

Description

Title of Invention: A NOVEL PHTALAZINONE DERIVATIVES AND MANUFACTURING PROCESS THEREOF

Technical Field

- [1] The present invention relates to phtalazinone derivates, isomers, pharmaceutically acceptable salt thereof and on its study for medicinal uses.

Background Art

- [2] The interest in Poly ADP ribose polymerase(PARP) inhibitors is increasing in accordance with the detection of a high rate of BRCA1 or BRCA2 gene mutation due to the recent genetic breast and ovarian cancer. In general, with BRCA genetic mutations the breast cancer risk is 5 times higher, and one of them in particular, the probability of a considerable risk for TNBC (Triple-negative breast cancer) is increasing. TNBC accounted for 15% of breast cancer patients is related to the lacks of estrogen receptors, progesterone receptors. As there has been no special treatment until now, the target of TNBC contains significant market potential.
- [3] The PARP is the one of repairing enzyme for damaged single-stranded DNA breakes. In case of inhibition of PARP, the damage of single strand consecutively generates defects in double-stranded DNA. At this point, the defects of double strand can be recovered by BRCA protein complex. Thus in general, eventhough the one of the DNA repairing paths is not working, most of cell can be alive. But the cancer patients who inheritantly lost repairing path of BRCA protein complex by the mutation of BRCA1/BRCA2 can increase dependancy on the PARP pathway of DNA repairing. Especially, as the possibility of defects in DNA replication in case of cancer cell is higher than normal cell, the cancer cell has higher dependance on PARP path than normal cell. In other words, the PARP inhibitors fundamentally block the repairing system of cancer cell following apoptosis of cancer cell.
- [4] To date, 18 members of the PARP family have been identified and characterized, with PARP-1 being the most thoroughly studied and PARP-2 being its closest relative. Despite the large number of enzymes in this family, PARP-1 accounts for >90% of the ADP-ribosylation within the cell. Because of the structural homology between PARP-1 and PARP-2, most PARP-1 inhibitors also inhibit PARP-2. The PARP-1 enzyme is a 113 kDa protein with three major structural domains, a DNA binding domain with two zinc fingers, a 55 kDa catalytic domain, which utilizes nicotinamide adenine dinucleotide(NAD⁺) as a substrate to construct polymers of ADP-ribose on histones and other nuclear acceptor proteins including the automodification domain of PARP-1 itself. It is published and generally accepted that the catalytic activity of PARP-1 is

stimulated by DNA damage caused by peroxidation, irradiation, and DNA-damaging chemicals, chemotherapeutic agents. Toward this end, PARP-1 enzyme binds to damaged DNA and stimulates polymerization of ADP-ribose resulting in the unwinding of DNA from histones and exposing the damaged DNA for repairing. Accordingly, PARP-1 is associated with DNA repairing and maintenance.

- [5] TNBC breast cancer is associated with BRCA1 and BRCA2 gene mutations. The central role of the BRCA gene is the recovery of double stranded break (DSB) through homologous recombination(HR). PARP-1 inhibition will lead to an increase in single strand breaks(SSB), the preponderance of these SSBs will eventually lead to increased DSBs. The increase of DSBs in BRCA1/BRCA2 gene mutation cancer patients in the presence of HR deficient cell types leads to chromosomal aberrations and instability of the genome resulting in cell death.
- [6] A conventionally known PARP inhibitor Olaparib (WO2002036576, WO2003093261, US2004876080, US2005059663) are developed for the treatment of cancer, such as, specifically, stomach cancer, ovarian cancer, breast cancer.
- [7] Following four patents are published with modified phenyl group of phtalazinone structure (WO2007138351, WO2007138355, WO2009063244, and WO2009112832).
- [8] Since 2011 pharmaceutical companies from China and India published various patent with modified derivates of Olaparib (WO2012019426A1, WO2012019427A1, WO2012019430A1, WO2012071684A1, WO2012072033A1 and WO2012014221).
- [9] As anticancer agents PARP inhibitors, has been progressed with respect to the prior published clinical literature, has a new mechanism of action for the treatment of cancer. PARP inhibitors are development as first target for personalized medicine based on personal genetic mutation so that worldwide attention is focused. PARP inhibitors have been reported to exhibit in particular a significant effect on cancer caused by genetic mutations in BRCA1 / 2, and the present invention with new mechanism for the treatment of cancer patients with genetic variation in BRCA1 / 2 genes is expected to open a new chapter.

Disclosure of Invention

Technical Problem

- [10] An object of the present invention is to provide a novel phtalazinone derivative and a process method for preparing.
- [11] In addition, the object of the present invention is to provide medical use for useful treatment of diseases improved by PARP inhibition, or cancers caused by generic defect of BRCA1, BRCA2, and ERG fusion gene.
- [12] However, the technical objects to be achieved in the present invention are not limited to those stated above and other objects may be clearly understood to those skilled in

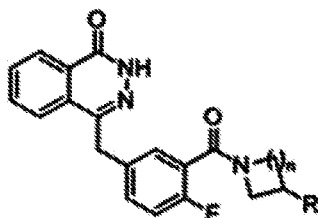
the art from the following description.

Solution to Problem

- [13] To solve the problem described above, the present invention provides a compound represented by Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof.

[14] [Formula I]

[15]

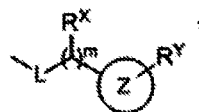


[16] wherein,

[17] n is 1 or 2,

[18] R is or

[19] Wherein, when the R is



[20] m is 0, 1 or 2,

[21] L is oxygen, methylene, carbonyl, CONHCH₂, NR^{c1}CH₂, NR^{c2}CO, NR^{c3}, CONR^{c4} or CH₂NR^{c5}(especially, R^{c1}, R^{c2}, R^{c3}, R^{c4} and R^{c5} is each independently oxygen, C₁₋₄ alkylamine, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl or 3-8 membered heterocycle),

[22] R^x is hydrogen, cyano, hydroxyl, trifluoromethyl, C₁₋₆ alkyl or C₃₋₈ cycloalkyl,

[23] R^y is hydrogen, amide, cyano, hydroxyl, trifluoromethyl, halo, ester, C₁₋₄ alkylamine, C₁₋₆ alkyl, C₁₋₆ methoxyalkyl or C₂₋₆ alkynyl,

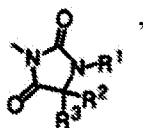
[24] Z is unsubstituted, C₁₋₆ alkyl, C₁₋₆ methoxyalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, C₆₋₁₀ aromatic cycle or 3-8 membered heterocycle having 1-3 nitrogens,

[25] wherein, when the R is

[26] p and q is each independently from 1 to 3,

[27] W is CR^{d1}R^{d2} or NR^{d3}(especially, R^{d1}, R^{d2} and R^{d3} is each independently hydrogen, fluoro or C₁₋₆ alkyl),

[28]



[29] R^1 , R^2 and R^3 is each independently hydrogen or C_{1-6} alkyl.

[30] The present invention provides a pharmaceutical composition for treating cancers comprising the compound represented by Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof.

[31] The present invention provides a preparation method of the compound represented by Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof.

Advantageous Effects of Invention

[32] The compounds of the present invention are highly active in the suppression of PARP, and according to its pharmaceutical compositions are expected to be useful for therapeutic applications which are improved by suppression of PARP activity, and cancer with mutated BRCA1, BRCA2 and ERG fusion gene in mono or combination treatment with radiation and with chemotherapy.

Best Mode for Carrying out the Invention

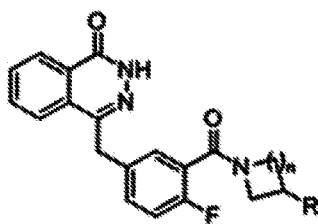
[33] Hereinafter, the present invention will be described in detail.

[34]

[35] The present invention provides a compound represented by Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof.

[36] [Formula I]

[37]



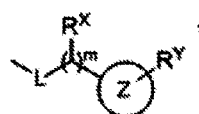
[38] wherein,

[39] n is 1 or 2,

[40] R is



[41] Wherein, when the R is

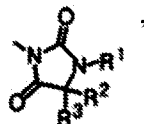


[42] m is 0, 1 or 2,

- [43] L is oxygen, methylene, carbonyl, CONHCH₂, NR^{c1}CH₂, NR^{c2}CO, NR^{c3}, CONR^{c4} or CH₂NR^{c5}(especially, R^{c1}, R^{c2}, R^{c3}, R^{c4} and R^{c5} is each independently oxygen, C₁₋₄ alkylamine, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl or 3-8 membered heterocycle),
- [44] R^x is hydrogen, cyano, hydroxyl, trifluoromethyl, C₁₋₆ alkyl or C₃₋₈ cycloalkyl,
- [45] R^y is hydrogen, amide, cyano, hydroxyl, trifluoromethyl, halo, ester, C₁₋₄ alkylamine, C₁₋₆ alkyl, C₁₋₆ methoxyalkyl or C₂₋₆ alkynyl,
- [46] Z is unsubstituted, C₁₋₆ alkyl, C₁₋₆ methoxyalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, C₆₋₁₀ aromatic cycle or 3-8 membered heterocycle having 1-3 nitrogens,
- [47] wherein, when the R is



- [48] p and q is each independently from 1 to 3,
- [49] W is CR^{d1}R^{d2} or NR^{d3}(especially, R^{d1}, R^{d2} and R^{d3} is each independently hydrogen, fluoro or C₁₋₆ alkyl),
- [50] wherein, when the R is



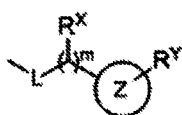
- [51] R¹, R² and R³ is each independently hydrogen or C₁₋₆ alkyl.

[52]

- [53] In the present invention, the compound of Formula I is preferably selected from i) or Vii) disclosed below:

[54]

- [55] i) In case, R is



CO, NR^{c3}, CONR^{c4} or CH₂NR^{c5}(especially, R^{c1}, R^{c2}, R^{c3}, R^{c4} and R^{c5} is each independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkynyl or C₃₋₈ cycloalkyl), R^x is hydrogen, cyano, hydroxyl, trifluoromethyl, methyl, ethyl or cyclopropyl, R^y is hydrogen, dimethylamide, cyano, hydroxyl, trifluoromethyl, halo, ethylester, dimethylamine, methyl, methoxymethyl or propargyl, Z is unsubstituted, C₁₋₆ alkyl, C₁₋₆ methoxyalkyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aromatic cycle or 3-8 membered heterocycle having 1-3 nitrogens.

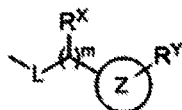
- [56] ii) In case, R is



or NR^{d3}(especially R^{d1}, R^{d2} and R^{d3} is each independently hydrogen, fluoro or methyl).

*C1C(=O)N(C1)C(=O)N(R1)C2(R2)C(R3)C(=O)N2

[58] iv) In case, R is $\mathbf{R}^x$, L is $\text{NR}^{\text{cl}}\text{CH}_2$, CONR^{c4} or $\text{CH}_2\text{NR}^{\text{c5}}$ (especially, R^{cl} ,



Chemical structures representing various substituents (R groups) for the synthesis of polymers, including aromatic, heterocyclic, and aliphatic groups, as well as functionalized and branched structures.

[59]

[76] N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)-

- N-methylcyclopropanecarboxamide; (I-12)
- [77] (S)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide; (I-13)
- [78] 3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)-5,5-dimethylimidazolidine-2,4-dione; (I-14)
- [79] (R)-3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione; (I-15)
- [80] (R)-1-ethyl-3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione; (I-16)
- [81] 4-(4-fluoro-3-(3-(4-fluoropiperidine-1-carbonyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-17)
- [82] 4-(3-(3-(3,3-difluoroazetidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-18)
- [83] 4-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-19)
- [84] 4-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-20)
- [85] (R)-N-(cyclopropylmethyl)-1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidine-3-carboxamide; (I-21)
- [86] 4-(4-fluoro-3-(3-(pyrrolidine-1-carbonyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-22)
- [87] (R)-4-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-23)
- [88] (S)-4-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-24)
- [89] 4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-25)
- [90] 4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-26)
- [91] 4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-27)
- [92] 4-(3-(3-(cyclohexylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-28)
- [93] (R)-4-(3-(3-(cyclopropylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-29)
- [94] (R)-4-(3-(3-(cyclobutylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-30)
- [95] (R)-4-(3-(3-(cyclopentylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(

- 2H)-one; (I-31)
- [96] 4-(4-fluoro-3-(3-(isopropylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-32)
- [97] 4-(3-(3-((cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-33)
- [98] 4-(3-(3-(bis(cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-34)
- [99] 4-(4-fluoro-3-(3-(isobutylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-35)
- [100] 4-(4-fluoro-3-(3-((1-hydroxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-36)
- [101] 4-(4-fluoro-3-(3-(neopentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-37)
- [102] 4-(3-(3-((2,2-dimethylcyclopentyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-38)
- [103] ethyl
2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclopent-1-enecarboxylate; (I-39)
- [104] 4-(4-fluoro-3-(3-(pentan-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-40)
- [105] 4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-41)
- [106] 4-(3-(3-((1-cyclopropylethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-42)
- [107] 4-(3-(3-(bicyclo[2.2.1]heptan-2-ylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-43)
- [108] 4-(3-(3-(sec-butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-44)
- [109] 4-(3-(3-((dicyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-45)
- [110] 4-(4-fluoro-3-(3-((4-methylpentan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-46)
- [111] 4-(4-fluoro-3-(3-((3-hydroxybutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-47)
- [112] 4-(4-fluoro-3-(3-(pentan-2-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-48)
- [113] 4-(4-fluoro-3-(3-((1-(1-methylcyclopropyl)ethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-49)

- [114] 4-(4-fluoro-3-(3-((3,3,3-trifluoro-2-methylpropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-50)
- [115] 4-(3-(3-(allylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-51)
- [116] 4-(4-fluoro-3-(3-(isopentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-52)
- [117] 4-(3-(3-(butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-53)
- [118] 4-(4-fluoro-3-(3-((3-methylbut-2-en-1-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-54)
- [119] 4-(3-(3-((cyclopentylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-55)
- [120] 4-(4-fluoro-3-(3-((4,4,4-trifluorobutyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-56)
- [121] 4-(4-fluoro-3-(3-(pentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-57)
- [122] 4-(3-(3-((2-cyclopropylethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-58)
- [123] 4-(4-fluoro-3-(3-(propylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-59)
- [124] 4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-60)
- [125] (R)-4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-61)
- [126] (S)-4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-62)
- [127] (S)-4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-63)
- [128] (R)-4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-64)
- [129] 4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-65)
- [130] 4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-66)
- [131] (S)-4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-67)
- [132] (R)-4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-68)

- [133] 4-(3-(3-(cyclopropyl(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-69)
- [134] 4-(3-(3-(cyclopropyl(ethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-70)
- [135] 4-(3-(3-(cyclobutyl(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-71)
- [136] 4-(3-(3-(cyclopentyl(prop-2-yn-1-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-72)
- [137] 4-(3-(3-(3,3-difluoropyrrolidin-1-yl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-73)
- [138] 4-(4-fluoro-3-(3-(4-fluoropiperidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-74)
- [139] 4-(3-([1,3'-biazetidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-75)
- [140] 4-(4-fluoro-3-(3-(pyrrolidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-76)
- [141] 4-(4-fluoro-3-(3-(piperidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-77)
- [142] 4-(4-fluoro-3-(3-(4-methylpiperazin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-78)
- [143] 4-(4-fluoro-3-(3-(phenylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-79)
- [144] 4-(4-fluoro-3-(3-((1-(trifluoromethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-80)
- [145] 4-(4-fluoro-3-(3-(prop-2-yn-1-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-81)
- [146] (S)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-82)
- [147] (R)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-83)
- [148] 4-(4-fluoro-3-(3-((1-(hydroxymethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-84)
- [149] 4-(4-fluoro-3-(3-((1-methylcyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-85)
- [150] (R)-4-(3-(3-((3,3-dimethylbutan-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-86)
- [151] (S)-4-(3-(3-((3,3-dimethylbutan-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-87)
- [152] (R)-4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthal

- azin-1(2H)-one; (I-88)
- [153] (S)-4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-89)
- [154] 4-(4-fluoro-3-(3-((1-(methoxymethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-90)
- [155] 4-(3-(3-(but-3-yn-1-ylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-91)
- [156] 4-(4-fluoro-3-(3-((2-methylallyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-92)
- [157] 4-(4-fluoro-3-(3-((3-hydroxy-2,2-dimethylpropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-93)
- [158] 1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)methyl)cyclopropanecarbonitrile; (I-94)
- [159] 4-(4-fluoro-3-(3-((2,2,2-trifluoroethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-95)
- [160] (R)-4-(4-fluoro-3-(3-(pyrrolidin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-96)
- [161] (S)-4-(4-fluoro-3-(3-(pyrrolidin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-97)
- [162] 1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclopentanecarbonitrile; (I-98)
- [163] 1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclobutanecarbonitrile; (I-99)
- [164] 2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)propanenitrile; (I-100)
- [165] 2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)butanenitrile; (I-101)
- [166] 2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)-3-methylbutanenitrile; (I-102)
- [167] 2-cyclopropyl-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)acetonitrile; (I-103)
- [168] 4-(4-fluoro-3-(3-((1-(trifluoromethyl)cyclobutyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-104)
- [169] (S)-4-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-105)
- [170] (S)-4-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-106)
- [171] 4-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalaz

- in-1(2H)-one; (I-107)
- [172] 4-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-108)
- [173] 4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-109)
- [174] (S)-4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-110)
- [175] (S)-4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-111)
- [176] (S)-4-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-112)
- [177] (S)-4-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-113)
- [178] 4-(3-(3-((6-chloropyridazin-3-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-114)
- [179] 4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-115)
- [180] 4-(3-(3-(cyclobutyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-116)
- [181] 4-(4-fluoro-3-(3-(pyridazin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-117)
- [182] (R)-4-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-118)
- [183] (R)-4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-119)
- [184] (R)-4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-120)
- [185] (R)-4-(3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-121)
- [186] (R)-4-(4-fluoro-3-(3-(pyridazin-3-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-122)
- [187] (R)-4-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-123)
- [188] (R)-4-(4-fluoro-3-(3-(thiazol-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-124)
- [189] (R)-4-(3-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-125)
- [190] (R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-

- 3-yl)amino)pyrimidine-5-carbonitrile; (I-126)
- [191] (R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)amino)nicotinonitrile; (I-127)
- [192] (R)-4-(4-fluoro-3-(3-(pyridin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-128)
- [193] (R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)amino)-N,N-dimethylnicotinamide; (I-129)
- [194] (R)-4-(3-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-130)
- [195] (R)-4-(4-fluoro-3-(3-((5-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-131)
- [196] (R)-4-(4-fluoro-3-(3-((4-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-132)
- [197] 4-(3-(3-(benzylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-133)
- [198] 4-(4-fluoro-3-(3-((3,3,3-trifluoropropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-134)
- [199] (R)-4-(3-(3-(azetidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-135)
- [200] (R)-4-(3-([1,3'-bipyrrolidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-136)
- [201] (R)-4-(4-fluoro-3-(3-(piperidin-1-yl)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-137)
- [202] (R)-4-(4-fluoro-3-(3-(p-tolylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-138)
- [203] (R)-4-(4-fluoro-3-(3-(phenylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-139)
- [204] 4-(4-fluoro-3-(3-(pyrrolidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-140)
- [205] 4-(4-fluoro-3-(3-(piperidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-141)
- [206] 4-(3-(3-(azetidin-1-ylmethyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-142)
- [207] 4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-143)
- [208] 4-(4-fluoro-3-(3-((isopropylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-144)
- [209] 4-(3-(3-(((cyclopropylmethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)ph

- thalazin-1(2H)-one; (I-145)
- [210] 4-(4-fluoro-3-(3-((isobutylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-146)
- [211] 4-(3-(3-((tert-butylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-147)
- [212] 4-(3-(3-((cyclobutylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-148)
- [213] 4-(4-fluoro-3-(3-((prop-2-yn-1-ylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-149)
- [214] 4-(4-fluoro-3-(3-((phenylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-150)
- [215] 1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)methyl)amino)methyl)cyclopropanecarbonitrile; (I-151)
- [216] 1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)methyl)amino)cyclopropanecarbonitrile; (I-152)
- [217] 4-(3-(3-((cyclopropyl(prop-2-yn-1-yl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-153)
- [218] 4-(3-(3-((cyclopropyl(methyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-154)
- [219] 4-(3-(3-((cyclopropyl(ethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-155)
- [220] 4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-156)
- [221] 4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-157)
- [222] 4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-158)
- [223] 4-(4-fluoro-3-(3-(isopropylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-159)
- [224] 4-(3-(3-((cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-160)
- [225] 4-(4-fluoro-3-(3-(isobutylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-161)
- [226] 4-(4-fluoro-3-(3-((1-hydroxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-162)
- [227] 4-(3-(3-(butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-163)
- [228] 4-(3-([1,3'-biazetidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hy-

- drochloride; (I-164)
- [229] (R)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-165)
- [230] 1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclobutanecarbonitrile hydrochloride; (I-166)
- [231] (R)-4-(3-(3-(azetidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-167)
- [232] 4-(4-fluoro-3-(3-(pyrrolidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-168)
- [233] 4-(4-fluoro-3-(3-(piperidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-169)
- [234] 4-(3-(3-(azetidin-1-ylmethyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-170)
- [235] 4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-171)
- [236] 4-(4-fluoro-3-(3-((isopropylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-172)
- [237] 4-(3-(3-(((cyclopropylmethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-173)
- [238] 4-(4-fluoro-3-(3-((isobutylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-174)
- [239] 4-(3-(3-((cyclobutylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-175) and
- [240] 4-(4-fluoro-3-(3-((prop-2-yn-1-ylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-176).
- [241]
- [242] In the present invention, "C₁₋₄ alkylamine" is a saturated hydrocarbonyl amine with linear or branched chains of 1~4 carbon atoms. Exemplary alkylamines include, but are not limited, to methylamine, ethylamine, propylamine, butylamine, 1-methylethylamine, diethylamine or dimethylamine.
- [243] In the present invention, "C₁₋₆ alkyl" is a saturated hydrocarbonyl amine with linear or branched chains of 1-6 carbon atoms. Exemplary alkyl include, but are not limited, to methyl, ethyl, propyl, butyl, pentyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, 1-methylbutyl, 1,1-dimethylpropyl, 1-methylpentyl or 1,1-dimethylbutyl.
- [244] In the present invention, "C₁₋₆ alkoxy" is an OR group with R as defined above. Exemplary alkoxy with 1-6 carbon atoms include, but are not limited, to methoxy, ethoxy, propoxy, butoxy, 1-methylethoxy, 1,1-dimethylethoxy, 1-methylpropoxy,

2-methylpropoxy or cyclopropylmethoxy.

- [245] In the present invention, "halo C₁₋₆ alkyl" is intended as a C₁₋₆ alkyl radical having one or more hydrogen atoms replaced by a halogen atom as defined above. Exemplary haloalkyl include, but are not limited, to difluoromethyl or trifluoromethyl.
- [246] In the present invention, "halo" is intended as bromine, fluorine, or chlorine atom.
- [247] In the present invention, "C₂₋₆ alkenyl" is intended as a linear or branched hydrocarbon chain of 2-6 carbon atoms and at least one carbon-carbon double bond. Alkenyls have a "cis" or "trans" and "E" or "Z" double bond configuration. Exemplary alkenyl include, but are not limited, to crotyl(-CH₂CH=CHCH₃), vinyl(-CH=CH₂) or allyl(-CH₂CH=CH₂).
- [248] In the present invention, "C₂₋₆ alkynyl" is intended as a linear or branched hydrocarbon radical with 2-6 carbon atoms and at least one carbon-carbon triple bond. Exemplary alkynyl include, but are not limited, to ethynyl(-C≡CH) or propargyl(-CH₂C≡CH).
- [249] In the present invention, "C₃₋₈ cycloalkyl" is intended as a saturated hydrocarbon ring with 3-8 carbon atoms. Exemplary cycloalkyl include, but are not limited, to cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
- [250] In the present invention, "C₃₋₈ cycloalkenyl" is intended as an unsaturated hydrocarbon ring with 3-8 carbon atoms and at least one carbon-carbon double bond. Alkenyls have a "cis" or "trans" and "E" or "Z" double bond configuration. Exemplary cycloalkenyl include, but are not limited, to cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1,3-cyclohexadiene, 1,4-cyclohexadiene, cycloheptenyl, cyclooctenyl or 1,5-cyclooctadiene.
- [251] In the present invention, "C₆₋₁₀ aromatic cycle" is intended as an aromatic hydrocarbon radical with 6-10 carbon atoms. Exemplary aromatic ring include, but are not limited, to phenyl or naphthyl.
- [252] In the present invention, "heterocycle" is intended as a saturated or partially unsaturated hydrocarbon mono-tricyclic ring with at least one nitrogen atom. Exemplary mono heterocycles with 5-6 atoms include, but are not limited, to pyrrolidinyl, piperidinyl, pyrrollyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl. Also, exemplary bicyclic aromatic ring include, but are not limited, to benzothiazolyl, benzoxazolyl, benzoxazinone, benzoxadiazolyl, 1,3-benzodioxolyl, benzofuryl, benzopyrazinyl, indolyl, indazolyl, benzimidazolyl, benzopyranyl, pyrolopyridinyl, furopyridinyl, or imidazothiazolyl.
- [253] The term "pharmaceutically acceptable," as used herein, when referring to a component of a pharmaceutical composition means that the component, when administered to an animal, does not have undue adverse effects such as excessive

toxicity, irritation, or allergic response commensurate with a reasonable benefit/risk ratio.

[254] The term "treatment" as used herein covers any treatment of a disease in a mammal, particularly a human, and includes inhibiting the disease, i.e., arresting its development; or relieving the disease, i.e. causing regression of the disease and/or its symptoms or conditions and slowing disease progression.

[255] The term "therapeutically effective amount" means an amount of a compound of the present invention that ameliorates, attenuates or eliminates a particular disease or condition or prevents or delays the onset of a particular disease or condition. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic.

[256] The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic-mixture or a racemate.

[257] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

[258] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[259] The phrase "pharmaceutically acceptable salt" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the invention. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate "mesylate", ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate(i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate))

salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion.

[260] If the compound of the invention is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[261] If the compound of the invention is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine(primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include, but are not limited to, organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

[262]

[263] In another aspect, the present invention provides a method of preparing the compound represented by Formula I or a pharmaceutically approved salt thereof.

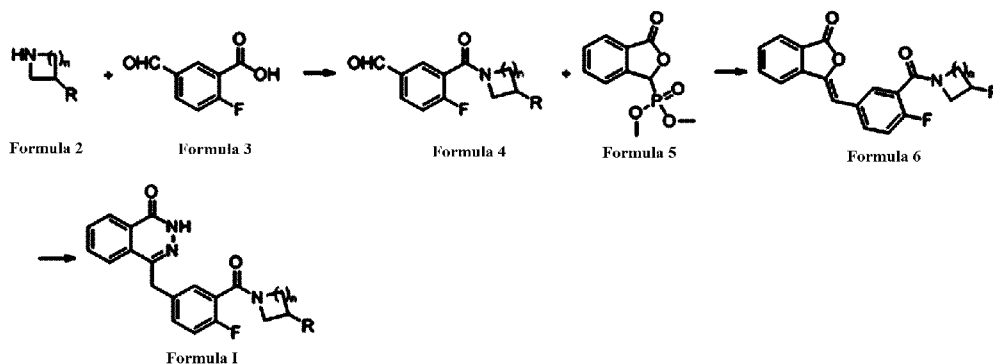
[264]

[265] A preparation method of the present invention is shown in the following.

[266]

[267] [Scheme 1]

[268]



[269]

[270] The compound of Formula I of the present invention, as shown in Scheme 1, can be prepared by series of steps from the compound of Formula 2.

[271]

[272] n and R, illustrated in Scheme 1, are defined as below:

[273]

[274] Wherein,

[275] n is 1 or 2;

[276] R is , or ,

[277] Wherein, when the R is ,

[278] m is 0, 1 or 2,

[279] L is oxygen, methylene, carbonyl, CONHCH₂, NR^{c1}CH₂, NR^{c2}CO, NR^{c3}, CONR^{c4} or CH₂NR^{c5}(especially, R^{c1}, R^{c2}, R^{c3}, R^{c4} and R^{c5} is each independently oxygen, C₁₋₄ alkylamine, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl or 3-8 membered heterocycle),

[280] R^x is hydrogen, cyano, hydroxyl, trifluoromethyl, C₁₋₆ alkyl or C₃₋₈ cycloalkyl,

[281] R^y is hydrogen, amide, cyano, hydroxyl, trifluoromethyl, halo, ester, C₁₋₄ alkylamine, C₁₋₆ alkyl, C₁₋₆ methoxyalkyl or C₂₋₆ alkynyl,

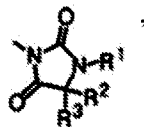
[282] Z is unsubstituted, C₁₋₆ alkyl, C₁₋₆ methoxyalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, C₆₋₁₀ aromatic cycle or 3-8 membered heterocycle having 1-3 nitrogens,

[283] wherein, when the R is ,

[284] p and q is each independently from 1 to 3,

[285] W is CR^{d1}R^{d2} or NR^{d3}(especially, R^{d1}, R^{d2} and R^{d3} is each independently hydrogen, fluoro or C₁₋₆alkyl),

[286] wherein, when the R is



[287] R¹, R² and R³ is each independently hydrogen or C₁₋₆alkyl.

[288]

[289] The preparation method of the Formula I comprise:

[290]

[291] Preparing a compound of Formula 4 from a compound of Formula 2 and 3 which reacted with amide coupling reaction(Step 1)

[292] Preparing a compound of Formula 6 from a compound of Formula 4 and 5 which reacted with olefination reaction(Step 2)

[293] Preparing a compound of Formula I from a compound of Formula 6 and hydrazine monohydrate which reacted with condensation reaction(Step 3)

[294]

[295] Each step of the above preparation method is described in more detail as follows.

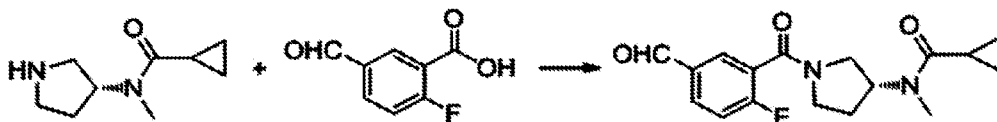
[296]

[297] i) The compound of Formula 4 can be prepared from Formula 2 by amide coupling in the above Step 1. An Amide coupling reaction is carried out with 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(EDCI) and 4-(Dimethylamino)pyridine(DMAP) or O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU) and N,N-diisopropyl ethylamine(DIPEA). Examples of solvents useful in the reaction include chloroform or dimethylformamide. The reaction is heated to 20~35°C for 1~30 hours, so as to obtain the compound of Formula 4.

[298]

[299] Example of preparing the compound of Formula 4 from the compound of Formula 2 and 3 by amide coupling in the above Step 1 is illustrated below.

[300]



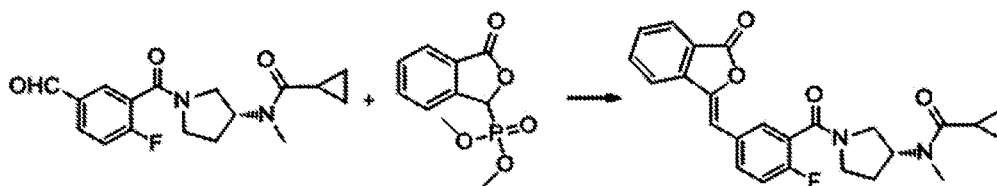
[301]

[302] ii) The compound of Formula 6 can be prepared from Formula 4 by olefination in the above Step 2. An olefination reaction is carried out with Formula 5 in basic condition. Examples of solvent useful in the reaction include THF. The reaction is cooled to 0°C for 1~5 hours, so as to obtain the compound of Formula 6.

[303]

[304] Example of preparing the compound of Formula 6 from the compound of Formula 4 and 5 by olefination in the above Step 2 is illustrated below.

[305]



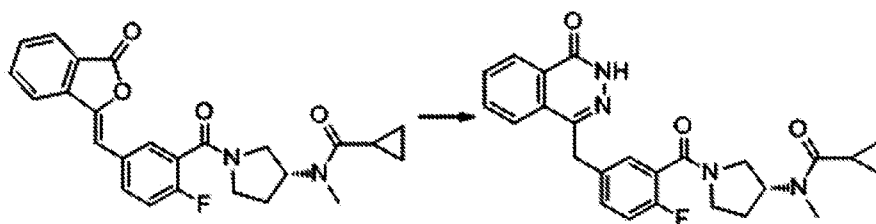
[306]

[307] iii) The compound of Formula I can be prepared from Formula 6 by condensation in the above Step 3. A condensation reaction is carried out with hydrazine monohydrate. Example of solvent useful in the reaction includes water. The reaction is heated to 30~70°C for 20 hours, so as to obtain the compound of Formula I.

[308]

[309] Example of preparing the compound of Formula I from the compound of Formula 6 by condensation in the above Step 3 is illustrated below.

[310]



[311]

[312] In another aspect, the present invention provides another method of preparing the compound represented by Formula I or a pharmaceutically approved salt thereof.

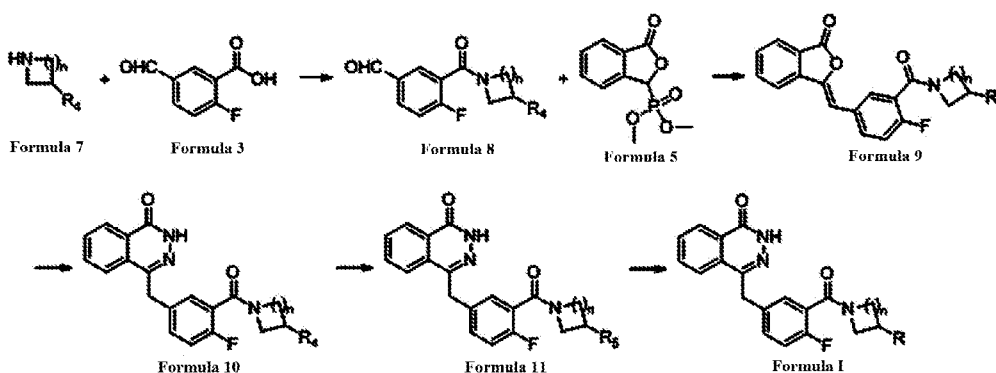
[313]

[314] Besides, another preparation method of the present invention is shown in the following.

[315]

[316] [Scheme 2]

[317]



[318]

[319] The compound of Formula I of the present invention, as shown in Scheme 2, can be prepared by series of steps from the compound of Formula 1.

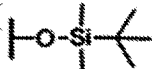
[320]

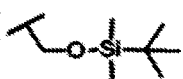
[321] n, R₄ and R₅, illustrated in Scheme 2, are defined as below:

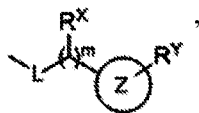
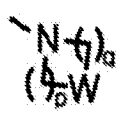
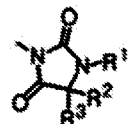
[322]

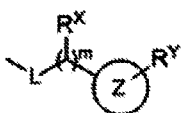
[323] Wherein,

[324] n is 1 or 2;

[325] R₄ and R₅ is each independently tert-butyldimethylsiloxy() , tert-

butyldimethylsiloxymethyl() , benzylcarbamate, amine, CH₂OH or hydroxyl;

[326] R is ,  or 

[327] wherein, when the R is ,

[328] m is 0, 1 or 2,

[329] L is oxygen, methylene, carbonyl, CONHCH₂, NR^{c1}CH₂, NR^{c2}CO, NR^{c3}, CONR^{c4} or CH₂NR^{c5} (especially, R^{c1}, R^{c2}, R^{c3}, R^{c4} and R^{c5} is each independently oxygen, C₁₋₄ alkylamine, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl or 3-8 membered heterocycle),

[330] R^x is hydrogen, cyano, hydroxyl, trifluoromethyl, C₁₋₆ alkyl or C₃₋₈ cycloalkyl,

[331] R^y is hydrogen, amide, cyano, hydroxyl, trifluoromethyl, halo, ester, C₁₋₄ alkylamine, C₁₋₆ alkyl, C₁₋₆ methoxyalkyl or C₂₋₆ alkynyl,

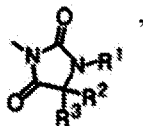
[332] Z is unsubstituted, C₁₋₆ alkyl, C₁₋₆ methoxyalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, C₆₋₁₀ aromatic cycle or 3-8 membered heterocycle having 1-3 nitrogens,

[333] wherein, when the R is ,

[334] p and q is each independently from 1 to 3,

[335] W is CR^{d1}R^{d2} or NR^{d3} (especially, R^{d1}, R^{d2} and R^{d3} is each independently hydrogen, fluoro or C₁₋₆ alkyl),

[336]



[337] R^1 , R^2 and R^3 is each independently hydrogen or C_{1-6} alkyl.

[338]

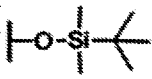
[339] Another preparation method of the Formula I comprises

[340]

[341] Preparing a compound of Formula 8 from a compound of Formula 7 and 3 which reacted with amidecoupling reaction(Step 1)

[342] Preparing a compound of Formula 9 from a compound of Formula 8 and 5 which reacted with olefination reaction(Step 2)

[343] Preparing a compound of Formula 10 from a compound of Formula 9 and hydrazine monohydrate which reacted with condensation reaction(Step 3)

[344] Preparing a compound of Formula 11 from a compound of Formula 10 which reacted with carboxybenzyl or tert-butyldimethylsiloxy() deprotection

reaction(Step 4)

[345] Preparing a compound of Formula I from a compound of Formula 11 which reacted with amide coupling, substitution and reductive amination reaction(Step 5)

[346]

[347] Each step of the above preparation method is described in more detail as follows.

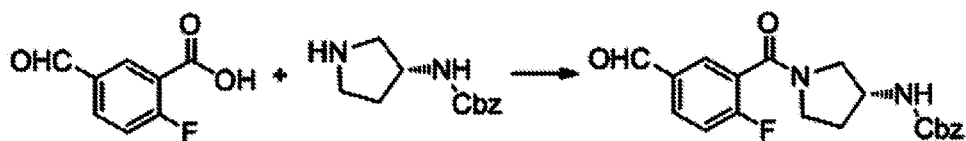
[348]

[349] i) The compound of Formula 8 can be prepared from Formula 7 by amide coupling in the above Step 1. An Amide coupling reaction is carried out with 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(EDCI) and 4-(Dimethylamino)pyridine(DMAP) or O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU) and N,N-diisopropyl ethylamine(DIPEA). Examples of solvents useful in the reaction include chloroform or dimethylformamide. The reaction is heated to 20~35°C for 1~30 hours, so as to obtain the compound of Formula 8.

[350]

[351] Example of preparing the compound of Formula 8 from the compound of Formula 7 and 3 by amide coupling in the above Step 1 is illustrated below.

[352]



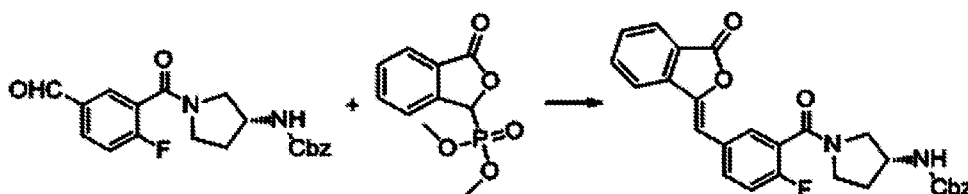
[353]

[354] ii) The compound of Formula 9 can be prepared from Formula 8 by olefination in the above Step 2. An olefination reaction is carried out with Formula 5 in basic condition. Examples of solvent useful in the reaction include THF. The reaction is cooled to 0°C for 1~5 hours, so as to obtain the compound of Formula 9.

[355]

[356] Example of preparing the compound of Formula 9 from the compound of Formula 8 and 5 by olefination in the above Step 2 is illustrated below.

[357]



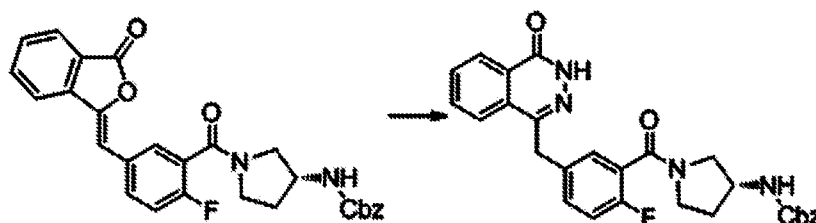
[358]

[359] iii) The compound of Formula 10 can be prepared from Formula 9 by condensation in the above Step 3. A condensation reaction is carried out with hydrazine monohydrate. Example of solvent useful in the reaction includes water. The reaction is heated to 30~70°C for 20 hours, so as to obtain the compound of Formula 10.

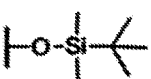
[360]

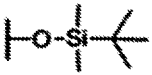
[361] Example of preparing the compound of Formula 10 from the compound of Formula 9 by condensation in the above Step 3 is illustrated below.

[362]



[363]

[364] iv) The compound of Formula 11 can be prepared from Formula 10 by carboxybenzyl or tert-butyloxycarbonyl() deprotection in the above Step 4. A

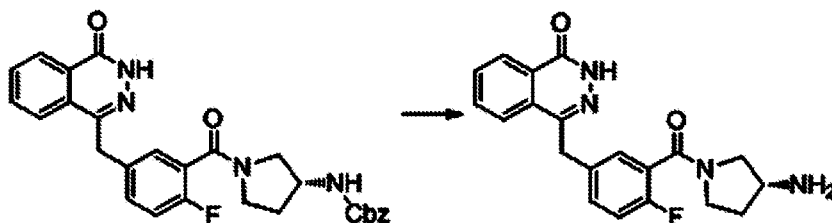
carboxybenzyl or tert-butyldimethylsiloxy() deprotection reaction is

carried out with Pd/C under N₂ gas or 1M solution of tetra-n-butylammonium fluoride in THF(TBAF), so as to obtain the compound of Formula 11.

[365]

[366] Example of preparing the compound of Formula 11 from the compound of Formula 10 by condensation in the above Step 4 is illustrated below.

[367]



[368]

[369] v) The compound of Formula I can be prepared from Formul 11 by amide coupling, substitution and reductive amination reaction.

[370]

[371] A step 5 of the Scheme 2 is described in more detail as follows.

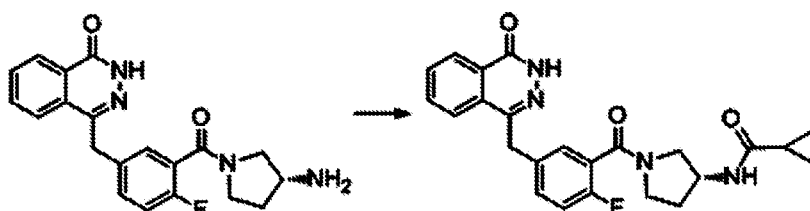
[372]

[373] In Step 5 of the preparation method, the compound of Formula I can be prepared with amide coupling, substitution and reductive amination.

[374]

[375] In the above amide coupling reaction, the reaction is carried out with 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(EDCI) and 4-(Dimethylamino)pyridine(DMAP) or O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU) and N,N-diisopropyl ethylamine(DIPEA). Examples of solvents useful in the reaction include chloroform or dimethylformamide, so as to obtain the compound of Formula I. An example is illustrated below.

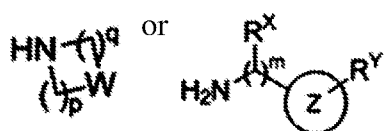
[376]



[377]

[378] Besides, In the Step 5, the compound of Formula I can be prepared with from substitution.

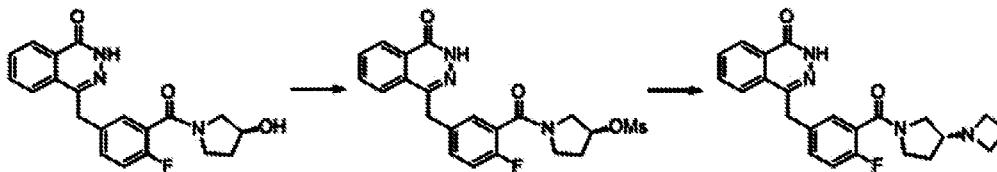
[379] In the above substitution reaction, mesylate compound is prepared from alcohol compound by reaction with methanesulfonyl chloride in dichloromethane. And then, desired functional group can be introduced by reaction of mesylate compound with



(In above Scheme, p, q, m, W, Z, R^x and R^y, are the

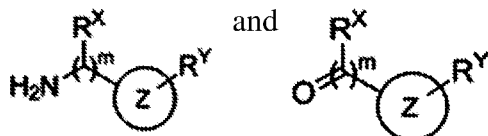
same as defined in Formula I). An example of preparing the compound of Formula I form the compound of Formula 8 by substitution in the present invention is illustrated below(The R^{c6} substitution is introduced with K₂CO₃ and R^{c6}-I).

[380]



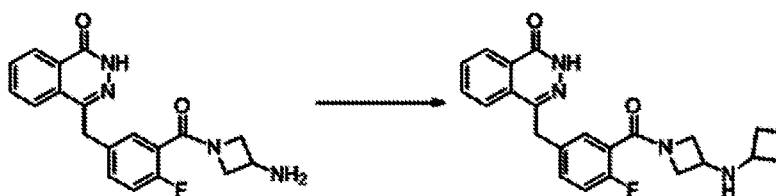
[381]

[382] Besides, in the above reductive amination reaction, the compound of Formula I can be prepared from



and R^y , are the same as defined in Formula I). The reaction is carried out with sodium triacetoxyborohydride and acetic acid for overnight. Examples of solvent useful in the reaction include chloroform or dichloromethane. An example of preparing the compound of Formula I is illustrated below (The $\text{R}^{\text{c}4}$ substitution is introduced with K_2CO_3 and $\text{R}^{\text{c}4}\text{-I}$ in dimethylformamide).

[383]



[384]

[385] In addition, the present invention provides a pharmaceutical composition for treating cancers comprising the compound of Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof. The cancers may be caused by PARP activity, or generic defect of BRCA1, BRCA2, and ERG fusion gene. Exemplary cancers include, but are not limited to breast cancer, ovarian cancer, pancreatic cancer, gastric cancer, lung cancer, colorectal cancer, brain tumor, prostate cancer and Ewings sarcoma. As used herein, the term "generic defect" is intended as gene mutation, gene deficiency or defect of gene expression, but is not limited thereto.

[386] The present invention provides a method of treating cancers in a subject in need thereof, comprising administering an effective amount of the pharmaceutical composition to the subject. The dosage of pharmaceutical composition of the present invention may vary depending on the patient's weight, age, gender, physical condition, diet, the time and mode of administration, excretion rates, and the severity of illness. Mammals (including human) are desirable for the individual without limit.

[387] Compounds of the invention intended for pharmaceutical use may be administered as a solid or liquid, such as a tablet, capsule, solution or suspension. Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such

compositions and methods for their preparation may be found, for example, in Remingtons Pharmaceutical Sciences, 19th Edition(Mack Publishing Company, 1995).

[388] The present invention provides compound, specifically, active in inhibiting the activity of PARP. Compounds of the invention can be used in cancer treatment through inhibition of PARP. Exemplary include lung cancer, gastrointestinal cancer, prostate cancer, uterine cancer, or especially breast cancer, or ovarian cancer.

[389] Compounds of the invention may be combined in a pharmaceutical combination formulation, or dosing regimen as combination therapy, with a second compound having anti-cancer properties or at least two kinds of pharmaceutical active ingredients.

[390] The examples of agents include: oxaliplatin(ELOXATIN®, Sanofi), bortezomib(VELCADE®, Millennium Pharm.), sunitinib(SUNITINIB®, SU11248, Pfizer), letrozole(FEMARA®, Novartis), imatinib mesylate(GLEEVEC®, Novartis), XL-518(Mek inhibitor, Exelixis, WO 2007/044515), ARRY-886(Mek inhibitor, AZD6244, Array BioPharma, Astra Zeneca), SF-1126(PI3K inhibitor, Semaphore Pharmaceuticals), BEZ-235(PI3K inhibitor, Novartis), XL-147(PI3K inhibitor, Exelixis), PTK787/ZK 222584(Novartis), fulvestrant(FASLODEX®, AstraZeneca), leucovorin(folinic acid), rapamycin(sirolimus, RAPAMUNE®, Wyeth), lapatinib(TYKERB®, GSK572016, Glaxo Smith Kline), lonafarnib(SARASAR®, SCH 66336, Schering Plough), sorafenib(NEXAVAR®, BAY43-9006, Bayer Labs), gefitinib(IRESSA®, AstraZeneca), irinotecan(CAMPTOSAR®, CPT-11, Pfizer), tipifarnib(ZARNESTRA®, Johnson & Johnson), ABRAXANE®(Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel(American Pharmaceutical Partners, Schaumberg, IL), vandetanib(rINN, ZD6474, ZACTIMA®, AstraZeneca), chlorambucil, AG1478, AG1571(SU 5271; Sugen), temsirolimus(TORISEL®, Wyeth), pazopanib(GlaxoSmithKline), canfosfamide(TELCYTA®, Telik), thiotepa and cyclophosphamide(CYTOXAN®, NEOSAR®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylmelamine; acetogenins(especially bullatacin and bullatacinone); a camptothecin(including the synthetic analog topotecan); bryostatin; callystatin; CC-1065(including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins(particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin(including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine,

chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics(e.g., calicheamicin, calicheamicin gamma II, calicheamicin omega II (Angew Chem. Intl. Ed. Engl. (1994) 33:183-186); dynemicin, dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), acla-cinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, morpholino-doxorubicin, cyanomorpholino-dox-orubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, nemorubicin, marcellomycin, mitomycins such as mitomycin C, my-cophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanol, testolactone; anti-adrenals such as aminog-lutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mi-toxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK polysaccharide complex(JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes(especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; ara-binoside("Ara-C"); cyclophosphamide; thiotepa; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide(VP-16); ifosfamide; mitoxantrone; vincristine; vi-norelbine(NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine(XELODA®, Roche); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine(DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[391] For instance, compounds of the invention, especially formula I or pharmaceutically acceptable salt can be administered simultaneously, gradually, or individually with at

least one of therapeutic agents.

[392]

[393] **Oral Administration**

[394] In one embodiment, the compounds of the invention may be administered orally.

Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual, or sublingual administration by which the compound enters the blood stream directly from the mouth.

[395] Formulations suitable for oral administration include solid plugs, solid microparticulates, semi-solid and liquid(including multiple phases or dispersed systems) such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids, emulsions or powders; lozenges(including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches. Liquid(including multiple phases and dispersed systems) formulations include emulsions, suspensions, solutions, syrups and elixirs. Such formulations may be presented as fillers in soft or hard capsules(made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

[396] The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

[397] The immediate release portion may comprise a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, powdered cellulose, loweralkyl-substituted hydroxypropyl cellulose, polacrillin potassium, starch, pregelatinized starch, sodium alginate, and mixtures thereof. Generally, the disintegrant will comprise from 1 wt% to 80 wt%, preferably from 5 wt% to 60 wt% of the layer.

[398] Examples of matrix materials, fillers, or diluents include lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, compressible sugar, microcrystalline cellulose, powdered cellulose, starch, pregelatinized starch, dextrates, dextran, dextrin, dextrose, maltodextrin, calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, poloxamers, polyethylene oxide, hydroxypropyl methyl cellulose and mixtures thereof.

[399] When preparing dosage forms incorporating the compositions of the invention, the compounds may also be blended with conventional excipients such as binders, including gelatin, pregelatinized starch, and the like; lubricants, such as hydrogenated

vegetable oil, stearic acid, and the like; diluents, such as lactose, mannose, and sucrose; disintegrants, such as carboxymethylcellulose and sodium starch glycolate; suspending agents, such as povidone, polyvinyl alcohol, and the like; absorbants, such as silicon dioxide; preservatives, such as methylparaben, propylparaben, and sodium benzoate; surfactants; such as sodium lauryl sulfate, polysorbate 80, and the like; flavorants; and sweeteners. If present, the surfactants would comprise of 0.2 wt% to 5 wt% and the absorbants would comprise from 0.2 wt% to 1 wt%. Other excipients include one or more of: anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

- [400] Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.
- [401] The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).
- [402] Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release
- [403]
- [404] **Parenteral Administration**
- [405] The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous.
- [406] Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques. An example of a needle free injection is Powderject™.
- [407] Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably, to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile nonaqueous solution or as a powdered, dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.
- [408] The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.
- [409] A proper dosage form such as combination with solubility enhancer can increase solubility of compound of formula I used in non-oral solution.

[410] Formulations for parenteral administration may be formulated to be immediate and/or modified/controlled re-lease. Controlled/modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and pro-programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

[411]

[412] **Local Administration**

[413] The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used.

[414]

[415] **Does**

[416] In human patients, the precise daily dose administered depends on various factors such as the age, sex, weight and condition of the patient being treated. The amount of dose can be selected within the bounds of goal achieving treatment effect without harmful or serious adverse effect.

[417] For instance, the dosage of the compound of invention may be administered in an effective amount ranging from 0.05 to 1000mg daily on patients. The following dosage levels and other dosage levels herein are for the average human subject having a weight range of about 65 to 70kg. The skilled person will readily be able to determine the dosage levels required for a subject whose weight falls outside this range, such as children and the elderly.

[418]

[419] The present invention explains, but are not limited, in detail through the following examples and experimental examples.

[420]

[421] **[Example]**

[422] **<Example 1>**

(R)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-1)

[423]

[424] Step 1 : Preparation of

((R)-benzyl(1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)carbamate

[425] 2-fluoro-5-formylbenzoic acid (220mg, 0.91mmol), O-

(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 384mg, 1.01mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.52mL, 2.98mmol) was added to a solution of (R)-benzyl pyrrolidin-3-ylcarbamate(200mg, 0.91mmol) in DMF(5mL) and stirred for 12 hours. The reaction mixture was concentrated in vacuum, added dichloromethane and washed sat. NH₄Cl(ag) and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum and purified using silica chromatography to give the intermediate compound (R)-benzyl (1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)carbamate(229mg, 68%).

[426]

[427] Step 2 : Preparation of (R,Z)-benzyl(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)carbamate

[428] The intermediate compound(Step 1)(236mg, 0.62mmol) and triethylamine(0.12mL, 0.81mmol) was added to a solution of dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(220mg, 0.91mmol) in THF(1.7mL) and stirred for 5 hours at 0°C. The reaction mixture was concentrated in vacuum then the white residue was slurried in water for 30 minutes, filtered, washed with water, hexane and ether, and dried to yield the intermediate compound (R,Z)-benzyl (1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)carbamate(164mg, 59%).

[429]

[430] Step 3 : Preparation of (R)-benzyl(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)carbamate

[431] Hydrazine monohydrate(19uL, 0.38mmol) was added to a suspension of the intermediate compound(Step 2)(164mg, 0.35mmol) in water(1.5mL) and stirred for 2 hours at 40°C. The reaction was cooled to room temperature and concentrated in vacuum. Water was added to the reaction mixture and the product was extracted into dichloromethane. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum and purified using silica chromatography to give (R)-benzyl(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)carbamate(100mg,47%).

[432]

[433] Step 4 : Preparation of (R)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[434] The intermediate compound(step 3)(100mg, 0.20mmol) and 10 wt. % Pd/C (10mg) in methanol(30mL) was hydrogenated at atmosphere for 6h. The reaction mixture was

filtered, evaporated in vacuum and purified using silica chromatography to afford the title compound(63mg, 85%).

[435] ¹H-NMR (DMSO, 400MHz): δ 12.60(s, 1H), 8.26 (d, 1H), 7.97 (d, 1H), 7.89 (t, 1H), 7.83 (t, 1H), 7.50-7.44 (m, 1H), 7.40 (d, 1H), 7.21 (t, 1H), 4.37 (s, 2H), 3.79-3.67 (m, 1H), 3.59-3.33 (m, 3H), 3.29-3.06 (m, 3H).

[436]

[437] **<Example 2>**

(S)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-2)

[438]

[439] Step 1 : Preparation of

(S)-benzyl(1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)carbamate

[440] This compound was made using the procedure described for example 1(Step 1). Thus, (S)-benzylpyrrolidine-3-ylcarbamate(150mg, 0.68mmol) was reacted with 2-fluoro-5-formyl benzoic acid(114mg, 0.68 mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 335mg, 0.88mmol) and N,N-diisopropyl ethyl amine(DIPEA, 0.24mL, 1.36 mmol) to afford the intermediate compound (S)- benzyl (1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)carbamate(156mg, 62%).

[441]

[442] Step 2 : Preparation of

(S,Z)-benzyl(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)carbamate

[443] This compound was made using the procedure described for example 1(Step 2). Thus, this intermediate compound(Step 1) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(102mg, 0.42mmol) and triethyl amine(88uL, 0.63mmol) to afford the intermediate compound (S,Z)- benzyl (1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)carbamate(117mg, 57%).

[444]

[445] Step 3 : Preparation of

(S)-benzyl(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)carbamate

[446] This compound was made using the procedure described for example 1(Step 3). Thus, this intermediate compound(Step 2) was reacted with hydrazine monohydrate(24uL, 0.48mmol) to afford the intermediate compound (S)- benzyl (1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)carbamate(58mg, 48%).

[447]

[448] Step 4 : Preparation of

(S)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[449]

This compound was made using the procedure described for example 1(Step 4).

Thus, this intermediate compound(Step 3)(58mg, 0.12mmol) was reacted with 10 wt. % Pd/C(6mg) to afford the title compound(39mg, 88%).

[450]

¹H-NMR (DMSO, 400MHz): δ 12.60 (s, 1H), 8.26 (d, 1H), 7.97 (d, 1H), 7.89 (t, 1H), 7.83 (t, 1H), 7.50-7.44 (m, 1H), 7.40 (d, 1H), 7.21 (t, 1H), 4.37 (s, 2H), 3.79-3.67 (m, 1H), 3.59-3.33 (m, 3H), 3.29-3.06 (m, 3H).

[451]

[452] <Example 3>

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-3)

[453]

[454] Step 1 : Preparation of benzyl(1-(2-fluoro-5-formylbenzoyl)azetidin-3-yl)carbamate

[455]

This compound was made using the procedure described for example 1(Step 1).

Thus, benzyl azetidine-3-ylcarbamate(500mg, 2.42mmol) was reacted with 2-fluoro-5-formyl benzoic acid (408mg, 2.42 mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 1.20g, 3.15mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.84mL, 4.85mmol) to afford the intermediate compound benzyl (1-(2-fluoro-5-formylbenzoyl)azetidin-3-yl)carbamate(604mg, 70%).

[456]

[457] Step 2 : Preparation of

(Z)-benzyl(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)azetidin-3-yl)carbamate

[458]

This compound was made using the procedure described for example 1(Step 2).

Thus, this intermediate compound(Step 1)(604mg, 1.69mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(410mg, 1.69mmol) and triethylamine(0.35mL, 2.54mmol) to afford the intermediate compound (Z)-benzyl (1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)azetidin-3-yl)carbamate(497mg, 62%).

[459]

[460] Step 3 : Preparation of

benzyl(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)carbamate

[461]

This compound was made using the procedure described for example 1(Step 3).

Thus, this intermediate compound(Step 2)(497mg, 1.05mmol) was reacted with hydrazine monohydrate(0.1mL, 2.1mmol) to afford the intermediate compound benzyl

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)carbamate(261mg, 51%).

[462]

[463] Step 4 : Preparation of

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[464] This compound was made using the procedure described for example 1(Step 4).

Thus, this intermediate compound(Step 3)(261mg, 0.54mmol) was reacted with 10 wt. % Pd/C(30mg) to afford the title compound(174mg, 91%).

[465] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.27-8.25 (m, 1H), 7.97 (d, 1H), 7.91-7.81 (m, 2H), 7.48-7.44 (m, 1H), 7.41-7.39 (m, 1H), 7.21 (t, 1H), 4.33 (s, 2H), 4.15-4.10 (m, 2H), 3.66-3.59 (m, 3H).

[466]

[467] <Example 4>

(R)-4-(4-fluoro-3-(3-hydroxypyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
(I-4)

[468]

[469] Step 1 : Preparation of

(R)-3-(3-(((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[470] This compound was made using the procedure described for example 1(Step 1).

Thus, (R)-3-(((tert-butyldimethylsilyl)oxy)pyrrolidine(300mg, 1.49mmol) was reacted with 2-fluoro-5-formyl benzoic acid(250mg, 1.49mmol), O-

(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 734mg, 1.93mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.52mL, 2.97mmol) to afford the intermediate compound

(R)-3-(3-(((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(377mg, 72%).

[471]

[472] Step 2 : Preparation of

(R,Z)-3-(3-(3-(((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one

[473] This compound was made using the procedure described for example 1(Step 2).

Thus, this intermediate compound(Step 1)(377mg, 1.07mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(260mg, 1.07mmol) and triethylamine(0.22mL, 1.61mmol) to afford the intermediate compound

(R,Z)-3-(3-(3-(((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one(300mg, 60%).

[474]

[475] Step 3 : Preparation of

((R)-4-(3-(3-((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[476] This compound was made using the procedure described for example 1(Step 3). Thus, this intermediate compound(Step 2)(300 mg, 0.64mmol) was reacted with hydrazine monohydrate(63uL, 1.28mmol) to afford the intermediate compound (R)-4-(3-(3-((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(148mg, 48%).

[477]

[478] Step 4 : Preparation of
(R)-4-(4-fluoro-3-(3-hydroxypyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[479] The intermediate compound(step 3)(148mg, 0.30mmol) in THF (3mL) cooled to 0°C was added 1M solution of tetra-n-butylammonium fluoride in THF(TBAF, 0.60mL, 0.60mmol), and the mixture was stirred at room temperature for 3h. The reaction mixture was concentrated in vacuum, added dichloromethane and washed with sat. NH₄Cl(ag) and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum and purified using silica chromatography to afford the title compound(101mg,92%).

[480] ¹H-NMR (DMSO, 400MHz): δ 12.61(s, 1H), 8.25 (d, 1H), 7.98 (d, 1H), 7.87 (t, 1H), 7.82 (t, 1H), 7.51-7.45 (m, 1H), 7.40 (d, 1H), 7.21 (t, 1H), 4.37 (s, 2H), 3.79-3.65 (m, 2H), 3.59-3.28 (m, 5H).

[481]

[482] <Example 5>
(S)-4-(4-fluoro-3-(3-hydroxypyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
(I-5)

[483]

[484] Step 1 : Preparation of
(S)-3-(3-((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[485] This compound was made using the procedure described for example 1(Step 1). Thus, (S)-3-((tert-butyldimethylsilyl)oxy)pyrrolidine(300mg, 1.49mmol) was reacted with 2-fluoro-5-formyl benzoic acid(250mg, 1.49mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 734mg, 1.93mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.52mL, 2.97mmol) to afford the intermediate compound (S)-3-(3-((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(377mg, 72%).

[486]

[487] Step 2 : Preparation of
(S,Z)-3-(3-(3-((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzyliden

e)isobenzofuran-1(3H)-one

[488] This compound was made using the procedure described for example 1(Step 2). Thus, this intermediate compound(Step 1)(377mg, 1.07mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(260mg, 1.07mmol) and triethylamine(0.22mL, 1.61mmol) to afford the intermediate compound (S,Z)-3-(3-(3-((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzyliden e)isobenzofuran-1(3H)-one(300mg, 60%).

[489]

[490] Step 3 : Preparation of
(S)-4-(3-(3-((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[491] This compound was made using the procedure described for example 1(Step 3). Thus, this intermediate compound(Step 2)(300 mg, 0.64mmol) was reacted with hydrazine monohydrate(63uL, 1.28mmol) to afford the intermediate compound (S)-4-(3-(3-((tert-butyldimethylsilyl)oxy)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(148mg, 48%).

[492]

[493] Step 4 : Preparation of
(S)-4-(4-fluoro-3-(3-hydroxypyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[494] This compound was made using the procedure described for example 4(Step 4). Thus, this intermediate compound(Step 3)(144 mg, 0.30 mmol) was reacted with a 1M solution of tetra-n-butylammonium fluoride in THF(TBAF, 0.60 mL, 0.60 mmol) to afford the title compound(101mg, 92%).

[495] ¹H-NMR (DMSO, 400MHz): δ 12.61(s, 1H), 8.25 (d, 1H), 7.98 (d, 1H), 7.87 (t, 1H), 7.82 (t, 1H), 7.51-7.45 (m, 1H), 7.40 (d, 1H), 7.21 (t, 1H), 4.37 (s, 2H), 3.79-3.65 (m, 2H), 3.59-3.28 (m, 5H).

[496]

[497] <Example 6>
4-(4-fluoro-3-(3-hydroxyazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-6)

[498]

[499] Step 1 : Preparation of
3-(3-((tert-butyldimethylsilyl)oxy)azetidine-1-carbonyl)-4-fluorobenzaldehyde

[500] This compound was made using the procedure described for example 1(Step 1). Thus, 3-((tert-butyldimethylsilyl)oxy)azetidine(300mg, 1.60mmol) was reacted with 2-fluoro-5-formyl benzoic acid(269mg, 1.60mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 789mg, 2.08mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.56mL, 3.20mmol) to afford the intermediate compound

3-(3-((tert-butyldimethylsilyl)oxy)azetidine-1-carbonyl)-4-fluorobenzaldehyde(378mg, 70%).

[501]

[502] Step 2 : Preparation of
(Z)-3-(3-(3-((tert-butyldimethylsilyl)oxy)azetidine-1-carbonyl)-4-fluorobenzylidene)is
obenzofuran-1(3H)-one

[503] This compound was made using the procedure described for example 1(Step 2). Thus, this intermediate compound(Step 1)(378mg, 1.12mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(271mg, 1.12mmol) and triethylamine(0.23mL, 1.68mmol) to afford the intermediate compound (Z)-3-(3-(3-((tert-butyldimethylsilyl)oxy)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one(284mg, 56%).

[504]

[505] Step 3 : Preparation of
4-(3-(3-((tert-butyldimethylsilyl)oxy)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-
1(2H)-one

[506] This compound was made using the procedure described for example 1(Step 3). Thus, this intermediate compound(Step 2)(284 mg, 0.62mmol) was reacted with hydrazine monohydrate(61uL, 1.26mmol) to afford the intermediate compound 4-(3-(3-((tert-butyldimethylsilyl)oxy)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(149mg, 51%).

[507]

[508] Step 4 : Preparation of
4-(4-fluoro-3-(3-(hydroxyazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[509] This compound was made using the procedure described for example 4(Step 4). Thus, this intermediate compound(Step 3)(149mg, 0.32mmol) was reacted with a 1M solution of tetra-n-butylammonium fluoride in THF(TBAF, 0.64mL, 0.64mmol) to afford the title compound(98mg, 92%).

[510] ¹H-NMR (DMSO, 400MHz): δ 12.60 (s, 1H), 8.27-8.26 (m, 1H), 7.96 (d, 1H), 7.91-7.81 (m, 2H), 7.48-7.45 (m, 1H), 7.41-7.39 (m, 1H), 7.20 (t, 1H), 4.33 (s, 2H), 4.15-4.11 (m, 3H), 3.66-3.58 (m, 2H).

[511]

[512] <Example 7>
4-(4-fluoro-3-(3-(hydroxymethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-o
ne; (I-7)

[513]

[514] Step 1 : Preparation of
3-(3-(((tert-butyldimethylsilyl)oxy)methyl)azetidine-1-carbonyl)-4-fluorobenzaldehyde

[515] This compound was made using the procedure described for example 1(Step 1). Thus, 3-(((tert-butyldimethylsilyl)oxy)methyl)azetidine(300mg, 1.60mmol) was reacted with 2-fluoro-5-formyl benzoic acid(269mg, 1.60mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 789mg, 2.08mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.56mL, 3.20mmol) to afford the intermediate compound 3-(3-(((tert-butyldimethylsilyl)oxy)methyl)azetidine-1-carbonyl)-4-fluorobenzaldehyde (378mg, 72%).

[516]

[517] Step 2 : Preparation of (Z)-3-(3-(3-(((tert-butyldimethylsilyl)oxy)methyl)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one

[518] This compound was made using the procedure described for example 1(Step 2). Thus, this intermediate compound(Step 1)(378mg, 1.12mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(271mg, 1.12mmol) and triethylamine(0.23mL, 1.68mmol) to afford the intermediate compound (Z)-3-(3-(3-(((tert-butyldimethylsilyl)oxy)methyl)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one(284mg, 56%).

[519]

[520] Step 3 : Preparation of 4-(3-(3-(((tert-butyldimethylsilyl)oxy)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)pht halazin-1(2H)-one

[521] This compound was made using the procedure described for example 1(Step 3). Thus, this intermediate compound(Step 2)(284mg, 0.63mmol) was reacted with hydrazine monohydrate(61uL, 1.25mmol) to afford the intermediate compound 4-(3-(3-(((tert-butyldimethylsilyl)oxy)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)pht halazin-1(2H)-one(149mg, 51%).

[522]

[523] Step 4 : Preparation of 4-(4-fluoro-3-(3-(hydroxymethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[524] This compound was made using the procedure described for example 4(Step 4). Thus, this intermediate compound(Step 3)(149mg, 0.32mmol) was reacted with a 1M solution of tetra-n-butylammonium fluoride in THF(TBAF, 0.64mL, 0.64mmol) to afford the title compound(98mg, 92%).

[525] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.28-8.26 (m, 1H), 7.97 (d, 1H), 7.92-7.81 (m, 2H), 7.49-7.45 (m, 1H), 7.42-7.39 (m, 1H), 7.21 (t, 1H), 4.33 (s, 2H), 4.15-4.11 (m, 3H), 3.66-3.58 (m, 2H), 3.47 (m, 2H).

[526]

[527] **<Example 8>**

(R)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)cyclopropanecarboxamide; (I-8)

[528]

[529] Step 1 : Preparation of

(R)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)cyclopropanecarboxamide

[530] Cyclopropanecarboxylic acid(20uL, 0.28mmol),

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(EDCI, 66mg, 0.42mmol) and 4-(Dimethylamino)pyridine(DMAP, 68 mg, 0.56 mmol) was added to a solution of

(R)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 1)(100mg, 0.28mmol) in dichloromethane(1.5mL) and stirred for 12 hours. The reaction mixture was concentrated in vacuum, added dichloromethane and washed sat. NH₄Cl(ag) and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum and purified using silica chromatography to afford title compound(83mg,68%).

[531] ¹H-NMR (CDCl₃,400MHz): δ 10.36 (d,1H), 8.46 (m,1H), 7.79 (m,2H), 7.71 (m,1H), 7.35 (m,1H), 7.32 (m,1H), 7.04 (q,1H), 5.89 (m,1H), 4.60 (q,0.3H), 4.45 (q,0.7H), 4.26 (d,2H), 3.82 (m,1H), 3.65 (m,1H), 3.51 (m,1H), 3.40 (m,1H), 3.18 (m,1H), 2.28 (m,2H), 1.61 (m,1H), 0.98 (m,1H), 0.96 (m,2H), 0.74 (m,2H).

[532]

[533] **<Example 9> N-**

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)cyclopropanecarboxamide; (I-9)

[534]

[535] Step 1 : Preparation of N-

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)cyclopropanecarboxamide

[536] This compound was made using the procedure described for example 8(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(100mg, 0.28mmol) was reacted with cyclopropanecarboxylic acid(20uL, 0.28mmol), 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(EDCI, 66mg, 0.42mmol) and 4-(Dimethylamino)pyridine(DMAP, 68mg, 0.56mmol) to afford the title compound(78mg, 62%).

[537] ¹H-NMR (MeOD, 400MHz): δ 8.39 (dd, 1H), 7.94 (dd, 1H), 7.85-7.80 (m, 2H), 7.52-7.45 (m, 2H), 7.17-7.12 (m, 1H), 4.63-4.53 (m, 1H), 4.44-4.37 (m, 3H), 4.30-4.21

(m, 1H), 4.01-3.89 (m, 2H), 1.59-1.52 (m, 1H), 0.92-0.78 (m, 4H).

[538]

[539] **<Example 10>**

(S)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)cyclopropanecarboxamide; (I-10)

[540]

[541] Step 1 : Preparation of

(S)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)cyclopropanecarboxamide

[542] This compound was made using the procedure described for example 8(Step 1).

Thus,

(S)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 2)(100mg, 0.28mmol) was reacted with cyclopropanecarboxylic acid(20uL, 0.28mmol), 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(EDCI, 66mg, 0.42mmol) and 4-(Dimethylamino)pyridine(DMAP, 68mg, 0.56mmol) to afford the title compound(77mg, 65%).

[543]

¹H-NMR (CDCl₃, 400MHz): δ 9.55 (s, 0.6H), 9.52 (s, 0.6H), 8.46 (d, 1H), 7.82-7.71 (m, 3H), 7.38-7.26 (m, 2H), 7.04 (q, 1H), 5.75 (m, 1H), 4.60 (m, 0.4H), 4.42 (m, 0.6H), 4.28 (s, 0.8H), 4.27 (s, 1.2H), 3.92-3.64 (m, 2.4H), 3.56-3.33 (m, 1H), 3.17 (dd, 0.6H), 2.33-2.16 (m, 1H), 1.93 (m, 1H), 1.32 (m, 1H), 0.96 (m, 2H), 0.75 (m, 2H).

[544]

[545] **<Example 11>**

(R)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide; (I-11)

[546]

[547] Step 1 : Preparation of

(R)-N-(1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide

[548]

2-fluoro-5-formylbenzoic acid(350mg, 2.08mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 1.02g, 2.79mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.72mL, 4.16mmol) was added to a solution of (R)-N-methyl-N-(pyrrolidin-3-yl)cyclopropanecarboxamide(350mg, 2.08mmol) in DMF(5 mL) and stirred for 12 hours. The reaction mixture was concentrated in vacuum, added dichloromethane and washed sat. NH₄Cl(ag) and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum and purified using silica chromatography to afford the intermediate compound (R)-N-(1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide

de(470mg,72%).(R)-benzyl(1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)carbamate(229mg,68%).

[549]

[550] Step 2 : Preparation of (R,Z)-N-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide

[551] Triethylamine(0.38mL, 2.21mmol) was added drop-wide to a solution of the intermediate compound(Step 1)(470mg, 1.48mmol) and dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(357mg, 1.48mmol) in THF(1.7mL) and stirred for 5 hours at 0°C. The reaction mixture was concentrated in vacuum then the white residue was slurried in water for 30 minutes, filtered, washed with water, hexane and ether, and dried to afford the intermediate compound (R,Z)-N-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide(398mg, 62%).

[552]

[553] Step 3 : Preparation of (R)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide

[554] Hydrazine monohydrate(90uL, 1.83mmol) was added to a suspension of the intermediate compound(Step 2)(398mg, 0.92mmol) in ethanol(1.5mL) and stirred at 40°C for 2 hours. The reaction was cooled to room temperature and concentrated in vacuum. Water was added to the reaction mixture and the product was extracted into dichloromethane. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum and purified using silica chromatography to afford the title compound(184mg,45%).

[555] ¹H-NMR (CDCl₃,400MHz): δ 5.35 (q, 0.7H), 4.78 (q, 0.3H), 3.65 (m, 1H), 3.51 (m, 1H), 3.40 (m, 1H), 3.01 (s, 3H), 2.28 (m, 2H), 1.61 (m, 1H), 0.98 (m, 1H), 0.96 (m, 2H), 0.74 (m, 2H).

[556]

[557] **<Example 12> N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)-N-methylcyclopropanecarboxamide; (I-12)**

[558]

[559] Step 1 : Preparation of N-(1-(2-fluoro-5-formylbenzoyl)azetidin-3-yl)-N-methylcyclopropanecarboxamide

[560] This compound was made using the procedure described for example 11(Step 1). Thus, N-(azetidin-3-yl)-N-methylcyclopropanecarboxamide(200mg, 1.30mmol) was reacted with 2-fluoro-5-formyl benzoic acid(218mg, 1.30mmol), O-

(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 640mg, 1.68mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.45mL, 2.59mmol) to afford the intermediate compound N-(1-(2-fluoro-5-formylbenzoyl)azetidin-3-yl)-N-methylcyclopropanecarboxamide(256mg, 65%).

[561]

[562] Step 2 : Preparation of

(Z)-N-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)azetidin-3-yl)-N-methylcyclopropanecarboxamide

[563] This compound was made using the procedure described for example 11(Step 2). Thus, this intermediate compound(Step 1)(256mg, 0.84mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(204mg, 0.84mmol) and triethylamine(0.17mL, 1.26mmol) to afford the intermediate compound (Z)-N-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)azetidin-3-yl)-N-methylcyclopropanecarboxamide(202mg, 57%).

[564]

[565] Step 3 : Preparation of N-

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)-N-methylcyclopropanecarboxamide

[566] This compound was made using the procedure described for example 11(Step 3). Thus, this intermediate compound(Step 2)(202mg, 0.48mmol) was reacted with hydrazine monohydrate(46uL, 0.96mmol) to afford the title compound (106mg, 51%).

[567] ¹H-NMR (MeOD, 400MHz): δ 8.39 (dd, 1H), 7.94 (dd, 1H), 7.85-7.80 (m, 2H), 7.52-7.45 (m, 2H), 7.17-7.12 (m, 1H), 4.63-4.53 (m, 1H), 4.44-4.37 (m, 3H), 4.30-4.21 (m, 1H), 4.01-3.89 (m, 2H), 3.26 (s, 3H), 1.59-1.52 (m, 1H), 0.92-0.78 (m, 4H).

[568]

[569] **<Example 13>**

(S)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide; (I-13)

[570]

[571] Step 1 : Preparation of

(S)-N-(1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide

[572] This compound was made using the procedure described for example 11(Step 1). Thus, (S)-N-methyl-N-(pyrrolidin-3-yl)cyclopropanecarboxamide(350mg, 2.08mmol) was reacted with 2-fluoro-5-formyl benzoic acid(349mg, 2.08mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 1.02mg, 2.70mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.72mL, 4.16mmol) to

afford the intermediate compound

(S)-N-(1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide(470mg, 71%).

[573]

[574] Step 2 : Preparation of

(S,Z)-N-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide

[575] This compound was made using the procedure described for example 11(Step 2).

Thus, this intermediate compound(Step 1)(470mg, 1.48mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(357mg, 1.48mmol) and triethylamine (0.31mL, 2.12mmol) to afford the intermediate compound (S,Z)-N-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide(397mg, 62%).

[576]

[577] Step 3 : Preparation of

(S)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide

[578] This compound was made using the procedure described for example 11(Step 3).

Thus, this intermediate compound(Step 2)(397mg, 0.92mmol) was reacted with hydrazine monohydrate(90uL, 1.83mmol) to afford the title compound (185mg, 45%).

[579] ¹H-NMR (CDCl₃, 400MHz): δ 10.13 (s, 0.5H), 9.97 (s, 0.5H), 8.46 (s, 1H), 7.81-7.70 (m, 3H), 7.37 (m, 1H), 7.30 (m, 1H), 7.03 (q, 1H), 5.34 (m, 0.5H), 5.13 (m, 0.5H), 4.27 (d, 2H), 3.88 (m, 0.5H), 3.78 (m, 0.5H), 3.66-3.34 (m, 3H), 3.20-3.14 (m, 3.5H), 2.98-2.82 (m, 0.5H), 2.20-2.06 (m, 1H), 1.78-1.65 (m, 1H), 1.06-0.92 (m, 2H), 0.81 (m, 2H).

[580]

[581] <Example 14>

3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)-5,5-dimethylimidazolidine-2,4-dione; (I-14)

[582]

[583] Step 1 : Preparation of

3-(3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)azetidine-1-carbonyl)-4-fluorobenzaldehyde

[584] This compound was made using the procedure described for example 11(Step 1).

Thus, 3-(azetidin-3-yl)-5,5-dimethylimidazolidine-2,4-dione(150mg, 0.82mmol) was reacted with 2-fluoro-5-formyl benzoic acid(137mg, 0.82mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 403mg, 1.06mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.29mL, 1.63mmol) to

afford the intermediate compound

3-(3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)azetidine-1-carbonyl)-4-fluorobenzaldehyde(152mg, 56%).

[585]

[586] Step 2 : Preparation of

(Z)-3-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)azetidin-3-yl)-5,5-dimethylimidazolidine-2,4-dione

[587] This compound was made using the procedure described for example 11(Step 2).

Thus, this intermediate compound(Step 1)(152mg, 0.45mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(111mg, 0.45mmol) and triethylamine(96uL, 0.68mmol) to afford the intermediate compound (Z)-3-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)azetidin-3-yl)-5,5-dimethylimidazolidine-2,4-dione(89mg, 43%).

[588]

[589] Step 3 : Preparation of

3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)-5,5-dimethylimidazolidine-2,4-dione

[590] This compound was made using the procedure described for example 11(Step 3).

Thus, this intermediate compound(Step 2)(89mg, 0.19mmol) was reacted with hydrazine monohydrate(20uL, 0.39mmol) to afford the title compound (47mg, 51%).

[591] ¹H-NMR (MeOD, 400MHz): δ 8.36-8.35 (m, 1H), 7.92 (t, 1H), 7.98 (d, 1H), 7.90-7.82 (m, 2H), 7.48-7.43 (m, 2H), 7.22 (t, 1H), 4.34 (s, 2H), 4.07-4.03 (m, 1H), 3.94 (t, 1H), 3.85-3.76 (m, 2H), 3.27-3.23 (m, 1H), 1.32 (s, 6H).

[592]

[593] <Example 15>

(R)-3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione: (I-15)

[594]

[595] Step 1 : Preparation of

(R)-3-(3-(2,5-dioxoimidazolidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[596] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-3-(pyrrolidin-3-yl)imidazolidine-2,4-dione(150mg, 0.88mmol) was reacted with 2-fluoro-5-formyl benzoic acid(149mg, 0.88 mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 437mg, 1.15mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.31mL, 1.77mmol) to afford the intermediate compound (R)-3-(3-(2,5-dioxoimidazolidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(158mg, 56%).

[597]

[598] Step 2 : Preparation of
(R,Z)-3-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione

[599] This compound was made using the procedure described for example 11(Step 2). Thus, this intermediate compound(Step 1)(158mg, 0.50mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(120mg, 0.50mmol) and triethylamine(58uL, 0.42mmol) to afford the intermediate compound (R,Z)-3-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione(93mg, 43%).

[600]

[601] Step 3 : Preparation of
(R)-3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione

[602] This compound was made using the procedure described for example 11(Step 3). Thus, this intermediate compound(Step 2)(93mg, 0.21mmol) was reacted with hydrazine monohydrate(21uL, 0.43mmol) to afford the title compound (54mg, 56%).

[603] ¹H-NMR (MeOD, 400MHz): δ 8.35-8.32 (m, 1H), 7.91 (t, 1H), 7.86-7.77 (m, 2H), 7.47-7.38 (m, 2H), 7.16-7.10 (m, 1H), 4.80-4.58 (m, 1H), 4.35 (d, 2H), 3.98-3.94 (m, 2H), 3.68-3.60 (m, 1H), 3.51-3.45 (m, 2H), 2.50-2.32 (m, 1H), 2.24-2.12 (m, 2H).

[604]

[605] <Example 16>
(R)-1-ethyl-3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione; (I-16)

[606]

[607] Step 1 : Preparation of
(R)-3-(3-(3-ethyl-2,5-dioxoimidazolidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[608] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-1-ethyl-3-(pyrrolidin-3-yl)imidazolidine-2,4-dione(200mg, 1.01mmol) was reacted with 2-fluoro-5-formyl benzoic acid(170mg, 1.01mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 500mg, 1.31mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.35mL, 2.02mmol) to afford the intermediate compound (R)-3-(3-(3-ethyl-2,5-dioxoimidazolidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(197mg, 56%).

[609]

[610] Step 2 : Preparation of

(R,Z)-1-ethyl-3-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione

[611] This compound was made using the procedure described for example 11(Step 2). Thus, this intermediate compound(Step 1)(197mg, 0.56mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(137mg, 0.56 mmol) and triethylamine(0.12mL, 0.85mmol) to afford the intermediate compound (R,Z)-1-ethyl-3-(1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione(134mg, 51%).

[612]

[613] Step 3 : Preparation of

(R)-1-ethyl-3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione

[614] This compound was made using the procedure described for example 11(Step 3). Thus, this intermediate compound(Step 2)(134mg, 0.29mmol) was reacted with hydrazine monohydrate(28uL, 0.58mmol) to afford the title compound (66mg, 48%).

[615] ¹H-NMR (MeOD, 400MHz): δ 8.37-8.34 (m, 1H), 7.92 (t, 1H), 7.87-7.80 (m, 2H), 7.49-7.43 (m, 1H), 7.41-7.39 (m, 1H), 7.17-7.11 (m, 1H), 4.78-4.59 (m, 1H), 4.37 (d, 2H), 3.94 (s, 2H), 3.87 (d, 2H), 3.84-3.79 (m, 1H), 3.67-3.60 (m, 1H), 3.47-3.35 (m, 2H), 2.59-2.44 (m, 1H), 2.19 (d, 2H), 1.20-1.13 (m, 3H).

[616]

[617] <Example 17>

4-(4-fluoro-3-(3-(4-fluoropiperidine-1-carbonyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-17)

[618]

[619] Step 1 : Preparation of

4-fluoro-3-(3-(4-fluoropiperidine-1-carbonyl)azetidine-1-carbonyl)benzaldehyde

[620] This compound was made using the procedure described for example 11(Step 1). Thus, azetidin-3-yl(4-fluoropiperidin-1-yl)methanone(200mg, 1.07mmol) was reacted with 2-fluoro-5-formyl benzoic acid(180mg, 1.07mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 529mg, 1.40mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.37mL, 2.14mmol) to afford the intermediate compound 4-fluoro-3-(3-(4-fluoropiperidine-1-carbonyl)azetidine-1-carbonyl)benzaldehyde(216mg, 60%).

[621]

[622] Step 2 : Preparation of

(Z)-3-(4-fluoro-3-(3-(4-fluoropiperidine-1-carbonyl)azetidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one

[623] This compound was made using the procedure described for example 11(Step 2). Thus, this intermediate compound(Step 1)(261mg, 0.64mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(156mg, 0.64mmol) and triethylamine(0.13mL, 0.96mmol) to afford the intermediate compound (Z)-3-(4-fluoro-3-(3-(4-fluoropiperidine-1-carbonyl)azetidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one(140mg, 48%).

[624]

[625] Step 3 : Preparation of
4-(4-fluoro-3-(3-(4-fluoropiperidine-1-carbonyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[626] This compound was made using the procedure described for example 11(Step 3). Thus, this intermediate compound(Step 2)(140mg, 0.31mmol) was reacted with hydrazine monohydrate(30uL, 0.62mmol) to afford the title compound(76mg, 53%).

[627] ¹H-NMR (MeOD, 400MHz): δ 8.36 (d, 1H), 7.95 (d, 1H), 7.79-7.90 (m, 2H), 7.45-7.60 (m, 2H), 7.15 (t, 1H), 4.37 (s, 2H), 4.32 (d, 1H), 4.15-4.27 (m, 3H), 3.70-3.88 (m, 2H), 3.41-3.62 (m, 2H), 3.27-3.36 (m, 2H), 1.76-1.94 (m, 4H).

[628]

[629] <Example 18>
4-(3-(3-(3,3-difluoroazetidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-18)

[630]

[631] Step 1 : Preparation of
3-(3-(3,3-difluoroazetidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzaldehyde

[632] This compound was made using the procedure described for example 11(Step 1). Thus, azetidin-3-yl(3,3-difluoroazetidin-1-yl)methanone(200mg, 1.14mmol) was reacted with 2-fluoro-5-formyl benzoic acid(190mg, 1.14mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 560mg, 1.47mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.41mL, 2.27mmol) to afford the intermediate compound 3-(3-(3,3-difluoroazetidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzaldehyde(222mg, 60%).

[633]

[634] Step 2 : Preparation of
(Z)-3-(3-(3-(3,3-difluoroazetidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one

[635] This compound was made using the procedure described for example 11(Step 2). Thus, this intermediate compound(Step 1)(222mg, 0.68mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(164mg, 0.68mmol) and

triethylamine(0.14mL, 1.02mmol) to afford the intermediate
(Z)-3-(3-(3-(3,3-difluoroazetidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one(145mg, 48%).

[636]

[637] Step 3 : Preparation of
4-(3-(3-(3,3-difluoroazetidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[638] This compound was made using the procedure described for example 11(Step 3). Thus, this intermediate compound(Step 2)(145mg, 0.33mmol) was reacted with hydrazine monohydrate(31uL, 0.65mmol) to afford the title compound (79mg, 53%).

[639] ¹H-NMR (MeOD, 400MHz): δ 8.36 (d, 1H), 7.94 (d, 1H), 7.79-7.89 (m, 2H), 7.46-7.58 (m, 2H), 7.14 (t, 1H), 4.46-4.64 (m, 2H), 4.25-4.40 (m, 5H), 4.05-4.23 (m, 3H), 3.51-3.59 (m, 1H).

[640]

[641] <Example 19>
4-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-19)

[642]

[643] Step 1 : Preparation of
3-(3-(3,3-difluoropyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzaldehyde

[644] This compound was made using the procedure described for example 11(Step 1). Thus, azetidin-3-yl(3,3-difluoropyrrolidin-1-yl)methanone(200mg, 1.05mmol) was reacted with 2-fluoro-5-formyl benzoic acid(176mg, 1.05mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 518mg, 1.05mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.37mL, 1.37mmol) to afford the intermediate compound
3-(3-(3,3-difluoropyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzaldehyde(214mg, 60%).

[645]

[646] Step 2 : Preparation of
(Z)-3-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one

[647] This compound was made using the procedure described for example 11(Step 2). Thus, this intermediate compound(Step 1)(214mg, 0.63mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(152mg, 0.63mmol) and triethylamine (0.13mL, 0.94mmol) to afford the intermediate compound
(Z)-3-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one(138mg, 48%).

[648]

[649] Step 3 : Preparation of
4-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[650] This compound was made using the procedure described for example 11(Step 3). Thus, this intermediate compound(Step 2)(138mg, 0.31mmol) was reacted with hydrazine monohydrate(30uL, 0.62mmol) to afford the title compound(75mg, 53%).

[651] ¹H-NMR (MeOD, 400MHz): δ 8.36 (d, 1H), 7.95 (d, 1H), 7.80-7.90 (m, 2H), 7.45-7.54 (m, 2H), 7.15 (t, 1H), 4.38 (s, 2H), 4.29-4.36 (m, 2H), 4.16-4.28 (m, 3H), 3.58-3.85 (m, 4H), 2.36-2.51 (m, 2H).

[652]

[653] <Example 20>
4-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-20)

[654]

[655] Step 1 : Preparation of
3-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[656] This compound was made using the procedure described for example 11(Step 1). Thus, (3,3-difluoropyrrolidin-1-yl)(pyrrolidin-3-yl)methanone(210mg, 1.03mmol) was reacted with 2-fluoro-5-formyl benzoic acid(172mg, 1.03mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 507mg, 1.33mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.36mL, 2.05mmol) to afford the intermediate compound 3-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(218mg, 60%).

[657]

[658] Step 2 : Preparation of
(Z)-3-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one

[659] This compound was made using the procedure described for example 11(Step 2). Thus, this intermediate compound(Step 1)(218mg, 0.62mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(149mg, 0.62mmol) and triethylamine(0.13mL, 0.93mmol) to afford the intermediate compound (Z)-3-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one(139mg, 48%).

[660]

[661] Step 3 : Preparation of

4-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[662] This compound was made using the procedure described for example 11(Step 3). Thus, this intermediate compound(Step 2)(139mg, 0.30mmol) was reacted with hydrazine monohydrate(29uL, 0.59mmol) to afford the title compound (76mg, 53%).

[663] ¹H-NMR (DMSO, 400MHz): δ 12.60 (s, 1H), 8.26 (d, 1H), 7.98 (d, 1H), 7.90 (t, 1H), 7.86-7.80 (m, 1H), 7.46-7.37 (m, 2H), 7.22 (t, 1H), 4.33 (s, 2H), 4.08-3.98 (m, 1H), 3.79-3.67 (m, 2H), 3.64-3.42 (m, 3H), 3.32-3.16 (m, 2H), 2.49-2.32 (m, 2H), 2.23-2.04 (m, 1H), 1.97-1.87 (m, 1H), 1.18 (t, 1H).

[664]

[665] **<Example 21>**

(R)-N-(cyclopropylmethyl)-1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidine-3-carboxamide; (I-21)

[666]

[667] Step 1 : Preparation of

(R)-N-(cyclopropylmethyl)-1-(2-fluoro-5-formylbenzoyl)pyrrolidine-3-carboxamide

[668] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-N-(cyclopropylmethyl)pyrrolidine-3-carboxamide(300mg, 1.78mmol) was reacted with 2-fluoro-5-formyl benzoic acid(299mg, 1.78mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 879mg, 2.32mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.63mL, 3.57mmol) to afford the intermediate compound (R)-N-(cyclopropylmethyl)-1-(2-fluoro-5-formylbenzoyl)pyrrolidine-3-carboxamide(266mg, 47%).

[669]

[670] Step 2 : Preparation of

(R,Z)-N-(cyclopropylmethyl)-1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidine-3-carboxamide

[671] This compound was made using the procedure described for example 11(Step 2). Thus, this intermediate compound(Step 1)(266mg, 0.84mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(203mg, 0.84mmol) and triethylamine (0.18mL, 1.26mmol) to afford the intermediate compound (R,Z)-N-(cyclopropylmethyl)-1-(2-fluoro-5-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidine-3-carboxamide(186mg, 51%).

[672]

[673] Step 3 : Preparation of

(R)-N-(cyclopropylmethyl)-1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidine-3-carboxamide

[674] This compound was made using the procedure described for example 11(Step 3). Thus, this intermediate compound(Step 2)(186mg, 0.43mmol) was reacted with hydrazine monohydrate(42uL, 0.85mmol) to afford the title compound (84mg, 44%).

[675] ¹H-NMR (MeOD, 400MHz): δ 8.36-8.34 (m, 1H), 7.93 (t, 1H), 7.88-7.78 (m, 2H), 7.47-7.39 (m, 2H), 7.14 (t, 1H), 4.37 (s, 2H), 3.82-3.53 (m, 2H), 3.49-3.33 (m, 2H), 3.12-2.96 (m, 3H), 2.22-1.96 (m, 2H), 0.99-0.88 (m, 1H), 0.52-0.44 (m, 2H), 2.24-2.02 (m, 2H).

[676]

[677] **<Example 22>**

4-(4-fluoro-3-(3-(pyrrolidine-1-carbonyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-22)

[678]

[679] Step 1 : Preparation of

4-fluoro-3-(3-(pyrrolidine-1-carbonyl)azetidine-1-carbonyl)benzaldehyde

[680] This compound was made using the procedure described for example 11(Step 1). Thus, azetidin-3-yl(pyrrolidin-1-yl)methanone(200mg, 1.30mmol) was 2-fluoro-5-formyl benzoic acid(218mg, 1.30mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 639mg, 1.69mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.45mL, 2.59mmol) to afford the intermediate 4-fluoro-3-(3-(pyrrolidine-1-carbonyl)azetidine-1-carbonyl)benzaldehyde(244mg, 62%).

[681]

[682] Step 2 : Preparation of

(Z)-3-(4-fluoro-3-(3-(pyrrolidine-1-carbonyl)azetidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one

[683] This compound was made using the procedure described for example 11(Step 2). Thus, this intermediate compound(Step 1)(244mg, 0.80mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(194mg, 0.80mmol) and triethylamine(0.17mL, 1.21mmol) to afford the intermediate compound (Z)-3-(4-fluoro-3-(3-(pyrrolidine-1-carbonyl)azetidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one(172mg, 51%).

[684]

[685] Step 3 : Preparation of

4-(4-fluoro-3-(3-(pyrrolidine-1-carbonyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[686] This compound was made using the procedure described for example 11(Step 3). Thus, this intermediate compound(Step 2)(172mg, 0.42mmol) was reacted with

hydrazine monohydrate(40uL, 0.82mmol) to afford the title compound (97mg, 55%).

[687] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.37 (m, 1H), 7.24 (d, 1H), 7.80-7.90 (m, 2H), 7.49 (m, 2H), 7.14 (t, 1H), 4.37 (s, 2H), 4.32 (t, 1H), 4.22 (m, 3H), 3.71 (m, 1H), 3.44 (m, 2H), 3.30-3.44 (m, 2H), 1.86-1.97(m, 4H).

[688]

[689] **<Example 23>**

(R)-4-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-23)

[690]

[691] Step 1 : Preparation of

(R)-3-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzaldehyde

[692] This compound was made using the procedure described for example 11(Step 1).

Thus, (R)-azetidin-3-yl(3-(dimethylamino)pyrrolidin-1-yl)methanone(200mg, 1.05mmol) was reacted with 2-fluoro-5-formyl benzoic acid(176mg, 2.05mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 515mg, 1.36mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.52mL, 2.98mmol) to afford the intermediate compound (R)-3-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzaldehyde(150mg, 42%).

[693]

[694] Step 2 : Preparation of

(R,Z)-3-(3-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one

[695] This compound was made using the procedure described for example 11(Step 2).

Thus, this intermediate compound(Step 1)(150mg, 0.44mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(106mg, 0.44mmol) and triethylamine(92uL, 0.65mmol) to afford the intermediate compound (R,Z)-3-(3-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one(102mg, 51%).

[696]

[697] Step 3 : Preparation of

(R)-4-(3-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[698] This compound was made using the procedure described for example 11(Step 3).

Thus, this intermediate compound(Step 2)(102mg, 0.22mmol) was reacted with hydrazine monohydrate(21uL, 0.45mmol) to afford the title compound (53mg, 50%).

[699] ¹H-NMR (MeOD, 400MHz): δ 8.36 (m, 1H), 7.94-7.92 (m, 1H), 7.89-7.80 (m, 2H),

7.56-7.39 (m, 2H), 7.16 (t, 1H), 4.36 (s, 2H), 4.20-4.03 (m, 2H), 3.96-3.80 (m, 2H), 3.67 (m, 1H), 3.44 (t, 2H), 3.39-3.32 (m, 2H), 2.98-2.90 (m, 1H), 2.10 (s, 6H), 1.82-1.80 (m, 2H).

[700]

[701] **<Example 24>**

(S)-4-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-24)

[702]

[703] Step 1 : Preparation of

(S)-3-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzaldehyde

[704]

This compound was made using the procedure described for example 11(Step 1). Thus, (S)-azetidin-3-yl(3-(dimethylamino)pyrrolidin-1-yl)methanone(200mg, 1.05mmol) was reacted with 2-fluoro-5-formyl benzoic acid(176mg, 2.05mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 515mg, 1.36mmol) and N,N-diisopropyl ethylamine(DIPEA, 0.52mL, 2.98mmol) to afford the intermediate compound (S)-3-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzaldehyde(150mg, 42%).

[705]

[706] Step 2 : Preparation of

(S,Z)-3-(3-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one

[707]

This compound was made using the procedure described for example 11(Step 2). Thus, this intermediate compound(Step 1)(150mg, 0.44mmol) was reacted with dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(106mg, 0.44mmol) and triethylamine(92uL, 0.65mmol) to afford the intermediate compound (S,Z)-3-(3-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzylidene)isobenzofuran-1(3H)-one(102mg, 51%).

[708]

[709] Step 3 : Preparation of

(S)-4-(3-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[710]

This compound was made using the procedure described for example 11(Step 3). Thus, this intermediate compound(Step 2)(102mg, 0.22mmol) was reacted with hydrazine monohydrate(21uL, 0.45mmol) to afford the title compound(53mg, 50%).

[711]

¹H-NMR (MeOD, 400MHz): δ 8.36 (m, 1H), 7.94-7.92 (m, 1H), 7.89-7.80 (m, 2H), 7.56-7.39 (m, 2H), 7.16 (t, 1H), 4.36 (s, 2H), 4.20-4.03 (m, 2H), 3.96-3.80 (m, 2H),

3.67 (m, 1H), 3.44 (t, 2H), 3.39-3.32 (m, 2H), 2.98-2.90 (m, 1H), 2.10 (s, 6H), 1.82-1.80 (m, 2H).

[712]

[713] **<Example 25>**

4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-25)

[714]

[715] Step 1 : Preparation of

4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[716]

Cyclobutanone(42uL, 0.57mmol) was added to a solution of 4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(100mg, 0.28mmol) in 1,2-dichloroethane(2mL) and stirred for 30min then acetic acid(32uL, 0.56mmol) and triacetoxyborohydride(118mg, 0.56mmol) was added to the reaction mixture at 0°C and stirred for 12 hours. The reaction mixture was concentrated in vacuum, added 2N NaOH(aq) and extracted into dichloromethane. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum and purified using silica chromatography to afford the title compound(82mg,72%).

[717]

¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.26 (d, 1H), 7.97 (d, 1H), 7.89 (t, 1H), 7.83 (t, 1H), 7.50-7.21 (m, 2H), 7.21 (t, 1H), 4.33 (s, 2H), 4.10 (t, 1H), 3.97 (t, 1H), 3.67-3.51 (m, 3H), 3.08 (m, 1H), 2.76 (m, 1H), 1.99 (t, 2H), 1.69-1.46 (m, 4H).

[718]

[719] **<Example 26>**

4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-26)

[720]

[721] Step 1 : Preparation of

4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[722]

This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with (1-ethoxycyclopropoxy)trimethylsilane(51uL, 0.57mmol) and sodium triacetoxyborohydride(248mg, 1.17mmol) to afford the title compound(152mg, 68%).

[723]

¹H-NMR (MeOD, 400MHz): δ 8.36 (d, 1H), 7.93 (d, 1H), 7.79-7.89 (m, 2H), 7.48-7.54 (m, 1H), 7.42 (d, 1H), 7.15 (t, 1H), 4.00-4.05 (m, 2H), 3.75-3.80 (m, 2H), 3.34-3.39 (m, 1H), 3.12 (s, 2H), 1.32-1.36 (m, 1H), 0.64-0.72 (m, 2H), 0.41-0.46 (m, 2H).

[724]

[725] **<Example 27>**

4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-27)

[726]

[727] Step 1 : Preparation

of 4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[728] This compound was made using the procedure described for example 25(Step 1).
Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with cyclopentanone(51uL, 0.57mmol) and sodium triacetoxyborohydride(248mg, 1.178mmol) to afford the title compound(240mg, 66%).

[729] ¹H-NMR (DMSO, 400MHz): δ 12.60(s, 1H), 8.26 (d, 1H), 7.97 (d, 1H), 7.89 (t, 1H), 7.83 (t, 1H), 7.44-7.50 (m, 1H), 7.40 (d, 1H), 7.21 (t, 1H), 4.33 (s, 2H), 4.13 (t, 1H), 4.00 (t, 1H), 3.54-3.70 (m, 3H), 2.82-2.91 (m, 1H), 1.52-1.67 (m, 4H), 1.43 (brs, 2H), 1.10-1.27 (m, 2H).

[730]

[731] **<Example 28>**

4-(3-(3-(cyclohexylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-28)

[732]

[733] Step 1 : Preparation of

4-(3-(3-(cyclohexylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[734] This compound was made using the procedure described for example 25(Step 1).
Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with cyclohexanone(59uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(203mg, 82%).

[735] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.26 (d, 1H), 7.97 (d, 1H), 7.91-7.81 (m, 2H), 7.49-7.45 (m, 1H), 7.41-7.39 (m, 1H), 7.21 (t, 1H), 4.33 (s, 2H), 4.16-3.98 (m, 2H), 3.67-3.58 (m, 3H), 2.33-2.26 (m, 1H), 1.72-1.61 (m, 4H), 1.52 (d, 1H), 1.23-1.06 (m, 3H), 1.00-0.90 (m, 2H).

[736]

[737] **<Example 29>**

(R)-4-(3-(3-(cyclopropylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-29)

[738]

[739] Step 1 : Preparation of

(R)-4-(3-(3-(cyclopropylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[740] This compound was made using the procedure described for example 25(Step 1).

Thus,

(R)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 1)(200mg, 0.54mmol) was reacted with (1-ethoxycyclopropoxy)trimethylsilane(49uL, 0.54mmol) and sodium triacetoxymborohydride(247mg, 1.17mmol) to afford the title compound(142mg, 65%).

[741] ¹H-NMR (DMSO, 400MHz): δ 12.60 (s, 1H), 8.27-8.25 (m, 1H), 7.97 (d, 1H), 7.89-7.82 (m, 2H), 7.44-7.33 (m, 2H), 7.22 (t, 1H), 4.32 (s, 2H), 3.29-3.23 (m, 2H), 3.15-2.99 (m, 1H), 2.06-1.73 (m, 3H), 1.24 (s, 1H), 0.39-0.13 (m, 4H).

[742]

[743] <Example 30>

(R)-4-(3-(3-(cyclobutylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-30)

[744]

[745] Step 1 : Preparation of

(R)-4-(3-(3-(cyclobutylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[746] This compound was made using the procedure described for example 25(Step 1).

Thus,

(R)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 1)(200mg, 0.54mmol) was reacted with cyclobutanone(41uL, 0.54mmol) and sodium triacetoxymborohydride(247mg, 1.17mmol) to afford the title compound(163mg, 72%).

[747] ¹H-NMR (DMSO, 400MHz): δ 12.60 (s, 1H), 8.26 (d, 1H), 7.97 (d, 1H), 7.89 (t, 1H), 7.83 (t, 1H), 7.44-7.50 (m, 1H), 7.40 (d, 1H), 7.21 (t, 1H), 4.37 (s, 2H), 3.79-3.67 (m, 1H), 3.59-3.33 (m, 3H), 3.29-3.06 (m, 3H), 2.76 (m, 1H), 1.99 (t, 2H), 1.69-1.46(m, 4H).

[748]

[749] <Example 31>

(R)-4-(3-(3-(cyclopentylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-31)

[750]

[751] Step 1 : Preparation of

(R)-4-(3-(3-(cyclopentylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[752] This compound was made using the procedure described for example 25(Step 1).

Thus,

(R)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 1)(200mg, 0.54mmol) was reacted with cyclopentanone(48uL, 0.54mmol) and sodium triacetoxymethylborohydride(247mg, 1.17mmol) to afford the title compound(190mg, 81%).

[753] ¹H-NMR (DMSO, 400MHz): δ 12.60 (s, 1H), 8.26 (d, 1H), 7.97 (d, 1H), 7.89 (t, 1H), 7.83 (t, 1H), 7.44-7.50 (m, 1H), 7.40 (d, 1H), 7.21 (t, 1H), 4.37 (s, 2H), 3.79-3.67 (m, 1H), 3.59-3.33 (m, 3H), 3.29-3.06 (m, 3H), 2.82-2.91 (m, 1H), 1.52-1.67 (m, 4H), 1.43 (brs, 2H), 1.10-1.27 (m, 2H).

[754]

[755] **<Example 32>**

4-(4-fluoro-3-(3-(isopropylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-32)

[756]

[757] Step 1 : Preparation of

4-(4-fluoro-3-(3-(isopropylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[758] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with acetone(42uL, 0.57mmol) and sodium triacetoxymethylborohydride(247mg, 1.17mmol) to afford the title compound(123mg, 55%).

[759] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.27-8.25 (m, 1H), 7.97 (d, 1H), 7.91-7.81 (m, 2H), 7.48-7.44 (m, 1H), 7.41-7.39 (m, 1H), 7.21 (t, 1H), 4.33 (s, 2H), 4.15-4.10 (m, 2H), 3.66-3.59 (m, 3H), 3.17 (d, 1H), 2.68-2.61 (m, 1H), 0.92-0.83 (m, 6H).

[760]

[761] **<Example 33>**

4-(3-(3-((cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-33)

[762]

[763] Step 1 : Preparation of

4-(3-(3-((cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[764] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with cyclopropanecarbaldehyde(42uL, 0.57mmol) and sodium triacetoxymethylborohydride(247mg, 1.17mmol) to afford the title

compound(153mg, 66%).

[765] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.28-7.97 (m, 2H), 7.91-7.81 (m, 2H), 7.48-7.40 (m, 2H), 7.22 (m, 1H), 4.33 (s, 2H), 4.13-3.98 (m, 2H), 3.70-3.56 (m, 3H), 2.29 (m, 2H), 0.83-0.72 (m, 1H), 0.37-0.32 (m, 2H), 0.06 (m, 2H).

[766]

[767] **<Example 34>**

4-(3-(3-(bis(cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-34)

[768]

[769] Step 1 : Preparation of

4-(3-(3-(bis(cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[770] This compound was made using the procedure described for example 25(Step 1). Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with cyclopropanecarbaldehyde(84uL, 1.14mmol) and sodium triacetoxyborohydride (247mg, 1.17mmol) to afford the title compound(116mg, 43%).

[771] ¹H-NMR (DMSO, 400MHz): δ 12.57 (s, 1H), 8.23 (m, 1H), 7.97-7.77 (m, 3H), 7.47-7.36 (m, 2H), 7.18 (m, 1H), 4.29 (s, 2H), 3.99 (m, 1H), 3.88-3.58 (m, 4H), 2.38-2.31 (m, 4H), 0.77 (m, 2H), 0.38 (s, 2H), 0.36 (s, 2H), 0.01 (s, 4H).

[772]

[773] **<Example 35>**

4-(4-fluoro-3-(3-(isobutylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-35)

[774]

[775] Step 1 : Preparation of

4-(4-fluoro-3-(3-(isobutylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[776] This compound was made using the procedure described for example 25(Step 1). Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with isobutyraldehyde(52uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(194mg, 83%).

[777] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.35 (m, 1H), 7.95-7.93 (m, 1H), 7.89-7.82 (m, 2H), 7.51-7.49 (m, 1H), 7.45-7.43 (m, 1H), 7.15 (t, 1H), 4.38 (s, 2H), 4.28-4.26 (m, 1H), 4.16-4.12 (m, 1H), 3.88-3.84 (m, 1H), 3.79-3.75 (m, 1H), 3.66-3.64 (m, 1H), 2.31-2.28 (m, 2H), 1.71-1.68 (m, 1H), 0.91 (dd, 6H).

[778]

[779] <Example 36>

4-(4-fluoro-3-(3-((1-hydroxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-36)

[780]

[781] Step 1 : Preparation of

4-(4-fluoro-3-(3-((1-hydroxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[782] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 1-hydroxypropan-2-one(39uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(82mg, 35%).

[783] ¹H-NMR (MeOD, 400MHz): δ 8.36-8.34 (m, 1H), 7.94-7.92 (m, 1H), 7.88-7.81 (m, 2H), 7.50-7.49 (m, 1H), 7.46-7.44 (m, 1H), 7.16-7.11 (m, 1H), 4.36 (s, 2H), 4.35-4.33 (m, 1H), 4.20-4.17 (m, 1H), 3.90-3.3.83 (m, 3H), 3.46-3.43 (m, 1H), 3.39-3.36 (m, 1H), 2.77-2.75 (m, 1H), 1.95 (s, 1H), 1.02 (q, 3H).

[784]

[785] <Example 37>

4-(4-fluoro-3-(3-(neopentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-37)

[786]

[787] Step 1 : Preparation of

4-(4-fluoro-3-(3-(neopentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[788] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with pivalaldehyde(62uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(185mg, 77%).

[789] ¹H-NMR (MeOD, 400MHz): δ 8.34 (m, 1H), 7.92-7.78 (m, 3H), 7.50-7.43 (m, 2H), 7.13 (t, 1H), 4.35 (s, 2H), 4.29-4.10 (m, 2H), 3.88-3.75 (m, 2H), 3.62 (m, 1H), 2.23 (m, 2H), 0.91 (s, 9H).

[790]

[791] <Example 38>

4-(3-(3-((2,2-dimethylcyclopentyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-38)

[792]

[793] Step 1 : Preparation of
4-(3-(3-((2,2-dimethylcyclopentyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[794] This compound was made using the procedure described for example 25(Step 1).
Thus,
4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 2,2-dimethylcyclopentanone(72uL, 0.57mmol) and sodium triacetoxyborohydride(247 mg, 1.17mmol) to afford the title compound(99mg, 39%).

[795] ¹H-NMR (MeOD, 400MHz): δ 8.35 (m, 1H), 7.93-7.79 (m, 3H), 7.51-7.42 (m, 2H), 7.14 (t, 1H), 4.36(s, 2H), 4.30-4.10 (m, 2H), 3.90-3.68 (m, 3H), 2.43 (m, 1H), 1.95-1.82 (m, 1H), 1.68-1.28 (m, 5H), 1.01 (d, 3H), 0.84 (s, 3H).

[796]

[797] <Example 39> ethyl
2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclopent-1-enecarboxylate; (I-39)

[798]

[799] Step 1 : Preparation of
ethyl2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclopent-1-enecarboxylate

[800] This compound was made using the procedure described for example 25(Step 1).
Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with ethyl 2-oxocyclopentanecarboxylate(85uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(64mg, 23%).
[801] ¹H-NMR (CDCl₃,400MHz): δ 11.44 (s, 1H), 8.48 (m, 1H), 7.80-7.73 (m, 3H), 7.55 (m, 1H), 7.34-7.28 (m, 1H), 7.01 (t, 1H), 4.50 (t, 1H), 4.39-4.27 (m, 4H), 4.15 (m, 2H), 4.01 (m, 2H), 2.52-2.38 (m, 4H), 1.86-1.80 (m, 2H), 1.28 (t, 3H).

[802]

[803] <Example 40>
4-(4-fluoro-3-(3-(pentan-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-40)

[804]

[805] Step 1 : Preparation of
4-(4-fluoro-3-(3-(pentan-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[806] This compound was made using the procedure described for example 25(Step 1).
Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with pentan-3-one(48uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(46mg, 19%).

[807] ¹H-NMR (CDCl₃,400MHz): δ 11.32 (br, 1H), 8.47 (m, 1H), 7.77-7.72 (m, 3H), 7.51 (m, 1H), 7.32-7.31 (m, 1H), 7.00 (t, 1H), 4.39 (m, 1H), 4.29 (s, 2H), 4.17 (m, 1H), 3.85-3.74 (m, 3H), 2.36 (m, 1H), 2.06 (br, 1H), 1.38 (m, 4H), 0.87 (dd, 6H).

[808]

[809] **<Example 41>**

4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-41)

[810]

[811] Step 1 : Preparation of

4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[812] This compound was made using the procedure described for example 25(Step 1). Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 3-methylbutan-2-one(61uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(125mg, 52%).

[813] ¹H-NMR (CDCl₃, 400MHz): δ 11.22 (s, 1H), 8.50-8.45 (m, 1H), 7.79-7.71 (m, 3H), 7.52-7.50 (m, 1H), 7.33-7.29 (m, 1H), 7.01 (t, 1H), 4.38 (m, 1H), 4.29 (s, 2H), 4.21-4.13 (m, 1H), 3.86-3.72 (m, 3H), 2.50-2.40 (m, 1H), 1.66-1.55 (m, 1H), 0.94-0.84 (m, 9H).

[814]

[815] **<Example 42>**

4-(3-(3-((1-cyclopropylethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-42)

[816]

[817] Step 1 : Preparation of

4-(3-(3-((1-cyclopropylethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[818] This compound was made using the procedure described for example 25(Step 1). Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 1-cyclopropylethanone(56uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(239mg, 43%).

[819] ¹H-NMR (CDCl₃, 400MHz): δ 11.18 (s, 1H), 8.49-8.47 (m, 1H), 7.79-7.72 (m, 3H), 7.52-7.50 (m, 1H), 7.33-7.29 (m, 1H), 7.01 (t, 1H), 4.40 (m, 1H), 4.29 (s, 2H), 3.79 (m, 1H), 1.93 (br, 1H), 1.83 (m, 1H), 1.14 (m, 3H), 0.70-0.40 (m, 3H), 0.15-0.04 (m, 2H).

[820]

[821] **<Example 43>**

4-(3-(3-(bicyclo[2.2.1]heptan-2-ylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-43)

[822]

[823] Step 1 : Preparation of

4-(3-(3-(bicyclo[2.2.1]heptan-2-ylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[824] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with norcamphor(62mg, 0.57mmol) and sodium triacetoxymethylborohydride(247mg, 1.17mmol) to afford the title compound(48mg, 19%).

[825] ¹H-NMR (MeOD, 400MHz): δ 8.37 (d, 1H), 7.92 (d, 1H), 7.82-7.88 (m, 2H), 7.48-7.50 (m, 1H), 7.41-7.43 (m, 1H), 7.14 (t, 1H), 4.38 (s, 2H), 4.28-4.37 (m, 1H), 4.09-4.26 (m, 1H), 3.70-3.91 (m, 2H), 3.61-3.69 (m, 1H), 2.88-2.95 (m, 1H), 2.14-2.23 (m, 2H), 1.73-1.94 (m, 2H), 1.48-1.71 (m, 2H), 1.22-1.40 (m, 4H).

[826]

[827] **<Example 44>**

4-(3-(3-(sec-butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-44)

[828]

[829] Step 1 : Preparation of

4-(3-(3-(sec-butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[830] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with butan-2-one(51uL, 0.57mmol) and sodium triacetoxymethylborohydride (247mg, 1.17mmol) to afford the title compound(74mg, 32%).

[831] ¹H-NMR (CDCl₃, 400MHz): δ 10.58 (s, 1H), 8.49-8.45 (m, 1H), 7.80-7.71 (m, 3H), 7.52-7.49 (dd, 1H), 7.33-7.30 (m, 1H), 7.01 (t, 1H), 4.44-4.35 (m, 1H), 4.28 (s, 2H), 4.22-4.14 (m, 1H), 3.86-3.73 (m, 3H), 2.59-2.52 (m, 1H), 1.48-1.24 (m, 3H), 1.02-0.98 (m, 3H), 0.91-0.86 (m, 3H).

[832]

[833] **<Example 45>**

4-(3-(3-((dicyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-45)

[834]

[835] Step 1 : Preparation of

4-(3-(3-((dicyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[836] This compound was made using the procedure described for example 25(Step 1). Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with dicyclopropylmethanone(43uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(28mg, 11%).

[837] ¹H-NMR (CDCl₃, 400MHz): δ 10.63 (s, 1H), 8.50-8.45 (m, 1H), 7.87-7.71 (m, 3H), 7.52-7.50 (m, 1H), 7.33-7.31 (m, 1H), 7.01 (t, 1H), 4.41-4.37 (m, 1H), 4.28 (s, 2H), 4.20-4.16 (m, 1H), 3.99-3.93 (m, 1H), 3.89-3.76 (m, 2H), 1.74 (br, 1H), 1.08 (t, 1H), 0.85-0.77 (m, 2H), 0.54-0.42 (m, 4H), 0.24-0.18 (m, 2H), 0.08-0.04 (m, 2H).

[838]

[839] **<Example 46>**

4-(4-fluoro-3-(3-((4-methylpentan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-46)

[840]

[841] Step 1 : Preparation of

4-(4-fluoro-3-(3-((4-methylpentan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[842] This compound was made using the procedure described for example 25(Step 1). Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 4-methylpentan-2-one(57mg, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(104mg, 42%).

[843] ¹H-NMR (MeOD, 400MHz): δ 8.37-8.35 (m, 1H), 7.95-7.92 (m, 1H), 7.87-7.82 (m, 2H), 7.51-7.49 (m, 1H), 7.45-7.43 (m, 1H), 7.16 (q, 1H), 4.37 (s, 2H), 4.34-4.32 (m, 1H), 4.19-4.17 (m, 1H), 3.84-3.82 (m, 3H), 2.78-2.76 (m, 1H), 1.71-1.68 (m, 1H), 1.32-1.27 (m, 2H), 1.03-0.99 (m, 3H), 0.92-0.86 (m, 6H).

[844]

[845] **<Example 47>**

4-(4-fluoro-3-(3-((3-hydroxybutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-47)

[846]

[847] Step 1 : Preparation of

4-(4-fluoro-3-(3-((3-hydroxybutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[848] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 3-hydroxybutan-2-one(49uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(60mg, 25%).

[849] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.36 (m, 1H), 7.94-7.92 (m, 1H), 7.88-7.80 (m, 2H), 7.52-7.49 (m, 1H), 7.46-7.44 (m, 1H), 7.16-7.11 (m, 1H), 4.37 (s, 2H), 4.35-4.32 (m, 1H), 4.19-4.16 (m, 1H), 3.91-3.89 (m, 3H), 2.04-1.99 (m, 2H), 1.15-1.12 (m, 3H), 0.12-0.95 (m, 3H).

[850]

[851] **<Example 48>**

4-(4-fluoro-3-(3-(pentan-2-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-48)

[852]

[853] Step 1 : Preparation of

4-(4-fluoro-3-(3-(pentan-2-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[854] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with pentan-2-one(49mg, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(113mg, 51%).

[855] ¹H-NMR (CDCl₃, 400MHz): δ 10.55 (s, 1H), 8.49-8.45 (m, 1H), 7.80-7.71 (m, 3H), 7.50 (d, 1H), 7.33-7.29 (m, 1H), 7.01 (t, 1H), 4.42-4.36 (m, 1H), 4.21-4.11 (m, 1H), 3.85-3.72 (m, 3H), 2.66-2.59 (m, 1H), 1.40-1.25 (m, 5H), 1.02-0.98 (m, 3H), 0.92-0.88 (m, 3H).

[856]

[857] **<Example 49>**

4-(4-fluoro-3-(3-((1-(1-methylcyclopropyl)ethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-49)

[858]

[859] Step 1 : Preparation of

4-(4-fluoro-3-(3-((1-(1-methylcyclopropyl)ethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[860] This compound was made using the procedure described for example 25(Step 1).
Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 1-(1-methylcyclopropyl)ethanone(63uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(37mg, 16%).

[861] ¹H-NMR (CDCl₃, 400MHz): δ 10.22 (s, 1H), 8.48-8.45 (m, 1H), 7.78-7.71 (m, 3H), 7.50-7.49 (m, 1H), 7.33-7.29 (m, 1H), 7.02 (t, 1H), 4.40-4.34 (m, 1H), 4.27 (s, 2H), 4.15 (t, 1H), 3.84-3.73 (m, 3H), 1.85-1.79 (m, 1H), 1.41 (br, 1H), 1.10-1.07 (dd, 3H), 0.97-0.95 (d, 3H).

[862]

[863] **<Example 50>**

4-(4-fluoro-3-(3-((3,3,3-trifluoro-2-methylpropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-50)

[864]

[865] Step 1 : Preparation of

4-(4-fluoro-3-(3-((3,3,3-trifluoro-2-methylpropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[866] This compound was made using the procedure described for example 25(Step 1).
Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 3,3,3-trifluoro-2-methylpropanal(0.1uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(137mg, 52%).

[867] ¹H-NMR (MeOD, 400MHz): δ 8.26 (d, 1H), 7.72-7.84 (m, 3H), 7.33-7.41 (m, 2H), 7.04 (t, 1H), 4.28 (s, 2H), 4.18 (t, 1H), 4.02-4.05 (m, 1H), 3.71-3.76 (m, 1H), 3.63-3.67 (m, 1H), 3.54-3.58 (m, 1H), 2.65-2.70 (m, 1H), 2.32-2.38 (m, 2H), 1.05-1.07 (m, 3H).

[868]

[869] **<Example 51>**

4-(3-(3-(allylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-51)

[870]

[871] Step 1 : Preparation of

4-(3-(3-(allylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[872] This compound was made using the procedure described for example 25(Step 1).
Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with acrylaldehyde(38uL, 0.57mmol) and sodium

triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(147mg, 66%).

[873] ¹H-NMR (CDCl₃, 400MHz): δ 10.02 (s, 1H), 8.40-8.38 (m, 1H), 7.72-7.64 (m, 3H), 7.44-7.42 (m, 1H), 7.25-7.22 (m, 1H), 6.97-6.93 (m, 1H), 5.79 (m, 1H), 5.13-5.03 (m, 2H), 4.30-4.27 (m, 1H), 4.20 (s, 2H), 4.10-4.08 (m, 1H), 3.83-3.79 (m, 1H), 3.72-3.65 (m, 2H), 3.14 (d, 2H).

[874]

[875] **<Example 52>**

4-(4-fluoro-3-(3-(isopentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-52)

[876]

[877] Step 1 : Preparation of

4-(4-fluoro-3-(3-(isopentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[878] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 3-methylbutanal(61uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(190mg, 79%).

[879] ¹H-NMR (CDCl₃, 400MHz): δ 10.14 (s, 1H), 8.47-8.45 (m, 1H), 7.79-7.71 (m, 3H), 7.50 (m, 1H), 7.33-7.29 (m, 1H), 7.02 (t, 1H), 4.36 (t, 1H), 4.27 (s, 2H), 4.18 (t, 1H), 3.88-3.68 (m, 3H), 2.56 (m, 2H), 1.62 (m, 1H), 1.51 (br, 1H), 1.38-1.35 (m, 2H), 0.90-0.88 (dd, 6H).

[880]

[881] **<Example 53>**

4-(3-(3-(butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-53)

[882]

[883] Step 1 : Preparation of

4-(3-(3-(butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[884] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with butyraldehyde(51uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(198mg, 85%).

[885] ¹H-NMR (CDCl₃, 400MHz): δ 10.28 (s, 1H), 8.40-8.38 (m, 1H), 7.72-7.66 (m, 1H), 7.44-7.41 (m, 1H), 7.24-7.22 (m, 1H), 6.97-6.92 (m, 1H), 4.30-4.27 (m, 1H), 4.20 (s, 2H), 4.11-4.09 (m, 1H), 3.81-3.79 (m, 1H), 3.72-3.70 (m, 1H), 3.64-3.62 (m, 1H), 2.50-2.46 (m, 2H), 2.02 (s, 1H), 1.40-1.37(m, 2H), 1.30-1.24 (m, 2H), 0.86-0.80 (m, 5H).

[886]

[887] **<Example 54>**

4-(4-fluoro-3-(3-((3-methylbut-2-en-1-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-54)

[888]

[889] Step 1 : Preparation of

4-(4-fluoro-3-(3-((3-methylbut-2-en-1-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[890] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 3-methylbut-2-enal(55uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(146mg, 61%).

[891] ¹H-NMR (MeOD, 400MHz): δ 8.36 (d, 1H), 7.79-7.94 (m, 3H), 7.43-7.51 (m, 2H), 7.13 (t, 1H), 5.19 (brs, 1H), 4.37 (s, 2H), 4.26 (t, 1H), 4.13 (t, 1H), 3.83-3.87 (m, 1H), 3.74-3.78 (m, 1H), 3.63-3.66 (m, 1H), 3.11 (d, 2H), 1.71 (s, 3H), 1.64 (s, 3H).

[892]

[893] **<Example 55>**

4-(3-(3-((cyclopentylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-55)

[894]

[895] Step 1 : Preparation of

4-(3-(3-((cyclopentylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[896] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with cyclopentanecarbaldehyde(61uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(178mg, 72%).

[897] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.36 (m, 1H), 7.94-7.93 (m, 1H), 7.89-7.82 (m, 2H), 7.51-7.43 (m, 2H), 7.17-7.12 (m, 1H), 4.38 (s, 2H), 4.29-4.28 (m, 1H), 4.15-4.13 (m, 1H), 3.88-3.87 (m, 1H), 3.79-3.77 (m, 1H), 3.66-3.64 (m, 1H), 2.45-2.42 (m, 2H), 1.98-1.95 (m, 1H), 1.81-1.79 (m, 2H), 1.65-1.56 (m, 4H), 1.18-1.16 (m, 2H).

[898]

[899] **<Example 56>**

4-(4-fluoro-3-(3-((4,4,4-trifluorobutyl)amino)azetidine-1-carbonyl)benzyl)phthala

zin-1(2H)-one; (I-56)

[900]

[901] Step 1 : Preparation of4-(4-fluoro-3-(3-((4,4,4-trifluorobutyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[902] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 4,4,4-trifluorobutanal(72mg, 0.57mmol) and sodium triacetoxymethylborohydride(247mg, 1.17mmol) to afford the title compound(111mg, 42%).

[903] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.35 (m, 1H), 7.95-7.92 (m, 1H), 7.89-7.82 (m, 2H), 7.52-7.50 (m, 1H), 7.45-7.43 (m, 1H), 7.17-7.12 (m, 1H), 4.37 (s, 2H), 4.30-4.28 (m, 1H), 4.16-4.14 (m, 1H), 3.86-3.83 (m, 1H), 3.78-3.76 (m, 1H), 3.68-3.66 (m, 1H), 2.58-2.55 (m, 2H), 2.24-2.17 (m, 2H), 1.74-1.68 (m, 2H).

[904]

[905] **<Example 57>****4-(4-fluoro-3-(3-(pentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-57)**

[906]

[907] Step 1 : Preparation of4-(4-fluoro-3-(3-(pentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[908] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with pentanal(61uL, 0.57mmol) and sodium triacetoxymethylborohydride(247mg, 1.17mmol) to afford the title compound(200mg, 83%).

[909] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.35 (m, 1H), 7.94-7.92 (m, 1H), 7.89-7.82 (m, 2H), 7.51-7.49 (m, 1H), 7.45-7.43 (m, 1H), 7.17-7.12 (m, 1H), 4.37 (s, 2H), 4.30-4.28 (m, 1H), 4.17-4.15 (m, 1H), 3.88-3.86 (m, 1H), 3.80-3.78 (m, 1H), 3.69-3.67 (m, 1H), 2.53-2.49 (m, 2H), 1.51-1.47 (m, 2H), 1.35-1.29 (m, 4H), 0.91 (t, 3H).

[910]

[911] **<Example 58>****4-(3-(3-((2-cyclopropylethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-58)**

[912]

[913] Step 1 : Preparation of4-(3-(3-((2-cyclopropylethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1

(2H)-one

[914] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with 2-cyclopropylacetaldehyde(48mg, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(240mg, 69%).

[915] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.36 (m, 1H), 7.95-7.93 (m, 1H), 7.89-7.82 (m, 2H), 7.52-7.50 (m, 1H), 7.45-7.43 (m, 1H), 7.17-7.15 (m, 1H), 4.38 (s, 2H), 4.30-4.29 (m, 1H), 4.15-4.14 (m, 1H), 3.87-3.86 (m, 1H), 3.78-3.77 (m, 1H), 3.68-3.66 (m, 1H), 2.60-2.56 (m, 2H), 1.39-1.34 (m, 2H), 0.72-0.71 (m, 1H), 0.46-0.42 (m, 2H), 0.06-0.04 (m, 2H).

[916]

[917] **<Example 59>**

4-(4-fluoro-3-(3-(propylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-59)

[918]

[919] Step 1 : Preparation of

4-(4-fluoro-3-(3-(propylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[920] This compound was made using the procedure described for example 25(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 0.57mmol) was reacted with propionaldehyde(42uL, 0.57mmol) and sodium triacetoxyborohydride(247mg, 1.17mmol) to afford the title compound(191mg, 85%).

[921] ¹H-NMR (MeOD, 400MHz): δ 10.39 (s, 1H), 8.47-8.45 (m, 1H), 7.80-7.72 (m, 3H), 7.51-7.48 (m, 1H), 7.33-7.29 (m, 1H), 7.04-6.99 (m, 1H), 4.39-4.34 (m, 1H), 4.27 (s, 2H), 4.19-4.17 (m, 1H), 3.89-3.85 (m, 1H), 3.81-3.77 (m, 1H), 3.71-3.70 (m, 1H), 2.55-2.50 (m, 2H), 1.52-1.47 (m, 2H), 0.94-0.91 (m, 3H).

[922]

[923] **<Example 60>**

4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-60)

[924]

[925] Step 1 : Preparation of

4-(4-fluoro-3-(3-((pyridin-4-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[926] isonicotinaldehyde(26uL, 0.28mmol) was added to a solution of

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(100mg, 0.28mmol) in 1,2-dichloroethane(1.1mL) and stirred for 30min then acetic acid(31uL, 0.54 mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) was added to the reaction mixture at 0°C and stirred for 12 hours. The reaction mixture was concentrated in vacuum, added 2N NaOH(aq) and extracted into dichloromethane. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum and purified using silica chromatography to afford the intermediate compound 4-(4-fluoro-3-(3-((pyridin-4-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(108mg,87%).

[927]

[928] Step 2 : Preparation of

4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[929] K₂CO₃(51mg,0.48mmol) and iodomethane(33uL,0.48mmol) was added to a solution of the intermediate compound(Step1)(108mg,0.24mmol) in DMF(1.5mL) and stirred for 3 hours. The reaction mixture was concentrated in vacuum, added dichloromethane and washed sat. NH₄Cl(aq) and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum and purified using silica chromatography to afford the title compound(99mg,91%).

[930] ¹H-NMR (MeOD, 400MHz): δ 8.47 (d, 2H), 8.36 (d, 2H), 7.94 (d, 1H), 7.78-7.91 (m, 2H), 7.40-7.55 (m, 3H), 7.15 (t, 1H), 4.38 (s, 2H), 4.18-4.25 (m, 1H), 3.97-4.14 (m, 2H), 3.80-3.90 (m, 1H), 3.42-3.54 (m, 3H), 2.08(s, 3H).

[931]

[932] <Example 61>

(R)-4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-61)

[933]

[934] Step 1 : Preparation of

(R)-4-(4-fluoro-3-(3-((pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[935] This compound was made using the procedure described for example 60(Step 1).

Thus,

(R)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 1)(100mg, 0.28mmol) was reacted with isonicotinaldehyde(26uL, 0.28mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound

(R)-4-(4-fluoro-3-(3-((pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(106mg, 83%).

[936]

[937] Step 2 : Preparation of

(R)-4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[938] This compound was made using the procedure described for example 60(Step 2). Thus, this intermediate compound(Step 1)(106mg, 0.23mmol) was reacted with K_2CO_3 (51mg, 0.48mmol) and iodomethane(33uL, 0.48mmol) to afford the title compound(98mg, 91%).

[939] ^1H -NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.51-8.47 (m, 2H), 8.26 (t, 1H), 7.97 (m, 1H), 7.92-7.78 (m, 2H), 7.45-7.33 (m, 3H), 7.24 (m, 2H), 4.32 (s, 2H), 3.76 (m, 1H), 3.51 (m, 3H), 3.30 (s, 2H), 3.08 (m, 1H), 1.92 (s, 3H), 1.81(m, 2H), 1.19 (m, 1H).

[940]

[941] <Example 62>

(S)-4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-62)

[942]

[943] Step 1 : Preparation of

(S)-4-(4-fluoro-3-(3-((pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[944] This compound was made using the procedure described for example 60(Step 1). Thus, (S)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 2)(100mg, 0.23mmol) was reacted with isonicotinaldehyde(33uL, 0.23mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound (S)-4-(4-fluoro-3-(3-((pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(106mg, 83%).

[945]

[946] Step 2 : Preparation of

(S)-4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[947] This compound was made using the procedure described for example 60(Step 2). Thus, this intermediate compound(Step 1)(106mg, 0.24mmol) was reacted with K_2CO_3 (51mg, 0.48mmol) and iodomethane(33uL, 0.48mmol) to afford the title compound(98mg, 91%).

[948] ^1H -NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.51-8.47 (m, 2H), 8.26 (t, 1H), 7.97 (m, 1H), 7.92-7.78 (m, 2H), 7.45-7.33 (m, 3H), 7.24 (m, 2H), 4.32 (s, 2H), 3.76 (m, 1H), 3.51 (m, 3H), 3.30 (s, 2H), 3.08 (m, 1H), 1.92 (s, 3H), 1.81(m, 2H), 1.19 (m, 1H).

[949]

[950] **<Example 63>**

(S)-4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-63)

[951]

[952] Step 1 : Preparation of

(S)-4-(4-fluoro-3-(3-((pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[953] This compound was made using the procedure described for example 60(Step 1).

Thus,

(S)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 2)(100mg, 0.23mmol) was reacted with picolinaldehyde(33uL, 0.23mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound

(S)-4-(4-fluoro-3-(3-((pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(85mg, 81%).

[954]

[955] Step 2 : Preparation of

(S)-4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[956] This compound was made using the procedure described for example 60(Step 2).

Thus, this intermediate compound(Step 1)(85mg, 0.19mmol) was reacted with K₂CO₃ (51mg,0.37mmol) and iodomethane(23uL,0.37mmol) to afford the title compound(79mg, 88%).

[957]

¹H-NMR (MeOD, 400MHz): δ 10.82 (s, 0.4H), 10.40 (s, 0.6H), 8.62 (dd, 1H), 8.46 (m, 1H), 7.75 (m, 3H), 7.52 (m, 1H), 7.37 (m, 2H), 7.17 (m, 1H), 7.0 (m, 1H), 4.15 (s, 2H), 3.96 (m, 1H), 3.89 (m, 1H), 3.74 (d, 1H), 3.63 (m, 2H), 3.46 (m, 1H), 3.41 (m, 1H), 2.21 (s, 2H), 1.93 (m, 3H).

[958]

[959] **<Example 64>**

(R)-4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-64)

[960]

[961] Step 1 : Preparation of

(R)-4-(4-fluoro-3-(3-((pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[962] This compound was made using the procedure described for example 60(Step 1).

Thus,

(R)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 1)(100mg, 0.23mmol) was reacted with picolinaldehyde(33uL, 0.23mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound

(R)-4-(4-fluoro-3-(3-((pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(85mg, 81%).

[963]

[964] Step 2 : Preparation of

(R)-4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[965] This compound was made using the procedure described for example 60(Step 2).

Thus, this intermediate compound(Step 1)(85mg, 0.19mmol) was reacted with K₂CO₃ (51mg, 0.37mmol) and iodomethane(23uL, 0.37mmol) to afford the title compound(79mg, 88%).

[966] ¹H-NMR (MeOD, 400MHz): δ 10.82 (s, 0.4H), 10.40 (s, 0.6H), 8.62 (dd, 1H), 8.46 (m, 1H), 7.75 (m, 3H), 7.52 (m, 1H), 7.37 (m, 2H), 7.17 (m, 1H), 7.0 (m, 1H), 4.15 (s, 2H), 3.96 (m, 1H), 3.89 (m, 1H), 3.74 (d, 1H), 3.63 (m, 2H), 3.46 (m, 1H), 3.41 (m, 1H), 2.21 (s, 2H), 1.93 (m, 3H).

[967]

[968] <Example 65>

4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-65)

[969]

[970] Step 1 : Preparation of

4-(4-fluoro-3-(3-((pyridin-2-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[971] This compound was made using the procedure described for example 60(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(100mg, 0.28mmol) was reacted with picolinaldehyde(26uL, 0.28mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound 4-(4-fluoro-3-(3-((pyridin-2-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(108mg, 87%).

[972]

[973] Step 2 : Preparation of

4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[974] This compound was made using the procedure described for example 60(Step 2).

Thus, this intermediate compound(Step 1)(108mg, 0.24mmol) was reacted with K₂CO₃ (51mg, 0.48mmol) and iodomethane(33uL,0.48mmol) to afford the title compound(99mg, 91%).

[975] ¹H-NMR (MeOD, 400MHz): δ 8.47 (d, 1H), 8.35 (d, 1H), 7.94 (d, 1H), 7.78-7.89 (m, 3H), 7.43-7.54 (m, 3H), 7.30-7.35 (m, 1H), 7.14 (t, 1H), 4.38 (s, 2H), 4.17-4.22 (m, 1H), 3.95-4.06 (m, 2H), 3.87-3.94 (m, 1H), 3.57 (s, 2H), 3.44-3.51 (m, 1H), 2.18 (s, 3H).

[976]

[977] **<Example 66>**

4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-66)

[978]

[979] Step 1 : Preparation of

4-(4-fluoro-3-(3-((pyridin-3-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[980] This compound was made using the procedure described for example 60(Step 1). Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(100mg, 0.28mmol) was reacted with nicotinaldehyde(26uL, 0.28mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound 4-(4-fluoro-3-(3-((pyridin-3-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(108mg, 87%).

[981]

[982] Step 2 : Preparation of

4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[983] This compound was made using the procedure described for example 60(Step 2). Thus, this intermediate compound(Step 1)(108mg, 0.24mmol) was reacted with K₂CO₃ (51mg, 0.48mmol) and iodomethane(33uL, 0.48mmol) to afford the title compound(99mg, 91%).

[984] ¹H-NMR (MeOD, 400MHz): δ 8.43-8.51 (m, 2H), 8.36 (d, 1H), 7.94 (d, 1H), 7.79-7.90 (m, 3H), 7.48-7.53 (m, 1H), 7.39-7.48 (m, 2H), 7.15 (t, 1H), 4.38 (s, 2H), 4.18-4.25 (m, 1H), 3.96-4.10 (m, 2H), 3.89-3.96 (m, 1H), 3.39-3.56 (m, 2H), 2.06 (s, 3H).

[985]

[986] **<Example 67>**

(S)-4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-67)

[987]

[988] Step 1 : Preparation of

(S)-4-(4-fluoro-3-(3-((pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[989] This compound was made using the procedure described for example 60(Step 1).

Thus,

(S)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 2)(100mg, 0.23mmol) was reacted with nicotinaldehyde(26uL, 0.23mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound

(S)-4-(4-fluoro-3-(3-((pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(86mg, 82%).

[990]

[991] Step 2 : Preparation of

(S)-4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[992] This compound was made using the procedure described for example 60(Step 2).

Thus, this intermediate compound(Step 1)(86mg, 0.19mmol) was reacted with K₂CO₃(52mg, 0.38mmol) and iodomethane(24uL, 0.38mmol) to afford the title compound(98mg, 91%).

[993] ¹H-NMR (MeOD, 400MHz): δ 10.36 (s, 0.4H), 10.01 (s, 0.6H), 8.46 (m, 3H), 7.73 (m, 3H), 7.40 (m, 1H), 7.38 (m, 3H), 7.04 (m, 1H), 4.27 (s, 2H), 3.89 (m, 1H), 3.67 (m, 3H), 3.47 (m, 3H), 3.12 (m, 1H), 2.13 (m, 5H), 1.87 (m, 1H).

[994]

[995] **<Example 68>**

(R)-4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-68)

[996]

[997] Step 1 : Preparation of

(R)-4-(4-fluoro-3-(3-((pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[998] This compound was made using the procedure described for example 60(Step 1).

Thus,

(R)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 1)(100mg, 0.23mmol) was reacted with nicotinaldehyde(26uL, 0.23mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound

(R)-4-(4-fluoro-3-(3-((pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthal

azin-1(2H)-one(86mg, 82%).

[999]

[1000] Step 2 : Preparation of

(R)-4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)
phthalazin-1(2H)-one

[1001] This compound was made using the procedure described for example 60(Step 2).

Thus, this intermediate compound(Step 1)(86mg, 0.19mmol) was reacted with K_2CO_3 (52mg, 0.38mmol) and iodomethane(24uL, 0.38mmol) to afford the title compound(98mg, 91%).

[1002] ^1H -NMR (MeOD, 400MHz): δ 10.36 (s, 0.4H), 10.01 (s, 0.6H), 8.46 (m, 3H), 7.73 (m, 3H), 7.40 (m, 1H), 7.38 (m, 3H), 7.04 (m, 1H), 4.27 (s, 2H), 3.89 (m, 1H), 3.67 (m, 3H), 3.47 (m, 3H), 3.12 (m, 1H), 2.13 (m, 3H), 1.87 (m, 1H).

[1003]

[1004] **<Example 69>**

4-(3-(3-(cyclopropyl(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-69)

[1005]

[1006] Step 1 : Preparation of

4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1007] This compound was made using the procedure described for example 60(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(100mg, 0.23mmol) was reacted with (1-ethoxycyclopropoxy)trimethylsilane(46uL, 0.23mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound

4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one (58mg, 71%).

[1008]

[1009] Step 2 : Preparation of

4-(3-(3-(cyclopropyl(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1010] This compound was made using the procedure described for example 60(Step 2).

Thus, this intermediate compound(Step 1)(58mg, 0.16mmol) was reacted with K_2CO_3 (44mg, 0.32mmol) and iodomethane(33uL, 0.32mmol) to afford the title compound(62mg, 95%).

[1011] ^1H -NMR (MeOD, 400MHz): δ 8.32-8.39 (d, 1H), 7.89-7.95 (d, 1H), 7.78-7.88 (m, 2H), 7.46-7.53 (m, 1H), 7.39-7.45 (m, 1H), 7.14 (t, 1H), 4.37 (s, 2H), 4.14-4.22 (m, 1H), 4.05-4.13 (m, 2H), 3.98-4.03 (m, 2H), 3.54-3.63 (m, 1H), 2.26 (s, 3H), 0.34-0.56

(m, 4H).

[1012]

[1013] **<Example 70>**

4-(3-(3-(cyclopropyl(ethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-70)

[1014]

[1015] Step 1 : Preparation of

4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1016] This compound was made using the procedure described for example 60(Step 1) to afford the intermediate compound

4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one (58mg, 71%).

[1017]

[1018] Step 2 : Preparation of

4-(3-(3-(cyclopropyl(ethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1019] This compound was made using the procedure described for example 60(Step 2). Thus, this intermediate compound(Step 1)(58mg, 0.16mmol) was reacted with K₂CO₃ (44mg, 0.32mmol) and iodoethane(33uL, 0.32mmol) to afford the title compound(58mg,91%).

[1020] ¹H-NMR (MeOD, 400MHz): δ 8.32-8.40 (m, 1H), 7.90-7.95 (m, 1H), 7.77-7.89 (m, 2H), 7.46-7.54 (m, 1H), 7.30-7.45 (m, 1H), 7.14 (t, 1H), 4.36 (s, 2H), 3.95-4.24 (m, 4H), 3.73-3.84 (m, 1H), 2.60-2.71 (m, 2H), 1.68-1.78 (m, 1H), 1.19-1.26 (m, 1H), 1.01-1.10 (m, 3H), 0.35-0.58 (m, 4H).

[1021]

[1022] **<Example 71>**

4-(3-(3-(cyclobutyl(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-71)

[1023]

[1024] Step 1 : Preparation of

4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1025] This compound was made using the procedure described for example 60(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(100mg, 0.23mmol) was reacted with cyclobutanone(17uL, 0.23mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound 4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(84mg, 90%).

[1026]

[1027] Step 2 : Preparation of
4-(3-(3-(cyclobutyl(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1028] This compound was made using the procedure described for example 60(Step 2). Thus, this intermediate compound(Step 1)(84mg, 0.21mmol) was reacted with K₂CO₃ (57mg, 0.41mmol) and iodomethane(25uL, 0.41mmol) to afford the title compound(82mg, 93%).

[1029] ¹H-NMR (MeOD, 400MHz): δ 8.36 (d, 1H), 7.93 (d, 1H), 7.79-7.89 (m, 2H), 7.48-7.54 (m, 1H), 7.42 (d, 1H), 7.15 (t, 1H), 4.37 (s, 2H), 4.08-4.18 (m, 1H), 3.98-4.04 (m, 1H), 3.89-3.99 (m, 2H), 3.35-3.43 (m, 1H), 2.80-2.90 (m, 1H), 2.06 (s, 3H), 1.81-1.97 (m, 4H), 1.59-1.72 (m, 2H).

[1030]

[1031] <Example 72>
4-(3-(3-(cyclopentyl(prop-2-yn-1-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-72)

[1032]

[1033] Step 1 : Preparation of
4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1034] This compound was made using the procedure described for example 60(Step 1). Thus,
4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(100mg, 0.23mmol) was reacted with cyclopentanone(20uL, 0.23mmol) and sodium triacetoxyborohydride(114mg, 0.54mmol) to afford the intermediate compound 4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one (74mg, 77%).

[1035]

[1036] Step 2 : Preparation of
4-(3-(3-(cyclopentyl(prop-2-yn-1-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1037] This compound was made using the procedure described for example 60(Step 2). Thus, this intermediate compound(Step 1)(74mg, 0.18mmol) was reacted with K₂CO₃ (49mg, 0.35mmol) and 1N solution of propargyl bromide in toluene(0.35mL, 0.35mmol) to afford the title compound(67mg, 81%).

[1038] ¹H-NMR (CDCl₃, 400MHz): δ 10.32 (s, 1H), 8.48-8.46 (m, 1H), 7.80-7.71 (m, 3H), 7.51-7.48 (m, 1H), 7.33-7.29 (m, 1H), 7.01 (t, 1H), 4.29-4.25 (m, 3H), 4.12-3.99 (m, 3H), 3.81-3.74 (m, 1H), 3.52-3.39 (m, 2H), 2.96-2.89 (m, 1H), 2.16 (m, 1H), 1.83-1.51 (m, 6H), 1.41-1.30 (m, 2H)

[1039]

[1040] **<Example 73>**

4-(3-(3-(3,3-difluoropyrrolidin-1-yl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-73)

[1041]

[1042] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1043] 4-(4-fluoro-3-(3-hydroxyazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(example 6)(200mg, 0.57mmol) was dissolved in dichloromethane (2.5mL) and 1,4-dioxane(1mL). Dess-Martin periodinane(DMP, 484mg, 1.14mmol) was added at 0°C, after stirring at room temperature for 12h. The reaction mixture added dichloromethane and washed with aqueous sodium hydroxide and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum to afford the intermediate compound 4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(162mg, 81%).

[1044]

[1045] Step 2 : Preparation of

4-(3-(3-(3,3-difluoropyrrolidin-1-yl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1046] 3,3-difluoropyrrolidine(43uL, 0.46mmol) was added to a solution of the intermediate compound(Step 1)(162mg, 0.46mmol) in 1,2-dichloroethane/methanol(2mL/1mL) and stirred for 30min then acetic acid(31uL, 0.54mmol) and sodium triacetoxymethylborohydride(227mg, 1.07mmol) was added to the reaction mixture at 0°C and stirred for 12 hours. The reaction mixture was concentrated in vacuum, added 2N NaOH(aq) and extracted into dichloromethane. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuum and purified using silica chromatography to afford the title compound(134mg, 66%).

[1047] ¹H-NMR (DMSO, 400MHz): δ 12.62 (s, 1H), 8.26 (d, 1H), 7.99 (d, 1H), 7.90 (t, 1H), 7.84 (t, 1H), 7.45 (d, 2H), 7.23 (t, 1H), 4.33 (s, 2H), 4.11 (m, 1H), 4.07-0.03 (m, 1H), 3.96 (t, 1H), 3.89-3.85 (m, 1H), 3.81-3.78 (m, 1H), 2.90 (t, 2H), 2.69-2.65 (m, 2H), 2.30-2.19 (m, 2H).

[1048]

[1049] **<Example 74>**

4-(4-fluoro-3-(3-(4-fluoropiperidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-74)

[1050]

[1051] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1052] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1053]

[1054] Step 2 : Preparation of

4-(4-fluoro-3-(3-(4-fluoropiperidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1055] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with 4-fluoropiperidine(43uL, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(145mg, 72%).

[1056] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.26 (d, 1H), 7.99 (d, 1H), 7.89 (t, 1H), 7.83 (t, 1H), 7.48-7.42 (m, 2H), 7.22 (t, 1H), 4.78-4.60 (m, 1H), 4.33 (s, 2H), 4.05-4.01 (m, 1H), 3.91 (t, 1H), 3.81-3.77 (m, 1H), 3.74-3.70 (m, 1H), 2.41-2.31 (m, 2H), 2.25-2.12 (m, 2H), 1.91-1.77 (m, 2H), 1.75-1.64 (m, 2H).

[1057]

[1058] **<Example 75>**

4-(3-([1,3'-biazetidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-75)

[1059]

[1060] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1061] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1062]

[1063] Step 2 : Preparation of

4-(3-([1,3'-biazetidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1064] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with azetidine(28uL, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(113mg, 74%).

[1065] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.26 (d, 1H), 7.78 (d, 1H), 7.89 (t, 1H), 7.83 (t, 1H), 7.45 (m, 2H), 7.22 (t, 1H), 4.33 (d, 2H), 4.11 (m, 1H), 3.97 (t, 1H), 3.87 (t, 1H), 3.68 (m, 1H), 3.60 (t, 1H), 3.10 (m, 4H), 1.95 (t, 2H).

[1066]

[1067] **<Example 76>**

4-(4-fluoro-3-(3-(pyrrolidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-76)

[1068]

[1069] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1070] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1071]

[1072] Step 2 : Preparation of

4-(4-fluoro-3-(3-(pyrrolidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1073] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with pyrrolidine(38uL, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(159mg, 85%).

[1074] ¹H-NMR (MeOD, 400MHz): δ 8.37-8.35 (m, 1H), 7.94 (d, 1H), 7.98 (d, 1H), 7.92-7.82 (m, 2H), 7.48-7.42 (m, 2H), 7.22 (t, 1H), 4.34 (s, 2H), 4.07-4.03 (m, 1H), 3.94 (t, 1H), 3.85-3.81 (m, 1H), 3.76-3.73 (m, 1H), 3.27-3.23 (m, 1H), 2.38 (d, 4H), 1.69 (s, 4H).

[1075]

[1076] <Example 77>

4-(4-fluoro-3-(3-(piperidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one ; (I-77)

[1077]

[1078] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1079] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1080]

[1081] Step 2 : Preparation of

4-(4-fluoro-3-(3-(piperidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1082] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with piperidine(43uL, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(162mg, 85%).

[1083] ¹H-NMR (DMSO, 400MHz): δ 12.62 (s, 1H), 8.25 (d, 1H), 8.01 (d, 1H), 7.88 (t, 1H), 7.82 (t, 1H), 7.48-7.39 (m, 2H), 7.21 (t, 1H), 4.33 (s, 2H), 4.10-4.08 (m, 1H), 3.95 (t, 1H), 3.85 (t, 1H), 3.69-3.65 (m, 1H), 3.61-3.55 (m, 1H), 2.42 (t, 4H), 1.55-1.49 (m, 6H).

[1084]

[1085] **<Example 78>**

4-(4-fluoro-3-(3-(4-methylpiperazin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-78)

[1086]

[1087] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1088] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1089]

[1090] Step 2 : Preparation of

4-(4-fluoro-3-(3-(4-methylpiperazin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1091] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with 1-methylpiperazine(50uL, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(90mg, 45%).

[1092] ¹H-NMR (MeOD, 400MHz): δ 8.37-8.35 (m, 1H), 7.95-7.93 (m, 1H), 7.89-7.81 (m, 2H), 7.57-7.40 (m, 2H), 7.15 (t, 1H), 4.38 (s, 2H), 4.21-4.02 (m, 2H), 3.97-3.82 (m, 2H), 3.65 (m, 1H), 2.94-2.80 (m, 6H), 2.59 (s, 3H).

[1093]

[1094] **<Example 79>**

4-(4-fluoro-3-(3-(phenylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-79)

[1095]

[1096] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1097] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1098]

[1099] Step 2 : Preparation of

4-(4-fluoro-3-(3-(phenylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1100] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with aniline(42uL, 0.46mmol), titanium(IV) epoxide(Ti[OCH₂(CH₃)₄], 96mL, 46mmol) and sodium triacetoxyborohydride(227mg, 1.0mmol) to afford the title compound(43mg,

22%).

[1101] ¹H-NMR (DMSO, 400MHz): δ 12.60 (s, 1H), 8.25 (d, 1H), 7.97 (d, 1H), 7.89 (t, 1H), 7.82 (t, 1H), 7.41 (m, 1H), 7.33 (m, 1H), 7.23 (t, 1H), 7.06 (t, 2H), 6.59 (d, 2H), 6.51 (t, 1H), 4.38 (m, 1H), 4.33 (s, 2H), 4.28-4.19(m, 2H), 3.80 (dd, 1H), 3.70 (m, 1H).

[1102]

[1103] **<Example 80>**

4-(4-fluoro-3-(3-((1-(trifluoromethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-80)

[1104]

[1105] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1106] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1107]

[1108] Step 2 : Preparation of

4-(4-fluoro-3-(3-((1-(trifluoromethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1109] This compound was made using the procedure described for example 73(Step 2). Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with 1-(trifluoromethyl)cyclopropylamine(74mg, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound (51mg, 24%).

[1110] ¹H-NMR (MeOD, 400MHz): δ 8.25 (d, 1H), 7.83(d, 1H), 7.71-7.76 (m, 2H), 7.33-7.39(m, 1H), 7.31-7.40 (m, 1H), 7.03 (t, 1H), 4.25 (s, 2H), 4.20-4.26 (m, 1H), 4.01-4.06(m, 1H), 3.66-3.80(m, 3H), 0.97-0.99(m, 2H), 0.81-0.83(m, 2H).

[1111]

[1112] **<Example 81>**

4-(4-fluoro-3-(3-(prop-2-yn-1-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-81)

[1113]

[1114] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1115] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1116]

[1117] Step 2 : Preparation of

4-(4-fluoro-3-(3-(prop-2-yn-1-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-

one

[1118] This compound was made using the procedure described for example 73(Step 2). Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with propargylamine(29uL, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(134mg, 66%).

[1119] ¹H-NMR (CDCl₃, 400MHz): δ 10.40 (s, 1H), 8.48-8.46 (m, 1H), 7.79-7.71 (m, 3H), 7.52-7.50 (m, 1H), 7.32-7.30 (m, 1H), 7.02 (t, 1H), 4.43-4.38 (m, 1H), 4.28 (s, 2H), 4.23-4.20 (m, 1H), 4.00-3.93 (m, 1H), 3.88-3.85 (m, 2H), 3.42 (q, 2H), 2.21 (m, 1H).

[1120]

[1121] **<Example 82>**

(S)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-82)

[1122]

[1123] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1124] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1125]

[1126] Step 2 : Preparation of

(S)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1127] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with (S)-1-methoxypropane-2-amine(48uL, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(125mg, 64%).

[1128] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.35 (m, 1H), 7.95-7.93 (m, 1H), 7.89-7.82 (m, 2H), 7.52-7.50 (m, 1H), 7.45-7.43 (m, 1H), 7.14 (t, 1H), 4.38 (s, 2H), 4.12-4.10 (m, 1H), 4.18-4.15 (m, 1H), 3.84-3.77 (m, 3H), 3.22-3.19 (m, 1H), 2.89-2.87 (m, 1H), 2.03 (s, 3H), 1.00 (t, 3H).

[1129]

[1130] **<Example 83>**

(R)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-83)

[1131]

[1132] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1133] This compound was made using the procedure described for example 73(Step 1) to

afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1134]

[1135] Step 2 : Preparation of

(R)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1136] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with (R)-1-methoxypropane-2-amine(48uL, 0.4mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(125mg, 64%).

[1137] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.35 (m, 1H), 7.95-7.93 (m, 1H), 7.89-7.82 (m, 2H), 7.52-7.50 (m, 1H), 7.45-7.43 (m, 1H), 7.14 (t, 1H), 4.38 (s, 2H), 4.12-4.10 (m, 1H), 4.18-4.15 (m, 1H), 3.84-3.77 (m, 3H), 3.22-3.19 (m, 1H), 2.89-2.87 (m, 1H), 2.03 (s, 3H), 1.00 (t, 3H).

[1138]

[1139] **<Example 84>**

4-(4-fluoro-3-(3-((1-(hydroxymethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-84)

[1140]

[1141] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1142] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1143]

[1144] Step 2 : Preparation of

4-(4-fluoro-3-(3-((1-(hydroxymethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1145] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with (1-aminocyclopropyl)methanol(40mg, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(84mg, 43%).

[1146] ¹H-NMR (MeOD, 400MHz): δ 8.35-8.34 (m, 1H), 7.95-7.82 (m, 3H), 7.51-7.44 (m, 2H), 7.13 (t, 1H), 4.37-4.33 (m, 3H), 4.19-4.17 (m, 1H), 3.90-3.86 (m, 3H), 1.29-1.27 (m, 1H), 0.57-0.54 (m, 2H), 0.52-0.50 (m, 2H).

[1147]

[1148] **<Example 85>**

4-(4-fluoro-3-(3-((1-methylcyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthal

azin-1(2H)-one; (I-85)

[1149]

[1150] Step 1 : Preparation of4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1151] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1152]

[1153] Step 2 : Preparation of4-(4-fluoro-3-(3-((1-methylcyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1154] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with 1-methylcyclopropanamine(43uL, 0.46mmol) and sodium triacetoxy-borohydride(227mg, 1.07mmol) to afford the title compound(35mg, 19%).

[1155] ¹H-NMR (MeOD, 400MHz): δ 8.36 (d, 1H), 7.93(d, 1H), 7.80-7.86(m, 2H), 7.42-7.52(m, 2H), 7.14(t, 1H), 4.32-4.37(m, 3H), 4.16(t, 1H), 3.78-3.88(m, 3H), 1.29(s, 3H), 0.51-0.57(m, 2H, 0.33-0.39(m, 2H).

[1156]

[1157] **<Example 86>****(R)-4-(3-(3-((3,3-dimethylbutan-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-86)**

[1158]

[1159] Step 1 : Preparation of4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1160] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1161]

[1162] Step 2 : Preparation of(R)-4-(3-(3-((3,3-dimethylbutan-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1163] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with (R)-3,3-dimethylbutan-2-amine(55uL, 0.46mmol) and sodium triacetoxy-borohydride(227mg, 1.07mmol) to afford the title compound(110mg, 55%).

[1164] ¹H-NMR (MeOD, 400MHz): δ 8.39(d, 1H), 7.87-8.38(m, 3H), 7.43-7.53(m, 2H), 7.17(t, 1H), 4.41(s, 2H), 4.28-4.40(m, 1H), 4.09-4.18(m, 1H), 3.71-3.90(m, 3H),

2.17-2.27(m, 1H), 0.94-0.98(m, 12H).

[1165]

[1166] **<Example 87>**

(S)-4-(3-(3-((3,3-dimethylbutan-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-87)

[1167]

[1168] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1169] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1170]

[1171] Step 2 : Preparation of

(S)-4-(3-(3-((3,3-dimethylbutan-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1172] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with (S)-3,3-dimethylbutan-2-amine(55uL, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(110mg, 55%).

[1173] ¹H-NMR (CDCl₃, 400MHz): δ 10.28 (d, 1H), 8.48-8.46 (m, 1H), 7.79-7.70 (m, 3H), 7.50 (d, 1H), 7.32-7.28 (m, 1H), 7.01 (t, 1H), 4.43-4.32 (m, 1H), 4.27 (s, 2H), 4.21-4.09 (m, 1H), 3.84-3.70 (m, 3H), 2.26-2.14 (m, 1H), 0.96-0.90 (m, 3H), 0.88-0.86 (dd, 9H).

[1174]

[1175] **<Example 88>**

(R)-4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-88)

[1176]

[1177] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1178] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1179]

[1180] Step 2 : Preparation of

(R)-4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1181] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with (R)-3-methylbutan-2-amine(53uL, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(113mg, 58%).

[1182] ¹H-NMR (MeOD, 400MHz): δ 8.39 (d, 1H), 7.83-8.38 (m, 3H), 7.44-7.52 (m, 2H), 7.17 (t, 1H), 4.63 (brs, 2H), 4.40 (s, 2H), 3.76-3.86 (m, 3H), 2.44-2.46 (m, 1H), 1.64-1.67 (m, 1H), 0.86-0.96 (m, 9H).

[1183]

[1184] **<Example 89>**

(S)-4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-89)

[1185]

[1186] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1187] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1188]

[1189] Step 2 : Preparation of

(S)-4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1190] This compound was made using the procedure described for example 73(Step 2).

Thus, this intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with (S)-3-methylbutan-2-amine(53uL, 0.46mmol) and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(113mg, 58%).

[1191] ¹H-NMR (CDCl₃, 400MHz): δ 10.61 (s, 1H), 8.48-8.46 (m, 1H), 7.80-7.71 (m, 3H), 7.53-7.47 (m, 1H), 7.32-7.30 (m, 1H), 7.01 (t, 1H), 4.38 (m, 1H), 4.28 (s, 2H), 4.15 (m, 1H), 3.84-3.71 (m, 3H), 2.45 (m, 1H), 1.59 (m, 1H), 0.94-0.83 (m, 9H).

[1192]

[1193] **<Example 90>**

4-(4-fluoro-3-(3-((1-(methoxymethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-90)

[1194]

[1195] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1196] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1197]

[1198] Step 2 : Preparation of
4-(4-fluoro-3-(3-((1-(methoxymethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)
phthalazin-1(2H)-one

[1199] This compound was made using the procedure described for example 73(Step 2). Thus, the intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with 1-(methoxymethyl)cyclopropanamine(46mg, 0.46mmol), and sodium triacetoxymethylborohydride(227mg, 1.07mmol) to afford the title compound(78mg, 39%)

[1200] ¹H-NMR (MeOD, 400MHz): δ 8.37-8.35 (m, 1H), 7.95-7.93 (m, 1H), 7.89-7.82 (m, 2H), 7.50-7.43 (m, 2H), 7.16-7.13 (m, 1H), 4.37 (s, 2H), 7.36-7.33 (m, 1H), 7.15-7.14 (m, 1H), 3.87-3.82 (m, 3H), 3.31 (s, 3H), 1.29 (br, 2H), 0.60-0.59 (m, 2H), 0.53-0.51 (m, 2H).

[1201]

[1202] **<Example 91>**

4-(3-(3-(but-3-yn-1-ylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-91)

[1203]

[1204] Step 1 : Preparation of
4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1205] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound
4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1206]

[1207] Step 2 : Preparation of
4-(3-(3-(but-3-yn-1-ylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1208] This compound was made using the procedure described for example 73(Step 2). Thus, the intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with but-3-yn-1-amine(38uL, 0.46mmol), and sodium triacetoxymethylborohydride(227mg, 1.07mmol) to afford the title compound(145mg, 78%).

[1209] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.35 (m, 1H), 7.94-7.82 (m, 3H), 7.52-7.43 (m, 2H), 7.17-7.14 (m, 1H), 4.37 (s, 2H), 4.32-4.29 (m, 1H), 4.15-4.13 (m, 1H), 3.88-3.69 (m, 3H), 2.69-2.66 (m, 2H), 2.34-2.31 (m, 3H).

[1210]

[1211] **<Example 92>**

4-(4-fluoro-3-(3-((2-methylallyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-92)

[1212]

[1213] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1214] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1215]

[1216] Step 2 : Preparation of

4-(4-fluoro-3-(3-((2-methylallyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1217] This compound was made using the procedure described for example 73(Step 2).

Thus, the intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with 2-methylprop-2-en-1-amine(35uL, 0.46mmol), and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(83mg, 45%).

[1218] ¹H-NMR (MeOD, 400MHz): δ 8.38 (d, 1H), 8.36 (d, 1H), 7.81-7.95 (m, 2H), 7.44-7.50 (m, 1H), 7.11-7.17 (m, 1H), 4.38 (brs, 2H), 4.26-4.30 (m, 1H), 4.11-4.13 (m, 1H), 3.85-3.88 (m, 1H), 3.76-3.78 (m, 1H), 3.66-3.69 (m, 1H), 3.34 (s, 2H), 3.08 (s, 2H), 1.25 (s, 3H).

[1219]

[1220] **<Example 93>**

4-(4-fluoro-3-(3-((3-hydroxy-2,2-dimethylpropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-93)

[1221]

[1222] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1223] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1224]

[1225] Step 2: Preparation of

4-(4-fluoro-3-(3-((3-hydroxy-2,2-dimethylpropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1226] This compound was made using the procedure described for example 73(Step 2).

Thus, the intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with 3-amino-2,2-dimethylpropan-1-ol(47mg, 0.46mmol), and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(24mg, 12%).

[1227] ¹H-NMR (CDCl₃, 400MHz): δ 11.53 (br, 1H), 8.46 (m, 1H), 7.78-7.72 (m, 3H), 7.51-7.49 (m, 1H), 7.34-7.29 (m, 1H), 7.01 (t, 1H), 4.36-4.32 (m, 3H), 4.18-4.10 (m, 1H), 3.90-3.78 (m, 2H), 3.67 (m, 1H), 2.53-2.45 (m, 5H), 0.93 (s, 3H), 0.91 (s, 3H).

[1228]

[1229] **<Example 94>**

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)methyl)cyclopropanecarbonitrile; (I-94)

[1230]

[1231] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1232] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1233]

[1234] Step 2 : Preparation of

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)methyl)cyclopropanecarbonitrile

[1235] This compound was made using the procedure described for example 73(Step 2). Thus, the intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with 1-(aminomethyl)cyclopropanecarbonitrile(44mg, 0.46mmol), and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(91mg, 46%).

[1236] ¹H-NMR (MeOD, 400MHz): δ 8.38 (dd, 1H), 8.00 (d, 1H), 7.83-7.92 (m, 2H), 7.54-7.62 (m, 2H), 7.14 (t, 1H), 4.41 (s, 2H), 4.28-4.36 (m, 1H), 4.14-4.18 (m, 1H), 3.71-3.81 (m, 3H), 1.35 (s, 4H).

[1237]

[1238] **<Example 95>**

4-(4-fluoro-3-(3-((2,2,2-trifluoroethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-95)

[1239]

[1240] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1241] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1242]

[1243] Step 2 : Preparation of

4-(4-fluoro-3-(3-((2,2,2-trifluoroethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1244] This compound was made using the procedure described for example 73(Step 2). Thus, the intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with 2,2,2-trifluoroethaneamine(36uL, 0.46mmol), and sodium triacetoxyborohydride(227mg, 1.07mmol) to afford the title compound(200mg, 60%).

[1245] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.35 (m, 1H), 7.95-7.92 (m, 1H), 7.89-7.82 (m, 2H), 7.52-7.50 (m, 1H), 7.45-7.43 (m, 1H), 7.17-7.12 (m, 1H), 4.37 (s, 2H), 4.30-4.28 (m, 1H), 4.16-4.14 (m, 1H), 3.86-3.83 (m, 1H), 3.78-3.76 (m, 1H), 3.68-3.66 (m, 1H), 2.90-2.83 (m, 2H).

[1246]

[1247] **<Example 96>**

(R)-4-(4-fluoro-3-(3-(pyrrolidin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-96)

[1248]

[1249] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1250] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1251]

[1252] Step 2 : Preparation of

(R)-tert-butyl-3-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)amino)pyrrolidin-1-carboxylate

[1253] The intermediate compound(Step 1, 162mg, 0.46mmol) was added to a solution of (R)-tert-butyl-3-aminopyrrolidin-1-carboxylate(25uL, 0.46mmol) in dichloromethane(3mL), methanol(1mL) and stirred for 30min then acetic acid(36uL, 0.69mmol) and sodium triacetoxyborohydride(144mg, 0.69mmol) was added to the reaction mixture at 0°C and stirred for 12 hours. The reaction mixture was concentrated in vacuo, added 2N NaOH(aq) and extracted into dichloromethane. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuo and purified using silica chromatography to afford (R)-tert-butyl-3-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)amino)pyrrolidin-1-carboxylate(122mg, 43%).

[1254]

[1255] Step 3 : Preparation of

(R)-4-(4-fluoro-3-(3-(pyrrolidin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1256] The intermediate compound(Step 2)(122mg, 0.20mmol) in dichloromethane(4mL) cooled to 0°C was added 1.0 N HCl solution(0.40mL, 0.40mmol), and the mixture was stirred at room temperature for 3h. The reaction mixture was concentrated in vacuo, added dichloromethane and washed with 2N NaOH(aq) and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuo and purified using silica chromatography to afford the title compound(76mg, 90%).

[1257] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.36 (m, 1H), 7.95-7.83 (m, 3H), 7.54 (m, 1H), 7.44-7.42 (m, 1H), 7.25 (t, 1H), 4.38 (s, 2H), 4.35-4.33 (m, 1H), 4.19-4.17 (m, 1H), 3.78-3.77 (m, 1H), 3.74-3.71 (m, 2H), 3.36-3.21 (m, 2H), 3.17-3.08 (m, 2H), 2.09-1.99 (m, 1H), 1.82-1.79 (m, 1H), 1.28 (s, 1H).

[1258]

[1259] **<Example 97>**

(S)-4-(4-fluoro-3-(3-(pyrrolidin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-97)

[1260]

[1261] Step 1 : Preparation of

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1262] This compound was made using the procedure described for example 73(Step 1) to afford the intermediate compound

4-(4-fluoro-3-(3-oxoazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(81mg, 162%).

[1263]

[1264] Step 2 : Preparation of

(S)-tert-butyl-3-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)amino)pyrrolidin-1-carboxylate

[1265] This compound was made using the procedure described for example 96(Step 2).

Thus, the intermediate compound(Step 1)(162mg, 0.46mmol) was reacted with (S)-tert-butyl-3-aminopyrrolidin-1-carboxylate(25uL, 0.46mmol), and sodium triacetoxymethylborohydride(144mg, 0.69mmol) to afford the title compound(122mg, 43%).

[1266]

[1267] Step 3 : Preparation of

(S)-4-(4-fluoro-3-(3-(pyrrolidin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1268] This compound was made using the procedure described for example 96(Step 3).

Thus, the intermediate compound(Step 2)(122mg, 0.20mmol) was reacted with 1.0 N HCl solution(0.40mL, 0.40mmol) to afford the title compound(76mg, 90%).

[1269] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.36 (m, 1H), 7.95-7.83 (m, 3H), 7.54 (m, 1H), 7.44-7.42 (m, 1H), 7.25 (t, 1H), 4.38 (s, 2H), 4.35-4.33 (m, 1H), 4.19-4.17 (m, 1H), 3.78-3.77 (m, 1H), 3.74-3.71 (m, 2H), 3.36-3.21 (m, 2H), 3.17-3.08 (m, 2H), 2.09-1.99 (m, 1H), 1.82-1.79 (m, 1H), 1.28 (s, 1H).

[1270]

[1271] **<Example 98>**

1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclopentanecarbonitrile; (I-98)

[1272]

[1273] Step 1 : Preparation of
1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclopentanecarbonitrile

[1274] Cyclopentanone(79uL, 1.17mmol) was added to a solution of 4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(200mg, 1.17mmol) in 1,2-dichloroethane(6mL) and stirred for 30min then acetic acid(67uL, 1.17mmol) and trimethylsilyl cyanide(0.30mL, 2.34mmol) was added to the reaction mixture at 0°C and stirred for 12 hours. The reaction mixture was concentrated in vacuo, added 2N NaOH(aq) and extracted into dichloromethane. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuo and purified using silica chromatography to afford the title compound(328mg, 63%).

[1275] ¹H-NMR (MeOD, 400MHz): δ 8.36 (m, 1H), 7.93-7.79 (m, 3H), 7.51-7.43 (m, 2H), 7.14 (t, 1H), 4.43-4.39 (m, 1H), 4.36 (s, 2H), 4.25 (m, 1H), 3.96-3.91 (m, 3H), 2.10-2.02 (m, 2H), 1.86-1.76 (m, 6H).

[1276]

[1277] **<Example 99>**

1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclobutanecarbonitrile; (I-99)

[1278]

[1279] Step 1 : Preparation of
1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclobutanecarbonitrile

[1280] This compound was made using the procedure described for example 98(Step 1). Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 1.17mmol) was reacted with cyclobutanone(87uL, 1.17mmol), trimethylsilyl cyanide(0.30mL, 2.34mmol) to afford the title compound(293mg, 58%).

[1281] ¹H-NMR (MeOD, 400MHz): δ 8.35 (m, 1H), 7.92-7.78 (m, 3H), 7.50-7.43 (m, 2H), 7.13 (t, 1H), 4.41-4.39 (m, 1H), 4.36 (s, 2H), 4.23 (m, 1H), 3.98-3.92 (m, 2H), 3.85-3.78(m, 1H), 2.48-2.41 (m, 2H), 2.20-2.02 (m, 2H).

[1282]

[1283] **<Example 100>**

2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)propanenitrile; (I-100)

[1284]

[1285] Step 1 : Preparation of
2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)propanenitrile

[1286] This compound was made using the procedure described for example 98(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 1.17mmol) was reacted with acetaldehyde(70uL, 1.17mmol), trimethylsilyl cyanide(0.30mL, 2.34mmol) to afford the title compound(336mg, 71%).

[1287] ¹H-NMR (MeOD, 400MHz): δ 8.36 (m, 1H), 7.94-7.79 (m, 3H), 7.50-7.44 (m, 2H), 7.14 (t, 1H), 4.41-4.17 (m, 4H), 4.00-3.93 (m, 1H), 3.89-3.66 (m, 3H), 1.42 (d, 3H).

[1288]

[1289] **<Example 101>**

2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)butanenitrile; (I-101)

[1290]

[1291] Step 1 : Preparation of

2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)butanenitrile

[1292] This compound was made using the procedure described for example 98(Step 1).

Thus, 4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one (example 3, 200mg, 1.17mmol) was reacted with propionaldehyde(84uL, 1.17mmol), trimethylsilyl cyanide(0.30mL, 2.34 mmol) to afford the title compound(294mg, 60%).

[1293] ¹H-NMR (MeOD, 400MHz): δ 8.35 (m, 1H), 7.94-7.80 (m, 3H), 7.49-7.44 (m, 2H), 7.14 (t, 1H), 4.40-4.16 (m, 4H), 4.00-3.91 (m, 1H), 3.88-3.76 (m, 2H), 3.61-3.50 (m, 1H), 1.79-1.68 (m, 2H), 1.08-1.01 (m, 3H).

[1294]

[1295] **<Example 102>**

2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)-3-methylbutanenitrile; (I-102)

[1296]

[1297] Step 1 : Preparation of

2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)-3-methylbutanenitrile

[1298] This compound was made using the procedure described for example 98(Step 1).

Thus,

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 3)(200mg, 1.17mmol) was reacted with isobutylaldehyde(0.1mL, 1.17mmol), trimethylsilyl cyanide(0.30mL, 2.34mmol) to afford the title compound(294mg, 58%).

[1299] ¹H-NMR (MeOD, 400MHz): δ 8.34 (m, 1H), 7.92-7.78 (m, 3H), 7.49-7.44 (m, 2H), 7.13 (t, 1H), 4.39-4.15 (m, 4H), 4.02-3.96 (m, 1H), 3.88-3.76 (m, 2H), 3.46-3.39 (dd, 1H), 1.93 (m, 1H), 1.04-0.87 (m, 6H).

[1300]

[1301] **<Example 103>**

2-cyclopropyl-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)acetonitrile; (I-103)

[1302]

[1303] Step 1 : Preparation of

2-cyclopropyl-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)acetonitrile

[1304] This compound was made using the procedure described for example 98(Step 1). Thus, 4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one (example 3)(200mg, 1.17mmol) was reacted with cyclopropanecarbaldehyde(79uL, 1.17mmol), trimethylsilyl cyanide(0.30mL, 2.34mmol) to afford the title compound(409mg, 81%).

[1305] ¹H-NMR (MeOD, 400MHz): δ 8.35 (m, 1H), 7.93-7.78 (m, 3H), 7.50-7.44 (m, 2H), 7.13 (t, 1H), 4.40-4.17 (m, 4H), 4.01-3.79 (m, 3H), 3.42-3.37 (dd, 1H), 1.17 (m, 1H), 0.65-0.42 (m, 4H).

[1306]

[1307] **<Example 104>**

4-(4-fluoro-3-(3-((1-(trifluoromethyl)cyclobutyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-104)

[1308]

[1309] Step 1 : Preparation of

4-(4-fluoro-3-(3-((1-(trifluoromethyl)cyclobutyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1310] This compound was made using the procedure described for example 98(Step 1). Thus, 4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one (example 3)(200mg, 1.17mmol) was reacted with cyclobutanone(79uL, 1.17mmol), trifluoromethyltrimethylsilane(0.30mL, 2.34mmol) to afford the title compound(328mg, 63%).

[1311] ¹H-NMR (MeOD, 400MHz): δ 8.26 (d, 1H), 7.72-7.84 (m, 3H), 7.34-7.41 (m, 2H), 7.04 (t, 1H), 7.71-7.76 (m, 2H), 7.33-7.39 (m, 1H), 7.31-7.40 (m, 1H), 7.03 (t, 1H), 4.25 (s, 2H), 4.20-4.26 (m, 1H), 4.01-4.06 (m, 1H), 3.66-3.80 (m, 3H), 0.97-0.99 (m, 2H), 0.81-0.83 (m, 2H).

[1312]

[1313] **<Example 105>**

(S)-4-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-105)

[1314]

[1315] Step 1 : Preparation of

(S)-4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzaldehyde

[1316] This compound was made using the procedure described for example 11(Step 1).

Thus, (S)-N-methyl-N-(pyrrolidin-3-yl)pyrimidine-2-amine(200mg, 1.12mmol) was reacted with 2-fluoro-5-formylbenzoic acid(188mg, 1.12mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 553mg, 1.46mmol), N,N-diisopropyl ethylamine(DIPEA, 0.40mL, 2.24mmol) to afford

(S)-4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzaldehyde(154mg, 43%).

[1317]

[1318] Step 2 : Preparation of

(S,Z)-3-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)aminopyrrolidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one

[1319] This compound was made using the procedure described for example 11(Step 2).

Thus, the intermediate compound(Step 1)(154mg, 0.47mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(114mg, 0.47mmol), triethylamine(98uL, 0.47mmol) to afford intermediate compound

(S,Z)-3-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)aminopyrrolidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one(107mg, 51%).

[1320]

[1321] Step 3 : Preparation of

(S)-4-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phtalazin-1(2H)-one

[1322] This compound was made using the procedure described for example 11(Step 3).

Thus, the intermediate compound(Step 2)(107mg, 0.24mmol) was reacted with hydrazine monohydrate(23uL, 0.48mmol) to afford title compound(55mg, 50%).

[1323] ¹H-NMR (CDCl₃, 400MHz): δ 9.96 (d, 1H), 8.45 (m, 1H), 8.43 (dd, 2H), 7.75 (m, 3H), 7.39 (m, 1H), 7.31 (m, 1H), 7.02 (m, 1H), 6.52 (q, 1H), 5.53 (m, 1H), 4.26 (d, 2H), 3.93 (m, 1H), 3.66 (m, 1H), 3.44 (m, 1H), 3.27 (m, 1H), 3.10 (s, 1.3H), 3.04 (s, 1.7H), 2.21 (m, 1H), 2.06 (m, 1H).

[1324]

[1325] <Example 106>

(S)-4-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phtalazin-1(2H)-one; (I-106)

[1326]

[1327] Step 1 : Preparation of

(S)-4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzaldehyde

[1328] This compound was made using the procedure described for example 11(Step 1). Thus, (S)-N-ethyl-N-(pyrrolidin-3-yl)pyrimidine-2-amine(200mg, 1.12mmol) was reacted with 2-fluoro-5-formylbenzoic acid(175mg, 1.04mmol), O-(benzotriazole-1-yl)-N,N,N,N-tetramethyluronium hexafluorophosphate(HBTU, 512mg, 1.35mmol), N,N-diisopropyl ethylamine(DIPEA, 0.36mL, 2.08mmol) to afford (S)-4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzaldehyde(149mg, 42%).

[1329]

[1330] Step 2 : Preparation of (S,Z)-3-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one

[1331] This compound was made using the procedure described for example 11(Step 2). Thus, intermediate compound(Step 1)(149mg, 0.43mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(105mg, 0.43mmol), triethylamine(92uL, 0.66mmol) to afford (S,Z)-3-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one(102mg, 51%).

[1332]

[1333] Step 3 : Preparation of (S)-4-(3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1334] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(102mg, 0.22mmol) was reacted with hydrazine monohydrate(21uL, 0.45mmol) to afford title compound(53mg, 50%).

[1335] ¹H-NMR (CDCl₃, 400MHz): δ 10.63 (d, 1H), 8.49 (m, 1H), 8.32 (dd, 2H), 7.73 (m, 3H), 7.39 (m, 1H), 7.28 (m, 1H), 7.02 (m, 1H), 6.50 (m, 1H), 5.13 (dt, 1H), 4.29 (d, 2H), 3.95 (m, 1H), 3.58 (m, 2H), 3.46 (m, 2H), 3.27 (m, 1H), 2.23 (m, 1H), 2.09 (m, 1H), 1.93 (dt, 3H).

[1336]

[1337] <Example 107>

4-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-107)

[1338]

[1339] Step 1 : Preparation of 4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzaldehyde

[1340] This compound was made using the procedure described for example 11(Step 1). Thus, N-(azetidin-3-yl)-N-methylpyrimidine-2-amine(200mg, 1.12mmol) was reacted

with 2-fluoro-5-formylbenzoic acid(204mg, 1.22mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, HBTU, 600mg, 1.58mmol), N,N-diisopropyl ethylamine(DIPEA, 0.42mL, 2.44mmol) to afford 4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzaldehyde(149mg, 42%).

[1341]

[1342] Step 2 : Preparation of

(Z)-3-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one

[1343] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(202mg, 0.65mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(156mg, 0.65mmol), triethylamine(0.13mL, 0.96mmol) to afford intermediate compound (Z)-3-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one(169mg, 61%).

[1344]

[1345] Step 3 : Preparation of

4-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1346] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(169mg, 0.39mmol) was reacted with hydrazine monohydrate(38uL, 0.79mmol) to afford title compound(89mg, 51%).

[1347] ¹H-NMR (CDCl₃, 400MHz): δ 8.53 (dd, 1H), 8.31 (d, 2H), 7.80-7.70 (m, 3H), 7.54 (dd, 1H), 7.34-7.30 (m, 1H), 7.10-7.03 (m, 1H), 6.55 (t, 1H), 5.48-5.41 (m, 1H), 4.52-4.45 (m, 1H), 4.39-4.27 (m, 4H), 4.23-4.12 (m, 1H), 3.21 (s, 3H).

[1348]

[1349] **<Example 108>**

4-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-108)

[1350]

[1351] Step 1 : Preparation of

4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzaldehyde

[1352] This compound was made using the procedure described for example 11(Step 1). Thus, N-(azetidin-3-yl)-N-ethylpyrimidine-2-amine(200mg, 1.12mmol) was reacted with 2-fluoro-5-formylbenzoic acid(188mg, 1.12mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 553mg, 1.45mmol), N,N-diisopropyl ethylamine(DIPEA, 0.39mL, 2.24mmol) to

afford

4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzaldehyde(195mg, 53%).

[1353]

[1354] Step 2 : Preparation of

(Z)-3-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one

[1355] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(195mg, 0.59mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(144mg, 0.59mmol), triethylamine(0.12mL, 0.89mmol) to afford intermediate compound (Z)-3-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl) benzylidene)isobenzofuran-1(3H)-one(161mg, 61%).

[1356]

[1357] Step 3 : Preparation of

4-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1358] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(161mg, 0.36mmol) was reacted with hydrazine monohydrate(36uL, 0.73mmol) to afford title compound(84mg, 51%).

[1359] ¹H-NMR (CDCl₃, 400MHz): δ 8.53 (dd, 1H), 8.31 (d, 2H), 7.80-7.70 (m, 3H), 7.54 (dd, 1H), 7.34-7.30 (m, 1H), 7.10-7.03 (m, 1H), 6.55 (t, 1H), 5.09-5.01 (m, 1H), 4.55-4.46 (m, 1H), 4.44-4.28 (m, 4H), 4.20-4.13 (m, 1H), 3.82-3.63 (m, 2H), 1.18 (t, 3H).

[1360]

[1361] **<Example 109>**

4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-109)

[1362]

[1363] Step 1 : Preparation of

4-fluoro-3-(3-(pyrimidin-2-ylamino)azetidine-1-carbonyl)benzaldehyde

[1364] This compound was made using the procedure described for example 11(Step 1). Thus, N-(azetidin-3-yl)-pyrimidine-2-amine(220mg, 1.46mmol) was reacted with 2-fluoro-5-formylbenzoic acid(246mg, 1.46mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 722mg, 1.90mmol), N,N-diisopropyl ethylamine(DIPEA, 0.51mL, 2.93 mmol) to afford 4-fluoro-3-(3-(pyrimidin-2-ylamino)azetidine-1-carbonyl)benzaldehyde(233mg, 53%).

[1365]

[1366] Step 2 : Preparation of

(Z)-3-(4-fluoro-3-(3-(pyrimidin-2-ylamino)azetidine-1-carbonyl)benzylidene)isofuran-1(3H)-one

[1367] This compound was made using the procedure described for example 11(Step 2).

Thus, the intermediate compound(Step 1)(233mg, 0.78mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(188mg, 0.78mmol), triethylamine(0.16mL, 1.16mmol) to afford intermediate compound (Z)-3-(4-fluoro-3-(3-(pyrimidin-2-ylamino)azetidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(197mg, 61%).

[1368]

[1369] Step 3 : Preparation of

4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1370] This compound was made using the procedure described for example 11(Step 3).

Thus, the intermediate compound(Step 2)(197mg, 0.47mmol) was reacted with hydrazine monohydrate(46uL, 0.95mmol) to afford title compound(104mg, 51%).

[1371] ¹H-NMR (DMSO, 400MHz): δ 7.45 (d, 2H), 7.41 (d, 1H), 7.14 (d, 1H), 7.06-6.96 (m, 3H), 6.63-6.62 (m, 2H), 6.40-6.35 (m, 1H), 5.80 (t, 1H), 3.78-3.70 (m, 1H), 3.49-3.44 (m, 3H), 3.40-3.36 (m, 1H), 3.12-3.08 (m, 1H), 3.05-3.01 (m, 1H).

[1372]

[1373] <Example 110>

(S)-4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-110)

[1374]

[1375] Step 1 : Preparation of

(S)-4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzaldehyde

[1376] This compound was made using the procedure described for example 11(Step 1).

Thus, (S)-N-(pyrrolidin-3-yl)pyrimidine-2-amine(300mg, 1.82mmol) was reacted with 2-fluoro-5-formylbenzoic acid(307mg, 1.82mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 900mg, 2.38mmol), N,N-diisopropyl ethylamine(DIPEA, 0.64mL, 3.65mmol) to afford (S)-4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzaldehyde(252mg, 44%).

[1377]

[1378] Step 2 : Preparation of

(S,Z)-3-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzylidene)isofur

an-1(3H)-one

[1379] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(252mg, 0.80mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(195mg, 0.80mmol), triethylamine(0.17mL, 1.20mmol) to afford intermediate compound (S,Z)-3-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(138mg, 40%).

[1380]

[1381] Step 3 : Preparation of

(S)-4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1382] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(138mg, 0.32mmol) was reacted with hydrazine monohydrate(32uL, 0.65mmol) to afford title compound(73mg, 51%).

[1383] ¹H-NMR (CDCl₃, 400MHz): δ 10.74 (d, 1H), 8.46 (m, 1H), 8.32 (dd, 2H), 7.73 (m, 3H), 7.40 (m, 1H), 7.28 (m, 1H), 7.01 (q, 1H), 6.60 (m, 1H), 5.60 (m, 1H), 4.60 (m, 1H), 4.27 (d, 2H), 4.03 (dd, 0.4H), 3.84 (m, 0.6H), 3.73 (m, 1H), 3.49 (m, 1H), 3.41 (m, 1H), 3.25 (m, 1H), 2.28 (m, 1H), 1.95 (m, 1H).

[1384]

[1385] **<Example 111>**

(S)-4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-111)

[1386]

[1387] Step 1 : Preparation of

(S)-3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[1388] This compound was made using the procedure described for example 11(Step 1). Thus, (S)-6-chloro-N-methyl-N-(pyrrolidin-3-yl)pyridazin-3-amine(120mg, 0.71mmol) was reacted with 2-fluoro-5-formylbenzoic acid(118mg, 0.71mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 348mg, 0.91mmol), N,N-diisopropyl ethylamine(DIPEA, 0.25mL, 1.41mmol) to afford (S)-3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(115 mg, 45%).

[1389]

[1390] Step 2 : Preparation of

(S,Z)-3-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one

[1391] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(115mg, 0.31mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(77mg, 0.31mmol), triethylamine(66uL, 0.48mmol) to afford intermediate compound (S,Z)-3-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one(85mg, 56%).

[1392]

[1393] Step 3 : Preparation of
(S)-4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1394] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(85mg, 0.18mmol) was reacted with hydrazine monohydrate(17uL, 0.36mmol) to afford title compound(46mg, 52%).

[1395] ¹H-NMR (CDCl₃, 400MHz): δ 10.68 (d, 1H), 8.45 (m, 1H), 7.76 (m, 3H), 7.37 (m, 1H), 7.28 (m, 1H), 6.83 (d, 1H), 7.05 (q, 1H), 6.83 (q, 1H), 5.57 (m, 0.4H), 5.39 (m, 0.6H), 4.29 (d, 2H), 3.92 (m, 1H), 3.66 (m, 2H), 3.50 (m, 1H), 3.26 (m, 1H), 2.91 (s, 1.5H), 2.96 (s, 1.5H), 2.24 (m, 2H).

[1396]

[1397] <Example 112>
(S)-4-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-112)

[1398]

[1399] Step 1 : Preparation of
(S)-3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[1400] This compound was made using the procedure described for example 11(Step 1). Thus, (S)-6-chloro-N-(pyrrolidin-3-yl)pyridazin-3-amine(200mg, 1.01mmol) was reacted with 2-fluoro-5-formylbenzoic acid(169mg, 1.01mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 496mg, 1.31mmol), N,N-diisopropyl ethylamine(DIPEA, 0.35mL, 2.01mmol) to afford (S)-3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(158mg, 45%).

[1401]

[1402] Step 2 : Preparation of
(S,Z)-3-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one

[1403] This compound was made using the procedure described for example 11(Step 2).

Thus, the intermediate compound(Step 1)(158mg, 0.45mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(109mg, 0.45mmol), triethylamine(95uL, 0.68mmol) to afford intermediate compound (S,Z)-3-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one(117mg, 56%).

[1404]

[1405] Step 3 : Preparation of

(S)-4-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1406] This compound was made using the procedure described for example 11(Step 3).

Thus, the intermediate compound(Step 2)(117mg, 0.25mmol) was reacted with hydrazine monohydrate(25uL, 0.50mmol) to afford title compound(64mg, 52%).

[1407] ¹H-NMR (CDCl₃, 400MHz): δ 10.83 (d, 1H), 8.41 (m, 1H), 7.72 (m, 3H), 7.35 (m, 1H), 7.02 (m, 2H), 6.67 (dd, 1H), 5.37 (m, 1H), 4.57 (m, 1H), 4.27 (dd, 2H), 3.77 (m, 1H), 3.43 (m, 2H), 3.23 (m, 2H), 2.02 (m, 1H).

[1408]

[1409] <Example 113>

(S)-4-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-113)

[1410]

[1411] Step 1 : Preparation of

(S)-4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzaldehyde

[1412] This compound was made using the procedure described for example 11(Step 1). Thus, (S)-N-methyl-N-(pyrrolidin-3-yl)pyridazin-3-amine(200mg, 1.22mmol) was reacted with 2-fluoro-5-formylbenzoic acid(204mg, 1.22mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 600mg, 1.58mmol), N,N-diisopropyl ethylamine(DIPEA, .42mL, 2.43mmol) to afford (S)-4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzaldehyde(172mg, 45%).

[1413]

[1414] Step 2 : Preparation of

(S,Z)-3-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one

[1415] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(172mg, 0.55mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(132mg, 0.55mmol), triethylamine(0.12mL, 0.55mmol) to afford intermediate compound (S,Z)-3-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one.

ne)isofuran-1(3H)-one(132mg, 56%).

[1416]

[1417] Step 3 : Preparation of

(S)-4-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1418] This compound was made using the procedure described for example 11(Step 3).

Thus, the intermediate compound(Step 2)(132mg, 0.31mmol) was reacted with hydrazine monohydrate(30uL, 0.61mmol) to afford title compound(71mg, 52%).

[1419] ¹H-NMR (CDCl₃, 400MHz): δ 10.68 (d, 1H), 8.6 (m, 1H), 8.45 (m, 1H), 7.75 (m, 3H), 7.37 (m, 2H), 7.20 (m, 1H), 7.04 (m, 1H), 6.67 (dd, 1H), 4.65 (m, 2H), 4.27 (d, 2H), 3.91 (m, 2H), 3.48 (m, 1H), 3.22 (m, 1H), 2.40 (m, 1H), 2.02 (m, 1H).

[1420]

[1421] <Example 114>

4-(3-(3-((6-chloropyridazin-3-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-114)

[1422]

[1423] Step 1 : Preparation of

3-(3-((6-chloropyridazin-3-yl)amino)azetidine-1-carbonyl)-4-fluorobenzaldehyde

[1424] This compound was made using the procedure described for example 11(Step 1).

Thus, N-(azetidin-3-yl)-6-chloropyridazin-3-amine(200mg, 1.08mmol) was reacted with 2-fluoro-5-formylbenzoic acid(182mg, 1.08mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 534mg, 1.40mmol), N,N-diisopropyl ethylamine(DIPEA, 0.38mL, 2.17mmol) to afford

3-(3-((6-chloropyridazin-3-yl)amino)azetidine-1-carbonyl)-4-fluorobenzaldehyde(184 mg, 51%).

[1425]

[1426] Step 2 : Preparation of

(Z)-3-(3-(3-((6-chloropyridazin-3-yl)amino)azetidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one

[1427] This compound was made using the procedure described for example 11(Step 2).

Thus, the intermediate compound(Step 1)(184mg, 0.55mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(133mg, 0.55mmol), triethylamine(0.12mL, 0.83mmol) to afford intermediate compound

(Z)-3-(3-(3-((6-chloropyridazin-3-yl)amino)azetidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one(146mg, 59%).

[1428]

[1429] Step 3 : Preparation of

4-(3-(3-((6-chloropyridazin-3-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1430] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(146mg, 0.33mmol) was reacted with hydrazine monohydrate(32uL, 0.66mmol) to afford title compound(82mg, 54%).

[1431] ¹H-NMR (CDCl₃, 400MHz): δ 10.16 (s, 1H), 8.47-8.42 (m, 1H), 7.79-7.67 (m, 4H), 7.47 (dd, 1H), 7.35-7.31 (m, 1H), 7.18 (d, 1H), 7.04-6.99 (m, 1H), 6.72 (d, 1H), 5.29-5.25 (m, 1H), 4.87-4.73 (m, 1H), 4.65-4.59 (m, 1H), 4.47-4.43 (m, 1H), 4.31-4.26 (m, 3H), 4.09-4.05 (m, 1H), 3.92-3.88 (m, 1H).

[1432]

[1433] **<Example 115>**

4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-115)

[1434]

[1435] Step 1 : Preparation of

3-(3-((6-chloropyridazin-3-yl)(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzaldehyde

[1436] This compound was made using the procedure described for example 11(Step 1). Thus, N-(azetidin-3-yl)-6-chloro-N-methylpyridazin-3-amine(200mg, 1.00mmol) was reacted with 2-fluoro-5-formylbenzoic acid(169mg, 1.00mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 496mg, 1.31mmol), N,N-diisopropyl ethylamine(DIPEA, 0.35mL, 2.01mmol) to afford 3-(3-((6-chloropyridazin-3-yl)(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzaldehyde(179mg, 51%).

[1437]

[1438] Step 2 : Preparation of

(Z)-3-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one

[1439] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(179mg, 0.51mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(124mg, 0.51mmol), triethylamine(0.11mL, 0.77mmol) to afford intermediate compound (Z)-3-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one(140mg, 59%).

[1440]

[1441] Step 3 : Preparation of

4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)

phthalazin-1(2H)-one

[1442] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(140mg, 0.30mmol) was reacted with hydrazine monohydrate(30uL, 0.60mmol) to afford title compound(78mg, 54%).

[1443] ¹H-NMR (CDCl₃, 400MHz): δ 10.16 (s, 1H), 8.47-8.42 (m, 1H), 7.79-7.67 (m, 4H), 7.47 (dd, 1H), 7.35-7.31 (m, 1H), 7.18 (d, 1H), 7.04-6.99 (m, 1H), 6.72 (d, 1H), 5.21-5.15 (m, 1H), 4.87-4.73 (m, 1H), 4.65-4.59 (m, 1H), 4.47-4.43 (m, 1H), 4.31-4.26 (m, 3H), 4.09-4.05 (m, 1H), 3.92-3.88 (m, 1H), 3.06 (s, 3H).

[1444]

[1445] **<Example 116>**

4-(3-(3-(cyclobutyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-116)

[1446]

[1447] Step 1 : Preparation of

3-(3-(cyclobutyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzaldehyde

[1448] This compound was made using the procedure described for example 11(Step 1). Thus, N-(azetidin-3-yl)-N-cyclobutylpyrimidine-2-amine(500mg, 2.44mmol) was reacted with 2-fluoro-5-formylbenzoic acid(411mg, 2.44mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 1.2g, 3.18mmol), N,N-diisopropyl ethylamine(DIPEA, 0.86mL, 4.89mmol) to afford 3-(3-(cyclobutyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzaldehyde(442mg, 51%).

[1449]

[1450] Step 2 : Preparation of

(Z)-3-(3-(3-(cyclobutyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one

[1451] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(442mg, 1.24mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(302mg, 1.24mmol), triethylamine(0.26mL, 1.87mmol) to afford intermediate compound (Z)-3-(3-(3-(cyclobutyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one(288mg, 49%).

[1452]

[1453] Step 3 : Preparation of

4-(3-(3-(cyclobutyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1454] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(288mg, 0.62mmol) was reacted with

hydrazine monohydrate(60uL, 1.22mmol) to afford title compound(124mg, 42%).

[1455] ¹H-NMR (CDCl₃, 400MHz): δ 8.46-8.44 (m, 1H), 8.28 (d, 2H), 7.75-7.72 (m, 3H), 7.52-7.49 (m, 1H), 7.36-7.28 (m, 1H), 7.04-6.99 (m, 1H), 6.55 (t, 1H), 4.97-4.90 (m, 1H), 4.82-4.74 (m, 1H), 4.66-4.62 (m, 1H), 4.47-4.43 (m, 1H), 4.31-4.26 (m, 3H), 4.17-4.13 (m, 1H), 2.25-2.01 (m, 5H).

[1456]

[1457] **<Example 117>**

4-(4-fluoro-3-(3-(pyridazin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-117)

[1458]

[1459] Step 1 : Preparation of

4-fluoro-3-(3-(pyridazin-3-ylamino)azetidine-1-carbonyl)benzaldehyde

[1460] This compound was made using the procedure described for example 11(Step 1). Thus, N-(azetidin-3-yl)pyridazin-3-amine(200mg, 1.33mmol) was reacted with 2-fluoro-5-formylbenzoic acid(224mg, 1.33mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 656mg, 1.73mmol), N,N-diisopropyl ethylamine(DIPEA, 0.46mL, 2.66mmol) to afford 4-fluoro-3-(3-(pyridazin-3-ylamino)azetidine-1-carbonyl)benzaldehyde(203mg, 51%).

[1461]

[1462] Step 2 : Preparation of

(Z)-3-(4-fluoro-3-(3-(pyridazin-3-ylamino)azetidine-1-carbonyl)benzylidene)isofuran-1(3H)-one

[1463] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(203mg, 0.68mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(164mg, 0.68mmol), triethylamine(0.14mL, 1.02mmol) to afford intermediate compound (Z)-3-(4-fluoro-3-(3-(pyridazin-3-ylamino)azetidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(172mg, 61%).

[1464]

[1465] Step 3 : Preparation of

4-(4-fluoro-3-(3-(pyridazin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1466] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(172mg, 0.41mmol) was reacted with hydrazine monohydrate(40uL, 0.82mmol) to afford title compound(93mg, 52%).

[1467] ¹H-NMR (CDCl₃, 400MHz): δ 10.86 (s, 1H), 8.58-8.57 (m, 1H), 8.44 (d, 1H), 7.78-7.69 (m, 3H), 7.48-7.46 (m, 1H), 7.35-7.31 (m, 1H), 7.18-7.15 (m, 1H), 7.00 (t,

1H), 6.70 (d, 1H), 5.68 (brs, 1H), 4.81-4.74 (m, 1H), 4.61-4.42 (m, 2H), 4.26 (s, 2H), 4.11-4.07 (m, 1H), 3.93-3.90 (m, 1H).

[1468]

[1469] **<Example 118>**

(R)-4-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)phthalazin-1(2H)-one; (I-118)

[1470]

[1471] Step 1 : Preparation of

(R)-3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[1472]

This compound was made using the procedure described for example 11(Step 1). Thus, (R)-6-chloro-N-(pyrrolidin-3-yl)pyridazin-3-amine(200mg, 1.00mmol) was reacted with 2-fluoro-5-formylbenzoic acid(169mg, 1.00mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 496mg, 1.31mmol), N,N-diisopropyl ethylamine(DIPEA, 0.35mL, 2.01mmol) to afford (R)-3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(179mg, 51%).

[1473]

[1474] Step 2 : Preparation of

(R,Z)-3-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one

[1475]

This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(179mg, 0.51mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(124mg, 0.51mmol), triethylamine(0.1mL, 0.77mmol) to afford intermediate compound (R,Z)-3-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one(146mg, 61%).

[1476]

[1477] Step 3 : Preparation of

(R)-4-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1478]

This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(146mg, 0.31mmol) was reacted with hydrazine monohydrate(30uL, 0.31mmol) to afford title compound(78mg, 52%).

[1479]

¹H-NMR (CDCl₃, 400MHz): δ 10.85 (s, 0.6H), 10.61 (s, 0.4H), 8.43 (m, 1H), 7.79-7.66 (m, 3.5H), 7.32 (m, 1.5H), 7.15-6.98 (m, 2H), 6.69 (d, 0.4H), 6.58 (d, 0.6H), 5.37 (t, 1H), 4.65 (m, 0.4H), 4.58 (m, 0.6H), 4.26 (d, 2H), 3.99-3.83 (m, 1H), 3.79-3.66

(m, 2H), 3.43 (m, 0.5H), 3.25 (dd, 0.5H), 2.32 (m, 1H), 2.04 (m, 1H).

[1480]

[1481] <Example 119>

(R)-4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-119)

[1482]

[1483] Step 1 : Preparation of

(R)-3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[1484] This compound was made using the procedure described for example 11(Step 1).

Thus, (R)-6-chloro-N-methyl-N-(pyrrolidin-3-yl)pyridazin-3-amine(200mg, 0.94mmol) was reacted with 2-fluoro-5-formylbenzoic acid(158mg, 0.94mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 463mg, 1.22mmol), N,N-diisopropyl ethylamine(DIPEA, 0.33mL, 1.88mmol) to afford

(R)-3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(174mg, 51%).

[1485]

[1486] Step 2 : Preparation of

(R,Z)-3-(3-(3-((6-chloropyridazin-3-yl)methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one

[1487] This compound was made using the procedure described for example 11(Step 2).

Thus, the intermediate compound(Step 1)(174mg, 0.48mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(116mg, 0.48mmol), triethylamine(0.1mL, 0.72mmol) to afford intermediate compound (R,Z)-3-(3-(3-((6-chloropyridazin-3-yl)methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one(140mg, 61%).

[1488]

[1489] Step 3 : Preparation of

(R)-4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1490] This compound was made using the procedure described for example 11(Step 3).

Thus, the intermediate compound(Step 2)(140mg, 0.29mmol) was reacted with hydrazine monohydrate(29uL, 0.59mmol) to afford title compound(74mg, 52%).

[1491]

¹H-NMR (CDCl₃, 400MHz): δ 10.42 (s, 0.6H), 10.29 (s, 0.4H), 8.46 (m, 1H), 7.81-7.70 (m, 3H), 7.38 (m, 1H), 7.34-7.24 (m, 1H), 7.22 (d, 1H), 7.03 (m, 1H), 6.82 (dd, 1H), 5.58 (m, 0.5H), 5.41 (m, 0.5H), 4.29 (s, 0.8H), 4.28 (s, 1.2H), 3.92 (m, 1H), 3.74-3.61 (m, 2H), 3.44 (m, 0.5H), 3.26 (dd, 0.5H), 2.99 (s, 1.2H), 2.94 (s, 1.8H),

2.32-2.04 (m, 2H).

[1492]

[1493] <Example 120>

(R)-4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-120)

[1494]

[1495] Step 1 : Preparation of

(R)-4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzaldehyde

[1496] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-N-(pyrrolidin-3-yl)pyrimidine-2-amine(200mg, 1.22mmol) was reacted with 2-fluoro-5-formylbenzoic acid(205mg, 1.22mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 600mg, 1.58mmol), N,N-diisopropyl ethylamine(DIPEA, 0.42mL, 2.44mmol) to afford (R)-4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzaldehyde(195mg, 51%).

[1497]

[1498] Step 2 : Preparation of

(R,Z)-3-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one

[1499] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(195mg, 0.62mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(150mg, 0.62mmol), triethylamine(0.13mL, 0.94mmol) to afford intermediate compound (R,Z)-3-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(163mg, 61%).

[1500]

[1501] Step 3 : Preparation of

(R)-4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1502] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(163mg, 0.38mmol) was reacted with hydrazine monohydrate(37uL, 0.76mmol) to afford title compound(88mg, 52%).

[1503] ¹H-NMR (CDCl₃, 400MHz): δ 10.73 (s, 0.6H), 10.51 (s, 0.4H), 8.42 (s, 1H), 8.30 (dd, 2H), 7.78-7.68 (m, 3H), 7.41 (m, 1H), 7.28 (m, 1H), 7.03 (q, 1H), 6.59 (m, 1H), 5.57 (dd, 1H), 4.63 (m, 0.4H), 4.53 (m, 0.6H), 4.27 (s, 0.8H), 4.26 (s, 1.2H), 4.02 (dd, 0.4H), 3.88-3.68 (m, 1.6H), 3.62 (dd, 0.4H), 3.52-3.40 (m, 1H), 3.26 (d, 0.6H), 2.37-2.24 (m, 1H), 2.08-1.95 (m, 1H).

[1504]

[1505] **<Example 121>**

(R)-4-(3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-121)

[1506]

[1507] Step 1 : Preparation of

(R)-3-(3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[1508] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-N-ethyl-N-(pyrrolidin-3-yl)pyrimidine-2-amine(220mg, 1.14mmol) was reacted with 2-fluoro-5-formylbenzoic acid(158mg, 0.94mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 564mg, 1.49mmol), N,N-diisopropyl ethylamine(DIPEA, 0.40mL, 2.29mmol) to afford (R)-3-(3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(200mg, 51%).

[1509]

[1510] Step 2 : Preparation of

(R,Z)-3-(3-(3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one

[1511] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(200mg, 0.58mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(141mg, 0.58mmol), triethylamine(0.12mL, 0.87mmol) to afford intermediate compound (R,Z)-3-(3-(3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one(163mg, 61%).

[1512]

[1513] Step 3 : Preparation of

(R)-4-(3-(3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1514] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(163mg, 0.36mmol) was reacted with hydrazine monohydrate(34uL, 0.72mmol) to afford title compound(87mg, 52%).

[1515] ¹H-NMR (CDCl₃, 400MHz): δ 10.43 (s, 0.5H), 10.38 (s, 0.5H), 8.47 (m, 1H), 8.30 (m, 2H), 7.81-7.68 (m, 3H), 7.39 (dd, 1H), 7.28 (m, 1H), 7.03 (m, 1H), 6.51 (m, 1H), 5.37-5.18 (m, 1H), 4.29 (s, 0.8H), 4.27 (s, 1.2H), 4.02-3.90 (m, 1H), 3.67-3.53 (m, 2H), 3.52-3.37 (m, 2.5H), 3.27 (t, 0.5H), 2.22 (m, 1H), 2.13 (m, 1H), 1.22 (t, 1.5H), 1.16 (t, 1.5H).

[1516]

[1517] **<Example 122>**

(R)-4-(4-fluoro-3-(3-(pyridazin-3-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-122)

[1518]

[1519] Step 1 : Preparation of

(R)-4-fluoro-3-(3-(pyridazin-3-ylamino)pyrrolidine-1-carbonyl)benzaldehyde

[1520] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-N-(pyrrolidin-3-yl)pyridazin-3-amine(200mg, 1.34mmol) was reacted with 2-fluoro-5-formylbenzoic acid(225mg, 1.34mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 660mg, 1.74mmol), N,N-diisopropyl ethylamine(DIPEA, 0.47mL, 2.68mmol) to afford (R)-4-fluoro-3-(3-(pyridazin-3-ylamino)pyrrolidine-1-carbonyl)benzaldehyde(214mg, 51%).

[1521]

[1522] Step 2 : Preparation of

(R,Z)-3-(4-fluoro-3-(3-(pyridazin-3-ylamino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one

[1523] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(214mg, 0.68mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(165mg, 0.68mmol), triethylamine(0.14mL, 1.02 mmol) to afford intermediate compound (R,Z)-3-(4-fluoro-3-(3-(pyridazin-3-ylamino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(179mg, 61%).

[1524]

[1525] Step 3 : Preparation of

(R)-4-(4-fluoro-3-(3-(pyridazin-3-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1526] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(179mg, 0.42mmol) was reacted with hydrazine monohydrate(41uL, 0.84mmol) to afford title compound(97mg, 52%).

[1527] ¹H-NMR (CDCl₃, 400MHz): δ 10.88 (s, 0.6H), 10.49 (s, 0.4H), 8.58 (m, 1H), 8.44 (m, 1H), 7.74 (m, 3H), 7.39-7.25 (m, 2H), 7.17 (m, 1H), 7.02 (m, 1H), 6.71 (d, 0.4H), 6.63 (d, 0.6H), 5.30 (m, 0.4H), 5.00 (m, 0.6H), 4.28 (s, 0.8H), 4.26 (s, 1.2H), 4.02 (m, 0.6H), 3.87 (m, 1.4H), 3.79-3.64 (m, 1H), 3.52-3.42 (m, 0.5H), 3.25 (m, 0.5H), 2.43-2.26 (m, 1H), 2.07 (m, 1H).

[1528]

[1529] **<Example 123>**

(R)-4-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-123)

[1530]

[1531] Step 1 : Preparation of

(R)-4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzaldehyde

[1532] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-N-methyl-N-(pyrrolidin-3-yl)pyridazin-3-amine(200mg, 1.12mmol) was reacted with 2-fluoro-5-formylbenzoic acid(188mg, 1.12mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 553mg, 1.46mmol), N,N-diisopropyl ethylamine(DIPEA, 0.39mL, 2.24mmol) to afford (R)-4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzaldehyde(187mg, 51%).

[1533]

[1534] Step 2 : Preparation of

(R,Z)-3-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one

[1535] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(187mg, 0.57mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(138mg, 0.57mmol), triethylamine(0.12mL, 0.86mmol) to afford intermediate compound (R,Z)-3-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(155mg, 61%).

[1536]

[1537] Step 3 : Preparation of

(R)-4-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1538] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(155mg, 0.35mmol) was reacted with hydrazine monohydrate(34uL, 0.70mmol) to afford title compound(83mg, 52%).

[1539] ¹H-NMR (CDCl₃, 400MHz): δ 10.70 (s, 0.6H), 10.25 (s, 0.4H), 8.61 (m, 1H), 8.46 (m, 1H), 7.81-7.70 (m, 3H), 7.39 (m, 1H), 7.33-7.21 (m, 2H), 7.08-6.97 (m, 1H), 6.81 (m, 1H), 5.74 (m, 0.4H), 5.52 (m, 0.6H), 4.29 (s, 0.8H), 4.27 (s, 1.2H), 3.92 (m, 1H), 3.75-3.63 (m, 2H), 3.52-3.39 (m, 0.4H), 3.24 (dd, 0.6H), 2.99 (s, 1.2H), 2.94 (s, 1.8H), 2.25 (m, 1H), 2.08 (m, 1H).

[1540]

[1541] **<Example 124>**

(R)-4-(4-fluoro-3-(3-(thiazol-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-

1(2H)-one; (I-124)

[1542]

[1543] Step 1 : Preparation of(R)-4-fluoro-3-(3-(thiazol-2-ylamino)pyrrolidine-1-carbonyl)benzaldehyde

[1544] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-N-(pyrrolidine-3-yl)thiazol-2-amine(200mg, 1.18mmol) was reacted with 2-fluoro-5-formylbenzoic acid(198mg, 1.18mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 582mg, 1.54mmol), N,N-diisopropyl ethylamine(DIPEA, 0.42mL, 2.36mmol) to afford (R)-4-fluoro-3-(3-(thiazol-2-ylamino)pyrrolidine-1-carbonyl)benzaldehyde(170mg, 45%).

[1545]

[1546] Step 2 : Preparation of(R,Z)-3-(4-fluoro-3-(3-(thiazol-2-ylamino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one

[1547] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(170mg, 0.53mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(128mg, 0.53mmol), triethylamine(0.11mL, 0.80mmol) to afford intermediate compound (R,Z)-3-(4-fluoro-3-(3-(thiazol-2-ylamino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(125mg, 54%).

[1548]

[1549] Step 3 : Preparation of(R)-4-(4-fluoro-3-(3-(thiazol-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1550] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(125mg, 0.29mmol) was reacted with hydrazine monohydrate(28uL, 0.57mmol) to afford title compound(67mg, 52%).

[1551] ¹H-NMR (MeOD, 400 MHz): δ 8.36 (m, 1H), 7.85 (m, 3H), 7.39 (m, 2H), 7.15 (m, 1H), 6.96 (dd, 1H), 6.58 (dd, 1H), 4.41 (m, 2H), 3.71 (m, 3H), 3.40 (m, 1H), 3.21 (m, 1H), 2.29 (m, 1H), 2.04 (m, 1H).

[1552]

[1553] **<Example 125>****(R)-4-(3-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-125)**

[1554]

[1555] Step 1 : Preparation of

(R)-3-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

- [1556] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-5-ethynyl-N-(pyrrolidin-3-yl)pyrimidine-2-amine(230mg, 1.22mmol) was reacted with 2-fluoro-5-formylbenzoic acid(205mg, 1.22mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 602mg, 1.59mmol), N,N-diisopropyl ethylamine(DIPEA, 0.43mL, 2.44mmol) to afford (R)-3-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(210mg, 51%).

[1557]

- [1558] Step 2 : Preparation of (R,Z)-3-(3-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one

- [1559] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 2)(210mg, 0.62mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(150mg, 0.62mmol), triethylamine(0.13mL, 0.93mmol) to afford intermediate compound (R,Z)-3-(3-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzylidene)isofuran-1(3H)-one(164mg, 58%).

[1560]

- [1561] Step 3 : Preparation of (R)-4-(3-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

- [1562] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(164mg, 0.36mmol) was reacted with hydrazine monohydrate(36uL, 0.72mmol) to afford title compound(103mg, 61%).

- [1563] ¹H-NMR (CDCl₃, 400MHz): δ 10.10-0.93 (dd, 1H), 8.41-8.38 (m, 3H), 7.78-7.68 (m, 3H), 7.41-7.37 (m, 1H), 7.32-7.27 (m, 1H), 7.04-7.02 (m, 1H), 5.48-5.44 (m, 1H), 4.66-4.51 (m, 1H), 4.27 (s, 2H), 4.03 (m, 0.5H), 3.85-3.39 (m, 3H), 3.28-3.26 (m, 0.5H), 3.19 (m, 2H), 2.40-2.23 (m, 1H), 2.17-1.93 (m, 1H).

[1564]

- [1565] **<Example 126>**
(R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)amino)pyrimidine-5-carbonitrile; (I-126)

[1566]

- [1567] Step 1 : Preparation of (R)-2-((1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)amino)pyrimidine-5-carbonitrile

[1568] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile(230mg, 1.22mmol) was reacted with 2-fluoro-5-formylbenzoic acid(205mg, 1.22mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 602mg, 1.59mmol), N,N-diisopropyl ethylamine(DIPEA, 0.43mL, 2.44mmol) to afford (R)-3-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(210mg, 51%).

[1569]

[1570] Step 2 : Preparation of (R,Z)-2-((1-(2-fluoro-5-((3-oxoisofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)amino)pyrimidine-5-carbonitrile

[1571] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(210mg, 0.63mol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(150mg, 0.63mmol), triethylamine(0.13mL, 0.93mmol) to afford intermediate compound (R,Z)-2-((1-(2-fluoro-5-((3-oxoisofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)amino)pyrimidine-5-carbonitrile(164mg, 58%).

[1572]

[1573] Step 3 : Preparation of (R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)amino)pyrimidine-5-carbonitrile

[1574] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(164mg, 0.36mmol) was reacted with hydrazine monohydrate(164mg, 0.36mmol) to afford title compound(103mg, 61%).

[1575] ¹H-NMR (CDCl₃, 400MHz): δ 9.93-9.81 (m, 1H), 8.50-8.43 (m, 2H), 7.79-7.62 (m, 3H), 7.41-7.27 (m, 3H), 7.07-6.99 (m, 1H), 5.83-5.76 (m, 1H), 4.71-4.55 (m, 1H), 4.27 (d, 2H), 4.05-4.00 (m, 0.5H), 3.88-3.62 (m, 2H), 3.52-3.44 (m, 1H), 3.29-3.25 (m, 0.5H), 2.42-2.28 (m, 1H), 2.09-1.96 (m, 1H).

[1576]

[1577] **<Example 127>**

(R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)amino)nicotinonitrile; (I-127)

[1578]

[1579] Step 1 : Preparation of (R)-2-((1-(2-fluoro-5-formylbenzoyl)pyrrolidine-3-yl)amino)nicotinonitrile

[1580] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-2-(pyrrolidin-3-ylamino)nicotinonitrile(300mg, 1.59mmol) was reacted with

2-fluoro-5-formylbenzoic acid(205mg, 1.22 mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 785mg, 2.07mmol), N,N-diisopropyl ethylamine(DIPEA, 0.55mL, 3.18mmol) to afford (R)-2-((1-(2-fluoro-5-formylbenzoyl)pyrrolidine-3-yl)amino)nicotinonitrile(275mg, 51%).

[1581]

[1582] Step 2 : Preparation of

(R,Z)-2-((1-(2-fluoro-5-((3-oxoisofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidine-3-yl)amino)nicotinonitrile

[1583] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(275mg, 0.81mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(196mg, 0.81mmol), triethylamine(1.7mL, 1.22mmol) to afford intermediate compound (R,Z)-2-((1-(2-fluoro-5-((3-oxoisofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidine-3-yl)amino)nicotinonitrile(155mg, 42%).

[1584]

[1585] Step 3 : Preparation of

(R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)amino)nicotinonitrile

[1586] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(155mg, 0.34mmol) was reacted with hydrazine monohydrate(34uL, 0.68mmol) to afford title compound(78 mg, 49%).

[1587] ¹H-NMR (DMSO, 400 MHz): δ 12.59 (d, 1H), 8.28 (m, 2H), 7.85 (m, 4H), 7.38 (m, 2H), 7.22 (m, 2H), 6.72 (m, 1H), 4.57 (m, 1H), 4.32 (d, 2H), 3.75 (m, 1H), 3.46 (m, 2H), 3.21 (m, 1H), 2.10 (m, 2H).

[1588]

[1589] **<Example 128>**

(R)-4-(4-fluoro-3-(3-(pyridin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-128)

[1590]

[1591] Step 1 : Preparation of

(R)-4-fluoro-3-(3-(pyridin-2-ylamino)pyrrolidine-1-carbonyl)benzaldehyde

[1592] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-N-(pyrrolidin-3-yl)pyridine-2-amine(250mg, 0.92mmol) was reacted with 2-fluoro-5-formylbenzoic acid(154mg, 0.92mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 453mg, 1.19mmol), N,N-diisopropyl ethylamine(DIPEA, 0.32mL, 1.83mmol) to

afford

(R)-4-fluoro-3-(3-(pyridin-2-ylamino)pyrrolidine-1-carbonyl)benzaldehyde(178mg, 62%).

[1593]

[1594] Step 2 : Preparation of

(R,Z)-3-(4-fluoro-3-(3-(pyridin-2-ylamino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one

[1595] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(178mg, 0.57mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(138mg, 0.57mmol), triethylamine(0.12mL, 0.85mmol) to afford intermediate compound (R,Z)-3-(4-fluoro-3-(3-(pyridin-2-ylamino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(144mg, 59%).

[1596]

[1597] Step 3 : Preparation of

(R)-4-(4-fluoro-3-(3-(pyridin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1598] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(144mg, 0.34mmol) was reacted with hydrazine monohydrate(33uL, 0.67mmol) to afford title compound(91mg, 61%).

[1599] ¹H-NMR (MeOD, 400MHz): δ 8.35-8.31(m, 1H), 7.95-7.93(m, 1H), 7.88-7.81(m, 2H), 7.76-7.73(m, 1H), 7.45-7.39(m, 3H), 7.34-7.32(m, 1H), 7.15-7.08(m, 2H), 4.67-4.30 (m, 1H), 4.38-4.31 (d, 2H), 3.98-3.12 (m, 5H), 2.35-2.19 (m, 1H), 2.06-1.88 (m, 1H).

[1600]

[1601] **<Example 129>**

(R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)amino)-N,N-dimethylnicotinamide; (I-129)

[1602]

[1603] Step 1 : Preparation of

(R)-2-((1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)amino)-N,N-dimethylnicotinamide

[1604] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-N,N-dimethyl-2-(pyrrolidin-3-ylamino)nicotinamide(320mg, 1.36mmol) was reacted with 2-fluoro-5-formylbenzoic acid(300mg, 1.36mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 673mg, 1.77mmol), N,N-diisopropyl ethylamine(DIPEA, 0.48mL, 2.73mmol) to afford

(R)-2-((1-(2-fluoro-5-formylbenzoyl)pyrrolidin-3-yl)amino)-N,N-dimethylnicotinamide(220mg, 42%).

[1605]

[1606] Step 2 : Preparation of

(R,Z)-2-((1-(2-fluoro-5-((3-oxoisofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)amino)-N,N-dimethylnicotinamide

[1607] This compound was made using the procedure described for example 11(Step 2).

Thus, the intermediate compound(Step 1)(220mg, 0.57mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(139mg, 0.57mmol), triethylamine(0.2mL, 0.86mmol) to afford intermediate compound (R,Z)-2-((1-(2-fluoro-5-((3-oxoisofuran-1(3H)-ylidene)methyl)benzoyl)pyrrolidin-3-yl)amino)-N,N-dimethylnicotinamide(109mg, 38%).

[1608]

[1609] Step 3 : Preparation of

(R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)amino)-N,N-dimethylnicotinamide

[1610] This compound was made using the procedure described for example 11(Step 3).

Thus, the intermediate compound(Step 2)(109mg, 0.22mmol) was reacted with hydrazine monohydrate(22uL, 0.44mmol) to afford title compound(39mg, 35%).

[1611] ¹H-NMR (MeOD, 400 MHz): δ 8.36 (m, 1H), 7.88 (m, 4H), 7.44 (m, 3H), 7.13 (m, 1H), 6.69 (m, 1H), 4.56 (m, 1H), 4.36 (d, 2H), 3.85 (m, 1H), 3.55 (m, 2H), 3.21 (m, 1H), 3.02 (s, 6H), 2.30 (m, 1H), 2.07 (m, 1H).

[1612]

[1613] <Example 130>

(R)-4-(3-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-130)

[1614]

[1615] Step 1 : Preparation of

(R)-3-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde

[1616] This compound was made using the procedure described for example 11(Step 1).

Thus, (R)-5-bromo-N-(pyrrolidin-3-yl)pyrimidine-2-amine(320mg, 1.32mmol) was reacted with 2-fluoro-5-formylbenzoic acid(221mg, 1.32mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 649mg, 1.71mmol), N,N-diisopropyl ethylamine(DIPEA, 0.46mL, 2.63mmol) to afford

(R)-3-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzaldehyde(274mg, 53%).

[1617]

[1618] Step 2 : Preparation of

(R,Z)-3-(4-fluoro-3-(3-((5-bromopyrimidin-2-yl)aminopyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one

[1619] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(274mg, 0.70mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(169mg, 0.70mmol), triethylamine(0.15mL, 1.04mmol) to afford intermediate compound (R,Z)-3-(4-fluoro-3-(3-((5-bromopyrimidin-2-yl)aminopyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(217mg, 61%).

[1620]

[1621] Step 3 : Preparation of

(R)-4-(4-fluoro-3-(3-((5-bromopyrimidin-2-yl)aminopyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1622] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(217mg, 0.43mmol) was reacted with hydrazine monohydrate(45uL, 0.86mmol) to afford title compound(131mg, 59%).

[1623] ¹H-NMR (CDCl₃, 400MHz): δ 9.93-9.81 (m, 1H), 8.50-8.43 (m, 2H), 7.79-7.62 (m, 3H), 7.41-7.27 (m, 3H), 7.07-6.99 (m, 1H), 5.83-5.76 (m, 1H), 4.71-4.55 (m, 1H), 4.27 (d, 2H), 4.05-4.00 (m, 0.5H), 3.88-3.62 (m, 2H), 3.52-3.44 (m, 1H), 3.29-3.25 (m, 0.5H), 2.42-2.28 (m, 1H), 2.09-1.96 (m, 1H).

[1624]

[1625] <Example 131>

(R)-4-(4-fluoro-3-(3-((5-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-131)

[1626]

[1627] Step 1 : Preparation of

(R)-4-fluoro-3-(3-((5-(trifluoromethyl)pyridin-2-yl)aminopyrrolidine-1-carbonyl)benzaldehyde

[1628] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-N-(pyrrolidin-3-yl)-5-(trifluoromethyl-2-amine(200mg, 0.86mmol) was reacted with 2-fluoro-5-formylbenzoic acid(145mg, 0.86mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 426mg, 1.12mmol), N,N-diisopropyl ethylamine(DIPEA, 0.31mL, 1.72mmol) to afford (R)-4-fluoro-3-(3-((5-(trifluoromethyl)pyridin-2-yl)aminopyrrolidine-1-carbonyl)benzaldehyde (174mg, 53%).

[1629]

[1630] Step 2 : Preparation of
(R,Z)-3-(4-fluoro-3-(3-((5-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one

[1631] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(174mg, 0.46mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(111mg, 0.46mmol), triethylamine(96uL, 0.69mmol) to afford intermediate compound
 R,Z)-3-(4-fluoro-3-(3-((5-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(139mg, 61%).

[1632]

[1633] Step 3 : Preparation of
(R)-4-(4-fluoro-3-(3-((5-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1634] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(139mg, 0.28mmol) was reacted with hydrazine monohydrate(28uL, 0.56mmol) to afford title compound(85mg, 59%).

[1635] ¹H-NMR (DMSO, 400 MHz): δ 12.59 (d, 1H), 8.29 (m, 2H), 7.85 (m, 3H), 7.62 (m, 2H), 7.39 (m, 2H), 7.20 (m, 1H), 6.58 (m, 1H), 4.38 (m, 1H), 4.32 (d, 2H), 3.75 (m, 1H), 3.47 (m, 2H), 3.21 (m, 1H), 2.20 (m, 1H), 1.92 (m, 1H).

[1636]

[1637] <Example 132>
(R)-4-(4-fluoro-3-(3-((4-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-132)

[1638]

[1639] Step 1 : Preparation of
(R)-4-fluoro-3-(3-((4-(trifluoromethyl)pyridin-2-yl)aminopyrrolidine-1-carbonyl)benzaldehyde

[1640] This compound was made using the procedure described for example 11(Step 1). Thus, (R)-N-(pyrrolidin-3-yl)-4-(trifluoromethyl)pyridine-2-amine(200mg, 0.86mmol) was reacted with 2-fluoro-5-formylbenzoic acid(145mg, 0.86mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 426mg, 1.12mmol), N,N-diisopropyl ethylamine(DIPEA, 0.31mL, 1.72mmol) to afford
 (R)-4-fluoro-3-(3-((4-(trifluoromethyl)pyridin-2-yl)aminopyrrolidine-1-carbonyl)benzaldehyde(174mg, 53%).

[1641]

[1642] Step 2 : Preparation of
(R,Z)-3-(4-fluoro-3-(3-((4-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl

)benzylidene)isofuran-1(3H)-one

[1643] This compound was made using the procedure described for example 11(Step 2). Thus, the intermediate compound(Step 1)(174mg, 0.46mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(111mg, 0.46mmol), triethylamine(96uL, 0.69mmol) to afford intermediate compound (R,Z)-3-(4-fluoro-3-(3-((4-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzylidene)isofuran-1(3H)-one(139mg, 61%).

[1644]

[1645] Step 3 : Preparation of (R)-4-(4-fluoro-3-(3-((4-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1646] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(139mg, 0.28mmol) was reacted with hydrazine monohydrate(28uL, 0.56mmol) to afford title compound(85mg, 59%).

[1647] ¹H-NMR (DMSO, 400 MHz): δ 12.59 (d, 1H), 8.29 (m, 2H), 7.85 (m, 3H), 7.62 (m, 2H), 7.39 (m, 2H), 7.20 (m, 1H), 6.58 (m, 1H), 4.38 (m, 1H), 4.32 (d, 2H), 3.75 (m, 1H), 3.47 (m, 2H), 3.21 (m, 1H), 2.20 (m, 1H), 1.92 (m, 1H).

[1648]

[1649] **<Example 133>**
4-(3-(3-(benzylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-133)

[1650]

[1651] Step 1 : Preparation of 4-(3-(3-(benzylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1652] Benzyl bromide(0.10mL, 0.86mmol) and K₂CO₃(119mg, 0.86mmol) was added to a suspension of the example 3 product(150mg, 0.43mmol) in dimethylformamide(DMF, 8mL) and stirred for 8 hours at 80°C. The reaction was cooled to room temperature and concentrated in vacuo, added dichloromethane and washed a solution of sodium bicarbonate and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuo and purified using silica chromatography to afford title compound(86mg, 45%).

[1653] ¹H-NMR (CDCl₃, 400MHz): δ 10.17 (s, 1H), 8.47-8.46 (m, 1H), 7.82-7.72 (m, 3H), 7.54-7.50 (m, 1H), 7.37-7.31 (m, 5H), 7.06-7.01 (m, 1H), 4.37-4.32 (m, 1H), 4.29 (s, 2H), 4.19-4.16 (m, 1H), 3.89-3.73 (m, 5H).

[1654]

[1655] **<Example 134>**
4-(4-fluoro-3-(3-((3,3,3-trifluoropropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-134)

[1656]

[1657] Step 1 : Preparation of

4-(4-fluoro-3-(3-((3,3,3-trifluoropropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1658] This compound was made using the procedure described for example 133(Step 1). Thus, 4-(3-(3-aminoazetidin-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(150mg, 0.43mmol) was reacted with 3-bromo-1,1,1-trifluoropropan(0.25mL, 0.86mmol), K₂CO₃(119mg, 0.86mmol) to afford title compound(98mg,51%).

[1659] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.35 (m, 1H), 7.95-7.92 (m, 1H), 7.89-7.82 (m, 2H), 7.52-7.50 (m, 1H), 7.45-7.43 (m, 1H), 7.17-7.12 (m, 1H), 4.37 (s, 2H), 4.30-4.28 (m, 1H), 4.16-4.14 (m, 1H), 3.86-3.83 (m, 1H), 3.78-3.76 (m, 1H), 3.68-3.66 (m, 1H), 2.48-2.42 (m, 2H), 1.92-1.85 (m, 2H).

[1660]

[1661] <Example 135>

(R)-4-(3-(3-(azetidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-135)

[1662]

[1663] Step 1 : Preparation of

(S)-1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidine-3-yl methanesulfonate

[1664] The example 5 intermediate compound (S)-4-(4-fluoro-3-(3-hydroxypyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(539 mg, 1.25mmol) in dichloromethane (7mL) cooled to 0°C was added triethylamine (0.1mL, 1.50mmol), methanesulfonyl chloride (MsCl, 0.11mL, 1.38mmol), and the mixture was stirred at room temperature for 3h. The reaction mixture was concentrated in vacuo, added dichloromethane and washed with aqueous sodium bicarbonate and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuo to afford (S)-1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidine-3-yl methanesulfonate(434mg, 78%).

[1665]

[1666] Step 2 : Preparation of

(R)-4-(3-(3-(azetidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1667] The intermediate compound(Step 1)(434mg, 0.97mmol) in dimethylformamide(DMF, 5mL) was added azetidine(0.20mL, 2.93mmol), Li₂CO₃(216mg, 2.93mmol) and the mixture was stirred at 80°C for 16h. The reaction mixture was concentrated in vacuo, added dichloromethane and washed with aqueous ammonium

chloride and water. The combined organic layers were dried over MgSO_4 , filtered, evaporated in vacuo and purified using silica chromatography to afford the title compound(117mg,45%).

[1668] $^1\text{H-NMR}$ (DMSO, 400MHz): δ 12.61 (s, 1H), 8.26 (d, 1H), 7.96 (t, 1H), 7.91-7.80(m, 2H), 7.46-7.35 (m, 1H), 7.25-7.18 (m, 1H), 4.33 (s, 2H), 3.73-3.58 (m, 1H), 3.44-3.39 (m, 1H), 3.27-3.19 (m, 1H), 3.13-3.08 (m, 1H), 2.98 (t, 1H), 2.86 (d, 1H), 2.77-2.61 (m, 1H), 2.16 (t, 2H), 2.03 (t, 2H), 1.77-1.62 (m, 2H).

[1669]

[1670] **<Example 136>**

(R)-4-(3-([1,3'-bipyrrolidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-136)

[1671]

[1672] Step 1 : Preparation of

(S)-1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidine-3-yl methansulfonate

[1673] The intermediate compound

(S)-1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidine-3-yl methansulfonate was made using the procedure described for example 135(Step 1) in a yield of 78%(434mg).

[1674]

[1675] Step 2 : Preparation of

(R)-4-(3-([1,3'-bipyrrolidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1676] This compound was made using the procedure described for example 135(Step 2).

Thus, the intermediate compound(Step 1)(434mg, 0.97mmol) was reacted with pyrrolidine(0.22mL, 2.93mmol), Li_2CO_3 (216mg, 2.93mmol) to afford title compound(130mg,32%).

[1677] $^1\text{H-NMR}$ (MeOD, 400MHz): δ 8.35 (d, 1H), 7.93 (d, 1H), 7.90-7.79 (m, 2H), 7.54-7.44 (m, 1H), 7.42-7.37 (m, 1H), 7.18-7.11 (m, 1H), 4.37 (s, 2H), 3.85-3.74 (m, 1H), 2.65 (t, 2H), 2.57-2.50 (m, 1H), 2.40 (t, 1H), 2.23-2.07 (m, 1H), 1.97-1.90 (m, 1H), 1.85 (m, 2H), 1.76 (m, 2H).

[1678]

[1679] **<Example 137>**

(R)-4-(4-fluoro-3-(3-(piperidin-1-yl)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-137)

[1680]

[1681] Step 1 : Preparation of

(S)-1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidine-3-yl methansulfonate

[1682] The intermediate compound
(S)-1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidine-3-yl
methansulfonate was made using the procedure described for example 135(Step 1) in a
yield of 78%(434mg).

[1683]

[1684] Step 2 : Preparation of
(R)-4-(4-fluoro-3-(3-(piperidin-1-yl)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-o
ne

[1685] This compound was made using the procedure described for example 135(Step 2).
Thus, the intermediate compound(Step 1)(434mg, 0.97mmol) was reacted with
piperidine(0.10mL, 2.93mmol), Li₂CO₃(216mg, 2.93mmol) to afford title
compound(88mg,21%).

[1686] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 8.26 (d, 1H), 7.97 (d, 1H), 7.91-7.80
(m, 2H), 7.46-7.39 (m, 1H), 7.38-7.35 (m, 1H), 7.25-7.19 (m, 1H), 4.32 (s, 2H),
3.75-3.59 (m, 1H), 3.39-3.36 (m, 0.5H), 3.29-3.12 (m, 2H), 2.97 (t, 0.5H), 2.83-2.71
(m, 1H), 2.42-2.28 (m, 3H), 2.15-1.98 (m, 2H), 1.73-1.63 (m, 1H), 1.51-1.29 (m, 6H).

[1687]

[1688] <Example 138>
(R)-4-(4-fluoro-3-(3-(p-tolylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H
)-one; (I-138)

[1689]

[1690] Step 1 : Preparation of
(R)-4-fluoro-3-(3-(p-tolylamino)pyrrolidine-1-carbonyl)benzaldehyde

[1691] This compound was made using the procedure described for example 11(Step 1).
Thus, (R)-4-fluoro-3-(3-(p-tolylamino)pyrrolidine-1-carbonyl)benzaldehyde(200mg,
1.13mmol) was reacted with 2-fluoro-5-formylbenzoic acid(190mg, 1.13mmol), O-
(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU,
559mg, 1.48mmol), N,N-diisopropyl ethylamine(DIPEA, 0.40mL, 2.27mmol) to
afford (R)-4-fluoro-3-(3-(p-tolylamino)pyrrolidine-1-carbonyl)benzaldehyde(230mg,
62%).

[1692]

[1693] Step 2 : Preparation of
(R,Z)-3-(4-fluoro-3-(3-(p-tolylamino)pyrrolidine-1-carbonyl)benzylidene)isobenzofura
n-1(3H)-one

[1694] This compound was made using the procedure described for example 11(Step 2).
Thus, the intermediate compound(Step 1)(230mg, 0.70mmol) was reacted with
dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(170mg, 0.70mmol), tri-
ethylamine(0.15mL, 1.10mmol) to afford intermediate compound

(R,Z)-3-(4-fluoro-3-(3-(p-tolylamino)pyrrolidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one(190mg, 61%).

[1695]

[1696] Step 3 : Preparation of

(R)-4-(4-fluoro-3-(3-(p-tolylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1697] This compound was made using the procedure described for example 11(Step 3).

Thus, the intermediate compound(Step 2)(190mg, 0.43mmol) was reacted with hydrazine monohydrate(42uL, 0.86mmol) to afford title compound(129mg, 66%).

[1698] ¹H-NMR (DMSO, 400 MHz): δ 12.59 (d, 1H), 8.26 (m, 1H), 7.85 (m, 3H), 7.60 (m, 1H), 7.36 (m, 1H), 7.20 (m, 1H), 6.88 (dd, 2H), 6.48 (dd, 2H), 5.60 (m, 1H), 4.32 (d, 2H), 3.91 (m, 2H), 3.52 (m, 2H), 3.11 (m, 1H), 2.14 (m, 1H), 2.12 (s, 3H), 1.90 (m, 1H).

[1699]

[1700] <Example 139>

(R)-4-(4-fluoro-3-(3-(phenylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-139)

[1701]

[1702] Step 1 : Preparation of

(R)-4-fluoro-3-(3-(phenylamino)pyrrolidine-1-carbonyl)benzaldehyde

[1703] This compound was made using the procedure described for example 11(Step 1).

Thus, (R)-N-phenylpyrrolidine-3-amine(200mg, 1.23mmol) was reacted with 2-fluoro-5-formylbenzoic acid(207mg, 1.23mmol), O-(benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate(HBTU, 607mg, 1.60mmol), N,N-diisopropyl ethylamine(DIPEA, 0.43mL, 2.46mmol) to afford (R)-4-fluoro-3-(3-(phenylamino)pyrrolidine-1-carbonyl)benzaldehyde(238mg, 62%).

[1704]

[1705] Step 2 : Preparation of

(R,Z)-3-(4-fluoro-3-(3-(phenylamino)pyrrolidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one

[1706] This compound was made using the procedure described for example 11(Step 2).

Thus, the intermediate compound(Step 1)(238mg, 0.76mmol) was reacted with dimethyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate(185mg, 0.76mmol), triethylamine(0.16mL, 1.14mmol) to afford intermediate compound (R,Z)-3-(4-fluoro-3-(3-(phenylamino)pyrrolidine-1-carbonyl)benzylidene)isobenzofuran-1(3H)-one(200mg, 61%).

[1707]

[1708] Step 3 : Preparation of

(R)-4-(4-fluoro-3-(3-(phenylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1709] This compound was made using the procedure described for example 11(Step 3). Thus, the intermediate compound(Step 2)(200mg, 0.47mmol) was reacted with hydrazine monohydrate(46uL, 0.94mmol) to afford title compound(136mg, 66%).

[1710] ¹H-NMR (MeOD, 400MHz): δ 8.39-8.34 (m, 1H), 7.97-7.70 (m, 3H), 7.50-7.33 (m, 2H), 7.19-7.07 (m, 3H), 6.70-6.57(m, 3H), 4.40 (s, 1H), 4.33 (s, 1H), 4.17-4.05 (m, 1H), 3.95-3.79 (m, 1H), 3.72-3.47 (m, 2H), 3.41-3.16 (m, 1H), 2.37-2.20 (m, 1H), 2.09-1.91 (m, 1H).

[1711]

[1712] <Example 140>

4-(4-fluoro-3-(3-(pyrrolidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-140)

[1713]

[1714] Step 1 : Preparation of

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methylmethansulfonate

[1715] The intermediate compound(example 7)

4-(4-fluoro-3-(3-(hydroxymethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(460mg, 1.25mmol) in dichloromethane (7mL) cooled to 0°C was added triethylamine (0.1mL, 1.50mmol), methanesulfonyl chloride (MsCl, 0.11mL, 1.38mmol), and the mixture was stirred at room temperature for 3h. The reaction mixture was concentrated in vacuo, added dichloromethane and washed with aqueous sodium bicarbonate and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuo to afford (1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methylmethansulfonate(417mg, 75%).

[1716]

[1717] Step 2 : Preparation of

4-(4-fluoro-3-(3-(pyrrolidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1718] The intermediate compound(Step 1)(417mg, 0.94mmol) in 1,4-dioxane(5mL) was added pyrrolidine(0.27mL, 4.00mmol) and the mixture was stirred at 80°C for 16h. The reaction mixture was concentrated in vacuo, added dichloromethane and washed with aqueous ammonium chloride and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuo and purified using silica chromatography to afford the title compound(138mg,35%).

[1719] ¹H-NMR (CDCl₃, 400MHz): δ 9.85 (s, 1H), 8.46-8.44 (m, 1H), 7.78-7.70 (m, 3H), 7.49-7.47 (m, 1H), 7.32-7.27 (m, 1H), 7.03-6.98 (m, 1H), 4.29-4.24 (m, 3H), 4.14-4.10 (t, 1H), 3.85-3.77 (m, 2H), 2.91-2.64 (m, 3H), 2.48 (s, 4H), 1.77 (s, 4H).

[1720]

[1721] **<Example 141>**

4-(4-fluoro-3-(3-(piperidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-141)

[1722]

[1723] Step 1 : Preparation of

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1724] The intermediate compound

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1725]

[1726] Step 2 : Preparation of

4-(4-fluoro-3-(3-(piperidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1727] This compound was made using the procedure described for example 140(Step 2).

Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with piperidine(0.44mL, 4.00mmol) to afford title compound(138mg, 35%).

[1728] ¹H-NMR (CDCl₃, 400MHz): δ 9.94 (s, 1H), 8.46 (m, 1H), 7.78-7.70 (m, 3H), 7.50-7.48 (m, 1H), 7.31-7.27 (m, 1H), 7.01 (t, 1H), 4.27-4.23 (t, 1H), 4.26 (s, 2H), 7.13-4.09 (t, 1H), 3.83-3.70 (m, 2H), 2.88-2.84 (m, 1H), 2.57-2.55 (m, 2H), 2.32 (s, 4H), 1.54 (s, 4H), 1.42 (s, 2H).

[1729]

[1730] **<Example 142>**

4-(3-(3-(azetidin-1-ylmethyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-142)

[1731]

[1732] Step 1 : Preparation of

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1733] The intermediate compound

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1734]

[1735] Step 2 : Preparation of

4-(3-(3-(azetidin-1-ylmethyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1736] This compound was made using the procedure described for example 140(Step 2). Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with azetidine(0.28mL, 4.00mmol) to afford title compound(154mg, 41%).

[1737] ¹H-NMR (MeOD, 400 MHz): δ 8.36 (d, 1H), 7.94 (d, 1H), 7.84 (m, 2H), 7.50 (m, 2H), 7.13 (t, 1H), 4.38 (s, 2H), 4.19 (t, 1H), 4.09 (m, 1H), 3.74 (m, 2H), 3.30 (m, 4H), 2.69 (m, 3H), 2.14 (t, 2H).

[1738]

[1739] **<Example 143>**

4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-143)

[1740]

[1741] Step 1 : Preparation of

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazine-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1742] The intermediate compound (1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1743]

[1744] Step 2 : Preparation of

4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1745] This compound was made using the procedure described for example 140(Step 2). Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with cyclopropylamine(0.28mL, 4.00mmol) to afford title compound(206mg, 54%).

[1746] ¹H-NMR (CDCl₃, 400MHz): δ 10.03 (s, 1H), 8.47-8.45 (m, 1H), 7.80-7.71 (m, 3H), 7.52-7.48 (m, 1H), 7.32-7.28 (m, 1H), 7.01 (t, 1H), 4.27 (s, 2H), 4.26-4.22 (m, 1H), 4.10 (t, 1H), 3.85-3.81 (m, 1H), 3.73-3.70 (m, 1H), 2.99-2.88 (m, 2H), 2.81-2.72 (m, 1H), 2.07 (m, 1H), 1.57 (br, 1H), 0.45-0.41 (m, 2H), 0.29-0.26 (m, 2H).

[1747]

[1748] **<Example 144>**

4-(4-fluoro-3-(3-((isopropylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-144)

[1749]

[1750] Step 1 : Preparation of
(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazine-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1751] The intermediate compound
 (1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1752]

[1753] Step 2 : Preparation of
4-(4-fluoro-3-(3-((isopropylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1754] This compound was made using the procedure described for example 140(Step 2). Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with isopropylamine(0.34mL, 4.00mmol) to afford title compound(234mg, 61%).

[1755] ¹H-NMR (CDCl₃, 400MHz): δ 10.20 (br, 1H), 8.47-8.45 (m, 1H), 7.80-7.70 (m, 3H), 7.51-7.49 (dd, 1H), 7.32-7.28 (m, 1H), 7.01 (t, 1H), 4.27 (s, 2H), 4.28-4.23 (m, 1H), 4.12 (t, 1H), 3.84-3.81 (dd, 1H), 3.75-3.71 (dd, 1H), 2.88-2.69 (m, 4H), 1.05-1.03 (dd, 6H).

[1756]

[1757] **<Example 145>**
4-(3-(3-(((cyclopropylmethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-145)

[1758]

[1759] Step 1 : Preparation of
(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazine-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1760] The intermediate compound
 (1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1761]

[1762] Step 2 : Preparation of
4-(3-(3-(((cyclopropylmethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1763] This compound was made using the procedure described for example 140(Step 2). Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with cyclopropylmethylamine(0.34mL, 4.00mmol) to afford title compound(189mg, 48%).

[1764] ¹H-NMR (CDCl₃, 400MHz): δ 10.36 (br, 1H), 8.47-8.45 (m, 1H), 7.80-7.71 (m, 3H),

7.51-7.49 (m, 1H), 7.32-7.28 (m, 1H), 7.01 (t, 1H), 4.27-4.24 (m, 3H), 4.13 (t, 1H), 3.86-3.75 (m, 2H), 2.94-2.75 (m, 3H), 2.48-2.46 (dd, 2H), 1.61 (br, 1H), 0.95-0.91 (m, 1H), 0.51-0.46 (m, 2H), 0.12-0.09 (m, 2H).

[1765]

[1766] **<Example 146>**

4-(4-fluoro-3-(3-((isobutylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-146)

[1767]

[1768] Step 1 : Preparation of

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazine-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1769] The intermediate compound

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1770]

[1771] Step 2 : Preparation of

4-(4-fluoro-3-(3-((isobutylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1772] This compound was made using the procedure described for example 140(Step 2).

Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with 2-methylpropan-1-amine(0.40mL, 4.00mmol) to afford title compound(207mg, 52%).

[1773] ¹H-NMR (CDCl₃, 400MHz): δ 10.69 (br, 1H), 8.47-8.45 (m, 1H), 7.80-7.71 (m, 3H),

7.50-7.48 (m, 1H), 7.32-7.28 (m, 1H), 7.00 (t, 1H), 4.27-4.23 (m, 3H), 4.14 (t, 1H), 3.86-3.78 (m, 2H), 2.93-2.78 (m, 3H), 2.45 (s, 1H), 2.44 (s, 1H), 1.81-1.71 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H).

[1774]

[1775] **<Example 147>**

4-(3-(3-((tert-butylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-147)

[1776]

[1777] Step 1 : Preparation of

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazine-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1778] The intermediate compound

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1779]

[1780] Step 2 : Preparation of

4-(3-(3-((tert-butylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1781] This compound was made using the procedure described for example 140(Step 2).

Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with 2-methylpropan-2-amine(0.42mL, 4.00mmol) to afford title compound(71mg, 18%).

[1782] ¹H-NMR (CDCl₃, 400MHz): δ 10.49 (br, 1H), 8.47-8.45 (m, 1H), 7.80-7.72 (m, 3H), 7.52-7.48 (m, 1H), 7.31-7.28 (m, 1H), 7.01 (t, 1H), 4.27-4.22 (m, 3H), 4.14 (t, 1H), 2.90-2.75 (m, 3H), 1.14 (s, 9H).

[1783]

[1784] **<Example 148>**

4-(3-(3-((cyclobutylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-148)

[1785]

[1786] Step 1 : Preparation of

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazine-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1787] The intermediate compound

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1788]

[1789] Step 2 : Preparation of

4-(3-(3-((cyclobutylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1790] This compound was made using the procedure described for example 140(Step 2).

Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with cyclobutylamine(0.43mL, 4.00mmol) to afford title compound(138mg, 35%).

[1791] ¹H-NMR (CDCl₃, 400MHz): δ 10.33 (br, 1H), 8.47-8.45 (m, 1H), 7.80-7.71 (m, 3H), 7.50-7.48 (m, 1H), 7.31-7.28 (m, 1H), 7.00 (t, 1H), 4.27-4.22 (m, 3H), 4.11 (t, 1H), 3.83-3.72 (m, 2H), 3.23 (m, 1H), 2.83-2.72 (m, 3H), 2.23-2.17 (m, 2H), 1.71-1.62 (m, 5H).

[1792]

[1793] **<Example 149>**

4-(4-fluoro-3-(3-((prop-2-yn-1-ylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-149)

[1794]

[1795] Step 1 : Preparation of
(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazine-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1796] The intermediate compound
 (1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1797]

[1798] Step 2 : Preparation of
4-(4-fluoro-3-(3-((prop-2-yn-1-ylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1799] This compound was made using the procedure described for example 140(Step 2). Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with propargylamine(0.27mL, 4.00mmol) to afford title compound(163mg, 43%).

[1800] ¹H-NMR (CDCl₃, 400MHz): δ 10.61 (s, 1H), 8.48-8.46 (m, 1H), 7.80-7.71 (m, 3H), 7.51-7.49 (m, 1H), 7.32-7.28 (m, 1H), 7.01 (t, 1H), 4.28-4.24 (m, 3H), 4.12 (t, 1H), 3.88-3.76 (m, 2H), 3.43 (m, 2H), 3.00-2.87 (m, 2H), 2.78-2.72 (m, 1H), 2.27-2.23 (m, 1H), 1.45 (br, 1H).

[1801]

[1802] **<Example 150>**
4-(4-fluoro-3-(3-((phenylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one; (I-150)

[1803]

[1804] Step 1 : Preparation of
(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazine-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1805] The intermediate compound
 (1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1806]

[1807] Step 2 : Preparation of
4-(4-fluoro-3-(3-((phenylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one

[1808] This compound was made using the procedure described for example 140(Step 2). Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with aniline(0.36mL, 4.00mmol) to afford title compound(45mg, 11%).

[1809] ¹H-NMR (CDCl₃, 400MHz): δ 11.25 (s, 1H), 8.48-8.46 (m, 1H), 7.77-7.70 (m, 3H),

7.51-7.49 (dd, 1H), 7.33-7.29 (m, 1H), 7.17 (t, 2H), 7.00 (t, 1H), 6.72 (t, 1H), 6.59 (m, 2H), 4.31-4.27 (m, 3H), 4.17-4.09 (m, 1H), 3.39-3.78 (m, 2H), 3.41-3.31 (m, 2H), 2.95-2.89 (m, 1H).

[1810]

[1811] **<Example 151>**

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)methyl)amino)methyl)cyclopropanecarbonitrile; (I-151)

[1812]

[1813] Step 1 : Preparation of

1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazine-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1814] The intermediate compound

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1815]

[1816] Step 2 : Preparation of

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)methyl)amino)methyl)cyclopropanecarbonitrile

[1817] This compound was made using the procedure described for example 140(Step 2).

Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with 1-(aminomethyl)cyclopropanecarbonitrile(384mg, 4.00mmol) to afford title compound(121mg, 29%).

[1818] ¹H-NMR (MeOD, 400MHz): δ 8.36(d, 1H), 7.82-7.95(m, 3H), 7.44-7.46(m, 2H), 7.13(t, 1H), 4.37(s, 2H), 4.21(t, 1H), 4.10(t, 1H), 3.74-3.85(m, 2H), 2.80-2.87(m, 3H), 2.68-2.70(m, 2H), 1.20(s, 2H), 0.95(s, 2H).

[1819]

[1820] **<Example 152>**

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)methyl)amino)cyclopropanecarbonitrile; (I-152)

[1821]

[1822] Step 1 : Preparation of

1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazine-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate

[1823] The intermediate compound

(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidine-3-yl)methyl methansulfonate was made using the procedure described for example 140(Step 1) in a yield of 75%(417mg).

[1824]

[1825] Step 2 : Preparation of

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)methyl)amino)cyclopropanecarbonitrile

[1826] This compound was made using the procedure described for example 140(Step 2). Thus, the intermediate compound(Step 1)(417mg, 0.94mmol) was reacted with 1-aminocyclopropanecarbonitrile(474mg, 4.00mmol) to afford title compound(44mg, 11%).

[1827] ¹H-NMR (CDCl₃, 400MHz): δ 10.39 (s, 1H), 8.48-8.46 (m, 1H), 7.77-7.72 (m, 3H), 7.53-7.49 (m, 1H), 7.35-7.29 (m, 1H), 7.02 (t, 1H), 4.28 (s, 2H), 4.27-4.09 (m, 2H), 3.86-3.69 (m, 2H), 2.75 (m, 1H), 1.90 (m, 1H), 1.64 (s, 2H), 1.23 (m, 2H), 1.00 (m, 2H).

[1828]

[1829] **<Example 153>**

4-(3-(3-((cyclopropyl(prop-2-yn-1-yl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-153)

[1830]

[1831] Step 1 : Preparation of

4-(3-(3-((cyclopropyl(prop-2-yn-1-yl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1832] 4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(example 144)(126mg, 0.52mmol) in dimethylformamide(DMF, 3mL) was added Na₂CO₃(63mg, 1.56mmol), 3-bromoprop-1-yn(0.16mL, 2.60mmol) and the mixture was stirred at room temperature for 3h. The reaction mixture was concentrated in vacuo, added dichloromethane and washed with aqueous ammonium chloride and water. The combined organic layers were dried over MgSO₄, filtered, evaporated in vacuo and purified using silica chromatography to afford the title compound(190mg,82%).

[1833] ¹H-NMR (CDCl₃, 400MHz): δ 11.08 (s, 1H), 8.49-8.47 (m, 1H), 7.79-7.71 (m, 3H), 7.51-7.49 (m, 1H), 7.32-7.29 (m, 1H), 7.01 (t, 1H), 4.29 (s, 2H), 4.26-4.05 (m, 2H), 3.83-3.68 (m, 2H), 3.40 (m, 2H), 2.96-2.87 (m, 3H), 2.23 (m, 1H), 1.98-1.95 (m, 1H), 0.53-0.48 (m, 2H), 0.34-0.31 (m, 2H).

[1834]

[1835] **<Example 154>**

4-(3-(3-((cyclopropyl(methyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-154)

[1836]

[1837] Step 1 : Preparation of

4-(3-(3-((cyclopropyl(methyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1838] This compound was made using the procedure described for example 153(Step 1). Thus, the intermediate compound(example 144) 4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)-phthalazin-1(2H)-one(150mg, 0.34mmol) was reacted with Na₂CO₃(78mg, 0.74mmol) and methyl iodide(46uL, 0.74mmol) to afford the title compound(121mg,85%).

[1839] ¹H-NMR (CDCl₃, 400MHz): δ 10.91 (s, 1H), 8.49-8.47 (m, 1H), 7.79-7.71 (m, 3H), 7.51-7.49 (m, 1H), 7.32-7.28 (m, 1H), 7.00 (t, 1H), 4.28 (s, 2H), 4.26-4.04 (m, 2H), 3.81-3.66 (m, 2H), 2.96-2.87 (m, 1H), 2.81-2.74 (m, 3H), 1.03 (m, 1H), 0.49-0.41 (m, 2H), 0.34-0.26 (m, 2H).

[1840]

[1841] **<Example 155>**

4-(3-(3-((cyclopropyl(ethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one; (I-155)

[1842]

[1843] Step 1 : Preparation of

4-(3-(3-((cyclopropyl(ethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one

[1844] This compound was made using the procedure described for example 153(Step 1). Thus, the intermediate compound(example 144)

4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)-phthalazin-1(2H)-one(150mg, 0.34mmol) was reacted with Na₂CO₃(78mg, 0.74mmol) and ethyl iodide(49uL, 0.74mmol) to afford the title compound(113mg,77%).

[1845] ¹H-NMR (CDCl₃, 400MHz): δ 10.60 (s, 1H), 8.48-8.46 (m, 1H), 7.79-7.71 (m, 3H), 7.51-7.49 (m, 1H), 7.32-7.28 (m, 1H), 7.01 (t, 1H), 4.28 (s, 2H), 4.26-4.04 (m, 2H), 3.81-3.66 (m, 2H), 2.96-2.87 (m, 1H), 2.81-2.74 (m, 2H), 2.65-2.60 (m, 2H), 1.64 (m, 1H), 1.03 (m, 1H), 0.49-0.41 (m, 2H), 0.34-0.26 (m, 2H).

[1846]

[1847] **<Example 156>**

4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-156)

[1848]

[1849] Step 1 : Preparation of

4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride

[1850] The intermediate compound(example 25)

4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(

100 mg, 0.25 mmol) in dichloromethane (3mL) cooled to 0°C was added 1N solution of hydrochloric acid (0.50mL, 0.50mmol). After stirring at room temperature for 1h, the solvents were evaporated to afford title compound (102mg, 93%).

[1851] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 9.23 (d, 2H), 8.26 (d, 1H), 7.97 (d, 1H), 7.89 (t, 1H), 7.83 (t, 1H), 7.50-7.21 (m, 2H), 7.21 (t, 1H), 4.33 (s, 2H), 4.10 (t, 1H), 3.97 (t, 1H), 3.67-3.51 (m, 3H), 3.08 (m, 1H), 2.76 (m, 1H), 1.99 (t, 2H), 1.69-1.46(m, 4H).

[1852]

[1853] **<Example 157>**

4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-157)

[1854]

[1855] Step 1 : Preparation of

4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride

[1856] This compound was made using the procedure described for example 156(Step 1).

Thus, the intermediate compound(example 26)

4-(3-(3-(cyclopropylcyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(100mg, 0.25mmol) was reacted with 1N solution of hydrochloric acid(0.50mL, 0.50mmol) to afford the title compound(97mg, 91%).

[1857] ¹H-NMR (MeOD, 400MHz): δ 8.36 (d, 1H), 7.93 (d, 1H), 7.79-7.89 (m, 2H), 7.48-7.54 (m, 1H), 7.42 (d, 1H), 7.15 (t, 1H), 4.00-4.05 (m, 2H), 3.75-3.80 (m, 2H), 3.34-3.39 (m, 1H), 3.12 (s, 2H), 1.32-1.36 (m, 1H), 0.64-0.72 (m, 2H), 0.41-0.46 (m, 2H).

[1858]

[1859] **<Example 158>**

4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-158)

[1860]

[1861] Step 1 : Preparation of

4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride

[1862] This compound was made using the procedure described for example 156(Step 1).

Thus, the intermediate compound(example 27)

4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one (117mg, 0.24mmol) was reacted with 1N solution of hydrochloric acid(0.48mL, 0.48mmol) to afford the title compound(99mg, 90%).

[1863] ¹H-NMR (DMSO, 400MHz): δ 12.60(s, 1H), 9.23 (d, 2H), 8.26 (d, 1H), 7.97 (d, 1H),

7.89 (t, 1H), 7.83 (t, 1H), 7.44-7.50 (m, 1H), 7.40 (d, 1H), 7.21 (t, 1H), 4.33 (s, 2H), 4.13 (t, 1H), 4.00 (t, 1H), 3.54-3.70 (m, 3H), 2.82-2.91 (m, 1H), 1.52-1.67 (m, 4H), 1.43 (brs, 2H), 1.10-1.27 (m, 2H).

[1864]

[1865] **<Example 159>**

4-(4-fluoro-3-(3-(isopropylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-159)

[1866]

[1867] Step 1 : Preparation of

4-(4-fluoro-3-(3-(isopropylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride

[1868] This compound was made using the procedure described for example 156(Step 1).

Thus, the intermediate compound(example 32)

4-(4-fluoro-3-(3-(isopropylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(100mg, 0.25mmol) was reacted with 1N solution of hydrochloric acid(0.50mL, 0.50mmol) to afford the title compound(102mg, 95%).

[1869] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 9.23 (d, 2H), 8.27-8.25 (m, 1H), 7.97 (d, 1H), 7.91-7.81 (m, 2H), 7.48-7.44 (m, 1H), 7.41-7.39 (m, 1H), 7.21 (t, 1H), 4.33 (s, 2H), 4.15-4.10 (m, 2H), 3.66-3.59 (m, 3H), 3.17 (d, 1H), 2.68-2.61 (m, 1H), 0.92-0.83 (m, 6H).

[1870]

[1871] **<Example 160>**

4-(3-(3-((cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-160)

[1872]

[1873] Step 1 : Preparation of

4-(3-(3-((cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride

[1874] This compound was made using the procedure described for example 156(Step 1).

Thus, the intermediate compound(example 33)

4-(3-(3-((cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(100mg, 0.25mmol) was reacted with 1N solution of hydrochloric acid(0.50mL, 0.50mmol) to afford the title compound(98mg, 89%).

[1875] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 9.23 (d, 2H), 8.28-7.97 (m, 2H), 7.91-7.81 (m, 2H), 7.48-7.40 (m, 2H), 7.22 (m, 1H), 4.33 (s, 2H), 4.13-3.98 (m, 2H), 3.70-3.56 (m, 3H), 2.29 (m, 2H), 0.83-0.72 (m, 1H), 0.37-0.32 (m, 2H), 0.06 (m, 2H).

[1876]

[1877] **<Example 161>**

4-(4-fluoro-3-(3-(isobutylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-161)

[1878]

[1879] Step 1 : Preparation of

4-(4-fluoro-3-(3-(isobutylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride

[1880] This compound was made using the procedure described for example 156(Step 1).

Thus, the intermediate compound(example 35)

4-(4-fluoro-3-(3-(isobutylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(100mg, 0.24mmol) was reacted with 1N solution of hydrochloric acid(0.48mL, 0.48mmol) to afford the title compound(101mg, 95%).

[1881] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.35 (m, 1H), 7.95-7.93 (m, 1H), 7.89-7.82 (m, 2H), 7.51-7.49 (m, 1H), 7.45-7.43 (m, 1H), 7.15 (t, 1H), 4.38 (s, 2H), 4.28-4.26 (m, 1H), 4.16-4.12 (m, 1H), 3.88-3.84 (m, 1H), 3.79-3.75 (m, 1H), 3.66-3.64 (m, 1H), 2.31-2.28 (m, 2H), 1.71-1.68 (m, 1H), 0.91 (dd, 6H).

[1882]

[1883] **<Example 162>**

4-(4-fluoro-3-(3-((1-hydroxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-162)

[1884]

[1885] Step 1 : Preparation of

4-(4-fluoro-3-(3-((1-hydroxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride

[1886] This compound was made using the procedure described for example 156(Step 1).

Thus, the intermediate compound(example 36)

4-(4-fluoro-3-(3-((1-hydroxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(100mg, 0.24mmol) was reacted with 1N solution of hydrochloric acid(0.48mL, 0.48mmol) to afford the title compound(91mg, 85%).

[1887] ¹H-NMR (MeOD, 400MHz): δ 8.36-8.34 (m, 1H), 7.94-7.92 (m, 1H), 7.88-7.81 (m, 2H), 7.50-7.49 (m, 1H), 7.46-7.44 (m, 1H), 7.16-7.11 (m, 1H), 4.36 (s, 2H), 4.35-4.33 (m, 1H), 4.20-4.17 (m, 1H), 3.90-3.83 (m, 3H), 3.46-3.43 (m, 1H), 3.39-3.36 (m, 1H), 2.77-2.75 (m, 1H), 1.95 (s, 1H), 1.02 (q, 3H).

[1888]

[1889] **<Example 163>**

4-(3-(3-(butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-163)

[1890]

[1891] Step 1 : Preparation of

4-(3-(3-(butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-onehydrochloride

[1892] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 53)

4-(3-(3-(butylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(100mg, 0.24mmol) was reacted with 1N solution of hydrochloric acid(0.48mL, 0.48mmol) to afford the title compound(104mg, 98%).

[1893] ¹H-NMR (CDCl₃, 400MHz): δ 10.28 (s, 1H), 9.19 (d, 2H), 8.40-8.38 (m, 1H), 7.72-7.66 (m, 1H), 7.44-7.41 (m, 1H), 7.24-7.22 (m, 1H), 6.97-6.92 (m, 1H), 4.30-4.27 (m, 1H), 4.20 (s, 2H), 4.11-4.09 (m, 1H), 3.81-3.79 (m, 1H), 3.72-3.70 (m, 1H), 3.64-3.62 (m, 1H), 2.50-2.46 (m, 2H), 2.02 (s, 1H), 1.40-1.37(m, 2H), 1.30-1.24 (m, 2H), 0.86-0.80 (m, 5H).

[1894]

[1895] **<Example 164>**

4-(3-([1,3'-biazetidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-164)

[1896]

[1897] Step 1 : Preparation of

4-(3-([1,3'-biazetidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-onehydrochloride

[1898] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 75)

4-(3-([1,3'-biazetidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(100mg, 0.25mmol) was reacted with 1N solution of hydrochloric acid(0.50mL, 0.50mmol) to afford the title compound(88mg, 82%).

[1899] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 9.23 (d, 2H), 8.26 (d, 1H), 7.78 (d, 1H), 7.89 (t, 1H), 7.83 (t, 1H), 7.45 (m, 2H), 7.22 (t, 1H), 4.33 (d, 2H), 4.11 (m, 1H), 3.97 (t, 1H), 3.87 (t, 1H), 3.68 (m, 1H), 3.60 (t, 1H), 3.10 (m, 4H), 1.95 (t, 2H).

[1900]

[1901] **<Example 165>**

(R)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-165)

[1902]

[1903] Step 1 : Preparation of

(R)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-onehydrochloride

[1904] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 83)

(R)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(117mg, 0.23mmol) was reacted with 1N solution of hydrochloric acid(0.46mL, 0.46mmol) to afford the title compound(93mg, 88%).

[1905] ¹H-NMR (MeOD, 400MHz): δ 8.38-8.35 (m, 1H), 7.95-7.93 (m, 1H), 7.89-7.82 (m, 2H), 7.52-7.50 (m, 1H), 7.45-7.43 (m, 1H), 7.14 (t, 1H), 4.38 (s, 2H), 4.12-4.10 (m, 1H), 4.18-4.15 (m, 1H), 3.84-3.77 (m, 3H), 3.22-3.19 (m, 1H), 2.89-2.87 (m, 1H), 2.03 (s, 3H), 1.00 (t, 3H).

[1906]

[1907] **<Example 166>**

1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclobutanecarbonitrile hydrochloride; (I-166)

[1908]

[1909] Step 1 : Preparation of

1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclobutanecarbonitrilehydrochloride

[1910] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 99)

1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclobutanecarbonitrile(100mg, 0.23mmol) was reacted with 1N solution of hydrochloric acid(0.46mL, 0.46mmol) to afford the title compound(86mg, 79%).

[1911] ¹H-NMR (MeOD, 400MHz): δ 8.35 (m, 1H), 7.92-7.78 (m, 3H), 7.50-7.43 (m, 2H), 7.13 (t, 1H), 4.41-4.39 (m, 1H), 4.36 (s, 2H), 4.23 (m, 1H), 3.98-3.92 (m, 2H), 3.85-3.78(m, 1H), 2.48-2.41 (m, 2H), 2.20-2.02(m, 2H).

[1912]

[1913] **<Example 167>**

(R)-4-(3-(3-(azetidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-167)

[1914]

[1915] Step 1 : Preparation of

(R)-4-(3-(3-(azetidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-onehydrochloride

[1916] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 135)

(R)-4-(3-(3-(azetidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(100mg, 0.24mmol) was reacted with 1N solution of hydrochloric acid(0.48mL, 0.48mmol) to afford the title compound(99mg, 93%).

[1917] ¹H-NMR (DMSO, 400MHz): δ 12.61 (s, 1H), 9.23 (d, 2H), 8.26 (d, 1H), 7.96 (t, 1H), 7.91-7.80(m, 2H), 7.46-7.35 (m, 1H), 7.25-7.18 (m, 1H), 4.33 (s, 2H), 3.73-3.58 (m,

1H), 3.44-3.39 (m, 1H), 3.27-3.19 (m, 1H), 3.13-3.08 (m, 1H), 2.98 (t, 1H), 2.86 (d, 1H), 2.77-2.61 (m, 1H), 2.16 (t, 2H), 2.03 (t, 2H), 1.77-1.62 (m, 2H).

[1918]

[1919] **<Example 168>**

4-(4-fluoro-3-(3-(pyrrolidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-168)

[1920]

[1921] Step 1 : Preparation of

4-(4-fluoro-3-(3-(pyrrolidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride

[1922] This compound was made using the procedure described for example 156(Step 1).

Thus, the intermediate compound(example 140) -

(4-fluoro-3-(3-(pyrrolidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(100mg, 0.23mmol) was reacted with 1N solution of hydrochloric acid(0.46mL, 0.46mmol) to afford the title compound(96mg, 91%).

[1923] ¹H-NMR (CDCl₃, 400MHz): δ 9.85 (s, 1H), 9.19 (d, 2H), 8.46-8.44 (m, 1H), 7.78-7.70 (m, 3H), 7.49-7.47 (m, 1H), 7.32-7.27 (m, 1H), 7.03-6.98 (m, 1H), 4.29-4.24 (m, 3H), 4.14-4.10 (t, 1H), 3.85-3.77 (m, 2H), 2.91-2.64 (m, 3H), 2.48 (s, 4H), 1.77 (s, 4H).

[1924]

[1925] **<Example 169>**

4-(4-fluoro-3-(3-(piperidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-169)

[1926]

[1927] Step 1 : Preparation of

4-(4-fluoro-3-(3-(piperidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride

[1928] This compound was made using the procedure described for example 156(Step 1).

Thus, the intermediate compound(example 142)

4-(4-fluoro-3-(3-(piperidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(100mg, 0.23mmol) was reacted with 1N solution of hydrochloric acid(0.46mL, 0.46mmol) to afford the title compound(105mg, 97%).

[1929] ¹H-NMR (CDCl₃, 400MHz): δ 9.94 (s, 1H), 9.19 (d, 2H), 8.46 (m, 1H), 7.78-7.70 (m, 3H), 7.50-7.48 (m, 1H), 7.31-7.27 (m, 1H), 7.01 (t, 1H), 4.27-4.23 (t, 1H), 4.26 (s, 2H), 7.13-4.09 (t, 1H), 3.83-3.70 (m, 2H), 2.88-2.84 (m, 1H), 2.57-2.55 (m, 2H), 2.32 (s, 4H), 1.54 (s, 4H), 1.42 (s, 2H).

[1930]

[1931] **<Example 170>**

4-(3-(3-(azetidin-1-ylmethyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-170)

[1932]

[1933] Step 1 : Preparation of

4-(3-(3-(azetidin-1-ylmethyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride

[1934] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 143)

4-(3-(3-(azetidin-1-ylmethyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(100mg, 0.24mmol) was reacted with 1N solution of hydrochloric acid(0.48mL, 0.48mmol) to afford the title compound(101mg, 95%).

[1935] ¹H-NMR (400 MHz, MeOD): δ 8.36 (d, 1H), 7.94 (d, 1H), 7.84 (m, 2H), 7.50 (m, 2H), 7.13 (t, 1H), 4.38 (s, 2H), 4.19 (t, 1H), 4.09 (m, 1H), 3.74 (m, 2H), 3.30 (m, 4H), 2.69 (m, 3H), 2.14 (t, 2H).

[1936]

[1937] **<Example 171>**

4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-171)

[1938]

[1939] Step 1 : Preparation of

4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride

[1940] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 25)

4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(100mg, 0.25mmol) was reacted with 1N solution of hydrochloric acid(0.50mL, 0.50mmol) to afford the title compound(99mg, 91%).

[1941] ¹H-NMR (CDCl₃, 400MHz): δ 10.03 (s, 1H), 9.18 (d, 2H), 8.47-8.45 (m, 1H), 7.80-7.71 (m, 3H), 7.52-7.48 (m, 1H), 7.32-7.28 (m, 1H), 7.01 (t, 1H), 4.27 (s, 2H), 4.26-4.22 (m, 1H), 4.10 (t, 1H), 3.85-3.81 (m, 1H), 3.73-3.70 (m, 1H), 2.99-2.88 (m, 2H), 2.81-2.72 (m, 1H), 2.07 (m, 1H), 1.57 (br, 1H), 0.45-0.41 (m, 2H), 0.29-0.26 (m, 2H).

[1942]

[1943] **<Example 172>**

4-(4-fluoro-3-(3-((isopropylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-172)

[1944]

[1945] Step 1 : Preparation of

4-(4-fluoro-3-(3-((isopropylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-onehydrochloride

- [1946] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 145)
4-(4-fluoro-3-(3-((isopropylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(100mg, 0.24mmol) was reacted with 1N solution of hydrochloric acid(0.48mL, 0.48mmol) to afford the title compound(95mg, 89%).
- [1947] ¹H-NMR (CDCl₃, 400MHz): δ 10.20 (br, 1H), 9.19 (d, 2H), 8.47-8.45 (m, 1H), 7.80-7.70 (m, 3H), 7.51-7.49 (dd, 1H), 7.32-7.28 (m, 1H), 7.01 (t, 1H), 4.27 (s, 2H), 4.28-4.23 (m, 1H), 4.12 (t, 1H), 3.84-3.81 (dd, 1H), 3.75-3.71 (dd, 1H), 2.88-2.69 (m, 4H), 1.05-1.03 (dd, 6H).

[1948]

[1949] **<Example 173>**

4-(3-(3-(((cyclopropylmethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-173)

[1950]

[1951] Step 1 : Preparation of

4-(3-(3-(((cyclopropylmethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-onehydrochloride

- [1952] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 146)
4-(3-(3-(((cyclopropylmethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(100mg, 0.23mmol) was reacted with 1N solution of hydrochloric acid(0.46mL, 0.46mmol) to afford the title compound(94mg, 90%).
- [1953] ¹H-NMR (CDCl₃, 400MHz): δ 10.36 (br, 1H), 9.18 (d, 2H), 8.47-8.45 (m, 1H), 7.80-7.71 (m, 3H), 7.51-7.49 (m, 1H), 7.32-7.28 (m, 1H), 7.01 (t, 1H), 4.27-4.24 (m, 3H), 4.13 (t, 1H), 3.86-3.75 (m, 2H), 2.94-2.75 (m, 3H), 2.48-2.46 (dd, 2H), 1.61 (br, 1H), 0.95-0.91 (m, 1H), 0.51-0.46 (m, 2H), 0.12-0.09 (m, 2H).

[1954]

[1955] **<Example 174>**

4-(4-fluoro-3-(3-((isobutylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-174)

[1956]

[1957] Step 1 : Preparation of

4-(4-fluoro-3-(3-((isobutylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-onehydrochloride

- [1958] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 147)

4-(4-fluoro-3-(3-((isobutylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(100mg, 0.23mmol) was reacted with 1N solution of hydrochloric acid(0.46mL, 0.46mmol) to afford the title compound(101mg, 93%).

[1959] ¹H-NMR (CDCl₃, 400MHz): δ 10.69 (br, 1H), 9.20 (d, 2H), 8.47-8.45 (m, 1H), 7.80-7.71 (m, 3H), 7.50-7.48 (m, 1H), 7.32-7.28 (m, 1H), 7.00 (t, 1H), 4.27-4.23 (m, 3H), 4.14 (t, 1H), 3.86-3.78 (m, 2H), 2.93-2.78 (m, 3H), 2.45 (s, 1H), 2.44 (s, 1H), 1.81-1.71 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H).

[1960]

[1961] **<Example 175>**

4-(3-(3-((cyclobutylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; (I-175)

[1962]

[1963] Step 1 : Preparation of

4-(3-(3-((cyclobutylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-onehydrochloride

[1964] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 149)

4-(3-(3-((cyclobutylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one(100mg, 0.24mmol) was reacted with 1N solution of hydrochloric acid(0.48mL, 0.48mmol) to afford the title compound(99mg, 91%).

[1965] ¹H-NMR (CDCl₃, 400MHz): δ 10.33 (br, 1H), 9.19 (d, 2H), 8.47-8.45 (m, 1H), 7.80-7.71 (m, 3H), 7.50-7.48 (m, 1H), 7.31-7.28 (m, 1H), 7.00 (t, 1H), 4.27-4.22 (m, 3H), 4.11 (t, 1H), 3.83-3.72 (m, 2H), 3.23 (m, 1H), 2.83-2.72 (m, 3H), 2.23-2.17 (m, 2H), 1.71-1.62 (m, 5H).

[1966]

[1967] **<Example 176>**

4-(4-fluoro-3-(3-((prop-2-yn-1-ylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride; (I-176)

[1968]

[1969] Step 1 : Preparation of

4-(4-fluoro-3-(3-((prop-2-yn-1-ylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-onehydrochloride

[1970] This compound was made using the procedure described for example 156(Step 1). Thus, the intermediate compound(example 150)

4-(4-fluoro-3-(3-((prop-2-yn-1-ylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one(100mg, 0.25mmol) was reacted with 1N solution of hydrochloric acid(0.50mL, 0.50mmol) to afford the title compound(96mg, 88%).

[1971] ¹H-NMR (CDCl₃,400MHz): δ 10.61 (s, 1H), 9.19 (d, 2H), 8.48-8.46 (m, 1H),

7.80-7.71 (m, 3H), 7.51-7.49 (m, 1H), 7.32-7.28 (m, 1H), 7.01 (t, 1H), 4.28-4.24 (m, 3H), 4.12 (t, 1H), 3.88-3.76 (m, 2H), 3.43 (m, 2H), 3.00-2.87 (m, 2H), 2.78-2.72 (m, 1H), 2.27-2.23 (m, 1H), 1.45 (br, 1H).

[1972]

[1973] **<Experiment 1> In vitro test for antitumoral activity**

[1974] To evaluate the in vitro test, the invented compounds (from I-1 to I-155) were determined as follows and showed table 1, 2, 3, 4 and 5.

[1975]

[1976] 1. Determination of Cellular PAR levels

[1977] Cellular PAR assay was performed to measure cellular PARP inhibitory activity of the compounds in the present invention. Hela human cervical cancer cells cultured in Minimum Essential Medium with Earle's Balanced Salts (MEM/EBSS) containing 10% FBS were seeded into 96-well cell culture plates, and incubated for 1 day at 37°C under 5% CO₂ atmosphere. After the invented compounds serially diluted in DMSO were added to each well, and then DNA damage was provoked by addition of H₂O₂ solution in H₂O. Cellular PAR levels were determined and EC₅₀ was calculated by using PAR antibody and detection solution.

[1978] Table 1

[Table 1]

Compound	EC ₅₀	Compound	EC ₅₀	Compound	EC ₅₀
	Cellular PAR[EC ₅₀ , nM]		Cellular PAR[EC ₅₀ , nM]		Cellular PAR[EC ₅₀ , nM]
WO2004080976A1 Example 168	A	I-56	A	I-106	C
		I-57	A	I-107	A
I-8	B	I-58	A	I-108	B
I-9	B	I-59	A	I-109	A
I-10	A	I-60	B	I-110	A
I-11	B	I-61	A	I-111	B
I-12	A	I-62	A	I-112	B
I-13	A	I-63	B	I-113	B
I-14	B	I-64	B	I-114	B
I-15	C	I-65	B	I-115	B
I-16	C	I-66	A	I-116	B
I-17	A	I-67	B	I-118	B
I-18	A	I-68	B	I-119	C
I-19	A	I-69	A	I-120	A
I-20	B	I-70	A	I-121	C
I-21	B	I-71	A	I-122	B
I-22	A	I-72	C	I-123	B
I-23	C	I-73	A	I-124	B
I-24	C	I-74	A	I-125	B
I-25	A	I-75	A	I-126	A
I-26	A	I-76	A	I-127	C
I-27	A	I-77	A	I-128	A
I-28	A	I-78	B	I-129	D
I-29	B	I-79	A	I-130	A
I-30	B	I-80	A	I-131	B
I-31	A	I-81	A	I-132	A

I-32	A	I-82	A	I-133	B
I-33	A	I-83	A	I-134	B
I-34	C	I-84	B	I-135	A
I-35	A	I-85	A	I-136	A
I-36	B	I-86	A	I-137	B
I-37	A	I-87	B	I-138	B
I-38	A	I-88	A	I-139	B
I-39	B	I-89	A	I-140	A
I-40	A	I-90	A	I-141	A
I-41	A	I-91	A	I-142	A
I-42	A	I-92	A	I-143	A
I-43	A	I-93	B	I-144	A
I-44	A	I-94	B	I-145	A
I-45	A	I-95	A	I-146	A
I-46	A	I-96	C	I-147	B
I-47	B	I-97	C	I-148	A
I-48	A	I-98	A	I-149	A
I-49	A	I-99	A	I-150	B
I-50	A	I-100	A	I-151	B
I-51	A	I-101	A	I-152	D
I-52	A	I-102	A	I-153	B
I-53	A	I-103	B	I-154	A
I-54	A	I-104	A	I-155	A
I-55	A	I-105	A		

[1979] Range A: $EC_{50} \leq 5nM$

[1980] Range B: $5nM < EC_{50} \leq 50nM$

[1981] Range C: $50nM < EC_{50} \leq 300nM$

[1982] Range D: $300nM < EC_{50} \leq 1,000nM$

[1983] Range E: $EC_{50} > 1,000nM$

[1984]

[1985] According to the above table 1, the compounds in the present invention showed potent cellular PARP inhibitory activity in cellular PAR assay.

[1986]

[1987] 2. Cell viability assay (MDA-MB-436)

[1988] Cell viability assay was performed by using MDA-MB-436 cell line to measure cytotoxicity of compounds in the present invention. MDA-MB-436 breast cancer cell line was seeded into 96-well plates at 37°C under 5% CO₂ atmosphere using DMEM/F12(Gibco) containing 10% FBS(Hyclone). After 24hr incubation, cells were treated with the invented compounds at various concentrations for 6 days. The medium was changed every 3 day. 6 days later, A fluorescence reagent was used to determine the IC₅₀ values.

[1989] Table 2

[Table 2]

Compound	IC ₅₀	Compound	IC ₅₀	Compound	IC ₅₀
	MDA-MB-436[nM]		MDA-MB-436[nM]		MDA-MB-436[nM]
WO200408097 6A1Example 168	B	I-59	B	I-111	D
		I-61	C	I-112	D
I-14	C	I-66	C	I-113	D
I-19	C	I-69	C	I-114	D
I-22	C	I-70	C	I-115	D
I-24	D	I-71	C	I-116	D
I-25	B	I-73	C	I-118	D
I-26	B	I-74	B	I-120	A
I-27	A	I-75	B	I-121	D
I-28	B	I-76	B	I-124	C
I-29	D	I-77	C	I-125	A
I-30	C	I-78	D	I-126	B
I-31	B	I-79	C	I-128	B
I-32	A	I-80	A	I-129	D
I-33	A	I-81	C	I-130	A
I-34	D	I-82	B	I-131	C
I-35	A	I-83	B	I-132	A
I-36	B	I-84	C	I-133	C
I-37	B	I-85	A	I-134	C
I-38	B	I-86	B	I-135	B
I-39	D	I-87	D	I-136	B
I-40	B	I-88	A	I-137	C
I-41	A	I-89	B	I-138	D
I-42	A	I-90	C	I-140	A
I-43	B	I-91	C	I-141	B
I-44	A	I-92	B	I-142	B

I-45	B	I-93	C	I-143	A
I-46	B	I-94	D	I-144	A
I-48	A	I-95	C	I-145	B
I-49	B	I-96	D	I-146	B
I-50	C	I-98	D	I-147	D
I-51	B	I-99	B	I-148	A
I-52	A	I-100	D	I-149	A
I-53	A	I-101	D	I-150	C
I-54	B	I-102	D	I-151	D
I-55	B	I-103	D	I-153	D
I-56	D	I-104	D	I-154	D
I-57	B	I-109	D	I-155	C
I-58	B	I-110	D		

[1990] Range A: $IC_{50} \leq 5nM$

[1991] Range B: $5nM < IC_{50} \leq 50nM$

[1992] Range C: $50nM < IC_{50} \leq 300nM$

[1993] Range D: $300nM < IC_{50} \leq 1,000nM$

[1994] Range E: $IC_{50} > 1,000nM$

[1995]

[1996] According to the above table 2, the compounds in the present invention showed potent growth inhibition of cancer cells in cell cytotoxicity assay using MDA-MB-436 breast cancer cell line.

[1997]

[1998] 3. Cell viability assay (Capan-1)

[1999] Cell viability assay was performed by using Capan-1 cell line to measure cytotoxicity of compounds in the present invention. Capan-1 pancreatic cancer cell line was seeded into 96-well plates at 37°C under 5% CO₂ atmosphere using IMDM(Sigma) containing 10% FBS(Hyclone). After 24hr incubation, cells were treated with the invented compounds at various concentrations for 10 days. After 7-day incubation, the medium was changed. 10 days later, A fluorescence reagent was used to determine the IC₅₀ values.

[2000] Table 3

[Table 3]

Compound	IC ₅₀ ,	Compound	IC ₅₀ ,	Compound	IC ₅₀ ,
	Capan-1[nM]		Capan-1[nM]		Capan-1[nM]
WO200408097 6A1Example 168	D	I-40	D	I-132	B
		I-36	D	I-140	D
I-25	D	I-41	D	I-141	D
I-26	D	I-42	D	I-142	D
I-27	C	I-43	D	I-143	C
I-28	D	I-44	D	I-146	D
I-31	C	I-53	D	I-149	D
I-32	C	I-80	C	I-99	D
I-33	D	I-82	D	I-100	D
I-35	D	I-83	D		

[2001] Range A: IC₅₀ ≤ 5nM

[2002] Range B: 5nM < IC₅₀ ≤ 50nM

[2003] Range C: 50nM < IC₅₀ ≤ 300nM

[2004] Range D: 300nM < IC₅₀ ≤ 1,000nM

[2005] Range E: IC₅₀ > 1,000nM

[2006]

[2007] According to the above table 3, the compounds in the present invention showed potent growth inhibition of cancer cells in cell cytotoxicity assay using Capan-1 pancreatic cancer cell line.

[2008]

[2009] 4. Cell viability assay (LNCap)

[2010] Cell viability assay was performed by using LNCaP cell line to measure cytotoxicity of compounds in the present invention. LNCaP prostate cancer cell line was seeded into 96-well plates at 37°C under 5% CO₂ atmosphere using RPMI-1640(Hyclone) containing 10% FBS(Hyclone). After 24hr incubation, cells were treated with the invented compounds at various concentrations for 11 days. The medium was changed every 3 to 4 day. 11 days later, A fluorescence reagent was used to determine the IC₅₀ values.

[2011] Table 4

[Table 4]

Compound	IC ₅₀
	LNCap [nM]
WO2004080976A1Example 168	E
I-27	C
I-32	C
I-33	D
I-35	E
I-53	E
I-80	C
I-83	E
I-99	D
I-114	B
I-131	B
I-146	E
I-149	E

[2012] Range A: IC₅₀ ≤ 5nM

[2013] Range B: 5nM < IC₅₀ ≤ 50nM

[2014] Range C: 50nM < IC₅₀ ≤ 300nM

[2015] Range D: 300nM < IC₅₀ ≤ 1,000nM

[2016] Range E: IC₅₀ > 1,000nM

[2017]

[2018] According to the above table 4, the compounds in the present invention showed potent growth inhibition of cancer cells in cell cytotoxicity assay using LNCaP prostate cancer cell line.

[2019]

[2020] 5. Tankyrase-1 enzyme assay

[2021] Tankyrase-1 enzyme assay was performed to determine Tankyrase-1 inhibitory activity of compounds in the present invention. The enzymatic reaction was conducted by coating the plate with substrates of tankyrase-1, and then the plate was washed. Compounds in the present invention serially diluted in DMSO were added to the reaction buffer activating tankyrase-1, and incubated for 1 hr at room temperature. After stopping the reaction, the plate was washed, and streptavidin-HRP was added to each well. IC₅₀ was calculated by adding chemiluminescent substrate and immediately

reading the sample in a microplate reader(Biotek).

[2022] Table 5

[Table 5]

Compound	IC ₅₀
	Tankyrase-1 [nM]
WO2004080976A1Example 168	E
I-27	E
I-32	E
I-33	E
I-99	D
I-114	E
I-130	C
I-147	E
I-150	E

[2023] Range A: IC₅₀ ≤ 5nM

[2024] Range B: 5nM < IC₅₀ ≤ 50nM

[2025] Range C: 50nM < IC₅₀ ≤ 300nM

[2026] Range D: 300nM < IC₅₀ ≤ 1,000nM

[2027] Range E: IC₅₀ > 1,000nM

[2028]

[2029] According to the above table 5, the compounds in the prevent invention exhibited strong inhibitory activity against tankyrase-1.

[2030]

[2031] **<Experiment 2> In vivo test for antitumoral activity**

[2032] To evaluate the in vivo antitumoral efficacy, the invented compounds(I-80~171) was determined as a result to follows.

[2033] Capan-1 Human pancreatic cancer cells were established as subcutaneous xenografts by injection of 8 X 10⁶ cells into the flanks of adult female Balb/c nude mice. Mice with established tumors (160-250mm³) were selected for study (n=6/treatmentgroup). The test compounds were formulated in DW and administered orally (po) at a dose of 30~200mg/kg. The vehicle alone was administered to control groups. Animals were dosed 5 days per week (Monday through Friday) for 3 consecutive weeks.

[2034]

[2035] Animals were weighed and tumor size was determined twice weekly by caliper measurements, and tumor volumes were calculated(volume = [l x w²]/2(mm³),where l and w

refer to the larger and smaller dimensions collected at each measurement). The mean tumor volumes of each group were calculated. The change in mean treated tumor volume was divided by the change in mean control tumor volume, multiplied by 100 and subtracted from 100% to give the tumor growth inhibition for each group.

[2036] Table 6

[Table 6]

Compound	Dose	Schedule	%TGI
WO2004080976A1Example 168	200mg/kg	po qd x 5	53.5
I-80	100mg/kg	po qd x 5	75.9
	200mg/kg		103.9
I-159	100mg/kg	po qd x 5	59.4
	200mg/kg		69.4
I-158	100mg/kg	po qd x 5	44.9
	200mg/kg		80.9
I-160	100mg/kg	po qd x 5	55.8
	200mg/kg		88.2
I-171	30mg/kg	po qd x 5	42.1
	60mg/kg		69.7

[2037] As can be seen from table 6, the selected compounds showed useful tumor growth inhibition.

[2038]

[2039] **<Experiment 3> Mouse Pharmacokinetics**

[2040] To evaluate the pharmacokinetics test, the invented compounds (from I-25 to I-1171) were determined as follows. Blood samples are collected at 15, 30, 60, 120, 240, 480, 1140 min. Quantification is by using a LC-MS/MS method specific to the selected compound. Pharmacokinetics parameters are calculated using WinNonLin compartmental analysis software.

[2041] Table 7

[Table 7]

Compound	AUC[min*ng/mL]	Compound	AUC[min*ng/mL]
WO2004080976A 1Example 168	39,927	I-135	9,175
I-25	49,858	I-140	17,724
I-26	200,772	I-141	11,588
I-27	28,302	I-142	5,325
I-30	31,280	I-143	40,367
I-33	61,268	I-146	65,532
I-35	135,283	I-148	28,290
I-53	74,937	I-149	10,138
I-75	28,516	I-159	28,302
I-80	121,308	I-160	135,283
I-83	34,044	I-161	61,268
I-99	35,139	I-171	40,367
I-120	30,582		

[2042] As can be seen from table 7, the selected compounds showed significant pharmacokinetics in Balb/c male mice.

[2043]

[2044] **<Experiment 4> Solubility test**

[2045] To evaluate the solubility, the invented compounds(I-159, I-161 and I-171) was determined as follows. The compounds was dissolve in water(1mL, 10mL and 100mL) at 25°C under an atmospheric pressure.

[2046] Table 8

[Table 8]

Compound	Solvent by volume for one part of soluble by weight.	
WO2004080976 A1example 168	From 1000 to 10000mL	Very slightly soluble
I-159	From 30 to 100mL	Sparingly soluble
I-161	From 30 to 100mL	Sparingly soluble
I-171	From 30 to 100mL	Sparingly soluble

[2047] As can be seen form Table 8. The invented compounds showed significant solubility.

[2048]

[2049] It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

Industrial Applicability

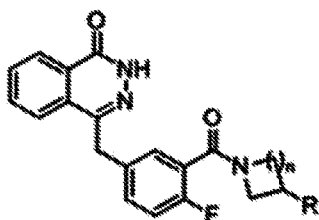
[2050] The compounds of the present invention are highly active in the suppression of PARP, and according to its pharmaceutical compositions are expected to be useful for therapeutic applications which are improved by suppression of PARP activity, and cancer with mutated BRCA1, BRCA2 and ERG fusion gene in mono or combination treatment with radiation and with chemotherapy.

Claims

[Claim 1]

A compound represented by Formula I, racemic, enantiomer, diastereoisomer thereof, or pharmaceutically acceptable salt thereof.

[Formula I]



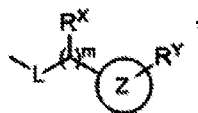
In the present Formula I,

n is 1 or 2,

R is



Wherein, when the R is



m is 0, 1 or 2,

L is oxygen, methylene, carbonyl, CONHCH_2 , $\text{NR}^{\text{c1}}\text{CH}_2$, $\text{NR}^{\text{c2}}\text{CO}$, NR^{c3} , CONR^{c4} or $\text{CH}_2\text{NR}^{\text{c5}}$ (especially, R^{c1} , R^{c2} , R^{c3} , R^{c4} and R^{c5} is each independently oxygen, C_{1-4} alkylamine, C_{1-6} alkyl, C_{1-6} alkoxy, halo C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl or 3-8 membered heterocycle),

R^{X} is hydrogen, cyano, hydroxyl, trifluoromethyl, C_{1-6} alkyl or C_{3-8} cycloalkyl,

R^{Y} is hydrogen, amide, cyano, hydroxyl, trifluoromethyl, halo, ester, C_{1-4} alkylamine, C_{1-6} alkyl, C_{1-6} methoxyalkyl or C_{2-6} alkynyl,

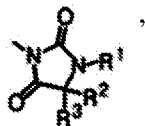
Z is unsubstituted, C_{1-6} alkyl, C_{1-6} methoxyalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-10} aromatic cycle or 3-8 membered heterocycle having 1-3 nitrogens,

wherein, when the R is



p and q is each independently from 1 to 3,

W is $\text{CR}^{\text{d1}}\text{R}^{\text{d2}}$ or NR^{d3} (especially, R^{d1} , R^{d2} and R^{d3} is each independently hydrogen, fluoro or C_{1-6} alkyl),



R^1 , R^2 and R^3 is each independently hydrogen or C_{1-6} alkyl.

[Claim 2]

The compound according to claim 1,

wherein, L is methylene, carbonyl, $CONHCH_2$, $NR^{c1}CH_2$, $NR^{c2}CO$, NR^{c3} , $CONR^{c4}$ or CH_2NR^{c5} (especially, R^{c1} , R^{c2} , R^{c3} , R^{c4} and R^{c5} is each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkynyl or C_{3-8} cycloalkyl),

R^X is hydrogen, cyano, hydroxyl, trifluoromethyl, methyl, ethyl or cyclopropyl,

R^Y is hydrogen, dimethylamide, cyano, hydroxyl, trifluoromethyl, halo, ethylester, dimethylamine, methyl, methoxymethyl or propargyl,

Z is unsubstituted, C_{1-6} alkyl, C_{1-6} methoxyalkyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aromatic cycle or 3-8 membered heterocycle having 1-3 nitrogens,

p and q is each independently 1 or 2,

W is $CR^{d1}R^{d2}$ or NR^{d3} (especially R^{d1} , R^{d2} and R^{d3} is each independently hydrogen, fluoro or methyl),

R^1 , R^2 and R^3 is each independently hydrogen, methyl or ethyl.

[Claim 3]

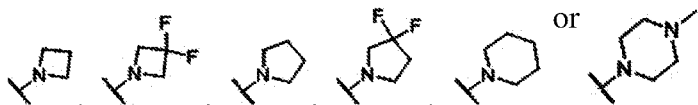
The compound according to claim 1,

wherein, L is $NR^{c1}CH_2$, $CONR^{c4}$ or CH_2NR^{c5} (especially, R^{c1} , R^{c4} and R^{c5} is each independently hydrogen, methyl, ethyl, propyl, propargyl or cyclopropyl),

Z is

The compound according to claim 1,

wherein, the present R is



[Claim 7]

The compound according to claim 1,

wherein, the compound represented by Formula I is selected from the group consisting of the following compounds:

(R)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(S)-4-(3-(3-aminopyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(3-(3-aminoazetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-hydroxypyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(S)-4-(4-fluoro-3-(3-hydroxypyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-hydroxyazetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(hydroxymethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)cyclopropanecarboxamide;

N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)cyclopropanecarboxamide;

(S)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)cyclopropanecarboxamide;

(R)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide;

N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)-N-methylcyclopropanecarboxamide;

(S)-N-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)-N-methylcyclopropanecarboxamide;

3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)-5,5-dimethylimidazolidine-2,4-dione;

(R)-3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)

yl)pyrrolidin-3-yl)imidazolidine-2,4-dione;
(R)-1-ethyl-3-(1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)imidazolidine-2,4-dione;
4-(4-fluoro-3-(3-(4-fluoropiperidine-1-carbonyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
4-(3-(3-(3,3-difluoroazetidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(3-(3-(3,3-difluoropyrrolidine-1-carbonyl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
(R)-N-(cyclopropylmethyl)-1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidine-3-carboxamide;
4-(4-fluoro-3-(3-(pyrrolidine-1-carbonyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
(R)-4-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
(S)-4-(3-(3-(3-(dimethylamino)pyrrolidine-1-carbonyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(3-(3-(cyclohexylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
(R)-4-(3-(3-(cyclopropylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
(R)-4-(3-(3-(cyclobutylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
(R)-4-(3-(3-(cyclopentylamino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(4-fluoro-3-(3-(isopropylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
4-(3-(3-((cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(3-(3-(bis(cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

enzy)phthalazin-1(2H)-one;
 4-(4-fluoro-3-(3-(isobutylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
 4-(4-fluoro-3-(3-((1-hydroxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
 4-(4-fluoro-3-(3-(neopentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
 4-(3-(3-((2,2-dimethylcyclopentyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
 ethyl
 2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclopent-1-enecarboxylate;
 4-(4-fluoro-3-(3-(pentan-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
 4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
 4-(3-(3-((1-cyclopropylethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
 4-(3-(3-(bicyclo[2.2.1]heptan-2-ylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
 4-(3-(3-(sec-butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
 4-(3-(3-((dicyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
 4-(4-fluoro-3-(3-((4-methylpentan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
 4-(4-fluoro-3-(3-((3-hydroxybutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
 4-(4-fluoro-3-(3-(pentan-2-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
 4-(4-fluoro-3-(3-((1-(1-methylcyclopropyl)ethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
 4-(4-fluoro-3-(3-((3,3,3-trifluoro-2-methylpropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
 4-(3-(3-(allylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
 4-(4-fluoro-3-(3-(isopentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(3-(3-(butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(4-fluoro-3-(3-((3-methylbut-2-en-1-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
4-(3-(3-((cyclopentylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(4-fluoro-3-(3-((4,4,4-trifluorobutyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
4-(4-fluoro-3-(3-(pentylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
4-(3-(3-((2-cyclopropylethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(4-fluoro-3-(3-(propylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
(R)-4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
(S)-4-(4-fluoro-3-(3-(methyl(pyridin-4-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
(S)-4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
(R)-4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
4-(4-fluoro-3-(3-(methyl(pyridin-2-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
(S)-4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
(R)-4-(4-fluoro-3-(3-(methyl(pyridin-3-ylmethyl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;
4-(3-(3-(cyclopropyl(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(3-(3-(cyclopropyl(ethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;
4-(3-(3-(cyclobutyl(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(3-(3-(cyclopentyl(prop-2-yn-1-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(3-(3-(3,3-difluoropyrrolidin-1-yl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(4-fluoropiperidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(3-([1,3'-biazetidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(pyrrolidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(piperidin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(4-methylpiperazin-1-yl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(phenylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((1-(trifluoromethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(prop-2-yn-1-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(S)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((1-(hydroxymethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((1-methylcyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(3-(3-((3,3-dimethylbutan-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(S)-4-(3-(3-((3,3-dimethylbutan-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(S)-4-(4-fluoro-3-(3-((3-methylbutan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((1-(methoxymethyl)cyclopropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(3-(3-(but-3-yn-1-ylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((2-methylallyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((3-hydroxy-2,2-dimethylpropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)methyl)cyclopropanecarbonitrile;

4-(4-fluoro-3-(3-((2,2,2-trifluoroethyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-(pyrrolidin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(S)-4-(4-fluoro-3-(3-(pyrrolidin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclopentanecarbonitrile;

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclobutanecarbonitrile;

2-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)propanenitrile;

2-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)butanenitrile;

2-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)-3-methylbutanenitrile;

2-cyclopropyl-2-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)acetonitrile;

4-(4-fluoro-3-(3-((1-(trifluoromethyl)cyclobutyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(S)-4-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(S)-4-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(methyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(ethyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(S)-4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(S)-4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(S)-4-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(S)-4-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(3-(3-((6-chloropyridazin-3-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(3-(3-(cyclobutyl(pyrimidin-2-yl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(pyridazin-3-ylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(3-(3-((6-chloropyridazin-3-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(R)-4-(3-(3-((6-chloropyridazin-3-yl)(methyl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-(pyrimidin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(3-(3-(ethyl(pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-(pyridazin-3-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-(methyl(pyridazin-3-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-(thiazol-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(3-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzyl)pyrrolidin-3-yl)amino)pyrimidine-5-carbonitrile;

(R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzyl)pyrrolidin-3-yl)amino)nicotinonitrile;

(R)-4-(4-fluoro-3-(3-(pyridin-2-ylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-2-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)pyrrolidin-3-yl)amino)-N,N-dimethylnicotinamide;

(R)-4-(3-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-((5-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-((4-(trifluoromethyl)pyridin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(3-(3-(benzylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((3,3,3-trifluoropropyl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(3-(3-(azetidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(R)-4-(3-([1,3'-bipyrrolidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-(piperidin-1-yl)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-(p-tolylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

(R)-4-(4-fluoro-3-(3-(phenylamino)pyrrolidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(pyrrolidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-(piperidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(3-(3-(azetidin-1-ylmethyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((isopropylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(3-(3-(((cyclopropylmethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((isobutylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(3-(3-((tert-butylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(3-(3-((cyclobutylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((prop-2-yn-1-ylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

4-(4-fluoro-3-(3-((phenylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one;

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)methyl)amino)methyl)cyclopropanecarbonitrile;

1-(((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)methyl)amino)cyclopropanecarbonitrile;

4-(3-(3-((cyclopropyl(prop-2-yn-1-yl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(3-(3-((cyclopropyl(methyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(3-(3-((cyclopropyl(ethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one;

4-(3-(3-(cyclobutylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;

4-(3-(3-(cyclopropylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;

4-(3-(3-(cyclopentylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;

4-(4-fluoro-3-(3-(isopropylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride;

4-(3-(3-((cyclopropylmethyl)amino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;

4-(4-fluoro-3-(3-(isobutylamino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride;

4-(4-fluoro-3-(3-((1-hydroxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride;

4-(3-(3-(butylamino)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;

4-(3-([1,3'-biazetidine]-1'-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;

(R)-4-(4-fluoro-3-(3-((1-methoxypropan-2-yl)amino)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride;

1-((1-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)azetidin-3-yl)amino)cyclobutanecarbonitrile hydrochloride;

(R)-4-(3-(3-(azetidin-1-yl)pyrrolidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;
 4-(4-fluoro-3-(3-(pyrrolidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride;
 4-(4-fluoro-3-(3-(piperidin-1-ylmethyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride;
 4-(3-(3-(azetidin-1-ylmethyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;
 4-(3-(3-((cyclopropylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;
 4-(4-fluoro-3-(3-((isopropylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride;
 4-(3-(3-(((cyclopropylmethyl)amino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride;
 4-(4-fluoro-3-(3-((isobutylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride;
 4-(3-(3-((cyclobutylamino)methyl)azetidine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one hydrochloride; and
 4-(4-fluoro-3-(3-((prop-2-yn-1-ylamino)methyl)azetidine-1-carbonyl)benzyl)phthalazin-1(2H)-one hydrochloride.

- [Claim 8] A pharmaceutical composition for treating cancers comprising the compound according to any one of claims 1-7.
- [Claim 9] The pharmaceutical composition according to claim 8, wherein the cancers are caused by genetic defect of BRCA1, BRCA2, and ERG fusion gene.
- [Claim 10] The pharmaceutical composition according to claim 9, wherein the cancers are selected from the group consisting of breast cancer, ovarian cancer, pancreatic cancer, gastric cancer, lung cancer, colorectal cancer, brain tumor, prostate cancer and Ewings sarcoma.
- [Claim 11] A use of the compound according to any one of claims 1-7 for manufacturing a medicament for treating cancers.
- [Claim 12] The use according to claim 11, wherein the cancers are caused by genetic defect of BRCA1, BRCA2, and ERG fusion gene.
- [Claim 13] The use according to claim 12, wherein the cancers are selected from the group consisting of breast cancer, ovarian cancer, pancreatic cancer, gastric cancer, lung cancer, colorectal cancer, brain tumor, prostate cancer and Ewings sarcoma.