-5-ylmethyl triethylammonium bromide (0.29 g, 0.61 mmol), and diisopropylethyl amine (79 mg, 0.61 mmol) in MeCN (6 mL) was heated to 55°C for 12 hours and concentrated *in vacuo*. The residue was dissolved in dichloromethane and washed with water (2 × 50 mL). The dichloromethane portion was dried over Na_2SO_4 and concentrated *in vacuo* to give 0.33 g (yield: 99%) of Compound **260E** as an oil. It was used in the next step without further purification. $(M+H)^+ = 545$

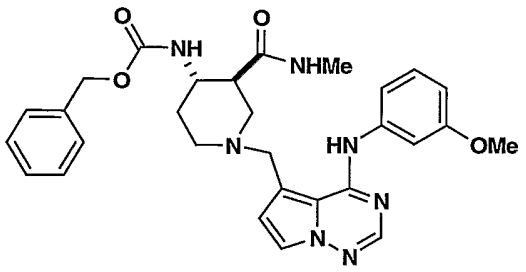
260F. Preparation of (3*S*,4*S*)-4-(benzyloxycarbonyl)-1-((4-(3-methoxyphenylamino)-pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)piperidine-3-carboxylic acid



260F

A solution of **260E** (95 mg, 0.18 mmol) in MeOH/THF/water (1/1/0.5 mL) at room temperature was treated with LiOH monohydrate (75 mg, 1.8 mmol). The reaction mixture was stirred for 18 hours, quenched with saturated NH_4Cl (5 mL), and extracted with EtOAc (3 × 15 mL). The EtOAc layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 80 mg (yield: 89%) of Compound **260F** as a film. It was used in the next step without further purification. Mass $(M+H)^+ = 531$

260G. Preparation of benzyl (3*S*,4*S*)-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-*f*][1,2,4]triazin-5-yl)methyl)-3-(methylcarbamoyl)piperidin-4-ylcarbamate



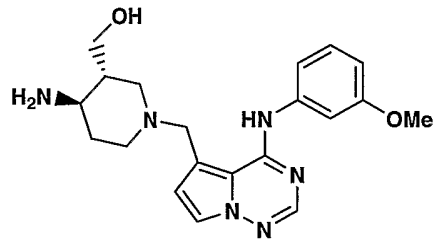
260G

A solution of **260F** (40 mg, 0.075 mmol) in DMF (0.8 mL) at room temperature was treated with diisopropylethylamine (10 mg, 0.075 mmol), Bop Reagent (59 mg, 0.11 mmol), then 2N methylamine in THF (0.12 mL, 0.23 mmol). The reaction mixture was stirred for 16 hours, quenched with water, and concentrated. The resulting suspension was dissolved in MeOH, and purified by preparative HPLC (YMC ODS-A 5um, 20 x 100 mm, solvent A 10% MeOH-90% H_2O-0.1% TFA, solvent B 90% MeOH-10% H_2O-0.1% TFA, gradient 0-100%B, 12 minutes). The desired fractions were concentrated to remove most of the MeOH, neutralized by saturated $NaHCO_3$ to *p*H 10 and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give 38 mg (yield: 93%) of **260G** as a solid. Mass $(M+H)^+ = 544$.

A solution of **260G** (38 mg, 0.070 mmol) in MeOH (2 mL) at room temperature was treated with 5% Pd/C (10 mg). The reaction mixture was stirred under a hydrogen atmosphere for 16 hours. The catalyst was removed by filtration. The filtrate was concentrated *in vacuo* to give 25 mg (yield: 87%) of Compound **260** as a solid. It had an analytic HPLC retention time = 1.71 min (Phenomenex Su C18 4.6 x 50 mm column 10-90% aqueous methanol containing 0.2% H_3PO_4, 4min grad. monitored at 220 nm). Mass $[M+H]^+ = 410$.

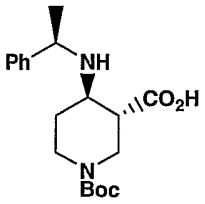
EXAMPLE 261

((3R,4R)-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-f][1,2,4]-triazin-5-yl)methyl)-4-((R)-1-phenylethylamino)piperidin-3-yl)methanol



261

261A. Preparation of(3R,4R)-1-(tert-butoxycarbonyl)-4-((R)-1-phenylethylamino)-piperidine-3-carboxylic acid

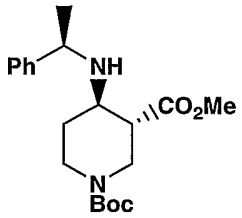


261A

A mixture of **252D** (460 mg, 1.22 mmol) and NaOEt (1.25 mL, 21% wt in EtOH) in EtOH (10 ml) was stirred at 50°C for 3 hrs, then at RT for about 48 hours.

The reaction mixture was concentrated *in vacuo*, followed by the addition of water. The mixture was acidified with 1N HCl to *p*H 4-5 and the solid was collected by filtration, washed with water and dried to give 300 mg (yield: 71%) of **252A**. It had an analytical HPLC retention time = 2.065 min. (Chromolith SpeedROD column 4.5 x50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 min, 4 mL/min, monitoring at 220 nm). Mass $(M+1)^+ = 349$.

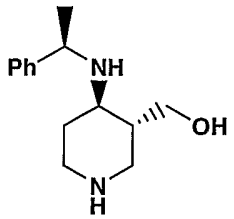
261B. Preparation of (3R,4R)-1-tert-butyl 3-methyl 4-((R)-1-phenylethylamino)-piperidine-1,3-dicarboxylate



261B

To a solution of **261A** (280 mg, 0.80 mmol) in 6 mL of 1:1 CH_2Cl_2/MeOH was added a solution of $TMSCHN_2$ (0.82 ml, 1.64 mmol, 2N in hexane). The mixture was stirred at room temperature for 30 min, then concentrated *in vacuo* and purified by flash chromatography (hexane/EtOAc: 80:20) on silica gel to give Compound **261B** as an oil. It had an analytical HPLC retention time = 2.187 min. (Chromolith SpeedROD column 4.5 x50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 min, 4 mL/min, monitoring at 220 nm). Mass $(M+1)^+ = 363$.

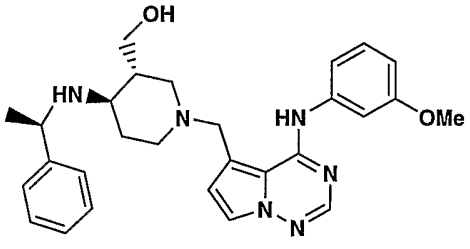
261C. Preparation of ((3R,4R)-4-((R)-1-phenylethylamino) piperidin-3-yl)methanol



261C

To a solution of **261B** (270 mg, 0.75 mmol) was added $LiBH_4$ (15.5 mg, 0.71 mmol). The mixture was heated to reflux for 1.0 hr. HPLC showed still some starting material remaining. More $LiBH_4$ (15.5 mg, 0.71 mmol) was added, and the mixture was heated for another 2.0 hrs. After cooling to room temperature, ice water was added, and the mixture was concentrated *in vacuo* to remove the THF. The aqueous residue was extracted with EtOAc (x 3) and the combined extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The residue was taken into 2 mL of CH_2Cl_2 and 2 mL of TFA was added. The mixture was stirred at room temperature for 30 min. The mixture was concentrated *in vacuo,* followed by drying under high vacuum overnight to afford **261C** as an oil. It had an analytical HPLC retention time = 0.590 min. (Chromolith SpeedROD column 4.5 x50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 min, 4 mL/min, monitoring at 220 nm) and a LC/MS M^++1 = 235. This material was used directly in the next reaction step without further purification.

261D. Preparation of ((3R,4R)-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-f][1,2,4]-triazin-5-yl)methyl)-4-((R)-1-phenylethylamino)piperidin-3-yl)methanol



261D

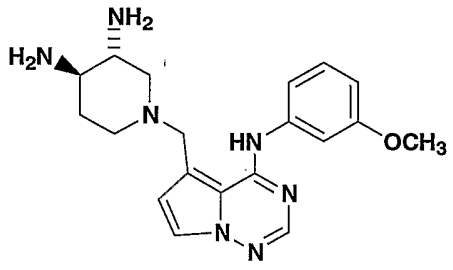
Compound **261D** was prepared from **261C** in a similar process as used for Compound **146E**. It had an analytical HPLC retention time = 1.761 min. (Chromolith

SpeedROD column 4.5 x50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 min, 4 mL/min, monitoring at 220 nm) and a LC/MS M^++1 = 487.

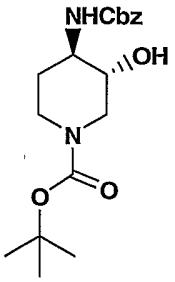
A mixture of **261D** (160 mg, 0.33 mmol), 10% Pd/C (39 mg) and ammonium formate (166 mg, 2.63 mmol) in MeOH (15 ml) was heated to reflux for 1.0 hr. After cooling to room temperature, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in water, basified with aqueous $NaHCO_3$ and extracted with EtOAc (3x). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give 64 mg (yield: 51%) of Compound **261** as a solid (64 mg, 51%). It had an analytical HPLC retention time = 1.137 min. (Chromolith SpeedROD column 4.5 x50 mm, 10-90% aqueous methanol containing 0.1% TFA over 4 min, 4 mL/min, monitoring at 220 nm) and a LC/MS M^++1 = 383.

EXAMPLE 262

rac-(3*R*,4*R*)-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3,4-diamine



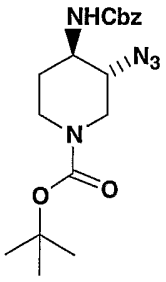
262A. Preparation of (3R,4R)-*tert*-butyl 4-(benzyloxycarbonyl)-3-hydroxypiperidine-1-carboxylate



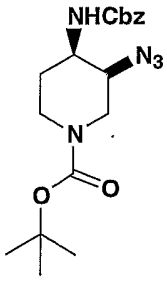
262A

To a stirred mixture of Compound **249A** (1.40 g, 6.47 mmoL) in 10 mL of CH_2Cl_2 was added Et_3N (1.08 mL, 7.76 mmoL), followed by Cbz-OSu (1.69 g, 6.80 mmoL). The reaction mixture was stirred at room temperature for 16 hrs and then diluted with 300 mL of EtOAc. The organic layer was washed with 5% citric acid solution (2x 40 mL), 5% K_2CO_3 solution (2x 40 mL) and brine (40 mL) and dried ($MgSO_4$). The residue was filtered and concentrated *in vacuo* to afford 2.25 g (yield: 99%) of Compound **262A**. It had an analytical HPLC retention time = 3.02 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 351.

262B/C. Preparation of (3*R*,4*R*)-*tert*-butyl 3-azido-4-(benzyloxycarbonyl) piperidine-1-carboxylate



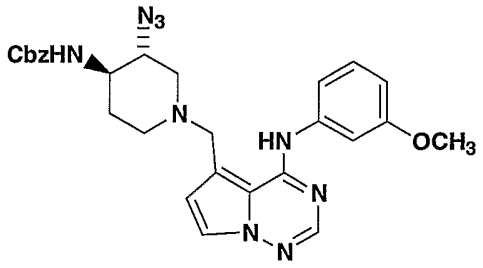
262B (cis)
Diastereomer A



262C (trans)
Diastereomer B

To a stirred solution of Compound **262A** (2.23 g, 6.36 mmoL)and Et_3N (1.20 mL, 0.83 mmoL) in 30 mL of CH_2Cl_2 under nitrogen at 0°C was added and methanesulfonyl chloride (0.49 mL, 6.36 mmoL) over 5 min. The mixture was stirred at 0°C for 35 min and then diluted with 40 mL of CH_2Cl_2. The mixture was washed with water (2x 25 mL), brine (20 mL) and dried ($MgSO_4$). The mixture was filtered and concentrated *in vacuo* to afford the crude mesylate. To the mesylate in 20 mL of DMSO was added NaN_3 (1.65 g, 25.5 mmoL). The mixture was heated at 90°C for 17 h and cooled to room temperature. The mixture was diluted with 200 mL of EtOAc and washed with water (4x 200 mL), saturated $NaHCO_3$ solution (40 mL), brine (40 mL) and dried ($MgSO_4$). Filtration, concentration *in vacuo,* followed by flash chromatography (15-50% EtOAc in hexane) on silica gel gave 696 mg (29%) of **262B** (***Diastereomer A***, Rf = 0.65) and **262C** (***Diastereomer B***, Rf = 0.70). **262B** had an analytical HPLC retention time = 3.51 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 376. **262C** had an analytical HPLC retention time = 3.51 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 376.

262D. Preparation of benzyl (3*R*,4*R*)-3-azido-1-((4-(3-methoxyphenylamino) pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)piperidin-4-ylcarbamate



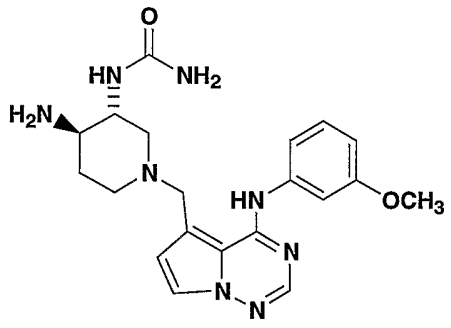
262D

Compound **262D** was prepared from Compound **262B** in a similar process as described for Compound **247A**. It had an analytical HPLC retention time = 2.96 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 528.

Compound **262** was prepared from Compound **262D** in a similar process as described for Compound **249A**. It had an analytical HPLC retention time = 1.27 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 368.

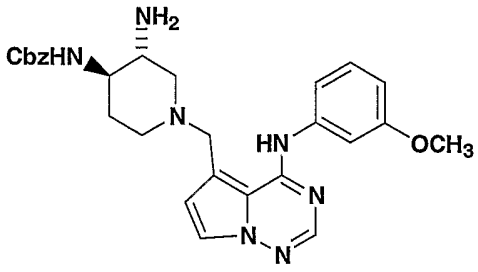
EXAMPLE 263

rac-N-[(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]urea



263

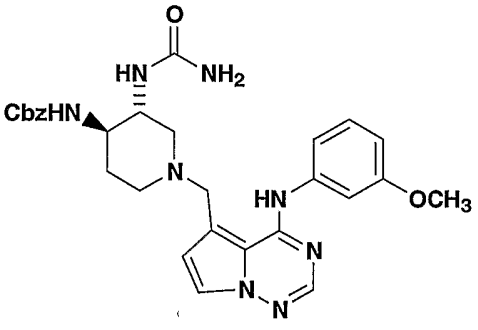
263A. Preparation of benzyl (3*R*,4*R*)-3-amino-1-((4-(3-methoxyphenylamino) pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)piperidin-4-ylcarbamate (Chiral, Diastereomer **A**):



263A

Compound **263A** was prepared from Compound **262C** in a similar process as described as used for Compound **146E**. It had an analytical HPLC retention time = 2.71 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 502.

263B. Preparation of benzyl (3*R*,4*R*)-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)-3-ureidopiperidin-4-ylcarbamate



263B

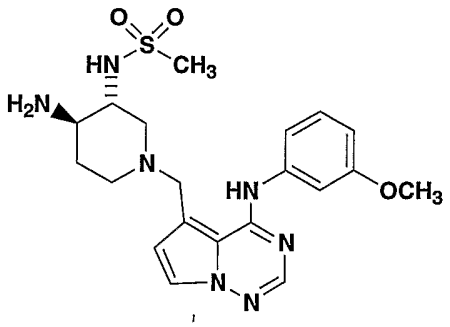
To a stirred mixture of Compound **263A** (77.0 mg, 0.15 mmoL) in 2 mL of CH_2Cl_2 at 0°C was added trichloroacetylisocyanate (28.9 mg, 0.18 mmoL). The mixture was stirred at 0°C for 30 min, and 1 mL of methanol was added. This mixture was then concentrated *in vacuo* to give a crude oil. This crude material was

dissolved in 3 mL of methanol and 2 mL of 20% K_2CO_3 solution was added. The mixture was stirred at room temperature for 2 h, then diluted with 10 mL of water. It was concentrated *in vacuo* to remove methanol and then extracted with EtOAc (3x 15 mL). The combined EtOAc extracts were washed with brine (10 mL) and dried ($MgSO_4$). Filtration followed by concentration *in vacuo* afforded 70 mg (yield: 84%) of Compound **263B**. It had an analytical HPLC retention time = 2.51 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 545.

Compound **263** was prepared from Cmpound **263B** in a similar way as described for compound **249A**. It had an analytical HPLC retention time = 1.32 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 411.

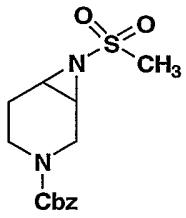
EXAMPLE 264

rac-N-[(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]methanesulfonamide



264

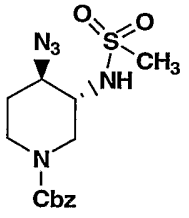
264A. Preparation of benzyl 7-(methylsulfonyl)-3,7-diaza-bicyclo[4.1.0]heptane-3-carboxylate (racemic)



264A

To a stirred mixture of benzyl 3,7-diaza-bicyclo[4.1.0]heptane-3-carboxylate (410 mg, 1.77 mmoL, prepared as shown in Tetrahedron Letters, 43(23), 4289-4293, 2002) in 5 mL of CH_2Cl_2 was added triethylamine (0.74 mL, 5.31 mmoL), followed by methanesulfonyl chloride (0.18 mL, 2.30 mmoL). The mixture was stirred at room temperature for 2.5 h and then diluted with 120 mL of EtOAc. This mixture was washed with 5% citric acid solution (3x 30 mL), saturated $NaHCO_3$ solution (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give Compound **264A** in quantitative yield. It had an analytical HPLC retention time = 2.56 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS $M^+ + Na = 333$.

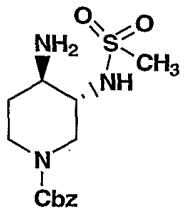
264B. Preparation of (3R,4R)-*rel*-benzyl 4-azido-3-(methylsulfonamido)piperidine-1-carboxylate:



264B

To a stirred mixture of compound **264A** (549 mg, 1.77 mmoL) in 4 mL of DMSO was added NaN_3 (458 mg, 7.08 mmoL). The mixture was stirred at room temperature for 2 h, and diluted with 80 mL of EtOAc. The mixture was washed with water (3x 100 mL), saturated $NaHCO_3$ solution (40 mL), and brine (40 mL). The EtOAc layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 530 mg (yield: 85%) of Compound **264B**. It had an analytical HPLC retention time = 2.90 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 354.

264C. Preparation of (3R,4R)-*rel*-benzyl 4-amino-3-(methylsulfonamido)piperidine-1-carboxylate:

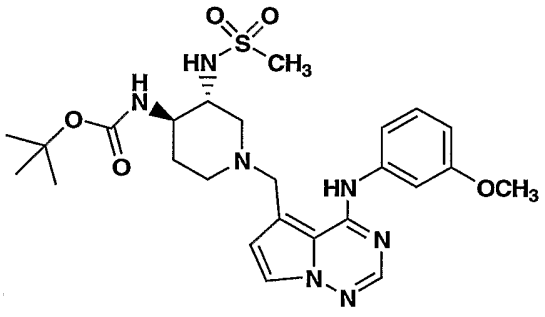


264C

To a stirred mixture of Compound **264B** (530 mg, 1.50 mmoL) in 6 mL of THF and 1 mL of water was added Ph_3P (900 mg, 3.43 mmoL). The reaction mixture was heated at 70°C for 15 h and cooled to room temperature. This mixture was concentrated *in vacuo*, diluted with 15 mL of 2N HCl solution, and then washed with $CHCl_3$ (3x 20 mL). The aqueous was basified to pH 12 by the addition of 50% NaOH solution, saturated with NaCl, and then extracted with EtOAc (3x 25 mL). The combined EtOAc extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered

and concentrated *in vacuo* to give 490 mg (yield: 100%) of Compound **264C**. It had an analytical HPLC retention time = 1.67 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 328.

264D. Preparation of tert-butyl (3R,4R)-*rel*-1-((4-(3-methoxyphenylamino) pyrrolo[1,2-f][1,2,4]triazin-5-yl)methyl)-3-(methylsulfonamido)piperidin-4-ylcarbamate



264D

To a stirred solution of compound **264C** (490 mg, 1.50 mmoL) in 6 mL of CH_2Cl_2 was added Et_3N (0.63 mL, 4.50 mmoL), followed by di-*t-butyl* dicarbonate (390 mg, 1.80 mmoL). The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with 60 mL of EtOAc, washed with saturated $NaHCO_3$ solution (2x 15 mL) and brine (15 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude intermediate. The crude intermediate was purified by flash chromatography (hexane-EtOAc) on silica gel to give 131 mg of pure meterial. To this intermediate in 6 mL of methanol under nitrogen was added 20%$Pd(OH)_2/C$ (30 mg). The reaction mixture was purged with hydrogen several times and stirred under hydrogen atmosphere for 18 h. The catalyst was removed by filtration using a 4 μM polycarbonate film and rinsed with MeOH

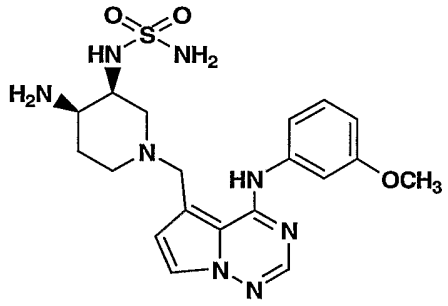
(4x 10 mL). The combined filtrates were concentrated *in vacuo* to give 89 mg of crude amine intermediate.

Compound **264D** was prepared from this intermediate in a similar process as described for **146E**. It had an analytical HPLC retention time = 2.72 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 546.

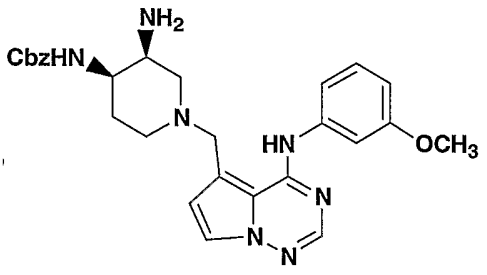
To a stirred solution of compound **264D** (120 mg, 0.22 mmoL) in 3 mL of CH_2Cl_2 was added TFA (2.5 mL, 32.4 mmoL). The mixture was stirred at room temperature for 40 min, concentrated *in vacuo*, and purified by a prep HPLC to give 71 mg (yield: 73%) of Compound **264**. It had an analytical HPLC retention time = 1.54 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 446.

EXAMPLE 265

N-[(3S,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]methanesulfonamide



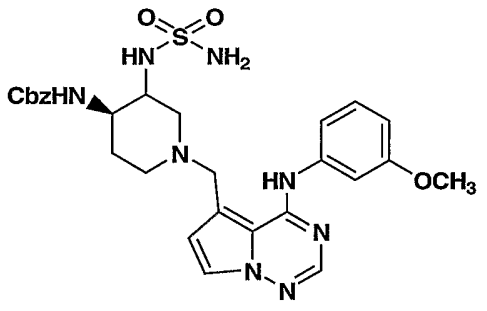
Preparation of compound **265A**



265A

Compound **265A** was prepared from compound **262C** (chiral, regioisomer B) in a similar way as described for compound **262D**. It had an analytical HPLC retention time = 2.73 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 502.

Preparation of compound **265B**



265B

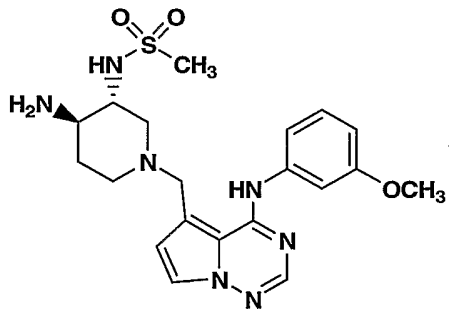
To a stirred mixture of compound **265A** (60.0 mg, 0.12 mmoL) and Et_3N (0.05 mL, 0.36 mmoL) in 4 mL of DCM was added methanesulfonyl chloride (15.0 mg, 0.13 mmoL). This reaction mixture was stirred at room temperature for 20 h and then diluted with 100 mL of EtOAc. The mixture was washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL). The EtOAc layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 70 mg of compound **265B** in a quantitative yield. Compound **265B** has an analytical HPLC retention time = 2.61 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 580.

Compound **265** was prepared from compound **265B** (chiral, regioisomer B) in a similar way as described for Compound **249A**. The structure of Compound **265** was assigned based on comparison of ^{1}H-NMR from that of Compound **264**.The compound had an analytical HPLC retention time = 1.50 min. (Phenomenox S5 C18-HC 4.6 x 50 mm column, 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 ml/min, monitoring at 220 nm) and a LC/MS M^++1 = 446.

EXAMPLE 266

N-[(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]methanesulfonamide

(*Enantiomer A*)



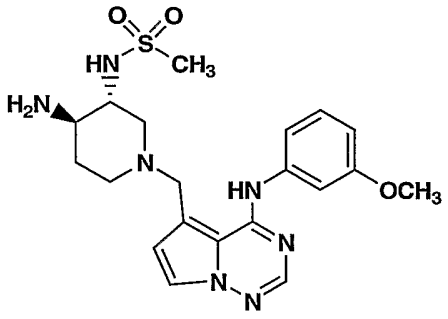
266 (*Enantiomer A*)

Compound **266** was obtained from **264** by a chrial preparative HPLC separation as the first eluted peak with >99% ee. Compound **127A** an HPLC retention time = 6.3 min (Chiral Pak, AD 250x4.6 mm column, 10 micron, 220 nM, 0.8 mL/min, EtOH as eluant). LC/MS M^++1 = 446.

EXAMPLE 267

N-[(3*S*,4*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]methanesulfonamide

(*Enantiomer B*)



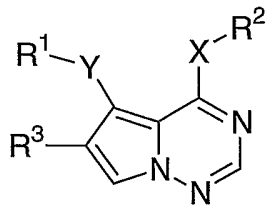
267 *(Enantiomer B)*

Compound **267** was obtained from **264** by a chiral preparative HPLC separation as the second eluted peak with >99% ee. Compound **267** had an HPLC retention time = 7.9 min (Chiral Pak, AD 250x4.6 mm column, 10 micron, 220 nM, 0.8 mL/min, EtOH as eluant). LC/MS M^++1 = 446.

Claims

We claim

1. A compound of formula I



(I)

wherein

R^1 is cycloalkyl or substituted cycloalkyl, aryl or substituted aryl, heterocyclyl or substituted heterocyclyl;

R^2 is aryl, substituted aryl, heteroaryl or substituted heteroaryl, heterocyclyl or substituted heterocyclyl;

R^3 is hydrogen, alkyl or substituted alkyl;

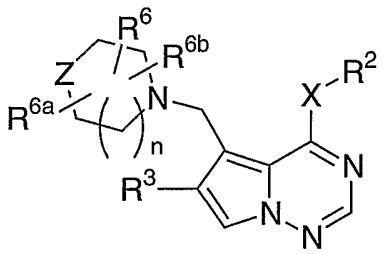
X is a direct bond, $-NR^3-$ or -O- ;

Y is a direct bond, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl;

or a pharmaceutically acceptable salt or stereoisomer thereof,

with the proviso that R^2 is not indazolyl or substituted indazolyl.

2. A compound of the formula



(II)

wherein

X is a direct bond, $-NR^3-$ or -O- ;

Z is $\overset{R^6}{\underset{|}{-CH-}}$ or $-NR^7-$;

R^2 is aryl or substituted aryl, heteroaryl or substituted heteroaryl,

R^3, R^4 and R^5 are independently selected from hydrogen, alkyl and substituted alkyl;

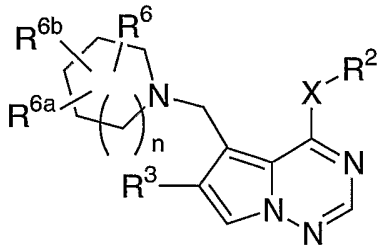
R^6, R^{6a} and R^{6b} are independently selected from the group consisting of one or more hydrogen, halogen, alkyl, alkoxy, aryloxy, -CN, $-NH_2$, -OH, -COOH, $-CH_2OR^5$, $-CONHSO_2R^5$, $-CONR^4R^5$, -NHalkyl, -NHCOalkyl, $-NR^4SO_2$alkyl, $-NR^4SO_2NR^4R^5$, $-OCONR^4R^5$, $-CF_3$ and $-OCF_3$, two of which may be attached to the same ring carbon atom provided that the resultant compound is chemically stable;

R^7 is hydrogen, alkyl or $-NH_2$, and

n is 0, 1, 2 or 3;

or a pharmaceutically acceptable salt or stereoisomer thereof.

3. A compound of the formula



(III)

wherein

X is a direct bond, $-NR^3-$ or -O- ;

R^2 is aryl or substituted aryl, heteroaryl or substituted heteroaryl,

R^3, R^4 and R^5 are independently selected from hydrogen, alkyl and substituted alkyl;

R^6, R^{6a} and R^{6b} are independently selected from the group consisting of one or more hydrogen, halogen, alkyl, alkoxy, aryloxy, -CN, $-NH_2$, -OH, -COOH, $-CH_2OR^5$,

-$CONHSO_2R^5$, -$CONR^4R^5$, -NHalkyl, -NHCOalkyl, -NR^4SO_2alkyl, -$NR^4SO_2NR^4R^5$, -$OCONR^4R^5$,-CF_3 and -OCF_3, two of which may be attached to the same ring carbon atom provided that the resultant compound is chemically stable; and

n is 0, 1, 2 or 3;

or a pharmaceutically acceptable salt or stereoisomer thereof.

4. The compound according to claim 3 wherein

R^2 is phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, oxazole, substituted oxazole, thiazole, substituted thiazole, pyrazinyl or substituted pyrazinyl;

R^6, R^{6a} and R^{6b} are independently selected from the group consisting of one or more hydrogen, -NH_2, OH, alkoxy, -$CONR^4R^5$, -NR^4SO_2alkyl, -$NR^4SO_2NR^4R^5$, -$OCONR^4R^5$, -NHalkyl and -NHCOalkyl;

X is –NH-;and

n is 1 or 2.

5. A compound selected from the group consisting of

5-[(4-Amino-1-piperidinyl)methyl]-N-(3-chloro-4-fluorophenyl)pyrrolo[2,1-f][1,2,4]triazine-4-amine,

5-[(4-Amino-1-piperidinyl)methyl]-N-2-naphthalenylpyrrolo[2,1-f][1,2,4]triazin-4-amine,

5-[(4-Amino-1-piperidinyl)methyl]-N-phenylpyrrolo[2,1-f][1,2,4]triazin-4-amine,

5-[(4-Amino-1-piperidinyl)methyl]-N-(3-methoxyphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine,

5-[(4-Amino-1-piperidinyl)methyl]-N-(3-ethynylphenyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine,

5-[(4-aminopiperidin-1-yl)methyl]-*N*-(4-fluoro-3-methoxyphenyl)pyrro-lo[2,1-*f*][1,2,4]triazin-4-amine,

(3R,4R)-4-amino-1-[[4-[(3-chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol,

(3S,4S)-4-amino-1-[[4-[(3-chloro-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol,

(3R,4R)-4-amino-1-[[4-[(3-methoxyphenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol,

(3S,4S)-4-amino-1-[[4-[(3-methoxyphenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol,

(3R,4R)-4-amino-1-[[4-[(3-methoxy-4-fluorophenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*]-[1,2,4]-triazin-5-yl}-methyl)piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-ethoxyphenyl)-amino]-pyrrolo[2,1-*f*]-[1,2,4]triazin-5-yl}-methyl)piperidin-3-ol

(3*R*,4*R*)-4-amino-1-{[4-(2-naphthylamino)-pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl]methyl}piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxy-4-methyl-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-bromophenyl)amino]pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-fluoro-5-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol,

(3*S*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol,

(3*R*,4*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-ol

(3*S*,4*R*)-4-amino-1-({4-[(3-chlorophenyl)amino]-pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-ol,

(3*S*,4*R*)-4-amino-1-({4-[(3-chloro-4-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-ol,

(3*S*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl) amino]pyrrolo[2,1-*f*][1, 2,4]triazin-5-yl}methyl) piperidin-3-ol,

(3*R*,4*S*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1, 2,4]triazin-5-yl}methyl)piperidin-3-ol,

(3*R*,4*S*)-4-amino-1-({4-[(3-chlorophenyl)amino]pyrrolo[2,1-*f*][1,2,4]-triazin-5-yl}methyl)-piperidin-3-ol,

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl carbamate,

(3*R*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1, 2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate,

(3*R*,4*R*)-4-amino-1-({4-[(3-chloro-4-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate,

(3*S*,4*R*)-4-amino-1-({4-[(3-chloro-4-fluoro-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate,

(3*S*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1, 2,4]triazin-5-yl}-methyl)piperidin-3-yl carbamate,

(3*S*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-3-methylpiperidin-3-ol,

(3R/*S*,5R/*S*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3,5-diol,

(3*S*,5*S*)-4-amino-1-({4-[(4-fluoro-3-methoxy-phenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}-methyl)piperidine-3,5-diol,

(3*R*,5*R*)-4-amino-1-({4-[(3-ethynylphenyl)-amino]pyrrolo[2,1-*f*][1, 2,4]triazin-5-yl}methyl)piperidine-3,5-diol,

5-{[(3*R*,4*R*)-4-amino-3-methoxypiperidin-1-yl]methyl}-*N*-(3-methoxyphenyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine,

5-(((4aR,8aR)-*rel*-hexahydro-1H-pyrido[3,4-b][1,4]oxazin-6(7H)-yl)methyl)-N-(3-methoxyphenyl)pyrrolo[1,2-f][1,2,4]triazin-4-amine,

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-(methylsulfonyl)piperidine-3-carboxamide,

(3*R*,4*R*)-4-amino-1-({4-[(3-ethynylphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-methylpiperidine-3-carboxamide,

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)-*N*-methylpiperidine-3-carboxamide,

(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidine-3-carboxamide,

((3R,4R)-1-((4-(3-methoxyphenylamino)pyrrolo[1,2-f][1,2,4]-triazin-5-yl)methyl)-4-((R)-1-phenylethylamino)piperidin-3-yl)methanol,

N-[(3R,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]urea,

N-[(3*R*,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]methanesulfonamide, and

N-[(3S,4*R*)-4-amino-1-({4-[(3-methoxyphenyl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-5-yl}methyl)piperidin-3-yl]methanesulfonamide,

or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition comprising one or more compounds of claim 1 and a pharmaceutically acceptable carrier.

7. A pharmaceutical composition comprising one or more compounds of claim 2 and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition comprising one or more compounds of claim 3 and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition comprising one or more compounds of claim 5 and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition comprising one or more compounds according to claim 1 in combination with a pharmaceutically acceptable carrier and one or more other anti-cancer or cytotoxic agent.

11. The pharmaceutical composition according to claim 10 wherein said anti-cancer or cytotoxic agent is selected from the group consisting of tamoxifen, toremifene, raloxifene, droloxifene, iodoxifene, megestrol acetate, anastrozole, letrozole, borazole, exemestane, flutamide, nilutamide, bicalutamide, cyproterone acetate, gosereline acetate, leuprolide, finasteride, metalloproteinase inhibitors, inhibitors of urokinase plasminogen activator receptor function, growth factor

antibodies, growth factor receptor antibodies, bevacizumab, cetuximab, trastuzumab, erlotinib, tyrosine kinase inhibitors, serine/threonine kinase inhibitors, methotrexate, 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, cisplatin, carboplatin, nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa, vincristine, vinorelbine, vinblastine, vinflunine paclitaxel, docetaxel, epothilone analogs, discodermolide analogs, eleutherobin analogs, etoposide, teniposide, amsacrine, topotecan, flavopyridol, bortezomib and biological response modifiers.

12. A method for treating a proliferative disease, comprising administering to a mammalian species in need thereof, a therapeutically effective amount of one or more compound according to claim 1.

13. The method of claim 12 wherein the proliferative disease is selected from the group consisting of cancer, psoriasis and rheumatoid arthritis.

14. The method of claim 13 wherein the proliferative disease is cancer.

15. The method of claim 14 further comprising administering to a warm-blooded species in need thereof, a therapeutically effective amount of one or more other anti-cancer or cytotoxic agent in combination with one or more compound according to claim 1.

16. The method of claim 15 wherein said anti-cancer or cytotoxic agent is selected from the group consisting of tamoxifen, toremifene, raloxifene, droloxifene, iodoxifene, megestrol acetate, anastrozole, letrozole, borazole, exemestane, flutamide, nilutamide, bicalutamide, cyproterone acetate, gosereline acetate, leuprolide, finasteride, metalloproteinase inhibitors, inhibitors of urokinase plasminogen activator receptor function, growth factor antibodies, growth factor receptor antibodies, bevacizumab, cetuximab, trastuzumab, erlotinib, tyrosine kinase inhibitors, serine/threonine kinase inhibitors, methotrexate, 5-fluorouracil, purine and adenosine

analogues, cytosine arabinoside, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, cisplatin, carboplatin, nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa, vincristine, vinorelbine, vinblastine, vinflunine paclitaxel, docetaxel, epothilone analogs, discodermolide analogs, eleutherobin analogs, etoposide, teniposide, amsacrine, topotecan, flavopyridols, proteasome inhibitors including bortezomib and biological response modifiers.

17. A method of modulating receptor tyrosine kinase activity which comprises administering to a mammalian species in need thereof, an effective amount of one or more compound according to claim 1.

18. The method of claim 17 wherein said receptor tyrosine kinase is selected from the group consisting of HER1, HER2 and HER4.

19. A method for treating diseases associated with signal transduction pathways operating through growth factor receptors, which comprises administering to a mammalian species in need thereof a therapeutically effective amount of one or more compound according to claim 1.

20. A method for identifying kinase ATP-competitive inhibitors which comprises selecting a compound as defined in Claim 1, that binds in the adenine pocket, the ribose pocket, the phosphate binding pocket, specificity region 1 and specificity region 2 of the kinase as shown in Figure 2, wherein the group occupying the ribose and/or the phosphate binding pocket can interact with one or more of the absolutely conserved residues involved in phosphate binding.

21. The method according to Claim 20 wherein the group interacts with residues Asn818 and/or Asp 831 (HER1 numbering) or the correponding residues in a different kinase of the ribose/phosphate binding pockets.

FIG. 1

X-ray structure of HER1, color-coded by key elements of a typical kinase.

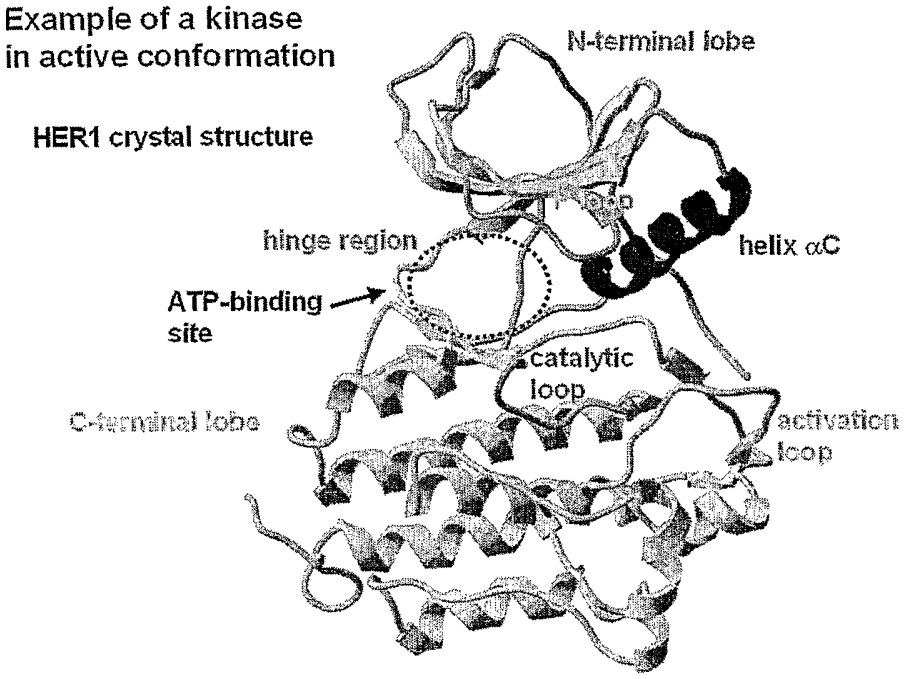
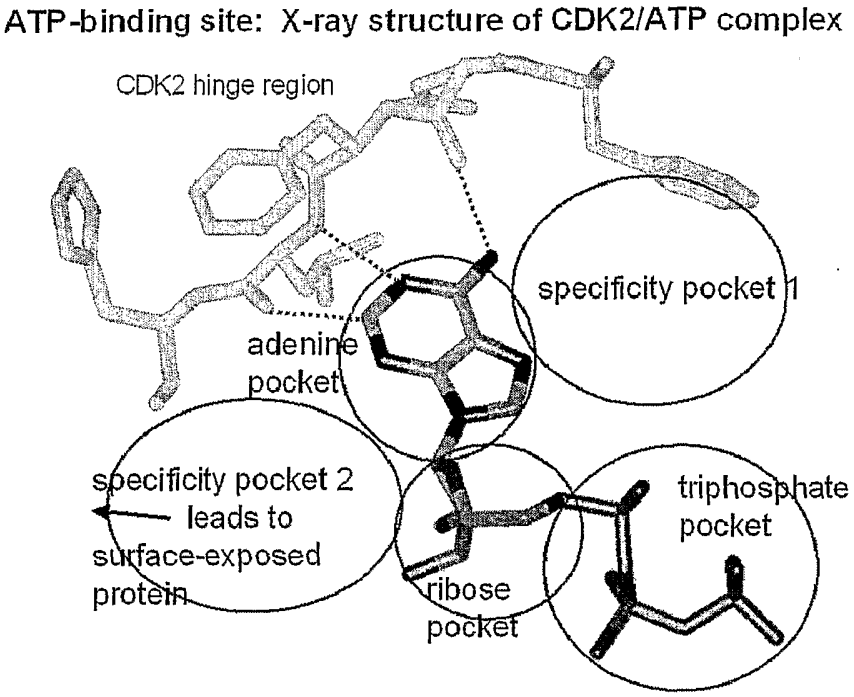


FIG. 2

X-ray structure of CDK2 complexed with ATP. Different regions of a typical ATP-binding site are delineated.



INTERNATIONAL SEARCH REPORT

Int ›nal Application No
PCT/US2004/043169

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 C07D519/00 A61K31/53 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 03/042172 A (BRISTOL-MYERS SQUIBB COMPANY; MASTALERZ, HAROLD; ZHANG, GUIFEN; TARRAN) 22 May 2003 (2003-05-22) claims; examples 14,19,34-37,53-56,58,63-73,83,86,123	2,3,7,8 1-21
Y	WO 00/71129 A (BRISTOL-MYERS SQUIBB COMPANY) 30 November 2000 (2000-11-30) cited in the application claims; examples	1-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 2005	13/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fazzi, R

3

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US2004/043169

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,5(part), 6, 9(part), 10-21

Claim 1 and dependent upon disclose pyrrolotriazine compounds of general formula (I) and their use in the treatment of cancer.

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2. claims: 2, 5(part), 7, 9(part)

Claim 2 and dependent upon disclose pyrrolotriazine compounds of general formula (II) and their use in the treatment of cancer.

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3. claims: 3, 4, 5(part), 8, 9(part)

Claim 3 and dependent upon disclose pyrrolotriazine compounds of general formula (III) and their use in the treatment of cancer.

INTERNATIONAL SEARCH REPORT

In ınal Application No
PCT/US2004/043169

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