

(19) **DANMARK**

(10) **DK/EP 2938598 T3**



(12) **Oversættelse af  
europæisk patentskrift**

Patent- og  
Varemærkestyrelsen

- 
- (51) Int.Cl.: *C 07 D 237/32 (2006.01)*      *A 61 K 31/502 (2006.01)*      *A 61 P 35/00 (2006.01)*  
*C 07 D 487/04 (2006.01)*      *C 07 D 491/048 (2006.01)*      *C 07 D 495/04 (2006.01)*  
*C 07 D 498/04 (2006.01)*      *C 07 D 513/04 (2006.01)*
- (45) Oversættelsen bekendtgjort den: **2017-02-13**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-12-21**
- (86) Europæisk ansøgning nr.: **13828996.2**
- (86) Europæisk indleveringsdag: **2013-12-23**
- (87) Den europæiske ansøgnings publiceringsdag: **2015-11-04**
- (86) International ansøgning nr.: **IN2013000794**
- (87) Internationalt publikationsnr.: **WO2014102817**
- (30) Prioritet: **2012-12-31 IN MM37422012**
- (84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**
- (73) Patenthaver: **Cadila Healthcare Limited, Zydus Tower , Satellite Cross Roads, Ahmedabad 380 015, Gujarat, Indien**
- (72) Opfinder: **SRIVASTAVA, Brijesh, K., Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380015, Gujarat, Indien**  
**DESAI, Ranjit, C., Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, Indien**  
**PATEL, Pankaj, R, Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380015, Gujarat, Indien**
- (74) Fuldmægtig i Danmark: **Zacco Denmark A/S, Arne Jacobsens Allé 15, 2300 København S, Danmark**
- (54) Benævnelse: **Substitueret phthalazin-1(2H)-on-derivater som selektive hæmmere af poly-(adp-ribose-)polymerase-1**
- (56) Fremdragne publikationer:  
**WO-A1-2008/083027**  
**WO-A1-2009/004356**  
**WO-A1-2009/063244**  
**WO-A1-2009/093032**  
**WO-A1-2012/019426**  
**WO-A1-2012/019427**  
**WO-A1-2012/071684**  
**WO-A2-2007/138351**  
**US-A1- 2005 059 663**  
**US-A1- 2008 269 234**

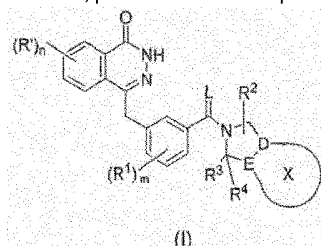
Fortsættes ...



## DESCRIPTION

### FIELD OF THE INVENTION

[0001] The present invention relates to novel compounds of general formula (I), and pharmaceutical compositions containing them. The present disclosure also relates to processes for preparing the novel compounds of general formula (I), their stereoisomers, regioisomers, their tautomeric forms, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutical compositions containing them, and novel intermediates involved in their synthesis.



[0002] The present invention is further directed to compounds which cause selective inhibition of the poly (ADP-ribose) polymerase-1.

### BACKGROUND & PRIOR ART

[0003] Exploitation of synthetic lethal relationship is a trustworthy therapeutic strategy to target genetic differences between tumor and normal cells which eventually provide large therapeutic window for the treatment of cancer. Poly (ADP-ribose) polymerase-1 (PARP-1, 113 kDa) is a prototype member of the 17 member PARP protein superfamily. PARP-1 is a nuclear protein whose zinc finger DNA binding domain localizes PARP-1 to the site of DNA damage. This NAD dependent enzyme catalyzes poly (ADP-ribosylation) of proteins, involved in the detection and repair of DNA damage. It plays a frontal role in the decision of a cell to live or to die in a stress situation [Senthil kumar B., Rajmohan, et al., Mol. Cell. Biol. 2009, 29(15), 4116-4129]. The primary structure of the enzyme is highly conserved in eukaryotes with human enzyme having 92% homology with mouse enzyme at the level of amino acid sequence and a 50 amino acid block showing 100% homology between vertebrates [Virag Laszlo and Szabo Csaba, Pharmacol. Reviews 2002, 54(3), 375-429]. Studies on the molecular mechanism of PARP-1 suggests that, it is involved in various DNA related functions including gene amplifications, cell division, differentiation, apoptosis, DNA base excision repair and also effects on telomere length and chromosome stability [d'Adda di Fagogna et al., Nature Gen. 1999, 23(10), 76-80].

[0004] It has been reported that PARP-1 modulates DNA repair and other processes and can produce long chains of poly (ADP-ribose) within the cell nucleus which is central to its activity [Althaus, F. R.; Richter, C. Mol. Biol., Biochem. Biophys. 1987, 37, 1-237]. Different studies on knock out mouse models, report that the deletion of PARP-1 impairs DNA repair but is not embryonically lethal. Double knock out PARP-1 and PARP-2 mice die during early embryogenesis, which shows that PARP-2 as the closest homolog of PARP-1 (62% identical in its catalytic domain to PARP-1) & plays a major role in the DNA repair during the absence of PARP-1 enzyme [Ratnam Kapil and Law Jenifer A. Clin. Cancer Res. 2007, 17(5), 1383-1388]. A group of scientists from Newcastle University and University of Konstanz, in British Journal of Cancer 2009, 101(2), 256 - 26, claims to be the first to directly compare PARP-1 polymorphisms, cellular levels of PARP-1 protein and PARP activity in a systematic way and reveals that PARP activity depends on other factors beside the level of protein and the active site SNP.

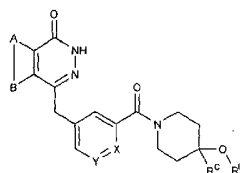
[0005] In a recent review from Free Radical Biology & Medicine 2009, 47, 13-26 suggests that PARP inhibitors could be used not only as chemo/radiotherapy sensitizers, but also as single agents to selectively kill cancers which are due to defect in DNA repair, specifically cancers with mutations in the breast cancer-associated gene (BRCA1 and BRCA2). PARP becomes activated in response to oxidative DNA damage and depletes cellular energy pools, thus leading to cellular dysfunction in various tissues. The activation of PARP may also induce various cell death processes and promotes an inflammatory response associated with multiple organ failure.

[0006] Recently some of the investigators have demonstrated in Biochem. Pharmacol. 2009, 77, 1348-1357 that PARP inhibitors combined with DNA-damage inducing cytostatic agents like taxol can lead to effective tumor therapy through activation of PI-3-kinase-Akt pathway.

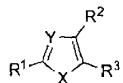
[0007] The American Society of Clinical Oncology held its Annual Meeting in Orlando, Florida (May 29-June 2, 2009) and as reported in Eur. J. Cancer 2009, 45, 1897 - 1901 that two drugs Olaparib and BSI-201 from a new class of targeted agents called poly (ADP-ribose) polymerase (PARP) inhibitors have demonstrated significant activity against hard-to treat breast cancers, according to findings from two separate phase II trials.

[0008] Several small molecules that specifically target PARP-1 enzyme as an inhibitor are being investigated and among them BSI 201 (BiPar) is in Phase III clinical trial and AG 14699 (Cancer Res. UK), AZD 2281 (KuDOS), ABT 888 (Abbott) are in Phase II clinical trial, with promising initial results. However, special attention must be paid to the possibility that enhanced therapeutic efficacy might be accompanied by increased off-target effects because of effect on DNA-repair mechanism in normal tissues. Recent findings have thrust poly(ADP-ribose) polymerases (PARPs) into the limelight as potential chemotherapeutic targets as described in Nature Reviews Cancer 4 March 2010, 1-9. Crystal Structure of the Catalytic Domain of Human PARP2 in Complex with PARP Inhibitor ABT-888 reported by [Herwig Schuler et al., Pharmacol. Biochemistry 2010, 49, 1056-1058]

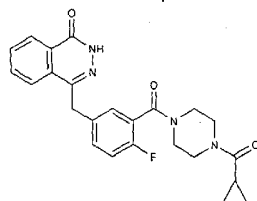
[0009] Novel compounds which are selective PARP-1 inhibitors, their preparation and their use in medicine have also been reported in WO 2002036576, WO 2006039545, WO 2007062413, WO 2004080976, WO 2009093032, WO 2008047082, WO 2001042219, WO 2005066163, WO 2006106326, WO 2008146035, WO 2006021801, US 20090192156, WO 2012019427, WO 2012071684, WO 2012019426, WO 2012072033, which are incorporated as references in their entirety. Synthesis of pthalazinone derivatives of the following general formula and having the potential to inhibit PARP for the treatment of cancer or for potentiating tumor cells for the treatment with ionizing radiation or chemotherapeutic agents has been disclosed in US 2009/0192156 A1 and WO 2009/093032 A1.



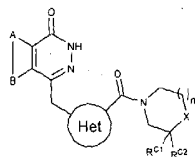
[0010] Synthesis of thiophene carboxamide class of compounds as the combination of CHK and PARP inhibitors for the treatment of cancer is disclosed in WO 2008146035 A1 and WO 2005066163 A2. Representative compounds have the following general formula,



[0011] Wherein X is selected from NH, S and O. Y is selected from CH or N. Crystalline form and improved method for the synthesis of particular pthalazinone derivatives and use of the crystalline form as PARP-1 inhibitor has been reported in WO 2008047082. Representative compounds have the following structure:

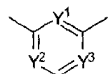


[0012] Synthesis of 4-heteroaryl/methyl substituted pthalazinone derivatives has been disclosed in WO 2006021801 A1 and WO 2004080976 A1 for use in treating cancer or other diseases ameliorated by the inhibition of PARP.

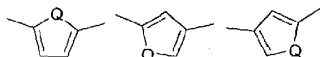


wherein, A and B together represent an optionally substituted, fused aromatic ring; X can be NR<sup>X</sup> or CR<sup>X</sup>R<sup>Y</sup>; if X= NR<sup>X</sup> then n is 1 or 2 and if X= CR<sup>X</sup>R<sup>Y</sup> then n is 1; R<sup>X</sup> is selected from the group consisting of H, optionally substituted C<sub>1-20</sub> alkyl, C<sub>1-20</sub> aryl, C<sub>3-</sub>

20) heterocyclyl, thioamido, ester, acyl, and sulfonyl groups;  $R^Y$  is selected from H, hydroxyl, amino;  $R^X$  and  $R^Y$  may together form a spiro  $C_{3-7}$  cycloalkyl or heterocyclyl group;  $R^{C1}$  and  $R^{C2}$  are independently selected from the group consisting of H and  $C_{1-4}$  alkyl;  $R^1$  is selected from H and halo; And Het is selected from



where  $Y^1$  is selected from CH and N,  $Y^2$  is selected from CH and N,  $Y^3$  is selected from CH, CF and N, where one or two of  $Y^1$ ,  $Y^2$ , and  $Y^3$  can be N; and



wherein Q is O or S.

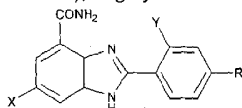
**[0013]** Optimization of Phenyl-Substituted Benzimidazole Carboxamide Poly(ADP-Ribose) 5-Benzamidoisoquinolin-1-ones and 5-( $\omega$ -Carboxyalkyl)isoquinolin-1-ones as Isoform-Selective Inhibitors of Poly(ADP-ribose) Polymerase 2 (PARP-2) has been described in J. Med. Chem. 2011, 54, 2049-2059 by Peter T. Sunderland et. al. Tumor Growth Inhibition by Olaparib in BRCA2 Germline-Mutated Patient-Derived Ovarian Cancer Tissue Xenografts has been recently published in Clin Cancer Res 2011, 17, 783-791.

**[0014]** Simultaneous determination of ABT-888, a poly (ADP-ribose) polymerase inhibitor, and its metabolite in human plasma by liquid chromatography/tandem mass spectrometry has been described in Journal of Chromatography B, 2011, 878, 333-339.

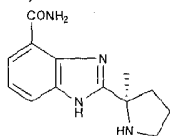
**[0015]** "Evolution of Poly(ADP-ribose)Polymerase-1(PARP-1) inhibitors, From Concept to Clinic" a review article by Dana V. Ferraris has been published in J. Med. Chem. 2010, 53, 4561-4584, which describes in details of the efforts by different pharmaceutical industries and academic institutions in the development of the PARP 1 inhibitors.

**[0016]** "Development of substituted 6-[4-fluoro-3-(piperazin-1-ylcarbonyl)benzyl]-4,5-dimethylpyridazin-3-(2H)-ones as potent poly(ADP-ribose)polymerase -1(PARP-1) inhibitors active in BRCA deficient cells " article has been published by Federica Ferrigno et al. in Bioorg. Med. Chem. Lett. 2010, 20, 1100-1105.

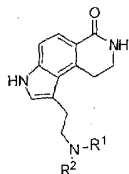
**[0017]** 'Polymerase Inhibitors: Identification of (S)-2-(2-Fluoro-4-(pyrrolidin-2-yl)phenyl)-1H-benzimidazole-4-carboxamide (A-966492), a highly Potent and Efficacious Inhibitor' has been described in J. Med. Chem., 2010, 53, 3142-3153.



**[0018]** Design, synthesis of Quinoline-8-carboxamides, a new class of Poly (adenosine-diphosphate-ribose) polymerase-1 (PARP-1) Inhibitor has been described in J. Med. Chem. 2009, 52, 868-877. Synthesis of 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide as a Poly (ADP-ribose) Polymerase (PARP) Inhibitor has been disclosed in J. Med. Chem. 2009, 52, 514-523.

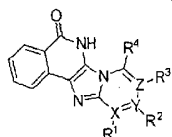


**[0019]** Synthesis of aminoethyl pyrrolo dihydroisoquinolinones as novel poly (ADP-ribose) polymerase-1 inhibitors has been described in Bioorg. Med. Chem. Lett. 2009, 19, 4042-4045. Representative compounds have the following general formula.

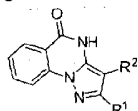


**[0020]** Synthesis of isoquinolinone-based tetracycles as poly (ADP-ribose) polymerase-1 (PARP-1) inhibitors inhibitors has been

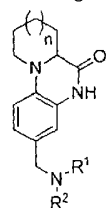
described in Bioorg. Med. Chem. Lett. 2009, 19, 7537-7541. Representative compounds have the following general formula.



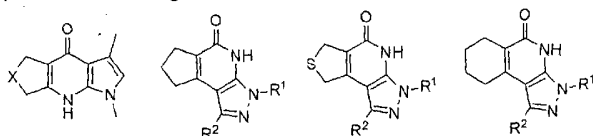
[0021] Identification of substituted pyrazolo[1,5-a]quinazolin-5(4H)-one as potent poly(ADP-ribose)polymerase-1 (PARP-1) inhibitors has been described in Bioorg. Med. Chem. Lett. 2009, 19, 4196-4200. Representative compounds have the following general formula



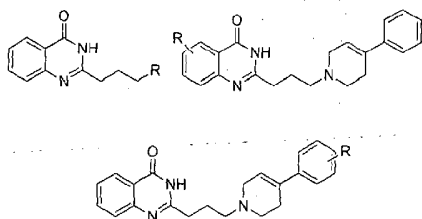
[0022] Synthesis of novel tricyclic quinoxalinone as the inhibitors of poly (ADP-ribose) polymerase-1 (PARP-1) has been stated in Bioorg. Med. Chem. Lett. 2009, 19, 4050-4054. Representative compounds have the following general formula.



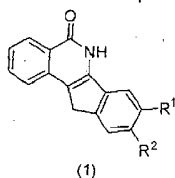
[0023] Identification of ring-fused pyrazolo pyridin-2-ones as novel poly (ADP-ribose) polymerase-1 inhibitors has been published in Bioorg. Med. Chem. Lett. 2008, 18, 5126-5129. This describes compounds of the following general formula.



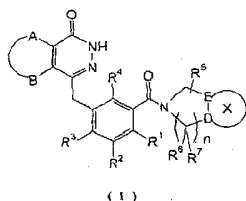
[0024] Discovery of Orally Active and Brain-Penetrable Quinoxalinone Inhibitors of Poly (ADP-ribose) polymerase has been disclosed in J. Med. Chem. 2004, 47, 4151-4154 and describes compounds of the following general formula.



[0025] Discovery of potent Poly(ADP-ribose) Polymerase-1 Inhibitors from the modification of Indeno[1,2-c]isoquinolinone and the described compounds of the following general formula I has been reported in J. Med. Chem. 2005, 48, 5100-5103.

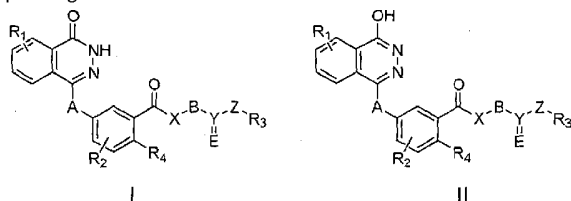


[0026] WO 2012 019426 discloses PARP inhibitors of the following general formula (I)



wherein: A and B are connected together to the carbon atoms to form a cycloalkyl group, heterocyclic group, aryl or heteroaryl group. Each of the ring atoms D or E is independently selected from C or N atoms; when n is 1, D and E are connected to one another to accomplish 6 ~ 10-membered ring X; This specification is incorporated as reference in its entirety.

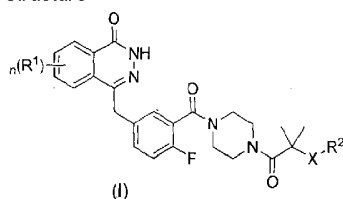
[0027] WO 2012 072033 discloses compounds of formula I or II, their isomers, salts, solvates, chemically protected form, and prodrugs:



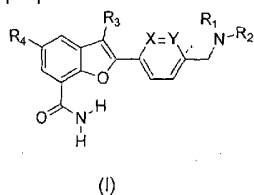
wherein the substituents are as defined in the specification which is incorporated in entirety as reference.

[0028] New Gen Therapeutics, Inc has published a patent WO 2012166983 and disclosed tricyclic inhibitors of poly(ADP-ribose)polymerase.

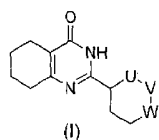
[0029] Substituted 4-(4-fluoro-3-(piperazine-1-carbonyl)benzyl)phthalazin-1(2H)-one derivatives as Poly (ADP-ribose) polymerase-1 inhibitors has been published in WO 2012014221 by Cadila Healthcare Ltd. and discloses the following general structure



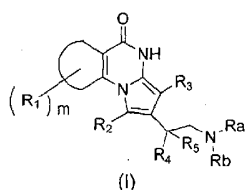
[0030] Shanghai Institute of Materia Medica, Chinese Academy of Science disclosed 2-Arylbenzofuran-7-formamide compounds preparation method and use thereof in patent WO 2013117120 and mentions the following formula:



[0031] Merck disclosed tetrahydro-quinazolinone derivatives as tankyrase and PARP inhibitors in patent WO 2013/117288 and mentions the following general structure



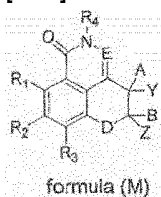
[0032] Novel compounds having PARP inhibitory activity has been disclosed by Santen Pharmaceutical Co. Ltd. in a patent WO 2013/008872 and the following formula has been disclosed.



[0033] Fused tetra or penta- cyclic pyridophthalazinones as PARP inhibitors have been reported by Belgena, Ltd. in a patent WO 2013097226.

[0034] AstraZeneca AB has published a patent US 8475842 for immediate release pharmaceutical formation of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one.

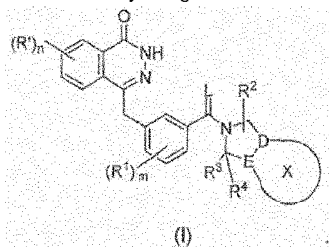
[0035] BioMarin recently published a patent US 2013/0053365 and disclosed the formula (M)



[0036] Though several compounds have been reported in the literature as PAR-1 inhibitors, very few have actually shown actual clinical benefits and none have been approved so far. Looking at the large unmet medical needs, there appears a need for developing further compounds which have better safety and efficacy profile. We herein disclose a new series of compounds which shows potential as PAR-1 inhibitors.

#### SUMMARY OF THE INVENTION

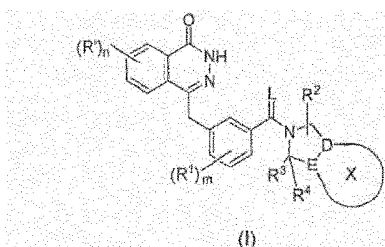
[0037] The present invention describes novel compounds useful as poly (ADP-ribose) polymerase-I inhibitors. The compounds are defined by the general formula (I) below.



[0038] The compounds of the present invention act by inhibiting PARP1 enzyme to prevent the process of DNA repair and induce cell mediated apoptosis. As a result of compromised repair, WARP-1 deficient or inhibited cells are more sensitive to DNA damaging agents ( $\gamma$  radiation, topoisomerase inhibitors, and alkylating agents). The compounds of the present invention are selective inhibitors of the poly (ADP-ribose) polymerase-1.

#### OBJECTS OF THE INVENTION

[0039] The main object of the present invention is to provide novel compounds of general formula (I), pharmaceutical compositions containing them and their use in medicine.

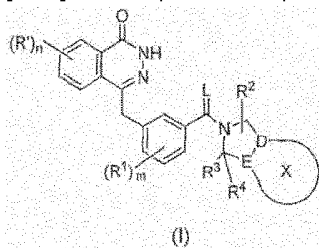


**[0040]** Another object of the present disclosure is to provide a process for the preparation of novel compounds of general formula (I), their stereoisomers, regioisomers and their tautomeric forms, novel intermediates involved in their synthesis, pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

**[0041]** Another object of the present disclosure is to provide a method of treatment of diseases which can be treated or whose symptoms can be reversed with by administering a therapeutically effective & non-toxic amount of the compound of formula (I) or their pharmaceutically acceptable compositions to the mammals.

#### DETAILED DESCRIPTION OF THE INVENTION

**[0042]** The compound of the present invention are defined by the general formula (I) below.



wherein  $R^1$  at each occurrence is independently selected from H, halogen, or the groups selected from  $(C_1-C_{12})$ alkyl, haloalkyl, cycloalkyl, alkylthio or the group  $(OSO_2)$  alkyl, wherein each of these groups may be further substituted by suitable substituents selected from hydroxyl, oxo, halo, thio, nitro, amino, alkyl, alkoxy, haloalkyl and haloalkoxy groups;

$R'$  at each occurrence is independently selected from halogen, alkyl, alkoxy, hydroxyl, haloalkyl, haloalkoxy, cyano, thioalkyl, cycloalkyl groups;

$m = 1-4$ ;

$L = -O, -S, -NH$ ;

$n = 0-4$ ;

$R^2$  is selected from substituent groups consisting of hydrogen atom, hydroxyl, alkyl, cycloalkyl, oxo,  $C(O)OR^5$ ,  $-C(O)R^5$ , or  $-C(O)NR^6R^7$ , wherein said alkyl or cycloalkyl groups are further substituted by one or more substituents groups selected from halogen, hydroxyl, alkyl or alkoxy.

$R^3$  and  $R^4$  are each independently selected from the groups such as hydrogen atom, alkyl, hydroxyl, alkoxy, cycloalkyl,  $-C(O)OR^5$ ,  $-OC(O)R^5$ ,  $-O(CH_2)_pC(O)OR^5$ ,  $-C(O)R^5$ ,  $-NHC(O)R^5$ ,  $-NR^6R^7$ ,  $-OC(O)NR^6R^7$  or  $-C(O)NR^6R^7$ , alternatively,  $R^3$  and  $R^4$  together form an oxo group;

each of ring atoms 'D' and 'E' is independently selected from C or N atoms;

'D' and 'E' are connected to one another to form 5 membered ring 'X', wherein 'X' is selected from heterocyclyl and heteroaryl, wherein heterocyclyl and heteroaryl are substituted with one or more suitable substituents selected from hydrogen, cyano, halogen, hydroxyl, oxo, optionally substituted groups selected from alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, benzyl,  $OR^5$ ,  $-C(O)OR^5$ ,  $-OC(O)R^5$ ,  $-O(CH_2)_pC(O)OR^5$ ,  $C(O)R^5$ ,  $S(O)_qR^5$ ,  $-NHC(O)R^5$ ,  $NR^6R^7$ ,  $-OC(O)NR^6R^7$  or  $-C(O)NR^6R^7$ , and

wherein the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or benzyl group may each be independently substituted further with one or more substituents selected from alkyl, halogen, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo,  $-C(O)OR^5$ ,  $-OC(O)R^5$ ,  $O(CH_2)_pC(O)OR^5$ ,  $-C(O)R^5$ ,  $-S(O)_qR^5$ ,  $-NHC(O)R^5$ ,  $NR^6R^7$ ,  $-OC(O)NR^6R^7$  or  $-C(O)NR^6R^7$  groups.

[0043] In another embodiment, the substituents on ring X are selected from alkyl, halogen, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl or heteroaryl, benzyl, oxo,  $OR^5$ ,  $-C(O)OR^5$ ,  $-OC(O)R^5$ ,  $-O(CH_2)_pC(O)OR^5$ ,  $C(O)R^5$ ,  $S(O)_qR^5$ ,  $-NHC(O)R^5$ ,  $NR^6R^7$ ,  $-OC(O)NR^6R^7$  or  $-C(O)NR^6R^7$ , wherein the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or benzyl are each independently substituted further with one or more substituents selected from alkyl, halogen, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, oxo,  $-C(O)OR^5$ ,  $-OC(O)R^5$ ,  $O(CH_2)_pC(O)OR^5$ ,  $-C(O)R^5$ ,  $-S(O)_qR^5$ ,  $-NHC(O)R^5$ ,  $NR^6R^7$ ,  $-OC(O)NR^6R^7$  or  $-C(O)NR^6R^7$  substituent.

[0044]  $R^5$  at each occurrence is independently selected from hydrogen atom, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl groups; wherein said alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl groups are each independently optionally substituted by one or more substituents selected from alkyl, halogen, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, carboxylic acid or carboxylic acid ester substituents.

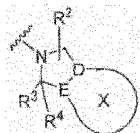
[0045] Each of  $R^6$  or  $R^7$  at each occurrence are independently selected from the groups consisting of hydrogen atom, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl groups; wherein said alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl groups are each independently optionally further substituted by one or more substituents selected from alkyl, halogen, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, carboxylic acid or carboxylic acid ester substituents;

alternatively,  $R^6$  and  $R^7$  are joined together with the nitrogen atom to form a heterocyclic ring; wherein said heterocyclic ring contains one or more heteroatoms selected from N, O,  $S(O)_q$ , furthermore the stated heterocyclic ring is optionally further substituted with one or more substituents selected from alkyl, halogen, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, carboxylic acid or carboxylic acid ester substituted substituents;

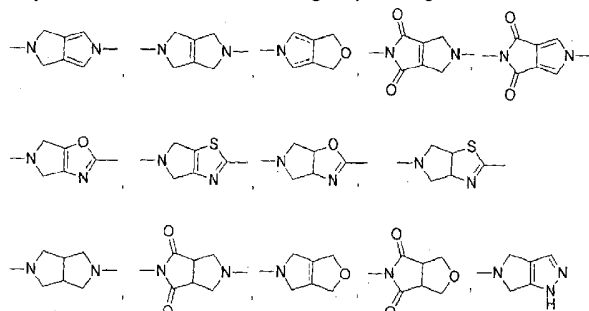
q is 0, 1 or 2 and p is 0, 1 or 2.

[0046] Suitable substituents wherever applicable and where substituents are not specifically mentioned are hydroxyl, oxo, halo, thio, nitro, amino, alkyl, alkoxy, haloalkyl or haloalkoxy groups.

[0047] The preferred heterocycle representing



may be selected from the following bicyclic rings mentioned below



[0048] In another preferred embodiment, the groups representing the above may further be selected from those described hereinafter.

[0049] The "aryl" may be selected from phenyl, naphthyl, tetrahydronaphthyl, indenyl, dihydroindenyl, biphenyl groups and each of these groups may be optionally substituted with one or more substituents selected from hydrogen, halogen, alkyl, alkoxy, hydroxyl, haloalkyl, haloalkoxy, cyano, thioalkyl, cycloalkyl groups; "Heteroaryl" or "heteroaromatic" is selected from suitable single

or fused mono, bi or tricyclic aromatic heterocyclic radicals containing one or more hetero atoms selected from O, N or S, more preferably the groups are selected from pyridyl, thienyl, furyl, pyrrolyl, indolyl, indolyl, pyridofuranyl, pyridothienyl, thienopyrimidyl, quinolinyl, pyrimidinyl, pyrazolyl, quinazolinyl, pyridazinyl, purinyl groups, each of these groups may be further optionally substituted with one or more substituents selected from hydrogen, halogen, alkyl, alkoxy, hydroxyl, haloalkyl, haloalkoxy, aryl, aralkyl, cyano, alkylthio, thioalkyl groups;

**[0050]** "Heterocyclyl" may be selected from suitable saturated, partially saturated or unsaturated aromatic or non-aromatic mono, bi or tricyclic radicals, containing one or more heteroatoms selected from nitrogen, sulfur and oxygen, more preferably selected from aziridinyl, azetidiny, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxapinyl, thiazepinyl, oxazolidinyl, thiazolidinyl, dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, benzopyranyl, benzopyranonyl, benzodihydrofuranyl, benzodihydrothienyl, pyrazolopyrimidonyl, azaquinazolinoyl, thienopyrimidonyl, quinazolonyl, pyrimidonyl, benzoxazinyl, benzoxazinonyl, benzothiazinyl, benzothiazinonyl, thienopiperidinyl groups, each of these groups may be optionally substituted with one or more substituents selected from hydrogen, halogen, alkyl, alkoxy, hydroxyl, haloalkyl, haloalkoxy, aryl, aralkyl, cyano, alkylthio, thioalkyl groups.

**[0051]** In a further embodiment the groups, radicals described above may be selected from:

- the term "alkyl" used either alone or in combination with other radicals, denotes a linear or branched radical containing one to six carbons, selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, amyl, *t*-amyl, *n*-pentyl, *n*-hexyl, and the like;
- the term "alkoxy" used either alone or in combination with other radicals, is selected from groups containing an alkyle radical, as defined above, attached directly to an oxygen atom, more preferably groups selected from methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, pentyloxy, hexyloxy, and the like;
- the term "haloalkyl," is selected from an alkyl radical, as defined above, suitably substituted with one or more halogens; such as fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, mono or polyhalo substituted methyl, ethyl, propyl, butyl, pentyl or hexyl groups;
- "Haloalkoxy" is selected from suitable haloalkyl, as defined above, directly attached to an oxygen atom, more preferably groups selected from fluoromethoxy, chloromethoxy, fluoroethoxy, chloroethoxy and the like;
- the term "alkylthio" used either alone or in combination with other radicals, denotes a straight or branched or cyclic monovalent substituent comprising an alkyl group as defined above, linked through a divalent sulfur atom having a free valence bond from the sulfur atom, more preferably the groups may be selected from methylthio, ethylthio, propylthio;
- the term "aralkyl," represents an aryl group as defined above attached to an alkyl group as described above;
- "Heteroaralkyl" and "heterocyclclakyl" represents heteroaryl and heterocyclcl groups respectively as defined above attached to an alkyl group as defined above.

**[0052]** The compounds of formula (I) may optionally be converted to their suitable pharmaceutically acceptable salts by processes as are known in the art. The novel compounds of the present invention can further be, formulated into suitable pharmaceutically acceptable compositions by combining with suitable excipients by techniques and processes and concentrations as are well known.

**[0053]** The compounds of the present invention modulate PARP-1 receptor and are useful as a therapeutic target for many diseases and especially for the treatment of cancer.

**[0054]** The compounds prepared according to present invention include, but are not limited to:

Example 1: 4-(3-(5-benzyl-octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

Example 2: 2-benzyl-5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl) benzoyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;

Example 3: 4-(4-fluoro-3-(1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl) benzyl)phthalazin-1(2H)-one;

Example 4: 4-(3-(5-(cyclopropanecarbonyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

Example 5: 4-(3-(1-(cyclopropylmethyl)-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

Example 6: 4-(3-(5-(cyclopropylmethyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

- Example 7: 4-(4-fluoro-3-(5-(2,2,2-trifluoroethyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl)phthalazin-1(2H)-one;
- Example 8: 4-(3-(5-(cyclopropylmethyl)-1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
- Example 9: 4-(3-(5-benzyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;
- Example 10: 4-(4-fluoro-3-(5-(2-((3-fluorophenyl)thio)-2-methylpropanoyl) octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl)phthalazin-1(2H)-one;
- Example 11: 2-benzyl-5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl) benzoyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
- Example 12: 4-(3-(1-(cyclopropanecarbonyl)-1,4,5,6-tetrahydropyrrolo[3,4-c] pyrazole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
- Example 13: tert-butyl 5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl) benzoyl) hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate;
- Example 14: 4-(4-fluoro-3-(hexahydro-1H-furo[3,4-c]pyrrole-5-carbonyl) benzyl)phthalazin-1(2H)-one;
- Example 15: 4-(4-fluoro-3-(octahydropyrrolo[3,4-c]pyrrole-2-carbonyl) benzyl) phthalazin-1 (2H)-one;
- Example 16: 4-(4-fluoro-3-(5-(methylsulfonyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one;
- Example 17: 4-(4-fluoro-3-(1-(methylsulfonyl)-1,4,5,6-tetrahydropyrrolo[3,4-c] pyrazole-5-carbonyl)benzyl)phthalazin-1 (2H)-one;
- Example 18: 4-(3-(5-benzyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
- Example 19: 4-(3-(5-(2,4-difluorobenzyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one;
- Example 20: 4-(3-(5,6-dihydro-4H-furo[3,4-c]pyrrole-5-carbonyl)-4-fluorobenzyl) phthalazin-1 (2H)-one;
- Example 21: 4-(4-fluoro-3-(5-methyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl) benzyl)phthalazin-1(2H)-one;
- Example 22: 5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl) tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
- Example 24: 4-(4-fluoro-3-(5-(4-fluorobenzyl)octahydropyrrolo[3,4-e]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one;
- Example 25: 4-(4-fluoro-3-(5-(2-fluorobenzyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one;
- Example 26: 4-(4-fluoro-3-(5-(2-(4-(4-fluoro-3-(5-((6-methoxypyridin-2-yl)methyl) octahydropyrrolo [3,4-c]pyrrole-2-carbonyl)benzyl)phthalazin-1(2H)-one;
- Example 27: 5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)-2-methyl tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
- Example 28: 4-(4-fluoro-3-(1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl)phthalazin-1(2H)-one compound with 4-(4-fluoro-3-(2-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl)phthalazin-1(2H)-one (1:3);
- Example 29: 4-(3-(2,2-dioxido-3,4,5,6-tetrahydro-1H-thieno[3,4-c]pyrrole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
- Example 30: 4-(3-(5,6-dihydro-4H-thieno[3,4-c]pyrrole-5-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one;
- Example 31: 4-(4-fluoro-3-(1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl) benzyl)phthalazin-1(2H)-one;
- Example 32: 4-(4-fluoro-3-(5-phenyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl) benzyl)phthalazin-1(2H)-one;
- Example 33: 4-(4-fluoro-3-(5-methyl-1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one;
- Example 34: 4-(3-((3aR,8bR)-decahydropyrrolo[3,4-a]pyrrolizine-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
- Example 35: 4-(4-fluoro-3-(2-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl)phthalazin-1(2H)-one;
- Example 36: 4-(4-fluoro-3-(1-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one;
- Example 37: 2-((5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl) benzoyl) hexahydropyrrolo [3,4-c]pyrrole-2(1H)-yl)methyl)-

6-methoxypyridine-1-oxide; Example 38: 4-(3-(5-(difluoromethyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

Example 40: Mixture of 1 & 2 Ethyl 4-(3-(2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

Example 41: 4-(3-(2-ethyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

Example 42: 4-(3-(1-ethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

Example 43: 4-(4-fluoro-3-(1-isopropyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one;

Example 44: Mixture of (1 & 2 isopropyl) 4-(4-fluoro-3-(1,4,5,6-tetrahydropyrrolo [3,4-c]pyrazole-5-carbonyl)benzyl)phthalazin-1(2H)-one;

Example 45: 4-(4-fluoro-3-(2-isopropyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one;

Example 47: 4-(4-fluoro-3-(5-(2-methoxyethyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one;

Example 50: 4-(4-fluoro-3-(1-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one hydrobromide;

Example 51: 4-(4-fluoro-3-(1-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one hydrochloride;

Example 52: 4-(4-fluoro-3-(1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one sulfate;

Example 53: 4-(4-fluoro-3-(1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one 4-methylbenzenesulfonate;

Example 54: 4-(4-fluoro-3-(1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one benzenesulfonate;

Example 55: 5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)-2-isopropyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-2-ium hydrogensulfate;

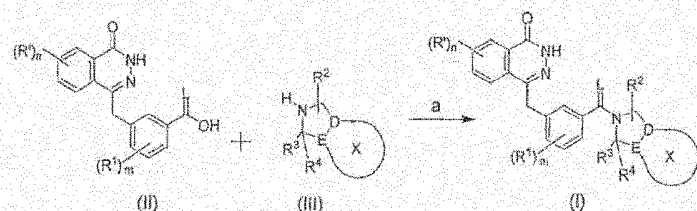
Example 56: 4-(3-(1-cyclopropyl-1,4,5,6-tetrahydropyrrolo [3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one;

[0055] Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

[0056] The compounds of the present invention may be prepared using the methods described below, together with conventional techniques known to those skilled in the art of organic synthesis, or variations thereon as appreciated by those skilled in the art. Referred methods include, but are not limited to those described below, where all symbols are as defined earlier.

[0057] The compounds of the present invention can be prepared according to the following schemes 1

Scheme 1:



<sup>a</sup> Reagents and condition: DMF, TBTU, triethylamine, 0-27 °C, 2-6 h

**Synthesis of compound of general formula (I)**

**General process of preparation:**

[0058] The Compounds of the general formula (II) can be synthesized by processes reported for e.g. in J. Med. Chem. 2008, 51, 6581-6591 with suitable modifications/alterations as required which are within the skills of a skilled person.

[0059] Compounds of the general formula (I) can be synthesized by coupling the compounds of the general formula (III) with the compounds of the general formula (II), using suitable coupling agents such as 0-(Benzotriazol-1-yl)-NNN',N-tetramethyluronium-tetrafluoroborate(TBTU),dimethylaminopyridine(DMAP), dicyclohexylcarbodiimide (DCC), hydroxybenzotriazole (HOBT.H<sub>2</sub>O), and 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC. HCl) & the like in the presence of organic bases such as DIPEA, TEA, pyridine, & the like in the solvents such as tetrahydrofuran, dimethyl formamide, dichloromethane, chloroform & the like or their suitable mixtures at ambient temperature.

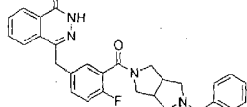
[0060] The invention is further exemplified by the following non-limiting examples which are provided for exemplifying the invention and should not be construed as limiting the scope of the invention in any ways. It will be appreciated that the other embodiments which are not exemplified can be easily practiced by a skilled person using his routine skills after reading the specific examples provided below. Such changes/alterations/modifications etc. which may be required to practice the full scope of the invention as described and claimed in the present invention are well within the scope of a person skilled in the art.

[0061] Unless otherwise specified, <sup>1</sup>H NMR spectral data given in the examples are recorded using a 400 MHz spectrometer (Bruker Topspin 2.0) and reported in δ scale. Tetra methyl silane is used as the internal standard.

#### Example 1

##### Synthesis of 4-(3-(5-benzyltetrahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one.

[0062]



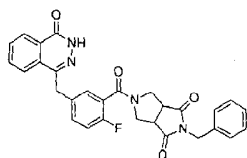
[0063] To a solution of 2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoic acid (1 g, 3.35 mmol) in dry DMF (15 mL) was added TBTU (1.292 g, 4.02 mmol) at room temperature under atmosphere of nitrogen. To this 2-benzyltetrahydropyrrolo[3,4-c]pyrrole (0.678 g, 3.35 mmol) and DIPEA (1.32 mL, 6.71 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. The progress of reaction was checked by TLC by using mobile phase 5 % methanol in chloroform. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with water, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and solvents were evaporated on a rotatory evaporator under reduced pressure to crude solid which was purified by the flash column chromatography using eluent chloroform : methanol (97 : 3) to afford 4-(3-(5-benzyltetrahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one as white solid (1.19 g, 74 %).

<sup>1</sup>H-NMR(400 MHz, DMSO-*d*<sub>6</sub>)δ 12.59 (s, 1H), 8.25 (dd, *J* = 7.6 Hz & 0.6 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.86 - 7.80 (m, 2H), 7.35 (m, 1H), 7.32 (dd, 1H), 5.29 - 7.24 (m, 4H), 7.23 - 7.20 (m, 2H), 4.32 (s, 2H), 3.63 (m, 1H), 3.47 (m, 1H), 3.46 (m, 2H), 3.36 (m, 1H), 2.9 (dd, 1H), 2.60 - 2.8 (m, 3H), 2.51 - 2.49 (m, 2H), 2.1 (m, 1H).

#### Example 2

**2-benzyl-5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl) tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione.**

[0064]

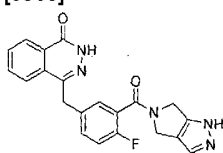


**[0065]**  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.59 (s, 1H), 8.25 (d,  $J = 7.6$  Hz, 1H), 7.80-7.89(m, 3H), 7.41 - 7.43 (m, 1H), 7.13 - 7.40 (m, 7H), 4.55 (s, 2H), 4.26 (s, 2H), 4.15-4.17 (brd, 1H), 3.50-3.62 (m, 4H), 3.37-3.40 (brd, 1H).

### Example 3

**4-(4-fluoro-3-(1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one.**

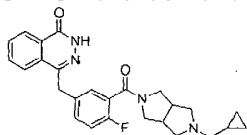
**[0066]**



**[0067]**  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.74 (s, 1H), 12.58 (s, 1H), 8.25 (d,  $J = 7.6$  Hz, 1H), 7.97 (dd,  $J = 8$  & 3.6 Hz, 1H), 7.80 - 7.90 (m, 2H), 7.42-7.59 (m, 3H), 7.25 (t,  $J = 9$  Hz, 1H), 4.56 (s, 2H), 4.35 (s, 2H), 4.25-4.29 (brd, 2H).

### Example 4

**[0068]** 4-(3-(5-(cyclopropanecarbonyl) octahydropyrrolo [3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one.

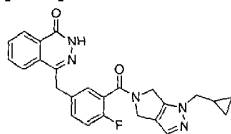


**[0069]**  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.59 (s, 1H), 8.24 (d,  $J = 1.2$  Hz, 1H), 7.96 (dd,  $J = 8$  & 4.8 Hz, 1H), 7.82 - 7.90 (m, 2H), 7.40 (dd,  $J = 6.8$  & 5.2 Hz, 2H), 7.23 (dd,  $J = 9.6$  & 3.6 Hz, 2H), 4.32 (s, 2H), 3.89-3.90 (brt, 1H), 3.70-3.80 (m, 1 H), 3..50-3.60 (m, 1H), 3.40-3.49 (m, 2H), 3.22-3.26 (m, 2H), 3.11 - 3.16 (m, 2H), 2.90-3.0 (m, 1H), 1.17-1.25 (m, 1H), 0.69-0.72 (brt, 4H).

### Example 5

**4-(3-(1-(cyclopropylmethyl)-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one**

**[0070]**



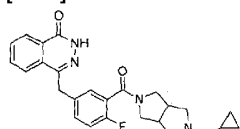
**[0071]**  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  12.77 (brs, 1H), 8.30 (d,  $J = 7.6$  Hz, 1H), 8.03 (dd,  $J = 7.6$  & 4.8 Hz, 1H), 7.83-7.91 (m,

2H), 7.46-7.58 (m, 3H), 7.24-7.29 (brt, 1H), 4.57 (s, 2H), 4.37 (s, 2H), 4.25-4.29 (brd, 2H), 4.0 (d, J= 7.2 Hz, 2H), 1.12-1.19 (m, 1H), 0.35-0.47 (m, 4H).

#### Example 6

#### 4-(3-(5-(cyclopropylmethyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[0072]

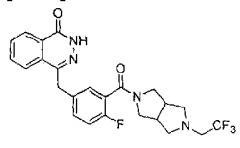


[0073] <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.30 (s, 1H), 8.44-8.47 (m, 1H), 7.70-7.79 (m, 3H), 7.35 (dd, J= 6.4 & 2.4 Hz, 1H), 7.26-7.31 (m, 1H), 7.0-7.05 (brt, 1H), 4.27 (s, 2H), 3.75-3.76 (brd, 2H), 3.45-3.47 (m, 1H), 2.88-3.24 (m, 4H), 2.36-2.52 (m, 5H), 0.98 (brs, 1H), 0.56-0.58 (brd, 2H), 0.19-0.58 (brd, 2H).

#### Example 7

#### 4-(4-fluoro-3-(5-(2,2,2-trifluoroethyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl)phthalazin-1(2H)-one

[0074]

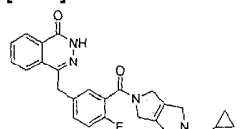


[0075] <sup>1</sup>H NMR (400 MHz, In CDCl<sub>3</sub>): δ 10.28 (s, 1H), 8.45-8.47 (m, 1H), 7.70=7.77 (m, 3H), 7.36 (dd, J=6.4 & 2.4, 1H), 7.26-7.29 (m, 1H), 6.99-7.04 (m, 1H), 4.27 (s, 2H), 3.86-3.91 (m, 1 H), 3.61-3.65 (m, 1 H), 3.48-3.53 (m, 1 H), 3.15-3.19 (m, 1H), 3.0-3.07 (m, 1H), 2.86-2.99 (m, 1H), 2.69-2.82 (m, 3H), 2.50-2.53 (m, 1H)

#### Example 8

#### 4-(3-(5-(cyclopropylmethyl)-1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[0076]

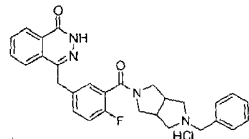


[0077] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (s, 1H), 8.27 - 8.25 (m, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.91 - 7.87 (m, 1H), 7.83 (dd, J = 7.6 Hz & 1.2 Hz, 1H), 7.42 (dd, J = 10.4 Hz & 5.2 Hz, 2H), 7.26 - 7.22 (m, 1H), 4.32 (s, 2H), 4.23 (s, 2H), 3.92 (s, 2H), 3.78 - 3.46 (m, 3H), 3.42 (s, 1H), 2.69 - 2.66 (m, 2H), 1.0 - 0.7 (m, 1H), 0.5 - 0.035 (m, 2H), 0.2 (m, 2H).

## Example 9

## 4-(3-(5-benzyl-octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride

[0078]

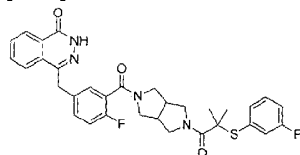


[0079]  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ ):  $\delta$  12.62 (s, 1H), 10.81 (s, 1H), 8.26 (m, 1H), 8.32 - 7.98 (m, 1H), 7.87 - 7.61 (m, 1H), 7.59 (dd, 1H), 7.53 (dd, 2H), 7.44 (m, 4H), 7.38 - 7.35 (m, 1H), 7.27 - 7.19 (m, 1H), 4.39 - 4.31 (m, 4H), 3.72 (d, 1H), 3.28 (m, 1H), 3.16 (m, 2H), 2.99 - 2.89 (m, 2H), 2.73 - 2.49 (m, 2H).

## Example 10

## 4-(4-fluoro-3-(5-(2-((3-fluorophenyl)thio)-2-methylpropanoyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl)phthalazin-1(2H)-one

[0080]

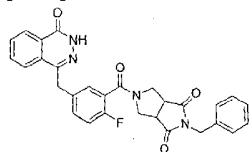


[0081]  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ ):  $\delta$  12.58 (s, 1H), 8.25 (d,  $J = 6.4$  Hz, 1H), 7.90 (d, 1H), 7.88 (t, 1H), 7.82 (t, 1H), 7.37 (d,  $J = 6.4$  Hz, 1H), 7.34 (m, 2H), 7.19 (t, 2H), 7.1 (m, 2H), 4.45 (d, 2H), 4.39 (t, 4H), 4.30 (s, 2H), 3.43 - 3.36 (m, 3H), 3.17 (d, 2H), 1.4 (s, 6H).

## Example 11

## 2-benzyl-5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl) tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione

[0082]

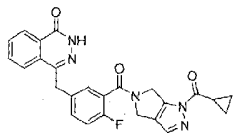


[0083]  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ ):  $\delta$  12.59 (s, 1H), 8.25 (dd,  $J = 7.6$  Hz & 0.6 Hz, 1H), 7.94 (d,  $J = 7.6$  Hz, 1H), 7.86 - 7.80 (m, 2H), 7.35 (m, 1H), 7.32 (dd, 1H), 5.29 - 7.24 (m, 4H), 7.23 - 7.20 (m, 2H), 4.32 (s, 2H), 3.63 (m, 1H), 3.47 (m, 1H), 3.46 (m, 2H), 3.36 (m, 1H), 2.9 (dd, 1H), 2.60 - 2.8 (m, 3H), 2.51 - 2.49 (m, 2H), 2.1 (m, 1H)

## Example 12

4-(3-(1-(cyclopropanecarbonyl)-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[0084]

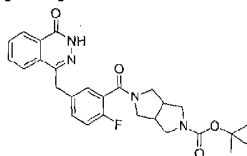


[0085] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.57-12.60 (brd, 2H), 8.26 (d, J= 7.6 Hz, 1H), 7.97 (d, J= 7.6 Hz, 1H), 7.69-7.92 (m, 3H), 7.45-7.49 (m, 2H), 7.25-7.30(brt, 1H), 4.80(brs, 2H), 4.37 (brs, 2H), 4.34 (s, 2H), 4.28(brs,1H), 2.97-3.0 (m, 1H), 1.07-1.23 (m, 4H).

## Example 13

tert-butyl 5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl) hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxyate

[0086]

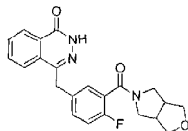


[0087] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (s, 1H), 8.25 (t, J = 8 Hz, 1H), 7.97 (d, J = 8 Hz, 1H), 7.82 - 7.88 (m, 2H), 7.39 - 7.41 (m, 2H), 7.21 - 7.23 (brt, 1H), 4.32 (s, 2H), 3.68 (brs, 1H), 3.50 (brd, 2H), 3.39-3.41 (brd, 2H), 3.00-3.03 (brt, 2H), 2.81-2.89 (brd, 2H), 1.39 (s, 9H).

## Example 14

4-(4-fluoro-3-(hexahydro-1H-furo[3,4-c]pyrrole-5-carbonyl)benzyl)phthalazin-1(2H)-one

[0088]

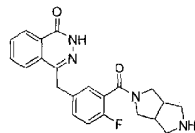


[0089] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (s, 1H), 8.26 (dd, J= 7.6 & 0.8 Hz, 1H), 7.97 (d, J= 8 Hz, 1H), 7.80-7.89 (m, 2H), 7.39-7.43 (m, 1H), 8.35 (dd, J= 6.4 & 2 Hz, 1H), 7.19-7.23 (brt, 1H), 4.32 (s, 2H), 3.74-3.78 (m, 1H), 3.64-3.69 (m, 2H), 3.33-3.55 (m, 4H), 3.01-3.02 (m, 2H), 2.91-3.07 (m, 2H).

## Example 15

## 4-(4-fluoro-3-(octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl)phthalazin-1(2H)-one

[0090]

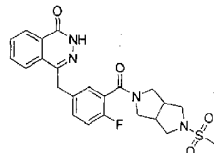


[0091] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.60 (s, 1H), 8.26 (dd, J = 7.6 & 0.8 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.82 - 7.88 (m, 2H), 7.32 - 7.34 (m, 1H), 7.18 - 7.23 (m, 1H), 4.32 (s, 2H), 3.67-3.72 (m, 1H), 3.30-3.40 (m, 2H), 2.77-2.96 (m, 2H), 2.58-2.73 (m, 4H), 2.41-2.44 (m, 1H).

## Example 16

## 4-(4-fluoro-3-(5-(methylsulfonyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one

[0092]

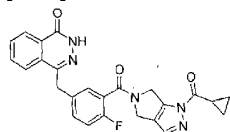


[0093] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.58 (s, 1H), 8.26 (dd, J = 8 & 1.2 Hz, 1H), 7.96 (d, J = 8 Hz, 1H), 7.82 - 7.89 (m, 2H), 7.39-7.41 (brd, 2H), 7.19-7.24 (m, 1H), 4.32 (s, 2H), 3.69-3.74 (m, 1H), 3.39-3.50 (m, 5H), 2.98-3.15 (m, 4H), 2.91 (s, 3H).

## Example 17

## 4-(4-fluoro-3-(1-(methylsulfonyl)-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl)phthalazin-1(2H)-one

[0094]

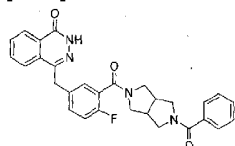


[0095] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (brd, 1H), 8.26 (d, J = 7.6 Hz, 1H), 7.97 (d, J = 8 Hz, 1H), 7.72-7.90 (m, 3H), 7.47-7.50 (m, 2H), 7.29-7.30 (m, 1H), 4.81 (brs, 1H), 4.58 (brs, 2H), 4.34 (brs, 1H), 3.52-3.57 (brd, 3H).

## Example 18

## 4-(3-(5-benzoyloctahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one

[0096]

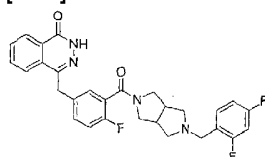


[0097] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (s, 1 H), 8.25 (d, J = 7.2 Hz, 1H), 7.80 - 7.96 (m, 3H), 7.23-7.50 (m, 7H), 7.21-7.23 (m, 1H), 4.30- 4.33 (brd, 2H), 3.38-3.75 (m, 5H).

**Example 19**

**4-(3-(5-(2,4-difluorobenzyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one**

[0098]

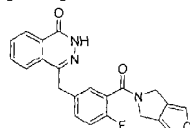


[0099] <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 12.59 (s, 1H), 8.44-8.46 (m, 1H), 7.69-7.78 (m, 3H), 7.31-7.37 (m, 2H), 7.26-7.29 (m, 1H), 6.99-7.04 (brt, 1H), 6.75-6.86 (m, 2H), 4.27 (s, 2H), 3.83-3.88 (m, 1H), 3.60-3.66 (m, 4H), 3.14-3.18 (m, 1H), 2.51-2.88 (m, 5H), 2.33-2.35 (m, 1H).

**Example 20**

**4-(3-(5,6-dihydro-4H-furo[3,4-c]pyrrole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one**

[0100]

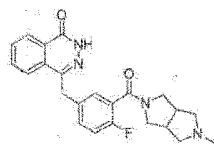


[0101] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (s, 1H), 8.26 (dd, J = 7.6 Hz & 1.2 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.91 - 7.87 (m, 1H), 7.85-7.81 (m, 1H), 7.53 (d, J = 1.2 Hz, 1H), 7.46 - 7.42 (m, 2H), 7.41 - 7.40 (d, J = 1.2 Hz, 1H), 7.28 - 7.23 (m, 1H), 4.56 (s, 2H), 4.34 (s, 2H), 4.26 (s, 2H).

**Example 21**

**4-(4-fluoro-3-(5-methyloctahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl)phthalazin-1(2H)-one**

[0102]

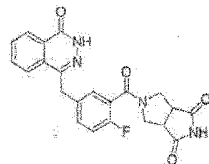


**[0103]**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.90 (s, 1H), 8.44-8.47 (m, 1H), 7.70-7.79 (m, 3H), 7.27-7.52 (m, 2H), 6.99-7.04 (brq, 1H), 4.26 (s, 2H), 3.85-3.90 (m, 1H), 3.62-3.64 (m, 1H), 3.44-3.51 (m, 1H), 3.19-3.21 (m, 1H), 2.73-2.97 (m, 4H).

**Example 22**

**5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione**

**[0104]**

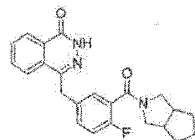


**[0105]**  $^1\text{H NMR}$ (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  12.58 (s, 1H), 11.4(s, 1H), 8.26 (dd,  $J = 7.6 \text{ Hz} \ \& \ 0.8 \text{ Hz}$ , 1H), 7.87 - 7.96 (m, 2H), 7.80-7.85 (m, 1H), 7.41-7.43 (m, 1H), 7.37 (dd,  $J = 6.4 \text{ Hz} \ \& \ 2.4 \text{ Hz}$ , 1H), 7.20- 7.24 (brt, 1H), 4.31 (s, 2H), 4.09-4.12 (brd, 1H), 3.38-3.58 (m, 5H).

**Example 23 (not claimed)**

**4-(4-fluoro-3-(octahydrocyclopenta[c]pyrrole-2-carbonyl)benzyl)phthalazin-1(2H)-one**

**[0106]**

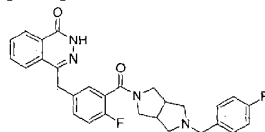


**[0107]**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  10.04 (s, 1H), 8.44-8.46 (m, 1H), 7.70-7.77 (m, 3H), 7.24-7.33 (brt, 1H), 7.01-7.03 (m, 1H), 6.99-7.03 (brt, 1H), 4.26 (s, 2H), 3.79-3.84 (m, 1H), 3.43-3.49 (m, 2H), 3.0-3.04 (m, 1H), 2.60-2.72 (m, 2H), 1.49-1.88 (m, 6H).

**Example 24**

**4-(4-fluoro-3-(5-(4-fluorobenzyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one**

**[0108]**

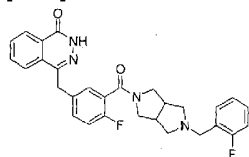


[0109] <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.18 (s, 1H), 8.44-8.46 (m, 1H), 7.69-7.76 (m, 3H), 7.33-7.35 (m, 1H), 7.25-7.34 (m, 3H), 6.96-7.04 (m, 3H), 4.27 (s, 2H), 3.83-3.88 (m, 1H), 3.45-3.64 (m, 4H), 3.13-3.17 (m, 1H), 2.80-2.90 (m, 2H), 2.62-2.63 (m, 1H), 2.49-2.52 (m, 2H), 2.28-2.31 (m, 1H).

**Example 25**

**4-(4-fluoro-3-(5-(2-fluorobenzyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one**

[0110]



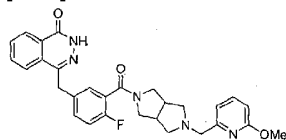
[0111] <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.09 (s, 1H), 8.44-8.46 (m, 1H), 7.69-7.76 (m, 3H), 7.34-7.37 (m, 2H), 7.21-7.28 (m, 2H), 6.99-7.12 (m, 3H), 4.26 (s, 2H), 3.84-3.89 (m, 1H), 3.59-3.65 (m, 3H), 3.45-3.50 (m, 1H), 3.14-3.18 (m, 1H), 2.8-2.9 (m, 2H), 2.67-2.69 (m, 1H), 2.53-2.61 (m, 2H), 2.33-2.36 (m, 1H).

**Example 26**

**4-(4-fluoro-3-(5-(2-(4-(4-fluoro-3-(5-((6-methoxypyridin-2-yl)methyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl)phthalazin-1(2H)-one**

**octahydropyrrolo[3,4-c]pyrrole-2-**

[0112]

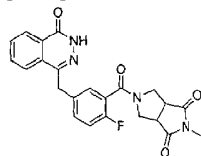


[0113] <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.19 (s, 1H), 8.43-8.46 (m, 1H), 7.69-7.76 (m, 3H), 7.51-7.55 (m, 1H), 7.34-7.36 (m, 1H), 7.26-7.28 (m, 1H), 7.0-7.04 (brt, 1H), 6.95 (d, J = 6.8 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.26 (s, 2H), 3.91 (s, 3H), 3.85-3.91 (m, 1H), 3.18-3.22 (m, 1H), 2.60-2.79 (m, 5H), 2.08-2.44 (m, 1H).

**Example 27**

**5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)-2-methyl tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione**

[0114]

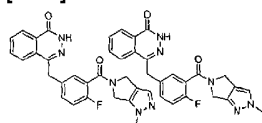


[0115] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 10.17 (s, 1H), 8.45-8.47 (m, 1H), 7.74-7.82 (m, 2H), 7.69-7.71 (m, 1H), 7.26-7.34 (m, 2H), 7.02-7.06 (m, 1H), 4.45-4.49 (brd, 1H), 4.26 (s, 2H), 3.58-3.69 (m, 2H), 3.36-3.46 (m, 2H), 3.0 (s, 3H).

**Example 28**

Mixture of 4-(4-fluoro-3-(1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl)phthalazin-1(2H)-one compound with 4-(4-fluoro-3-(2-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl)phthalazin-1(2H)-one (1:3)

[0116]

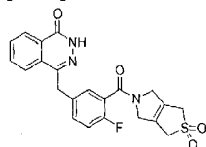


[0117] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (s, 1H), 8.24-8.27 (m, 1H), 7.96-7.99 (m, 1H), 7.81-7.90 (m, 2H), 7.43-7.56 (m, 3H), 7.23-7.27 (m, 1H), 4.54 (s, 2H), 4.33 (s, 2H), 4.23-4.27 (brd, 2H), 3.82 (s, 3H).

**Example 29**

4-(3-(2,2-dioxido-3,4,5,6-tetrahydro-1H-thieno[3,4-c]pyrrolo-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[0118]

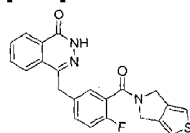


[0119] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.58 (s, 1H), 8.27 (d, J = 7.6 Hz, 1H), 7.98 (d, J = 8 Hz, 1H), 7.91 (dd, J = 14 Hz & 6.8 Hz, 1H), 7.85 - 7.81 (m, 1H), 7.45-7.44 (m, 2H), 7.28 - 7.23 (m, 1H), 4.35 - 4.32 (d, 4H), 4.06 (s, 2H), 4.007 (s, 2H), 3.88 (s, 2H).

**Example 30**

4-(3-(5,6-dihydro-4H-thieno[3,4-c]pyrrolo-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[0120]

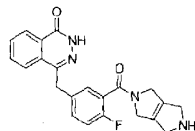


[0121] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.58 (s, 1H), 8.26 (dd, J = 8 Hz & 1.2 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.91 - 7.87 (m, 1H), 7.85 - 7.81 (m, 1H), 7.46-7.43 (m, 2H), 7.29 - 7.23 (m, 2H), 7.16 (m, 1H), 4.59 (s, 2H), 4.34 (s, 2H), 4.29 (s, 2H).

## Example 31

## 4-(4-fluoro-3-(1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one

[0122]

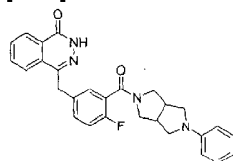


[0123] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (s, 1H), 8.26 (m, J = 7.6 Hz & 1.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.90 - 7.84 (m, 1H), 7.82 - 7.80 (m, 1H), 7.44 - 7.40 (m, 2H), 7.22 - 7.21 (m, 1H), 4.32 (s, 2H), 4.26 - 4.19 (d, 2H), 3.96 - 3.87 (d, 2H), 3.63 - 3.59 (d, 2H), 3.58 - 3.48 (d, 2H).

## Example 32

## 4-(4-fluoro-3-(5-phenyloctahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl)phthalazin-1(2H)-one

[0124]

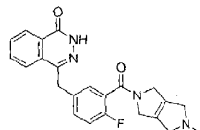


[0125] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.58 (s, 1H), 8.25 (dd, J=7.6 & 1.2 Hz, 1H), 7.95 (d, J=7.6 Hz, 1H), 7.80-7.85 (m, 2H), 7.36-7.42 (m, 2H), 7.14-7.23 (m, 3H), 6.62 (t, J=7.6 Hz, 1H), 6.52 (d, J=8 Hz, 2H), 4.31 (s, 2H), 3.74-3.79 (m, 1H), 3.42-3.48 (m, 3H), 3.32-3.36 (m, 1H), 3.18-3.22 (m, 1H), 2.96-3.10 (m, 4H)

## Example 33

## 4-(4-fluoro-3-(5-methyl-1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl) benzyl) phthalazin-1(2H)-one

[0126]

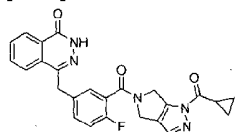


[0127] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (s, 1H), 8.26 (dd, J = 8 Hz & 0.8 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.90 - 7.86 (m, 1H), 7.84 - 7.80 (m, 1H), 7.43 - 7.40 (m, 2H), 7.25 - 7.21 (m, 1H), 4.32 (s, 2H), 4.19 (s, 2H), 3.58 (s, 2H), 3.43 (s, 2H), 2.42 (s, 3H).

## Example 34

4-(3-((3a*R*,8*bR*)-decahydropyrrolo[3,4-*a*]pyrrolizine-2-carbonyl)-4-fluorobenzyl) phthalazin-1(2*H*)-one

[0128]

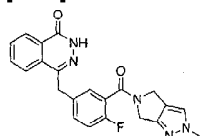


[0129] <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 10.5 - 10.2 (d, 1H), 8.44 - 8.46 (m, 1H), 7.71 - 7.77 (m, 3H), 7.41 - 7.38 (m, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.02 - 6.99 (m, 1H), 4.24 (s, 2H), 3.89 - 0.88 (m, 15H).

## Example 35

4-(4-fluoro-3-(2-methyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzyl) phthalazin-1(2*H*)-one

[0130]

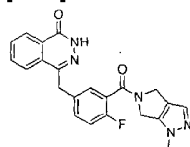


[0131] <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.02 (s, 1H), 8.44-8.46 (m, 1H), 7.69-7.79 (m, 3H), 7.29-7.40 (m, 2H), 7.04-7.17 (m, 2H), 4.73-4.77 (brd, 2H), 4.37-4.39 (brd, 2H), 4.28 (s, 2H), 3.89-3.90 (brd, 2H).

## Example 36

4-(4-fluoro-3-(1-methyl-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzyl) phthalazin-1(2*H*)-one

[0132]

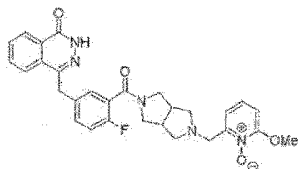


[0133] <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.98 (s, 1H), 8.44-8.47 (m, 1H), 7.70-7.80 (m, 3H), 7.31-7.40 (m, 2H), 7.06-7.30 (m, 2H), 4.72-4.78 (brd, 2H), 4.37-4.44 (brd, 2H), 4.28-4.29 (brd, 2H), 3.73-3.85 (brd, 3H).

## Example 37

2-((5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl) hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)methyl)-6-methoxypyridine-1-oxide

[0134]

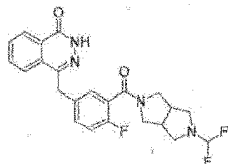


**[0135]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.70 (s, 1H), 8.26 (d, J = 8.8 Hz, 1H), 8.83-8.91 (m, 3H), 7.67-7.70 (m, 1H), 7.41-7.45 (m, 1H), 7.28-7.30 (m, 1H), 7.16-7.23 (m, 1H), 6.82 (d, J = 8 Hz, 1H), 4.40-4.41 (brd, 2H), 4.31 (s, 2H), 3.82 (s, 3H), 3.70-3.73 (brd, 1H), 3.37-3.47 (m, 3H), 3.12-3.25 (m, 3H), 2.99-3.02 (brd, 1H).

**Example 38**

**4-(3-(5-(difluoromethyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one**

**[0136]**

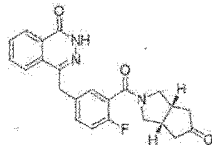


**[0137]** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.25 (s, 1H), 8.45-8.47 (m, 1H), 8.21-8.24 (m, 1H), 7.71-7.79 (m, 3H), 7.30-7.32 (m, 1H), 7.26-7.29 (m, 1H), 7.01-7.05 (m, 1H), 4.27 (s, 2H), 3.87-3.93 (m, 1H), 3.73-3.82 (m, 1H), 3.56-3.70 (m, 1H), 3.46-3.50 (m, 1H), 3.30-3.34 (m, 1H), 3.18-3.23 (m, 1H), 2.92-2.95 (m, 1H).

**Example 39 (not claimed)**

**4-(4-fluoro-3-((3aR,6aS)-5-oxooctahydrocyclopenta[c]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one**

**[0138]**

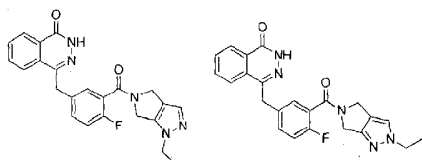


**[0139]** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.63 (s, 1H), 8.47-8.49 (m, 1H), 7.72-7.81 (m, 3H), 7.37-7.39 (m, 1H), 7.30-7.33 (m, 1H), 7.02-7.04 (brt, 1H), 4.30 (s, 2H), 3.95-4.00 (m, 1H), 3.55-3.65 (m, 2H), 3.18-3.22 (m, 1H), 2.94-3.10 (m, 2H), 2.44-2.61 (m, 2H), 2.22-2.28 (m, 1H), 2.08-2.18 (m, 1H).

**Example 40**

**Mixture of 1 & 2 Ethyl 4-(3-(2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one**

**[0140]**

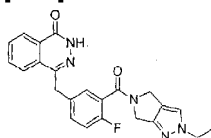


**[0141]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.60 (s, 1 H), 8.25 (t, 1H), 7.99 (dd, J = 7.6 Hz & 4 Hz, 1H), 7.91 - 7.87 (m, 1H), 7.85 - 7.81 (m, 1H), 7.61 - 7.42 (m, 3H), 7.28-7.23 (m, 1H), 5.31 (s, 1H), 4.55 (d, 1H), 4.52 - 4.43 (d, 2H), 4.34 (s, 2H), 4.28-4.20 (t, 2H), 4.14 - 4.08 (m, 2H), 3.39 - 3.35 (m, 2H), 1.67 - 1.10 (m, 6H).

#### Example 41

#### 4-(3-(2-ethyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one

**[0142]**

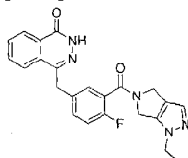


**[0143]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (s, 1H), 8.26 (d, J = 8 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.61 (s, 1H), 7.46 (d, J = 5.6 Hz, 2H), 5.25 (m, 1H), 4.55 (s, 2H), 4.33 (s, 2H), 4.26 (d, 2H), 4.10 (q, 2H), 1.36 - 1.32 (m, 3H).

#### Example 42

#### 4-(3-(1-ethyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl) phthalazin-1(2H)-one

**[0144]**

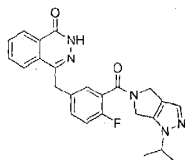


**[0145]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 10.37 - 10.34 (d, 2H), 8.47 - 8.45 (dd, 1 H), 7.82 - 7.22 (m, 3H), 7.41 - 7.33 (m, 2H), 7.20 (s, 1H), 7.13 - 6.99 (m, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 4.46 (s, 1H), 4.37 (s, 1H), 4.37-4.31 (d, 2H), 4.15 (q, 2H), 1.48 (t, 2 H), 1.37 (t, 1H).

#### Example 43

#### 4-(4-fluoro-3-(1-isopropyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl)phthalazin-1(2H)-one

**[0146]**

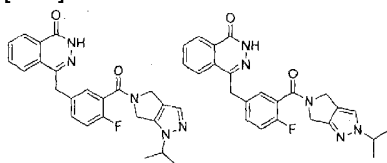


**[0147]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.56 (s, 1H), 8.24 (d, J = 7.6 Hz, 1H), 7.95 (t, 1H), 7.87 (t, 1H), 7.81 (t, 1H), 7.46 - 7.42 (m, 2H), 7.27 - 7.22 (m, 1H), 7.15 (s, 1H), 4.74 (s, 1H), 4.48 (s, 1H), 4.45 (m, 1H), 4.32 (s, 2H), 4.30 - 4.26 (m, 1H), 4.16 (s, 1H), 1.37 (d, 3H), 1.23 (t, 3H).

**Example 44**

**Mixture of (1& 2 isopropyl) 4-(4-fluoro-3-(1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl)phthalazin-1(2H)-one**

**[0148]**

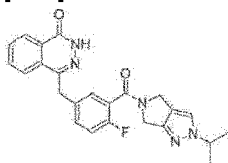


**[0149]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.58 (s, 1H), 8.26 (d, J = 7.6 Hz, 1H), 7.98 (d, J = 8 Hz, 1H), 7.91 - 7.81 (m, 2H), 7.48 - 7.42 (m, 2H), 7.29 - 7.23 (m, 1H), 7.17 (s, 1H), 4.55 (s, 1H), 4.49-4.44 (m, 1H), 4.33 (s, 2H), 4.29 (s, 1H), 4.24 (s, 1H), 1.40 (dd, 5H), 1.25 (t, 1H).

**Example 45**

**4-(4-fluoro-3-(2-isopropyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one**

**[0150]**

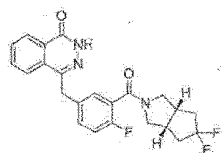


**[0151]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.57 (s, 1H), 8.26 (d, J = 7.6 Hz & 1.2 Hz, 1H), 7.98 (t, 1H), 7.91 - 7.87 (m, 1H), 7.85 - 7.81 (m, 1H), 7.64 - 7.50 (d, 1H), 7.46-7.42 (m, 2H), 7.27 (t, 1H), 4.55 (s, 2H), 4.49 - 4.46 (m, 1H), 4.33 (s, 2H), 4.29 (s, 1H), 4.24 (s, 1H), 1.40 - 1.38 (dd, 6H).

**Example 46 (not claimed)**

**4-(3-((3aR,6aS)-5,5-difluorooctahydrocyclopenta[c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one**

**[0152]**

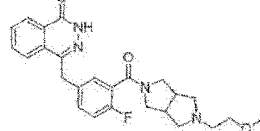


**[0153]**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  10.07 (s, 1H), 8.45-8.47 (m, 1H), 7.70-7.79 (m, 3H), 7.35-7.37 (m, 1H), 7.24-7.31 (m, 1H), 7.01-7.05 (brt, 1H), 4.27 (s, 2H), 3.82-3.87 (m, 1H), 3.65-3.70 (m, 1H), 3.51-3.56 (m, 1H), 3.18-3.22 (m, 1H), 2.80-2.94 (m, 2H), 2.26-2.45 (m, 2H), 1.87-2.08 (m, 2H).

**Example 47**

**4-(4-fluoro-3-(5-(2-methoxyethyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzyl) phthalazin-1(2H)-one**

**[0154]**

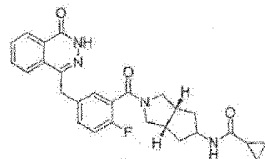


**[0155]**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  10.25 (s, 1H), 8.44-8.47 (m, 1H), 7.71-7.79 (m, 3H), 7.34-7.36 (m, 1H), 7.26-7.30 (m, 1H), 6.99-7.04 (brt, 1H), 4.27 (s, 2H), 3.64-3.79 (m, 2H), 3.50-3.53 (m, 2H), 3.42-3.47 (m, 1H), 3.36 (s, 3H), 3.16-3.18 (brd, 1H), 2.80-2.97 (m, 2H), 2.64-2.68 (m, 2H), 2.41-2.42 (brd, 1H).

**Example 48 (not claimed)**

**N-((3aR,6aS)-2-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)octahydrocyclopenta[c]pyrrol-5-yl)cyclopropanecarboxamide**

**[0156]**

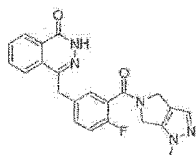


**[0157]**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  10.38 (s, 1H), 8.44-8.46 (m, 1H), 7.72-7.78 (m, 3H), 7.42-7.44 (m, 1H), 7.26-7.29 (m, 1H), 6.98-7.03 (brt, 1H), 5.57 (brd, 1H), 4.40-4.42 (m, 1H), 4.27 (s, 2H), 3.79-3.85 (m, 1H), 3.48-3.60 (m, 2H), 3.06-3.10 (m, 1H), 2.78-2.85 (m, 2H), 1.90-2.00 (m, 1H), 1.70-1.88 (m, 1H), 1.00-1.03 (m, 2H), 0.83-0.90 (m, 1H), 0.73-0.75 (m, 2H)

**Example 50**

**4-(4-fluoro-3-(1-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one hydrobromide**

**[0158]**



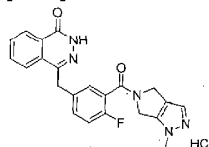
**[0159]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59 (d, J = 3.6 Hz, 1H), 8.26(d, J = 7.6 Hz, 1H), 8.005 - 7.92 (m, 1H), 7.911 - 7.87 (m, 1H), 7.85 - 7.81 (m, 1H), 7.48 - 7.43 (m, 2H), 7.30 - 7.25 (m, 1H), 7.15 (brs, 1H), 4.69 (s, 1H), 4.53 (s, 1H), 4.42 (s, 1H), 4.34 (s, 2H), 4.21 (s, 1H), 3.78 - 3.66 (brd, 3H).

#### Example 51

**4-(4-fluoro-3-(1-methyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) hydrochloride**

**phthalazin-1(2H)-one**

**[0160]**

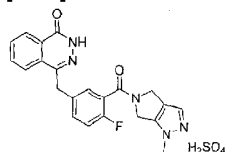


**[0161]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59-12.59 (d, J = 3.6Hz, 1H), 8.26 (d, J = 7.6Hz, 1H), 7.98 (t, J = 8Hz, 1H), 7.89 (t, J = 3.4Hz, 1H), 7.83 (t, J = 7.4Hz, 1H), 7.43-7.48 (m, 2H), 7.26-7.28 (m, 1H), 7.15-7.27 (brd, 1H), 4.53-4.69 (brd, 2H), 4.34 (s, 2H), 4.21-4.42 (brd, 2H), 3.66-3.78 (brd, 3H).

#### Example 52

**4-(4-fluoro-3-(1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one sulfate**

**[0162]**



**[0163]** <sup>1</sup>H NMR (400 MHz DMSO-d<sub>6</sub>): δ 12.59-12.58 (d, J = 3.2Hz, 1H), 8.26 (d, J = 8Hz, 1H), 7.97 (m, 1H), 7.89 (m, 1H), 7.84 (m, 1H), 7.48-7.43 (m, 2H), 7.15 (s, 1H), 4.53 (s, 1H), 4.41 (s, 1H), 4.34 (s, 2H), 4.21 (s, 1H), 3.78 (s, 3H), 3.73 (m, 1H).

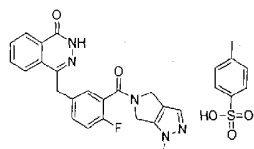
#### Example 53

**4-(4-fluoro-3-(1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) 4-methylbenzenesulfonate**

**phthalazin-1(2H)-one**

**4-**

**[0164]**



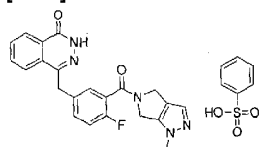
**[0165]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59-12.58 (d, J = 3.2Hz, 1H), 8.26 (d, J = 7.6Hz, 1H), 7.98 (m, 1H), 7.904 (m, 1H), 7.87-7.81 (m, 1H), 7.48-7.43 (m, 4H), 7.3-7.28 (m, 1H), 7.11 (m, 2H), 4.69 (s, 1H), 4.53 (s, 1H), 4.41 (s, 1H), 4.21 (s, 1H), 3.72 (s, 3H), 2.28 (s, 3H)

**Example 54**

**4-(4-fluoro-3-(1-methyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl)phthalazin-1(2H)-one benzenesulfonate**

**phthalazin-1(2H)-one**

**[0166]**

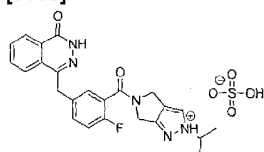


**[0167]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.59-12.59 (d, J = 3.2Hz, 1H), 8.26 (d, J = 8Hz, 1H), 7.87-7.92 (m, 1H), 7.83 (t, J = 7.6Hz, 1H), 7.58-7.61 (m, 2H), 7.43-7.48 (m, 2H), 7.15-7.34 (m, 7H), 4.53-4.69 (brd, 2H), 4.34 (s, 2H), 4.21-4.41 (brd, 2H), 3.66-3.78 (brd, 3H).

**Example 55**

**5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)-2-isopropyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-2-ium hydrogensulfate**

**[0168]**

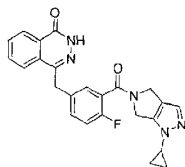


**[0169]** <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.58 (s, 1H), 8.26 (dd, J = 8 Hz & 1.2 Hz, 1H), 7.98 (dd, J = 7.6 Hz & 2.4 Hz, 1H), 7.91 - 7.87 (m, 1 H), 7.85 - 7.81 (m, 1H), 7.64-7.51 (brd, 1H), 7.47 - 7.42 (m, 2H), 7.28 - 7.23 (m, 1H), 4.55 (s, 2H), 4.51 - 4.45 (m, 1H), 4.33 (s, 2H), 4.29 - 4.24 (brd, 2H), 1.40 - 1.38 (brd, 4H).

**Example 56**

**4-(3-(1-cyclopropyl-1,4,5,6-tetrahydropyrrolo [3,4-c]pyrazole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one**

**[0170]**

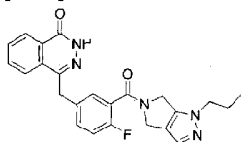


[0171]  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  12.58 (d,  $J = 2.4$  Hz, 1H), 8.24 (d,  $J = 7.6$  Hz, 1H), 7.98 - 7.37 (m, 1H), 7.89 - 7.85 (m, 1H), 7.81 (t, 1H), 7.47 - 7.39 (m, 2H), 7.28 - 7.22 (m, 1H), 7.14 (d, 1H), 4.70 (s, 1H), 4.48 (s, 1H), 4.42 (s, 2H), 4.32 (s, 2H), 4.16 (s, 1H), 3.57 - 3.44 (m, 1H), 0.98-0.82 (m, 4H).

[0172] The following compounds can be synthesized following the same procedure as described for example 1 and are considered to be encompassed within the scope of the present invention.

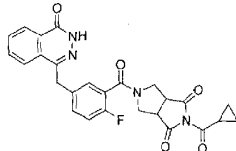
**4-(4-fluoro-3-(1-propyl-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)benzyl) phthalazin-1(2H)-one**

[0173]



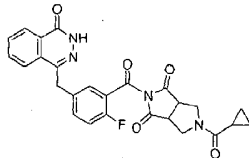
**2-(cyclopropanecarbonyl)-5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione**

[0174]



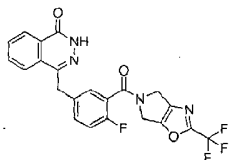
**5-(cyclopropanecarbonyl)-2-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione**

[0175]



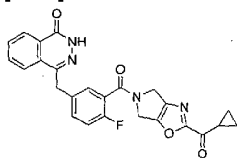
**4-(4-fluoro-3-(2-(trifluoromethyl)-5,6-dihydro-4H-pyrrolo[3,4-d]oxazole-5-carbonyl)benzyl)phthalazin-1(2H)-one**

[0176]



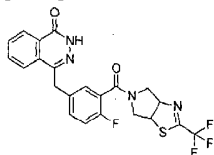
4-(3-(2-(cyclopropanecarbonyl)-5,6-dihydro-4H-pyrrolo[3,4-d]oxazole-5-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[0177]



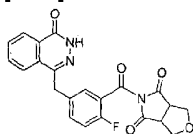
4-(4-fluoro-3-(2-(trifluoromethyl)-4,5,6,6a-tetrahydro-3aH-pyrrolo[3,4-d]thiazole-5-carbonyl)benzyl)phthalazin-1(2H)-one

[0178]



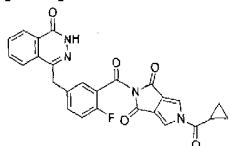
5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)dihydro-1H-furo[3,4-c]pyrrole-4,6(5H,6aH)-dione

[0179]



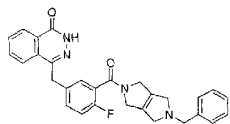
5-(cyclopropanecarbonyl)-2-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolo[3,4-c]pyrrole-1,3(2H,5H)-dione

[0180]



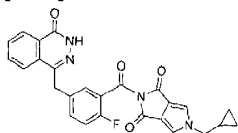
4-(3-(5-benzyl-1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[0181]



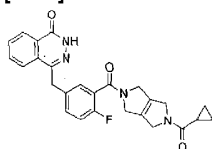
**5-(cyclopropylmethyl)-2-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolo[3,4-c]pyrrole-1,3(2H,5H)-dione**

[0182]



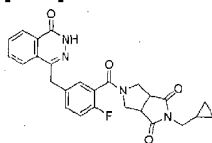
**4-(3-(5-(cyclopropanecarbonyl)-1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one**

[0183]



**2-(cyclopropylmethyl)-5-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione**

[0184]



#### Biological activity- *In vitro* study

##### *In vitro* study

[0185] Potentiation of cell killing activity of Methyl Methane Sulphonate (MMS) by selected compounds according to present invention was evaluated in MCF-7 cell line obtained from National Centre for Cell Science, Pune, by using MTT assay according to general protocol described in Methods in Molecular Biology, Volume-43, *In vitro* Toxicity Testing Protocol, Chapter-6, page:137-149. Compounds were tested for PARP 1 activity based on percent cell survival of MCF-7 cells with alkylating agent MMS.

[0186] The compounds were tested for PARP-1 inhibitory activity by using HT universal colorimetric PARP assay kit obtained from Trevigen, following manufacturer's protocol.

[0187] The results of the compounds are provided in Table 1.

[0188] Result of Table 1 shows that the compounds are found to possess PARP 1 inhibitory activity, thus have potential to be developed as compounds for therapeutic use.

#### In vivo study

[0189] On basis of the in vitro data, the ability of selected compounds to potentiate the antitumor activity of the methylating chemotherapeutic agent, temozolomide, was evaluated in an SW 620 tumor model.

[0190] Animals bearing SW 620 xenograft tumors were treated with the compounds in combination with TMZ (50 mg/Kg, po) once daily for 5 consecutive days, after which the tumors were left to grow out. A considerable inhibition of tumor volumes as compared with that of the TMZ alone group was observed for the TMZ plus compounds combinations (mean values given as relative tumor volumes (RTV) [table 2]. The compounds did not exacerbate the systemic toxicity of TMZ, with a maximum mean body weight loss of 9-10% on day 6 with full recovery of body weight within 3 days and with no mortalities, which indicates that the combination therapy was well tolerated by compounds under the dosing regimen.

[0191] Female athymic nude mice were used for antitumor *in vivo* studies. SW620 colorectal tumor cells ( $1 \times 10^7$  cells per animal) were implanted s.c. into one flank of each mouse. When tumors were palpable (10-12 days after implantation), animals were treated (n= 6-8/group) with five daily doses of temozolomide administered per os as a suspension in 0.5% methyl cellulose at 50 mg/kg either alone or in combination with a five daily per os administrations of PARP inhibitor at different doses. Tumor growths were measured using two-dimensional caliper measurements. Tumor volume was calculated using the equation  $a^2 \times b / 2$ , where a is the smallest measurement and b is the largest. Data are presented as median relative tumor volumes (RTV), defined as the calculated tumor volume divided by the calculated tumor volume on the initial day of treatment (day 0). Thus, on day 0, the RTV value is 1 and RTV4 is when the tumor is four times as large as its initial value. Control animals were treated with vehicle (15 tween 80 in methyl cellulose) alone tumor growth delay (TGD) = Time to RTV4 in treated group - time to RTV4 control.

**Table 1:** In-Vitro PARP-1 activity

Compound	PARP-1 activity in vitro IC50(nM) <sup>a</sup>	Compound	PARP-1 activity in vitro IC50(nM) <sup>a</sup>
Olaparib	8.39±2.3	Compound 29	18.43
Compound 1	11.54	Compound 30	9.87
Compound 2	8.41	Compound 31	24.25
Compound 3	14.55	Compound 32	11.54
Compound 6	46.71	Compound 33	28.5
Compound 7	38.63	Compound 34	11.68
Compound 9	23.97	Compound 35	29.87
Compound 12	14.15	Compound 36	27.87
Compound 14	46.45	Compound 38	90.95
Compound 15	11.64	Compound 39	54.52
Compound 16	103.8	Compound 40	9.9
Compound 17	30.27	Compound 41	8.9
Compound 19	34.41	Compound 42	48.6
Compound 20	11.78	Compound 43	55.1
Compound 21	22.56	Compound 44	19.87
Compound 22	20.22	Compound 45	13.8
Compound 23	67.85	Compound 46	27.8
Compound 24	9.85	Compound 47	48.3
Compound 25	27.81	Compound 48	74.5
Compound 26	35.95	Compound 54	15.4
Compound 27	12.47	Compound 55	13.23
Compound 28	20.73		

a PARP 1 IC<sub>50</sub> are estimation as calculated from a 4 point dose response curve

**Table 2:** In vivo antitumor efficacy of compounds in combination with temozolomide (TMZ) in an SW620 tumor model<sup>b</sup>.

Compounds	Median time to RTV4(days)	Tumor growth delay(days)
Vehicle(control)	10	
Temozolomide (50 mg/kg, po)	22	12
TMZ (50 mg/kg, po) + example 20 (50 mg/kg, po)	43	33
TMZ (50 mg/kg, po) + example 35 (10 mg/kg, po)	50	40
TMZ (50 mg/kg, po) + example 36 (10 mg/kg, po)	37	27
TMZ (50 mg/kg, po) + example 36 (30 mg/kg, po)	44	34
TMZ (50 mg/kg, po) + example 36 (100 mg/kg, po)	65	55

<sup>b</sup> Mice were orally dosed once daily for 5 consecutive days. The compounds were administered 45 min before TMZ.

## REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

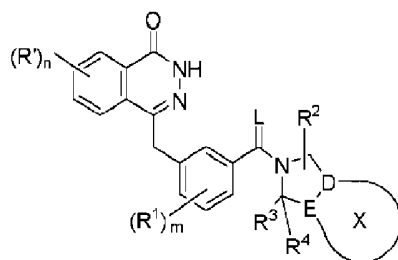
### Patent documents cited in the description

- [WO2002036676A \[0009\]](#)
- [WO2006039545A \[0009\]](#)
- [WO2007062413A \[0009\]](#)
- [WO2004080976A \[0009\]](#)
- [WO2009093032A \[0009\]](#)
- [WO2008047082A \[0009\] \[0011\]](#)
- [WO2001042219A \[0009\]](#)
- [WO2005066163A \[0009\]](#)
- [WO2006106326A \[0009\]](#)
- [WO2008146035A \[0009\]](#)
- [WO2006021801A \[0009\]](#)
- [US20090192156A \[0009\]](#)
- [WO2012019427A \[0009\]](#)
- [WO2012071684A \[0009\]](#)
- [WO2012019426A \[0009\] \[0026\]](#)
- [WO2012072033A \[0009\] \[0027\]](#)
- [US20090192156A1 \[0009\]](#)
- [WO2009093032A1 \[0009\]](#)
- [WO2008146035A1 \[0010\]](#)
- [WO2005066163A2 \[0010\]](#)
- [WO2006021801A1 \[0012\]](#)
- [WO2004080976A1 \[0012\]](#)
- [WO2012166983A \[0028\]](#)
- [WO2012014221A \[0029\]](#)

- [WO2013117120A](#) [0030]
- [WO2013117288A](#) [0031]
- [WO2013008872A](#) [0032]
- [WO2013097226A](#) [0033]
- [US8475842B](#) [0034]
- [US20130053365A](#) [0035]

#### Non-patent literature cited in the description

- **SENTHIL KUMAR B., RAJMOHAN et al.** Mol. Cell. Biol., 2009, vol. 29, 154116-4129 [0003]
- **VIRAG LASZLOSZABO CSABA** Pharmacol. Reviews, 2002, vol. 54, 3375-429 [0003]
- **D'ADDI FAGOGNA et al.** Nature Gen., 1999, vol. 23, 1076-80 [0003]
- **ALTHAUS, F. R. RICHTER, C.** Mol. Biol., Biochem. Biophys., 1987, vol. 37, 1-237 [0004]
- **RATNAM KAPILLAW JENIFER A.** Clin. Cancer Res., 2007, vol. 17, 51383-1388 [0004]
- British Journal of Cancer, 2009, vol. 101, 2256-26 [0004]
- Free Radical Biology & Medicine, 2009, vol. 47, 13-26 [0005]
- Biochem. Pharmacol., 2009, vol. 77, 1348-1357 [0006]
- Eur. J. Cancer, 2009, vol. 45, 1897-1901 [0007]
- Nature Reviews Cancer, 2010, 1-9 [0008]
- **HERWIG SCHULER et al.** Pharmacol. Biochemistry, 2010, vol. 49, 1056-1058 [0008]
- **PETER T. SUNDERLAND** J. Med. Chem., 2011, vol. 54, 2049-2059 [0013]
- Clin Cancer Res, 2011, vol. 17, 783-791 [0013]
- Journal of Chromatography B, 2011, vol. 878, 333-339 [0014]
- **DANA V. FERRARIS** Evolution of Poly(ADP-ribose) Polymerase-1 (PARP-1) inhibitors, From Concept to Clinic J. Med. Chem., 2010, vol. 53, 4561-4584 [0015]
- **FEDERICA FERRIGNO et al.** Development of substituted 6-[4-fluoro-3-(piperazin-1-ylcarbonyl)benzyl]-4,5-dimethylpyridazin-3-(2H)-ones as potent poly(ADP-ribose) polymerase -1 (PARP-1) inhibitors active in BRCA deficient cells Bioorg. Med. Chem. Lett., 2010, vol. 20, 1100-1105 [0016]
- Polymerase Inhibitors: Identification of (S)-2-(2-Fluoro-4-(pyrrolidin-2-yl)phenyl)-1H-benzimidazole-4-carboxamide (A-966492), a highly Potent and Efficacious Inhibitor J. Med. Chem., 2010, vol. 53, 3142-3153 [0017]
- J. Med. Chem., 2009, vol. 52, 868-877 [0018]
- J. Med. Chem., 2009, vol. 52, 514-523 [0018]
- Bioorg. Med. Chem. Lett., 2009, vol. 19, 4042-4045 [0019]
- Bioorg. Med. Chem. Lett., 2009, vol. 19, 7537-7541 [0020]
- Bioorg. Med. Chem. Lett., 2009, vol. 19, 4196-4200 [0021]
- Bioorg. Med. Chem. Lett., 2009, vol. 19, 4050-4054 [0022]
- Bioorg. Med. Chem. Lett., 2008, vol. 18, 5126-5129 [0023]
- J. Med. Chem., 2004, vol. 47, 4151-4154 [0024]
- J. Med. Chem., 2005, vol. 48, 5100-5103 [0025]
- J. Med. Chem., 2008, vol. 51, 6581-6591 [0058]
- Methods in Molecular Biology In vitro Toxicity Testing Protocol vol. 43, 137-149 [0185]

**Patentkrav****1. Forbindelse med strukturen i den almene formel (I)**

5

(I)

hvor  $R^1$  ved hver forekomst uafhængigt er udvalgt blandt H, halogen, eller grupperne udvalgt blandt  $(C_1-C_{12})$ alkyl, haloalkyl, cycloalkyl, alkylthio eller  $(OSO_2)$ alkyl-gruppen, hvor hver af disse grupper er yderligere substitueret med egnede substituer udvalgt blandt hydroxyl-, oxo-, halo-, thio-, nitro-, amino-, alkyl-, alkoxy-, haloalkyl- og haloalkoxygrupper;

10

$R'$  ved hver forekomst uafhængigt er udvalgt blandt halogen-, alkyl-, alkoxy-, hydroxyl-, haloalkyl-, haloalkoxy-, cyano-, thioalkyl-, cycloalkylgrupper;

$m = 1-4$ ;  $L = -O, -S, -NH$ ;  $n = 0-4$ ;

$R^2$  er udvalgt blandt substituentgrupper bestående af hydrogenatom, hydroxyl, alkyl, cycloalkyl, oxo,  $C(O)OR^5$ ,  $-C(O)R^5$  eller  $-C(O)NR^6R^7$ , hvor alkyl- og cycloalkylgrupperne yderligere er substitueret med en eller flere substituer udvalgt blandt halogen-, hydroxyl-, alkyl- eller alkoxygrupper;

15

$R^3$  og  $R^4$  hver især uafhængigt er udvalgt blandt hydrogenatom, alkyl, hydroxyl, alkoxy, cycloalkyl,  $-C(O)OR^5$ ,  $-OC(O)R^5$ ,  $-O(CH_2)_pC(O)OR^5$ ,  $-C(O)R^5$ ,  $-NHC(O)R^5$ ,  $-NR^6R^7$ ,  $-OC(O)NR^6R^7$  eller  $-C(O)NR^6R^7$  eller alternativt,  $R^3$  og  $R^4$  tilsammen danner en oxogruppe;

20

hver af ringatomerne 'D' og 'E' uafhængigt er udvalgt blandt C- eller N-atomer;

'D' og 'E' er forbundet med hinanden for at danne en 5-leddet ring 'X', hvor 'X' er udvalgt blandt heterocyclyl og heteroaryl, hvor heterocyclyl og heteroaryl er substitueret med en eller flere egnede substituer udvalgt blandt hydrogen-, cyano-, halogen-, hydroxyl-, oxo-, eventuelt substituerede grupper udvalgt blandt alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, benzyl,  $OR^5$ ,  $-C(O)OR^5$ ,  $-OC(O)R^5$ ,  $-O(CH_2)_pC(O)OR^5$ ,  $C(O)R^5$ ,  $S(O)_qR^5$ ,  $-NHC(O)R^5$

30

NR<sup>6</sup>R<sup>7</sup>, -OC(O)NR<sup>6</sup>R<sup>7</sup> eller -C(O)NR<sup>6</sup>R<sup>7</sup>, og hvor alkyl-, cycloalkyl-, heterocyclyl-, aryl-, heteroaryl- eller benzylgruppen hver især uafhængigt kan være yderligere substitueret med en eller flere substituenten udvalgt blandt alkyl-, halogen-, hydroxyl-, alkoxy-, cycloalkyl-, heterocyclyl-, aryl-, heteroaryl-, oxo-,  
 5 -C(O)OR<sup>5</sup>-, -OC(O)R<sup>5</sup>-, O(CH<sub>2</sub>)<sub>p</sub>C(O)OR<sup>5</sup>-, -C(O)R<sup>5</sup>-, -S(O)<sub>q</sub>R<sup>5</sup>-, -NHC(O)R<sup>5</sup>-, NR<sup>6</sup>R<sup>7</sup>-, -OC(O)NR<sup>6</sup>R<sup>7</sup>- eller -C(O)NR<sup>6</sup>R<sup>7</sup>-grupper;

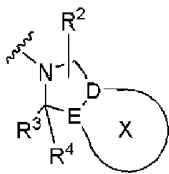
R<sup>5</sup> ved hver forekomst uafhængigt er udvalgt blandt hydrogenatom, eventuelt substituerede grupper udvalgt blandt alkyl-, cycloalkyl-, heterocyclyl-, aryl- eller heteroarylgrupper, hvor de eventuelle substituenten er udvalgt blandt  
 10 alkyl, halogen, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, carboxylsyre eller carboxylsyreester;

hver af R<sup>6</sup> eller R<sup>7</sup> ved hver forekomst uafhængigt er udvalgt blandt H, eventuelt substituerede grupper udvalgt blandt alkyl, cycloalkyl, heterocyclyl, aryl eller heteroaryl, hvor de eventuelle substituenten uafhængigt er udvalgt  
 15 blandt alkyl, halogen, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, carboxylsyre eller carboxylsyreester;

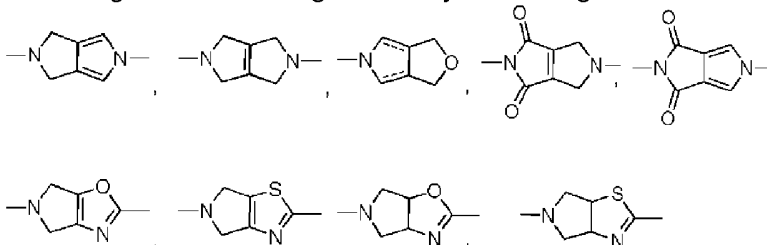
eller R<sup>6</sup> og R<sup>7</sup> er forbundet med hinanden sammen med nitrogenatomet for at danne en heterocyclylring; hvor heterocyclylringen indeholder et eller flere heteroatomer udvalgt blandt N, O, S(O)<sub>q</sub>, q er 0, 1 eller 2 og p er 0, 1 eller 2.

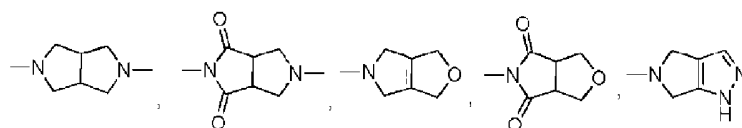
20

2. Forbindelse ifølge krav 1, hvor heterocyclussen, der betegner



25 er udvalgt blandt de følgende bicykliske ringe nævnt nedenfor

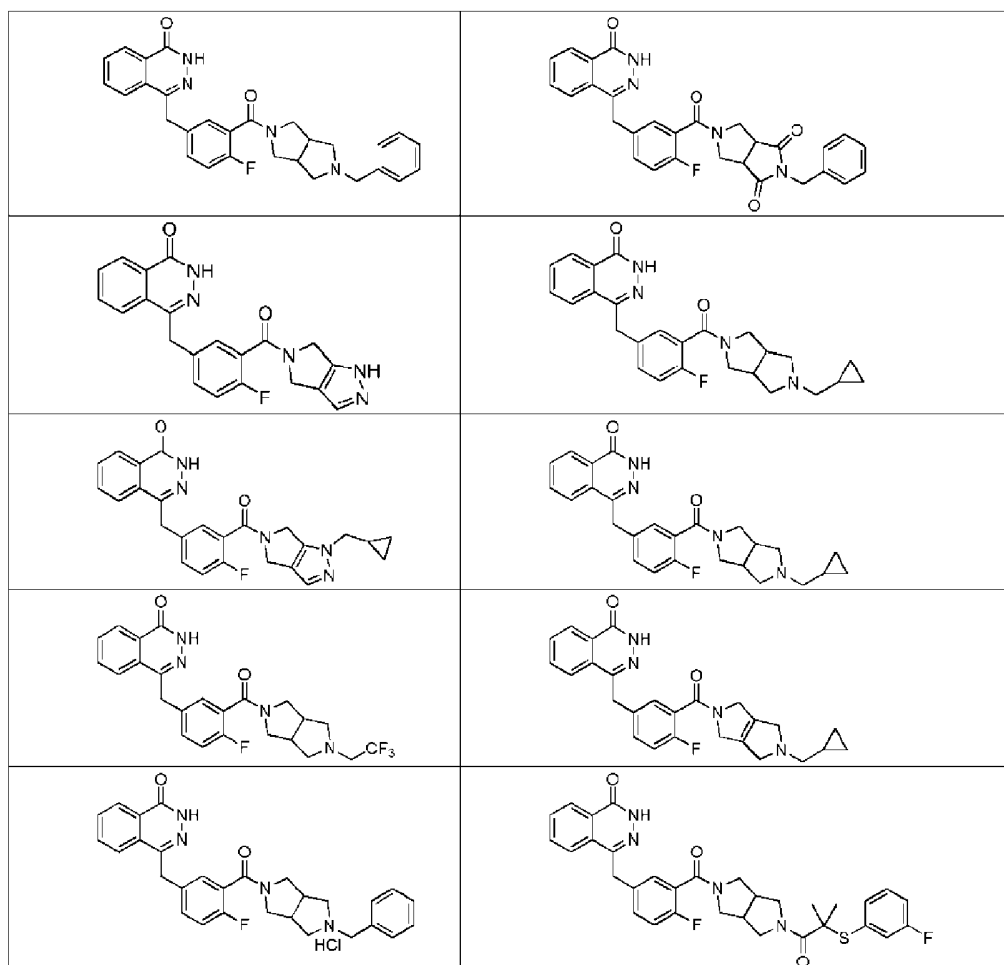


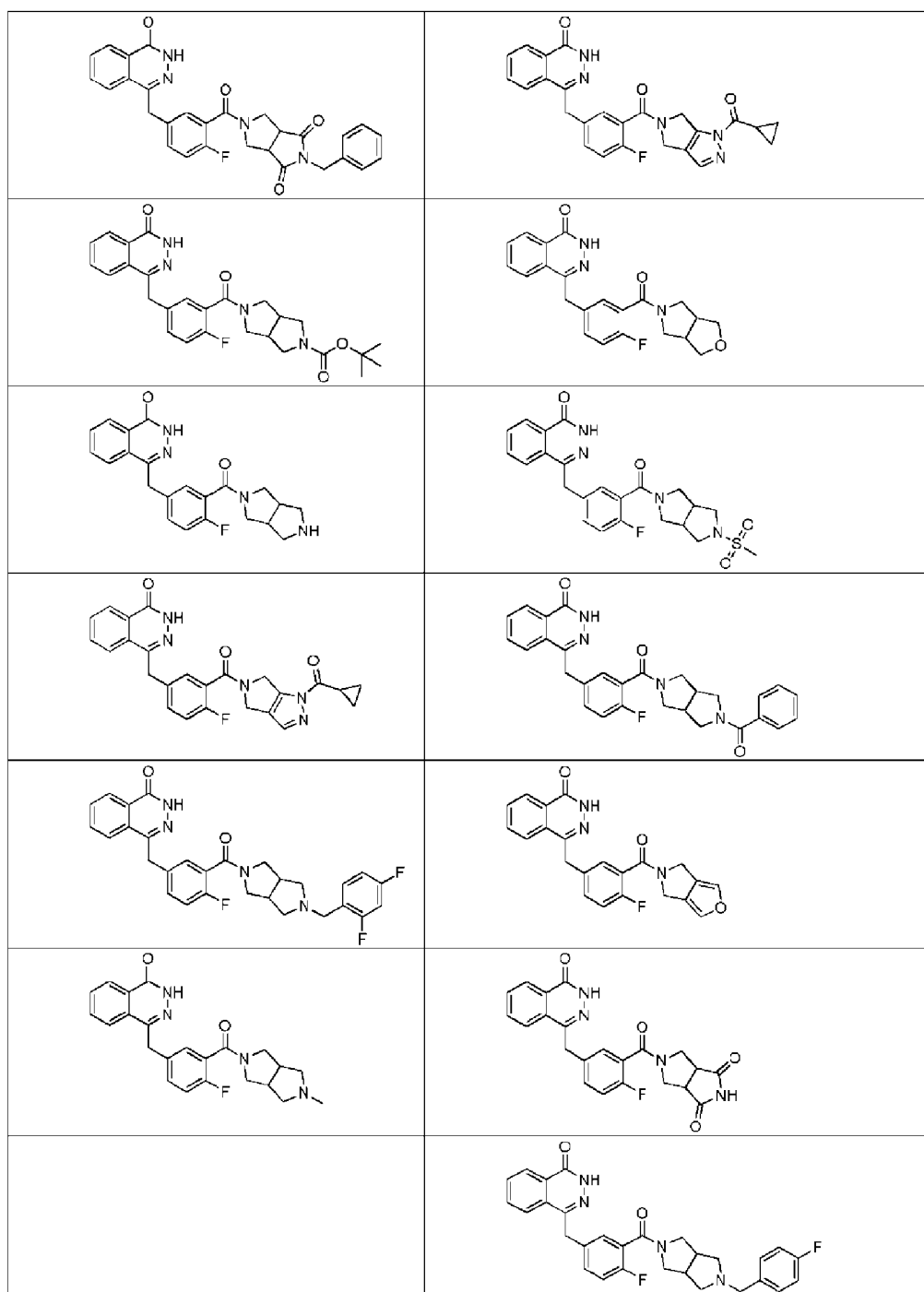


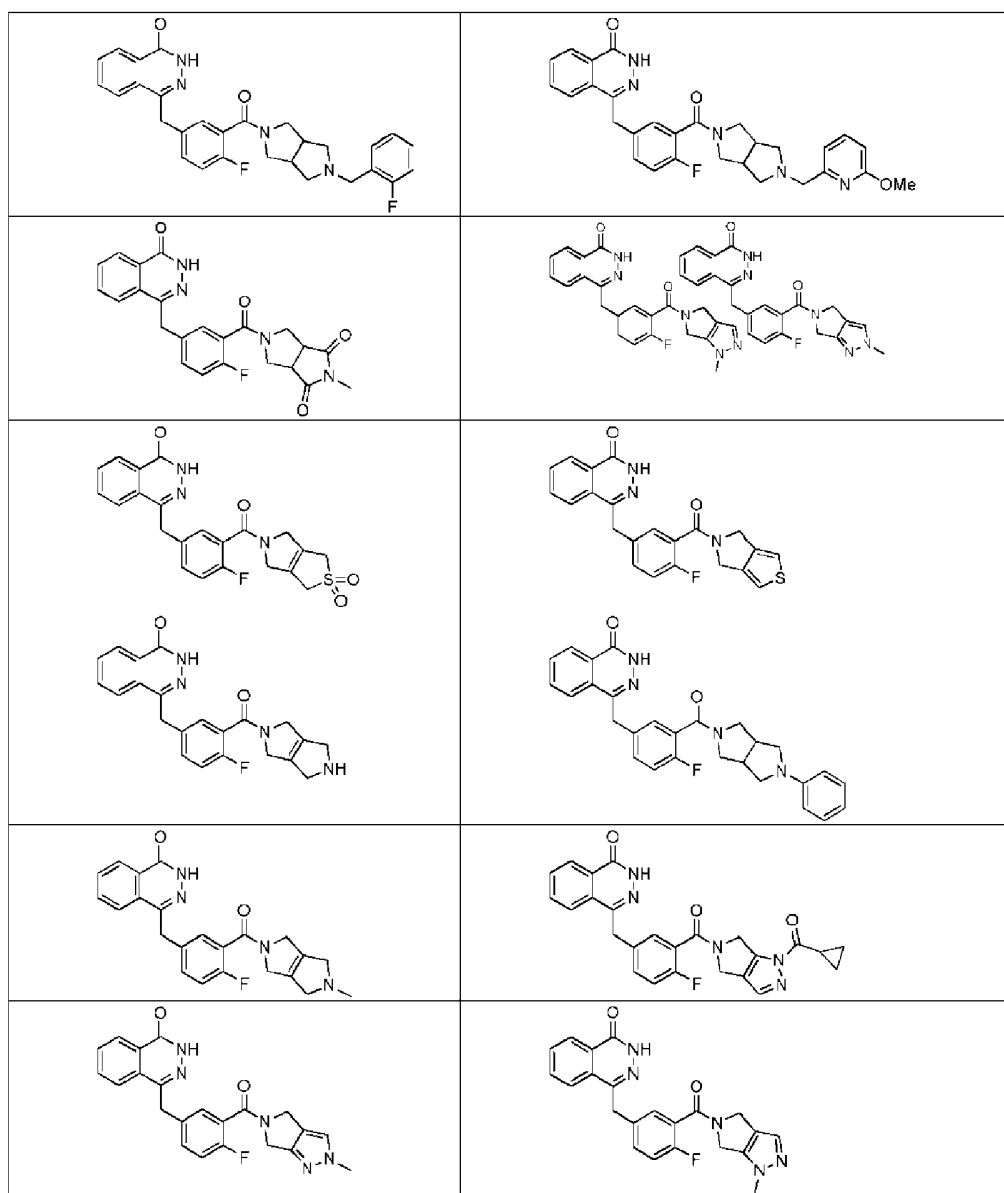
- 3.** Forbindelse ifølge krav 1, hvor substituerterne på ring X er udvalgt blandt halogen, hydroxyl, oxo, eventuelt substituerede grupper udvalgt blandt alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, benzyl,  $\text{OR}^5$ ,  $-\text{C}(\text{O})\text{OR}^5$ ,  $-\text{OC}(\text{O})\text{R}^5$ ,  $-\text{O}(\text{CH}_2)_p\text{C}(\text{O})\text{OR}^5$ ,  $\text{C}(\text{O})\text{R}^5$ ,  $\text{S}(\text{O})_q\text{R}^5$ ,  $-\text{NHC}(\text{O})\text{R}^5$ ,  $\text{NR}^6\text{R}^7$ ,  $-\text{OC}(\text{O})\text{NR}^6\text{R}^7$  eller  $-\text{C}(\text{O})\text{NR}^6\text{R}^7$ , hvor hver af  $\text{R}^5$ ,  $\text{R}^6$  og  $\text{R}^7$  er som defineret i krav 1, og hvor alkyl-, cycloalkyl-, heterocyclyl-, aryl-, heteroaryl- eller benzylgruppen hver især uafhængigt yderligere er substitueret med en eller flere substituerter udvalgt blandt alkyl-, halogen-, hydroxyl-, alkoxy-, cycloalkyl-, heterocyclyl-, aryl-, heteroaryl-, oxo-,  $-\text{C}(\text{O})\text{OR}^5$ -,  $-\text{OC}(\text{O})\text{R}^5$ -,  $\text{O}(\text{CH}_2)_p\text{C}(\text{O})\text{OR}^5$ -,  $-\text{C}(\text{O})\text{R}^5$ -,  $-\text{S}(\text{O})_q\text{R}^5$ -,  $-\text{NHC}(\text{O})\text{R}^5$ -,  $\text{NR}^6\text{R}^7$ -,  $-\text{OC}(\text{O})\text{NR}^6\text{R}^7$ - eller  $-\text{C}(\text{O})\text{NR}^6\text{R}^7$ -grupper.
- 4.** Forbindelse ifølge krav 1, hvor "aryl"-grupperne er udvalgt blandt phenyl-, naphthyl-, tetrahydronaphthyl-, indenyl-, dihydroindenyl-, biphenylgrupper; og/eller hvor heteroaryl- eller den heteroaromatiske gruppe er udvalgt blandt pyridyl-, thienyl-, furyl-, pyrrolyl-, indolinyll-, indolyl-, pyridofuranyl-, pyridothienyl-, thienopyrimidyl-, quinolinyll-, pyrimidinyl-, pyrazolyl-, quinazolinyll-, pyridazinyl-, purinylgrupper; og/eller hvor heterocyclylgruppen er udvalgt blandt aziridinyl-, azetidinyll-, pyrrolidinyl-, imidazolidinyl-, piperidinyl-, piperazinyl-, 2-oxopiperidinyl-, 4-oxopiperidinyl-, 2-oxopiperazinyl-, 3-oxopiperazinyl-, morpholinyl-, thiomorpholinyl-, 2-oxomorpholinyl-, azepinyl-, diazepinyl-, oxapinyl-, thiazepinyl-, oxazolidinyl-, thiazolidinyl-, dihydrothiophen-, dihydropyran-, dihydrofuran-, dihydrothiazol-, benzopyranyl-, benzopyranonyll-, benzodihydrofuranyl-, benzodihydrothienyl-, pyrazolopyrimidonyll-, azaquinazolinyll-, thienopyrimidonyll-, quinazolonyll-, pyrimidonyll-, benzoxazinyl-, benzoxazinonyll-, benzothiazinyl-, benzothiazinonyll-, thienopiperidinylgrupper.
- 5.** Forbindelse ifølge krav 1, hvor substituerterne på arylgrupper uafhængigt er udvalgt blandt hydrogen-, halogen-, alkyl-, alkoxy-, hydroxyl-, haloalkyl-, haloalkoxy-, cyano-, thioalkyl-, cycloalkylgrupper; og/eller hvor substituerterne på heteroaryl- eller heteroaromatiske grupper er udvalgt blandt hydrogen-, halogen-, alkyl-, alkoxy-, hydroxyl-, haloalkyl-, haloalkoxy-, aryl-, aralkyl-, cy-

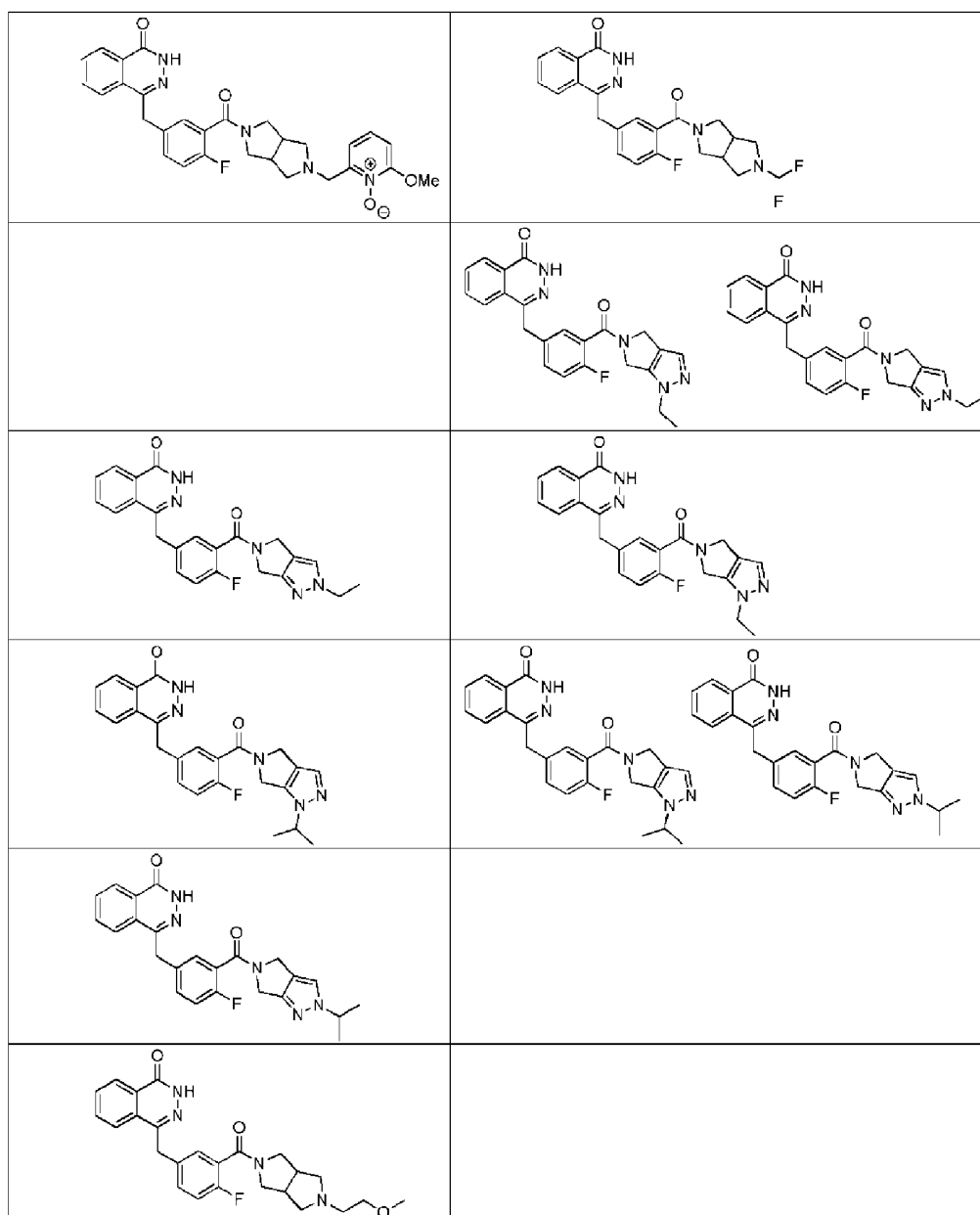
ano-, alkylthio-, thioalkylgrupper; og/eller hvor substituenterne på heterocyclgrupper er udvalgt blandt hydrogen-, halogen-, alkyl-, alkoxy-, hydroxyl-, haloalkyl-, haloalkoxy-, aryl-, aralkyl-, cyano-, alkylthio-, thioalkylgrupper.

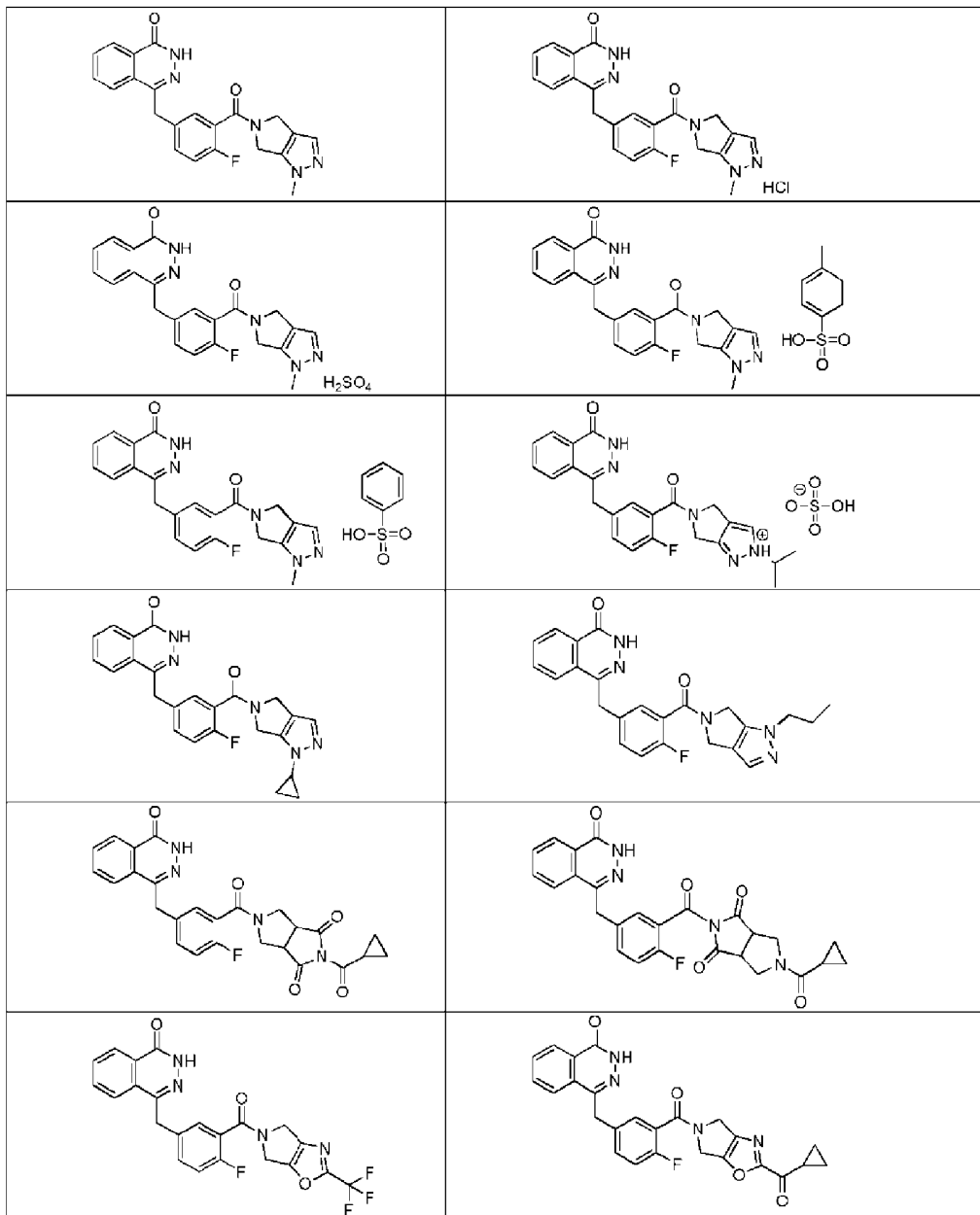
5 **6.** Forbindelse ifølge krav 1 udvalgt fra gruppen bestående af:

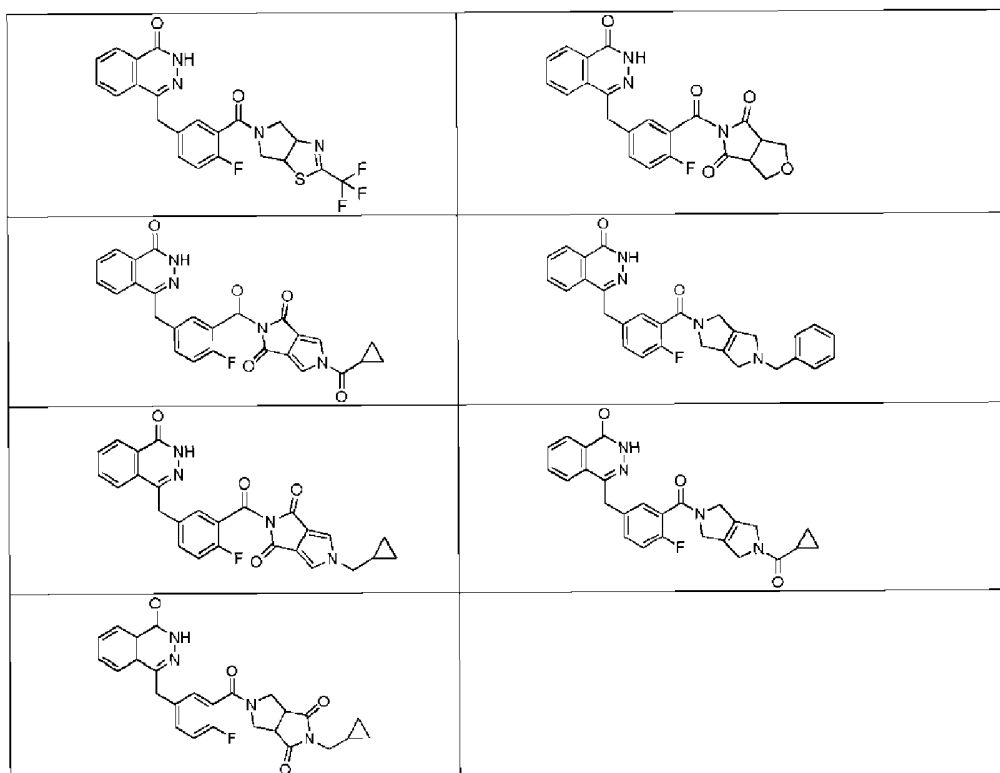






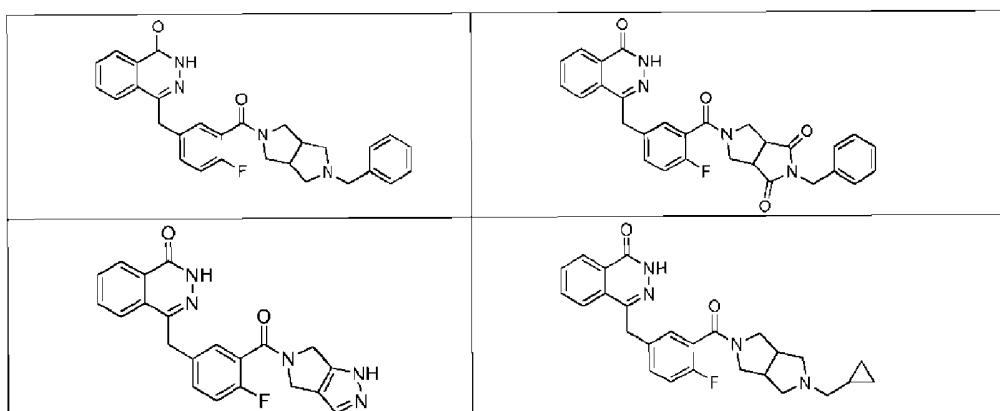


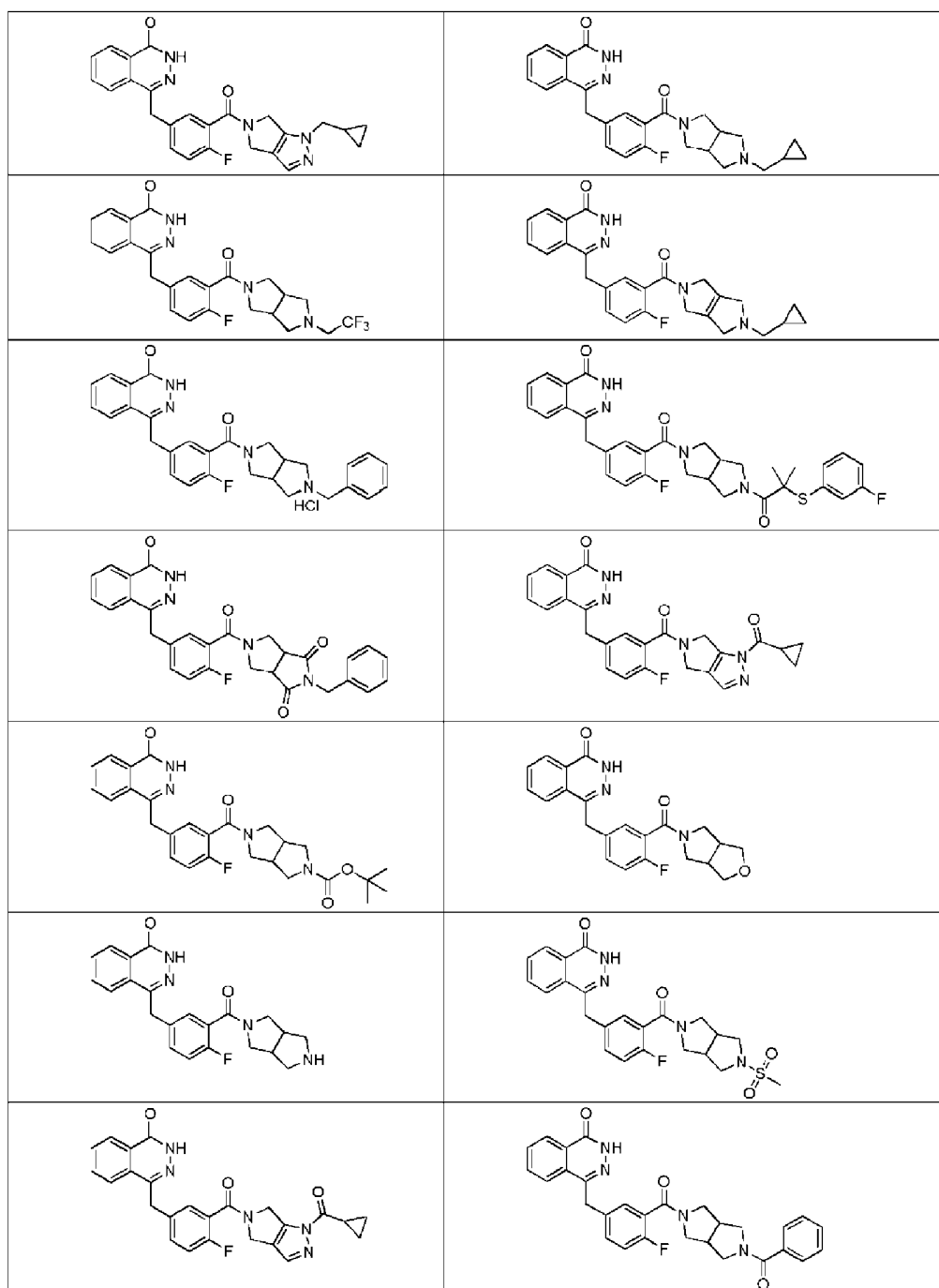


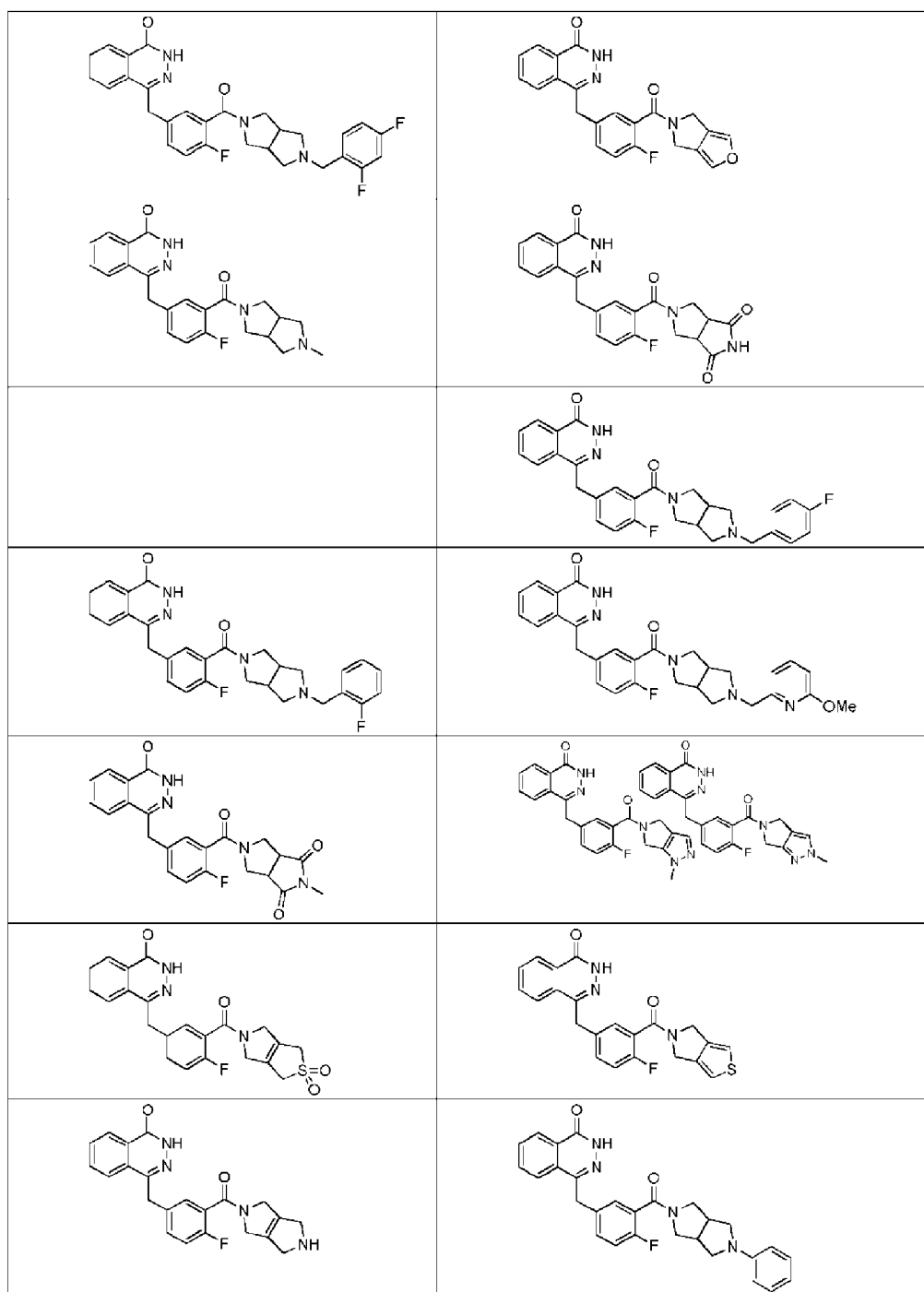


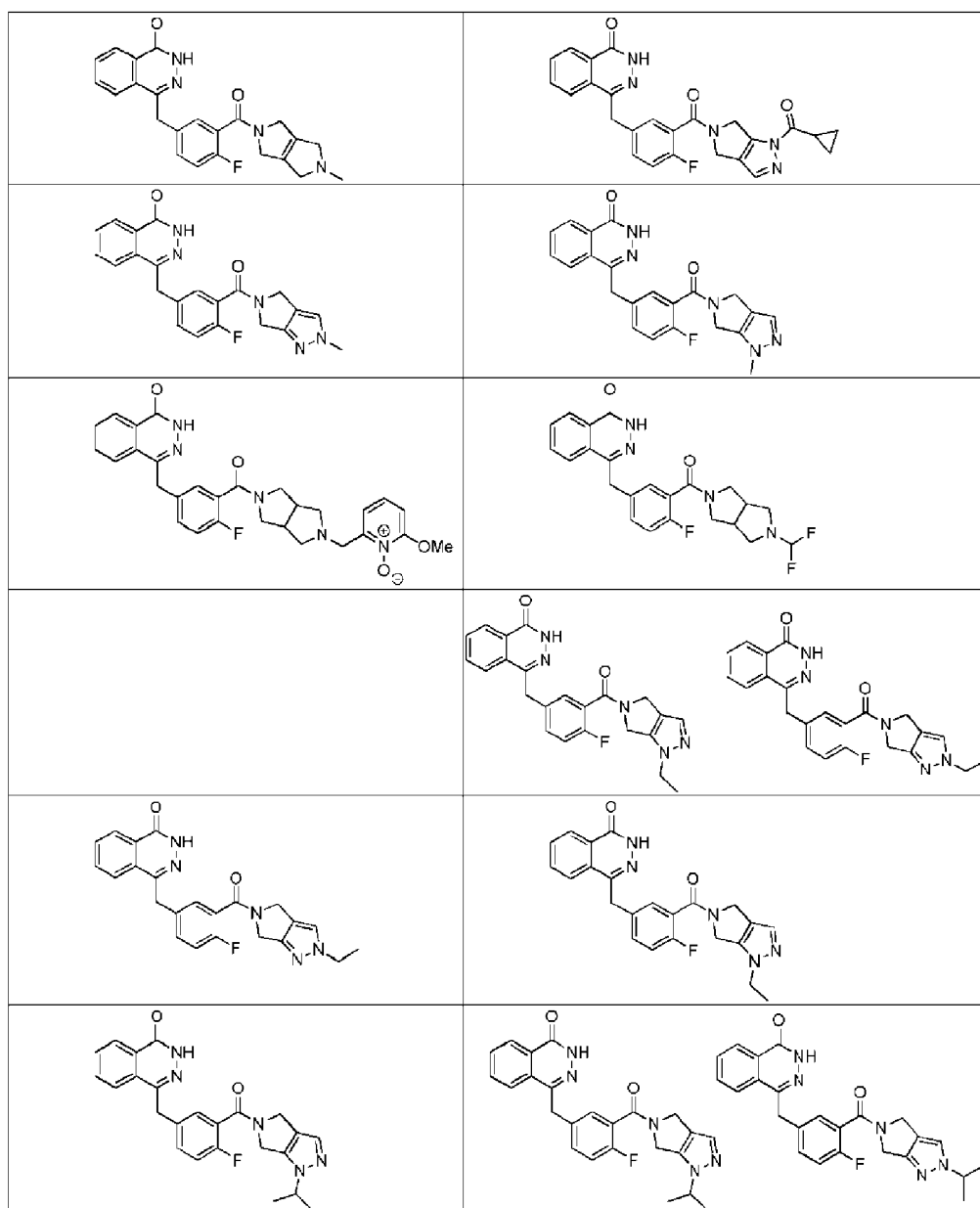
7. Forbindelse ifølge et af de foregående krav udvalgt fra gruppen bestående af:

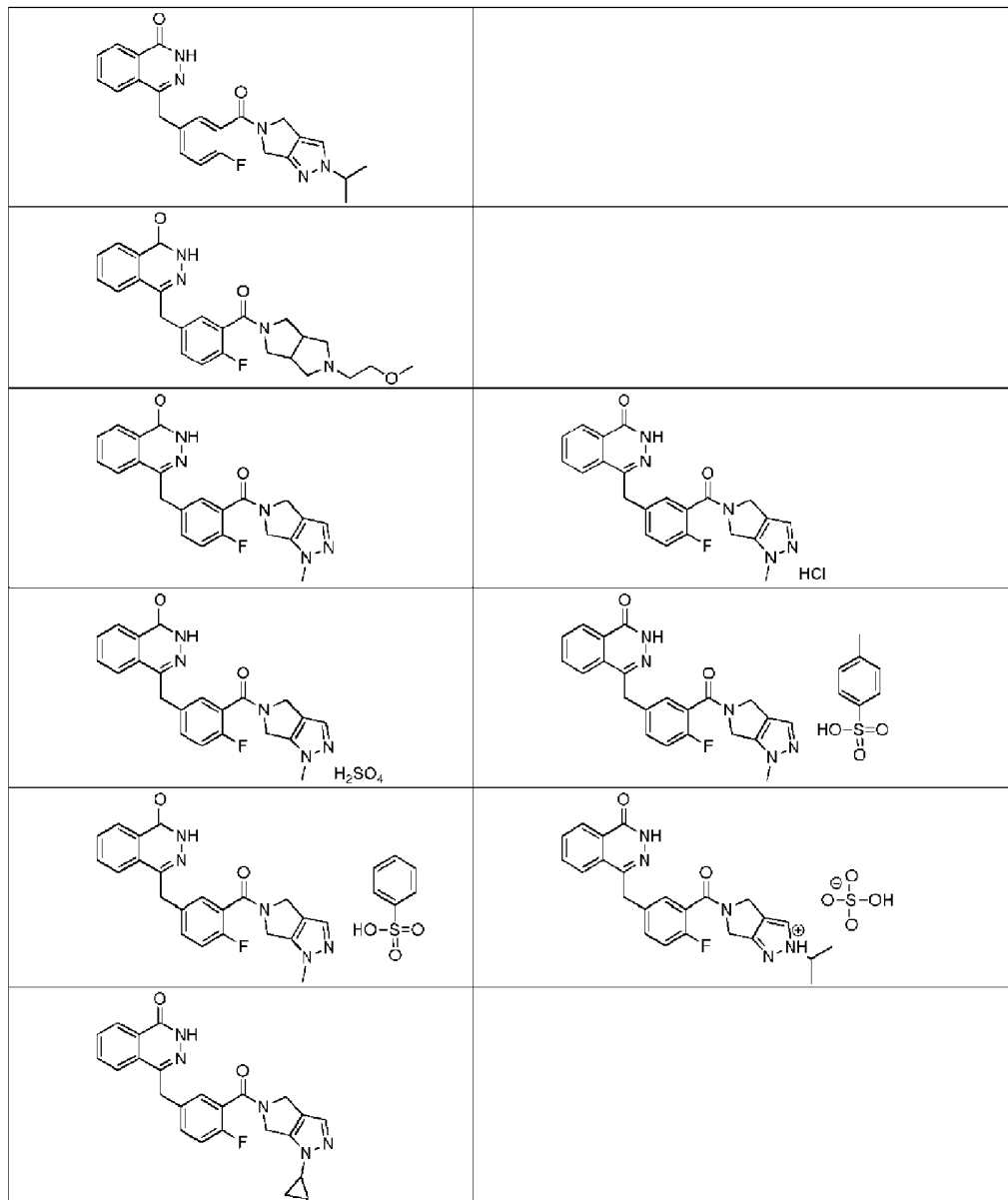
5











8. Farmaceutisk sammensætning omfattende en terapeutisk virksom mængde af en forbindelse med Formel (I) ifølge et af de foregående krav og eventuelt en eller flere farmaceutisk acceptable bærere, fortyndingsmidler eller hjælpestoffer.

9. Forbindelse med Formel (I) ifølge et af kravene 1 til 7 til anvendelse ved behandling af cancer.

**10.** Farmaceutisk sammensætning omfattende en forbindelse med Formel (I) ifølge et af kravene 1 til 7 sammen med en eller flere farmaceutisk acceptable bærere, fortyndingsmidler eller hjælpestoffer til anvendelse ved behandling af cancer.