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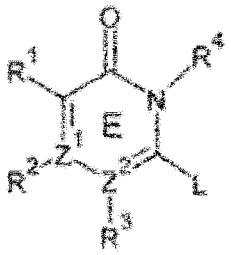
(56) Documents Cited:
EP 4105207 A1 **WO 2023/156386 A2**
WO 2023/019259 A1 **WO 2023/004280 A1**
WO 2019/084026 A1 **WO 2005/040159 A1**
US 20050080111 A1

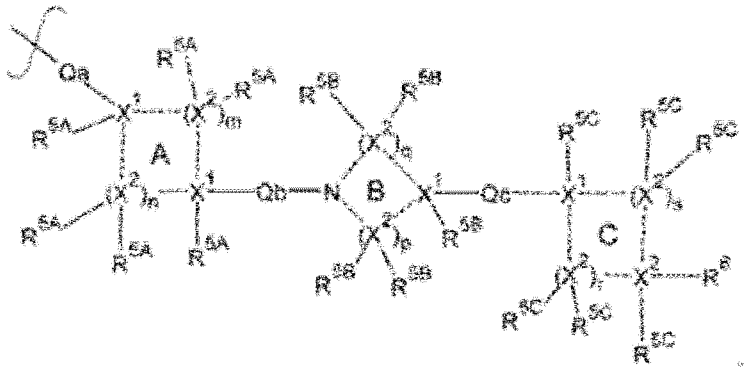
(58) Field of Search:
Other: **CAS ONLINE**

(54) Title of the Invention: **PARP1 inhibitor compounds**
Abstract Title: **Heterocyclic PARP1 inhibitor compounds and their use in the treatment of cancer**

(57) A PARP1 inhibitor compound has a structure of:



R^1 and R^4 are independently selected from H and an organic group. R^2 and R^3 are independently absent, H, or an organic group. Z^1 and Z^2 are independently C or N. L has the structure:



Each X^1 is independently selected from C and N. Each X^2 is independently selected from C, N, O and S. Integers n, m, p, q, and s are each in a range of 0-6, provided that m + n, p + q, and r + s are each integers in the range of 2 to 6. Each R^{5a}, R^{5b}, R^{5c}, and R^6 is independently absent, H, or an organic group. Qa, Qb, Qc are each independently a bond or an organic linker. The compounds are poly(ADP-ribose) polymerase (PARP) inhibitors and are useful in medicine, e.g., for use in treating cancer. Also provided are composition and kits comprising the compounds, and methods of synthesising the compounds.

GB 2630970 A

PARP1 Inhibitor Compounds

Technical Field

The present invention relates to PARP1 inhibitor compounds, and in particular to PARP1 inhibitor compounds for use in medicine. The inhibitors of the invention may be used in pharmaceutical compositions, and in particular pharmaceutical compositions for treating a cancer. The invention also relates to methods of manufacture of such inhibitors, and methods of treatment using such inhibitors.

Background

The family of poly(ADP-ribose) polymerases (PARPs) consists of 17 PARP proteins that catalyse the transfer of ADP-ribose to target proteins, a posttranslational process termed PARylation. Target protein modification by PARylation causes significant changes to function and as such PARPs play an important role in many cellular processes such as chromatin remodelling, transcription, replication, recombination, cell cycle progression and DNA damage repair (Kamaletdinova, T. *et al. Cell.* 2019; 8: 1625).

PARP1 and 2 are the most widely studied PARP enzymes, primarily due to their role in DNA damage repair, in particular in the base excision repair (BER) process of DNA single-strand breaks (Ngoi, YL. *et al. Cancer J.* 2021; 27: 521-528). PARP1 is activated by DNA damage breaks, and the subsequent PARylation of target proteins leads to recruitment of additional factors that initiate repair of DNA lesions. Auto-PARylation of PARP triggers the release of bound PARP from the DNA allowing other DNA repair proteins access to complete lesion repair. This highlights the critical role PARP plays in enabling a cancer cell to repair DNA damage caused by exogenous agents such as radiation therapy and chemotherapeutic agents.

Inhibition of PARP enzymes has been utilised as a strategy to selectively kill cancer cells that harbour genetic defects in complementary DNA damage repair pathways (Farmer, H. *et al. Nature.* 2005; 434: 917–921). This synthetic lethality approach has been demonstrated successfully in tumours with epigenetic modifications or deleterious mutations in BRCA1 and

BRCA2, two functionally redundant tumour suppressor proteins involved in DNA double-strand break (DSB) repair by homologous recombination (HR) (Lord, CJ. and Ashworth, A. *Science.* 2017; 355: 1152–1158). Such tumours with HR deficiency (HRD) are dependent on PARP function for survival – following PARP inhibition in these tumours, DSB breaks will be processed by alternative error-prone repair pathways leading to genomic instability and cancer cell death.

The inhibition of PARP can trap the inactivated PARP at the sites of DNA damage. This leads to replication fork stalling and subsequent collapse in S-phase when the fork reaches the site of the trapped PARP, resulting in the generation of genotoxic DNA double-strand breaks. It is believed that this PARP1-DNA trapping can lead to the selective death of cancer cells harbouring HRD (Farmer, H. *et al. Nature.* 2005; 434: 917–921).

This strategy has led to the successful approval of several PARP inhibitors for the treatment of cancers with HRD, such as in BRCA1/2-mutated breast, ovarian and prostate cancer, as well as in ovarian and prostate cancer harbouring genomic consequences of HRD, and ovarian cancer in the maintenance setting where platinum sensitivity acts as a surrogate for HRD (Fong, PC. *et al. N. Engl. J. Med.* 2009; 361: 123–134).

It has recently been shown that genomic instability, in the form of unrepaired DNA double-strand breaks or micronuclei disruption can trigger innate immune system activation via the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS), leading to generation of cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) and induction of dimerization of Stimulator of interferon genes (STING). STING subsequently translocates from the endoplasmic reticulum to the Golgi where it recruits and activates TANK-binding kinase 1 (TBK1). TBK1 phosphorylates interferon regulatory transcription factor 3 (IRF3) which drives the production of type I interferons and supports the induction of an adaptive immune response (Zhu, Y. *et al. Mol. Cancer.* 2019, 18: 152).

For example, PARP inhibitor-induced STING pathway activation and anti-tumour immune responses have been demonstrated in multiple tumour models, providing rationale for exploiting combinations of PARP inhibitors with immunotherapies for improved therapeutic

efficacy (Sen, T. *et al. Cancer Discov.* 2019; 9: 646–661). For example, the PARP inhibitor Olaparib was also recently shown to induce synthetic lethal effects in combination with a synthetic cyclic dinucleotide STING agonist in DNA damage repair deficient cancer cells and a BRCA-deficient breast cancer model (Pantelidou, C. *et al.* 2021: bioRxiv 2021.01.26.428337v1).

Overall, modulation of nucleic acid sensing pathways via multiple mechanisms has been shown to promote anti-tumour efficacy in a variety of cell and animal models thus demonstrating therapeutic potential for augmenting efficacy of immunotherapies and overcoming resistance to immune checkpoint blockade through use of PARP inhibitors. There are numerous clinical trials ongoing combining PARP inhibitors with immunotherapies (reviewed in Chabanon, RM, *et al. Nat. Rev. Cancer*. 2021; 21: 701-717).

Recently, PARP1 has also been shown to bind the Epstein Barr Virus (EBV) genome and that PARP1 inhibition can alter EBV chromatin structure and latent gene expression (Morgan, SM. *et al. Nat. Commun.* 2022; 13: 187). Hence, PARP1 inhibitors may play a role in cancers where EBV plays a contributing role such as Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal and gastrointestinal cancers. Interestingly, EBV has also been shown to be a causative factor in multiple sclerosis (MS) whereby EBV infection greatly increases the risk of subsequent MS (Bjornevik, K. *et al. Science* (2021); 375: 296-301).

First-generation PARP inhibitors generally demonstrate non-selective activity at PARP1 and 2. Haematological toxicities such as anaemia, neutropenia and thrombocytopenia are associated with clinical use of these molecules which restricts their use in combination with cytotoxic chemotherapies and other targeted agents due to dose-limiting cytopenias (LaFargue, CJ. *et al. Lancet Oncol.* 2019, 20, e15–e28). Evidence from pre-clinical mouse studies strongly suggests that PARP2 inhibition is a major driver of these haematological toxicities, with PARP2 being particularly linked to erythrogenesis in mice (Farrés, J. *et al. Blood.* 2013; 122: 44-54). In addition, PARP2 function has been shown to be dispensable for anti-tumour activity in HRD mouse cancer models (Ronson, G E. *et al. Nat. Commun.* 2018, 9: 746). Taken together, these data suggest an unmet medical need for the development of inhibitors with improved selectivity for PARP1 over PARP2 and other PARPs, thus providing

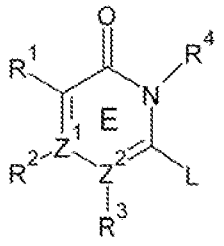
expanded therapeutic utility (1) as single agents and (2) in combination with other anti-cancer agents.

To date, two PARP1-selective inhibitors, AZD5305 and AZD9574, have entered clinical development. AZD5305 was described as a potent PARP1 inhibitor and trapper with 500-fold selectivity over PARP2 and less off-target activity against secondary pharmacology targets than first-generation PARP inhibitors (Johannes, JW. *et al. J. Med. Chem.* 2021; 64: 14498-14512). Importantly, significantly less haematotoxicity was observed for AZD5305 in rodent models than with first-generation PARP inhibitors, confirming the reported pathogenic role of PARP2 in haematologic toxicity (Illuzzi, G. *et al. Clin. Cancer Res.* 2022; CCR-22-0301).

Having regard to the above, it is an aim of the present invention to provide PARP1 inhibitors, and in particular PARP1 inhibitors for use in medicine. It is a further aim to provide pharmaceutical compositions comprising such inhibitors, and in particular to provide compounds and pharmaceutical compositions for treating a cancer. It is also an aim to provide methods of synthesis of the compounds.

Summary

In one aspect, there is provided a PARP1 inhibitor compound for use in medicine. The PARP1 inhibitor compound has the following structure:



wherein:

R^1 is selected from H and a substituted or unsubstituted organic group;

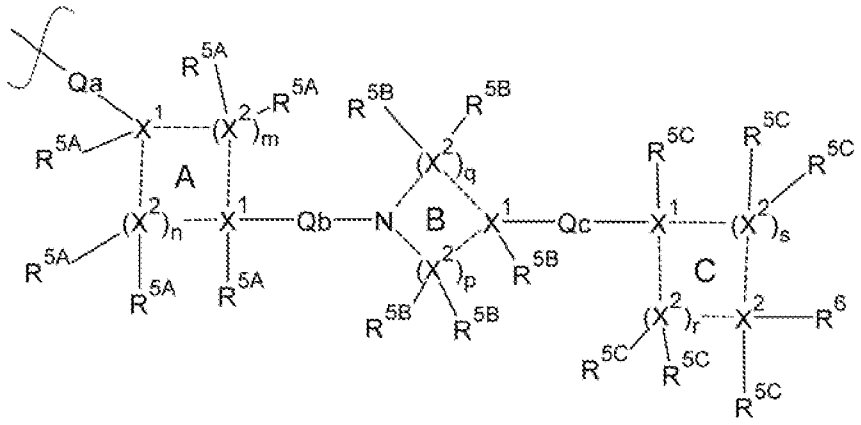
R^2 is absent or selected from H and a substituted or unsubstituted organic group;

R^3 is absent or selected from H and a substituted or unsubstituted organic group;

R^4 is selected from H and a substituted or unsubstituted organic group;

Z^1 and Z^2 are each independently selected from C and N; and

L is a group having the following structure:



wherein:

each X^1 is independently selected from C and N;

each X^2 is independently selected from C, N, O and S;

n is a number selected from 0, 1, 2, 3, 4, 5 and 6; and m is a number selected from 0, 1, 2, 3, 4, 5 and 6; with the proviso that m + n is a number selected from 2, 3, 4, 5, and 6;

p is a number selected from 0, 1, 2, 3, 4, 5 and 6; and q is a number selected from 0, 1, 2, 3, 4, 5 and 6; with the proviso that p + q is a number selected from 2, 3, 4, 5, and 6;

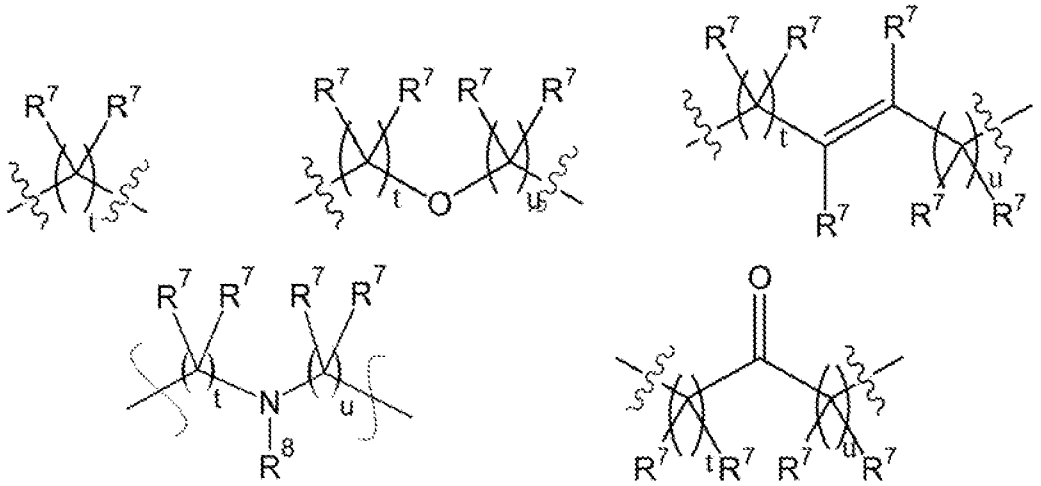
r is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; s is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; with the proviso that r + s is a number selected from 2, 3, 4, 5, and 6;

each R^{5A}, R^{5B}, and R^{5C} is independently absent or selected from H and a substituted or unsubstituted organic group; and

R^6 is absent or selected from H and a substituted or unsubstituted organic group;

the lines forming rings A, B and C each independently represent single or double bonds such that each ring is independently saturated, unsaturated, or aromatic; and

each of Qa, Qb, and Qc is independently selected from a bond and a group having a structure independently selected from:



wherein:

t is a number selected from 0, 1, 2, 3, 4 and 5; and u is independently a number selected from 0, 1, 2, 3, 4 and 5; with the proviso that t + u is a number selected from 0, 1, 2, 3, 4, 5 and 6; and

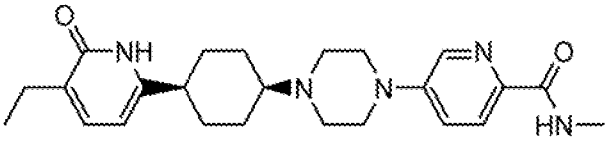
each R^7 and R^8 is independently selected from H and a substituted or unsubstituted organic group.

Another aspect provides a pharmaceutical composition comprising a PARP1 inhibitor compound as defined herein.

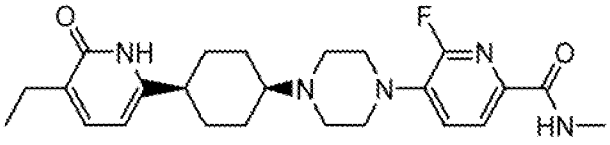
A further aspect provides a pharmaceutical kit for treating a cancer. The kit comprises a PARP1 inhibitor compound as defined herein, and a further agent for treating cancer. The compound and the further agent are suitable for administration simultaneously, sequentially or separately.

Another aspect provides a method of treating a disease and/or a condition and/or a disorder, which method comprises administering to a patient a compound, a composition or a kit as provided herein.

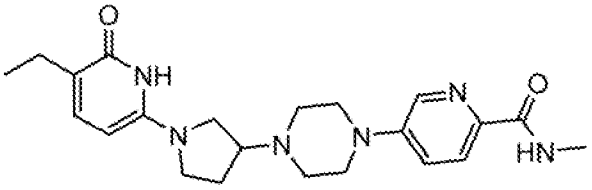
Still another aspect provides a compound selected from:



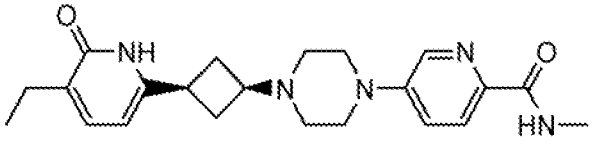
1*cis*



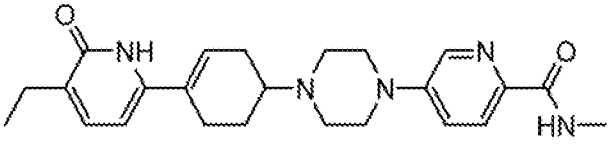
2*cis*



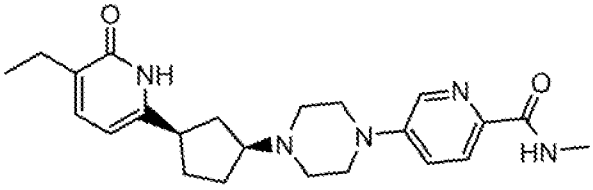
3



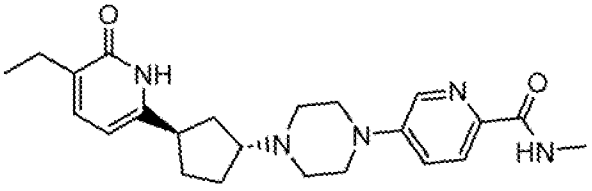
4cis



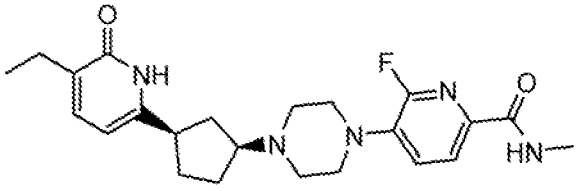
5



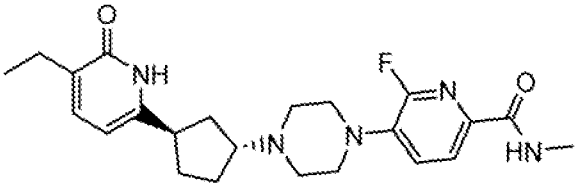
6cis



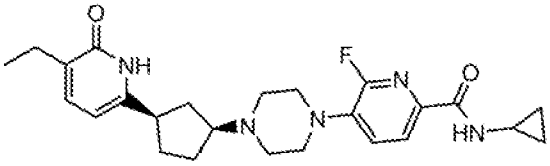
6trans



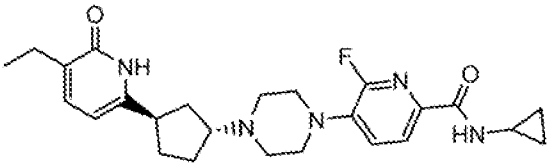
7*cis*



7trans



8cis



8trans

Another aspect provides a method of synthesis of a PARP1 inhibitor compound as provided herein. The method comprises conducting a reaction between a first reactant comprising ring E bearing a first portion of group L and a second reactant comprising a remainder of group L, to form the PARP1 inhibitor compound.

This Summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This Summary is not intended to identify

key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter. Nor is the claimed subject matter limited to implementations that solve any or all of the disadvantages noted herein.

Detailed Description

General Definitions

The verb 'to comprise' is used herein as shorthand for 'to include or to consist of'. In other words, although the verb 'to comprise' is intended to be an open term, the replacement of this term with the closed term 'to consist of' is explicitly contemplated, particularly where used in connection with chemical compositions.

It will be appreciated that some compounds disclosed herein may be ionisable, i.e. some compounds may be weak acids, weak bases, or ampholytes. Representations of the free forms of ionisable compounds are intended to encompass the corresponding ionised forms. Ionisable compounds may be in free form, or in the form of a pharmaceutically-acceptable salt.

A compound is considered to be a PARP1 inhibitor if its presence is capable of preventing or reducing the ability of immobilised PARP1 to undergo auto-poly-ADP ribosylation (AutoPARylation) following incubation with biotinylated-NAD+ as compared to the same process in its absence. Typically, the compound is considered to be a PARP1 inhibitor if it has an IC50 < 10 μM in a suitable assay. A suitable assay may be conducted using 2 nM PARP1, 2 μM biotin-NAD+ assay solution in 20 mM HEPES (pH 7.5), 100 mM NaCl, 2 mM DTT, 0.1 % BSA (w/v), 0.02 % Tween (v/v) assay buffer. PARylation may take place for 2 h at room temperature and may be detected using a dissociation-enhanced lanthanide fluorescence immunoassay (DELFIA) readout. A particularly suitable assay is described in the Examples below. Preferably, the compound has an IC50 < 1 μM, more preferably < 100 nM and most preferably < 10 nM in the PARP1 inhibitor assay.

A compound is considered to be a selective PARP1 inhibitor if its presence is capable of displacing or reducing the ability of a high affinity Cy5 fluorescent dye-labelled chemical probe to bind to PARP1 whilst displacing the same chemical probe at PARP2 with at least 10-fold weaker activity. Typically, the compound is considered to be a selective PARP1 inhibitor if it has an IC50 < 10 μM in this assay at PARP1 with at least 10-fold selectivity preference over PARP2. A suitable such assay may be conducted for 1 h at room temperature using 10 nM PARP1 or PARP2, Tb-cryptate antibody and PARP1/2 binding probe in 20 mM HEPES (pH 7.5), 100 mM NaCl, 2 mM DTT, 0.1 % BSA (w/v), 0.02 % Tween (v/v) assay buffer. Probe binding displacement may be detected using homogeneous time-resolved fluorescence. A particularly suitable assay is described in the Examples below. Preferably the selectivity preference of PARP1 over PARP2 is at least 50-fold, more preferably at least 100-fold.

A compound is also considered to be a selective PARP1 inhibitor if it has an IC50 < 10 μM at PARP1 with at least 10-fold selectivity preference over PARP2 in NanoBRET assays demonstrating cellular target engagement. These assays are based on bioluminescence resonance energy transfer (BRET) between a Nano-luc-tagged protein (e.g. PARP1 or PARP2) and a fluorescent group on a high affinity NAD+ competitive binding probe. Such cellular probe displacement assays can be utilised to measure inhibitor affinities and selectivity ratios at PARP1 and 2. A particularly suitable assay is described in the Examples below. Preferably the selectivity preference of PARP1 over PARP2 is at least 50-fold, more preferably at least 100-fold.

The expression "substituted or unsubstituted organic group" is used herein as a synonym for "substituent". Example organic groups are discussed in more detail hereinbelow.

Where it is said that an organic group is "substituted", it is meant that an H in the organic group is replaced by a further organic group.

A dotted line in a structural formula represents a covalent bond of any appropriate non-zero order, most typically a single bond or a double bond. As will be appreciated, systems comprising multiple double bonds may be conjugated or aromatic.

Except where the configuration of a particular bond is directly illustrated, all formulae herein are shown in non-stereoisomeric form and are intended to represent all possible stereoisomers of a particular structure, including all possible isolated enantiomers corresponding to the formula, all possible mixtures of enantiomers corresponding to the formula, all possible mixtures of diastereomers corresponding to the formula, all possible mixtures of epimers corresponding to the formula and all possible racemic mixtures corresponding to the formula. In addition to this, all formulae herein are intended to represent all tautomeric forms equivalent to the corresponding formula.

The term "aliphatic ring" is used herein in the broad sense of a ring in which all bonds between ring atoms are single bonds. An aliphatic ring may be carbocylic or heterocyclic, and may be substituted or unsubstituted.

Compound numbering

Various ones of the compounds provided herein are enantiomeric or diastereomeric. Where a suffix is applied to a compound number, the suffix indicates stereochemistry. A compound number without a suffix denotes a compound having the indicated structural formula without defining stereochemistry.

The suffix 'rac' in a compound number denotes a racemic mixture.

The suffixes 'cis' and 'trans' denotes compounds which are A ring cis and A ring trans, as explained in the section "stereochemistry" hereinbelow. In the case of diastereomeric compounds, the cis and trans suffixes may refer to pairs of diastereomers having the indicated configuration of the A ring. Nuclear Overhauser Effect nuclear magnetic resonance spectroscopy ("NOE NMR") may be used to determine the stereochemistry of compounds as described herein.

The suffix 'a' in a compound number denotes an enantiomer eluted as a first fraction when a mixture of two enantiomers is separated by supercritical fluid chromatography ("SFC") using a chiral column.

The suffix 'b' in a compound number denotes an enantiomer eluted as a second fraction when a mixture of two enantiomers is separated by supercritical fluid chromatography ("SFC") using a chiral column.

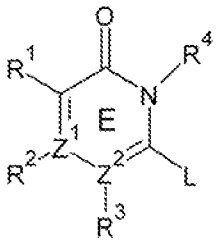
Some structural formulae presented herein illustrate stereochemistry assigned by the applicant. In the event of any discrepancy between order of elution (as represented by compound numbering) and assigned stereochemistry, the order of elution takes precedence.

By way of illustration, Example 3 hereinbelow describes the synthesis of compound **6**. Compound **6** is obtained as a mixture of diastereomers. In a first separation step, the diastereomers are separated into two fractions by prep-HPLC. The first fraction to be eluted comprises a pair of enantiomers **6cis-a** and **6cis-b**. The second fraction comprises a pair of enantiomers **6trans-a** and **6trans-b**. In a second separation step, the mixture of **6cis-a** and **6cis-b** is passed through a Regis (R,R)-Whelk-O chiral chromatography column under the conditions indicated above. The first fraction to be eluted in the second separation step comprises compound **6cis-a**, and the second fraction comprises compound **6cis-b**. Separately, the mixture of **6trans-a** and **6trans-b** is passed through a Daicel CHIRALPAK chiral chromatography column under the conditions indicated above to obtain compounds **6trans-a** (eluted first) and **6trans-b** (eluted second).

Discussion

Provided herein are PARP1 inhibitor compounds having monocyclic head groups. Also provided are kits and compositions comprising such compounds, and medical uses of the compounds, compositions, and kits.

The PARP1 inhibitor compounds have a structure according to the following general formula:



wherein:

R^1 is selected from H and a substituted or unsubstituted organic group;

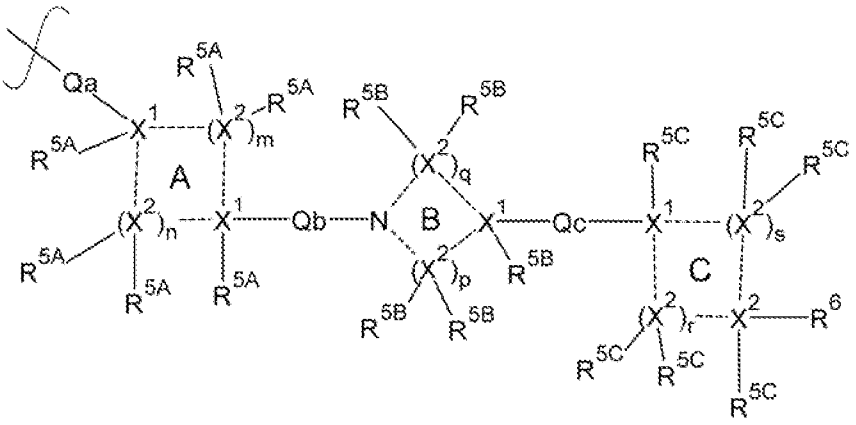
R^2 is absent or selected from H and a substituted or unsubstituted organic group;

R^3 is absent or selected from H and a substituted or unsubstituted organic group;

R^4 is selected from H and a substituted or unsubstituted organic group;

Z^1 and Z^2 are each independently selected from C and N; and

L is a group having the following structure:



wherein:

each X^1 is independently selected from C and N;

each X^2 is independently selected from C, N, O and S;

n is a number selected from 0, 1, 2, 3, 4, 5 and 6; and m is a number selected from 0, 1, 2, 3, 4, 5 and 6; with the proviso that m + n is a number selected from 2, 3, 4, 5, and 6;

p is a number selected from 0, 1, 2, 3, 4, 5 and 6; and q is a number selected from 0, 1, 2, 3, 4, 5 and 6; with the proviso that p + q is a number selected from 2, 3, 4, 5, and 6;

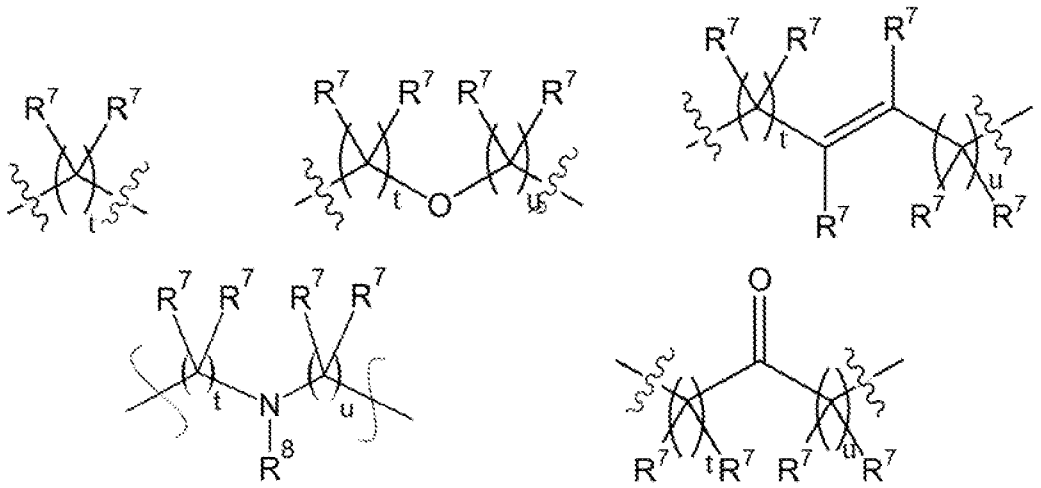
r is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; s is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; with the proviso that r + s is a number selected from 2, 3, 4, 5, and 6;

each R^{5A}, R^{5B}, and R^{5C} is independently absent or selected from H and a substituted or unsubstituted organic group; and

R^6 is absent or selected from H and a substituted or unsubstituted organic group;

the lines forming rings A, B and C each independently represent single or double bonds such that each ring is independently saturated, unsaturated, or aromatic; and

each of Qa, Qb, and Qc is independently selected from a bond and a group having a structure independently selected from:



wherein:

t is a number selected from 0, 1, 2, 3, 4 and 5; and u is independently a number selected from 0, 1, 2, 3, 4 and 5; with the proviso that t + u is a number selected from 0, 1, 2, 3, 4, 5 and 6; and

each R^7 and R^8 is independently selected from H and a substituted or unsubstituted organic group.

The PARP1 inhibitor compounds provided herein may be selective for PARP1 over PARP2. Selective inhibition of PARP1 over PARP2 reduces PARP2 associated side effects including one or more haematological toxicities such as anaemia, neutropenia and thrombocytopenia. This may enable treatment of cancer patients with reduced haematological side effects. Alternatively or additionally, this may enable higher doses of PARP1 inhibitors to be

administered to patients and for such inhibitors to be administered in combination with chemotherapeutic agents.

The PARP1 inhibitor compounds provided herein have monocyclic head groups. Comparative compounds have bicyclic head groups, with the groups at positions R^1 and R^2 being fused to form a ring. Without wishing to be bound by theory, it is believed that the PARP1 inhibitor compounds with monocyclic head groups may have improved physicochemical and pharmacokinetic properties, and potentially central nervous system ("CNS") penetrating activity. Compounds provided herein may therefore be particularly useful for the treatment of a cancer of the brain (such as gliomas, glioblastomas, medulloblastomas, craniopharyngioma, ependymoma, and astrocytoma) or spinal cord.

The improved pharmacokinetics and improved CNS penetration may at least in part be due to improved physicochemical properties of the molecules compared to those having bicyclic head groups, as well as modifying the conformation of the molecule: the head groups of bicyclic head groups tend to be flatter and more lipophilic.

Substituents

The expression "R^5 group" refers generally to groups R^{5A}, R^{5B}, and R^{5C}. An "R^{5A}" group is an R^5 group which is attached to ring A, and so on. Some of the formulae presented herein use more specific identifiers for R^5 groups. For example, "R^{5A1}" identifies a subset of R^{5A} groups.

In the compounds provided herein, various ones of the R^2, R^3, and R^5 groups may be absent, with dotted lines in the structural formulae presented herein representing covalent bonds of any non-zero order. As will be appreciated, the number of ring bonds and the number of substituents are selected such that the Z^1, Z^2, X^1, and X^2 atoms maintain a stable valency. Maintaining a stable valency means ensuring that an atom has its normal (typically most common) valency in organic compounds (i.e. 2 for oxygen; 2 or 6 for sulfur; 3 or 4 for nitrogen; and 4 for carbon).

When an X^1 or X^2 atom is N, that atom most preferably has a valency of 3. Compounds in which an X^1 or X^2 atom is tetravalent N are also contemplated. Tetravalent N is positively charged, and such compounds may have a counterion.

Typically, each of rings A, B, and C includes at most a single tetravalent N. Preferably, the PARP1 inhibitor compound includes at most one tetravalent N, and more preferably no tetravalent N.

Each R^5 group may be absent or present, and may be the same or different. For the avoidance of doubt, where the number of R^5 groups may vary according to the choice of corresponding X group, the following provisos typically apply:

i) When an X^1 is N, its corresponding R^5 is absent.

ii) When an X^1 is C and is double bonded to an adjacent ring atom, its corresponding R^5 is absent.

iii) When an X^1 is C and is not double bonded to an adjacent ring atom, its corresponding R^5 is present.

iv) When an X^2 is O, its corresponding R^5 / R^6 groups are both absent.

v) When an X^2 is S, its corresponding R^5 /R^6 groups are both absent or are both selected from =O and =NR^{10}, where R^{10} is H or a substituted or unsubstituted organic group, preferably a C1 to C3 alkyl group.

vi) When an X^2 is N and is doubled bonded to an adjacent ring atom, the or each corresponding R^5 / R^6 is absent.

vii) When an X^2 is N and not doubled bonded to an adjacent ring atom, exactly one corresponding R^5 / R^6 is present.

viii) When an X^2 is C and is double bonded to an adjacent ring atom, exactly one corresponding R^5 / R^6 is present.

ix) When an X^2 is C and is not double bonded to an adjacent ring atom, both corresponding R^5 groups or both the corresponding R^5 and R^6 are present.

The substituents (i.e. R groups; R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8) are not especially limited, provided that they do not prevent the PARP1 inhibitory function from occurring. The substituents are selected from H and a substituted or unsubstituted organic group. Thus, both

above and in the following, the terms 'substituent' and 'organic group' are not especially limited and may be any functional group or any atom, especially any functional group or atom common in organic chemistry.

Any R^5 or R^6 group may form a ring with any other R^5 or R^6 group on an adjacent and/or proximal atom, although in most embodiments this is not preferred, except where explicitly stated. Thus, the following substituents may together form a ring: an R^{5A} with another R^{5A}; an R^B with another R^{5B}; an R^C with another R^{5C}; or an R^{5C} with R^6. In the present context, an adjacent and/or proximal atom may mean another atom directly bonded to an atom (adjacent) or may be two atoms with only a single atom in between (proximal), or may mean two atoms close enough sterically to be capable of forming a ring (proximal). Preferably R^5 / R^6 groups attached to the same atom do not together form a ring, although this is not excluded.

The PARP1 inhibitor compounds provided herein have monocyclic head groups. None of R^1, R^2, R^3, and R^4 forms a ring with any other R group.

A single R^5 or R^6 group on an atom, or two R^5 / R^6 groups on the same atom, may form a group which is double bonded to that atom. Accordingly, an R^5 or R^6 group, or two R^5 / R^6 groups attached to the same atom, may together form a =O group, or a $=C(R')_2$ group (wherein each R' group is the same or different and is H or an organic group, preferably H or a straight or branched C_1-C_6 alkyl group). This is more typical in cases where the R groups are attached to a C atom, such that together they form a C=O group or a $C=C(R')_2$ group. Thus in some cases an X^2 group which is C may bear a =O group.

'Substituent' and 'organic group' may have any of the following meanings.

The organic group may comprise any one or more atoms from any of groups IIIA, IVA, VA, VIA or VIIA of the Periodic Table, such as a B, Si, N, P, O, or S atom (e.g. OH, OR, NH_2, NHR, NR_2, SH, SR, SO_2R, SO_3H, PO_4H_2) or a halogen atom (e.g. F, Cl, Br or I) where R is a linear or branched lower hydrocarbon (1-6 C atoms) or a linear or branched higher hydrocarbon (7 C atoms or more, e.g. 7-40 C atoms).

The organic group preferably comprises a hydrocarbon group. The hydrocarbon group may comprise a straight chain, a branched chain or a cyclic group. Independently, the hydrocarbon group may comprise an aliphatic or an aromatic group. Also independently, the hydrocarbon group may comprise a saturated or unsaturated group.

When the hydrocarbon comprises an unsaturated group, it may comprise one or more alkene functionalities and/or one or more alkyne functionalities. When the hydrocarbon comprises a straight or branched chain group, it may comprise one or more primary, secondary and/or tertiary alkyl groups.

When the hydrocarbon comprises a cyclic group it may comprise an aromatic ring, a non-aromatic ring, an aliphatic ring, a heterocyclic group, and/or fused ring derivatives of these groups. The ring may be fully saturated, partially saturated, or fully unsaturated. The cyclic group may thus comprise a benzene, naphthalene, anthracene, phenanthrene, phenalene, biphenylene, pentalene, indene, *as*-indacene, *s*-indacene, acenaphthylene, fluorene, fluoranthene, acephenanthrylene, azulene, heptalene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyrrolidine, furan, oxetane, tetrahydrofuran, 2-aza-tetrahydrofuran, 3-aza-tetrahydrofuran, oxazole, isoxazole, furazan, 1,2,4-oxadiazol, 1,3,4-oxadiazole, thiophene, isothiazole, thiazole, thiolane, pyridine, pyridazine, pyrimidine, pyrazine, piperidine, 2-azapiperidine, 3-azapiperidine, piperazine, pyran, tetrahydropyran, 2-azapyran, 3-azapyran, 4-azapyran, 2-aza-tetrahydropyran, 3-aza-tetrahydropyran, morpholine, thiopyran, 2-azathiopyran, 3-azathiopyran, 4-azathiopyran, thiane, indole, indazole, benzimidazole, 4-azaindole, 5-azaindole, 6-azaindole, 7-azaindole, isoindole, 4-azaisoindole, 5-azaisoindole, 6-azaisoindole, 7-azaisoindole, indolizine, 1-azaindolizine, 2-azaindolizine, 3-azaindolizine, 5-azaindolizine, 6-azaindolizine, 7-azaindolizine, 8-azaindolizine, 9-azaindolizine, purine, carbazole, carboline, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, quinoline, cinnoline, quinazoline, quinoxaline, 5-azaquinoline, 6-azaquinoline, 7-azaquinoline, isoquinoline, phthalazine, 6-azaisoquinoline, 7-azaisoquinoline, pteridine, chromene, isochromene, acridine, phenanthridine, perimidine, phenanthroline, phenoxazine, xanthene, phenoxanthiin, and/or thianthrene, as well as regioisomers of the above groups. These groups may generally be attached at any point in the

group, and also may be attached at a hetero-atom or at a carbon atom. In some instances particular attachment points are preferred, such as at 1-yl, 2-yl and the like, and these are specified explicitly where appropriate. All tautomeric ring forms are included in these definitions. For example pyrrole is intended to include 1*H*-pyrrole, 2*H*-pyrrole and 3*H*-pyrrole.

The number of carbon atoms in the hydrocarbon group is not especially limited, but preferably the hydrocarbon group comprises from 1-40 C atoms. The hydrocarbon group may thus be a lower hydrocarbon (1-6 C atoms) or a higher hydrocarbon (7 C atoms or more, e.g. 7-40 C atoms). The lower hydrocarbon group may be a methyl, ethyl, propyl, butyl, pentyl or hexyl group or regioisomers of these, such as isopropyl, isobutyl, tert-butyl, etc. The number of atoms in the ring of the cyclic group is not especially limited, but preferably the ring of the cyclic group comprises from 3-10 atoms, such as 3, 4, 5, 6, 7, 8, 9 or 10 atoms.

The groups comprising heteroatoms described above, as well as any of the other groups defined above, may comprise one or more heteroatoms from any of groups IIIA, IVA, VA, VIA or VIIA of the Periodic Table, such as a B, Si, N, P, O, or S atom or a halogen atom (e.g. F, Cl, Br or I). Thus, the substituent may comprise one or more of any of the common functional groups in organic chemistry, such as hydroxy groups, carboxylic acid groups, ester groups, ether groups, aldehyde groups, ketone groups, amine groups, amide groups, imine groups, thiol groups, thioether groups, sulfate groups, sulfonic acid groups, sulfonyl groups, and phosphate groups etc. The substituent may also comprise derivatives of these groups, such as carboxylic acid anhydrides and carboxylic acid halides.

In addition, any substituent may comprise a combination of two or more of the substituents and/or functional groups defined herein.

Typically, when one or more of R^1, R^2, R^3, R^4, R^{5A} (e.g., R^{5A1}, R^{5A2}, R^{5A3}), R^{5B}, R^{5C} (e.g., R^{5C1}), R^6, R^7, R^{51}, and R^{52} is a substituted or unsubstituted organic group, the or each substituted or unsubstituted organic group is independently selected from:

deuterium;

a halogen (such as –F, -Cl, -Br and –I);

a nitrile group;

a substituted or unsubstituted linear or branched C_1-C_6 alkyl group

(such as Me, Et, Pr, i-Pr, n-Bu, i-Bu, t-Bu, pentyl and hexyl);

a substituted or unsubstituted linear or branched C_1-C_6 alkyl-aryl group

(such as –CH_2Ph, -CH_2(2,3 or 4)F-Ph, -CH_2(2,3 or 4)Cl-Ph, -CH_2(2,3 or 4)Br-Ph, -CH_2(2,3 or 4)I-Ph, -CH_2CH_2Ph, -$CH_2CH_2CH_2$Ph, -$CH_2CH_2CH_2CH_2$Ph, -$CH_2CH_2CH_2CH_2CH_2$Ph, and -$CH_2CH_2CH_2CH_2CH_2CH_2$Ph);

a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group

(such as -CH_2F, -CH_2Cl, -CH_2Br, -CH_2I, -CHF_2, -CF_3, -CCl_3 -CBr_3, -Cl_3, -CH_2CH_2F, -CH_2CF_3, -CH_2CCl_3, -CH_2CBr_3, and -CH_2Cl_3);

NH_2 or a substituted or unsubstituted linear or branched primary secondary or tertiary C_1-C_6 amine group

(such as -NMeH, -NMe_2, -NEtH, -NEtMe, -NEt_2, -NPrH, -NPrMe, -NPrEt, -NPr_2, -NBuH, -NBuMe, -NBuEt, –CH_2-NH_2, -CH_2-NMeH, -CH_2-NMe_2, -CH_2-NEtH, -CH_2-NEtMe, -CH_2-NEt_2, -CH_2-NPrH, -CH_2-NPrMe, and –CH_2-NPrEt);

a substituted or unsubstituted amino-aryl group

(such as -NH-Ph, -NH-(2,3 or 4)F-Ph, -NH-(2,3 or 4)Cl-Ph, -NH-(2,3 or 4)Br-Ph, -NH-(2,3 or 4)I-Ph, -NH-(2,3 or 4)Me-Ph, -NH-(2,3 or 4)Et-Ph, -NH-(2,3 or 4)Pr-Ph, -NH-(2,3 or 4)Bu-Ph, NH-(2,3 or 4)OMe-Ph, -NH-(2,3 or 4)OEt-Ph, -NH-(2,3 or 4)OPr-Ph, -NH-(2,3 or 4)OBu-Ph, -NH-2,(3,4,5 or 6)F_2-Ph, -NH-2,(3,4,5 or 6)Cl_2-Ph, -NH-2,(3,4,5 or 6)Br_2-Ph, -NH-2,(3,4,5 or 6)I_2-Ph, -NH-2,(3,4,5 or 6)Me_2-Ph, -NH-2,(3,4,5 or 6)Et_2-Ph, -NH-2,(3,4,5, or 6)Pr_2-Ph, -NH-2,(3,4,5 or 6)Bu_2-Ph),

a substituted or unsubstituted cyclic amine or amido group

(such as pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, 2-keto-pyrrolidinyl, 3-keto-pyrrolidinyl, 2-keto-piperidinyl, 3-keto-piperidinyl, and 4-keto-piperidinyl);

a substituted or unsubstituted cyclic C_3-C_8 alkyl group

(such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl);

an -OH group;

a substituted or unsubstituted linear or branched C_1-C_6 alcohol group (such as –CH_2OH, -CH_2CH_2OH, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2OH$, -$CH_2CH_2CH_2OH$, -$CH_2CH_2CH_2CH_2OH$, -$CH(CH_3)CH_2CH_2OH$, -$CH(CH_3)CH(CH_3)OH$, -$CH(CH_2CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2CH_2CH_2CH_2CH_2OH$, and -$CH_2CH_2CH_2CH_2CH_2CH_2OH$);

a substituted or unsubstituted linear or branched C_1-C_6 carboxylic acid group (such as -COOH, -CH_2COOH, -CH_2CH_2COOH, -$CH_2CH_2CH_2COOH$, -$CH_2CH_2CH_2CH_2COOH$, and -$CH_2CH_2CH_2CH_2CH_2COOH$);

a substituted or unsubstituted linear or branched carbonyl group (such as -(CO)Me, -(CO)Et, -(CO)Pr, -(CO)iPr, -(CO)nBu, -(CO)iBu, -(CO)tBu, -(CO)Ph, -(CO)CH_2Ph, -(CO)CH_2OH, -(CO)CH_2OCH_3, -(CO)CH_2NH_2, -(CO)CH_2NHMe, -(CO)CH_2NMe_2, -(CO)-cyclopropyl, -(CO)-1,3-epoxypropan-2-yl; -(CO)NH_2, -(CO)NHMe, -(CO)NMe_2, -(CO)NHEt, -(CO)NEt_2, -(CO)-pyrollidine-N-yl, -(CO)-morpholine-N-yl, -(CO)-piperazine-N-yl, -(CO)-N-methyl-piperazine-N-yl, -(CO)$NHCH_2CH_2OH$, -(CO)$NHCH_2CH_2OMe$, -(CO)$NHCH_2CH_2NH_2$, -(CO)$NHCH_2CH_2NHMe$, and -(CO)$NHCH_2CH_2NMe_2$);

a substituted or unsubstituted linear or branched C_1-C_6 carboxylic acid ester group (such as -COOMe, -COOEt, -COOPr, -COO-i-Pr, -COO-n-Bu, -COO-i-Bu, -COO-t-Bu, -CH_2COOMe, -CH_2CH_2COOMe, -$CH_2CH_2CH_2COOMe$, and -$CH_2CH_2CH_2CH_2COOMe$);

a substituted or unsubstituted linear or branched C_1-C_6 amide group (such as -CO-NH_2, -CO-NMeH, -CO-NMe_2, -CO-NEtH, -CO-NEtMe, -CO-NEt_2, -CO-NPrH, -CO-NPrMe, and -CO-NPrEt);

a substituted or unsubstituted linear or branched C_1-C_7 amino carbonyl group (such as -NH-CO-Me, -NH-CO-Et, -NH-CO-Pr, -NH-CO-Bu, -NH-CO-pentyl, -NH-CO-hexyl, -NH-CO-Ph, -NMe-CO-Me, -NMe-CO-Et, -NMe-CO-Pr, -NMe-CO-Bu, -NMe-CO-pentyl, -NMe-CO-hexyl, -NMe-CO-Ph);

a substituted or unsubstituted linear or branched C_1-C_7 alkoxy or aryloxy group (such as –OMe, -OEt, -OPr, -O-i-Pr, -O-n-Bu, -O-i-Bu, -O-t-Bu, -O-pentyl, -O-hexyl, -OCH_2F, -$OCHF_2$, -OCF_3, -OCH_2Cl, -$OCHCl_2$, -$OCCl_3$, -O-Ph, -O-CH_2-Ph,

-O-CH_2-(2,3 or 4)-F-Ph, -O-CH_2-(2,3 or 4)-Cl-Ph, –CH_2OMe, –CH_2OEt, –CH_2OPr, –CH_2OBu, -CH_2CH_2OMe, -$CH_2CH_2CH_2OMe$, -$CH_2CH_2CH_2CH_2OMe$, and -$CH_2CH_2CH_2CH_2CH_2OMe$);

a substituted or unsubstituted linear or branched aminoalkoxy group (such as –OCH_2NH_2, -OCH_2NHMe, -OCH_2NMe_2, -OCH_2NHEt, -OCH_2NEt_2, -$OCH_2CH_2NH_2$, -OCH_2CH_2NHMe, -$OCH_2CH_2NMe_2$, -OCH_2CH_2NHEt, and -$OCH_2CH_2NEt_2$);

a substituted or unsubstituted sulfonyl group (such as -SO_2Me, -SO_2Et, -SO_2Pr, -SO_2iPr, -SO_2Ph, -SO_2-(2,3 or 4)-F-Ph, -SO_2-cyclopropyl, -$SO_2CH_2CH_2OCH_3$, -SO_2NH_2, -SO_2NHMe, -SO_2NMe_2, -SO_2NHEt, -SO_2NEt_2, -SO2-pyrrolidine-N-yl, -SO_2-morpholine-N-yl, -SO_2NHCH_2OMe,and -$SO_2NHCH_2CH_2OMe$);

a substituted or unsubstituted aminosulfonyl group (such as –$NHSO_2Me$, -$NHSO_2Et$, - $NHSO_2Pr$, -$NHSO_2iPr$, -$NHSO_2Ph$, -$NHSO_2$-(2,3 or 4)-F-Ph, -$NHSO_2$-cyclopropyl, -$NHSO_2CH_2CH_2OCH_3$);

a substituted or unsubstituted aromatic group (such as Ph-, 2-F-Ph-, 3-F-Ph-, 4-F-Ph-, 2-Cl-Ph-, 3-Cl-Ph-, 4-Cl-Ph-, 2-Br-Ph-, 3-Br-Ph-, 4-Br-Ph-, 2-I-Ph-, 3-I-Ph, 4-I-Ph-, 2,(3,4,5 or 6)-F_2-Ph-, 2,(3,4,5 or 6)-Cl_2-Ph-, 2,(3,4,5 or 6)-Br_2-Ph-, 2,(3,4,5 or 6)-I_2-Ph-, 2,(3,4,5 or 6)-Me_2-Ph-, 2,(3,4,5 or 6)-Et_2-Ph-, 2,(3,4,5 or 6)-Pr_2-Ph-, 2,(3,4,5 or 6)-Bu_2-Ph-, 2,(3,4,5 or 6)-$(CN)_2$-Ph-, 2,(3,4,5 or 6)-$(NO_2)_2$-Ph-, 2,(3,4,5 or 6)-$(NH_2)_2$-Ph-, 2,(3,4,5 or 6)-$(MeO)_2$-Ph-, 2,(3,4,5 or 6)-$(CF_3)_2$-Ph-, 3,(4 or 5)-F_2-Ph-, 3,(4 or 5)-Cl_2-Ph-, 3,(4 or 5)-Br_2-Ph-, 3,(4 or 5)-I_2-Ph-, 3,(4 or 5)-Me_2-Ph-, 3,(4 or 5)-Et_2-Ph-, 3,(4 or 5)-Pr_2-Ph-, 3,(4 or 5)-Bu_2-Ph-, 3,(4 or 5)-$(CN)_2$-Ph-, 3,(4 or 5)-$(NO_2)_2$-Ph-, 3,(4 or 5)-$(NH_2)_2$-Ph-, 3,(4 or 5)-$(MeO)_2$-Ph-, 3,(4 or 5)-$(CF_3)_2$-Ph-, 2-Me-Ph-, 3-Me-Ph-, 4-Me-Ph-, 2-Et-Ph-, 3-Et-Ph-, 4-Et-Ph-, 2-Pr-Ph-, 3-Pr-Ph-, 4-Pr-Ph-, 2-Bu-Ph-, 3-Bu-Ph-, 4-Bu-Ph-, 2-(CN)-Ph-, 3-(CN)-Ph-, 4-(CN)-Ph-, 2-(NO_2)-Ph-, 3-(NO_2)-Ph-, 4-(NO_2)-Ph-, 2-(NH_2)-Ph-, 3-(NH_2)-Ph-, 4-(NH_2)-Ph-, 2-MeO-Ph-, 3-MeO-Ph-, 4-MeO-Ph-, 2-$(NH_2$-CO)-Ph-, 3-$(NH_2$-CO)-Ph-, 4-$(NH_2$-CO)-Ph-, 2-CF_3-Ph-, 3-CF_3-Ph-, 4-CF_3-Ph-, 2-CF_3O-Ph-, 3-CF_3O-Ph-, and 4-CF_3O-Ph-);

a saturated or unsaturated, substituted or unsubstituted, heterocyclic group, optionally an aromatic heterocyclic group or a non-aromatic heterocyclic group (such as pyrrole-1-yl, pyrrole-2-yl, pyrrole-3-yl, pyrazole-1-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazole-5-yl, imidazole-1-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, 1,2,3-triazole-1-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-1-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazine-3-yl, pyridazine-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-6-yl, pyrazine-2-yl, pyrrolidine-1-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-1-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, 2-azapiperidine-1-yl, 2-azapiperidine-3-yl, 2-azapiperidine-4-yl, 3-azapiperidine-1-yl, 3-azapiperidine-2-yl, 3-azapiperidine-4-yl, 3-azapiperidine-5-yl, piperazine-1-yl, piperazine-2-yl, furan-2-yl, furan-3-yl, pyran-2-yl, pyran-3-yl, pyran-4-yl, 2-azapyran-2-yl, 2-azapyran-3-yl, 2-azapyran-4-yl, 2-azapyran-5-yl, 2-azapyran-6-yl, 3-azapyran-2-yl, 3-azapyran-4-yl, 3-azapyran-5-yl, 3-azapyran-6-yl, 4-azapyran-2-yl, 4-azapyran-3-yl, 4-azapyran-4-yl, 4-azapyran-5-yl, 4-azapyran-6-yl, oxetan-2-yl, oxetan-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-2-yl, 2-aza-tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-4-yl, 2-aza-tetrahydrofuran-5-yl, 3-aza-tetrahydrofuran-2-yl, 3-aza-tetrahydrofuran-3-yl, 3-aza-tetrahydrofuran-4-yl, 3-aza-tetrahydrofuran-5-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, 2-aza-tetrahydropyran-2-yl, 2-aza-tetrahydropyran-3-yl, 2-aza-tetrahydropyran-4-yl, 2-aza-tetrahydropyran-5-yl, 2-aza-tetrahydropyran-6-yl, 3-aza-tetrahydropyran-2-yl, 3-aza-tetrahydropyran-3-yl, 3-aza-tetrahydropyran-4-yl, 3-aza-tetrahydropyran-5-yl, 3-aza-tetrahydropyran-6-yl, morpholine-2-yl, morpholine-3-yl, morpholine-4-yl, thiophen-2-yl, thiophen-3-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl, thiopyran-2-yl, thiopyran-3-yl, thiopyran-4-yl, 2-azathiopyran-2-yl, 2-azathiopyran-3-yl, 2-azathiopyran-4-yl, 2-azathiopyran-5-yl, 2-azathiopyran-6-yl, 3-azathiopyran-2-yl, 3-azathiopyran-4-yl,

3-azathiopyran-5-yl, 3-azathiopyran-6-yl, 4-azathiopyran-2-yl, 4-azathiopyran-3-yl, 4-azathiopyran-4-yl, 4-azathiopyran-5-yl, 4-azathiopyran-6-yl, thiolane-2-yl, thiolane-3-yl, thiane-2-yl, thiane-3-yl, thiane-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, furazan-3-yl, (1,3,4-oxadiazol)-2-yl, (1,3,4-oxadiazol)-5-yl, (1,2,4-oxadiazol)-3-yl, (1,2,4-oxadiazol)-5-yl; and tetrazole-1-yl, tetrazole-2-yl, tetrazole-5-yl).

A pair of R^{5A} groups attached to different atoms may together form a ring with ring A atoms.

A pair of R^{5B} groups attached to different atoms may together form a ring with ring B atoms.

A pair of R^{5C} groups attached to different atoms may together form a ring with ring C atoms.

An R^{5C} group and an R^{6} group attached to different atoms may together form a ring with ring C atoms.

R5 groups (R^{5A}, such as R^{5A1}, R^{5A2}, R^{5A3}; R^{5B}; or R^{5C}, such as R^{5C1}) may in particular be absent or selected from:

H,

deuterium,

a halogen (such as –F, -Cl, -Br, and –I; preferably F or Cl),

a nitrile group,

a substituted or unsubstituted C_1-C_6 alkyl group,

a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group (preferably CF_3 or CHF_2),

a cyclopropyl group,

an -OH group,

a substituted or unsubstituted linear or branched C_1-C_6 alcohol group,

a substituted or unsubstituted linear or branched C_1-C_7 amino carbonyl group (such as -NH-CO-Me),

an -NH_2 group,

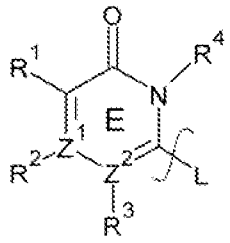
a substituted or unsubstituted C_1-C_6 amino group, and

a substituted or unsubstituted C_1-C_6 alkoxy group.

When a pair of R^{5A} groups attached to different atoms together forms a ring with ring A atoms and/or a pair of R^{5B} groups attached to different atoms together forms a ring with ring B atoms and/or a pair R^{5C} groups attached to different atoms together forms a ring with ring C atoms, each of the pair of R^{5A}, R^{5B} or R^{5C} groups independently comprises -CH_2- or -CH_2CH_2-, or the pair of groups together comprise -CH=CH-CH=CH- or -NH-CO-NH-.

Ring E

Ring E (also referred to as the "head group") of the compounds provided herein has a structure of:



where:

Z^1 and Z^2 are each independently selected from C and N;

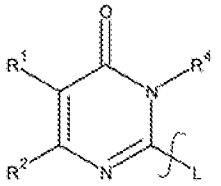
R^1 is selected from H and a substituted or unsubstituted organic group;

R^2 is absent or selected from H and a substituted or unsubstituted organic group;

R^3 is absent or selected from H and a substituted or unsubstituted organic group; and

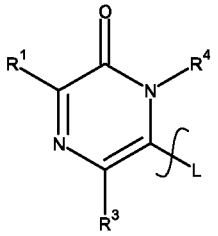
R^4 is selected from H and a substituted or unsubstituted organic group.

Ring E may have a structure of:



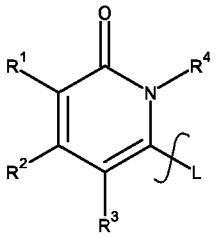
R^1, R^2 and R^4 each being independently selected from H and a substituted or unsubstituted organic group.

Alternatively, ring E may have a structure of:



R^1, R^3 and R^4 each being independently selected from H and a substituted or unsubstituted organic group;

Preferably, ring E has a structure of:



R^1, R^2, R^3 and R^4 each being independently selected from H and a substituted or unsubstituted organic group.

Generally, the following provisos apply to the selection of R^2 and R^3:

R^2 is absent when Z^1 is N. R^2 is selected from H and a substituted or unsubstituted organic group when Z^1 is C.

R^3 is absent when Z^2 is N. R^3 is selected from H and a substituted or unsubstituted organic group when Z^1 is C.

R^1 and R^2 may each be independently selected from:

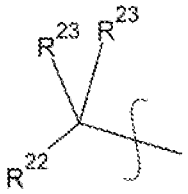
H;

a C1 to C6 alkyl, aminoalkyl, alkoxy or haloalkyl group;

a C3 to C6 cycloalkyl group;

a halogen group;

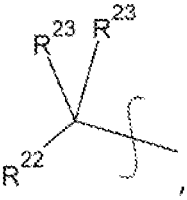
and



wherein R^{22} is selected from H, a C1 to C6 alkyl, cycloalkyl, alkoxy, or haloalkyl group, and a halogen group, and each R^{23} is independently selected from H and a substituted or unsubstituted organic group, and each R^{23} is preferably selected from H, a C1 to C6 alkyl, aminoalkyl, alkoxy or haloalkyl group, and a halogen group. Usually, at least one R^{23} is H.

In most implementations, at least one of R^1 and R^2 is not H. Preferably, R^1 is a substituted or unsubstituted organic group and R^2 is H.

Preferably, at least one of R^1, R^2, R^3 and R^{22} is selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -F, -Cl, $-CH_2CF_3$, $-CH_2CH_2F$, $-CH_2CH_2OH$, methoxy, methoxymethyl, methoxyethyl, isopropyl, cyclopropyl or cyclopropylmethyl.

At least one of R^1 and R^2 may be  , with each R^{23} being independently selected from H, F, C1 to C3 alkyl, and C1 to C3 fluoroalkyl.

R^1 may in particular be selected from H, C1 to C3 alkyl, C1 to C3 alkoxy, and C1 to C3 haloalkyl. Most preferably, R^1 is an ethyl group.

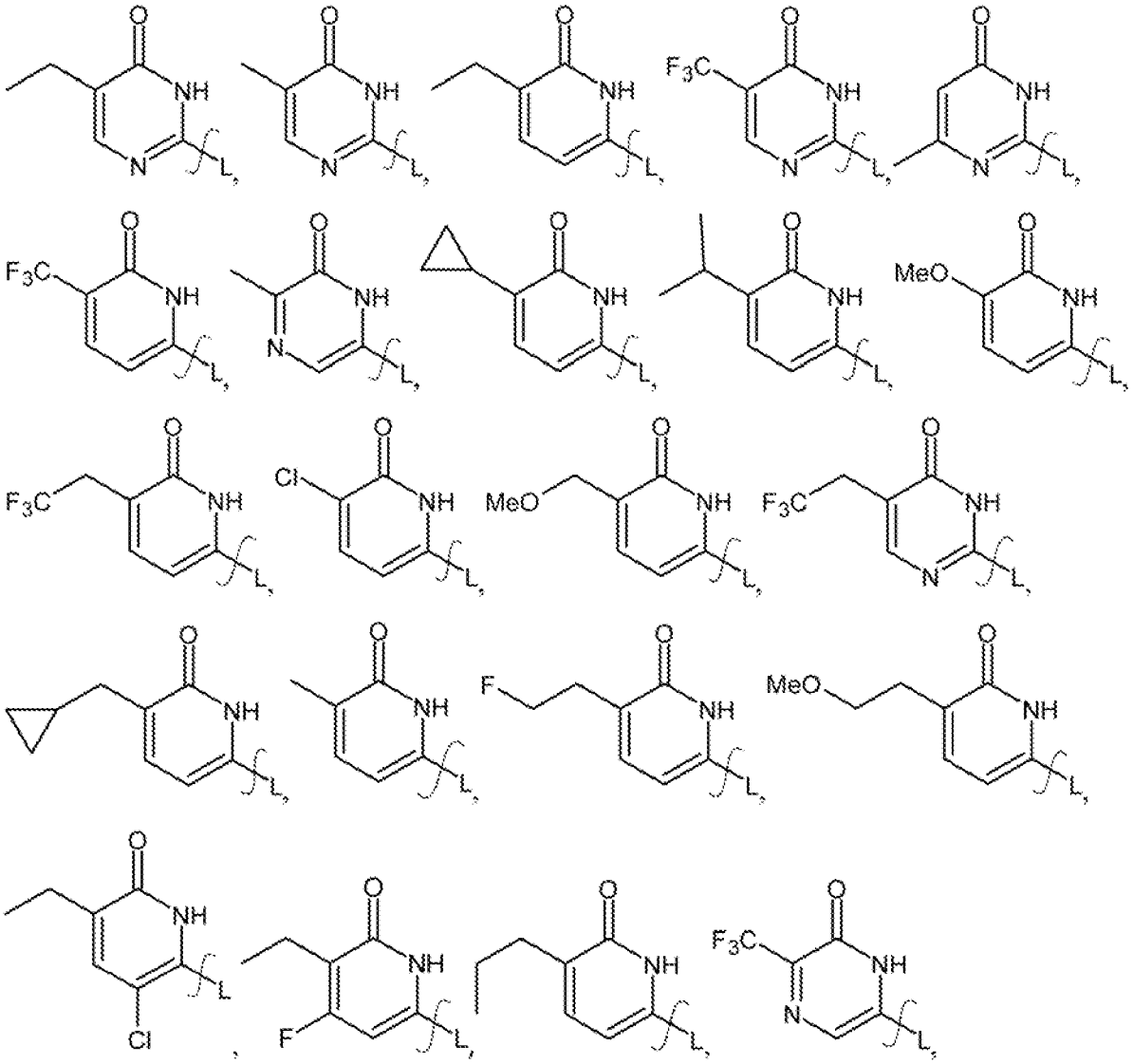
R^2 may in particular be selected from H, CH_3, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, -F, -Cl, $-CH_2CF_3$, $-CH_2CH_2F$, $-CH_2CH_2OH$, methoxy, methoxymethyl, methoxyethyl, isopropyl, cyclopropyl and cyclopropylmethyl. R^2 is most preferably H.

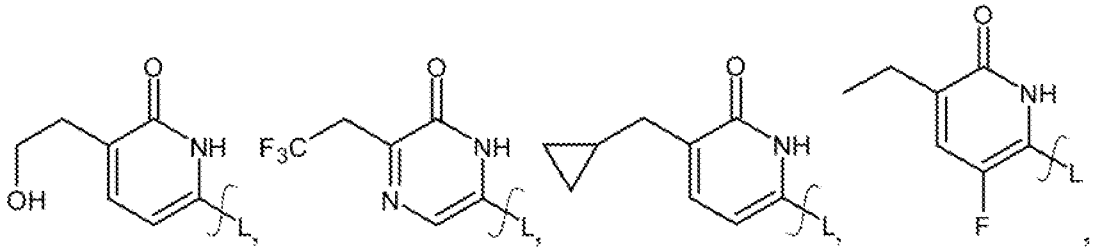
R^3 may in particular be selected from H, halogen, C1 to C3 alkyl, C1 to C3 haloalkyl, C1 to C3 alcohol, and C1 to C3 aminoalkyl. R^3 is most preferably H.

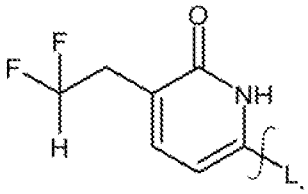
R^4 may in particular be selected from H, C1 to C3 alkyl, and C1 to C3 haloalkyl. R^4 is most preferably H.

In one class of example compounds, Z^1 and Z^2 are each C; and R^2 and R^3 are each independently selected from H, C1 to C3 alkyl, and C1 to C3 haloalkyl. In compounds of this class, R^2 and R^3 are optionally each H.

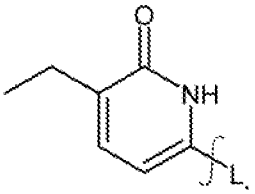
The E ring may have a structure selected from:







The most preferred E ring has the structure:



Rings A, B, and C - general

Rings A and C are each independently carbocylic or heterocyclic.

Variable atoms which are part of the skeleton of the A, B and C rings are generically referred to as "X" atoms. Each X^1 atom is independently selected from C and N. Each X^2 atom is independently selected from C, N, O, and S; with C and N being particularly preferred.

Each X^1 and X^2 atom is independently selected. One or more, and most preferably all, of the following provisos may apply:

Typically, at least one X group per ring is C. When an A, B or C ring is 4-membered, that ring typically includes at most one heteroatom. When an A, B or C ring is 5 or 6-membered, that ring typically includes at most three heteroatoms, optionally at most two heteroatoms.

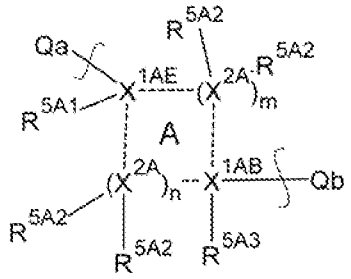
Each of rings A, B, and C individually may comprise at most three heteroatoms.

The compound is typically not a quaternary ammonium compound. An X^1 atom which is N typically does not bear an R^5 group. An X^2 atom which is N typically bears at most one R^5 group.

The compound is free of O-O, S-S, and S-O bonds between X^2 atoms. When an X^2 is O or S, its adjacent ring atoms are C or N. More generally, the compound may be free of O-O bonds and S-S bonds.

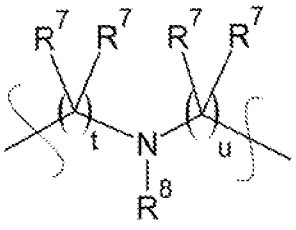
Ring A

Ring A of the PARP1 inhibitor compound has the general structure:

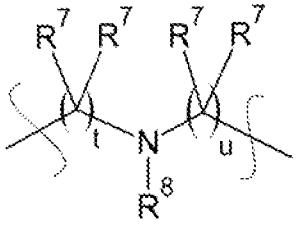


X^{1AE} is the X^1atom that is connected to ring E via linker Qa, and X^{1AB} is the X^1 atom that is connected to ring B via linker Qb. X^{2A} denotes an X^2 atom which is part of ring A.

X^{1AE} may be C or N, and is preferably C.

When Qa is  and u=0, X^{1AE} is C. When X^{1AE} is N, R^{5A1} is typically absent.

X^{1AB} may be C or N, and is preferably C.

Rings A and B are most typically not connected via an N-N bond. To this end, when Qb is a bond or  and t=0, X^{1AB} is C. When X^{1AB} is N, R^{5A3} is typically absent.

Each X^{2A} atom is independently selected from C, N, O, and S; with C and N being particularly preferred. The X^{2A} groups are selected such that ring A is free of O-O, O-S, and S-S bonds. Particularly preferably, all of the X^{2A} atoms are C.

Ring A is a 4, 5, 6, 7, or 8 membered ring. To this end, n is 0 or an integer in the range 1 to 6; m is 0 or an integer in the range 1 to 6, and n and m sum to an integer in the range 2 to 6.

In particular, ring A may be a 4, 5, or 6 membered ring, and is preferably a 5 or 6 membered ring. Put differently, n+m may sum to an integer in the range 2 to 4.

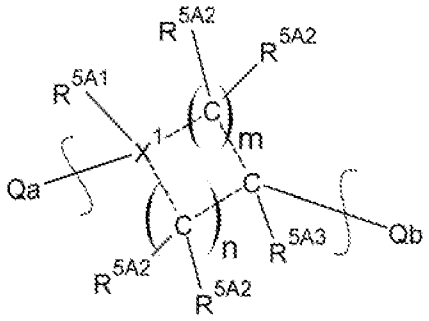
Preferably, both n and m are at least 1. In other words, it is preferable for X^{1AE} and X^{1AB} to be non-adjacent.

The R^{5A} groups (R^{5A1}, R^{5A2}, and R^{5A3}) are each independently absent or selected from H and a substituted or unsubstituted organic group. Ring A may be a saturated ring, an unsaturated non-aromatic ring, or an aromatic ring depending upon the number of R^{5A} groups present.

In most implementations, no more than one of the R^{5A} groups is a substituted or unsubstituted organic group.

When an R^{5A} group is present, that R^{5A} group is most preferably H.

Ring A may for example have a structure of formula:



where:

m is 1 or 2;

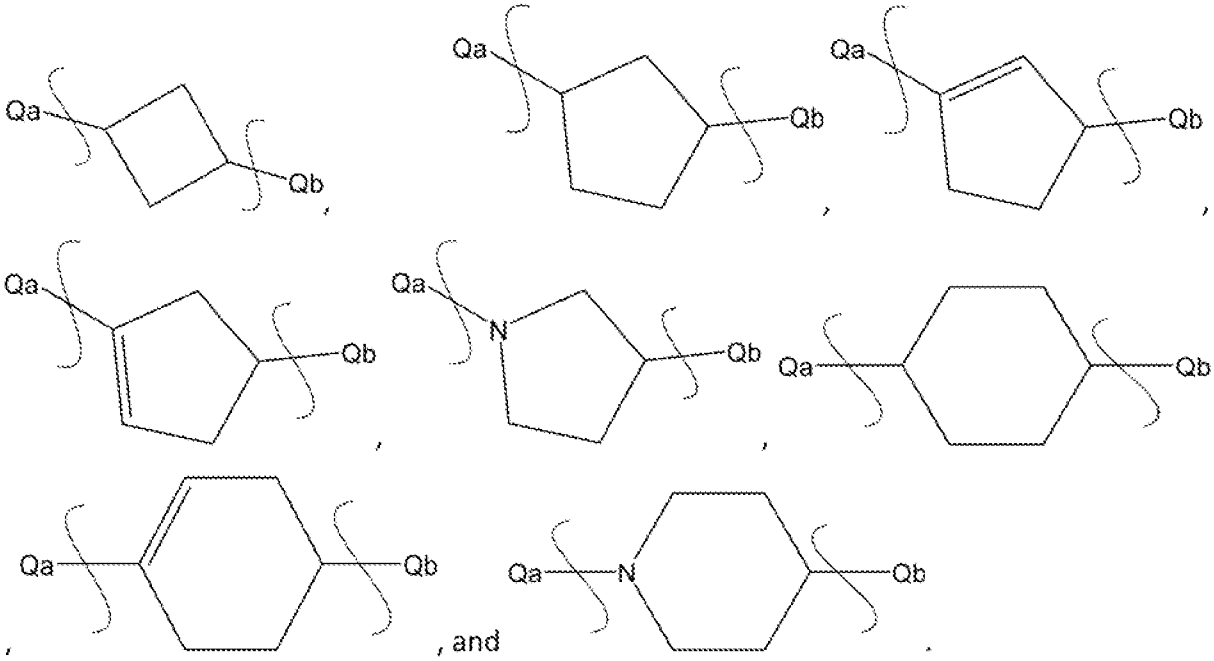
n is 1 or 2;

each R^{5A2} and R^{5A3} independently is absent or selected from H and a substituted or unsubstituted organic group; and

i) X1 is C and R^{5A1} is absent or selected from H and a substituted or unsubstituted organic group; or

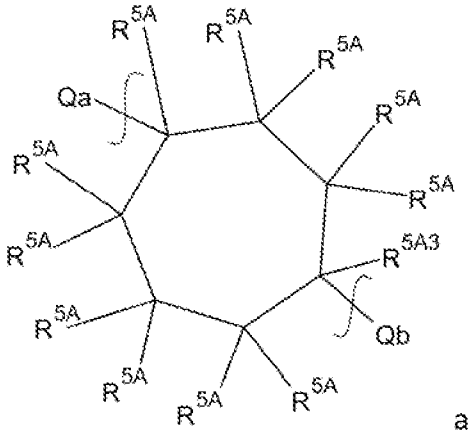
ii) X1 is N and R^{5A1} is absent. In such compounds, ring A is preferably an aliphatic ring (i.e., all bonds between X atoms are single bonds) and R^{5A3} is H. Optionally, each R^{5A2} is H.

Particularly preferably, ring A may have a structure selected from:

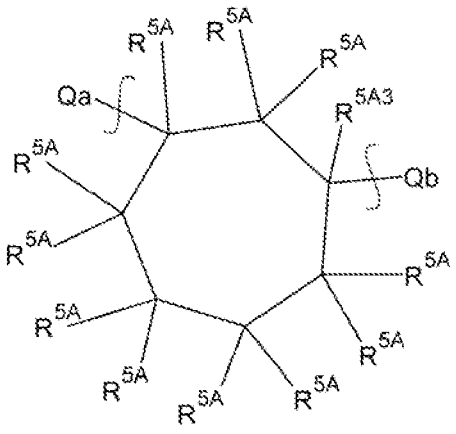


, and .

In other examples, ring A is a substituted or unsubstituted 7-membered aliphatic carbocycle or heterocycle, optionally a cycloheptane, further optionally a cycloheptane having structure selected from:

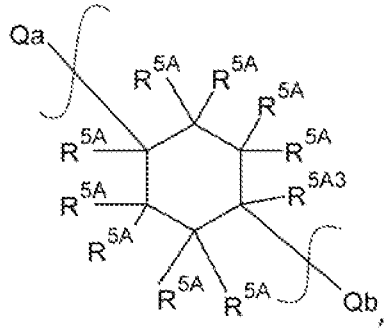


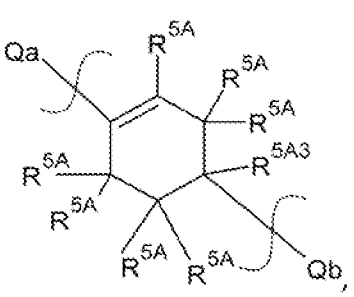
and

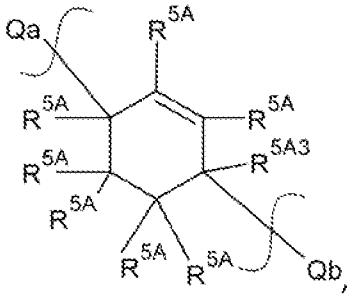


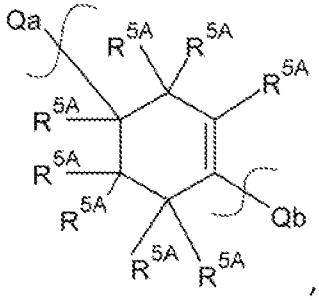
each R^{5A} and R^{5A3} being independently selected from H and a substituted or unsubstituted organic group, wherein R^{5A3} is most preferably H.

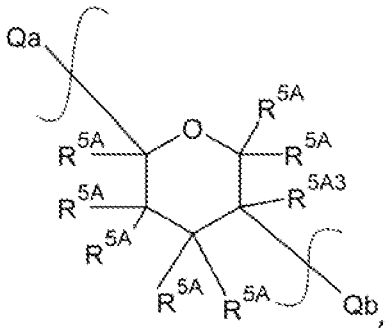
Alternatively, ring A may be a substituted or unsubstituted 6-membered aliphatic carbocycle or heterocycle, optionally a cyclohexane or tetrahydropyran and further optionally having a structure selected from:

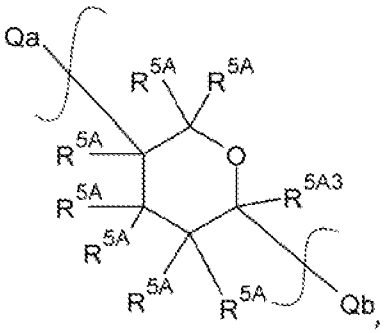


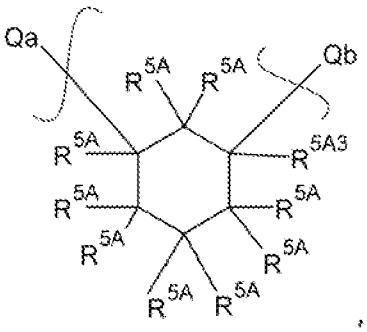












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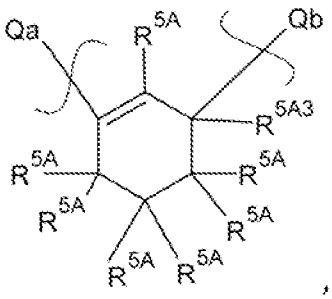

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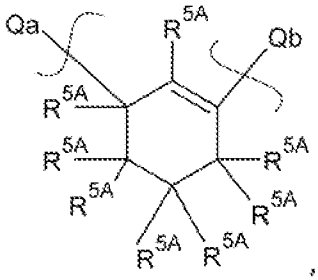

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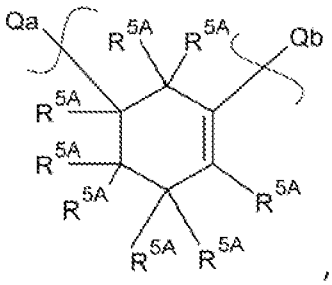

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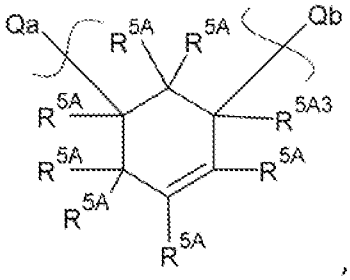

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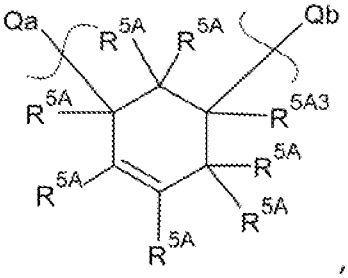

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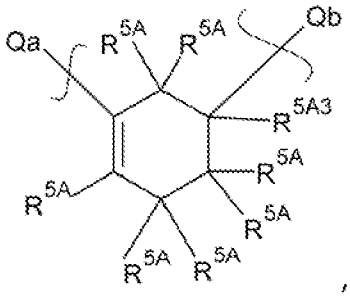

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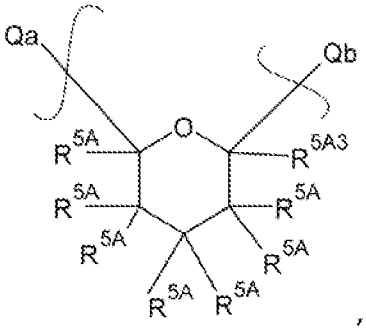

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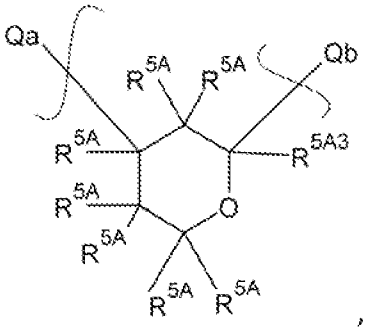

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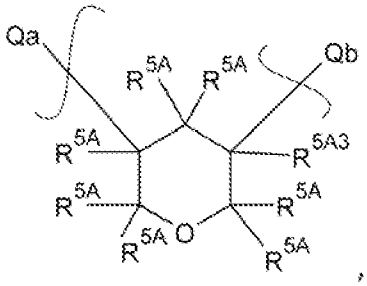

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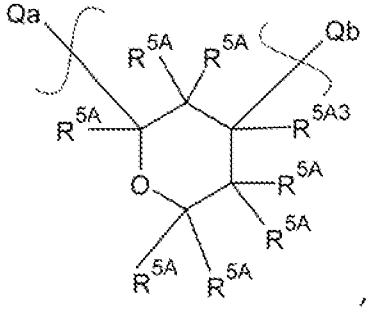
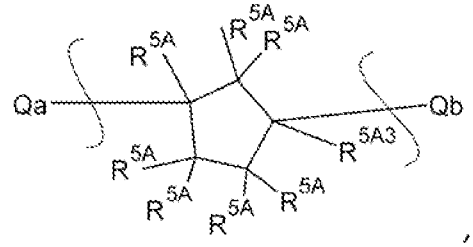


,

each R^{5A} and R^{5A3} being independently selected from H and a substituted or unsubstituted organic group, wherein R^{5A3} is most preferably H.

In accordance with another possibility, ring A may be a substituted or unsubstituted 5-membered aliphatic carbocycle or heterocycle, optionally a cyclopentane, cyclopentene, or a tetrahydrofuran, and further optionally having a structure selected from:



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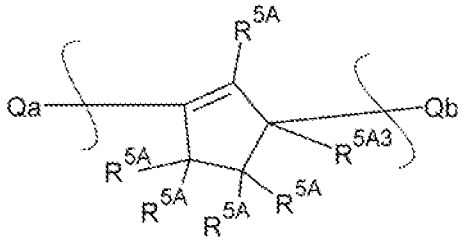

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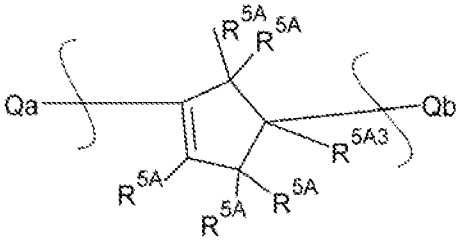

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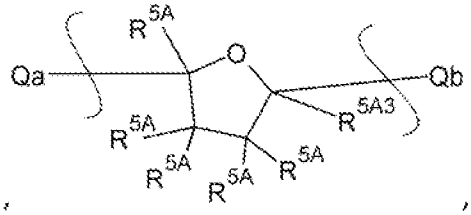

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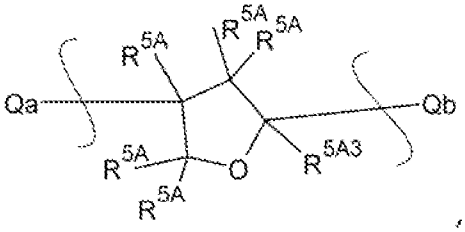

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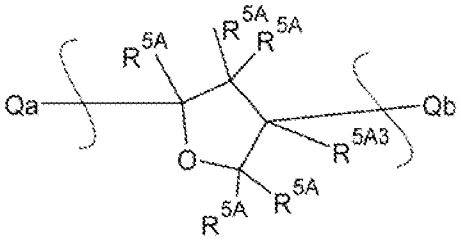
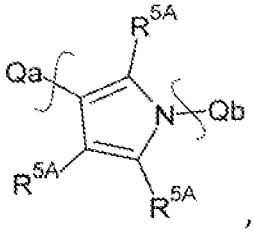
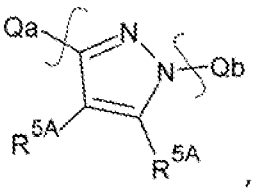


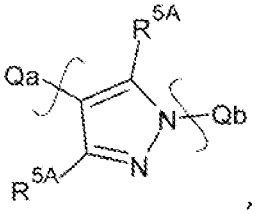
, and

each R^{5A} and R^{5A3} being independently selected from H and a substituted or unsubstituted organic group, wherein R^{5A3} is most preferably H.

In still further examples, ring A may be a 5-membered aromatic ring, optionally a pyrrole or pyrazole, and further optionally having a structure selected from:



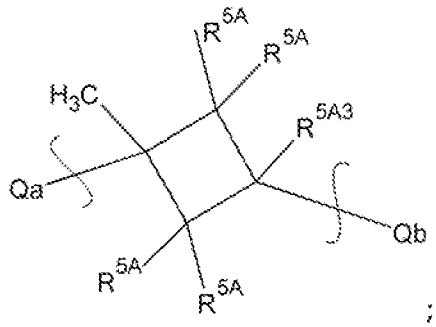
,


, and


,

each R^{5A} being independently selected from H and a substituted or unsubstituted organic group.

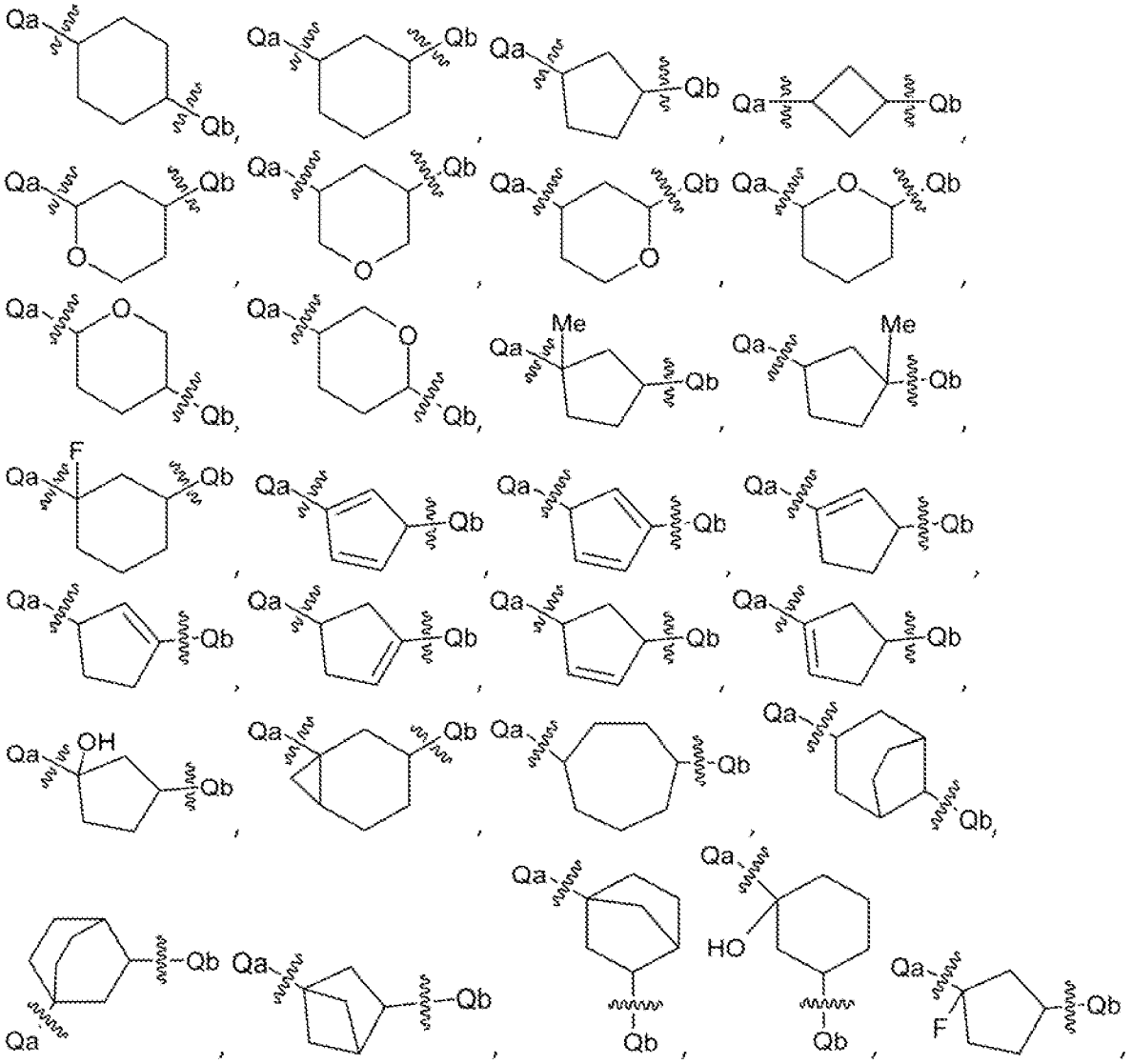
Other example compounds include those in which ring A is a substituted or unsubstituted cyclobutane, optionally having a structure of:

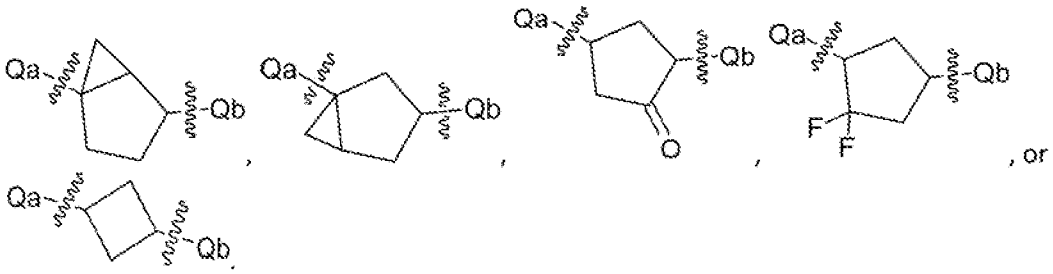


;

each R^{5A} and R^{5A3} being independently selected from H and a substituted or unsubstituted organic group, wherein R^{5A3} is most preferably H.

More specific examples of ring A structures include:

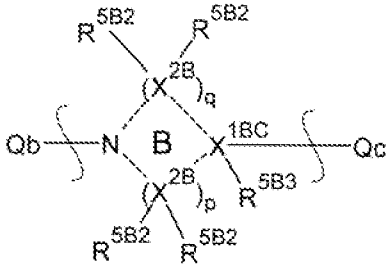




, , , , or .

Ring B

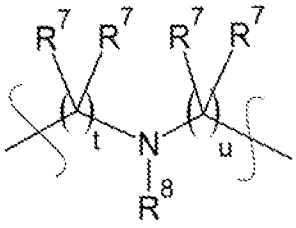
Ring B of the PARP1 inhibitor compound has a structure of:



X^{1BC} is the X^1 atom that is connected to ring C via linker Qc. X^{2B} denotes an X^2 atom which is part of ring B.

X^{1BC} may be C or N, and is preferably N. When X^{1BC} is N, R^{5B3} is typically absent.

Rings B and C are most typically not connected via an N-N bond. When Qc is



and t=0, X^{1BC} is C. When Qc is a bond, no more than one of X^{1BC} and $X1^{CB}$ is N.

Each X^{2B} atom is independently selected from C, N, O, and S; with C and N being preferred. The X^{2B} atoms are selected such that ring B is free of O-O, O-S, and S-S bonds. Particularly preferably, all of the X^{2B} atoms are C.

Ring B may be a 4, 5, 6, 7, or 8 membered ring. To this end, p is 0 or an integer in the range 1 to 6; q is 0 or an integer in the range 1 to 6, and p and q sum to an integer in the range 2 to 6.

In particular, ring B may be a 5 or 6 membered ring, and is particularly preferably a 6 membered ring. Put differently, p and q may sum to 3 or 4, preferably 4.

Preferably, both p and q are at least 1. In other words, X^{1BC} is preferably not adjacent to the N atom that connects to linker Qa.

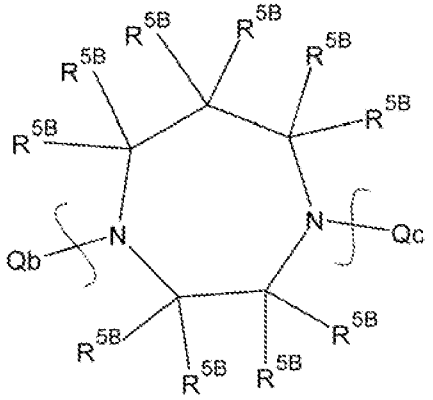
When ring B is a 6-membered ring, it is preferable for p to be 2 and q to be 2.

The R^{5B} groups (R^{5B2}, R^{5B3}) are each independently absent or selected from H and a is independently absent or selected from H and a substituted or unsubstituted organic group. Ring B may be a saturated ring, an unsaturated non-aromatic ring, or an aromatic ring depending upon the number of R^{5B} groups present. Ring B is preferably a saturated heterocycle.

In most implementations, no more than one of the R^{5B} groups is a substituted or unsubstituted organic group.

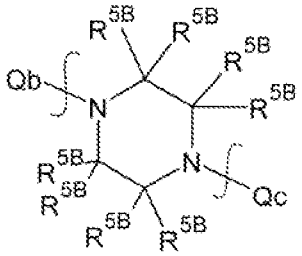
When an R^{5B} group is present, that R^{5B} group is most preferably H. Preferably, all R^{5B} groups are present and all R^{5B} groups are H.

Ring B may be a 7-membered saturated heterocyclic ring, optionally a homopiperazine having a structure:



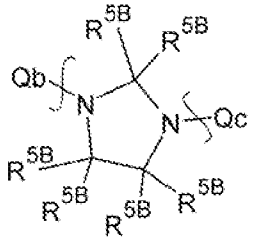
each R^{5B} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5B} is H.

Alternatively, ring B may be a 6-membered saturated heterocyclic ring, optionally a piperazine, further optionally a piperazine having a structure:



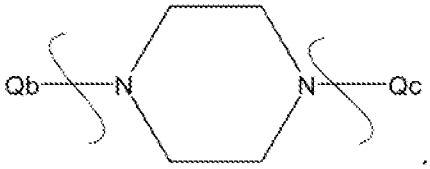
each R^{5B} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5B} is H.

In accordance with another possibility, ring B may be a 5-membered saturated heterocyclic ring, optionally an imidazolidine, further optionally an imidazolidine having a structure:



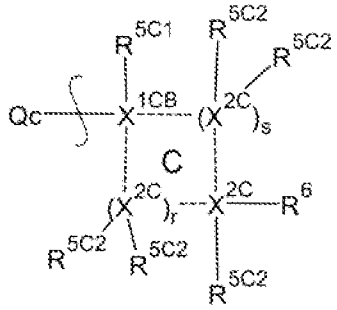
each R^{5B} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5B} is H.

It is particularly preferred for ring B to have a structure of:



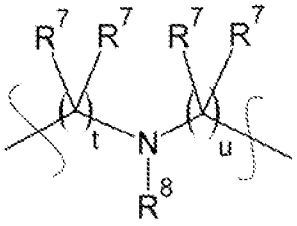
Ring C

Ring C of the PARP1 inhibitor compound has a structure of:



X^{1CB} denotes the X^1 atom of ring C which connects to ring B via linker Qc. X^{2C} denotes an X^2 atom of ring C.

X^{1CB} may be C or N, and is preferably C. When X^{1CB} is N, R5C1 is typically absent.



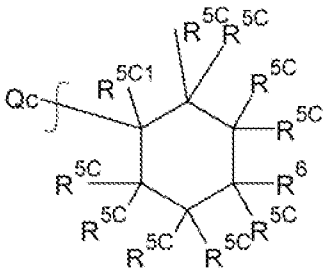
When Qc is and u=0, X^{1CB} is N. When atom X^{1BC} of ring B is N and Qc is a bond, X^{1CB} is C.

Ring C may be a 4, 5, 6, 7, or 8 membered ring. To this end, r is 0 or an integer in the range 1 to 6; s is 0 or an integer in the range 1 to 6, and r and s sum to an integer in the range 2 to 6.

It is preferable for each of r and s to be at least 1.

In particular, ring C may be a 5 or 6 membered ring, and is particularly preferably a 6 membered ring. Put differently, p and q may sum to 3 or 4, preferably 4.

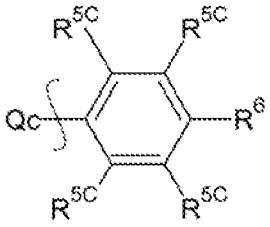
Ring C may be a 6-membered aliphatic ring, optionally a 6-membered aliphatic ring having structure:



each R^{5C} and R^{5C1} being independently selected from H and a substituted or unsubstituted organic group, preferably wherein R^{5C1} is H, more preferably wherein R^{5C1} and each R^{5C} is H.

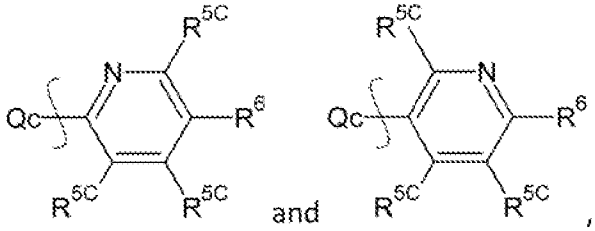
Alternatively, ring C may be a 6-membered aromatic ring, optionally selected from:

iia) a phenyl group, optionally having formula:



each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

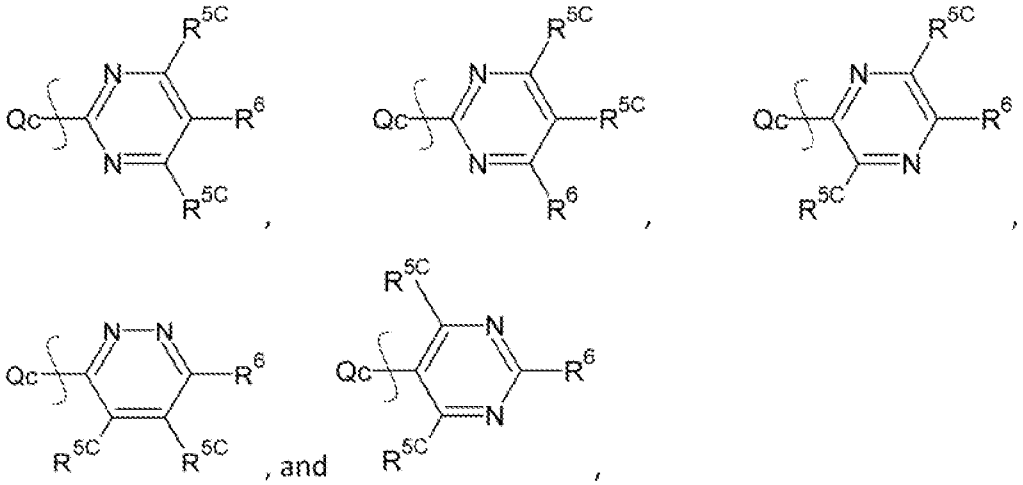
iib) a pyridine group, optionally having a formula selected from:



each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

and

iic) a diazine group, optionally having a formula selected from:

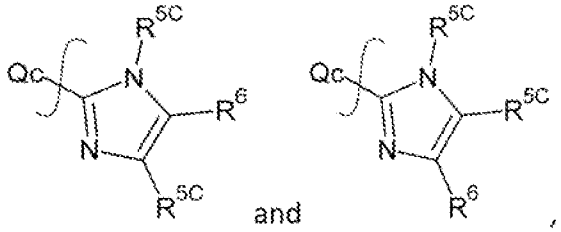


, and

each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H.

In further examples, ring C may be a 5-membered aromatic ring, optionally selected from:

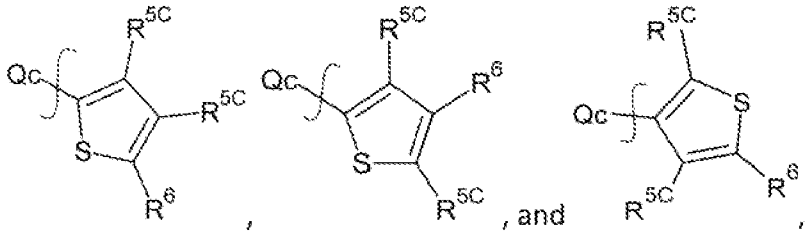
iiia) an imidazole group, optionally an imidazole group having a structure of:



and

each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

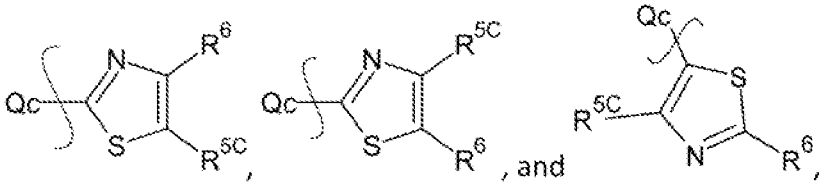
iiib) a thiophene group, optionally having a structure selected from:



, and

each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

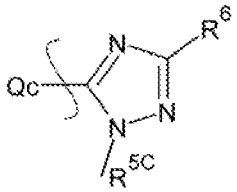
iiic) a thiazole group, optionally having a structure selected from:



each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

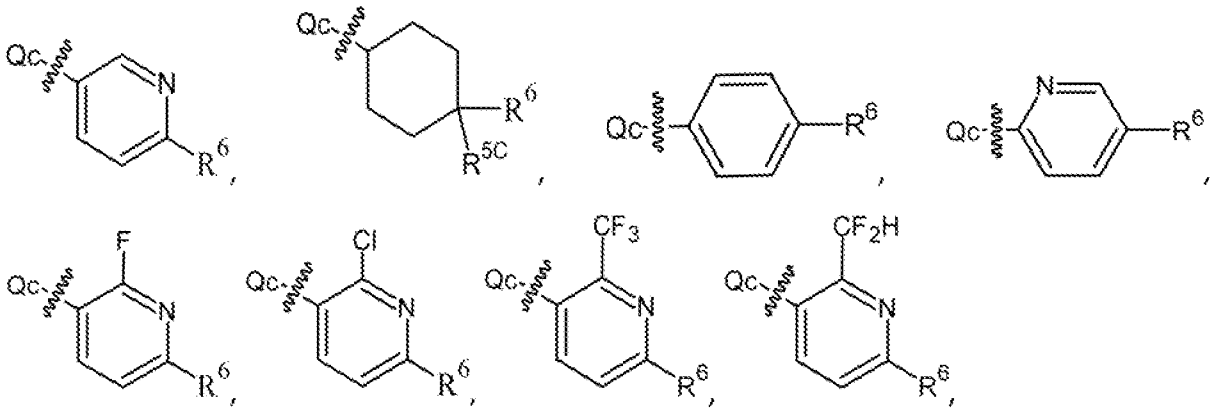
and

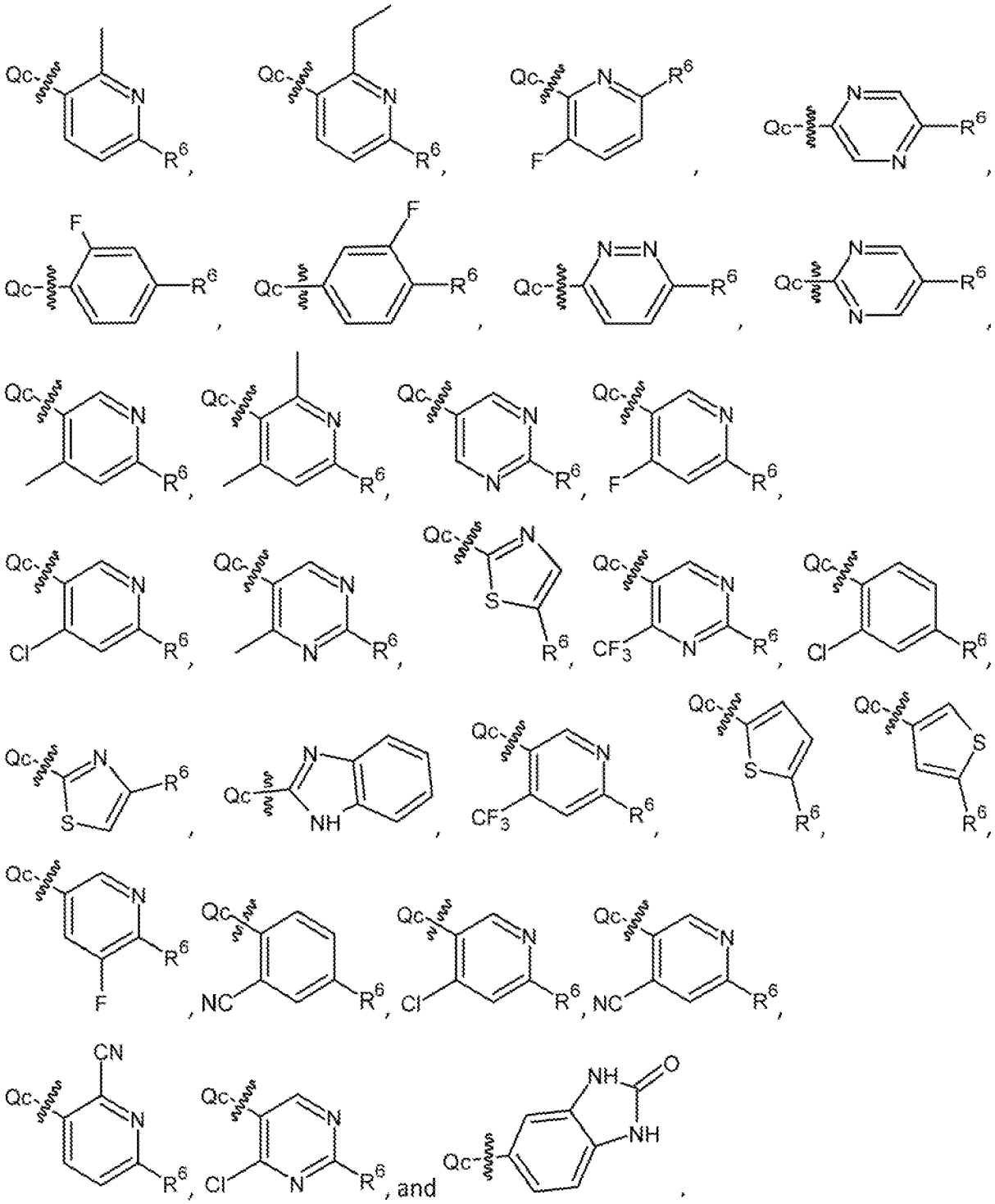
iiid) a triazole, optionally a triazole of formula:



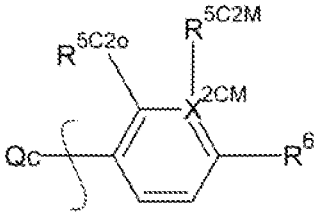
R^{5C} being selected from H and a substituted or unsubstituted organic group, optionally wherein R^{5C} is H.

In particular, ring C may have a structure selected from:





It is preferable for ring C to be a 6-membered aromatic ring. In particular, ring C may have a structure of:



where:

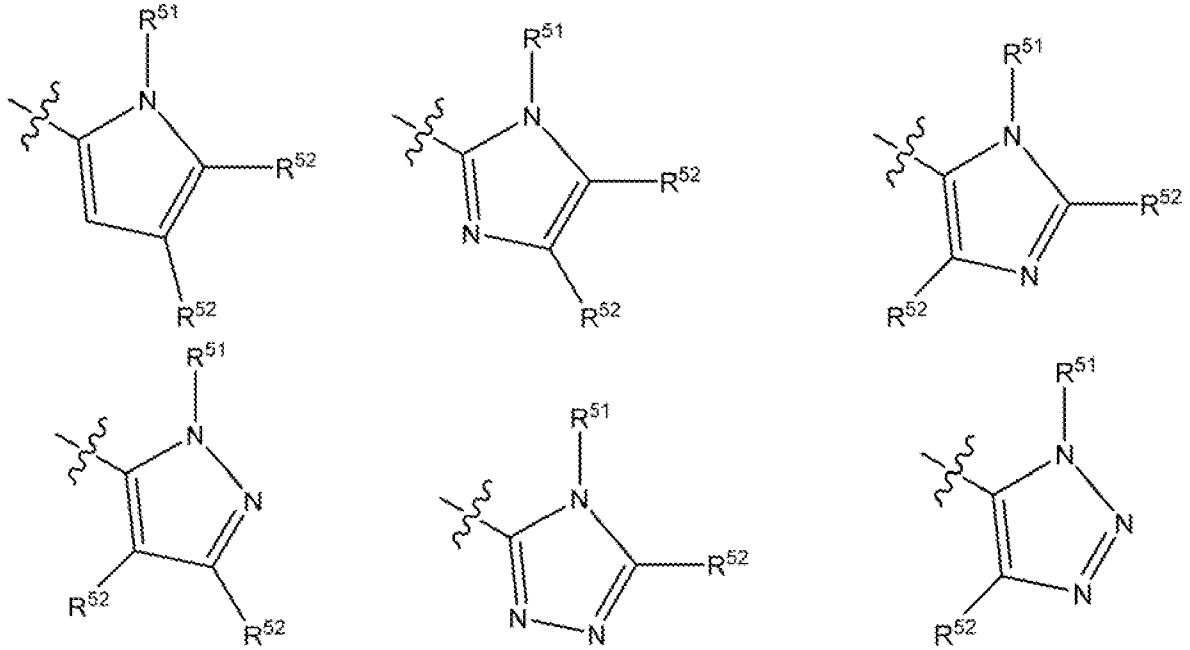
R^{5C2o} is selected from H and a halogen; and

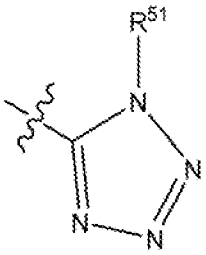
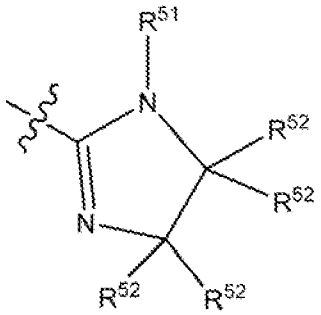
i) X^{2CM} is C and R^{5C2} is H; or

ii) X^{2CM} is N and $R5^{C2M}$ is absent.

Preferably, R^{5C2o} is a halogen, with F being the preferred halogen.

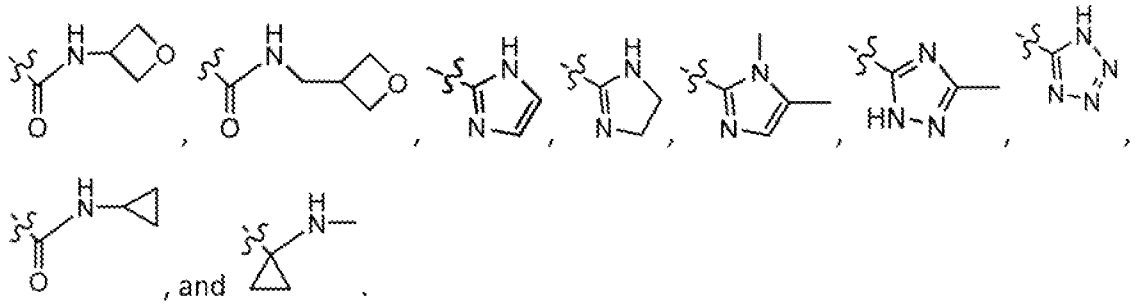
In the PARP1 inhibitor compounds provided herein, R^6 is absent or selected from H and a substituted or unsubstituted organic group. Preferably, R^6 is selected from H, -F, -Cl, -Br, -I, -CN, $-CONR^{51}R^{51}$, $-NR^{51}COR^{52}$, $-SO_2NR^{51}R^{51}$, $-NR^{51}SO_2R^{52}$, $-O-CR^{52}R^{52}R^{52}$, $-CR^{52}R^{52}NR^{51}R^{51}$ and any of the following structures:

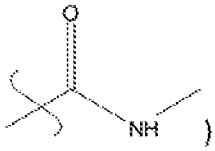
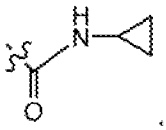


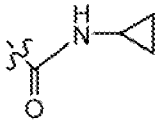
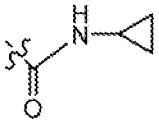



wherein R^{51} and R^{52} are each independently selected from H and a substituted or unsubstituted organic group. R^{51} and R^{52} are preferably each independently selected from H, a halogen, C1 to C3 alkyl, and C1 to C3 haloalkyl. For example, R^{51} and R^{52} may each be H.

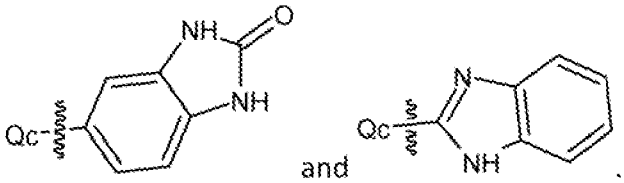
In particular, R^6 may be selected from -F, -Cl, -CN, $-CONH_2$, -CONHMe, -CONHEt, $-CONMe_2$, -CONHCOMe, $-CONHCH_2-CH_2OMe$, $-CONH-CH_2-CH_2F$, $-CONH-CH_2-CF_3$, $-CONH-CH_2-CHF_2$, $-OCHF_2$, -NHCOMe, $-NHSO_2Me$, $-SO_2NHMe$, $-CONHSO_2Me$,



The most preferred R^6 groups are CONHMe (i.e. ) and  .

Where a compound, L group, or C ring substructure is depicted as having R^6 = CONHMe, replacement of the R^6 group with  is contemplated. Likewise, where a compound, L group, or C ring substructure is depicted as having R^6 =  , replacement of the R^5 group with CONHMe is contemplated.

In some examples, R^6 and one R^{5C} group together form a ring. For example, ring C may have a structure selected from:

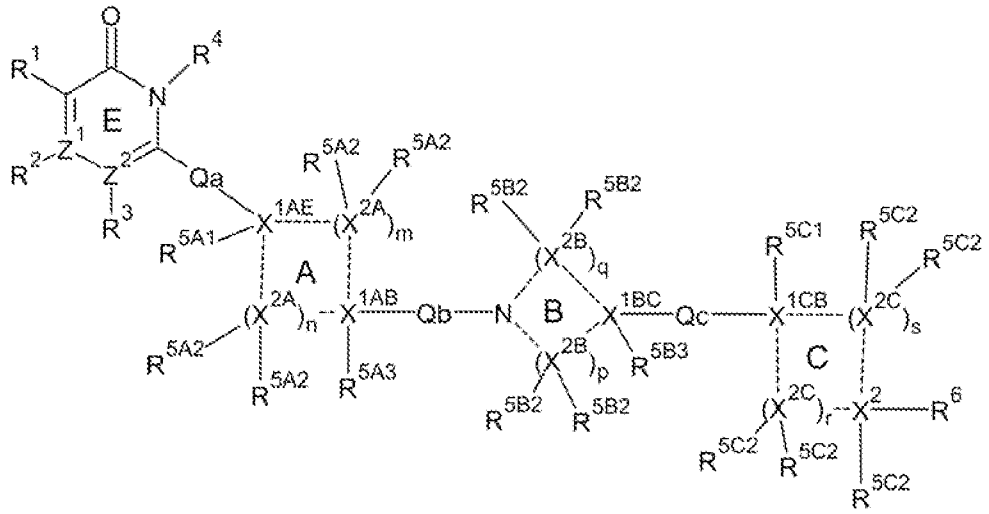


and

Typically however, ring C is not a fused ring system and no R^{5C} group forms a ring with another R^{5C} or R^6 group.

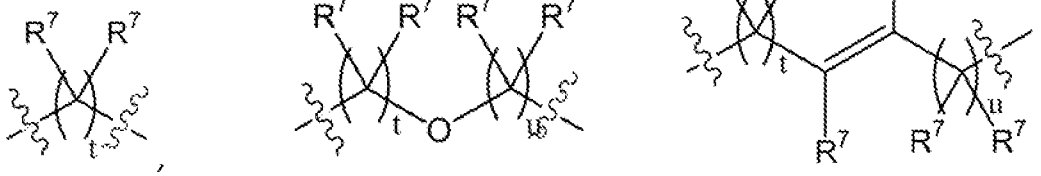
Linkers (Q groups)

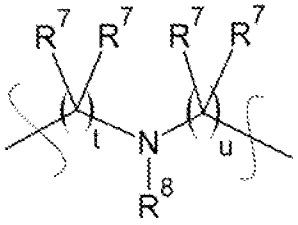
As shown in the formula below, the E, A, B, and C rings are connected by linkers Qa, Qb, and Qc:



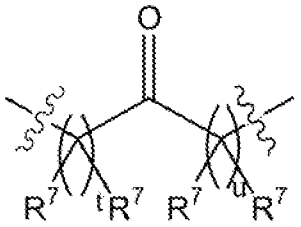
The linkers may be referred to herein generically as "Q groups". Qa, Qb, and Qc and rings A to C may be referred to collectively as group L.

Each linker is independently selected from a bond and a group having a structure independently selected from:





and

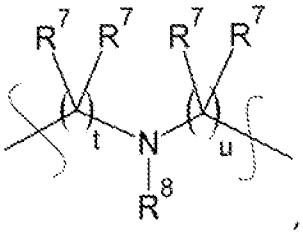


where:

t is a number selected from 0, 1, 2, 3, 4 and 5; and u is independently a number selected from 0, 1, 2, 3, 4 and 5; with the proviso that t + u is a number selected from 0, 1, 2, 3, 4, 5 and 6; and

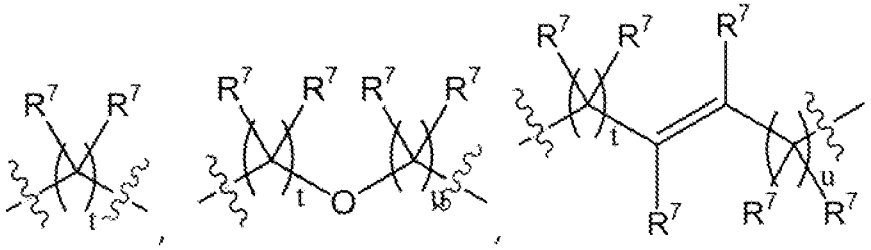
each R^7 and R^8 is independently selected from H and a substituted or unsubstituted organic group.

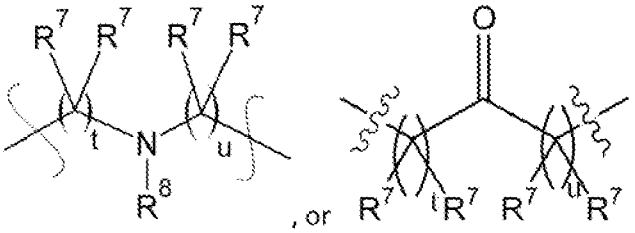
When a Q group is



, t and u are selected such that the Q group connects to the rings via C-N bonds and not N-N bonds. Typically, t is at least 1 and u is at least 1.

For example, at least one of Qa, Qb, and Qc may be:





, or

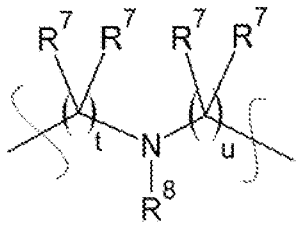
where t + u is at least one; and

where R^7 is selected from H, a halogen (such as –F, -Cl, -Br, and –I, preferably -F), a substituted or unsubstituted C_1-C_6 alkyl group, a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group (preferably CF_3), an -NH_2 group or a substituted or unsubstituted C_1-

C_6 amino group, an -OH group or a substituted or unsubstituted linear or branched C_1-C_6 alcohol group and a substituted or unsubstituted C_1-C_6 alkoxy group.

In particular, R^7 may be selected from H, a halogen (preferably F), a substituted or unsubstituted C_1-C_6 alkyl group or a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group.

When at least one of Qa, Qb and Qc has a structure of:



R^8 may be selected from:

H;

a substituted or unsubstituted linear or branched C_1-C_6 alkyl group

(such as Me, Et, Pr, i-Pr, n-Bu, i-Bu, t-Bu, pentyl and hexyl);

a substituted or unsubstituted linear or branched C_1-C_6 alkyl-aryl group

(such as --CH_2Ph, -CH_2(2,3 or 4)F-Ph, -CH_2(2,3 or 4)Cl-Ph, -CH_2(2,3 or 4)Br-Ph, -CH_2(2,3 or 4)I-Ph, -CH_2CH_2Ph, -$CH_2CH_2CH_2$Ph, -$CH_2CH_2CH_2CH_2$Ph, -$CH_2CH_2CH_2CH_2CH_2$Ph, and -$CH_2CH_2CH_2CH_2CH_2CH_2$Ph);

a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group

(such as -CH_2F, -CF3, -CH_2CH_2F and -CH_2CF_3);

a substituted or unsubstituted cyclic amine or amido group

(such as pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, 2-keto-pyrrolidinyl, 3-keto-pyrrolidinyl, 2-keto-piperidinyl, 3-keto-piperidinyl, and 4-keto-piperidinyl);

a substituted or unsubstituted cyclic C_3-C_8 alkyl group

(such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl);

a substituted or unsubstituted linear or branched C_2-C_6 alcohol group

(such as -CH_2CH_2OH, -$CH(CH_3)CH_2$OH, -$C(CH_3)_2$OH, -$CH_2CH_2CH_2$OH,

$-CH_2CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2CH_2OH$, $-CH(CH_3)CH(CH_3)OH$, $-CH(CH_2CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2CH_2CH_2CH_2OH$, and $-CH_2CH_2CH_2CH_2CH_2CH_2OH$);

a substituted or unsubstituted linear or branched C_2-C_6 carboxylic acid group (such as $-CH_2COOH$, $-CH_2CH_2COOH$, $-CH_2CH_2CH_2COOH$, $-CH_2CH_2CH_2CH_2COOH$, and $-CH_2CH_2CH_2CH_2CH_2COOH$);

a substituted or unsubstituted linear or branched carbonyl group (such as -(CO)Me, -(CO)Et, -(CO)Pr, -(CO)-i_Pr, -(CO)-n-Bu, -(CO)-i-Bu, -(CO)-t-Bu, -(CO)Ph, $-(CO)CH_2Ph$, $-(CO)CH_2OH$, $-(CO)CH_2OCH_3$, $-(CO)CH_2NH_2$,$-(CO)CH_2NHMe$, $-(CO)CH_2NMe_2$, -(CO)-cyclopropyl, -(CO)-1,3-epoxypropan-2-yl; $-(CO)NH_2$, -(CO)NHMe, $-(CO)NMe_2$, -(CO)NHEt, $-(CO)NEt_2$, -(CO)-pyrollidine-N-yl, -(CO)-morpholine-N-yl, -(CO)-piperazine-N-yl, -(CO)-N-methyl-piperazine-N-yl, $-(CO)NHCH_2CH_2OH$, $-(CO)NHCH_2CH_2OMe$, $-(CO)NHCH_2CH_2NH_2$, $-(CO)NHCH_2CH_2NHMe$, and $-(CO)NHCH_2CH_2NMe_2$);

a substituted or unsubstituted linear or branched C_1-C_6 carboxylic acid ester group (such as -COOMe, -COOEt, -COOPr, -COO-i-Pr, -COO-n-Bu, -COO-i-Bu, -COO-t-Bu, $-CH_2COOMe$, $-CH_2CH_2COOMe$, $-CH_2CH_2CH_2COOMe$, and $-CH_2CH_2CH_2CH_2COOMe$);

a substituted or unsubstituted linear or branched C_1-C_6 amide group (such as $-CO-NH_2$, -CO-NMeH, $-CO-NMe_2$, -CO-NEtH, -CO-NEtMe, $-CO-NEt_2$, -CO-NPrH, -CO-NPrMe, and -CO-NPrEt);

a substituted or unsubstituted sulfonyl group (such as $-SO_2Me$, $-SO_2Et$, $-SO_2Pr$, $-SO_2iPr$, $-SO_2Ph$, $-SO_2$-(2,3 or 4)-F-Ph, $-SO_2$-cyclopropyl, $-SO_2CH_2CH_2OCH_3$), $-SO_2NH_2$, $-SO_2NHMe$, $-SO_2NMe_2$, $-SO_2NHEt$, $-SO_2NEt_2$, $-SO_2$-pyrrolidine-N-yl, $-SO_2$-morpholine-N-yl, $-SO_2NHCH_2OMe$, and $-SO_2NHCH_2CH_2OMe$);

a substituted or unsubstituted aromatic group (such as Ph-, 2-F-Ph-, 3-F-Ph-, 4-F-Ph-, 2-Cl-Ph-, 3-Cl-Ph-, 4-Cl-Ph-, 2-Br-Ph-, 3-Br-Ph-, 4-Br-Ph-, 2-I-Ph-, 3-I-Ph, 4-I-Ph-, 2,(3,4,5 or 6)-F_2-Ph-, 2,(3,4,5 or 6)-Cl_2-Ph-, 2,(3,4,5 or 6)-Br_2-Ph-, 2,(3,4,5 or 6)-I_2-Ph-, 2,(3,4,5 or 6)-Me_2-Ph-, 2,(3,4,5 or 6)-Et_2-Ph-, 2,(3,4,5 or 6)-Pr_2-Ph-,

2,(3,4,5 or 6)-Bu_2-Ph-, 2,(3,4,5 or 6)-$(CN)_2$-Ph-, 2,(3,4,5 or 6)-$(NO_2)_2$-Ph-, 2,(3,4,5 or 6)-$(NH_2)_2$-Ph-, 2,(3,4,5 or 6)-$(MeO)_2$-Ph-, 2,(3,4,5 or 6)-$(CF_3)_2$-Ph-, 3,(4 or 5)-F_2-Ph-, 3,(4 or 5)-Cl_2-Ph-, 3,(4 or 5)-Br_2-Ph-, 3,(4 or 5)-I_2-Ph-, 3,(4 or 5)-Me_2-Ph-, 3,(4 or 5)-Et_2-Ph-, 3,(4 or 5)-Pr_2-Ph-, 3,(4 or 5)-Bu_2-Ph-, 3,(4 or 5)-$(CN)_2$-Ph-, 3,(4 or 5)-$(NO_2)_2$-Ph-, 3,(4 or 5)-$(NH_2)_2$-Ph-, 3,(4 or 5)-$(MeO)_2$-Ph-, 3,(4 or 5)-$(CF_3)_2$-Ph-, 2-Me-Ph-, 3-Me-Ph-, 4-Me-Ph-, 2-Et-Ph-, 3-Et-Ph-, 4-Et-Ph-, 2-Pr-Ph-, 3-Pr-Ph-, 4-Pr-Ph-, 2-Bu-Ph-, 3-Bu-Ph-, 4-Bu-Ph-, 2-(CN)-Ph-, 3-(CN)-Ph-, 4-(CN)-Ph-, 2-(NO_2)-Ph-, 3-(NO_2)-Ph-, 4-(NO_2)-Ph-, 2-(NH_2)-Ph-, 3-(NH_2)-Ph-, 4-(NH_2)-Ph-, 2-MeO-Ph-, 3-MeO-Ph-, 4-MeO-Ph-, 2-$(NH_2$-CO)-Ph-, 3-$(NH_2$-CO)-Ph-, 4-$(NH_2$-CO)-Ph-, 2-CF_3-Ph-, 3-CF_3-Ph-, 4-CF_3-Ph-, 2-CF_3O-Ph-, 3-CF_3O-Ph-, and 4-CF_3O-Ph-); and

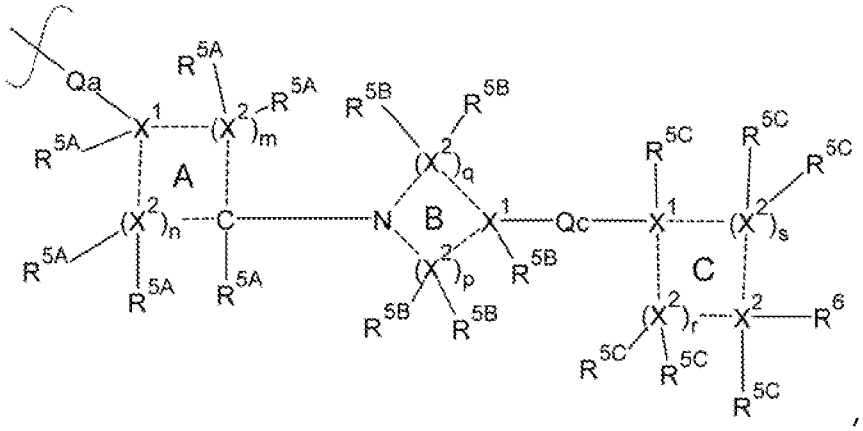
a substituted or unsubstituted heterocyclic group

(such as pyrrole-2-yl, pyrrole-3-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazole-5-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazine-3-yl, pyridazine-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-6-yl, pyrazine-2-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, 2-azapiperidine-3-yl, 2-azapiperidine-4-yl, 3-azapiperidine-2-yl, 3-azapiperidine-4-yl, 3-azapiperidine-5-yl, piperazine-2-yl, furan-2-yl, furan-3-yl, pyran-2-yl, pyran-3-yl, pyran-4-yl, 2-azapyran-3-yl, 2-azapyran-4-yl, 2-azapyran-5-yl, 2-azapyran-6-yl, 3-azapyran-2-yl, 3-azapyran-4-yl, 3-azapyran-5-yl, 3-azapyran-6-yl, 4-azapyran-2-yl, 4-azapyran-3-yl, 4-azapyran-5-yl, 4-azapyran-6-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-4-yl, 2-aza-tetrahydrofuran-5-yl, 3-aza-tetrahydrofuran-2-yl, 3-aza-tetrahydrofuran-4-yl, 3-aza-tetrahydrofuran-5-yl, tetrahydropyran-2-yl, oxetan-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, 2-aza-tetrahydropyran-3-yl, 2-aza-tetrahydropyran-4-yl, 2-aza-tetrahydropyran-5-yl, 2-aza-tetrahydropyran-6-yl, 3-aza-tetrahydropyran-2-yl, 3-aza-tetrahydropyran-4-yl,

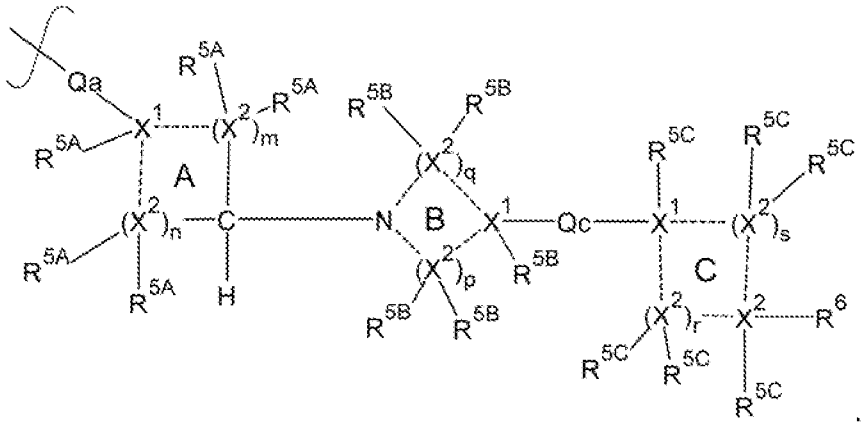
3-aza-tetrahydropyran-5-yl, 3-aza-tetrahydropyran-6-yl, morpholine-2-yl, morpholine-3-yl, thiophen-2-yl, thiophen-3-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl, thiopyran-2-yl, thiopyran-3-yl, thiopyran-4-yl, 2-azathiopyran-3-yl, 2-azathiopyran-4-yl, 2-azathiopyran-5-yl, 2-azathiopyran-6-yl, 3-azathiopyran-2-yl, 3-azathiopyran-4-yl, 3-azathiopyran-5-yl, 3-azathiopyran-6-yl, 4-azathiopyran-2-yl, 4-azathiopyran-3-yl, 4-azathiopyran-5-yl, 4-azathiopyran-6-yl, thiolane-2-yl, thiolane-3-yl, thiane-2-yl, thiane-3-yl, thiane-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, furazan-3-yl, (1,3,4-oxadiazol)-2-yl, (1,3,4-oxadiazol)-5-yl, (1,2,4-oxadiazol)-3-yl, (1,2,4-oxadiazol)-5-yl; and tetrazole-5-yl).

In particular, R^8 may be selected from H, a substituted or unsubstituted C_1-C_6 alkyl group or a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group.

Optionally, Qa is a bond or -CH_2-, and preferably Qa is a bond. Group L may have a structure of:



and optionally group L may have a structure of:



Optionally, Qb is a bond or -CH_2-, and preferably Qb is a bond.

Optionally, Qc is a bond or -CH_2-, and preferably Qc is a bond.

Preferably, Qa, Qb and Qc are each independently selected from a bond and -CH_2-. Most preferably, Qa, Qb, and Qc are each bonds.

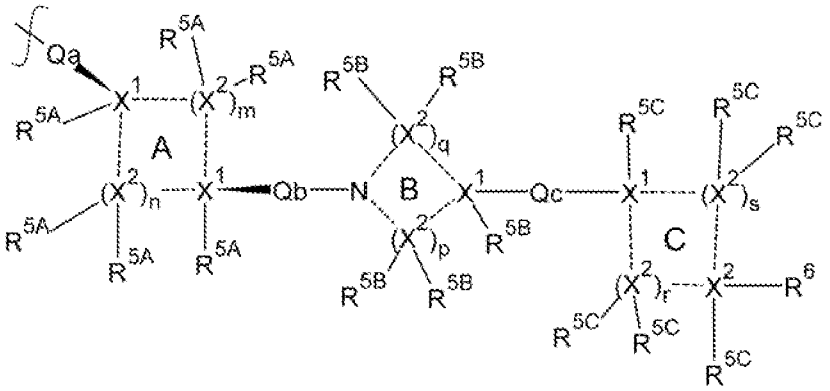
Group L of the PARP1 inhibitor compound

Stereochemistry

Various ones of the PARP1 inhibitor compounds provided herein may include one or more chiral centres.

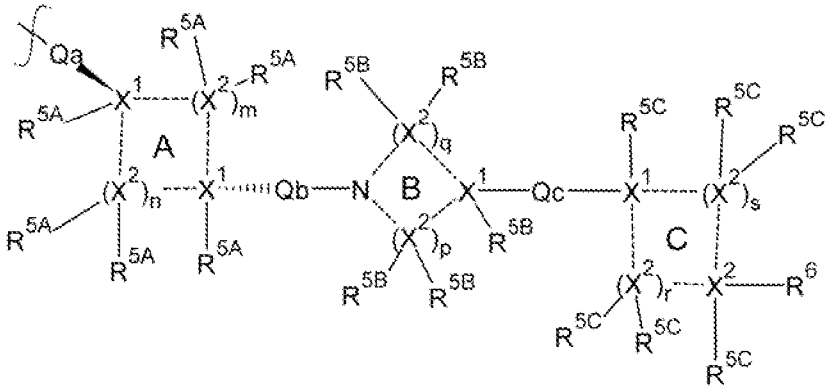
Without wishing to be bound by theory, it is believed that the configuration of rings E and B with respect to the A ring may influence the activity of the PARP1 inhibitor compound.

In the context of the present disclosure, where it is said that a PARP1 inhibitor compound is "A ring cis" or has a cis configuration of the A ring this means that the L group of the compound has a structure of:



where ring A is a saturated or unsaturated aliphatic carbocycle or heterocycle.

Where it is said that a PARP1 inhibitor compound is "A ring trans" or has a *trans* configuration of the A ring, this means that the L group of the compound has a structure of:



where ring A is a saturated or unsaturated aliphatic carbocycle or heterocycle.

In examples where ring A is a saturated 6-membered ring (n+m = 4, optionally n=m=2), the compound is preferably A ring cis. In such compounds, the A ring cis isomer may display greater PARP1 inhibition activity than the corresponding A ring trans isomer.

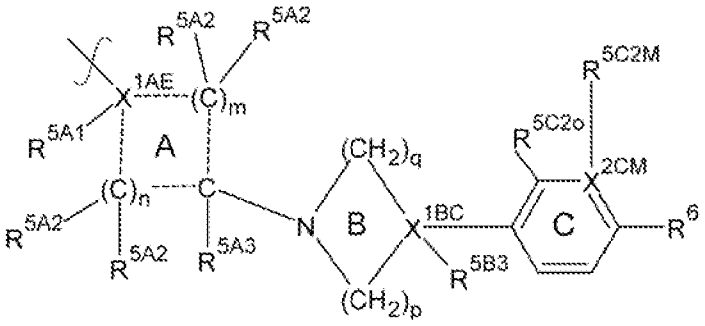
In examples where ring A is a saturated 5-membered ring (n+m = 3), the compound is preferably A ring trans. In such compounds, the A ring trans isomer may display greater PARP1 inhibition activity than the corresponding A ring cis isomer.

In some of the compounds provided herein, ring A is an aromatic ring. When ring A is aromatic, the PARP1 inhibitor compound is neither A ring cis nor A ring trans.

The PARP1 inhibitor compounds described herein may be provided in the form of an isolated enantiomer, a mixture of two or more enantiomers, a mixture of two or more diastereomers and/or epimers, or a racemic mixture.

Example L groups

In particular, group L may have a structure of:



where:

m is 1 or 2;

n is 1 or 2;

X^{1AE} is C and R^{5A1} is H, or X^{1AE} is N and R^{5A1} is absent;

each R^{5A2} is independently absent or H;

R^{5A3} is absent or H;

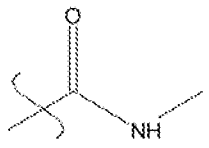
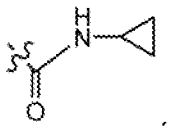
p is 1 or 2;

q is 1 or 2;

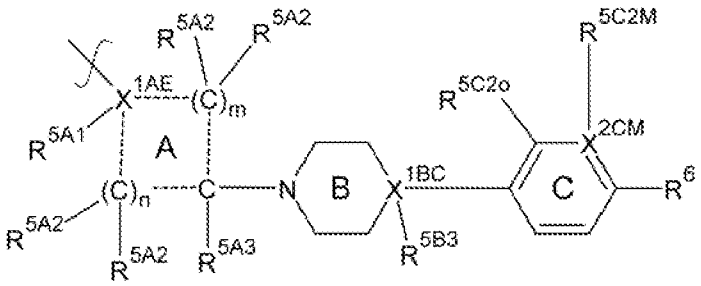
X^{1BC} is C and R^{5B3} is H, or X^{1BC} is N and R^{5B3} is absent;

R^{5C2o} is H or a halogen, optionally F;

X^{2CM} is N and R^{5C2M} is absent, or X^{2CM} is C and R^{52CM} is H; and

R^6 is selected from  and  .

In particular, p may be 2 and q may be 2, such that group L has a structure of:



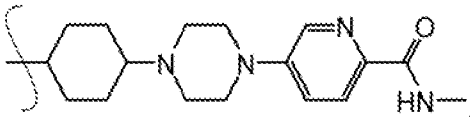
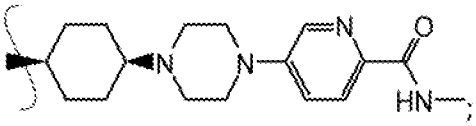
Preferably, X^{1BC} is N and R^{5B3} is absent.

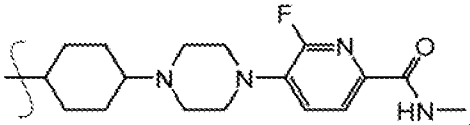
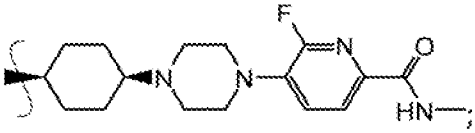
Ring A is preferably selected from: cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, and cyclohexenyl.

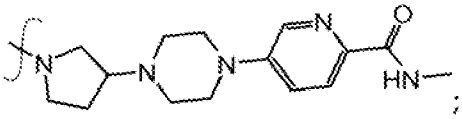
When ring A is a saturated 5-membered ring (e.g., cyclopentyl), the compound is preferably A ring trans.

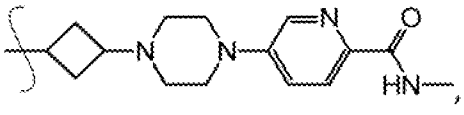
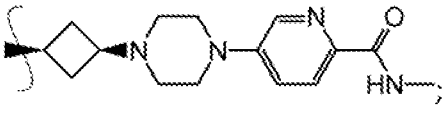
When ring A is a saturated 6-membered ring (e.g., cyclohexyl), the compound is preferably A ring cis.

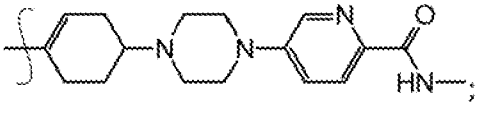
Group L may in particular be selected from:

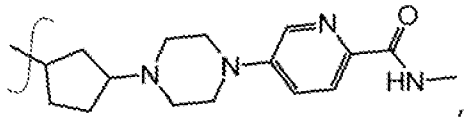
i)  , optionally  ;

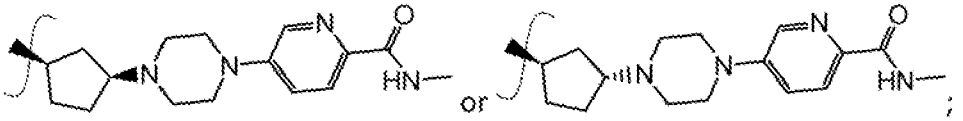
ii)  , optionally  ;

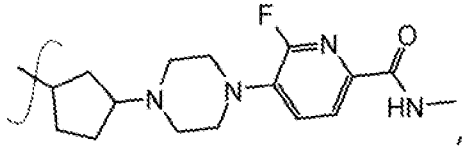
iii)  ;

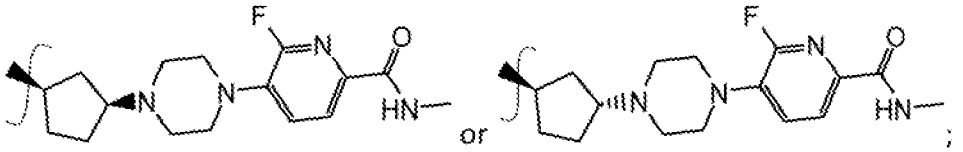
iv)  , optionally  ;

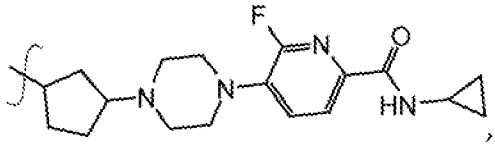
v)  ;

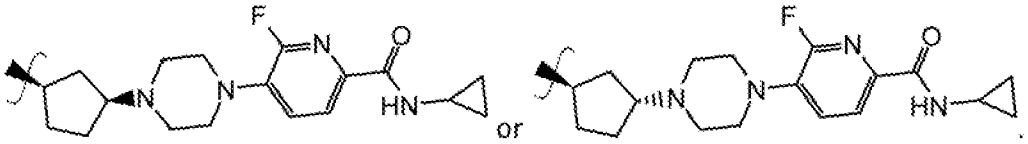
vi)  , optionally



vii)  , optionally

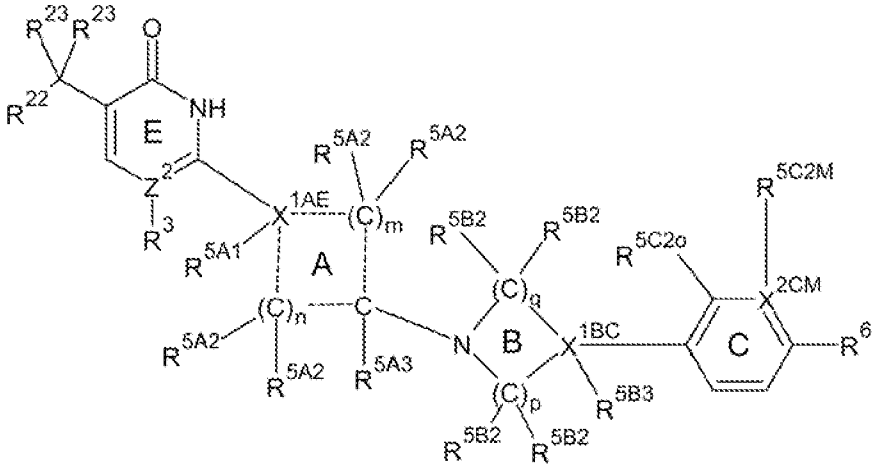


viii)  , optionally



Example Compounds

Example PARP1 inhibitor compounds provided herein include those having a structure of:



where:

each R^{23} is independently selected from H or a halogen (e.g., F);

R^{22} is selected from H, methyl, and halomethyl (e.g., CH_2F, CHF_2, CF_3);

Z^2 is C and R^3 is H, or Z^2 is N and R^3 is absent;

m is 1 or 2;

n is 1 or 2;

X^{1AE} is C and R^{5A1} is absent or H, or X^{1AE} is N and R^{5A1} is absent;

each R^{5A2} is independently absent or H;

R^{5A3} is absent or H;

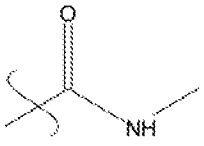
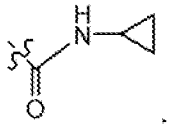
p is 1 or 2;

q is 1 or 2;

X^{1BC} is C and R^{5B3} is H, or X^{1BC} is N and R^{5B3} is absent;

R^{5C2o} is H or a halogen, optionally F;

X^{2CM} is N and R^{5C2M} is absent, or X^{2CM} is C and R^{52CM} is H; and

R^6 is selected from  and  .

Preferably, each R^{23} is H and R^{22} is methyl.

Preferably, Z^2 is C and R^3 is H.

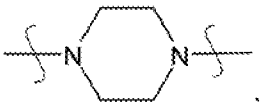
Preferably, X^{1AE} is C and R^{5A1} is H.

Ring A is preferably selected from cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, and cyclohexenyl.

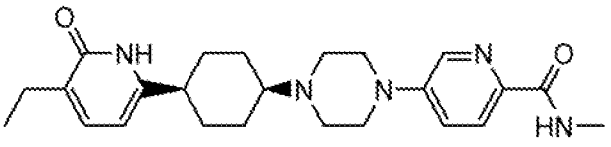
When ring A is a saturated 5-membered ring (e.g., cyclopentyl), the compound is preferably A ring trans.

When ring A is a saturated 6-membered ring (e.g., cyclohexyl), the compound is preferably A ring cis.

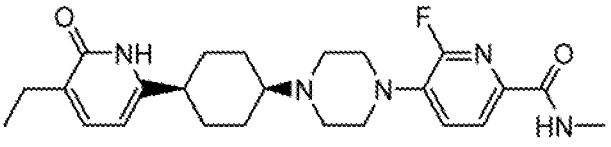
Ring B is preferably a piperazine:



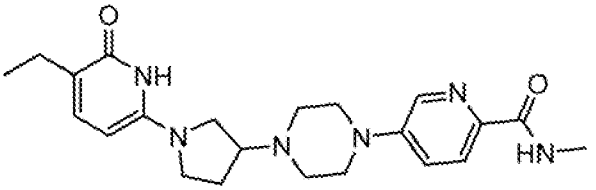
The PARP1 inhibitor compound may in particular have a structure selected from:



1cis



2cis



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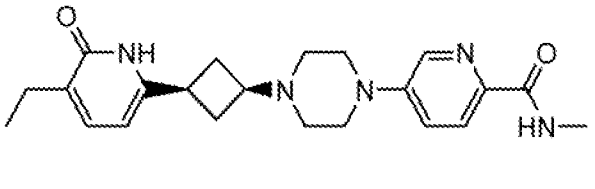
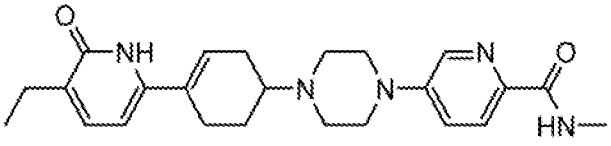
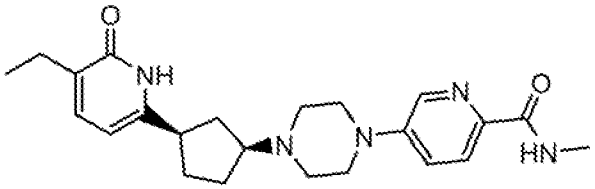


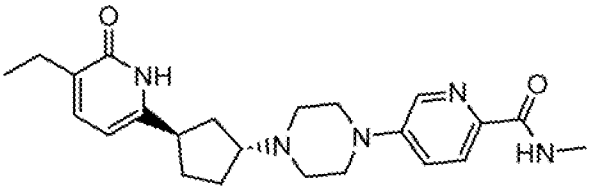
4cis



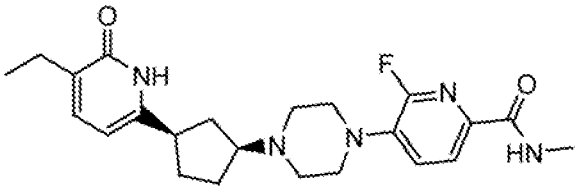
5



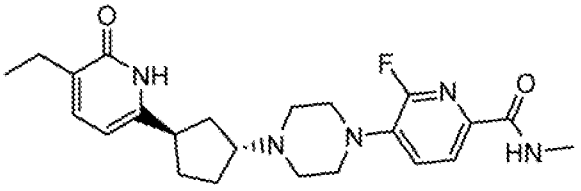
6cis



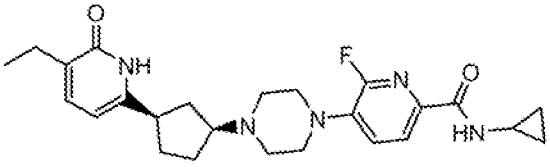
6trans



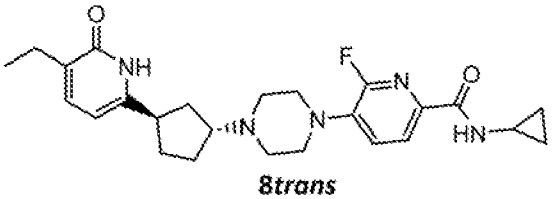
7cis



7trans



8cis



8trans

5

Medical Uses

The compounds described herein may be for use in medicine. In the context of the present invention, the medicinal use is not especially limited, provided that it is a use which is facilitated by the PARP1 inhibitory effect of the compound. Thus, the compounds of the invention may be for use in any disease, condition or disorder that may be prevented, ameliorated or treated using a PARP1 inhibitor.

In particular, the PARP1 inhibitor compound may be for use in treating a cancer. The nature of the cancer is not especially limited, provided that the cancer is one which may be treated, prevented or ameliorated by using a PARP1 inhibitor. The cancer may comprise a solid or liquid tumour.

For example, the cancer selected from: a cancer of the eye, brain (such as gliomas, glioblastomas, medulloblastomas, craniopharyngioma, ependymoma, and astrocytoma), spinal cord, kidney, mouth, lip, throat, oral cavity, nasal cavity, small intestine, colon, parathyroid gland, gall bladder, head and neck, breast, bone, bile duct, cervix, heart, hypopharyngeal gland, lung, bronchus, liver, skin, ureter, urethra, testicles, vagina, anus, laryngeal gland, ovary, thyroid, oesophagus, nasopharyngeal gland, pituitary gland, salivary gland, prostate, pancreas, adrenal glands; an endometrial cancer, oral cancer, melanoma, neuroblastoma, gastric cancer, an angiomatosis, a hemangioblastoma, a pheochromocytoma, a pancreatic cyst, a renal cell carcinoma, Wilms' tumour, squamous cell carcinoma, sarcoma, osteosarcoma, Kaposi sarcoma, rhabdomyosarcoma, hepatocellular carcinoma, PTEN Hamartoma-Tumor Syndromes (PHTS) (such as Lhermitte-Duclos disease, Cowden syndrome, Proteus syndrome, and Proteus-like syndrome), leukaemias and lymphomas (such as acute lymphoblastic leukaemia, chronic lymphocytic leukaemia, acute myelogenous leukaemia, chronic myelogenous leukaemia, hairy cell leukaemia, T-cell prolymphocytic leukaemia (T-PLL), large granular lymphocytic leukaemia, adult T-cell leukaemia, juvenile myelomonocytic leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, mantle lymphoma, follicular lymphoma, primary effusion lymphoma, AIDS-related lymphoma, diffuse B cell lymphoma, Burkitt lymphoma, cutaneous T-cell lymphoma, nasopharyngeal and gastrointestinal cancers.

In addition, the compounds described herein may be of use in cancers where Epstein Barr Virus, EBV, plays a contributing role such as Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal and gastrointestinal cancers.

The compounds described herein may be provided for use in for treating a cancer which is deficient in DNA damage response repair pathways, in particular in Homologous Recombination ("HR") dependent DNA Double Strand Break ("DSB") DNA repair activity. Components of HR dependent DNA DSB repair pathways and other DNA damage response pathways include but are not limited to the following proteins: ATM, ATR, ERCC1, XRCC1, XRCC2, XRCC3, RAD51, RAD51L1, RAD51C, RAD51D, RAD51L3, DMC1, RAD52, RAD54L, RAD54B, RAD50, MRE11A, NBS1, BRCA1, BRCA2, FANCP (SLX4), FEN1, PALB2, PBRM1, SMARCA4, ARID1A, ARID1B, FANCD2, BLM. Other components involved in HR dependent DNA DSB repair include regulatory factors such as ESMY (Hughes-Davies, L. *et al. Cell.* 2003; 115: 523-535). A cancer which is deficient in HR-dependent DNA DSB repair typically becomes dependent on alternative DSB pathway repair mechanisms. Such cancers include but are not limited to cancers of the ovary, prostate, breast, lung, gastrointestine, blood and pancreas.

The cancer cells may have a BRCA1 and/or BRCA2 deficient phenotype, i.e. the cancer cells may be deficient in BRCA1 and/or 2 function. The deficiency may arise by means of mutation, polymorphism or epigenetic silencing in the encoding nucleic acids or by means of mutation, polymorphism, amplification in a gene encoding a regulatory factor, e.g. the ESMY gene which encodes a BRCA2 regulatory factor (Hughes-Davies, L. *et al. Cell.* 2003; 115: 523-535). Amplification of the ESMY gene is associated with breast and ovarian cancer. Carriers of mutations in the tumour suppressor BRCA1 and/or BRCA2 genes are known to have an elevated risk of developing certain cancers including ovarian, prostate and breast. Wild-type alleles of BRCA1 and/or BRCA2 are frequently lost in tumours of heterozygous carriers (Jasin, M. *et al. Oncogene.* 2002; 21: 8981-93) and their detection, as a means of patient selection, is well known in the art (Radice, PJ. *et al. Exp. Clin. Cancer. Res.* 2002; 21: 9-12; Chappnis, PO and Foulkes WO. *Cancer Treat Res.* 2002; 107: 29-59).

The compounds provided herein may be administered to a patient who is undergoing radiotherapy and/or chemotherapy using a further agent for treating cancer.

For example, the PARP1 inhibitor compound may be administered in conjunction with a further agent for treating cancer.

The further agent for treating cancer may be selected from: anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase I inhibitors, topoisomerase II inhibitors, antimetabolites, senolytic agents, hormones and hormone analogues, signal transduction pathway inhibitors, other DNA damage repair pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, antibody-drug conjugates, immunotherapeutic agents, hormone deprivation therapy, proapoptotic agents, radioligand therapies, anti-angiogenic agents, and cell cycle signalling inhibitors.

In particular, the further agent may comprise an immunotherapeutic agent selected from: an anti-tumour vaccine; an oncolytic virus; an immune stimulatory antibody such as anti-CTLA4, anti-PD1, anti-PDL-1, anti-OX40, anti-41BB, anti-CD27, anti-CD40, anti-LAG3, anti-TIM3, and anti-GITR; a pattern recognition receptor agonist such as a STING, TLR-9 or RIG-I Helicase agonist; an IDO or TDO inhibitor; a novel adjuvant; a peptide; a cytokine; a chimeric antigen receptor T cell therapy (CAR-T); a small molecule immune modulator; and a tumour microenvironment modulator.

Pharmaceutical Compositions

Another aspect provides a pharmaceutical composition comprising the PARP1 inhibitor compound as defined above.

Typically, the composition includes a pharmaceutically acceptable additive and/or excipient.

In the pharmaceutical composition, the PARP1 inhibitor compound as defined above may be present in the form described above, but may alternatively be in a form suitable for improving bioavailability, solubility, and/or activity, and/or may be in a form suitable for improving formulation. Thus, the compound may be in the form of a pharmaceutically acceptable salt, hydrate, acid, ester, or other alternative suitable form.

Typically, the composition is for use in medicine, e.g. for use in treating a disease, condition or disorder as defined above.

For example, the pharmaceutical composition may be for use in treating a cancer. The composition may further comprise a further agent for treating cancer. The further agent for treating cancer is not especially limited, provided that it affords some utility for cancer treatment.

The further agent for treating cancer may comprise one or more chemotherapeutic agents such as anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase I inhibitors, topoisomerase II inhibitors, antimetabolites, senolytic agents, hormones and hormone analogues, signal transduction pathway inhibitors, other DNA damage repair pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, antibody-drug conjugates, immunotherapeutic agents, hormone-deprivation therapies, proapoptotic agents, radioligand therapies, anti-angiogenic agents, and cell cycle signalling inhibitors.

In particular, the further agent for treating cancer may comprise an immunotherapeutic agent selected from: an anti-tumour vaccine; an oncolytic virus; an immune stimulatory antibody such as anti-CTLA4, anti-PD1, anti-PDL-1, anti-OX40, anti-41BB, anti-CD27, anti-CD40, anti-LAG3, anti-TIM3, and anti-GITR; a pattern recognition receptor agonist such as a STING, TLR-9 or RIG-I Helicase agonist; an IDO or TDO inhibitor; a novel adjuvant; a peptide; a cytokine; a chimeric antigen receptor T cell therapy (CAR-T); a small molecule immune modulator; and a tumour microenvironment modulator.

Kits

Another aspect provides a pharmaceutical kit for treating a cancer. The pharmaceutical kit comprises a PARP1 inhibitor compound as defined herein, and a further agent for treating cancer. The compound and the further agent are suitable for administration simultaneously, sequentially or separately.

The further agent for treating cancer may be any of the further agents for treating cancer identified above in the discussion of the pharmaceutical composition.

In particular, the further agent for treating cancer may comprise one or more chemotherapeutic agents selected from: anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase I inhibitors, topoisomerase II inhibitors, antimetabolites, senolytic agents, hormones and hormone analogues, signal transduction pathway inhibitors, other DNA damage repair pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, antibody-drug conjugates, hormone-deprivation therapies, radioligand therapies, antiangiogenic agents, immunotherapeutic agents (such as selected from an anti-tumour vaccine, an oncolytic virus, an immune stimulatory antibody such as anti-CTLA4, anti-PD1, anti-PDL-1, anti-OX40, anti-41BB, anti-CD27, anti-CD40, anti-LAG3, anti-TIM3, and anti-GITR, a pattern recognition receptor agonist such as a STING, TLR-9 or RIG-I Helicase agonist, an IDO or TDO inhibitor, a novel adjuvant, a peptide, a cytokine, a chimeric antigen receptor T cell therapy (CAR-T), a small molecule immune modulator, tumour microenvironment modulators), proapoptotic agents and cell cycle signalling inhibitors.

Methods of Treatment

Another aspect of the invention provides a method of treating a disease and/or a condition and/or a disorder, which method comprises administering to a patient (or subject) a PARP1 inhibitor compound, or a composition, or a kit as defined herein. The method is typically a method for treating any disease condition or disorder mentioned herein. In typical embodiments, the method is a method for treating a cancer.

The patient may be any animal, preferably a mammal. For example, the patient may be a human, canine, equine or feline; and is preferably a human.

The method may comprise administering to the patient (or subject) a compound or a composition as defined above and a further agent for treating cancer as defined above. The

compound or composition and the further agent may be administered simultaneously, sequentially or separately, depending upon the agents and patients involved, and the disease to be treated (e.g., the type of cancer to be treated).

The patient may be undergoing treatment using ionising radiation.

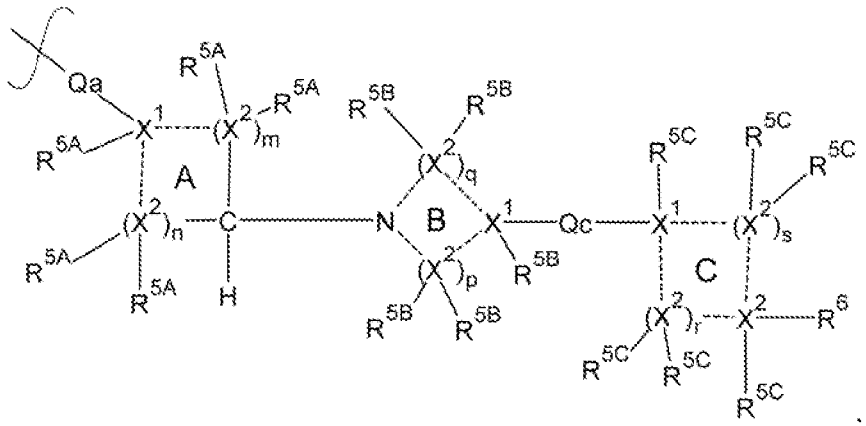
Methods of synthesising PARP1 inhibitor compounds

Also provided are methods for synthesising the PARP1 inhibitor compounds as defined herein. In general, the method comprises conducting a reaction between: (i) a first reactant comprising ring E bearing a first portion of group L, and (ii) a second reactant comprising a remainder of group L, to form the PARP1 inhibitor compound. The skilled person may select reaction conditions with reference to known synthesis techniques depending on the appropriate starting materials. The method may comprise one or more additional steps. Exemplary synthesis methodology is shown in the Examples hereinbelow.

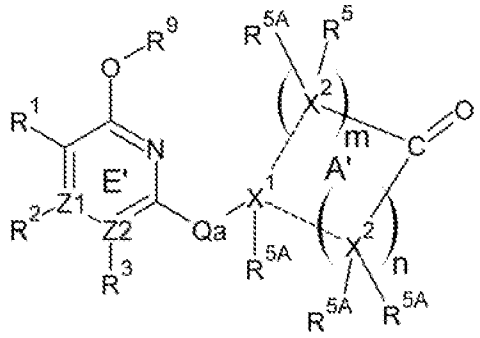
In one example method, the first reactant comprises ring E and ring A, and the second reactant comprises a Qb precursor bearing a reactive group, which method comprises joining ring A to the Qb precursor. In this method, the reactive group of the Qb precursor may comprise a carbonyl group, an alkyl halide, or an alkyl sulfonate. The reaction may comprise alkylation, reductive amination. or amide formation so as to form group L.

In another example method, the first reactant comprises ring E, ring A, Qa, and ring B, and the second reactant comprises a ring C derivative bearing a leaving group such as a halide or sulfonate. In this method, the reaction may comprise a nucleophilic substitution reaction, such as a nucleophilic aromatic substitution reaction, so as to form group L.

A particularly preferred method is for synthesising a PARP1 inhibitor compound where L is a group having a structure of:

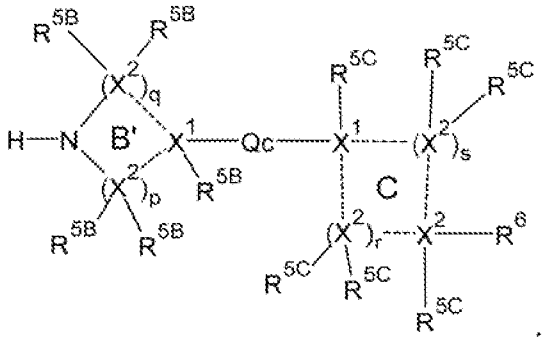


In the preferred method, the first reactant has a structure of:



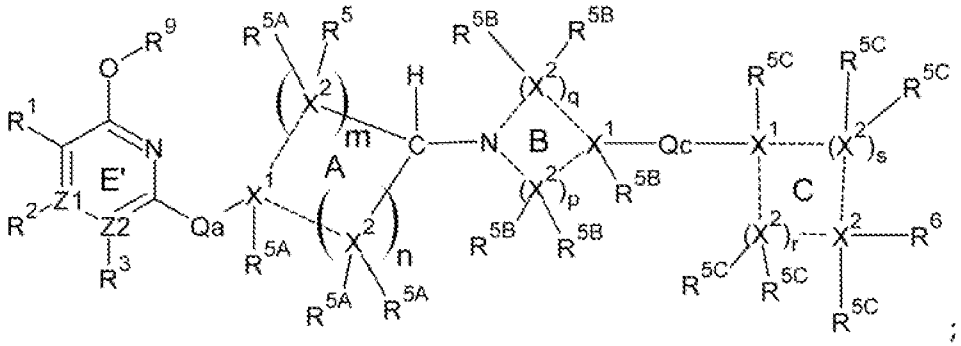
where R9 is a protecting group. R9 is most typically a methyl group. Other examples of protecting groups include acetyl, tert-butyl, benzoyl; benzyl; p-methoxybenzyl; p-methoxyphenyl, methoxymethyl, ethoxyethyl, methoxyethoxymethyl; methylthiomethyl, trityl; methoxytrityl; dimethoxytrityl, pivaloyl, tetrahydropyranyl, tetrahydrofuran, and silyl groups (such as trimethylsilyl, tert-butyldimethylsilyl, tri-iso-propylsilyloxymethyl, and triisopropylsilyl).

The second reactant in the preferred method has a structure of:



In the preferred method, conducting the reaction comprises:

i) coupling the first reagent and the second reagent using a reducing agent in the presence of an acid to obtain an intermediate product having a structure of:



; and

ii) subsequently deprotecting ring E' to form the PARP1 inhibitor compound.

The reducing agent and acid used in step i) may be selected as appropriate. Examples of suitable reducing agents include sodium borohydride, sodium cyanoborohydride, and sodium triacetoxyborohydride. The acid may be a weak acid, optionally a weak organic acid such as acetic acid.

The conditions used for deprotection step ii) may be selected as appropriate based on the nature of the protecting group R^9. For example, in implementations where R^9 is a methyl group, deprotection may be performed trimethylsilyl iodide ("TMSI") or boron tribromide in an appropriate solvent (such as dichloromethane, acetonitrile, or chloroform). Other acids or Lewis acids may be used.

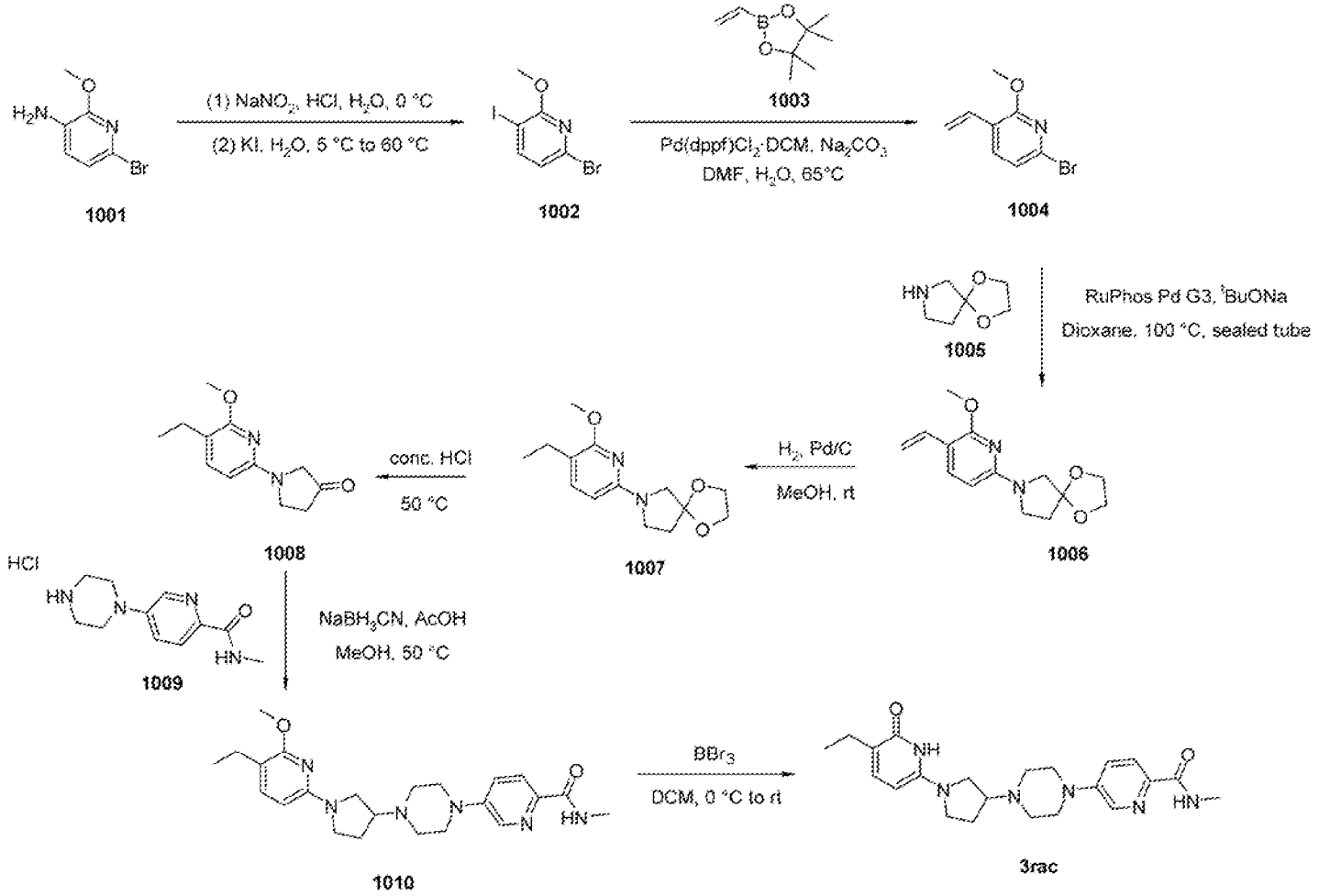
In some implementations of the preferred method, rings A, B', and B are all saturated rings, and optionally the X1 of rings B and B' is N.

The PARP1 inhibitor compound may be obtained in the form of a mixture of two or more structural isomers. The method may further comprise separating the structural isomers. For example, the method may further comprise comprising separating structural isomers of the PARP1 inhibitor compound using chiral supercritical fluid chromatography ("SFC") and/or chiral high-performance liquid chromatography ("HPLC").

When the PARP1 inhibitor compound is diastereomeric, separation may proceed in two stages. In a first stage, two pairs of stereoisomers may be isolated by HPLC. In a second stage, individual stereoisomers may be isolated from the pairs of stereoisomers by SFC.

Examples

Example 1: Synthesis of 3rac



SCHEME 1

Preparation of 6-bromo-3-iodo-2-methoxypyridine (1002)

The following three solutions A-C were prepared:

A: a solution of $NaNO_2$ (3.4 g, 0.049 mol) in H_2O (100 mL).

B: a solution of 6-bromo-2-methoxypyridin-3-amine **1001** (10 g, 0.049 mol) in conc. HCl: H_2O = 1:1 (80 mL).

C: a solution of KI (24.56 g, 0.15 mol) in H_2O (450 mL).

A was added to **B** dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. Then the reaction mixture was added to **C** dropwise at 0 °C. The mixture was heated at 60 °C for 2 h. The resulting mixture was diluted with water (200 mL) and extracted with EtOAc (500 mL x 3). The combined organic phases were washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (eluting with EtOAc/PE, 0 % to 50 %) to give 6-bromo-3-iodo-2-methoxypyridine **1002** (8.9 g, 90 % purity, 58 % yield) as a white solid.

LCMS (ESI) calcd for C_6H_5BrINO $[M + H]^+$ m/z 313.86, no MS signal found.

Preparation of 6-bromo-2-methoxy-3-vinylpyridine (1004)

To a solution of 6-bromo-3-iodo-2-methoxypyridine **1002** (1 g, 0.0032 mol) in DMF/H_2O = 5:1 (50 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane **1003** (0.50 g, 0.0032 mol), Na_2CO_3 (1.01 g, 0.0096 mol) and Pd(dppf)Cl_2·DCM (0.26 g, 0.00032 mol) under N_2. The mixture was heated at 65 °C for 2 hours. The resulting mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic phases were washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (eluting with EtOAc/PE, 0% to 100%) to give 6-bromo-2-methoxy-3-vinylpyridine **1004** (600 mg, 90 % purity, 78 % yield) as a white solid.

LCMS (ESI) calcd for C_8H_8BrNO $[M + H]^+$ m/z 213.98, no signal found

Preparation of 7-(6-methoxy-5-vinylpyridin-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonane (1006)

To a solution of 6-bromo-2-methoxy-3-vinylpyridine **1004** (600 mg, 0.0028 mol) and 1,4-dioxa-7-azaspiro[4.4]nonane **1005** (0.41 g, 0.0031 mol) in Dioxane (20 mL) was added ^{t}BuONa (0.89 g, 0.0084 mol) and RuPhos Pd G3 (0.24 g, 0.00024 mol) in a sealed tube. The mixture was heated at 100 °C for 2 hours. The resulting mixture was concentrated and purified by silica gel column chromatography (eluting with EtOAc/PE, 0% to 100%) to give 7-(6-methoxy-5-vinylpyridin-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonane **1006** (250 mg, 90% purity, 30% yield) as a white solid.

LCMS (ESI) calcd for $C_{14}H_{18}N_2O_3$ $[M + H]^+$ m/z 263.13, found 262.92.

Preparation of 7-(5-ethyl-6-methoxypyridin-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonane (1007)

To a solution of 7-(6-methoxy-5-vinylpyridin-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonane **1006** (250 mg, 0.96 mmol) in MeOH (20 mL) was added 10% Pd/C (25 mg). The mixture was evacuated and backfilled with hydrogen three times and then charged with hydrogen. The resulting mixture was stirred at room temperature for 2 hours. Then the mixture was filtered through celite and concentrated under vacuum to give crude 7-(5-ethyl-6-methoxypyridin-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonane **1007** (250 mg, 90 % purity, 90 % yield) which was used directly in next step without further purification.

LCMS (ESI) calcd for $C_{14}H_{20}N_2O_3$ $[M + H]^+$ m/z 265.15, found 264.95.

Preparation of 1-(5-ethyl-6-methoxypyridin-2-yl)pyrrolidin-3-one (1008)

A solution of 7-(5-ethyl-6-methoxypyridin-2-yl)-1,4-dioxa-7-azaspiro[4.4]nonane **1007** (200 mg, 0.76 mmol) in conc. HCl (12 mL) was stirred at 50 °C for 12 h. Then the resulting mixture was adjusted to pH 7-8 with aq. $NaHCO_3$ and extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine, dried over sodium sulfate, concentrated to give crude 1-(5-ethyl-6-methoxypyridin-2-yl)pyrrolidin-3-one **1008** (130 mg, 90 % purity, 70 % yield) as a white solid.

LCMS (ESI) calcd for $C_{12}H_{16}N_2O_2$ $[M + H]^+$ m/z 221.12, found 221.20.

Preparation of 5-(4-(1-(5-ethyl-6-methoxypyridin-2-yl)pyrrolidin-3-yl)piperazin-1-yl)-N-methylpicolinamide (1010)

To a solution of 1-(5-ethyl-6-methoxypyridin-2-yl)pyrrolidin-3-one **1008** (120 mg, 0.45 mmol) and N-methyl-5-(piperazin-1-yl)picolinamide **1009** (117 mg, 0.45 mmol) in MeOH (10 mL) was added AcOH (0.1 mL). Then $NaBH_3CN$ (29 mg, 0.45 mmol) was added to the mixture. The mixture was heated at 50 °C for 1 hour. The resulting mixture was quenched with water (1 mL), concentrated, and purified by silica gel column chromatography (eluting with MeOH/DCM, 0 % to 10 %) to give 5-(4-(1-(5-ethyl-6-methoxypyridin-2-yl)pyrrolidin-3-yl)piperazin-1-yl)-N-methylpicolinamide **1010** (100 mg, 90 % purity, 38 % yield) as a white solid.

LCMS (ESI) calcd for $C_{23}H_{32}N_6O_2$ $[M + H]^+$ m/z 425.26, found 425.25.

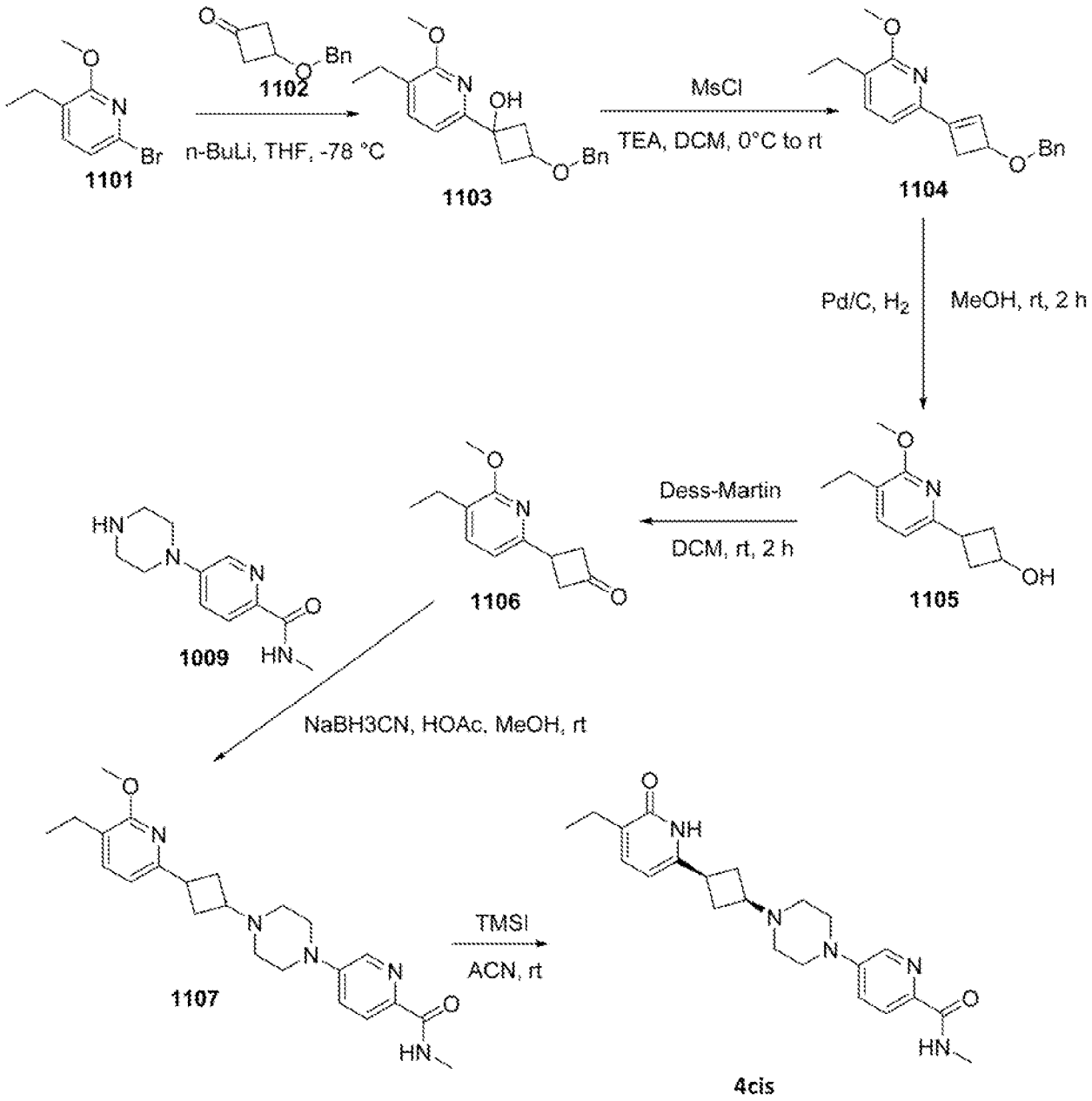
Preparation of 5-(4-(1-(5-ethyl-6-oxo-1,6-dihydropyridin-2-yl)pyrrolidin-3-yl)piperazin-1-yl)-N-methylpicolinamide (3rac)

To a solution of 5-(4-(1-(5-ethyl-6-methoxypyridin-2-yl)pyrrolidin-3-yl)piperazin-1-yl)-N-methylpicolinamide **1010** (100 mg, 0.24 mmol) in DCM (10 mL) was added BBr_3 (118 mg, 0.47 mmol) at 0 °C. The mixture was stirred at rt for 2 hours. The resulting mixture was diluted with water (10 mL) and extracted with EtOAc (50 mL x 3). The combined organic phases were washed with brine, dried over sodium sulfate, concentrated, and purified by prep-HPLC (Gemini 5 μm C18 column, 150 × 21.2 mm, eluting with 5 % to 95 % $MeCN/H_2O$ containing 0.1% FA) to give 5-(4-(1-(5-ethyl-6-oxo-1,6-dihydropyridin-2-yl)pyrrolidin-3-yl)piperazin-1-yl)-N-methylpicolinamide **3rac** (11.9 mg, 99% purity, 13% yield) as a white solid.

^1H NMR (400 MHz, DMSO-d_6, ppm) δ: 10.20 (s, 1 H), 8.44-8.36 (m, 1 H), 8.28 (d, *J* = 2.4 Hz, 1 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.44-7.37 (m, 1 H), 7.11 (d, *J* = 7.6 Hz,1 H), 5.39 (s, 1 H), 3.65-3.57 (m, 1 H), 3.52-3.42 (m, 1 H), 3.37-3.33 (m, 3 H), 3.30-3.22 (m, 2 H), 3.19-3.09 (m, 1 H), 2.94 (d, *J* = 4.8 Hz, 1 H), 2.78 (d, *J* = 4.8 Hz, 3 H), 2.68-2.60 (m, 2 H), 2.60-2.53 (m, 2 H), 2.34-2.25 (m, 2 H), 2.23-2.14 (m, 1 H), 1.89-1.77 (m, 1 H), 1.03 (t, *J* = 7.4 Hz, 3 H).

LCMS (ESI) calcd for $C_{22}H_{30}N_6O_2$ $[M + H]^+$ m/z 411.24, found 411.25.

*Example 2: Synthesis of **4cis***



SCHEME 2

Preparation of 3-(benzyloxy)-1-(5-ethyl-6-methoxypyridin-2-yl)cyclobutan-1-ol (1103)

To a solution of 6-bromo-3-ethyl-2-methoxypyridine **1101** (800 mg, 12.41 mmol) in THF (15 mL) was added n-BuLi (2.5 M in hexane, 2.22 mL, 5.55 mmol) dropwise at -78°C under an atmosphere of N_2. After addition, the solution was stirred at -78°C for 30 minutes. Then 3-(benzyloxy)cyclobutan-1-one (**1102**, 984 mg, 5.55 mmol) was added dropwise. The resulting solution was slowly warmed to room temperature and stirred for 2 hours. The final mixture

was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. (20 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 80: 20) to give 3-(benzyloxy)-1-(5-ethyl-6-methoxypyridin-2-yl)cyclobutan-1-ol **1103** (400 mg, 32 % yield) as a colorless oil.

LCMS (ESI) calcd for $C_{19}H_{24}NO_3$ $[M + H]^+$ m/z 314.17, found 314.10.

Preparation of 6-(3-(benzyloxy)cyclobut-1-en-1-yl)-3-ethyl-2-methoxypyridine (1104)

To a solution of 3-(benzyloxy)-1-(5-ethyl-6-methoxypyridin-2-yl)cyclobutan-1-ol (**1103**, 400 mg, 1.27 mmol) and TEA (257 mg, 2.54 mmol) in DCM (10 mL) was added MsCl (292 mg, 2.54 mmol) at 0°C. The resulting solution was slowly warmed to room temperature and stirred for 2 hours. The reaction mixture was added to water and then extracted with EtOAc (10 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 90: 10) to give 6-(3-(benzyloxy)cyclobut-1-en-1-yl)-3-ethyl-2-methoxypyridine **1104** (120 mg, 30 % yield) as a colorless oil.

LCMS (ESI) calcd for $C_{19}H_{22}NO_2$ $[M + H]^+$ m/z 296.16, found 296.05.

Preparation of 3-(5-ethyl-6-methoxypyridin-2-yl)cyclobutan-1-ol (1105)

To a solution of 6-(3-(benzyloxy)cyclobut-1-en-1-yl)-3-ethyl-2-methoxypyridine **1104** (120 mg, 0.40 mmol) in MeOH (10 mL) was added Pd/C (5 mg, 0.04 mmol). The mixture was stirred at room temperature under H_2 for 2 h. The reaction mixture was concentrated under reduced pressure to give 3-(5-ethyl-6-methoxypyridin-2-yl)cyclobutan-1-ol **1105** (70 mg, 60 % yield) as a yellow solid.

LCMS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M + H]^+$ m/z 208.13, found 208.05.

Preparation of 3-(5-ethyl-6-methoxypyridin-2-yl)cyclobutan-1-one (1106)

To a solution of 3-(5-ethyl-6-methoxypyridin-2-yl)cyclobutan-1-ol **1105** (60 mg, 0.29 mmol) in DCM (5 mL) was added Dess-Martin reagent (368 g, 0.87 mmol). The reaction mixture was

stirred at room temperature for 2 h. The reaction mixture was added into sodium hypochlorite solution and then extracted with EtOAc (5 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 80: 20) to give 3-(5-ethyl-6-methoxypyridin-2-yl)cyclobutan-1-one **1106** (35 mg, 37 % yield) as a yellow oil.

LCMS (ESI) calcd for $C_{12}H_{16}NO_2$ $[M + H]^+$ m/z 206.11, found 205.94.

Preparation of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclobutyl)piperazin-1-yl)-N-methylpicolinamide (1107)

To a solution of give 3-(5-ethyl-6-methoxypyridin-2-yl)cyclobutan-1-one **1106** (30 mg, 0.15 mmol) and N-methyl-5-(piperazin-1-yl)pyridine-2-carboxamide **1009** (32 mg, 0.15 mmol) in MeOH (5 mL) was added sodium triacetoxyborohydride (77 mg, 0.37 mmol). The mixture was stirred at 50 °C for 1 h. Sodium cyanoborohydride (11 mg, 0.18 mmol) was added at 50 °C. The mixture was stirred at 50 °C for 3 h. Saturated NH_4Cl aqueous (2 mL) was added. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 97 : 3) to give 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclobutyl)piperazin-1-yl)-N-methylpicolinamide **1107** (40 mg, 7 % yield) as a white solid.

LCMS (ESI) calcd for $C_{23}H_{32}N_5O_2$ $[M + H]^+$ m/z 409.25, found 410.72.

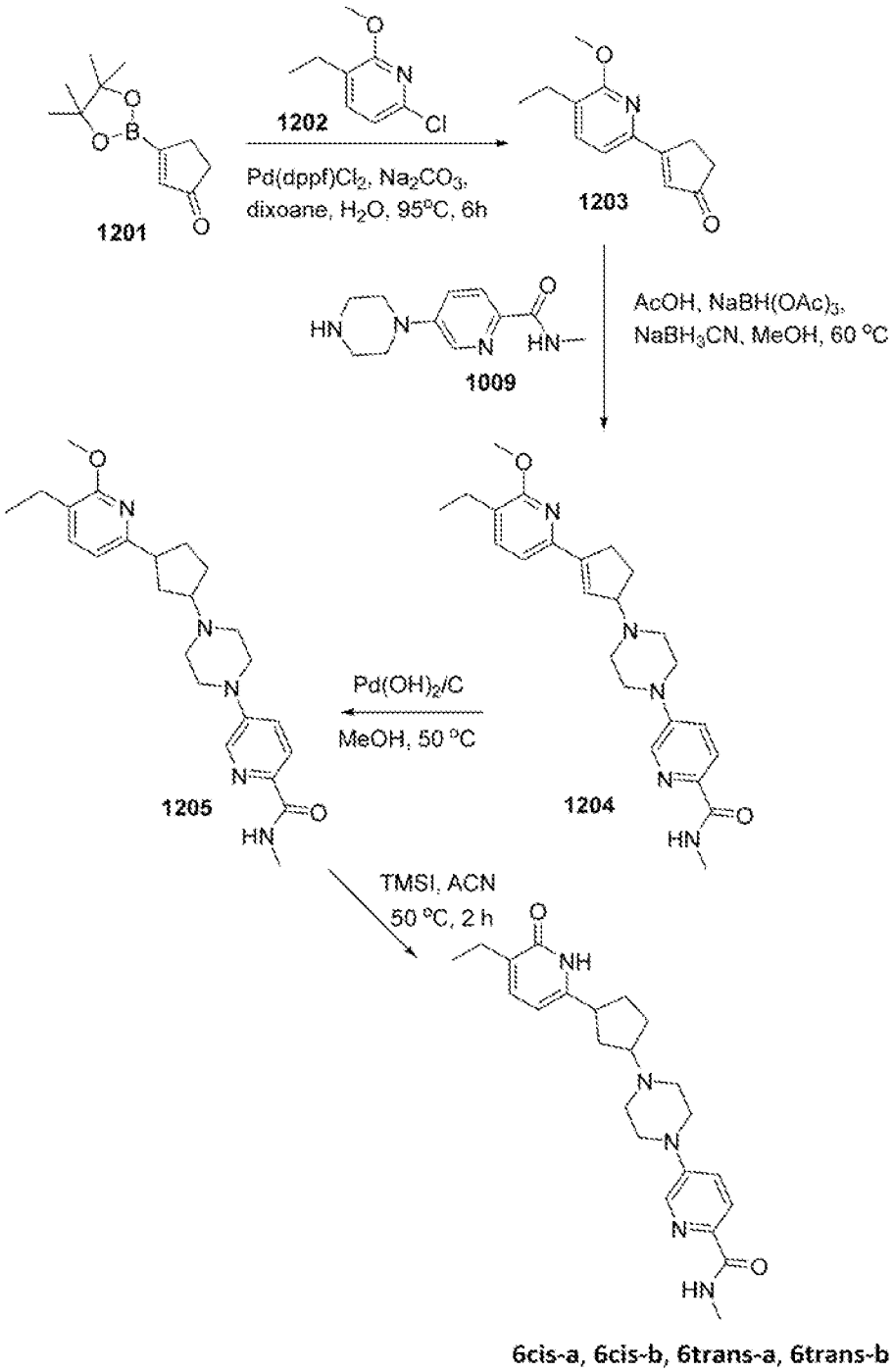
Preparation of 5-(4-((1s,3s)-3-(5-ethyl-6-oxo-1,6-dihydropyridin-2-yl)cyclobutyl)piperazin-1-yl)-N-methylpicolinamide (4cis)

To a solution of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclobutyl)piperazin-1-yl)-N-methylpicolinamide **1107** (40 mg, 0.10 mmol) in ACN (5 mL) was added TMSI (58.65 mg, 0.29 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (Column: Gemini 5um C18 150*21.2mm; Mobile phase: ACN/H_2O [0.1 %(FA)] = 20/80) to give 5-(4-((1s,3s)-3-(5-ethyl-6-oxo-1,6-dihydropyridin-2-yl)cyclobutyl)piperazin-1-yl)-N-methylpicolinamide **4cis** (5 mg, 13 % yield) as a white solid.

^{1}HNMR(400MHz, DMSO-d_6) δ 11.53 (s, 1 H), 8.40 (q, *J* = 4.4 Hz, 1 H), 8.29 (d, *J* = 2.4 Hz, 1 H), 7.84 (d, *J* = 8.8 Hz, 1 H), 7.41 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.19 (d, *J* = 7.2Hz, 1H), 5.98 (d, *J* = 6.8 Hz, 1 H), 3.49-3.37 (m, 4 H), 3.05-2.97 (m, 1 H), 2.87-2.74 (m, 4 H), 2.59-2.52 (m, 2 H), 2.48-2.40 (m, 4 H), 2.34 (q, *J* = 7.2 Hz, 2 H), 2.08-1.84 (m, 2 H), 1.06 (t, *J* = 7.2 Hz, 3 H).

LCMS (ESI) calcd for $C_{22}H_{30}N_5O_2$ $[M + H]^+$ m/z 396.23, found 396.25.

Example 3: Synthesis of **6cis-a, 6cis-b, 6trans-a, 6trans-b**



SCHEME 3

Preparation of 3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-one (1203)

To a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-one **1201** (200 mg, 0.96 mmol) and 6-chloro-3-ethyl-2-methoxypyridine **1202** (197 mg, 1.15 mmol) in dioxane (5 mL) and H_2O (0.5 mL) was added $Pd(dppf)Cl_2$ (70 mg, 0.10 mmol) and sodium

carbonate (255 mg, 2.40 mmol) at room temperature. The reaction mixture stirred under nitrogen at 95 °C for 6 h. After cooling to ambient temperature, the mixture was filtered through celite and the filtrate was concentrated under vacuum. The residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 85 : 15) to give product of 3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-one **1203** (90 mg, 43 % yield) as a white solid.

LCMS (ESI) calcd for $C_{13}H_{15}NO_2$ $[M + H]^+$ m/z 218.12, found 218.00.

Preparation of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylpicolinamide (1204)

To a solution of 3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-one **1203** (90 mg, 0.42 mmol) and N-methyl-5-(piperazin-1-yl)picolinamide **1009** (110 mg, 0.50 mmol) in MeOH (5 mL) was added two drops of acetic acid at room temperature and stirred for 10 min. $NaBH(OAc)_3$ (220 mg, 1.04 mmol) was added to the reaction mixture and stirred at 60 °C for 1 h. $NaBH_3CN$ (261 mg, 4.15 mmol) was added to the reaction mixture and stirred at 60 °C for 15h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 95 : 5) to give product of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylpicolinamide **1204** (85 mg, 49 % yield) as faint yellow oil.

LCMS (ESI) calcd for $C_{24}H_{31}N_5O_2$ $[M + H]^+$ m/z 422.26, found 422.25.

Preparation of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopentyl)piperazin-1-yl)-N-methylpicolinamide (1205)

To a solution of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-N-methylpicolinamide **1204** (85 mg, 0.20 mmol) in MeOH (5 mL) was added $Pd(OH)_2/C$ (20 mg). The mixture was evacuated and backfilled with hydrogen three times and then charged with hydrogen. The resulting mixture was stirred at 50 °C for 3 h. Then the mixture was filtered through celite and concentrated under vacuum to give crude 5-(4-(3-(5-ethyl-6-

methoxypyridin-2-yl)cyclopentyl)piperazin-1-yl)-N-methylpicolinamide **1205** (80 mg, 93 % yield) as faint yellow oil.

LCMS (ESI) calcd for $C_{24}H_{33}N_5O_2$ $[M + H]^+$ m/z 424.27, found 424.15.

Preparation of 5-(4-(3-(5-ethyl-6-oxo-1,6-dihydropyridin-2-yl)cyclopentyl)piperazin-1-yl)-N-methylpicolinamide (6cis-a, 6cis-b, 6trans-a, 6trans-b)

To a solution of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopentyl)piperazin-1-yl)-N-methylpicolinamide **1205** (80 mg, 0.19 mmol) in ACN (4 mL) was added TMSI (113 mg, 0.57 mmol). The mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (Gemini 5 µm C18 150*21.2 mm, mobile phase: ACN - H_2O (0.1 % FA), gradient: 2 % - 95 %) to afford the first fraction as **6cis-a / 6cis-b** racemic mixture (cis stereochemistry assumed across cyclopentane based on NOE experiments) (10 mg, 95 % purity, white solid) and the second fraction as **6trans-a / 6trans-b** racemic mixture (trans stereochemistry assumed across cyclopentane based on NOE experiments) (3 mg, 95 % purity, white solid).

6cis-a / 6cis-b racemic mixture

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.19 (d, *J* = 2.4 Hz, 1 H), 8.10 (d, *J* = 8.8 Hz, 1 H), 7.83 (d, *J* = 4.8 Hz, 1 H), 7.69 (d, *J* = 7.2 Hz, 1 H), 7.29 (d, *J* = 2.4 Hz, 1 H), 6.82 (d, *J* = 7.2 Hz, 1 H), 4.20-3.36 (m, 8 H), 3.24 (dt, *J* = 14.8, 10.8 Hz, 2 H), 3.02 (d, *J* = 5.2 Hz, 3 H), 2.66-2.54 (m, 3 H), 2.39 (dd, *J* = 22.0, 11.2 Hz, 2H), 2.31-2.19 (m, 2H), 2.10-2.00 (m, 1H), 1.22 (t, *J* = 7.4 Hz, 3H).

LCMS (ESI) calcd for $C_{23}H_{31}N_5O_2$ $[M + H]^+$ m/z 410.26, found 410.20.

6trans-a / 6trans-b racemic mixture

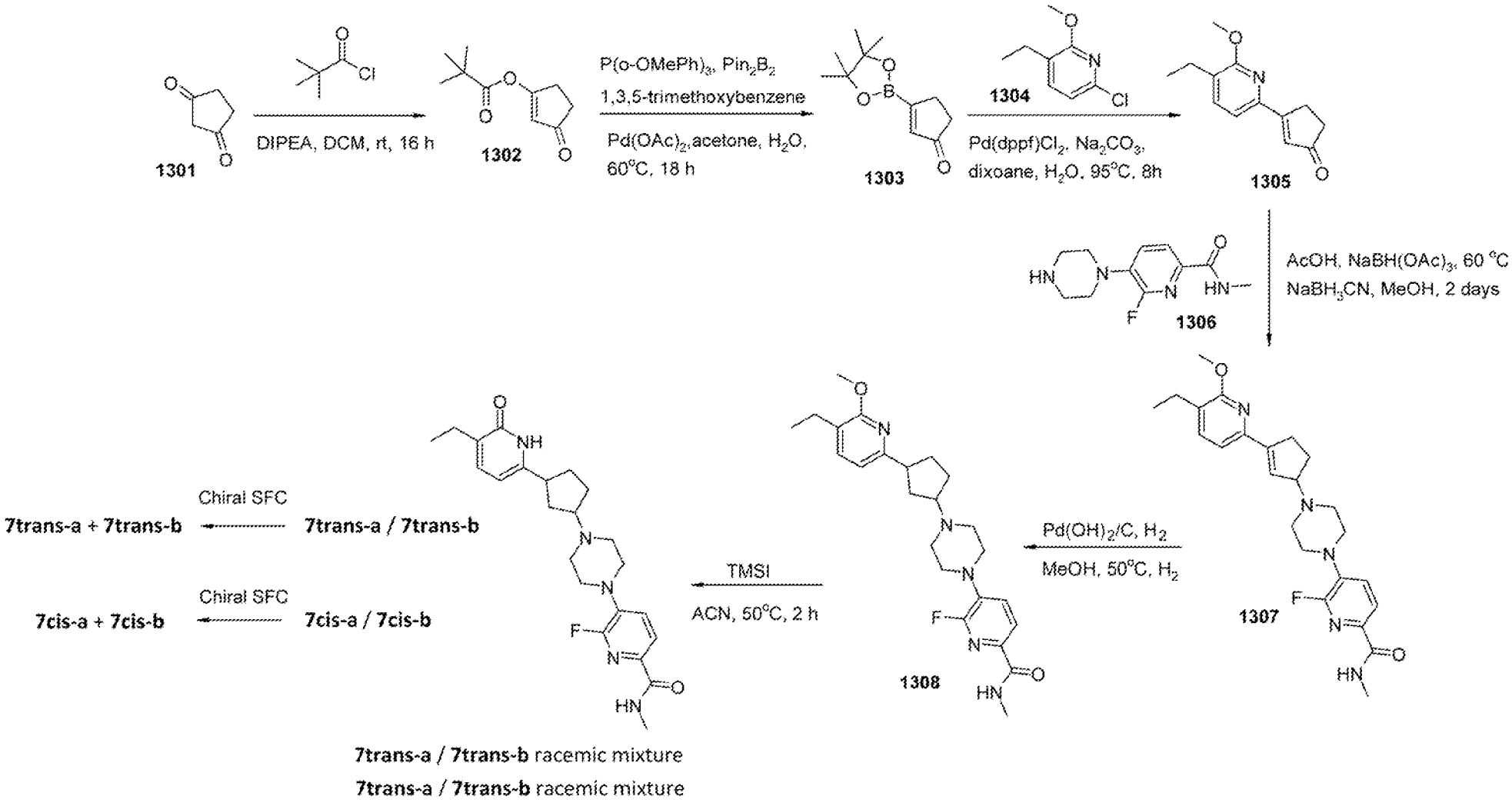
^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.74 (s, 1 H), 8.17 (s, 1 H), 8.06 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.78 (s, 1 H), 7.25-7.15 (m, 2 H), 6.02 (dd, *J* = 6.4, 2.0 Hz, 1 H), 3.37 (s, 3 H), 3.22-2.96 (m, 5 H), 2.71 (s, 3 H), 2.57-2.48 (m, 2 H), 2.27-1.98 (m, 4 H), 1.86-1.58 (m, 4 H), 1.18 (td, *J* = 7.2, 2.4 Hz, 3 H).

LCMS (ESI) calcd for $C_{23}H_{31}N_5O_2$ $[M + H]^+$ m/z 410.26, found 410.40.

The **6cis-a / 6cis-b** racemic mixture was separated by SFC (Column: Regis (R,R)-Whelk-O 1, 250 mm × 20 mm I.D., 5 µmm; Mobile phase: CO_2/MeOH[0.1 %(NH_3)(7 M solution in MeOH)] = 65/35) and concentrated under reduced pressure to afford the first fraction as **6cis-a** (white solid) and the second fraction as **6cis-b** (white solid).

The **6trans-a / 6trans-b** racemic mixture was separated by SFC (Column: Daicel CHIRALPAK IJ SFC 250 mm × 20 mm I.D., 5 µmm; Mobile phase: CO_2/MeOH[0.1 %(NH_3)(7 M solution in MeOH)] = 60/40) and concentrated under reduced pressure to afford the first fraction as **6trans-a** (white solid) and the second fraction as **6trans-b** (white solid).

*Example 4: Synthesis of **7cis-a**, **7cis-b**, **7trans-a** and **7trans-b***



SCHEME 4

Preparation of 3-oxocyclopent-1-en-1-yl pivalate (1302)

To a solution of cyclopentane-1,3-dione **1301** (8 g, 81.6 mmol) and DIPEA (21.09 g, 163.2 mmol) in DCM (160 mL) was added pivaloyl chloride (10.77 g, 89.8 mmol) slowly at 0 °C. The reaction mixture stirred at room temperature for 16 h. The mixture was diluted with water (400 mL) and extracted with EtOAc (400 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated in vacuo to get crude product, which was purified by flash column chromatography (PE/EtOAc = 100: 0 to 70: 30) to afford product of 3-oxocyclopent-1-en-1-yl pivalate **1302** (12 g, 81 % yield) as faint yellow oil.

LCMS (ESI) calcd for $C_{10}H_{14}O_3$ $[M + H]^+$ m/z 183.12, found 183.00.

Preparation of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-one (1303)

To a solution of 3-oxocyclopent-1-en-1-yl 2,2-dimethylpropanoate **1302** (8 g, 43.9 mmol), B_2Pin_2 (22.3 g, 87.9 mmol), palladium diacetate (863 mg, 3.52 mmol) and Tri-o-tolylphosphine (1.2 g, 3.9 mmol) in acetone (80 mL) and H_2O (8 mL) was added 1,3,5-trimethoxybenzene (3.7 g, 22.0 mmol). The reaction mixture was stirred at 60 °C for 18 hours. After cooling to room temperature, the reaction mixture was poured into water (800 mL), The aqueous phase was washed with EtOAc (600 mL) 3 times. The water layers were concentrated under reduced pressure to give product of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-one **1303** (2 g, 22 % yield) as a white solid.

LCMS (ESI) calcd for $C_{24}H_{31}N_5O_2$ $[M-72 + H]^+$ m/z 126, found N/A.

Preparation of 3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-one (1305)

To a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-one **1303** (2.0 g, 9.6 mmol) and 6-chloro-3-ethyl-2-methoxypyridine **1304** (1.6 g, 9.6 mmol) in dioxane (50 mL) and H_2O (5 mL) were added $Pd(dppf)Cl_2$ (351 mg, 0.48 mmol) and sodium carbonate (2.5 g, 24.0 mmol) at room temperature. The reaction mixture stirred under nitrogen at 95 °C for 8 h. After cooling to ambient temperature, the mixture was filtered through celite and the filtrate was concentrated under vacuum. The residue was diluted with water and extracted

with EtOAc. The combined organic layers were washed with water and brine, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 85 : 15) to give product of 3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-one **1305** (450 mg, 22 % yield) as a white solid.

LCMS (ESI) calcd for $C_{13}H_{15}NO_2$ [M + H] + m/z 218.12, found 218.00.

Preparation of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide (1307)

To a solution of 3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-one **1305** (186 mg, 0.85 mmol) and 6-fluoro-N-methyl-5-(piperazin-1-yl)picolinamide **1306** (243 mg, 1.02 mmol) in MeOH (5 mL) was added two drops of acetic acid at room temperature and stirred for 10 min. NaBH (OAc)$_3$ (433 mg, 2.04 mmol) was added to the reaction mixture and stirred at 60 °C for 1 h. $NaBH_3CN$ (534 mg, 8.5 mmol) was added to the reaction mixture and stirred at 60 °C for 2 days. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 95 : 5) to give crude product of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide **1307** (200 mg, 54 % yield) as faint yellow oil.

LCMS (ESI) calcd for $C_{24}H_{30}FN_5O_2$ $[M + H]^+$ m/z 440.25, found 440.20.

Preparation of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopentyl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide (1308)

To a solution of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopent-2-en-1-yl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide **1307** (200 mg, 0.46 mmol) in MeOH (5 mL) was added $Pd(OH)_2/C$ (80 mg). The mixture was evacuated and backfilled with hydrogen three times and then charged with hydrogen. The resulting mixture was stirred at 50 °C for 5 h. Then the mixture was filtered through celite and concentrated under vacuum to give crude product. The crude product was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 95 : 5) to give product of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopentyl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide **1308** (125 mg, 63% yield) as a faint yellow oil.

LCMS (ESI) calcd for $C_{24}H_{32}FN_5O_2$ $[M + H]^+$ m/z 442.26, found 442.25.

Preparation of 5-(4-(3-(5-ethyl-6-oxo-1,6-dihydropyridin-2-yl)cyclopentyl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide (7trans-a/7trans-b/7cis-a/7cisb)

To a solution of 5-(4-(3-(5-ethyl-6-methoxypyridin-2-yl)cyclopentyl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide **1308** (125 mg, 0.283 mmol) in ACN (5 mL) was added TMSI (170 mg, 0.85 mmol). The mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (Gemini 5 μm C18 150*21.2mm, mobile phase: ACN - H_2O (0.05 % $NH_3.H_2O$), gradient: 25 % - 95 %) to afford the first fraction as a racemic mixture of **7trans-a** and **7trans-b** (23 mg, white solid) and the second fraction as a racemic mixture of **7cis-a** and **7cis-b** (33 mg, white solid).

7trans-a / 7trans-b

LCMS (ESI) calcd for $C_{23}H_3FN_5O_2$ $[M + H]^+$ m/z 428.25, found 428.20.

7cis-a / 7cis-b

LCMS (ESI) calcd for $C_{23}H_3FN_5O_2$ $[M + H]^+$ m/z 428.25, found 428.20.

Preparation of 5-(4-(3-(5-ethyl-6-oxo-1,6-dihydropyridin-2-yl)cyclopentyl)piperazin-1-yl)-6-fluoro-N-methylpicolinamide (7trans-a, 7trans-b, 7cis-a and 7cis-b)

The racemic mixture of **7trans-a** and **7trans-b** was separated by SFC (Column: Daicel CHIRALPAK IH SFC 250 mm × 20 mm I.D., 5 μmm; Mobile phase: CO_2/MeOH[0.1 %(NH_3)(7 M solution in MeOH)] = 70/30) and concentrated under reduced pressure to afford the first fraction as **7trans-a** (3.85 mg, 99 % purity, ee%: 100, white solid) and the second fraction as **7trans-b** (5.43 mg, 99 % purity, ee%: 100, white solid).

7trans-a

^{1}H NMR (400 MHz, MeOD, ppm) δ 7.90 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.52 (dd, *J* = 10.4, 8.4 Hz, 1 H), 7.35 (d, *J* = 7.2 Hz, 1 H), 6.23 (d, *J* = 7.2 Hz, 1 H), 3.29-3.24 (m, 4 H), 3.17-3.09 (m, 1 H), 2.96-2.87 (m, 4 H), 2.79-2.68 (m, 4 H), 2.48 (q, *J* = 7.6 Hz, 2 H), 2.18-2.04 (m, 3 H), 2.00-1.92 (m, 1H), 1.78-1.59 (m, 2 H), 1.16 (t, *J* = 7.6 Hz, 3 H).

Assigned trans-stereochemistry based on NOE experiments.

LCMS (ESI) calcd for $C_{23}H_3FN_5O_2$ [M + H] $^+$ m/z 428.25, found 428.20.

7trans-b

^{1}H NMR (400 MHz, MeOD, ppm) δ 7.90 (d, *J* = 8.0 Hz, 1 H), 7.61-7.42 (m, 1 H), 7.35 (d, *J* = 7.2 Hz, 1 H), 6.22 (d, *J* = 6.8 Hz, 1 H), 3.29-3.22 (m, 4 H), 3.17-3.08 (m, 1 H), 2.99-2.83 (m, 4 H), 2.80-2.65 (m, 4 H), 2.48 (q, *J* = 7.6 Hz, 2 H), 2.20-2.04 (m, 3 H), 2.00-1.91 (m, 1 H), 1.78-1.58 (m, 2 H), 1.16 (t, *J* = 7.6 Hz, 3 H).

Assigned trans-stereochemistry based on NOE experiments.

LCMS (ESI) calcd for $C_{23}H_3FN_5O_2$ [M + H] $^+$ m/z 428.25, found 428.20.

The racemic mixture of **7cis-a** and **7cis-b** was separated by SFC (Column: Daicel CHIRALPAK IH SFC 250 mm × 20 mm I.D., 5 µmm; Mobile phase: CO_2/MeOH[0.1 %(NH_3)(7 M solution in MeOH)] = 70/30) and concentrated under reduced pressure to afford the first fraction as **7cis-a** (6.20 mg, 98 % purity, ee%: 100, white solid) and the second fraction as **7cis-b** (5.34 mg, 98 % purity, ee%: 99, white solid).

7cis-a

^{1}H NMR (400 MHz, MeOD, ppm) δ 7.91 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.57 (dd, *J* = 10.4, 8.2 Hz, 1 H), 7.31 (d, *J* = 6.8 Hz, 1 H), 6.21 (d, *J* = 6.8 Hz, 1 H), 3.54-3.42 (m, 2 H), 3.40-3.33 (m, 2 H), 3.19-3.11 (m, 1 H), 2.91 (s, 3 H), 2.84-2.72 (m, 5 H), 2.46 (q, *J* = 7.6 Hz, 2 H), 2.25-2.14 (m, 2 H), 2.05-1.98 (m, 1 H), 1.90-1.79 (m, 2 H), 1.76-1.65 (m, 1 H), 1.14 (t, *J* = 7.6 Hz, 3 H).

Assigned cis-stereochemistry based on NOE experiments.

LCMS (ESI) calcd for $C_{23}H_3FN_5O_2$ [M + H] $^+$ m/z 428.25, found 428.20.

7cis-b

^{1}H NMR (400 MHz, MeOD, ppm) δ 7.91 (d, *J* = 8.0 Hz, 1 H), 7.57 (dd, *J* = 10.4, 8.2 Hz, 1 H), 7.31 (d, *J* = 6.8 Hz, 1 H), 6.21 (d, *J* = 6.8 Hz, 1 H), 3.52-3.42 (m, 2 H), 3.40-3.33 (m, 2 H), 3.19-3.11 (m, 1 H), 2.91 (s, 3 H), 2.84-2.74 (m, 5H), 2.46 (q, *J* = 7.6 Hz, 2 H), 2.25-2.14 (m, 2 H), 2.05-1.98 (m, 1 H), 1.89-1.79 (m, 2 H), 1.76-1.64 (m, 1 H), 1.14 (t, *J* = 7.6 Hz, 3 H).

Assigned cis-stereochemistry based on NOE experiments.

LCMS (ESI) calcd for $C_{23}H_3FN_5O_2$ $[M + H]^+$ m/z 428.25, found 428.20.

Example 5 - Assays

Exemplary compounds of the invention were prepared and tested to determine their effect as PARP1 and PARP2 inhibitors. Typical assays are described below.

Example 5A. PARP1 biochemical dissociation-enhanced lanthanide fluorescence immunoassay (DELFIA assay)

Optiplate HB 384-well plates were coated with anti-FLAG antibody, supplied as a 4 mg/ml solution, using a Na_2CO_3/HCO_3 coating buffer at pH 9.6, overnight at 4°C, in order to achieve a final immobilisation per well of 0.3 μg. Wells were then washed 3 x 5 min in coating wash buffer (PBS/0.05 % Tween (v/v)), and blocked with 2 % BSA (w/v) in coating wash buffer overnight at 4°C. Prior to assay, wells were washed 3 x 5 min in coating wash buffer. For the assay 20 μl of 2.5 nM recombinant full length human N-terminally FLAG-tagged PARP1 was added to each well of the 384-well plate for 30 min at room temperature followed by addition of 50 nL of compound solution in DMSO using pintool technology. Following incubation for 30 min at room temperature, 5 μl of 10 μM biotin-NAD^+ and 10 nM activation DNA (sequence shown below) in solution in 20 mM HEPES (pH 7.5), 100 mM NaCl, 2 mM DTT, 0.1 % BSA (w/v), 0.02 % Tween (v/v) assay buffer. Auto-PARylation proceeded for 2 h at room temperature prior to the addition of 5 μl of 12 mM NAD^+ quenching solution. After 30 min at room temperature, assay solution was removed and following washing 5 times for 3 min, 100 μl of a 1:1000 dilution of DELFIA Eu-N1 Streptavidin reagent was added. Plates were then

incubated for 30 min at room temperature. Reaction mixture was removed and plates washed 5 times for 3 min prior to the addition of 25 µl DELFIA enhancement solution. Following incubation for 30 min at room temperature, fluorescence was measured on a Pherastar FS (Ex337 nm, Em620 nm; integration start 60 µs; integration time 400 µs).

Typically compounds were tested from 20 µM at 3-fold dilution intervals in 12-point concentration-response curves to determine IC_{50} values. Data was analysed using ActivityBase software and replicate values for the low (without enzyme, 0.2 % DMSO) and high (0.2 % DMSO) % controls were averaged and the data obtained from the test compounds expressed as a % of 100 % using the below formulae:

% value = 100-(100*((high control - unknown) / (high control - low control))

% data was fitted to a non-linear regression equation (log inhibitor vs response-variable slope 4-parameters) to obtain IC_{50} values.

The IC_{50} values for a variety of test compounds are shown in Table 1.

Activation DNA sequence:

Duplex Sequences

5'-ACCCTGCTGTGGGC/deoxyU/GGAGAACAAGGTGAT-3' (SEQ ID NO:1)

5'-ATCACCTTGTTCTCCAHGCCCACAGCAGGGT-3' (SEQ ID NO:2)

```
  5'- ACCCTGCTGTGGGCGGAGAACAAGGTGAT -3'(SEQ ID NO:3)
      |     || |   ||||||||||||||||
3'- TGGGACGACACCCGHACCTCTTGTTCCACTA -5'
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Example 5B. PARP1 probe displacement homogeneous time-resolved fluorescence assay (HTRF assay)

10 nM full length N-terminally FLAG-tagged PARP1 was incubated with 2 nM Anti-FLAG Tb-cryptate antibody and PARP1/2 Cy5 fluorescent dye-labelled binding probe (10-fold probe K_d = 270 nM) in 20 mM HEPES (pH 7.5), 100 mM NaCl, 2 mM DTT, 0.1 % BSA (w/v), 0.02 % Tween (v/v) assay buffer for 40 min at room temperature. A Cy5-labelled binding probe is shown below and described in Papeo, G. *et al. J. Biomol. Screen.* 2014; 19:1212-1219. 6 µl of this

reaction mixture was then transferred to each well of a black non-binding surface 384-well plate and 35 nl of compound solution in DMSO was then added using pintool technology. Following incubation for 1 h at room temperature, fluorescence was measured on a Pherastar FS (Ex 337 nm, Em620 nm, em665 nm; integration start 60µs; integration time 400µs) using the HTRF module.

Typically compounds were tested from 58.5 µM at factor 3 dilution intervals in 12-point concentration-response curves to determine IC_{50} values. Data was analysed using ActivityBase software and replicate values for the low (without enzyme but with probe and Tb-cryptate antibody, 0.6% DMSO) and high (0.6 % DMSO) % controls were averaged and the data obtained from the test compounds expressed as a % of 100 % using the below formulae:

%activity = 100*(value – low control) / (high control – low control)

%activity data was fitted to a non-linear regression equation to obtain IC50 values

K_d values were calculated using Cheng-Prussoff formula:

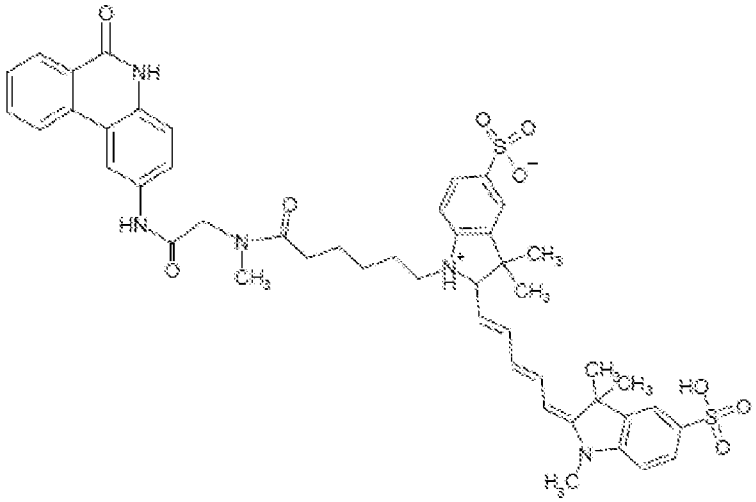
$IC_{50} = (1+ ([\text{probe concentration}]/[Km_{probe}]))*K_d$

Therefore $K_d = IC_{50} / (1+[[\text{probe concentration}]/[Km_{probe}]))$; using probe at 10 x K_m, this equated to $K_d = IC_{50}/11$

Example 5C. PARP2 probe displacement homogeneous time-resolved fluorescence assay (HTRF assay)

This assay was performed under identical conditions as for PARP1, except that N-terminally FLAG-tagged PARP2 (amino acids 1-583) was used instead of PARP1, and PARP1/2 binding probe was used at 10-fold probe K_d = 540 nM. Data analysis was performed identical as for PARP1.

Cy5 probe structure:



NanoBRET cellular target occupancy assay

NanoBRET assays were employed to demonstrate cellular target engagement and selectivity at PARP1 and PARP2. These assays are based on bioluminescence resonance energy transfer (BRET) between a Nano-luc-tagged protein (eg PARP1 or PARP2) and a fluorescent group on a high affinity NAD^+ competitive binding probe. Such cellular probe displacement assays can be utilised to measure inhibitor affinities and selectivity ratios at PARP1 and 2.

Frozen HEK293 cells transiently transfected with either PARP1-NanoLuc® fusion or PARP2-NanoLuc® fusion constructs (Promega) were thawed and dispensed as a suspension in 384-well microplates each at a density of 1750 cells per well. NanoBRET™ TE PARP Tracer-01 was then added to final concentrations of 11 and 2 nM for PARP1 and PARP2 assays, respectively. Compounds were added from 25 µM at factor 3 dilution intervals in 12-point concentration-response curves and plates were incubated for 2 hours at 37°C. BRET ratios were then measured using a NanoBRET module (LUM 610-LP 450-80) and PHERAstar FS or FSX reader following addition of NanoBRET™ Nano-Glo® Substrate and Extracellular NanoLuc® Inhibitor according to manufacturer's instructions. Kd values were calculated using Cheng-Prussoff formula:

$$IC50 = (1+ ([\text{tracer concentration}]/[Km_{tracer}])) * Kd$$

Binned potency, affinity and selectivity data for a variety of test compounds are shown in Table 1 where DELFIA and Probe Displacement HTRF assays were used. Binned potency, affinity and selectivity data for a subset of test compounds where the NanoBRET assay was used are shown in Table 1.

TABLE 1

Results of Parp 1/2 assays for selected compounds (DELFIA and Probe Displacement HTRF)

Compound	PARP1 DELFIA	PARP1 HTRF	PARP2 HTRF	Selectivity
1*cis*	++	++	-	+
2*cis*	++	++	+	-
3	++++	++++	-	+++
4*cis*	+++	+++	-	+++
5	++	++	+	-
6cis-a	++++	++++	+	+++
6cis-b	++++	++++	++	+++
6trans-a	+++	+++	+	++
6trans-b	++++	++++	++	+++
7cis-a	++++	++++	+	+++
7cis-b	++++	++++	++	+++
7trans-a	+++	+++	-	+++
7trans-b	++++	++++	++	+++
8cis-a	++++	++++	+	+++
8cis-b	++++	++++	++	+++
8trans-a	+++	+++	-	+++
8trans-b	++++	++++	++	+++

TABLE 2

Results of Parp 1/2 assays for selected compounds (NanoBRET)

Compound	PARP1 NanoBRET	PARP2 NanoBRET	Selectivity
6cis-a	++++	+	+++
6cis-b	++++	++	+++

6trans-b	++++	++	+++
7trans-b	++++	+	+++
8trans-b	++++	++	+++

Key

DELFIA, Probe Displacement HTRF and NanoBRET assay categories:

- indicates IC_{50} or K_d value above 10 μM

+ indicates IC_{50} or K_d value above 1 μM up to 10 μM

++ indicates IC_{50} or K_d value above 100 nM up to 1 μM

+++ indicates IC_{50} or K_d value above 10 nM up to 100 nM

++++ indicates IC_{50} or K_d value of 10 nM or less

Selectivity categories:

- indicates a value of less than 10

+ indicates a value of 10 to less than 50

++ indicates a value of 50 to less than 100

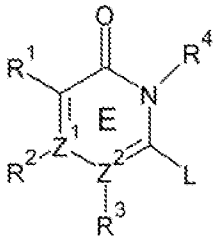
+++ indicate a value of at least 100

The selectivity values relate to the selectivity preference of PARP1 over PARP2. They are calculated from the ratio of K_d values for PARP1 and PARP2 inhibition as K_d (PARP2) / K_d (PARP1).

Other variants or use cases of the disclosed techniques may become apparent to the person skilled in the art once given the disclosure herein. The scope of the disclosure is not limited by the described embodiments but only by the accompanying claims.

Claims

1. A PARP1 inhibitor compound for use in medicine, which compound comprises a structure of:



wherein:

R^1 is selected from H and a substituted or unsubstituted organic group;

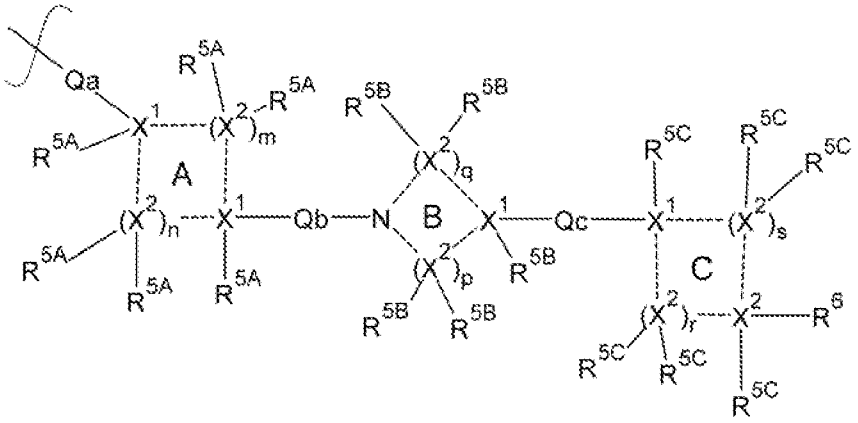
R^2 is absent or selected from H and a substituted or unsubstituted organic group;

R^3 is absent or selected from H and a substituted or unsubstituted organic group;

R^4 is selected from H and a substituted or unsubstituted organic group;

Z^1 and Z^2 are each independently selected from C and N; and

L is a group having a structure of:



wherein:

each X^1 is independently selected from C and N;

each X^2 is independently selected from C, N, O and S;

n is a number selected from 0, 1, 2, 3, 4, 5 and 6; and m is a number selected from 0, 1, 2, 3, 4, 5 and 6; with the proviso that m + n is a number selected from 2, 3, 4, 5, and 6;

p is a number selected from 0, 1, 2, 3, 4, 5 and 6; and q is a number selected from 0, 1, 2, 3, 4, 5 and 6; with the proviso that p + q is a number selected from 2, 3, 4, 5, and 6;

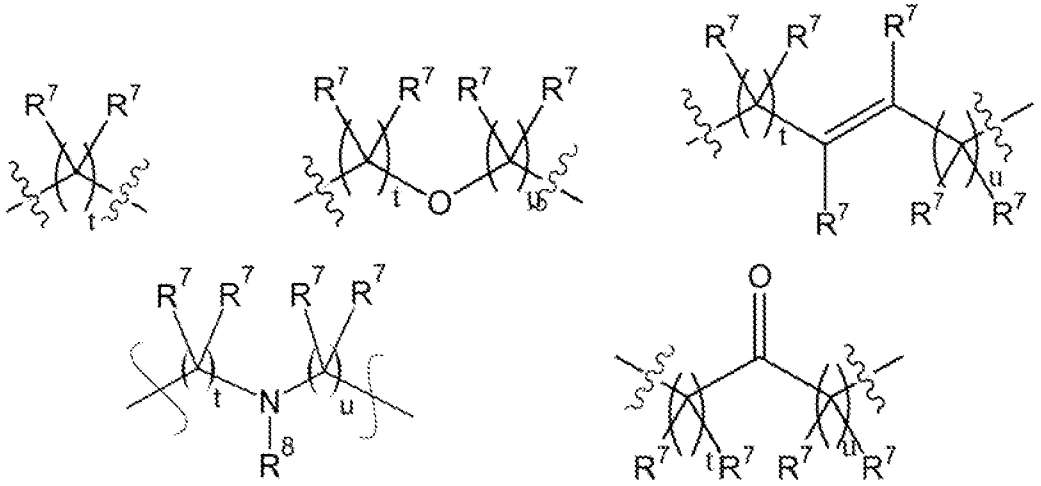
r is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; s is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; with the proviso that r + s is a number selected from 2, 3, 4, 5, and 6;

each R^{5A}, R^{5B}, and R^{5C} is independently absent or selected from H and a substituted or unsubstituted organic group; and

R^6 is absent or selected from H and a substituted or unsubstituted organic group;

the lines forming rings A, B and C each independently represent single or double bonds such that each ring is independently saturated, unsaturated, or aromatic; and

each of Qa, Qb, and Qc is independently selected from a bond and a group having a structure independently selected from:



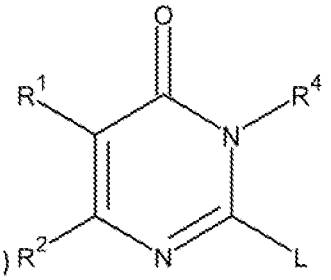
wherein:

t is a number selected from 0, 1, 2, 3, 4 and 5; and u is independently a number selected from 0, 1, 2, 3, 4 and 5; with the proviso that t + u is a number selected from 0, 1, 2, 3, 4, 5 and 6; and

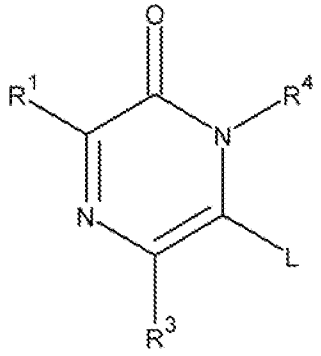
each R^7 and R^8 is independently selected from H and a substituted or unsubstituted organic group.

2. The PARP1 inhibitor compound for use according to claim 1, wherein each X^2 is independently selected from C and N.

3. The PARP1 inhibitor compound for use according to claim 1 or claim 2, wherein the compound has a structure selected from:

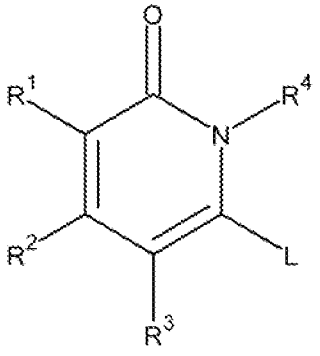
i) 

R^1, R^2 and R^4 each being independently selected from H and a substituted or unsubstituted organic group;

ii) 

R^1, R^3 and R^4 each being independently selected from H and a substituted or unsubstituted organic group;

and preferably:

iii) 

R^1, R^2, R^3 and R^4 each being independently selected from H and a substituted or unsubstituted organic group.

4. The PARP1 inhibitor compound for use according to any preceding claim, wherein R^1 and R^2 are each independently selected from:

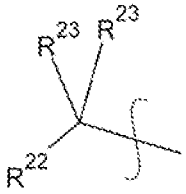
H;

a C1 to C6 alkyl, aminoalkyl, alkoxy or haloalkyl group;

a C3 to C6 cycloalkyl group;

a halogen group;

and

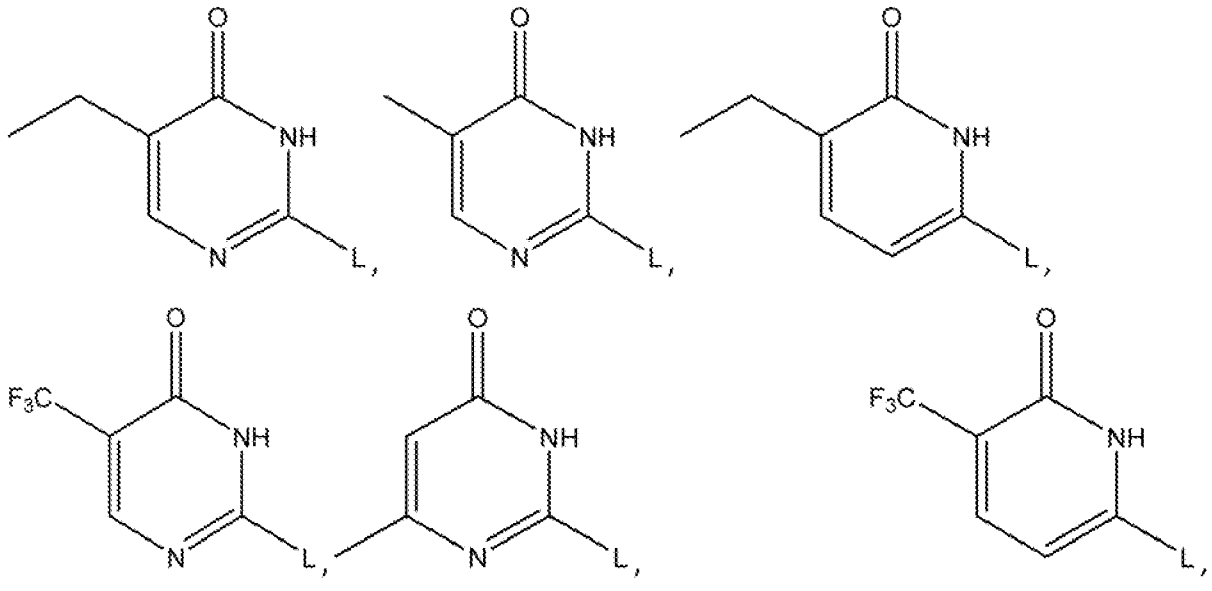


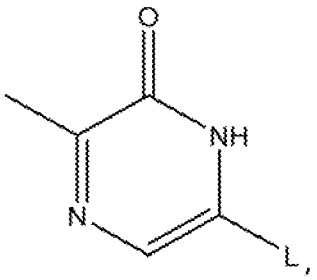
wherein R^{22} is selected from H, a C1 to C6 alkyl, cycloalkyl, alkoxy, or haloalkyl group, and a halogen group, and each R^{23} is independently selected from H and a substituted or unsubstituted organic group, preferably wherein each R^{23} is independently selected from H, a C1 to C6 alkyl, aminoalkyl, alkoxy or haloalkyl group, and a halogen group, and preferably wherein at least one R^{23} is H;

with the proviso that at least one of R^1 and R^2 is not H, and preferably R^2 is H.

5. The PARP1 inhibitor compound for use according to claim 4, wherein at least one of R^1, R^2, R^3 and R^{22} is selected from -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -CH_2F, -CHF_2, -CF_3, -F, -Cl, -CH_2CF_3, -CH_2CH_2F, -CH_2CH_2OH, methoxy, methoxymethyl, methoxyethyl, isopropyl, cyclopropyl or cyclopropylmethyl.

6. The PARP1 inhibitor compound for use according to claim 5, having a structure selected from:

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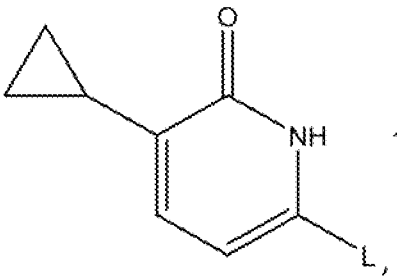
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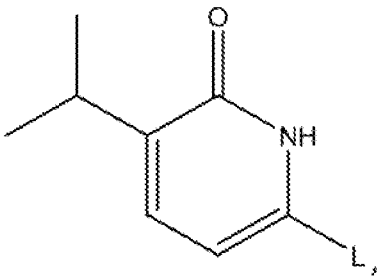
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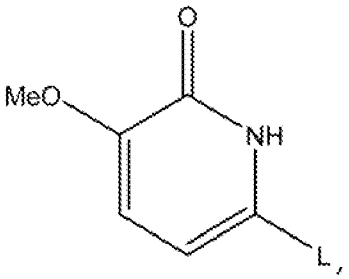
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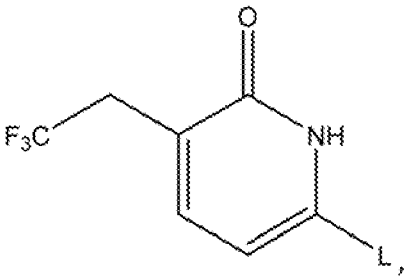
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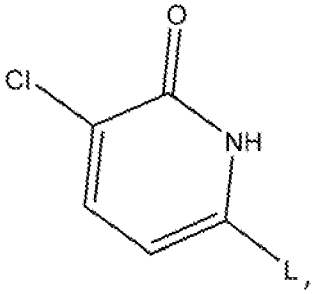
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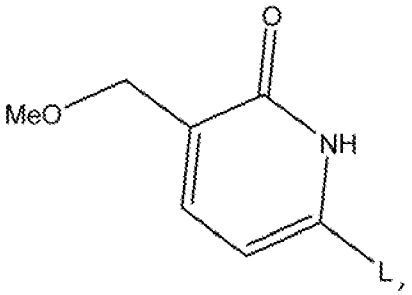
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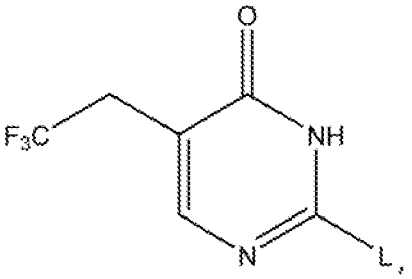
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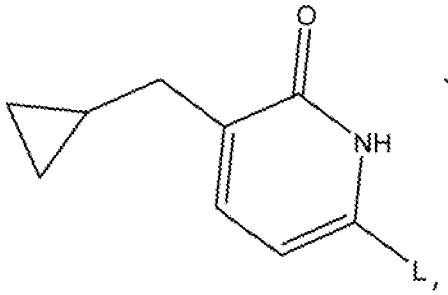
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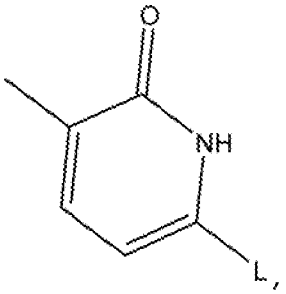
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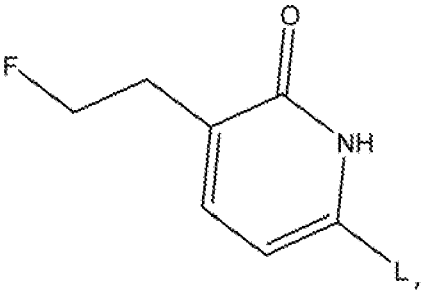
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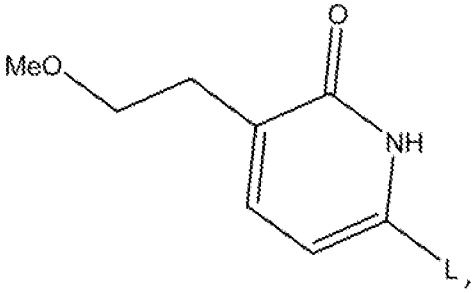
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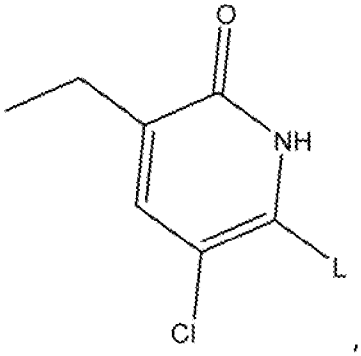
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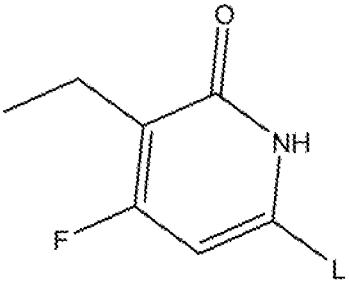
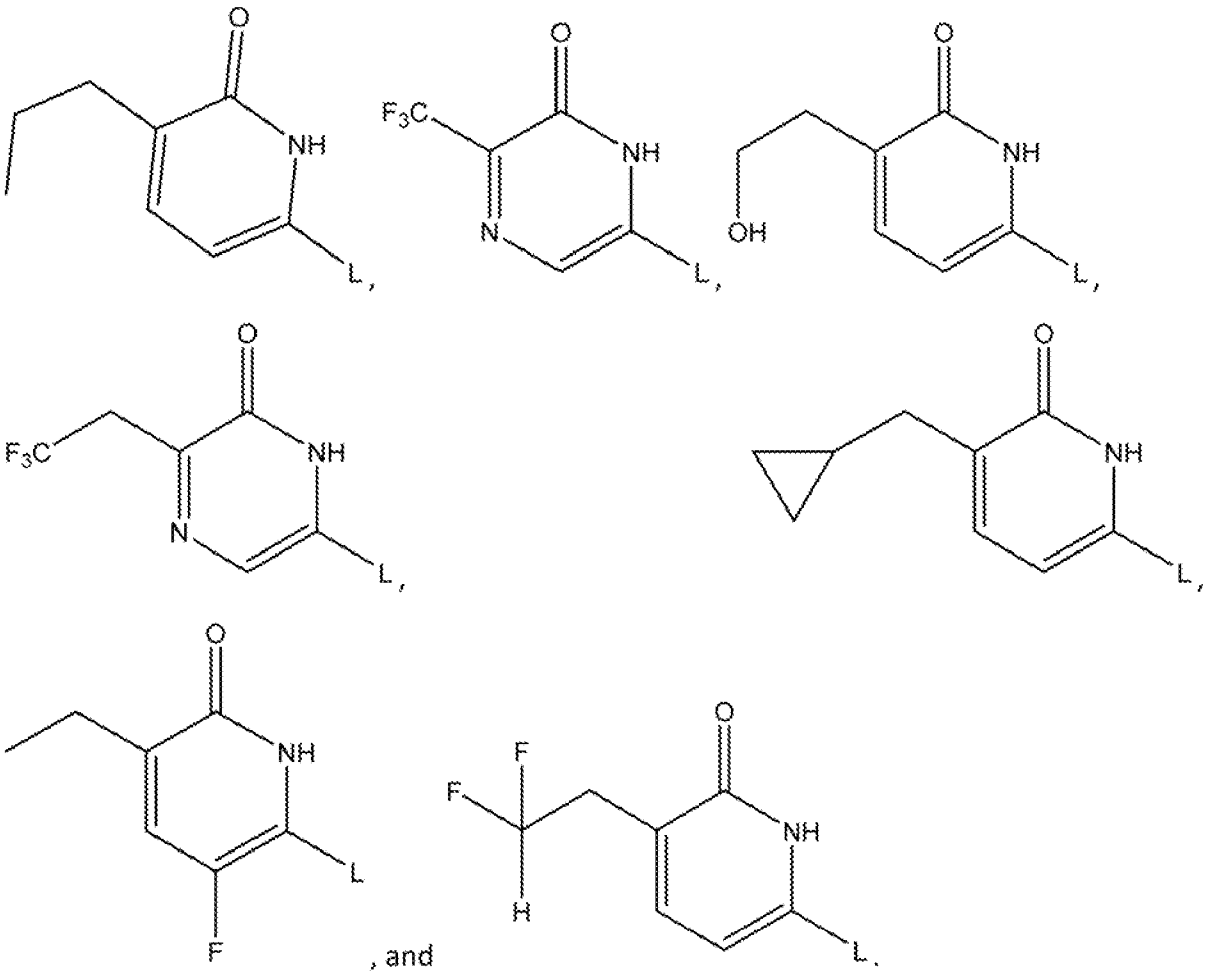
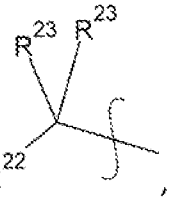

O
NH
F
L



, and

7. The PARP1 inhibitor compound for use according to any of claims 4 to 6, wherein at least one of R^1 and R^2 is 

, and each R^{23} is independently selected from H, F, C1 to C3 alkyl or C1 to C3 fluoroalkyl.

8. The PARP1 inhibitor compound for use according to any of claims 4 to 7, wherein R^1 is selected from H, C1 to C3 alkyl, C1 to C3 alkoxy, and C1 to C3 haloalkyl.

9. The PARP1 inhibitor compound for use according to claim 8, wherein R^1 is an ethyl group.

10. The PARP1 inhibitor compound for use according to any preceding claim, wherein R^3 is selected from H, halogen, C1 to C3 alkyl, C1 to C3 haloalkyl, C1 to C3 alcohol or C1 to C3 aminoalkyl.

11. The PARP1 inhibitor compound for use according to claim 10, wherein:

Z1 and Z2 are each C; and

R^2 and R^3 are each independently selected from H, C1 to C3 alkyl, and C1 to C3 haloalkyl;

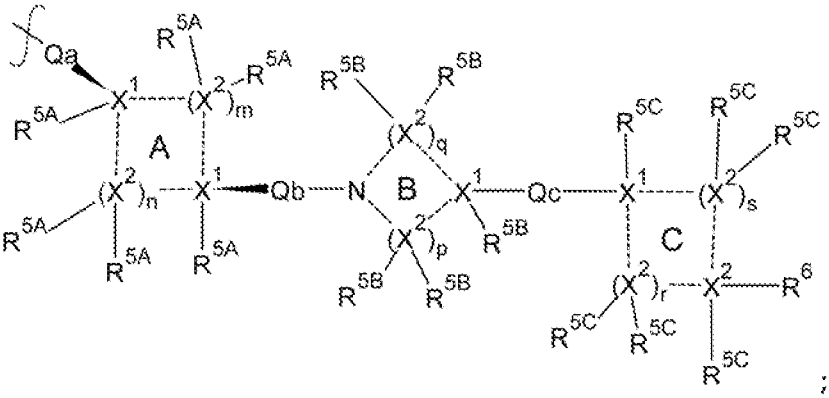
optionally wherein R^2 and R^3 are each H.

12. The PARP1 inhibitor compound for use according to any preceding claim, wherein R^4 is selected from H, C1 to C3 alkyl, and C1 to C3 haloalkyl.

preferably wherein R^4 is H.

13. The PARP1 inhibitor compound for use according to any preceding claim, wherein ring A is an aromatic ring.

14. The PARP1 inhibitor compound for use according to any of claims 1 to 12, wherein L has a structure of:

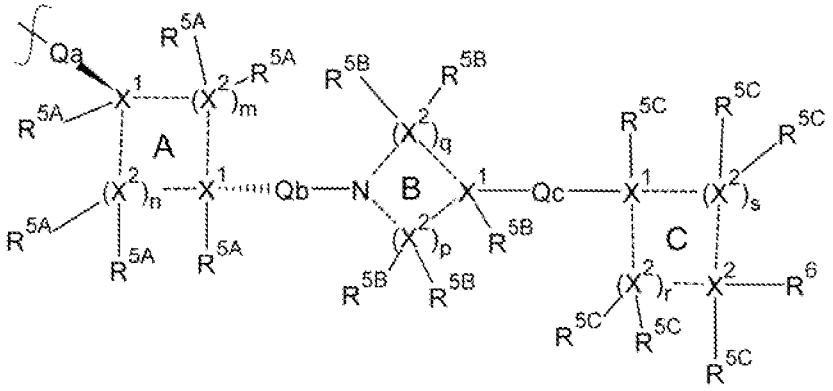


; and

wherein ring A is a saturated or unsaturated aliphatic carbocycle or heterocycle.

15. The PARP1 inhibitor compound for use according to claim 14, wherein ring A is a 6-membered saturated or unsaturated aliphatic carbocycle or heterocycle.

16. The PARP1 inhibitor compound for use according to any of claims 1 to 12, wherein L has a structure of:



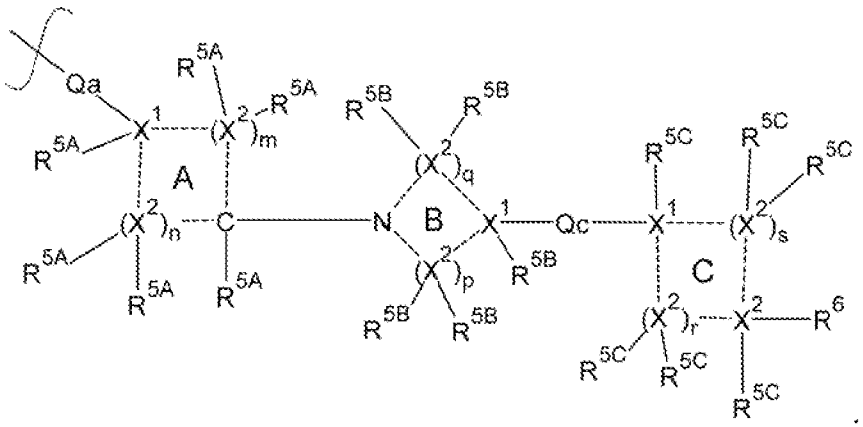
wherein ring A is a saturated or unsaturated aliphatic carbocycle or heterocycle.

17. The PARP1 inhibitor compound for use according to claim 16, wherein ring A is a 5-membered saturated or unsaturated aliphatic carbocycle or heterocycle.

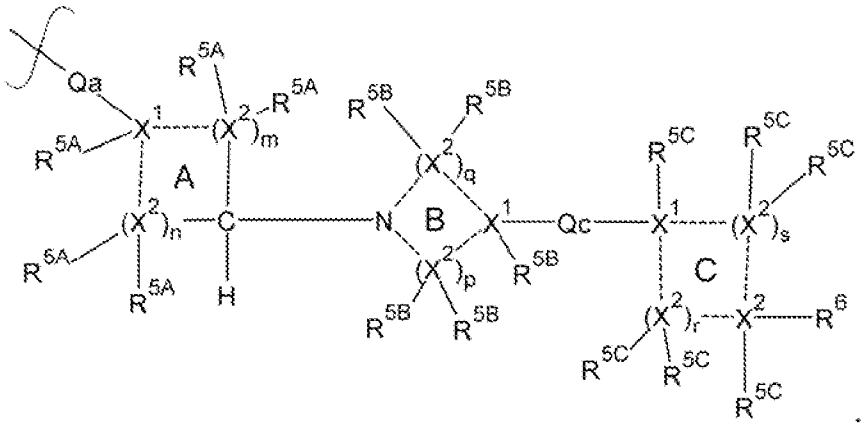
18. The PARP1 inhibitor compound for use according to any preceding claim, wherein Qa is a bond or -CH_2-,

optionally wherein Qa is a bond.

19. The PARP1 inhibitor compound for use according to any preceding claim, wherein L is a group having a structure of:



20. The PARP1 inhibitor compound for use according to claim 19, wherein L is a group having a structure of:

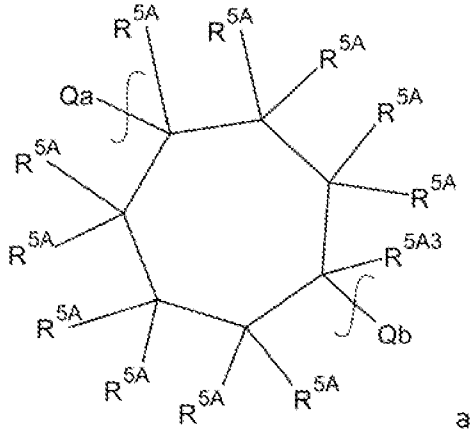


21. The PARP1 inhibitor compound for use according to claim 20, wherein ring B is a saturated heterocycle.

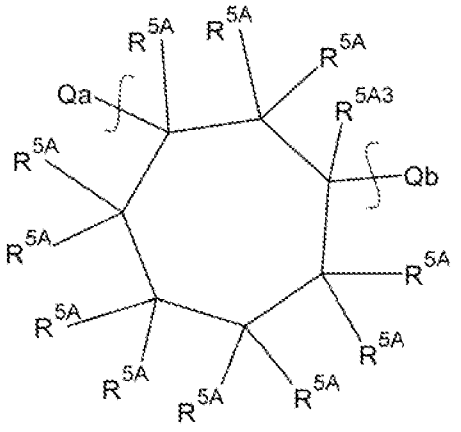
22. The PARP1 inhibitor compound according to any preceding claim, wherein both n and m are at least 1.

23. The PARP1 inhibitor compound for use according to claim 22, wherein:

i) ring A is a substituted or unsubstituted 7-membered aliphatic carbocycle or heterocycle, optionally a cycloheptane, further optionally a cycloheptane having a structure selected from:

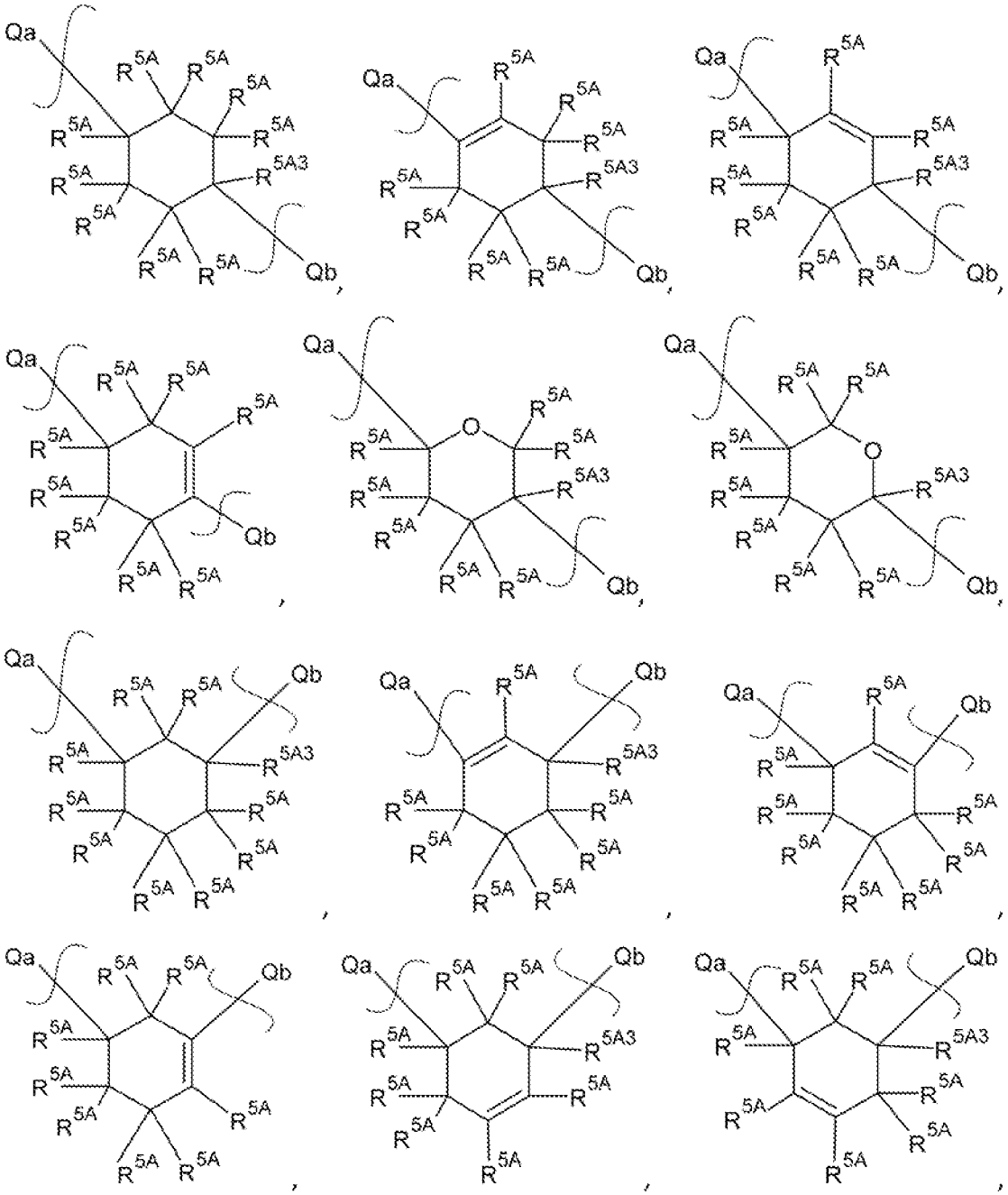


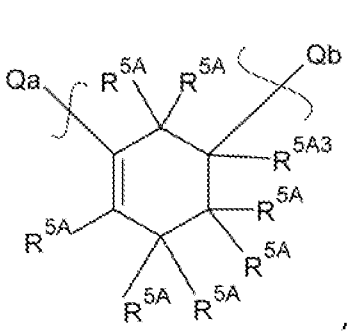
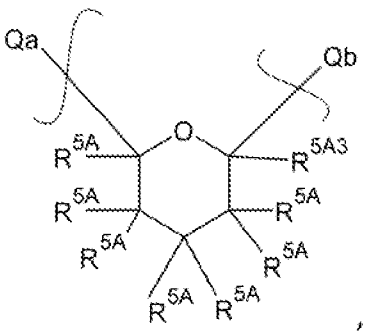
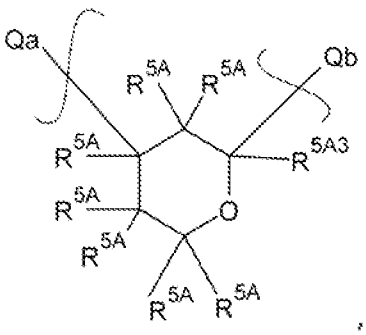
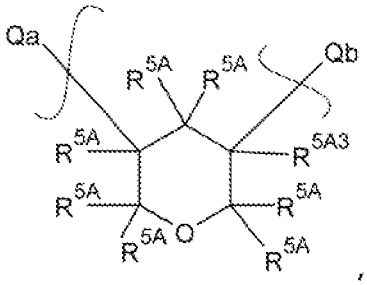
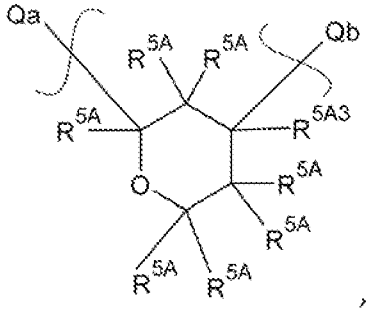
and



each R^{5A} and R^{5A3} being independently selected from H and a substituted or unsubstituted organic group, wherein R^{5A3} is most preferably H; or

ii) wherein ring A is a substituted or unsubstituted 6-membered aliphatic carbocycle or heterocycle, optionally a cyclohexane or tetrahydropyran and further optionally having a structure selected from:

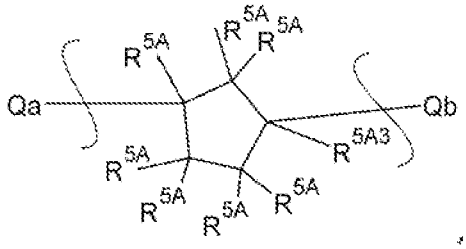
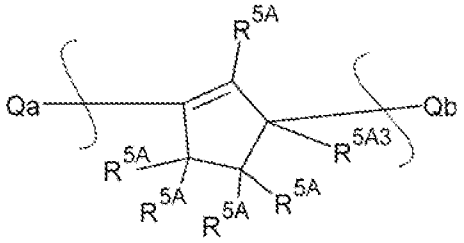
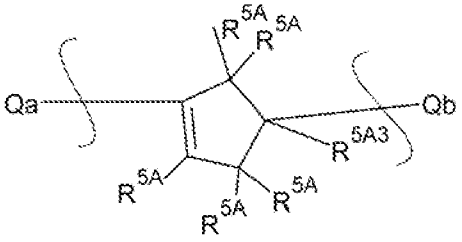
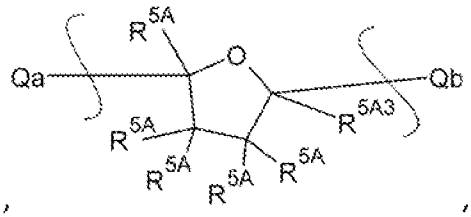
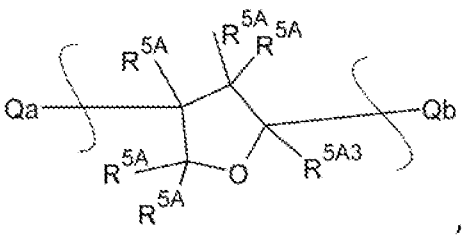
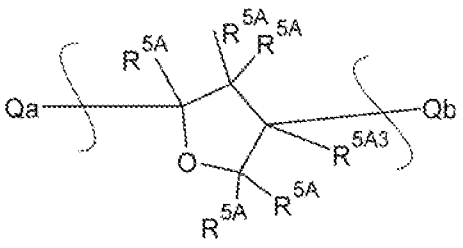


, and

each R^{5A} and R^{5A3} being independently selected from H and a substituted or unsubstituted organic group, wherein R^{5A3} is most preferably H; or

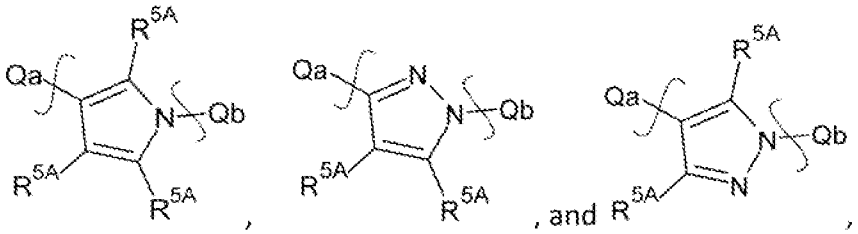
iii) ring A is a substituted or unsubstituted 5-membered aliphatic carbocycle or heterocycle, optionally a cyclopentane, cyclopentene, or a tetrahydrofuran, and further optionally having a structure selected from:

, and

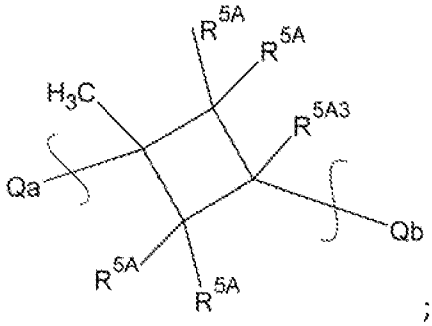
each R^{5A} and R^{5A3} being independently selected from H and a substituted or unsubstituted organic group, wherein R^{5A3} is most preferably H; or

iv) ring A is a 5-membered aromatic ring, optionally a pyrrole or pyrazole, and further optionally having a structure selected from:



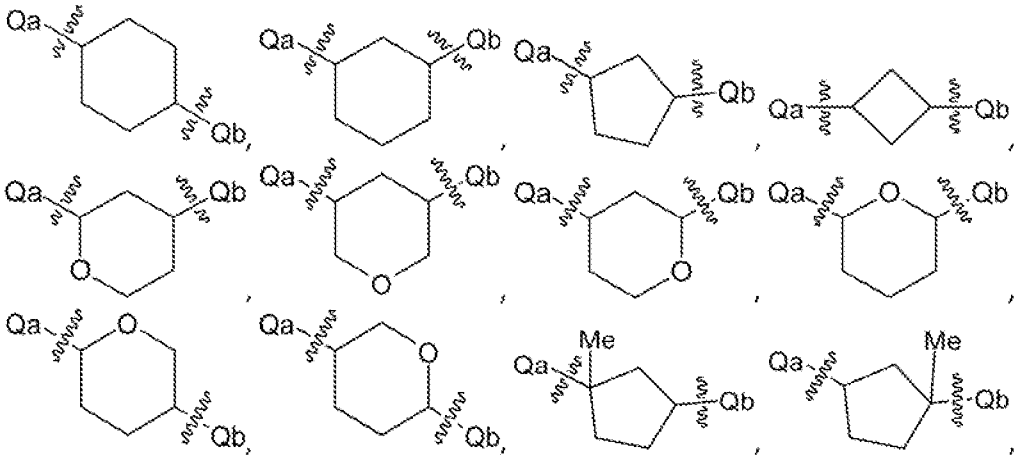
each R^{5A} being independently selected from H and a substituted or unsubstituted organic group; and

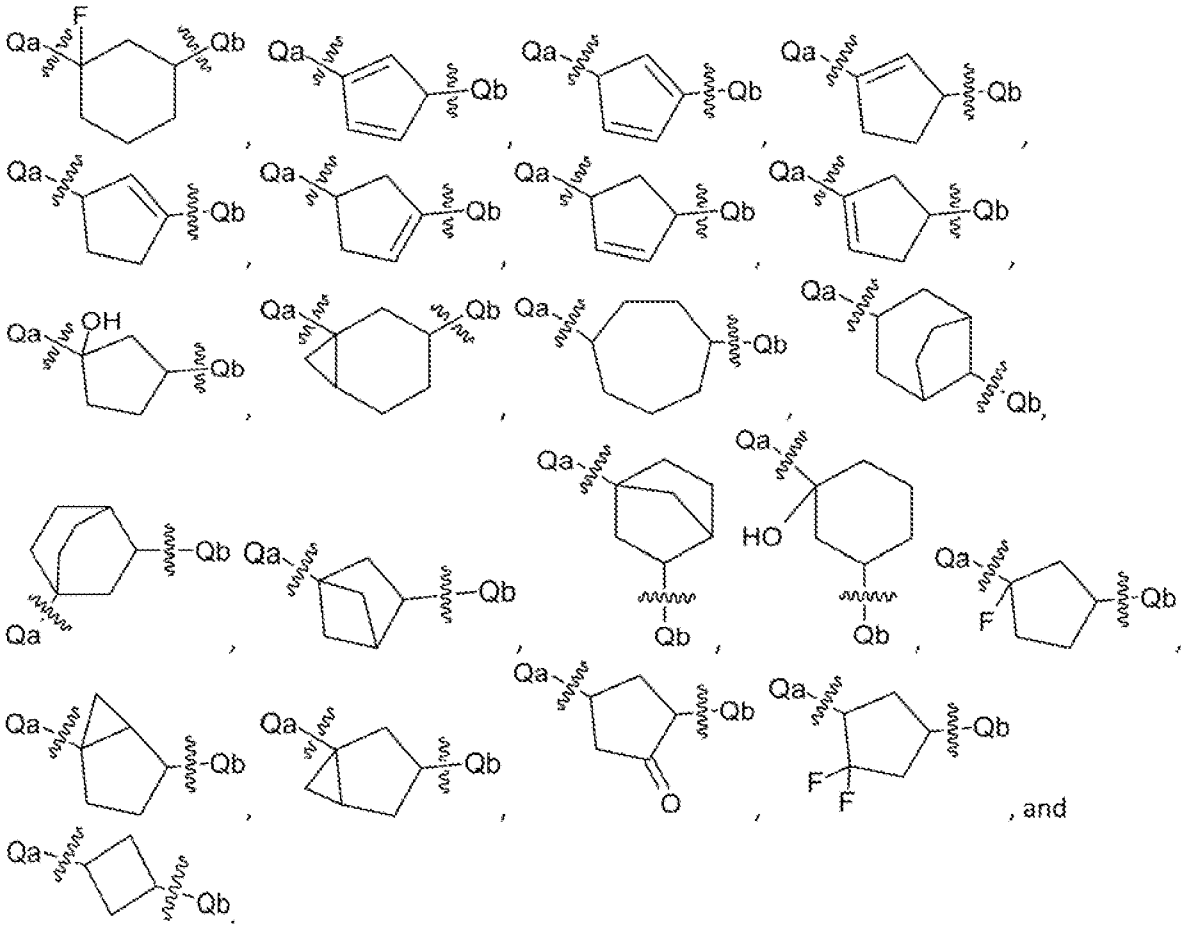
v) ring A is a substituted or unsubstituted cyclobutane, optionally having a structure of:



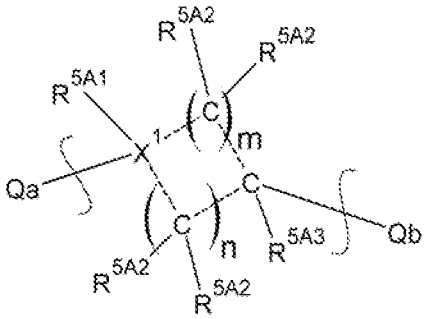
each R^{5A} and R^{5A3} being independently selected from H and a substituted or unsubstituted organic group, wherein R^{5A3} is most preferably H.

24. The PARP1 inhibitor compound for use according to claim 23, wherein ring A has a structure selected from:





25. The PARP1 inhibitor compound for use according to claim 22, wherein ring A has a structure of:



wherein:

m is 1 or 2;

n is 1 or 2;

each R^{5A2} and R^{5A3} independently is absent or selected from H and a substituted or unsubstituted organic group, preferably wherein the ring A is an aliphatic ring and R^{5A3} is H;

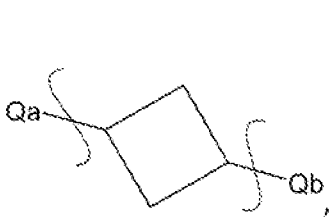
and wherein:

i) X1 is C and R^{5A1} is selected from H and a substituted or unsubstituted organic group; or

ii) X1 is N and R^{5A1} is absent.

26. The PARP1 inhibitor compound for use according to claim 25, wherein each R^{5A2} independently is absent or H.

27. The PARP1 inhibitor compound for use according to claim 26, wherein ring A has a structure selected from:



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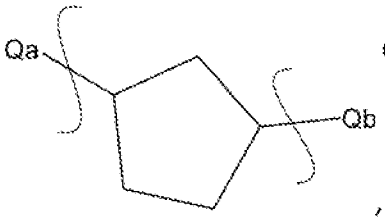

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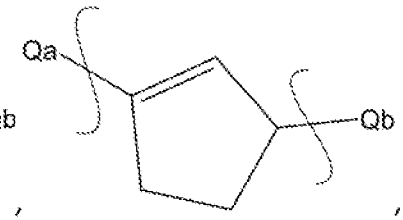

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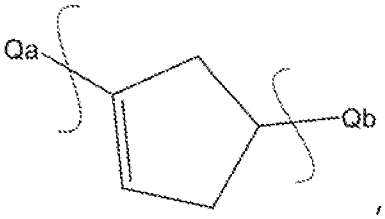

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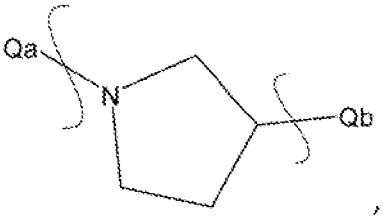

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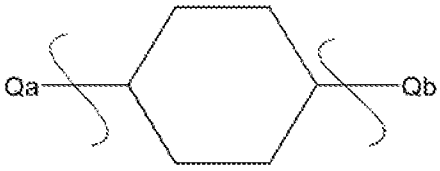

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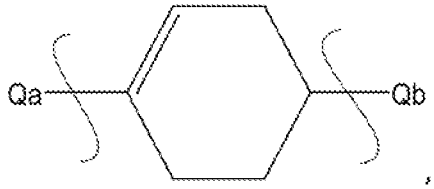

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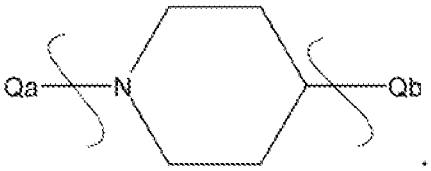


, and .

28. The PARP1 inhibitor compound for use according to any preceding claim, wherein Qb is a bond or $-CH_2-$,

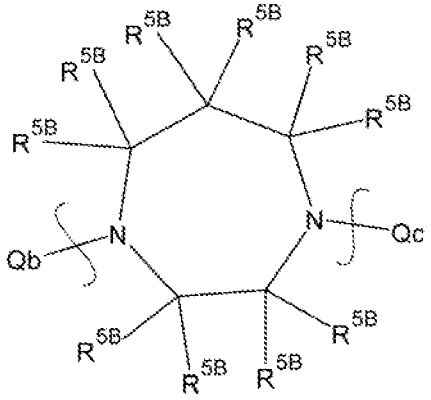
optionally wherein Qb is a bond.

29. The PARP1 inhibitor compound for use according to any preceding claim, wherein both p and q are at least 1;

optionally wherein p and q sum to 3 or 4, and further optionally wherein p is 2 and q is 2.

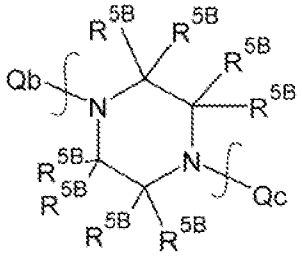
30. The PARP1 inhibitor compound for use according to claim 29, wherein:

i) ring B is a 7-membered saturated heterocyclic ring, optionally a homopiperazine having a structure of:



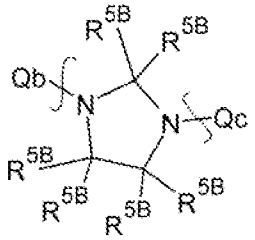
each R^{5B} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5B} is H;

ii) ring B is a 6-membered saturated heterocyclic ring, optionally a piperazine, further optionally a piperazine having a structure of:



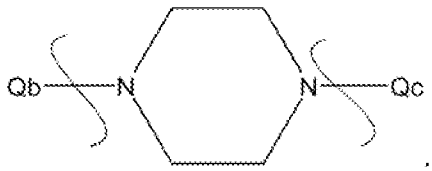
each R^{5B} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5B} is H; or

iii) ring B is a 5-membered saturated heterocyclic ring, optionally an imidazolidine, further optionally an imidazolidine having a structure of:



each R^{5B} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5B} is H.

31. The PARP1 inhibitor compound for use according to claim 30, wherein ring B has a structure of:



32. The PARP1 inhibitor compound for use according to any preceding claim, wherein Qc is a bond or -CH_2-,

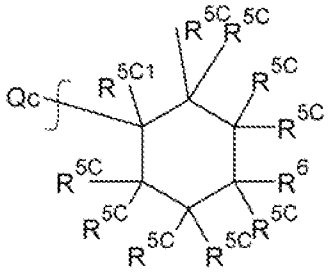
optionally wherein Qc is a bond.

33. The PARP1 inhibitor compound for use according to any preceding claim, wherein both r and s are at least 1,

optionally wherein r and s sum to 3 or 4.

34. The PARP1 inhibitor compound for use according to claim 33, wherein:

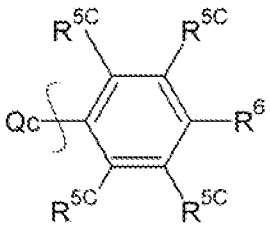
i) ring C is a 6-membered aliphatic ring, optionally a 6-membered aliphatic ring having structure of:



each R^{5C} and R^{5C1} being independently selected from H and a substituted or unsubstituted organic group, preferably wherein R^{5C1} is H, more preferably wherein R^{5C1} and each R^{5C} is H;

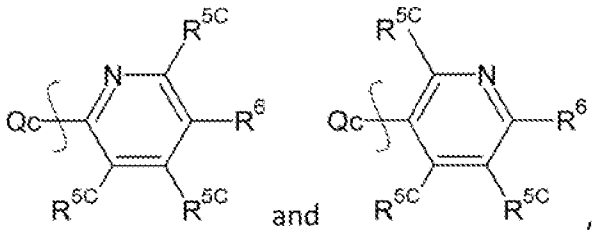
ii) ring C is a 6-membered aromatic ring, optionally selected from:

iia) a phenyl group, optionally having a structure of:



each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

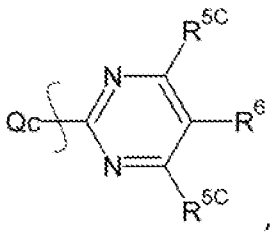
iib) a pyridine group, optionally having a structure selected from:

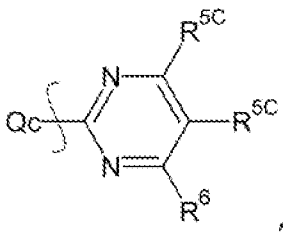


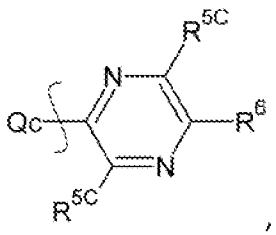
and

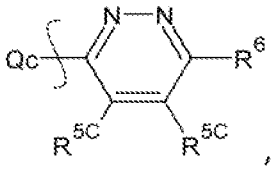
each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

iic) a diazine group, optionally having a structure selected from:

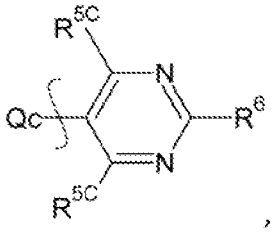








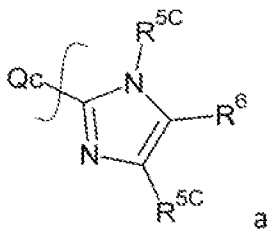
, and



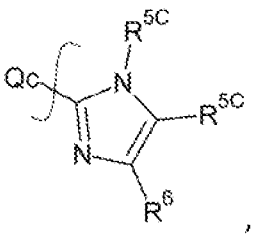
each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

iii) ring C is a 5-membered aromatic ring, optionally selected from:

iiia) an imidazole group, optionally an imidazole group having a structure selected from:

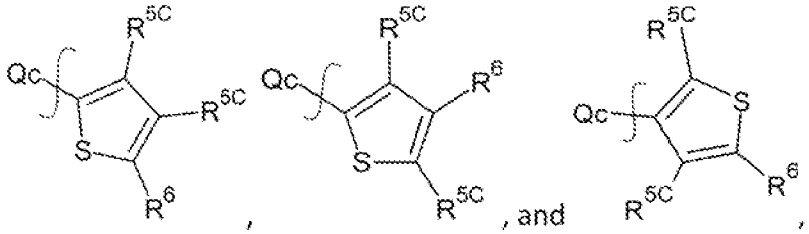


and



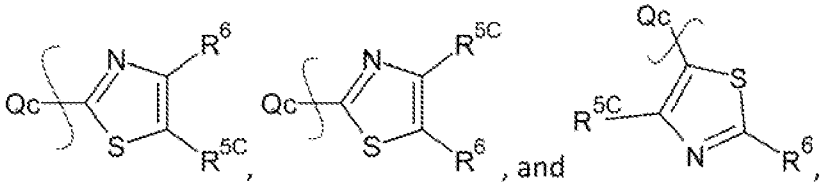
each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

iiib) a thiophene group, optionally having a structure selected from:



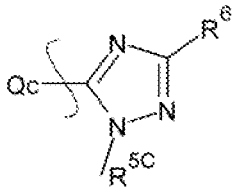
each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

iiic) a thiazole group, optionally having a structure selected from:



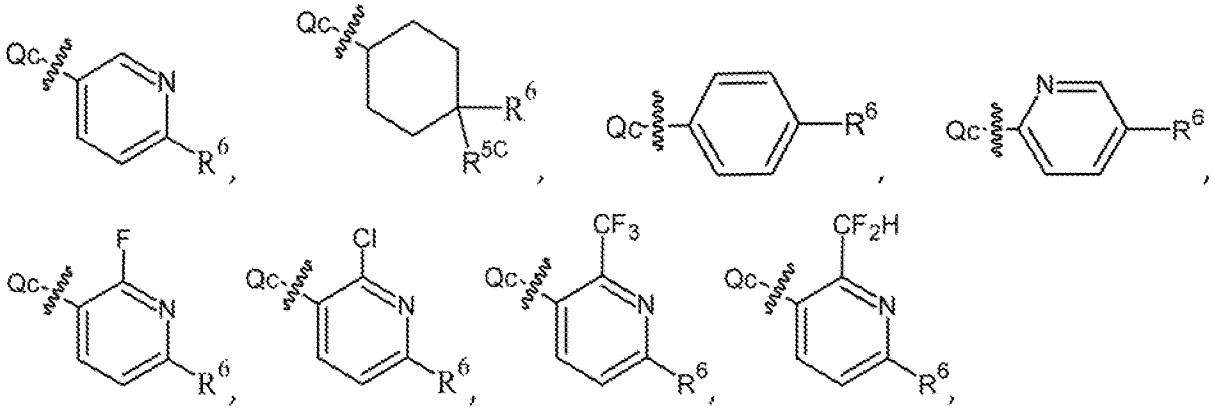
each R^{5C} being independently selected from H and a substituted or unsubstituted organic group, optionally wherein each R^{5C} is H;

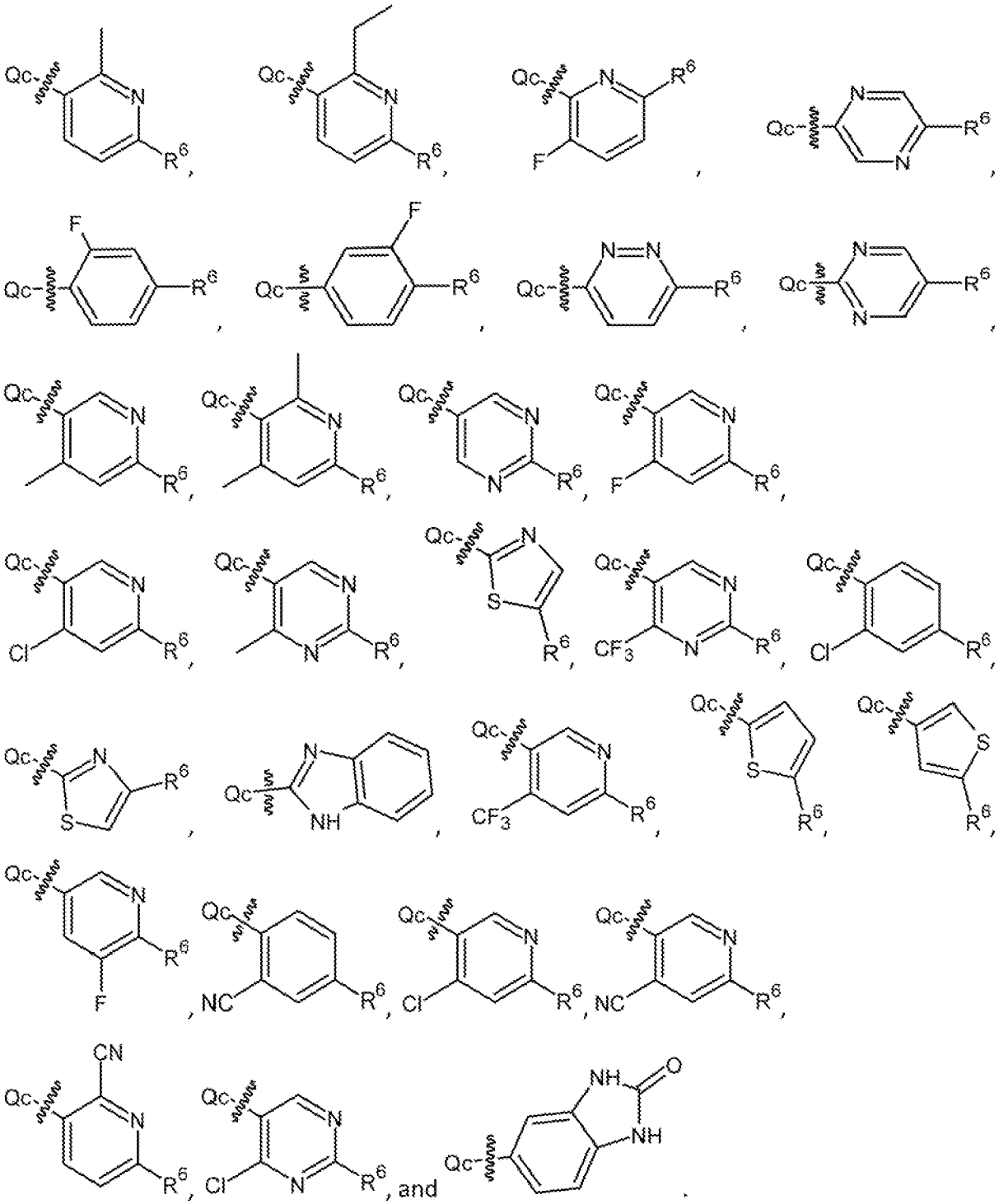
iiid) a triazole, optionally a triazole having a structure of:



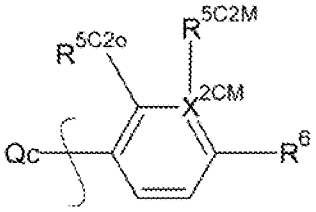
R^{5C} being selected from H and a substituted or unsubstituted organic group, optionally wherein R^{5C} is H.

35. The PARP1 inhibitor compound for use according to claim 34, wherein ring C has a structure selected from:





36. The PARP1 inhibitor compounds for use according to claim 34, wherein ring C has a structure of:



wherein:

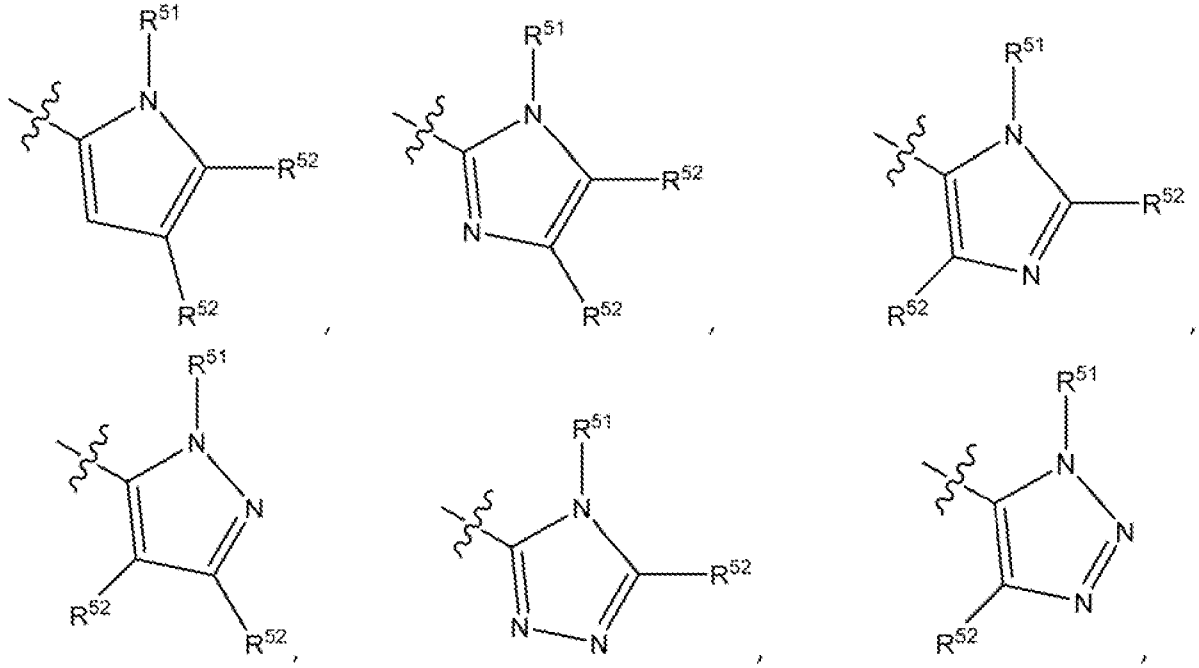
R^{5C2o} is selected from H and a halogen; and

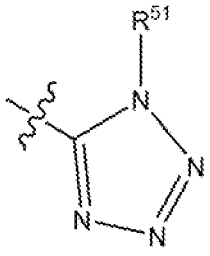
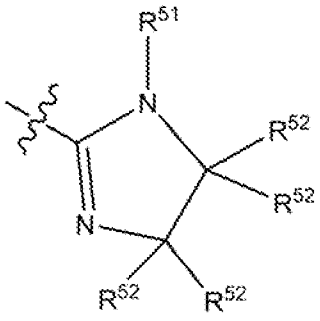
i) X^{2CM} is C and R^{5C2M} is H; or

ii) X^{2CM} is N and $R5^{C2M}$ is absent.

37. The PARP1 inhibitor compound for use according to claim 33, wherein R^{5C1} is a halogen, optionally wherein R^{5C1} is F.

38. The PARP1 inhibitor compound for use according to any preceding claim, wherein R^6 is selected from H, -F, -Cl, -Br, -I, -CN, $-CONR^{51}R^{51}$, $-NR^{51}COR^{52}$, $-SO_2NR^{51}R^{51}$, $-NR^{51}SO_2R^{52}$, $-O-CR^{52}R^{52}R^{52}$, $-CR^{52}R^{52}NR^{51}R^{51}$, and any of the following structures:

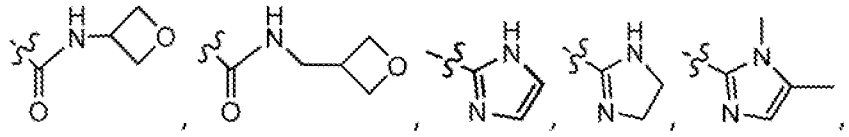


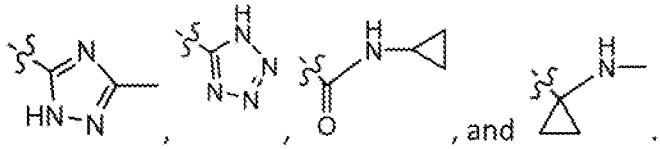



, and

wherein R^{51} and R^{52} are each independently selected from H and a substituted or unsubstituted organic group, optionally wherein R^{51} and R^{52} are each independently selected from H, a halogen, C1 to C3 alkyl, and C1 to C3 haloalkyl.

39. The PARP1 inhibitor compound for use according to claim 38, wherein R^6 is selected from -F, -Cl, -CN, -$CONH_2$, -CONHMe, -CONHEt, -$CONMe_2$, -CONHCOMe, -$CONHCH_2$-CH_2OMe, -CONH-CH_2-CH_2F, -CONH-CH_2-CF_3, -CONH-CH_2-CHF_2, -$OCHF_2$, -NHCOMe, -$NHSO_2$Me, -SO_2NHMe, -$CONHSO_2$Me,



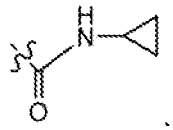


, and

.

40. The PARP1 inhibitor compound for use according to claim 39, wherein R^6 is CONHMe.

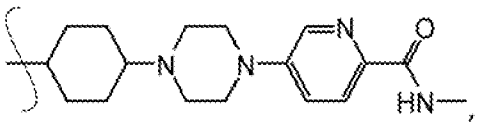
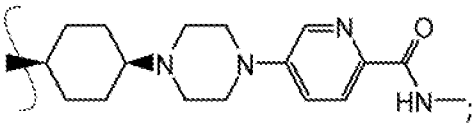
41. The PARP1 inhibitor compound for use according to claim 39, wherein R^6 is

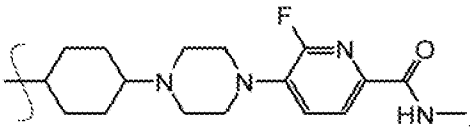
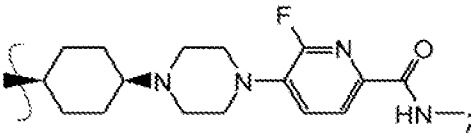


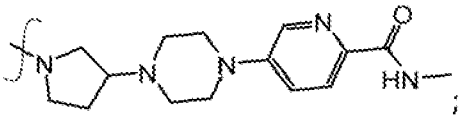
.

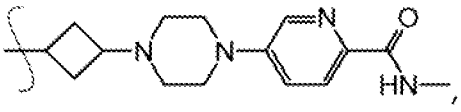
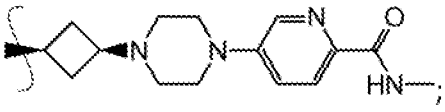
42. The PARP1 inhibitor compound for use according to any of claims 1 to 37, wherein R^6 and one R^{SC} group together form a ring.

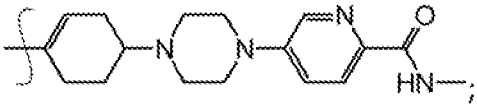
43. The PARP1 inhibitor compound for use according to any of claims 1 to 12, wherein group L is selected from:

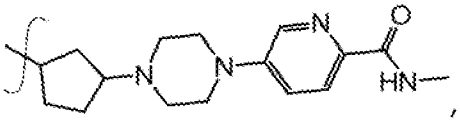
i)  , optionally  ;

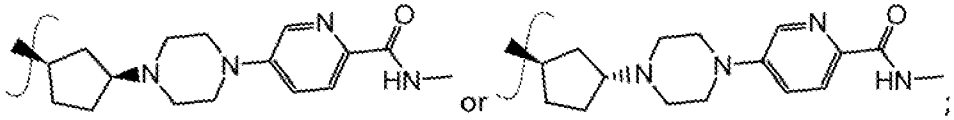
ii)  , optionally  ;

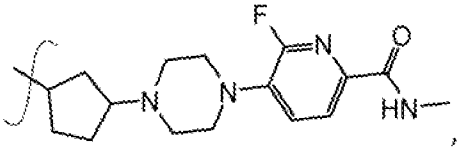
iii)  ;

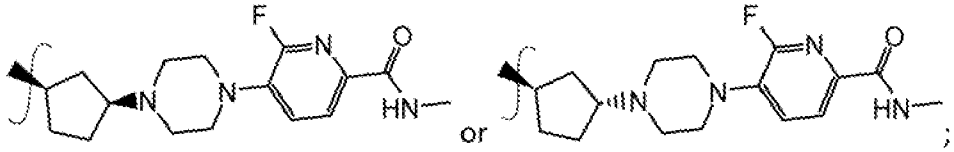
iv)  , optionally  ;

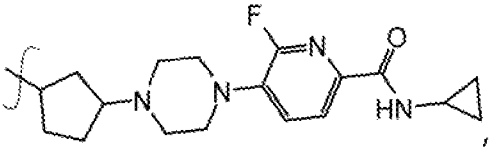
v)  ;

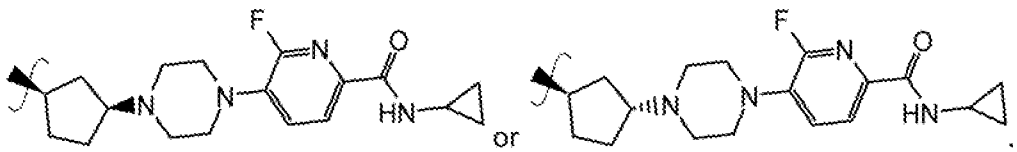
vi)  , optionally

 ;

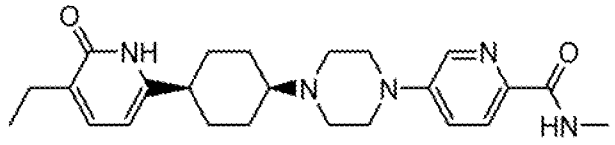
vii)  , optionally

 ;

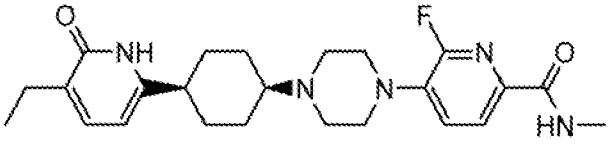
viii)  , optionally

 .

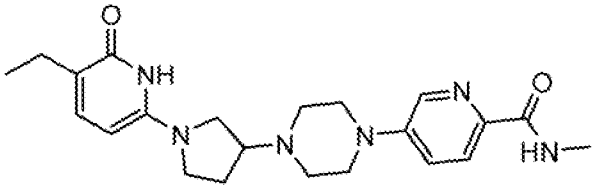
44. The PARP1 inhibitor compound for use according to claim 43, wherein the compound has a structure selected from:



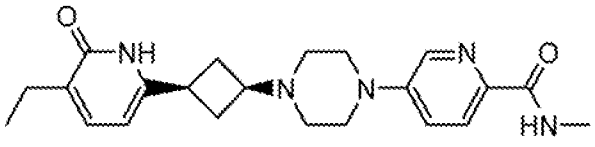
1*cis*



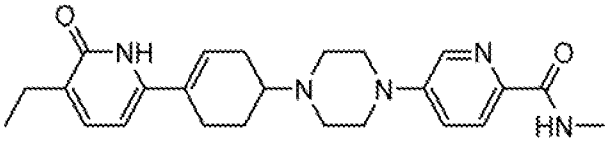
2*cis*



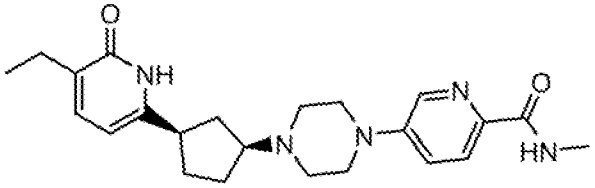
3



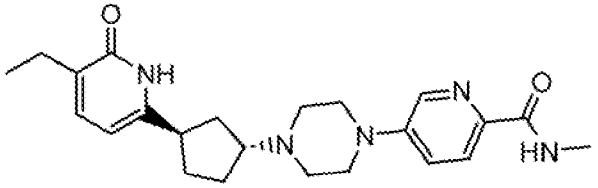
4*cis*



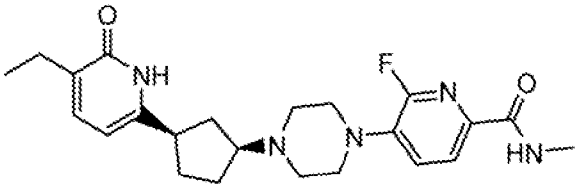
5



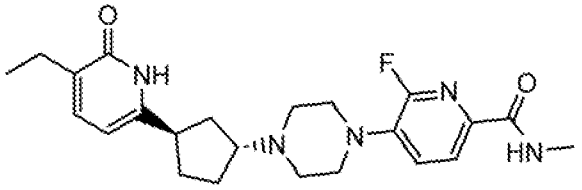
6*cis*



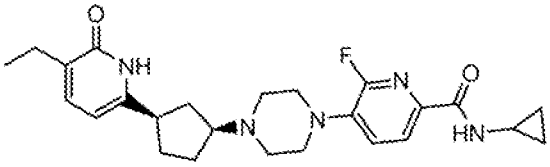
6*trans*



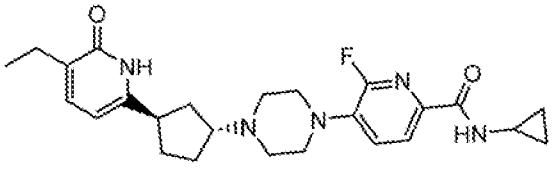
7*cis*



7*trans*



8*cis*



8*trans*

45. The PARP1 inhibitor compound for use according to any preceding claim, wherein when one or more of R^1, R^2, R^3, R^4, R^{5A} (e.g., R^{5A1}, R^{5A2}, R^{5A3}), R^{5B}, R^{5C}, R^6, R^7, R^{S1}, R^{S2}, R^{S3} is a substituted or unsubstituted organic group, the or each substituted or unsubstituted organic group is independently selected from:

deuterium;

a halogen (such as –F, -Cl, -Br and –I);

a nitrile group;

a substituted or unsubstituted linear or branched C_1-C_6 alkyl group

(such as Me, Et, Pr, i-Pr, n-Bu, i-Bu, t-Bu, pentyl and hexyl);

a substituted or unsubstituted linear or branched C_1-C_6 alkyl-aryl group

(such as –CH_2Ph, -CH_2(2,3 or 4)F-Ph, -CH_2(2,3 or 4)Cl-Ph, -CH_2(2,3 or 4)Br-Ph, -CH_2(2,3 or 4)I-Ph, -CH_2CH_2Ph, -$CH_2CH_2CH_2$Ph, -$CH_2CH_2CH_2CH_2$Ph, -$CH_2CH_2CH_2CH_2CH_2$Ph, and -$CH_2CH_2CH_2CH_2CH_2CH_2$Ph);

a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group

(such as -CH_2F, -CH_2Cl, -CH_2Br, -CH_2I, -CHF_2, -CF_3, -CCl_3 -CBr_3, -Cl_3, -CH_2CH_2F, -CH_2CF_3, -CH_2CCl_3, -CH_2CBr_3, and -CH_2Cl_3);

NH_2 or a substituted or unsubstituted linear or branched primary secondary or tertiary C_1-C_6 amine group

(such as -NMeH, -NMe_2, -NEtH, -NEtMe, -NEt_2, -NPrH, -NPrMe, -NPrEt, -NPr_2, -NBuH, -NBuMe, -NBuEt, –CH_2-NH_2, -CH_2-NMeH, -CH_2-NMe_2, -CH_2-NEtH, -CH_2-NEtMe, -CH_2-NEt_2, -CH_2-NPrH, -CH_2-NPrMe, and –CH_2-NPrEt);

a substituted or unsubstituted amino-aryl group

(such as -NH-Ph, -NH-(2,3 or 4)F-Ph, -NH-(2,3 or 4)Cl-Ph, -NH-(2,3 or 4)Br-Ph, -NH-(2,3 or 4)I-Ph, -NH-(2,3 or 4)Me-Ph, -NH-(2,3 or 4)Et-Ph, -NH-(2,3 or 4)Pr-Ph, -NH-(2,3 or 4)Bu-Ph, NH-(2,3 or 4)OMe-Ph, -NH-(2,3 or 4)OEt-Ph, -NH-(2,3 or 4)OPr-Ph, -NH-(2,3 or 4)OBu-Ph, -NH-2,(3,4,5 or 6)F_2-Ph, -NH-2,(3,4,5 or 6)Cl_2-Ph, -NH-2,(3,4,5 or 6)Br_2-Ph, -NH-2,(3,4,5 or 6)I_2-Ph, -NH-2,(3,4,5 or 6)Me_2-Ph, -NH-2,(3,4,5 or 6)Et_2-Ph, -NH-2,(3,4,5, or 6)Pr_2-Ph, -NH-2,(3,4,5 or 6)Bu_2-Ph),

a substituted or unsubstituted cyclic amine or amido group

(such as pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, 2-keto-pyrrolidinyl, 3-keto-pyrrolidinyl, 2-keto-piperidinyl, 3-keto-piperidinyl, and 4-keto-piperidinyl);

a substituted or unsubstituted cyclic C_3-C_8 alkyl group

(such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl);

an -OH group;

a substituted or unsubstituted linear or branched C_1-C_6 alcohol group (such as –CH_2OH, -CH_2CH_2OH, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2OH$, -$CH_2CH_2CH_2OH$, -$CH_2CH_2CH_2CH_2OH$, -$CH(CH_3)CH_2CH_2OH$, -$CH(CH_3)CH(CH_3)OH$, -$CH(CH_2CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2CH_2CH_2CH_2CH_2OH$, and -$CH_2CH_2CH_2CH_2CH_2CH_2OH$);

a substituted or unsubstituted linear or branched C_1-C_6 carboxylic acid group (such as -COOH, -CH_2COOH, -CH_2CH_2COOH, -$CH_2CH_2CH_2COOH$, -$CH_2CH_2CH_2CH_2COOH$, and -$CH_2CH_2CH_2CH_2CH_2COOH$);

a substituted or unsubstituted linear or branched carbonyl group (such as -(CO)Me, -(CO)Et, -(CO)Pr, -(CO)iPr, -(CO)nBu, -(CO)iBu, -(CO)tBu, -(CO)Ph, -(CO)CH_2Ph, -(CO)CH_2OH, -(CO)CH_2OCH_3, -(CO)CH_2NH_2, -(CO)CH_2NHMe, -(CO)CH_2NMe_2, -(CO)-cyclopropyl, -(CO)-1,3-epoxypropan-2-yl; -(CO)NH_2, -(CO)NHMe, -(CO)NMe_2, -(CO)NHEt, -(CO)NEt_2, -(CO)-pyrollidine-N-yl, -(CO)-morpholine-N-yl, -(CO)-piperazine-N-yl, -(CO)-N-methyl-piperazine-N-yl, -(CO)$NHCH_2CH_2OH$, -(CO)$NHCH_2CH_2OMe$, -(CO)$NHCH_2CH_2NH_2$, -(CO)$NHCH_2CH_2$NHMe, and -(CO)$NHCH_2CH_2NMe_2$);

a substituted or unsubstituted linear or branched C_1-C_6 carboxylic acid ester group (such as -COOMe, -COOEt, -COOPr, -COO-i-Pr, -COO-n-Bu, -COO-i-Bu, -COO-t-Bu, -CH_2COOMe, -CH_2CH_2COOMe, -$CH_2CH_2CH_2$COOMe, and -$CH_2CH_2CH_2CH_2$COOMe);

a substituted or unsubstituted linear or branched C_1-C_6 amide group (such as -CO-NH_2, -CO-NMeH, -CO-NMe_2, -CO-NEtH, -CO-NEtMe, -CO-NEt_2, -CO-NPrH, -CO-NPrMe, and -CO-NPrEt);

a substituted or unsubstituted linear or branched C_1-C_7 amino carbonyl group (such as -NH-CO-Me, -NH-CO-Et, -NH-CO-Pr, -NH-CO-Bu, -NH-CO-pentyl, -NH-CO-hexyl, -NH-CO-Ph, -NMe-CO-Me, -NMe-CO-Et, -NMe-CO-Pr, -NMe-CO-Bu, -NMe-CO-pentyl, -NMe-CO-hexyl, -NMe-CO-Ph);

a substituted or unsubstituted linear or branched C_1-C_7 alkoxy or aryloxy group (such as –OMe, -OEt, -OPr, -O-i-Pr, -O-n-Bu, -O-i-Bu, -O-t-Bu, -O-pentyl, -O-hexyl, -OCH_2F, -$OCHF_2$, -OCF_3, -OCH_2Cl, -$OCHCl_2$, -$OCCl_3$, -O-Ph, -O-CH_2-Ph,

-O-CH_2-(2,3 or 4)-F-Ph, -O-CH_2-(2,3 or 4)-Cl-Ph, –CH_2OMe, –CH_2OEt, –CH_2OPr, –CH_2OBu, -CH_2CH_2OMe, -$CH_2CH_2CH_2OMe$, -$CH_2CH_2CH_2CH_2OMe$, and -$CH_2CH_2CH_2CH_2CH_2OMe$);

a substituted or unsubstituted linear or branched aminoalkoxy group

(such as –OCH_2NH_2, -OCH_2NHMe, -OCH_2NMe_2, -OCH_2NHEt, -OCH_2NEt_2, -$OCH_2CH_2NH_2$, -OCH_2CH_2NHMe, -$OCH_2CH_2NMe_2$, -OCH_2CH_2NHEt, and -$OCH_2CH_2NEt_2$);

a substituted or unsubstituted sulfonyl group

(such as -SO_2Me, -SO_2Et, -SO_2Pr, -SO_2iPr, -SO_2Ph, -SO_2-(2,3 or 4)-F-Ph, -SO_2-cyclopropyl, -$SO_2CH_2CH_2OCH_3$, -SO_2NH_2, -SO_2NHMe, -SO_2NMe_2, -SO_2NHEt, -SO_2NEt_2, -SO2-pyrrolidine-N-yl, -SO_2-morpholine-N-yl, -SO_2NHCH_2OMe,and -$SO_2NHCH_2CH_2OMe$);

a substituted or unsubstituted aminosulfonyl group

(such as –$NHSO_2Me$, -$NHSO_2Et$, - $NHSO_2Pr$, -$NHSO_2iPr$, -$NHSO_2Ph$, -$NHSO_2$-(2,3 or 4)-F-Ph, -$NHSO_2$-cyclopropyl, -$NHSO_2CH_2CH_2OCH_3$);

a substituted or unsubstituted aromatic group

(such as Ph-, 2-F-Ph-, 3-F-Ph-, 4-F-Ph-, 2-Cl-Ph-, 3-Cl-Ph-, 4-Cl-Ph-, 2-Br-Ph-, 3-Br-Ph-, 4-Br-Ph-, 2-I-Ph-, 3-I-Ph, 4-I-Ph-, 2,(3,4,5 or 6)-F_2-Ph-, 2,(3,4,5 or 6)-Cl_2-Ph-, 2,(3,4,5 or 6)-Br_2-Ph-, 2,(3,4,5 or 6)-I_2-Ph-, 2,(3,4,5 or 6)-Me_2-Ph-, 2,(3,4,5 or 6)-Et_2-Ph-, 2,(3,4,5 or 6)-Pr_2-Ph-, 2,(3,4,5 or 6)-Bu_2-Ph-, 2,(3,4,5 or 6)-$(CN)_2$-Ph-, 2,(3,4,5 or 6)-$(NO_2)_2$-Ph-, 2,(3,4,5 or 6)-$(NH_2)_2$-Ph-, 2,(3,4,5 or 6)-$(MeO)_2$-Ph-, 2,(3,4,5 or 6)-$(CF_3)_2$-Ph-, 3,(4 or 5)-F_2-Ph-, 3,(4 or 5)-Cl_2-Ph-, 3,(4 or 5)-Br_2-Ph-, 3,(4 or 5)-I_2-Ph-, 3,(4 or 5)-Me_2-Ph-, 3,(4 or 5)-Et_2-Ph-, 3,(4 or 5)-Pr_2-Ph-, 3,(4 or 5)-Bu_2-Ph-, 3,(4 or 5)-$(CN)_2$-Ph-, 3,(4 or 5)-$(NO_2)_2$-Ph-, 3,(4 or 5)-$(NH_2)_2$-Ph-, 3,(4 or 5)-$(MeO)_2$-Ph-, 3,(4 or 5)-$(CF_3)_2$-Ph-, 2-Me-Ph-, 3-Me-Ph-, 4-Me-Ph-, 2-Et-Ph-, 3-Et-Ph-, 4-Et-Ph-, 2-Pr-Ph-, 3-Pr-Ph-, 4-Pr-Ph-, 2-Bu-Ph-, 3-Bu-Ph-, 4-Bu-Ph-, 2-(CN)-Ph-, 3-(CN)-Ph-, 4-(CN)-Ph-, 2-(NO_2)-Ph-, 3-(NO_2)-Ph-, 4-(NO_2)-Ph-, 2-(NH_2)-Ph-, 3-(NH_2)-Ph-, 4-(NH_2)-Ph-, 2-MeO-Ph-, 3-MeO-Ph-, 4-MeO-Ph-, 2-$(NH_2$-CO)-Ph-, 3-$(NH_2$-CO)-Ph-, 4-$(NH_2$-CO)-Ph-, 2-CF_3-Ph-, 3-CF_3-Ph-, 4-CF_3-Ph-, 2-CF_3O-Ph-, 3-CF_3O-Ph-, and 4-CF_3O-Ph-);

a saturated or unsaturated, substituted or unsubstituted, heterocyclic group, optionally an aromatic heterocyclic group or a non-aromatic heterocyclic group

(such as pyrrole-1-yl, pyrrole-2-yl, pyrrole-3-yl, pyrazole-1-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazole-5-yl, imidazole-1-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, 1,2,3-triazole-1-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-1-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazine-3-yl, pyridazine-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-6-yl, pyrazine-2-yl, pyrrolidine-1-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-1-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, 2-azapiperidine-1-yl, 2-azapiperidine-3-yl, 2-azapiperidine-4-yl, 3-azapiperidine-1-yl, 3-azapiperidine-2-yl, 3-azapiperidine-4-yl, 3-azapiperidine-5-yl, piperazine-1-yl, piperazine-2-yl, furan-2-yl, furan-3-yl, pyran-2-yl, pyran-3-yl, pyran-4-yl, 2-azapyran-2-yl, 2-azapyran-3-yl, 2-azapyran-4-yl, 2-azapyran-5-yl, 2-azapyran-6-yl, 3-azapyran-2-yl, 3-azapyran-4-yl, 3-azapyran-5-yl, 3-azapyran-6-yl, 4-azapyran-2-yl, 4-azapyran-3-yl, 4-azapyran-4-yl, 4-azapyran-5-yl, 4-azapyran-6-yl, oxetan-2-yl, oxetan-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-2-yl, 2-aza-tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-4-yl, 2-aza-tetrahydrofuran-5-yl, 3-aza-tetrahydrofuran-2-yl, 3-aza-tetrahydrofuran-3-yl, 3-aza-tetrahydrofuran-4-yl, 3-aza-tetrahydrofuran-5-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, 2-aza-tetrahydropyran-2-yl, 2-aza-tetrahydropyran-3-yl, 2-aza-tetrahydropyran-4-yl, 2-aza-tetrahydropyran-5-yl, 2-aza-tetrahydropyran-6-yl, 3-aza-tetrahydropyran-2-yl, 3-aza-tetrahydropyran-3-yl, 3-aza-tetrahydropyran-4-yl, 3-aza-tetrahydropyran-5-yl, 3-aza-tetrahydropyran-6-yl, morpholine-2-yl, morpholine-3-yl, morpholine-4-yl, thiophen-2-yl, thiophen-3-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl, thiopyran-2-yl, thiopyran-3-yl, thiopyran-4-yl, 2-azathiopyran-2-yl, 2-azathiopyran-3-yl, 2-azathiopyran-4-yl, 2-azathiopyran-5-yl, 2-azathiopyran-6-yl, 3-azathiopyran-2-yl, 3-azathiopyran-4-yl,

3-azathiopyran-5-yl, 3-azathiopyran-6-yl, 4-azathiopyran-2-yl, 4-azathiopyran-3-yl, 4-azathiopyran-4-yl, 4-azathiopyran-5-yl, 4-azathiopyran-6-yl, thiolane-2-yl, thiolane-3-yl, thiane-2-yl, thiane-3-yl, thiane-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, furazan-3-yl, (1,3,4-oxadiazol)-2-yl, (1,3,4-oxadiazol)-5-yl, (1,2,4-oxadiazol)-3-yl, (1,2,4-oxadiazol)-5-yl; and tetrazole-1-yl, tetrazole-2-yl, tetrazole-5-yl);

wherein:

a pair of R^{5A} groups attached to different atoms may together form a ring with ring A atoms; and/or

a pair of R^{5B} groups attached to different atoms may together form a ring with ring B atoms, and/or

a pair of R^{5C} groups attached to different atoms may together form a ring with ring C atoms; and/or

an R^{5C} group and an R^6 group attached to different atoms may together form a ring with ring C atoms.

46. The PARP1 inhibitor compound for use according to any preceding claim, wherein each of R^{5A} (e.g., R^{5A1}, R^{5A2}, R^{5A3}), R^{5B}, and R^{5C} is independently absent or selected from:

H,

deuterium,

a halogen (such as –F, -Cl, -Br, and –I; preferably F or Cl),

a nitrile group,

a substituted or unsubstituted C_1-C_6 alkyl group,

a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group (preferably CF_3 or CHF_2),

a cyclopropyl group,

an -OH group,

a substituted or unsubstituted linear or branched C_1-C_6 alcohol group,

a substituted or unsubstituted linear or branched C_1-C_7 amino carbonyl group (such as -NH-CO-Me),

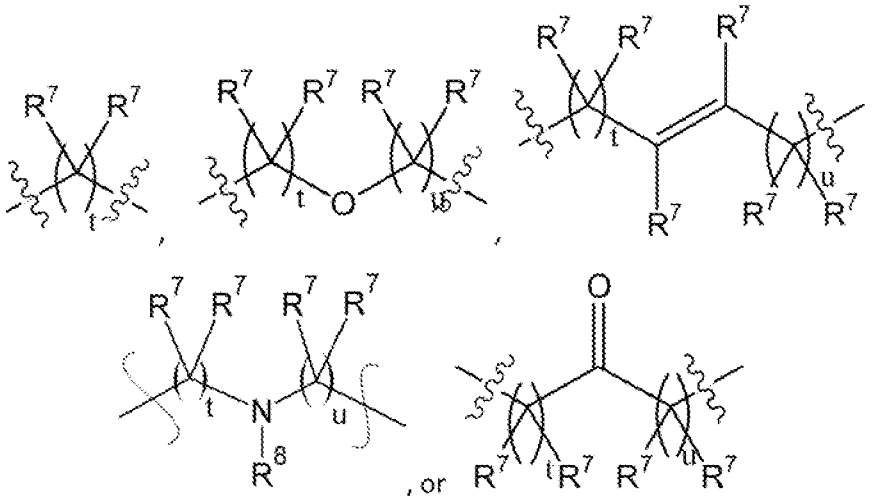
an $-NH_2$ group,

a substituted or unsubstituted C_1-C_6 amino group, and

a substituted or unsubstituted C_1-C_6 alkoxy group;

wherein, when a pair of R^{5A} groups attached to different atoms together forms a ring with ring A atoms and/or a pair of R^{5B} groups attached to different atoms together forms a ring with ring B atoms and/or a pair R^{5C} groups attached to different atoms together forms a ring with ring C atoms, each of the pair of R^{5A}, R^{5B} or R^{5C} groups independently comprises -CH_2- or -CH_2CH_2-, or the pair of groups together comprise -CH=CH-CH=CH- or -NH-CO-NH-.

47. The PARP1 inhibitor compound for use according to any preceding claim, wherein at least one of Qa, Qb, and Qc is:

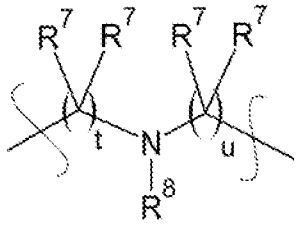


wherein t + u is at least 1; and

wherein R^7 is selected from H, a halogen (such as –F, -Cl, -Br, and –I, preferably -F), a substituted or unsubstituted C_1-C_6 alkyl group, a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group (preferably CF_3), an -NH_2 group or a substituted or unsubstituted C_1-C_6 amino group, an -OH group or a substituted or unsubstituted linear or branched C_1-C_6 alcohol group and a substituted or unsubstituted C_1-C_6 alkoxy group.

48. The PARP1 inhibitor compound for use according to claim 44, wherein R^7 is selected from: H; a halogen, optionally F; a substituted or unsubstituted C_1-C_6 alkyl group; or a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group.

49. The PARP1 inhibitor compound for use according to any preceding claim, wherein at least one of Qa, Qb and Qc has a structure of:



and wherein R^8 is selected from:

H;

a substituted or unsubstituted linear or branched C_1-C_6 alkyl group

(such as Me, Et, Pr, i-Pr, n-Bu, i-Bu, t-Bu, pentyl and hexyl);

a substituted or unsubstituted linear or branched C_1-C_6 alkyl-aryl group

(such as -CH_2Ph, -CH_2(2,3 or 4)F-Ph, -CH_2(2,3 or 4)Cl-Ph, -CH_2(2,3 or 4)Br-Ph, -CH_2(2,3 or 4)I-Ph, -CH_2CH_2Ph, -$CH_2CH_2CH_2$Ph, -$CH_2CH_2CH_2CH_2$Ph, -$CH_2CH_2CH_2CH_2CH_2$Ph, and -$CH_2CH_2CH_2CH_2CH_2CH_2$Ph);

a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group

(such as -CH_2F, -CF3, -CH_2CH_2F and -CH_2CF_3);

a substituted or unsubstituted cyclic amine or amido group

(such as pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, 2-keto-pyrrolidinyl, 3-keto-pyrrolidinyl, 2-keto-piperidinyl, 3-keto-piperidinyl, and 4-keto-piperidinyl);

a substituted or unsubstituted cyclic C_3-C_8 alkyl group

(such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl);

a substituted or unsubstituted linear or branched C_2-C_6 alcohol group

(such as -CH_2CH_2OH, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2OH$, -$CH_2CH_2CH_2OH$, -$CH_2CH_2CH_2CH_2OH$, -$CH(CH_3)CH_2CH_2OH$, -$CH(CH_3)CH(CH_3)OH$, -$CH(CH_2CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2CH_2CH_2CH_2CH_2OH$, and -$CH_2CH_2CH_2CH_2CH_2CH_2OH$);

a substituted or unsubstituted linear or branched C_2-C_6 carboxylic acid group

(such as -CH_2COOH, -CH_2CH_2COOH, -$CH_2CH_2CH_2COOH$, -$CH_2CH_2CH_2CH_2COOH$, and -$CH_2CH_2CH_2CH_2CH_2COOH$);

a substituted or unsubstituted linear or branched carbonyl group (such as -(CO)Me, -(CO)Et, -(CO)Pr, -(CO)-i_Pr, -(CO)-n-Bu, -(CO)-i-Bu, -(CO)-t-Bu, -(CO)Ph, -(CO)CH_2Ph, -(CO)CH_2OH, -(CO)CH_2OCH_3, -(CO)CH_2NH_2,-(CO)CH_2NHMe, -(CO)CH_2NMe_2, -(CO)-cyclopropyl, -(CO)-1,3-epoxypropan-2-yl; -(CO)NH_2, -(CO)NHMe , -(CO)NMe_2, -(CO)NHEt, -(CO)NEt_2, -(CO)-pyrollidine-N-yl, -(CO)-morpholine-N-yl, -(CO)-piperazine-N-yl, -(CO)-N-methyl-piperazine-N-yl, -(CO)NHCH$_2$CH$_2$OH, -(CO)NHCH$_2$CH$_2$OMe, -(CO)NHCH$_2$CH$_2$NH$_2$, -(CO)NHCH$_2$CH$_2$NHMe, and -(CO)NHCH$_2$CH$_2$NMe$_2$);

a substituted or unsubstituted linear or branched C_1-C_6 carboxylic acid ester group (such as -COOMe, -COOEt, -COOPr, -COO-i-Pr, -COO-n-Bu, -COO-i-Bu, -COO-t-Bu, -CH$_2$COOMe, -CH$_2$CH$_2$COOMe, -CH$_2$CH$_2$CH$_2$COOMe, and -CH$_2$CH$_2$CH$_2$CH$_2$COOMe);

a substituted or unsubstituted linear or branched C_1-C_6 amide group (such as -CO-NH_2, -CO-NMeH, -CO-NMe_2, -CO-NEtH, -CO-NEtMe, -CO-NEt_2, -CO-NPrH, -CO-NPrMe, and -CO-NPrEt);

a substituted or unsubstituted sulfonyl group (such as -SO_2Me, -SO_2Et, -SO_2Pr, -SO_2iPr, -SO_2Ph, -SO_2-(2,3 or 4)-F-Ph, -SO_2-cyclopropyl, -$SO_2CH_2CH_2OCH_3$), -SO_2NH_2, -SO_2NHMe, -SO_2NMe_2, -SO_2NHEt, -SO_2NEt_2, -SO_2-pyrrolidine-N-yl, -SO_2-morpholine-N-yl, -SO_2NHCH$_2$OMe, and -SO_2NHCH$_2$CH$_2$OMe);

a substituted or unsubstituted aromatic group (such as Ph-, 2-F-Ph-, 3-F-Ph-, 4-F-Ph-, 2-Cl-Ph-, 3-Cl-Ph-, 4-Cl-Ph-, 2-Br-Ph-, 3-Br-Ph-, 4-Br-Ph-, 2-I-Ph-, 3-I-Ph, 4-I-Ph-, 2,(3,4,5 or 6)-F_2-Ph-, 2,(3,4,5 or 6)-Cl_2-Ph-, 2,(3,4,5 or 6)-Br_2-Ph-, 2,(3,4,5 or 6)-I_2-Ph-, 2,(3,4,5 or 6)-Me_2-Ph-, 2,(3,4,5 or 6)-Et_2-Ph-, 2,(3,4,5 or 6)-Pr_2-Ph-, 2,(3,4,5 or 6)-Bu_2-Ph-, 2,(3,4,5 or 6)-$(CN)_2$-Ph-, 2,(3,4,5 or 6)-$(NO_2)_2$-Ph-, 2,(3,4,5 or 6)-$(NH_2)_2$-Ph-, 2,(3,4,5 or 6)-$(MeO)_2$-Ph-, 2,(3,4,5 or 6)-$(CF_3)_2$-Ph-, 3,(4 or 5)-F_2-Ph-, 3,(4 or 5)-Cl_2-Ph-, 3,(4 or 5)-Br_2-Ph-, 3,(4 or 5)-I_2-Ph-, 3,(4 or 5)-Me_2-Ph-, 3,(4 or 5)-Et_2-Ph-, 3,(4 or 5)-Pr_2-Ph-, 3,(4 or 5)-Bu_2-Ph-, 3,(4 or 5)-$(CN)_2$-Ph-, 3,(4 or 5)-$(NO_2)_2$-Ph-, 3,(4 or 5)-$(NH_2)_2$-Ph-, 3,(4 or 5)-$(MeO)_2$-Ph-, 3,(4 or 5)-$(CF_3)_2$-Ph-, 2-Me-Ph-, 3-Me-Ph-, 4-Me-Ph-, 2-Et-Ph-, 3-Et-Ph-, 4-Et-Ph-, 2-Pr-Ph-, 3-Pr-Ph-, 4-Pr-Ph-, 2-Bu-Ph-, 3-Bu-Ph-,

4-Bu-Ph-, 2-(CN)-Ph-, 3-(CN)-Ph-, 4-(CN)-Ph-, 2-(NO_2)-Ph-, 3-(NO_2)-Ph-, 4-(NO_2)-Ph-, 2-(NH_2)-Ph-, 3-(NH_2)-Ph-, 4-(NH_2)-Ph-, 2-MeO-Ph-, 3-MeO-Ph-, 4-MeO-Ph-, 2-(NH_2-CO)-Ph-, 3-(NH_2-CO)-Ph-, 4-(NH_2-CO)-Ph-, 2-CF_3-Ph-, 3-CF_3-Ph-, 4-CF_3-Ph-, 2-CF_3O-Ph-, 3-CF_3O-Ph-, and 4-CF_3O-Ph-); and

a substituted or unsubstituted heterocyclic group

(such as pyrrole-2-yl, pyrrole-3-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazole-5-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazine-3-yl, pyridazine-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-6-yl, pyrazine-2-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, 2-azapiperidine-3-yl, 2-azapiperidine-4-yl, 3-azapiperidine-2-yl, 3-azapiperidine-4-yl, 3-azapiperidine-5-yl, piperazine-2-yl, furan-2-yl, furan-3-yl, pyran-2-yl, pyran-3-yl, pyran-4-yl, 2-azapyran-3-yl, 2-azapyran-4-yl, 2-azapyran-5-yl, 2-azapyran-6-yl, 3-azapyran-2-yl, 3-azapyran-4-yl, 3-azapyran-5-yl, 3-azapyran-6-yl, 4-azapyran-2-yl, 4-azapyran-3-yl, 4-azapyran-5-yl, 4-azapyran-6-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-4-yl, 2-aza-tetrahydrofuran-5-yl, 3-aza-tetrahydrofuran-2-yl, 3-aza-tetrahydrofuran-4-yl, 3-aza-tetrahydrofuran-5-yl, tetrahydropyran-2-yl, oxetan-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, 2-aza-tetrahydropyran-3-yl, 2-aza-tetrahydropyran-4-yl, 2-aza-tetrahydropyran-5-yl, 2-aza-tetrahydropyran-6-yl, 3-aza-tetrahydropyran-2-yl, 3-aza-tetrahydropyran-4-yl, 3-aza-tetrahydropyran-5-yl, 3-aza-tetrahydropyran-6-yl, morpholine-2-yl, morpholine-3-yl, thiophen-2-yl, thiophen-3-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl, thiopyran-2-yl, thiopyran-3-yl, thiopyran-4-yl, 2-azathiopyran-3-yl, 2-azathiopyran-4-yl, 2-azathiopyran-5-yl, 2-azathiopyran-6-yl, 3-azathiopyran-2-yl, 3-azathiopyran-4-yl, 3-azathiopyran-5-yl, 3-azathiopyran-6-yl, 4-azathiopyran-2-yl, 4-azathiopyran-3-yl, 4-azathiopyran-5-yl, 4-azathiopyran-6-yl, thiolane-2-yl, thiolane-3-yl,

thiane-2-yl, thiane-3-yl, thiane-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, furazan-3-yl, (1,3,4-oxadiazol)-2-yl, (1,3,4-oxadiazol)-5-yl, (1,2,4-oxadiazol)-3-yl, (1,2,4-oxadiazol)-5-yl; and tetrazole-5-yl).

50. The PARP1 inhibitor compound for use according to claim 49, wherein R^8 is selected from H, a substituted or unsubstituted linear or branched C_1-C_6 alkyl group, and a substituted or unsubstituted linear or branched C_1-C_6 halogenated alkyl group.

51. The PARP1 inhibitor compound for use according to any preceding claim, which compound comprises:

an isolated enantiomer, or

a mixture of two or more enantiomers, or

a mixture of two or more diastereomers, and/or epimers, or

a racemic mixture, or

a tautomer of the compound.

52. The PARP1 inhibitor compound for use according to any preceding claim, which is selective for PARP1 over PARP2.

53. The PARP1 inhibitor compound for use according to any preceding claim, which is for use in treating a cancer.

54. The PARP1 inhibitor compound for use according to claim 53, wherein the cancer is selected from: a cancer of the eye, brain (such as gliomas, glioblastomas, medulloblastomas, craniopharyngioma, ependymoma, and astrocytoma), spinal cord, kidney, mouth, lip, throat, oral cavity, nasal cavity, small intestine, colon, parathyroid gland, gall bladder, head and neck, breast, bone, bile duct, cervix, heart, hypopharyngeal gland, lung, bronchus, liver, skin, ureter, urethra, testicles, vagina, anus, laryngeal gland, ovary, thyroid, oesophagus, nasopharyngeal gland, pituitary gland, salivary gland, prostate, pancreas, adrenal glands; an endometrial cancer, oral cancer, melanoma, neuroblastoma, gastric cancer, an angiomatosis, a hemangioblastoma, a pheochromocytoma, a pancreatic cyst, a renal cell carcinoma, Wilms'

tumour, squamous cell carcinoma, sarcoma, osteosarcoma, Kaposi sarcoma, rhabdomyosarcoma, hepatocellular carcinoma, PTEN Hamartoma-Tumor Syndromes (PHTS) (such as Lhermitte-Duclos disease, Cowden syndrome, Proteus syndrome, and Proteus-like syndrome), leukaemias and lymphomas (such as acute lymphoblastic leukaemia, chronic lymphocytic leukaemia, acute myelogenous leukaemia, chronic myelogenous leukaemia, hairy cell leukaemia, T-cell prolymphocytic leukaemia (T-PLL), large granular lymphocytic leukaemia, adult T-cell leukaemia, juvenile myelomonocytic leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, mantle lymphoma, follicular lymphoma, primary effusion lymphoma, AIDS-related lymphoma, diffuse B cell lymphoma, Burkitt lymphoma, cutaneous T-cell lymphoma, nasopharyngeal and gastrointestinal cancers;

optionally wherein the cancer is a cancer of the brain or spinal cord.

55. The PARP1 inhibitor compound for use according to claim 53 or claim 54, wherein the cancer is deficient in a DNA damage response repair pathway, such as Homologous Recombination dependent DNA Double Strand Break DNA repair activity.

56. The PARP1 inhibitor compound for use according to any of claims 53 to 55, wherein the cancer is deficient in BRCA1 and/or BRCA2 function.

57. The PARP1 inhibitor compound for use according to any of claims 53 to 56, which is to be administered in conjunction with a further agent for treating cancer; optionally wherein the further agent for treating cancer is selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase I inhibitors, topoisomerase II inhibitors, antimetabolites, senolytic agents, hormones and hormone analogues, signal transduction pathway inhibitors, other DNA damage repair pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, antibody-drug conjugates, immunotherapeutic agents, hormone deprivation therapy, proapoptotic agents, radioligand therapies, cell cycle signalling inhibitors, and anti-angiogenic agents.

58. The PARP1 inhibitor compound for use according to claim 57, wherein the further agent is an immunotherapeutic agent selected from: an anti-tumour vaccine; an oncolytic virus; an immune stimulatory antibody such as anti-CTLA4, anti-PD1, anti-PDL-1, anti-OX40, anti-41BB,

anti-CD27, anti-CD40, anti-LAG3, anti-TIM3, and anti-GITR; a pattern recognition receptor agonist such as a STING, TLR-9 or RIG-I Helicase agonist; an IDO or TDO inhibitor; a novel adjuvant; a peptide; a cytokine; a chimeric antigen receptor T cell therapy (CAR-T); a small molecule immune modulator; and a tumour microenvironment modulator.

59. A pharmaceutical composition comprising a PARP1 inhibitor compound as defined in any of claims 1 to 52.

60. A pharmaceutical composition according to claim 59, further comprising a pharmaceutically acceptable additive and/or excipient, and/or wherein the compound is in the form of a pharmaceutically acceptable salt, hydrate, acid, ester, or other alternative form of the compound.

61. The pharmaceutical composition according to claim 59 or claim 60, further comprising a further agent for treating cancer; optionally wherein the further agent for treating cancer is selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase I inhibitors, topoisomerase II inhibitors, antimetabolites, senolytic agents, hormones and hormone analogues, signal transduction pathway inhibitors, other DNA damage repair pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, antibody-drug conjugates, immunotherapeutic agents, hormone deprivation therapy, proapoptotic agents, radioligand therapies, anti-angiogenic agents, and cell cycle signalling inhibitors.

62. The pharmaceutical composition according to claim 61, wherein the further agent comprises an immunotherapeutic agent selected from: an anti-tumour vaccine; an oncolytic virus; an immune stimulatory antibody such as anti-CTLA4, anti-PD1, anti-PDL-1, anti-OX40, anti-41BB, anti-CD27, anti-CD40, anti-LAG3, anti-TIM3, and anti-GITR; a pattern recognition receptor agonist such as a STING, TLR-9 or RIG-I Helicase agonist; an IDO or TDO inhibitor; a novel adjuvant; a peptide; a cytokine; a chimeric antigen receptor T cell therapy (CAR-T); a small molecule immune modulator; and a tumour microenvironment modulator.

63. The pharmaceutical composition according to any of claims 59 to 62, for use in treating a cancer.

64. A pharmaceutical kit for treating a cancer, which pharmaceutical kit comprises:

a) a PARP1 inhibitor compound as defined in any of claims 1 to 51; and

b) a further agent for treating cancer;

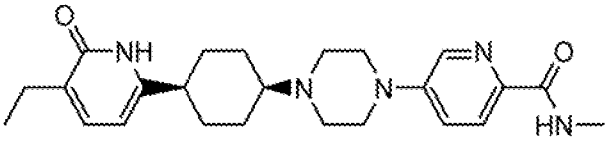
wherein the compound and the further agent are suitable for administration simultaneously, sequentially or separately; and

optionally wherein the further agent for treating cancer is selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase I inhibitors, topoisomerase II inhibitors, antimetabolites, senolytic agents, hormones and hormone analogues, signal transduction pathway inhibitors, other DNA damage repair pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, antibody-drug conjugates, hormone-deprivation therapy, immunotherapeutic agents (such as selected from an anti-tumour vaccine; an oncolytic virus; an immune stimulatory antibody such as anti-CTLA4, anti-PD1, anti-PDL-1, anti-OX40, anti-41BB, anti-CD27, anti-CD40, anti-LAG3, anti-TIM3, and anti-GITR; a pattern recognition receptor agonist such as a STING, TLR-9 or RIG-I Helicase agonist; an IDO or TDO inhibitor; a novel adjuvant; a peptide; a cytokine; a chimeric antigen receptor T cell therapy (CAR-T); a small molecule immune modulator; a tumour microenvironment modulator), proapoptotic agents, radioligand therapies, anti-angiogenic agents, and cell cycle signalling inhibitors.

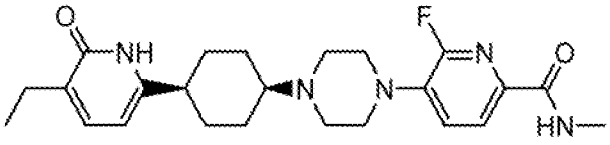
65. A method of treating a disease and/or a condition and/or a disorder, which method comprises administering to a patient a PARP1 inhibitor compound, a composition or a kit as defined in any preceding claim.

66. The method according to claim 65, wherein the patient is an animal, preferably a mammal, optionally a human, canine, equine or feline; and preferably a human.

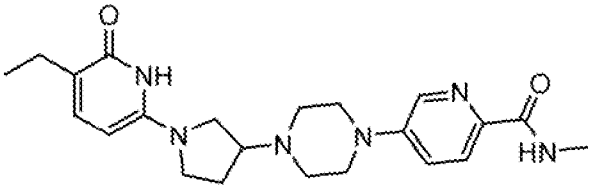
67. A compound selected from:



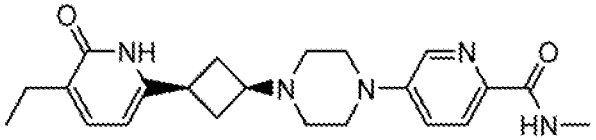
1*cis*



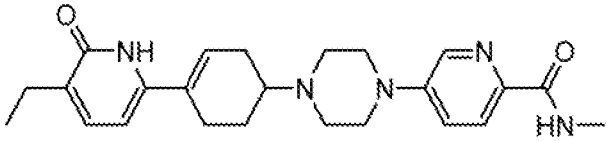
2*cis*



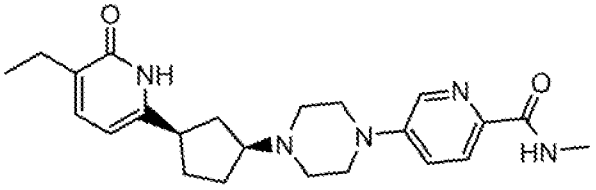
3



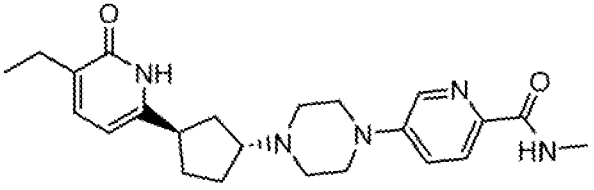
4*cis*



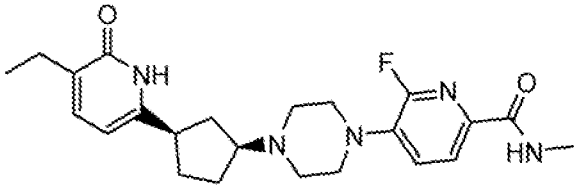
5



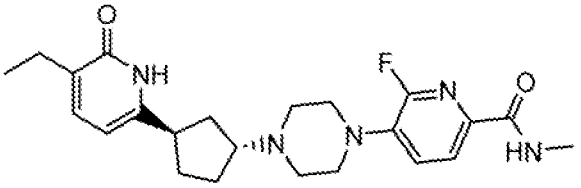
6*cis*



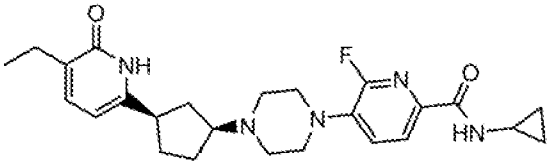
6*trans*



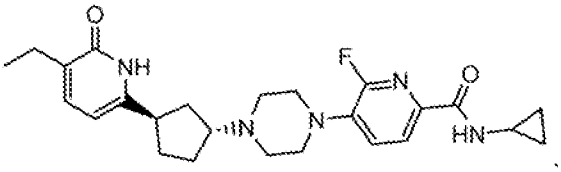
7*cis*



7*trans*



8*cis*



8*trans*

68. The compound according to claim 67, which compound comprises:

an isolated enantiomer, or

a mixture of two or more enantiomers, or

a mixture of two or more diastereomers, and/or epimers, or

a racemic mixture, or

a tautomer of the compound.

69. A method of synthesising a PARP1 inhibitor compound as defined in any of claims 1 to 52, which method comprises conducting a reaction between:

i) a first reactant comprising ring E bearing a first portion of group L and

ii) a second reactant comprising a remainder of group L,

to form the PARP1 inhibitor compound.

70. A method according to claim 69, wherein the first reactant comprises ring E and ring A, and the second reactant comprises a Qb precursor bearing a reactive group, which method comprises joining ring A to the Qb precursor.

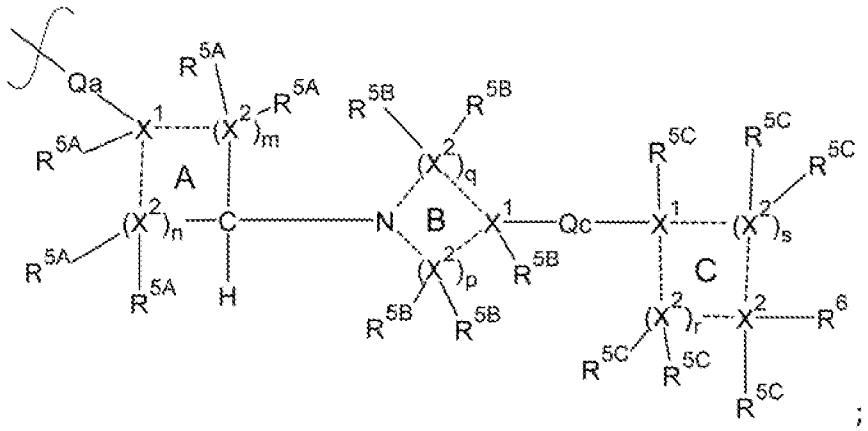
71. A method according to claim 70, wherein the reactive group of the Qb precursor comprises a carbonyl group, an alkyl halide, or an alkyl sulfonate.

72. A method according to any of claims 69 to 71, wherein the reaction comprises alkylation, reductive amination or amide formation so as to form group L.

73. A method according to claim 72, wherein the first reactant comprises ring E, ring A, Qa, and ring B, and the second reactant comprises a ring C derivative bearing a leaving group such as a halide or sulfonate.

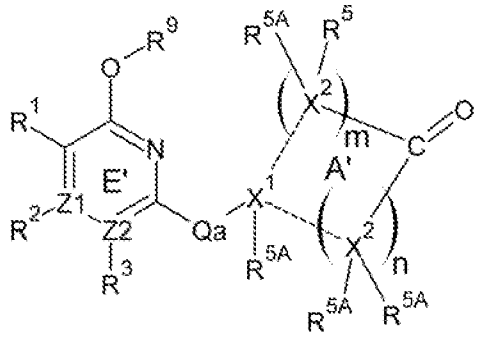
74. A method according to claim 70 or claim 71, wherein the reaction comprises a nucleophilic substitution reaction, such as a nucleophilic aromatic substitution reaction, so as to form group L.

75. The method according to any of claims 69 to 71, which method is to synthesise a PARP1 inhibitor compound wherein L is a group having a structure of:



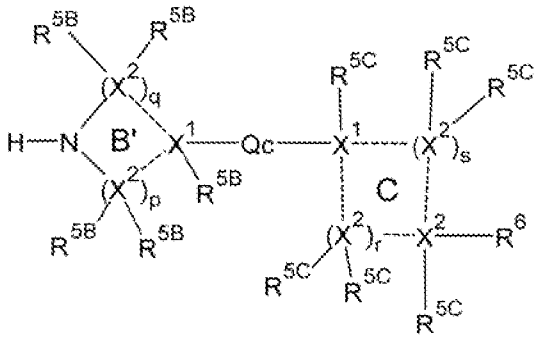
;

wherein the first reactant has a structure of:



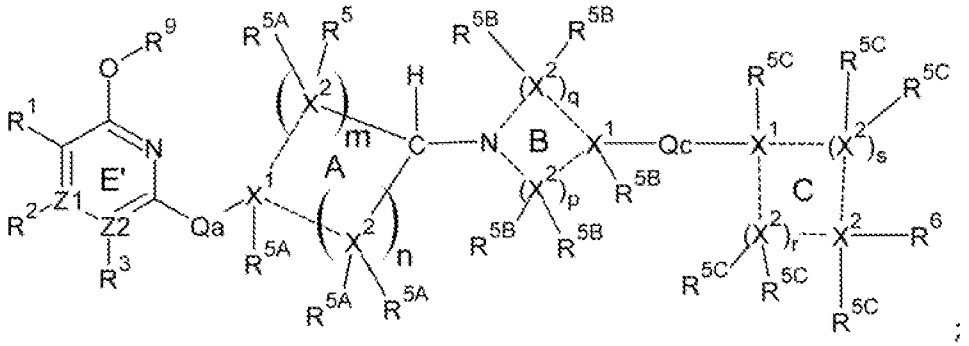
R^9 being a protecting group, optionally a C1 to C6 alkyl group, and preferably a methyl group;

wherein the second reactant has a structure of:



wherein conducting the reaction comprises:

i) coupling the first reagent and the second reagent using a reducing agent in the presence of an acid to obtain an intermediate product having a structure of:



;

and

ii) subsequently deprotecting ring E' to form the PARP1 inhibitor compound.

76. The method according to claim 75, wherein rings A, B', and B are all saturated rings.

77. The method according to claim 76, wherein the X1 of rings B and B' is N.

78. The method according to any of claims 75 to 77, further comprising separating structural isomers of the PARP1 inhibitor compound using chiral supercritical fluid chromatography and/or chiral high-performance liquid chromatography.

Intellectual Property Office

Application No:	GB2308970.9	**Examiner:**	Dr S. David Evans
Claims searched:	1-78	**Date of search:**	8 December 2023

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X,E	1, 53-66, 69-78 at least	WO 2023/156386 A2 (DUKE STREET BIO LTD) See Chem. Abs. Acc. No. 2023:1741809 and the whole document.
X	1, 53-66 at least	WO 2023/019259 A1 (DECIPHERA PHARMACEUTICALS LLC) See Chem. Abs. Acc. No. 2023:317177 and the entire document, but particularly the Markush structure of Formula I in claim 1.
X	1, 53-66 at least	WO 2023/004280 A1 (UNIV LELAND STANFORD JUNIOR) See Chem. Abs. Acc. No. 2023:178514 and the whole document, but especially the generic structures in claim 1.
X	1, 53-66 at least	EP 4105207 A1 (BETTA PHARMACEUTICALS CO LTD) See Chem. Abs. Acc. No. 2021:1804230 and the entire document, but particularly the Markush structure of Formula I in claim 1.
X	1, 53-66 at least	WO 2019/084026 A1 (GENENTECH INC) See Chem. Abs. Acc. No. 2019:867547 and the whole document, but especially the generic structure of formula (I) in claim 1.
X	1, 53-66 at least	WO 2005/040159 A1 (ASTRAZENECA) See Chem. Abs. Acc. No. 2005:395305 and the entire document, but particularly the Markush structure of formula (I) in claim 1.
X	1, 53-66 at least	US 2005/080111 A1 (BAYNE et al) See Chem. Abs. Acc. No. 2005:325708 and the entire document, but especially the generic structure of formula (I) in claim 1.

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Intellectual Property Office

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC[X] :

Worldwide search of patent documents classified in the following areas of the IPC

The following online and other databases have been used in the preparation of this search report

CAS ONLINE

International Classification:

Subclass	Subgroup	Valid From
C07D	0401/12	01/01/2006
A61K	0031/444	01/01/2006
A61P	0035/00	01/01/2006
C07D	0403/14	01/01/2006