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(54) **Title:** CRYSTALLINE DIPEPTIDES USEFUL IN THE SYNTHESIS OF ELAMIPRETIDE

(57) **Abstract:** Disclosed are crystalline forms of L-Lys(Boc)-Phe-NH₂ and Boc-D-Arg-DMT.



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Crystalline Dipeptides Useful in the Synthesis of Elamipretide

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application No. 62/651,430, filed April 2, 2018.

BACKGROUND OF THE INVENTION

[0001] Elamipretide (MTP-131) is a mitochondria-targeting peptide compound with therapeutic potential for treating diseases associated with mitochondrial dysfunction. Elamipretide contains four-amino acid residues and has been synthesized according to typical linear and convergent solution phase peptide synthesis methods. The synthetic routes to generate elamipretide that have been used to date require the preparation of various differentially protected peptides, such that certain protecting groups are selectively removed in order to subject the deprotected compound to peptide coupling, while other protecting groups remain to prevent unwanted side reactions. Even with protecting groups such coupling reactions and related steps generate impurities. Thus, there exists a need to develop new methods to purify elamipretide that allow the purification after coupling reactions. Crystallization of the desired reaction products are one method of achieving the necessary purification.

SUMMARY OF THE INVENTION

[0002] Disclosed are crystalline forms of L-Lys(Boc)-Phe-NH₂ and Boc-D-Arg-DMT, wherein DMT is an abbreviation for dimethyltyrosine, which are intermediates in the synthesis of elamipretide.

BRIEF DESCRIPTION OF THE DRAWINGS

[0003] **Figure 1** is the XRPD pattern of crystalline L-Lys(Boc)-Phe-NH₂.

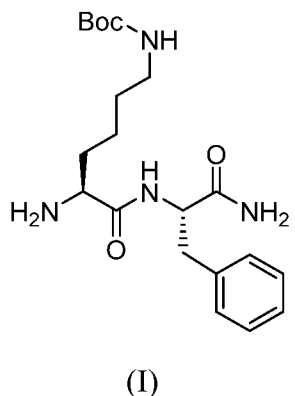
[0004] **Figure 2** is the XRPD pattern crystalline Boc-D-Arg-DMT.

DETAILED DESCRIPTION OF THE INVENTION

[0005] Elamipretide has been shown to have various therapeutic effects in diseases related to mitochondrial dysfunction. Previous synthetic routes to elamipretide presented challenges with respect to scale-up due to reliance on chromatographic separations to enrich levels of desired intermediates. Herein are disclosed crystalline forms of L-Lys(Boc)-Phe-NH₂ and

Boc-D-Arg-DMT, which can be used as purified intermediates in the synthesis of elamipretide.

[0006] One aspect of the present invention relates to crystalline forms of Compound (I):



which compound is also known as L-Lys(Boc)-Phe-NH₂.

[0007] A crystalline form of Compound (I) can be used in the synthesis of elamipretide.

[0008] In certain embodiments, a polymorph of the crystalline form is characterized by powder X-ray diffraction (XRD). θ represents the diffraction angle, measured in degrees. In certain embodiments, the diffractometer used in XRD measures the diffraction angle as two times the diffraction angle θ . Thus, in certain embodiments, the diffraction patterns described herein refer to X-ray intensity measured against angle 2θ .

[0009] In certain embodiments, a crystalline form of Compound (I) is not solvated (e.g., the crystal lattice does not comprise molecules of a solvent). In certain alternative embodiments, a crystalline form of Compound (I) is solvated. In some cases, the solvent is water.

[0010] In one aspect, the invention features a crystalline form of Compound (I) which has characteristic peaks in the powder X-ray diffraction (XRPD) pattern as shown in Figure 1.

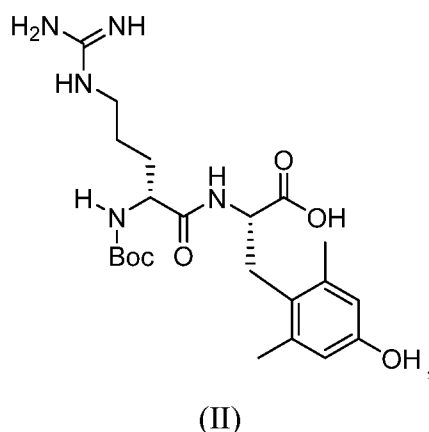
[0011] In another aspect, the invention features a crystalline form of Compound (I) which has characteristic peaks in the powder X-ray diffraction (XRPD) pattern at values of two theta ($^{\circ} 2\theta$) as shown in Table 1.

[0012] In another aspect, the invention features a crystalline form of Compound (I) which has characteristic peaks in the powder X-ray diffraction (XRPD) pattern at values of two theta ($^{\circ} 2\theta$) of: 4.7, 6.2, 12.4, 15.8, 16.5, 18.0, 18.2, 18.8, and 19.8.

[0013] In another aspect, the invention features a crystalline form of Compound (I) which has characteristic peaks in the powder X-ray diffraction (XRPD) pattern at values of two theta ($^{\circ} 2\theta$) of: 4.7, 6.2, 11.3, 12.4, 13.3, 15.0, 15.8, 16.5, 17.0, 17.7, 18.0, 18.2, 18.8, 19.8, 22.0, and 22.8.

[0014] The relative intensity, as well as the two theta value, of each peak in Table 1, as well as in Figure 1, may change or shift under certain conditions, although the crystalline form is the same. One of ordinary skill in the art should be able to determine readily whether a given crystalline form is the same crystalline form as described in Table 1, as well as in Figure 1, by comparing their XRPD data.

[0015] One aspect of the present invention relates to a crystalline form of Compound (II):



which compound is also known as Boc-D-Arg-DMT, and may also be drawn in the form of a zwitterion.

[0016] A crystalline form of Compound (II) can be used in the synthesis of elamipretide.

[0017] In certain embodiments, a polymorph of the crystalline form is characterized by powder X-ray diffraction (XRD). θ represents the diffraction angle, measured in degrees. In certain embodiments, the diffractometer used in XRD measures the diffraction angle as two times the diffraction angle θ . Thus, in certain embodiments, the diffraction patterns described herein refer to X-ray intensity measured against angle 2θ .

[0018] In certain embodiments, a crystalline form of Compound (II) is not solvated (e.g., the crystal lattice does not comprise molecules of a solvent). In certain alternative embodiments, a crystalline form of Compound (II) is solvated. In some cases, the solvent is water.

[0019] In one aspect, the invention features a crystalline form of Compound (II) which has characteristic peaks in the powder X-ray diffraction (XRPD) pattern as shown in Figure 2.

[0020] In another aspect, the invention features a crystalline form of Compound (II) which has characteristic peaks in the powder X-ray diffraction (XRPD) pattern at values of two theta ($^{\circ} 2\theta$) as shown in Table 2.

[0021] In another aspect, the invention features a crystalline form of Compound (II) which has characteristic peaks in the powder X-ray diffraction (XRPD) pattern at values of two theta ($^{\circ} 2\theta$) of : 9.3, 12.1, 16.6, 17.6, 18.0, 18.8, and 19.4.

[0022] In another aspect, the invention features a crystalline form of Compound (II) which has characteristic peaks in the powder X-ray diffraction (XRPD) pattern at values of two theta ($^{\circ} 2\theta$) of : 9.3, 12.1, 13.7, 16.3, 16.6, 17.6, 18.0, 18.8, 19.4, 21.3, 23.0, 24.2, and 25.1.

[0023] The relative intensity, as well as the two theta value, of each peak in Table 2, as well as in Figure 2, may change or shift under certain conditions, although the crystalline form is the same. One of ordinary skill in the art should be able to determine readily whether a given crystalline form is the same crystalline form as described in Table 1, as well as in Figure 1, by comparing their XRPD data.

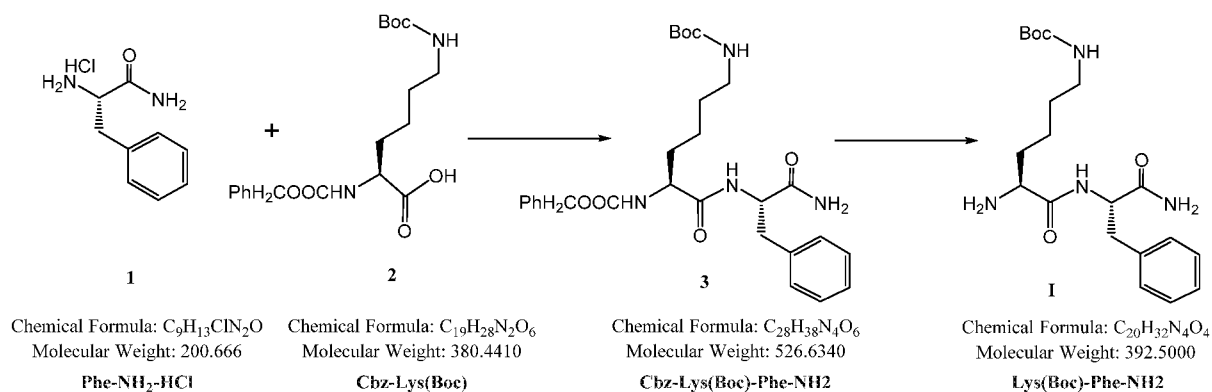
EXAMPLES

Materials and methods

Name	RM0858 General Method (2007)
Parent	2Theta
Sample Name	S-18-0011862 SOC-109
File Name	RM0858 General Method (2007)
Scan Type	Coupled TwoTheta/Theta
Scan Mode	Continuous PSD fast
Start	2.000
End	40.016
Step Size	0.050
Time per Step	192.00
Anode	Cu
k α 1	1.54
Generator kV	40.0
Generator mA	40.0
PSD Opening	2.940
Detector Slit Opening	
Primary Soller slit	2.500
Secondary Soller slit	2.500
Sample rotation speed	15.000
Divergence Slit	0.500
Antiscatter Slit	3.000
Slit Mode	Fixed

Example 1. *L*-Lys(Boc)-Phe-NH₂ (Compound I)

- Exemplary synthetic route



Synthesis of Compound 3

Name	Amount (g)	Volume (mL)	MW (g/mol)	Molar Equiv	Moles	Density g/mL	BR Charge Amt (kg)	kg/kg
Phe-NH ₂ HCl	950.00	950.00	200.67	1.00	4.734	-	7.030	
Cbz-Lys(Boc)-OH	1891.11	1891.11	380.44	1.05	4.971	-	13.990	1.99
HOBt-H ₂ O	797.48	797.48	153.14	1.10	5.208	-	5.900	0.84
Dimethylacetamide (DMAc)	3736.49	3987.71	87.12	-	-	0.937	27.650	3.93
N-Methylmorpholine (NMM)	957.72	1041.00	101.15	2.00	9.468	0.920	7.080	1.01
EDCI	952.91	952.91	191.70	1.05	4.971	-	7.050	1.00
Anhydrous Ethyl Alcohol (EtOH)	750.50	951.20	46.07	-	-	0.789	5.550	0.79
Acetonitrile (ACN)	11202.70	14252.80	84.93	-	-	0.786	82.900	11.79
Acetonitrile (ACN)	11202.70	14252.80	85.93	-	-	0.786	82.900	11.79

	Operation	Charge	Units
	Inert the reactor with nitrogen.		
1	Charge Compound 1 to reactor.	950.00	g
2	Charge Compound 2 to reactor.	1891.11	g
3	Charge HOBt-H ₂ O to reactor.	797.48	g
4	Charge DMAc to reactor.	3736.49	g
5	Adjust solution to target 22 °C (19 to 25 °C) with agitation.		
6	Agitate for 10-15 min at 22 °C (19 to 25 °C).		
7	Slowly charge NMM to reactor with moderate agitation.	957.72	g
8	Adjust solution to target 7 °C (4 to 10 °C) with agitation.		
9	Slowly charge EDCI to reactor with vigorous agitation.	952.91	g
10	Adjust solution to target 7 °C (4 to 10 °C) with vigorous agitation.		
11	Charge EtOH to reactor with vigorous agitation.	750.50	g
12	Adjust solution to target 22 °C (19 to 25 °C) with vigorous agitation.		
13	Agitate vigorously for ≥1 h at 22 °C (19 to 25 °C).		
	IPC for Reaction Completion (≤ 1.0% Phe-NH ₂ remaining)	0.169% a/a	
CRYSTALLIZATION			
15	Charge ACN to the reactor with vigorous agitation.	11202.70	g
16	Agitate vigorously for ≥5 h at 22 °C (19 to 25 °C).		
17	Verify crystallization successful.		
18	Filter the reaction to isolate the product (SCC-175).		
19	Wash the product cake with ACN and combine with mother liquor.	11202.70	g
20	Dry the product with agitation and nitrogen bleed for at least 17 h.		

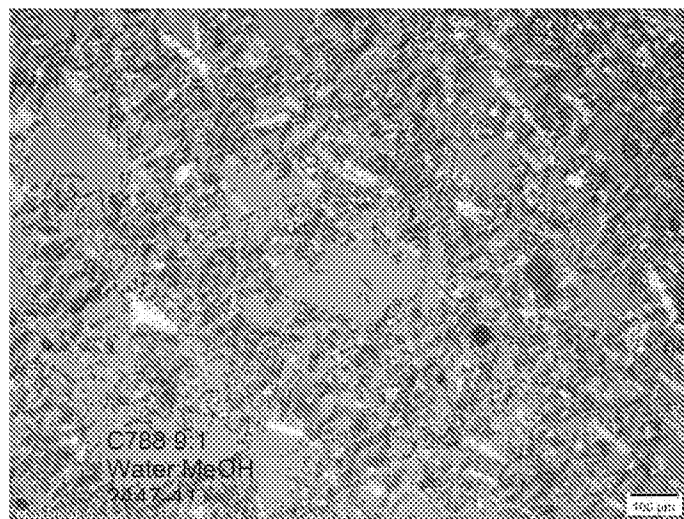
Synthesis of Compound I

Name	Amt	Volume (mL)	MW (g/mol)	Molar Equiv	Density g/mL	BR Charge Amt	units	kg/kg
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Compound 3	2000.00	2000.00	526.63	1.00		15.700	kg	
10% Pd/C (50% w/w wet)	200.00	200.00	106.42	10% w/w	-	3.140	kg	0.20
Anhydrous Methyl Alcohol (MeOH)	14191.08	17918.03	32.04	-	0.792	111.400	kg	7.10
Anhydrous Methyl Alcohol (MeOH)	7000.00	8838.38	32.04	-	0.792	54.950	kg	3.50
Water	7000.00	7000.00	18.02		1.000	54.950	kg	3.50
Water	8000.00	8000.00	18.02		1.000	62.800	kg	4.00
MeOH-Water (1:9) Solution	8000.00	7896.00			0.987	62.800	kg	4.00
Water (1:9 MeOH-water make-up)	9000.00	9000.00	18.02		1.000	NA		NA
Anhydrous Methyl Alcohol (MeOH) (1:9 MeOH-water make-up)	792.00	1000.00	33.04	-	0.792	NA		NA

	Operation	Charge	Units
	REACTION (30 L Hydrogenator Main Reactor)		
	Inert the hydrogenation reactor with nitrogen.		
1	Charge Pd/C (10%, 50% w/w water, 20A597) to reactor.	200.00	g
2	Charge Compound 3 to reactor.	2000.00	g
3	Charge MeOH to the reactor.	14191.08	g
4	Adjust solution to target 22 °C (19 to 25 °C) with agitation.		
	Inert the hydrogenation reactor with nitrogen.		
5	Pressurize the reactor with hydrogen (20-25 psi).		
6	Agitate for ≥6 h at 22 °C (19 to 25 °C) and 20-25 psi hydrogen.		
	Note: Maintain the pressure at 20-25 psi hydrogen.		
7	De-pressurize the reactor and inert with nitrogen at 22 °C (19 to 25 °C).		
	IPC for Reaction Completion (≤ 0.5% SCC-175 remaining)	0.09% a/a	
9	Filter the reaction to remove catalyst.		
10	Rinse the filter cake with MeOH and combine with filtrate.	7000.00	g
	DISTILLATION (30L ChemGlass Jacketed Main Reactor)		
11	Distill the reaction at ≤45 °C (100-200 Torr vacuum) to target.		
	Note: Distillation target = 1.5-2.5 mL/g SCC-175 charge.	5000.00	mL
	PRECIPITATION (30L ChemGlass Jacketed Main Reactor)		
	ISOLATION (12L Allen Glass Filter w/30 micron ChemGlass teflon frit)		
12	Charge water to reactor with moderate agitation at 40 °C over 30-60 min.	7000.00	g
13	Agitate the reaction at at 40 °C until crystallization observed.		
14	Verify crystallization successful.		
15	Charge water to reactor with moderate agitation at 40 °C over 30-60 min.	8000.00	g
16	Adjust the reaction to 22 °C (20 to 25 °C) over 30-60 min.		
17	Filter the reaction to isolate the product (SCC-169).		
18	Wash the product cake with MeOH-water (1:9).	8000.00	g
19	Dry the product with agitation and nitrogen bleed for at least 17 h.		

- *Microscopy of Compound I Product Slurry:*



- *Preliminary Single-Solvent Solubility of Compound I:*

Solvent	Solubility (mg/mL) ^A
EtOH (SDAG-7)	154.8
THF	84.5
<i>i</i> PrOAc	5.1
MeOAc	18.2
Water	4.1

^ASolubility was determined by HPLC (response curve).

- *Preliminary Precipitation Studies (MeOH/Water) of Compound I:*

Precipitation Studies					
Experiment	MeOH / Water	Addition Mode	Precip (Y/N)	Concentration (mL/g)	Solubility (mg/mL)
1 ^A	1:3	Normal	Y	10	7.0
2 ^A	1:5	Normal	Y	10	5.0
3 ^A	1:9	Normal	Y	10	3.6
4 ^A	1:19	Normal	Y	10	2.7
5 ^B	1:3	Reverse	N	80	---
+ 2 parts water	1:5	Normal	Y	120	ND

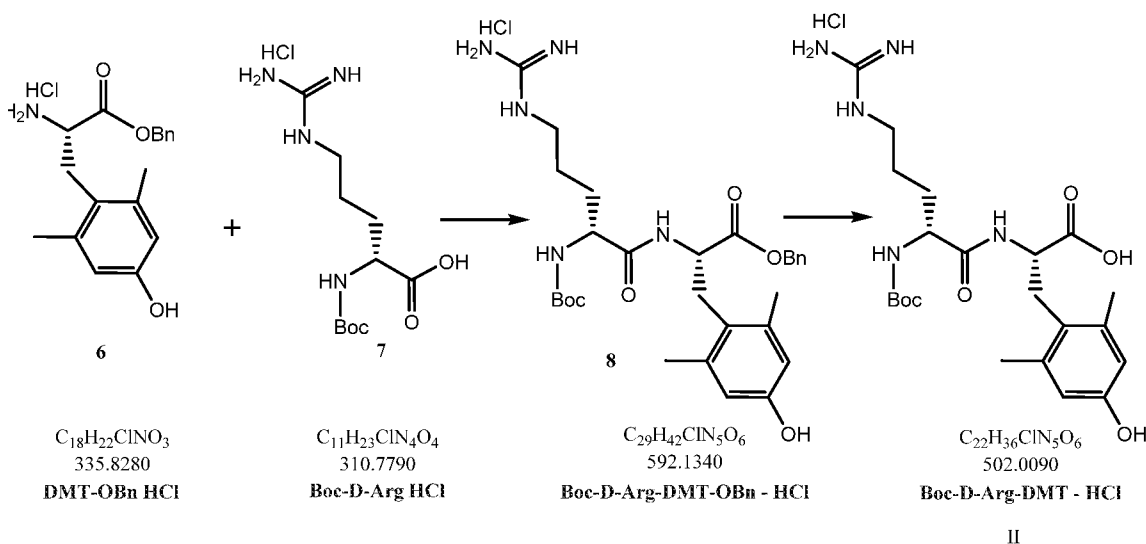
^AExperiments were conducted on 500 mg scale where the initial solution in MeOH (via 2447-41) was concentrated to a residue followed by charging MeOH/water at 25 °C.

^BExperiment was conducted on 40 mg scale where the initial solution in MeOH (via 2447-41) was charged directly to water. An additional charge of water was required to enable precipitation.

- *In Process Precipitation Results (MeOH/Water) of Compound I:*

Precipitation Results				
Experiment	MeOH / Water	Concentration (mL/g)	Solubility (mg/mL)	Total Losses
2447-41 ^A	1:9	13	2.5	5.7%
2447-47 ^A	1:5	10	4.2	6.2%

Example 2. Boc-D-Arg-DMT-OH



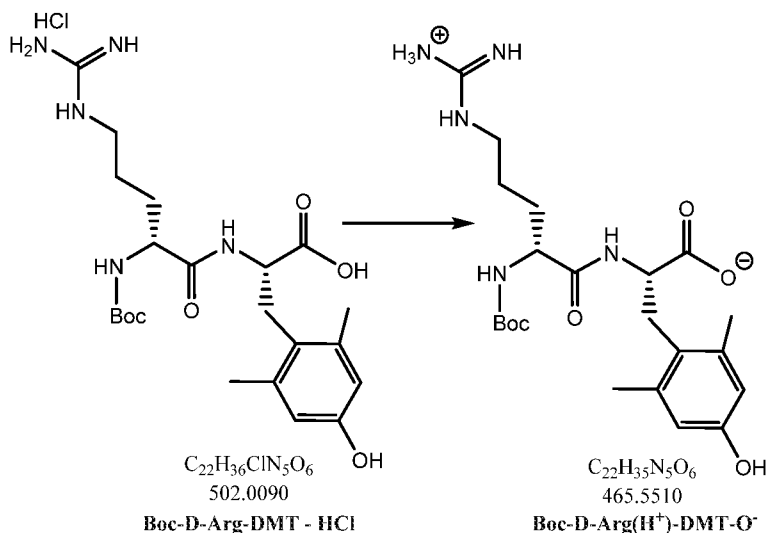
- *Manufacturing Process to Produce Compound 8*

Step	Operation
1	Charge DMT-OBn HCl (1 eq) and Boc-D-Arg-OH HCl (1.05 eq) to the reactor.
2	Charge HOBT (0.1 eq) and DCM (8.5 L/kg of DMT-OBn HCl) to the reactor.
3	Adjust temperature to about 22±3°C and charge NMM (2.0 eq) to the reactor
4	Adjust temperature to about 15±3°C and charge EDCI (1.05 eq) to the reactor.
5	Adjust temperature to about 15°C and agitate.
5	Charge EtOH (1.5 L/kg of DMT-OBn HCl) to the reactor
7	Agitate for a minimum of 5 hours at 15±3°C
8	Sample for in-process control reaction completion test, if reaction is not complete, charge additional EDCI, stir for a minimum of 1 hour and repeat the in-process control test until criterion for completion is met.
9	Charge 15% EtOH in DCM.
10	Charge 1M HCl.
11	Adjust temperature to ambient and agitate.
12	Stop agitation and separate layers
13	Wash organic layer successively with brine, 1 M HCl, brine and then brine again
14	Reduce volume via vacuum distillation
15	Adjust temperature to ambient
16	Charge EtOH and reduce volume via vacuum distillation
17	Sample for in-process control DCM content test, Repeat EtOH addition and volume reduction by vacuum distillation until the in-process control limit for DCM is met
18	Adjust temperature to ambient
19	Sample the product for in-process control test for SCC-192 purity and content

- *Manufacturing Process to Produce the HCl salt of Compound II*

Step	Operation
1	Charge the ethanol solution of Boc-D-Arg-DMT-OBn HCl (SCC-192)
2	Charge 10% Pd/C, 50% wet (w/w) (20 wt. %)
3	Charge EtOH (7L/kg of SCC-192)
4	Agitate and begin hydrogenation around ambient temperature
5	Step 2B In-Process Control 1: Test for reaction completion
5	Filter suspension through filter aid and wash filter cake three times with EtOH
7	Reduce volume via vacuum distillation
8	Adjust temperature to ambient
9	Charge THF and reduce volume via vacuum distillation
10	Adjust temperature to ambient
11	Charge THF and reduce volume via vacuum distillation
12	Adjust temperature to ambient
13	Charge THF and reduce volume via vacuum distillation
14	Step 2B In-Process Control 2: Test for EtOH content
15	Charge iPrOAc and agitate at ambient temperature
16	Filter and wash solids three times with iPrOAc
17	Dry the product under vacuum and nitrogen
18	Sample the product for in-process control test for purity
19	Step 2B In-Process Control 3: Test for Purity

- *Preparation of the Zwitterionic Form of Compound II*



1. The crude HCl salt is suspended in CH₃OH/H₂O (1/1, v/v)
2. The suspension is heated to 45~50°C.
3. After the clear solution is formed, an aqueous solution of Na₂CO₃ (1.2 eq.) is added. During the addition, the solid begins to precipitate.
4. The suspension is stirred for 1 h at 45°C, and then cooled to 15°C and stirred for an additional hour.

5. The solid is isolated by filtration and dried to provide Compound II with high purity (99.4 area %) by HPLC. The calculated w/w assay correcting for residual solvents, water content and residue on ignition for this demonstration run was 98.7%.

Formation of zwitterionic compound led to high purity material that was stable, easily handled, and highly crystalline.

Example 3. Crystalline L-Lys(Boc)-Phe-NH₂ – XRPD Peak List

Angle	d Value	Net Intensity	Gross Intensity	Rel. Intensity
4.704	18.77211	9559	11528	100.0 %
5.230	16.88407	624	2301	6.5 %
5.648	15.83394	862	2340	9.0 %
6.200	14.24402	7663	8912	80.2 %
6.650	13.28057	394	1456	4.1 %
7.056	12.81772	508	1460	5.3 %
7.709	11.45860	1161	1869	12.1 %
8.553	10.33046	2135	2771	22.3 %
9.402	9.38869	2473	3673	25.9 %
9.922	8.90729	2627	3266	27.5 %
10.503	8.57920	1435	1897	15.0 %
11.292	7.82975	3301	3848	34.5 %
11.758	7.52244	1985	2530	20.8 %
12.205	7.24594	2827	3370	29.6 %
12.452	7.10259	4581	5123	47.9 %
12.655	6.98916	2764	3305	28.9 %
13.270	6.68655	4117	4658	43.1 %
13.778	6.42221	795	1330	8.3 %
14.133	6.26164	333	666	3.5 %
14.462	6.11961	682	1413	9.2 %
14.957	5.91833	3726	4255	39.0 %
15.796	5.61997	7404	7928	77.5 %
16.263	5.44580	2360	2881	24.7 %
16.504	5.36683	5366	5895	56.1 %
16.961	5.22337	2930	3447	30.7 %
17.107	5.17917	2585	3100	27.0 %
17.658	5.01859	3807	4320	39.8 %
17.956	4.93596	4360	4871	45.6 %

18.210	4.86777	4451	4960	46.6 %
18.832	4.70852	8963	9469	93.8 %
19.561	4.53460	3331	3830	34.8 %
19.802	4.47896	7877	8375	82.4 %
20.265	4.37865	1989	2483	20.8 %
20.715	4.28449	1746	2237	18.3 %
21.514	4.12715	1756	2241	18.4 %
21.958	4.04471	4087	4568	42.7 %
22.807	3.89590	3856	4331	40.3 %
23.398	3.79891	779	1248	8.1 %
23.660	3.75740	835	1303	8.7 %
24.306	3.65896	726	1169	7.6 %
25.050	3.55198	2158	2614	22.6 %
25.462	3.49548	764	1217	8.0 %
25.709	3.46234	1227	1677	12.6 %
26.016	3.42222	714	1161	7.5 %
26.319	3.38357	521	966	5.5 %
26.713	3.33445	662	1103	6.9 %
27.411	3.25119	709	1143	7.4 %
28.356	3.14493	831	1256	8.7 %
28.808	3.09664	340	761	3.6 %
30.662	2.91341	740	1142	7.7 %
31.492	2.83854	649	1041	6.8 %
35.876	2.50109	376	740	3.9 %
36.369	2.46832	362	723	3.8 %

Example 4. Crystalline Boc-D-Arg-DMT– XRPD Peak List

Angle	d Value	Net Intensity	Gross intensity	Ref. Intensity
9.293	10.70488	3779	4204	15.0 %
9.353	9.44784	20863	21225	82.9 %
12.104	7.30592	20016	20338	79.6 %
12.809	6.90584	2797	3126	11.1 %
13.756	6.43269	11432	11758	45.4 %
15.709	5.63659	909	1235	3.6 %
16.307	5.43127	7503	7839	29.8 %
16.656	5.35006	12773	13103	50.8 %
16.725	5.29845	2495	2825	9.9 %
17.557	5.04740	22493	22824	89.4 %
18.006	4.92236	25154	25485	100.0 %
18.756	4.72740	18203	18534	72.4 %
18.908	4.68953	4809	5141	19.1 %
19.414	4.56848	12725	13056	50.6 %
20.716	4.28417	899	1231	3.6 %
21.259	4.17597	5974	6406	20.2 %
22.357	3.97329	3830	4161	15.2 %
23.009	3.86218	7511	7842	29.9 %
23.163	3.83895	2203	2533	8.8 %
23.511	3.78085	4659	4989	18.5 %
24.208	3.67354	7257	7585	28.8 %
24.809	3.58598	1940	2268	7.7 %
25.060	3.55054	5827	6054	22.4 %
25.767	3.45478	970	1297	3.9 %
26.009	3.42308	1418	1744	5.6 %
26.457	3.36813	255	580	1.0 %
26.721	3.33347	181	485	0.6 %
27.783	3.21073	1862	2185	7.4 %

28.111	3.17181	1182	1503	4.7 %
28.263	3.15505	366	687	1.5 %
29.111	3.06507	2546	2864	10.1 %
29.311	3.04456	1100	1418	4.4 %
29.662	3.00931	616	933	2.4 %
29.912	2.98476	1550	1866	6.2 %
30.212	2.95583	1607	1922	6.4 %
30.865	2.89475	1913	2228	7.6 %
31.414	2.84540	1565	1876	6.2 %
31.695	2.82084	468	778	1.9 %
32.865	2.73926	657	963	2.6 %
32.915	2.71901	296	602	1.2 %
33.805	2.64939	326	632	1.3 %
34.165	2.62230	670	976	2.7 %
34.977	2.56330	485	795	1.9 %
36.166	2.48167	798	1113	3.2 %
36.514	2.45883	611	927	2.4 %
36.813	2.43955	364	682	1.4 %
37.466	2.39851	173	502	0.7 %
37.966	2.36808	901	1257	3.6 %
38.221	2.35285	394	764	1.6 %
38.576	2.33202	878	1266	3.5 %
39.114	2.30117	394	810	1.6 %
39.516	2.27866	363	801	1.4 %

INCORPORATION BY REFERENCE

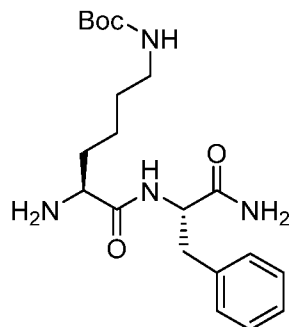
All U.S. patents and U.S. and PCT published patent applications mentioned in the description above are incorporated by reference herein in their entirety.

EQUIVALENTS

Having now fully described the present invention in some detail by way of illustration and examples for the purposes of clarity of understanding, it will be obvious to one of ordinary skill in the art that the same can be performed by modifying or changing the invention within a range of conditions, formulations and other parameters without affecting the scope of the invention or any specific embodiment thereof, and that such modifications or changes are intended to be encompassed within the scope of the appended claims.

We claim:

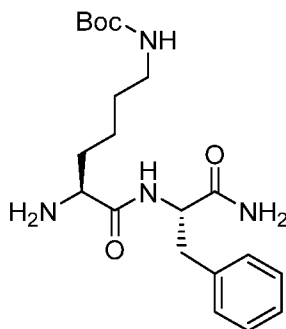
1. A crystalline form of Compound (I),



(I),

wherein said crystalline form has characteristic peaks in its XRPD pattern at values of two theta as described in Table 1.

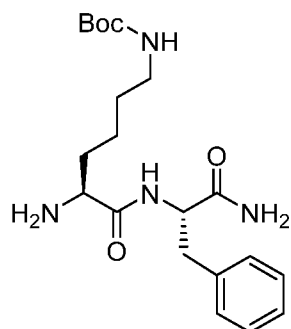
2. A crystalline form of Compound (I),



(I),

wherein said crystalline form has characteristic peaks in its XRPD pattern at values of two theta as described in Figure 1.

3. A crystalline form of Compound (I),

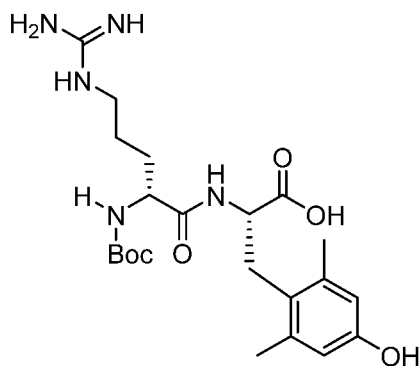


(I),

wherein said crystalline form has characteristic peaks in its XRPD pattern at values of two theta theta ($^{\circ} 2\theta$) of: 4.7, 6.2, 12.4, 15.8, 16.5, 18.0, 18.2, 18.8, and 19.8.

4. The crystalline form of claim 3, wherein said crystalline form has characteristic peaks in its XRPD pattern at values of two theta ($^{\circ} 2\theta$) of: 4.7, 6.2, 11.3, 12.4, 13.3, 15.0, 15.8, 16.5, 17.0, 17.7, 18.0, 18.2, 18.8, 19.8, 22.0, and 22.8.

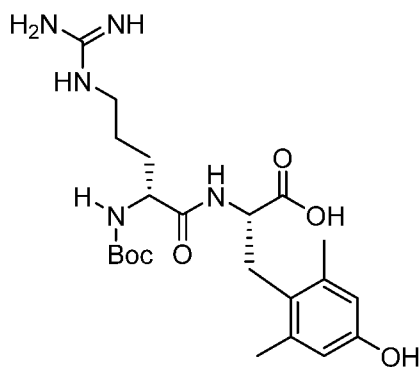
5. A crystalline form of Compound (II),



(II),

wherein said crystalline form has characteristic peaks in its XRPD pattern at values of two theta as described in Table 2.

6. A crystalline form of Compound (II),



(II),

wherein said crystalline form has characteristic peaks in its XRPD pattern at values of two theta as described in Figure 2.

FIG. 1

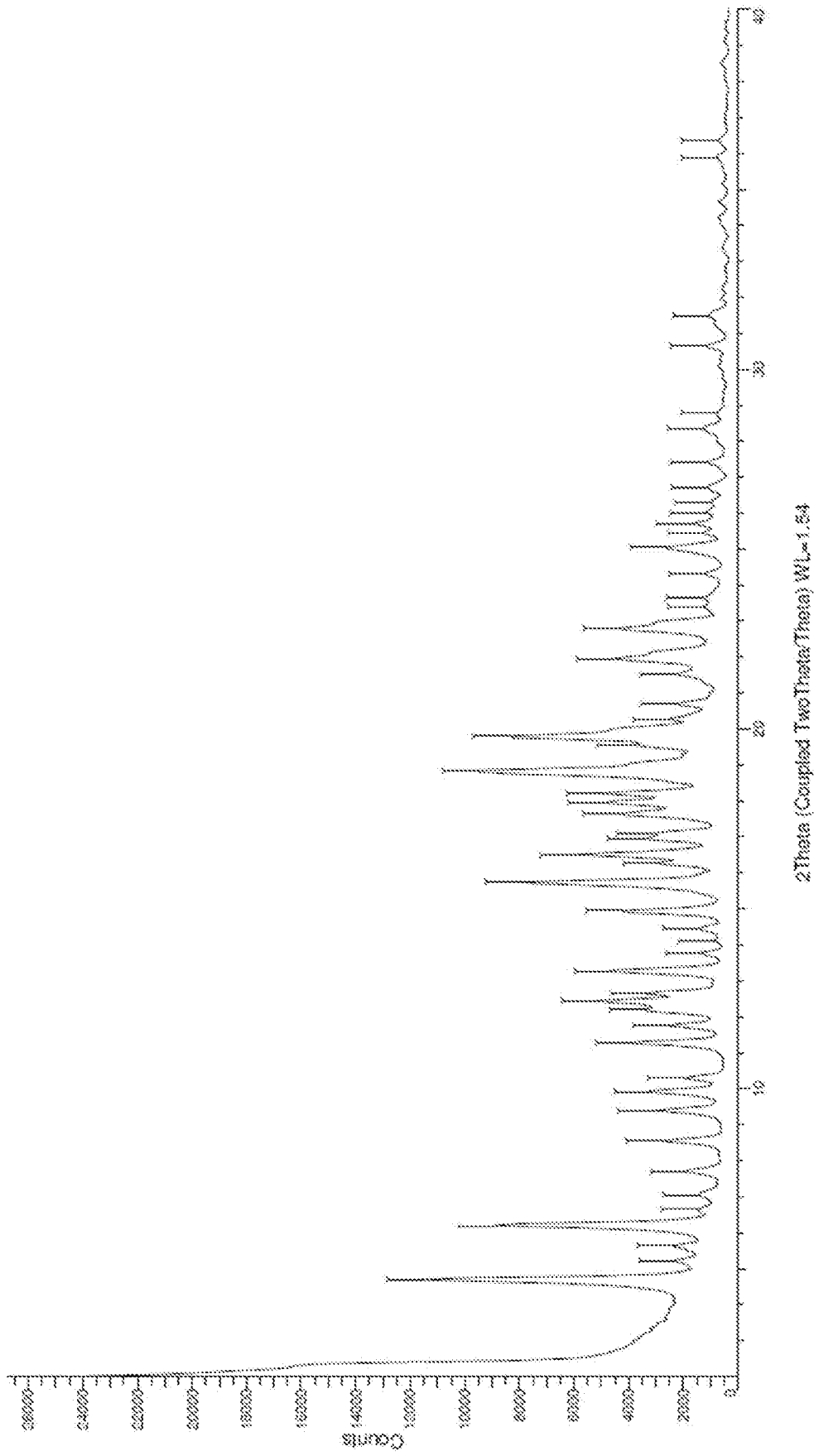
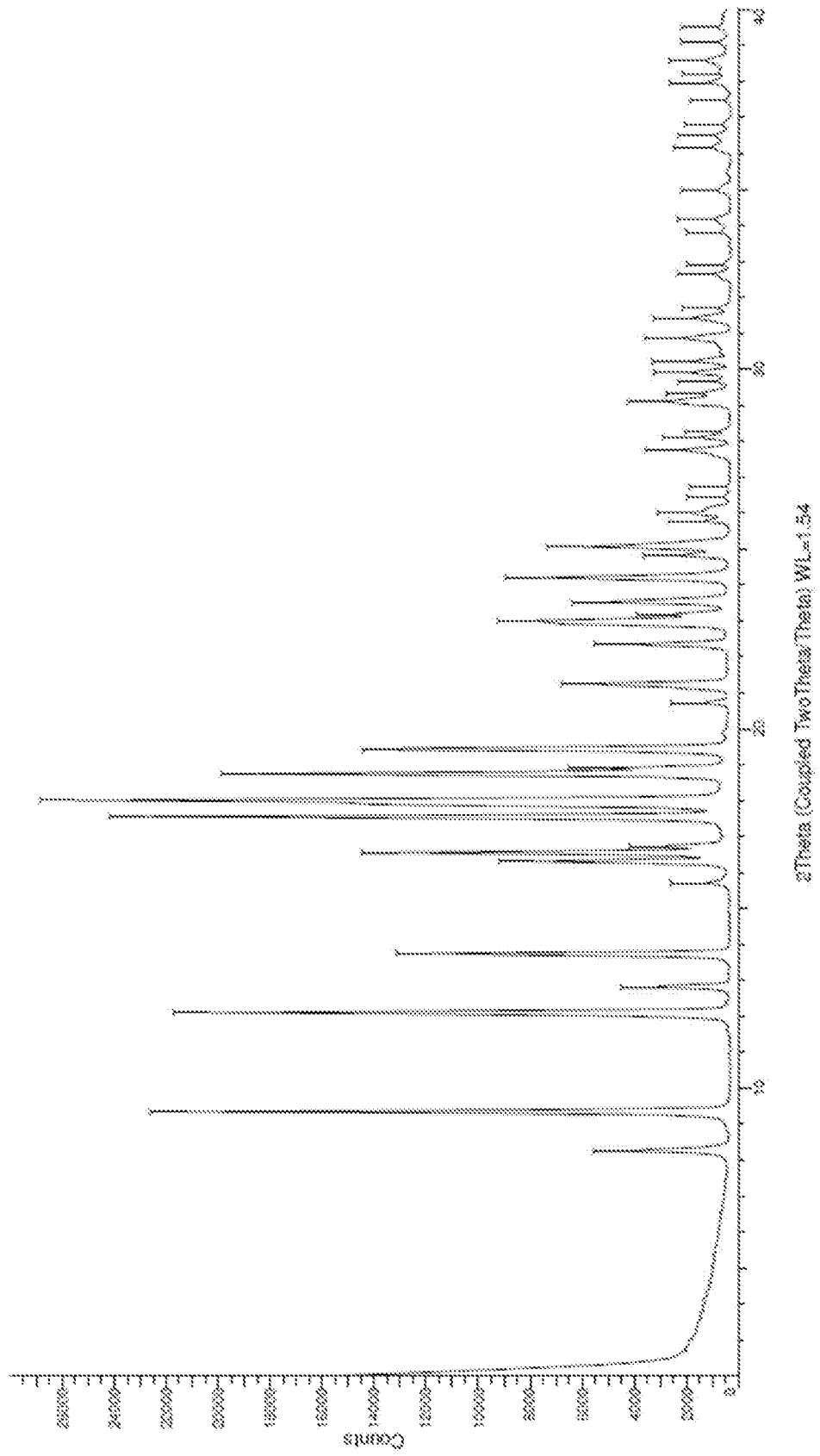


FIG. 2



INTERNATIONAL SEARCH REPORT

International application No. PCT/US 19/24617
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A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - C07K 5/068; C07K 5/087; C07K 5/11 (2019.01)
 CPC - C07K 5/06086; C07K 5/0812; C07K 5/1019

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)
 See Search History Document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017/156403 A1 (Stealth Biotherapeutics) 14 September 2017 (14.09.2017) entire document especially para [0039], claims 1-47	1-8
A	WO 2018/034901 A1 (Stealth Biotherapeutics) 22 February 2018 (22.02.2018) entire document especially page 19, in 1-4	1-8
A	US 2017/0152289 A1 (Flamma SpA) 01 June 2017 (01.06.2017) entire document especially para [0041]	1-8
E/A	US 2019/0202861 A1 (Stealth Biotherapeutics) 04 July 2019 (04.07.2019) entire document	1-8
P/A	WO 2018/187400 A1 (Stealth Biotherapeutics) 11 October 2018 (11.10.2018) entire document	1-8

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance	"I" 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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 15 July 2019	Date of mailing of the international search report 02 AUG 2019
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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/24617

Box No. 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. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

- 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 No. 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:

---please see supplemental box ---

- 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
- 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 and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/24617

Box III: lack of unity

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-4 directed towards a crystalline form of Compound (I).

Group II: Claims 5-8 directed towards a crystalline form of Compound (II)

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I requires a compound of formula (I), not required by group II.

Group II requires a crystalline form of Compound (II), not required by group I.

Shared Technical Features:

Groups I-II share the technical feature of dipeptide portion of formula I and II.

However, this shared technical feature do not provide a contribution over the prior art, as being anticipated by WO 2018/034901 A1 to Stealth biotherapeutics (hereinafter 'Stealth') which taches dipeptide portion of formula I and II (see page 13, scheme 1, product formula)

As the technical features were known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups. Groups I-II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.