

rearrangements that are a hallmark of cancer. In response to RS, ATR triggers arrest of the cell cycle in the S and G2/M stages by phosphorylation of CHK1.

ATR can prevent cancer development, as the ATR checkpoint response might limit the expansion of precancerous cells undergoing RS as a result of oncogene activation. Moreover, because the ATR–CHK1 checkpoint pathway serves to ensure cell survival after RS, a normal and robust ATR–CHK1 checkpoint may be a mechanism of resistance to chemotherapy and may allow cancer cells to survive with high endogenous levels of RS.

Inhibition of ATR–CHK1 pathway components could potentially enhance the effectiveness of replication inhibitors. In addition, ATR inhibition may be particularly toxic for cells with high levels of RS, such as those expressing oncogenes or lacking tumour suppressors. In these cells, strong limitation of ATR activity (for example, by use of an ATR inhibitor) would generate lethal amounts of RS leading to cell death.

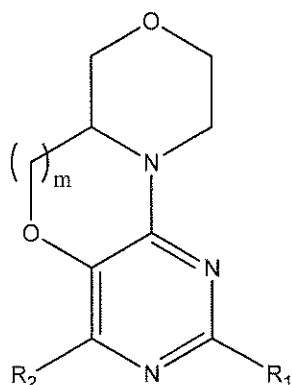
A potential advantage of sensitizing cells in this way would be the capacity to lower the doses of the replication inhibitors. This would result in reduced toxicity to haematological and gastrointestinal organ systems among others, if the normal cells are not sensitized to the same extent. Specificity of the replication inhibitor for causing cancer cell death may be assisted by the fact that untransformed cells have more robust S and G2 checkpoints than tumour cells. For example, many cancers have mutations in p53 or other components of the p53 pathway, leading to reliance on the S and G2 checkpoints to arrest the cell cycle and provide for repair and survival. Inhibition of the S and G2 checkpoints may then preferentially kill these p53 deficient tumour cells.

The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

There is a lack of potent inhibitors of ATR. Therefore, a need exists for chemical entities that selectively inhibit ATR for clinical use or for further study of the ATR response.

Summary of the Invention

In one aspect, there is provided a chemical entity selected from compounds of formula (I)



2. (I)

wherein

R_1 is selected from aryl or heteroaryl;

R_2 is selected from $NR_3SO_2R_3$, alkyl, cycloalkyl, aryl and heteroaryl; wherein R_3 is independently selected at each occurrence from H, alkyl optionally substituted by 1, 2 or 3 halo atoms, cycloalkyl optionally substituted by 1, 2 or 3 halo atoms and heterocycloalkyl optionally substituted by 1, 2 or 3 halo atoms; and m is 1 or 2; alkyl is a linear saturated hydrocarbon having up to 10 carbon atoms (C_1 - C_{10}) or a branched saturated hydrocarbon of between 3 and 10 carbon atoms (C_3 - C_{10}); cycloalkyl is a mono- or bi-cyclic saturated C_3 - C_{10} hydrocarbon, which may optionally be fused to an aryl group; or cycloalkyl is adamantyl; heterocycloalkyl is a C-linked or N-linked 3-10 membered saturated mono- or bi-cyclic ring, which contains 1, 2, 3 or 4 ring heteroatoms independently selected from N, S and O, wherein an N or S atom in the ring may be substituted with oxygen to form an N-oxide, sulfoxide or sulfone group;

aryl is phenyl, biphenyl or naphthyl; and

heteroaryl is a 5, 6, 9 or 10, 12, 13 or 14 membered mono-, bi- or tri-cyclic aromatic ring, which may contain 1, 2, 3 or 4 ring heteroatoms independently selected from N, S and O;

and pharmaceutically acceptable salts, solvates and stereoisomers thereof.

In another aspect, there is provided a pharmaceutical composition comprising a chemical entity as disclosed above and a pharmaceutically acceptable carrier, diluent or excipient.

In another aspect, there is provided a chemical entity as disclosed above for use in medicine.

In another aspect, there is provided a chemical entity as disclosed above for use in a method of treatment of a disease or condition in which ATR activity is implicated.

In another aspect, there is provided use of a chemical entity as disclosed above in the manufacture of a medicament for the treatment of a disease or condition in which ATR activity is implicated.

In another aspect, there is provided a combination product comprising:

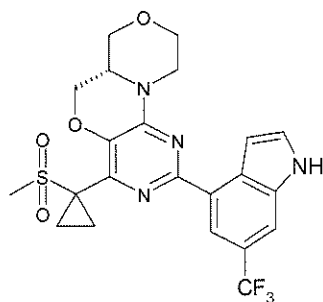
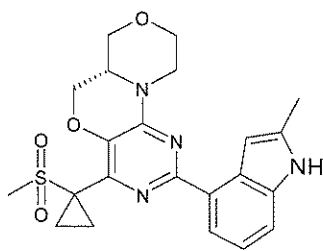
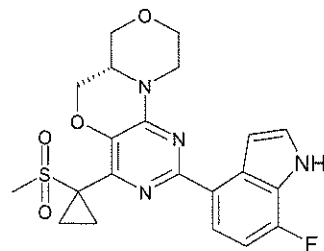
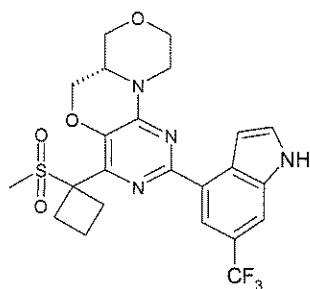
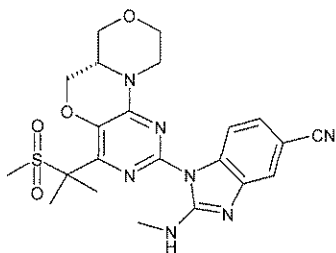
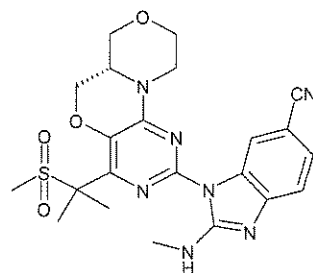
(A) a chemical entity as disclosed above; and

(B) another therapeutic agent that is useful in the treatment of in the treatment of cancer and/or a proliferative disease,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Detailed Disclosure

The present invention relates to a series of tricyclic chemical entities that are inhibitors of ATR. These chemical entities demonstrate good selectivity for ATR and are potentially useful in the



and pharmaceutically acceptable salts, solvates and stereoisomers thereof.

- 5 14. A pharmaceutical composition comprising a chemical entity as claimed in any one of claims 1 to ~~13~~¹³⁴³ and a pharmaceutically acceptable carrier, diluent or excipient.
- 15 15. A chemical entity as claimed in any one of claims 1 to ~~13~~¹³⁴³ for use in medicine.
- 10 ~~16. A method of treatment of a disease or condition in which ATR activity is implicated comprising administration to a subject in need thereof a therapeutically effective amount of a chemical entity as claimed in any one of claims 1 to 13.~~
- 15 ~~17.16.~~ A chemical entity as claimed in any one of claims 1 to ~~13~~¹³⁴³ for use in a method of treatment of a disease or condition in which ATR activity is implicated.
- 20 ~~18.17.~~ Use of a chemical entity as claimed in any one of claims 1 to ~~13~~¹³⁴³ in the manufacture of a medicament for the treatment of a disease or condition in which ATR activity is implicated.
- ~~19.18.~~ The method of claim ~~16~~, chemical entity as claimed in claim ~~17~~¹⁶ or use of as claimed in claim ~~17~~¹⁸, wherein the disease or condition in which ATR activity is implicated is a disease or condition associated with increased proliferation, such as cancer.

~~20-19.~~ The ~~method or chemical entity~~ or use of claim ~~189~~, wherein the disease or condition in which ATR activity is implicated is endometrial cancer, colon cancer or stomach cancer.

~~21-20.~~ A combination product comprising:

(A) a chemical entity as claimed in any one of claims 1 to ~~1313~~; and

(B) another therapeutic agent that is useful in the treatment of in the treatment of cancer and/or a proliferative disease,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.