

[00042] ADCs will provide a means of delivering Bcl-xL inhibitors that would be difficult to deliver in unconjugated form. Due to their low cell permeability, once inside the cell, the Bcl-xL inhibitors will be unlikely to “leak” out of the cell.

[00042a] In one aspect, there is provided the use of an ADC as described herein, or a pharmaceutically acceptable salt thereof, effective to provide therapeutic benefit in the manufacture of a medicament for treating a disease involving dysregulated intrinsic apoptosis, wherein the antibody of the ADC binds a cell surface receptor on a cell whose intrinsic apoptosis is dysregulated.

[00042b] In one aspect, there is provided the use of an ADC as described herein, or a pharmaceutically acceptable salt thereof, that is capable of binding a cell surface receptor or a tumor associated antigen expressed on the surface of the cancer cells, in an amount effective to provide therapeutic benefit in the manufacture of a medicament for treating cancer.

[00042c] In one aspect, there is provided the use of an ADC as described herein, or a pharmaceutically acceptable salt thereof, that is capable of binding the tumor, in an amount effective to sensitize the tumor cell to a standard cytotoxic agent and/or radiation, in the manufacture of a medicament for sensitizing a tumor to standard cytotoxic agents and/or radiation.

4. DETAILED DESCRIPTION

[00043] The present disclosure concerns Bcl-xL inhibitors having low cell permeability, ADCs comprising the inhibitors, synthons useful for synthesizing the ADCs, compositions comprising the inhibitors or ADCs, and various methods of using the inhibitors and ADCs.

[00044] As will be appreciated by skilled artisans, the ADCs disclosed herein are “modular” in nature. Throughout the instant disclosure, various specific embodiments of the various “modules” comprising the ADCs, as well as the synthons useful for synthesizing the ADCs, are described. As specific non-limiting examples, specific embodiments of antibodies, linkers, and Bcl-xL inhibitors that may comprise the ADCs and synthons are described. It is intended that all of the specific embodiments described may be combined with each other as though each specific combination were explicitly described individually.

[00045] It will also be appreciated by skilled artisans that the various Bcl-xL inhibitors, ADCs and/or ADC synthons described herein may be in the form of salts, and in certain embodiments, particularly pharmaceutically acceptable salts. The compounds of the present disclosure that possess a sufficiently acidic, a sufficiently basic, or both functional groups, can react with any of a number of

[00046] inorganic bases, and inorganic and organic acids, to form a salt. Alternatively, compounds that are inherently charged, such as those with a quaternary nitrogen, can form a salt with an appropriate counterion, e.g., a halide such as a bromide, chloride, or fluoride.

[00047] Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, *etc.* Base addition salts include those derived from inorganic bases, such as ammonium and alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like.

[00048] In the disclosure below, if both structural diagrams and nomenclature are included and if the nomenclature conflicts with the structural diagram, the structural diagram controls.

82. A method of making an ADC, comprising contacting a synthon according to **any one of claims 62-76**, or a pharmaceutically acceptable salt thereof, with an antibody under conditions in which the synthon covalently links to the antibody.

83. A method of inhibiting Bcl-xL activity in a cell that expresses Bcl-xL, comprising contacting the cell with an ADC according to **any one of claims 34-58 and 77-78**, or a pharmaceutically acceptable salt thereof, that is capable of binding the cell, under conditions in which the ADC binds the cell.

84. A method of inducing apoptosis in a cell which expresses Bcl-xL, comprising contacting the cell with an ADC according to **any one of claims 34-58 and 77-78**, or a pharmaceutically acceptable salt thereof, that is capable of binding the cell, under conditions in which the ADC binds the cell.

85. Use of an ADC according to **any one of claims 34-58 and 77-78**, or a pharmaceutically acceptable salt thereof, effective to provide therapeutic benefit in the manufacture of a medicament for treating a disease involving dysregulated intrinsic apoptosis, wherein the antibody of the ADC binds a cell surface receptor on a cell whose intrinsic apoptosis is dysregulated.

86. Use of an ADC according to **any one of claims 34-58 and 77-78**, or a pharmaceutically acceptable salt thereof, that is capable of binding a cell surface receptor or a tumor associated antigen expressed on the surface of the cancer cells, in an amount effective to provide therapeutic benefit in the manufacture of a medicament for treating cancer.

87. The use of **claim 86** in which the ADC is to be administered as monotherapy.

88. The use of **claim 86** in which the ADC is to be administered adjunctive to another chemotherapeutic agent radiation therapy.

89. The use of **claim 86** in which the cancer being treated is a tumorigenic cancer.

90. The use of **claim 89** in which the cancer being treated is a blood cancer.

91. The use of **claim 89** in which the ADC is to be administered as monotherapy.

92. The use of **claim 89** in which the ADC is to be administered adjunctive to standard chemotherapy and/or radiation therapy.

93. The use of **claim 92** in which the ADC is to be administered concurrently with the initiation of the standard chemotherapy and/or radiation therapy.

94. The use of **claim 92** in which the ADC is to be administered prior to initiating the standard chemotherapy and/or radiation therapy.

95. The use of **any one of claims 91-94** in which the ADC is to be administered in an amount effective to sensitize the tumor cells to standard chemotherapy and/or radiation therapy.

96. Use of an ADC according to **any one of claims 34-58 and 77-78**, or a pharmaceutically acceptable salt thereof, that is capable of binding the tumor, in an amount effective to sensitize the tumor cell to a standard cytotoxic agent and/or radiation, in the manufacture of a medicament for sensitizing a tumor to standard cytotoxic agents and/or radiation.

97. The use of **claim 96** in which the tumor has become resistant to treatment with standard cytotoxic agents and/or radiation.

98. The use of **claim 96** in which the tumor has not been previously exposed to standard cytotoxic agents and/or radiation therapy.

99. The synthon of **claim 62**, selected from the group consisting of synthon examples 2.1, 2.2, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29, 2.30, 2.31, 2.32, 2.33, 2.34, 2.35, 2.36, 2.37, 2.38, 2.39, 2.40, 2.41, 2.42, 2.43, 2.44, 2.45, 2.46, 2.47, 2.48, 2.49, 2.50, 2.51, 2.52, 2.53, 2.54, 2.55, 2.56, 2.57, 2.58, 2.59, 2.60, 2.61, 2.62, 2.63, 2.64, 2.65, 2.66, 2.67, 2.68, 2.69, 2.77, 2.78, 2.79, 2.80, 2.81, 2.82, 2.83, 2.84, 2.85, 2.86, 2.87, 2.88, 2.89, 2.90, 2.91, 2.92, 2.93, 2.94, 2.95, 2.96, 2.97, 2.98, 2.101, 2.102, 2.103, 2.104, 2.105, 2.106, 2.107, 2.108, 2.109, 2.110, 2.111, 2.112, 2.113, 2.114, 2.115, 2.116, 2.117, 2.118, 2.119, 2.120, 2.121, 2.122, 2.123, 2.124, 2.125, 2.126, 2.127, 2.128, 2.129, 2.130, 2.131, 2.132, 2.133, 2.134, 2.135, 2.136, 2.137, 2.138, 2.139, 2.140, 2.141, 2.142, 2.143, 2.144, 2.145, 2.146, 2.147, 2.148, 2.149, 2.150, 2.151, 2.152, 2.153, 2.154, 2.155, 2.156, 2.157, 2.158, 2.159, 2.160, 2.161, 2.162, 2.163, 2.164, 2.166, 2.167, 2.168, 2.169, 2.170, 2.171, 2.172, 2.173, 2.174, 2.175, 2.176, and pharmaceutically acceptable salts thereof.

100. The ADC of **claim 34**, or a pharmaceutically acceptable salt thereof, wherein the drug is selected from the group consisting of W2.01, W2.02, W2.03, W2.04, W2.05, W2.06, W2.07, W2.08, W2.09, W2.10, W2.11, W2.12, W2.13, W2.14, W2.15, W2.16, W2.17, W2.18, W2.19,