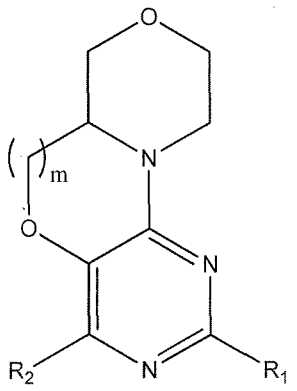


(I)

wherein

R_1 is ~~selected from aryl or heteroaryl~~ a bicyclic heteroaryl group optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halo, OH, CN, $COOR_4$, CF_3, NR_4R_4, NR_4COR_4, $(NR_4)_nSO_2R_4$, wherein n is 0 or 1, NHR_5, alkyl optionally substituted by 1, 2 or 3 halo atoms, O-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;

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~~and, wherein when R_2 is selected from alkyl, cycloalkyl, aryl and heteroaryl, then

said alkyl and cycloalkyl may optionally be substituted at each occurrence with 1, 2, 3, 4 or 5 substituents, wherein the substituents are independently selected from halo, OH, CN, $COOR_4$, CF_3, NR_4R_4, NR_4COR_4, $(NR_4)_nSO_2R_4$, wherein n is 0 or 1, alkyl optionally

substituted by 1, 2 or 3 halo atoms, cycloalkyl optionally substituted by 1,2 or 3 halo atoms, O-alkyl optionally substituted by 1, 2 or 3 halo atoms, and wherein two substituents on a single atom may be taken together with the atom to which they are attached to form a cyclic structure selected from cycloalkyl and heterocycloalkyl optionally substituted by 1, 2 or 3 groups selected from halo, $C(O)C_1$-C_4 alkyl, C(O)O-(C_1-C_4 alkyl) and C_1-C_4 alkyl optionally substituted with 1, 2 or 3 halo atoms;

said aryl and heteroaryl may be optionally substituted at each occurrence with 1, 2, 3, 4 or 5 substituents independently selected from halo, OH, CN, $COOR_4$, CF_3, NR_4R_4, NR_4COR_4, $(NR_4)_nSO_2R_4$, wherein n is 0 or 1, NHR_5, alkyl optionally substituted by 1, 2 or 3 halo atoms, O-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;

R_4 is independently selected at each occurrence from H, alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl, wherein alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2 or 3 substituents selected from halo, alkyl, O-alkyl, $N(C_1$-C_4alkyl$)_2$, $N(C_1$-C_4alkyl$)COC_1$-C_4alkyl, or the R_4 groups are taken together with the atom(s) to which they are attached to form a heterocycloalkyl, optionally substituted by 1, 2 or 3 halo atoms or, where a substituent comprising an R_4 group is present on an alkyl, cycloalkyl or heterocycloalkyl, the R_4 group may be taken together with a substituent on that alkyl, cycloalkyl or heterocycloalkyl to form a heterocycloalkyl optionally substituted by 1, 2 or 3 halo atoms; and

R_5 is independently selected from COalkyl, COaryl or COheteroaryl;

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, wherein said disease or condition in which ATR activity is implicated is selected from the group consisting of haematological malignancies, leukaemia, multiple myeloma, lymphomas, Hodgkin's disease, non-Hodgkin's lymphomas, mantle cell lymphoma, myelodysplastic syndromes, solid tumours and their metastases, breast cancer, lung cancer, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), squamous cell carcinoma, endometrial cancer, tumours of the central nervous system, gliomas, dysembryoplastic neuroepithelial tumour, glioblastoma multiforme, mixed gliomas, medulloblastoma, retinoblastoma, neuroblastoma, germinoma, teratoma, cancers of the gastrointestinal tract, gastric cancer, oesophagal cancer, hepatocellular (liver) carcinoma, cholangiocarcinomas, colon and rectal carcinomas, cancers of the small intestine, pancreatic cancers, cancers of the skin, melanomas, metastatic melanoma, thyroid cancers, cancers of the head and neck and cancers of the salivary glands, prostate, testis, ovary, cervix, uterus, vulva, bladder, kidney, renal cell carcinoma, clear cell and renal oncocytoma, squamous cell carcinomas, sarcomas, osteosarcoma, chondrosarcoma, leiomyosarcoma, soft tissue sarcoma, Ewing's sarcoma, gastrointestinal stromal tumour (GIST), Kaposi's sarcoma, and paediatric cancers, rhabdomyosarcomas and neuroblastomas.

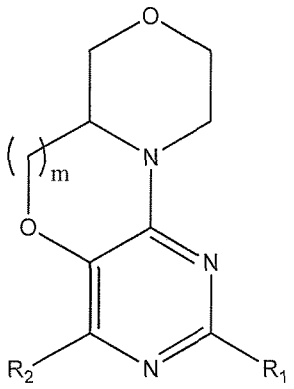
In another aspect, there is provided a combination product comprising:
(A) a chemical entity as disclosed above; and
(B) another therapeutic agent that is useful in the treatment of in the treatment of cancer and/or a proliferative disease,
wherein each of components (A) and (B) is formulated in admixture 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

CLAIMS

1. A chemical entity selected from compounds of formula (I)



(I)

wherein

R_1 is ~~selected from aryl or heteroaryl~~a bicyclic heteroaryl group optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from halo, OH, CN, $COOR_4$, CF_3, NR_4R_4, NR_4COR_4, $(NR_4)_nSO_2R_4$, wherein n is 0 or 1, NHR_5, alkyl optionally substituted by 1, 2 or 3 halo atoms, O-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;

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, wherein when R_2 is selected from alkyl, cycloalkyl, aryl and heteroaryl, then

said alkyl and cycloalkyl may optionally be substituted at each occurrence with 1, 2, 3, 4 or 5 substituents, wherein the substituents are independently selected from halo, OH, CN, $COOR_4$, CF_3, NR_4R_4, NR_4COR_4, $(NR_4)_nSO_2R_4$, wherein n is 0 or 1, alkyl optionally substituted by 1, 2 or 3 halo atoms, cycloalkyl optionally substituted by 1,2 or 3 halo atoms, O-alkyl optionally substituted by 1, 2 or 3 halo atoms, and wherein two substituents on a single atom may be taken together with the atom to which they are attached to form a cyclic structure selected from cycloalkyl and heterocycloalkyl optionally substituted by 1, 2 or 3 groups selected from halo, $C(O)C_1$-C_4 alkyl, $C(O)O$-(C_1-C_4 alkyl) and C_1-C_4 alkyl optionally substituted with 1, 2 or 3 halo atoms;

said aryl and heteroaryl may be optionally substituted at each occurrence with 1, 2, 3, 4 or 5 substituents independently selected from halo, OH, CN, $COOR_4$, CF_3, NR_4R_4, NR_4COR_4, $(NR_4)_nSO_2R_4$, wherein n is 0 or 1, NHR_5, alkyl optionally substituted by 1, 2 or 3 halo atoms, O-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;

R_4 is independently selected at each occurrence from H, alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl, wherein alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2 or 3 substituents selected from halo, alkyl, O-alkyl, $N(C_1$-C_4alkyl)$_2$, $N(C_1$-C_4alkyl)COC_1-C_4alkyl, or the R_4 groups are taken together with the atom(s) to which they are attached to form a heterocycloalkyl, optionally substituted by 1, 2 or 3 halo atoms or, where a substituent comprising an R_4 group is present on an alkyl, cycloalkyl or heterocycloalkyl, the R_4 group may be taken together with a substituent on that alkyl, cycloalkyl or heterocycloalkyl to form a heterocycloalkyl optionally substituted by 1, 2 or 3 halo atoms; and

R_5 is independently selected from COalkyl, COaryl or COheteroaryl;

and pharmaceutically acceptable salts, solvates and stereoisomers thereof.

~~2. A chemical entity as claimed in claim 1, wherein when any of R_1, R_2 and R_3 is selected from alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, then~~

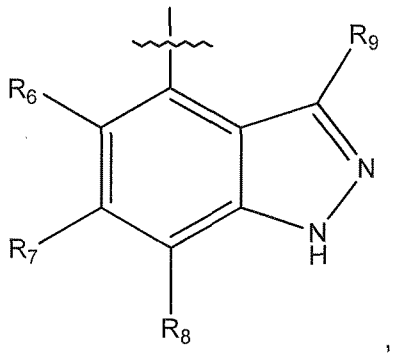
~~said alkyl, heterocycloalkyl and cycloalkyl may optionally be substituted at each occurrence with 1, 2, 3, 4 or 5 substituents, wherein the substituents are independently selected from halo, OH, CN, $COOR_4$, CF_3, NR_4R_4, NR_4COR_4, $(NR_4)_nSO_2R_4$, wherein n is 0 or 1, alkyl optionally substituted by 1, 2 or 3 halo atoms, cycloalkyl optionally substituted by 1,2 or 3 halo atoms, O-alkyl optionally substituted by 1, 2 or 3 halo atoms, and wherein two substituents on a single atom may be taken together with the atom to which they are attached to form a cyclic structure selected from cycloalkyl and heterocycloalkyl optionally substituted by 1, 2 or 3 groups selected from halo, $C(O)C_1$-C_4 alkyl, $C(O)O$-(C_1-C_4 alkyl) and C_1-C_4 alkyl optionally substituted with 1, 2 or 3 halo atoms;~~

~~said aryl and heteroaryl may be optionally substituted at each occurrence with 1, 2, 3, 4 or 5 substituents independently selected from halo, OH, CN, $COOR_4$, CF_3, NR_4R_4, NR_4COR_4, $(NR_4)_nSO_2R_4$, wherein n is 0 or 1, NHR_5, alkyl optionally substituted by 1, 2 or 3 halo atoms, O-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;~~

~~R_4 is independently selected at each occurrence from H, alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl, wherein alkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2 or 3 substituents selected from halo, alkyl, O-alkyl, $N(C_1$-C_4alkyl)$_2$, $N(C_1$-C_4alkyl)COC_1-C_4alkyl, or the R_4 groups are taken together with the atom(s) to which they are attached to form a heterocycloalkyl, optionally substituted by 1, 2 or 3 halo atoms or, where a substituent comprising an R_4 group is present on an alkyl, cycloalkyl or heterocycloalkyl, the R_4 group may be taken together with a substituent on that alkyl, cycloalkyl or heterocycloalkyl to form a heterocycloalkyl optionally substituted by 1, 2 or 3 halo atoms; and~~

~~R_5 is independently selected from COalkyl, COaryl or COheteroaryl.~~

~~3.~~2. A chemical entity as claimed in claim 1, wherein R_1 is selected from



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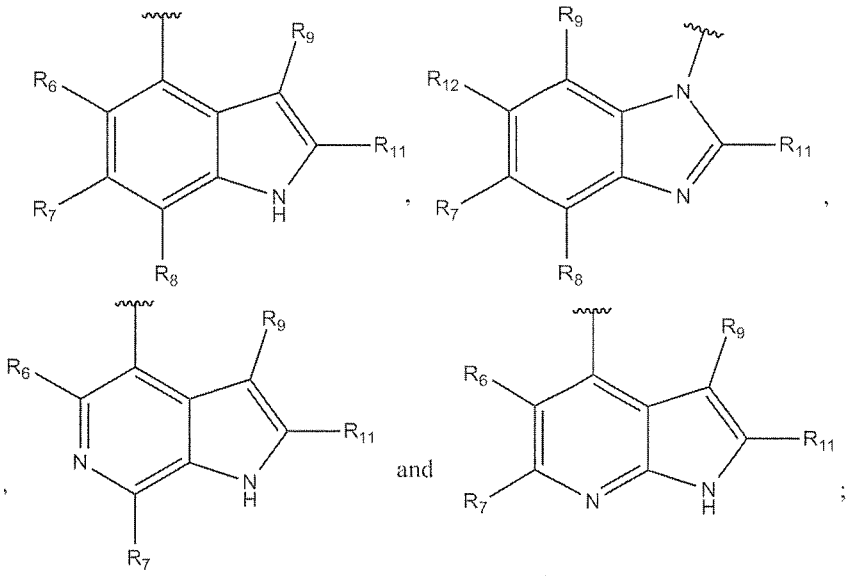


wherein

R_6 is selected from halo and H;

R_7, R_8 and R_9 are each independently selected from H; halo; CN; R_{10}; and OR_{10};

wherein R_{10} is $(C_1\text{-}C_6)$alkyl optionally substituted with 1, 2 or 3 halo atoms;

R_{11} is selected from H, R_{10}, NR_4R_4 and NR_4COR_4;

wherein R_4 is independently selected at each occurrence from H or alkyl optionally substituted by 1, 2 or 3 halo atoms, or the R_4 groups are taken together with the atom(s) to which they are attached to form heterocycloalkyl, optionally substituted by 1, 2 or 3 halo atoms; and

R_{12} is selected from H, halo, OR_{10} or R_{10}.

~~4.~~3. A chemical entity as claimed in claim ~~3~~2, wherein

R_6 is selected from H and halo;

R_7, R_8 and R_9 are selected from H, halo, CN, $O(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_6)$alkyl optionally substituted by one or more halo atoms;

R_{11} is selected from H, $(C_1\text{-}C_6)$alkyl, NR_4R_4 and NR_4COR_4; and

R_{12} is selected from H, halo, $(C_1\text{-}C_6)$alkyl and $O(C_1\text{-}C_6)$alkyl.

~~5.~~4. A chemical entity as claimed in claim ~~3~~2, wherein R_6, R_7, R_8, R_9 and R_{12} are H; and R_{11} is selected from $(C_1\text{-}C_6)$alkyl, NR_4R_4 and NR_4COR_4.

~~6.~~5. A chemical entity as claimed in claim ~~3~~2, wherein R_6, R_8, R_9, R_{11} and R_{12} are H; and R_7 is selected from halo, CN, $O(C_1\text{-}C_6)$alkyl, and $(C_1\text{-}C_6)$alkyl optionally substituted by 1, 2 or 3 halo atoms.

7.6. A chemical entity as claimed in claim 32, wherein R_6, R_7, R_8, R_9, R_{11} and R_{12} are H.

8.7. A chemical entity as claimed in any preceding claim, wherein R_2 is selected from $NR_3SO_2R_3$, alkyl and cycloalkyl;

wherein alkyl and cycloalkyl is substituted with at least one substituent selected from $(NR_4)_nSO_2R_4$, wherein n is 0 or 1, OH and CN; and

wherein alkyl and cycloalkyl is further optionally substituted with 1 or 2 substituents independently selected from halo, CN, $COOR_4$, CF_3, $(C_1$-$C_6)$alkyl optionally substituted by 1, 2 or 3 halo atoms, cycloalkyl optionally substituted by 1, 2 or 3 halo atoms, and $O(C_1$-$C_6)$alkyl optionally substituted by 1, 2 or 3 halo atoms, or with 2 substituents on a single atom that are taken together with the atom to which they are attached to form a cyclic structure selected from cycloalkyl and heterocycloalkyl optionally substituted by 1, 2 or 3 groups selected from halo, C_1-C_4 alkyl, $C(O)C_1$-C_4 alkyl and $C(O)O$-C_1-C_4 alkyl.

9.8. A chemical entity as claimed in claim 87 wherein R_2 is $(CH_2)_pC(R_{13})_2(CH_2)_qQ$, wherein Q is $(NR_4)_nSO_2R_4$, OH or CN, wherein p and q are independently 0, 1 or 2, and wherein (i) R_{13} is independently selected at each occurrence from the group consisting of H and $(C_1$-$C_4)$alkyl, or (ii) one R_{13} is selected from the group consisting of H and $(C_1$-$C_4)$alkyl or the other R_{13} is taken together with R_4, if present, to form a 3-6 membered heterocycloalkyl optionally substituted by 1, 2 or 3 halo atoms, or (iii) the R_{13} groups are taken together with the carbon to which they are attached form a cyclic structure selected from $(C_3$-$C_6)$cycloalkyl and 3-6 membered heterocycloalkyl, optionally substituted by 1, 2 or 3 groups selected from halo, C_1-C_4 alkyl, $C(O)C_1$-C_4 alkyl and $C(O)O$-C_1-C_4 alkyl.

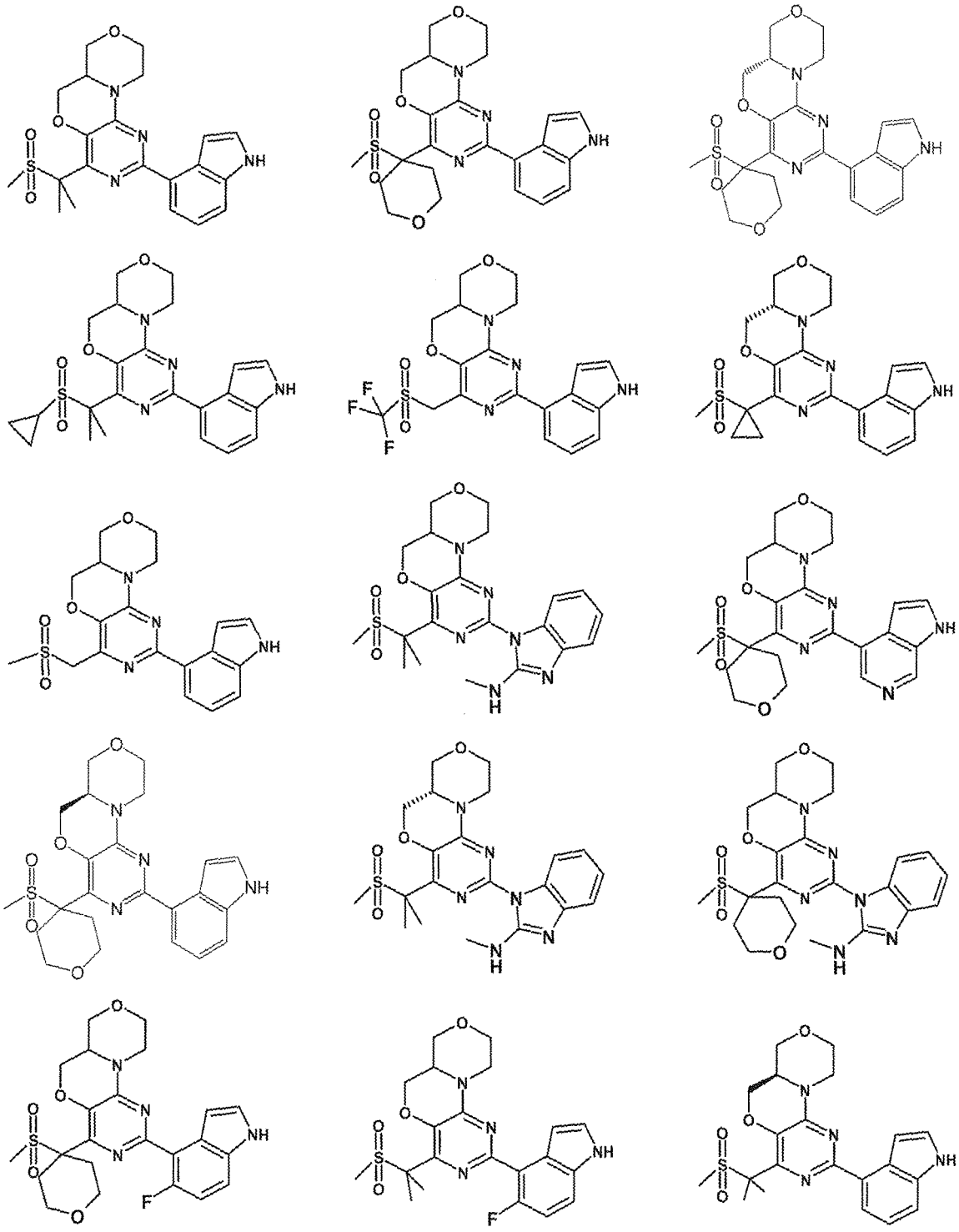
10.9. A chemical entity as claimed in claim 98, wherein both R_{13} groups are H, wherein both R_{13} groups are methyl or wherein the R_{13} groups are taken together with the carbon to which they are attached form cyclopropanyl, cyclobutyl, tetrahydropyranyl, piperidinyl, N-ethoxycarbonylpiperidinyl or *N*-methylpiperidinyl.

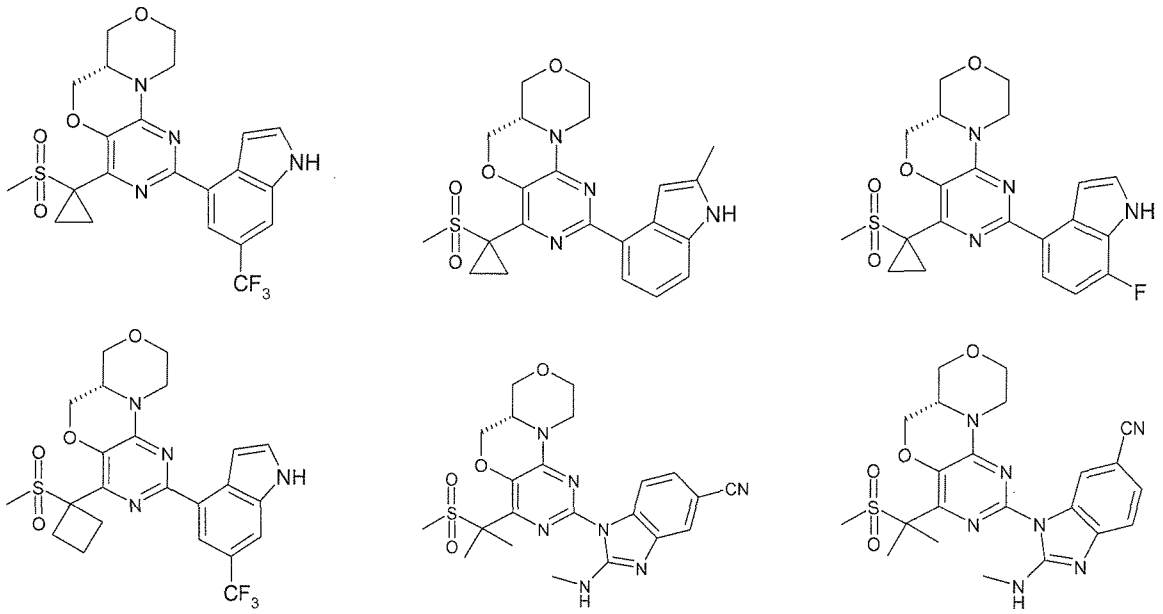
11.10. A chemical entity as claimed in claim 109, wherein Q is SO_2R_4.

12.11. A chemical entity as claimed in any preceding claim, wherein when m is 1 the mandatory chiral centre in the chemical entity of formula (I) is in the (*S*) configuration and wherein

when m is 2 the mandatory chiral centre in the chemical entity of formula (I) is in the (*R*) configuration.

~~13.~~12. A chemical entity as claimed in claim 1, selected from the group consisting of:





and pharmaceutically acceptable salts, solvates and stereoisomers thereof.

~~14.~~13. A pharmaceutical composition comprising a chemical entity as claimed in any one of claims 1 to ~~13~~ 12 and a pharmaceutically acceptable carrier, diluent or excipient.

~~15.~~14. A chemical entity as claimed in any one of claims 1 to ~~13~~ 12 for use in medicine.

~~16.~~15. A chemical entity as claimed in any one of claims 1 to ~~13~~ 12 for use in a method of treatment of a disease or condition in which ATR activity is implicated.

~~17.~~16. Use of a chemical entity as claimed in any one of claims 1 to ~~13~~ 12 in the manufacture of a medicament for the treatment of a disease or condition in which ATR activity is implicated, wherein said disease or condition in which ATR activity is implicated is selected from the group consisting of haematological malignancies, leukaemia, multiple myeloma, lymphomas, Hodgkin's disease, non-Hodgkin's lymphomas, mantle cell lymphoma, myelodysplastic syndromes, solid tumours and their metastases, breast cancer, lung cancer, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), squamous cell carcinoma, endometrial cancer, tumours of the central nervous system, gliomas, dysembryoplastic neuroepithelial tumour, glioblastoma multiforme, mixed gliomas, medulloblastoma, retinoblastoma, neuroblastoma, germinoma, teratoma, cancers of the gastrointestinal tract, gastric cancer, oesophagal cancer, hepatocellular (liver) carcinoma, cholangiocarcinomas, colon and rectal carcinomas, cancers of the small

intestine, pancreatic cancers, cancers of the skin, melanomas, metastatic melanoma, thyroid cancers, cancers of the head and neck and cancers of the salivary glands, prostate, testis, ovary, cervix, uterus, vulva, bladder, kidney, renal cell carcinoma, clear cell and renal oncocytoma, squamous cell carcinomas, sarcomas, osteosarcoma, chondrosarcoma, leiomyosarcoma, soft tissue sarcoma, Ewing's sarcoma, gastrointestinal stromal tumour (GIST), Kaposi's sarcoma, and paediatric cancers, rhabdomyosarcomas and neuroblastomas.

~~18.~~17. The chemical entity as claimed in claim 15~~16 or use of as claimed in claim 17~~, wherein the disease or condition in which ATR activity is implicated is ~~a disease or condition associated with increased proliferation, such as cancer~~selected from the group consisting of haematological malignancies, leukaemia, multiple myeloma, lymphomas, Hodgkin's disease, non-Hodgkin's lymphomas, mantle cell lymphoma, myelodysplastic syndromes, solid tumours and their metastases, breast cancer, lung cancer, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), squamous cell carcinoma, endometrial cancer, tumours of the central nervous system, gliomas, dysembryoplastic neuroepithelial tumour, glioblastoma multiforme, mixed gliomas, medulloblastoma, retinoblastoma, neuroblastoma, germinoma, teratoma, cancers of the gastrointestinal tract, gastric cancer, oesophagal cancer, hepatocellular (liver) carcinoma, cholangiocarcinomas, colon and rectal carcinomas, cancers of the small intestine, pancreatic cancers, cancers of the skin, melanomas, metastatic melanoma, thyroid cancers, cancers of the head and neck and cancers of the salivary glands, prostate, testis, ovary, cervix, uterus, vulva, bladder, kidney, renal cell carcinoma, clear cell and renal oncocytoma, squamous cell carcinomas, sarcomas, osteosarcoma, chondrosarcoma, leiomyosarcoma, soft tissue sarcoma, Ewing's sarcoma, gastrointestinal stromal tumour (GIST), Kaposi's sarcoma, and paediatric cancers, rhabdomyosarcomas and neuroblastomas.

~~19.~~18. The use as claimed in claim 16 or chemical entity ~~or use~~ of claim ~~18~~17, wherein the disease or condition in which ATR activity is implicated is endometrial cancer, colon cancer or stomach cancer.

~~20.~~19. A combination product comprising:

(A) a chemical entity as claimed in any one of claims 1 to ~~13~~12; 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.