

HETEROARYL PYRIDONE AND AZA-PYRIDONE COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional application filed under 37 CFR §1.53(b), claims the benefit
5 under 35 USC §119(e) of U.S. Provisional Application Serial No. 61/555,393 filed on 3
November 2011, which is incorporated by reference in entirety.

FIELD OF THE INVENTION

The invention relates generally to compounds for treating disorders mediated by
Bruton's Tyrosine Kinase (Btk) including inflammation, immunological, and cancer, and
10 more specifically to compounds which inhibit Btk activity. The invention also relates to
methods of using the compounds for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of
mammalian cells, or associated pathological conditions.

BACKGROUND OF THE INVENTION

Protein kinases, the largest family of human enzymes, encompass well over 500
15 proteins. Bruton's Tyrosine Kinase (Btk) is a member of the Tec family of tyrosine kinases,
and is a regulator of early B-cell development as well as mature B-cell activation, signaling,
and survival.

B-cell signaling through the B-cell receptor (BCR) can lead to a wide range of biological
outputs, which in turn depend on the developmental stage of the B-cell. The magnitude and
20 duration of BCR signals must be precisely regulated. Aberrant BCR-mediated signaling can
cause dysregulated B-cell activation and/or the formation of pathogenic auto-antibodies
leading to multiple autoimmune and/or inflammatory diseases. Mutation of Btk in humans
results in X-linked agammaglobulinaemia (XLA). This disease is associated with the
impaired maturation of B-cells, diminished immunoglobulin production, compromised T-
25 cell-independent immune responses and marked attenuation of the sustained calcium sign
upon BCR stimulation. Evidence for the role of Btk in allergic disorders and/or autoimmune
disease and/or inflammatory disease has been established in Btk-deficient mouse models.
For example, in standard murine preclinical models of systemic lupus erythematosus (SLE),
Btk deficiency has been shown to result in a marked amelioration of disease progression.
30 Moreover, Btk deficient mice can also be resistant to developing collagen-

A “solvate” refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethylacetate, acetic acid, and ethanolamine.

5 The term “EC₅₀” is the half maximal effective concentration” and denotes the plasma concentration of a particular compound required for obtaining 50% of the maximum of a particular effect in vivo.

10 The term “Ki” is the inhibition constant and denotes the absolute binding affinity of a particular inhibitor to a receptor. It is measured using competition binding assays and is equal to the concentration where the particular inhibitor would occupy 50% of the receptors if no competing ligand (e.g. a radioligand) was present. Ki values can be converted logarithmically to pKi values (-log Ki), in which higher values indicate exponentially greater potency.

15 The term “IC₅₀” is the half maximal inhibitory concentration and denotes the concentration of a particular compound required for obtaining 50% inhibition of a biological process in vitro. IC₅₀ values can be converted logarithmically to pIC₅₀ values (-log IC₅₀), in which higher values indicate exponentially greater potency. The IC₅₀ value is not an absolute value but depends on experimental conditions e.g. concentrations employed, and can be converted to an absolute inhibition constant (Ki) using the Cheng-Prusoff equation (Biochem. Pharmacol. (1973) 22:3099). Other percent inhibition parameters, such as IC₇₀, IC₉₀, etc.,
20 may be calculated.

 The terms “compound of this invention,” and “compounds of the present invention” and “compounds of Formula I” include compounds of Formulas I and stereoisomers, geometric isomers, tautomers, solvates, ~~metabolites~~, and pharmaceutically acceptable salts and ~~prodrugs~~ thereof.

25 Any formula or structure given herein, including Formula I compounds, is also intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

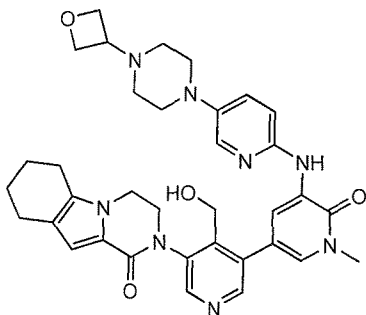
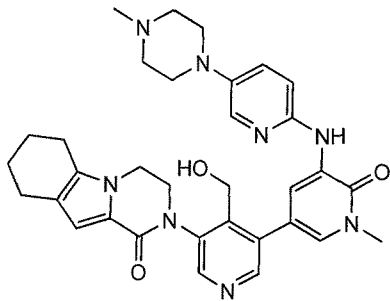
 Any formula or structure given herein, including Formula I compounds, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds.
30 Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, but not limited to 2H (deuterium, D), 3H (tritium), 11C, 13C, 14C, 15N, 18F, 31P,

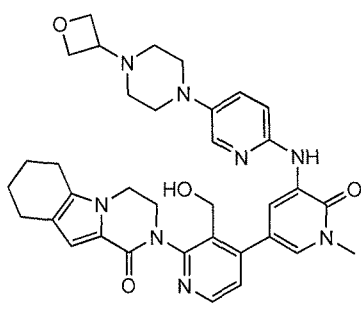
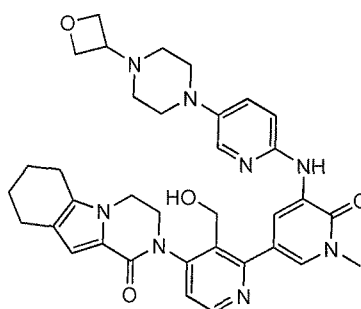
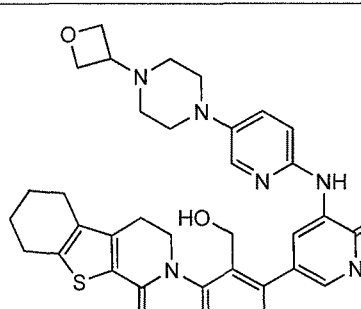
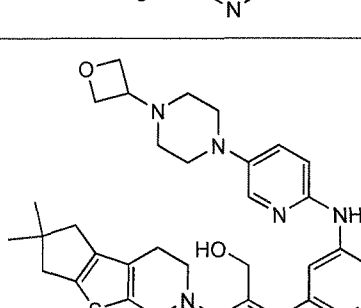
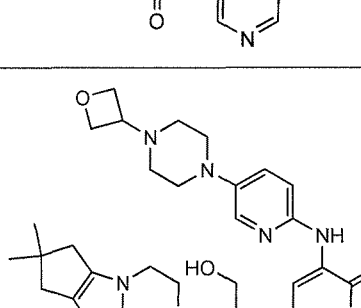
384 well format. Data can be recorded by luminometer or CCD camera imaging device. The luminescence output is presented as relative light units (RLU), measured over time.

The anti-proliferative efficacy of Formula I exemplary compounds and combinations with chemotherapeutic agents are measured by the CellTiter-Glo[®] Assay (Example 908) against certain hematological tumor cell lines. EC₅₀ values are established for the tested compounds and combinations.

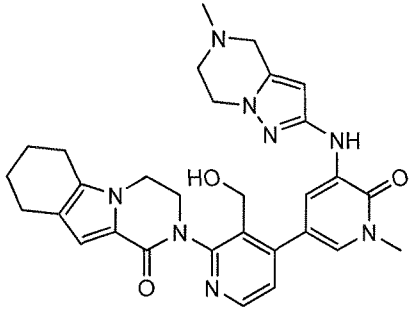
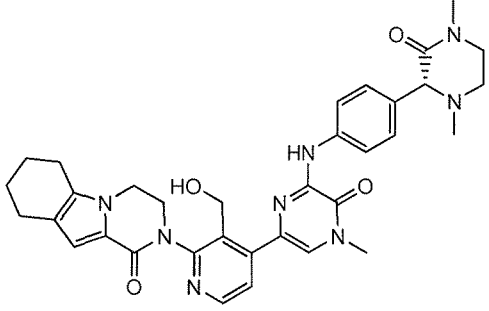
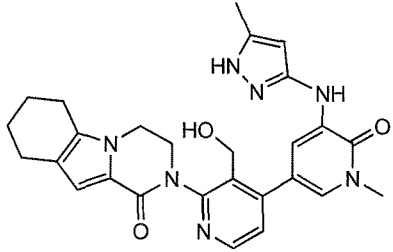
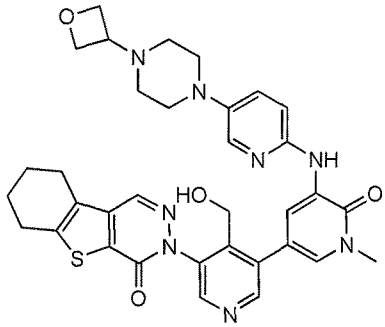
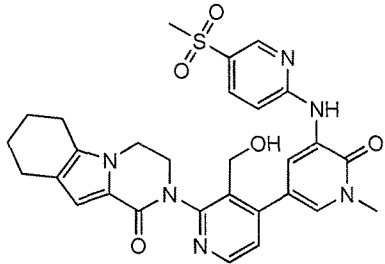
Exemplary Formula I compounds in Tables 1 and 2 were made, characterized, and tested for inhibition of Btk according to the methods of this invention, and have the following structures and corresponding names (ChemDraw Ultra, Version 9.0.1, and ChemBioDraw, Version 11.0, CambridgeSoft Corp., Cambridge MA) (where * refers to reference examples). Where more than one name is associated with a Formula I compound or intermediate, the chemical structure shall define the compound.

Table 1.

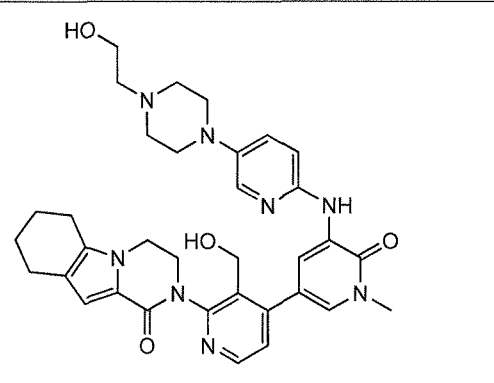
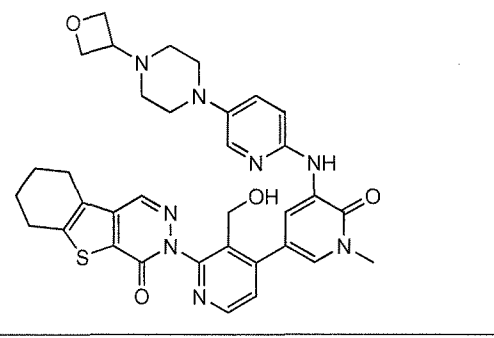
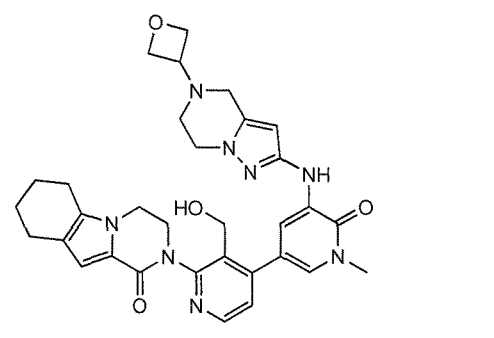
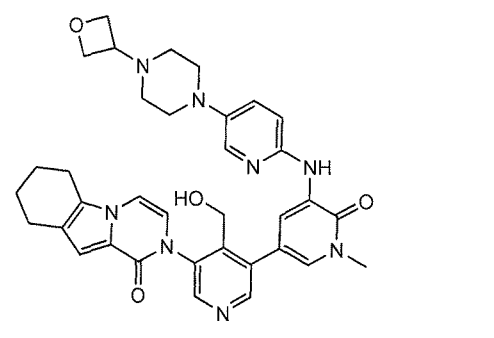
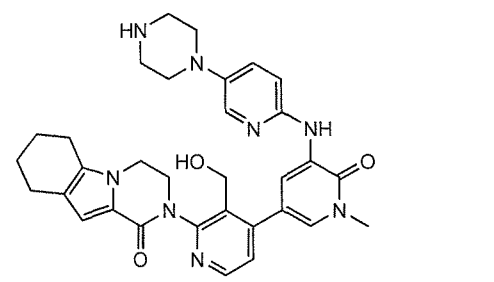
No.	Structure	IUPAC_Name	Mol Weight	CD69 Hu Blood FACS IC70 (μM)
101 *		2-{4-Hydroxymethyl-1'-methyl-5'-[5-(4-oxetan-3-yl)piperazin-1-yl]-pyridin-2-ylamino}-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	636.74	0.132
102 *		2-{4-Hydroxymethyl-1'-methyl-5'-[5-(4-methylpiperazin-1-yl)-pyridin-2-ylamino]-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	594.71	0.132

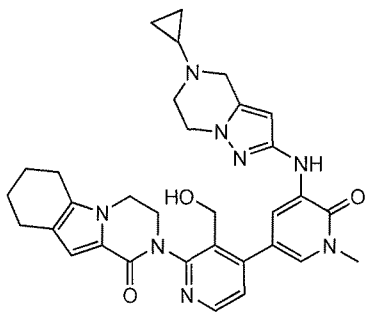
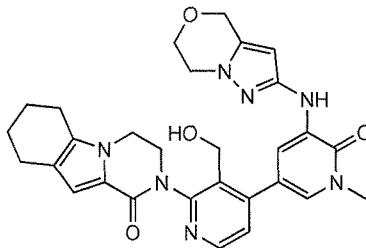
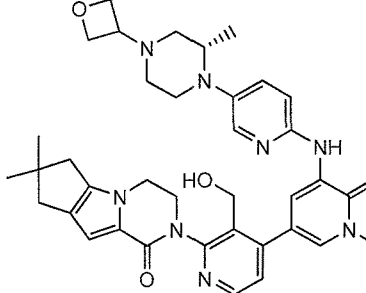
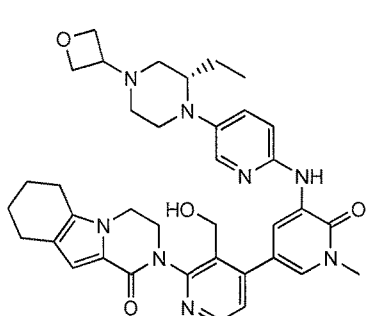
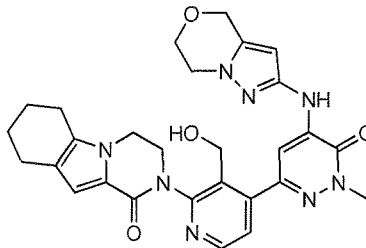
103 * —		2-(3-(Hydroxymethyl)-4-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)pyridin-2-yl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	636.74	0.0776
104 * —		2-(3-(Hydroxymethyl)-2-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)pyridin-4-yl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	636.74	0.793
105 * —		2-{4-Hydroxymethyl-1'-methyl-5'-[5-(4-(oxetan-3-yl)piperazin-1-yl)-pyridin-2-ylamino]-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl}-3,4,5,6,7,8-hexahydro-2H-benzo[4,5]thieno[2,3-c]pyridin-1-one	653.79	0.0654
106 * —		6-{4-Hydroxymethyl-1'-methyl-5'-[5-(4-(oxetan-3-yl)piperazin-1-yl)-pyridin-2-ylamino]-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl}-2,2-dimethyl-2,3,5,6-tetrahydro-1H,4H-8-thia-6-azacyclopenta[a]inden-7-one	667.82	0.0576
107		2-{4-Hydroxymethyl-1'-methyl-5'-[5-(4-(oxetan-3-yl)piperazin-1-yl)-pyridin-2-ylamino]-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	650.77	0.0216

108		2-{3'-Hydroxymethyl-1-methyl-5-[5-(4-oxetan-3-ylpiperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	650.77	0.0319
109 * —		6-{3'-Hydroxymethyl-1-methyl-5-[5-(4-oxetan-3-ylpiperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-2,2-dimethyl-2,3,5,6-tetrahydro-1H,4H-8-thia-6-aza-cyclopenta[a]inden-7-one	667.82	0.0501
110 * —		2-{3'-Hydroxymethyl-1-methyl-5-[6-(4-methylpiperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	594.71	2.7
111 * —		2-{3'-Hydroxymethyl-1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	609.68	0.131
112 * —		2-{4-Hydroxymethyl-1'-methyl-5'-[5-(4-oxetan-3-ylpiperazin-1-yl)-pyridin-2-ylamino]-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl}-2,3,5,6,7,8-hexahydro-4H-2,4b-diaza-fluoren-1-one	636.74	0.492

113 * —		2-[3'-Hydroxymethyl-1-methyl-5-(5-methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	554.64	0.0625
114 * —		2-(4-{6-[4-((R)-1,4-Dimethyl-3-oxo-piperazin-2-yl)-phenylamino]-4-methyl-5-oxo-4,5-dihydro-pyrazin-2-yl}-3-hydroxymethyl-pyridin-2-yl)-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	622.72	0.0802
115 * —		2-[3'-Hydroxymethyl-1-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	499.56	0.286
116 * —		3-{4-Hydroxymethyl-1'-methyl-5'-[5-(4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl}-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one	652.77	0.377
117 * —		2-[3'-Hydroxymethyl-5-(5-methanesulfonyl-pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	574.65	0.396

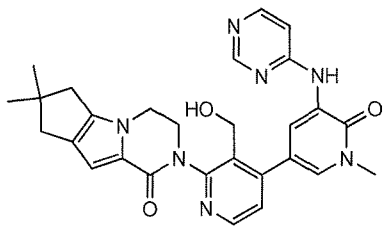
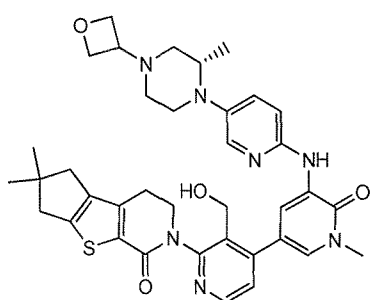
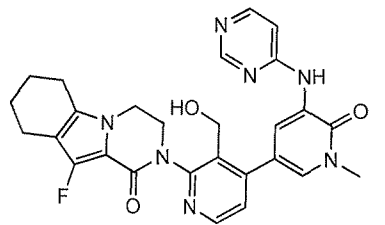
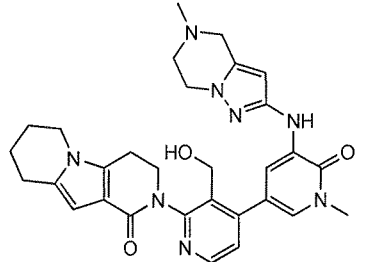
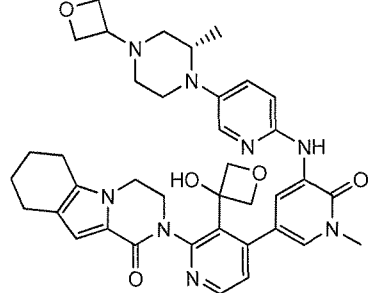
118 * —		2-[5-(5-Cyclopropyl-1H-pyrazol-3-ylamino)-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	525.60	0.608
119 * —		2-{3'-Hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	650.77	0.0356
120 * —		2-(3'-Hydroxymethyl-5-{5-[4-(2-hydroxy-2-methyl-propyl)-piperazin-1-yl]-pyridin-2-ylamino}-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl)-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	652.79	0.283
121 * —		2-{3'-Hydroxymethyl-1-methyl-5-[5-(4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-6,7,8,9-tetrahydro-2H-pyrazino[1,2-a]indol-1-one	634.73	0.0323
122 * —		2-{5-[5-((2S,5R)-2,5-Dimethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	664.80	0.0127

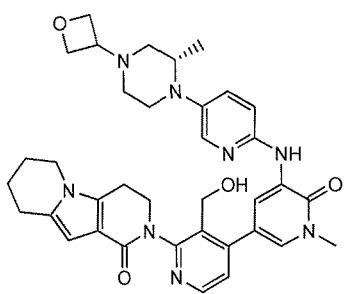
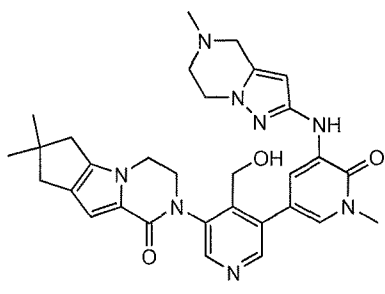
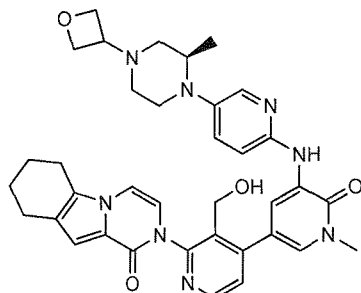
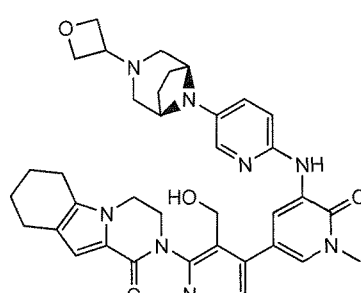
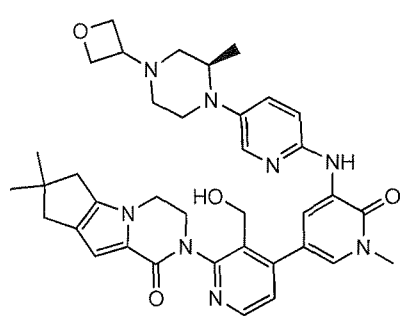
123 * —		2-(5-{5-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-pyridin-2-ylamino}-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl)-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	624.73	0.0331
124 * —		3-{3'-Hydroxymethyl-1-methyl-5-[5-(4-oxetan-3-yl)-piperazin-1-yl]-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one	652.77	0.0362
125 * —		2-[3'-Hydroxymethyl-1-methyl-5-(5-oxetan-3-yl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	596.68	0.0873
126 * —		2-{4-Hydroxymethyl-1'-methyl-5'-[5-(4-oxetan-3-yl)-piperazin-1-yl]-pyridin-2-ylamino]-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl}-6,7,8,9-tetrahydro-2H-pyrazino[1,2-a]indol-1-one	634.73	0.138
127 * —		2-[3'-Hydroxymethyl-1-methyl-6-oxo-5-(5-piperazin-1-yl-pyridin-2-ylamino)-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	580.68	0.141

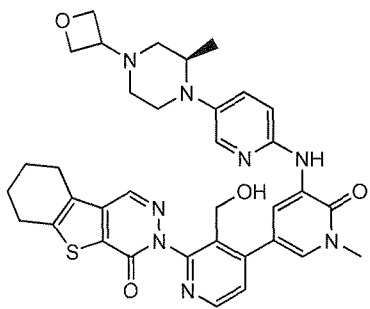
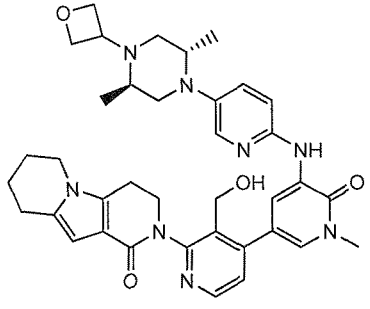
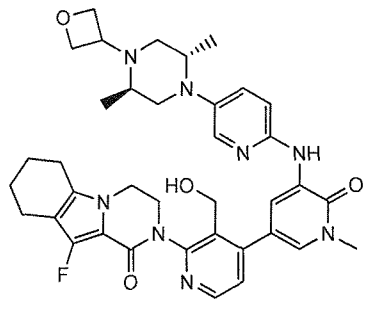
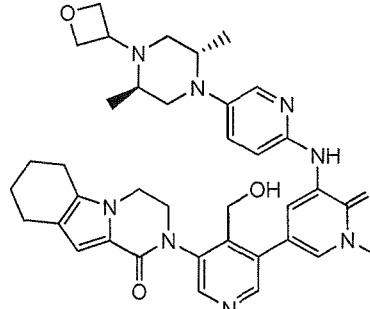
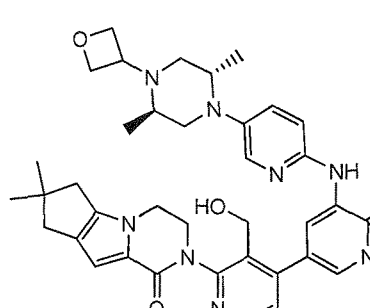
128 * —		2-[5-(5-Cyclopropyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	580.68	0.0918
129 * —		2-[5-(6,7-Dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	541.60	0.0917
130		2-{3'-Hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	664.80	0.012
131 * —		2-{5-[5-((S)-2-Ethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	664.80	0.0155
132 * —		2-{4-[5-(6,7-Dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydro-pyridazin-3-yl]-3-hydroxymethyl-pyridin-2-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	542.59	0.263

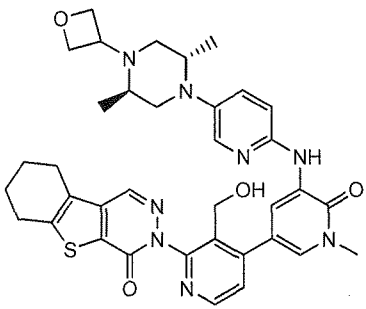
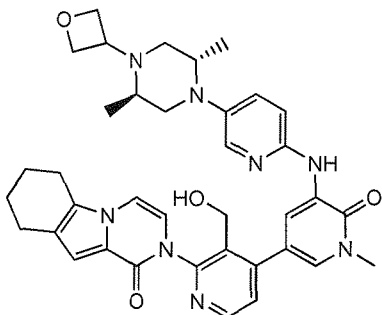
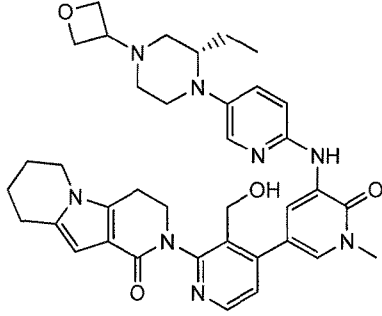
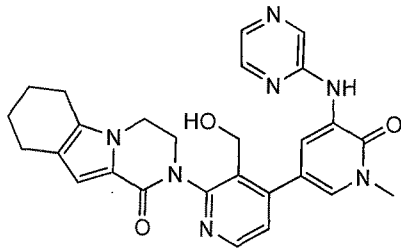
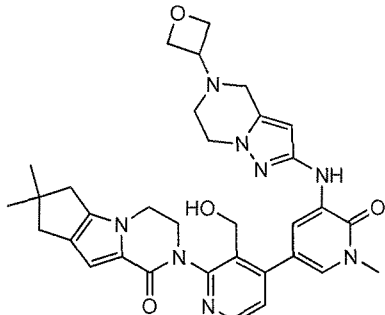
133 * —		2-{3-Hydroxymethyl-4-[1-methyl-5-(5-methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydro-pyridazin-3-yl]-pyridin-2-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	555.63	0.227
134 * —		10-Fluoro-2-{3'-hydroxymethyl-1-methyl-5-[5-(4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	654.73	0.0944
135 * —		10-Fluoro-2-{3'-hydroxymethyl-1-methyl-5-(5-methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	572.63	0.107
136 * —		10-Fluoro-2-{3'-hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	668.76	0.030
137 * —		2-{3'-Hydroxymethyl-1-methyl-5-[5-((R)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	650.77	0.0646

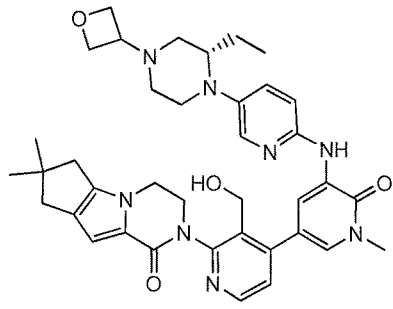
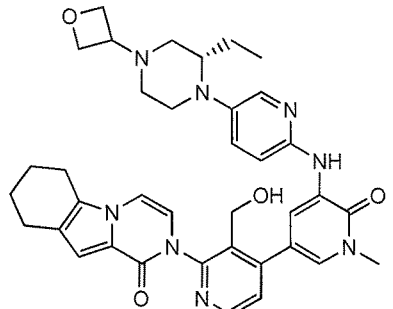
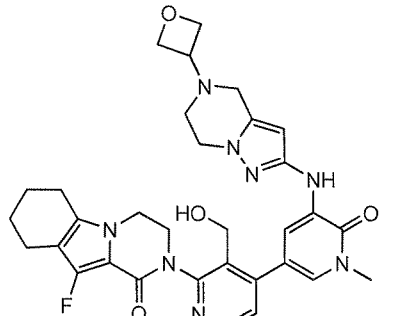
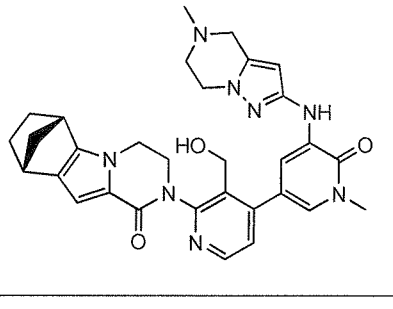
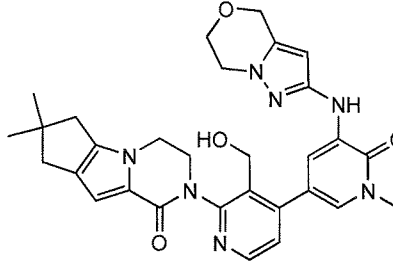
138 * —		2-[4-Hydroxymethyl-1'-methyl-5'-(5-methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	554.64	0.353
139 * —		2-{3'-Hydroxymethyl-1-methyl-5-[5-(4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-2,3,5,6,7,8-hexahydro-4H-2,4b-diaza-fluoren-1-one	636.74	0.326
140 * —		7,7-Difluoro-2-{3'-hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	686.75	0.308
141		2-[3'-Hydroxymethyl-1-methyl-5-(5-methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	568.67	0.0266
142 * —		2-[3'-Hydroxymethyl-1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	497.55	2.1
143 * —		6-[3'-Hydroxymethyl-1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-2,2-dimethyl-2,3,5,6-tetrahydro-1H,4H-8-thia-6-aza-cyclopenta[a]inden-7-one	528.63	0.0309

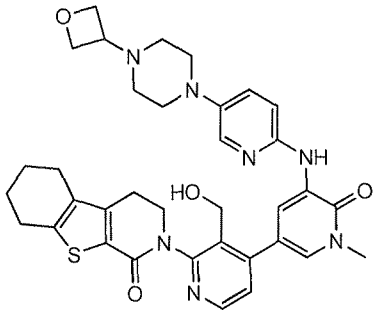
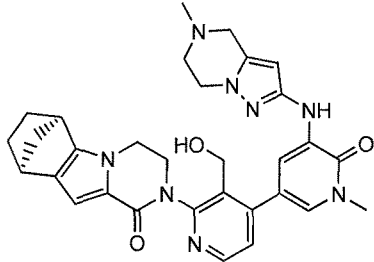
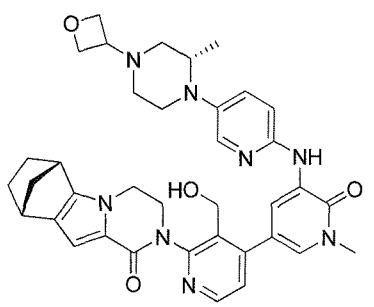
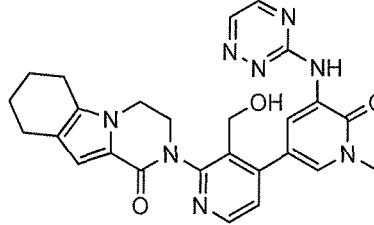
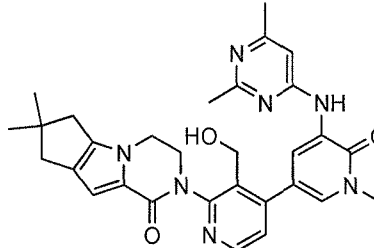
144		2-[3'-Hydroxymethyl-1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	511.58	0.106
145 * —		6-{3'-Hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-2,2-dimethyl-2,3,5,6-tetrahydro-1H,4H-8-thia-6-aza-cyclopenta[a]inden-7-one	681.85	0.0147
146 * —		10-Fluoro-2-[3'-hydroxymethyl-1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	515.54	0.0856
147 * —		2-[3'-Hydroxymethyl-1-methyl-5-(5-methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-2,3,5,6,7,8-hexahydro-4H-2,4b-diaza-fluoren-1-one	554.64	0.32
148 * —		2-{3'-(3-Hydroxy-oxetan-3-yl)-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	692.81	5

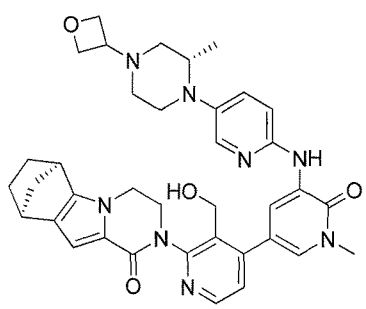
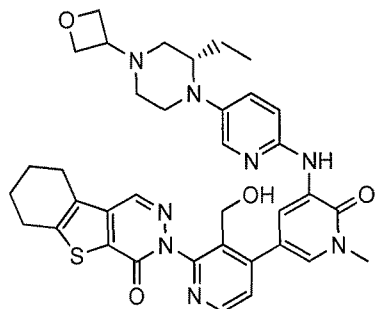
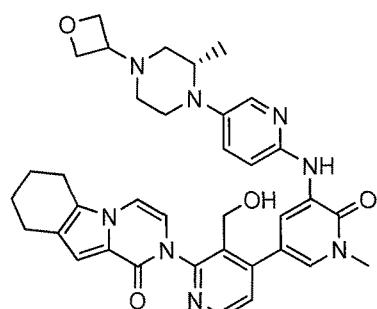
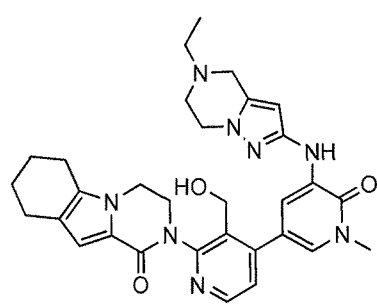
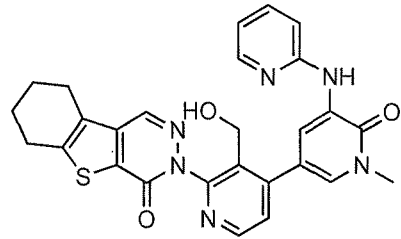
149 *		2-{3'-Hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-2,3,5,6,7,8-hexahydro-4H-2,4b-diaza-fluoren-1-one	650.77	0.0454
150		2-[4-Hydroxymethyl-1'-methyl-5'-(5-methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl]-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	568.67	0.0316
151 *		2-{3'-Hydroxymethyl-1-methyl-5-[5-((R)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-6,7,8,9-tetrahydro-2H-pyrazino[1,2-a]indol-1-one	648.75	0.0455
152 *		2-{3'-Hydroxymethyl-1-methyl-5-[5-(((1S,5R)-3-oxetan-3-yl-3,8-diaza-bicyclo[3.2.1]oct-8-yl)-pyridin-2-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	662.78	0.188
153		2-{3'-Hydroxymethyl-1-methyl-5-[5-((R)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	664.80	0.0238

154 * —		3-{3'-Hydroxymethyl-1-methyl-5-[5-((R)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one	666.79	0.0374
155 * —		2-{5-[5-((2S,5R)-2,5-Dimethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-2,3,5,6,7,8-hexahydro-4H-2,4b-diaza-fluoren-1-one	664.80	0.0454
156 * —		2-{5-[5-((2S,5R)-2,5-Dimethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-10-fluoro-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	682.79	0.0145
157 * —		2-{5'-[5-((2S,5R)-2,5-Dimethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-4-hydroxymethyl-1'-methyl-6'-oxo-1',6'-dihydro-[3,3']bipyridinyl-5-yl}-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	664.80	0.0298
158		2-{5-[5-((2S,5R)-2,5-Dimethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	678.82	0.020

159 * —		3-{5-[5-((2S,5R)-2,5-Dimethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one	680.82	0.082
160 * —		2-{5-[5-((2S,5R)-2,5-Dimethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-6,7,8,9-tetrahydro-2H-pyrazino[1,2-a]indol-1-one	662.78	0.0547
161 * —		2-{5-[5-((S)-2-Ethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-2,3,5,6,7,8-hexahydro-4H-2,4b-diaza-fluoren-1-one	664.80	0.064
162 * —		2-[3'-Hydroxymethyl-1-methyl-6-oxo-5-(pyrazin-2-ylamino)-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	497.55	0.434
163		2-[3'-Hydroxymethyl-1-methyl-5-(5-oxetan-3-yl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	610.71	0.0228

164		2-{5-[5-((S)-2-Ethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	678.82	0.029
165 * —		2-{5-[5-((S)-2-Ethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-6,7,8,9-tetrahydro-2H-pyrazino[1,2-a]indol-1-one	662.78	0.0417
166 * —		10-Fluoro-2-[3'-hydroxymethyl-1-methyl-5-(5-oxetan-3-yl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-3,4,6,7,8,9-hexahydro-2H-pyrazino[1,2-a]indol-1-one	614.67	0.155
167 * —		2-(3-(hydroxymethyl)-4-(1-methyl-5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)pyridin-2-yl)-3,4,6,7,8,9-hexahydro-6,9-methanopyrazino[1,2-a]indol-1(2H)-one	566.65	0.119
168		2-[5-(6,7-Dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-ylamino)-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	555.63	0.0635

169 * —		2-{3'-Hydroxymethyl-1-methyl-5-[5-(4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-3,4,5,6,7,8-hexahydro-2H-benzo[4,5]thieno[2,3-c]pyridin-1-one	653.79	0.206
170 * —		2-(3-(hydroxymethyl)-4-(1-methyl-5-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)pyridin-2-yl)-3,4,6,7,8,9-hexahydro-6,9-methanopyrazino[1,2-a]indol-1(2H)-one	566.65	0.335
171 * —		(1 <i>S</i> ,11 <i>R</i>)-6-[3-(Hydroxymethyl)-4-[1-methyl-5-({5-[(2 <i>S</i>)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]pyridin-2-yl} amino)-6-oxo-1,6-dihydropyridin-3-yl]pyridin-2-yl]-3,6-diazatetracyclo[9.2.1.0 ^{2,10} .0 ^{3,8}]tetradeca-2(10),8-dien-7-one	662.78	0.036
172 * —		2-(4-(5-(1,2,4-triazin-3-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-3-(hydroxymethyl)pyridin-2-yl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	498.54	5
173		2-[5-(2,6-Dimethyl-pyrimidin-4-ylamino)-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	539.63	1

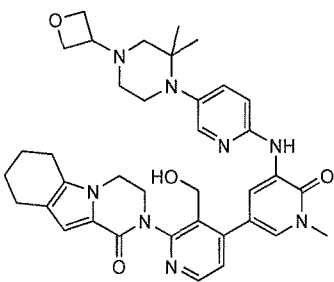
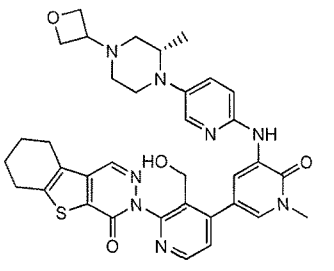
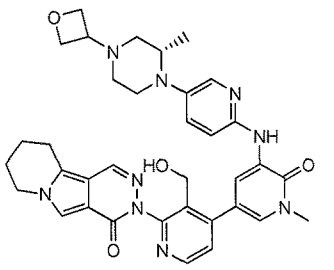
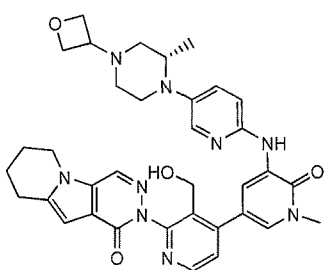
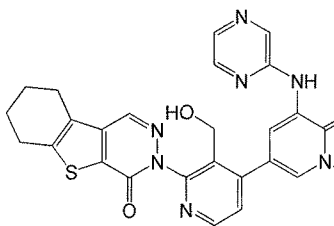
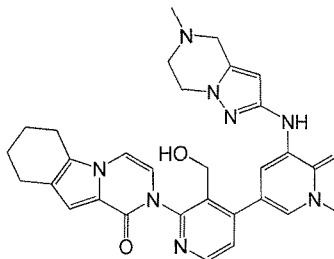
174 * —		(1R,11S)-6-[3-(Hydroxymethyl)-4-[1-methyl-5-({5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]pyridin-2-yl} amino)-6-oxo-1,6-dihydropyridin-3-yl]pyridin-2-yl]-3,6-diazatetracyclo[9.2.1.0 ^{2,10} .0 ^{3,8}]tetradeca-2(10),8-dien-7-one	662.78	0.101
175 * —		3-{5-[5-((S)-2-Ethyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-3'-hydroxymethyl-1-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one	680.82	0.0466
176 * —		(S)-2-(3-(hydroxymethyl)-4-(1-methyl-5-(5-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)pyridin-2-yl)-6,7,8,9-tetrahydropyrazino[1,2-a]indol-1(2H)-one	648.75	0.0375
177 * —		2-(4-(5-(5-ethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-3-(hydroxymethyl)pyridin-2-yl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	568.67	0.107
178 * —		3-[3'-Hydroxymethyl-1-methyl-6-oxo-5-(pyridin-2-ylamino)-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one	512.58	1.1

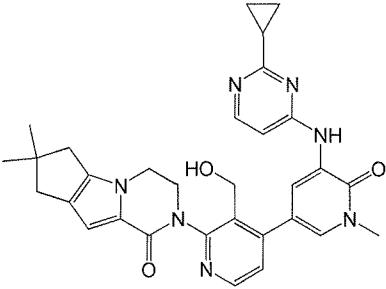
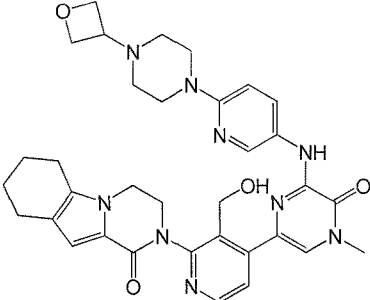
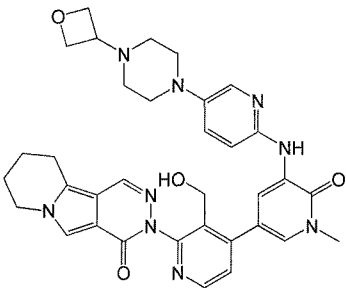
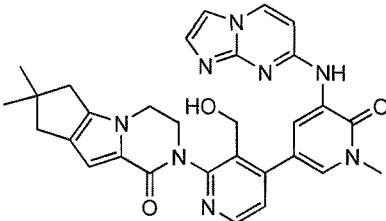
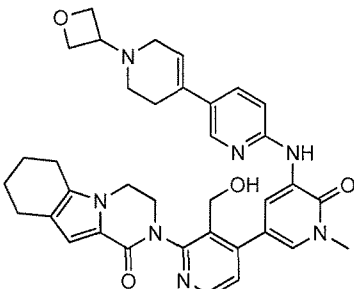
179		2-[3'-Hydroxymethyl-1-methyl-5-(2-methyl-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl)-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	525.60	0.209
180		2-[3'-Hydroxymethyl-1-methyl-5-(6-methyl-pyrimidin-4-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	525.60	0.245
181 * —		3-[3'-Hydroxymethyl-1-methyl-5-(5-methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazin-2-ylamino)-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one	570.67	0.144
182 * —		3-[3'-Hydroxymethyl-1-methyl-6-oxo-5-(pyrimidin-4-ylamino)-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-6,7,8,9-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyridazin-4-one	513.57	0.813
183 * —		10-fluoro-2-(3-(hydroxymethyl)-4-(1-methyl-6-oxo-5-(pyridin-2-ylamino)-1,6-dihydropyridin-3-yl)pyridin-2-yl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	514.55	0.906
184 * —		6-[3'-Hydroxymethyl-1-methyl-6-oxo-5-(pyrazin-2-ylamino)-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-2,2-dimethyl-2,3,5,6-tetrahydro-1H,4H-8-thia-6-azacyclopenta[a]inden-7-one	528.63	0.601

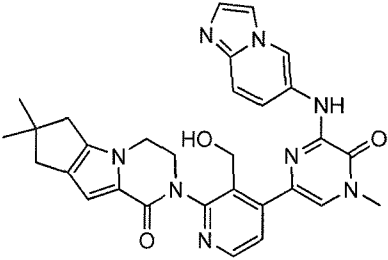
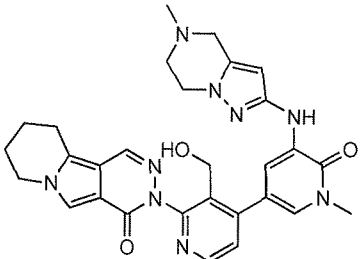
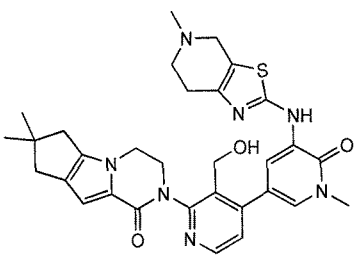
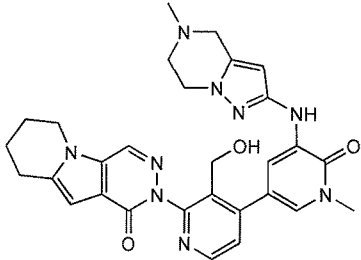
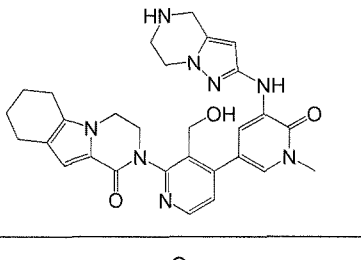
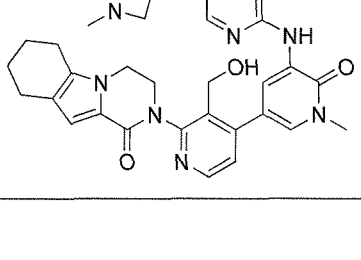
185		2-{3-Hydroxymethyl-4-[6-(imidazo[1,2-a]pyridin-7-ylamino)-4-methyl-5-oxo-4,5-dihydro-pyrazin-2-yl]-pyridin-2-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	550.61	1.3
186 * —		10-fluoro-2-(3-(hydroxymethyl)-4-(4-methyl-5-oxo-6-(pyridin-3-ylamino)-4,5-dihydro-pyrazin-2-yl)pyridin-2-yl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	515.54	1.6
187 * —		2-(4-(5-(5-(2,2-dimethyl-4-oxetan-3-yl)piperazin-1-yl)pyridin-2-ylamino)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-3-(hydroxymethyl)pyridin-2-yl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	664.80	0.0451
188		2-[3'-Hydroxymethyl-1-methyl-6-oxo-5-(pyrazin-2-ylamino)-1,6-dihydro-[3,4']bipyridinyl-2'-yl]-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	511.57	0.601
189 * —		2-(3-(hydroxymethyl)-4-(1-methyl-5-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyrazin-2-ylamino)-6-oxo-1,6-dihydropyridin-3-yl)pyridin-2-yl)-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1(2H)-one	637.73	0.652

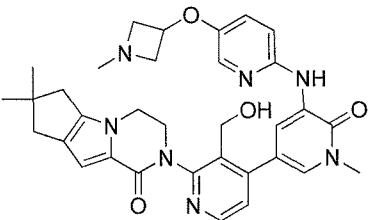
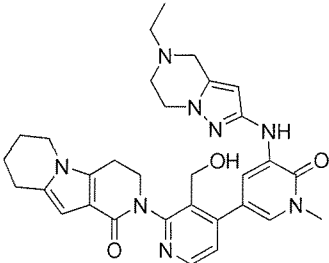
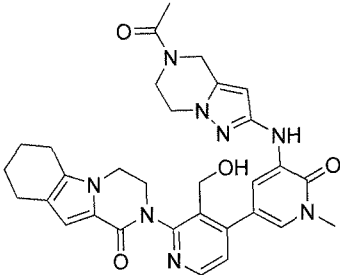
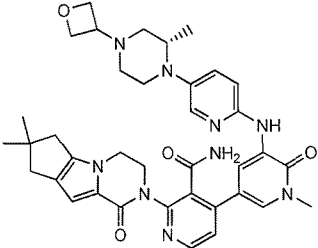
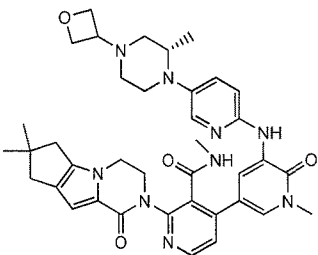
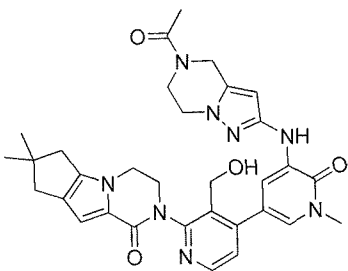
Table 2.

No.	Structure	IUPAC Name	CD69 Hu Blood FACS (IC70)

190 *		2-[4-[5-[[5-[2,2-dimethyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.0704
191 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-6,7,8,9-tetrahydrobenzothiopheno[2,3-d]pyridazin-4-one	0.0435
192 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,8,9,10-tetrahydropyridazino[4,5-a]indolizin-4-one	1.1
193 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-6,7,8,9-tetrahydropyridazino[4,5-b]indolizin-1-one	0.0995
194 *		3-[3-(hydroxymethyl)-4-[1-methyl-6-oxo-5-(pyrazin-2-ylamino)-3-pyridyl]-2-pyridyl]-6,7,8,9-tetrahydrobenzothiopheno[2,3-d]pyridazin-4-one	1.2
195 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-6,7,8,9-tetrahydropyrazino[1,2-a]indol-1-one	0.101

196		3-[4-[5-[(2-cyclopropylpyrimidin-4-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.325
197 *		2-[3-(hydroxymethyl)-4-[4-methyl-6-[[6-[4-(oxetan-3-yl)piperazin-1-yl]-3-pyridyl]amino]-5-oxo-pyrazin-2-yl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	2.3
198 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,8,9,10-tetrahydropyridazino[4,5-a]indolizin-4-one	6
199		3-[3-(hydroxymethyl)-4-[5-(imidazo[1,2-a]pyrimidin-7-ylamino)-1-methyl-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.934
200 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[1-(oxetan-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.636

201		3-[3-(hydroxymethyl)-4-[6-(imidazo[1,2-a]pyridin-6-ylamino)-4-methyl-5-oxo-pyrazin-2-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	3.3
202 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,8,9,10-tetrahydropyridazino[4,5-a]indolizin-4-one	7.3
203		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-2-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0605
204 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-6,7,8,9-tetrahydropyridazino[4,5-b]indolizin-1-one	0.436
205 *		2-[3-(hydroxymethyl)-4-[1-methyl-6-oxo-5-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.114
206 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(1-methylazetidin-3-yl)oxy-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.15

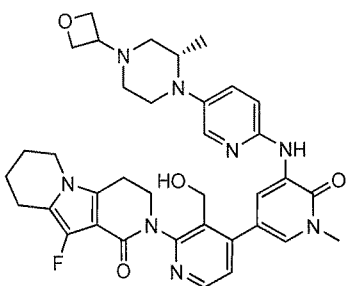
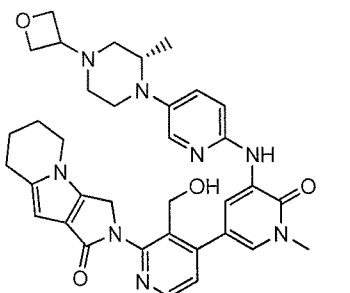
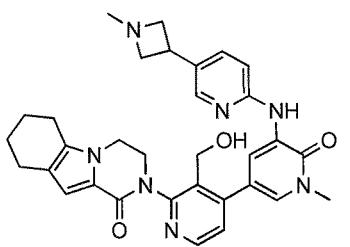
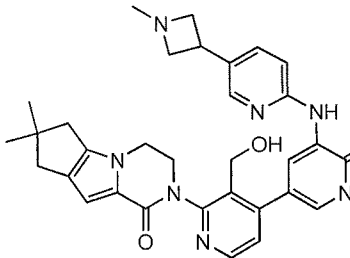
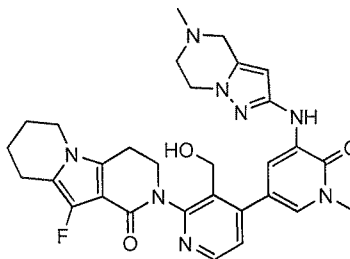
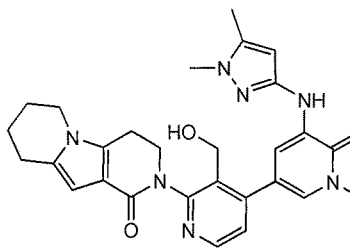
207		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(1-methylazetidin-3-yl)oxy-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.0414
208 *		2-[4-[5-[(5-ethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1-one	0.58
209 *		2-[4-[5-[(5-acetyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.116
210 *		2-(7,7-dimethyl-4-oxo-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-3-yl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]pyridine-3-carboxamide	0.914
211 *		2-(7,7-dimethyl-4-oxo-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-3-yl)-N-methyl-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]pyridine-3-carboxamide	2.1
212		3-[4-[5-[(5-acetyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.0152

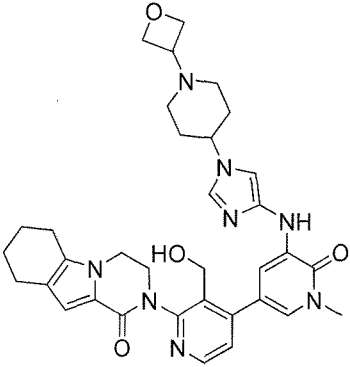
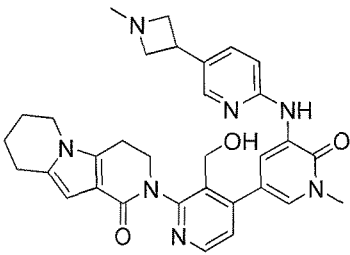
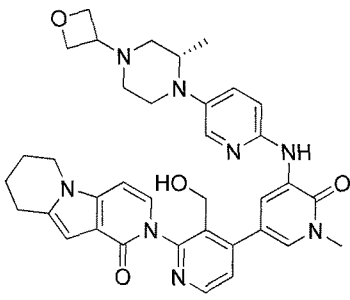
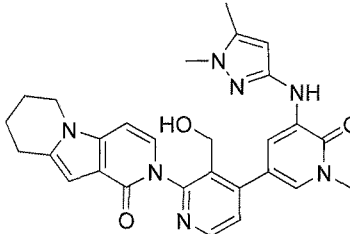
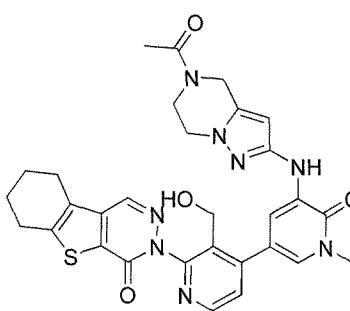
213 *		10-fluoro-2-[3-(hydroxymethyl)-4-[1-methyl-5-[(2-methylpyrimidin-4-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.62
214		3-[4-[5-(6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-ylamino)-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.124
215		3-[4-(hydroxymethyl)-5-[1-methyl-5-[(2-methylpyrimidin-4-yl)amino]-6-oxo-3-pyridyl]-3-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.457
216 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-2-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-6,7,8,9-tetrahydrobenzothiopheno[2,3-d]pyridazin-4-one	0.357
217 *		2-[3-(hydroxymethyl)-4-[5-(1H-imidazo[4,5-b]pyridin-5-ylamino)-1-methyl-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	2.9
218		3-[4-[5-[(1,5-dimethylpyrazol-3-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0741

219		3-[4-[6-(3-aminoanilino)-4-methyl-5-oxo-pyrazin-2-yl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.204
220 *		5-[2-(3,4,6,7,8,9-hexahydro-1H-pyrazino[1,2-a]indol-2-yl)-3-(hydroxymethyl)-4-pyridyl]-1-methyl-3-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]pyridin-2-one	1.6
221		3-[4-[5-[(6-amino-2-pyridyl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.121
222		3-[3-(hydroxymethyl)-4-[5-[(2-methylpyrimidin-4-yl)amino]-6-oxo-1H-pyridin-3-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.178
223 *		10-fluoro-2-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-2-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.43
224		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-pyridazin-3-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0307

225		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(2-methylpyrimidin-4-yl)amino]-6-oxo-pyridazin-3-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.766
226		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(morpholine-4-carbonyl)-2-pyridyl]amino]-6-oxo-pyridazin-3-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.117
227 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(morpholine-4-carbonyl)-2-pyridyl]amino]-6-oxo-pyridazin-3-yl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.73
228 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]pyrazin-2-yl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.369
229		3-[4-[5-[(2-ethylpyrimidin-4-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.583
230 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]pyrazin-2-yl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-6,7,8,9-tetrahydrobenzothiopheno[2,3-d]pyridazin-4-one	0.179

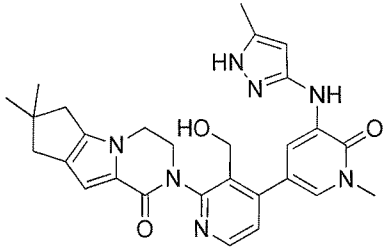
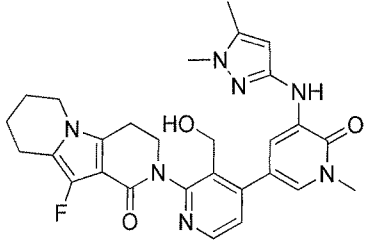
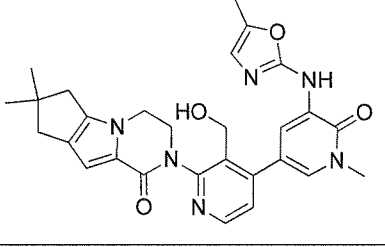
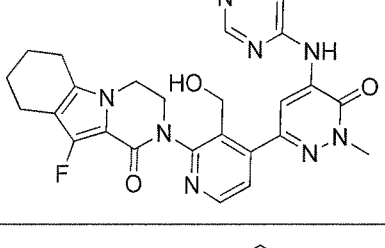
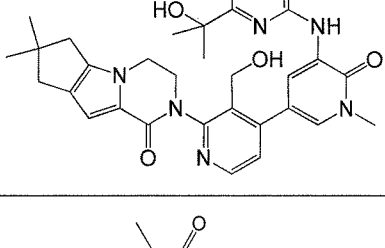
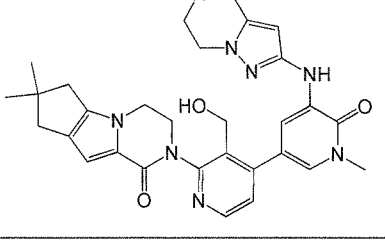
231 *		10-fluoro-2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-pyridazin-3-yl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.0624
232 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(1-methyl-4-piperidyl)-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.0518
233		3-[3-(hydroxymethyl)-4-[1-methyl-6-oxo-5-(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-ylamino)-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0657
234 *		2-[4-[5-[(5-acetyl-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-10-fluoro-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.183
235		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]pyrazin-2-yl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.112
236		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(1-methyl-4-piperidyl)-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0336

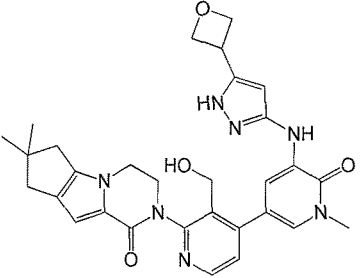
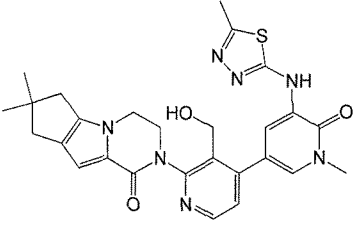
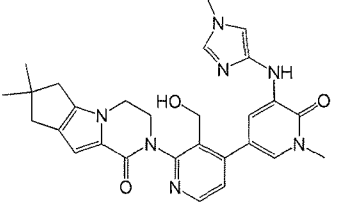
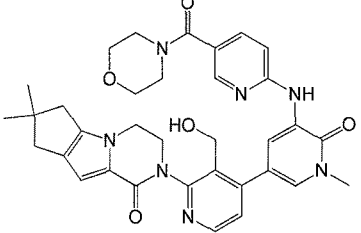
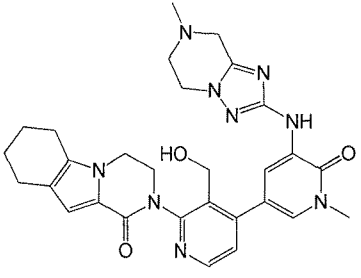
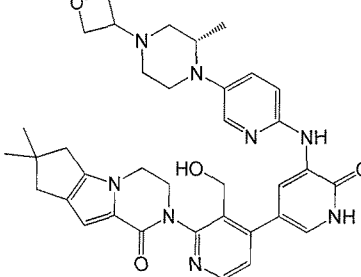
237 *		10-fluoro-2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1-one	0.0461
238 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-5,6,7,8-tetrahydro-1H-pyrrolo[3,4-b]indolizin-3-one	5
239 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(1-methylazetidin-3-yl)-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.153
240		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(1-methylazetidin-3-yl)-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0229
241 *		10-fluoro-2-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1-one	0.19
242 *		2-[4-[5-[(1,5-dimethylpyrazol-3-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1-one	1.2

243 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[1-[1-(oxetan-3-yl)-4-piperidyl]imidazol-4-yl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	2.8
244 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(1-methylazetidin-3-yl)-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1-one	0.138
245 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-6,7,8,9-tetrahydropyrido[3,4-b]indolizin-1-one	0.065
246 *		2-[4-[5-[(1,5-dimethylpyrazol-3-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-6,7,8,9-tetrahydropyrido[3,4-b]indolizin-1-one	1.7
247 *		3-[4-[5-[(5-acetyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-6,7,8,9-tetrahydrobenzothiopheno[2,3-d]pyridazin-4-one	0.145

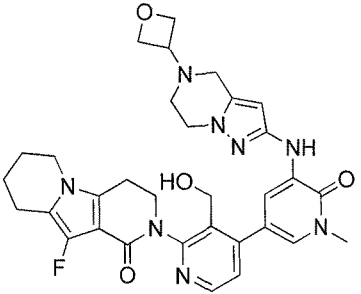
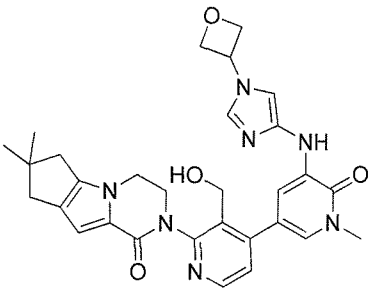
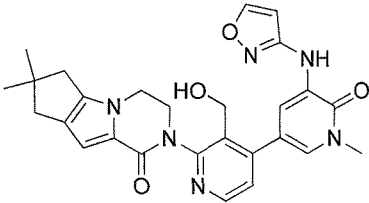
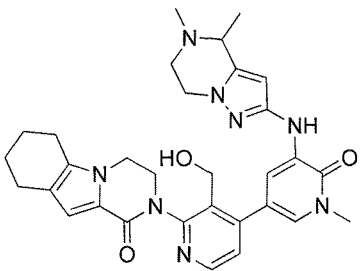
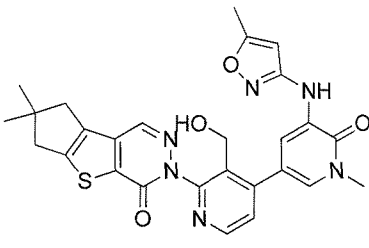
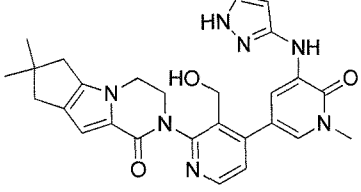
248		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(3R)-3-methylmorpholin-4-carbonyl]-2-pyridyl]amino]-6-oxo-pyridazin-3-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.0703
249		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(3R)-3-methylmorpholin-4-carbonyl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.0177
250 *		2-[4-[5-[(5,6-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.171
251			
252		3-[4-[5-[(1-ethyl-5-methyl-pyrazol-3-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.252
253		3-[3-(hydroxymethyl)-4-[5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-1H-pyridazin-3-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.0164

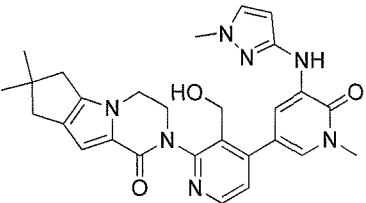
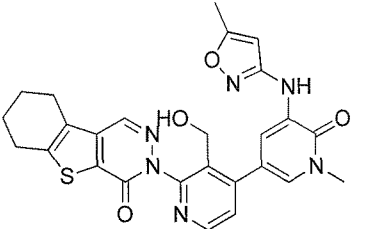
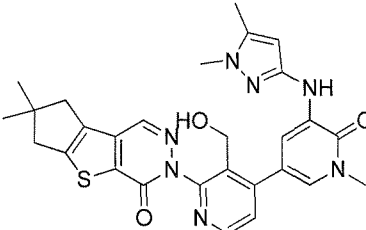
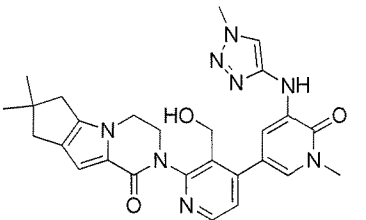
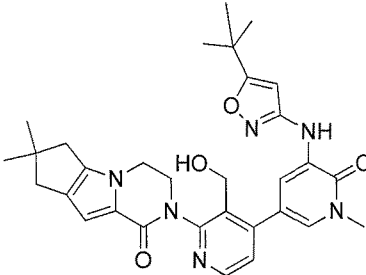
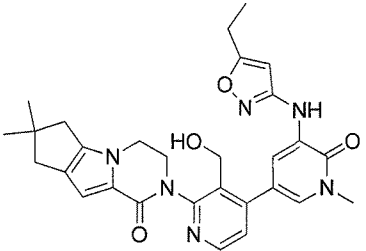
254 *		3-[4-[5-[(5-acetyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]thieno[1,3-c]pyridin-4-one	0.0373
255 *		2-[4-[5-[(5-acetyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-10-fluoro-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.094
256		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(3S)-3-methylmorpholine-4-carbonyl]-2-pyridyl]amino]-6-oxo-pyridazin-3-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.08
257		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(3S)-3-methylmorpholine-4-carbonyl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0216
258 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(morpholine-4-carbonyl)-2-pyridyl]amino]-6-oxo-pyridazin-3-yl]-2-pyridyl]-6,7,8,9-tetrahydrobenzothiopheno[2,3-d]pyridazin-4-one	0.646
259 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(morpholine-4-carbonyl)-2-pyridyl]amino]-6-oxo-pyridazin-3-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]thieno[1,3-c]pyridin-4-one	0.301

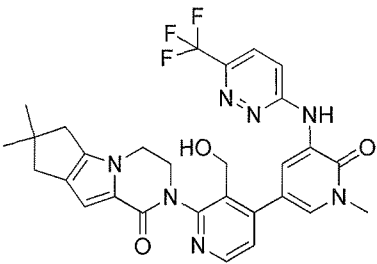
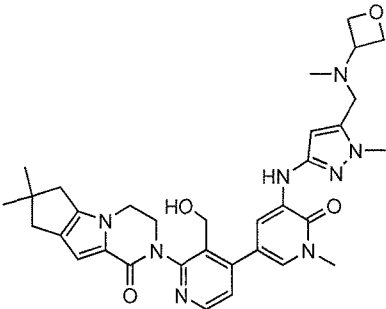
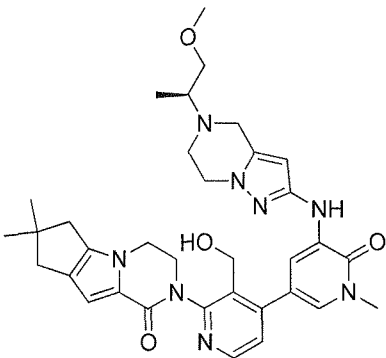
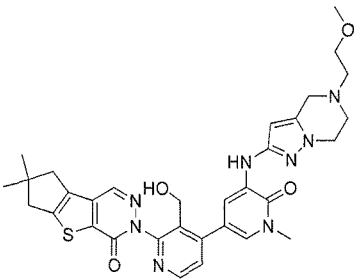
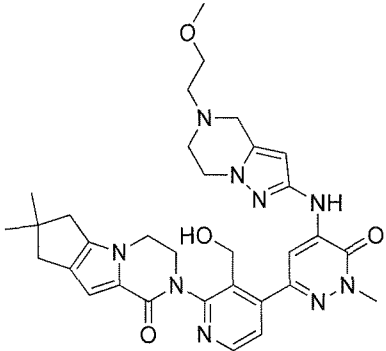
260		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-1H-pyrazol-3-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0606
261 *		2-[4-[5-[(1,5-dimethylpyrazol-3-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-10-fluoro-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1-one	2.9
262		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methoxy-1H-pyrazol-2-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.577
263 *		10-fluoro-2-[3-(hydroxymethyl)-4-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)pyridazin-3-yl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	2.2
264		3-[3-(hydroxymethyl)-4-[5-[[2-(1-hydroxy-1-methylethyl)pyrimidin-4-yl]amino]-1-methyl-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.653
265		3-[3-(hydroxymethyl)-4-[1-methyl-6-oxo-5-[(5-propanoyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0091

266		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(oxetan-3-yl)-1H-pyrazol-3-yl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0293
267		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.225
268		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(1-methylimidazol-4-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.212
269		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(morpholine-4-carbonyl)-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0251
270 *		2-[3-(hydroxymethyl)-4-[1-methyl-5-[(7-methyl-6,8-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	5.9
271		3-[3-(hydroxymethyl)-4-[5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-1H-pyridin-3-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0245

278		3-[4-[5-[(5-cyclopropyl-2-pyridyl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	3.2
279		3-[3-(hydroxymethyl)-4-[1-methyl-6-oxo-5-[[5-(trifluoromethyl)-2-pyridyl]amino]-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	2.1
280		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[1-methyl-5-(morpholine-4-carbonyl)pyrazol-3-yl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.0141
281		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-2-pyridyl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.718
282 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]-2-pyridyl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-6,8-dihydrocyclopenta[3,4]thieno[1,3-d]pyridazin-4-one	0.0174
283		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methylisoxazol-3-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.143

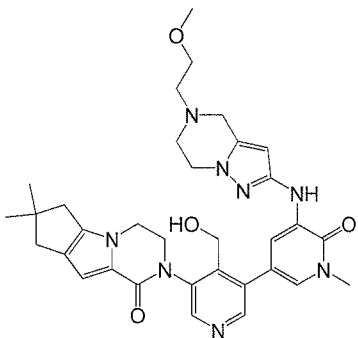
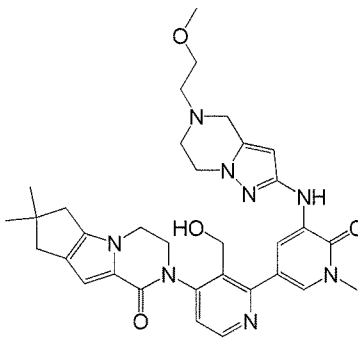
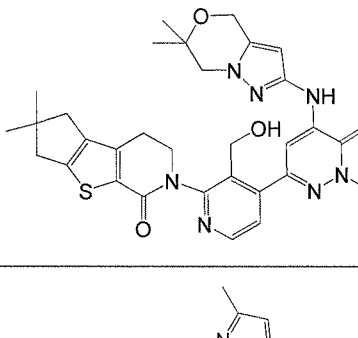
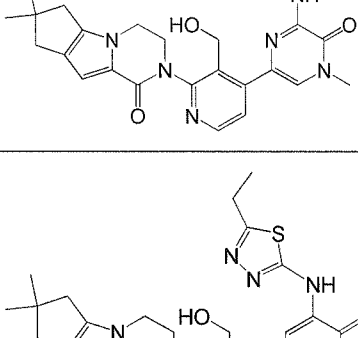
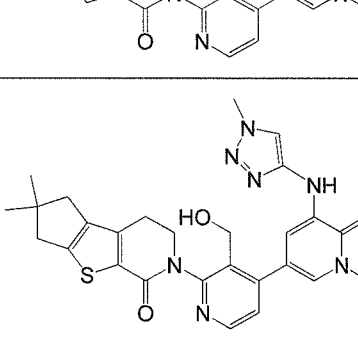
284 *		10-fluoro-2-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-(oxetan-3-yl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1-one	0.131
285		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[1-(oxetan-3-yl)imidazol-4-yl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.175
286		3-[3-(hydroxymethyl)-4-[5-(isoxazol-3-ylamino)-1-methyl-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.167
287 *		2-[4-[5-[(4,5-dimethyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.127
288 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methylisoxazol-3-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-6,8-dihydrocyclopenta[3,4]thieno[1,3-d]pyridazin-4-one	0.229
289		3-[3-(hydroxymethyl)-4-[1-methyl-6-oxo-5-(1H-pyrazol-3-ylamino)-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.214

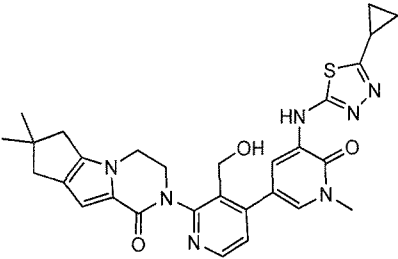
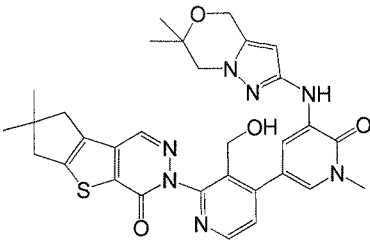
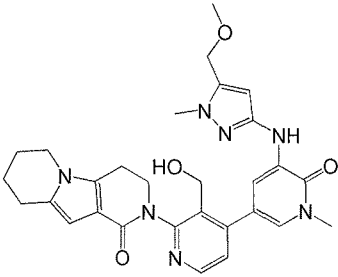
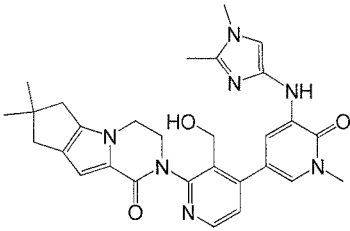
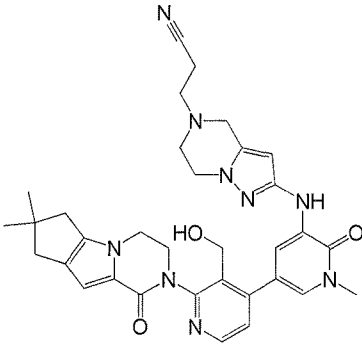
290		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(1-methylpyrazol-3-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.113
291 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methylisoxazol-3-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-6,7,8,9-tetrahydrobenzothiopheno[2,3-d]pyridazin-4-one	0.843
292 *		3-[4-[5-[(1,5-dimethylpyrazol-3-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-6,8-dihydrocyclopenta[3,4]thieno[1,3-d]pyridazin-4-one	0.118
293		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(1-methyltriazol-4-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.0691
294		3-[4-[5-[(5-tert-butylisoxazol-3-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.276
295		3-[4-[5-[(5-ethylisoxazol-3-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.134

301		3-[3-(hydroxymethyl)-4-[1-methyl-6-oxo-5-[[6-(trifluoromethyl)pyridazin-3-yl]amino]-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	1.3
302		3-[3-(hydroxymethyl)-4-[1-methyl-5-[[1-methyl-5-[[methyl(oxetan-3-yl)amino]methyl]pyrazol-3-yl]amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0228
303		(S)-2-(3'-(hydroxymethyl)-5-((5-(1-methoxypropan-2-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)amino)-1-methyl-6-oxo-1,6-dihydro-[3,4'-bipyridin]-2'-yl)-7,7-dimethyl-2,3,4,6,7,8-hexahydro-1H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	0.0179
304 *		3-[3-(hydroxymethyl)-4-[5-[[5-(2-methoxyethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]amino]-1-methyl-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-6,8-dihydrocyclopenta[3,4]thieno[1,3-d]pyridazin-4-one	0.04
305		3-[3-(hydroxymethyl)-4-[5-[[5-(2-methoxyethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]amino]-1-methyl-6-oxo-pyridazin-3-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0832

306		3-[3-(hydroxymethyl)-4-[5-[(6-methoxypyridazin-3-yl)amino]-1-methyl-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.602
307		3-[4-[6-[(1,3-dimethylindazol-5-yl)amino]-4-methyl-5-oxo-pyrazin-2-yl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	
308 *		3-[3-(hydroxymethyl)-4-[5-[[5-(2-methoxyethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]amino]-1-methyl-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]thieno[1,3-c]pyridin-4-one	0.0546
309		3-[3-(hydroxymethyl)-4-[5-[[5-(3-methoxypropyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]amino]-1-methyl-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.0398
310		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methylisothiazol-3-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo [3,5-b]pyrazin-4-one	0.119

317 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(5-methyl-6-oxo-4,7-dihydropyrazolo[1,5-a]pyrazin-2-yl)amino]-6-oxo-3-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]thieno[1,3-c]pyridin-4-one	0.0586
318		(R)-2-(5-((4,5-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)amino)-3'-(hydroxymethyl)-1-methyl-6-oxo-1,6-dihydro-[3,4'-bipyridin]-2'-yl)-7,7-dimethyl-2,3,4,6,7,8-hexahydro-1H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	0.108
319		(S)-2-(5-((4,5-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)amino)-3'-(hydroxymethyl)-1-methyl-6-oxo-1,6-dihydro-[3,4'-bipyridin]-2'-yl)-7,7-dimethyl-2,3,4,6,7,8-hexahydro-1H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one	0.0167
320		3-[4-[5-[[5-[(3S,5R)-3,5-dimethylmorpholine-4-carbonyl]-2-pyridyl]amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0468
321		3-[4-[5-[[5-[(3S,5R)-3,5-dimethylmorpholine-4-carbonyl]-2-pyridyl]amino]-1-methyl-6-oxo-pyridazin-3-yl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.112
322 *		2-[4-[5-[[5-[(3S,5R)-3,5-dimethylmorpholine-4-carbonyl]-2-pyridyl]amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-3,4,6,7,8,9-hexahydropyrazino[1,2-a]indol-1-one	0.0796

328		3-[4-(hydroxymethyl)-5-[[5-[(2-methoxyethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]amino]-1-methyl-6-oxo-3-pyridyl]-3-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0124
329		3-[3-(hydroxymethyl)-2-[[5-[(2-methoxyethyl)-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-2-yl]amino]-1-methyl-6-oxo-3-pyridyl]-4-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.11
330 *		3-[4-[5-[(6,6-dimethyl-4,7-dihydropyrazolo[5,1-c][1,4]oxazin-2-yl)amino]-1-methyl-6-oxo-pyridazin-3-yl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]thieno[1,3-c]pyridin-4-one	0.235
331		3-[3-(hydroxymethyl)-4-[4-methyl-6-[(3-methylisothiazol-5-yl)amino]-5-oxo-pyrazin-2-yl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	
332		3-[4-[5-[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.0919
333 *		3-[3-(hydroxymethyl)-4-[1-methyl-5-[(1-methyl-1,2,4-triazol-4-yl)amino]-6-oxo-3-pyridyl]-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]thieno[1,3-c]pyridin-4-one	0.209

334		3-[4-[5-[(5-cyclopropyl-1,3,4-thiadiazol-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.193
335 *		3-[4-[5-[(6,6-dimethyl-4,7-dihydropyrazolo[5,1-c][1,4]oxazin-2-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-6,8-dihydrocyclopenta[3,4]thieno[1,3-d]pyridazin-4-one	0.0528
336 *		2-[3-(hydroxymethyl)-4-[5-[[5-(methoxymethyl)-1-methyl-pyrazol-3-yl]amino]-1-methyl-6-oxo-3-pyridyl]-2-pyridyl]-3,4,6,7,8,9-hexahydropyrido[3,4-b]indolizin-1-one	0.33
337		3-[4-[5-[(1,2-dimethylimidazol-4-yl)amino]-1-methyl-6-oxo-3-pyridyl]-3-(hydroxymethyl)-2-pyridyl]-7,7-dimethyl-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-4-one	0.613
338		3-[2-[[5-[2-(7,7-dimethyl-4-oxo-1,2,6,8-tetrahydrocyclopenta[3,4]pyrrolo[3,5-b]pyrazin-3-yl)-3-(hydroxymethyl)-4-pyridyl]-1-methyl-2-oxo-3-pyridyl]amino]-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl]propanenitrile	0.0178

The compounds of Formula I may be employed alone or in combination with other therapeutic agents for the treatment of a disease or disorder described herein, such as inflammation or a hyperproliferative disorder (e.g., cancer). In certain embodiments, a compound of Formula I is combined in a pharmaceutical combination formulation, or dosing regimen as combination therapy, with an additional, second therapeutic compound that has anti-inflammatory or anti-hyperproliferative properties or that is useful for treating an inflammation, immune-response disorder, or hyperproliferative disorder (e.g., cancer). The additional therapeutic may be an anti-inflammatory agent, an immunomodulatory agent, chemotherapeutic agent, an apoptosis-enhancer, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders. The second therapeutic agent may be an NSAID anti-inflammatory agent. The second therapeutic agent may be a chemotherapeutic agent. The second compound of the pharmaceutical combination formulation or dosing regimen preferably has complementary activities to the compound of Formula I such that they do not adversely affect each other. Such compounds are suitably present in combination in amounts that are effective for the purpose intended. In one embodiment, a composition of this invention comprises a compound of Formula I, or a stereoisomer, tautomer, solvate, ~~metabolite, or pharmaceutically acceptable salt or pro-drug thereof,~~ in combination with a therapeutic agent such as an NSAID.

The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes coadministration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities.

Suitable dosages for any of the above coadministered agents are those presently used and may be lowered due to the combined action (synergy) of the newly identified agent and other therapeutic agents or treatments.

The combination therapy may provide "synergy" and prove "synergistic", i.e., the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined, unit dosage formulation; (2) delivered by alternation or in

parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., by different injections in separate syringes, separate pills or capsules, or separate infusions. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e., serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

In a particular embodiment of therapy, a compound of Formula I, or a stereoisomer, tautomer, solvate, ~~metabolite~~, or pharmaceutically acceptable salt or ~~prodrug~~ thereof, may be combined with other therapeutic, hormonal or antibody agents such as those described herein, as well as combined with surgical therapy and radiotherapy. Combination therapies according to the present invention thus comprise the administration of at least one compound of Formula I, or a stereoisomer, tautomer, solvate, ~~metabolite~~, or pharmaceutically acceptable salt or ~~prodrug~~ thereof, and the use of at least one other cancer treatment method. The amounts of the compound(s) of Formula I and the other pharmaceutically active therapeutic agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

METABOLITES OF COMPOUNDS OF FORMULA I

Also falling within the scope of this invention are the *in vivo* metabolic products of Formula I described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of Formula I, including compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

Metabolite products typically are identified by preparing a radiolabelled (e.g., ¹⁴C or ³H) isotope of a compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS, LC/MS or NMR analysis. In

5. A volume of CellTiter-Glo Reagent equal to the volume of cell culture medium present in each well is added.

6. The contents are mixed for 2 minutes on an orbital shaker to induce cell lysis.

7. The plate is incubated at room temperature for 10 minutes to stabilize the
5 luminescence signal.

8. Luminescence is recorded and reported in graphs as RLU = relative luminescence units.

10 Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. Accordingly, all suitable modifications and equivalents may be considered to fall within the scope of the invention as defined by the claims that follow. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

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