

**METHODS AND COMPOSITIONS FOR TREATING
MALIGNANT PERIPHERAL NERVE SHEATH TUMORS**

BACKGROUND OF THE DISCLOSURE

Cross-reference to related applications

[0001] This application claims priority from U.S. Provisional Application No. 63/518,312, filed August 8, 2023, and from U.S. Provisional Application No. 63/588,563, filed October 6, 2023, the disclosure of each of which is hereby incorporated by reference in its entirety.

Field of the Disclosure

[0002] This disclosure relates to methods of treating cancer. This disclosure further relates to treating cancer in a subject with compounds that are inhibitors of protein arginine N-methyl transferase 5 (PRMT5). More particularly, this disclosure relates to treatment of malignant peripheral nerve sheath tumors (MPNST).

Description of Related Art

[0003] PRMT5 is a type II arginine methyltransferase that catalyzes the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to an omega-nitrogen of the guanidino function of protein L-arginine residues (omega-monomethylation) and the transfer of a second methyl group to the other omega-nitrogen, yielding symmetric dimethylarginine (sDMA). PRMT5 forms a complex with methylosome protein 50 (MEP50), which is required for substrate recognition and orientation and is also required for PRMT5-catalyzed histone 2A and histone 4 methyltransferase activity (e.g., see Ho *et al.* (2013) *PLoS ONE* 8(2): e57008).

[0004] Homozygous deletions of p16/CDKN2a are prevalent in cancer and these mutations commonly involve the co-deletion of adjacent genes, including the gene encoding methylthioadenosine phosphorylase (MTAP). It is estimated that approximately 15% of all human cancers have a homozygous deletion of the MTAP gene (e.g., see Firestone & Schramm (2017) *J. Am. Chem Soc.* 139(39):13754-13760).

[0005] Cells lacking MTAP activity have elevated levels of the MTAP substrate, methylthioadenosine (MTA), which is a potent inhibitor of PRMT5. Inhibition of PRMT5 activity results in reduced methylation activity and increased sensitivity of cellular proliferation to PRMT5 depletion or loss of activity. Hence, the loss of MTAP activity reduces methylation activity of PRMT5 making the cells selectively dependent on PRMT5 activity.

[0006] Malignant peripheral nerve sheath tumors are a form of cancer of the connective tissue or sheath that surrounds and protects peripheral nerves. Malignant peripheral nerve sheath tumors were previously named neurofibrosarcomas.

[0007] Malignant peripheral nerve sheath tumors grow in any of the soft tissues of the body, such as muscle, fat, tendons, ligaments, lymph and blood vessels, nerves, and other tissue that connects and supports the body. MPNST grows quickly and can spread to other parts of the body.

[0008] Despite importance of treating MPNST, effective therapies for treating this cancer remain elusive. Thus, there remains a need to develop new therapies to treat MPNST.

SUMMARY OF THE DISCLOSURE

[0009] One aspect of the disclosure provides methods for treating malignant peripheral nerve sheath tumors (MPNST) in a subject. Such methods include administering to the subject a therapeutically effective amount of a PRMT5 inhibitor.

[0010] In another aspect, the disclosure provides methods for reducing the size of malignant peripheral nerve sheath tumors (MPNST) in a subject. Such methods include administering to the subject a therapeutically effective amount of a PRMT5 inhibitor.

[0011] These and other features and advantages of the present invention will be more fully understood from the following detailed description taken together with the accompanying claims. It is noted that the scope of the claims is defined by the recitations therein and not by the specific discussion of features and advantages set forth in the present description.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0012] Before the disclosed processes and materials are described, it is to be understood that the aspects described herein are not limited to specific embodiments, and as such can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and, unless specifically defined herein, is not intended to be limiting.

[0013] In view of the present disclosure, the methods and compositions described herein can be configured by the person of ordinary skill in the art to meet the desired need. The present disclosure provides improvements in treating cancer in a subject. As used herein,

the terms “subject” or “patient” are used interchangeably, refers to any animal, including mammals, and most preferably humans.

[0014] It has been unexpectedly discovered that administration of a PRMT5 inhibitor as disclosed herein is useful for treating malignant peripheral nerve sheath tumors (MPNST).

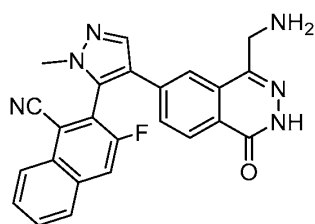
[0015] The methods provided herein may be used for the treatment of a wide variety of cancer including tumors, including malignant peripheral nerve sheath tumors (MPNST). The methods involve administration of a PRMT5 inhibitor to a patient or subject in need of such treatment.

[0016] A “PRMT5 inhibitor” as used herein refers to compounds of the disclosure as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of PRMT5, particularly, in the presence of bound MTA *in vitro* or *in vivo* or in cells in the presence of elevated levels of MTA. In certain embodiments, the PRMT5 inhibitor is an MTA-cooperative PRMT5 inhibitor.

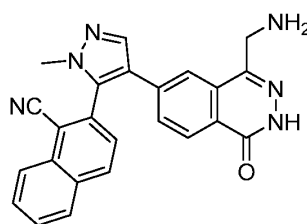
[0017] In certain embodiments, the PRMT5 inhibitor of the disclosure is any one of the PRMT5 inhibitors disclosed in published International Patent Application No. WO 2021/050915 A1, published 18 March 2021, which is incorporated by reference in its entirety.

[0018] In certain other embodiments, the PRMT5 inhibitor of the disclosure is any one of the PRMT5 inhibitors disclosed in published International Patent Application No. WO/2022/192745, published 15 September 2022, which is incorporated by reference in its entirety.

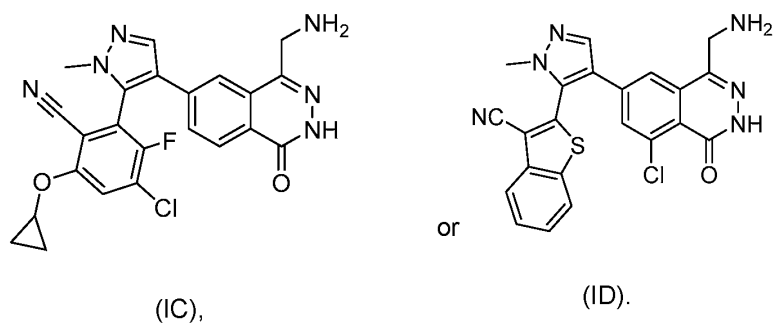
[0019] For example, the PRMT5 inhibitor in the methods of the disclosure as described herein is a compound having formula (IA), (IB), (IC) or (ID)



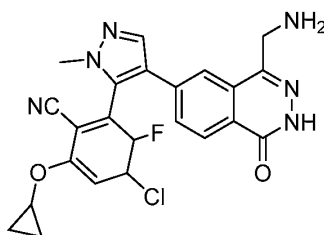
(IA),



(IB),

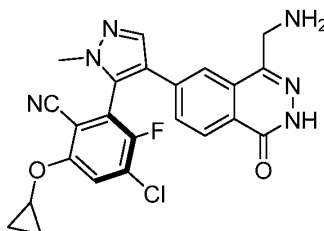


[0020] In one embodiment the PRMT5 inhibitor is a compound of the formula:



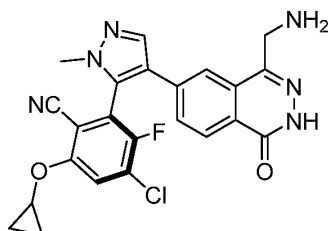
or a pharmaceutically acceptable salt thereof.

[0021] In another embodiment, the PRMT5 inhibitor is a compound of the formula:

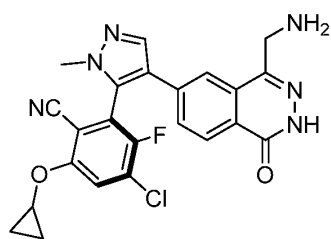


or a pharmaceutically acceptable salt thereof.

[0022] In another embodiment, the PRMT5 inhibitor is a pharmaceutically acceptable salt of a compound of the formula:

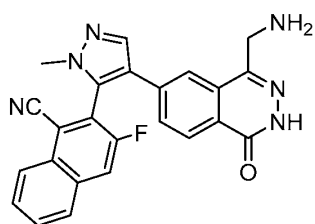


[0023] In another embodiment, the PRMT5 inhibitor is a compound of the formula:

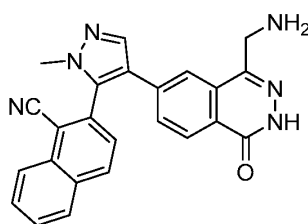


(MRTX1719).

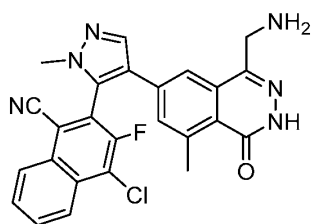
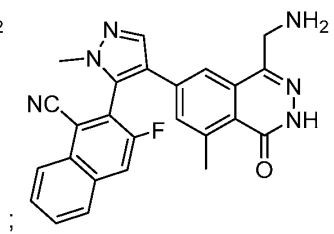
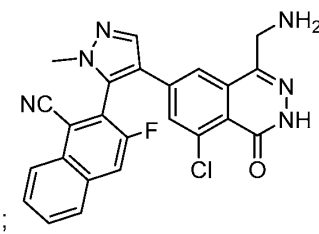
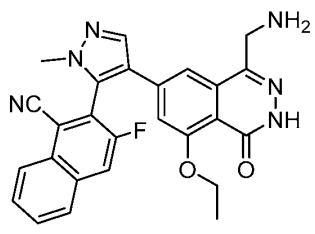
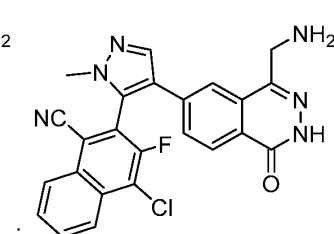
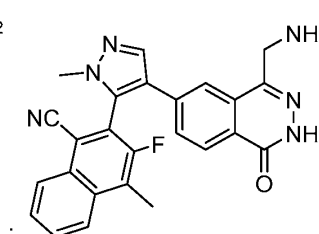
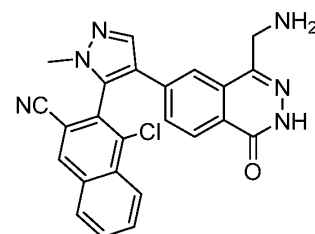
[0024] In other embodiments of the methods of the disclosure as described herein, the PRMT5 inhibitor is:



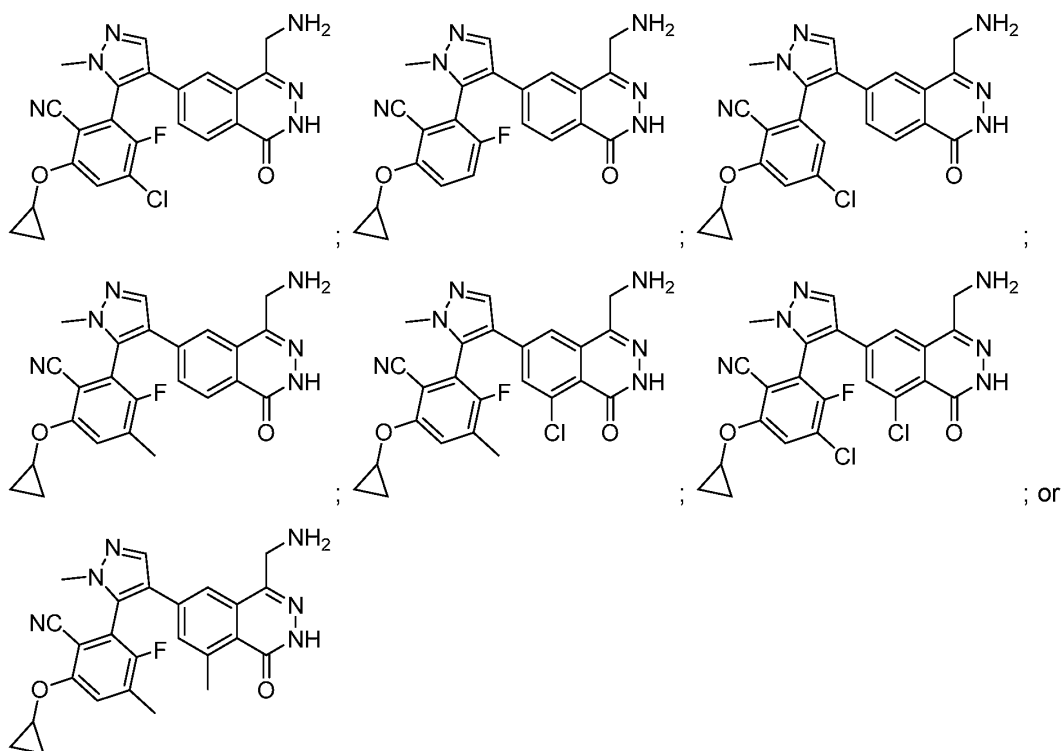
(MRTX9768);



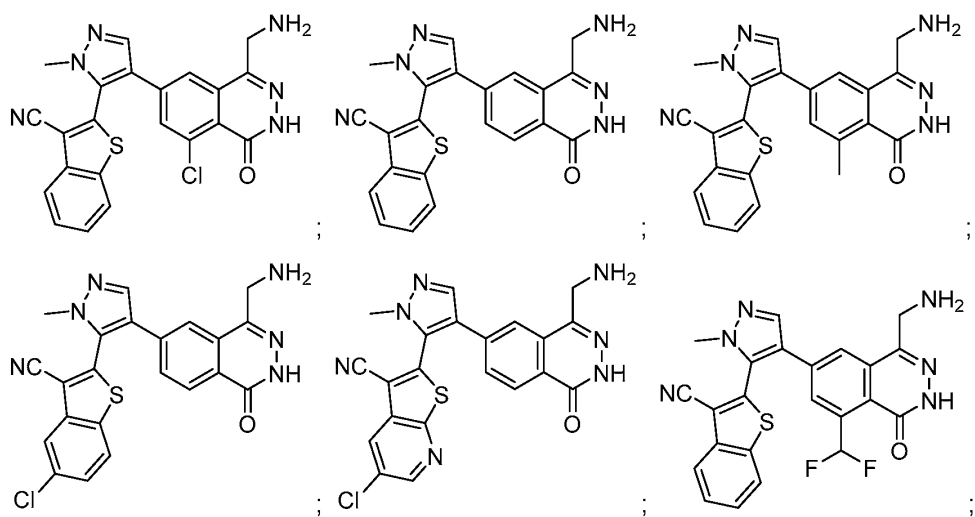
(MRTX7477);

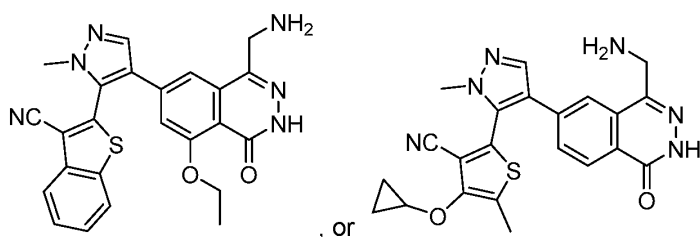


[0025] In certain embodiments of the methods of the disclosure as described herein, the PRMT5 inhibitor is:



[0026] In certain embodiments of the methods of the disclosure as described herein, the PRMT5 inhibitor is:





[0027] The PRMT5 inhibitor of the disclosure may be synthesized according to procedures set forth in published International Patent Application No. WO 2021/050915, or published International Patent Application No. WO/2022/192745.

[0028] The PRMT5 inhibitor of the disclosure may be provided as a pharmaceutical composition comprising a therapeutically effective amount of such inhibitor and a pharmaceutically acceptable carrier, excipient, and/or diluents. The PRMT5 inhibitor of the disclosure may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain embodiments, The PRMT5 inhibitor of the disclosure are administered intravenously in a hospital setting. In certain other embodiments, administration may preferably be by the oral route.

[0029] The characteristics of the carrier will depend on the route of administration. As used herein, the term “pharmaceutically acceptable” means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, pharmaceutical compositions of the disclosure may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington’s Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, Pa., 1990.

[0030] The PRMT5 inhibitor of the disclosure are administered in a therapeutically effective amount. As used herein, the phrase “therapeutically effective amount” or “effective amount” refers to the amount of active agent that elicits the biological or medicinal response that is being sought in a tissue, system, subject or human by a researcher, medical doctor or other clinician. In general, the therapeutically effective amount is sufficient to deliver the biological or medicinal response to the subject without causing serious toxic effects. A dose of the active agent may be in the range from about 0.01 to 300 mg/kg per day, such as 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg/kg body weight of the recipient per day. A typical topical dosage will range from 0.01 to 3% wt/wt in a suitable carrier.

[0031] In certain embodiments of the methods of the disclosure, the therapeutically effective amount of the PRMT5 inhibitor is in the range of about 0.01 to 300 mg/kg per day. For example, in certain embodiments, the therapeutically effective amount of the PRMT5 inhibitor is in the range of about 0.1 to 100 mg/kg per day, or 25 to 100 mg/kg per day, or 50 to 100 mg/kg per day.

[0032] In certain embodiments, the therapeutically effective amount of the PRMT5 inhibitor is less than 1% of, e.g., less than 10%, or less than 25%, or less than 50% of the clinically-established therapeutic amount (e.g., such as the amount required when the PRMT5 inhibitor is administered by itself).

[0033] The PRMT5 inhibitor may also be administered in combination with another anticancer compound or therapy. Combination therapy is intended to embrace administration of each agent in a sequential manner, a substantially simultaneous manner or in a single dosage form. Each combination therapy is administered in a regimen that will provide beneficial effects of the drug combination. Each compound of the combination therapy can be formulated as a separate composition such that separate compositions are given sequentially or in a substantially simultaneous manner, such as in a single dosage form having a fixed ratio of the active agents or in multiple or a separate dosage forms for each agent. The disclosure is not limited in the sequence of administration: the PRMT5 inhibitor of the disclosure may be administered either prior to or after (i.e., sequentially), or at the same time (i.e., simultaneously) as administration of an additional anti-cancer compound.

[0034] The methods of disclosure are useful as a first-line treatment. Thus, in certain embodiments of the methods of the disclosure, the subject has not previously received another first-line of therapy.

[0035] The methods of disclosure are also useful as a first-line maintenance or a second-line treatment. Thus, in certain embodiments of the methods of the disclosure, the subject has previously completed another first-line of therapy. For example, the methods of the disclosure, in certain embodiments, may provide a delay in progression and relapse of cancer in subjects that have previously completed another first-line chemotherapy. For example, in certain embodiments, the subject has previously completed a platinum- and/or taxane-based chemotherapy (e.g., carboplatin, cisplatin, oxaliplatin, paclitaxel, docetaxel, and the like). In certain embodiments of the methods of the disclosure, the subject has previously completed another first-line chemotherapy and is in partial response to such chemotherapy.

EXAMPLES

[0036] The Examples that follow are illustrative of specific embodiments of the process of the disclosure, and various uses thereof. They are set forth for explanatory purposes only, and are not to be taken as limiting the scope of the disclosure.

[0037] Example 1: In Vitro Proliferation Assay

[0038] Viability assays were performed using the *MTAP* deleted human MPNST (Malignant Peripheral Nerve Sheath Tumor) cell lines HS-PSS and sNF96.2. To conduct the assays, on Day 0, an optimized cell number for each cell line was plated in 96-well plates and incubated overnight at 37°C plus 5% CO₂. The following day baseline CTG (CellTiter-Glo; Promega cat. No. G7573) readings were collected from designated wells and assay plates were treated with DMSO (as the control) or a dose response of MRTX1719. The cells were then incubated at 37°C plus 5% CO₂ for five days. After this duration of treatment, CTG readings were collected. The MRTX1719 relative viability IC₅₀ values for each cell line were calculated using the end of treatment CTG values after Day 0 baseline subtraction for each cell line using GraphPad PRISM software. The results of these assays are shown in FIG. 1A and 1B and the IC₅₀ for each cell line is shown in Table 1.

[0039] Table 1.

Cell Line	IC ₅₀ (nM)	Treatment duration (Days)
HS-PSS	35	6
sNF96.2	23	7

[0040] Example 2: In Vivo Tumor Growth Inhibition Study

[0041] Immunocompromised nude/nude mice were inoculated in the hind flank with patient derived tumor samples harboring an *MTAP* deletion. When mean tumor volumes reached ~ 90 mm³ in size, the mice were divided into two groups of 5 mice each. The first group was administered vehicle only (0.5% Methylcellulose (4000cps) + 0.2% TWEEN80 in water). The second group was administered a single agent dose of MRTX1719 at the indicated dose for the indicated treatment duration. The dosing used is reported in Table 2.

[0042] Tumor volumes were measured using a caliper every two – three days and tumor volumes calculated by the formula: $V = (0.5)a \times b^2$ where a and b are the long and short perpendicular diameters of the tumor, respectively. Percent tumor growth inhibition (TGI) was calculated by the formula:

$\% \text{ TGI} = (1 - (\text{Average treatment group final volume} - \text{Average treatment group initial volume}) / (\text{Average vehicle group final volume} - \text{Average vehicle group initial volume})) \times 100$

The tumor volumes were measured over 28 days on study, and the average tumor volumes (mm³) of each treatment group are shown in Table 2. MRTX1719 treatment for 28 days resulted in 97% TGI.

[0043] Table 2.

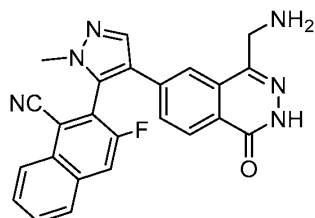
Study Day	Vehicle Average Tumor Volumes (mm ³)	MRTX1719 (100 mg/kg p.o. q.d.) Average Tumor Volume (mm ³)
0	86	86
4	97	100
7	125	106
11	179	117
14	220	120
18	271	126
21	289	117
25	303	110
28	347	95

[0044] All experimental data management and reporting procedures were in strict accordance with applicable standards and procedures. Animals were checked daily for morbidity and mortality. At the time of routine monitoring, the animals were checked for any effects of tumor growth and treatment on behavior such as mobility, food and water consumption, body weight gain/loss (body weights were measured twice per week), and any other abnormalities.

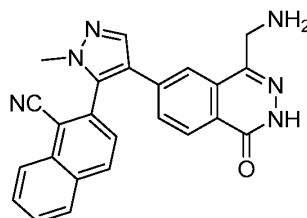
[0045] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be incorporated within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated herein by reference for all purposes.

What is claimed is:

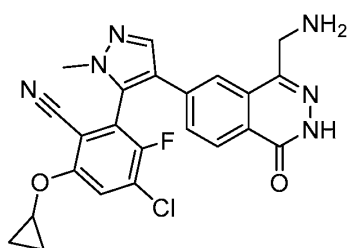
1. A method for treating malignant peripheral nerve sheath tumors in a subject, the method comprising administering to the subject a therapeutically effective amount of a protein arginine N-methyl transferase 5 (PRMT5) inhibitor which is a compound having formula (IA), (IB), (IC) or (ID)



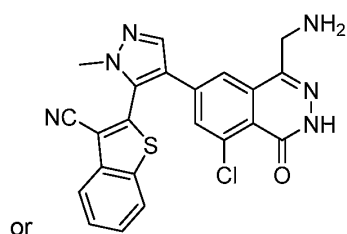
(IA),



(IB),



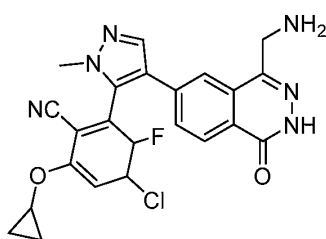
(IC),



or

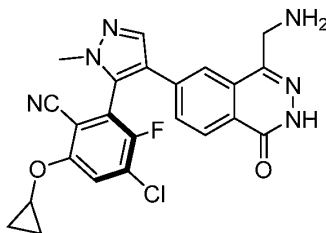
(ID).

2. The method of claim 1, wherein the PRMT5 inhibitor is:



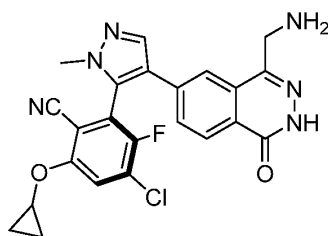
or a pharmaceutically acceptable salt thereof.

3. The method of claim 1, wherein the PRMT5 inhibitor is:

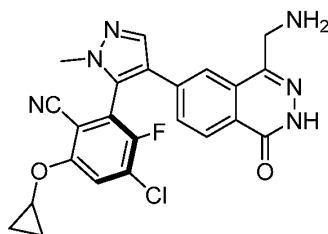


or a pharmaceutically acceptable salt thereof.

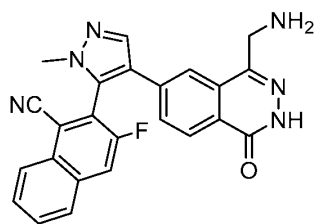
4. The method of claim 1, wherein the PRMT5 inhibitor is a pharmaceutically acceptable salt of a compound of the formula:



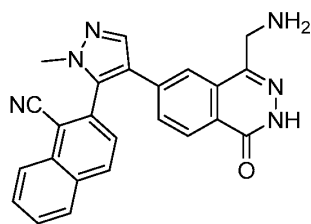
5. The method of claim 1, wherein the PRMT5 inhibitor is a compound of the formula:



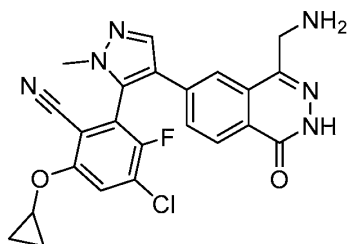
6. A method for reducing the size of malignant peripheral nerve sheath tumors in a subject, the method comprising administering to the subject a therapeutically effective amount of a protein arginine N-methyl transferase 5 (PRMT5) inhibitor which is a compound having formula (IA), (IB), (IC) or (ID)



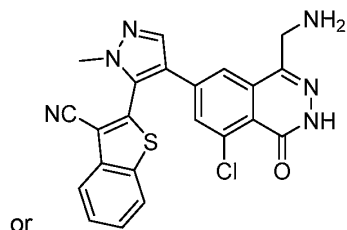
(IA),



(IB),

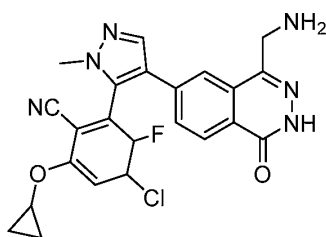


(IC),



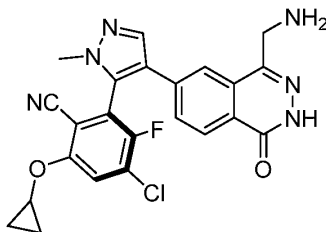
(ID).

7. The method of claim 6, wherein the PRMT5 inhibitor is:



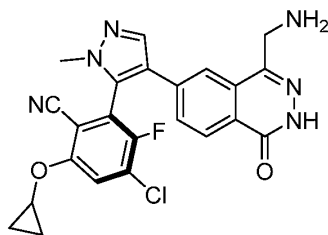
or a pharmaceutically acceptable salt thereof.

8. The method of claim 6, wherein the PRMT5 inhibitor is:



or a pharmaceutically acceptable salt thereof.

9. The method of claim 6, wherein the PRMT5 inhibitor is a pharmaceutically acceptable salt of a compound of the formula:



10. The method of claim 6, wherein the PRMT5 inhibitor is a compound of the formula:

