



(51) International Patent Classification:

C07D 487/14 (2006.01) *C07D 401/12* (2006.01)
C07D 487/04 (2006.01) *A61P 11/00* (2006.01)
A61K 31/4545 (2006.01) *A61P 37/08* (2006.01)

(21) International Application Number:

PCT/EP2015/064498

(22) International Filing Date:

26 June 2015 (26.06.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1411581.0 30 June 2014 (30.06.2014) GB

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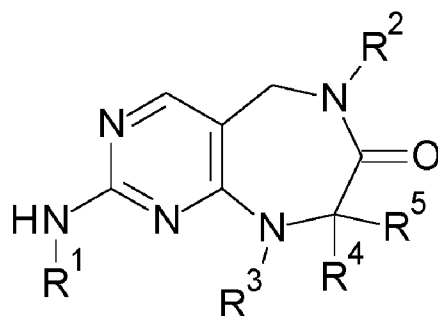
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: COMPOUNDS INHIBITING THE ENZYME MONOPOLAR SPINDLE 1 KINASE, PHARMACEUTICAL COMPOSITIONS AND USES THEREOF



(I)

(57) Abstract: The present invention relates to compounds able to inhibit the Monopolar Spindle 1 kinase (Mps-1 or TTK), according to the general formula (I), wherein R¹, R², R³, R⁴, and R⁵ are as defined in the specification. The present application also relates to a process for their preparation, pharmaceutical compositions comprising them, and to their use as therapeutic agents, in particular for the treatment of cancer.

COMPOUNDS INHIBITING THE ENZYME MONOPOLAR SPINDLE 1 KINASE, PHARMACEUTICAL COMPOSITIONS AND USES THEREOF

FIELD OF INVENTION

5 The present invention relates to compounds able to inhibit the Monopolar Spindle 1 kinase (Mps-1 or TTK), to a process for their preparation, pharmaceutical compositions comprising them, and to their use as therapeutic agents, in particular for the treatment of cancer.

BACKGROUND OF THE INVENTION

The Monopolar Spindle 1 kinase (Mps-1), also known as Tyrosine Threonine kinase (TTK), is a serine/threonine kinase protein, which appear to be involved in the regulation of an evolutionarily conserved regulator of mitotic progression called Spindle Assembly Checkpoint (SAC).

15 Several crucial observations suggest that inhibiting the SAC may lead to selective killing of cancer cells: cells containing supernumerary centrosomes (SCs), a very frequent alteration in tumours, often undergo a multipolar mitosis [Nigg, E. A. *Nat. Rev. Cancer* 2, 815–25 (2002)]. The cell progeny of a multipolar division invariably die within 1-2 generations [Ganem, N. J. *et al. Nature* 460, 278–82 (2009)]. To survive, cells with SCs
20 rely on a suppression pathway that allows the creation of a bipolar spindle, thus avoiding the dire consequences of multipolar divisions [Silkworth, W. T., *et al. PLoS One* 4, e6564 (2009)]. Suppression of multipolarity requires the SAC [Kwon, M. *et al. Genes Dev.* 22, 2189–203 (2008)]. Inhibition of the SAC has been shown to be synthetically lethal with the presence of supernumerary centrosomes [Kwon, M. *et al. Genes Dev.* 22, 2189–203
25 (2008)]. Hence SAC kinases may be considered novel drug targets for anti-cancer therapies.

Biochemical and genetic evidence has demonstrated a fundamental role for Mps-1 in centrosome duplication in *S. cerevisiae* and in regulation of the SAC in all organisms [Abrieu, A. *et al. Cell* 106, 83–93 (2001); Stucke, V. M., *et al. EMBO J.* 21, 1723–32
30 (2002)]. In cancer cells, small molecule kinase inhibitors of Mps-1 prevent correct assembly of the SAC, promote premature anaphase and induce aneuploidy followed by cell death. These inhibitors show antiproliferative activity on a range of tumour cell types

and have anti-tumour activity in mouse tumour xenograft models [Tardif, K. D. *et al.* Mol. Cancer Ther. 10, 2267–75 (2011); Colombo, R. *et al.* Cancer Res. 70, 10255–64 (2010); Kwiatkowski, N. *et al.* Nat. Chem. Biol. 6, 359–68 (2010)].

Based on these findings, inhibitors of Mps-1 represent valuable compounds that should
5 be useful either as single agents or in combination with other drugs for the treatment of proliferative diseases such as cancer.

Different inhibitors of Mps-1 are known in prior art: WO2012032031 discloses imidazopiperazine derivatives; WO2014009219, WO2012136531, and WO2012123745
10 disclose various fused pyridines; WO2012101032, WO2009067547, WO2010111406, WO2012013557, WO2014037750 and WO2014037751 disclose different fused pyrimidine compounds.

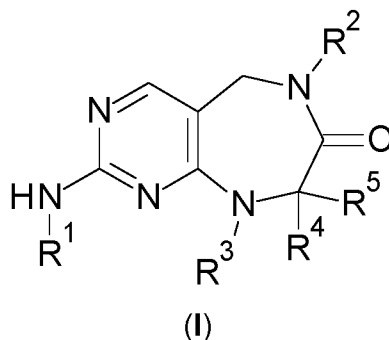
Xiang, J., *et al.* [J. Comb. Chem. 12, 503–9 (2010)] report the preparation of 8,9-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7(6H)-ones, but no biological characterizations are disclosed.

15 Despite the progress that have been made in the protein kinase inhibition field, the searches continues for new therapeutic agents active in regulating protein kinase activity, to enrich the still largely inadequate therapeutic armamentarium for cancer treatment and prevent the possible resistance issues of current best compounds.

The inventors found a novel series of bicyclic pyrimidines, which have valuable
20 pharmaceutical properties, in particular, the ability to inhibit protein kinases, more particularly, the ability of inhibiting the Mps-1 protein kinase.

SUMMARY OF THE INVENTION

According to the present invention there is provided a compound, endowed with a potent
25 Mps-1 inhibitory activity, of general formula (I):



wherein:

R¹ is a phenyl, optionally substituted by 1 to 3 groups selected from: C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, cyano, heterocycloalkyl, CONR⁶R⁷;

5 R² is hydrogen, C₁₋₃ alkyl optionally substituted by cyano or methoxy;

R³ is hydrogen, C₁₋₃ alkyl, C₃₋₆ cycloalkyl, heterocycloalkyl, indanyl, CH₂R⁸,

R⁴, R⁵ are, independently, hydrogen; C₁₋₃ alkyl, phenyl, CH₂R⁸; or R⁴ and R⁵ together with the carbon atom to which they are bound form a C₃₋₆ cycloalkyl ring; or, R⁴ and R³ together with the carbon and nitrogen atoms to which they are respectively bound, form a pyrrolidine or piperidine ring;

R⁶ and R⁷ are, independently, hydrogen; heterocycloalkyl; or R⁶ and R⁷ together with the nitrogen atom to which they are bound form a heterocycloalkyl ring;

R⁸ is phenyl; or heteroaryl optionally substituted by one to three substituents, selected from C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, cyano; or R⁸ is 1,3-benzodioxolyl or 2,2-difluoro-1,3-benzodioxolyl;

wherein the phenyl in R⁴, R⁵ and R⁸ may be optionally substituted by one to three substituents, selected from C₁₋₃ alkyl, C₁₋₃ alkoxy, or halogen;

wherein the heterocycloalkyl in R¹ and R⁶, or the heterocycloalkyl ring formed by R⁶ and R⁷ together with the nitrogen atom to which they are bound, is optionally substituted with one to three substituents, selected from C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, hydroxy group, pyrrolidinyl, morpholinyl, piperidinyl or 2-oxo-2-heterocycloalkyl-ethyl; or stereoisomers or pharmaceutically acceptable salts thereof.

The term "halogen" refers to fluoro, chloro, bromo, or iodo. The "halogen" is preferably fluoro or chloro.

The term "C₁₋₃ alkyl" refers to methyl, ethyl, *n*-propyl and *iso*-propyl.

The term "C₃₋₆ cycloalkyl" refers to a saturated monocyclic hydrocarbon ring system having three to six carbon atoms and zero heteroatoms. Suitable examples of C₃₋₆-cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "C₁₋₃ alkoxy" refers to methoxy, ethoxy, n-propoxy and *iso*-propoxy.

The term "C₁₋₃ haloalkyl" refers to a straight or branched hydrocarbon chain radical, which is substituted by one or more halogen atoms and having from one to three carbon atoms. Suitable examples of C₁₋₃ haloalkyl include fluoromethyl, fluoroethyl, fluoropropyl, difluoromethyl, difluoroethyl, trifluoromethyl and trifluoroethyl. The "C₁₋₃ haloalkyl" group is preferably trifluoromethyl.

The term "C₁₋₃ haloalkoxy" refers to a straight or branched O-C₁₋₃ haloalkyl, where haloalkyl is defined herein. Suitable examples of "C₁₋₆ haloalkoxy" groups are OCF₃, OCHF₂ or OCH₂F.

The term "heteroaryl" means a monocyclic- or bicyclic 5-10 membered aromatic ring comprising carbon atoms, hydrogen atoms, and one or more heteroatoms, preferably, 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. As is well known to those skilled in the art, heteroaryl rings have less aromatic character than their all-carbon counter parts. Thus, for the purposes of the invention, a heteroaryl group need only have some degree of aromatic character. Illustrative examples of heteroaryl groups include, but are not limited to pyridinyl, pyrazolyl, imidazolyl, (1,2,3)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, indazolyl, indolyl, benzoimidazolyl, 1,3-benzodioxolyl, and the like.

The terms "heterocycloalkyl" or "heterocyclic ring" represents a mono or bicyclic saturated or partially saturated non-aromatic ring system of, respectively, 5 to 10 members, which contains one or more heteroatoms selected from nitrogen, oxygen, and sulphur. Examples of such heterocycles include, but are not limited to: pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl.

A heterocycloalkyl can be unsubstituted or substituted with one to three suitable substituents, selected from C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, hydroxy group, pyrrolidinyl, morpholinyl, piperidinyl.

According to the meanings provided to R⁴, R⁵, and R⁸, a phenyl can be optionally substituted by one to three suitable substituents, selected from C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen.

In a preferred embodiment R² is methyl.

In another preferred embodiment R³ is selected from the group consisting of: C₅₋₆ cycloalkyl, 5-6 membered heterocycloalkyl, indanyl, or CH₂R⁸ wherein R⁸ is as defined

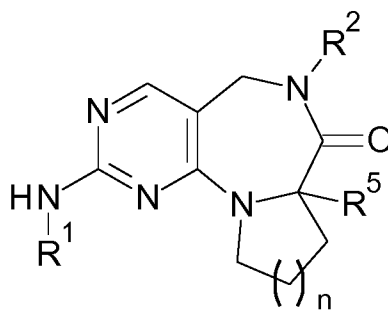
herein above.

In still another preferred embodiment R^2 is methyl; R^3 is C_{5-6} cycloalkyl, 5-6 membered heterocycloalkyl, indanyl, or CH_2R^8 wherein R^8 is as defined herein above.

The term " C_{5-6} cycloalkyl" refers to a saturated monocyclic hydrocarbon ring system having five to six carbon atoms and zero heteroatoms. Suitable examples of C_{5-6} -cycloalkyl groups include cyclopentyl and cyclohexyl.

The terms "5-6 membered heterocycloalkyl" represents a mono saturated or partially saturated non-aromatic ring system of, respectively, 5 to 6 members, which contains one or more heteroatoms selected from nitrogen, oxygen, and sulphur. Examples of such heterocycles include, but are not limited to: pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, or morpholinyl.

In one embodiment of the invention R^4 and R^3 together with the carbon and nitrogen atoms to which they are respectively bound, form a pyrrolidine or piperidine ring originating a compound of formula (Ia), wherein R^1 , R^2 and R^5 are as described herein above, and n is 1 or 2;



(Ia)

or stereoisomers or pharmaceutically acceptable salts thereof.

In a preferred embodiment the compound of formula (I) is selected from:

- 1) 9-cyclopentyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 2) 9-benzyl-6-methyl-2-[[4-(morpholin-4-yl)phenyl]amino]-5H,6H,7H,8H,9H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 3) 9-cyclopentyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 4) 9-cyclopentyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-

7-one;

- 5) 9-benzyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 6) 9-benzyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 7) 9-cyclopentyl-2-[4-(4-methylpiperazin-1-yl)anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 8) 4-[(9-cyclopentyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide;
- 9) 9-benzyl-2-[4-(4-methylpiperazin-1-yl)anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 10) 4-[(9-benzyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide;
- 11) 9-isopropyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 12) 4-[(9-isopropyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide;
- 13) 9-methyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 14) 4-[(9-methyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide;
- 15) 9-cyclopentyl-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 16) 9-cyclopentyl-2-(2-methoxy-4-morpholino-anilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 17) 8-benzyl-2-(2-methoxy-4-morpholino-anilino)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
- 18) 8-benzyl-9-methyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 19) 8-benzyl-2-(2-methoxy-4-morpholino-anilino)-9-methyl-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
- 20) 2-(4-morpholinoanilino)-5,6,7a,8,9,10-hexahydro-7H-pyrimido[5,4-f]pyrrolo[1,2-

- a)[1,4]diazepin-7-one;
- 21) 8-benzyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
- 22) 9-cyclopentyl-6-ethyl-2-(2-methoxy-4-morpholino-anilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 23) 9-cyclopentyl-6-ethyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 24) 9-cyclopentyl-2-[2-methoxy-4-(4-morpholino-1-piperidyl)anilino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 25) 2-(2-methoxy-4-morpholino-anilino)-8-phenyl-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
- 26) 2-(2-methoxy-4-morpholino-anilino)-9-[(3-methoxyphenyl)methyl]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 27) 2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-9-[(3-methoxyphenyl)methyl]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 28) 9-indan-2-yl-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 29) 2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-9-indan-2-yl-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 30) 9-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 31) 2-(2-methoxy-4-morpholino-anilino)-6-methyl-9-tetrahydropyran-4-yl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 32) 2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6-methyl-9-tetrahydropyran-4-yl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 33) 9-(1,3-benzodioxol-5-ylmethyl)-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 34) 9-(1,3-benzodioxol-5-ylmethyl)-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 35) 9-(1,3-benzodioxol-4-ylmethyl)-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 36) 9-(1,3-benzodioxol-4-ylmethyl)-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-

- phenyl]amino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 37) 8-(1H-indol-3-ylmethyl)-2-[(2-methoxy-4-morpholino-phenyl)amino]-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one
- 38) 2-[[4-(4-hydroxy-1-piperidyl)-2-methoxy-phenyl]amino]-8-(1H-indol-3-ylmethyl)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
- 5 39) 9-cyclopentyl-6-methyl-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 40) 9-cyclopentyl-6-ethyl-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 10 41) 2-(9-cyclopentyl-2-[[4-(morpholin-4-yl)phenyl]amino]-7-oxo-5H,6H,7H,8H,9H-pyrimido[4,5-e][1,4]diazepin-6-yl)acetonitrile;
- 42) 9-cyclopentyl-6-(2-methoxyethyl)-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 43) 8-benzyl-6,9-dimethyl-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 15 44) 8-benzyl-2-(4-morpholinoanilino)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
- 45) 9-cyclopentyl-2-[2-methoxy-4-(4-methylpiperazine-1-carbonyl)anilino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 20 46) 4-[(9-cyclopentyl-6-methyl-7-oxo-5,8-dihydropyrimido[4,5-e][1,4]diazepin-2-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide;
- 47) 9-cyclopentyl-6-methyl-2-[4-(4-methylpiperazine-1-carbonyl)-2-(trifluoromethoxy)anilino]-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
- 48) 2-(4-morpholinoanilino)spiro[6,9-dihydro-5H-pyrimido[4,5-e][1,4]diazepine-8,1'-cyclopropane]-7-one;
- 25 49) 8-methyl-2-(4-morpholinoanilino)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
- 50) 8-methyl-2-[4-(4-methylpiperazin-1-yl)anilino]-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
- 30 51) 9-(1H-imidazol-2-ylmethyl)-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one and
- 52) 9-cyclopentyl-2-[2-methoxy-4-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-1-piperidyl]anilino]6-

methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one.

or stereoisomers or pharmaceutically acceptable salts thereof.

In a further embodiment the compounds of the invention are for use as Monopolar Spindle 1 kinase (Mps-1 or TTK) inhibitor.

5 In a further embodiment the compounds of the invention are for use as medicament.

In a further embodiment the compounds of the invention are for use in the treatment and/or prevention of proliferative diseases and/or conditions.

In a further embodiment the compounds of the invention are for use in the treatment and/or prevention of cancer.

10 In a further embodiment the compounds of the invention are for use in the treatment and/or prevention of lymphoma, hepatocellular carcinoma, pancreatic cancer, brain tumour, breast cancer, lung cancer, colon cancer, cervical cancer, prostate cancer, kidney cancer, osteosarcoma, nasopharyngeal cancer, oral cancer, melanoma and ovarian cancer.

15 "Pharmaceutically acceptable salt" comprise a conventional non-toxic salt obtained by salification of a compound of formula (I) with inorganic acids (e.g. hydrochloric, hydrobromic, sulphuric or phosphoric acids), or with organic acids (e.g. acetic, propionic, succinic, benzoic, sulfanilic, 2-acetoxy-benzoic, cinnamic, mandelic, salicylic, glycolic, lactic, oxalic, malic, maleic, malonic, fumaric, tartaric, citric, p-toluenesulfonic, 20 methanesulfonic, ethanesulfonic, or naphthalensulfonic acids).

For reviews on suitable pharmaceutical salts see Berge S. M. et al., J. Pharm. Sci. 1977, 66, 1-19; Gould P. L. Int. J. Pharm 1986, 33, 201-217; and Bighley et al. Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York 1996, Volume 13, page 453-497.

25 Other salts, which are not pharmaceutically acceptable, for example the trifluoroacetate salt, may be useful in the preparation of compounds of this invention and these form a further aspect of the invention. The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I).

In addition, the compounds of the present invention can exist in unsolvated as well as in 30 solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like and these forms are also included within the scope of the present invention.

The compounds of formula (I) of the invention have asymmetric carbon atoms and may

therefore exist as individual optical isomers, as racemic mixtures or as any other mixture comprising a majority of one of the two optical isomers, which are all to be intended as within the scope of the present invention.

Likewise, it is understood that compounds of the invention may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

The invention also includes all suitable isotopic variations of a compound of formula (I) of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature.

Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Certain isotopic variations of the invention, for example, those in which a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated ^3H , and carbon-14 ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

It is a further embodiment of the invention a pharmaceutical composition comprising at least one compound as defined herein above or stereoisomers, a hydrate, solvate, or pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient and/or diluent, and optionally a further therapeutic agent.

Non-exhaustive examples of a suitable further therapeutic agent include: antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example platin derivatives like cis-platin, carboplatin, oxaliplatin, lobaplatin, satraplatin, nedaplatin, heptaplatin; nitrogen mustard such as chlorambucil, melphalan, chlormethine, cyclophosphamide, ifosfamide,

trofosfamide, uramustine, bendamustine, estramustine; busulphan, temozolomide or nitrosoureas); antimetabolites (for example antifolates such as aminopterin, methotrexate, pemetrexed, raltitrexed); purines such as cladribine, clofarabine, fludarabine, mercaptopurine, pentostatin, thioguanine; pyrimidines like capecitabine, cytarabine, 5 fluorouracil, floxuridine, gemcitabine; azacitidine, decitabine; cytosine arabinoside or hydroxyurea; antitumour antibiotics (for example anthracyclines like aclarubicin, amrubicin, daunomycin, doxorubicin, epirubicin, idarubicin, valrubicin, zorubicine; mitoxantrone; or antibiotics from streptomyces like actinomycin, bleomycin, mitomycin, or plicamycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, 10 vindesine or vinorelbine; taxoids like docetaxel, paclitaxel or tesetaxel; epothilones like ixabepilone) and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide; amsacrine, camptothecin, irinotecan, rubitecan, and topotecan); cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and idoxifene), oestrogen receptor down regulators (for example fulvestrant), 15 antiandrogens (for example bicalutamide, flutamide, nilutamide, liarozole or cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuporelin or buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5-alpha-reductase such as finasteride;

20 agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors and inhibitors of urokinase plasminogen activator receptor function); inhibitors of growth factor function, for example growth factor antibodies, growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab, the anti-erbB1 antibody cetuximab and panitumumab, the anti IGF1R antibody figitumumab), farnesyl 25 transferase inhibitors, MEK inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example enzastaurin, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, sorafenib, sunitinib, regorafenib, everolimus, sirolimus or temsirolimus;

antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, for example the anti-vascular endothelial cell growth factor antibody 30 bevacizumab [AvastinTM], lenalidomide or thalidomide;

cell cycle inhibitors including for example CDK inhibitors (for example flavopiridol, roscovitine) and other inhibitors of cell cycle checkpoints; inhibitors of aurora kinase and

other kinases involved in mitosis and cytokinesis regulation;

proteasome inhibitors (for example lactacystin, bortezomib, epoxomicin);

HSP90 inhibitors (for example 17-AAG, AT-13387, KOS-953, KOS-1022, CNF-1010, CNF-2024, IPI-504, IPI-926, SNX 5422, STA-9090, VER-52296, PU-H17 or XL-888);

- 5 histone deacetylase inhibitors (for example SAHA, PXD101, JNJ-16241199, JNJ-26481585, SB939, ITF-2357, LBH589, PCI-24781, valproic acid, butyric acid, MS-275, MGCD0103 or FK-228); selective COX-2 inhibitors (for example celecoxib), or non selective NSAIDs (for example diclofenac, flurbiprofen, ibuprofen, ketoprofen, or naproxen).

- 10 In another aspect, a compound of general formula (I) can be used in combination with radiation therapy.

In yet another aspect, a compound of general formula (I) may be administered in combination with standard chemotherapy combinations such as, but not restricted to, CMF (cyclophosphamide, methotrexate and 5-fluorouracil), CAF (cyclophosphamide, 15 doxorubicin and 5-fluorouracil), AC (doxorubicin and cyclophosphamide), FEC (5-fluorouracil, epirubicin, and cyclophosphamide), ACT or ATC (doxorubicin, cyclophosphamide, and paclitaxel), or CMFP (cyclophosphamide, methotrexate, 5-fluorouracil and prednisone).

- 20 Preferably the pharmaceutical composition as defined above is in the form of tablets, capsules, oral preparations, powders, granules, pills, injectable or infusible liquid solutions, suspensions, emulsions, suppositories, ointments, creams, lotions, gels, pastes, transdermal delivery devices.

- The compounds of formula (I) can be pharmaceutically formulated according to known methods. The pharmaceutical compositions can be chosen on the basis of the treatment 25 requirements. Such compositions are prepared by blending and are suitably adapted to oral or parenteral administration, and as such can be administered in the form of tablets, capsules, oral preparations, powders, granules, pills, injectable, or infusible liquid solutions, suspensions, or suppositories.

- 30 Tablets and capsules for oral administration are normally presented in unit dose form and contain conventional excipients such as binders, fillers (including cellulose, mannitol, lactose), diluents, tableting agents, lubricants (including magnesium stearate), detergents, disintegrants (e.g. polyvinylpyrrolidone and starch derivatives such as sodium glycolate

starch), coloring agents, flavoring agents, and wetting agents (for example sodium lauryl sulfate).

The oral solid compositions can be prepared by conventional methods of blending, filling or tableting. The blending operation can be repeated to distribute the active principle throughout compositions containing large quantities of fillers. Such operations are conventional.

Oral liquid preparations can be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or can be presented as a dry product for reconstitution with water or with a suitable vehicle before use. Such liquid preparations can contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel, or hydrogenated edible fats; emulsifying agents, such as lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which can include edible oils), such as almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, such as methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired, conventional flavoring or coloring agents. Oral formulations also include conventional slow-release formulations such as enterically coated tablets or granules.

Pharmaceutical preparation for administration by inhalation can be delivered from an insufflator or a nebulizer pressurized pack.

For parenteral administration fluid unit dosages can be prepared, containing the compound and a sterile vehicle. The compound can be either suspended or dissolved, depending on the vehicle and concentration. The parenteral solutions are normally prepared by dissolving the compound in a vehicle, sterilising by filtration, filling suitable vials and sealing. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can also be dissolved in the vehicle. To increase stability, the composition can be frozen after having filled the vials and removed the water under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound can be suspended in the vehicle instead of being dissolved, and sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent can be included in the composition to facilitate uniform distribution of the compound of the invention.

For buccal or sublingual administration the compositions may be tablets, lozenges, pastilles, or gel.

The compounds can be pharmaceutically formulated as suppositories or retention enemas, e.g. containing conventional suppositories bases such as cocoa butter, polyethylene glycol, or other glycerides, for a rectal administration.

Another means of administering the compounds of the invention regards topical treatment. Topical formulations can contain for example ointments, creams, lotions, gels, solutions, pastes and/or can contain liposomes, micelles and/or microspheres. Examples of ointments include oleaginous ointments such as vegetable oils, animal fats, semisolid hydrocarbons, emulsifiable ointments such as hydroxystearin sulfate, anhydrous lanolin, hydrophilic petrolatum, cetyl alcohol, glycerol monostearate, stearic acid, water soluble ointments containing polyethylene glycols of various molecular weights. Creams, as known to formulation experts, are viscous liquids or semisolid emulsions, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase generally contains petrolatum and an alcohol such as cetyl or stearic alcohol. Formulations suitable for topical administration to the eye also include eye drops, wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient.

A further method of administering the compounds of the invention regards transdermal delivery. Typical transdermal formulations comprise conventional aqueous and non-aqueous vectors, such as creams, oils, lotions or pastes or can be in the form of membranes or medicated patches.

A reference for the formulations is the book by Remington ("Remington: The Science and Practice of Pharmacy", Lippincott Williams & Wilkins, 2000).

The compounds of the present invention may be employed alone as a sole therapy or in combination with other therapeutic agents for the treatment of the above-mentioned conditions.

The combination can be administered as separate compositions (simultaneous, sequential) of the individual components of the treatment or as a single dosage form containing both agents. When the compounds of this invention are in combination with others active ingredients, the active ingredients may be separately formulated into single-

ingredient preparations of one of the above-described forms and then provided as combined preparations, which are given at the same time or different times, or may be formulated together into a two- or more- ingredient preparation.

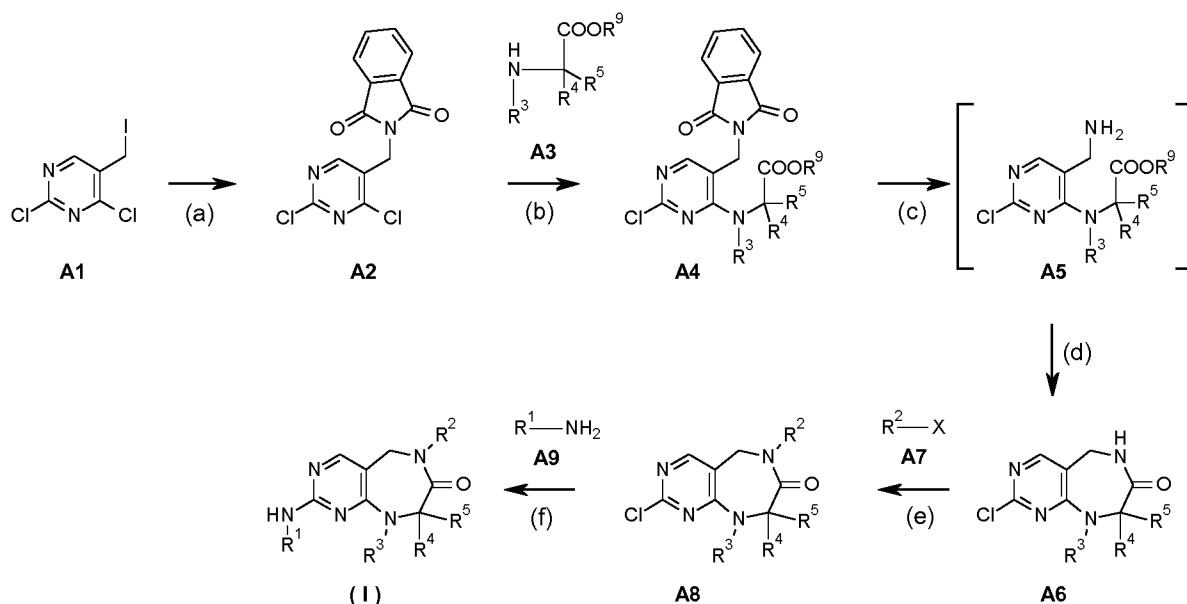
Compounds of general formula (I) may be administered to a patient in a total daily dose of, for example, from 0.001 to 1000 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose. The determination of optimum dosages for a particular patient is well known to one skilled in the art.

As is common practice, the compositions are normally accompanied by written or printed instructions for use in the treatment in question.

It is a further embodiment of the invention a kit comprising a compound as defined above and at least one therapeutic agent, preferably selected from the group consisting of: Mps1 inhibitors, antiproliferative/antineoplastic agents, cytostatic agents, agents which inhibit cancer cell invasion, inhibitors of growth factor function, antiangiogenic agents, cell cycle inhibitors, proteasome inhibitors, HSP90 inhibitors, selective COX-2 inhibitors histone deacetylase inhibitors, non selective NSAIDs or a chemotherapeutic agent for use in the treatment and/or prevention of cancer. Optionally, the compound of the invention and the at least one therapeutic agent are in separated containers.

It is a further embodiment of the present invention methods of synthesizing the compounds of general formula (I), and pharmaceutically acceptable salts, consisting in the reaction sequences outlined in Scheme A1 and Scheme A2:

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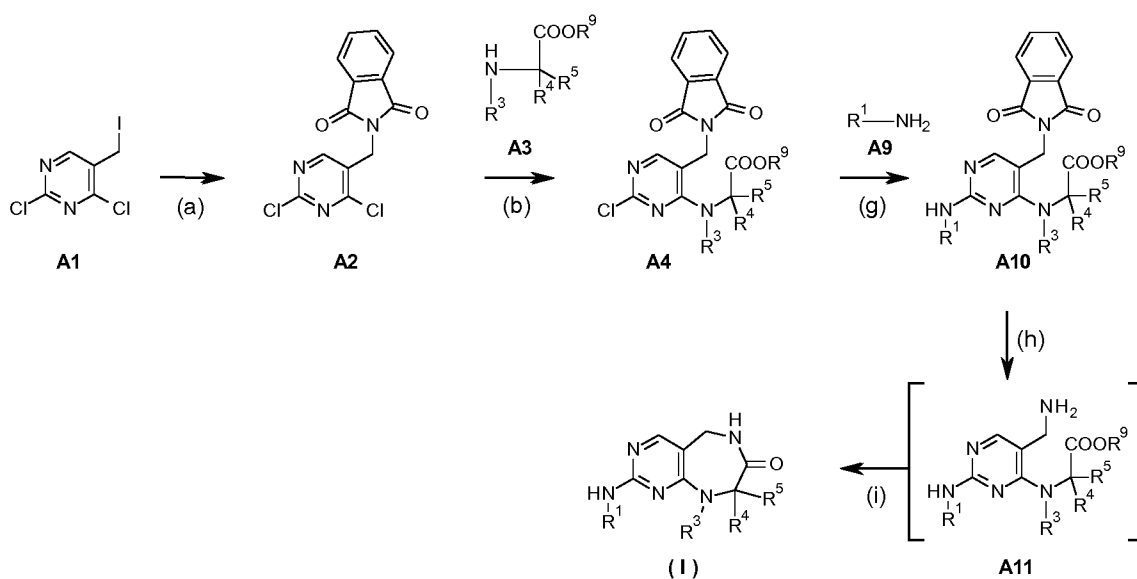
Scheme A1

wherein R^1 , R^2 , R^3 , R^4 and R^5 , are as defined herein above for formula (I), X is halogen, and R^9 is a methyl or ethyl. According to step (a) of the process, the 2-[(2,4-dichloropyrimidin-5-yl)methyl]isoindoline-1,3-dione **A2** is prepared by reaction of commercially available 2,4-dichloro-5-(iodomethyl)pyrimidine **A1** and potassium phthalimide in a suitable solvent, such as tetrahydrofuran or 1,4-dioxane at a temperature ranging from about 22°C to the reflux temperature of the reaction mixture. According to step (b) of the process, **A2** is then reacted with any suitable amino-ester of formula **A3** as to yield a compound of formula **A4**. The reaction is carried out in a suitable solvent, such as, for instance, tetrahydrofuran, 1,4-dioxane, dimethylformamide or N-methylpyrrolidinone in the presence of an opportune base such as triethylamine, N,N-diisopropylethylamine or pyridine at a temperature ranging from about 22°C and the reflux temperature of the reaction mixture. Preferably, the reaction is carried out in tetrahydrofuran in the presence of N,N-diisopropylethylamine. From the above, it is clear to the person skilled in the art that step (b) of the process may produce an admixture of regio-isomers; their separation to isolate the single isomer of formula **A4**, carried out according to conventional techniques, is still within the scope of the present invention. According to step (c) of the process, the phthalimido group of compounds of formula **A4** is removed by treatment with a suitable alkaline agent such as methylamine, ethylamine,

hydrazine, methylhydrazine, or phenylhydrazine in a solvent such as methanol, ethanol, tetrahydrofyrane, water, or a mixture thereof at a temperature ranging from about 22°C to the reflux temperature of the reaction mixture. Preferably, step (c) is carried out by treating a compound of formula **A4** with aqueous hydrazine in ethanol, tetrahydrofuran, or a mixture thereof at a temperature from about 22°C to the reflux temperature of the reaction mixture. Intra-molecular cyclization at step (d) may spontaneously occur in the reaction conditions above described for step (c), thus directly providing compounds of formula **A6**. Alternatively, according to step (d) of the process, an amino derivative of formula **A5** may be cyclized by treatment with a base such as, for instance, sodium methylate, sodium ethylate or potassium tert-butylate in a suitable solvent such as methanol, ethanol or tert-butanol at a temperature ranging from about 22°C and the reflux temperature of the reaction mixture. Preferably, step (d) is carried out by treating a compound of formula **A5** with sodium methylate in methanol, at a temperature from about 40°C to the reflux temperature of the reaction mixture. According to step (e) of the process, the lactamic nitrogen of a compound of formula **A6** may be alkylated to provide a compound of formula **A8** by reaction with a base such as, for instance, sodium hydride, potassium tert-butylate, lithium diisopropylamide and an opportune alkyl halide **A7** of formula R^2-X wherein R^2 is as defined above for compounds of formula (I) and X is halogen, preferably bromine or iodine. The reaction is carried out in a suitable solvent such as, for instance, tetrahydrofuran, N,N'-dimethylformamide or N,N'-dimethylacetamide at a temperature ranging from about -30°C to about 22°C. Preferably, step (e) is carried out by reaction of a compound of formula **A6**, sodium hydride, and a compound of formula **A7** in N,N'-dimethylacetamide at a temperature ranging from about -20°C to about 5°C. According to step (f) of the process, a 2-chloro-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one of formulae **A8** or **A6** may be coupled with an aniline **A9** of formula R^1-NH_2 wherein R^1 is as defined above to provide a compound of formula (I). The coupling reaction at step (f) may be carried out in a suitable solvent such as N,N'-dimethylformamide, dimethoxyethane, tert-butanol, 1,4-dioxane or acetonitrile in the presence of a catalyst such as, for example, palladium acetate or tris(dibenzylideneacetone)dipalladium, a base such as, for instance, potassium carbonate, potassium phosphate, or cesium carbonate and an organophosphorus ligand such as, for instance, 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) or 4,5-

Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) at a temperature ranging from about 22°C to about 180°C, optionally under microwave irradiation. Preferably, step (f) is carried out by reaction of a compound of formulae **A8** or **A6** with an aniline of formula R¹-NH₂ in the presence of potassium carbonate or cesium carbonate and catalytic amounts of tris(dibenzylideneacetone)dipalladium and 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene in tert-butanol or 1,4-dioxane at a temperature ranging from about 140°C to about 170°C, in sealed tube under microwave irradiation. Alternatively, step (f) of the process may be conveniently carried out by reaction of a compound of formulae **A8** or **A6** with an aniline **A9** of formula R¹-NH₂ in isopropyl alcohol at a temperature of about 160°C in sealed tube under microwave irradiation.

Alternatively, compounds of formula (I) can be prepared according to Scheme A2



Scheme A2

wherein R¹, R³, R⁴ and R⁵, are as defined herein above for formula (I), and R⁹ is a methyl or ethyl. According to step (g) of the process outlined in Scheme A2, a compound of formula **A4** obtained as described in Scheme A1 may be coupled with an aniline **A9** of formula R¹-NH₂ wherein R¹ is as defined above to provide a compound of formula **A10**. The coupling reaction at step (g) may be carried out in a suitable solvent such as N,N'-dimethylformamide, dimethoxyethane, tert-butanol, 1,4-dioxane or acetonitrile in the presence of a catalyst such as, for example, palladium acetate or tris(dibenzylideneacetone)dipalladium, a base such as, for instance, potassium carbonate, potassium phosphate, or cesium carbonate and an organophosphorus ligand such as, for

instance, 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) or 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) at a temperature ranging from about 22°C to about 180°C, optionally under microwave irradiation. Preferably, step (g) is carried out by reaction of a compound of formulae **A4** with an aniline of formula R^1-NH_2 in the presence of potassium carbonate or cesium carbonate and catalytic amounts of tris(dibenzylideneacetone)dipalladium and 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene in tert-butanol or 1,4-dioxane at a temperature ranging from about 140°C to about 170°C, in sealed tube under microwave irradiation. Alternatively, step (g) of the process may be conveniently carried out by reaction of a compound of formula **A4** with an aniline **A9** in isopropyl alcohol at a temperature of about 160°C in sealed tube under microwave irradiation.

According to step (h) of the process outlined in Scheme A2, the phthalimido group of compounds of formula **A10** is removed by treatment with a suitable alkaline agent such as methylamine, ethylamine, hydrazine, methylhydrazine, or phenylhydrazine in a solvent such as methanol, ethanol, tetrahydrofyrane, water, or a mixture thereof at a temperature ranging from about 22°C to the reflux temperature of the reaction mixture. Preferably, step (h) is carried out by treating a compound of formula **A10** with aqueous hydrazine in ethanol, tetrahydrofuran, or a mixture thereof at a temperature from about 22°C to the reflux temperature of the reaction mixture. Intra-molecular cyclization at step (i) may spontaneously occur in the reaction conditions above described for step (h), thus directly providing compounds of formula (I). Alternatively, according to step (i) of the process, an amino derivative of formula **A11** may be cyclized by treatment with a base such as, for instance, sodium methylate, sodium ethylate or potassium tert-butyrate in a suitable solvent such as methanol, ethanol or tert-butanol at a temperature ranging from about 22°C and the reflux temperature of the reaction mixture. Preferably, step (i) is carried out by treating a compound of formula **A11** with sodium methylate in methanol, at a temperature from about 40°C to the reflux temperature of the reaction mixture.

All of the compounds of formulae **A3**, **A7**, and **A9** are known or can be obtained according to known methods. As an example, the amino-esters of formula **A3** can be easily obtained by reaction between an amine of formula R^3NH_2 , wherein R^3 is as defined above for compounds of formula (I) and an opportune α -halogen acetate of formula XCH_2COOR^9 wherein R^9 is as defined above for compounds of formula **A3** and X is halogen, preferably

bromine. The reaction between an amine of formula R^3NH_2 and an opportune α -halogen acetate of formula XCH_2COOR^9 is carried out according to well-known operative conditions, in a suitable solvent, such as, for instance, tetrahydrofuran, 1,4-dioxane, or acetonitrile in the presence of an opportune proton scavenger such as triethylamine or N,N-diisopropylethylamine at a temperature ranging from about $-5^\circ C$ to about $22^\circ C$. Alternatively, the amino-esters of formula **A3** wherein R^3 is CH_2R^8 and R^8 is as defined above for formula (I) can be easily obtained by reaction between an opportune aldehyde of formula R^8CHO and a glycine ester of formula $NH_2-CH_2-COOR^9$ wherein R^9 is as defined above for compounds of formula **A3**.

The reaction between an aldehyde R^8CHO and a glycine ester of formula $NH_2-CH_2-COOR^9$ is carried out according to well-known operative conditions, in a suitable solvent, such as, for instance, methyl alcohol, ethyl alcohol, or 2,2,2-trifluoroethanol in the presence of an opportune reducing agent such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxymethylborohydride at a temperature ranging from about $10^\circ C$ to the reflux temperature of the reaction mixture.

When needed, the intermediate derivatives in Schemes A1 and A2 can be further manipulated using standard synthetic procedures.

As an additional example, compounds of formula (I), wherein the R^1 substituent is phenyl substituted by $CONR^6R^7$ or compound **52** can be conveniently prepared by coupling the opportune carboxylic acid and amine according to standard procedures well known in the art.

As it will be appreciated by the person skilled in the art, when, during the syntheses of compounds of formula (I) certain functional groups could give rise to unwanted side reactions, these groups need to be properly protected according to conventional techniques. Likewise, the conversion of these latter into the corresponding de-protected compounds may be carried out according to procedures well known to the person skilled in the art.

DETAILED DESCRIPTION OF THE INVENTION

EXPERIMENTAL PART

General methods

Reagents and solvents used, unless stated otherwise, were of commercially available

reagent grade quality and were used without further purification. Flash chromatography purifications were performed on Merck silica gel 60 (0.04–0.063 mm). Nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker 400 MHz spectrometer at 300K and are referenced in ppm (δ) relative to TMS. Coupling constants (J) are expressed in hertz (Hz). HPLC–MS experiments were performed either on an Acquity UPLC apparatus, equipped with a diode array and a Micromass SQD single quadrupole (Waters). The LC-MS experiments were performed according to the following methods:

Method A:

Column Acquity UPLC-BEH C18 (50 x 2.1 mm, 1.7 μm); Phase A: Milli-Q water/ CH_3CN 95/5 + 0.07% formic acid; Phase B: CH_3CN + 0.05% formic acid; flow rate: 0.6 ml/min; UV detection (DIODE array) from 210 to 400 nm; ESI+ detection in the 100-2000 m/z range; HPLC: Waters Acquity UPLC; MS: Waters SQD Single quadrupole (Waters).

Gradient: 0 min (A:98%, B:2%), 0-3.00 min (A:0%, B:100%), 3.00-3.50 min (A:0%, B:100%), 3.50-5.00 min (A:98%, B:2%).

UV detection wavelength: 254 nm.

Method B:

Column Acquity UPLC-BEH C18 (50 x 2.1 mm, 1.7 μm); Phase A: Milli-Q water/ CH_3CN 95/5 + 0.07% formic acid; Phase B: CH_3CN + 0.05% formic acid; flow rate: 0.6 ml/min; UV detection (DIODE array) from 210 to 400 nm; ESI+ detection in the 100-2000 m/z range; HPLC: Waters Acquity UPLC; MS: Waters SQD Single quadrupole (Waters).

Gradient: 0 min (A:98%, B:2%), 0-5.00 min (A:70%, B:30%), 5.00-5.50 min (A:0%, B:100%), 5.50-7.00 min (A:98%, B:2%). UV detection wavelength: 254 nm.

Method C:

Column Acquity UPLC-HSS T3 C18 (50 x 2.1 mm, 1.8 μm); Phase A: Milli-Q water/ CH_3CN 95/5 + 0.07% formic acid; Phase B: CH_3CN + 0.05% formic acid; flow rate: 0.6 ml/min; UV detection (DIODE array) from 210 to 400 nm; ESI+ detection in the 100-2000 m/z range; HPLC: Waters Acquity UPLC H-Class; MS: Waters SQD Single quadrupole (Waters).

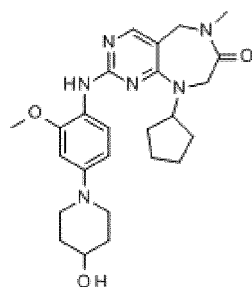
Gradient: 0 min (A:98%, B:2%), 0-3.00 min (A:0%, B:100%), 3.00-3.50 min (A:0%, B:100%), 3.50-5.00 min (A:98%, B:2%).

List of abbreviations:

TMS: tetramethylsilane; xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene;
 THF: tetrahydrofuran; DCM: dichloromethane; AcOEt: ethyl acetate; EDC: *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride; HOBT: 1-Hydroxybenzotriazole; DMF: *N,N*-dimethylformamide; (+)-BINAP: (R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl; MeOH: methyl alcohol; EtOH: ethyl alcohol; ADP: Adenosine diphosphate; ATP: Adenosine triphosphate; HEPES: 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; DTT: Dithiothreitol; DMSO: dimethyl sulfoxide;

Examples 1 and 2

10 9-cyclopentyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (1)

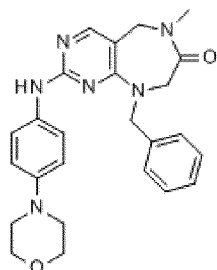


A mixture of 2-chloro-9-cyclopentyl-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (intermediate 68) (66 mg, 0.24 mmol), 1-(4-amino-3-methoxy-phenyl)piperidin-4-ol (55 mg, 0.25 mmol), tris(dibenzylideneacetone)dipalladium(0) (21.5 mg, 0.024 mmol), xantphos (27 mg, 0.047 mmol) and Cs₂CO₃ (153 mg, 0.47 mmol) in 1,4-dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 170 °C for 15 min. After cooling at room temperature the mixture was then filtered on a celite pad and the filtrate was concentrated and purified by flash chromatography (gradient: DCM/MeOH/NH₃aq from 98:2:0.2 to 96:4:0.4 to give 15 mg of the title compound.

¹H NMR (DMSO-d₆) δ: 7.80 (d, *J*=8.8 Hz, 1 H), 7.69 (s, 1 H), 7.30 (s, 1 H), 6.59 (d, *J*=2.0 Hz, 1 H), 6.43 (dd, *J*=2.4, 8.8 Hz, 1 H), 5.42–5.27 (m, 1 H), 4.66 (d, *J*=3.9 Hz, 1 H), 4.41 (s, 2 H), 4.12 (s, 2 H), 3.80 (s, 3 H), 3.64–3.54 (m, 1 H), 3.50–3.40 (m, 2 H), 2.89 (s, 3 H), 2.81–2.70 (m, 2 H), 1.88–1.42 (m, 12 H). LC-MS: Method B, *rt* = 2.10 min; *m/z* (ES⁺), (M + H)⁺ = 467.

By operating as above reported and by starting from the intermediate 119 the following compound was analogously prepared:

9-benzyl-6-methyl-2-{[4-(morpholin-4-yl)phenyl]amino}-5H,6H,7H,8H,9H-pyrimido[4,5-e][1,4]diazepin-7-one (2)

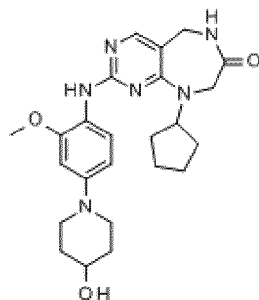


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^1H NMR (DMSO- d_6) δ : 8.82 (s, 1 H), 7.79 (s, 1 H), 7.41–7.35 (m, 2 H), 7.35–7.20 (m, 5 H), 6.74–6.68 (m, 2 H), 4.91 (s, 2 H), 4.47 (s, 2 H), 4.33 (s, 2 H), 3.76–3.63 (m, 4 H), 2.98–2.94 (m, 4 H), 2.93 (s, 3 H). LC-MS: Method C, r_t = 1.12 min; m/z (ES $^+$), (M + H) $^+$ = 440.

10 Examples 3 to 14 and Intermediate 117

9-cyclopentyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (3)



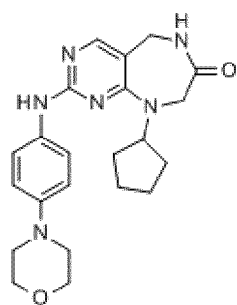
A mixture of ethyl 2-[cyclopentyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]pyrimidin-4-yl]amino]acetate (intermediate 53,) (95 mg, 0.151 mmol) and aqueous hydrazine (0.33 mmol) in MeOH (2 mL) and THF (2 mL) was stirred at the reflux temperature for about 4 h. The reaction mixture was concentrated under vacuum and the crude was taken up with DCM, filtered, and the resulting solution was concentrated and purified by flash chromatography (eluent DCM/MeOH/ NH_3 aq 95:5:0.5) to yield about 20 mg of the title compound.

^1H NMR (DMSO- d_6) δ : 8.18 (t, J =5.4 Hz, 1 H), 7.82 (d, J =8.8 Hz, 1 H), 7.67 (s, 1 H), 7.27 (s, 1 H), 6.59 (d, J =2.4 Hz, 1 H), 6.46–6.40 (m, 1 H), 5.41–5.29 (m, 1 H), 4.66 (d, J =4.4

Hz, 1 H), 4.15 (d, $J=5.4$ Hz, 2 H), 4.01 (s, 2 H), 3.80 (s, 3 H), 3.62–3.54 (m, 1 H), 3.48–3.40 (m, 2 H), 2.79–2.71 (m, 2 H), 1.85–1.78 (m, 2 H), 1.78–1.65 (m, 4 H), 1.60–1.43 (m, 6 H). LC-MS: Method C, $r_t = 0.69$ min; m/z (ES+), $(M + H)^+ = 453$.

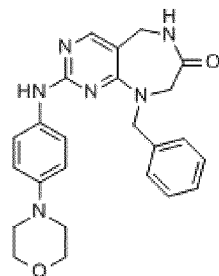
- 5 By operating as above reported and by starting from the suitable intermediates 54, 55, 56, 57, 81, 59, 87, 60, 82, 61, 83 and 67, the following compounds were analogously prepared:

9-cyclopentyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (4)



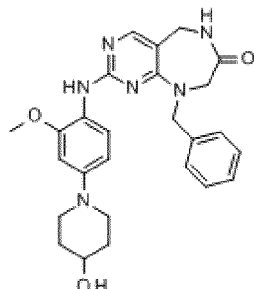
^1H NMR (DMSO- d_6) δ : 8.77 (s, 1 H), 8.25–8.12 (m, 1 H), 7.69 (s, 1 H), 7.58–7.48 (m, 2 H), 6.88–6.75 (m, 2 H), 5.50–5.35 (m, 1 H), 4.16 (d, $J=5.4$ Hz, 2 H), 4.02 (s, 2 H), 3.76–3.67 (m, 4 H), 3.04–2.93 (m, 4 H), 1.84–1.66 (m, 4 H), 1.56 (br. s., 4 H). LC-MS: Method A, $r_t = 1.08$ min; m/z (ES+), $(M + H)^+ = 409$.

9-benzyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (5)



^1H NMR (DMSO- d_6) δ : 8.79 (s, 1 H), 8.33–8.23 (m, 1 H), 7.76 (s, 1 H), 7.38 (d, $J=8.8$ Hz, 2 H), 7.34–7.26 (m, 4 H), 7.26–7.21 (m, 1 H), 6.76–6.66 (m, 2 H), 4.92 (s, 2 H), 4.23 (s, 2 H), 4.20 (d, $J=5.4$ Hz, 2 H), 3.73–3.67 (m, 4 H), 2.98–2.92 (m, 4 H). LC-MS: Method C, $r_t = 0.96$ min; m/z (ES+), $(M + H)^+ = 431$.

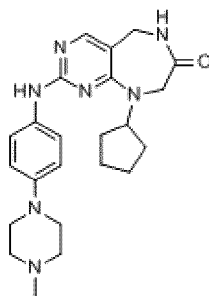
9-benzyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (6)



- 5 ^1H NMR (DMSO- d_6) δ : 8.25 (t, $J=5.6$ Hz, 1 H), 7.72 (s, 1 H), 7.63–7.54 (m, 1 H), 7.33–7.19 (m, 6 H), 6.55 (d, $J=2.4$ Hz, 1 H), 6.32–6.24 (m, 1 H), 4.85 (s, 2 H), 4.64 (d, $J=4.4$ Hz, 1 H), 4.23 (s, 2 H), 4.19 (d, $J=5.9$ Hz, 2 H), 3.76 (s, 3 H), 3.61–3.53 (m, 1 H), 3.45–3.37 (m, 2 H), 2.77–2.68 (m, 2 H), 1.84–1.75 (m, 2 H), 1.52–1.40 (m, 2 H). LC-MS: Method C, $r_t = 0.75$ min; m/z (ES $^+$), (M + H) $^+$ = 475.

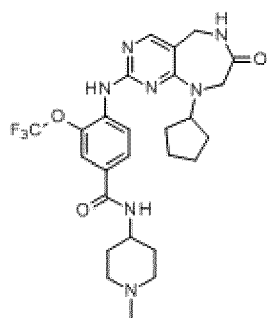
10

9-cyclopentyl-2-[4-(4-methylpiperazin-1-yl)anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (7)



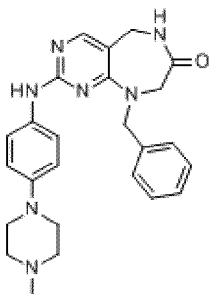
- 15 ^1H NMR (DMSO- d_6) δ : 8.75 (s, 1 H), 8.18 (t, $J=5.6$ Hz, 1 H), 7.69 (s, 1 H), 7.54–7.45 (m, 2 H), 6.88–6.75 (m, 2 H), 5.52–5.32 (m, 1 H), 4.16 (d, $J=5.4$ Hz, 2 H), 4.02 (s, 2 H), 3.07–2.97 (m, 4 H), 2.46–2.39 (m, 4 H), 2.21 (s, 3 H), 1.72 (br. s., 4 H), 1.55 (br. s., 4 H). LC-MS: Method C, $r_t = 0.52$ min; m/z (ES $^+$), (M + H) $^+$ = 422.

20 **4-[(9-cyclopentyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide (8)**



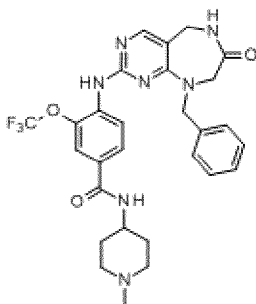
¹H NMR (DMSO-d₆) δ: 8.51 (s, 1 H), 8.30–8.18 (m, 3 H), 7.86–7.74 (m, 3 H), 5.40–5.28 (m, 1 H), 4.21 (d, *J*=5.4 Hz, 2 H), 4.06 (s, 2 H), 3.79–3.64 (m, 1 H), 2.82–2.71 (m, 2 H), 2.16 (s, 3 H), 1.98–1.88 (m, 2 H), 1.82–1.67 (m, 6 H), 1.64–1.48 (m, 6 H). LC-MS: Method C, rt = 0.73 min; *m/z* (ES⁺), (*M* + H)⁺ = 548.

9-benzyl-2-[4-(4-methylpiperazin-1-yl)anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (9)



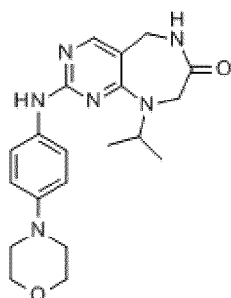
¹H NMR (DMSO-d₆) δ: 8.77 (s, 1 H), 8.26 (t, *J*=5.6 Hz, 1 H), 7.75 (s, 1 H), 7.41–7.20 (m, 7 H), 6.77–6.66 (m, 1 H), 4.92 (s, 2 H), 4.23 (s, 2 H), 4.20 (d, *J*=5.4 Hz, 2 H), 3.01 (br. s., 4 H), 2.53 (br. s., 4 H), 2.28 (br. s., 3 H). LC-MS: Method A, rt = 0.60 min; *m/z* (ES⁺), (*M* + H)⁺ = 444.

4-[(9-benzyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide (10)



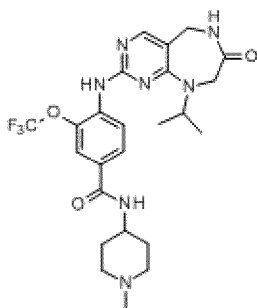
¹H NMR (DMSO-d₆) δ: 8.53 (s, 1 H), 8.34–8.28 (m, 1 H), 8.25 (d, *J*=6.8 Hz, 1 H), 8.00 (d, *J*=8.3 Hz, 1 H), 7.84 (s, 1 H), 7.78 (br. s., 1 H), 7.65 (d, *J*=8.8 Hz, 1 H), 7.34–7.18 (m, 5 H), 4.87 (br. s., 2 H), 4.28 (br. s., 2 H), 4.24 (d, *J*=3.9 Hz, 2 H), 3.71 (br. s., 1 H), 2.78 (br. s., 2 H), 2.18 (br. s., 3 H), 1.97 (br. s, 2 H), 1.82–1.69 (m, 2 H), 1.62–1.49 (m, 2 H). LC-MS: Method A, *rt* = 0.87 min; *m/z* (ES⁺), (*M* + *H*)⁺ = 570.

9-isopropyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-*e*][1,4]diazepin-7-one (11)



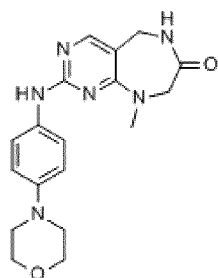
¹H NMR (DMSO-d₆) δ: 8.76 (s, 1 H), 8.21–8.10 (m, 1 H), 7.69 (s, 1 H), 7.57–7.47 (m, 2 H), 6.89–6.77 (m, 2 H), 5.36–5.23 (m, 1 H), 4.15 (d, *J*=5.4 Hz, 2 H), 4.03 (s, 2 H), 3.76–3.67 (m, 4 H), 3.04–2.96 (m, 4 H), 1.12 (d, *J*=6.8 Hz, 6 H). LC-MS: Method C, *rt* = 0.88 min; *m/z* (ES⁺), (*M* + *H*)⁺ = 383.

4-[(9-isopropyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-*e*][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide (12)



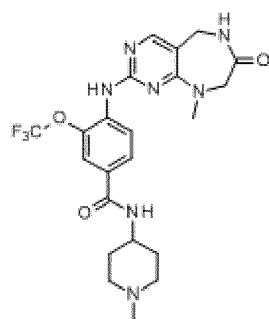
¹H NMR (DMSO-d₆) δ: 8.47 (s, 1 H), 8.31–8.16 (m, 3 H), 7.89–7.75 (m, 3 H), 5.28–5.12 (m, 1 H), 4.21 (d, *J*=5.4 Hz, 2 H), 4.07 (s, 2 H), 3.79–3.66 (m, 1 H), 2.83–2.72 (m, 2 H), 2.16 (s, 3 H), 2.00–1.87 (m, 2 H), 1.80–1.70 (m, 2 H), 1.64–1.50 (m, 2 H), 1.12 (d, *J*=6.8 Hz, 6 H). LC-MS: Method C, *rt* = 0.62 min; *m/z* (ES⁺), (*M* + *H*)⁺ = 522.

9-methyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one(13)



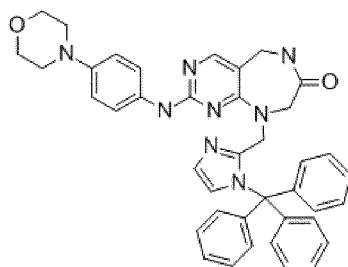
¹H NMR (DMSO-d₆) δ: 8.79 (s, 1 H), 8.27–8.16 (m, 1 H), 7.69 (s, 1 H), 7.59–7.51 (m, 2 H), 6.89–6.78 (m, 2 H), 4.21 (s, 2 H), 4.14 (d, *J*=5.9 Hz, 2 H), 3.76–3.68 (m, 4 H), 3.19 (s, 3 H), 3.04–2.95 (m, 4 H). LC-MS: Method A, *rt* = 0.73 min; *m/z* (ES⁺), (*M* + *H*)⁺ = 555.

4-[(9-methyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide (14)



¹H NMR (DMSO-d₆) δ: 8.48 (s, 1 H), 8.35–8.21 (m, 3 H), 7.88–7.76 (m, 3 H), 4.26 (s, 2 H), 4.19 (d, *J*=5.4 Hz, 2 H), 3.78–3.66 (m, 1 H), 3.18 (s, 3 H), 2.84–2.70 (m, 2 H), 2.17 (s, 3 H), 2.01–1.85 (m, 2 H), 1.80–1.70 (m, 2 H), 1.64–1.50 (m, 2 H). LC-MS: Method C, *rt* = 0.97 min; *m/z* (ES⁺), (*M* + *H*)⁺ = 494.

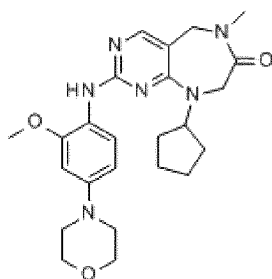
2-(4-morpholinoanilino)-9-[(1-tritylimidazol-2-yl)methyl]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (117)



LC-MS: Method A, rt = 1.45 min; m/z (ES+), (M + H)⁺ = 663.

Examples 15 to 38 and Intermediate 118

5 9-cyclopentyl-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (15)



10

A mixture of 2-chloro-9-cyclopentyl-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (intermediate 68,) (19 mg, 0.066 mmol) and 2-methoxy-4-morpholino-aniline (16 mg, 74 mmol) in isopropyl alcohol (0.3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 45 min. After cooling at room temperature the mixture was concentrated and purified by flash chromatography (eluent: DCM/MeOH/NH₃ aq. 98:1:1) to give 22 mg of the title compound.

15

¹H NMR (DMSO-d₆) δ: 7.89–7.82 (m, 1 H), 7.73–7.67 (s, 1 H), 7.35–7.26 (s, 1 H), 6.65–6.59 (s, 1 H), 6.47–6.39 (m, 1 H), 5.40–5.28 (m, 1 H), 4.44–4.40 (s, 2 H), 4.12 (s, 2 H), 3.81 (s, 3 H), 3.76–3.67 (m, 4 H), 3.08–3.02 (m, 4 H), 2.89 (s, 3 H), 1.79–1.46 (m, 8 H) .

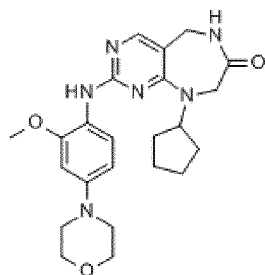
20

LC-MS: Method A, rt = 1.15 min; m/z (ES+), (M + H)⁺ = 453.

By operating as above reported and by starting from the suitable intermediates 80, 84, 68, 69, 79, 91, 85, 72, 73, 74, 75, 76, 77, and 86, the following compounds were analogously prepared:

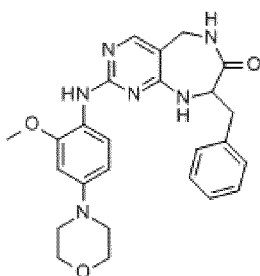
25

9-cyclopentyl-2-(2-methoxy-4-morpholino-anilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (16)



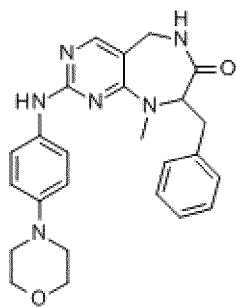
¹H NMR (DMSO-d₆) δ: 8.22–8.13 (m, 1 H), 7.86 (s, 1 H), 7.67 (s, 1 H), 7.30 (s, 1 H), 6.65–6.59 (m, 1 H), 6.47–6.39 (m, 1 H), 5.41–5.28 (m, 1 H), 4.19–4.10 (m, 2 H), 4.02 (s, 2 H),
 5 3.81 (s, 3 H), 3.77–3.69 (m, 4 H), 3.08–3.01 (m, 4 H), 1.82–1.43 (m, 8 H). LC-MS: Method A, rt = 1.09 min; m/z (ES+), (M + H)⁺ = 439.

8-benzyl-2-(2-methoxy-4-morpholino-anilino)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (17)



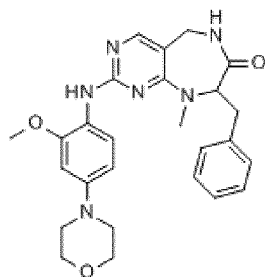
¹H NMR (DMSO-d₆) δ: 8.18–8.09 (m, 1 H), 8.03–7.95 (m, 1 H), 7.75–7.67 (s, 1 H), 7.42–7.13 (m, 6 H), 6.91–6.84 (m, 1 H), 6.64–6.58 (m, 1 H), 6.46–6.37 (m, 1 H), 4.92–4.85 (m, 1 H), 4.77–4.65 (m, 1 H), 3.80 (s, 3 H), 3.76–3.69 (m, 4 H), 3.67–3.56 (m, 1 H), 3.18–3.09 (m, 1 H), 3.07–2.99 (m, 4 H), 2.94–2.83 (m, 1 H). LC-MS: Method A, rt = 1.13 min; m/z
 15 (ES+), (M + H)⁺ = 461.

8-benzyl-9-methyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (18)



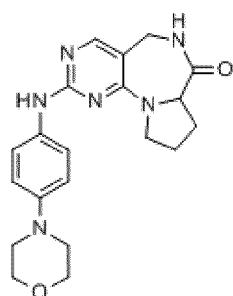
¹H NMR (DMSO-d₆) δ: 8.84 (s, 1 H), 8.13–8.03 (m, 1 H), 7.82 (s, 1 H), 7.53 (m, 2 H), 7.38–7.16 (m, 5 H), 6.83 (m, 2 H), 4.82–4.70 (m, 1 H), 4.44–4.31 (m, 1 H), 4.12–4.01 (m, 1 H), 3.75–3.68 (m, 4 H), 3.22 (m, 2 H), 3.07–2.95 (s,m, 7 H). LC-MS: Method A, rt = 1.18 min; m/z (ES⁺), (M + H)⁺ = 445.

8-benzyl-2-(2-methoxy-4-morpholino-anilino)-9-methyl-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (19)



¹H NMR (DMSO-d₆) δ: 8.14–8.04 (m, 1 H), 7.89 (m, 1 H), 7.80 (s, 1 H), 7.37–7.15 (m, 6 H), 6.62 (m, 1 H), 6.48–6.41 (m, 1 H), 4.81–4.71 (m, 1 H), 4.43–4.30 (m, 1 H), 4.12–4.02 (m, 1 H), 3.81 (s, 3 H), 3.76–3.69 (m, 4 H), 3.21 (m, 2 H), 3.08–2.96 (s,m, 7 H). LC-MS: Method A, rt = 1.22 min; m/z (ES⁺), (M + H)⁺ = 475.

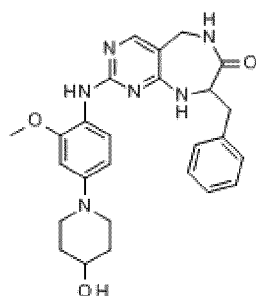
2-(4-morpholinoanilino)-5,6,7a,8,9,10-hexahydro-7H-pyrimido[5,4-f]pyrrolo[1,2-a][1,4]diazepin-7-one (20)



¹H NMR (DMSO-d₆) δ: 8.77 (s, 1 H), 8.27–8.15 (m, 1 H), 7.67 (s, 1 H), 7.58 (2m, 4 H), 5.09–5.02 (m, 1 H), 4.78–4.69 (m, 1 H), 3.75–3.68 (m, 4 H), 3.66–3.52 (2m, 3 H), 3.00 (m, 4 H), 2.45–2.33 (m, 1 H), 2.00–1.88 (m, 1 H), 1.88–1.74 (m, 2 H). LC-MS: Method A, rt = 0.85 min; m/z (ES+), (M + H)⁺ = 381.

5

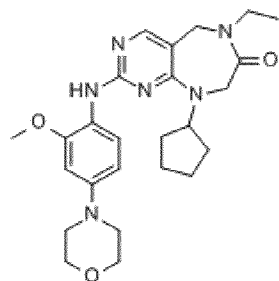
8-benzyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (21)



¹H NMR (DMSO-d₆) δ: 8.17–8.09 (m, 1 H), 7.97–7.90 (m, 1 H), 7.75–7.67 (s, 1 H), 7.41–7.17 (m, 5 H), 7.16–7.13 (s, 1 H), 6.88–6.84 (m, 1 H), 6.60–6.54 (m, 1 H), 6.45–6.34 (m, 1 H), 4.91–4.84 (m, 1 H), 4.75–4.68 (m, 1 H), 4.67–4.62 (m, 1 H), 3.79 (s, 3 H), 3.68–3.53 (m, 2 H), 3.49–3.38 (m, 2 H), 3.17–3.07 (m, 1 H), 2.94–2.84 (m, 1 H), 2.79–2.69 (m, 2 H), 1.87–1.73 (m, 2 H), 1.53–1.41 (m, 2 H). LC-MS: Method A, rt = 0.86 min; m/z (ES+), (M + H)⁺ = 475.

15

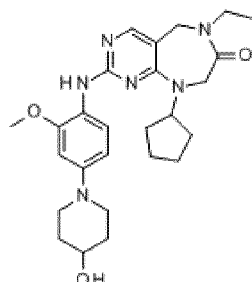
9-cyclopentyl-6-ethyl-2-(2-methoxy-4-morpholino-anilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (22)



¹H NMR (DMSO-d₆) δ: 7.90–7.84 (m, 1 H), 7.74 (s, 1 H), 7.31 (s, 1 H), 6.64–6.60 (m, 1 H), 6.47–6.40 (m, 1 H), 5.39–5.27 (m, 1 H), 4.44 (s, 2 H), 4.10 (s, 2 H), 3.81 (s, 3 H), 3.77–3.68 (m, 4 H), 3.41–3.34 (m, 2 H), 3.08–3.02 (m, 4H), 1.80–1.46 (m, 8 H), 1.05–0.95 (m, 3 H). LC-MS: Method A, rt = 1.25 min; m/z (ES+), (M + H)⁺ = 467.

20

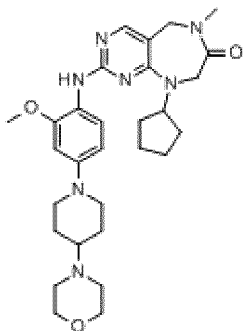
9-cyclopentyl-6-ethyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (23)



- 5 ¹H NMR (DMSO-d₆) δ: 7.72-7.69 (m, 1 H), 7.73 (s, 1 H), 7.28 (s, 1 H), 6.59-6.58 (m, 1 H), 6.46-6.36 (m, 1 H), 5.41-5.28 (m, 1 H), 4.69-4.63 (m, 1 H), 4.44 (s, 2 H), 4.10 (s, 2 H), 3.80 (s, 3 H), 3.62-3.53 (m, 1 H), 3.48-3.42 (m, 2 H), 3.40-3.33 (m, 2 H), 2.80-2.70 (m, 2 H), 1.86-1.42 (m, 12 H), 1.05-0.95 (m, 3 H). LC-MS: Method A, rt = 0.89 min; m/z (ES⁺), (M + H)⁺ = 481.

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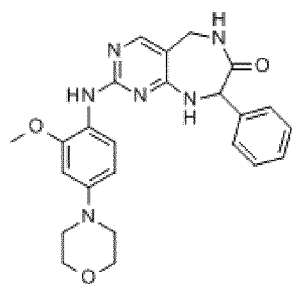
9-cyclopentyl-2-[2-methoxy-4-(4-morpholino-1-piperidyl)anilino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (24)



- 15 ¹H NMR (DMSO-d₆) δ: 7.85-7.76 (m, 1 H), 7.70 (s, 1 H), 7.42-7.25 (m, 1 H), 6.62-6.57 (m, 1 H), 6.48-6.38 (m, 1 H), 5.40-5.27 (m, 1 H), 4.42 (s, 2 H), 4.12 (s, 2 H), 3.80 (s, 3 H), 3.69-3.54 (2m, 6 H), 2.89 (s, 3 H), 2.66-2.55 (m, 2 H), 2.50 (m, 4 H), 2.32-2.18 (m, 1 H), 1.94-1.42 (m, 12 H). LC-MS: Method A, rt = 0.71 min; m/z (ES⁺), (M + H)⁺ = 536.

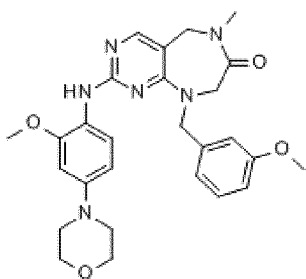
2-(2-methoxy-4-morpholino-anilino)-8-phenyl-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (25)

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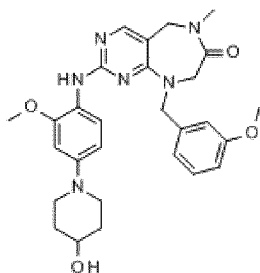
¹H NMR (DMSO-d₆) δ: 8.35–8.28 (m, 1 H), 7.98 (s, 1 H), 7.89–7.82 (m, 1 H), 7.67 (s, 1 H), 7.46–7.25 (m, 6 H), 6.66–6.62 (m, 1 H), 6.49–6.41 (m, 1 H), 5.12–5.06 (m, 1 H), 3.83 (s, 3 H), 3.78–3.69 (m, 4 H), 3.59–3.37 (m, 2 H), 3.10–3.01 (m, 4 H). LC-MS: Method A, rt = 0.94 min; m/z (ES⁺), (M + H)⁺ = 447.

2-(2-methoxy-4-morpholino-anilino)-9-[(3-methoxyphenyl)methyl]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (26)



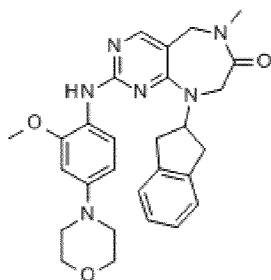
¹H NMR (DMSO-d₆) δ: 7.77 (s, 1 H), 7.68–7.59 (m, 1 H), 7.48–7.31 (br.s., 1 H), 7.25–6.76 (m, 4 H), 6.60–6.55 (m, 1 H), 6.34–6.25 (m, 1 H), 4.82 (s, 2 H), 4.46 (s, 2 H), 4.36 (s, 2 H), 3.80–3.66 (2s,m, 10 H), 3.05–2.98 (m, 4 H), 2.92 (s, 3 H). LC-MS: Method C, rt = 1.04 min; m/z (ES⁺), (M + H)⁺ = 505.

2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-9-[(3-methoxyphenyl)methyl]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (27)



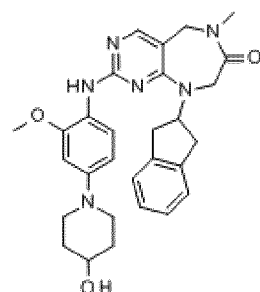
¹H NMR (DMSO-d₆) δ: 7.75 (m, 1 H), 7.63–7.56 (m, 1 H), 7.32 (s, 1 H), 7.24–6.76 (m, 4 H), 6.58–6.53 (m, 1 H), 6.32–6.24 (m, 1 H), 4.81 (s, 2 H), 4.69–4.62 (m, 1 H), 4.45 (s, 2 H), 4.35 (s, 2 H), 3.78–3.65 (2s, 6 H), 3.61–3.51 (m, 1 H), 3.46–3.36 (m, 2 H), 2.92 (s, 3 H), 2.78–2.67 (m, 2 H), 1.85–1.40 (2m, 4 H). LC-MS: Method A, rt = 0.80 min; m/z (ES⁺), (M + H)⁺ = 519.

9-indan-2-yl-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (28)



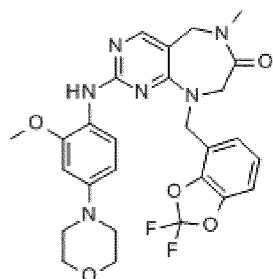
¹H NMR (DMSO-d₆) δ: 7.87–7.82 (m, 1 H), 7.75 (s, 1 H), 7.43–7.37 (m, 1 H), 7.28–7.14 (m, 4 H), 6.62–6.55 (m, 1 H), 6.42–6.34 (m, 1 H), 5.95–5.83 (m, 1 H), 4.44 (s, 2 H), 4.15 (s, 2 H), 3.79 (s, 3 H), 3.70 (m, 4 H), 3.17–2.97 (m, 8 H), 2.90 (s, 3 H). LC-MS: Method B, rt = 4.48 min; m/z (ES⁺), (M + H)⁺ = 501.

2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-9-indan-2-yl-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (29)

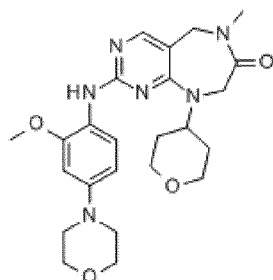


¹H NMR (DMSO-d₆) δ: 7.82–7.77 (m, 1 H), 7.74 (s, 1 H), 7.37 (s, 1 H), 7.28–7.14 (m, 4 H), 6.58–6.54 (m, 1 H), 6.40–6.33 (m, 1 H), 5.96–5.85 (m, 1 H), 4.67–4.61 (m, 1 H), 4.44 (s, 2 H), 4.15 (s, 2 H), 3.78 (s, 3 H), 3.61–3.50 (m, 1 H), 3.45–3.36 (m, 2 H), 3.16–2.97 (m, 4 H), 2.90 (s, 3 H), 2.75–2.65 (m, 2 H), 1.85–1.39 (m, 4 H). LC-MS: Method A, rt = 0.99 min; m/z (ES⁺), (M + H)⁺ = 515.

9-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (30)

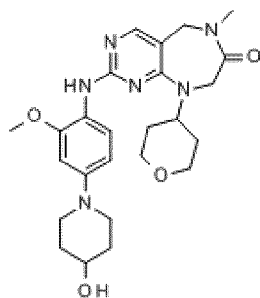


- 5 ^1H NMR (DMSO- d_6) δ : 7.80 (s, 1 H), 7.60–7.47 (m, 1 H), 7.36 (s, 1 H), 7.32–6.90 (3m, 3 H), 6.60–6.54 (m, 1 H), 6.24–6.16 (m, 1 H), 4.91 (s, 2 H), 4.52–4.39 (2s, 4 H), 3.76 (s, 3 H), 3.73–3.68 (m, 4 H), 3.04–2.97 (m, 4 H), 2.92 (s, 3 H). LC-MS: Method A, r_t = 1.13 min; m/z (ES $^+$), (M + H) $^+$ = 555.
- 10 **2-(2-methoxy-4-morpholino-anilino)-6-methyl-9-tetrahydropyran-4-yl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (31)**



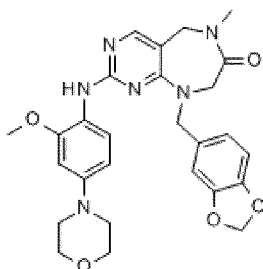
- ^1H NMR (DMSO- d_6) δ : 7.81–7.77 (m, 1 H), 7.73 (s, 1 H), 7.40 (s, 1 H), 6.65–6.60 (m, 1 H), 6.50–6.43 (m, 1 H), 5.06–4.90 (m, 1 H), 4.42 (s, 2 H), 4.16 (s, 2 H), 3.94 (m, 2 H), 3.81 (s, 3 H), 3.76–3.71 (m, 4 H), 3.34–3.29 (m, 2 H), 3.10–3.03 (m, 4 H), 2.89 (s, 3 H), 1.80–1.40 (2m, 4 H). LC-MS: Method A, r_t = 2.16 min; m/z (ES $^+$), (M + H) $^+$ = 469.
- 15

2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6-methyl-9-tetrahydropyran-4-yl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (32)



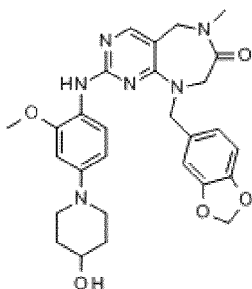
¹H NMR (DMSO-d₆) δ : 7.77–7.68 (m,s, 2 H), 7.37 (s, 1 H), 6.61–6.58 (m, 1 H), 6.48–6.43 (m, 1 H), 5.05–4.91 (m, 1 H), 4.68–4.64 (m, 1 H), 4.42 (s, 2 H), 4.16 (s, 2 H), 4.00–3.90 (m, 2 H), 3.79 (s, 3 H), 3.65–3.53 (m, 1 H), 3.50–3.42 (m, 2 H), 3.36–3.28 (m, 2 H), 2.89 (s, 3 H), 2.81–2.72 (m, 2 H), 1.88–1.38 (m, 8 H). LC-MS: Method B, rt = 1.23 min; m/z (ES⁺), (M + H)⁺ = 483.

9-(1,3-benzodioxol-5-ylmethyl)-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (33)



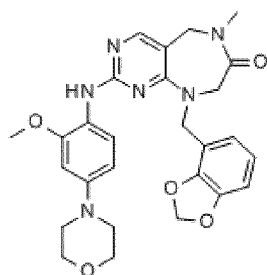
¹H NMR (DMSO-d₆) δ : 7.75 (s, 1 H), 7.67–7.62 (m, 1 H), 7.41 (s, 1 H), 6.85–6.69 (m, 3 H), 6.61–6.58 (m, 1 H), 6.38–6.32 (m, 1 H), 5.96 (s, 2 H), 4.71 (s, 2 H), 4.43 (s, 2 H), 4.31 (s, 2 H), 3.78 (s, 3 H), 3.73–3.69 (m, 4 H), 3.06–3.00 (m, 4 H), 2.90 (s, 3 H). LC-MS: Method A, rt = 1.15 min; m/z (ES⁺), (M + H)⁺ = 519.

9-(1,3-benzodioxol-5-ylmethyl)-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (34)



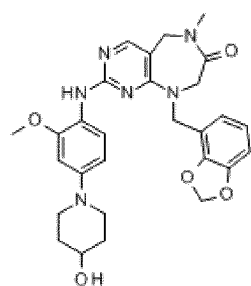
¹H NMR (DMSO-d₆) δ: 7.74 (s, 1 H), 7.64–7.56 (m, 1 H), 7.38 (s, 1 H), 6.83–6.70 (m, 3 H), 6.58–6.56 (m, 1 H), 6.38–6.29 (m, 1 H), 5.96 (s, 2 H), 4.71 (s, 2 H), 4.67–4.64 (m, 1 H), 4.43 (s, 2 H), 4.30 (s, 2 H), 3.77 (s, 3 H), 3.63–3.53 (m, 1 H), 3.47–3.37 (m, 2 H), 2.90 (s, 3 H), 2.80–2.68 (m, 2 H), 1.84–1.74 (m, 2 H), 1.53–1.40 (m, 2 H). LC-MS: Method A, rt = 0.91 min; m/z (ES⁺), (M + H)⁺ = 533.

9-(1,3-benzodioxol-4-ylmethyl)-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (35)



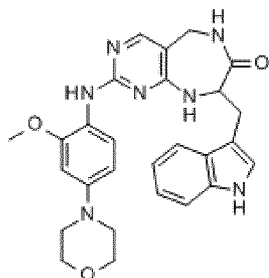
¹H NMR (DMSO-d₆) δ: 7.76 (s, 1 H), 7.68–7.62 (m, 1 H), 7.37 (s, 1 H), 6.83–6.62 (m, 3 H), 6.61–6.56 (m, 1 H), 6.35–6.27 (m, 1 H), 6.02 (s, 2 H), 4.78 (s, 1 H), 4.45 (s, 2 H), 4.35 (s, 2 H), 3.78 (s, 3 H), 3.74–3.68 (m, 4 H), 3.05–2.99 (m, 4 H), 2.91 (s, 3 H). LC-MS: Method A, rt = 1.17 min; m/z (ES⁺), (M + H)⁺ = 519.

9-(1,3-benzodioxol-4-ylmethyl)-2-[[4-(4-hydroxy-1-piperidyl)-2-methoxy-phenyl]amino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (36)



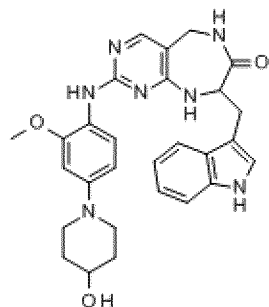
¹H NMR (DMSO-d₆) δ: 7.76 (s, 1 H), 7.64–7.55 (m, 1 H), 7.35 (s, 1 H), 6.84–6.61 (m, 3 H), 6.59–6.54 (m, 1 H), 6.33–6.26 (m, 1 H), 6.01 (s, 2 H), 4.78 (s, 2 H), 4.65 (d, J=4.4 Hz, 1 H), 4.44 (s, 2 H), 4.35 (s, 2 H), 3.77 (s, 3 H), 3.63–3.53 (m, 1 H), 3.46–3.37 (m, 2 H), 2.91 (s, 3 H), 2.77–2.69 (m, 2 H), 1.84–1.73 (m, 2 H), 1.53–1.39 (m, 2 H). LC-MS: Method A, rt = 0.87 min; m/z (ES⁺), (M + H)⁺ = 533.

8-(1H-indol-3-ylmethyl)-2-[(2-methoxy-4-morpholino-phenyl)amino]-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (37)



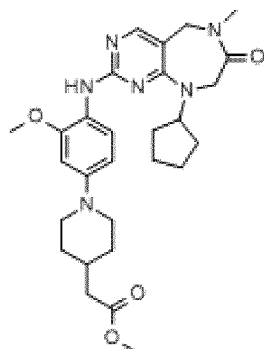
¹H NMR (DMSO-d₆) δ = 10.92–10.82 (m, 1 H), 8.19–8.14 (m, 1 H), 8.00 (d, *J*=8.8 Hz, 1 H), 7.71 (s, 1 H), 7.63–7.57 (m, 1 H), 7.36–7.31 (m, 1 H), 7.28 (d, *J*=2.2 Hz, 1 H), 7.17 (s, 1 H), 7.10–7.04 (m, 1 H), 7.02–6.95 (m, 1 H), 6.70–6.65 (m, 1 H), 6.62–6.56 (m, 1 H), 6.45–6.38 (m, 1 H), 4.90–4.83 (m, 1 H), 4.71–4.63 (m, 1 H), 3.75–3.71 (m, 4 H), 3.69–3.62 (m, 1 H), 3.28–3.19 (m, 1 H), 3.06–2.97 (m, 5 H). LC-MS: Method A, *rt* = 1.14 min; *m/z* (ES⁺), (*M* + *H*)⁺ = 500.

2-[[4-(4-hydroxy-1-piperidyl)-2-methoxy-phenyl]amino]-8-(1H-indol-3-ylmethyl)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (38)



¹H NMR (DMSO-d₆) δ: 10.86 (s, 1 H), 8.16 (t, *J*=6.0 Hz, 1 H), 7.94 (d, *J*=8.8 Hz, 1 H), 7.70 (s, 1 H), 7.61 (d, *J*=8.2 Hz, 1 H), 7.34 (d, *J*=7.7 Hz, 1 H), 7.29–6.96 (m, 4 H), 6.65 (d, *J*=2.7 Hz, 1 H), 6.57 (d, *J*=2.2 Hz, 1 H), 6.41 (dd, *J*=2.5, 9.1 Hz, 1 H), 4.86 (d, *J*=3.8 Hz, 1 H), 4.66 (d, *J*=3.8 Hz, 2 H), 3.78 (s, 3 H), 3.65 (d, *J*=9.3 Hz, 1 H), 3.58 (d, *J*=4.4 Hz, 1 H), 3.47–3.39 (m, 2 H), 3.21 (d, *J*=6.6 Hz, 1 H), 3.02 (d, *J*=7.7 Hz, 1 H), 2.78–2.71 (m, 2 H), 1.85–1.77 (m, 2 H), 1.53–1.42 (m, 2 H). LC-MS: Method A, *rt* = 0.87 min; *m/z* (ES⁺), (*M* + *H*)⁺ = 514.

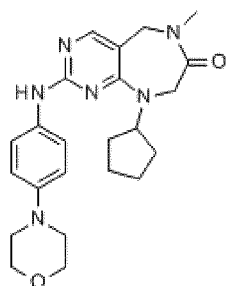
methyl 2-[1-[4-[(9-cyclopentyl-6-methyl-7-oxo-5,8-dihydropyrimido[4,5-e][1,4]diazepin-2-yl)amino]-3-methoxy-phenyl]-4-piperidyl]acetate (118)



¹H NMR (DMSO-d₆) δ: 7.84–7.77 (m, 1 H), 7.70 (s, 1 H), 7.31 (s, 1 H), 6.61–6.55 (m, 1 H), 6.46–6.40 (m, 1 H), 5.42–5.25 (m, 1 H), 4.42 (s, 2 H), 4.12 (s, 2 H), 3.80 (s, 3 H), 3.60 (s, m, 5 H), 2.89 (s, 3 H), 2.66–2.54 (m, 2 H), 2.31–2.27 (m, 2 H), 1.88–1.23 (m, 13 H). LC-MS: Method A, rt = 1.21 min; m/z (ES⁺), (M + H)⁺ = 523.

10 **Examples 39 to 47**

9-cyclopentyl-6-methyl-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (39)

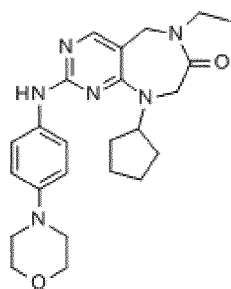


A mixture of 2-chloro-9-cyclopentyl-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (intermediate 68) (47 mg, 0.167 mmol), 4-morpholinoaniline (36 mg, 0.20 mmol), tris(dibenzylideneacetone)dipalladium(0) (12 mg, 0.012 mmol), xantphos (39 mg, 0.07 mmol) and K₂CO₃ (69 mg, 0.50 mmol) in tert-butyl alcohol (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 6 h. After cooling at room temperature the mixture was then filtered on a celite pad and the filtrate was concentrated and purified by flash chromatography (eluent: DCM/MeOH 97:3) to give 34 mg of the title compound.

^1H NMR (DMSO- d_6) δ : 8.84–8.76 (br. s., 1 H), 7.73 (s, 1 H), 7.56–6.76 (2m, 4 H), 5.49–5.33 (m, 1 H), 4.42 (s, 2 H), 4.13 (s, 2 H), 3.75–3.66 (m, 4 H), 3.03–2.96 (m, 4 H), 2.90 (s, 3 H), 1.79–1.48 (m, 8 H). LC-MS: Method A, r_t = 1.09 min; m/z (ES+), $(M + H)^+$ = 423.

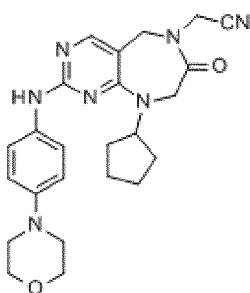
- 5 By operating as above reported and by starting from the suitable intermediates 68, 69, 70, 71, 84, and 78, the following compounds were analogously prepared:

9-cyclopentyl-6-ethyl-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (40)



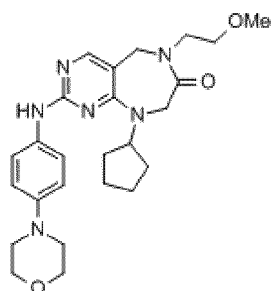
- 10 ^1H NMR (DMSO- d_6) δ : 8.80 (s, 1 H), 7.76 (s, 1 H), 7.56–6.77 (2m, 4 H), 5.51–5.35 (m, 1 H), 4.44 (s, 2 H), 4.11 (s, 2 H), 3.74–3.67 (m, 4 H), 3.37 (m, 2 H), 3.03–2.94 (m, 4 H), 1.78–1.47 (m, 8 H), 1.01 (m, 3 H). LC-MS: Method A, r_t = 1.19 min; m/z (ES+), $(M + H)^+$ = 437.

- 15 **2-(9-cyclopentyl-2-{[4-(morpholin-4-yl)phenyl]amino}-7-oxo-5H,6H,7H,8H,9H-pyrimido[4,5-e][1,4]diazepin-6-yl)acetonitrile (41)**



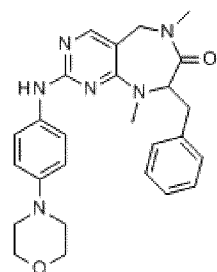
- ^1H NMR (DMSO- d_6) δ : 8.87 (s, 1 H), 7.75 (s, 1 H), 7.56–6.78 (2m, 4 H), 5.47–5.33 (m, 1 H), 4.60 (s, 2 H), 4.50 (s, 2 H), 4.20 (s, 2 H), 3.77–3.65 (m, 4 H), 3.03–2.95 (m, 4 H), 1.83–1.44 (m, 8 H). LC-MS: Method A, r_t = 1.20 min; m/z (ES+), $(M + H)^+$ = 448.
- 20

9-cyclopentyl-6-(2-methoxyethyl)-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (42)



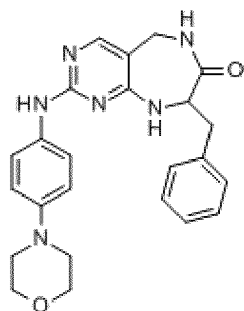
¹H NMR (DMSO-d₆) δ: 8.85–8.75 (br. s., 1 H), 7.72 (s, 1 H), 7.58–6.74 (2m, 4 H), 5.48–5.31 (m, 1 H), 4.47 (s, 2 H), 4.13 (s, 2 H), 3.76–3.67 (m, 4 H), 3.54–3.47 (m, 2 H), 3.41–3.35 (m, 2 H), 3.18 (s, 3 H), 3.03–2.95 (m, 4 H), 1.83–1.46 (m, 8 H). LC-MS: Method A, rt = 1.18 min; m/z (ES⁺), (M + H)⁺ = 467.

8-benzyl-6,9-dimethyl-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (43)



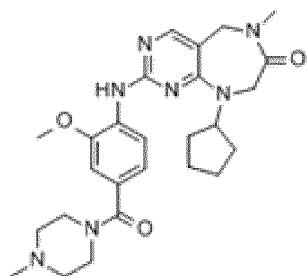
¹H NMR (DMSO-d₆) δ: 8.90–8.80 (br. s., 1 H), 7.84 (s, 1 H), 7.55–6.77 (m, 9 H), 5.05–4.96 (m, 1 H), 4.88–4.77 (m, 1 H), 4.23–4.12 (m, 1 H), 3.74–3.66 (m, 4 H), 3.25–3.19 (m, 2 H), 3.05–2.84 (m, 2s, 10 H). LC-MS: Method A, rt = 1.21 min; m/z (ES⁺), (M + H)⁺ = 459.

8-benzyl-2-(4-morpholinoanilino)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (44)



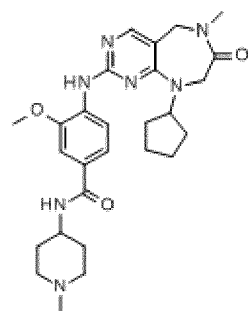
¹H NMR (CDCl₃) δ: 7.70 (s, 1 H), 7.42–6.81 (m, 10 H), 6.23 (br. s., 1 H), 5.04 (br. s., 1 H), 4.88–4.82 (m, 1 H), 4.77 (m, 1 H), 3.91–3.84 (m, 4 H), 3.79 (m, 1 H), 3.53–3.40 (m, 1 H), 3.16–3.07 (m, 4 H), 2.95 (m, 1 H). LC-MS: Method A, rt = 1.09 min; m/z (ES⁺), (M + H)⁺ = 431.

9-cyclopentyl-2-[2-methoxy-4-(4-methylpiperazine-1-carbonyl)anilino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (45)



¹H NMR (DMSO-d₆) δ: 8.33–8.25 (m, 1 H), 7.81 (s, 1 H), 7.60 (s, 1 H), 7.01–6.99 (m, 1 H), 6.96–6.90 (m, 1 H), 5.43–5.31 (m, 1 H), 4.47 (s, 2 H), 4.16 (s, 2 H), 3.88 (s, 3 H), 3.63–3.41 (m, 4 H), 2.91 (s, 3 H), 2.37–2.25 (m, 4 H), 2.19 (s, 3 H), 1.84–1.47 (m, 8 H). LC-MS: Method A, rt = 0.57 min; m/z (ES⁺), (M + H)⁺ = 494.

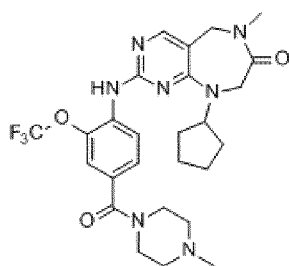
4-[(9-cyclopentyl-6-methyl-7-oxo-5,8-dihydropyrimido[4,5-e][1,4]diazepin-2-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (46)



^1H NMR (DMSO- d_6) δ : 8.37–8.31 (m, 1 H), 8.13–8.05 (m, 1 H), 7.83 (s, 1 H), 7.64–7.40 (s,m, 3 H), 5.44–5.31 (m, 1 H), 4.48 (s, 2 H), 4.17 (s, 2 H), 3.92 (s, 3 H), 3.78–3.66 (m, 1 H), 2.91 (s, 3 H), 2.81–2.71 (m, 2 H), 2.16 (s, 3 H), 1.97–1.86 (m, 2 H), 1.83–1.51 (m, 12 H). LC-MS: Method A, r_t = 0.67 min; m/z (ES $^+$), (M + H) $^+$ = 508.

5

9-cyclopentyl-6-methyl-2-[4-(4-methylpiperazine-1-carbonyl)-2-(trifluoromethoxy)anilino]-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (47)



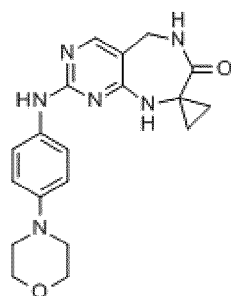
^1H NMR (DMSO- d_6) δ : 8.59 (s, 1 H), 8.11–8.08 (m, 1 H), 7.79 (s, 1 H), 7.38–7.30 (m, 2 H), 5.37–5.23 (m, 1 H), 4.46 (s, 2 H), 4.15 (s, 2 H), 3.71–3.41 (m, 4 H), 2.90 (s, 3 H), 2.40–2.24 (m, 4H), 2.19 (s, 3 H), 1.79–1.42 (m, 8 H). LC-MS: Method A, r_t = 0.75 min; m/z (ES $^+$), (M + H) $^+$ = 548.

10

Examples 48 to 50

2-(4-morpholinoanilino)spiro[6,9-dihydro-5H-pyrimido[4,5-e][1,4]diazepine-8,1'-cyclopropane]-7-one (48)

15



A mixture of ethyl 1-[[5-(aminomethyl)-2-(4-morpholinoanilino)pyrimidin-4-yl]amino]cyclopropanecarboxylate (intermediate 88) (34 mg, 0.082 mmol) and sodium methylate (6.7 mg, 0.12 mmol) in methyl alcohol (1 mL) was stirred at the reflux temperature for 2 h.

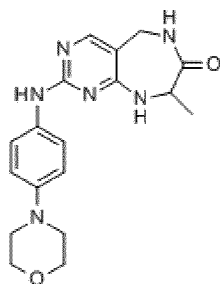
20

After cooling, the reaction mixture was concentrated under vacuum and the residue purified by silica gel chromatography (eluent DCM/MeOH/NH₄OHaq 64:6:0.6) to yield 22 mg of the target compound as a white solid.

¹H NMR (DMSO-d₆) δ: 8.68 (s, 1 H), 8.19–8.12 (m, 1 H), 7.79 (s, 1 H), 7.60–7.53 (m, 2 H), 7.43 (s, 1 H), 6.85–6.76 (m, 2 H), 4.20 (d, *J*=5.9 Hz, 2 H), 3.76–3.68 (m, 4 H), 3.03–2.92 (m, 4 H), 1.17–1.10 (m, 2 H), 1.07–0.98 (m, 2 H). LC-MS: Method C, *rt* = 0.68 min; *m/z* (ES⁺), (M + H)⁺ = 367.

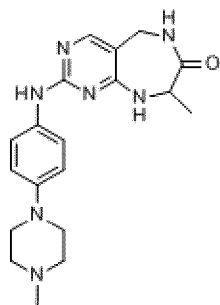
By operating as above reported and by starting from the suitable intermediates 89, 90 the following compounds were analogously prepared:

8-methyl-2-(4-morpholinoanilino)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (49)



¹H NMR (DMSO-d₆) δ: 8.72 (s, 1 H), 8.20 (br. s, 1 H), 7.79 (s, 1 H), 7.72–7.63 (m, 2 H), 6.95–6.83 (m, 3 H), 4.86–4.79 (m, 1 H), 4.78–4.70 (m, 1 H), 3.84–3.76 (m, 4 H), 3.72–3.64 (m, 1 H), 3.11–3.00 (m, 4 H), 1.30 (d, *J*=6.4 Hz, 3 H). LC-MS: Method A, *rt* = 0.74 min; *m/z* (ES⁺), (M + H)⁺ = 355.

8-methyl-2-[4-(4-methylpiperazin-1-yl)anilino]-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (50)

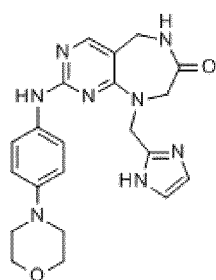


^1H NMR (DMSO- d_6) δ : 8.61 (s, 1 H), 8.18–8.07 (m, 1 H), 7.71 (s, 1 H), 7.62–7.52 (m, 2 H), 6.86–6.74 (m, 3 H), 4.79–4.71 (m, 1 H), 4.71–4.62 (m, 1 H), 3.67–3.55 (m, 1 H), 3.01 (br. s., 4 H), 2.43 (br. s., 4 H), 2.20 (s, 3 H), 1.22 (d, $J=6.4$ Hz, 3 H). LC-MS: Method A, $r_t=0.25$ min; m/z (ES+), $(M + H)^+ = 368$.

5

Example 51

9-(1H-imidazol-2-ylmethyl)-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (51)



10

A solution of 2-(4-morpholinoanilino)-9-[(1-tritylimidazol-2-yl)methyl]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (intermediate 117) (59 mg, 0.09 mmol) and trifluoroacetic acid (0.2 mL) in DCM (4 mL) was stirred at room temperature for 75 min. Then the reaction mixture was concentrated under reduced pressure and purified by reverse phase chromatography to yield 21 mg of the target compound as an off white solid.

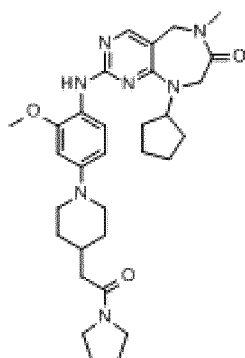
15

^1H NMR (DMSO- d_6) δ : 12.09 (br. s, 1 H), 8.83 (s, 1 H), 8.23 (t, $J=5.4$ Hz, 1 H), 7.76 (s, 1 H), 7.51–7.27 (m, 2 H), 7.01 (br. s., 2 H), 6.87–6.70 (m, 2 H), 4.87 (s, 2 H), 4.23 (s, 2 H), 4.16 (d, $J=5.4$ Hz, 2 H), 3.78–3.65 (m, 4 H), 3.07–2.93 (m, 4 H). LC-MS: Method A, $r_t=0.49$ min; m/z (ES+), $(M + H)^+ = 421$.

20

Example 52

9-cyclopentyl-2-[2-methoxy-4-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-1-piperidyl]anilino]6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (52)

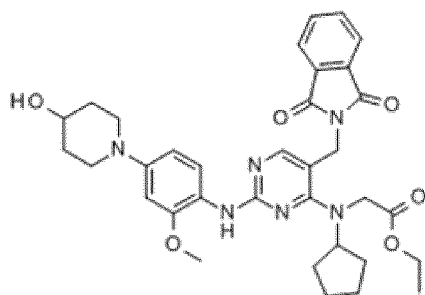


A mixture of 2-[1-[4-[(9-cyclopentyl-6-methyl-7-oxo-5,8-dihydropyrimido[4,5-e][1,4]diazepin-2-yl)amino]-3-methoxy-phenyl]-4-piperidyl]acetic acid (intermediate 116) (23 mg, 0.045 mmol), pyrrolidine (4.5 μ L), [dimethylamino(triazolo[4,5-b]pyridin-3-yloxy)methylene]-dimethyl-ammonium hexafluorophosphate (34.4 mg, 0.090 mmol), N-ethyl-N-isopropyl-propan-2-amine (120 mg, 0.92 mmol) in dry DMF was stirred under nitrogen atmosphere at room temperature for 1.5 h. The reaction was then quenched with water and then extracted with AcOEt. The combined organic layers were dried over sodium sulphate, filtered and evaporated. The residue was purified through column chromatography on silica gel (eluent DCM/MeOH/NH₄OH 98:1:1) followed by trituration in diethyl ether to give 16.8 mg of the target compound as a white powder.

¹H NMR (DMSO-d₆) δ : 7.82-7.78 (m, 1 H), 7.69 (s, 1 H), 7.31 (s, 1 H), 6.61-6.54 (m, 1 H), 6.46-6.39 (m, 1 H), 5.41-5.30 (m, 1 H), 4.42 (s, 2 H), 4.12 (s, 2 H), 3.80 (s, 3 H), 3.62-3.53 (m, 2 H), 3.41-3.37 (m, 2 H), 3.25-3.29 (m, 2 H), 2.89 (s, 3 H), 2.65-2.54 (m, 2 H), 2.17-2.22 (m, 2 H), 1.91-1.22 (m, 17 H). LC-MS: Method A, rt = 1.00 min; m/z (ES⁺), (M + H)⁺ = 562.

Intermediates 53 to 67

ethyl 2-[cyclopentyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]pyrimidin-4-yl]amino]acetate (53)



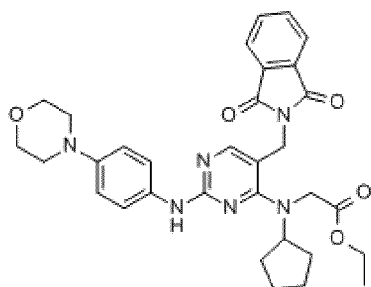
A mixture of ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]-cyclopentyl-amino]acetate (intermediate 99) (86 mg, 0.19 mmol), 1-(4-amino-3-methoxy-phenyl)piperidin-4-ol (45 mg, 0.20 mmol), tris(dibenzylideneacetone)dipalladium(0) (18 mg, 0.019 mmol), xantphos (23 mg, 0.04 mmol) and Cs₂CO₃ (127 mg, 0.39 mmol) in 1,4-dioxane (2.5 mL) was sealed in a microwave reaction tube and irradiated with microwave at 170 °C for 15 min. After cooling at room temperature the mixture was then filtered on a celite pad and the filtrate was concentrated and purified by silica gel chromatography

(eluent: DCM/MeOH:NH₄OHa_q 97:3:0.3) and trituration in diethyl ether to give 35 mg of the title compound.

LC-MS: Method A, rt = 1.40 min; m/z (ES⁺), (M + H)⁺ = 629.

- 5 By operating as above reported and by starting from the suitable intermediates 98, 99, 100, 101, 102, 103, and 104, the following compounds were analogously prepared:

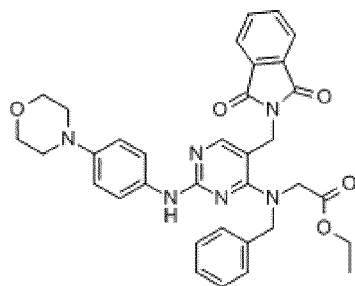
ethyl 2-[cyclopentyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-(4-morpholinoanilino)-pyrimidin-4-yl]amino]acetate (54)



- 10 ¹H NMR (CDCl₃) δ: 7.91–7.86 (m, 2 H), 7.82 (s, 1 H), 7.79–7.74 (m, 2 H), 7.39–7.33 (m, 2 H), 6.89–6.83 (m, 2 H), 4.84 (s, 2 H), 4.38–4.26 (m, 1 H), 4.16 (s, 2 H), 4.11 (q, J=6.8 Hz, 2 H), 3.90–3.82 (m, 4 H), 3.15–3.06 (m, 4 H), 2.07–1.94 (m, 2 H), 1.80–1.69 (m, 2 H), 1.68–1.59 (m, 4 H), 1.22–1.16 (m, 3 H). LC-MS: Method A, rt = 1.65 min; m/z (ES⁺), (M + H)⁺ = 585.

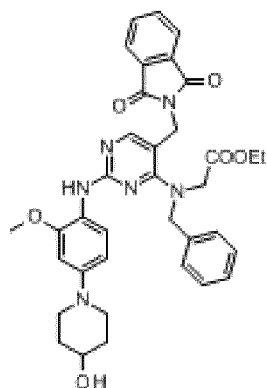
15

ethyl 2-[benzyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-(4-morpholinoanilino)-pyrimidin-4-yl]amino]acetate (55)



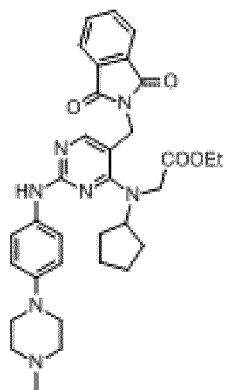
- 20 ¹H NMR (CDCl₃) δ: 7.87–7.81 (m, 2 H), 7.78 (s, 1 H), 7.77–7.71 (m, 2 H), 7.46–7.38 (m, 5 H), 7.38–7.34 (m, 2 H), 7.33–7.29 (m, 1 H), 6.88–6.82 (m, 2 H), 4.96–4.89 (m, 2 H), 4.71 (s, 2 H), 4.18 (s, 2 H), 4.16–4.08 (m, 2 H), 3.89–3.80 (m, 4 H), 3.14–3.07 (m, 4 H), 1.21 (t, J=7.1 Hz, 4 H). LC-MS: Method A, rt = 1.67 min; m/z (ES⁺), (M + H)⁺ = 607.

ethyl 2-[benzyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]pyrimidin-4-yl]amino]acetate (56)



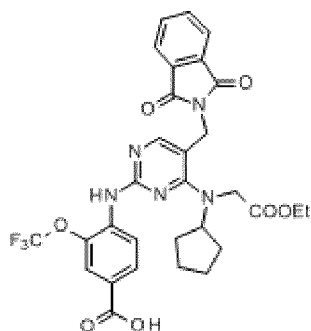
- 5 ^1H NMR (DMSO-d_6) δ : 7.87–7.81 (m, 4 H), 7.80 (s, 1 H), 7.73–7.68 (m, 1 H), 7.38–7.27 (m, 5 H), 7.24–7.19 (m, 1 H), 6.58 (d, $J=2.4$ Hz, 1 H), 6.39–6.33 (m, 1 H), 4.79 (s, 2 H), 4.66 (s, 2 H), 4.65 (d, $J=3.9$ Hz, 1 H), 4.12 (s, 2 H), 4.02 (q, $J=7.3$ Hz, 2 H), 3.79 (s, 3 H), 3.62–3.53 (m, 1 H), 3.47–3.40 (m, 2 H), 2.79–2.70 (m, 2 H), 1.85–1.75 (m, 2 H), 1.53–1.40 (m, 2 H), 1.14 (t, $J=7.1$ Hz, 3 H). LC-MS: Method A, $r_t = 1.57$ min; m/z (ES $^+$), (M + H) $^+$ = 651.
- 10

ethyl 2-[cyclopentyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-[4-(4-methylpiperazin-1-yl)anilino]pyrimidin-4-yl]amino]acetate (57)



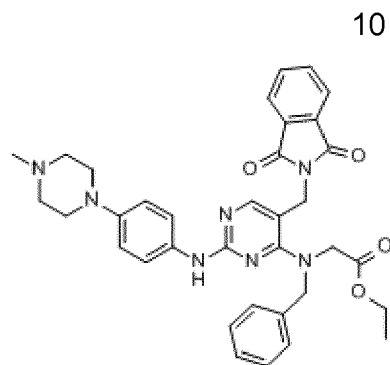
- 15 ^1H NMR (DMSO-d_6) δ : 8.89 (s, 1 H), 7.92–7.84 (m, 4 H), 7.83 (s, 1 H), 7.47–7.41 (m, 2 H), 6.83–6.76 (m, 2 H), 4.73 (s, 2 H), 4.35–4.21 (m, 1 H), 4.15 (s, 2 H), 4.04–3.90 (m, 2 H), 3.11–2.92 (m, 4 H), 2.43 (br. s., 4 H), 2.20 (s, 3 H), 1.88–1.76 (m, 2 H), 1.61 (br. s., 2 H), 1.50 (br. s., 4 H), 1.08 (t, $J=7.1$ Hz, 3 H). LC-MS: Method C, $r_t = 1.09$ min; m/z (ES $^+$), (M + H) $^+$ = 598.

ethyl 4-[[4-[cyclopentyl-(2-ethoxy-2-oxo-ethyl)amino]-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-2-yl]amino]-3-(trifluoromethoxy)benzoic acid (58)



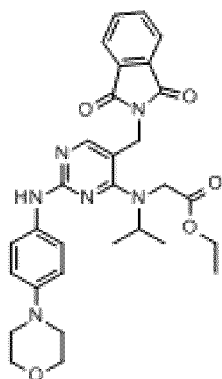
5 LC-MS: Method A, $r_t = 2.08$ min; m/z (ES⁺), $(M + H)^+ = 628$.

ethyl 2-[benzyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-[4-(4-methylpiperazin-1-yl)anilino]pyrimidin-4-yl]amino]acetate (59)



¹H NMR (DMSO-d₆) δ : 8.93 (s, 1 H), 7.88–7.79 (m, 5 H), 7.45–7.18 (m, 7 H), 6.80–6.73 (m, 2 H), 4.79 (s, 2 H), 4.68 (s, 2 H), 4.18 (s, 2 H), 3.99 (q, $J=6.8$ Hz, 2 H), 3.07–2.97 (m, 4 H), 2.46–2.39 (m, 4 H), 2.20 (s, 3 H), 1.10 (t, $J=7.1$ Hz, 3 H). LC-MS: Method A, $r_t = 1.28$ min; m/z (ES⁺), $(M + H)^+ = 620$.

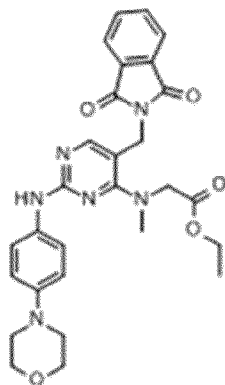
ethyl 2-[[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-(4-morpholinoanilino)pyrimidin-4-yl]-isopropyl-amino]acetate (60)



¹H NMR (CDCl₃) δ: 7.92–7.86 (m, 2 H), 7.82 (br. s., 1 H), 7.80–7.73 (m, 2 H), 7.39–7.33 (m, 2 H), 6.90–6.83 (m, 2 H), 4.82 (s, 2 H), 4.33–4.21 (m, 1 H), 4.18 (s, 2 H), 4.11 (q, *J*=7.3 Hz, 3 H), 3.92–3.82 (m, 4 H), 3.15–3.08 (m, 4 H), 1.32–1.29 (m, 6 H), 1.19 (t, *J*=7.1 Hz, 3 H). LC-MS: Method A, rt =1.52 min; *m/z* (ES⁺), (M + H)⁺ = 559.

ethyl 2-[[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-(4-morpholinoanilino)pyrimidin-4-yl]-methyl-amino]acetate (61)

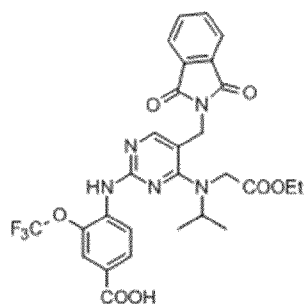
10



¹H NMR (CDCl₃) δ: 7.92–7.83 (m, 3 H), 7.80–7.71 (m, 2 H), 7.39–7.30 (m, 2 H), 6.90–6.79 (m, 2 H), 4.88 (s, 2 H), 4.22 (s, 2 H), 4.15 (q, *J*=7.3 Hz, 2 H), 3.91–3.81 (m, 4 H), 3.40 (s, 3 H), 3.14–3.07 (m, 4 H), 1.25–1.21 (m, 3 H). LC-MS: Method A, rt =1.36 min; *m/z* (ES⁺), (M + H)⁺ = 531.

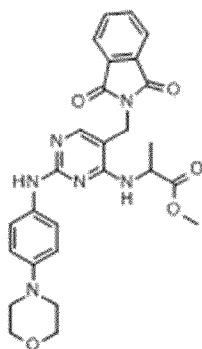
15

4-[[5-[(1,3-dioxoisindolin-2-yl)methyl]-4-[(2-ethoxy-2-oxo-ethyl)-isopropyl-amino]pyrimidin-2-yl]amino]-3-(trifluoromethoxy)benzoic acid (62)



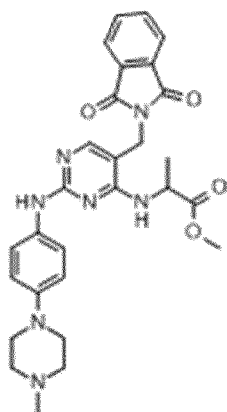
LC-MS: Method A, $r_t = 1.91$ min; m/z (ES⁺), $(M + H)^+ = 602$.

methyl 2-[[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-(4-morpholinoanilino)pyrimidin-4-yl]amino]propanoate (63)



¹H NMR (CDCl₃) δ : 7.98 (s, 1 H), 7.85–7.78 (m, 2 H), 7.72–7.65 (m, 2 H), 7.36–7.30 (m, 2 H), 7.06 (br. s, 1 H), 6.82–6.76 (m, 2 H), 4.63–4.52 (m, 3 H), 3.82–3.76 (m, 4 H), 3.57 (s, 3 H), 3.07–3.02 (m, 4 H), 1.52 (d, $J = 7.3$ Hz, 3 H). LC-MS: Method A, $r_t = 1.45$ min; m/z (ES⁺), $(M + H)^+ = 517$.

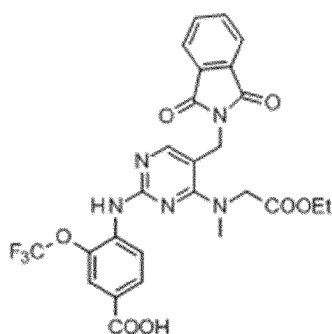
methyl (2-[[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-[4-(4-methylpiperazin-1-yl)anilino]pyrimidin-4-yl]amino]propanoate (64)



^1H NMR (CDCl_3) δ : 8.15 (s, 1 H), 7.92–7.83 (m, 2 H), 7.79–7.70 (m, 2 H), 7.44–7.38 (m, 2 H), 6.96 (br. s, 1 H), 6.92–6.85 (m, 2 H), 6.77–6.70 (m, 1 H), 4.71–4.60 (m, 3 H), 3.64 (s, 3 H), 3.27 (br. s., 4 H), 2.77 (br. s, 4 H), 2.49 (br. s., 3 H), 1.58 (d, $J=7.3$ Hz, 3 H). LC-MS:

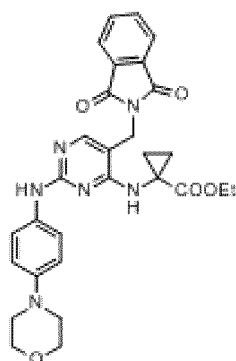
5 Method A, rt = 0.81 min; m/z (ES+), $(M + H)^+ = 530$.

4-[[5-[(1,3-dioxoisindolin-2-yl)methyl]-4-[(2-ethoxy-2-oxo-ethyl)-methyl-amino]pyrimidin-2-yl]amino]-3-(trifluoromethoxy)benzoic acid (65)



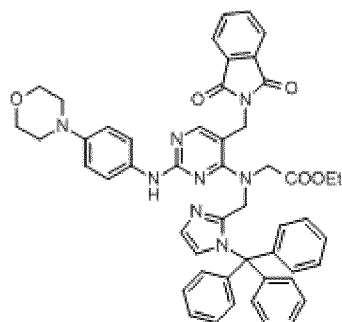
10 ^1H NMR ($\text{DMSO}-d_6$) δ : 13.06 (br. s., 1 H), 8.72 (br. s, 1 H), 8.22 (d, $J=8.8$ Hz, 1 H), 7.95 (s, 1 H), 7.91–7.84 (m, 4 H), 7.84–7.81 (m, 1 H), 7.78–7.72 (m, 1 H), 4.84 (s, 2 H), 4.23 (s, 2 H), 4.00–3.88 (m, 2 H), 3.26 (s, 3 H), 1.05 (t, $J=7.1$ Hz, 3 H). LC-MS: Method A, rt = 1.67 min; m/z (ES+), $(M + H)^+ = 574$.

15 **ethyl 1-[[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-(4-morpholinoanilino)pyrimidin-4-yl]amino]cyclopropanecarboxylate (66)**



¹H NMR (CDCl₃) δ: 8.03 (s, 1 H), 7.84–7.76 (m, 2 H), 7.72–7.62 (m, 2 H), 7.48–7.38 (m, 2 H), 7.15 (br. s., 1 H), 6.80–6.71 (m, 2 H), 4.52 (s, 2 H), 3.92 (q, *J*=7.3 Hz, 2 H), 3.81–3.75 (m, 4 H), 3.06–2.99 (m, 4 H), 1.65–1.56 (m, 2 H), 1.18–1.09 (m, 2 H), 0.90 (t, *J*=7.1 Hz, 3 H). LC-MS: Method A, *rt* = 1.42 min; *m/z* (ES⁺), (M + H)⁺ = 543.

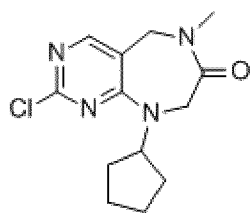
ethyl 2-[[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-(4-morpholinoanilino)pyrimidin-4-yl]-[(1-tritylimidazol-2-yl)methyl]amino]acetate (67)



¹H NMR (DMSO-*d*₆) δ: 8.82 (br. s., 1 H), 7.93–7.80 (m, 4 H), 7.59 (s, 1 H), 7.46–7.34 (m, 9 H), 7.33–7.28 (m, 2 H), 7.15–7.04 (m, 6 H), 6.96 (s, 1 H), 6.81 (s, 1 H), 6.75–6.68 (m, 2 H), 4.46 (s, 2 H), 3.90–3.80 (m, 4 H), 3.76–3.66 (m, 6 H), 3.01–2.91 (m, 4 H), 1.06 (t, *J*=7.3 Hz, 3 H). LC-MS: Method A, *rt* = 2.20 min; *m/z* (ES⁺), (M + H)⁺ = 839.

Intermediates 68 to 77 and 119

2-chloro-9-cyclopentyl-6-methyl-5,8-dihydropyrimido[4,5-*e*][1,4]diazepin-7-one (68)

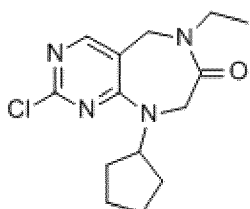


Sodium hydride (9.4 mg 60% slurry) was added under Nitrogen atmosphere to a cooled (-15°C) solution of 2-chloro-9-cyclopentyl-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (intermediate 80) (50 mg, 0.187 mmol) in dimethylacetamide (1 mL). After stirring at -15°C for 30 min, the reaction mixture was allowed to reach 0°C and methyl iodide (0.013 mL, 0.21 mmol) was added. After stirring at 0°C for 30 minutes the reaction was quenched with ice-water and extracted with AcOEt. The combined organic layers were washed with brine, dried over sodium sulphate, filtered and evaporated. Purification of the residue by column chromatography on silica gel (eluent DCM/MeOH 99:1) yielded 48 mg of the target product as a viscous oil.

¹H NMR (DMSO-d₆) δ: 7.92 (s, 1 H), 5.29–5.17 (m, 1 H), 4.56 (s, 2 H), 4.22 (s, 2 H), 2.90 (s, 3 H), 1.55 (m, 8 H). LC-MS: Method A, rt =1.40 min; m/z (ES+), (M + H)⁺ = 281.

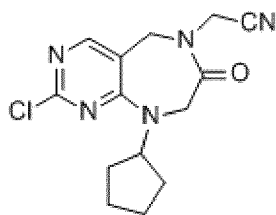
By operating as above reported and by starting from the suitable intermediates 80, 92, 93, 94, 95, 96, 97, and 120 and alkylating agents, the following compounds were analogously prepared:

2-chloro-9-cyclopentyl-6-ethyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (69)



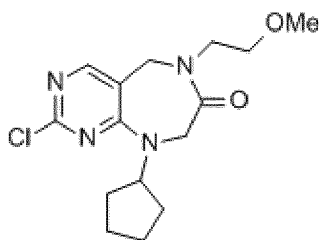
¹H NMR (DMSO-d₆) δ: 7.96 (s, 1 H), 5.30–5.15 (m, 1 H), 4.58 (s, 2 H), 4.21 (s, 2 H), 3.38 (m, 2 H), 1.55 (m, 8 H), 0.99 (m, 3 H). LC-MS: Method A, rt =1.52 min; m/z (ES+), (M + H)⁺ = 295.

2-(2-chloro-9-cyclopentyl-7-oxo-5,8-dihydropyrimido[4,5-e][1,4]diazepin-6-yl)-acetonitrile (70)



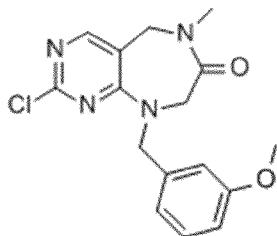
^1H NMR (DMSO- d_6) δ : 7.94 (s, 1 H), 5.29–5.16 (m, 1 H), 4.74 (s, 2 H), 4.50 (s, 2 H), 4.30 (s, 2 H), 1.81–1.45 (m, 8 H). LC-MS: Method A, r_t = 1.53 min; m/z (ES $^+$), (M + H) $^+$ = 306.

5 **2-chloro-9-cyclopentyl-6-(2-methoxyethyl)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (71)**



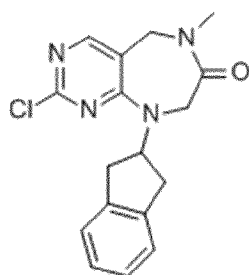
^1H NMR (DMSO- d_6) δ : 7.91 (s, 1 H), 5.28–5.19 (m, 1 H), 4.59 (s, 2 H), 4.23 (s, 2 H), 3.52 (m, 2 H), 3.35 (m, 2 H), 3.14 (s, 3 H), 1.82–1.47 (m, 8 H). LC-MS: Method A, r_t = 1.49 min; m/z (ES $^+$), (M + H) $^+$ = 325.

10 **2-chloro-9-[(3-methoxyphenyl)methyl]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (72)**



15 ^1H NMR (DMSO- d_6) δ : 7.99 (s, 1 H), 7.28–6.79 (m, 4 H), 4.81 (s, 2 H), 4.59 (s, 2 H), 4.44 (s, 2 H), 3.72 (s, 3 H), 2.92 (s, 3 H). LC-MS: Method A, r_t = 1.38 min; m/z (ES $^+$), (M + H) $^+$ = 333.

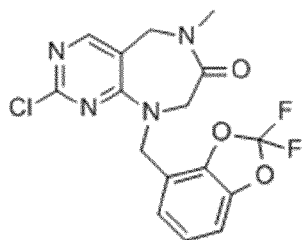
2-chloro-9-indan-2-yl-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (73)



¹H NMR (DMSO-d₆) δ: 7.98 (s, 1 H), 7.28–7.11 (m, 4 H), 5.88–5.73 (m, 1 H), 4.58 (s, 2 H), 4.24 (s, 2 H), 3.20–2.99 (m, 4 H), 2.91 (s, 3 H). LC-MS: Method A, rt =1.67 min; m/z (ES⁺), (M + H)⁺ = 328.

5

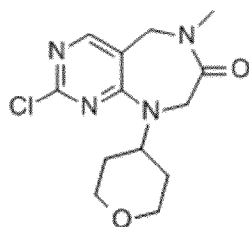
2-chloro-9-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (74)



¹H NMR (DMSO-d₆) δ = 8.02 (s, 1 H), 7.33–7.06 (3m, 3 H), 4.93 (s, 2 H), 4.59 (s, 2 H), 4.51 (s, 2 H), 2.78 (s, 3 H). LC-MS: Method A, rt =1.64 min; m/z (ES⁺), (M + H)⁺ = 383.

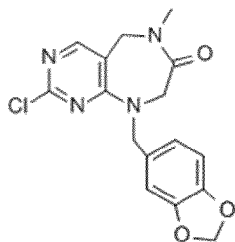
10

2-chloro-6-methyl-9-tetrahydropyran-4-yl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (75)

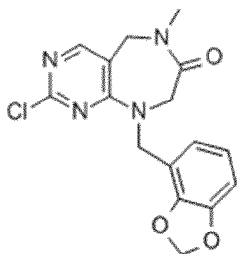


¹H NMR (DMSO-d₆) δ: 7.96 (s, 1 H), 4.99–4.85 (m, 1 H), 4.57 (s, 2 H), 4.27 (s, 2 H), 3.96–3.36 (2m, 4 H), 2.90 (s, 3 H), 1.86–1.41 (2m, 4 H). LC-MS: Method A, rt =0.96 min; m/z (ES⁺), (M + H)⁺ = 297.

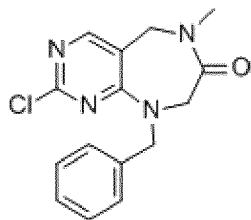
15

9-(1,3-benzodioxol-5-ylmethyl)-2-chloro-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (76)

¹H NMR (CDCl₃) δ: 7.82 (s, 1 H), 6.87–6.71 (m, 3 H), 5.96 (s, 2 H), 4.86 (s, 2 H), 4.39 (s, 2 H), 4.25 (s, 2 H), 3.06 (s, 3 H). LC-MS: Method A, rt = 1.40 min; m/z (ES+), (M + H)⁺ = 347.

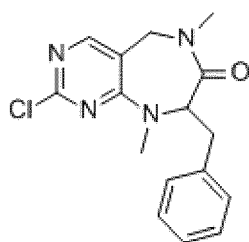
9-(1,3-benzodioxol-4-ylmethyl)-2-chloro-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (77)

¹H NMR (CDCl₃) δ: 7.79 (s, 1 H), 6.92–6.72 (m, 3 H), 5.97 (s, 2 H), 4.93 (s, 2 H), 4.45–4.30 (m, 4 H), 3.07 (s, 3 H). LC-MS: Method A, rt = 1.91 min; m/z (ES+), (M + H)⁺ = 347.

9-benzyl-2-chloro-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (119)

¹H NMR (DMSO-d₆) δ: 7.99 (s, 1 H), 7.36 - 7.24 (m, 5 H), 4.85 (s, 2 H), 4.59 (s, 2 H), 4.43 (s, 2 H), 2.92 (s, 3 H). LC-MS: Method A, rt = 1.44 min; m/z (ES+), (M + H)⁺ = 303.

Intermediate 78**8-benzyl-2-chloro-6,9-dimethyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one (78)**

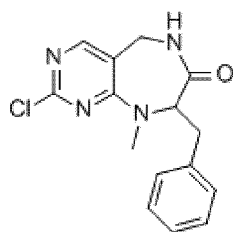


Sodium hydride (5 mg 60% slurry) was added under Nitrogen atmosphere to a cooled (-15°C) solution of 8-benzyl-2-chloro-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (intermediate 84) (29 mg, 0.10 mmol) in dimethylacetamide (0.5 mL). After stirring at -15°C for 30 min, the reaction mixture was allowed to reach 0°C and methyl iodide (0.0069 mL, 0.11 mmol) was added. After stirring at 0°C for 30 minutes the reaction was cooled down to -15°C and a second aliquot of sodium hydride (3 mg) was added. After stirring at -15°C for 30 min, the reaction mixture was allowed to reach 0°C and methyl iodide (0.004 mL) was added. After stirring at 0°C for 30 minutes the reaction was quenched with ice-water and extracted with AcOEt. The combined organic layers were washed with brine, dried over sodium sulphate, filtered and evaporated. Purification of the residue by column chromatography on silica gel (eluent DCM/MeOH 99:1) yielded 15 mg of the target product as a viscous oil.

¹H NMR (DMSO-d₆) δ: 8.04 (s, 1 H), 7.38–7.16 (m, 5 H), 5.16–5.07 (m, 1 H), 5.00–4.89 (m, 1 H), 4.42–4.23 (m, 1 H), 3.25 (m, 2 H), 3.03–2.85 (2s, 6 H). LC-MS: Method A, rt =1.49 min; m/z (ES+), (M + H)⁺ = 317.

Intermediate 79

8-benzyl-2-chloro-9-methyl-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (79)



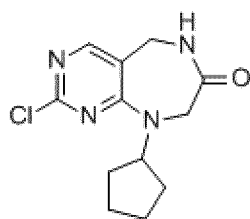
Sodium hydride (15 mg 60% slurry) was added under Nitrogen atmosphere to a cooled (-15°C) solution of 8-benzyl-2-chloro-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (intermediate 84) (100 mg, 0.36 mmol) in dimethylacetamide (1.7 mL). After stirring at -15°C for 30 min, the reaction mixture was allowed to reach 0°C and methyl iodide (0.024

mL, 0.38 mmol) was added. After stirring at 0°C for 30 minutes the reaction was quenched with ice-water and extracted with AcOEt. The combined organic layers were washed with brine, dried over sodium sulphate, filtered and evaporated. Purification of the residue by column chromatography on silica gel (eluent DCM/MeOH 99:1) yielded 86 mg of the target product as a viscous oil.

¹H NMR (DMSO-d₆) δ: 8.20 (m, 1 H), 8.05 (s, 1 H), 7.38–7.18 (m, 5 H), 4.92–4.83 (m, 1 H), 4.55–4.16 (m, 2 H), 3.24 (m, 2 H), 3.00 (s, 3 H). LC-MS: Method A, rt =1.39 min; m/z (ES+), (M + H)⁺ = 303.

Intermediates 80 and 120

2-chloro-9-cyclopentyl-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (80)

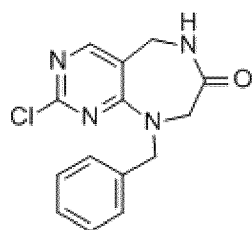


Hydrazine (2.2 mL of 1M solution in THF) was added to a solution of ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]-cyclopentyl-amino]acetate (intermediate 99) (641 mg, 1.45 mmol) in EtOH (10 mL). The resulting solution was stirred at 75°C for 2.5 h, then a further aliquot (4.4 mL) of hydrazine solution was added and the reaction mixture was stirred for additional 14 h at 70°C. A third aliquot of hydrazine solution (2.2 mL) was added and stirring was continued for 2 h at 80°C. Solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent DCM/MeOH 96:4) to give 176 mg of the target compound as a white powder.

¹H NMR (DMSO-d₆) δ: 8.34–8.24 (m, 1 H), 7.91 (s, 1 H), 5.30–5.17 (m, 1 H), 4.28 (m, 2 H), 4.12 (s, 2 H), 1.83–1.47 (m, 8 H). LC-MS: Method A, rt =1.29 min; m/z (ES+), (M + H)⁺ = 267.

By operating as above reported and by starting from the suitable intermediate 103 the following compound was analogously prepared:

9-benzyl-2-chloro-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (120)

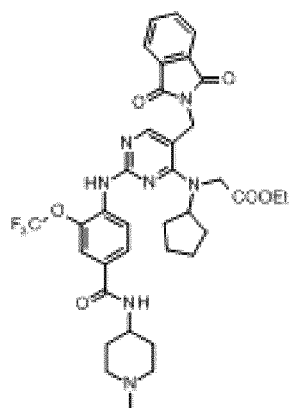


^1H NMR (DMSO-d_6) δ : 8.35 (t, J = 5.4 Hz, 1 H), 7.98 (s, 1 H), 7.39 - 7.20 (m, 5 H), 4.86 (s, 2 H), 4.34 (s, 2 H), 4.32 (d, J = 5.4 Hz, 2 H). Method A, t_r = 1.34 min; m/z (ES⁺), (M + H)⁺ = 289.

5

Intermediates 81 to 83

ethyl 2-[cyclopentyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-[4-[(1-methyl-4-piperidyl)carbamoyl]-2-(trifluoromethoxy)anilino]pyrimidin-4-yl]amino]acetate (81)

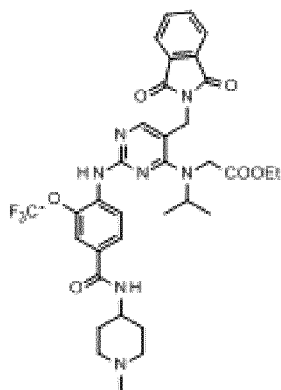


- 10 N-methylpiperidine (56 mg, 0.49 mmol), EDC (126 mg, 0.66 mmol) and HOBT (44 mg, 0.33 mmol) were added to a solution of 4-[[4-[cyclopentyl-(2-ethoxy-2-oxo-ethyl)amino]-5-[(1,3-dioxoisindolin-2-yl)methyl]-pyrimidin-2-yl]amino]-3-(trifluoromethoxy)benzoic acid (intermediate 58) (206 mg, 0.33 mmol) in THF(8 mL)/DMF(0.4 mL). After stirring at room temperature for 4 h and 30 min the reaction mixture was concentrated under reduced
- 15 pressure, the residue was taken up with saturated aqueous NaHCO_3 solution and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent DCM/MeOH/ NH_4OH aq. (95:5:0.5) to give the target product as a pale yellow solid (168 mg).
- 20 ^1H NMR (DMSO-d_6) δ : 8.57–8.48 (m, 1 H), 8.34–8.24 (m, 1 H), 8.19–8.11 (m, 1 H), 7.95–7.79 (m, 7 H), 4.79 (s, 2 H), 4.35–4.24 (m, 1 H), 4.13 (s, 2 H), 3.94–3.85 (m, 2 H), 3.78–

3.65 (m, 1 H), 2.82–2.72 (m, 2 H), 2.16 (s, 3 H), 1.99–1.88 (m, 2 H), 1.86–1.79 (m, 2 H), 1.77–1.70 (m, 2 H), 1.66–1.42 (m, 8 H), 1.02 (t, $J=7.1$ Hz, 3 H). LC-MS: Method C, $r_t=1.48$ min; m/z (ES⁺), (M + H)⁺ = 724.

- 5 By operating as above reported and by starting from the suitable intermediate 62 and 65 the following compounds were analogously prepared:

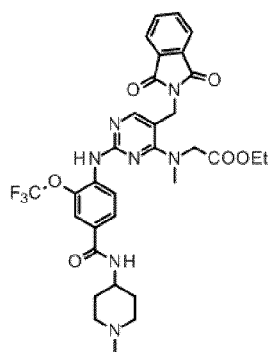
ethyl 2-[[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-[4-[(1-methyl-4-piperidyl)carbamoyl]-2-(trifluoromethoxy)anilino]pyrimidin-4-yl]-isopropyl-amino]acetate (82)



- 10 ¹H NMR (DMSO-d₆) δ : 8.54 (s, 1 H), 8.29 (d, $J=7.8$ Hz, 1 H), 8.15 (d, $J=8.8$ Hz, 1 H), 7.94 (s, 1 H), 7.92–7.81 (m, 6 H), 4.76 (s, 2 H), 4.22–4.16 (m, 1 H), 4.14 (s, 2 H), 3.88 (q, $J=6.8$ Hz, 2 H), 3.77–3.66 (m, 1 H), 2.81–2.72 (m, 2 H), 2.16 (s, 3 H), 1.98–1.87 (m, 2 H), 1.79–1.69 (m, 2 H), 1.63–1.51 (m, 2 H), 1.17 (d, $J=6.4$ Hz, 6 H), 1.01 (t, $J=7.1$ Hz, 3 H). LC-MS: Method C, $r_t=1.30$ min; m/z (ES⁺), (M + H)⁺ = 698.

15

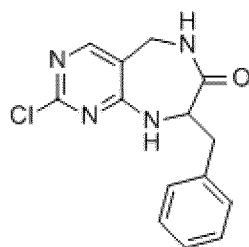
ethyl 2-[[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-[4-[(1-methyl-4-piperidyl)-carbamoyl]-2-(trifluoromethoxy)anilino]pyrimidin-4-yl]-methyl-amino]acetate (83)



¹H NMR (DMSO-d₆) δ: 8.58 (s, 1 H), 8.29 (d, *J*=7.8 Hz, 1 H), 8.11 (d, *J*=8.8 Hz, 1 H), 7.93 (s, 1 H), 7.91–7.84 (m, 4 H), 7.84–7.79 (m, 2 H), 4.83 (s, 2 H), 4.21 (s, 2 H), 3.96–3.88 (m, 2 H), 3.78–3.66 (m, 1 H), 3.25 (s, 3 H), 2.81–2.72 (m, 2 H), 2.15 (s, 3 H), 1.98–1.87 (m, 2 H), 1.78–1.69 (m, 2 H), 1.63–1.50 (m, 2 H), 1.05 (t, *J*=7.3 Hz, 3 H). LC-MS: Method C, rt = 1.18 min; *m/z* (ES⁺), (M + H)⁺ = 670.

Intermediates 84 to 86

8-benzyl-2-chloro-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (84)

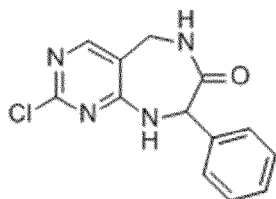


A solution of methyl 2-[[5-(aminomethyl)-2-chloro-pyrimidin-4-yl]amino]-3-phenylpropanoate (intermediate 114) (472 mg, 1.47 mmol) and sodium methylate (0.12 g, 2.2 mmol) in methanol (15 mL) was stirred at the reflux temperature for 2.5 h. After cooling, solvent was evaporated and the residue was taken up with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent DCM/MeOH (97:3) to give the target product as a white solid (203 mg).

¹H NMR (DMSO-d₆) δ: 8.26–8.19 (m, 1 H), 8.03 (m, 1 H), 7.94 (s, 1 H), 7.40–7.16 (m, 5 H), 5.01 (m, 1 H), 4.81 (m, 1 H), 3.78 (m, 1 H), 3.18–2.80 (m, 2 H). LC-MS: Method A, rt = 1.21 min; *m/z* (ES⁺), (M + H)⁺ = 289.

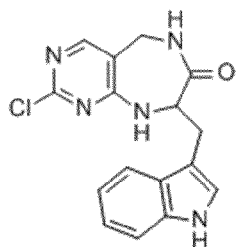
By operating as above reported and by starting from the suitable intermediates 112 and 113, the following compounds were analogously prepared:

2-chloro-8-phenyl-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (85)



¹H NMR (DMSO-d₆) δ: 8.85-8.78 (m, 1H), 8.47-8.41 (m, 1 H), 7.94 (s, 1 H), 7.47–7.25 (m, 5 H), 5.10-5.15 (m, 1 H), 3.84–3.43 (m, 2 H). LC-MS: Method A, rt =1.02 min; m/z (ES+), (M + H)⁺ = 275.

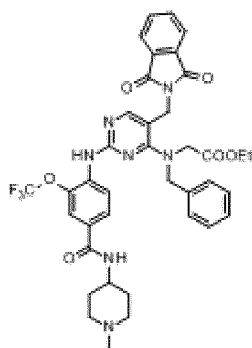
5 **2-chloro-8-(1H-indol-3-ylmethyl)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one (86)**



¹H NMR (CDCl₃) δ: 8.20 (br. s., 1 H), 7.82 (s, 1 H), 7.64–7.39 (m, 2 H), 7.30–7.13 (m, 3 H), 6.67 (t, J=6.1 Hz, 1 H), 5.63 (s, 1 H), 5.02–4.92 (m, 1 H), 4.85–4.74 (m, 1 H), 3.92–3.82 (m, 1 H), 3.60–3.48 (m, 1 H), 3.23–3.10 (m, 1 H). LC-MS: Method A, rt =1.21 min; m/z (ES+), (M + H)⁺ = 328.

Intermediate 87

15 **2-[benzyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-[4-[(1-methyl-4-piperidyl)carbamoyl]-2-(trifluoromethoxy)anilino]pyrimidin-4-yl]amino]acetate (87)**



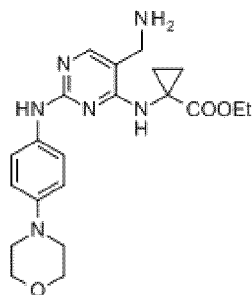
Palladium acetate (6.8 mg, 0.03 mmol), (+)-BINAP (19 mg, 0.03 mmol) and DMF (5 mL) were charged in a round-bottomed flask, flushed with nitrogen and stirred under nitrogen atmosphere for 30 minutes. The resulting mixture was added to a suspension of ethyl 2-[benzyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-iodo-pyrimidin-4-yl]amino]-acetate (intermediate 124) (153 mg, 0.275 mmol), 4-amino-N-(1-methyl-4-piperidyl)-3-

(trifluoromethoxy)benzamide (262 mg, 0.825 mmol) and potassium carbonate (380 mg, 2.75 mmol) in DMF (4.8 mL). The resulting mixture was stirred at 70 °C for 13 h. After cooling to r.t. the mixture was filtered on a pad of celite and washed with DCM. The filtrate was evaporated and the residue was purified by flash chromatography (elution gradient from 97:3:0.3 to 93:7:0.7 DCM/MeOH/NH₄OH) to yield about 70 mg of the target product.

¹H NMR (CDCl₃) δ: 8.54 (d, *J*=8.3 Hz, 1 H), 7.99 (s, 1 H), 7.87–7.80 (m, 2 H), 7.76–7.69 (m, 3 H), 7.58–7.51 (m, 1 H), 7.49–7.44 (m, 2 H), 7.42–7.36 (m, 2 H), 7.32–7.26 (m, 1 H), 6.00 (d, *J*=7.8 Hz, 1 H), 4.93 (s, 2 H), 4.75 (s, 2 H), 4.21–4.13 (m, 4 H), 4.04–3.94 (m, 1 H), 2.91–2.82 (m, 2 H), 2.33 (s, 3 H), 2.25–2.14 (m, 2 H), 2.09–1.98 (m, 2 H), 1.70–1.58 (m, 2 H), 1.23 (t, *J*=7.1 Hz, 3 H). LC-MS: Method A, *rt* = 1.76 min; *m/z* (ES⁺), (M + H)⁺ = 746.

Intermediates 88 to 90

ethyl 1-[[5-(aminomethyl)-2-(4-morpholinoanilino)pyrimidin-4-yl]amino]cyclopropanecarboxylate (88)



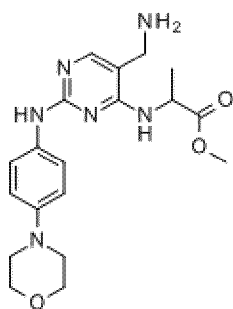
Hydrazine (0.012 mL, 0.25 mmol) was added to a suspension of ethyl 1-[[5-[(1,3-dioxisoindolin-2-yl)methyl]-2-(4-morpholinoanilino)pyrimidin-4-yl]amino]cyclopropanecarboxylate (intermediate 66) (61 mg, 0.11 mmol) in MeOH (1.5 mL) and THF (1 mL). The reaction mixture was stirred at the reflux temperature for 1 h, then a further aliquot (0.030 mL) of hydrazine was added and the reaction mixture was stirred for additional 4 h. After cooling, solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent DCM/MeOH/NH₄OH 95:5:0.5) to give 35 mg of the target compound as a white powder.

¹H NMR (DMSO-d₆) δ: 8.72 (s, 1 H), 7.78 (br. s, 1 H), 7.74 (s, 1 H), 7.67–7.61 (m, 2 H), 6.80–6.74 (m, 2 H), 3.98 (q, *J*=7.3 Hz, 2 H), 3.77–3.67 (m, 4 H), 3.51 (s, 2 H), 3.02–2.91 (m, 4 H), 1.56–1.48 (m, 2 H), 1.17–1.12 (m, 2 H), 1.03 (t, *J*=7.1 Hz, 3 H). LC-MS: Method A, *rt* = 0.74 min; *m/z* (ES⁺), (*M* + *H*)⁺ = 413.

5

By operating as above reported and by starting from the suitable intermediates 63 and 64, the following compounds were analogously prepared:

methyl 2-[[5-(aminomethyl)-2-(4-morpholinoanilino)pyrimidin-4-yl]amino]-propanoate (89)

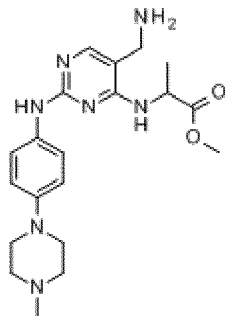


10

¹H NMR (DMSO-d₆) δ: 7.95 (s, 1 H), 7.51–7.32 (m, 4 H), 4.51 (q, *J*=6.8 Hz, 1 H), 4.09–3.93 (AB System: *V*_A=4.05, *V*_B=3.97, *J*_{AB}= 14.7 Hz, 2 H), 3.89 (br. s., 4 H), 3.47 (s, 3 H), 3.38 (br. s., 4 H), 1.47 (d, *J*=7.3 Hz, 3 H). LC-MS: Method A, *rt* = 0.69 min; *m/z* (ES⁺), (*M* + *H*)⁺ = 387.

15

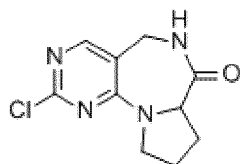
methyl (2S)-2-[[5-(aminomethyl)-2-[4-(4-methylpiperazin-1-yl)anilino]pyrimidin-4-yl]amino]propanoate (90)



m/z (ES⁺), (*M* + *H*)⁺ = 400.

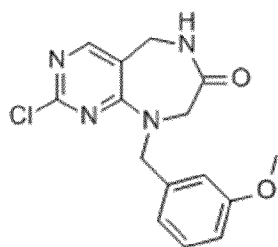
20

Intermediate 91

2-chloro-5,6,7a,8,9,10-hexahydro-7H-pyrimido[5,4-f]pyrrolo[1,2-a][1,4]diazepin-7-one (91)

Hydrazine (3.15 mL of 1M solution in THF) was added to a suspension of methyl 1-[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]pyrrolidine-2-carboxylate (intermediate 108) (630 mg, 1.56 mmol) in MeOH (8 mL). The resulting solution was stirred at 65°C for 16 h, then a further aliquot (9.5 mL) of hydrazine solution was added and the reaction mixture was stirred for additional 6 h at 70°C. A third aliquot of hydrazine solution (9.5 mL) was added and stirring was continued for 16 h at 80°C. Solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent DCM/MeOH 97:3) to give 285 mg of the target compound as a white powder.

¹H NMR (DMSO-d₆) δ: 8.40–8.27 (m, 1 H), 7.88 (s, 1 H), 5.23–5.12 (m, 1 H), 4.85–4.76 (m, 1 H), 3.83–3.72 (m, 1 H), 3.55–3.45 (m, 2 H), 2.44–2.34 (m, 1 H), 2.00–1.89 (m, 1 H), 1.88–1.72 (m, 2 H). LC-MS: Method A, rt = 0.86 min; m/z (ES⁺), (M + H)⁺ = 239.

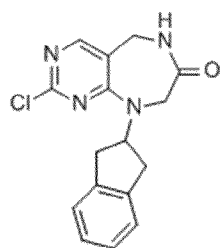
Intermediates 92 to 97**2-chloro-9-[(3-methoxyphenyl)methyl]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (92)**

Hydrazine (1.21 mL of 1M solution in THF) was added to a suspension of 2 ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]-[(3-methoxyphenyl)methyl]-amino]acetate (intermediate 109) (200 mg, 0.4 mmol) in EtOH (1.5 mL). The resulting solution was stirred at the reflux temperature for 1 h, then solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent DCM/MeOH 97:3) to give 68 mg of the target compound as a yellow oil.

^1H NMR (DMSO-d_6) δ : 8.39–8.31 (m, 1 H), 7.98 (s, 1 H), 7.28–6.78 (m, 4 H), 4.82 (s, 2 H), 4.38–4.27 (s,m, 4 H), 3.72 (s, 3 H). LC-MS: Method A, rt = 1.31 min; m/z (ES^+), $(\text{M} + \text{H})^+ = 319$.

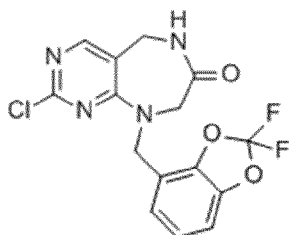
- 5 By operating as above reported and by starting from the suitable intermediate 105, 106, 107, 110, and 111, the following compounds were analogously prepared:

2-chloro-9-indan-2-yl-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (93)



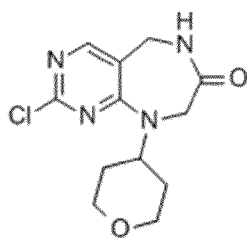
- 10 ^1H NMR (DMSO-d_6) δ : 8.36–8.30 (m, 1 H), 7.97 (s, 1 H), 7.28–7.13 (m, 4 H), 5.86–5.77 (m, 1 H), 4.33–4.27 (m, 2 H), 4.14 (s, 2 H), 3.21–2.99 (m, 4 H). LC-MS: Method A, rt = 1.54 min; m/z (ES^+), $(\text{M} + \text{H})^+ = 315$.

2-chloro-9-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (94)



- 15 ^1H NMR (DMSO-d_6) δ : 8.39–8.32 (m, 1 H), 8.00 (s, 1 H), 7.34–7.06 (3m, 3 H), 4.92 (s, 2 H), 4.43 (s, 2 H), 4.28–4.35 (m, 2 H). LC-MS: Method A, rt = 1.54 min; m/z (ES^+), $(\text{M} + \text{H})^+ = 369$.

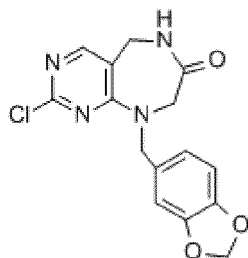
- 20 **2-chloro-9-tetrahydropyran-4-yl-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (95)**



¹H NMR (DMSO-d₆) δ: 8.31–8.22 (m, 1 H), 7.95 (s, 1 H), 4.99–4.87 (m, 1 H), 4.32–4.27 (m, 2 H), 4.17 (s, 2 H), 3.97–3.35 (2m, 4 H), 1.85–1.40 (2m, 4 H). LC-MS: Method A, rt = 0.87 min; m/z (ES⁺), (M + H)⁺ = 283.

5

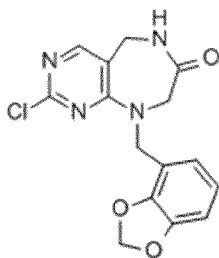
9-(1,3-benzodioxol-5-ylmethyl)-2-chloro-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (96)



¹H NMR (CDCl₃) δ = 7.84 (s, 1 H), 6.89–6.70 (m, 3 H), 6.23 (br. s., 1 H), 5.95 (s, 2 H), 4.89 (s, 2 H), 4.34 (d, J=6.4 Hz, 2 H), 4.20 (s, 2 H).

10

9-(1,3-benzodioxol-4-ylmethyl)-2-chloro-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one (97)



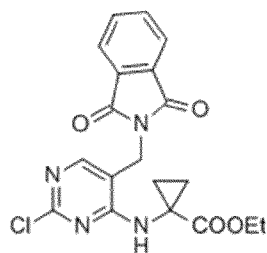
¹H NMR (DMSO-d₆) δ: 8.33 (t, J=5.5 Hz, 1 H), 7.97 (s, 1 H), 6.88–6.69 (m, 3 H), 6.01 (s, 2 H), 4.81 (s, 2 H), 4.33 (s, 2 H), 4.31–4.27 (m, 2 H). LC-MS: Method A, rt = 1.77 min; m/z (ES⁺), (M + H)⁺ = 333.

15

Intermediates 98 to 104

ethyl 1-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]amino]-cyclopropanecarboxylate (98)

20



ethyl 1-aminocyclopropanecarboxylate hydrochloride (0.278 g, 1.68 mmol) was added to a solution of 2-[(2,4-dichloropyrimidin-5-yl)methyl]isoindoline-1,3-dione (intermediate 115) (0.493 g, 1.6 mmol) and N-ethyl-N-isopropyl-propan-2-amine (0.62 g, 4.8 mmol) in dry

5 THF (6 mL) at room temperature and the mixture was stirred at the reflux temperature for 45 h. Then a second aliquot of ethyl 1-aminocyclopropanecarboxylate hydrochloride (1.6 mmol) was added and the mixture was refluxed under stirring for additional 24 h.

After cooling to room temperature the reaction mixture was concentrated and the residue taken up with water and extracted with ethyl acetate.

10 The organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent nHexane/AcOEt (70:30) to give 306 mg of the target compound as a white solid.

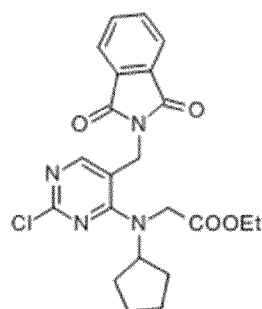
¹H NMR (CDCl₃) δ: 8.30 (s, 1 H), 7.91–7.85 (m, 2 H), 7.79–7.74 (m, 2 H), 7.26 (br. s, 1 H), 4.64 (s, 2 H), 4.05 (q, J=7.3 Hz, 2 H), 1.72–1.65 (m, 2 H), 1.22–1.18 (m, 2 H), 1.06 (t, J=7.1 Hz, 3 H). LC-MS: Method C, rt=1.89 min; m/z (ES+), (M + H)⁺ = 401.

15

By operating as above reported and by starting from intermediate 115, the following compounds were analogously prepared:

ethyl 2-[[2-chloro-5-[(1,3-dioxoisoindolin-2-yl)methyl]pyrimidin-4-yl]-cyclopentyl-amino]acetate (99)

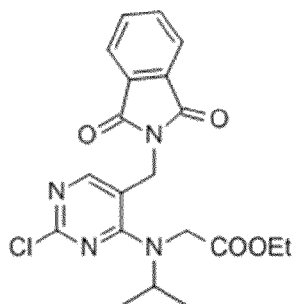
20



¹H NMR (CDCl₃) δ: 7.98 (s, 1 H), 7.93–7.87 (m, 2 H), 7.82–7.76 (m, 2 H), 4.89 (s, 2 H), 4.43–4.32 (m, 1 H), 4.23 (q, *J*=7.3 Hz, 2 H), 4.16 (s, 2 H), 2.11–1.99 (m, 2 H), 1.83–1.74 (m, 2 H), 1.73–1.61 (m, 4 H), 1.29 (t, *J*=7.1 Hz, 3 H). LC-MS: Method C, *rt* =2.52 min; *m/z* (ES+), (M + H)⁺ = 443.

5

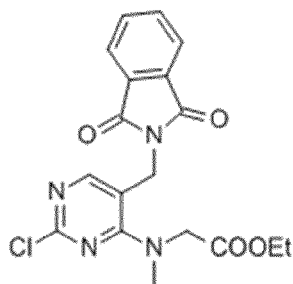
ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]-isopropyl-amino]acetate (100)



¹H NMR (CDCl₃) δ: 8.02 (s, 1 H), 7.94–7.86 (m, 2 H), 7.83–7.74 (m, 2 H), 4.87 (s, 2 H), 4.34–4.25 (m, 1 H), 4.21 (q, *J*=7.3 Hz, 2 H), 4.17 (s, 2 H), 1.32 (d, *J*=6.8 Hz, 6 H), 1.27 (t, *J*=7.1 Hz, 3 H). LC-MS: Method C, *rt* =2.07 min; *m/z* (ES+), (M + H)⁺ = 417.

10

ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]-methyl-amino]acetate (101)

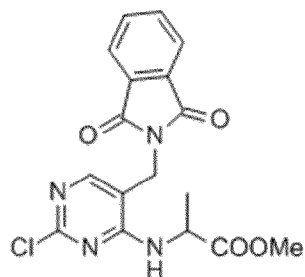


15

¹H NMR (CDCl₃) δ: 7.97 (s, 1 H), 7.85–7.76 (m, 2 H), 7.74–7.65 (m, 2 H), 4.86 (s, 2 H), 4.22–4.11 (m, 4 H), 3.35 (s, 3 H), 1.24 (t, *J*=7.1 Hz, 3 H). LC-MS: Method C, *rt* =1.85 min; *m/z* (ES+), (M + H)⁺ = 389.

methyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]amino]propanoate (102)

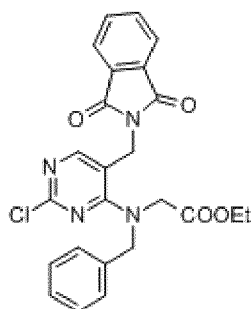
20



^1H NMR (CDCl_3) δ : 8.32 (s, 1 H), 7.98–7.72 (m, 4 H), 7.45 (d, $J=5.4$ Hz, 1 H), 4.84–4.75 (m, 1 H), 4.69 (s, 2 H), 3.75 (s, 3 H), 1.60 (d, $J=6.8$ Hz, 3 H). LC-MS: Method C, t_r = 1.79 min; m/z (ES^+), $(M + H)^+ = 375$.

5

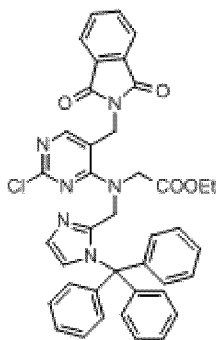
ethyl 2-[benzyl-[2-chloro-5-[(1,3-dioxoisoindolin-2-yl)methyl]pyrimidin-4-yl]amino]acetate (103)



^1H NMR (CDCl_3) δ : 8.00 (s, 1 H), 7.88–7.81 (m, 2 H), 7.78–7.71 (m, 2 H), 7.46–7.37 (m, 4 H), 7.33–7.28 (m, 1 H), 4.94 (s, 2 H), 4.76 (s, 2 H), 4.25 (q, $J=7.3$ Hz, 2 H), 4.14 (s, 2 H), 1.31 (t, $J=7.1$ Hz, 3 H). LC-MS: Method C, t_r = 2.26 min; m/z (ES^+), $(M + H)^+ = 465$.

10

ethyl 2-[2-chloro-5-[(1,3-dioxoisoindolin-2-yl)methyl]pyrimidin-4-yl]-[(1-tritylimidazol-2-yl)methyl]amino]acetate (104)

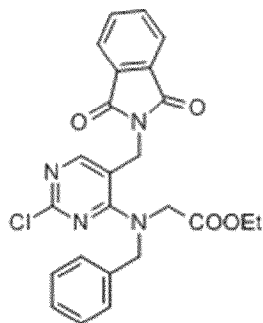


15

LC-MS: Method C, t_r = 2.40 min; m/z (ES^+), $(M + H)^+ = 697$.

Intermediates 103 to 107 and 121 to 123

ethyl 2-[benzyl-[2-chloro-5-[(1,3-dioxoisoindolin-2-yl)methyl]pyrimidin-4-yl]amino]acetate (103)



5

A mixture of 2-[(2,4-dichloropyrimidin-5-yl)methyl]isoindoline-1,3-dione (intermediate 115) (0.986 g, 3.2 mmol), ethyl 2-(benzylamino)acetate (0.649 g, 3.36 mmol), N-ethyl-N-isopropyl-propan-2-amine (0.827 g, 6.40 mmol) in tetrahydrofurane (13 mL) was sealed in a microwave reaction tube and irradiated with microwave at 130°C for 50 min. Then a second aliquot of ethyl 2-(benzylamino)acetate (0.8 mmol) was added and the mixture was irradiated at 140°C for additional 2.5 h.

10 After cooling to room temperature the reaction mixture was concentrated and the residue taken up with water and extracted with ethyl acetate.

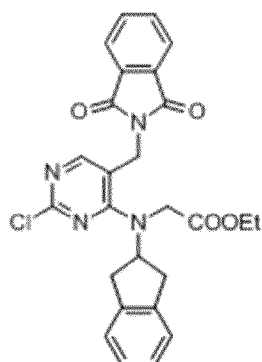
The organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent dichloromethane/AcOEt (97:3) to give 563 mg of the target compound as a white solid.

15 ¹H NMR (CDCl₃) δ: 8.44–8.33 (m, 1 H), 7.93–7.83 (m, 2 H), 7.79–7.68 (m, 2 H), 7.40–7.21 (m, 5 H), 5.03–4.90 (m, 2 H), 4.84 (s, 2 H), 4.34–4.09 (m, 4 H), 1.25 (t, J=6.1 Hz, 3 H). LC-MS: Method C, rt =2.18 min; m/z (ES+), (M + H)⁺ = 465.

20

By operating as above reported and by starting from intermediate 115, the following compounds were analogously prepared:

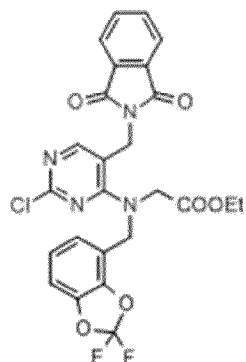
ethyl 2-[[2-chloro-5-[(1,3-dioxoisoindolin-2-yl)methyl]pyrimidin-4-yl]-indan-2-yl-amino]acetate (105)



^1H NMR (DMSO- d_6) δ : 8.08 (s, 1 H), 7.93–7.82 (m, 4 H), 7.26–7.11 (m, 4 H), 5.05–4.94 (m, 1 H), 4.88 (s, 2 H), 4.20 (s, 2 H), 4.10–4.03 (m, 2 H), 3.27–3.07 (m, 4 H), 1.16–1.10 (m, 3 H). LC-MS: Method C, r_t = 2.29 min; m/z (ES $^+$), (M + H) $^+$ = 491.

5

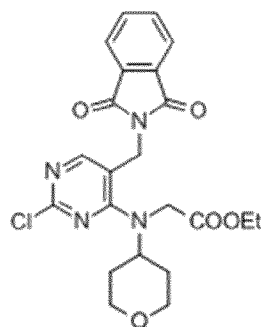
ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]amino]acetate (106)



^1H NMR (DMSO- d_6) δ : 8.13 (s, 1 H), 7.88–7.80 (m, 4 H), 7.31–7.07 (m, 3 H), 4.91 (s, 2 H), 4.79 (s, 2 H), 4.28 (s, 2 H), 4.12–4.05 (m, 2 H), 1.21–1.12 (m, 3 H). LC-MS: Method C, r_t = 2.28 min; m/z (ES $^+$), (M + H) $^+$ = 545.

10

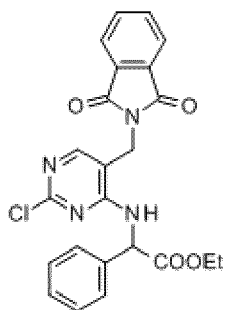
ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]-tetrahydropyran-4-yl-amino]acetate (107)



^1H NMR (DMSO- d_6) δ : 8.06 (s, 1 H), 7.95–7.80 (m, 4 H), 4.83 (s, 2 H), 4.22 (s, 2 H), 4.16–4.02 (m, 3 H), 3.91–3.84 (m, 2 H), 3.45–3.37 (m, 2 H), 3.91–3.84 (m, 4 H), 1.20–1.10 (m, 3 H). LC-MS: Method C, r_t = 1.75 min; m/z (ES $^+$), (M + H) $^+$ = 459.

5

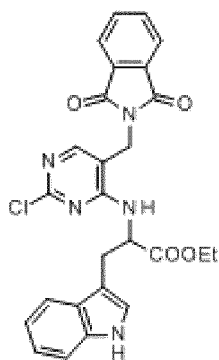
ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]amino]-2-phenylacetate (121)



^1H NMR (DMSO- d_6) δ : 8.09 (s, 1 H), 7.93–7.84 (m, 4 H), 7.69 - 7.63 (m, 1 H), 7.55 - 7.34 (m, 5 H), 5.60 - 5.54 (m, 1 H), 4.77 - 4.61 (m, 2 H), 4.20 - 3.96 (m, 2 H), 1.13 - 1.06 (m, 3 H). LC-MS: Method C, r_t = 2.10 min; m/z (ES $^+$), (M + H) $^+$ = 451.

10

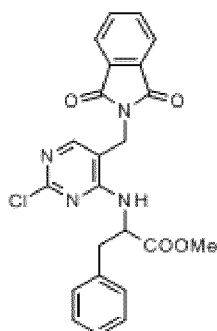
ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]amino]-3-(1H-indol-3-yl)propanoate(122)



15

¹H NMR (CDCl₃) δ: 8.25 (s, 1 H), 7.91 (br. s., 1 H), 7.79 - 7.69 (m, 4 H), 7.49 (d, J = 8.2 Hz, 1 H), 7.19 (d, J = 7.7 Hz, 1 H), 7.12 - 6.95 (m, 4 H), 5.13 - 5.04 (m, 1 H), 4.60 - 4.52 (m, 1 H), 4.48 - 4.42 (m, 1 H), 4.27 - 4.09 (m, 2 H), 3.52 (dd, J = 5.2, 14.5 Hz, 1 H), 3.36 (dd, J = 7.1, 14.8 Hz, 1 H), 1.32 - 1.16 (m, 3 H). LC-MS: Method C, rt = 2.08 min; m/z (ES+), (M + H)⁺ = 504.

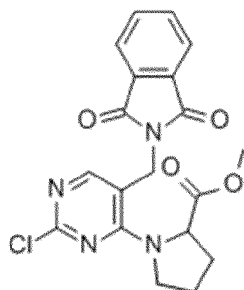
methyl-2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]amino]-3-phenyl-propanoate (123)



¹H NMR (DMSO-d₆) δ: 7.96 (s, 1 H), 7.94 - 7.82 (m, 4 H), 7.49 (m, 1 H), 7.30 - 7.06 (m, 5 H), 4.84 - 4.75 (m, 1 H), 4.67 - 4.44 (m, 2 H), 3.62 (s, 3 H), 3.25 - 3.03 (m, 2 H). LC-MS: Method C, rt = 2.04 min; m/z (ES+), (M + H)⁺ = 451.

Intermediate 108

methyl 1-[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]pyrrolidine-2-carboxylate (108)



A mixture of methyl pyrrolidine-2-carboxylate hydrochloride (0.395 g, 2.39 mmol), 2-[(2,4-dichloropyrimidin-5-yl)methyl]isoindoline-1,3-dione (intermediate 115) (0.70 g, 2.27 mmol), N-ethyl-N-isopropylpropan-2-amine (0.881 g, 6.81 mmol) in tetrahydrofuran (14 mL)

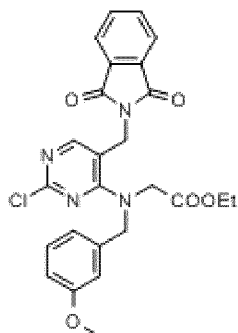
was sealed in a microwave reaction tube and irradiated with microwave at 130°C for 15 min. After cooling to room temperature the reaction mixture was concentrated and the residue taken up with water and extracted with ethyl acetate.

The organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent n-hexane/AcOEt (55:45) to give 652 mg of the target compound as a white solid.

¹H NMR (DMSO-d₆) δ: 7.94 (s, 1 H), 7.92–7.81 (m, 4 H), 4.96 (m, 2 H), 4.59 (m, 1 H), 4.01 (m, 2 H), 3.64 (s, 3 H), 2.29–2.18 (m, 1 H), 2.05–1.96 (m, 2 H), 1.94–1.86 (m, 1 H). LC-MS: Method C, rt =1.67 min; m/z (ES+), (M + H)⁺ = 401.

Intermediates 109 to 111

ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]-[(3-methoxyphenyl)methyl]amino]acetate (109)



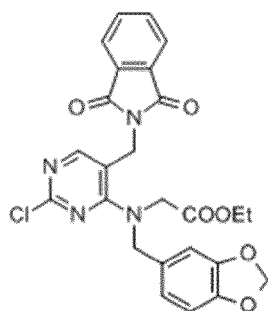
A mixture of ethyl 2-[(3-methoxyphenyl)methylamino]acetate (0.362 g, 1.62 mmol), 2-[(2,4-dichloropyrimidin-5-yl)methyl]isoindoline-1,3-dione (intermediate 115) (0.467 g, 1.55 mmol), N-ethyl-N-isopropyl-propan-2-amine (0.60 g, 4.64 mmol) in tetrahydrofuran (14 mL) was sealed in a microwave reaction tube and irradiated with microwave at 130°C for 70 min. After cooling to room temperature the reaction mixture was concentrated and the residue taken up with water and extracted with ethyl acetate.

The organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent n-hexane/AcOEt (55:45) to give 202 mg of the target compound as a white solid.

¹H NMR (DMSO-d₆) δ: 8.04 (s, 1 H), 7.88–7.80 (m, 4 H), 7.30–6.75 (3m, 4 H), 4.86 (s, 2 H), 4.76 (s, 2 H), 4.18 (s, 2 H), 4.14–4.07 (m, 2 H), 3.73 (s, 3 H), 1.22–1.12 (m, 3 H). LC-MS: Method A, rt =2.11 min; m/z (ES+), (M + H)⁺ = 495.

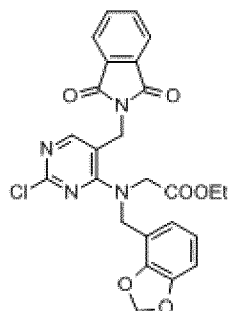
By operating as above reported and by starting from the suitable intermediate derivatives, the following compounds were analogously prepared:

ethyl 2-[1,3-benzodioxol-5-ylmethyl]-[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]amino]acetate (110)



^1H NMR (CDCl_3) δ = 8.00 (s, 1 H), 7.84 (qd, J =3.1, 5.6 Hz, 2 H), 7.79–7.68 (m, 2 H), 6.94–6.67 (m, 3 H), 5.99–5.89 (m, 2 H), 4.85–4.74 (m, 4 H), 4.29–4.18 (m, 2 H), 4.15–4.06 (m, 2 H), 1.37–1.21 (m, 3 H). LC-MS: Method A, r_t = 2.04 min; m/z (ES $^+$), (M + H) $^+$ = 509.

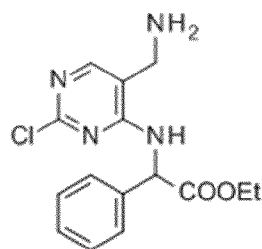
ethyl 2-[1,3-benzodioxol-4-ylmethyl]-[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]amino]acetate (111)



m/z (ES $^+$), (M + H) $^+$ = 509.

Intermediates 112 to 113

ethyl 2-[[5-(aminomethyl)-2-chloro-pyrimidin-4-yl]amino]-2-phenyl-acetate (112)

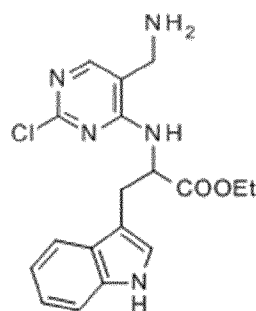


Hydrazine (2.32 mL of 1M solution in THF) was added to a solution of ethyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]amino]-2-phenylacetate (intermediate 121) (348 mg, 0.772 mmol) in MeOH (2.5 mL). The resulting solution was stirred at the reflux temperature for 75 min., then solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent DCM/MeOH 99:1) to give 159 mg of the target compound as a colorless oil.

^1H NMR (DMSO- d_6) δ : 7.91 (s, 1 H), 7.50–7.32 (m, 5 H), 5.54 (s, 1 H), 4.22–3.98 (m, 2 H), 3.78–3.68 (m, 2 H), 1.17–1.11 (m, 3 H). LC-MS: Method A, r_t = 0.99 min; m/z (ES $^+$), (M + H) $^+$ = 321.

By operating as above reported and by starting from the suitable intermediate 122 the following compound was analogously prepared:

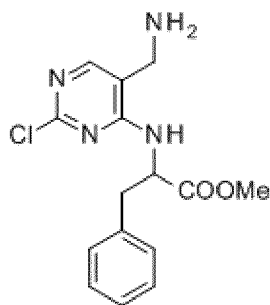
ethyl 2-[[5-(aminomethyl)-2-chloro-pyrimidin-4-yl]amino]-3-(1H-indol-3-yl)propanoate (113)



m/z (ES $^+$), (M + H) $^+$ = 374.

Intermediate 114

methyl 2-[[5-(aminomethyl)-2-chloro-pyrimidin-4-yl]amino]-3-phenyl-propanoate (114)

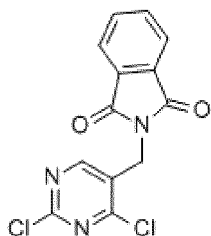


Hydrazine (7.5 mL of 1M solution in THF) was added to a solution of methyl 2-[[2-chloro-5-[(1,3-dioxoisindolin-2-yl)methyl]pyrimidin-4-yl]amino]-3-phenylpropanoate (1.13 g, 2.5 mmol) in MeOH (16 mL). The resulting solution was stirred at the reflux temperature for 16 h, then a further aliquot (5 mL) of hydrazine solution was added and the reaction mixture was refluxed under stirring for additional 5 h. A third aliquot of hydrazine solution (2.5 mL) was added and refluxing was continued for 16 h. Solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent DCM/MeOH 97:3) to give 285 mg of the target compound as a white powder.

¹H NMR (DMSO-d₆) δ: 7.88 (s, 1 H), 7.31–7.16 (m, 5 H), 4.77 (m, 1 H), 3.65–3.57 (s,m, 5 H), 3.20–3.03 (m, 2 H). LC-MS: Method A, rt =1.12 min; m/z (ES+), (M + H)⁺ = 321.

Intermediate 115

15 2-[(2,4-dichloropyrimidin-5-yl)methyl]isoindoline-1,3-dione (115)



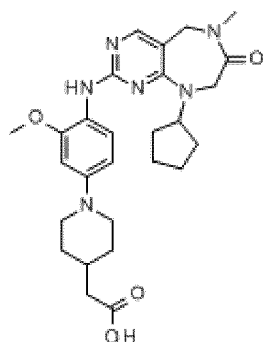
Potassium phthalimide (4.7 g, 25 mmol) was added to a solution of 2,4-dichloro-5-(iodomethyl)pyrimidine (7.3 g, 25 mmol) in THF (85 mL). The resulting mixture was stirred at the reflux temperature for 8h. After cooling the reaction mixture was filtered and concentrated under vacuum. The residue was taken up with water and extracted with ethyl acetate.

The organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was triturated with ethyl acetate to give the target compound as a white solid.

¹H NMR (DMSO-d₆) δ: 8.88 (s, 1 H), 7.93–7.82 (m, 4 H), 4.86 (s, 2 H). LC-MS: Method A, rt = 1.73 min; m/z (ES⁺), (M + H)⁺ = 308.

Intermediate 116

2-[1-[4-[(9-cyclopentyl-6-methyl-7-oxo-5,8-dihydropyrimido[4,5-e][1,4]diazepin-2-yl)amino]-3-methoxy-phenyl]-4-piperidyl]acetic acid (116)

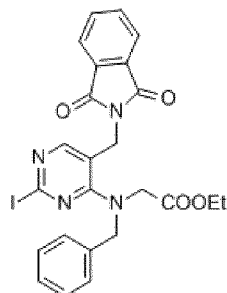


0.02 mL of a 2N solution of lithium hydroxide were added to a solution of methyl 2-[1-[4-[(9-cyclopentyl-6-methyl-7-oxo-5,8-dihydropyrimido[4,5-e][1,4]diazepin-2-yl)amino]-3-methoxy-phenyl]-4-piperidyl]acetate (intermediate. 118) (38 mg, 0.073 mmol) in MeOH (0.3 mL) and THF (0.3 mL). The resulting solution was stirred at room temperature for 40 h.

Volatiles were evaporated under vacuum and the remaining aqueous mixture was acidified with 1N HCl up to pH 5 and extracted with DCM. The organic layer was dried over sodium sulphate, filtered and evaporated to give 31.9 mg (off-white foam) of the target product.

¹H NMR (DMSO-d₆) δ: 12.24–11.90 (br. s., 1 H), 7.83–7.79 (m, 1 H), 7.70 (s, 1 H), 7.31 (s, 1 H), 6.6–6.57 (m, 1 H), 6.50–6.38 (m, 1 H), 5.44–5.25 (m, 1 H), 4.42 (s, 2 H), 4.12 (s, 2 H), 3.80 (s, 3 H), 3.65–3.52 (m, 2 H), 2.89 (s, 3 H), 2.64–2.55 (m, 2 H), 2.21–2.16 (m, 2 H), 1.82–1.19 (m, 13 H). LC-MS: Method A, rt = 0.89 min; m/z (ES⁺), (M+H)⁺ = 509.

Intermediate 124

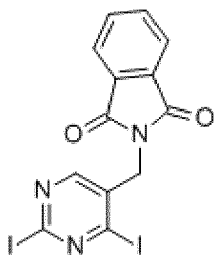
2-[benzyl-[5-[(1,3-dioxoisindolin-2-yl)methyl]-2-iodo-pyrimidin-4-yl]amino]-acetate (124)

5 ethyl 2-(benzylamino)acetate (0.335 g, 1.68 mmol) was added to a solution of 2-[(2,4-diiodopyrimidin-5-yl)methyl]isoindoline-1,3-dione (intermediate 125) (0.786 g, 1.6 mmol) and N-ethyl-N-isopropyl-propan-2-amine (0.62 g, 4.8 mmol) in dry THF (6 mL) at room temperature and the mixture was stirred at the reflux temperature for 24 h. Then a second aliquot of ethyl 2-(benzylamino)acetate (1.6 mmol) was added and the mixture was
10 refluxed under stirring for additional 24 h.

After cooling to room temperature the reaction mixture was concentrated and the residue taken up with water and extracted with ethyl acetate.

The organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (eluent DCM/AcOEt
15 (93:7) to give 200 mg of the target compound as a white solid.

LC-MS: Method A, rt =2.29 min; m/z (ES⁺), (M+H)⁺ = 557.

Intermediate 125**2-[(2,4-diiodopyrimidin-5-yl)methyl]isoindoline-1,3-dione (125)**

20 Cold HI (1.1 mL of a 57% aqueous solution) was added dropwise to a cooled (-5 °C), stirred solution of 2-[(2,4-dichloropyrimidin-5-yl)methyl]isoindoline-1,3-dione (intermediate 115,) (0.514 g, 1.65 mmol) in DCM (2 mL). The mixture was stirred at 0 °C for 1h and then

at room temperature for 5h. The mixture was cooled to 0 °C and a further aliquot of HI was added (1.1 mL). The reaction was stirred at 0 °C for 1 hour, and at r.t. for 5 h. The reaction mixture was then carefully neutralized with K₂CO₃ and washed with aqueous sodium metabisulfite. The organic layer was separated and the aqueous layer was
5 extracted with DCM. The combined organic layers were dried over sodium sulphate and the solvent was removed in vacuo to give 700 mg of off white solid that was used in the following synthetic step without further purification.

LC-MS: Method A, rt =1.97 min; m/z (ES+), (M+H)⁺ = 492.

10 Biochemical Assays

The inhibiting activity of putative Mps-1 inhibitors and the potency of selected compounds were determined through an assay based on the use of the ADP-Glo Kinase™ Assay technology (V9102 ,Promega, Madison WI 53711 USA).

N-terminal His-tagged human Mps-1 kinase domain (corresponding to residues 519-808
15 of the full length sequence GenBank accession number: NP_003309.2) was expressed in E.Coli and purified using standard affinity purification techniques. To get a fully activated enzyme, the protein was then subjected to auto-phosphorylation in presence of 1 mM ATP at 25°C for 1 hour in kinase buffer (HEPES 50 mM pH 7.5, MgCl₂ 5 mM, MnCl₂ 1 mM, DTT 1 mM, orthovanadate 100 µM); ATP was then removed with a desalting column.

20 As substrate for the kinase reaction, a fragment of human Mad1 protein (corresponding to residues 485-584 of the full length sequence (GenBank accession number: NP_001013859.1), His tagged expressed in E.Coli and purified using affinity chromatography techniques were used.

This method measures kinase activity by quantifying the amount of ADP produced during
25 a kinase reaction. The assay is performed in two steps: first, after the kinase reaction, an equal volume of ADP-Glo Reagent is added to terminate the kinase reaction and deplete the remaining ATP; second, the Kinase Detection Reagent is added to simultaneously convert ADP to ATP and allow the newly synthesized ATP to be measured using luciferase/luciferin reaction.

30 The light generated is measured using a luminometer (Infinite® F200, Tecan, 8708 Männedorf Schweiz). The luminescent signal generated is proportional to the ADP concentration produced and is correlated with kinase activity.

Kinase Assay conditions: 200 μ M Mad1 protein substrate (equal to the $K_{m_{app}}$ Mad1), 5nM Mps-1-Kinase Domain, and test compound in 100% DMSO were added in a final volume of 40 μ l kinase buffer (HEPES 50 mM pH 7.5, $MgCl_2$ 5 mM, $MnCl_2$ 1 mM, DTT 1 mM, orthovanadate 100 μ M) to each well of a 96 half area flat bottom white well plate.

- 5 The mixture was incubated for 15 minutes at room temperature to allow pre-binding of the test compounds to Mps-Kinase Domain before to start kinase reaction by the addition of 20 μ M ATP (equal to $2K_{m_{app}}$ ATP) (purchased from Sigma). After a reaction time of 30 minutes at room temperature, an half volume of reaction was transferred from the original plate into a new 96 well plate to be stopped by adding 20 μ l of ADP-Glo Reagent. The
- 10 resulting mixture was incubated 40minutes at room temperature. Then 40 μ l of Kinase Detection Reagent was added to each well and let stand 30 minutes before luminescence was read by a luminometer (Infinite® F200, Tecan).

- IC_{50} determination: inhibitors diluted in DMSO were tested at different concentrations ranging from 0.005 to 100 μ M (serial 1:3 dilutions). Control wells that produced a
- 15 maximum signal corresponding to maximum enzyme activity were created by adding 2.5% DMSO instead of test compound. Control wells that produced a minimum signal corresponding to fully inhibited enzyme were created by not adding enzyme to the reaction.

- Experimental data were analyzed by the computer program GraphPad Prism software
- 20 using the four parameter logistic equation:

$$y = bottom + (top - bottom) / (1 + 10^{((\log IC_{50} - x) * slope)})$$

where x is the logarithm of the inhibitor concentration, y is the response; y starts at bottom and goes to top with a sigmoid shape.

- RESULTS: IC_{50} for Mps-1 in Mps-1 inhibition assay according to the methods described**
- 25 above

The following compounds:

2, 4, 26, 27, 31, 33, 34, 37, 38, 39, 40, 46 and 47.

display IC_{50} values ranging from 3 μ M to 10 μ M.

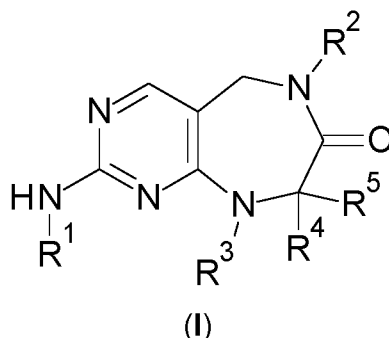
The following compounds:

- 30 1, 3, 15, 16, 22, 23, 24, 28, 29, 30, 32, 35, 36, 45, and 52.

display IC_{50} values below 3 μ M.

CLAIMS

1. A compound of formula (I)



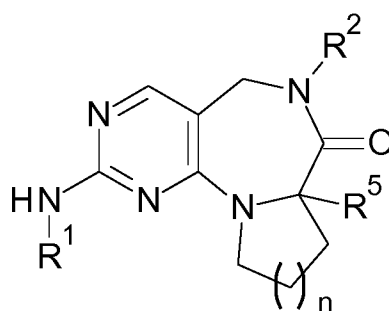
- 5 wherein:
- R¹ is a phenyl, optionally substituted by 1 to 3 groups selected from: C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, C₁₋₃ haloalkoxy, cyano, heterocycloalkyl, CONR⁶R⁷;
- R² is hydrogen, C₁₋₃ alkyl optionally substituted by cyano or methoxy;
- 10 R³ is hydrogen, C₁₋₃ alkyl, C₃₋₆ cycloalkyl, heterocycloalkyl, indanyl, CH₂R⁸,
- R⁴, R⁵ are, independently, hydrogen; C₁₋₃ alkyl, phenyl, CH₂R⁸; or R⁴ and R⁵ together with the carbon atom to which they are bound form a C₃₋₆ cycloalkyl ring; or, R⁴ and R³ together with the carbon and nitrogen atoms to which they are respectively bound, form a pyrrolidine or piperidine ring;
- 15 R⁶ and R⁷ are, independently, hydrogen; heterocycloalkyl; or R⁶ and R⁷ together with the nitrogen atom to which they are bound form a heterocycloalkyl ring;
- 20 R⁸ is phenyl or heteroaryl optionally substituted by one to three substituents, selected from C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, cyano; or R⁸ is 1,3-benzodioxolyl or 2,2-difluoro-1,3-benzodioxolyl;
- wherein the phenyl in R⁴, R⁵ and R⁸ may be optionally substituted by one to three substituents, selected from C₁₋₃ alkyl, C₁₋₃ alkoxy, or halogen;
- 25 wherein the heterocycloalkyl in R¹ and R⁶, or the heterocycloalkyl ring formed by R⁶ and R⁷ together with the nitrogen atom to which they are bound, is optionally substituted by

one to three substituents, selected from C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, hydroxy group, pyrrolidinyl, morpholinyl, piperidinyl or 2-oxo-2-heterocycloalkyl-ethyl; or stereoisomers or pharmaceutically acceptable salts thereof.

2. The compound according to claim 1, wherein R² is methyl.

5 3. The compound according to claim 1 or 2 wherein R³ is selected from the group consisting of: C₅₋₆ cycloalkyl, 5-6 membered heterocycloalkyl, indanyl, or CH₂R⁸ wherein R⁸ is as defined in claim 1.

4. The compound according to claim 1 having formula (Ia)



(Ia)

wherein: R¹, R² and R⁵ are as defined in claim 1, and n is 1 or 2 or stereoisomers or pharmaceutically acceptable salts thereof.

5. The compound according to claim 1, selected from the group consisting of:

9-cyclopentyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6-methyl-5,8-

15 dihydropyrimido[4,5-e][1,4]diazepin-7-one;

9-benzyl-6-methyl-2-[[4-(morpholin-4-yl)phenyl]amino]-5H,6H,7H,8H,9H-pyrimido[4,5-e][1,4]diazepin-7-one;

9-cyclopentyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;

20 9-cyclopentyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;

9-benzyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;

9-benzyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;

9-cyclopentyl-2-[4-(4-methylpiperazin-1-yl)anilino]-6,8-dihydro-5H-pyrimido[4,5-

25 e][1,4]diazepin-7-one;

4-[(9-cyclopentyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-

- methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide;
9-benzyl-2-[4-(4-methylpiperazin-1-yl)anilino]-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
4-[(9-benzyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide;
5 9-isopropyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
4-[(9-isopropyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide;
9-methyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
10 4-[(9-methyl-7-oxo-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-2-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide;
9-cyclopentyl-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
9-cyclopentyl-2-(2-methoxy-4-morpholino-anilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
15 8-benzyl-2-(2-methoxy-4-morpholino-anilino)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
8-benzyl-9-methyl-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
20 8-benzyl-2-(2-methoxy-4-morpholino-anilino)-9-methyl-6,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-7-one;
2-(4-morpholinoanilino)-5,6,7a,8,9,10-hexahydro-7H-pyrimido[5,4-f]pyrrolo[1,2-a][1,4]diazepin-7-one;
8-benzyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
25 9-cyclopentyl-6-ethyl-2-(2-methoxy-4-morpholino-anilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
9-cyclopentyl-6-ethyl-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
30 9-cyclopentyl-2-[2-methoxy-4-(4-morpholino-1-piperidyl)anilino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
2-(2-methoxy-4-morpholino-anilino)-8-phenyl-5,6,8,9-tetrahydropyrimido[4,5-

- e][1,4]diazepin-7-one;
 2-(2-methoxy-4-morpholino-anilino)-9-[(3-methoxyphenyl)methyl]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-9-[(3-methoxyphenyl)methyl]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 5 9-indan-2-yl-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-9-indan-2-yl-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 10 9-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 2-(2-methoxy-4-morpholino-anilino)-6-methyl-9-tetrahydropyran-4-yl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6-methyl-9-tetrahydropyran-4-yl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 15 9-(1,3-benzodioxol-5-ylmethyl)-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 9-(1,3-benzodioxol-5-ylmethyl)-2-[4-(4-hydroxy-1-piperidyl)-2-methoxy-anilino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 20 9-(1,3-benzodioxol-4-ylmethyl)-2-(2-methoxy-4-morpholino-anilino)-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 9-(1,3-benzodioxol-4-ylmethyl)-2-[[4-(4-hydroxy-1-piperidyl)-2-methoxy-phenyl]amino]-6-methyl-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 8-(1H-indol-3-ylmethyl)-2-[(2-methoxy-4-morpholino-phenyl)amino]-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one
 25 2-[[4-(4-hydroxy-1-piperidyl)-2-methoxy-phenyl]amino]-8-(1H-indol-3-ylmethyl)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
 9-cyclopentyl-6-methyl-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 30 9-cyclopentyl-6-ethyl-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 2-(9-cyclopentyl-2-[[4-(morpholin-4-yl)phenyl]amino]-7-oxo-5H,6H,7H,8H,9H-pyrimido[4,5-

- e][1,4]diazepin-6-yl)acetonitrile;
 9-cyclopentyl-6-(2-methoxyethyl)-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-
 e][1,4]diazepin-7-one;
 8-benzyl-6,9-dimethyl-2-(4-morpholinoanilino)-5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-
 5 one;
 8-benzyl-2-(4-morpholinoanilino)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
 9-cyclopentyl-2-[2-methoxy-4-(4-methylpiperazine-1-carbonyl)anilino]-6-methyl-5,8-
 dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 4-[(9-cyclopentyl-6-methyl-7-oxo-5,8-dihydropyrimido[4,5-e][1,4]diazepin-2-yl)amino]-3-
 10 methoxy-N-(1-methyl-4-piperidyl)benzamide;
 9-cyclopentyl-6-methyl-2-[4-(4-methylpiperazine-1-carbonyl)-2-(trifluoromethoxy)anilino]-
 5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one;
 2-(4-morpholinoanilino)spiro[6,9-dihydro-5H-pyrimido[4,5-e][1,4]diazepine-8,1'-
 cyclopropane]-7-one;
 15 8-methyl-2-(4-morpholinoanilino)-5,6,8,9-tetrahydropyrimido[4,5-e][1,4]diazepin-7-one;
 8-methyl-2-[4-(4-methylpiperazin-1-yl)anilino]-5,6,8,9-tetrahydropyrimido[4,5-
 e][1,4]diazepin-7-one;
 9-(1H-imidazol-2-ylmethyl)-2-(4-morpholinoanilino)-6,8-dihydro-5H-pyrimido[4,5-
 e][1,4]diazepin-7-one and
 20 9-cyclopentyl-2-[2-methoxy-4-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-1-piperidyl]anilino]6-methyl-
 5,8-dihydropyrimido[4,5-e][1,4]diazepin-7-one
 or stereoisomers or pharmaceutically acceptable salts thereof.
6. The compound according to any one of the previous claims for use as Monopolar
 Spindle 1 kinase (Mps-1 or TTK) inhibitor.
 - 25 7. The compound according to any one of the previous claims for use as medicament.
 8. The compound according to any one of the previous claims for use in the treatment
 and/or prevention of proliferative diseases and/or conditions.
 9. The compound according to any one of the previous claims for use in the treatment
 and/or prevention of cancer.
 - 30 10. The compound according to any one of the previous claims for use in the treatment
 and/or prevention of lymphoma, hepatocellular carcinoma, pancreatic cancer, brain
 tumour, breast cancer, lung cancer, colon cancer, cervical cancer, prostate cancer, kidney

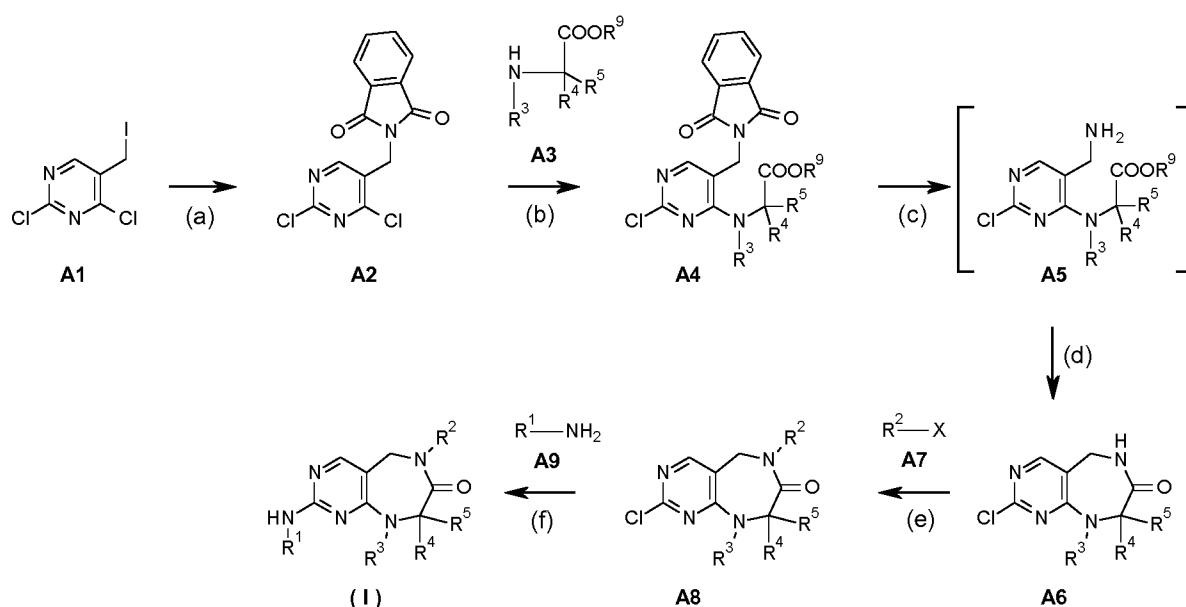
cancer, osteosarcoma, nasopharyngeal cancer, oral cancer, melanoma and ovarian cancer.

11. A pharmaceutical composition comprising the compound according to any one of the previous claims, or stereoisomers, a hydrate, solvate, or pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient and/or diluent.

12. The pharmaceutical composition according to claim 11 further comprising at least one therapeutic agent, preferably selected from the group consisting of: Mps-1 inhibitors, antiproliferative/antineoplastic agents, cytostatic agents, agents which inhibit cancer cell invasion, inhibitors of growth factor function, antiangiogenic agents, cell cycle inhibitors, proteasome inhibitors, HSP90 inhibitors, Selective COX-2 inhibitors, histone deacetylase inhibitors, non selective NSAIDs or chemotherapeutic agents.

13. The pharmaceutical composition according to claims 11 or 12, in the form of tablets, capsules, oral preparations, powders, granules, pills, injectable or infusible liquid, solutions, suspensions, emulsions, suppositories, ointments, creams, lotions, gels, pastes, transdermal delivery devices

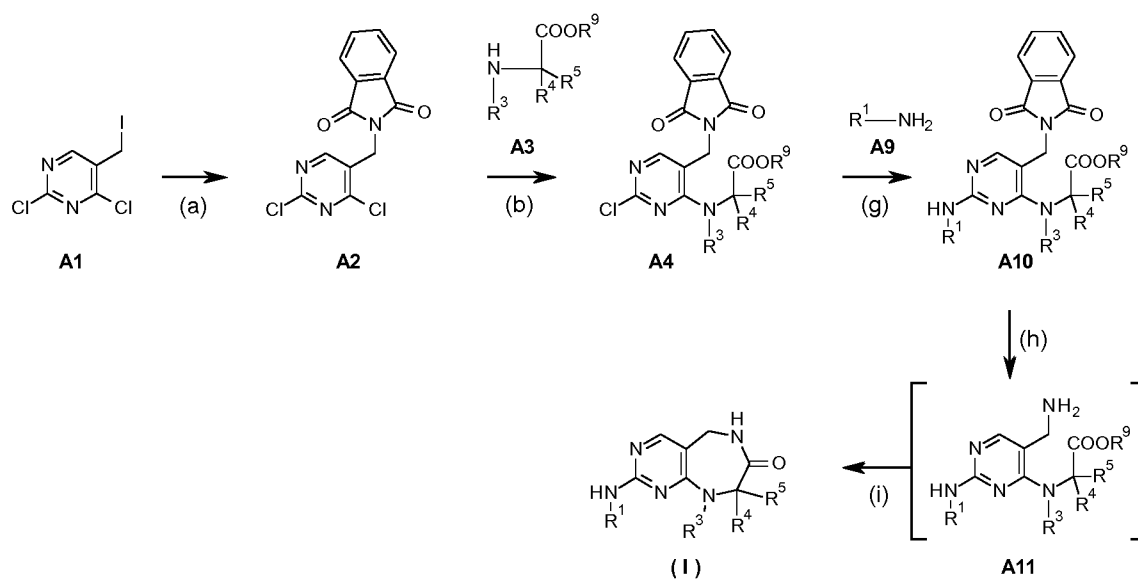
14. A process for obtaining a compound of formula (I) according to any of claims 1 to 5, the process comprising the preparation of compounds of formula **A2** by reaction of 2,4-dichloro-5-(iodomethyl)pyrimidine (**A1**) with potassium phthalimide, the reaction of a compound of formula **A2** with an amino-ester of formula **A3** in presence of a base to obtain a compound of formula **A4**, the removal of the phthalimido group of compounds of formula **A4** with an alkaline agent to obtain a compound of formula **A5**, which cyclizises to a compound of formula **A6**, the reaction of a compound of formula **A6** with an alkyl halide **A7** of formula **R²-X** in presence of a base to obtain a compound of formula **A8**, and finally react a compound of formula **A8** with an aniline **A9** of formula **R¹-NH₂** to obtain a compound of formula (I), as represented in **Scheme A1** below:

**Scheme A1**

wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined in claim 1, X is halogen, and R^9 is a methyl or ethyl.

15. A process for obtaining a compound of formula (I) according to any of claims 1 to 5, the process comprising the preparation of compounds of formula **A2** by reaction of 2,4-dichloro-5-(iodomethyl)pyrimidine (**A1**) with potassium phthalimide, the reaction of a compound of formula **A2** with an amino-ester of formula **A3** in presence of a base to obtain a compound of formula **A4**, the reaction a compound of formula **A4** with an aniline **A9** of formula R^1-NH_2 to obtain a compound of formula **A10**, the removal of the phthalimido group of compounds of formula **A10** with an alkaline agent to obtain a compound of formula **A11**, which cyclizises to a compound of formula (I), as represented in **Scheme A2** below:

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**Scheme A2**

wherein R¹, R², R³, R⁴ and R⁵ are as defined in claim 1, and R⁹ is a methyl or ethyl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/064498

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D487/14 C07D487/04 A61K31/4545 C07D401/12 A61P11/00 A61P37/08 ADD. According to International Patent Classification (IPC) or to both national classification and IPC														
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data														
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>US 2012/149898 A1 (KAY DAVID [GB] ET AL) 14 June 2012 (2012-06-14) the whole document -----</td> <td>1-15</td> </tr> <tr> <td>A</td> <td>US 2012/040961 A1 (GRAY NATHANAEL S [US] ET AL) 16 February 2012 (2012-02-16) the whole document -----</td> <td>1-15</td> </tr> <tr> <td>A</td> <td>US 2012/309747 A1 (CHARRIER JEAN-DAMIEN [GB] ET AL) 6 December 2012 (2012-12-06) the whole document -----</td> <td>1-15</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	US 2012/149898 A1 (KAY DAVID [GB] ET AL) 14 June 2012 (2012-06-14) the whole document -----	1-15	A	US 2012/040961 A1 (GRAY NATHANAEL S [US] ET AL) 16 February 2012 (2012-02-16) the whole document -----	1-15	A	US 2012/309747 A1 (CHARRIER JEAN-DAMIEN [GB] ET AL) 6 December 2012 (2012-12-06) the whole document -----	1-15
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Date of the actual completion of the international search 21 September 2015		Date of mailing of the international search report 19/10/2015												
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Lorenzo Varela, M												

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Information on patent family members

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