

inhibiting metastasis of a cancer in a patient in need thereof.

[0010h] In a tenth aspect, there is provided use of a compound of the first aspect or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for treating a subject having a cancer,

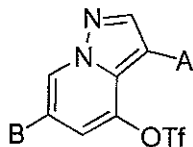
wherein (a) prior to such treating, the subject has been administered one or more doses of a RET inhibitor that is not a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof for a period of time and (b) a determination has been made whether a cancer cell in a sample obtained from the subject following such administration has at least one RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with a RET inhibitor that is not a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof of (a);
and wherein

(c) a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof is to be administered in monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with a RET inhibitor that is not a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof of (a).

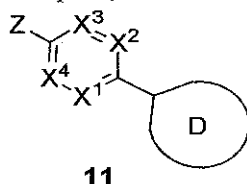
[0010i] In an eleventh aspect, there is provided use of a compound of the first aspect or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for treating a subject having a cancer, wherein

(a) after the subject has been administered one or more doses of a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof for a period of time;; (b) a determination has been made whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with a compound of General Formula I or a pharmaceutically acceptable salt

(a) for a compound of the first aspect where E is H and A, B, X¹, X², X³, X⁴, and D are as defined in the first aspect, coupling a corresponding compound having the formula



where A and B are as defined in the first aspect, with a compound having the formula 11



in the presence of a palladium catalyst and optionally a ligand and in the presence of a base, where Z is -B(OR^a)(OR^b) and R^a and R^b are H or (1-6C)alkyl, or R^a and R^b together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents

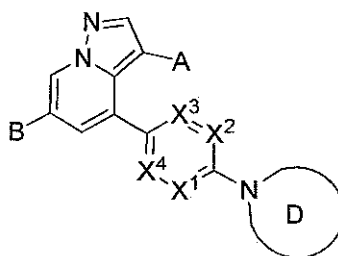
selected from (C1-C3 alkyl), the  ring is as defined for hetCyc¹, hetCyc² and hetCyc³ of Formula I, and X¹, X², X³ and X⁴ are as defined in the first aspect, followed by removal of a protecting group on the D ring if present; or

(b) for a compound of the first aspect where A, B, X¹, X², X³, X⁴, D and E are as defined in the first aspect with the exception that E is not hydrogen, functionalizing a corresponding compound having the formula

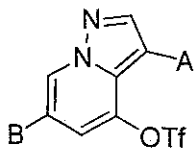


wherein the  moiety is as defined for hetCyc¹, hetCyc² and hetCyc³ of Formula I, and A, B, X¹, X², X³ and X⁴ are as defined for General Formula I; or

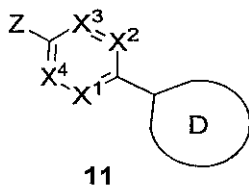
(c) for a compound of the first aspect where A is CN, D is as defined in the first aspect provided that the D ring is coupled to the ring defined by X¹, X², X³ and X⁴ through a ring nitrogen atom in the D ring, X¹, X², X³, X⁴ are as defined in the first aspect provided that at least one of X¹ and X² is nitrogen, and E is as defined in the first aspect, reacting a corresponding compound having the formula **15**



15



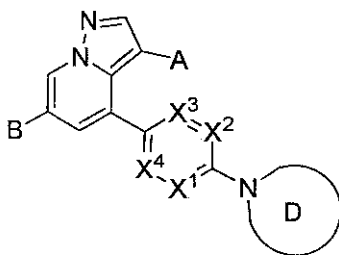
where A and B are as defined in claim 1, with a compound having the formula **11**



in the presence of a palladium catalyst and optionally a ligand and in the presence of a base, where Z is $-B(OR^a)(OR^b)$ and R^a and R^b are H or (1-6C)alkyl, or R^a and R^b together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents

selected from (C1-C3 alkyl), the  ring is as defined for hetCyc¹, hetCyc² and hetCyc³ of Formula I, and X¹, X², X³ and X⁴ are as defined in claim 1, followed by removal of a protecting group on the D ring if present; or

(b) for a compound of claim 1 where A, B, X¹, X², X³, X⁴, D and E are as defined in claim 1 with the exception that E is not hydrogen, functionalizing a corresponding compound having the formula



wherein the  moiety is as defined for hetCyc¹, hetCyc² and hetCyc³ of Formula I, and A, B, X¹, X², X³ and X⁴ are as defined for General Formula I; or

(c) for a compound of claim 1 where A is CN, D is as defined in claim 1 provided that the D ring is coupled to the ring defined by X¹, X², X³ and X⁴ through a ring nitrogen atom in the D ring, X¹, X², X³, X⁴ are as defined for claim 1 provided that at least one of X¹ and X² is nitrogen, and E is as defined in claim 1, reacting a corresponding compound having the formula **15**

wherein (a) prior to such treating, the subject has been administered one or more doses of a RET inhibitor that is not a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof for a period of time and (b) a determination has been made whether a cancer cell in a sample obtained from the subject following such administration has at least one RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with a RET inhibitor that is not a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof of (a);
and wherein

(c) a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof is to be administered in monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with a RET inhibitor that is not a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof of (a).

87. The use of claim 86, wherein the anticancer agent in (c) is another RET inhibitor.

88. The use of claim 87, wherein the anticancer agent in (c) is the same RET inhibitor administered in step (a).

89. The use of claim 86, wherein the subject is to be administered additional doses of the RET inhibitor that is not a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof of (a), and the subject is to be administered another anticancer agent.

90. The use of claim 89, wherein the anticancer agent is another RET inhibitor.