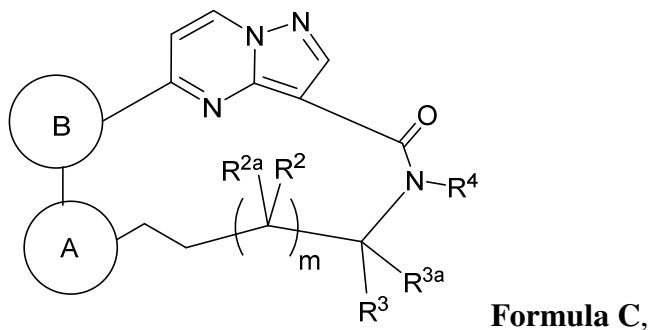


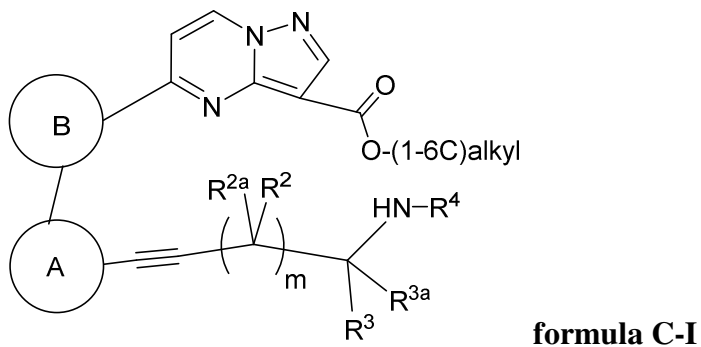
SUMMARY

Provided herein in some examples is a process for preparing a compound of Formula C:

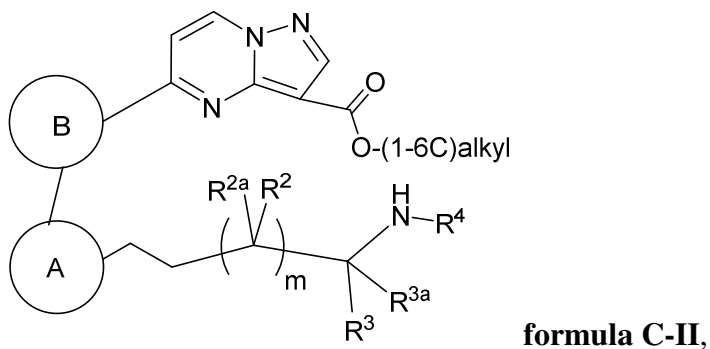


5 or a salt thereof. In some examples, the process comprises:

a) treating a compound of formula **C-I**



or a salt thereof, with a hydrogenation system to form a compound of formula **C-II**



10 or a salt thereof;

b) treating the compound of formula **C-II** or a salt thereof with a first strong base to form a compound of formula **C-III**

wherein the wavy line labeled 3 indicates the point of attachment to ring A and the wavy line labeled 4 indicates the point of attachment to the pyrazolo[1,5-a]pyrimidine ring;

R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH, provided that R^2 and R^{2a} are not both OH;

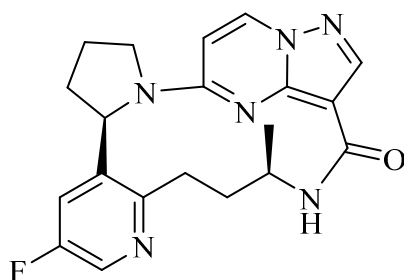
5 m is 0, 1 or 2;

R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

R^4 is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl); and

R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

10 Provided herein in some examples is a process for preparing a compound of
Formula I

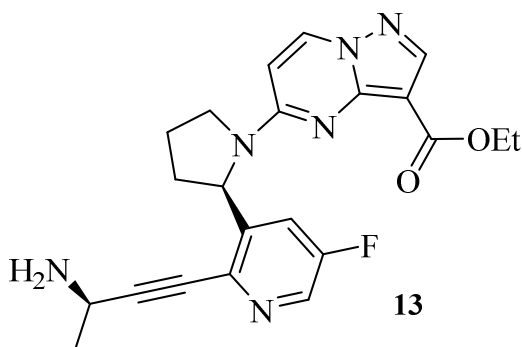


Formula I

or a salt thereof, comprising:

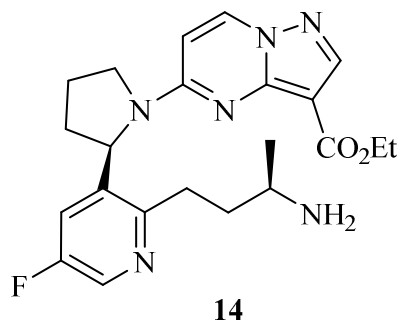
a) treating a compound of formula **13**

15



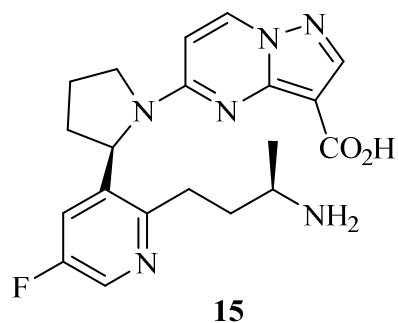
13

or a salt thereof with a hydrogenation system to form a compound of formula **14**



or a salt thereof;

b) treating the compound of formula **14** or a salt thereof with a first strong base to form a compound of formula **15**

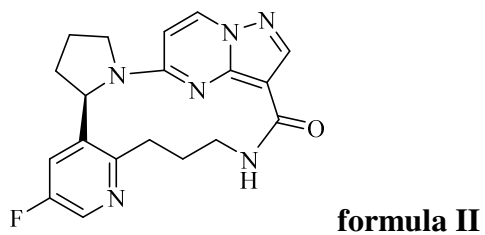


5

or a salt thereof; and

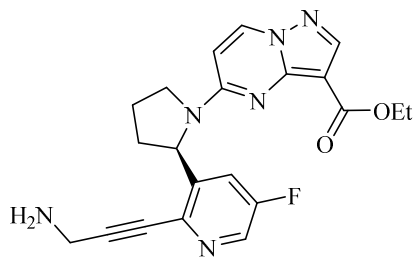
c) cyclizing the compound of formula **15** or a salt thereof with a coupling agent to form the compound of Formula **I** or a salt thereof.

Provided herein in some examples is a process for preparing a compound of
10 Formula **II**:

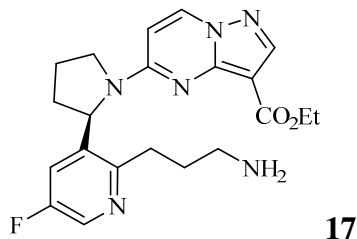


or a salt thereof, comprising:

a) treating a compound of formula **16**

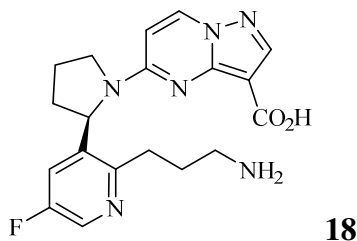


or a salt thereof with a hydrogenation system to form a compound of formula **17**



or a salt thereof;

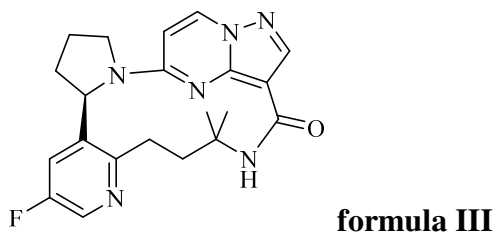
- 5 b) treating the compound of formula **17** or a salt thereof with a first strong base to form a compound of formula **18**



or a salt thereof; and

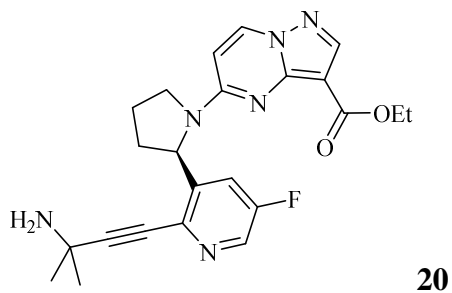
- 10 c) cyclizing the compound of formula **18** or a salt thereof with a coupling agent to form the compound of Formula **III** or a salt thereof.

Provided herein in some examples is a process for preparing a compound of Formula **III**:

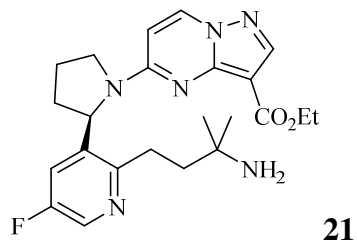


- 15 or a salt thereof, comprising:

a) treating a compound of formula **20**

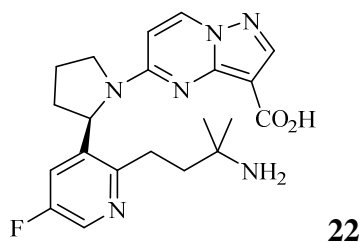


or a salt thereof with a hydrogenation system to form a compound of formula **21**



5 or a salt thereof;

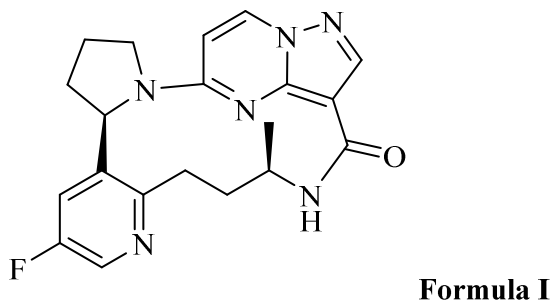
b) treating the compound of formula **21** or a salt thereof with a first strong base to form a compound of formula **22**



or a salt thereof; and

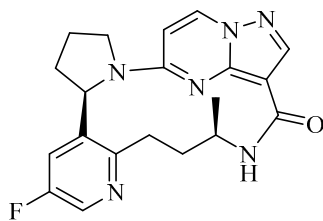
10 c) cyclizing the compound of formula **22** or a salt thereof with a coupling agent to form the compound of Formula **I** or a salt thereof.

Provided herein in some examples is a compound of Formula **I**



or a pharmaceutically acceptable salt, solvate or hydrate thereof.

The present disclosure in one example is directed to a solid form of (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosal(24),7,9,11,18(25),19,22-heptaen-17-one having the following structural formula:



(Compound 1).

5 The present disclosure is further directed to a crystalline form of Compound 1, such as a crystalline form of Compound 1 having Form I. In some examples, Form I has the XRPD peaks, in terms of 2-theta (2θ), at about 9.1, about 20.2 and about 24.9. In some examples, Form I has the XRPD peaks, in terms of 2-theta, at about 9.1, about 11.2, about 20.2 and about 24.9. In some examples, Form I has the XRPD peaks, in terms of 2-
10 theta, at about 9.1, about 11.2, about 13.4, about 14.8, about 20.2, and about 29.4. In some examples, Form I has the XRPD peaks, in terms of 2-theta, at about 9.1, about 11.2, about 13.4, about 14.8, about 18.3, about 18.6, about 20.2, about 23.6, about 24.9, and about 29.4. As used herein, the term “about” in conjunction with XRPD peaks refers to a variation of ±0.2. Thus, for example, a 2-theta value of “about 9.1” means a 2-theta
15 value of 9.1 ±0.2.

The present disclosure is further directed to salts of Compound 1.

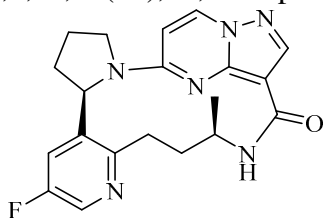
The present disclosure is further directed to crystalline forms of benzenesulfonic acid salt, citric acid salt, methanesulfonic acid salt, 1,2-ethane disulfonic acid salt, p-toluene sulfonic acid salt, oxalic acid salt, fumaric acid salt, L-malic acid salt, and
20 succinic acid salt of Compound 1.

In one example, the present disclosure is directed to a crystalline form of Compound 1 besylate. In some examples, the crystalline Compound 1 besylate has XRPD peaks, in terms of 2-theta, at about 8.1, about 13.4, and about 21.2. In some examples, the crystalline Compound 1 besylate has XRPD peaks, in terms of 2-theta, at
25 about 8.1, about 12.0, about 13.4, and about 21.2. In some examples, the crystalline Compound 1 besylate has XRPD peaks, in terms of 2-theta, at about 8.1, about 12.0, about 13.4, about 19.0, about 19.4, and about 21.2. In some examples, the crystalline Compound 1

besylate has XRPD peaks, in terms of 2-theta, at about 8.1, about 12.0, about 13.4, about 19.0, about 19.4, about 19.9, about 20.1, about 21.2, about 25.5, and about 32.7.

In another example, the present disclosure is directed to a crystalline form of Compound 1 citrate, such as crystalline Compound 1 citrate Form A. In some examples, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 20.7, about 21.6, and about 24.8. In some examples, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 8.9, about 20.7, about 21.6, and about 24.8. In some examples, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 8.9, about 11.1, about 14.4, about 15.4, about 20.7, about 21.6, and about 24.8. In some examples, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 8.9, about 11.1, about 13.9, about 14.4, about 15.4, about 19.2, about 20.7, about 21.6, about 24.8, and about 25.6.

In one aspect, the present disclosure refers to a crystalline form of (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosal(24),7,9,11,18(25),19,22-heptaen-17-one having the following structure:



The present disclosure is further directed to the hydrochloric acid salt, sulfuric acid salt, naphthalene-2-sulphonic acid salt, 2-hydroxy ethanesulfonic acid salt, L-aspartic acid salt, maleic acid salt, phosphoric acid salt, ethanesulfonic acid salt, L-glutamic acid salt, L-tartaric acid salt, D-glucuronic acid salt, hippuric acid salt, D-gluconic acid salt, DL-lactic acid salt, L-ascorbic acid salt, benzoic acid salt, benzenesulfonic acid salt, citric acid salt, methanesulfonic acid salt, 1,2-ethane disulfonic acid salt, p-toluene sulfonic acid salt, oxalic acid salt, fumaric acid salt, L-malic acid salt, and succinic acid salt of Compound 1.

The present disclosure is further directed to a hydrate or a solvate of Compound 1, or any one of the salts of Compound 1 described herein. In some examples, the hydrate or the solvate is crystalline.

The present disclosure is further directed to processes for preparing any one of the crystalline forms, solid forms, solvates, hydrates, or salts described herein. In one aspect, the present disclosure refers to a process for making a pharmaceutical composition comprising mixing a salt or crystalline form as described herein and a pharmaceutically acceptable carrier.

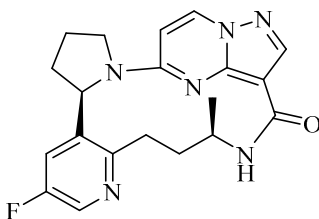
The present disclosure is further directed to pharmaceutical compositions comprising any one of the crystalline forms, solid forms, solvates, hydrates, or salts described herein, and at least one pharmaceutically acceptable carrier.

The present disclosure is further directed to therapeutic methods of using any one of the crystalline forms, solid forms, solvates, hydrates, or salts described herein. In one aspect, the present disclosure refers to use of the crystalline form as described herein in the manufacture of a medicament for treating a cancer mediated by a Trk kinase in a subject in need thereof.

Unless otherwise defined, all technical and scientific terms used herein have the

WE CLAIM:

1. A crystalline form of (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one having the following structure:



leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder glomus tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, leukemia lymphocytic, liver cholangiocarcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung small cell undifferentiated carcinoma, lung squamous cell carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, lymphoma, non-Hodgkin's lymphoma, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma, placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine adenocarcinoma, small intestine gastrointestinal stromal tumors (GISTs), soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma,

soft tissue perivascular epithelioid cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

9. The crystalline form of claim 1, wherein the crystalline form is characterized by a DTA thermogram characterized by an endothermal event at about 317 °C.
10. The crystalline form of claim 1, wherein the crystalline form is characterized by a DSC thermogram characterized by an endothermal event at about 317 °C.
11. The crystalline form of claim 1, wherein the crystalline form is characterized by a hygroscopicity characterized by a mass uptake of about 0.7% at 90% relative humidity as determined by dynamic vapor sorption analysis.