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(54) Title: KRAS G12D INHIBITORS

(57) Abstract: The present invention relates to compounds that inhibit KRas G12D. In particular, the present invention relates to compounds that inhibit the activity of KRas G12D, pharmaceutical compositions comprising the compounds and methods of use therefor.

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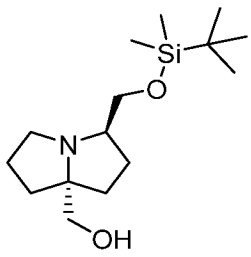
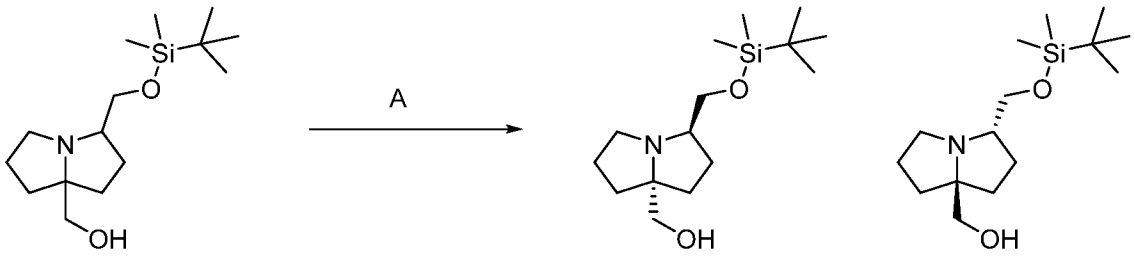


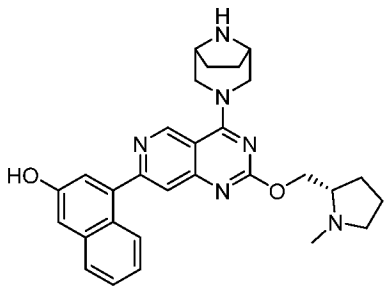
((3R,7aR)-3-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



A mixture of (3-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol was separated by Lotus Separations using chiral SFC using an AD-H (3x25 cm) column injecting with 1 mL of a 20 mg/ mL solution of compound in methanol eluting with 20% methanol/CO_2 at 100 bar of pressure with 70 mL/min. flow rate and monitoring 220 nM.

[0280] The following Examples are intended to illustrate further certain embodiments of the invention and are not intended to limit the scope of the invention.

EXAMPLE 1



4-(4-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol tris-hydrochloride salt

[01574] Briefly, 1L of 1.05X HBS-Mg buffer (262.5mM Bioultra Hepes, pH 7.5, 157.5mM NaCl, 105mM $MgCl_2$, 0.525mM TCEP, 0.0305% Brij-35) was prepared and filter sterilized using a 0.22µm bottle top filter. Approximately 50mL of 1.05X HBS-Mg buffer was removed and saved for future dilutions. A 50mL aliquot of DMSO (Sigma Aldrich DMSO Lot. #SHBK2079) was added and continued to stir for 10 minutes, creating the final 1.0X HBS-Mg buffer (250mM Bioultra Hepes pH 7.5, 150mM NaCl, 100mM $MgCl_2$, 0.5mM TCEP, 0.03% Brij-35).

[01575] Biacore T200 instrument was primed using 1.0X HBS-Mg buffer before docking a GE Streptavidin (SA) chip and then primed two additional times prior to beginning the immobilization step. All immobilized protein mixtures were created using 3-5mg/mL Biotinylated Avidin-tagged KRAS protein using the following immobilization settings: SA chip type, 1 flow cells per cycle, 720 second contact time, and 5ul/min flow rate. Normalization of the detector was also performed during the immobilization step using the GE BiaNormalize solution.

[01576] All compounds were diluted to 10mM in 100% DMSO prior to being diluted 20X in 1.05X buffer. Another 10X dilution was created using 1.0X buffer prior to performing a series of 3X dilutions to create a compound concentration curve using the following assay settings: 20C analysis temperature, General Settings=10Hz data collection rate and multi-detection; Assay Steps=all set to LMW kinetics; Cycle Types=LMW kinetics (60s contact time, 120s dissociation time, 100ul/min flow rate, extra wash after injection with 50% DMSO, flow path 1,2,3,4); Flow path detection=2-1, 4-3). Data evaluation was performed using the Biacore T200 Evaluation software and data fit to 1:1 binding model.

[01577] The results for exemplary compounds of Formula (I) are shown in Table 1. ND = not determined.

Table 1

Determination of KRas G12D K_D for Exemplary Compounds of Formula (I)

Example No.	K_D (nM)	Example No.	K_D (nM)
1	97.7	86	527559.5
2	2.4	87	195.8
3	8.3	88	15593.2

HEPES [pH 7.5], 5mM $MgCl_2$, 0.005% Tween-20 & 1 mM DTT). After a 60 minute incubation at 22°C, the reaction was measured using a PerkinElmer EnVision multimode plate reader via TR-FRET dual wavelength detection, and the percent of control (POC) calculated using a ratiometric emission factor. 100 POC is determined using no test compound and 0 POC is determined using a concentration of control compound that completely inhibits binding of the tracer to KRAS. The POC values were fit to a 4-parameter logistic curve and the IC_{50} value was determined as the concentration where the curve crosses 50 POC.

[01580] The results for exemplary compounds of Formula (I) are shown in Table 2. ND stands for "not determined."

Table 2

Binding to KRas G12D by Exemplary Compounds of Formula (I)

Example No.	IC_{50} (nM)	Example No.	IC_{50} (nM)
1	124.7	235	1.2
2	2.7	236	25.0
3	9.5	237	500.3
4	496.2	238	16.1
5	722.9	239	2.0
6	434.1	240	314.8
7	1867.3	241	79.2
8	1522.0	242	82.2
9	820.7	243	0.4
14	73.9	244	4.2
15	260.3	245	0.5
16	54.1	246	0.6
17	666.2	247	12.6
18	76.8	248	3.2
19	122.0	249	3.5
20	691.8	250	28.2
21	262.9	251	0.2
22	50.3	252	0.4
24	7.9	253	0.8
25	338.4	254	6.1
26	42.1	255	8.7
29	160.4	256	13.2
30	417.6	257	5.1