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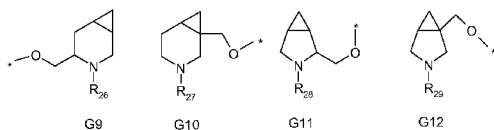
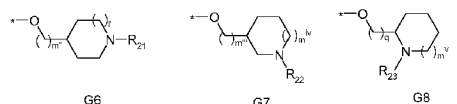
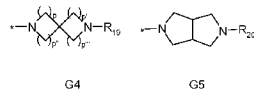
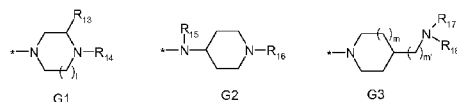
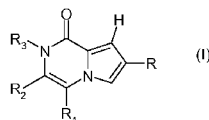
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[Continued on next page]

(54) Title: PYRROLO [1, 2-A] PYRAZINE DERIVATIVES AS VASOPRESSIN VIB RECEPTOR ANTAGONISTS



(57) Abstract: The present invention relates to novel compounds of formula (I) or salts thereof; wherein R is -X-[CH₂]_nCR₄R₅-Y; or a group G; R₁ is H or C1 -C4 alkyl; R₂ is aryl, heteroaryl or C3-C7 cycloalkyl, which may be substituted with one or more: halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, -CN; R₃ is -CH₂-C(=O)-NH-R₆; X is -CR₇R₈-, -O-, -NR₉-, -S-; Y is -NR₁₀R₁₁ R₄ is H or C1 -C4 alkyl; R₅ is H or C1 -C4 alkyl; R₆ is C1-C6 alkyl, C3-C6 cycloalkyl; C3-C6 cycloalkyl- (C1 -C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; R₇ is H or C1 -C4 alkyl; R₈ is H or C1 -C4 alkyl; R₉ is H or C1 -C4 alkyl; R₁₀ is H or C1 -C4 alkyl, or together with R₁₁ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR₁₂; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; R₁₁ is H or C1 -C4 alkyl; R₁₂ is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl- (C1 -C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; G is one of the groups selected from the list consisting of G1, G2, G3, G4, G5, G6, G7, G8, G9, G10, G11 and G12; R₁₃ is H or C1-C4 alkyl, or together with R₁₄ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR₂₄; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; R₁₄ R₁₆ is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl- (C1 -C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; R₁₅, R₁₇ correspond to H or C1-C4 alkyl and may assume different meanings; R₁₈ is H or C1-C4 alkyl, or together with R₁₇ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR₂₅; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅ is H,

C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl- (C1 -C2 alkyl); which may be substituted

[Continued on next page]



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- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
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by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; R₂₆, R₂₇, R₂₈, R₂₉ is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl- (C1 -C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; I, I' correspond to 1 or 2 and may assume different meanings; m, m', m'', m''', m^v, m^v correspond to 0, 1 or 2 and may assume different meanings; n is 1, 2 or 3; q is 1, 2 or 3; p, p', p'', p''' correspond to 0, 1, 2 or 3 and may assume different meanings; processes for their preparation, intermediates used in these processes, pharmaceutical compositions containing them and their use in therapy, as antagonists of V1b receptors, e.g. to treat depression and anxiety.

PYRROLO [1, 2-A] PYRAZINE DERIVATIVES AS VASOPRESSIN V1b RECEPTOR ANTAGONISTS

The present invention relates to novel compounds, processes for their preparation,
5 intermediates used in these processes, pharmaceutical compositions containing them and
their use in therapy, as V1b receptor antagonists.

Evidence has accumulated during the last two decades indicating that Arginine
Vasopressin (AVP) plays a major role in the regulation of the hypothalamic-pituitary-
10 adrenal (HPA) axis. In particular, the release of the adrenocorticotropin hormone (ACTH)
secretion from the pituitary gland is mediated by the V1b receptor subtype (Antoni, 1993,
Front Neuroendocrinol, 14:76-122). In rodents and in humans, AVP is a weak stimulus in
physiological conditions but it participates in the adaptation of the hypothalamic-pituitary-
adrenal (HPA) axis during stress through its ability to potentiate the stimulatory effect of
15 corticotrophin releasing factor (CRF) (Rivier and Vale, Nature, 1983, 305, 325-327). An
increased HPA axis activity is found in 40-70% of patients with major depression (Heuser
et al., 1996, Am J Psychiatry, 153:93-99). AVP synergies with CRF in maintaining this
overdrive and plays a major role in prolonged stressful states (Aguilera & Rabadan-Diehl,
2000, Regul Pept, 96, 23-29).

An emerging body of preclinical and clinical evidence demonstrates that CRF is the
physiological mediator of ACTH release under acute stressful conditions whereas AVP
represents the dynamic mediator of ACTH release and strongly potentiates CRH-induced
ACTH release. This situation may be altered in disease states where a dysregulation or
25 hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis is observed. In these
cases, the primary control of ACTH release may be shifted from CRH to AVP (Volpi et al.,
2004, Ann N Y Acad Sci, 1018:293-3014).

This suggests that the blockade of V1b receptors could be exploited as a possible
30 therapeutic strategy for the treatment of diseases that are characterized by an excessive
cortisol secretion, such as major depression (Scott & Dinan, 1998, Life Sci, 62:1985-1998)
and stress-related disorders (Griebel et al. 2003, Curr Drug Targets CNS Neurol Disord,
2:191-200). Furthermore, abnormally elevated HPA activity may results in an over
secretion of ACTH causing hypercortislaemia which predisposes to a metabolic syndrome
35 characterised by insulin resistance, hyperinsulinemia, impaired glucose tolerance,
dyslipideamia, obesity (in particular abdominal obesity) and non-insulin-dependent
diabetes mellitus (NIDDM).

AVP effects are mediated via 7-transmembrane G-protein coupled receptor subtypes: V1a
40 (mainly distributed in vascular wall, liver, kidney, platelet), V1b or V3 (mainly distributed in
anterior pituitary) and V2 (almost exclusively found in the kidney). Activation of V1a and
V1b receptors stimulates phosphatidylinositol (IP) hydrolysis and mobilises calcium; V2

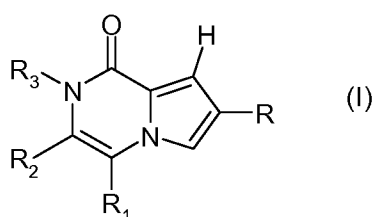
receptors are positively coupled to adenylyl cyclase. The human V1b receptor has a pharmacological profile clearly distinct from that of the human V1a and V2 receptors and activates several signalling pathways via different G proteins of the Gq, Gi and Gs families (Thibonnier et al., 1998, Adv Exp Med Biol, 449:251-276).

V1b mRNA is expressed in 90 % of corticotrope cells and immunohistochemical localisation reveals significant expression of V1b receptors in other brain area such as hippocampus, frontal, piriform and cingulate cortex, caudate putamen, medial habenula, central amygdala, hypothalamus and cerebellum in rats (Hernando et al., 2001, Endocrinology, 142:1659-1668). Recent tissue localisation studies indicate that the V1b receptor mRNA is not only present in anterior pituitary gland in human and rat, but also in other tissues, such as the adrenal medulla, pancreas, kidney, thymus, heart, lung and uterus (Lolait et al., 1995, Proc Natl Acad Sci U S A, 92:6783-6787).

Studies with V1b receptor knock out mice revealed not only changes in HPA axis regulation (Lolait et al., 2007, Endocrinology 148:849-856) as expected, but also profound modification of social behavior (Wersinger et al., 2002, Mol Psychiatry 7:975-984) and insulin release from the pancreas (Oshikawa et al., 2004, Mol Pharmacol 65:623-629). Taken together, these data strongly suggest that selective V1b receptor ligands could bring beneficial effects to different patient populations. The synthetic V1b receptor antagonist SSR149415 (Serradeil Le-Gal et al., 2002, J Pharmacol Exp Ther, 300:1122-1130) has been widely utilised in preclinical models and data obtained to date consistently support the potential therapeutic benefits that may derive from the blockade of V1b receptors in stress-related disorders (Griebel et al, 2002, Proc Natl Acad Sci U S A, 99: 6370-6375).

Thus, the object of the present invention is to provide novel compounds which are V1b antagonists.

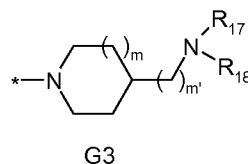
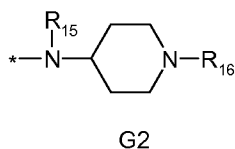
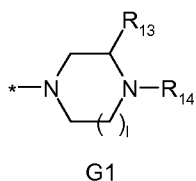
The present invention provides compounds of formula (I) or pharmaceutically acceptable salts or solvates thereof:



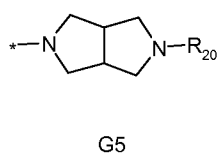
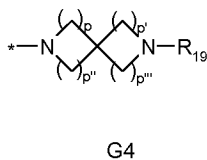
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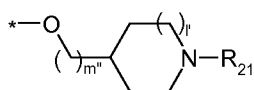
R is -X-[CH₂]_nCR₄R₅-Y; or a group G;
 R₁ is H or C1-C4 alkyl;

	R ₂	is aryl, heteroaryl or C3-C7 cycloalkyl, which may be substituted with one or more: halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, -CN;
5	R ₃	is -CH ₂ -C(=O)-NH-R ₆ ;
	X	is -CR ₇ R ₈ -, -O-, -NR ₉ -, -S-;
	Y	is -NR ₁₀ R ₁₁
	R ₄	is H or C1-C4 alkyl;
	R ₅	is H or C1-C4 alkyl;
10	R ₆	is C1-C6 alkyl, C3-C6 cycloalkyl; C3-C6 cycloalkyl-(C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;
	R ₇	is H or C1-C4 alkyl;
15	R ₈	is H or C1-C4 alkyl;
	R ₉	is H or C1-C4 alkyl;
	R ₁₀	is H or C1-C4 alkyl, or together with R ₁₁ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR ₁₂ ; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;
20		
	R ₁₁	is H or C1-C4 alkyl;
	R ₁₂	is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl-(C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;
25		
	G	is one of the groups selected from the list consisting of G1, G2, G3, G4, G5, G6, G7, G8, G9, G10, G11 and G12:
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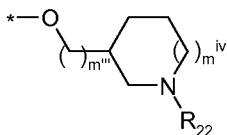


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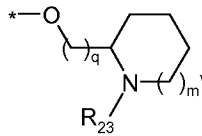




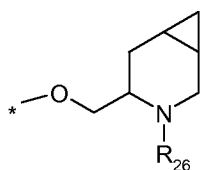
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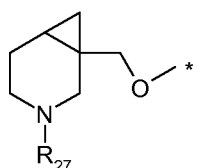
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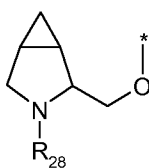
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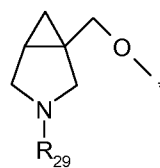
G9



G10



G11



G12

R₁₃

is H or C1-C4 alkyl, or together with R₁₄ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR₂₄; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;

R₁₄, R₁₆

is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl- (C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;

R₁₅, R₁₇

correspond to H or C1-C4 alkyl and may assume different meanings;

R₁₈

is H or C1-C4 alkyl, or together with R₁₇ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR₂₅; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;

R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅

is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl- (C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;

R₂₆, R₂₇, R₂₈, R₂₉

is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl- (C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;

l, l' correspond to 1 or 2 and may assume different meanings;
 m, m', m'', m''', m^{iv}, m^v correspond to 0, 1 or 2 and may assume different meanings;
 5 n is 1, 2 or 3;
 q is 1, 2 or 3;
 p, p', p'', p''' correspond to 0, 1, 2 or 3 and may assume different meanings.

10 The person skilled in the art would understand that for compounds of formula (I) the asterisk sign * is used in G groups to indicate the point of attachment of the group itself to the rest of the molecule.

The compounds of the present invention may be in the form of and/or may be
 15 administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge et al, J. Pharm. Sci., 1977, 66, 1-19.

Typically, a pharmaceutically acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by
 20 filtration or may be recovered by evaporation of the solvent.

Suitable pharmaceutically acceptable addition salts are formed from acids which form non-toxic salts and examples are hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, malate, fumarate,
 25 lactate, tartrate, citrate, formate, gluconate, succinate, pyruvate, oxalate, oxaloacetate, trifluoroacetate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and isethionate.

Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such
 30 as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases, including salts of primary, secondary and tertiary amines, such as isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexyl amine and N-methyl-D-glucamine.

35 Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound of formula (I) using conventional methods.

Those skilled in the art of organic chemistry will appreciate that many organic compounds
 40 can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a

complex with water is known as a "hydrate". Solvates of the compound of the invention are within the scope of the invention.

In addition, prodrugs are also included within the context of this invention.

- 5 As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and
10 Pergamon Press, 1987, and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference.

- The term prodrug also encompasses any covalently bonded carriers that release a
15 compound of structure (I) in vivo when such a prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or in vivo, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein amine groups are bonded to any group that, when administered to a patient, cleaves to form the
20 amine groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of amine functional groups of the compounds of structure (I).

- With regard to stereoisomers, the compounds of formula (I) may have one or more
25 asymmetric carbon atoms and may occur as racemates, racemic mixtures or diastereoisomeric mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

- When a specific enantiomer of a compound of formula (I) is required, this may be obtained
30 for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods, such as H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

- 35 Or a specific enantiomer may also be prepared from a corresponding optically pure intermediate.

- Separation of diastereoisomers, or cis and trans isomers, or syn and anti isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture.

40

Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the scope of the present invention.

The term C1-C6 alkyl as used herein as a group or a part of the group refers to a linear or branched alkyl group containing from 1 to 6 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert butyl, pentyl or hexyl.

5

The term C1-C4 alkyl as used herein as a group or a part of the group refers to a linear or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert butyl.

- 10 The term C3-C6 cycloalkyl group means a saturated monocyclic hydrocarbon ring of 3 to 6 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

The term C3-C7 cycloalkyl group means a saturated monocyclic hydrocarbon ring of 3 to 7 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

15

The term C4-C7 cycloalkyl group means a saturated monocyclic hydrocarbon ring of 4 to 7 carbon atom such as, for example, cyclobutyl, cyclopentyl, cyclohexyl; cycloheptyl.

- 20 The term 'C3-6cycloalkylC1-2alkyl' as used herein means an alkyl having one or two carbon atoms wherein one hydrogen atom is replaced with a C₃-C₆ cycloalkyl group as above defined, for example methylcyclopropane.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

25

The term halo C1-C4 alkyl means an alkyl group having one to 4 carbon atoms and wherein at least one hydrogen atom is replaced with halogen such as for example a trifluoromethyl group and the like.

- 30 The term C1-C4 alkoxy group may be a linear or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy and the like.

The term halo C1-C4 alkoxy group may be a C1-C4 alkoxy group as defined before substituted with at least one halogen, preferably fluorine, such as OCHF₂, or OCF₃.

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The term aryl means an aromatic carbocyclic moiety of 6 to 12 members. Representative aryl include (but are not limited to): phenyl, biphenyl or naphthyl.

- 40 The term heteroaryl means an aromatic heterocycle ring of 5 to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono-and bicyclic ring systems.

Representative heteroaryls include (but are not limited to): furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinoliny, isoquinoliny, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnoliny, phthalazinyl, triazolyl, tetrazolyl, quinazolinyl, benzodioxolyl, benzothiadiazolyl, benzooxadiazolyl, imidazo[1,2-a]pyrazinyl, isothiazolyl, thiadiazolyl, [1,2,4]thiazol[1,5-9]pyridinyl.

Representative 5-6 membered heteroaryls include (but are not limited to): furyl, thiophenyl, pyrrolyl, indolyl, pyridyl, oxazolyl, isooxazolyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, triazolyl, tetrazolyl, isothiazolyl, thiadiazolyl.

The 4-8 saturated or unsaturated heterocycle ring means a 4-8 mono-, bicyclic heterocycle ring which is either saturated, or unsaturated and one to four carbon atoms may be replaced by an heteroatom as defined above. Thus, the term include (but are not limited to): azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, hydantoinyl, hexahydro-1H-azepinyl and octahydroazocinyl.

In one embodiment, R is -X-[CH₂]_nCR₄R₅-Y or a group G. In another embodiment, R is -X-[CH₂]_nCR₄R₅-Y. In a further embodiment, R is a group G.

In one embodiment, R₁ is H or C1-C4 alkyl (for example methyl). In another embodiment, R₁ is H. In a further embodiment, R₁ is C1-C4 alkyl (for example methyl).

In one embodiment, R₂ is aryl, heteroaryl or C3-C7 cycloalkyl, which may be substituted with one or more: halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, -CN. In another embodiment, R₂ is aryl which may be substituted with one or more: halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, -CN. In a further embodiment, R₂ is a phenyl ring which may be substituted with one or more: halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy. In a still further embodiment, R₂ is a phenyl ring which m- or p- substituted with one or two: halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy

In one embodiment, R₃ is -CH₂-C(=O)-NH-R₆.

In one embodiment, X is -CR₇R₈-, -O-, -NR₉- or -S-. In another embodiment, X is -CR₇R₈-, -O- or -NR₉-. In a further embodiment, X is -CR₇R₈- or -O-. In a still further embodiment, X is -CR₇R₈-. In another embodiment, X is -O-.

In one embodiment, Y is -NR₁₀R₁₁.

In one embodiment, R₄ is H or C1-C4 alkyl. In another embodiment, R₄ is H.

In one embodiment, R₅ is H or C1-C4 alkyl. In another embodiment, R₅ is H.

In one embodiment, R₆ is C1-C6 alkyl, C3-C6 cycloalkyl; C3-C6 cycloalkyl-(C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy. In another embodiment, R₆ is C1-C6 alkyl, C3-C6 cycloalkyl or C3-C6 cycloalkyl-(C1-C2 alkyl). In a further embodiment, R₆ is C1-C6 alkyl. In a still further embodiment, R₆ is *i*-propyl or *t*-butyl.

In one embodiment, R₇ is H or C1-C4 alkyl. In another embodiment, R₇ is H.

In one embodiment, R₈ is H or C1-C4 alkyl. In another embodiment, R₈ is H.

In one embodiment, R₉ is H or C1-C4 alkyl.

In one embodiment, R₁₀ is H or C1-C4 alkyl or together with R₁₁ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR₁₂; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy. In another embodiment, R₁₀ is C1-C4 alkyl or together with R₁₁ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR₁₂; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy. In a still further embodiment, R₁₀ together with R₁₁ forms a 5-7 saturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR₁₂; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy.

In one embodiment, R₁₁ is H or C1-C4 alkyl.

In one embodiment, R₁₂ is H or C1-C6 alkyl (for example methyl).

In one embodiment, G is a group G1, G2, G3, G4, G5, G6, G7 or G8. In another, G is a group G1, G2, G3, G4, G5, G6, G7, G8 or G10. In a further embodiment, G is a group G1, G2, G3, G4, G6, G7 or G8. In a still further embodiment, G is a group G1, G3, G4 or G6. In a still further embodiment, G is a group G4 or G6.

In one embodiment, n is 1, 2 or 3. In another embodiment, n is 2.

In one embodiment, R is -X-[CH₂]_nCR₄R₅-Y or a group G; R₁ is H or C1-C4 alkyl (for example methyl); R₂ is a phenyl ring which may be substituted with one or more: halogen,

C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; X is $-\text{CR}_7\text{R}_8-$ or $-\text{O}-$; R_6 is C1-C6 alkyl, C3-C6 cycloalkyl; C3-C6 cycloalkyl-(C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; R_9 is H or C1-C4 alkyl; R_{10} is C1-C4 alkyl or together with R_{11} forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and $-\text{NR}_{12}$; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy; R_{11} is H or C1-C4 alkyl; R_{12} is H or C1-C6 alkyl (for example methyl); n is 1, 2 or 3.

- 10 In one embodiment, example compounds of the invention include:
 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[5-(1-piperidinyl)pentyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 15 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[1-methyl-4-(1-piperidinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[1-methyl-3-(1-piperidinyl)propyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-(1-methylethyl)-2-[3-[4-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 20 N-(1-methylethyl)-2-[1-oxo-3-phenyl-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[3-(1-piperidinyl)propyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 25 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-(4-morpholinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S/2R)-2-methyl-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one;
- 30 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S or 2R)-2-methyl-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one;
 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S or 2R)-2-methyl-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one;
- 35 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1,1-dimethylethyl)acetamide;
 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(cyclopropylmethyl)acetamide;
- 40 2-[7-{4-[Meso -2,6-dimethyl-1-piperidinyl]butyl}-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

- N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidiny)butyl]-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 2-[7-[4-(4,4-difluoro-1-piperidiny)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 5 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-(4-methyl-1-piperaziny)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-(1-methylethyl)-2-[3-(3-methylphenyl)-1-oxo-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{4-[4-(trifluoromethyl)-1-piperidiny]butyl}]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 10 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-[4-(methyloxy)-1-piperidiny]butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-ethyl-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 15 N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidiny)butyl]-3-[3-[(trifluoromethyl)oxy]phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 2-[3-(3-fluorophenyl)-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(3-chlorophenyl)-7-(4-methyl-1-piperaziny)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 20 2-[3-(3-chlorophenyl)-7-[4-(dimethylamino)-1-piperidiny]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(3-chlorophenyl)-7-(4-methylhexahydro-1H-1,4-diazepin-1-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 25 2-[3-(3-chlorophenyl)-7-[methyl(1-methyl-4-piperidiny)amino]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[7-[4-(dimethylamino)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 30 2-[3-(3-chlorophenyl)-4-methyl-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(3-chlorophenyl)-1-oxo-7-[4-(1-pyrrolidiny)-1-piperidiny]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[7-[4-(2,6-dimethyl-4-morpholiny)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 35 2-[3-(3-chlorophenyl)-7-[(1-methyl-3-piperidiny)methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(5-chloro-2-methylphenyl)-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 40 2-[3-(2-chlorophenyl)-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(3-chlorophenyl)-7-[2-(1-methyl-4-piperidiny)ethyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

- 2-[3-(3-chlorophenyl)-7-(2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-(2-methyl-2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 5 2-[3-(3-chlorophenyl)-7-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-{4-[2-(dimethylamino)ethyl]-1-piperidinyl}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[7-(1,4'-bipiperidin-1'-yl)-3-(3-chlorophenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 10 2-[3-(3-chlorophenyl)-7-(9-methyl-3,9-diazaspiro[5.5]undec-3-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-cyclobutylacetamide;
- 15 2-[3-(3-chlorophenyl)-7-{[2-(1-methyl-2-piperidinyl)ethyl]oxy}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chloro-4-fluorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- N-(1,1-dimethylethyl)-2-[1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 20 2-[3-(3-chlorophenyl)-7-[3-(dimethylamino)-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-[3-(dimethylamino)-1-pyrrolidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 25 2-[3-(3-chlorophenyl)-7-(9-methyl-2,9-diazaspiro[5.5]undec-2-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-{[(1-methyl-4-piperidinyl)methyl]oxy}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-(1-methyl-1,7-diazaspiro[4.4]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 30 2-[3-(3-chlorophenyl)-7-[(1-methyl-4-piperidinyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 35 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-[4-(trifluoromethyl)-1-piperidinyl]propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- N-cyclopropyl-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(2,2,2-trifluoroethyl)acetamide;
- 40 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

- N-(1,1-dimethylethyl)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 2-[3-(3-chlorophenyl)-1-oxo-7-(4-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 5 2-[3-(3-chlorophenyl)-7-[(1-cyclopentyl-4-piperidinyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S/3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 10 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(5-chloro-2-fluorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 15 2-[3-(3-chlorophenyl)-7-{[1-(1-methylethyl)-4-piperidinyl]oxy}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(3-chlorophenyl)-7-{[3-[(8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl]oxy}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-[3-(trifluoromethyl)-1-pyrrolidinyl]propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 20 2-[7-({[3-[(1R,5S)-3-azabicyclo[3.2.1]oct-3-yl]propyl]oxy}-3-(3-chlorophenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(1-methylethyl)acetamide;
 2-[3-(3-chlorophenyl)-7-{[3-(3-fluoro-1-piperidinyl)propyl]oxy}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 25 2-[3-(3-chlorophenyl)-7-{[3-[(8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl]oxy}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
 or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, example compounds of the invention include:

- 30 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[5-(1-piperidinyl)pentyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[1-methyl-4-(1-piperidinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 35 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[1-methyl-3-(1-piperidinyl)propyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 N-(1-methylethyl)-2-[3-[4-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
 40 N-(1-methylethyl)-2-[1-oxo-3-phenyl-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

- N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[3-(1-piperidiny)propyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 5 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-(4-morpholiny)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[2-[(1-methylethyl)amino]-2-propen-1-yl]-3-[3-(methyloxy)phenyl]-7-[4-[(2S/2R)-2-methyl-1-piperidiny]butyl]pyrrolo[1,2-a]pyrazin-1(2H)-one;
- 2-[2-[(1-methylethyl)amino]-2-propen-1-yl]-3-[3-(methyloxy)phenyl]-7-[4-[(2S or 2R)-2-methyl-1-piperidiny]butyl]pyrrolo[1,2-a]pyrazin-1(2H)-one;
- 10 2-[2-[(1-methylethyl)amino]-2-propen-1-yl]-3-[3-(methyloxy)phenyl]-7-[4-[(2S or 2R)-2-methyl-1-piperidiny]butyl]pyrrolo[1,2-a]pyrazin-1(2H)-one;
- 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 15 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1,1-dimethylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(cyclopropylmethyl)acetamide;
- 2-[7-[4-[Meso -2,6-dimethyl-1-piperidiny]butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 20 N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidiny)butyl]-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[7-[4-(4,4-difluoro-1-piperidiny)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 25 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-(4-methyl-1-piperaziny)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[3-(3-methylphenyl)-1-oxo-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[4-[4-(trifluoromethyl)-1-piperidiny]butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 30 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-[4-(methyloxy)-1-piperidiny]butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-ethyl-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 35 N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidiny)butyl]-3-[3-[[trifluoromethyl]oxy]phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[3-(3-fluorophenyl)-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-(4-methyl-1-piperaziny)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 40 2-[3-(3-chlorophenyl)-7-[4-(dimethylamino)-1-piperidiny]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

- 2-[3-(3-chlorophenyl)-7-(4-methylhexahydro-1H-1,4-diazepin-1-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-[methyl(1-methyl-4-piperidinyl)amino]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
5 2-[7-[4-(dimethylamino)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-4-methyl-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-1-oxo-7-[4-(1-pyrrolidinyl)-1-piperidinyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
10 2-[7-[4-(2,6-dimethyl-4-morpholinyl)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-[[1-(1-methyl-3-piperidinyl)methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
15 2-[3-(5-chloro-2-methylphenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(2-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-[[2-(1-methyl-4-piperidinyl)ethyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
20 2-[3-(3-chlorophenyl)-7-(2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-(2-methyl-2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
25 2-[3-(3-chlorophenyl)-7-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-[4-[2-(dimethylamino)ethyl]-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[7-(1,4'-bipiperidin-1'-yl)-3-(3-chlorophenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
30 2-[3-(3-chlorophenyl)-7-(9-methyl-3,9-diazaspiro[5.5]undec-3-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-cyclobutylacetamide;
35 2-[3-(3-chlorophenyl)-7-[[2-(1-methyl-2-piperidinyl)ethyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chloro-4-fluorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
N-(1,1-dimethylethyl)-2-[1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
40 2-[3-(3-chlorophenyl)-7-[3-(dimethylamino)-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

- 2-[3-(3-chlorophenyl)-7-[3-(dimethylamino)-1-pyrrolidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-(9-methyl-2,9-diazaspiro[5.5]undec-2-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 5 2-[3-(3-chlorophenyl)-7-[(1-methyl-4-piperidinyloxy)methyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-(1-methyl-1,7-diazaspiro[4.4]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-[(1-methyl-4-piperidinyloxy)methyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 10 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-[[3-(1-piperidinyloxy)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-[4-(trifluoromethyl)-1-piperidinyloxy]propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 15 N-cyclopropyl-2-[3-[3-(methoxy)phenyl]-1-oxo-7-[[3-(1-piperidinyloxy)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[3-[3-(methoxy)phenyl]-1-oxo-7-[[3-(1-piperidinyloxy)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(2,2,2-trifluoroethyl)acetamide;
- 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxo-7-[[3-(1-piperidinyloxy)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 20 N-(1,1-dimethylethyl)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-[[3-(1-piperidinyloxy)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-(4-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 25 2-[3-(3-chlorophenyl)-7-[(1-cyclopentyl-4-piperidinyloxy)methyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S/3R)-3-(trifluoromethyl)-1-piperidinyloxy]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyloxy]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 30 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyloxy]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(5-chloro-2-fluorophenyl)-1-oxo-7-[[3-(1-piperidinyloxy)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 35 2-[3-(3-chlorophenyl)-7-[[1-(1-methylethyl)-4-piperidinyloxy]methyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-[[3-[(8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-[3-(trifluoromethyl)-1-pyrrolidinyl]propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 40 2-[7-[[3-[(1R,5S)-3-azabicyclo[3.2.1]oct-3-yl]propyl]oxy]-3-(3-chlorophenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

2-[3-(3-chlorophenyl)-7-[[3-(3-fluoro-1-piperidinyl)propyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

2-[3-(3-chlorophenyl)-7-{{3-[(8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl}oxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

5 2-[7-[(1*R*,6*S*/1*S*,6*R*)-3-azabicyclo[4.1.0]hept-1-ylmethyl]oxy]-3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-[[[(1*R*,6*S*/1*S*,6*R*)-3-methyl-3-azabicyclo[4.1.0]hept-1-yl]methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

10 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-(((1*S*,6*R* or 1*R*,6*S*)-3-methyl-3-azabicyclo[4.1.0]hept-1-yl)methyl]oxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (Enantiomer 1);

2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-(((1*R*,6*S* or 1*S*,6*R*)-3-methyl-3-azabicyclo[4.1.0]hept-1-yl)methyl]oxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-

15 methylethyl)acetamide (Enantiomer 2);

or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, example compounds of the invention include:

20 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[5-(1-piperidinyl)pentyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[1-methyl-4-(1-piperidinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

25 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[1-methyl-3-(1-piperidinyl)propyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

N-(1-methylethyl)-2-[3-[4-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

30 N-(1-methylethyl)-2-[1-oxo-3-phenyl-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[3-(1-piperidinyl)propyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

35 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-(4-morpholinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

2-[2-[(1-methylethyl)amino]-2-propen-1-yl]-3-[3-(methyloxy)phenyl]-7-[4-[(2*S*/2*R*)-2-methyl-1-piperidinyl]butyl]pyrrolo[1,2-a]pyrazin-1(2H)-one;

40 2-[2-[(1-methylethyl)amino]-2-propen-1-yl]-3-[3-(methyloxy)phenyl]-7-[4-[(2*S* or 2*R*)-2-methyl-1-piperidinyl]butyl]pyrrolo[1,2-a]pyrazin-1(2H)-one;

2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

- 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1,1-dimethylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(cyclopropylmethyl)acetamide;
- 5 2-[7-{4-[Meso -2,6-dimethyl-1-piperidiny]butyl}-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidiny)butyl]-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 10 2-[7-[4-(4,4-difluoro-1-piperidiny)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-(4-methyl-1-piperaziny)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[3-(3-methylphenyl)-1-oxo-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 15 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{4-[4-(trifluoromethyl)-1-piperidiny]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-[4-(methyloxy)-1-piperidiny]butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-ethyl-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 20 N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidiny)butyl]-3-[3-[(trifluoromethyl)oxy]phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[3-(3-fluorophenyl)-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 25 2-[3-(3-chlorophenyl)-7-(4-methyl-1-piperaziny)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-[4-(dimethylamino)-1-piperidiny]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-(4-methylhexahydro-1H-1,4-diazepin-1-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 30 2-[3-(3-chlorophenyl)-7-[methyl(1-methyl-4-piperidiny)amino]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[7-[4-(dimethylamino)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 35 2-[3-(3-chlorophenyl)-4-methyl-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-[4-(1-pyrrolidiny)-1-piperidiny]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[7-[4-(2,6-dimethyl-4-morpholiny)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 40 2-[3-(3-chlorophenyl)-7-[(1-methyl-3-piperidiny)methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

or a pharmaceutically acceptable salt or solvate thereof.

In general, the compounds of formula (I) may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth in the Examples.

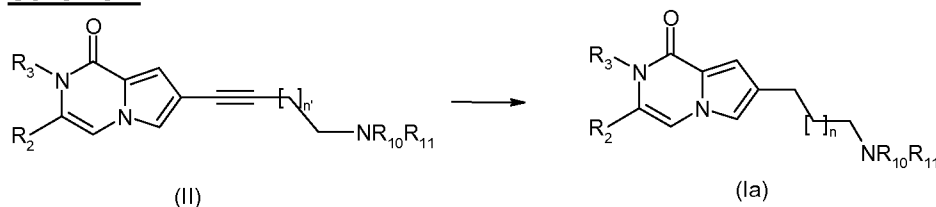
Compounds of formula (I), and salts or solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, R₂₇, R₂₈, R₂₉, X, Y, G, G₁, G₂, G₃, G₄, G₅, G₆, G₇, G₈, G₉, G₁₀, G₁₁, G₁₂, I, I', m, m', m'', m''', m^{iv}, m^v, n, q, p, p', p'', p''', have the meanings as previously defined for compounds of formula (I) unless otherwise stated.

Compounds of formula (Ia), which correspond to compounds of formula (I) as defined above wherein

R is -CH₂-[CH₂]_nCH₂-Y

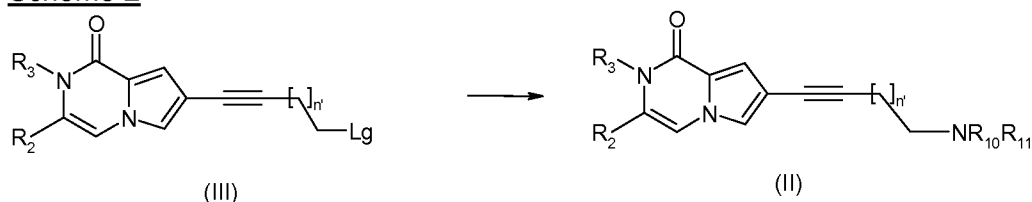
may be obtained from compounds of formula (II), wherein n' = n-1, according to Scheme 1, by hydrogenation procedure well described in the art, for example using Pd on charcoal as a catalyst and carrying out the reaction in protic solvents, such as ethanol, at atmospheric pressure and at RT.

Scheme 1



Compounds of formula (II) may be obtained according to Scheme 2 from compounds of formula (III), wherein Lg is a suitable leaving group, such as mesylate (OMs) or halogens (Cl, Br, I), by methods well known in the art, such as alkylation reactions of secondary amines, i.e. piperidine, using an inorganic base, e.g. K₂CO₃, and carrying out the reaction in aprotic solvents, such as MeCN, at temperature comprised between RT and 80 °C.

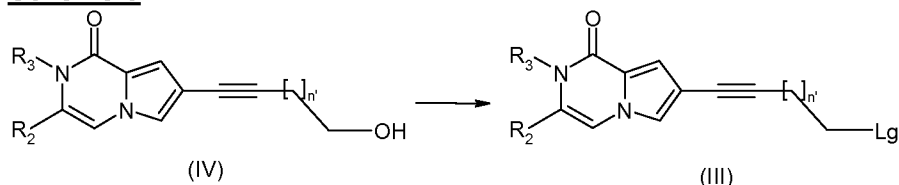
Scheme 2



Compounds of formula (III) may be obtained according to Scheme 3 from the corresponding alcohol intermediates (IV), wherein n' = n-1, by a variety of methods familiar to one skilled in the art. For example, wherein Lg = -OMs, mesyl chloride and TEA in aprotic solvents, e.g. DCM, at temperature comprised between 0 °C and RT can be

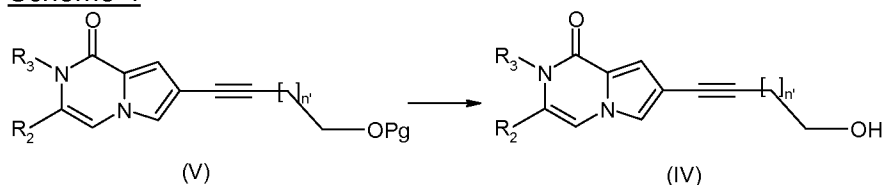
used. Wherein Lg = halides, e.g. Br, compounds of formula (IV) may be reacted with carbon tetrabromide (CBr₄) in the presence of triphenylphosphine and carrying out the reaction in aprotic solvents, such as DCM, at temperature comprised between 0 °C and RT.

Scheme 3



Compounds of formula (IV) may be obtained, according to Scheme 4, by compounds of formula (V), wherein Pg is a suitable protecting group and n' = n-1. For example, wherein Pg is a tert-butyl-dimethylsilyl (TBDMS) group its conversion in the corresponding alcohol, as well known in the art, may be carried out using tetrabutyl ammonium fluoride (TBAF) in aprotic solvents, such as THF, at RT.

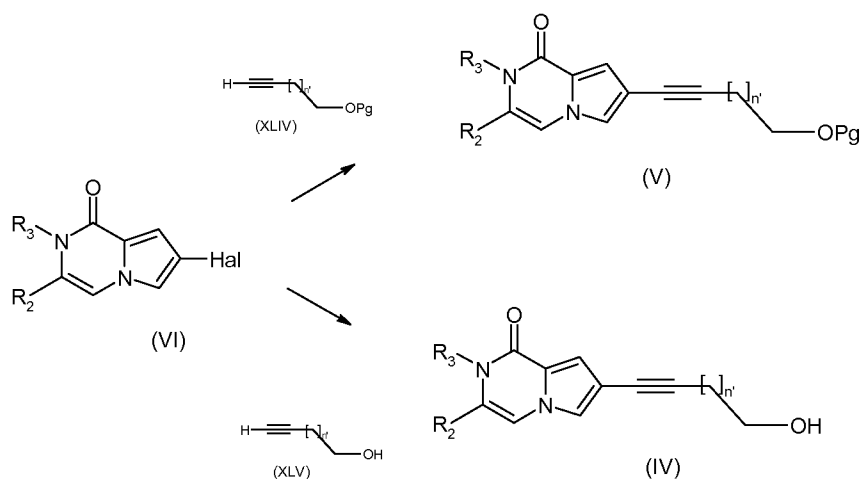
Scheme 4



Compounds of formula (V) may be obtained starting from compounds of formula (VI), wherein Hal is halide (i.e. I), according to Scheme 5 through a cross-coupling procedure, such as the Sonogashira reaction as reported in Journal of Organic Chemistry 2000, 65, 3274-83, using a suitable alkynyl alcohol O-protected of formula (XLIV), wherein n' = n-1 and i.e Pg = TBDMS.

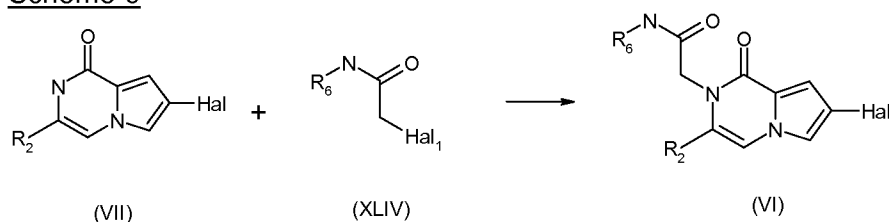
Compounds of formula (IV) may be alternatively prepared according to Scheme 5 starting from the corresponding alkynyl alcohol of formula (XLV), wherein n' = n-1, and a compound of formula (VI) as above defined.

Scheme 5



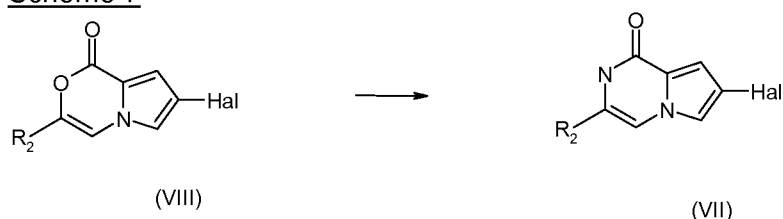
Compounds of formula (VI) may be obtained, according to Scheme 6, reacting compounds of formula (VII), wherein Hal is halide, with a suitable 2-halo-*N*-(alkylacetamides) of formula (XLIV) wherein Hal₁ is halide, following alkylation procedures well reported in the art, for example using 2-chloro-*N*-(1-methylethyl) acetamide, sodium hydride as a strong base and carrying out the reaction in aprotic solvents, e.g. DMF, at temperature comprised between RT and 80 °C.

10 Scheme 6



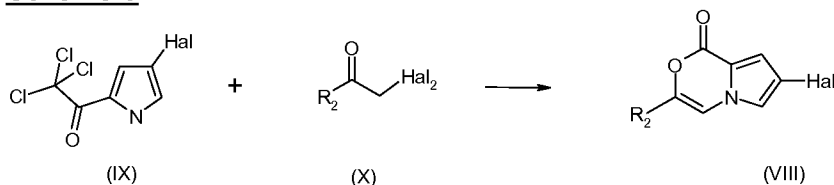
Compounds of formula (VII) may be obtained reacting compounds of formula (VIII), wherein Hal is halide, according to Scheme 7, with NH₄OAc in acetic acid at reflux temperature for several hours.

15 Scheme 7

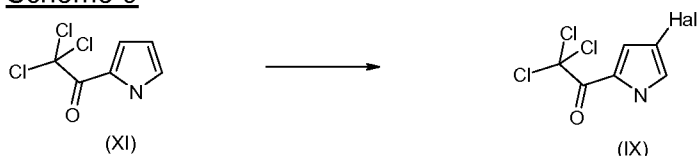


Compounds of formula (VIII) may be obtained reacting compounds of formula (IX), wherein Hal is halide (i.e. I), with compounds of formula (X), wherein Hal₂ is a halide (i.e. Br), according to Scheme 8, using an inorganic base, such as K₂CO₃, and carrying out the reaction in aprotic solvents, i.e. DMF, at RT.

Compounds of formula (X), wherein R₂ is an optionally substituted aryl and heteroaryl as reported above for compounds of formula (I), can be either commercially available or prepared following well known procedures described in the art.

Scheme 8

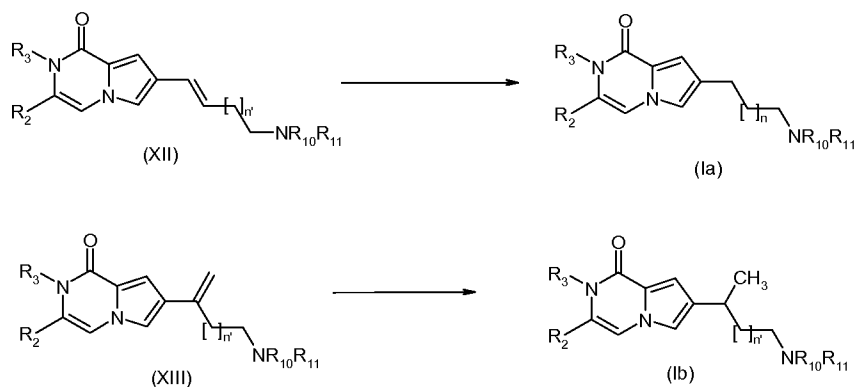
- 5 Compounds of formula (IX) could be obtained according to Scheme 9 starting from the commercial available 2-trichloroacetatepyrrole (XI). For example, the iodine derivative (Hal = I) may be prepared following the procedure reported in Organic & Biomolecular Chemistry (2006), 4(12), 2477-2482.

10 Scheme 9

Alternatively, compounds of formula (Ia), as defined above, and compounds of formula (Ib), which correspond to compounds of formula (I) as defined above wherein

- 15 R is $-\text{CH}(\text{CH}_3)-[\text{CH}_2]_n\text{CH}_2-\text{Y}$,

may be obtained from compounds of formula (XII) and compounds of formula (XIII) respectively, wherein $n'=n-1$, according to Scheme 10. Reaction conditions for Scheme 10 comprise usual hydrogenation procedure, for example using Pd on charcoal as a catalyst and carrying out the reaction in protic solvents, such as ethanol, at atmospheric pressure and at RT.

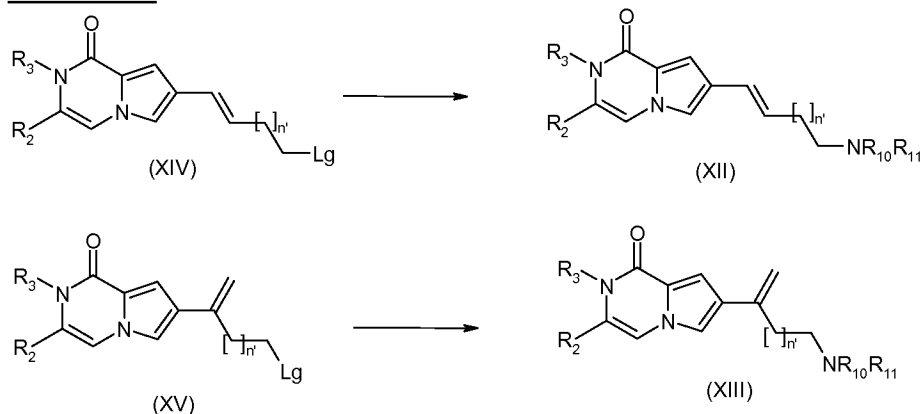
Scheme 10

25

Compounds of formula (XII) and (XIII) may be obtained respectively from compounds of formula (XIV) and (XV), wherein Lg is a suitable leaving group such as mesylate (OMs) or halogen (Cl, Br, I) and $n' = n-1$, according to Scheme 11, through usual alkylation

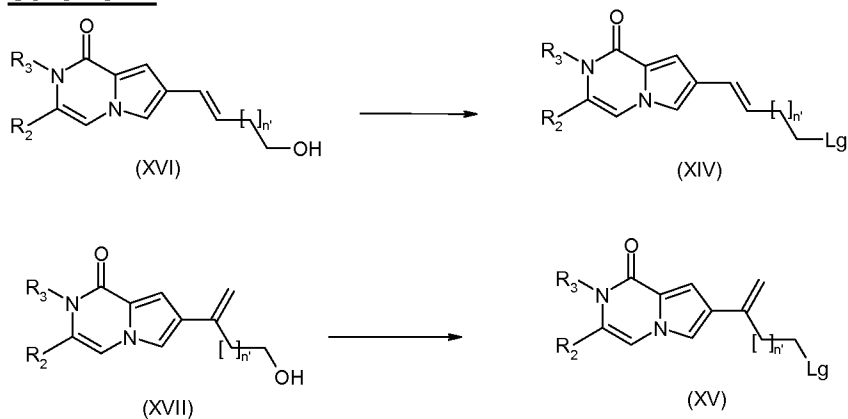
reactions with secondary amines, such as piperidine, in the presence of an inorganic base, such as K_2CO_3 , and carrying out the reaction in aprotic solvents, e.g. MeCN, at temperature comprised between RT and 80 °C.

5 Scheme 11

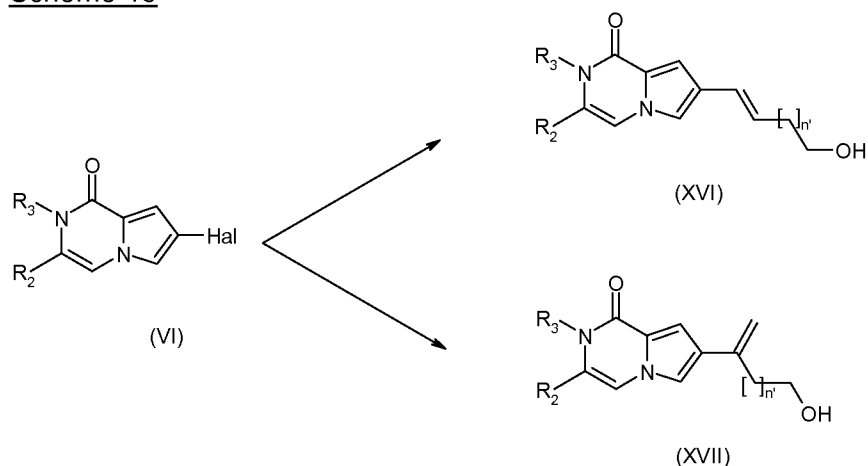


Compounds of formula (XIV) and (XV) may be obtained according to Scheme 12 respectively from the corresponding alcohol intermediates (XVI) and (XVII), wherein $n' = n-1$, by a variety of methods familiar to one skilled in the art. For example, wherein $Lg =$ -OMs, mesyl chloride and TEA in aprotic solvents, e.g. DCM, at temperature comprises between 0 °C and RT can be used. Wherein $Lg =$ halides, e.g. Br, compounds of formula (XVI) and (XVII) may be reacted with carbon tetrabromide in presence of triphenylphosphine and carrying out the reaction in aprotic solvents, such as DCM, at temperature comprised between 0 °C and RT.

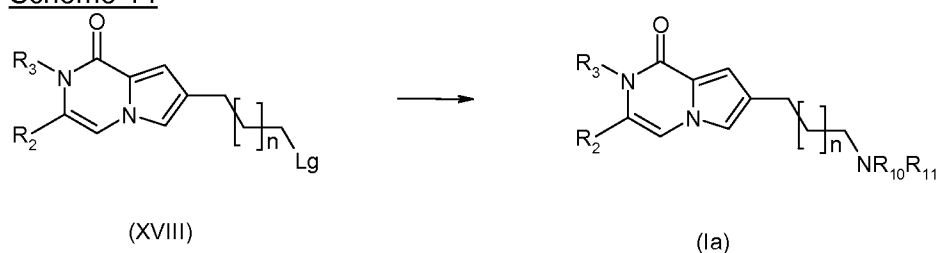
Scheme 12



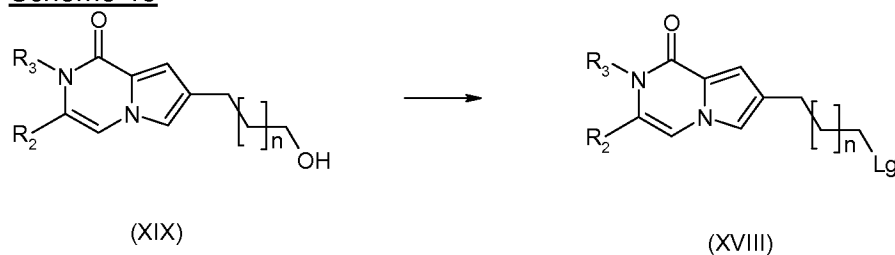
Compounds of formula (XVI) and (XVII) may be obtained according to Scheme 13 starting from compounds of formula (VI) through a Pd-catalyzed cross coupling methodology well known in the art, for example the Heck reaction, using the opportune alkenyl alcohols, a catalyst, e.g. palladium (II) acetate, a phosphine, e.g. tris(2-methylphenyl)phosphane, a base, e.g. TEA, in an aprotic solvent, e.g. DMF, at a temperature between 50 and 100 °C, for several hours.

Scheme 13

Compounds of formula (Ia), may be also obtained, according to Scheme 14, from compounds of formula (XVIII), wherein Lg is a suitable leaving group such as mesylate (OMs) or halogen (Cl, Br, I), by alkylation reaction using a secondary alkylamines, such as piperidine, in the presence of an inorganic base, e.g. K_2CO_3 , and carrying out the reaction in aprotic solvents, e.g. MeCN, at temperature comprised between RT and 80 °C.

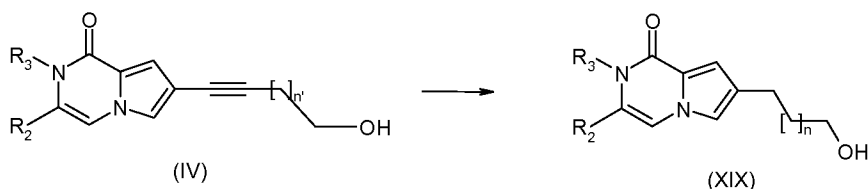
10 Scheme 14

Compounds of formula (XVIII) may be obtained, according to Scheme 15, starting from compounds of formula (XIX) by a variety of methods familiar to one skilled in the art.

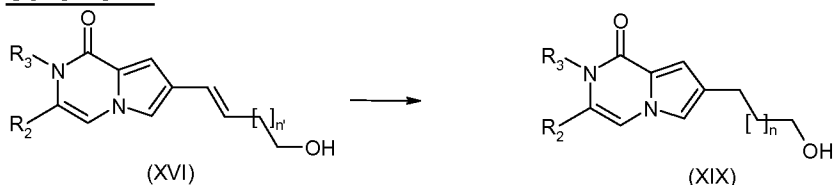
15 Scheme 15

Compounds of formula (XIX) may be obtained according to Scheme 16 from the corresponding alkynyl derivatives (IV), by hydrogenation procedure well described in the art, for example using Pd on charcoal as a catalyst and carrying out the reaction in protic solvents, such as ethanol, at atmospheric pressure and at RT.

Scheme 16



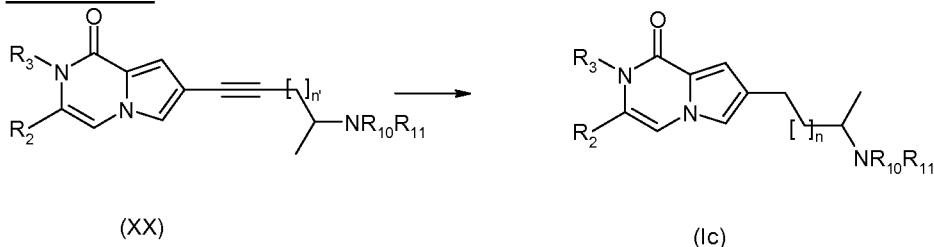
Compounds of formula (XIX) may be also prepared, according to Scheme 17, from compounds of formula (XVI), by hydrogenation procedure well described in the art, for example using Pd on charcoal as a catalyst and carrying out the reaction in protic solvents, such as ethanol at atmospheric pressure and at RT.

Scheme 17

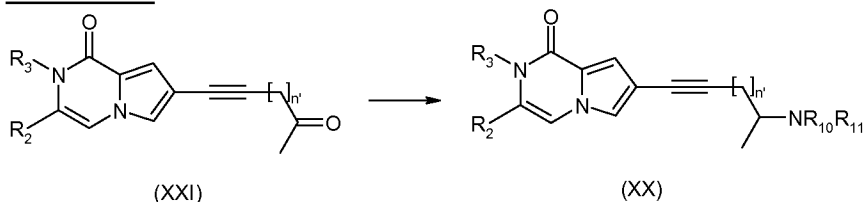
Compounds of formula (**Ic**), which correspond to compounds of formula (I) as defined above wherein

R is $-\text{CH}_2-[\text{CH}_2]_n\text{CH}(\text{CH}_3)-\text{Y}$,

may be obtained from compounds of formula (XX), wherein $n' = n-1$, according to Scheme 18, by hydrogenation procedure well described in the art, for example using Pd on charcoal as a catalyst and carrying out the reaction in protic solvents, such as ethanol at atmospheric pressure and at RT.

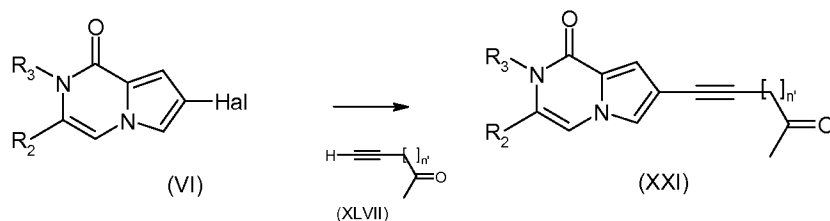
Scheme 18

Compounds of formula (XX) may be obtained, according to Scheme 19, from the corresponding aldehyde derivatives (XXI), wherein $n' = n-1$, by reductive amination procedure well described in the art, for example using a secondary amine, e.g. piperidine, using a reductive agent, e.g. NaBH_3CN , and carrying out the reaction in aprotic solvents, e.g. acetonitrile, at atmospheric pressure and at RT.

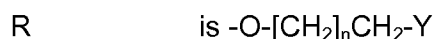
Scheme 19

Compounds of formula (XXI) may be obtained from compounds of formula (VI), wherein Hal is halide (e.g. I), according to Scheme 20 through a cross-coupling procedure with a compound of formula (XLVII), wherein $n' = n-1$, such as the Sonogashira reaction.

5 Scheme 20

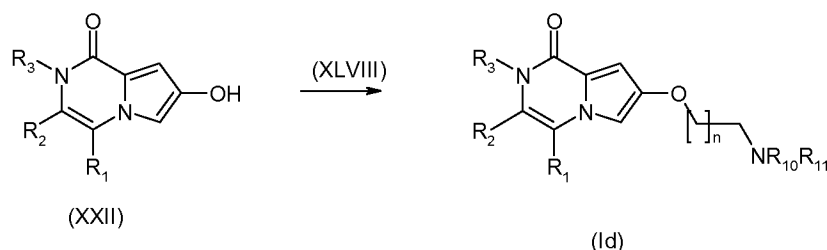


Compounds of formula (Id), which correspond to compounds of formula (I) as defined above wherein



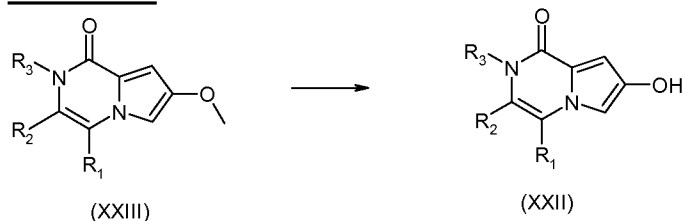
may be obtained from compounds of formula (XXII), according to Scheme 21, by usual alkylation methods well described in the art, using halo-alkylamines of formula $Hal[CH_2]_nCH_2NR_{10}R_{11}$ (XLVIII), such as 1-(3-chloropropyl)piperidine, and carrying out the reaction in presence of an inorganic base, such as K_2CO_3 , in aprotic solvents, e.g. DMF, at temperature comprised between RT and 80 °C.

Scheme 21



Compounds of formula (XXII) may be obtained, according to Scheme 22, from compounds of formula (XXIII) by reaction with a Lewis acid, such as boron tribromide (BBr_3), in aprotic solvent, e.g. DCM, at temperature comprised between -78 °C and RT.

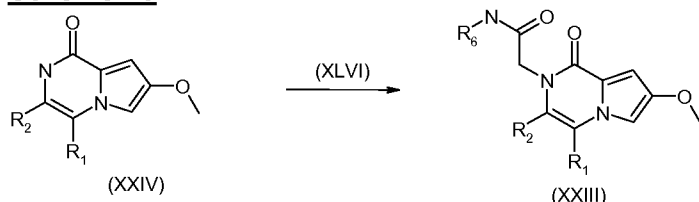
Scheme 22



Compounds of formula (XXIII) may be obtained, according to Scheme 23, from compounds of formula (XXIV) through alkylation procedures with a suitable 2-halo-*N*-(alkylacetamides) of formula (XLVI) as above defined. For example using 2-chloro-*N*-(1-

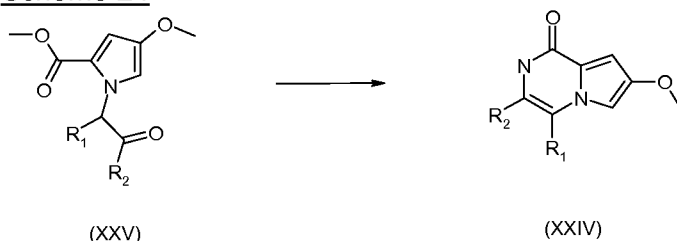
methylethyl) acetamide, sodium hydride as a strong base and carrying out the reaction in aprotic solvents, e.g. DMF, at temperature comprised between RT and 80 °C.

Scheme 23



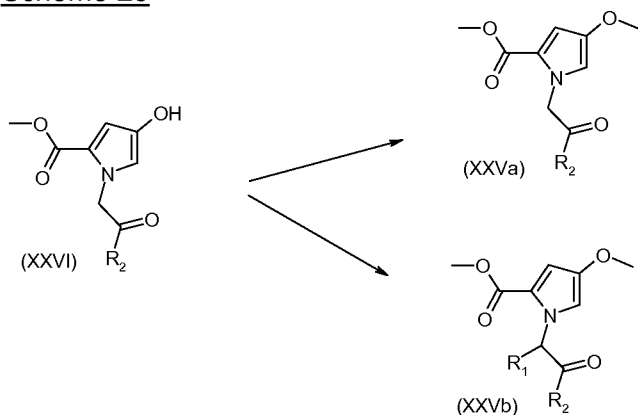
- 5 Compounds of formula (XXIV) may be obtained by reacting compounds of formula (XXV), according to Scheme 24, with NH₄OAc in acetic acid, at temperature comprised between 80 and 110 °C for several hours (24-48 h).

Scheme 24



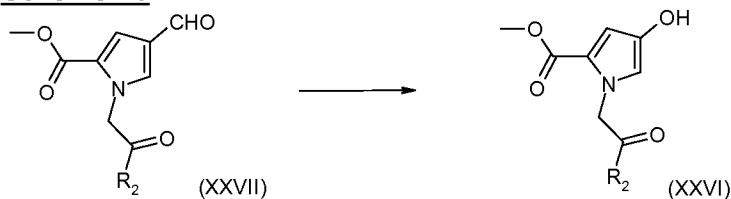
- 10 Compounds of formula (XXVa), i.e. compounds of formula (XXV) wherein R₁ is hydrogen, may be obtained, according to Scheme 25, from compounds of formula (XXVI) by reaction with an alkylant agent, such as dimethyl sulfate, in presence of an inorganic base, e.g. Cs₂CO₃, in aprotic solvents, such as DMF, at temperature comprised between 0 °C and
- 15 RT.
- Compounds of formula (XXVb), i.e. compounds of formula (XXV) wherein R₁ is not hydrogen, may be obtained, according to Scheme 25, from compounds of formula (XXVI), by reaction with an alkylant agent, such as methyl iodide, in presence of an inorganic base, e.g. Cs₂CO₃, in aprotic solvents, such as DMF at temperature comprised between -
- 20 30 °C and RT.

Scheme 25



Compounds of formula (XXVI) may be obtained from compounds of formula (XXVII), according to Scheme 26, following a modified Baeyer-Villiger procedure, in analogy to the method reported in Tetrahedron Letters (2000), 41(43), 8217-8220.

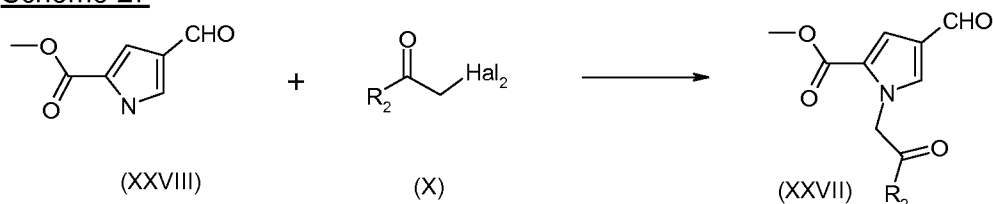
5 Scheme 26



Compounds of formula (XXVII) may be obtained, according to Scheme 27, from methyl 4-formyl-1H-pyrrole-2-carboxylate (XXVIII) by alkylation reaction with a suitable 2-halo-1-arylketone (X), wherein Hal₂ is halide (i.e. Br), such as 3-chlorophenacyl bromide, carrying out the reaction in aprotic solvents, e.g. MeCN, and using an inorganic base, such as K₂CO₃, usually at RT.

Methyl 4-formyl-1H-pyrrole-2-carboxylate (XXVIII) can be prepared following well known procedures described in the art, such as procedure reported in Tetrahedron Letters, 47(27), 4631-34; 2006.

15 Scheme 27

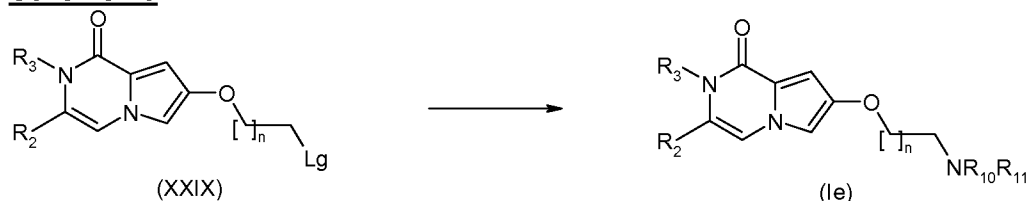


Compounds of formula (Ie), which correspond to compounds of formula (I) as defined above wherein

R is -O-[CH₂]_nCH₂-Y,
 R₁ is H

may be obtained, according to Scheme 28, by reacting compounds of formula (XXIX), wherein Lg is a suitable leaving group (such as halides or mesylate) with a secondary alkylamine, e.g. piperidine, using an inorganic base, such as K₂CO₃, in aprotic solvents, e.g. DMF, at temperature comprised between RT and 80 °C.

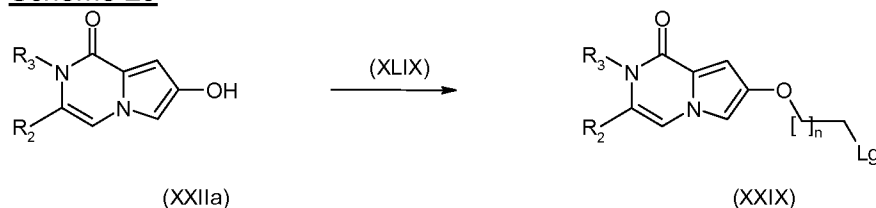
25 Scheme 28



Compounds of formula (XXIX) may be obtained starting from compounds (XXIIa), i.e. compounds of formula (XXII) wherein R₁ is hydrogen, according to Scheme 29. For example, wherein Lg is a halogen, compounds (XXIX) may be prepared by alkylation

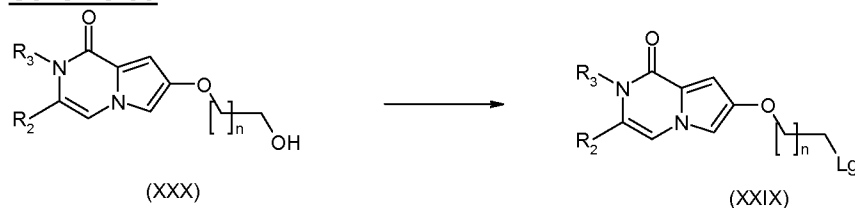
reaction with a di-haloalkyl derivatives of formula $\text{Hal}-[\text{CH}_2]_n\text{CH}_2\text{Lg}$ (XLIX), such as 1-bromo-3-chloropropane, using an inorganic base, such as K_2CO_3 , and carrying out the reaction in aprotic solvents, e.g. DMF, at temperature comprised between RT and 80 °C.

Scheme 29



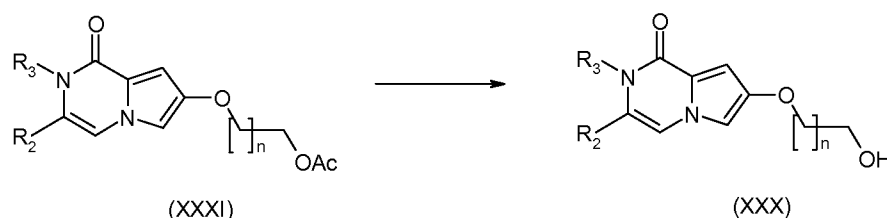
Compounds of formula (XXIX) may be also obtained according to Scheme 30, from the corresponding alcohol intermediates (XXX) by a variety of methods familiar to one skilled in the art. For example, wherein $\text{Lg} = -\text{OMs}$, mesyl chloride and TEA in aprotic solvents, i.e. DCM, at temperature comprises between 0 °C and RT can be used. Wherein $\text{Lg} =$ halides, e.g. Br, compounds of formula (XXX) may be reacted with carbon tetrabromide in presence of triphenylphosphine and carrying out the reaction in aprotic solvents, such as DCM, at temperature comprised between 0 °C and RT.

Scheme 30



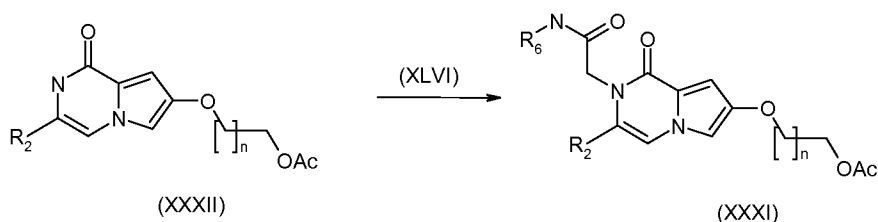
Compounds of formula (XXX) may be obtained, according to Scheme 31, by hydrolysis reaction of compounds (XXXI), for example using an inorganic base, such as LiOH , and carrying out the reaction in a mixture of aprotic and protic solvent, e.g. THF and water, at temperature comprised between RT and 60 °C.

Scheme 31



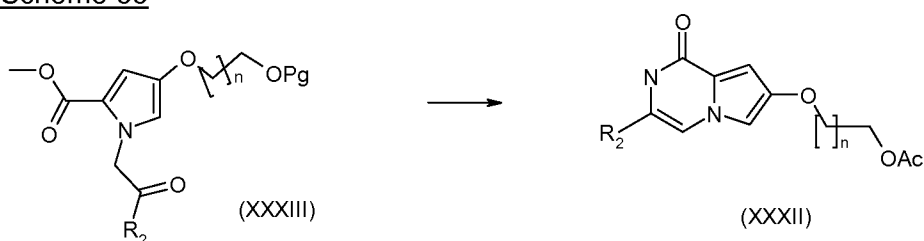
Compounds of formula (XXXI) may be obtained, according to Scheme 32, by compounds of formula (XXXII) through alkylation procedures with a suitable 2-halo-*N*-alkylacetamide of formula (XLVI) as above defined. For example, using 2-chloro-*N*-(1-methylethyl)acetamide, sodium hydride as a strong base and carrying out the reaction in aprotic solvents, e.g. DMF, at temperature comprised between 0 and 70 °C. An iodine derivative may be used to catalyse the reaction, such as sodium iodide.

Scheme 32



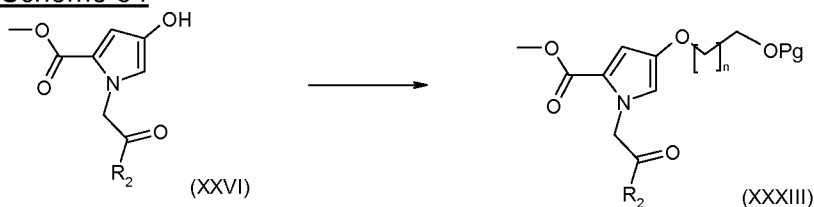
Compounds of formula (XXXII) may be prepared according to Scheme 33 by reaction of compounds of formula (XXXIII), wherein Pg is a suitable protecting group such as tert-butyltrimethylsilyl (TBDMS), with NH_4OAc in acetic acid at temperature comprised between 80 and 110 °C for several hours (24-48 h). This procedure involves the conversion of the -OPg group, wherein Pg is for example TBDMS, into alcohol and the consequent formation of its corresponding acetate derivative.

Scheme 33



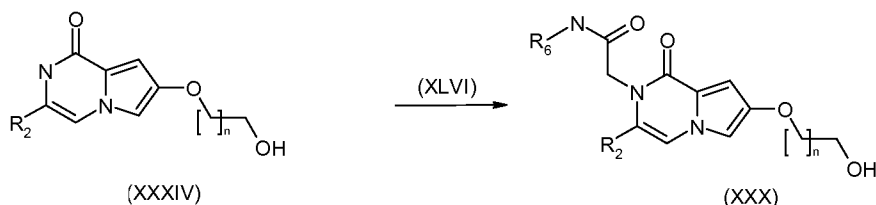
Compounds of formula (XXXIII) may be obtained, according to Scheme 34, treating compounds (XXVI) through procedures familiar to one skilled in the art. For example, wherein Pg = TBDMS (tert-butyltrimethylsilyl), through alkylation reaction with a suitable halo-alkylsilyl derivative, such as [(3-bromopropyl)oxy](1,1-dimethylethyl)dimethylsilane, using an inorganic base, e.g. K_2CO_3 , and carrying out the reaction in aprotic solvents, e.g. DMF, at temperature comprised between RT and 80 °C.

Scheme 34

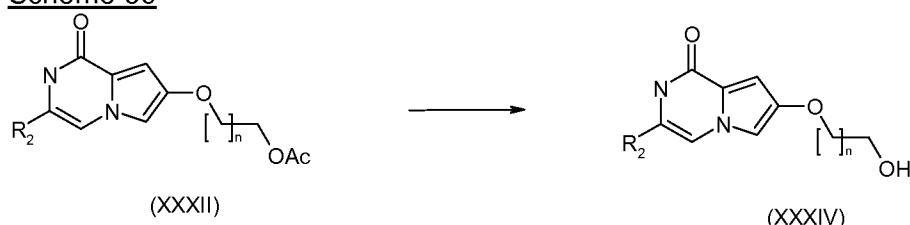


Compounds of formula (XXX), may be also obtained, according to Scheme 35, by reacting compounds of formula (XXXIV) with the appropriate 2-halo-N-alkylacetamide of formula (XLVI) as above defined, by alkylation methodology well known in the art. For example using 2-chloro-N-(1-methylethyl) acetamide and an inorganic base, such as K_2CO_3 , carrying out the reaction in aprotic solvents, e.g. MeCN at temperature comprised between RT and 80 °C.

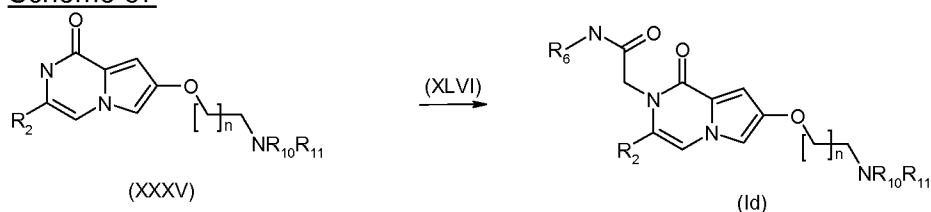
Scheme 35



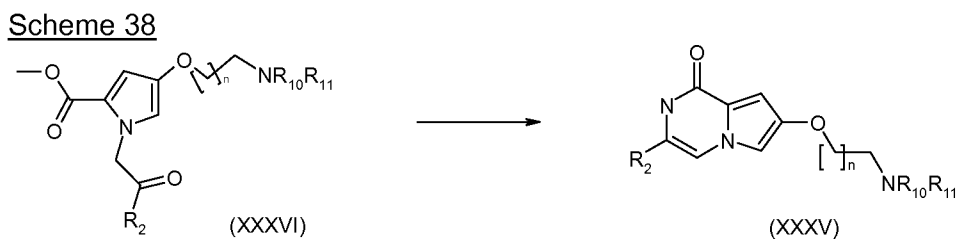
Compounds of formula (XXXIV) may be obtained, according to Scheme 36, by hydrolysis reaction of compounds (XXXII), for example using an inorganic base, such as LiOH, and carrying out the reaction in a mixture of aprotic and protic solvent, e.g. THF and water, at temperature comprised between RT and 60 °C.

Scheme 36

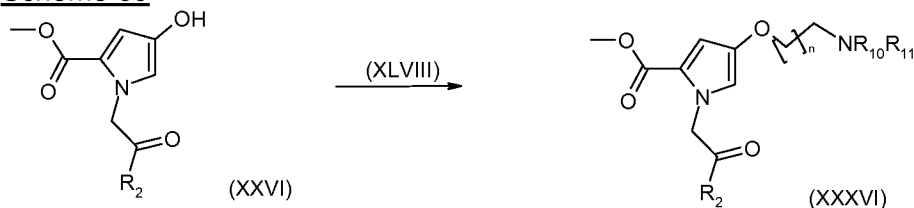
- Compounds of formula (Id), may be also obtained, according to Scheme 37, by reacting compounds of formula (XXXV) with a suitable 2-halo-N-alkylacetamide of formula (XLVI), as above defined such as 2-chloro-N-(1-methylethyl) acetamide, through alkylation procedures well known in the art, for example using an inorganic base, such as sodium hydroxy, a quaternary ammonium salt, e.g. tetrabutylammonium bromide, and an iodine derivative, such as sodium iodide, in aprotic solvents (e.g. THF) at temperature comprised between 0 °C and RT.

Scheme 37

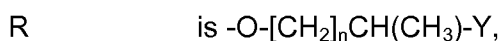
Compounds of formula (XXXV) may be obtained from compounds of formula (XXXVI), according to Scheme 38, by reaction with NH₄OAc in acetic acid at temperature comprised between 80 and 110 °C for several hours (24-48 h).



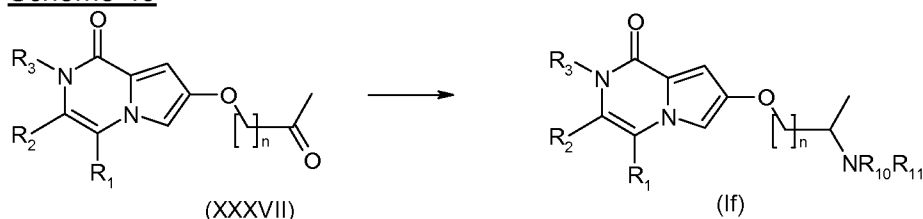
Compounds of formula (XXXVI) may be obtained from compounds of formula (XXVI), according to Scheme 39, by reaction with a suitable halo-alkylamine of formula Hal-[CH₂]_nCH₂NR₁₀R₁₁ (XLVIII) as above defined, such as 1-(3-chloropropyl)piperidine, in presence of an inorganic base, e.g. K₂CO₃, in aprotic solvents, such as MeCN, at temperature comprised between RT and 80 °C.

Scheme 39

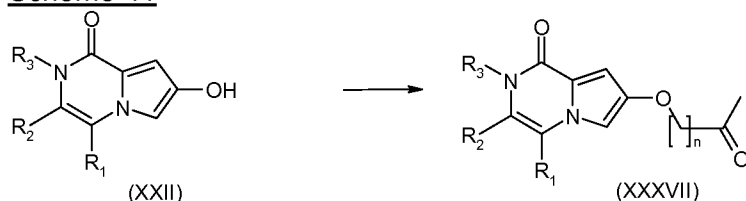
Compounds of formula (If), which correspond to compounds of formula (I) as defined above wherein



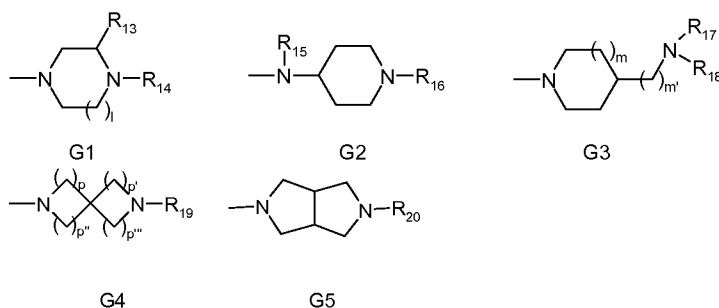
may be obtained from compounds of formula (XXXVII), according to Scheme 40, by reductive amination procedure well described in the art, for example using a secondary alkylamine, e.g. piperidine, using a reductive agent, e.g. NaBH₃CN, and carrying out the reaction in aprotic solvents, i.e. acetonitrile, at atmospheric pressure and at RT.

Scheme 40

Compounds of formula (XXXVII) may be obtained by usual alkylation methods well described in the art from compounds of formula (XXII), according to Scheme 41, using halo-alkylketone, such as 4-chloro-2-butanone, and carrying out the reaction in presence of an inorganic base, such as K₂CO₃, in aprotic solvents, e.g. DMF, at temperature comprises between RT and 80 °C.

Scheme 41

Compounds of formula (Ig), which correspond to compounds of formula (I) as defined above wherein R is a group G among the following G₁-G₅ groups

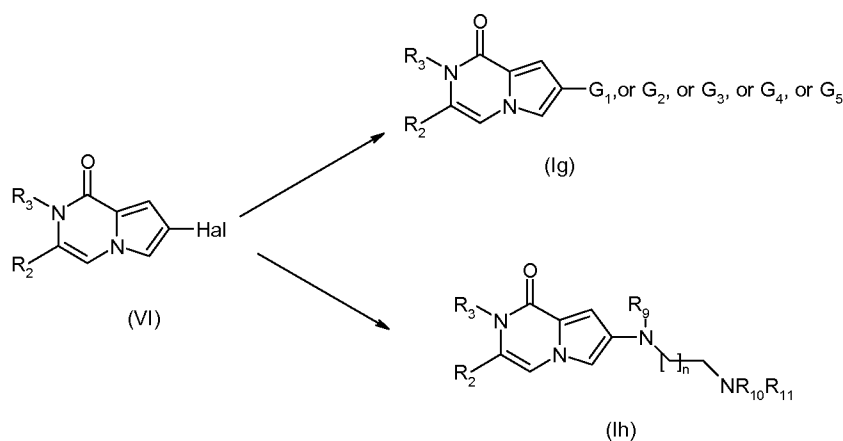


and compounds of formula (Ih), which correspond to compounds of formula (I) as defined above wherein

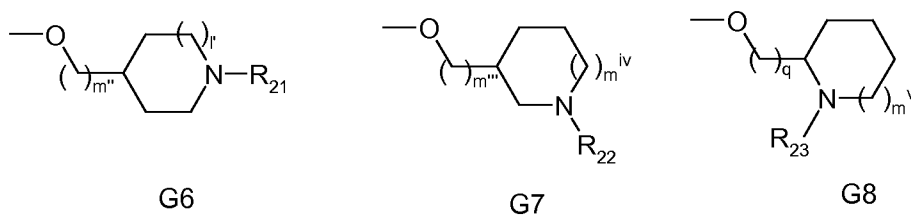
5 R is $-NR_9-[CH_2]_nCH_2-Y$,

may be obtained from compounds of formula (VI), wherein Hal is halide (e.g. I), and the appropriate amine according to Scheme 42, by Cu-catalyzed cross coupling methodology well known in the art, for example using CuI as catalyst, a secondary alkylamine, i.e. N-methyl piperidine, and carrying out the reaction in presence of a ligand, e.g. LD-proline, and of an inorganic base, e.g. K_2CO_3 , in aprotic solvents, e.g. DMSO, at temperature comprises between 80-100 °C (18-48 h).

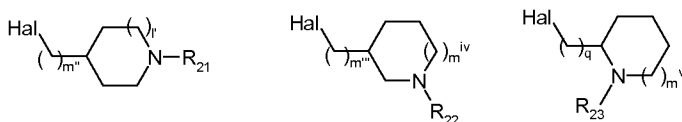
Scheme 42



Compounds of formula (II), which correspond to compounds of formula (I) as defined above wherein R is a group G among the following G₆-G₈ groups

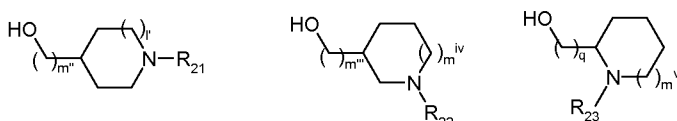


may be obtained from compounds of formula (XXII), according to Scheme 43, through alkylation reaction with an appropriate halo-alkylcycloamine derivative, such as 3-(chloromethyl)-1-methylpiperidine hydrochloride,



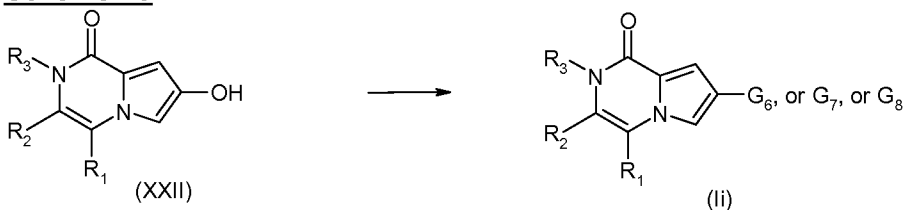
using an inorganic base, e.g. K_2CO_3 or Cs_2CO_3 , and carrying out the reaction in aprotic solvents, e.g. DMF or DMSO, at temperature comprises between RT and 80 °C.

- Compounds of formula (II), may be also obtained from compounds of formula (XXII), according to Scheme 43, by Mitsunobu reaction with a suitable hydroxy-alkylcycloamine derivative, such as 4-hydroxymethyl-pyridine hydrochloride,

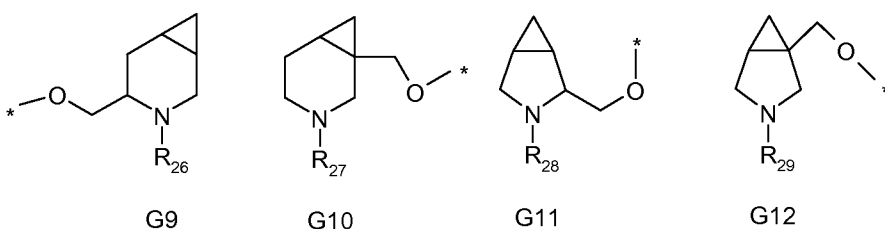


using triphenylphosphine and diethyl azodicarboxylate and carrying out the reaction in aprotic solvents, e.g. THF, at temperature comprises between 0 °C and RT.

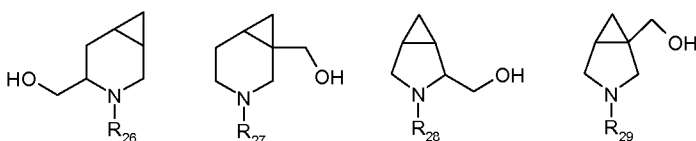
10 Scheme 43



Compounds of formula (In), which correspond to compounds of formula (I) as defined above wherein R is a group G among the following G_9 - G_{12} groups

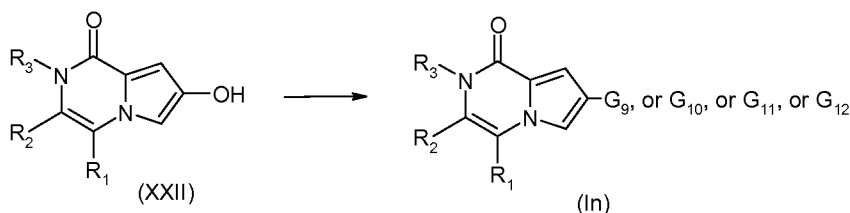


- and R_1 is C1-C4 alkyl, may be obtained from compounds of formula (XXII), according to Scheme 44, by Mitsunobu reaction with the appropriate hydroxy-alkylcycloamine derivative chosen among those listed below:



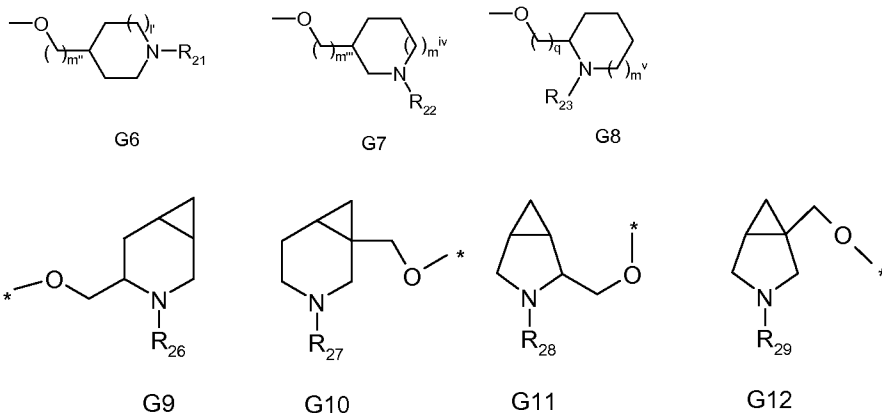
- using triphenylphosphine and diethyl azodicarboxylate and carrying out the reaction in aprotic solvents, e.g. THF or DCM, at temperature comprises between 0 °C and RT.

Scheme 44



Compounds of formula **(Im)**, which correspond to compounds of formula (I) as defined above wherein R is a group G among the following G₆-G₈ and G₉-G₁₂ groups

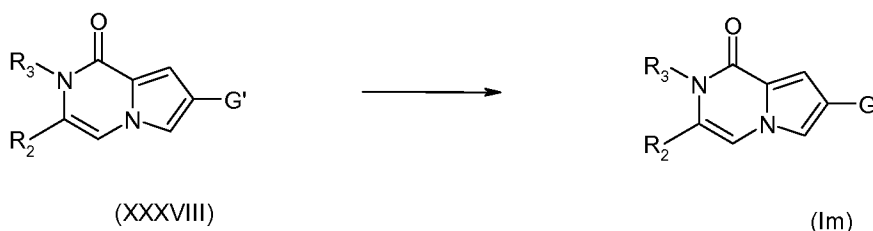
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and R₁ is H may be obtained, according to Scheme 45, by compounds of formula (XXXVIII), wherein G' corresponds to G₆, G₇, G₈, G₉, G₁₀, G₁₁ or G₁₂ in which R₂₁, R₂₂, R₂₃, R₂₆, R₂₇, R₂₈ R₂₉ are H, by reductive alkylation procedure well described in the art, for example using and aldehyde, e.g. formaldehyde, and a reductive agent, e.g. NaBH₃CN, carrying out the reaction in aprotic solvents, e.g. acetonitrile, at atmospheric pressure and at RT.

10

Scheme 45

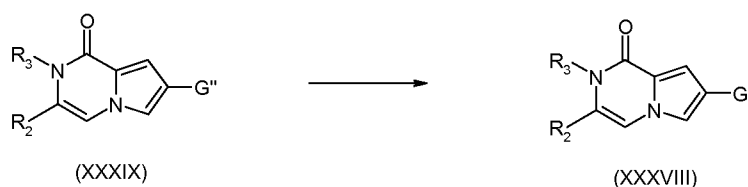


15

Compounds of formula (XXXVIII) may be obtained, according to Scheme 46, by compounds of formula (XXXIX), wherein G'' corresponds to G₆, G₇, G₈, G₉, G₁₀, G₁₁ or G₁₂ in which R₂₁, R₂₂, R₂₃, R₂₆, R₂₇, R₂₈ or R₂₉ are substituted with a nitrogen protecting group Pg₁. For example, wherein Pg₁ is a 1,1-dimethylethyl acetate (Boc) group its conversion in the corresponding amine, as well known in the art, may be carried out using trifluoroacetic acid in aprotic solvents, such as DCM, at RT.

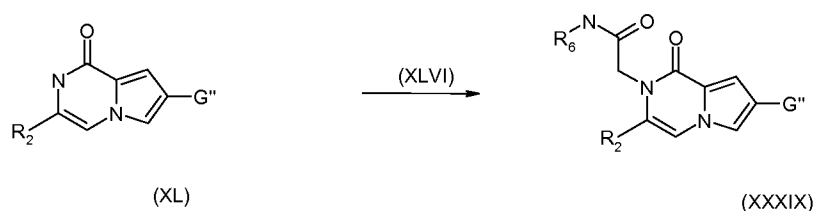
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Scheme 46



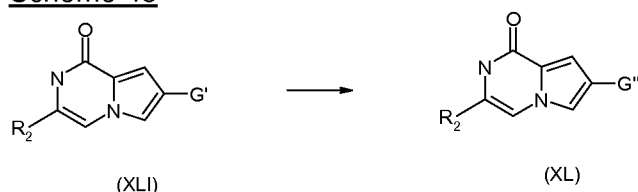
Compounds of formula (XXXIX) may be obtained, according to Scheme 47, by compounds of formula (XL), wherein $-G''$ is as above defined, through alkylation procedures with a suitable 2-halo-*N*-alkylacetamide of formula (XLVI) as above defined, for example using 2-chloro-*N*-(1-methylethyl) acetamide, sodium hydride as a strong base and carrying out the reaction in aprotic solvents, e.g. DMF, at temperature comprises between 0 and 70 °C. An iodine derivative may be used to catalyse the reaction, such as sodium iodide.

Scheme 47



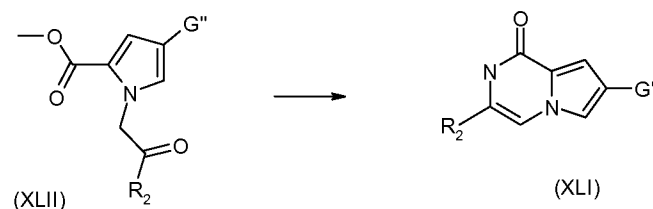
Compounds of formula (XL) may be prepared, according to Scheme 48, by reaction of compounds of formula (XLI), wherein G' is as above defined, by procedure well known to one skilled in the art. For example, wherein Pg_1 is a 1,1-dimethylethyl acetate (Boc) group, compound (XL) may be obtained reacting compound (XLI) with bis(1,1-dimethylethyl) dicarbonate (Boc_2O) carrying out the reaction in aprotic solvent, e.g. DCM, at RT.

Scheme 48

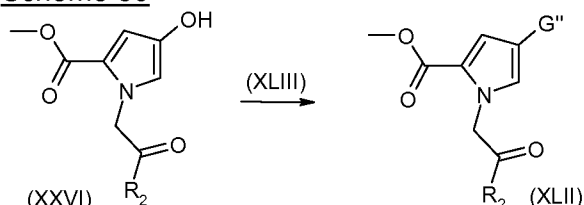


Compounds of formula (XLI) may be prepared, according to Scheme 49, by reaction of compounds of formula (XLII), wherein $-G''$ is as above defined, with NH_4OAc in acetic acid at temperature comprises between 80 and 110 °C for several hours (24-48 h).

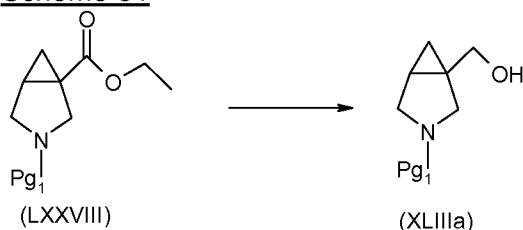
Scheme 49



Compounds of formula (XLII), may be obtained from compounds of formula (XXVI), according to Scheme 50, by Mitsunobu reaction with a suitable N-protecting group-hydroxy-alkylamine derivative of formula (XLIII) (HO-G'-Pg₁), such as N-Boc-4-hydroxymethylpiperidine, using triphenylphosphine and diethyl azodicarboxylate and carrying out the reaction in aprotic solvents, e.g. THF, at temperature comprises between 0 °C and RT.

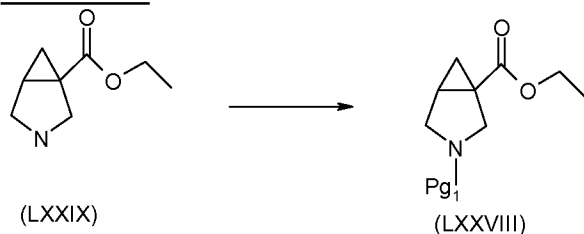
Scheme 50

Compounds of formula (XLIIIa), i.e. compound of formula (XLIII) as above define, wherein G' correspond to G₁₂ in which R₂₉ is H, may be obtained, according to Scheme 51, from compounds of formula (LXXVIII), wherein Pg₁ is a suitable N-protecting group, e.g. a 1,1-dimethylethyl acetate (Boc) group, by reduction, for example with diisobutyl aluminium hydride, in an aprotic solvent, e.g. toluene, at a temperature between -40 and -20 °C.

Scheme 51

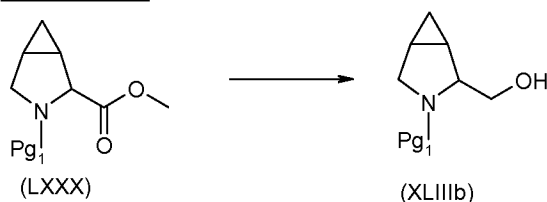
Compounds of formula (LXXVIII) may be obtained, according to Scheme 52, from compound of formula (LXXIX) by procedure well know to one skill in the art. For example, wherein Pg₁ is a 1,1-dimethylethyl acetate (Boc) group, compound (LXXVIII) may be obtained reacting compound (LXXIX) with bis(1,1-dimethylethyl) dicarbonate (Boc₂O) carrying out the reaction in aprotic solvent, e.g. DCM, at RT.

Compound of formula (LXXIX) may be prepared following the procedure reported in PCT Int. Appl. (2007) WO2007055093.

Scheme 52

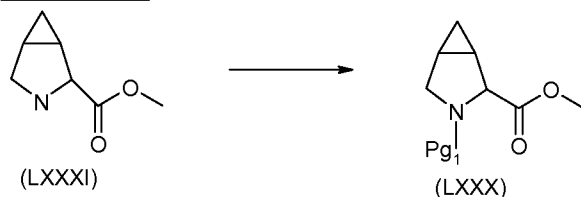
Compounds of formula (XLIIIb), i.e. compound of formula (XLIII) as above define, wherein G' correspond to G11 in which R₂₈ is H, may be obtained, according to Scheme 53, from compounds of formula (LXXX), wherein Pg₁ is a suitable N-protecting group, e.g. a 1,1-dimethylethyl acetate (Boc) group, by reduction, for example with diisobutyl aluminium hydride, in an aprotic solvent, e.g. toluene, at a temperature between -40 and -20 °C.

Scheme 53



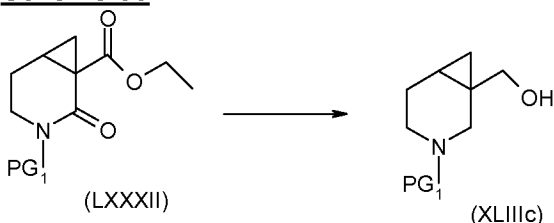
- Compounds of formula (LXXX) may be obtained, according to Scheme 54, from compound of formula (LXXXI) by procedure well know to one skill in the art. For example, wherein Pg₁ is a 1,1-dimethylethyl acetate (Boc) group, compound (LXXX) may be obtained reacting compound (LXXXI) with bis(1,1-dimethylethyl) dicarbonate (Boc₂O) carrying out the reaction in aprotic solvent, e.g. DCM, at RT. Compound of formula (LXXXI) is commercially available.

Scheme 54



- Compounds of formula (XLIIIc), i.e. compound of formula (XLIII) as above define, wherein G' correspond to G10 in which R₂₇ is H, may be obtained, according to Scheme 55, from compounds of formula (LXXXII), wherein Pg₁ is a suitable N-protecting group, e.g. a 1,1-dimethylethyl acetate (Boc) group, by reduction, for example, with lithium aluminium hydride in an aprotic solvent, e.g. THF, at a temperature between -40 and -20 °C.

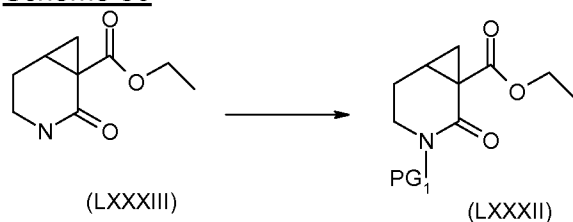
Scheme 55



- Compounds of formula (LXXXII) may be obtained, according to Scheme 56, from compound of formula (LXXXIII) by procedure well know to one skill in the art. For example, wherein Pg₁ is a 1,1-dimethylethyl acetate (Boc) group, compound (LXXXII) may be obtained reacting compound (LXXXIII) using bis(1,1-dimethylethyl) dicarbonate

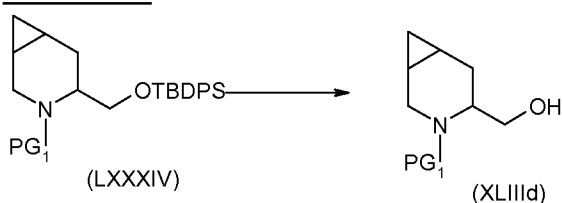
(Boc₂O) and carrying out the reaction in aprotic solvent, e.g. DCM, at RT. Compound of formula (LXXXIII) is commercially available.

Scheme 56



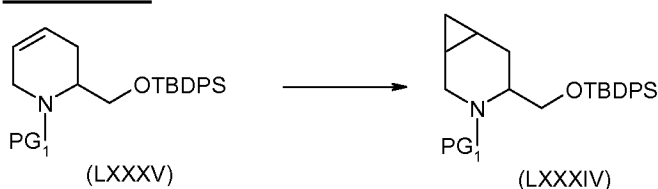
Compounds of formula (XLIIId), i.e. compound of formula (XLIII) as above define, wherein G' correspond to G9 in which R₂₆ is H, may be obtained, according to Scheme 57, from compounds of formula (LXXXIV), deprotecting the hydroxyl group with a procedure well know to one skilled in the art, such as using pyridine hydrofluoride at RT.

Scheme 57



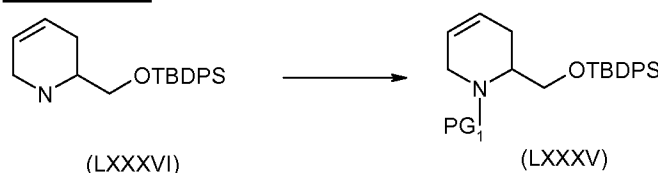
Compounds of formula (LXXXIV), may be obtained, according to Scheme 58, from compounds of formula (LXXXV), wherein Pg₁ is a suitable N-protecting group, e.g. a tosyl (Tos) group, by cyclopropanation using, for example, diethyl zinc, diiodomethane and trifluoroacetic acid in an aprotic solvent, e.g. DCM, at a temperature between 0 °C and RT.

Scheme 58



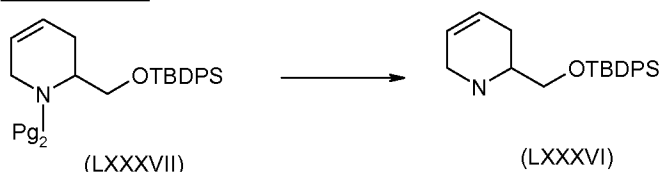
Compounds of formula (LXXXV), may be obtained, according to Scheme 59, from compounds of formula (LXXXVI) by procedure well know to one skill in the art. For example, wherein Pg₁ is a tosyl (Tos) group, compound (LXXXV) may be obtained reacting compound (LXXXVI) sing tosyl chloride and a base, e.g. TEA, carrying out the reaction in aprotic solvent, e.g. DCM, at RT.

Scheme 59



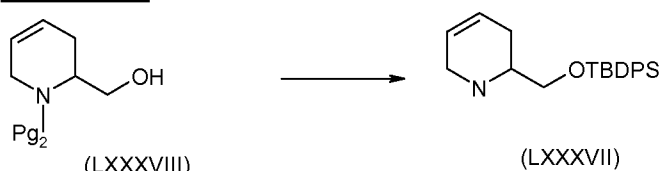
Compounds of formula (LXXXVI), may be obtained, according to Scheme 60, from compounds of formula (LXXXVII), wherein Pg₂ is a suitable N-protecting group such as 1,1-dimethylethyl acetate (Boc) group, by procedure well know to one skill in the art, for example using trifluoroacetic acid in aprotic solvent, e.g. DCM, at RT.

5

Scheme 60

Compounds of formula (LXXXVII), may be obtained, according to Scheme 61, from compounds of formula (LXXXVIII), wherein Pg₂ is a suitable N-protecting group such as 1,1-dimethylethyl acetate (Boc) group, by protection of the hydroxyl group using, for example, tert-butyl diisopropyl chloride and a base, e.g. imidazole, in aprotic solvent, e.g. DMF, at RT.

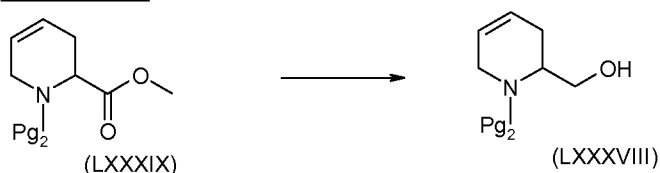
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Scheme 61

15

Compounds of formula (LXXXVIII), may be obtained, according to Scheme 62, from compounds of formula (LXXXIX), wherein Pg₂ is a suitable N-protecting group such as 1,1-dimethylethyl acetate (Boc) group, by reduction, for example, using lithium boro hydride in an aprotic solvent, e.g. THF, at RT.

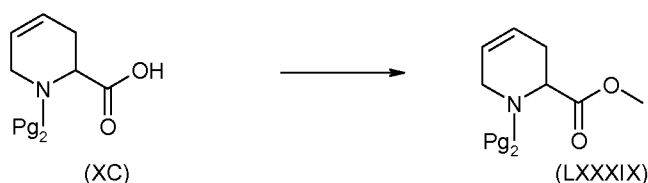
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Scheme 62

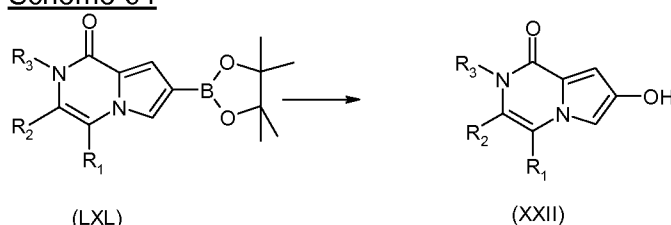
Compounds of formula (LXXXIX), may be obtained, according to Scheme 63, from compounds of formula (XC), wherein Pg₂ is a suitable N-protecting group such as 1,1-dimethylethyl acetate (Boc) group, by formation of the ester, for example, using a condensing reagent, e.g. o-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), MeOH and a base, e.g. diisopropyl ethyl amine, in an aprotic solvent, e.g. DMF, at RT.

25

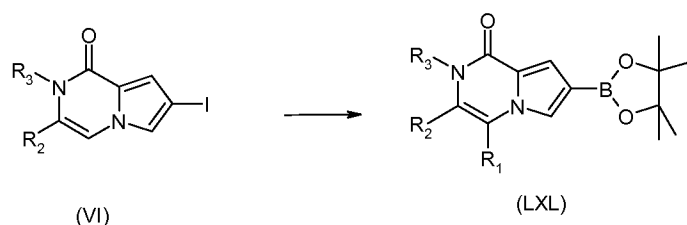
30 Scheme 63



Alternatively, compounds of formula (XXII), as above defined and wherein R₁ is hydrogen, may be obtained, according to Scheme 64, by oxidation of compounds of formula (LXL) in the presence of hydrogen peroxide, an appropriate base, such as NaOH, in an appropriate aqueous ambient, such as a mixture of THF and water, at room temperature.

Scheme 64

Compounds of formula (LXL) as above defined may be obtained, according to Scheme 65, by compounds of formula (VI) wherein Halogen is iodine, by reaction with bis (pinacolato)diboron under appropriate Suzuki conditions, for example in the presence of Pd(dppf)Cl₂·CH₂Cl₂, in DMF as a solvent, in the presence of potassium acetate and at an appropriate temperature, such as for example 90°C.

Scheme 65

In schemes 42, 43 and 50, the several derivatives described to introduce R being a group G in the molecule may be commercially available, may be prepared according to procedures described in the literature available to the person skilled in the art or may be prepared through the procedures described in the experimental section.

Those skilled in the art will appreciate that in the preparation of the compounds of the invention it may be necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be

used in a conventional manner. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butylloxycarbonyl (Boc), isopropylloxycarbonyl, cyclohexylloxycarbonyl) and alkyl type protecting groups (e.g. benzyl, trityl, chlorotriyl).

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula (I) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulphur, fluorine, iodine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I and ^{125}I .

Compounds of the present invention that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H , ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Isotopically labelled compounds of formula I and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

In a further aspect, the compounds of the present invention and their pharmaceutically acceptable salts and solvates may be useful in therapy. As such the compounds of the present invention may be useful for the manufacture of a medicament for the treatment or prevention of diseases influenced by modulation of the activity of the HPA axis. In particular the compounds may be useful for the manufacture of a medicament for the treatment of schizophrenia, anxiety, hot flushes, addiction, anorexia nervosa, stress-related disorders, sleep disorders, autistic spectrum disorders and Alzheimer's dementia. In one aspect the compounds may be useful for the manufacture of a medicament for the treatment of a metabolic syndrome characterised by insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidaemia, obesity (in particular abdominal obesity) and non-insulin-dependent diabetes mellitus (NIDDM). In a further aspect, the compounds of

the present invention may be useful for the manufacture of a medicament for the treatment or prevention of depression.

5 The present invention further includes a method for the treatment of a mammal, including a human, suffering from or liable to suffer from depression or any of the aforementioned disorders, which comprises administering an effective amount of a compound of the present invention or a pharmaceutically acceptable salt or solvate thereof.

10 Depression states in the treatment of which the compounds of the present invention and their pharmaceutically acceptable salts and solvates may be particularly useful are those classified as mood disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition- Text Revised, American Psychiatric Association, Washington D. C. (2000), including mood episodes, depressive disorders, bipolar disorders and other mood disorders.

15 The term "depression" includes:

20 Depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic
25 Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90): Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80);

30 The term "anxiety disorders" includes:

35 Anxiety disorders including Panic Attack; Panic Disorder including Panic Disorder without Agoraphobia (300.01) and Panic Disorder with Agoraphobia (300.21); Agoraphobia; Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29, formerly Simple Phobia) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (Social Anxiety Disorder, 300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02), Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced
40 Anxiety Disorder, Separation Anxiety Disorder (309.21), Adjustment Disorders with Anxiety (309.24) and Anxiety Disorder Not Otherwise Specified (300.00).

In a further aspect therefore, the present invention provides a method of treating a condition for which inhibition of V1b receptors is beneficial, which comprises administering to a mammal (e.g. human) in need thereof an effective amount of a compound of the present invention or a pharmaceutically acceptable salt or solvate thereof.

5

The invention also provides a compound of the present invention or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

10 The invention also provides a compound of the present invention or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of a condition in a mammal (e.g. Human) for which inhibition of V1b receptors is beneficial.

15 The invention also provides the use of a compound of the present invention or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a condition in a mammal (e.g. human) for which inhibition of V1b receptors is beneficial

In one embodiment, the above mentioned condition is depression.

20 "Treatment" includes prophylaxis, where this is appropriate for the relevant condition(s).

For use in medicine, the compounds of the present invention, or a pharmaceutically acceptable salt or solvate thereof, are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect a
25 pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. The pharmaceutical composition can be for use in the treatment of any of the conditions described herein.

30 Compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, may be administered by any convenient method, for example by oral, parenteral (e.g. intravenous), buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

35 Compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

40 A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as

polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

5 A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

10 A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

15 Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

20 Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed
25 container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a
30 compressed gas such as compressed air or an organic propellant such as a fluorochloro-hydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

35 Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

40 Compositions suitable for transdermal administration include ointments, gels and patches.

In one embodiment, the composition is in unit dose form such as a tablet, capsule or ampoule.

A suitable daily dose for any of the above mentioned disorders will be in the range of 0.001 to 50 mg per kilogram body weight of the recipient (e.g. a human) per day, preferably in the range of 0.01 to 20 mg per kilogram body weight per day. The desired dose may be presented as multiple sub-doses administered at appropriate intervals throughout the day.

Each dosage unit for oral administration contains for example from 1 to 250 mg (and for parenteral administration contains for example from 0.1 to 25 mg) of a compound of the invention calculated as the free base.

The compounds of the invention, or a pharmaceutically acceptable salt or solvate thereof, will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, for example between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, for example between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

The invention is further illustrated by the following non-limiting examples.

In the procedures that follow, after each starting material, reference to a Preparation or Example by number is typically provided. This is provided merely for assistance to the skilled chemist. The starting material may not necessarily have been prepared from the batch referred to.

Where reference is made to the use of a "similar" or "analogous" procedure, as will be appreciated by those skilled in the art, such a procedure may involve minor variation, for example reaction temperature, reagent/solvent amount, reaction time, work-up conditions or chromatographic purification conditions.

Compounds are named using ACD/Name PRO 6.02 chemical naming software (Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada).

All temperatures refer to °C.

Proton Magnetic Resonance (NMR) spectra are typically recorded either on Varian instruments at 300, 400 or 500 MHz, or on a Bruker instrument at 300 and 400 MHz.

Chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. The NMR spectra were recorded at a temperature ranging from 25 to 90°C. When more than one conformer was detected the chemical shifts for the most abundant one is reported.

Mass spectra (MS) are typically taken on a Agilent MSD 1100 Mass Spectrometer, operating in ES (+) and ES (-) ionization mode, or on an ion-trap Finnigan MS LCQ, operating in ES (+) and ES (-) ionization mode, or on an Agilent LC/MSD 1100 Mass Spectrometer, operating in ES (+) and ES (-) ionization mode coupled with HPLC instrument Agilent 1100 Series {LC/MS - ES (+): analysis performed on a Supelcosil ABZ +Plus (33x4.6 mm, 3 μ m); mobile phase: 100% [water +0.1% HCO₂H] for 1 min, then from 100% [water +0.1% HCO₂H] to 5% [water +0.1% HCO₂H] and 95% [CH₃CN] in 5 min, finally under these conditions for 2 min; T=40°C; flux= 1 mL/min;

LC/MS - ES (-): analysis performed on a Supelcosil ABZ +Plus (33x4.6 mm, 3 μ m); mobile phase: 100% [water +0.05% NH₃] for 1 min, then from 100% [water +0.05% NH₃] to 5% [water +0.05% NH₃] and 95% [CH₃CN] in 5 min, finally under these conditions for 2 min; T=40°C; flux= 1 mL/min}, or on a quadrupole Mass Spectrometer on a Shimadzu lcms 2010 or Agilent LC/MSD 1100 Series, operating in ES (+) and ES (-) ionization mode {LC/MS - ES (+): analysis performed on YMC ODS (50x2.0 mm, 5 μ m); mobile phase: from 90% [water +0.1% TFA] and 10% [CH₃CN+0.1% TFA] to 20% [water +0.1% TFA] and 80% [CH₃CN +0.1% TFA] in 2.5 min, finally under these conditions for 0.5min; T=50°C; flux= 1.0 mL/min;

LC/MS - ES (-): analysis performed on YMC ODS (50x2.0 mm, 5 μ m); mobile phase: from 90% [water +0.1% TFA] and 10% [CH₃CN+0.1% TFA] to 20% [water +0.1% TFA] and 80% [CH₃CN +0.1% TFA] in 3 min, finally under these conditions for 2 min; T=50°C; flux= 1.0 mL/min}, or on Shimadzu 20AB HPLC with PDA detector {column: YMC ODS 50x4.6 mm, 5 cm; mobile phase: 90% [water +0.1% TFA] and 10% [CH₃CN+0.1% TFA] to 20% [water +0.1% TFA] and 80% [CH₃CN +0.1% TFA] in 6 min, finally under these conditions for 2 min; T=40°C; flux= 3.0 mL/min}, or on a Agilent LC/MSD 1100 Mass Spectrometer, operating in ES (+) ionization mode coupled with HPLC instrument Agilent 1100 Series {LC/MS-ES (+): analysis performed on a Supelcosil ABZ+Plus (33x4.6 mm, 3 μ m); mobile phase: from 10%[CH₃CN+0.05%TFA] to 90 %[CH₃CN+0.05%TFA] and 10% [water] in 2.2 min, under these conditions for 2.8 min. T= 45 °C, flux = 0.9 mL/min}.

In the mass spectra only one peak in the molecular ion cluster is reported.

Total ion current (TIC) and DAD UV chromatographic traces together with MS and UV spectra associated with the peaks were taken on a UPLC/MS Acquity™ system equipped with 2996 PDA detector and coupled to a Waters Micromass ZQ™ mass spectrometer operating in positive or negative electrospray ionisation mode [UPLC/MS - ES (+ or -): analyses were performed using an Acquity™ UPLC BEH C18 column (50 x 2.1 mm, 1.7 μ m particle size). Mobile phase: solvent A - water + 0.1% HCO₂H / solvent B - CH₃CN + 0.06%

HCO₂H. Gradient 1: t = 0 min 3% B, t = 0.05 min 6% B, t = 0.57 min 70% B, t = 1.06 min 99% B, t = 1.449 min 99%, t = 1.45 min 3% B, stop time 1.5 min. or Gradient 2: t = 0 min 3% B, t = 1.06 min 99% B, t = 1.45 min 99% B, t = 1.46 min 3% B, stop time 1.5 min. Column T = 40 °C. Flow rate = 1.0 mL/min. Mass range: ES (+): 100-1000 amu. ES (-): 100-800 amu. UV detection range: 210-350 nm. The usage of this methodology is indicated by "UPLC" in the analytic characterization of the described compounds.

Flash silica gel chromatography was carried out on silica gel 230-400 mesh (supplied by Merck AG Darmstadt, Germany) or on silica gel 300-400 mesh supplied by SCRC (Sinopharm Chemical Reagent Co., Ltd.). or over Varian Mega Be-Si pre-packed cartridges or over pre-packed Biotage silica cartridges.

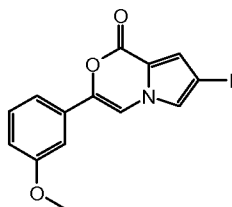
In a number of preparations, purification was performed using either Biotage manual flash chromatography (Flash+) or automatic flash chromatography (Horizon or SP1) systems. All these instruments work with Biotage Silica cartridges.

SPE-SCX cartridges are ion exchange solid phase extraction columns supplied by Varian. The eluent used with SPE-SCX cartridges is methanol followed by 2N ammonia solution in methanol.

SPE-Si cartridges are silica solid phase extraction columns supplied by Varian.

The following abbreviations are used in the text: dried refers to a solution dried over anhydrous sodium sulphate or by phase separator cartridge; BOC : *tert*-butoxycarbonyl; BOC₂O = di- *tert*-butoxycarbonyl anhydride; r.t. (RT) refers to room temperature; h = hour/hours; min = minute/minutes; Rt = retention time; DCM = dichloromethane; DMF = N,N'-dimethylformamide; DMSO = dimethylsulfoxide; DME = dimethoxyethane; MeOH = methanol; THF = tetrahydrofurane; EA, AcOEt or EtOAc = ethyl acetate; Cy = cyclohexane; Et₂O = diethyl ether; MeCN, ACN = acetonitrile; PE = petroleum ether; NH₃ = ammonia; Na₂SO₄ = sodium sulphate; MgSO₄ = magnesium sulphate; NaI = sodium iodide; TEA or Et₃N = triethylamine; NaOH = sodium hydroxide; KOH = potassium hydroxide; LiOH = lithium hydroxyde; NaH = sodium hydride; K₂CO₃ = potassium carbonate; Cs₂CO₃ = cesium carbonate; DMAP = 4-di(methylamino)pyridine; NaHCO₃ = sodium bicarbonate; TFA = trifluoroacetic acid; NH₄OAc = ammonium acetate; AcOH = acetic acid; HCl = hydrochloric acid; NaBH₃CN = sodium cyanoborohydride; BBr₃ = boron tribromide; Me₂SO₄ = dimethyl sulfate; Ac = acetyl; TPP = triphenylphosphine; DEAD = diethylazodicarboxylate; SCX Cartridge = Strong Cation Exchange Cartridge; HPLC: = high performance liquid chromatography, FC = flash chromatography; MCX: mixed mode-cation exchange cartridge; NH column: secondary amine functionalised silica cartridge.

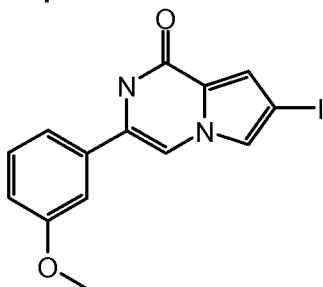
Preparation 1: 7-iodo-3-[3-(methyloxy)phenyl]-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (P1)



To a solution of 2,2,2-trichloro-1-(4-iodo-1H-pyrrol-2-yl)ethanone (200 mg, prepared in analogy with the method described in *Organic & Biomolecular Chemistry* 2006, 4(12), 2477-2482) in DMF (6 mL), potassium carbonate (245 mg) and 3-methoxyphenacyl bromide (203 mg) were added and the mixture was stirred at rt for 6h. Chilly water was added to the reaction mixture and the product was extracted with AcOEt. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was evaporated under vacuum. The crude obtained was purified by flash chromatography (eluent AcOEt: Cy=1:9) to give the title compound (120 mg) as light yellow solid.

MS (m/z): 368 [MH]⁺

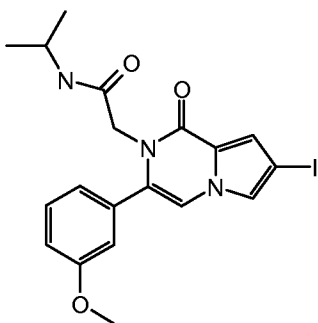
Preparation 2: 7-iodo-3-[3-(methoxy)phenyl]pyrrolo[1,2-a]pyrazin-1(2H)-one (P2)



To a solution of 7-iodo-3-[3-(methoxy)phenyl]-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (700 mg, prepared with an analogous procedure to that described in Procedure 1) in acetic acid (19 mL), ammonium acetate (2.2 g) was added and the mixture heated at reflux for 16h. Other ammonium acetate (2.2 g) was added and the solution heated at reflux for additional 24h. The solvent was evaporated under vacuum, the crude dissolved in water and DCM and the pH neutralized with potassium carbonate. The organic phase was separated from the aqueous phase, dried over Na₂SO₄ and the solvent evaporated under vacuum. The crude was purified by flash chromatography (eluent AcOEt: Cy=2:8) to give of the title compound (570mg).

MS (m/z): 367 [MH]⁺

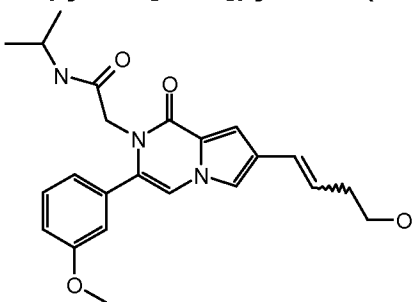
Preparation 3: 2-[7-iodo-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P3)



To a solution of 7-iodo-3-[3-(methyloxy)phenyl]pyrrolo[1,2-a]pyrazin-1(2H)-one (370 mg, P2) in dry DMF (10 mL), NaH (42.4 mg, 60% w/w) was added at 0 °C under nitrogen atmosphere. The mixture was stirred for 30 min at room temperature, that it was cooled down to 0 °C and NaI (227 mg) and 2-chloro-N-(1-methylethyl)acetamide (144 mg) were added and the mixture was stirred at 65 °C over night. Chilly water was added to the reaction mixture and the product was extracted with AcOEt. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent was evaporated under vacuum. The crude was purified by flash column chromatography on silica gel (eluent AcOEt:Cy with a gradient from 20% to 50% of AcOEt) to give the title compound (215 mg).

MS (m/z): 466 [MH]⁺

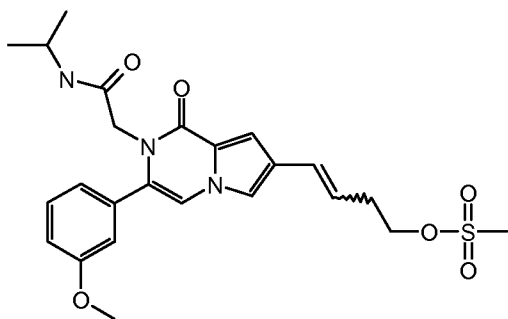
Preparation 4: 2-[7-[(1E/Z)-4-hydroxy-1-buten-1-yl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P4)



To a solution of 2-[7-iodo-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (215 mg, P3), palladium (II) acetate (10.4 mg) and tris(2-methylphenyl)phosphane (16.9 mg) in dry DMF (2.5 mL) were added under N₂ TEA (644 µL) and 3-buten-1-ol (199 µL). The resultant mixture was stirred at 100 °C for 3 h. The mixture was diluted with EtOAc, washed with chilly water and brine. The organic phase was dried over Na₂SO₄ anhydrous, filtered and evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent DCM/[DCM:MeOH = 95:5] with a gradient of DCM from 100% to 0%) to give the title compound (105 mg) containing an impurity not identified.

MS (m/z): 410 [MH]⁺

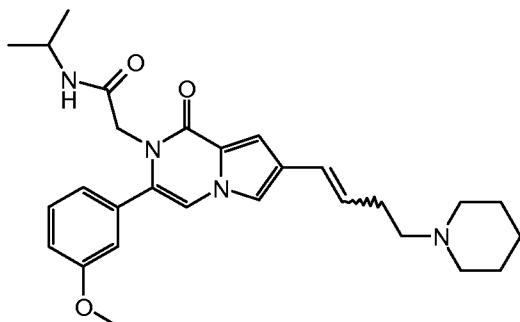
Preparation 5: (3E/Z)-4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]-3-buten-1-yl} methanesulfonate (P5)



To a solution of 2-[7-[(1*E/Z*)-4-hydroxy-1-buten-1-yl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1*H*)-yl]-N-(1-methylethyl)acetamide (105 mg, P4) in chloroform (2.5 ml) were added at 0 °C TEA (54 µl), DMAP (catalytic amount) and methansulphonyl chloride (24 µl). The mixture was stirred for 30 min at 0 °C and then warmed to room temperature and stirred over night. DCM was added and the organic layer was washed with 0.5M HCl (aq) and saturated NaHCO₃ aqueous solution. The organic phase was dried over Na₂SO₄ anhydrous, filtered and evaporated under reduced pressure to give the title compound (125 mg) as crude product that was used in the next reaction without further purification.

MS (m/z): 488 [MH]⁺

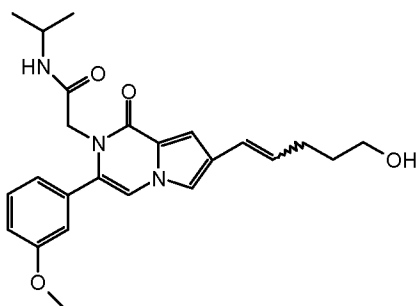
Preparation 6: *N*-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[(1*E/Z*)-4-(1-piperidinyl)-1-buten-1-yl]pyrrolo[1,2-a]pyrazin-2(1*H*)-yl]acetamide (P6)



A solution of (4*E/Z*)-5-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]-3-buten-1-yl} methanesulfonate (125 mg, P5), piperidine (76 µL) and potassium carbonate (177 mg) in acetonitrile (2 mL) was stirred at 80 °C for 8 h. The mixture was cooled down and it was partitioned between chilly water and EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ anhydrous, filtered and the solvent evaporated under reduced pressure to give the title compound (61 mg) as crude product that was used in the next reaction without further purification.

MS (m/z): 477 [MH]⁺

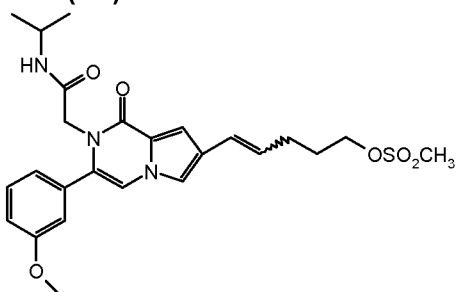
Preparation 7: 2-[7-[(1*E/Z*)-5-hydroxy-1-penten-1-yl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1*H*)-yl]-N-(1-methylethyl)acetamide (P7)



To a solution of 2-[7-iodo-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (260 mg, prepared with an analogous procedure to that described Preparation 3), palladium (II) acetate (13 mg) and tris(2-methylphenyl)phosphane (20 mg) in dry DMF (3 mL) were added under N₂ TEA (779 μ L, 5.590 mmol) and 4-penten-1-ol (289 μ L, 2.790 mmol). The resultant mixture was stirred at 80 °C for 14 h. Then palladium (II) acetate (13 mg), tris(2-methylphenyl)phosphane (20 mg) and 4-penten-1-ol (173 μ L) were sequentially added and the mixture was heated to 100 °C and allowed to stir for further 3 h. The mixture was diluted with EtOAc, washed with chilly water and brine. The organic phase was dried over Na₂SO₄ anhydrous, filtered and evaporated under reduced pressure to give 350 mg of crude product that was purified by flash column chromatography on silica gel with a gradient of DCM/DCM:MeOH = 9:1 (from 100% to 0% of DCM) as eluent affording the title compound (140 mg) containing an impurity not identified.

MS (m/z): 424 [MH]⁺

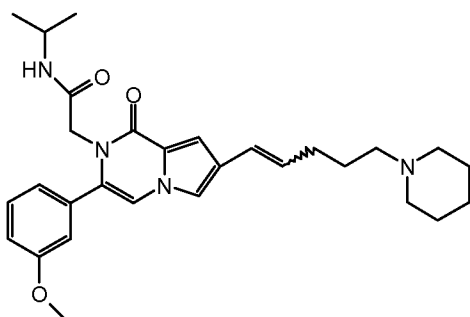
Preparation 8: (4E/Z)-5-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methoxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]-4-penten-1-yl} methanesulfonate (P8)



The title compound was prepared with an analogous procedure to that described in Preparation 5 in 215 mg yield from 2-[7-[(1E/Z)-5-hydroxy-1-penten-1-yl]-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (140 mg, P7).

MS (m/z): 502 [MH]⁺

Preparation 9: N-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-1-oxo-7-[(1E/Z)-5-(1-piperidiny)-1-penten-1-yl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (P9)

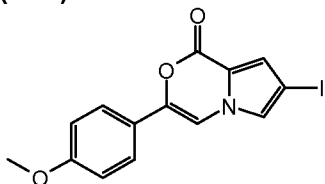


The title compound was prepared with an analogous procedure to that described in Preparation 6 in 165 mg yield from (4*E/Z*)-5-{2-{2-[(1-methylethyl)amino]-2-oxoethyl}-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-*a*]pyrazin-7-yl}-4-penten-1-yl

methanesulfonate (215 mg, P8).

MS (m/z): 491 [MH]⁺

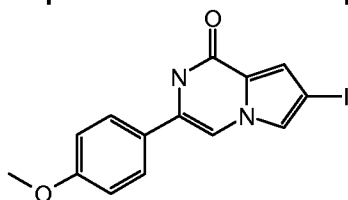
Preparation 10: 7-iodo-3-[4-(methyloxy)phenyl]-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (P10)



The title compound was prepared with an analogous procedure to that described in Preparation 1 in 5.6 g yield from 2,2,2-trichloro-1-(4-iodo-1*H*-pyrrol-2-yl)ethanone (8.1 g, prepared in analogy with the method described in *Organic & Biomolecular Chemistry* 2006, 4(12), 2477-2482).

MS (m/z): 386 [MH]⁺

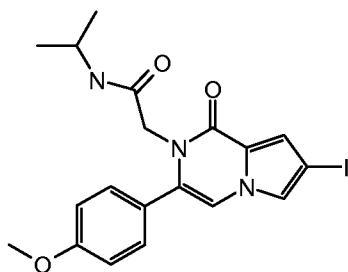
Preparation 11: 7-iodo-3-[4-(methyloxy)phenyl]pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (P11)



The title compound was prepared with an analogous procedure to that described in Preparation 2 in 2 g yield from 7-iodo-3-[4-(methyloxy)phenyl]-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (5.6 g, P10).

MS (m/z): 367 [MH]⁺

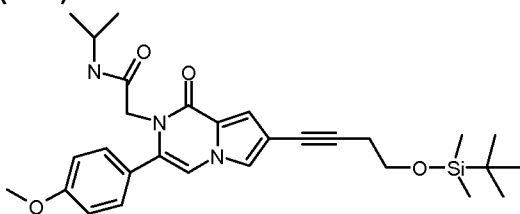
Preparation 12: 2-[7-iodo-3-[4-(methyloxy)phenyl]-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide (P12)



The title compound was prepared with an analogous procedure to that described in Preparation 3 in 1.4 g yield from 7-iodo-3-[4-(methyloxy)phenyl]pyrrolo[1,2-a]pyrazin-1(2H)-one (2 g, P11).

5 **MS (m/z):** 466 [MH]⁺

Preparation 13: 2-[7-(4-[[1,1-dimethylethyl](dimethyl)silyl]oxy)-1-butyn-1-yl]-3-[4-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P13)



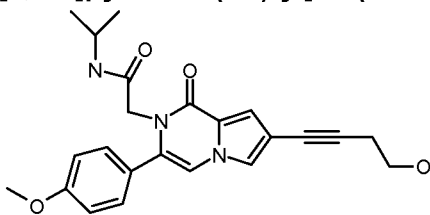
10

To a solution of 2-[7-iodo-3-[4-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (300 mg, P12) in diethylamine (2 mL) (3-butyn-1-yloxy)(1,1-dimethylethyl)dimethylsilane (0.213 mL, 1.032 mmol), bis(triphenylphosphine)palladium (II) chloride (45 mg) and copper iodide (74 mg) were added. This mixture was stirred at rt for 15 h under nitrogen atmosphere. Then the solvent was evaporated and the residue was purified by flash column chromatography on silica gel with a gradient of EtOAc/Cyclohexane as eluent to give the title compound as orange solid (150 mg).

15

MS (m/z): 522 [MH]⁺

20 **Preparation 14:** 2-[7-(4-hydroxy-1-butyn-1-yl)-3-[4-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P14)



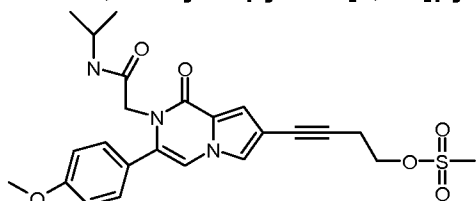
25

To a solution of 2-[7-(4-[[1,1-dimethylethyl](dimethyl)silyl]oxy)-1-butyn-1-yl]-3-[4-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (130 mg, P13) in THF (2 mL), tetrabutylammonium fluoride 1.0M in THF (0.374 mL) was added dropwise at 0 °C and the reaction mixture was stirred for 1 h at rt. Water was added to the mixture and the product extracted with EtOAc. The organic phase was dried over Na₂SO₄

anhydrous, filtered and evaporated under reduced pressure to give the title compound (90 mg) as crude material that was used in the next reaction without further purification.

MS (m/z): 408 [MH]⁺

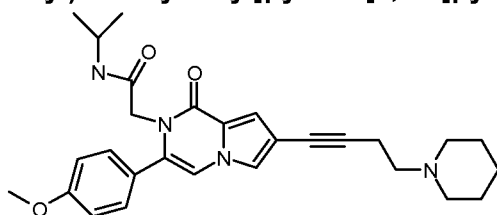
5 **Preparation 15:** 4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[4-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]-3-butyn-1-yl methanesulfonate (P15)



10 The title compound was prepared with an analogous procedure to that described in Preparation 5 in 120 mg yield as crude from 2-[7-(4-hydroxy-1-butyn-1-yl)-3-[4-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (90 mg, P14).

MS (m/z): 486 [MH]⁺

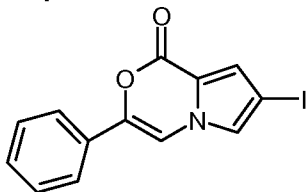
15 **Preparation 16:** N-(1-methylethyl)-2-[3-[4-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)-1-butyn-1-yl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (P16)



20 The title compound was prepared with an analogous procedure to that described in Preparation 6 in 123 mg yield as crude from 4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[4-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]-3-butyn-1-yl methanesulfonate (120 mg, P15).

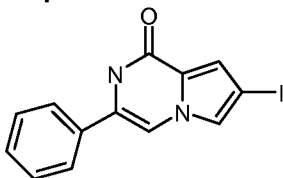
MS (m/z): 475 [MH]⁺.

Preparation 17: 7-iodo-3-phenyl-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (P17)



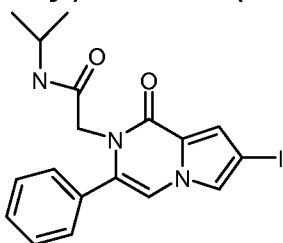
25 The title compound was prepared with an analogous procedure to that described in Preparation 1 in 2.7 g yield from 2,2,2-trichloro-1-(4-iodo-1H-pyrrol-2-yl)ethanone (3.37 g, prepared in analogy with the method described in *Organic & Biomolecular Chemistry* 2006, 4(12), 2477-2482).

MS (m/z): 338 [MH]⁺

Preparation 18: 7-iodo-3-phenylpyrrolo[1,2-a]pyrazin-1(2H)-one (P18)

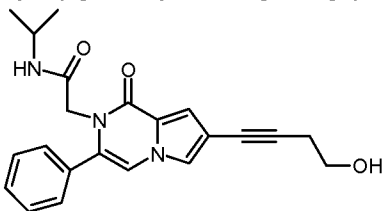
The title compound was prepared with an analogous procedure to that described in Preparation 2 in 1.26 g yield from 7-iodo-3-phenyl-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (1.68 g, P17).

MS (m/z): 337 [MH]⁺

Preparation 19: 2-(7-iodo-1-oxo-3-phenylpyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(1-methylethyl)acetamide (P19)

The title compound was prepared with an analogous procedure to that described in Preparation 3 in 0.7 g yield from 7-iodo-3-phenylpyrrolo[1,2-a]pyrazin-1(2H)-one (1.20 g, P18).

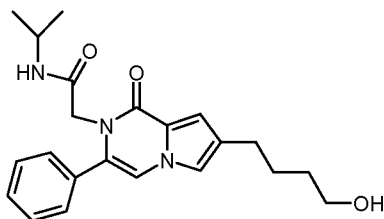
MS (m/z): 436 [MH]⁺

Preparation 20: 2-[7-(4-hydroxy-1-butyne-1-yl)-1-oxo-3-phenylpyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P20)

To a mixture of 2-(7-iodo-1-oxo-3-phenylpyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-(1-methylethyl)acetamide (653 mg, P19) in anhydrous triethylamine (25mL) and DMF (13mL) bis(triphenylphosphine)palladium (II) chloride (57 mg), cupper iodide (28.5 mg) and 3-butyn-1-ol (136 mg) were added under argon atmosphere. Then the reaction mixture was stirred at room temperature for 15h. The mixture was poured into ice-water (100mL) and extracted with DCM (2×150mL). The organic phase was washed with brine (150mL), dried over MgSO₄, filtered through celite and evaporated under vacuum to obtain the title compound (486mg).

MS (m/z): 378 [MH]⁺

Preparation 21: 2-[7-(4-hydroxybutyl)-1-oxo-3-phenylpyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P21)

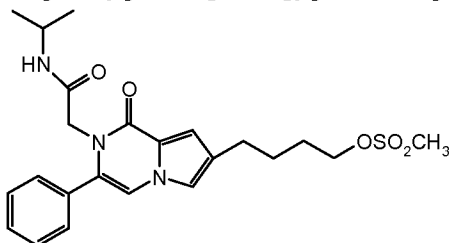


- 5 A mixture of 2-[7-(4-hydroxy-1-butyn-1-yl)-1-oxo-3-phenylpyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (435mg, P20) and palladium on carbon (10%, 0.30 g) in methanol (100 mL) was hydrogenated at atmospheric pressure at room temperature for 2h. The resulting suspension was filtered through a sinter glass funnel and the solvent was concentrated under vacuum to give a crude that was purified by flash chromatography on silica column (eluent PE: EtOAc = 1:2) to give the title compound (220mg).

¹HNMR(400 MHz, DMSO-d₆): δ 7.29-7.43(5H, m), 7.00 (1H, s), 6.94(1H, s), 6.84 (1H, s), 5.87-5.89(1H, m), 4.29(2H, s), 3.7.-4.06(1H, m), 3.66-3.68(2H, t), 2.62-2.66(2H,t), 1.59-1.75 (4H, m), 1.07-1.12 (6H,d).

15 **MS (m/z):** 382 [MH]⁺.

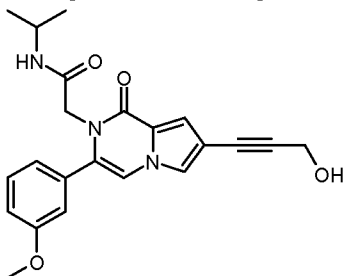
Preparation 22: 4-(2-{2-[(1-methylethyl)amino]-2-oxoethyl}-1-oxo-3-phenyl-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl)butyl methanesulfonate (P22)



- 20 The title compound was prepared with an analogous procedure to that described in Preparation 5 in 80 mg yield as crude beige solid from 2-[7-(4-hydroxybutyl)-1-oxo-3-phenylpyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (70 mg, P21).

MS (m/z): 460 [MH]⁺

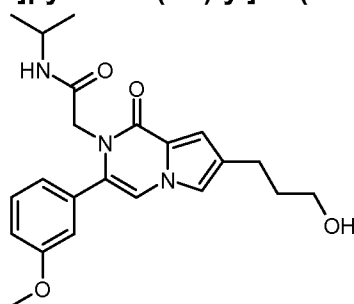
- 25 **Preparation 23: 2-[7-(3-hydroxy-1-propyn-1-yl)-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P23)**



The title compound was prepared with an analogous procedure to that described in Preparation 20 in 280 mg yield from 2-[7-iodo-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (390mg, prepared in analogy with the method described in P3).

5 **MS (m/z):** 394 [MH]⁺

Preparation 24: 2-[7-(3-hydroxypropyl)-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P24)

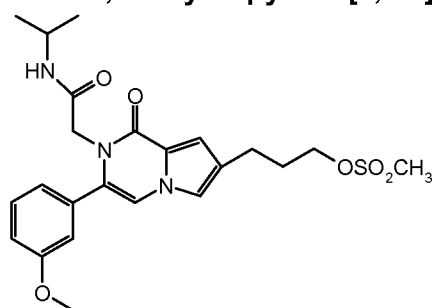


10 The title compound was prepared with an analogous procedure to that described in Preparation 21 in 208 mg yield from 2-[7-(3-hydroxy-1-propyn-1-yl)-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (280mg, P23).

15 **¹H-NMR(400 MHz, CDCl₃):** δ 7.25-7.36 (m, 1H), 6.88-7.00(m, 5H), 6.86 (s, 1H), 5.91(s, 1H), 4.26-4.30 (d, 2H), 3.99-4.03 (m, 1H), 3.82 (s, 3H), 3.64-3.74 (m, 2H), 2.67-2.72 (m, 2H), 1.56-1.92 (m, 2H), 1.11-1.12 (m, 7H).

MS (m/z): 398 [MH]⁺.

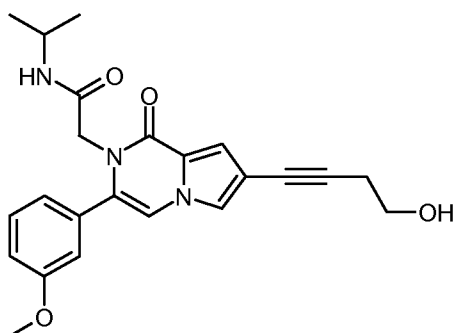
20 **Preparation 25:** 3-{2-{2-[(1-methylethyl)amino]-2-oxoethyl}-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl}propyl methanesulfonate (P25)



25 The title compound was prepared with an analogous procedure to that described in Preparation 5 in 145 mg yield as crude yellow oil from 2-[7-(3-hydroxypropyl)-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (70 mg, P24).

MS (m/z): 476 [MH]⁺

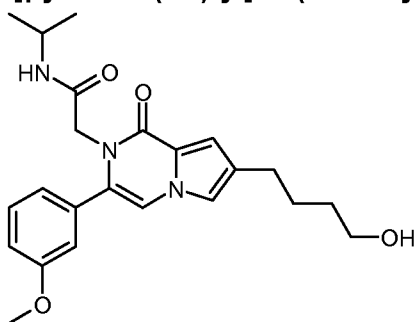
Preparation 26: 2-[7-(4-hydroxy-1-butyln-1-yl)-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P26)



The title compound was prepared with an analogous procedure to that described in Preparation 20 in 780 mg yield from 2-[7-iodo-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (900mg, prepared in analogy with the method described in P3).

MS (m/z): 408 [MH]⁺

Preparation 27: 2-[7-(4-hydroxybutyl)-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P27)

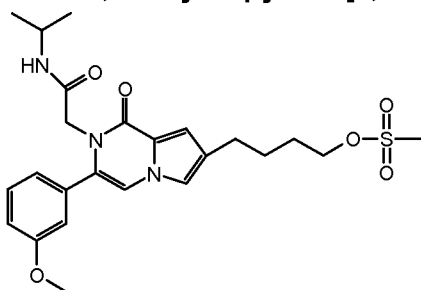


The title compound was prepared with an analogous procedure to that described in Preparation 21 in 360 mg yield from 2-[7-(4-hydroxy-1-butyne-1-yl)-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (780mg, P26).

¹HNMR (400 MHz, DMSO-d₆): δ 7.71(1H, m), 6.95-7.36(6H, m), 6.74(1H, s), 4.34(1H, t), 4.17(2H, s), 3.77(3H, s), 3.40(2H, q), 2.48-2.54(2H, m), 1.56-1.61(2H, m), 1.41-1.46 (2H, m), 0.95(6H, d).

MS (m/z): 412 [MH]⁺.

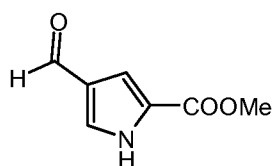
Preparation 28: 4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl}butyl methanesulfonate (P28)



The title compound was prepared with an analogous procedure to that described in Preparation 5 in 218 mg yield as crude yellow oil from -[7-(4-hydroxybutyl)-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (136 mg, prepared in analogy to P27).

5 **MS (m/z):** 490 [MH]⁺

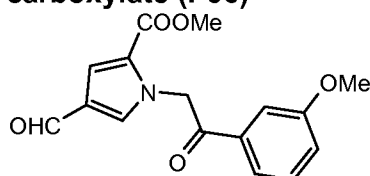
Preparation 29: methyl 4-formyl-1H-pyrrole-2-carboxylate (P29)



10 To a solution of methyl 1H-pyrrole-2-carboxylate (35 g) in DMF (80 mL) a solution of Vilsmeier reagent (synthesized as follow: phosphorus (III) oxychloride (85.12g) adding drop wise at 0 °C to DMF (40.88 g), then the solution was warmed to rt and stirred for 30 min) in DMF (20 mL) was added at rt and the reaction mixture was stirred for 16h. NaOH
15 4N solution was added slowly at 0 °C under stirring to the reaction mixture until pH=7, filtrated and washed several times with EA. The filtrate was extracted with EA for three times and the collected organic phase was washed with water, brine, dried over Na₂SO₄ and concentrated under vacuum. The crude product was combined with one other batch of crude product obtained with the same procedure starting from methyl 1H-pyrrole-2-carboxylate (15 g). The collected crude was purified by FC on silica gel to give the title
20 compound (32 g) as yellow solid.

¹H NMR (400 MHz, DMSO-d₆) δ: 3.77 (3H, s), 7.09 (1H, s), 7.77 (1H, s), 9.71 (1H, s), 12.6-12.7 (1H, b).

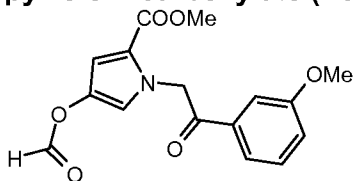
25 **Preparation 30: methyl 4-formyl-1-(2-(3-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (P30)**



To a solution of methyl 4-formyl-1H-pyrrole-2-carboxylate (10 g, P29) in acetonitrile (100 mL) K₂CO₃ (27.6 g) and 2-bromo-1-(3-methoxyphenyl)ethanone (14.9 g) were added and the suspension was stirred for 1h at room temperature. The reaction mixture was diluted
30 with EA (100ml), washed with water (three times) and brine, dried, filtrated and concentrated under vacuum to give the title compound (19.10 g) as yellow solid.

¹H NMR (400 MHz, DMSO-d₆), δ: 3.64 (3H, s), 3.81 (3H, s), 5.96 (2H, s), 7.295 (2H, m), 7.49 (2H, m), 7.62 (1H, d), 7.89 (1H, s), 9.74 (1H, s).

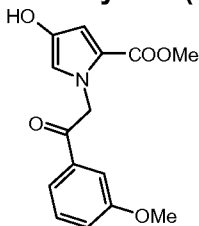
Preparation 31: methyl 4-(formyloxy)-1-(2-(3-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (P31)



To a solution of methyl 4-formyl-1-(2-(3-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (18.80 g, P30) in DCM (200mL) *meta*-chloroperbenzoic acid (18.71 g, 85 %) and TFA (702 mg) were added at 0 °C , then the mixture was warmed up at rt and stirred for 6h. Sodium thiosulfate solution was added, the two phases separated and the organic phase washed with sodium thiosulfate solution (three times), water, brine, dried, filtrated and concentrated under vacuum. The crude was purified by column chromatography on silica gel (eluted with PE:EA=8:1) to give the title compound (8.70 g) as yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.63 (3H, s), 3.83 (3H, s), 5.87 (2H, s), 6.84 (1H, d), 7.28 (2H, m), 7.50 (2H, m), 7.63 (1H, d), 8.46 (1H, s).

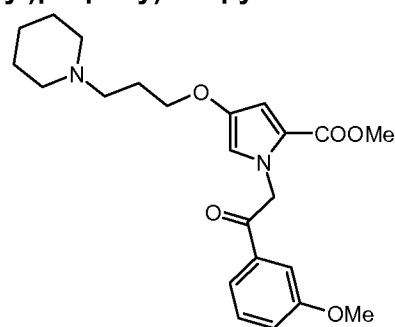
Preparation 32: methyl 4-hydroxy-1-(2-(3-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (P32)



To a solution of methyl 4-(formyloxy)-1-(2-(3-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (5.08 g, P31) in MeOH (30mL) Na₂CO₃ solution (2M, 10ml) was added and the mixture was stirred for five minutes. The mixture was concentrated under vacuum, the residue dissolve in EA, washed with water (three times), brine, dried and concentrated under vacuum to give the title compound (4.56 g) as grey solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.57 (3H, s), 4.02 (3H, s), 5.72 (2H, s), 6.32 (1H, d), 6.60 (1H, d), 7.26 (1H, dd), 7.48 (2H, m), 7.60 (1H, d), 8.52 (1H, s).

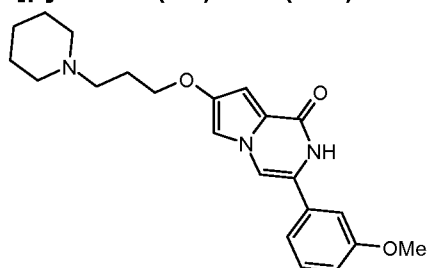
Preparation 33: methyl 1-(2-(3-methoxyphenyl)-2-oxoethyl)-4-(3-(piperidin-1-yl)propoxy)-1H-pyrrole-2-carboxylate (P33)



To the suspension of 1-(3-chloropropyl)piperidine hydrochloride (4.06g, P32) in CH₃CN (100ml) K₂CO₃ (5.45g, 39.5mmol) was added. The mixture was stirred for 0.5h then methyl 4-hydroxy-1-(2-(3-methoxyphenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (4.56g) and NaI (1.19g) were added and the mixture was heated to reflux temperature for 24h. The reaction mixture was cooled down to room temperature, diluted with EA, washed with water (three times), brine, dried and concentrated under vacuum. The crude was purified through a column chromatography on silica gel (eluted with DCM:MeOH=50:1) to give the title compound (3.44 g).

¹H NMR (400 MHz, DMSO-d₆) δ: 1.36 (2H, m), 1.50 (4H, m), 1.78 (2H, m), 2.46 (6H, m), 3.52 (3H, s), 3.79 (3H, m), 3.85 (2H, m), 5.73 (2H, s), 6.49 (1H, s), 6.78 (1H, s), 7.23 (1H, m), 7.48 (2H, m), 7.57 (1H, d).

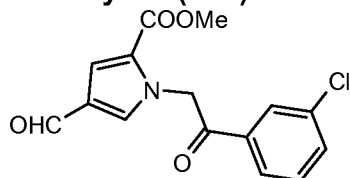
Preparation 34: 3-(3-methoxyphenyl)-7-(3-(piperidin-1-yl)propoxy)pyrrolo[1,2-a]pyrazin-1(2H)-one (P34)



To a solution of methyl 1-(2-(3-methoxyphenyl)-2-oxoethyl)-4-(3-(piperidin-1-yl)propoxy)-1H-pyrrole-2-carboxylate (3.00 g, P33) in AcOH (50ml) NH₄OAc (16.74 g) was added and the reaction was reflux for 16h. The mixture was cooled down to room temperature, diluted with EA (100ml), washed with the solution of NH₃·H₂O (three times), water, brine, dried, filtered and concentrated under vacuum. The crude was combined with one other batch of crude product obtained following the same synthetic procedure from methyl 1-(2-(3-methoxyphenyl)-2-oxoethyl)-4-(3-(piperidin-1-yl)propoxy)-1H-pyrrole-2-carboxylate (0.4 g, P33). The collected crude was purified by FC on silica column (eluent DCM:MeOH=10:0.5) to give the title compound (1.84 g) as yellow solid.

¹H NMR (400 MHz, DMSO-d₆) δ: 1.44 (2H, m), 1.56 (4H, m), 1.93 (2H, m), 2.54 (6H, m), 3.87 (3H, s), 4.03 (2H, t), 6.59 (1H, s), 6.98 (1H, d), 7.19 (1H, s), 7.25 (2H, m), 7.40 (1H, t), 7.71 (1H, s), 10.90 (1H, s).

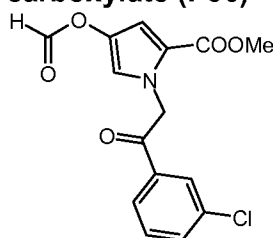
Preparation 35: methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (P35)



The title compound was prepared with an analogous procedure to that described in Preparation 30 in 4.69 g yield as yellow solid from methyl 4-formyl-1H-pyrrole-2-carboxylate (3.00 g, P29) and 2-bromo-1-(3-chlorophenyl)ethanone (4.58 g).

¹H NMR (400 MHz, DMSO-d₆), δ: 3.64 (3H, s), 5.97 (2H, s), 7.27 (2H, d), 7.60 (1H, t), 7.78 (1H, dd), 7.87 (1H, d), 7.96 (1H, dd), 8.04 (1H, d), 9.75 (1H, s).

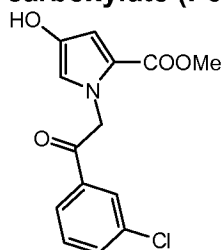
Preparation 36: methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-(formyloxy)-1H-pyrrole-2-carboxylate (P36)



To a solution of methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (5.34 g, P35) in DCM (150mL) *meta*-chloroperbenzoic acid (4.52 g, 85 % pure) and TFA (200 mg) were added at 0 °C, then the mixture was warmed up at rt and stirred for 4h. The reaction mixture was filtered and washed with DCM. The filtrate was washed with sodium thiosulfate solution (three times), water, brine, dried, filtrate and concentrated under vacuum. The crude was purified by column chromatography on silica gel (eluted with PE:EA=8:1) to give the title compound (3.00 g) as yellow solid.

¹H NMR (400 MHz, DMSO-d₆) δ: 3.63 (3H, s), 5.88 (2H, s), 6.84 (1H, d), 7.27 (1H, d), 7.63 (1H, t), 7.78 (1H, d), 7.97 (1H, d), 8.05 (1H, s), 8.46 (1H, s).

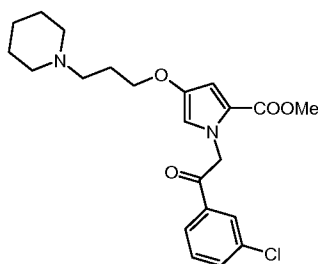
Preparation 37: methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-hydroxy-1H-pyrrole-2-carboxylate (P37)



The title compound was prepared with an analogous procedure to that described in Preparation 32 in 2.57 g yield as grey oil from methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-(formyloxy)-1H-pyrrole-2-carboxylate (3.00 g, P36)

¹H NMR (400 MHz, DMSO-d₆) δ: 3.54 (3H, s), 5.69 (2H, s), 6.30 (1H, s), 6.57 (1H, s), 7.58 (1H, t), 7.73 (1H, dd), 7.92 (1H, d), 7.98 (1H, s), 8.52 (1H, s).

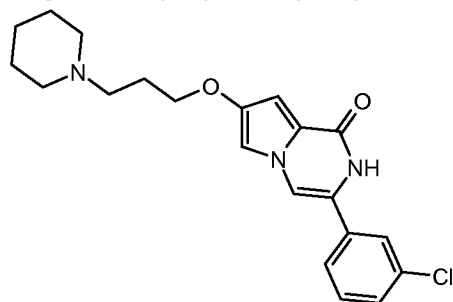
Preparation 38: methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-(3-(piperidin-1-yl)propoxy)-1H-pyrrole-2-carboxylate (P38)



The title compound was prepared with an analogous procedure to that described in Preparation 33 in 2.48 g yield as grey oil from 1-(3-chloropropyl)piperidine hydrochloride (2.26 g, P37).

- 5 **¹H NMR (400 MHz, DMSO-d₆)** δ: 1.36 (2H, m), 1.49 (4H, m), 1.82 (2H, m), 2.30-2.50 (6H, m), 3.56 (3H, s), 3.83 (2H, t), 5.73 (2H, s), 6.49 (1H, s), 6.78 (1H, s), 7.58 (1H, t), 7.75 (1H, t), 7.93 (1H, d), 7.95 (1H, s).

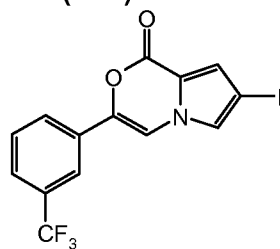
10 **Preparation 39: 3-(3-chlorophenyl)-7-(3-(piperidin-1-yl)propoxy)pyrrolo[1,2-a]pyrazin-1(2H)-one (P39)**



The title compound was prepared with an analogous procedure to that described in Preparation 34 in 1.51 g yield as white solid from methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-(3-(piperidin-1-yl)propoxy)-1H-pyrrole-2-carboxylate (2.48g, P38).

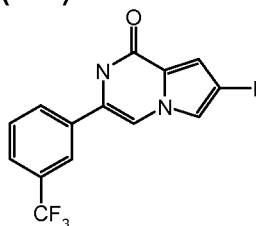
- 15 **¹H NMR (400 MHz, CD₃OD)** δ: 1.60 (2H, m), 1.79 (4H, m), 2.15 (2H, m), 3.02 (6H, m), 4.06 (2H, t), 6.68 (1H, s), 7.14 (1H, s), 7.45 (2H, m), 7.52 (2H, m), 7.63 (1H, s).

Preparation 40: 7-iodo-3-[3-(trifluoromethyl)phenyl]-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (P40)



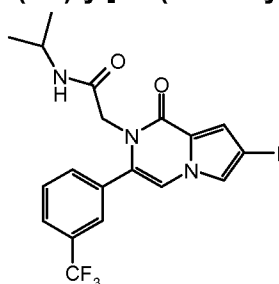
- 20 The title compound was prepared with an analogous procedure to that described in Preparation 1 in 0.4 g yield from 2,2,2-trichloro-1-(4-iodo-1H-pyrrol-2-yl)ethanone (0.5 g, prepared in analogy with the method described in *Organic & Biomolecular Chemistry* 2006, 4(12), 2477-2482) and 2-bromo-1-[3-(trifluoromethyl)phenyl]ethanone (0.8 g, prepared in analogy with the method described in JOC 45(24), 4989-90; 1980).
- 25

MS (m/z): 406 [MH]⁺

Preparation 41: 7-iodo-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-1(2H)-one (P41)


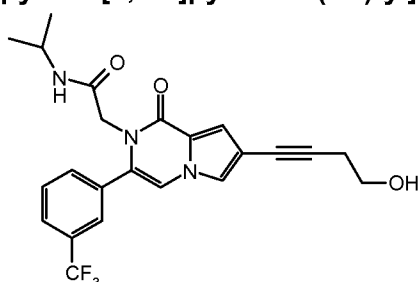
The title compound was prepared with an analogous procedure to that described in Preparation 2 in 0.9 g yield from 7-iodo-3-[3-(trifluoromethyl)phenyl]-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (0.9 g, prepared in analogy to P40).

MS (m/z): 405 [MH]⁺

Preparation 42: 2-[7-iodo-1-oxo-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P42)


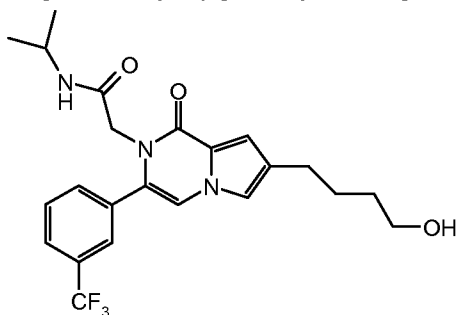
The title compound was prepared with an analogous procedure to that described in Preparation 3 in 130 mg yield from 7-iodo-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-1(2H)-one (530 mg, prepared in analogy to P41) and 2-bromo-N-(1-methylethyl)acetamide (248 mg).

MS (m/z): 503 [MH]⁺

Preparation 43: 2-[7-(4-hydroxy-1-butyn-1-yl)-1-oxo-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P43)


The title compound was prepared with an analogous procedure to that described in Preparation 20 in 150 mg yield from 2-[7-iodo-1-oxo-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (503mg, prepared in analogy to P42).

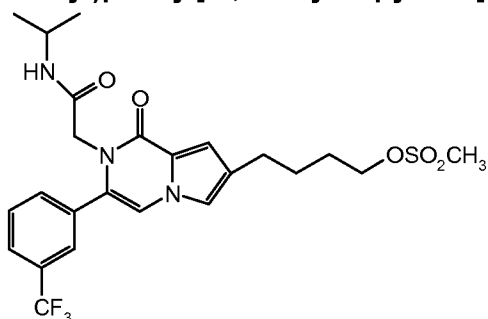
MS (m/z): 446 [MH]⁺

Preparation 44: 2-[7-(4-hydroxybutyl)-1-oxo-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P44)


The title compound was prepared with an analogous procedure to that described in Preparation 21 in 140 mg yield from 2-[7-(4-hydroxy-1-butyne-1-yl)-1-oxo-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (145mg, P43).

¹HNMR (400 MHz, CDCl₃): δ 7.80-7.67(m, 5H), 7.25-7.20 (d, 2H), 6.94 (s, 1H), 4.37 (s, 2H), 3.88-3.84 (m, 1H), 3.59-3.55 (t, 2H), 2.66-2.61 (t, 2H), 1.74-1.58 (m, 4H), 1.04-1.02 (d, 6H).

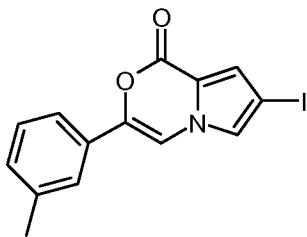
MS (m/z): 450 [MH]⁺

Preparation 45: 4-[2-{2-[(1-methylethyl)amino]-2-oxoethyl}-1-oxo-3-[3-(trifluoromethyl)phenyl]-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]butyl methanesulfonate (P45)


The title compound was prepared with an analogous procedure to that described in Preparation 5 in 92 mg yield as crude yellow solid from 2-[7-(4-hydroxybutyl)-1-oxo-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (75 mg, P44).

MS (m/z): 528 [MH]⁺

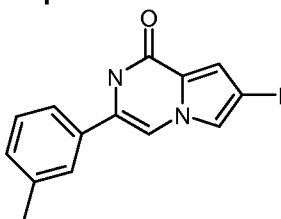
Preparation 46: 7-iodo-3-(3-methylphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (P46)



The title compound was prepared with an analogous procedure to that described in Preparation 1 in 2.3 g yield from 2,2,2-trichloro-1-(4-iodo-1H-pyrrol-2-yl)ethanone (2.89 g, prepared in analogy with the method described in *Organic & Biomolecular Chemistry* 2006, 4(12), 2477-2482).

MS (m/z): 352 [MH]⁺

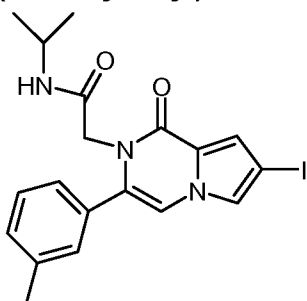
Preparation 47: 7-iodo-3-(3-methylphenyl)pyrrolo[1,2-a]pyrazin-1(2H)-one (P47)



The title compound was prepared with an analogous procedure to that described in Preparation 2 in 1.9 g yield from 7-iodo-3-(3-methylphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (2.39 g, P46).

MS (m/z): 351 [MH]⁺

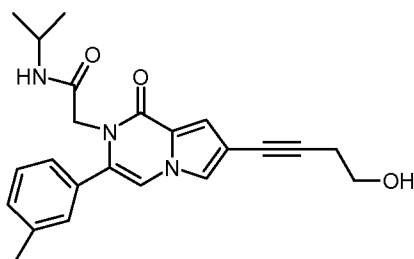
Preparation 48: 2-[7-iodo-3-(3-methylphenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P48)



The title compound was prepared with an analogous procedure to that described in Preparation 3 in 0.6 g yield from 7-iodo-3-(3-methylphenyl)pyrrolo[1,2-a]pyrazin-1(2H)-one (1.81 g, P47).

MS (m/z): 450 [MH]⁺

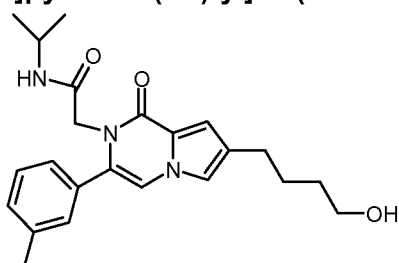
Preparation 49: 2-[7-(4-hydroxy-1-butyn-1-yl)-3-(3-methylphenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P49)



The title compound was prepared with an analogous procedure to that described in Preparation 20 in 0.42 g yield from 2-[7-iodo-3-(3-methylphenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (0.6 g, P48).

5 **MS (m/z):** 382 [MH]⁺

Preparation 50: 2-[7-(4-hydroxybutyl)-3-(3-methylphenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P50)



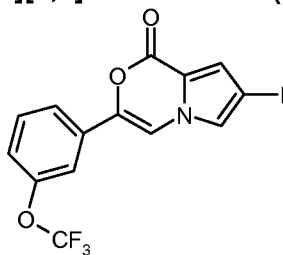
10 The title compound was prepared with an analogous procedure to that described in Preparation 21 in 0.42 g yield from 2-[7-(4-hydroxy-1-butyn-1-yl)-3-(3-methylphenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (0.42 g, P49).

¹HNMR (400 MHz, CHCl₃-d₆): δ 7.29-7.43(5H, m), 6.99 (1H, s), 6.93(1H, s), 6.84 (1H, s), 5.90-5.93(1H, m), 4.29(2H, s), 4.02-4.04(1H, m), 3.65-3.69(2H, t), 2.61-2.66(2H,t), 2.37(3H, s) 1.63-1.74 (4H, m), 1.11-1.14 (6H,d).

15

MS (m/z): 386 [MH]⁺.

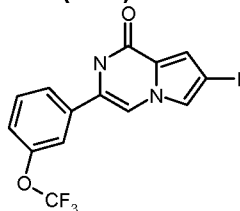
Preparation 51: 7-iodo-3-{3-[(trifluoromethoxy)phenyl]-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (P51)



20

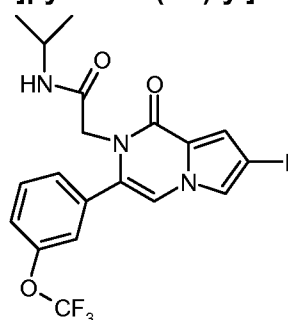
The title compound was prepared with an analogous procedure to that described in Preparation 1 in 3.8 g yield from 2,2,2-trichloro-1-(4-iodo-1H-pyrrol-2-yl)ethanone (2.4 g, prepared in analogy with the method described in *Organic & Biomolecular Chemistry* 2006, 4(12), 2477-2482).

25 **MS (m/z):** 421 [MH]⁺

Preparation 52: 7-iodo-3-{3-[(trifluoromethyl)oxy]phenyl}pyrrolo[1,2-a]pyrazin-1(2H)-one (P52)

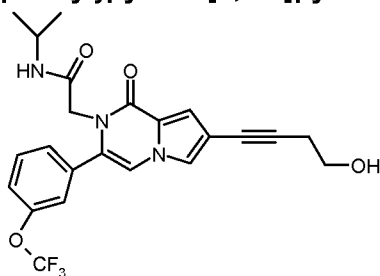
The title compound was prepared with an analogous procedure to that described in Preparation 2 in 3 g yield from 7-iodo-3-{3-[(trifluoromethyl)oxy]phenyl}-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (3.8 g, P51).

MS (m/z): 420 [MH]⁺

Preparation 53: 2-[7-iodo-1-oxo-3-{3-[(trifluoromethyl)oxy]phenyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P53)

The title compound was prepared with an analogous procedure to that described in Preparation 3 in 2.23 g yield from 7-iodo-3-{3-[(trifluoromethyl)oxy]phenyl}pyrrolo[1,2-a]pyrazin-1(2H)-one (0.53 g, P52).

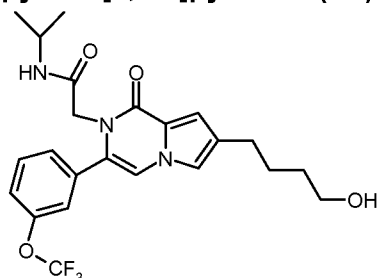
MS (m/z): 520 [MH]⁺

Preparation 54: 2-[7-(4-hydroxy-1-butyn-1-yl)-1-oxo-3-{3-[(trifluoromethyl)oxy]phenyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P54)

The title compound was prepared with an analogous procedure to that described in Preparation 20 in 0.23 g yield from 2-[7-iodo-1-oxo-3-{3-[(trifluoromethyl)oxy]phenyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (0.5 g, P53).

MS (m/z): 462 [MH]⁺

Preparation 55: 2-[7-(4-hydroxybutyl)-1-oxo-3-{3-[(trifluoromethyl)oxy]phenyl}-pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P55)

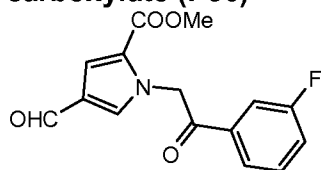


The title compound was prepared with an analogous procedure to that described in Preparation 21 in 40 mg yield from 2-[7-(4-hydroxy-1-butyn-1-yl)-1-oxo-3-{3-[(trifluoromethyl)oxy]phenyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (50 mg, P54).

¹H NMR (400 MHz, CDCl₃): δ 7.56-7.42(m, 4H), 7.25-7.20 (d, 2H), 6.94 (s, 1H), 4.36 (s, 2H), 3.88-3.84 (m, 1H), 3.59-3.55 (t, 2H), 2.63-2.61 (t, 2H), 1.74-1.58 (m, 4H), 1.06-1.04 (d, 6H).

MS (m/z): 466 [MH]⁺.

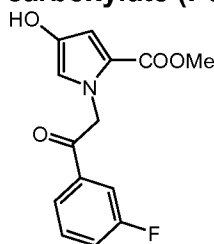
Preparation 56: methyl 1-[2-(3-fluorophenyl)-2-oxoethyl]-4-formyl-1H-pyrrole-2-carboxylate (P56)



The title compound was prepared with an analogous procedure to that described in Preparation 30 in 3.14 g yield as yellow solid from methyl 4-formyl-1H-pyrrole-2-carboxylate (1.75 g, P29) and 2-bromo-1-(3-fluorophenyl)ethanone (2.48 g).

¹H NMR (400 MHz, CDCl₃): δ: 9.83 (1H, s), 7.82 (1H, m), 7.70 (1H, m), 7.53 (2H, m), 7.45 (2H, m), 7.35 (1H, m), 5.77 (2H, s), 3.77 (3H, s).

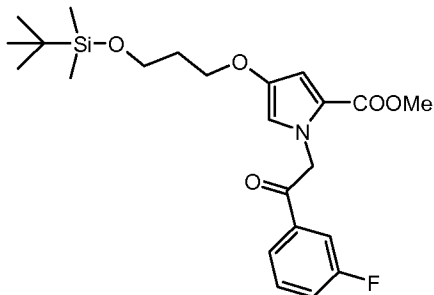
Preparation 57: methyl 1-(2-(3-fluorophenyl)-2-oxoethyl)-4-hydroxy-1H-pyrrole-2-carboxylate (P57)



The title compound was prepared with an analogous procedure to that described in Preparation 31 and Preparation 32 in 1.3 g yield as yellow solid from methyl 1-[2-(3-fluorophenyl)-2-oxoethyl]-4-formyl-1H-pyrrole-2-carboxylate (3.14 g, P56).

¹H NMR (400 MHz, DMSO-d₆) δ: 8.50 (1H, s), 7.85 (1H, m), 7.76 (1H, m), 7.50-7.65 (2H, m), 6.58 (1H, d), 6.31 (1H, d), 5.70 (2H, s), 3.55 (3H, s).

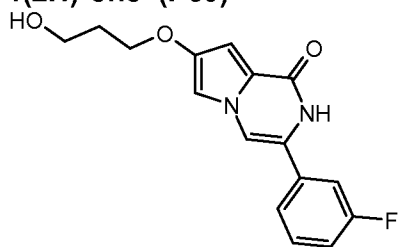
Preparation 58: methyl 4-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-1-[2-(3-fluorophenyl)-2-oxoethyl]-1H-pyrrole-2-carboxylate (P58)



To a solution of methyl 1-(2-(3-fluorophenyl)-2-oxoethyl)-4-hydroxy-1H-pyrrole-2-carboxylate (1.20 g, P57) in CH₃CN (50 mL) K₂CO₃ (0.90 g) was added and the mixture was stirred at room temperature for 45 min. Then (3-bromopropoxy)(tert-butyl)dimethylsilane (1.32 g) and NaI (0.13 g) were added and the mixture was heated to reflux for 16h. The mixture was cooled to room temperature and filtered. The filtrate was diluted with EA (200 ml), washed with water (3X30ml), the organic layer was dried (Na₂SO₄) and evaporated under reduced pressure to give the title compound (1.2 g).

¹H NMR (400 MHz, CDCl₃) δ: 7.72 (1H, m), 7.62 (1H, m), 7.29-7.48 (2H, m), 6.61 (1H, s), 6.40 (1H, s), 5.58 (2H, s), 3.94 (2H, m), 3.74 (2H, m), 3.65 (3H, s), 1.90 (2H, m), 0.85 (9H, s), 0.00 (6H, s).

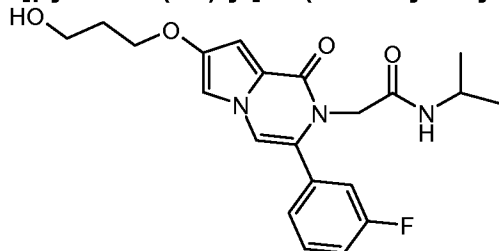
Preparation 59: 3-(3-fluorophenyl)-7-[(3-hydroxypropyl)oxy]pyrrolo[1,2-a]pyrazin-1(2H)-one (P59)



To a solution of methyl 4-(3-(tert-butyl dimethylsilyloxy)propoxy)-1-(2-(3-fluorophenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (1.20 g, P58) in AcOH (10 mL) NH₄OAc (6.17g) was added and the mixture was heated to reflux for 16h. The reaction mixture was cooled to room temperature, diluted with EA (200 mL) and washed with saturated aqueous NaHCO₃ (5X30 mL). The organic layer was dried (Na₂SO₄), filtered and evaporated and the residue was dissolved in THF (50 ml). A solution of 0.5M of LiOH in water (25 mL) was added. The mixture was stirred at room temperature for 2h, diluted with EA (300 ml) and washed with water (3X20 ml). The organic layer was dried (Na₂SO₄), filtered and evaporated under reduced pressure to give a crude that was purified by column on silica gel to give the title compound (400 mg).

¹H NMR (400 MHz, DMSO-d₆) δ: 7.79 (1H, s), 7.54-7.62 (3H, m), 7.26 (1H, m), 7.19 (1H, m), 6.62 (1H, s), 4.38 (1H, m), 4.10 (2H, m), 3.51 (2H, m), 1.90 (2H, m).

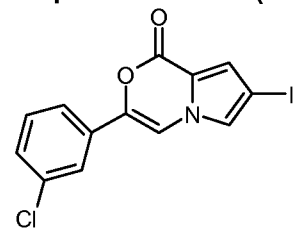
Preparation 60: 2-[3-(3-fluorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P60)



To a solution of 3-(3-fluorophenyl)-7-(3-hydroxypropoxy)pyrrolo[1,2-a]pyrazin-1(2H)-one (350 mg, P59) in CH₃CN (10 mL) K₂CO₃ (320 mg) and 2-chloro-N-isopropylacetamide (165 mg) were added. The mixture was heated to reflux for 16h, then cooled to room temperature and filtered. The filtrate was concentrated under vacuum and the residue was purified by preparative HPLC to give the product as salt which was neutralized with NaHCO₃ and extracted with EA (3X30 ml). The combined organic layers were dried (Na₂SO₄), filtered and evaporated under reduced pressure to give the title compound (45 mg)

¹H NMR (400 MHz, CD₃OD) δ: 8.32 (1H, s), 7.71-7.73 (2H, m), 7.31-7.42 (2H, m), 6.99 (1H, m), 6.53 (1H, s), 4.92 (2H, s), 4.13 (2H, t), 4.06 (1H, m), 3.75 (2H, t), 2.00 (2H, m), 1.16 (6H, d).

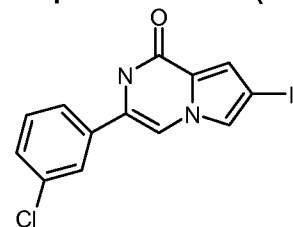
Preparation 61: 3-(3-chlorophenyl)-7-iodo-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (P61)



The title compound was prepared with an analogous procedure to that described in Preparation 1 in 1.91 g yield from 2,2,2-trichloro-1-(4-iodo-1H-pyrrol-2-yl)ethanone (2 g, prepared in analogy with the method described in *Organic & Biomolecular Chemistry* 2006, 4(12), 2477-2482).

MS (m/z): 371 [MH]⁺

Preparation 62: 3-(3-chlorophenyl)-7-iodopyrrolo[1,2-a]pyrazin-1(2H)-one (P62)

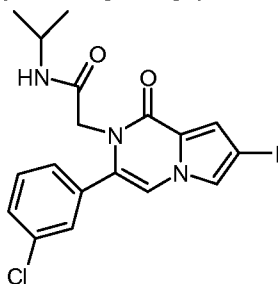


The title compound was prepared with an analogous procedure to that described in Preparation 2 in 3 g yield from 3-(3-chlorophenyl)-7-iodo-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (3.44 g, prepared in analogy to P61).

MS (m/z): 370 [MH]⁺

5

Preparation 63: 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P63)

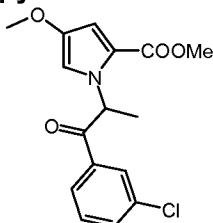


To a solution of 3-(3-chlorophenyl)-7-iodopyrrolo[1,2-a]pyrazin-1(2H)-one (3 g, P62) in DME (40 mL) and DMF (10 mL) NaH (60%, 0.48 g) was added at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 10min, then lithium bromide (1.75 g) was added and the mixture was stirred at rt for 15min. After cooling the mixture down at 0 °C, 2-chloro-N-(1-methylethyl)acetamide (1.65 g) and NaI (0.24 g) were added. The mixture was heated at 60 °C and stirred on. The reaction mixture was cooled down to rt and NaH (60%, 0.16 g) and 2-chloro-N-(1-methylethyl)acetamide (0.55 g) were added and the mixture was heated at 60 °C and stirred for 4,5 additional hours. DME was eliminated under reduced pressure and the crude was portioned between AcOEt and washed. Before the two phase separation the mixture was filtered. The solid was washed with AcOEt and dried under vacuum to give the title compound (2.2 g).

MS (m/z): 469 [MH]⁺

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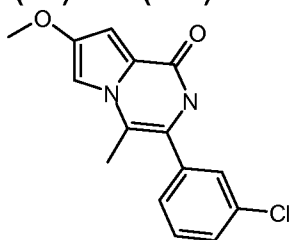
Preparation 64: methyl 1-[2-(3-chlorophenyl)-1-methyl-2-oxoethyl]-4-(methoxy)-1H-pyrrole-2-carboxylate (P64)



To a solution of methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-hydroxy-1H-pyrrole-2-carboxylate (1 g, prepared in analogy to P37) in DMF (20mL) Cs₂CO₃ (3.32g) and MeI (1.45 g) were added at -30 °C. The mixture was stirred for 3h increasing the temperature from -30 °C to room temperature. The mixture was partitioned between EA and water. The organic layer was washed with brine, dried over Na₂SO₄, filtered and the solvent was removed under vacuum to give the title compound (0.98 g) as brown oil which was used in next experiment without further purification.

30

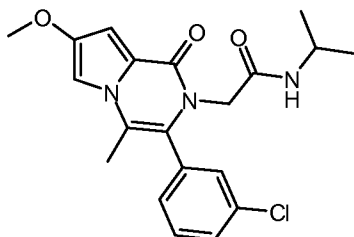
MS (m/z): 322 [MH]⁺

Preparation 65: 3-(3-chlorophenyl)-4-methyl-7-(methoxy)pyrrolo[1,2-a]pyrazin-1(2H)-one (P65)

The title compound was prepared with an analogous procedure to that described in Preparation 2 in 0.35 g yield from methyl 1-[2-(3-chlorophenyl)-1-methyl-2-oxoethyl]-4-(methoxy)-1H-pyrrole-2-carboxylate (0.98 g, P64).

¹H NMR (400 MHz, DMSO-d₆) δ: 2.16 (3H, s), 3.75 (3H, s), 6.58 (1H, s), 7.17 (1H, s), 7.39 (1H, m), 7.40-7.51 (3H, m), 10.698(1H, s).

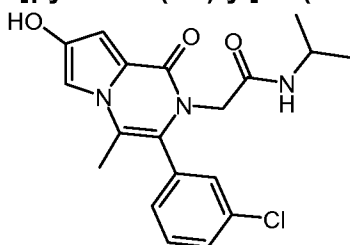
MS (m/z): 289 [MH]⁺

Preparation 66: 2-[3-(3-chlorophenyl)-4-methyl-7-(methoxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P66)

The title compound was prepared with an analogous procedure to that described in Preparation 3 in 0.29 g yield from 3-(3-chlorophenyl)-4-methyl-7-(methoxy)pyrrolo[1,2-a]pyrazin-1(2H)-one (0.35 g, P65).

¹H NMR (400 MHz, CDCl₃) δ: 1.13 (6H, d), 2.05 (3H, s), 3.86 (3H, s), 3.98 (1H, m), 4.24 (2H, s), 5.75 (1H, m), 6.82 (1H, d), 6.88 (1H, d), 7.24 (1H, m), 7.35 (1H, s), 7.417~7.481 (2H, m).

MS (m/z): 388 [MH]⁺

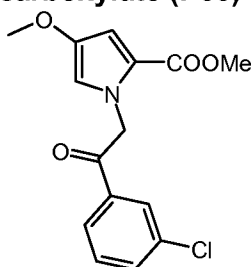
Preparation 67: 2-[3-(3-chlorophenyl)-7-hydroxy-4-methyl-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P67)

To a solution of 2-[3-(3-chlorophenyl)-4-methyl-7-(methyloxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (290 mg, P66) in DCM (8mL) BBr₃ (1.88 g) was added at -78 °C and the mixture was stirred at room temperature overnight. The mixture was adjusted to pH=7~8 with NaHCO₃ a.q. and partitioned between EA and water. The organic layer was dried with Na₂SO₄, filtered and concentrated. The crude product was purified by prepare HPLC to give the title compound (110 mg) as a yellow solid.

¹H NMR (400 MHz, CD₃OD) δ: 1.05 (6H, d), 2.03 (3H, s), 3.85 (1H, m), 4.19 (1H, d), 4.41 (1H, d), 6.65 (1H, s), 6.93 (1H, s), 7.30 (1H, m), 7.39 (1H, s), 7.45~7.59 (3H, m).

MS (m/z): 374 [MH]⁺

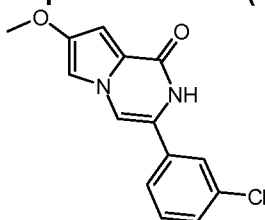
Preparation 68: methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-methoxy-1H-pyrrole-2-carboxylate (P68)



To a solution of methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-hydroxy-1H-pyrrole-2-carboxylate (5 g, prepared in analogy to P37) in DMF (80mL) Cs₂CO₃ (11.08 g) and Me₂SO₄ (8.57 g) were added at 0 °C. The mixture was stirred for 2h increasing the temperature from 0 °C to room temperature. The mixture was partitioned between EA and water. The organic layer was washed with brine, dried over Na₂SO₄, filtered and the solvent was removed under vacuum to give the title compound (11.2 g) as brown oil which was used in next experiment without further purification.

MS (m/z): 308 [MH]⁺

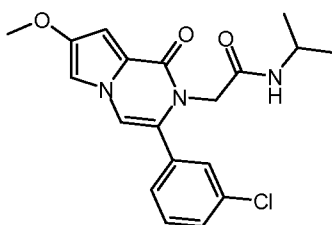
Preparation 69: 3-(3-chlorophenyl)-7-methoxypyrrolo[1,2-a]pyrazin-1(2H)-one (P69)



The title compound was prepared with an analogous procedure to that described in Preparation 2 in 3.33 g yield from methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-methoxy-1H-pyrrole-2-carboxylate (11 g, P68).

¹H NMR (400 MHz, DMSO-d₆) δ: 3.72 (3H, s), 6.53 (1H, s), 7.10 (1H, s), 7.46 (2H, m), 7.59 (1H, m), 7.71 (2H, m), 10.87 (1H, m).

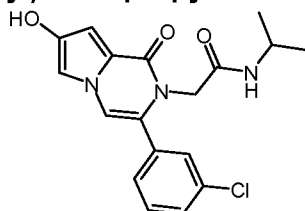
Preparation 70: 2-(3-(3-chlorophenyl)-7-methoxy-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-isopropylacetamide (P70)



The title compound was prepared with an analogous procedure to that described in Preparation 3 in 0.7 g yield from 3-(3-chlorophenyl)-7-methoxypyrrolo[1,2-a]pyrazin-1(2H)-one (3.33 g, P69).

- 5 **¹H NMR (400 MHz, CDCl₃)** δ : 1.08-1.13 (6H, d), 3.81 (3H, s), 4.00-4.06 (1H, m), 4.29 (2H, s), 5.87 (1H, m), 6.78-6.85 (3H, m), 7.36-7.39 (2H, m), 7.41-7.42 (2H, m).

Preparation 71: 2-(3-(3-chlorophenyl)-7-hydroxy-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-isopropylacetamide (P71)

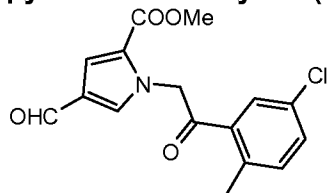


10

The title compound was prepared with an analogous procedure to that described in Preparation 67 in 35 mg yield from 2-(3-(3-chlorophenyl)-7-methoxy-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-isopropylacetamide (0.7 g, P70).

- 15 **¹H NMR (400 MHz, CD₃OD)** δ : 1.08-1.10 (6H, d), 3.89-3.93 (1H, m), 4.41 (2H, s), 6.61 (1H, m), 6.94 (1H, s), 7.17 (1H, s), 7.39-7.52 (4H, m).

Preparation 72: methyl 1-[2-(5-chloro-2-methylphenyl)-2-oxoethyl]-4-formyl-1H-pyrrole-2-carboxylate (P72)

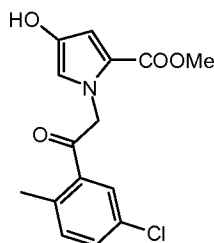


- 20 The title compound was prepared with an analogous procedure to that described in Preparation 30 in 0.70 g yield from methyl 4-formyl-1H-pyrrole-2-carboxylate (1.00 g, prepared with an analogous procedure to that described in P29) and 2-bromo-1-(5-chloro-2-methylphenyl)ethanone (2.42 g, P135).

MS (m/z): 320 [MH]⁺

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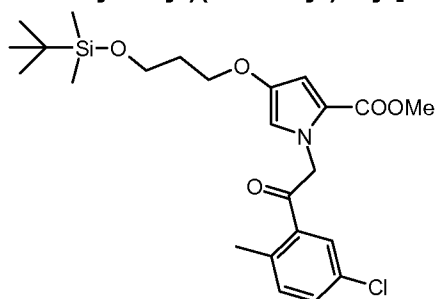
Preparation 73: methyl 1-[2-(5-chloro-2-methylphenyl)-2-oxoethyl]-4-hydroxy-1H-pyrrole-2-carboxylate (P73)



The title compound was prepared with an analogous procedure to that described in Preparation 31 and Preparation 32 in 17 mg yield from methyl 1-[2-(5-chloro-2-methylphenyl)-2-oxoethyl]-4-formyl-1H-pyrrole-2-carboxylate (32 mg, P72).

5 **MS (m/z):** 308 [MH]⁺

Preparation 74: methyl 1-[2-(5-chloro-2-methylphenyl)-2-oxoethyl]-4-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-1H-pyrrole-2-carboxylate (P74)

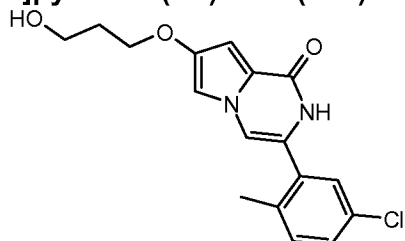


10 The title compound was prepared with an analogous procedure to that described in Preparation 58 in 202 mg yield from methyl 1-[2-(5-chloro-2-methylphenyl)-2-oxoethyl]-4-hydroxy-1H-pyrrole-2-carboxylate (286 mg, prepared with an analogous procedure to that described in P73).

MS (m/z): 480 [MH]⁺

15

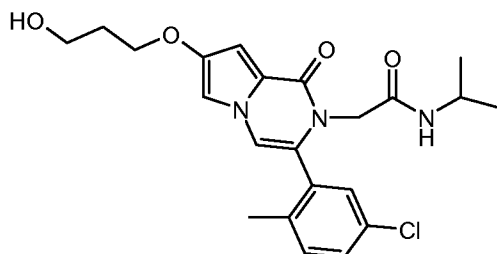
Preparation 75: 3-(5-chloro-2-methylphenyl)-7-[(3-hydroxypropyl)oxy]pyrrolo[1,2-a]pyrazin-1(2H)-one (P75)



20 The title compound was prepared with an analogous procedure to that described in Preparation 59 in 150 mg yield from methyl 1-[2-(5-chloro-2-methylphenyl)-2-oxoethyl]-4-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-1H-pyrrole-2-carboxylate (202 mg, P74).

MS (m/z): 333 [MH]⁺

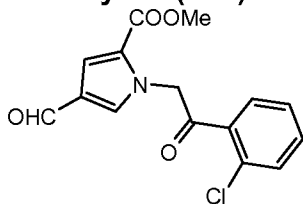
25 **Preparation 76: 2-[3-(5-chloro-2-methylphenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P76)**



To a solution of 3-(5-chloro-2-methylphenyl)-7-[(3-hydroxypropyl)oxy]pyrrolo[1,2-a]pyrazin-1(2H)-one (120 mg, P75) in DMF (100 mL) LiH (3mg) was added at 0°C. The mixture was stirred for 30min at room temperature and cooled to 0°C again. NaI (60mg) and 2-chloro-N-isopropylacetamide (68mg) were added and the reaction mixture was stirred overnight at 70 °C . Chilly water (100ml) was added to the reaction mixture and the mixture was extracted with EA (3×100ml). The organic phase was dried over MgSO₄ and evaporated. The residue was purified by gel silica column chromatography (eluent: MeOH/DCM= 1/20) to give the title compound (94mg).

MS (m/z): 432 [MH]⁺

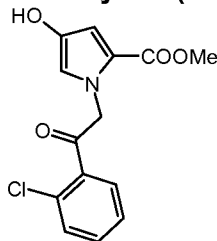
Preparation 77: methyl 1-(2-(2-chlorophenyl)-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (P77)



The title compound was prepared with an analogous procedure to that described in Preparation 30 in 3.45 g yield from methyl 4-formyl-1H-pyrrole-2-carboxylate (1.75 g , prepared with an analogous procedure to that described in P29) and 2-bromo-1-(2-chlorophenyl)ethanone (2.67 g, commercially available).

MS (m/z): 306 [MH]⁺

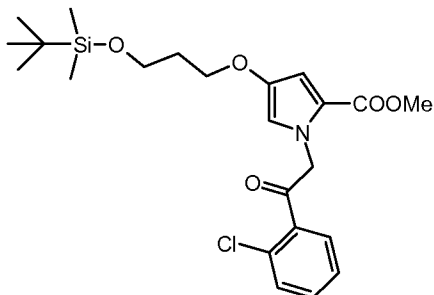
Preparation 78: methyl 1-(2-(2-chlorophenyl)-2-oxoethyl)-4-hydroxy-1H-pyrrole-2-carboxylate (P78)



The title compound was prepared with an analogous procedure to that described in Preparation 31 and Preparation 32 in 1.40 g yield from methyl 1-(2-(2-chlorophenyl)-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (3.40 g, P77).

¹H NMR (DMSO) δ: 8.54 (1H, s), 7.83 (1H, d), 7.56 (2H, m), 7.50 (1H, m), 6.63 (1H, d), 6.32 (1H, d), 5.55 (2H, s), 3.62 (3H, s).

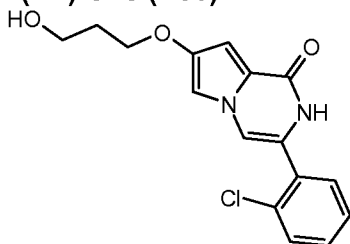
Preparation 79: methyl 4-(3-(tert-butyldimethylsilyloxy)propoxy)-1-(2-(2-chlorophenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (P79)



5 The title compound was prepared with an analogous procedure to that described in Preparation 58 in 1.2 g yield from methyl 1-(2-(2-chlorophenyl)-2-oxoethyl)-4-hydroxy-1H-pyrrole-2-carboxylate (1.40 mg, P78).

MS (m/z): 466 [MH]⁺

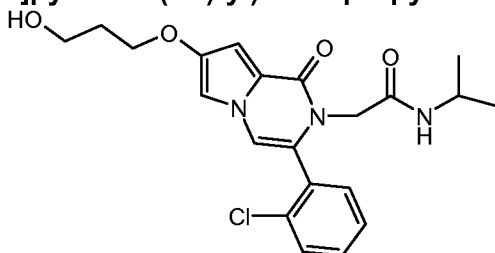
10 **Preparation 80: 3-(2-chlorophenyl)-7-(3-hydroxypropoxy)pyrrolo[1,2-a]pyrazin-1(2H)-one (P80)**



The title compound was prepared with an analogous procedure to that described in Preparation 59 in 500 mg yield from methyl 4-(3-(tert-butyldimethylsilyloxy)propoxy)-1-(2-(2-chlorophenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (1.20 g, P79).

15 **¹H NMR (DMSO)** δ: 7.39-7.55 (4H, m), 7.24 (2H, s), 7.11 (1H, d), 6.50 (1H, d), 4.50 (1H, t), 3.96 (2H, t), 3.51 (2H, t), 1.88 (2H, m).

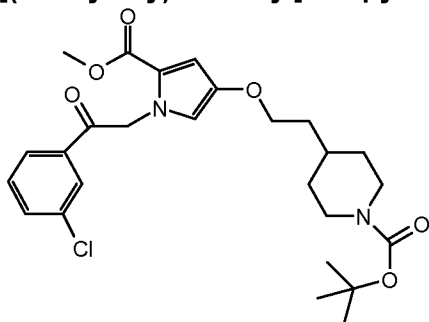
20 **Preparation 81: 2-(3-(2-chlorophenyl)-7-(3-hydroxypropoxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-isopropylacetamide (P81)**



The title compound was prepared with an analogous procedure to that described in Preparation 60 in 320 mg yield from 3-(2-chlorophenyl)-7-(3-hydroxypropoxy)pyrrolo[1,2-a]pyrazin-1(2H)-one (450 mg, P80).

25 **MS (m/z):** 418 [MH]⁺

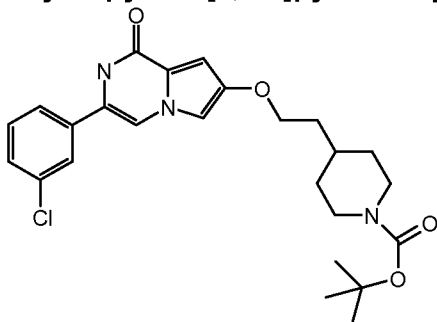
Preparation 82: 1,1-dimethylethyl 4-[2-({1-[2-(3-chlorophenyl)-2-oxoethyl]-5-[(methyloxy)carbonyl]-1H-pyrrol-3-yl}oxy)ethyl]-1-piperidinecarboxylate (P82)



To a stirred solution of methyl 1-[2-(3-chlorophenyl)-2-oxoethyl]-4-hydroxy-1H-pyrrole-2-carboxylate (50 mg, prepared with an analogous procedure to that described in P37), 1,1-dimethylethyl 4-(2-hydroxyethyl)-1-piperidinecarboxylate (94 mg, commercially available) and triphenylphosphine (107 mg) in THF (1.6 mL), at 0 °C and under a nitrogen atmosphere, diethyl azodicarboxylate (0.065 mL) was added. After 0.5h the ice-bath was removed and the reaction mixture was stirred 5h at RT. The reaction mixture was concentrated under vacuum and the residue was purified by Si FC (eluting with Cy/EA from 100% to 80% of Cy) to give the title compound (41 mg).

MS (m/z): 505 [MH]⁺

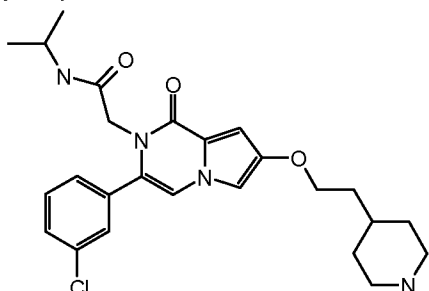
Preparation 83: 1,1-dimethylethyl 4-(2-{[3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]oxy}ethyl)-1-piperidinecarboxylate (P83)



A mixture of 1,1-dimethylethyl 4-[2-({1-[2-(3-chlorophenyl)-2-oxoethyl]-5-[(methyloxy)carbonyl]-1H-pyrrol-3-yl}oxy)ethyl]-1-piperidinecarboxylate (41 mg, P82), ammonium acetate (125 mg) and acetic acid (1.8 ml) in a sealed vial, was warmed at 110 °C and stirred for 24 h. The reaction mixture was concentrated under vacuum, the residue was taken-up with DCM and a saturated solution of K₂CO₃. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent removed under reduced pressure. The material so obtained was dissolved in DCM (2.0 mL) at RT and di-*tert*-butyl dicarbonate (0.043 mL) was added. After 12 h DCM (2 mL) and a saturated solution of NaHCO₃ were added to the mixture, the organic phase was washed with brine, dried over Na₂SO₄ and the solvent evaporated under vacuum. The crude product was purified by Si FC (eluting with Cy/EA from 100% to 50% of Cy) to give the title compound (32 mg).

MS (m/z): 472 [MH]⁺

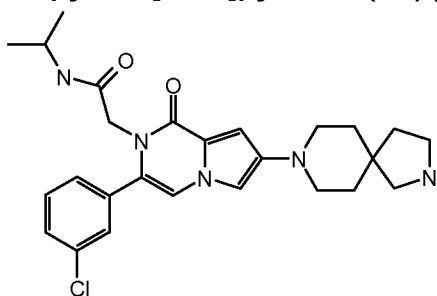
Preparation 84: 2-[3-(3-chlorophenyl)-1-oxo-7-{[2-(4-piperidinyl)ethyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P84)



To a stirred solution of 1,1-dimethylethyl 4-(2-{[3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]oxy}ethyl)-1-piperidinecarboxylate (32 mg, P83) in DMF (0.5 ml), at RT and under a nitrogen atmosphere, NaH (2.85 mg) was added. After 10 min, NaI (11.18 mg) and a solution of 2-chloro-N-(1-methylethyl)acetamide (10.11 mg) DMF (0.1 mL) were subsequently added and the reaction mixture was warmed to 65 °C and stirred overnight. Ether and water were added to the mixture, the organic phase was washed with brine, dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude material was purified by Si flash chromatography (eluting with Cy/EA from 80% to 40% of Cy) to give 10 mg of the corresponding N-Boc intermediate. This product was dissolved in DCM (0.4 mL) and trifluoroacetic acid (50 µl) was added. After 20 min the solution was concentrated under reduced pressure, the residue was taken up with DCM and a saturated solution of NaHCO₃, the organic phase washed with brine, dried over Na₂SO₄ and the solvent evaporated under vacuum to give the title compound (5mg).

MS (m/z): 471 [MH]⁺

Preparation 85: 2-[3-(3-chlorophenyl)-7-(2,8-diazaspiro[4.5]dec-8-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P85)

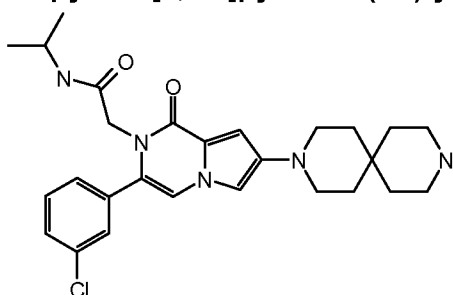


To a solution of 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (50 mg, prepared with an analogous procedure to that described in P63), K₂CO₃ (118 mg), copper (I) iodide (30.4 mg) and LD-proline (18.38 mg) in DMSO (2 ml), 2,8-diazaspiro[4.5]decane-2-carboxylic acid tert-butyl ester (147 mg, commercially available) was added and the mixture was heated to 80°C and stirred for 24h. Then one

more portion of copper (I) iodide (20 mg) was added and the mixture was stirred at 80 °C for additional 3h. The mixture was diluted with AcOEt and washed several times with a saturated solution of NH₄Cl. The organic phase was dried and evaporated. The residue was dissolved in dry DCM (1.5 ml) and trifluoroacetic acid (1 mL) was added at 0 °C. The mixture was stirred at RT for 1h. Solvent was evaporated under reduced pressure and the residue was purified by SCX cartridge (1g) eluting with NH₃ 2M in MeOH. Fractions containing the desired product were collected and evaporated, to give the title compound (15 mg) as yellow oil.

MS (m/z): 482 [MH]⁺

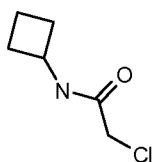
Preparation 86: 2-[3-(3-chlorophenyl)-7-(3,9-diazaspiro[5.5]undec-3-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P86)



The title compound was prepared with an analogous procedure to that described in Preparation 85 in 35 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (100 mg, prepared with an analogous procedure to that described in P63) and 1,1-dimethylethyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (310 mg, commercially available)

MS (m/z): 496 [MH]⁺

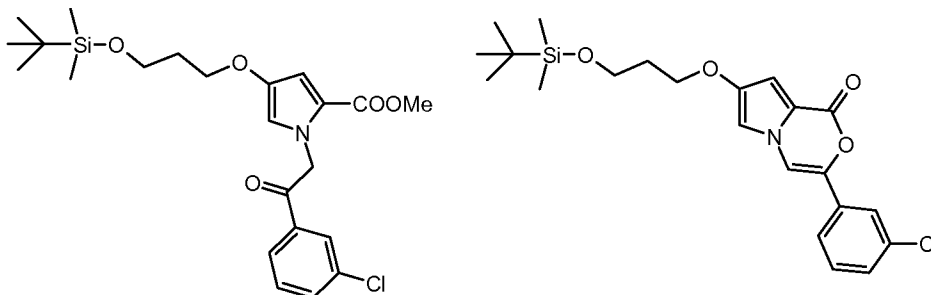
Preparation 87: 2-chloro-N-cyclobutylacetamide (P87)



To a solution of cyclobutanamine (1.3 g) in dry THF (80 mL) dry TEA (2.03 g) was added dropwise at room temperature. The reaction mixture was then cooled down to 0 °C and 2-chloroacetyl chloride (2.27 g) was added dropwise at the same temperature. After the addition was over, the solvent was removed under reduced pressure and the residue was diluted with water and extracted with EA. The organic layer was washed with aqueous HCl, saturated NaHCO₃ and saturated NH₄Cl, dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified by column chromatography (eluent PE:EA = 4:1) to give the title compound as a colourless solid (2.1 g).

¹H NMR (CDCl₃), δ: 0.788-0.825 (t, 3H), 1.012-1.028 (d, 2H), 1.35-1.42 (m, 2H), 3.61-3.68 (m, 1H), 3.96-4.02 (t, 2H), 7.98-8.00 (b, 1H).

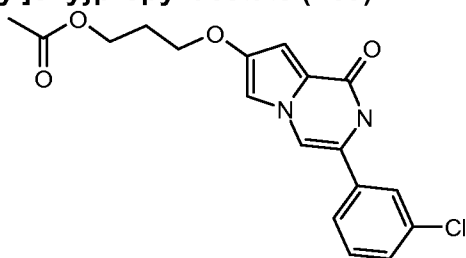
Preparation 88: methyl 1-[2-(3-chlorophenyl)-2-oxoethyl]-4-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-1H-pyrrole-2-carboxylate and 3-(3-chlorophenyl)-7-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (P88, mixture)



The mixture of title compounds were prepared with an analogous procedure to that described in Preparation 58 in 1.12 g yield from methyl 1-[2-(2-chlorophenyl)-2-oxoethyl]-4-hydroxy-1H-pyrrole-2-carboxylate (1 g, prepared with an analogous procedure to that described in P37).

MS (m/z): 434 [MH]⁺

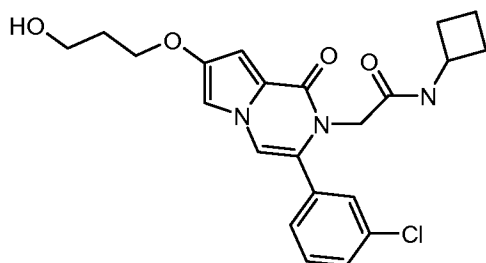
Preparation 89: 3-[(3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]oxy]propyl acetate (P89)



The title compound was prepared with an analogous procedure to that described in Preparation 2 in 255 mg yield from a mixture of methyl 1-[2-(3-chlorophenyl)-2-oxoethyl]-4-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-1H-pyrrole-2-carboxylate and 3-(3-chlorophenyl)-7-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (500 mg, P88).

MS (m/z): 361 [MH]⁺

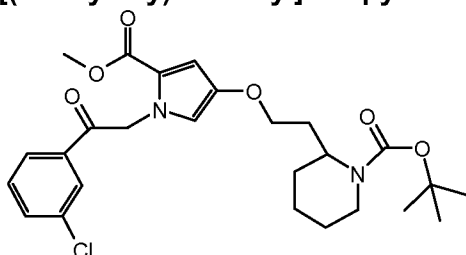
Preparation 90: 2-[3-(3-chlorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-cyclobutylacetamide (P90)



To a solution of 3-([3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]oxy)propyl acetate (250 g, P89) in acetone (30 mL) 2-chloro-N-cyclobutylacetamide (71 mg) and K₂CO₃ (144 mg) were added, then the reaction was stirred at 80°C for 12h. After cooling the mixture the solvent was evaporated in vacuo, H₂O was added and the mixture was extracted with EA. The organic layer was washed with brine, dried and concentrated under vacuum. The crude was dissolved in THF (5 mL) and an aqueous solution of lithium hydroxide (5 mg in 2ml H₂O) was added and the mixture was stirred at RT for 3h. Solvent was removed under reduced pressure, the residue was taken up with AcOEt and washed with water and brine. The organic phase was dried, filtered and evaporated under vacuum. The crude was purified by prep-HPLC to give the title compound (40mg) as white solid.

MS (m/z): 430 [MH]⁺

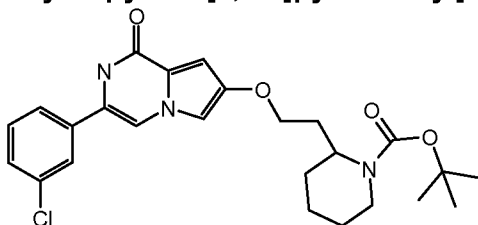
Preparation 91: 1,1-dimethylethyl 2-[2-({1-[2-(3-chlorophenyl)-2-oxoethyl]-5-[(methoxyloxy)carbonyl]-1H-pyrrol-3-yl}oxy)ethyl]-1-piperidinecarboxylate (P91)



The title compound was prepared with an analogous procedure to that described in Preparation 82 in 350 mg yield from methyl 1-[2-(3-chlorophenyl)-2-oxoethyl]-4-hydroxy-1H-pyrrole-2-carboxylate (350 mg, prepared with an analogous procedure to that described in P37) and 1,1-dimethylethyl 2-(2-hydroxyethyl)-1-piperidinecarboxylate (656 mg, commercially available)

MS (m/z): 505 [MH]⁺

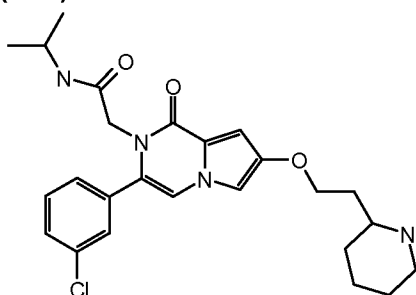
Preparation 92: 1,1-dimethylethyl 2-(2-{[3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]oxy}ethyl)-1-piperidinecarboxylate (P92)



The title compound was prepared with an analogous procedure to that described in Preparation 83 in 150 mg yield from 1,1-dimethylethyl 2-[2-(1-[2-(3-chlorophenyl)-2-oxoethyl]-5-[(methyloxy)carbonyl]-1H-pyrrol-3-yl)oxy)ethyl]-1-piperidinecarboxylate (350 mg, P91)

5 **MS (m/z):** 472 [MH]⁺

Preparation 93: 2-[3-(3-chlorophenyl)-1-oxo-7-{[2-(2-piperidinyl)ethyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P93)



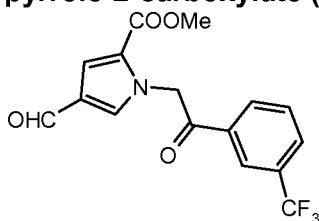
10

The title compound was prepared with an analogous procedure to that described in Preparation 83 in 48 mg yield from 1,1-dimethylethyl 2-(2-{[3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]oxy}ethyl)-1-piperidinecarboxylate (150 mg, P92)

MS (m/z): 471 [MH]⁺

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Preparation 94: methyl 4-formyl-1-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-1H-pyrrole-2-carboxylate (P94)



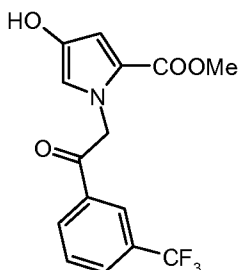
20

The title compound was prepared with an analogous procedure to that described in Preparation 30 in 4.7 g yield from methyl 4-formyl-1H-pyrrole-2-carboxylate (3 g, prepared with an analogous procedure to that described in P29) and 2-bromo-1-(3-trifluoromethylphenyl)ethanone (6.5 g, commercially available).

MS (m/z): 340 [MH]⁺

25

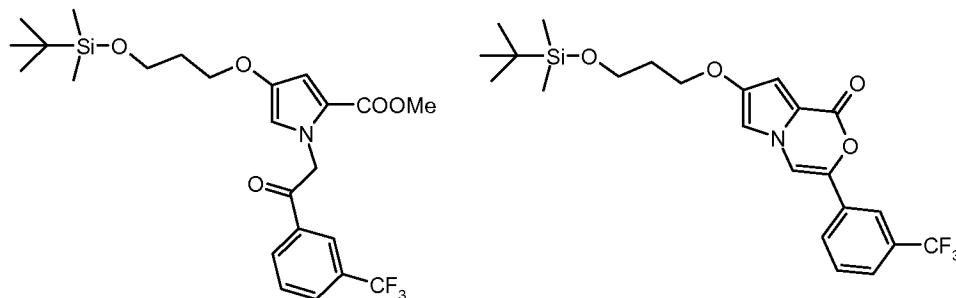
Preparation 95: methyl 4-hydroxy-1-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-1H-pyrrole-2-carboxylate (P95)



The title compound was prepared with an analogous procedure to that described in Preparation 31 and Preparation 32 in 2.1 g yield from methyl 4-formyl-1-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-1H-pyrrole-2-carboxylate (4.7 g, P94).

5 **MS (m/z):** 328 [MH]⁺

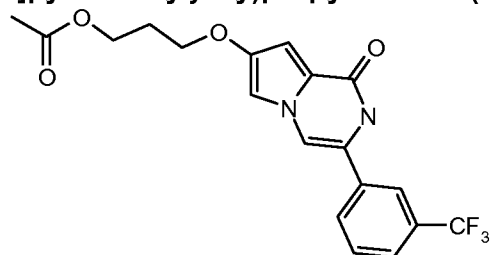
Preparation 96: methyl 4-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-1-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-1H-pyrrole-2-carboxylate and 7-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-3-[3-(trifluoromethyl)phenyl]-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (P96, mixture)



The mixture of title compounds were prepared with an analogous procedure to that described in Preparation 58 in 0.68 g yield from methyl 1-[2-(3-trifluoromethylphenyl)-2-oxoethyl]-4-hydroxy-1H-pyrrole-2-carboxylate (0.1 g, P95).

15 **MS (m/z):** 500 [MH]⁺

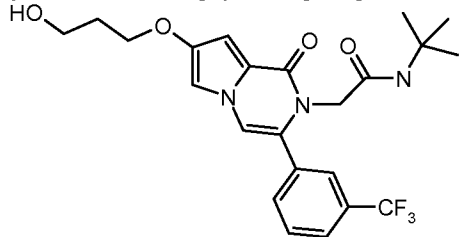
Preparation 97: 3-({1-oxo-3-[3-(trifluoromethyl)phenyl]-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl}oxy)propyl acetate (P97)



The title compound was prepared with an analogous procedure to that described in Preparation 2 in 280 mg yield from a mixture of methyl 4-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-1-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-1H-pyrrole-2-carboxylate and 7-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy]-3-[3-(trifluoromethyl)phenyl]-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (650 mg, P96).

MS (m/z): 395 [MH]⁺

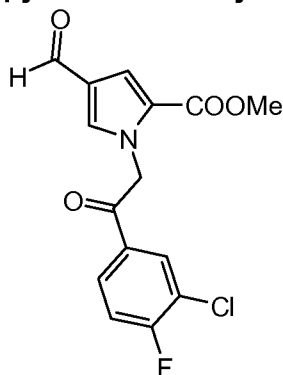
Preparation 98: *N*-(1,1-dimethylethyl)-2-[7-[(3-hydroxypropyl)oxy]-1-oxo-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide (P98)



To a solution of 3-({1-oxo-3-[3-(trifluoromethyl)phenyl]-1,2-dihydropyrrolo[1,2-*a*]pyrazin-7-yl}oxy)propyl acetate (50 mg, P97) and NaI (38.1 mg) in DMF (20 mL) LiH (4 mg) was added under argon at 0 °C. 2-chloro-*N*-(1,1-dimethylethyl)acetamide (31 mg) was added and the mixture was stirred at room temperature overnight. Ice-cold water was added to the reaction mixture and the product was extracted with EA. The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude was dissolved in THF and a solution of 0.5M of LiOH in water was added. The mixture was stirred at room temperature for 2h, diluted with EA and washed with water. The organic layer was dried (Na₂SO₄), filtered and evaporated under reduced pressure to give a crude that was purified by Pre-HPLC to give the title compound (12mg).

MS (m/z): 466 [MH]⁺

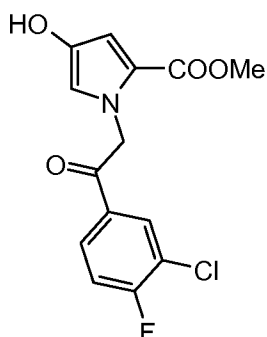
Preparation 99: methyl 1-(2-(3-chloro-4-fluorophenyl)-2-oxoethyl)-4-formyl-1*H*-pyrrole-2-carboxylate (P99)



The title compound was prepared with an analogous procedure to that described in Preparation 30 in 5.9 g yield from methyl 4-formyl-1*H*-pyrrole-2-carboxylate (2.5 g, prepared with an analogous procedure to that described in P29) and 2-bromo-1-(3-chloro-4-fluorophenyl)ethanone (4.1 g, commercially available)

¹H NMR (400 MHz, CDCl₃) δ: 3.75 (3H, s), 5.72 (2H, s), 7.25-7.31 (1H, m), 7.42-7.43 (2H, m), 7.89-7.91 (1H, m), 7.93-8.07 (1H, dd), 9.79 (1H, s).

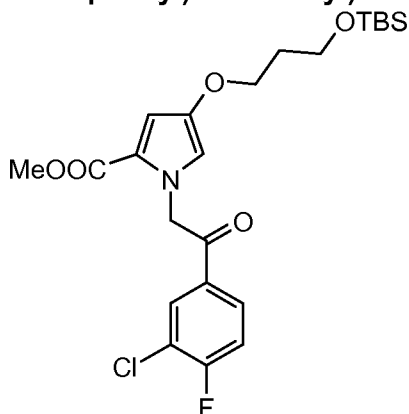
Preparation 100: methyl 1-(2-(3-chloro-4-fluorophenyl)-2-oxoethyl)-4-hydroxy-1*H*-pyrrole-2-carboxylate (P100)



The title compound was prepared with an analogous procedure to that described in Preparation 31 and Preparation 32 in 2.44g yield from methyl 1-(2-(3-chloro-4-fluorophenyl)-2-oxoethyl)-4-formyl-1H-pyrrole-2-carboxylate (5.9 g, P99).

- 5 **¹H NMR (CDCl₃)** δ: 3.69 (3H, s), 5.57 (2H, s), 6.46 (1H, d), 6.57 (1H, d), 7.22-7.26 (2H, m), 7.86-7.90 (1H, m), 8.03-8.05 (1H, dd).

Preparation 101: methyl 4-(3-(tert-butyldimethylsilyloxy)propoxy)-1-(2-(3-chloro-4-fluorophenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (P101)

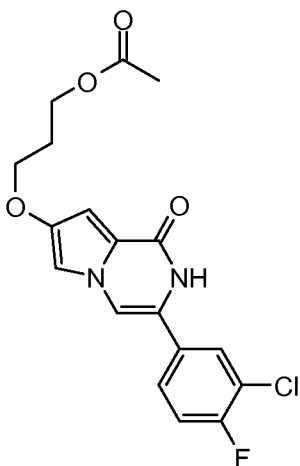


10

The title compound was prepared with an analogous procedure to that described in Preparation 58 in 20 mg yield from methyl 1-(2-(3-chloro-4-fluorophenyl)-2-oxoethyl)-4-hydroxy-1H-pyrrole-2-carboxylate (100 mg, P100).

- 15 **¹H NMR (CDCl₃)** δ: 0.05 (6H, s), 0.89 (9H, s), 1.90-2.00 (2H, m), 3.75 (3H, s), 3.76-3.81 (H, t), 3.94-4.00 (2H, t), 5.11 (2H, s), 6.46 (1H, s), 6.68 (1H, s), 7.26-7.80 (1H, m), 8.08 (1H, m).

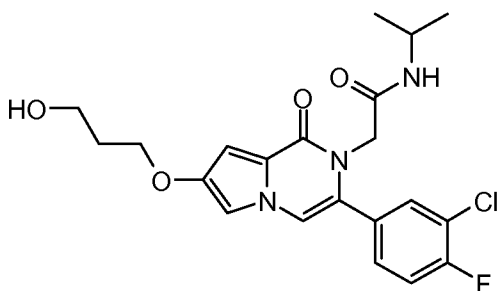
Preparation 102: 3-(3-(3-chloro-4-fluorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yloxy)propyl acetate (P102)



The title compound was prepared with an analogous procedure to that described in Preparation 2 in 160 mg yield from methyl 4-(3-(tert-butyldimethylsilyloxy)propoxy)-1-(2-(3-chloro-4-fluorophenyl)-2-oxoethyl)-1H-pyrrole-2-carboxylate (3 g, prepared with an analogous procedure to that described in P101).

MS (m/z): 380 [MH]⁺

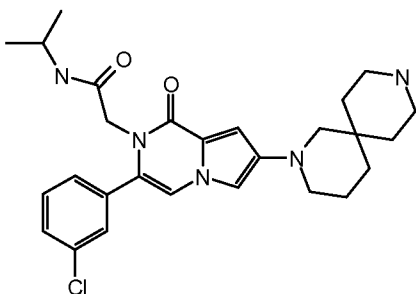
Preparation 103: 2-[3-(3-chloro-4-fluorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P103)



To a solution of 3-(3-(3-chloro-4-fluorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yloxy)propyl acetate (160 mg, P102) in CH₃CN (10 mL) K₂CO₃ (88 mg) and 2-chloro-N-isopropylacetamide (69 mg) were added and the mixture was heated to reflux for 16h, then cooled to RT and filtered. The filtrate was concentrated in vacuo, the crude was dissolved in THF (10 mL) and a 2M solution of LiOH in water (1 mL) was added. The mixture was stirred at RT for 16h, and then extracted with EA (20 mL X 5). The organic layer was dried, evaporated and the residue was combined with one other batch to give 260 mg of the crude product. The crude was purified by preparative HPLC to give the title compound (15 mg).

¹H NMR (400 MHz, CD₃OD) δ: 1.03-1.06 (6H, d), 1.83-1.91 (2H, m), 3.57-3.67 (2H, t), 3.75-3.85 (1H, m), 3.96-3.99 (2H, t), 4.29 (2H, s), 6.59 (1H, s), 6.96-7.01 (1H, s), 7.09 (1H, s), 7.20-7.28 (1H, t), 7.30-7.37 (1H, m), 7.50 (1H, m).

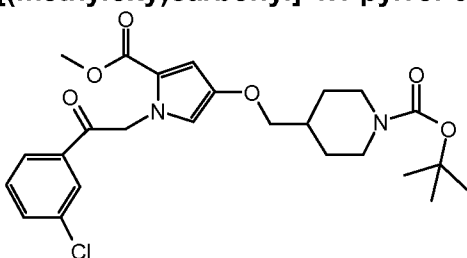
Preparation 104: 2-[3-(3-chlorophenyl)-7-(2,9-diazaspiro[5.5]undec-2-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P104)



The title compound was prepared with an analogous procedure to that described in Preparation 85 in 25 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (100 mg, were prepared with an analogous procedure to that described in P63) and 1,1-dimethylethyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (310 mg, prepared with a methodology well know to one skilled in the art from 2,9-diazaspiro[5.5]undecane, 2-(phenylmethyl)-; synthesis of 2,9-diazaspiro[5.5]undecane, 2-(phenylmethyl)- described in PCT Int. Appl. (2005) WO 2005097795)

MS (m/z): 496 [MH]⁺

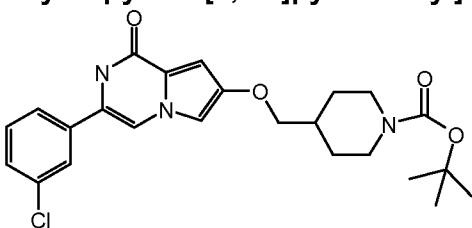
Preparation 105: 1,1-dimethylethyl 4-[(1-[2-(3-chlorophenyl)-2-oxoethyl]-5-[(methyloxy)carbonyl]-1H-pyrrol-3-yl)oxy)methyl]-1-piperidinecarboxylate (P105)



The title compound was prepared with an analogous procedure to that described in Preparation 82 in 139 mg yield from methyl 1-[2-(3-chlorophenyl)-2-oxoethyl]-4-hydroxy-1H-pyrrole-2-carboxylate (350 mg, prepared with an analogous procedure to that described in P37) and 1,1-dimethylethyl 4-(hydroxymethyl)-1-piperidinecarboxylate (620 mg, commercially available)

MS (m/z): 491 [MH]⁺

Preparation 106: 1,1-dimethylethyl 4-[(3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl)oxy)methyl]-1-piperidinecarboxylate (P106)



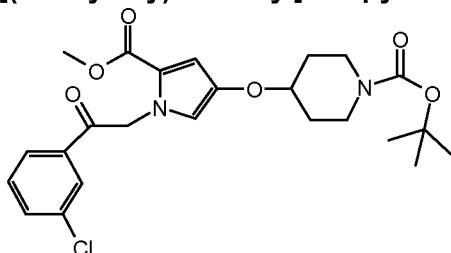
The title compound was prepared with an analogous procedure to that described in Preparation 83 in 42 mg yield from 1,1-dimethylethyl 4-[(1-[2-(3-chlorophenyl)-2-

oxoethyl]-5-[(methyloxy)carbonyl]-1H-pyrrol-3-yl}oxy)methyl]-1-piperidinecarboxylate (139 mg, P105)

MS (m/z): 458 [MH]⁺

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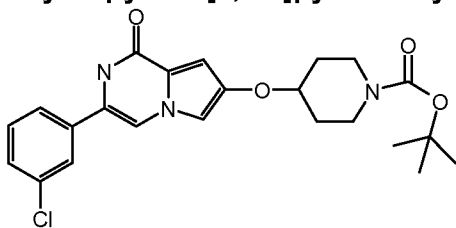
Preparation 107: 1,1-dimethylethyl 4-({1-[2-(3-chlorophenyl)-2-oxoethyl]-5-[(methyloxy)carbonyl]-1H-pyrrol-3-yl}oxy)-1-piperidinecarboxylate (P107)



To a stirred solution of methyl 1-[2-(3-chlorophenyl)-2-oxoethyl]-4-hydroxy-1H-pyrrole-2-carboxylate (0.85 g, prepared with an analogous procedure to that described in P37), 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate (0.88 g, commercially available) and triphenylphosphine (1.34 g) in THF (6 mL), at 0 °C and under a nitrogen atmosphere, a solution of di-tert-butyl azodicarboxylate (1.21 g, 5.25 mmol) in THF (2 mL) was added. After 0.5h the ice-bath was removed and the reaction mixture was stirred 5h at RT. Additional amounts of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate (90 mg), triphenylphosphine (140 mg) and di-tert-butyl azodicarboxylate (120 mg) were added at RT and the reaction mixture was stirred for other 4h. The reaction mixture was concentrated under vacuum and the residue was purified by FC (eluting with a gradient of Cy/EA from 0 to 20% of EA) to give 0.52 g of the title compound.

MS (m/z): 478 [MH]⁺

Preparation 108: 1,1-dimethylethyl 4-{{3-[3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrazolo[1,2-a]pyrazin-7-yl}oxy]-1-piperidinecarboxylate (P108)

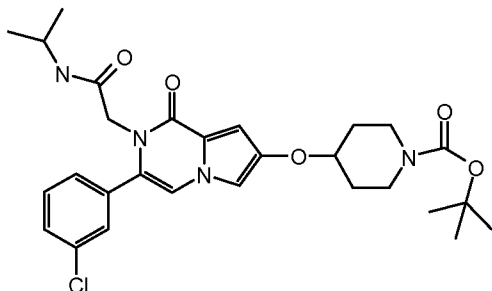


The title compound was prepared with an analogous procedure to that described in Preparation 83 in 72 mg yield from 1,1-dimethylethyl 4-({1-[2-(3-chlorophenyl)-2-oxoethyl]-5-[(methyloxy)carbonyl]-1H-pyrrol-3-yl}oxy)-1-piperidinecarboxylate (520 mg, P107)

MS (m/z): 444 [MH]⁺

30

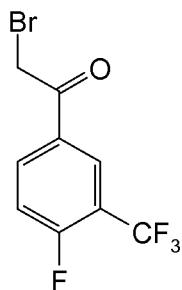
Preparation 109: 1,1-dimethylethyl 4-[(3-(3-chlorophenyl)-2-{2-[(1-methylethyl)amino]-2-oxoethyl}-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl)oxy]-1-piperidinecarboxylate (P109)



- 5 To a stirred solution of 1,1-dimethylethyl 4-[(3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl)oxy]-1-piperidinecarboxylate (72 mg, P108) in DME (1.3 mL) and DMF (0.3 mL), at RT and under a nitrogen atmosphere, sodium hydride (10 mg) was added portionwise. After 5 min, lithium bromide (35.0 mg) (fine powdered and dried) and NaI (5.0 mg) were subsequently added followed after 5 min by 2-chloro-N-(1-methylethyl)acetamide (36 mg). The reaction mixture was warmed to 65 °C and stirred for 7h. The reaction mixture was allowed to reach RT and concentrated under reduced pressure in order to remove the DME. The residue was taken-up with EA and cold water. The organic phase was washed with cold water, brine, dried over Na₂SO₄ and the solvent evaporated under vacuum. The crude product was purified by FC on silica (eluting with a gradient of Cy/EA from 20% to 70% of EA0) give 54 mg of the title compound (54 mg).

MS (m/z): 543 [MH]⁺

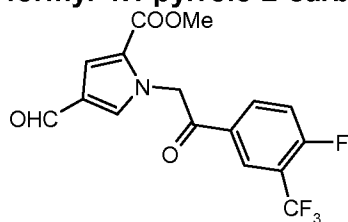
Preparation 109bis: 2-bromo-1-[4-fluoro-3-(trifluoromethyl)phenyl]ethanone (P109bis)



- 20 To a vigorously stirred refluxing solution of CuI₂ (15.17 g, 67.9 mmol) in EA (40 ml), a solution of 1-[4-fluoro-3-(trifluoromethyl)phenyl]ethanone (7 g, 34.0 mmol) in dry chloroform (50 ml) was added one pot, then the reaction mixture was refluxed for 6h. The mixture was cooled down to RT, filtered over a pad of celite and evaporated. The residue was partitioned between EA and saturated NaHCO₃ aqueous solution, then organic phase was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by FC on silica (eluting with Cy/EA from 10/0 to 8/2) to give 6.95 g of the title compound.

NMR (¹H, CDCl₃): δ 8.15 - 8.30 (m, 2 H), 7.30 – 7.39 (m, 1 H), 4.45 (s, 2 H).

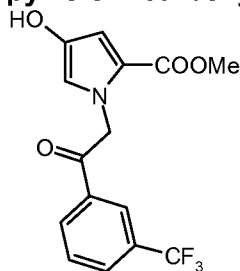
Preparation 110: methyl 1-{2-[4-fluoro-3-(trifluoromethyl)phenyl]-2-oxoethyl}-4-formyl-1H-pyrrole-2-carboxylate (P110)



The title compound was prepared with an analogous procedure to that described in Preparation 30 in 2.5 g yield from methyl 4-formyl-1H-pyrrole-2-carboxylate (2 g, prepared with an analogous procedure to that described in P29) and 2-bromo-1-[4-fluoro-3-(trifluoromethyl)phenyl]ethanone (4.28 g, commercially available or which may be prepared with an analogous procedure to that described in P109bis).

MS (m/z): 358 [MH]⁺

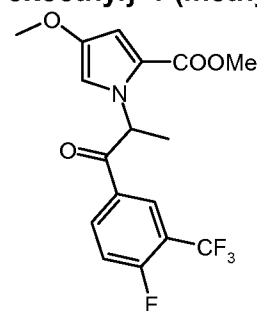
Preparation 111: methyl 4-hydroxy-1-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-1H-pyrrole-2-carboxylate (P111)



The title compound was prepared with an analogous procedure to that described in Preparation 31 and Preparation 32 in 1.84 g yield from methyl 4-formyl-1-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-1H-pyrrole-2-carboxylate (4.5 g, prepared with an analogous procedure to that described in P110).

MS (m/z): 346 [MH]⁺

Preparation 112: methyl 1-{2-[4-fluoro-3-(trifluoromethyl)phenyl]-1-methyl-2-oxoethyl}-4-(methoxy)-1H-pyrrole-2-carboxylate (P112)

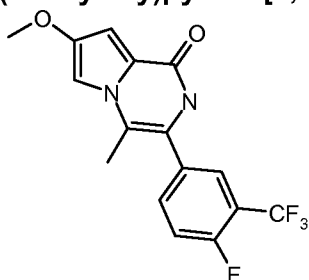


The title compound was prepared with an analogous procedure to that described in Preparation 64 in 771 mg yield from 1 methyl 1-(2-(3-chlorophenyl)-2-oxoethyl)-4-hydroxy-1H-pyrrole-2-carboxylate (1.73 g, P111)

MS (m/z): 374 [MH]⁺

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Preparation 113: 3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-7-(methoxy)pyrrolo[1,2-a]pyrazin-1(2H)-one (P113)



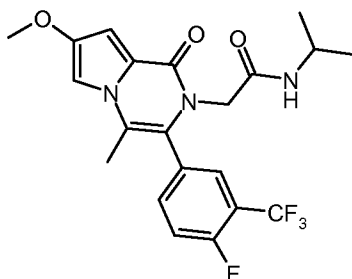
The title compound was prepared with an analogous procedure to that described in Preparation 2 in 0.66 g yield from methyl 1-{2-[4-fluoro-3-(trifluoromethyl)phenyl]-1-methyl-2-oxoethyl}-4-(methoxy)-1H-pyrrole-2-carboxylate (0.77 g, P112).

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MS (m/z): 341 [MH]⁺

Preparation 114: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-7-(methoxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P114)

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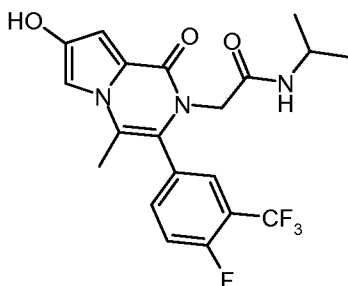


The title compound was prepared with an analogous procedure to that described in Preparation 109 in 0.36 g yield from 3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-7-(methoxy)pyrrolo[1,2-a]pyrazin-1(2H)-one (0.35 g, P113).

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MS (m/z): 440 [MH]⁺

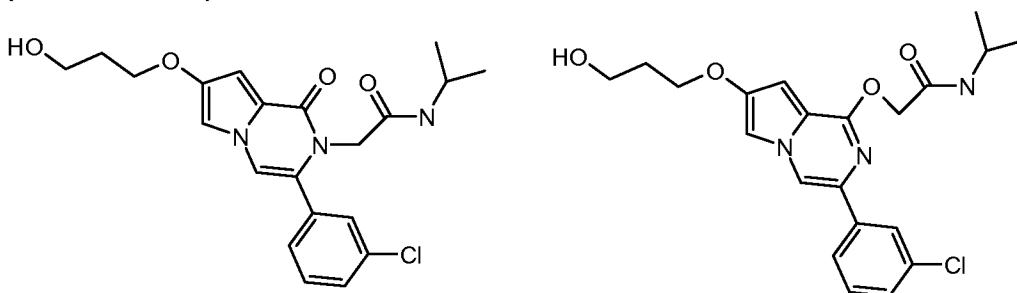
Preparation 115: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-hydroxy-4-methyl-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P115)



The title compound was prepared with an analogous procedure to that described in Preparation 67 in 0.34 g yield from 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-7-(methoxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (0.35 g, P114).

MS (m/z): 426 [MH]⁺

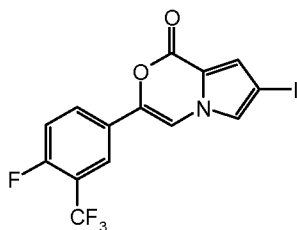
Preparation 116 : 2-[3-(3-chlorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide and 2-[(3-(3-chlorophenyl)-7-[(3-hydroxypropyl)oxy]pyrrolo[1,2-a]pyrazin-1-yl)oxy]-N-(1-methylethyl)acetamide (P116, mixture)



To a solution of 3-[(3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl)oxy]propyl acetate (0.4 g, prepared with an analogous procedure to that described in P89) in dry DMF (2.5 mL) and DME (10 mL) at 0°C under N₂ flux, NaH (0.053 g) was added. The mixture was stirred at 0°C for 10 min, then lithium bromide (0.241 g) (previously triturated and dried at high temperature) was added. The mixture was stirred at RT for 15 min, then 2-chloro-N-(1-methylethyl)acetamide (0.225 g) and NaI (0.033 g) were added and the mixture was warmed at 60°C and stirred at that temperature overnight. After cooling the mixture was diluted with AcOEt and washed with ice and brine. The organic phase was dried, filtered and evaporated affording a crude that was dissolved in THF (40 mL) and lithium hydroxide (10 mL) solution 0.5 M was added. The mixture was stirred at RT overnight. The mixture was concentrated under reduced pressure and the residue diluted with AcOEt and washed with water. The organic phase was dried, filtered and evaporated to give the mixture of title compounds.

MS (m/z): 418 [MH]⁺ . **UPLC:** Rt = 0.61 and 0.71 min.

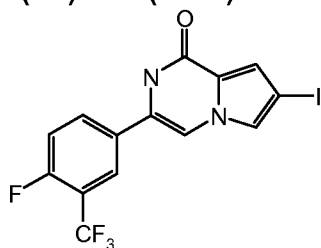
Preparation 117: 3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-iodo-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (P117)



The title compound was prepared with an analogous procedure to that described in Preparation 1 in 3.3 g yield from 2,2,2-trichloro-1-(4-iodo-1H-pyrrol-2-yl)ethanone (5.1 g, prepared in analogy with the method described in *Organic & Biomolecular Chemistry* 2006, 4(12), 2477-2482) and 2-bromo-1-[4-fluoro-3-(trifluoromethyl)phenyl]ethanone (4.3 g, commercially available).

MS (m/z): 424 [MH]⁺

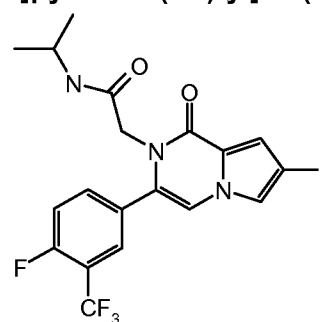
Preparation 118: 3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-iodopyrrolo[1,2-a]pyrazin-1(2H)-one (P118)



The title compound was prepared with an analogous procedure to that described in Preparation 2 in 2.22 g yield from 3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-iodo-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (3.25 g, P117).

MS (m/z): 423 [MH]⁺

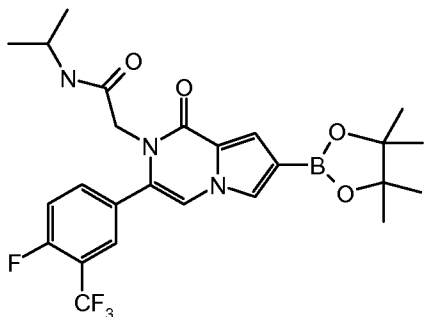
Preparation 119: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P119)



The title compound was prepared with an analogous procedure to that described in Preparation 109 in 1.36 g yield from 3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-iodopyrrolo[1,2-a]pyrazin-1(2H)-one (2.12 g, P118).

MS (m/z): 522 [MH]⁺

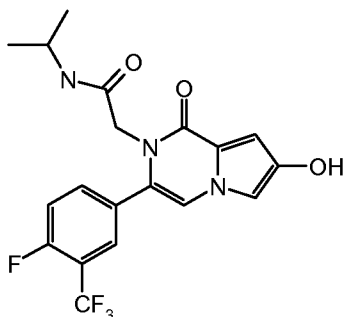
Preparation 120: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P120)



- 5 A stirred mixture of 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (200 mg, P119), bis(pinacolato)diboron (140 mg) and potassium acetate (180 mg) in DMF (3 ml) was degassed by repeated cycles of vacuum/nitrogen. [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (II) complex with dichloromethane (Pd(dppf)Cl₂·CH₂Cl₂) (40 mg) was added, the vessel was sealed and the resulting mixture was heated to 90 °C. The reaction mixture was diluted with ether, washed twice with water, brine, dried over Na₂SO₄ and the solvent evaporated under reduced pressure. The crude product was triturated with pentane, the mixture was filtered and the solid was washed with pentane and dried under vacuum to give the title compound (86 mg) as a light brown solid.

15 **MS (m/z):** 522 [MH]⁺

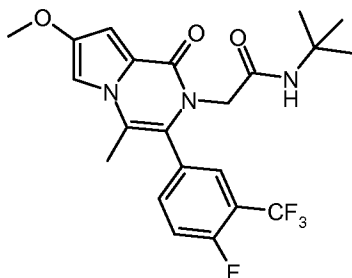
Preparation 121: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-hydroxy-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P121)



- 20 To a stirred solution of 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (0.69 g, P120) in THF (15 mL), at RT, a solution of NaOH (1.27 g) in Water (12 mL) was added followed by hydrogen peroxide (1.7 mL). The reaction was vigorously stirred for 15 min, the pH was brought to 6-7 with 1N HCl and the mixture was concentrated under reduced pressure. The residue was triturated with MeOH, the mixture was filtered, the filtered was concentrated under vacuum and the crude product was purified by FC on silica (eluting with a gradient of DCM/MeOH from 100% to 98% of DCM) to give the title compound (30 mg) as a light brown solid.

MS (m/z): 412 [MH]⁺

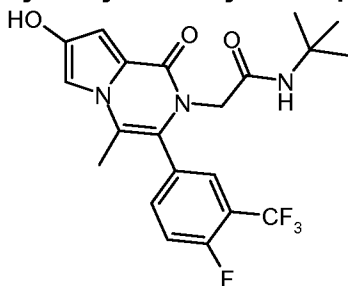
Preparation 122: *N*-(1,1-dimethylethyl)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-7-(methyloxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide (P122)



The title compound was prepared with an analogous procedure to that described in Preparation 109 in 0.324 g yield from 3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-7-(methyloxy)pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (0.313 g, P113) and 2-chloro-*N*-(1,1-dimethylethyl)acetamide (0.2 g, commercially available) .

MS (m/z): 454 [MH]⁺

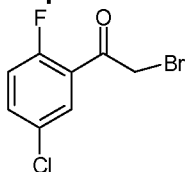
Preparation 123: *N*-(1,1-dimethylethyl)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-hydroxy-4-methyl-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide (P123)



The title compound was prepared with an analogous procedure to that described in Preparation 67 in 0.2 g yield from *N*-(1,1-dimethylethyl)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-7-(methyloxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide (0.324 g, P122).

MS (m/z): 426 [MH]⁺

Preparation 124: 2-bromo-1-(5-chloro-2-fluorophenyl)ethanone (P124)

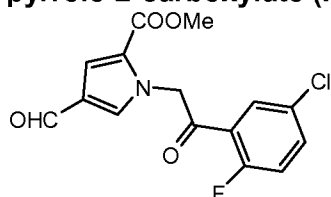


To a suspension of copper (II) bromide (14 g) in EA (100 mL) a solution of 1-(5-chloro-2-fluorophenyl)ethanone (5.4 g, commercially available) in chloroform was added dropwise and the mixture was reflux for 2.5 h. The suspension was filtered and the filtrate

concentrated under vacuum. The crude was purified by flash chromatography to give the title compound (6.45 g).

MS (m/z): 252 [MH]⁺

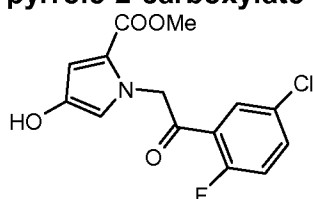
5 **Preparation 125: methyl 1-[2-(5-chloro-2-fluorophenyl)-2-oxoethyl]-4-formyl-1H-pyrrole-2-carboxylate (P125)**



10 The title compound was prepared with an analogous procedure to that described in Preparation 30 in 1.71 g yield from methyl 4-formyl-1H-pyrrole-2-carboxylate (0.92 g , prepared with an analogous procedure to that described in P29) 2-bromo-1-(5-chloro-2-fluorophenyl)ethanone (2.28 g, P124).

MS (m/z): 324 [MH]⁺

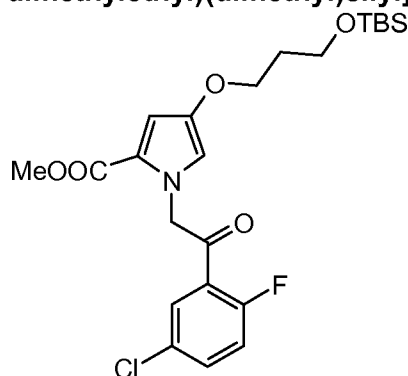
15 **Preparation 126: methyl 1-[2-(5-chloro-2-fluorophenyl)-2-oxoethyl]-4-hydroxy-1H-pyrrole-2-carboxylate (P126)**



The title compound was prepared with an analogous procedure to that described in Preparation 31 and Preparation 32 in 0.53 g yield from methyl 1-[2-(5-chloro-2-fluorophenyl)-2-oxoethyl]-4-formyl-1H-pyrrole-2-carboxylate (1.1 g, P125).

20 **MS (m/z):** 340 [MH]⁺

Preparation 127: methyl 1-[2-(5-chloro-2-fluorophenyl)-2-oxoethyl]-4-[(3-[(1,1-dimethylethyl)(dimethyl)silyl]oxy)propyl]oxy-1H-pyrrole-2-carboxylate (P127)

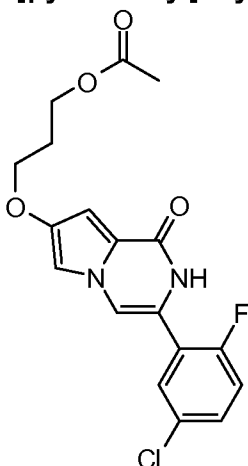


The title compound was prepared with an analogous procedure to that described in Preparation 58 in 60 mg yield from methyl 1-[2-(5-chloro-2-fluorophenyl)-2-oxoethyl]-4-hydroxy-1H-pyrrole-2-carboxylate (200 mg, P126).

MS (m/z): 484 [MH]⁺

5

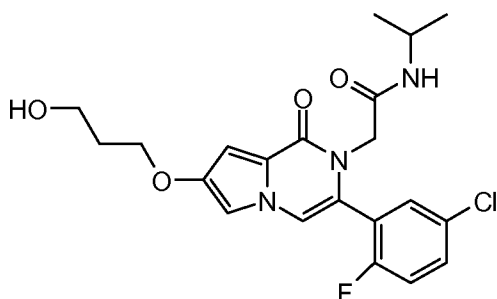
Preparation 128: 3-{[3-(5-chloro-2-fluorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]oxy}propyl acetate (P128)



The title compound was prepared with an analogous procedure to that described in Preparation 2 in 20 mg yield from methyl 1-[2-(5-chloro-2-fluorophenyl)-2-oxoethyl]-4-[(3-{{(1,1-dimethylethyl)(dimethyl)silyl}oxy}propyl)oxy]-1H-pyrrole-2-carboxylate (120 g, prepared with an analogous procedure to that described in P127).

MS (m/z): 379 [MH]⁺

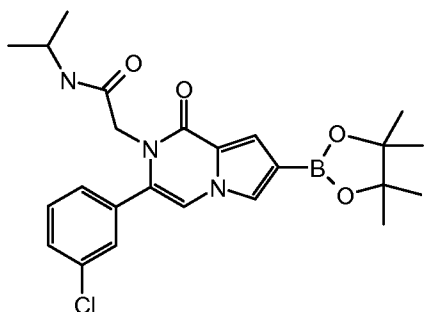
Preparation 129: 2-[3-(5-chloro-2-fluorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P129)



The title compound was prepared with an analogous procedure to that described in Preparation 98 in 10 mg yield from 3-{[3-(5-chloro-2-fluorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]oxy}propyl acetate (20 g, P128).

MS (m/z): 436 [MH]⁺

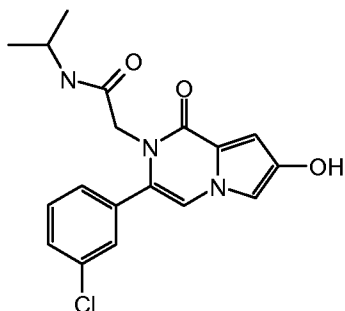
Preparation 130: 2-[3-(3-chlorophenyl)-1-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P130)



The title compound was prepared with an analogous procedure to that described in Preparation 120 in 0.89 g yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (1.53 g, prepared with an analogous procedure to that described in P63).

MS (m/z): 470 [MH]⁺

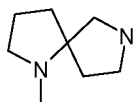
Preparation 131: 2-[3-(3-chlorophenyl)-7-hydroxy-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P131)



The title compound was prepared with an analogous procedure to that described in Preparation 121 in 0.22 g yield from 2-[3-(3-chlorophenyl)-1-oxo-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (0.86 g, P130).

MS (m/z): 412 [MH]⁺

Preparation 132: 1-methyl-1,7-diazaspiro[4.4]nonane (P132)

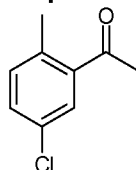


To a solution of 1,1-dimethylethyl 1,7-diazaspiro[4.4]nonane-7-carboxylate (49 mg, commercially available) in dry acetonitrile (2.2 mL), formaldehyde (0.032 mL) was added and the mixture was left stirring at rt 5min. Then sodium triacetoxyborohydride (92 mg) was added and the mixture stirred at rt for 40 min. The reaction was quenched with NaHCO₃ ss, solvent was eliminated under reduced pressure and the aqueous residue was extracted with DCM. Organic phase was washed with NH₄Cl ss and brine, filtered and concentrated under reduced pressure affording 1,1-dimethylethyl 1-methyl-1,7-diazaspiro[4.4]nonane-7-carboxylate that was combined with one other batch (95mg, total

amount). To a solution of 1,1-dimethylethyl 1-methyl-1,7-diazaspiro[4.4]nonane-7-carboxylate (95 mg) in dry DCM, trifluoroacetic acid (0.305 mL) was added and the mixture was stirred at rt for 18h. Afterwards solvent was eliminated under reduced pressure to give the title compound (156 mg).

5 **MS (m/z):** 157 [MH]⁺

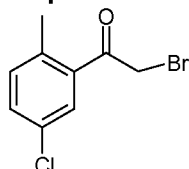
Preparation 134: 1-(5-chloro-2-methylphenyl)ethanone (P134)



10 To a suspension of magnesium (0.12 g) in THF (15 mL) 2-bromo-4-chlorotoluene (0.125 g, commercially available) was added and the mixture stirred for a few minutes. Then a solution of 2-bromo-4-chlorotoluene (0.9 g) in THF (85 mL) was added dropwise and the mixture stirred for 3h. The mixture was added dropwise to a solution of acetyl chloride (0.353 g) in THF (10 mL) at 0 °C. The mixture was stirred at RT for 5h. Chilly water was added to the reaction mixture and the pH adjusted at pH 6 with HCl 10% and the product
15 extracted with EA. The organic phase was dried and the solvent evaporated under vacuum to give the title compound (0.676 g) that was used in next step without further purification.

MS (m/z): 169 [MH]⁺

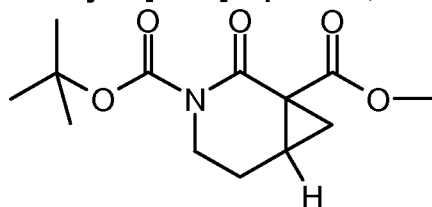
20 **Preparation 135: 2-bromo-1-(5-chloro-2-methylphenyl)ethanone (P135)**



The title compound was prepared with an analogous procedure to that described in Preparation 133 in 16 mg yield from 1-(5-chloro-2-methylphenyl)ethanone (5.4 g, prepared with an analogous procedure to that described in P134).

25 **MS (m/z):** 248 [MH]⁺

Preparation 136: 3-(1,1-dimethylethyl) 1-methyl (1R,6S/1S,6R)-2-oxo-3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate (P136)

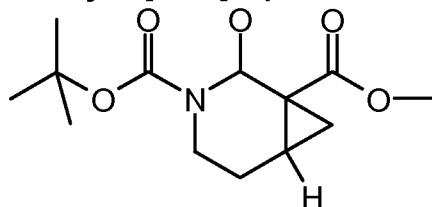


30 To a solution of methyl -2-oxo-3-azabicyclo[4.1.0]heptane-1-carboxylate (2.016 g, 11.92 mmol), whose preparation is described in Journal of Organic Chemistry (1974), 39(13),

1979-80, in a mixture Toluene (60 mL)/DCM (30mL), DMAP (2.184 g, 17.87 mmol) was added followed by BOC₂O (3.32 ml, 14.30 mmol). The resulting mixture was heated to reflux for 1.5 h, diluted with DCM and washed with brine. The organic layer was dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude product was purified by SPE-Si (50 g) column (eluting with Cy/AcOEt from 1/0 to 1/1) to give 2.24 g of the title product.

NMR (¹H, CDCl₃): δ 3.54 – 3.56 (m,s, 4 H), 3.5 (m, 1 H), 2.5 (m, 1 H), 2.05 (m, 1 H), 1.85 (m, 2 H), 1.65 (s, 9 H), 1.4 (m, 2 H)

10 **Preparation 137: 3-(1,1-dimethylethyl) 1-methyl (-2-hydroxy-3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate (P137)**

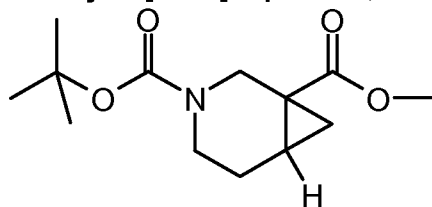


A solution 1M in THF of Superhydride (9.98 mL, 9.98 mmol) was added over 30 min to a solution of 3-(1,1-dimethylethyl) 1-methyl (1*R*,6*S*/1*S*,6*R*)-2-oxo-3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate (P136, 2.24 g, 8.32 mmol), in THF (20mL) cooled to -10 °C.

After 3.5 h the reaction mixture was diluted with water and extracted with AcOEt. The organic layer was dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude was purified by SPE-Si (25 g) column (eluting with Cyclohexane/AcOEt 7/3) to afford 1.373 g of the title product as mixture of diastereoisomers.

MS(*m/z*): 272.11 [MH]⁺.

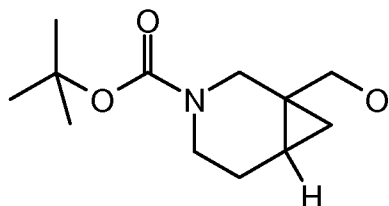
25 **Preparation 138: 3-(1,1-dimethylethyl) 1-methyl (1*R*,6*S*/1*S*,6*R*)-3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate (P138)**



A solution of 3-(1,1-dimethylethyl) 1-methyl 2-hydroxy-3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate (P137, 1.373g, 5.06 mmol) and TRIETHYLSILANE (0.808 mL, 5.06 mmol) in DCM (40mL) was cooled to -78 °C and BF₃OEt₂ (0.641 mL, 5.06 mmol) was then added dropwise under a nitrogen atmosphere. After 30 min, more TRIETHYLSILANE (0.808 mL, 5.06 mmol) and BF₃OEt₂ (0.641 mL, 5.06 mmol) were added. The resulting mixture was stirred an additional 1.5 h at - 78 °C. The reaction mixture was warmed at rt, diluted with DCM and washed with H₂O. The organic layer was dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude was purified by SPE-Si (5g) column (eluting with Cy/AcOEt from 100/0 to 95:5) to afford 878.2 mg of the title product.

NMR (¹H, CDCl₃): δ 3.82 - 4.12 (m, 2 H), 3.66 - 3.74 (m, 3 H), 3.51 (br. s., 1 H), 2.87 - 3.03 (m, 1 H), 1.94 - 2.08 (m, 1 H), 1.66 - 1.86 (m, 2 H), 1.44 - 1.53 (m, 9 H), 1.41 (dd, 1 H), 0.75 (dd, 1 H)

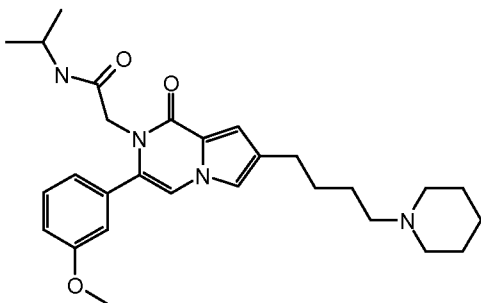
5 **Preparation 139: 1,1-dimethylethyl (1R,6S/1S,6R)-1-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (P139)**



10 To a stirred solution of 3-(1,1-dimethylethyl) 1-methyl 3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate (0.18 g, 0.705 mmol) (P138, racemic mixture) in anhydrous toluene (5 mL) at -20 °C and under a nitrogen atmosphere, (1M/THF) lithium aluminium hydride (0.705 mL, 0.705 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 15 min. Saturated NaHCO₃ was added to the reaction mixture that was then diluted with EA, the organic phase was washed with water, brine, dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude product was purified by FC on silica (eluting with Cy/EA from 1/0 to 6/4) to give 0.16 g of the title product as colourless oil.

NMR (¹H, CDCl₃): δ 3.85-2.90 (m, 6H), 1.95 (m, 1H), 1.68 (m, 1H), 0.97 (m, 1H), 0.63 (m, 1H), 0.37 (m, 1H). **MS(m/z):** 228.19 [MH]⁺.

20 **Example 1: N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidiny)-butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E1)**



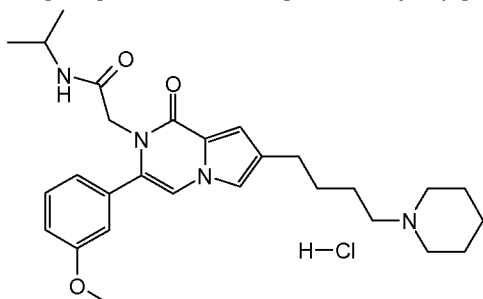
25 To a solution of N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[(1E/Z)-4-(1-piperidiny)-1-buten-1-yl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (61 mg, P6) in ethanol (2.4 mL) was added palladium on carbon (13.6 mg). The mixture was stirred under hydrogen atmosphere (1 atm) for 12 h at room temperature. The reaction was filtered over a pad of CELITE, washed with MeOH and the filtrate evaporated under vacuum. The crude obtained was purified by FC first on silica column (eluent DCM:MeOH:NH₃ acq=9:0.5:0.05) and then on NH column (eluent AcOEt:Cy=8:2) to give the title compound (35 mg).

¹H NMR (500 MHz, DMSO-*d*₆): δ ppm 7.73 (d, 1 H) 7.35 (t, 1 H) 7.20 - 7.26 (m, 2 H) 6.94 - 7.05 (m, 3 H) 6.74 (s, 1 H) 4.18 (s, 2 H) 3.67 - 3.79 (m, 4 H) 2.52 (t, 2 H) 2.10 - 2.33 (m, 6 H) 1.50 - 1.61 (m, 2 H) 1.27 - 1.49 (m, 8 H) 0.95 (d, 6 H).

MS (m/z): 479 [MH]⁺

5

Example 2 : N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)-butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E2)



N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (35 mg, E1) was dissolved in DCM (2 mL) and hydrogen chloride (1 M solution in Et₂O) (73 μL) was added. The solvent was evaporated and the residue thus obtained triturated with dry diethyl ether. Then diethyl ether was removed and the resultant solid dried under vacuum to provide the title compound (36 mg) as a white solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ ppm 9.29 (br. s., 1 H) 7.76 (d, 1 H) 7.36 (t, 1 H) 7.24 - 7.30 (m, 2 H) 7.03 (dd, 1 H) 6.94 - 7.00 (m, 2 H) 6.80 (s, 1 H) 4.17 (s, 2 H) 3.62 - 3.81 (m, 4 H) 3.19 - 3.37 (m, 2 H) 2.95 - 3.05 (m, 2 H) 2.73 - 2.88 (m, 2 H) 2.57 (t, 2 H) 1.20 - 1.81 (m, 10 H) 0.95 (d, 6 H).

MS (m/z): 479 [MH]⁺

20

Example 3: N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[5-(1-piperidinyl)pentyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E3) and

Example 4: N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[(1S/1R)-1-methyl-4-(1-piperidinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E4)

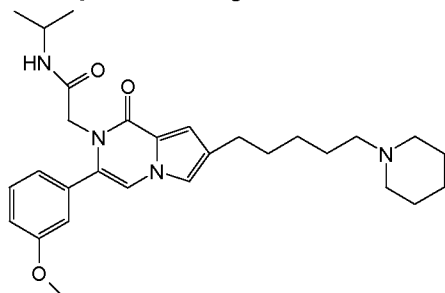
25

To a solution of N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[(1*E/Z*)-5-(1-piperidinyl)-1-penten-1-yl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (165 mg, P9) in ethanol (3.5 mL) was added palladium on carbon (36 mg). The mixture was stirred under hydrogen atmosphere (1 atm) for 5 h at room temperature. The reaction was filtered over a pad of celite, the filtrate evaporated under vacuum. The resulting crude was dissolved in ethanol (3.5 mL), palladium on carbon (36 mg) was added and the reaction stirred at room temperature under hydrogen atmosphere (1 atm) for 18 h. The reaction was filtered over celite and the filtrate evaporated under vacuum. The crude obtained was purified by SCX cartridge, eluting the compound with NH₃ (1 M in MeOH), and by several flash chromatography on NH column with a gradient of Cy:EtOAc (from 0% to 100% of EtOAc)

35

as eluent to afford a mixture of the title compounds (52 mg). The mixture was purified by preparative HPLC (chiral column chiralcel OD-H, eluent A: n-hexane, B: ethanol, gradient isocratic 13% B, flow rate 18 mL/min, detection UV at 220 nm; retention time given by analytical HPLC using a chiral column chiralcel OD-H (25 X 0.46 cm), eluent A: n-hexane; B: ethanol, gradient isocratic 13% B, flow rate 0.1 mL/min, detection UV at 210-340 nm) to give the two separate compounds (Rt = 8.4 min and Rt = 11.3 min):

Example 3: 15 mg as a white solid.

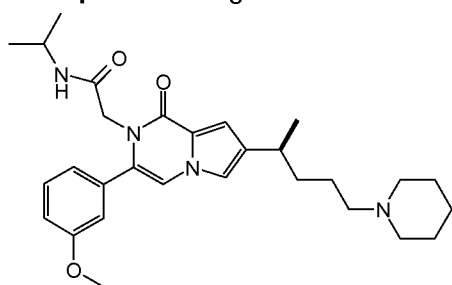


¹H NMR (400 MHz, CDCl₃): δ 1.16 (d, 6H), 1.33-1.42 (m, 2H), 1.50-1.71 (m, 10H), 2.24-2.48 (m, 6H), 2.62 (t, 2H), 3.85 (s, 3H), 3.97-4.14 (m, 1H), 4.32 (s, 2H), 5.94 (br d, 1H), 6.89 (s, 1H), 6.95 (s, 1H), 6.97-7.04 (m, 4H), 7.31-7.39 (m, 1H).

MS (m/z): 493 [MH]⁺

and

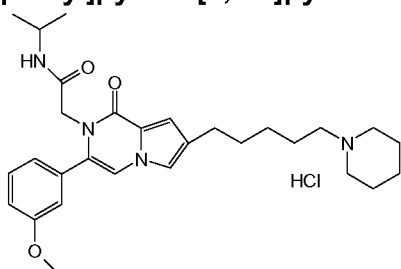
Example 4: 15 mg as a white solid.



¹H NMR (400 MHz, CDCl₃): δ ppm 7.35 (t, 1 H) 7.05 – 6.98 (m, 4 H) 6.95 (m, 1 H) 6.88 (s, 1 H) 6.00 (d, 1 H) 4.33 (m, 2 H) 4.15-4.01 (m, 1 H) 3.85 (s, 3 H) 2.80 (m, 1 H) 2.45 - 2.25 (m, 5 H) 1.65 - 1.40 (m, 10 H) 1.24 (d, 3 H) 1.15 (d, 6 H).

MS (m/z): 493 [MH]⁺

Example 5: N-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-1-oxo-7-[5-(1-piperidinyl)pentyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E5)

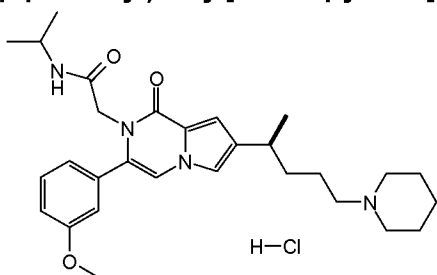


N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[5-(1-piperidiny)pentyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (15 mg, E3) was dissolved in DCM (2 mL) and hydrogen chloride (1.25M solution in MeOH) (25 μ L) was added. The solvent was evaporated and the residue thus obtained triturated with dry diethyl ether. Then diethyl ether was removed and the resultant solid dried under vacuum to provide the title compound (16 mg) as a white solid.

^1H NMR (500 MHz, DMSO- d_6): δ 0.96 (d, 6H), 1.23-1.40 (m, 3H), 1.56-1.82 (m, 9H), 2.56 (t, 2H), 2.75-2.85 (m, 2H), 2.93-3.01 (m, 2H), 3.36-3.42 (m, 2H), 3.69-3.79 (m, 1H), 3.75 (s, 3H), 4.18 (s, 2H), 6.78 (d, 1H), 6.95-7.00 (m, 2H), 7.03 (dd, 1H), 7.22-7.27 (m, 2H), 7.36 (t, 1H), 7.76 (d, 1H), 9.45 (br s, 1H).

MS (m/z): 493 [MH] $^+$

Example 6: N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[(1S/1R)-1-methyl-4-(1-piperidiny)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E6)

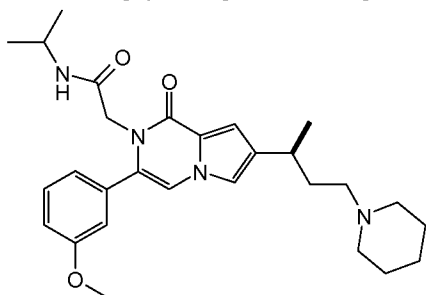


The title compound was prepared with an analogous procedure to that described in Example 5 in 16 mg yield as white solid from N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[(1S/1R)-1-methyl-4-(1-piperidiny)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (15 mg, E4).

^1H NMR (500 MHz, DMSO- d_6): δ 9.00 (br. s., 1 H) 7.74 (d, 1 H) 7.36 (t, 1 H) 7.14 - 7.29 (m, 2 H) 6.90 - 7.08 (m, 3 H) 6.83 (s, 1 H) 4.07 - 4.28 (m, 2 H) 3.68 - 3.79 (m, 4 H) 3.30 - 3.44 (m, 2 H) 2.91 - 3.07 (m, 2 H) 2.71 - 2.85 (m, 3 H) 1.30 - 1.87 (m, 10 H) 1.17 - 1.27 (m, 3 H) 0.95 (d, 6 H).

MS (m/z): 493 [MH] $^+$

Example 7: N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[(1S/1R)-1-methyl-3-(1-piperidiny)propyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E7)



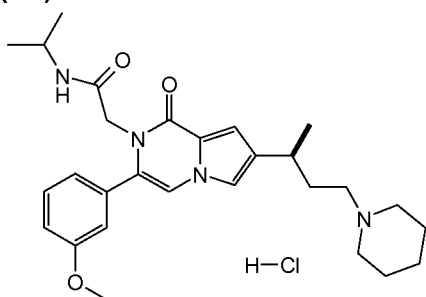
N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (30mg, E2, containing the title compound as

impurity) was purified by preparative HPLC (chiral column chiralcel OD-H, eluent A: n-hexane, B: Ethanol, gradient isocratic 35% B, flow rate 14 mL/min, detection UV at 225 nm; retention time given by analytical HPLC using a chiral column chiralcel OD-H (25 X 0.46 cm), eluent A: n-hexane; B: ethanol, gradient isocratic 35% B, flow rate 0.8 mL/min, detection UV at 210-340 nm) to give the title compound (2mg, Rt = 4.76 min)

¹H NMR (400 MHz, CDCl₃): δ 7.35 (t, 1 H) 7.05 – 6.98 (m, 4 H) 6.96 (m, 1 H) 6.88 (s, 1 H) 5.95 (broad s, 1 H) 4.32 (m, 2 H) 4.10-4.01 (m, 1 H) 3.84 (s, 3 H) 2.82 (m, 1 H) 2.47 - 2.21 (m, 5 H) 1.87 - 1.75 (m, 2 H) 1.64 - 1.55 (m, 4 H) 1.50 - 1.36 (m, 2 H) 1.28 (d, 3 H) 1.15 (d, 6 H).

MS (m/z): 479 [MH]⁺

Example 8: N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[(1S/1R)-1-methyl-3-(1-piperidinyl)propyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E8)

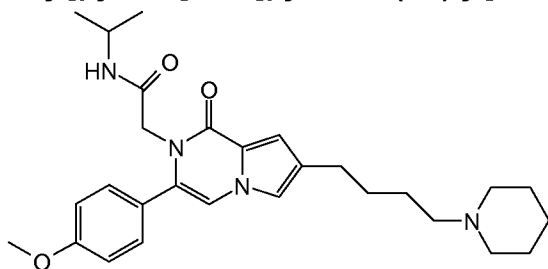


The title compound was prepared with an analogous procedure to that described in Example 2 in 2 mg yield as white solid from N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[(1S/1R)-1-methyl-3-(1-piperidinyl)propyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (2 mg, E7).

¹H NMR (500 MHz, (CD₃)₂O): δ 12.65 (br. s., 1 H) 7.32 - 7.43 (m, 2 H) 7.01 - 7.15 (m, 5 H) 6.87 - 6.89 (m, 1 H) 4.31 (s, 2 H) 3.91 - 4.01 (m, 1 H) 3.83 (s, 3 H) 3.37 - 3.48 (m, 2 H) 2.74 - 3.05 (m, 6 H) 2.10 - 2.34 (m, 4 H) 1.72 - 1.82 (m, 3 H) 1.46 (none, 1 H) 1.31 (d, 3 H) 1.07 (d, 6 H).

MS (m/z): 479 [MH]⁺

Example 9: N-(1-methylethyl)-2-[3-[4-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E9)



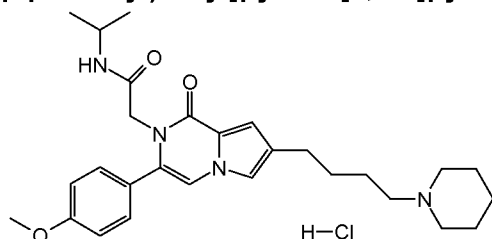
The title compound was prepared with an analogous procedure to that described in Example 1 in 25 mg yield as white solid from N-(1-methylethyl)-2-[3-[4-

(methoxy)phenyl]-1-oxo-7-[4-(1-piperidiny)-1-butyn-1-yl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (123 mg, P16).

¹H NMR (400 MHz, CDCl₃): δ 1.15 (d, 6H), 1.40-1.49 (m, 2H), 1.52-1.69 (m, 8H), 2.35-2.50 (m, 6H), 2.62 (t, 2H), 3.85 (s, 3H), 3.99-4.10 (m, 1H), 4.31 (s, 2H), 6.08-6.00 (m, 1H), 6.83 (s, 1H), 6.99-6.92 (m, 3H), 7.37-7.31 (m, 2H).

MS (m/z): 516 [MH]⁺

Example 10: N-(1-methylethyl)-2-[3-[4-(methoxy)phenyl]-1-oxo-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E10)

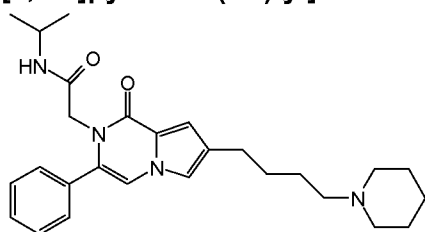


The title compound was prepared with an analogous procedure to that described in Example 2 in 25 mg yield as white solid from N-(1-methylethyl)-2-[3-[4-(methoxy)phenyl]-1-oxo-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (25 mg, E9).

¹H NMR (500 MHz, DMSO-d₆): δ 9.47 (br. s., 1 H) 7.75 (d, 1 H) 7.32 (d, 2 H) 7.25 (s, 1 H) 7.21 (s, 1 H) 7.00 (d, 2 H) 6.80 (s, 1 H) 4.18 (br. s., 2 H) 3.78 (s, 3 H) 3.68 - 3.79 (m, 1 H) 3.33 - 3.42 (m, 2 H) 2.95 - 3.07 (m, 2 H) 2.81 (q, 2 H) 2.59 (t, 2 H) 1.78 (d, 2 H) 1.63 - 1.73 (m, 5 H) 1.55 - 1.64 (m, 2 H) 1.29 - 1.42 (m, 1 H) 0.97 (d, 6 H).

MS (m/z): 516 [MH]⁺

Example 11: N-(1-methylethyl)-2-[1-oxo-3-phenyl-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E11)



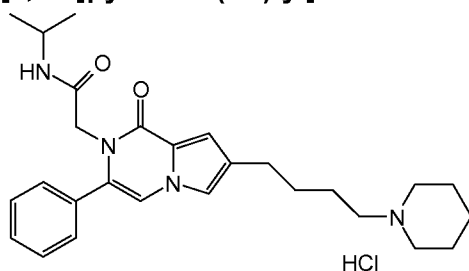
A stirring suspension of 4-(2-{2-[(1-methylethyl)amino]-2-oxoethyl}-1-oxo-3-phenyl-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl)butyl methanesulfonate (80 mg, P22), piperidine (52 µL) and potassium carbonate (120 mg) in acetonitrile (2 mL) was heated at 80 °C for 5 h. The reaction mixture was diluted with EtOAc and washed with chilly water and brine. The organic phase was dried over Na₂SO₄ anhydrous, filtered and evaporated under reduced pressure to provide 140 mg of crude material which was purified by silica gel flash column chromatography with a gradient of DCM/[DCM:MeOH:NH₃ (2.0M solution in MeOH) =90:9:1] (from 100% to 0% of DCM) as eluent to yield the title compound (35 mg) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 1.15 (d, 6H), 1.40-1.49 (m, 2H), 1.52-1.69 (m, 8H), 2.27-2.48 (m, 6H), 2.63 (t, 2H), 3.99-4.10 (m, 1H), 4.32 (s, 2H), 5.97 (br d, 1H), 6.86 (s, 1H), 6.95 (s, 1H), 7.01 (s, 1H), 7.42-7.48 (m, 5H).

MS (m/z): 449 [MH]⁺.

5

Example 12: N-(1-methylethyl)-2-[1-oxo-3-phenyl-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E12)



The title compound was prepared with an analogous procedure to that described in Example 5 in 35 mg yield as white solid from N-(1-methylethyl)-2-[1-oxo-3-phenyl-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (35 mg, E11).

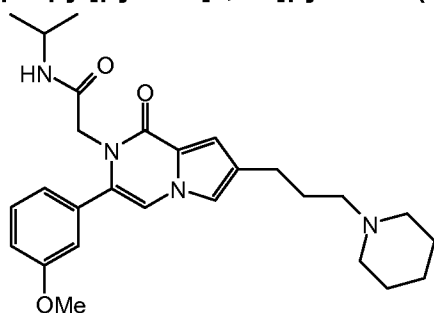
10

¹H NMR (500 MHz, DMSO-d₆): δ 0.95 (d, 6H), 1.30-1.75 (m, 10H), 2.55-3.08 (m, 8H), 3.68-3.79 (m, 1H), 4.19 (s, 2H), 6.79 (s, 1H), 7.25 (s, 2H), 7.39-7.50 (m, 5H), 7.74 (d, 1H), 9.10-10.10 (br s, 1H).

15

MS (m/z): 449 [MH]⁺.

Example 13: N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[3-(1-piperidiny)propyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E13)



The title compound was prepared with an analogous procedure to that described in Example 11 in 53 mg yield as a colourless oil from 3-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl}propyl methanesulfonate (145 mg, P25).

20

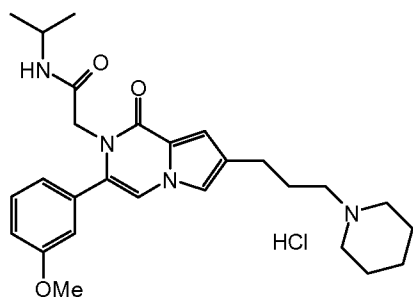
¹H NMR (400 MHz, CDCl₃): δ 1.14 (d, 6H), 1.39-1.55 (m, 2H), 1.59-1.70 (m, 4H), 1.83-1.96 (m, 2H), 2.31-2.54 (m, 6H), 2.64 (t, 2H), 3.83 (s, 3H), 3.95-4.13 (m, 1H), 4.32 (s, 2H), 5.97 (br d, 1H), 6.88 (s, 1H), 6.93-7.04 (m, 5H), 7.30-7.38 (m, 1H).

25

MS (m/z): 465 [MH]⁺.

Example 14: N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[3-(1-piperidiny)propyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E14)

30



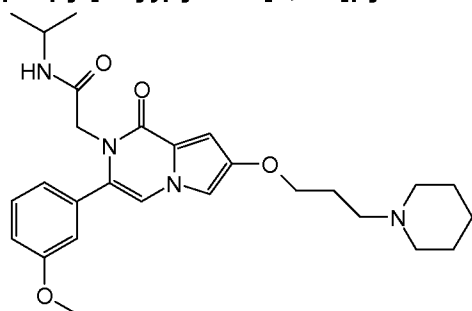
The title compound was prepared with an analogous procedure to that described in Example 5 in 56 mg yield from N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[3-(1-piperidinyl)propyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (53 mg, E13).

- 5 **¹H NMR (500 MHz, DMSO-d₆):** δ 0.96 (d, 6H), 1.32-1.61 (br s, 2H), 1.63-1.79 (s, 4H), 1.88-2.06 (s, 2H), 2.42-2.52 (t, 2H, under DMSO signal), 2.60 (t, 2H), 2.72-3.00 (br s, 4H), 3.69-3.79 (m, 4H), 4.19 (s, 2H), 6.83 (s, 1H), 6.94-7.08 (m, 3H), 7.28 (s, 2H), 7.32-7.37 (t, 1H), 7.77 (d, 1H). 9.44-10.08 (br s, 1H).

MS (m/z): 465 [MH]⁺

10

Example 15: N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E15)



15

To a suspension of 3-[3-(methyloxy)phenyl]-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-1(2H)-one (100 mg, P34), KOH (20.6 mg) and tetrabutylammonium bromide (25.4 mg) in THF (1.5 mL) were added, at 0°C under N₂, Nal (43.2 mg) and a solution of 2-chloro-N-(1-methylethyl)acetamide (39.1 mg) in THF (1 mL). The mixture was stirred at rt for 24h. Then 2-chloro-N-(1-methylethyl)acetamide (7 mg), tetrabutylammonium bromide (4 mg), KOH (3 mg) and Nal (8 mg) were added and the mixture was stirred at rt for other 24h.

20

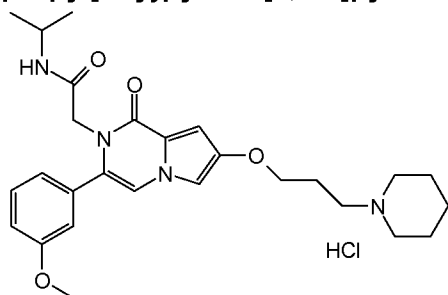
The mixture was diluted with DCM and washed with water. The organic phase was dried over anhydrous Na₂SO₄, filtered and evaporated under vacuum. The crude obtained was purified by SCX cartridge, eluting the desired product with NH₃ (1M in MeOH), and afterwards by FC on NH column, eluting with a gradient of Cy:AcOEt (from 100% to 0% of Cy), providing the title compound (22 mg) as oil.

25

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.31 (m, 1 H) 7.03-6.96 (m, 3 H) 6.84 (s, 1 H) 6.78 (m, 2 H) 6.01-5.90 (m, 1 H) 4.36-4.27 (m, 2 H) 4.17-4.10 (m, 1 H) 4.05-3.99 (m, 2 H) 3.84 (s, 3 H) 2.56 - 2.41 (m, 6 H) 2.03 - 1.96 (m, 2 H) 1.67 - 1.59 (m, 4 H) 1.51 - 1.42 (m, 2 H) 1.142 (d, 6 H).

MS (m/z): 481 [MH]⁺

Example 16: *N*-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide hydrochloride (E16)

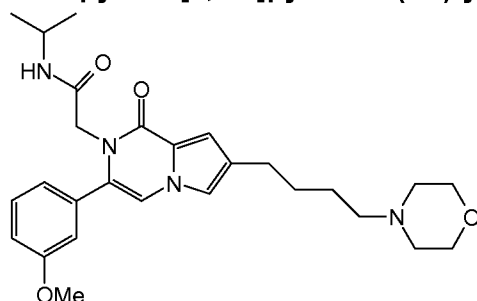


The title compound was prepared with an analogous procedure to that described in Example 5 in 22 mg yield as a white solid from *N*-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide (22 mg, E15).

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.35 (br. s., 1 H), 7.77 (d, 1 H), 7.38 (t, 1 H), 7.22 - 7.26 (m, 1 H), 7.15 (d, 1 H), 6.96 - 7.09 (m, 3 H), 6.56 - 6.62 (m, 1 H), 4.18 - 4.26 (m, 2 H), 3.99 - 4.09 (m, 2 H), 3.75 - 3.78 (m, 3 H), 3.69 - 3.82 (m, 1 H), 3.18 (br. s., 6 H), 1.76 (br. s., 8 H), 0.98 (d, 6 H).

MS (m/z): 481 [MH]⁺.

Example 17: *N*-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-(4-morpholinyl)butyl]-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide (E17)

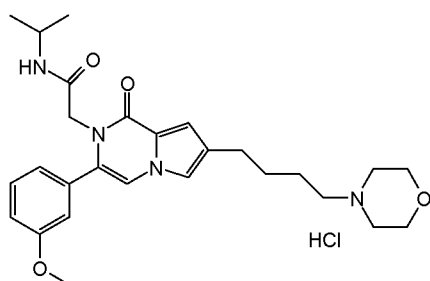


The title compound was prepared with an analogous procedure to that described in Example 11 in 24 mg yield as a colourless oil from 4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-*a*]pyrazin-7-yl}butyl methanesulfonate (73 mg, P28) and morpholine (39 μL).

¹H NMR (400 MHz, CDCl₃): δ 1.15 (d, 6H), 1.51-1.61 (m, 2H), 1.62-1.81 (m, 2H), 2.37 (t, 2H), 2.41-2.49 (m, 4H), 2.63 (t, 2H), 3.73 (t, 4H), 3.84 (s, 3H), 4.00-4.10 (m, 1H), 4.32 (s, 2H), 5.95 (br d, 1H), 6.88 (s, 1H), 6.94 (s, 1H), 6.97-7.03 (m, 4H), 7.30-7.39 (m, 1H).

MS (m/z): 481 [MH]⁺.

Example 18: *N*-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-(4-morpholinyl)butyl]-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide hydrochloride (E18)

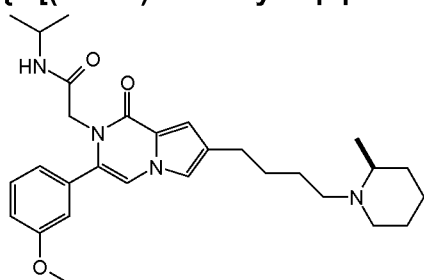


The title compound was prepared with an analogous procedure to that described in Example 2 in 22 mg yield as a white solid from N-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-7-[4-(4-morpholinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (22 mg, E17).

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.93 (br. s., 1 H) 7.76 (d, 1 H) 7.37 (t, 1 H) 7.23 - 7.29 (m, 2 H) 7.04 (dd, 1 H) 6.95 - 7.01 (m, 2 H) 6.81 (s, 1 H) 4.19 (s, 2 H) 3.86 - 4.06 (m, 2 H) 3.76 (s, 3 H) 3.51 - 3.80 (m, 3 H) 2.87 - 3.22 (m, 4 H) 2.54 - 2.63 (m, 2 H) 2.14 - 2.46 (m, 2 H) 1.49 - 1.77 (m, 4 H) 0.97 (d, 6 H).

MS (m/z): 481 [MH]⁺.

Example 19: 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methoxy)phenyl]-7-{4-[(2*S*/2*R*)-2-methyl-1-piperidiny]butyl}pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (E19)



To a suspension of 2-[7-(4-hydroxybutyl)-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (60 mg, prepared in analogy to P27), TEA (0.037 mL) and DMAP (1 mg) in dry chloroform (2 mL) at 0°C, methansulfonyl chloride (0.017 mL) was added dropwise, and the mixture was stirred at RT for 3h. Additional methansulphonyl chloride (10 µL) and TEA (20 µL) were added and the mixture was stirred for 1h. The mixture was diluted with DCM and washed with 0.5 M HCl and brine. The organic phase was dried and evaporated under vacuum. The crude obtained was dissolved in dry DMF (2.0 mL), potassium carbonate (101 mg) and 2-methylpiperidine (0.051 mL) were added and the mixture was stirred at 80°C for 7h, at RT for the weekend, then was heated to 80°C and stirred for additional 24h.

The mixture was cooled down, diluted with AcOEt and washed with ice and brine. The organic phase was dried and evaporated under vacuum and the crude purified by SCX cartridge and by flash chromatography on NH column eluting with Cy/AcOEt (from 100% to 0% of Cy), and affording the title compound (14 mg) as white solid.

¹H-NMR (400MHz, CDCl₃) δ: 7.35 (t, 1H); 7.02-6.98 (m, 4H); 6.94 (s, 1H); 6.88 (s, 1H); 5.95 (broad s, 1H); 4.32 (s, 2H); 4.1-4.01 (m, 1H); 3.84 (s, 3H); 2.9-2.83(m, 1H); 2.74-2.61

(m, 3H); 2.39-2.33 (m, 1H); 2.31-2.20 (m, 1H); 2.17-2.10 (m, 1H); 1.69-1.50 (m, 7H); 1.34-1.27 (m, 3H); 1.15 (d, 6H); 1.07 (d, 3H) ppm.

MS (m/z): 492 [MH]⁺

2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S/2R)-2-methyl-1-piperidiny]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one (14mg) was submitted to preparative HPLC using a chiral column chiralpack AD-H, 23x2cm, eluent A: n-hexane; B: ethanol, gradient isocratic 50%B, flow rate 14 mL/min, detection UV at 230 nm to give the separated enantiomers (retention times given were obtained using an analytical HPLC using a chiral column chiralpack AD-H, 25x0.46cm, eluent A: n-hexane; B: ethanol, gradient isocratic 50%B, flow rate 0.8 mL/min, detection UV at 230 nm):

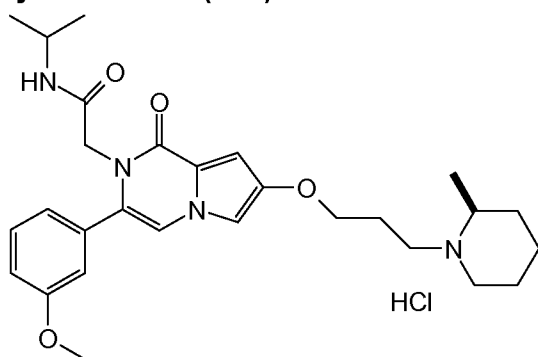
Example 20: 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S or 2R)-2-methyl-1-piperidiny]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one (E20)

Enantiomer 1 (Rt. = 17.92 min) in 4.8 mg yield as white solid;

Example 21: 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S or 2R)-2-methyl-1-piperidiny]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one (E21)

Enantiomer 2 (Rt. = 23.26 min) in 4.6 mg yield as white solid.

Example 22: 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S or 2R)-2-methyl-1-piperidiny]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one hydrochloride (E22)

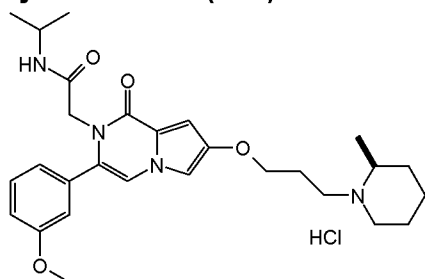


To a solution of 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S or 2R)-2-methyl-1-piperidiny]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one (4.8 mg, Enantiomer 1, E20) in DCM (0.5 mL) was added HCl (11 µL, 1M in Et₂O), the solvent was evaporated under vacuum and the residue triturated with Et₂O to give 5 mg of the title compound as white solid.

¹H-NMR (500 MHz, acetone-d₆) δ:12.57-12.09 (m, 1H); 7.40 (t, 1H); 7.34-7.28 (m, 1H); 7.18-7.12 (m, 2H); 7.13-6.99 (m, 3H); 6.87 (s, 1H); 4.35 (s, 2H); 4.06-3.89 (m, 1H); 3.85 (s, 3H); 3.49-3.38 (m, 1H); 3.31-2.98 (m, 3H); 2.97-2.84 (m, 1H); 2.76-2.67 (m, 2H); 2.32-1.48 (m, 10H); 1.48 (d, 3H); 1.09 (d, 6H).

MS (m/z): 492 [MH]⁺

Example 23: 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S or 2R)-2-methyl-1-piperidiny]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one hydrochloride (E23)



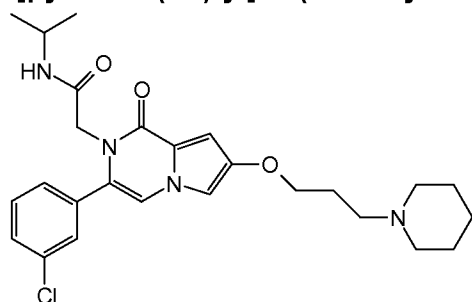
To a solution of 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S or 2R)-2-methyl-1-piperidiny]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one (4.6 mg, Enantiomer 2, E21) in DCM (0.5 mL) was added HCl (10.3 μ L, 1M in Et₂O), the solvent was evaporated under vacuum and the residue triturated with Et₂O to give 4.6 mg of the title compound as white solid.

¹H-NMR (500 MHz, acetone-d₆): δ 12.57-12.09 (m, 1H); 7.40 (t, 1H); 7.34-7.28 (m, 1H); 7.18-7.12 (m, 2H); 7.13-6.99 (m, 3H); 6.87 (s, 1H); 4.35 (s, 2H); 4.06-3.89 (m, 1H); 3.85 (s, 3H); 3.49-3.38 (m, 1H); 3.31-2.98 (m, 3H); 2.97-2.84 (m, 1H); 2.76-2.67 (m, 2H); 2.32-1.48 (m, 10H); 1.48 (d, 3H); 1.09

(d, 6H).

MS (m/z): 492 [MH]⁺

Example 24: 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E24)

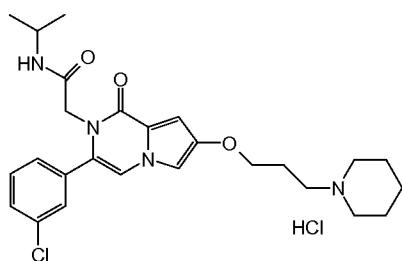


The title compound was prepared with an analogous procedure to that described in Example 15 in 35 mg yield from 3-[3-(methyloxy)phenyl]-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-1(2H)-one (300 mg, P39)

¹H NMR (400 MHz, CDCl₃): δ 7.46-7.38 (m, 4 H) 6.87 (s, 1 H) 6.78 (m, 2 H) 6.04 (d, 1 H) 4.23 (s, 2 H) 4.07 – 4.00 (m, 3 H) 2.852 - 2.40 (m, 6 H) 2.03 – 1.96 (m, 2 H) 1.65 - 1.60 (m, 4 H) 1.49 - 1.45 (m, 2 H) 1.14 (d, 6 H).

MS (m/z): 485 [MH]⁺.

Example 25: 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E25)

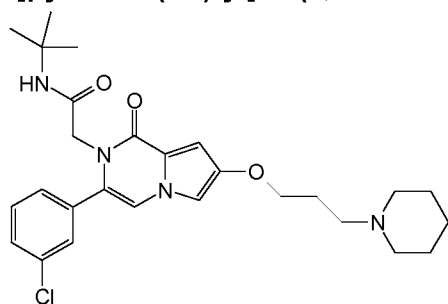


The title compound was prepared with an analogous procedure to that described in Example 2 in 35 mg yield as a white solid from 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (35 mg, E24).

¹H NMR (500 MHz, DMSO-d₆): δ 9.41 (s, 1 H) 7.80 (d, 1 H) 7.55 - 7.59 (m, 1 H) 7.48 - 7.53 (m, 2 H) 7.39 - 7.44 (m, 1 H) 7.29 (s, 1 H) 7.14 - 7.18 (m, 1 H) 6.60 - 6.64 (m, 1 H) 4.23 (s, 2 H) 4.05 (t, 2 H) 3.67 - 3.81 (m, 1 H) 3.42 - 3.54 (m, 2 H) 3.10 - 3.25 (m, 2 H) 2.80 - 2.98 (m, 2 H) 2.03 - 2.21 (m, 2 H) 1.56 - 1.89 (m, 5 H) 1.33 - 1.49 (m, 1 H) 0.98 (d, 6 H).

MS (m/z): 485 [MH]⁺.

Example 26: 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1,1-dimethylethyl)acetamide (E26)

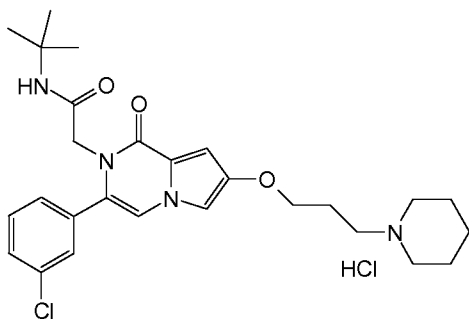


The title compound was prepared with an analogous procedure to that described in Example 15 in 62 mg yield as a yellow oil from 3-(3-chlorophenyl)-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-1(2H)-one (300 mg, P39).

¹H NMR (400 MHz, CDCl₃): δ 1.33 (s, 9H), 1.41-1.50 (m, 2H), 1.55-1.65 (m, 4H), 1.94-2.03 (m, 2H), 2.34-2.53 (m, 6H), 4.02 (t, 2H), 4.28 (s, 2H), 5.86 (s, 1H), 6.77-6.80 (m, 2H), 6.81 (s, 1H), 7.33-7.49 (m, 4H).

MS (m/z): 499 [MH]⁺.

Example 27: 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1,1-dimethylethyl)acetamide hydrochloride (E27)

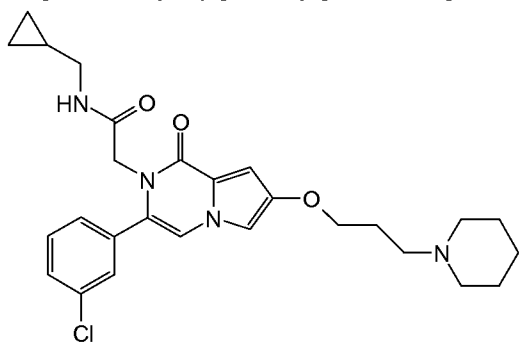


The title compound was prepared with an analogous procedure to that described in Example 5 in 64 mg yield from 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1,1-dimethylethyl)acetamide (62 mg, E26).

¹H NMR (500 MHz, DMSO-d₆): δ 1.16 (s, 9H), 1.30-2.24 (m, 8H), 2.71-3.65 (m, 6H), 3.94-4.07 (m, 2H), 4.22 (s, 2H), 6.59 (s, 1H), 7.13 (d, 1H), 7.26 (s, 1H), 7.39 (dt, 1H), 7.44-7.59 (m, 4H), 9.30 (br s, 1H).

MS (m/z): 499 [MH]⁺.

Example 28: 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(cyclopropylmethyl)acetamide (E28)

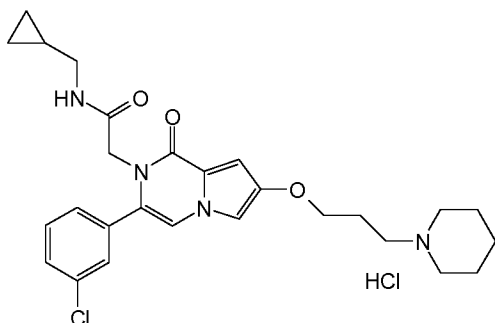


The title compound was prepared with an analogous procedure to that described in Example 15 in 68 mg yield as a yellow oil from 3-(3-chlorophenyl)-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-1(2H)-one (300 mg, P39).

¹H NMR (400 MHz, CDCl₃): δ 0.16-0.23 (m, 2H), 0.45-0.53 (m, 2H), 0.88-1.01 (m, 1H), 1.39-1.50 (m, 2H), 1.54-1.65 (m, 4H), 1.94-2.03 (m, 2H), 2.32-2.52 (m, 6H), 3.07-3.14 (dd, 2H), 4.02 (t, 2H), 4.36 (s, 2H), 6.32 (br t, 1H), 6.76-6.80 (m, 2H), 6.82 (s, 1H), 7.37-7.49 (m, 4H).

MS (m/z): 497 [MH]⁺.

Example 29: 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(cyclopropylmethyl)acetamide hydrochloride (E29)

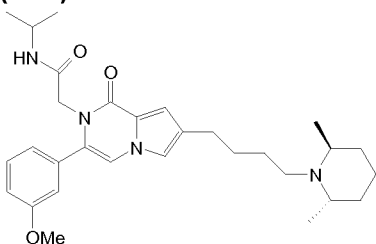


The title compound was prepared with an analogous procedure to that described in Example 5 in 63 mg yield from 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(cyclopropylmethyl)acetamide (63 mg, E28).

¹H NMR (500 MHz, DMSO-d₆): δ 0.06-0.12 (m, 2H), 0.33-0.40 (m, 2H), 0.71-0.88 (m, 1H), 1.30-2.20 (m, 8H), 2.88 (t, 2H), 3.05-3.31 (m, 6H), 4.02 (t, 2H), 4.25 (s, 2H), 6.60 (s, 1H), 7.14 (d, 1H), 7.28 (s, 1H), 7.39-7.58 (m, 4H), 8.02 (t, 1H), 9.29 (br s, 1H).

MS (m/z): 497 [MH]⁺.

Example 30: 2-[7-{4-[meso-2,6-dimethyl-1-piperidiny]butyl}-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E30)



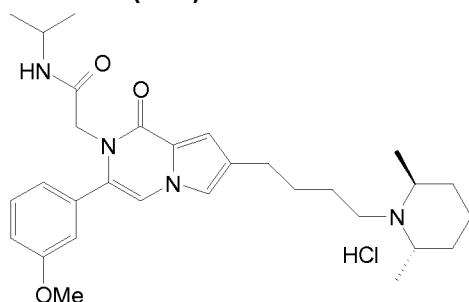
A stirring suspension of 4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl}butyl methanesulfonate (145 mg, P28), 2,6-dimethylpiperidine (120 μL) and potassium carbonate (205 mg) in acetonitrile (3 mL) was heated at 80 °C for 40 h. The reaction mixture was diluted with EtOAc and washed with chilly water and brine. The organic phase was dried over Na₂SO₄ anhydrous, filtered and evaporated under reduced pressure. To a solution of the obtained crude in DMF (2.5 mL) potassium carbonate (62 mg) and 2,6-dimethylpiperidine (40 μL) were added. The resultant mixture was stirred at 100 °C for 3 h, then cooled down, diluted with EtOAc and washed with chilly water and brine. The organic phase was dried over Na₂SO₄ anhydrous, filtered and evaporated under reduced pressure. The obtained crude material (98 mg) was purified by silica gel flash column chromatography with a gradient of DCM/[DCM:MeOH:NH₃ (2.0M solution in MeOH) = 90:9:1] (from 100% to 0% of DCM) as eluent to yield the title compound (42 mg) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 1.11-1.17 (m, 12H), 1.30-1.39 (m, 2H), 1.44-1.62 (m, 6H), 1.64-1.71 (m, 2H), 2.45-2.56 (m, 2H), 2.63 (t, 2H), 2.78-2.87 (m, 2H), 3.84 (s, 3H), 4.00-

4.10 (m, 1H), 4.33 (s, 2H), 5.99 (d, 1H), 6.88 (s, 1H), 6.94 (s, 1H), 6.96-7.04 (m, 4H), 7.35 (t, 1H).

MS (m/z): 507 [MH]⁺.

5 **Example 31: 2-[7-{4-[Meso -2,6-dimethyl-1-piperidiny]butyl}-3-[3-(methoxy)-phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E31)**

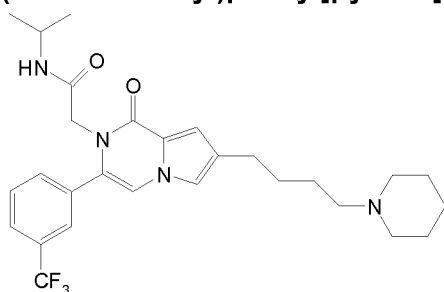


10 The title compound was prepared with an analogous procedure to that described in Example 5 in 32 mg yield as a white solid from 2-[7-{4-[meso-2,6-dimethyl-1-piperidiny]butyl}-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (42 mg, E30).

¹H NMR (500 MHz, DMSO-d₆): δ 0.97 (d, 6H), 1.16-1.32 (m, 6H), 1.40-1.89 (m, 10H), 2.61 (t, 2H), 2.89-3.34 (m, 4H), 3.70-3.81 (m, 1H), 3.76 (s, 3H), 4.19 (s, 2H), 6.80 (s, 1H), 6.95-7.07 (m, 3H), 7.23-7.30 (m, 2H), 7.37 (t, 1H), 7.74 (d, 1H), 9.10 (br s, 1H).

MS (m/z): 507 [MH]⁺.

Example 32: N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidiny)butyl]-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E30)

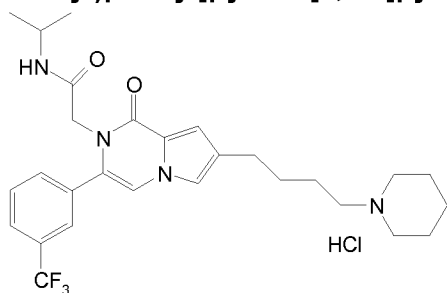


20 The title compound was prepared with an analogous procedure to that described in Example 11 in 30 mg yield as a white solid from 4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-1-oxo-3-[3-(trifluoromethyl)phenyl]-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl}butyl methanesulfonate (92 mg, P45).

25 **¹H NMR (400 MHz, CDCl₃):** δ 1.14 (d, 6H), 1.40-1.48 (m, 2H), 1.52-1.68 (m, 8H), 2.31-2.45 (m, 6H), 2.62 (t, 2H), 3.98-4.08 (m, 1H), 4.28 (s, 2H), 6.03 (br d, 1H), 6.87 (s, 1H), 6.95 (s, 1H), 7.01 (s, 1H), 7.56-7.64 (m, 1H), 7.68-7.78 (m, 3H).

MS (m/z): 517 [MH]⁺.

Example 33: N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidiny)butyl]-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E33)

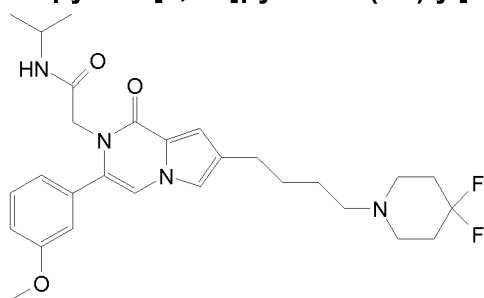


The title compound was prepared with an analogous procedure to that described in Example 5 in 26 mg yield from N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidiny)butyl]-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (30 mg, E32).

¹H NMR (400 MHz, DMSO-d₆): δ 0.95 (d, 6H), 1.32-1.82 (m, 10H), 2.56-3.05 (m, 8H), 3.66-3.77 (m, 1H), 4.22 (s, 2H), 6.85 (s, 1H), 7.27 (s, 1H), 7.38 (s, 1H), 7.68-7.81 (m, 4H), 7.87 (d, 1H), 9.12-9.42 (br s, 1H).

MS (m/z): 517 [MH]⁺.

Example 34: 2-[7-[4-(4,4-difluoro-1-piperidiny)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E34)

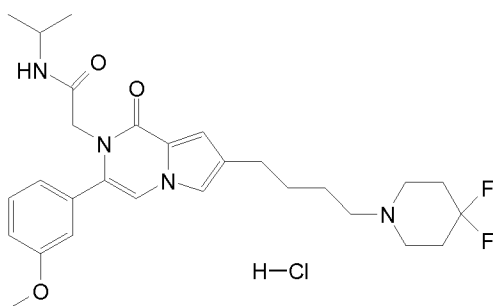


The title compound was prepared with an analogous procedure to that described in Example 11 in 34 mg yield as a white solid from 4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl}butyl methanesulfonate (110 mg, P28) and 4,4-difluoropiperidine (106 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.35 (t, 1H); 7.03-6.97 (m, 4H); 6.95 (s, 1H); 6.88 (s, 1H); 5.95 (d, 1H); 4.33 (s, 2H); 4.1-4.01 (m, 1H); 3.84 (s, 3H); 2.67-2.60 (m, 2H); 2.59-2.49 (m, 4H); 2.45-2.38 (m, 2H); 2.07-1.93 (m, 4H); 1.69-1.51 (m, 4H); 1.16-1.14 (d, 6H).

MS (m/z): 515 [MH]⁺.

Example 35: 2-[7-[4-(4,4-difluoro-1-piperidiny)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E35)

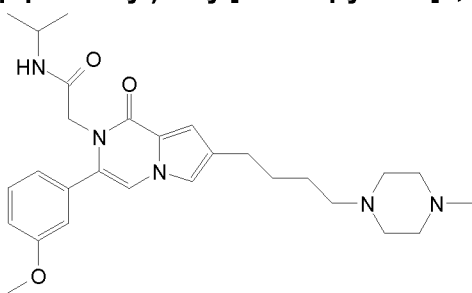


The title compound was prepared with an analogous procedure to that described in Example 5 in 32 mg yield from 2-[7-[4-(4,4-difluoro-1-piperidinyl)butyl]-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (35 mg, E34).

¹H NMR (500 MHz, DMSO-d₆): δ 10.14 (br. s., 1 H) 7.77 (d, 1 H) 7.38 (t, 1 H) 7.22 - 7.31 (m, 2 H) 6.94 - 7.10 (m, 3 H) 6.77 - 6.86 (m, 1 H) 4.20 (s, 2 H) 3.68 - 3.86 (m, 4 H) 3.51 - 3.67 (m, 2 H) 3.03 - 3.25 (m, 4 H) 2.55 - 2.66 (m, 2 H) 1.80 - 2.20 (m, 4 H) 1.53 - 1.75 (m, 4 H) 0.98 (d, 6 H).

MS (m/z): 515 [MH]⁺.

Example 36: *N*-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-7-[4-(4-methyl-1-piperazinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E36)

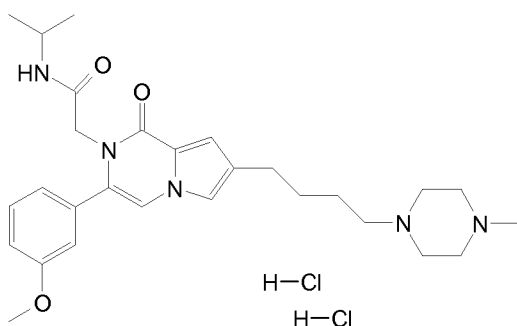


The title compound was prepared with an analogous procedure to that described in Example 11 in 43 mg yield as a white solid from 4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methoxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl}butyl methanesulfonate (90 mg, P28) and 1-methylpiperazine (55 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.35 (t, 1H); 7.04-6.97 (m, 4H); 6.94 (s, 1H); 6.88 (s, 1H); 5.95 (d, 1H); 4.32 (s, 2H); 4.1-4.01 (m, 1H); 3.84 (s, 3H); 2.72-2.36 (m, 12H); 2.31 (s, 3H); 1.71-1.51 (m, 4H); 1.16-1.14 (d, 6H).

MS (m/z): 494 [MH]⁺.

Example 37: *N*-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-7-[4-(4-methyl-1-piperazinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide dihydrochloride (E37)

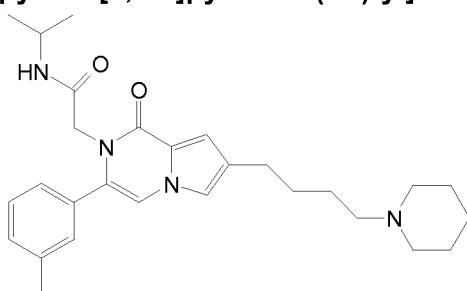


N-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-7-[4-(4-methyl-1-piperazinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (43 mg, E36) was dissolved in DCM (2 mL) and hydrogen chloride (1.25 M solution in MeOH) (69 μ L) was added. The solvent was evaporated and the residue thus obtained triturated with dry diethyl ether. Then diethyl ether was removed and the resultant solid dried under vacuum to provide the title compound (47 mg) as a white solid.

^1H NMR (500 MHz, DMSO- d_6): δ 10.04 - 12.33 (m, 2 H) 7.77 (d, 1 H) 7.38 (t, 1 H) 7.28 (s, 2 H) 6.95 - 7.11 (m, 3 H) 6.78 - 6.85 (m, 1 H) 4.21 (s, 2 H) 3.69 - 3.82 (m, 4 H) 3.17 - 3.50 (m, 10 H) 2.72 - 2.86 (m, 3 H) 2.56 - 2.65 (m, 2 H) 1.56 - 1.75 (m, 4 H) 0.98 (d, 6 H).

MS (m/z): 494 $[\text{MH}]^+$.

Example 38: N-(1-methylethyl)-2-[3-(3-methylphenyl)-1-oxo-7-[4-(1-piperidinyl)butyl]-pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E38)

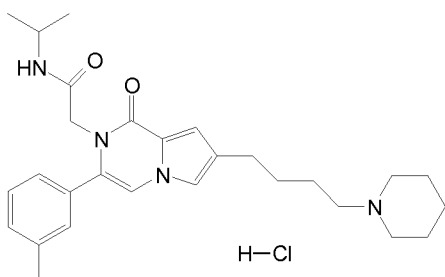


The title compound was prepared with an analogous procedure to that described in Example 19 in 30 mg yield as a white solid from 2-[7-(4-hydroxybutyl)-3-(3-methylphenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (70 mg, P50) and piperidine (85 mg).

^1H NMR (400 MHz, CDCl_3): δ 7.20-7.38 (m, 3H) 7.00 (s, 1H) 6.90 (s, 1H) 6.85 (1H) 5.95 (m, 1H) 4.30 (s, 2H) 4.05 (m, 1H) 2.64 (m, 2H) 2.29-2.43 (m, 9H) 1.40-1.70 (m, 10H) 1.18 (m, 6H).

MS (m/z): 463 $[\text{MH}]^+$.

Example 39: N-(1-methylethyl)-2-[3-(3-methylphenyl)-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E37)

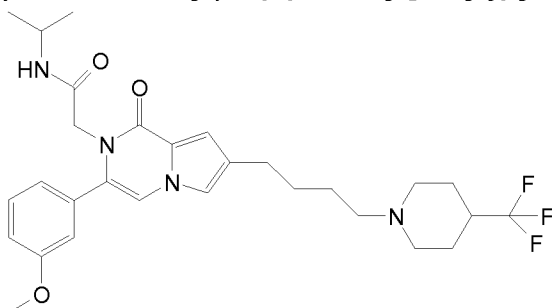


The title compound was prepared with an analogous procedure to that described in Example 2 in 30 mg yield from *N*-(1-methylethyl)-2-[3-(3-methylphenyl)-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1*H*)-yl]acetamide (30 mg, E38).

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.43 (br. s., 1 H) 7.75 (d, 1 H) 7.15 - 7.45 (m, 6 H) 6.76 - 6.86 (m, 1 H) 4.20 (s, 2 H) 3.69 - 3.81 (m, 1 H) 3.36 - 3.46 (m, 2 H) 2.99 - 3.09 (m, 2 H) 2.77 - 2.90 (m, 2 H) 2.61 (t, 2 H) 2.32 - 2.37 (m, 3 H) 1.75 - 1.86 (m, 2 H) 1.57 - 1.75 (m, 7 H) 1.31 - 1.45 (m, 1 H) 0.98 (d, 6 H).

MS (m/z): 463 [MH]⁺.

Example 40: *N*-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{4-[4-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1*H*)-yl]acetamide (E40)

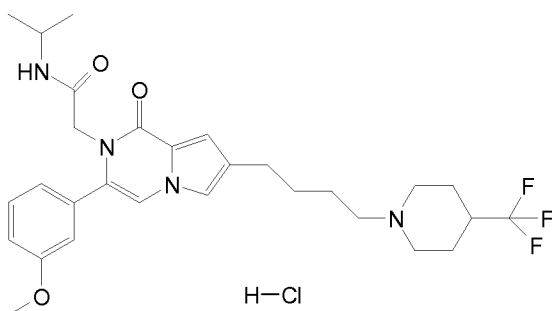


The title compound was prepared with an analogous procedure to that described in Example 11 in 34 mg yield as a white solid from 4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl}butyl methanesulfonate (85 mg, P28) and 4-(trifluoromethyl)piperidine hydrochloride (33 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.35 (t, 1H); 7.04-6.97 (m, 4H); 6.95 (s, 1H); 6.88 (s, 1H); 5.95 (d, 1H); 4.33 (s, 2H); 4.1-4.01 (m, 1H); 3.84 (s, 3H); 2.98-3.06 (m, 1H); 2.63 (t, 2H); 2.36 (t, 2H); 2.07-1.80 (m, 6H); 1.73-1.51 (m, 6H); 1.16-1.14 (d, 6H).

MS (m/z): 547 [MH]⁺.

Example 41: *N*-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{4-[4-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1*H*)-yl]acetamide hydrochloride (E41)

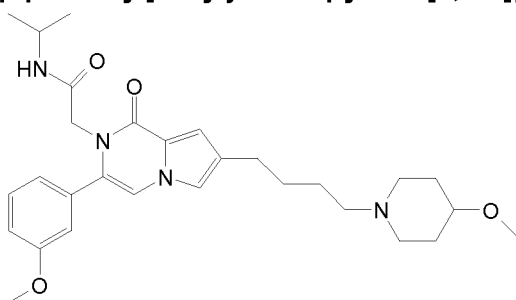


The title compound was prepared with an analogous procedure to that described in Example 5 in 35 mg yield from *N*-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-1-oxo-7-{4-[4-(trifluoromethyl)-1-piperidiny]butyl}pyrrolo[1,2-a]pyrazin-2(1*H*)-yl]acetamide (34 mg, E40).

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.54 (br. s., 1 H) 7.77 (d, 1 H) 7.40 (t, 1 H) 7.25 - 7.31 (m, 2 H) 6.94 - 7.12 (m, 3 H) 6.78 - 6.88 (m, 1 H) 4.21 (s, 2 H) 3.70 - 3.87 (m, 4 H) 3.46 - 3.67 (m, 2 H) 2.77 - 3.18 (m, 4 H) 2.57 - 2.66 (m, 2 H) 1.87 - 2.16 (m, 3 H) 1.54 - 1.87 (m, 6 H) 0.98 (d, 6 H).

MS (m/z): 547 [MH]⁺.

Example 42: *N*-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-7-{4-[4-(methoxy)-1-piperidiny]butyl}-1-oxopyrrolo[1,2-a]pyrazin-2(1*H*)-yl]acetamide (E42)

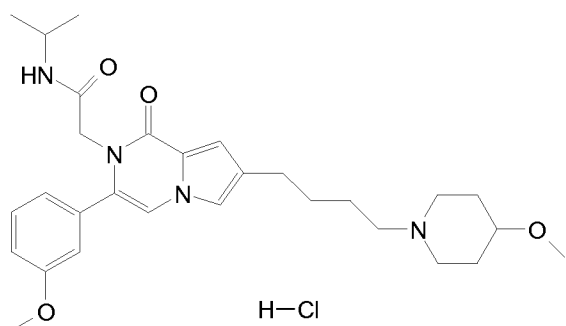


The title compound was prepared with an analogous procedure to that described in Example 19 in 21 mg yield as a white solid from 2-[7-(4-hydroxybutyl)-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide (70 mg, P27) and 4-(methoxy)piperidine (60.5 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.37 (t, 1H); 7.03-6.98 (m, 4H); 6.96 (s, 1H); 6.89 (s, 1H); 5.95 (m, 1H); 4.33 (s, 2H); 4.12-4.01 (m, 1H); 3.85 (s, 3H); 3.35 (s, 3H); 3.33-3.23 (m, 1H); 2.86-2.75 (m, 2H); 2.68-2.60 (m, 2H); 2.50-2.38 (m, 2H); 2.07-1.93 (m, 2H); 1.75-1.56 (m, 8H); 1.17-1.15 (d, 6H).

MS (m/z): 509 [MH]⁺.

Example 43: *N*-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-7-{4-[4-(methoxy)-1-piperidiny]butyl}-1-oxopyrrolo[1,2-a]pyrazin-2(1*H*)-yl]acetamide hydrochloride (E43)

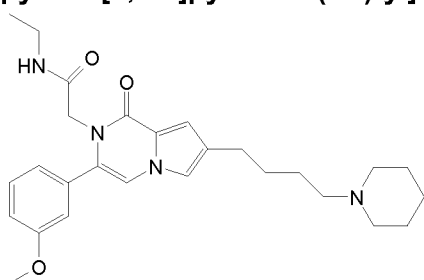


The title compound was prepared with an analogous procedure to that described in Example 2 in 21 mg yield from N-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-7-{4-[4-(methoxy)-1-piperidinyl]butyl}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (22 mg, E42).

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.34 (s, 1 H) 7.75 (d, 1 H) 7.37 (t, 1 H) 7.24 - 7.30 (m, 2 H) 6.95 - 7.07 (m, 3 H) 6.81 (s, 1 H) 4.20 (s, 2 H) 3.76 (s, 3 H) 3.69 - 3.78 (m, 1 H) 3.42 - 3.56 (m, 3 H) 3.25 (s, 3 H) 2.85 - 3.12 (m, 4 H) 2.60 (t, 2 H) 1.75 - 2.16 (m, 3 H) 1.47 - 1.71 (m, 5 H) 0.97 (d, 6 H)

MS (m/z): 509 [MH]⁺.

Example 44: N-ethyl-2-[3-[3-(methoxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]-pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E44)

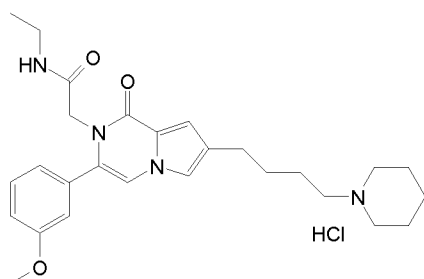


The title compound was prepared with an analogous procedure to that described in Example 15 in 45 mg yield as a white solid from 3-(3-methoxyphenyl)-7-(3-(piperidin-1-yl)propoxy)pyrrolo[1,2-a]pyrazin-1(2H)-one (200 mg, P34).

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.33 (m, 1 H) 7.04-6.97 (m, 3 H) 6.85 (s, 1 H) 6.80 (m, 2 H) 6.23-6.15 (m, 1 H) 4.36 (s, 1 H) 4.07-4.00 (m, 2 H) 3.85 (s, 3 H) 3.25-3.36 (m, 2 H) 2.54 - 2.37 (m, 6 H) 2.06 - 1.93 (m, 2 H) 1.66 - 1.56 (m, 6 H) 1.51 - 1.42 (m, 2 H) 1.15 (t, 3 H).

MS (m/z): 467 [MH]⁺.

Example 45: N-ethyl-2-[3-[3-(methoxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]-pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E45)



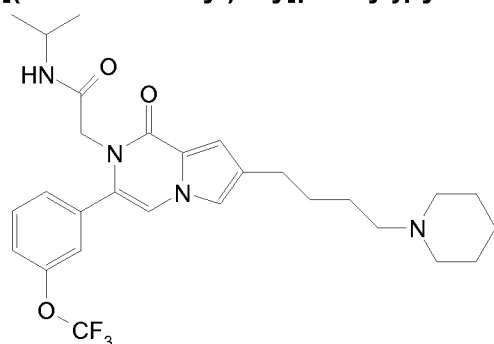
The title compound was prepared with an analogous procedure to that described in Example 2 in 48 mg yield from N-ethyl-2-[3-[3-(methoxy)phenyl]-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (45 mg, E44).

- 5 **¹H NMR (400 MHz, DMSO-d₆):** δ 7.77 (d, 1 H) 7.38 (t, 1 H) 7.28 (s, 2 H) 6.95 - 7.11 (m, 3 H) 6.78 - 6.85 (m, 1 H) 4.31-4.10 (m, 2 H) 4.10-3.96 (m, 2 H) 3.75 (s, 3 H) 3.50 - 3.40 (m, 2 H) 3.20-3.15 (m, 2 H) 3.10-2.96 (m, 2 H) 2.96 - 2.73 (m, 2 H) 2.28 - 2.01 (m, 2 H) 1.99 - 1.55 (m, 5 H) 1.47-1.29 (m, 1 H) 0.95 (t, 3 H).

MS (m/z): 466 [MH]⁺.

10

Example 46: *N*-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidinyl)butyl]-3-{3-[(trifluoromethyl)oxy]phenyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E46)



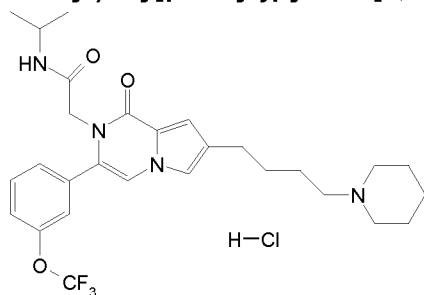
The title compound was prepared with an analogous procedure to that described in Example 19 in 29 mg yield as a white solid from (70 mg, P55) and piperidine (38 mg).

- 15 **¹H NMR (400 MHz, CDCl₃):** δ 7.3-7.5 (m, 4H) 7.00 (s, 1H), 6.95 (s, 1H) 6.89 (s, 1H) 5.98 (m, 1H) 4.30 (s, 2H) 4.05 (m, 1H) 2.65 (m, 2H) 2.29-2.51 (m, 6H) 1.50-1.70 (m, 8H) 1.39-4.9 (m, 2H) 1.15 (m, 6H).

MS (m/z): 533 [MH]⁺.

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Example 47: *N*-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidinyl)butyl]-3-{3-[(trifluoromethyl)oxy]phenyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E47)

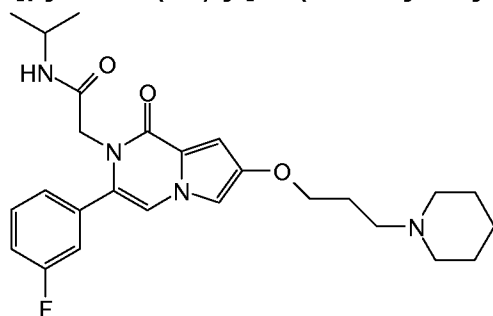


The title compound was prepared with an analogous procedure to that described in Example 2 in 28 mg yield from N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidinyl)butyl]-3-{3-[(trifluoromethyl)oxy]phenyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (29 mg, E46).

¹H NMR (500 MHz, DMSO-d₆): δ 9.42 (br. s., 1 H) 7.79 (d, 1 H) 7.61 (t, 1 H) 7.49 (t, 2 H) 7.42 - 7.45 (m, 1 H) 7.33 - 7.36 (m, 1 H) 7.25 - 7.29 (m, 1 H) 6.82 - 6.85 (m, 1 H) 4.22 (s, 2 H) 3.67 - 3.78 (m, 1 H) 3.39 (d, 2 H) 2.98 - 3.06 (m, 2 H) 2.75 - 2.87 (m, 2 H) 2.60 (t, 2 H) 1.74 - 1.83 (m, 2 H) 1.56 - 1.73 (m, 7 H) 1.31 - 1.42 (m, 1 H) 0.95 (d, 6 H).

MS (m/z): 533 [MH]⁺.

Example 48: 2-[3-(3-fluorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E48)

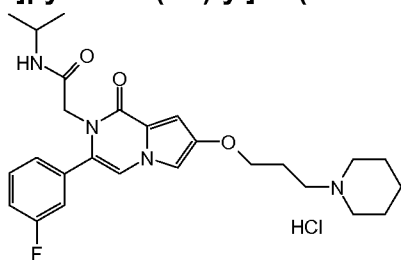


The title compound was prepared with an analogous procedure to that described in Example 19 in 12 mg yield from 2-[3-(3-fluorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (40 mg, P60) and piperidine (22 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.54-7.42 (m, 1 H) 7.27-7.15 (m, 2 H) 6.84 - 6.77 (m, 3 H) 5.86 (m, 1 H) 4.32 (s, 2 H) 4.10 - 4.02 (m, 3 H) 2.90 - 2.65 (m, 4 H) 2.25 - 2.15 (m, 2 H) 1.90 - 1.78 (m, 5 H) 1.75 - 1.50 (m, 3 H) 1.16 (d, 6 H).

MS (m/z): 469 [MH]⁺.

Example 49: 2-[3-(3-fluorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E49)



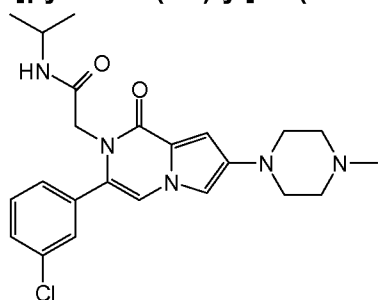
The title compound was prepared with an analogous procedure to that described in Example 2 in 12 mg yield as a white solid from 2-[3-(3-fluorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (12 mg, E48).

¹H NMR (500 MHz, DMSO-d₆): δ 9.51 (br. s., 1 H) 7.77 (d, 1 H) 7.51 (q, 1 H) 7.34 (t, 1 H) 7.25 - 7.30 (m, 3 H) 7.12 - 7.17 (m, 1 H) 6.59 - 6.64 (m, 1 H) 4.24 (s, 2 H) 4.04 (t, 2 H)

3.68 - 3.79 (m, 1 H) 3.41 - 3.51 (m, 2 H) 3.17 (br. s., 2 H) 2.82 - 2.95 (m, 2 H) 2.10 - 2.18 (m, 2 H) 1.76 - 1.86 (m, 2 H) 1.62 - 1.75 (m, 3 H) 1.32 - 1.44 (m, 1 H) 0.95 (d, 6 H).

MS (m/z): 469 [MH]⁺.

5 **Example 50: 2-[3-(3-chlorophenyl)-7-(4-methyl-1-piperazinyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E50)**



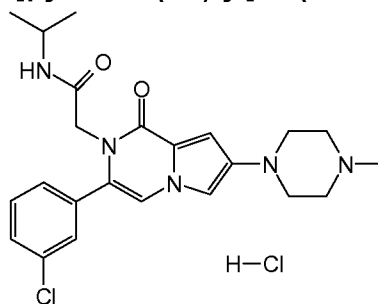
To a solution of 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (45 mg, prepared with an analogous procedure to that described in P63), potassium carbonate (26 mg), copper iodide (27 mg) and LD-proline (16 mg) in DMSO (1 mL) N-methylpiperidine (29 mg) was added and the mixture stirred at 80 °C for 18h. The reaction mixture was loaded on a SCX column, washed with methanol and the desired product eluted with NH₃ 1M in MeOH. The solvent was evaporated and the crude obtained purified by flash chromatography (eluent DCM:MeOH = 9:1) to give the title compound (7 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.46-7.36 (m, 4H); 6.84 (s, 1H); 6.79 (m, 1H); 6.68 (m, 1H); 5.95 (broad s, 1H); 4.31 (s, 2H); 4.1-4.01 (m, 1H); 3.12 (m, 4H); 2.61 (m, 4H); 2.38 (s, 3H); 1.17-1.15 (d, 6H) .

MS (m/z): 442 [MH]⁺.

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Example 51: 2-[3-(3-chlorophenyl)-7-(4-methyl-1-piperazinyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E51)



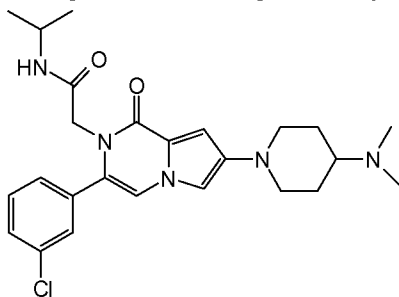
The title compound was prepared with an analogous procedure to that described in Example 2 in 6.4 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-(4-methyl-1-piperazinyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (6.7 mg, E50).

¹H NMR (500 MHz, DMSO-d₆): δ 10.08 (br. s., 1 H) 7.78 (d, 1 H) 7.57 (m, 1 H) 7.52 (m, 2 H) 7.39 (d, 1 H) 7.28 (s, 1 H) 7.07 (s, 1 H) 6.68 (s, 1 H) 4.2 (br. s., 2 H) 3.73 (m, 1 H) 2.88-3.69 (m, 6 H) 2.8 (s, 3 H) 0.96 (d, 6 H).

MS (m/z): 442 [MH]⁺.

5

Example 52: 2-[3-(3-chlorophenyl)-7-[4-(dimethylamino)-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E52)



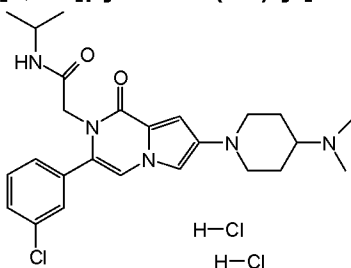
The title compound was prepared with an analogous procedure to that described in Example 50 in 18.5 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (100 mg, P63) and N,N-dimethyl-4-piperidine (82 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.45-7.37 (m, 4H); 6.83 (s, 1H); 6.79 (m, 1H); 6.68 (m, 1H); 5.93 (m, 1H); 4.31 (s, 2H); 4.1-4.01 (m, 1H); 3.59-3.53 (m, 2H); 2.69-2.63 (m, 2H); 2.34 (s, 6H); 2.30-2.27 (m, 1H); 1.92-1.80 (m, 2H); 1.75-1.65 (m, 2H); 1.17-1.15 (d, 6H).

15

MS (m/z): 470 [MH]⁺.

Example 53: 2-[3-(3-chlorophenyl)-7-[4-(dimethylamino)-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide dihydrochloride (E53)



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2-[3-(3-chlorophenyl)-7-[4-(dimethylamino)-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (18.5 mg, E52) was dissolved in DCM (2 mL) and hydrogen chloride (1 M solution in Et₂O) (86 μL) was added. The solvent was evaporated and the residue thus obtained triturated with dry diethyl ether. Then diethyl ether was removed and the resultant solid dried under vacuum to provide the title compound (21 mg) as a white solid.

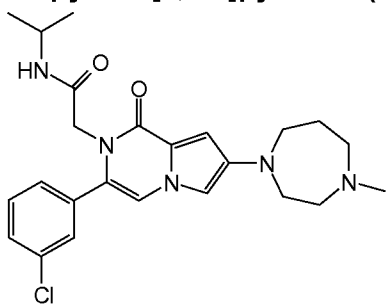
25

¹H NMR (400 MHz, DMSO-d₆): δ 10.20 (br. s., 1 H) 7.77 (d, 1 H) 7.53 - 7.58 (m, 1 H) 7.45 - 7.52 (m, 2 H) 7.39 (d, 1 H) 7.24 (s, 1 H) 7.05 (s, 1 H) 6.67 (s, 1 H) 4.21 (br. s., 2 H) 3.70 - 3.81 (m, 1 H) 3.63 - 3.69 (m, 2 H) 3.22 - 3.33 (m, 1 H) 2.74 (d, 6 H) 2.59 - 2.69 (m, 2 H) 2.02 - 2.12 (m, 2 H) 1.73 - 1.86 (m, 2 H) 0.97 (d, 6 H).

30

MS (m/z): 470 [MH]⁺.

Example 54: 2-[3-(3-chlorophenyl)-7-(4-methylhexahydro-1H-1,4-diazepin-1-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E54)

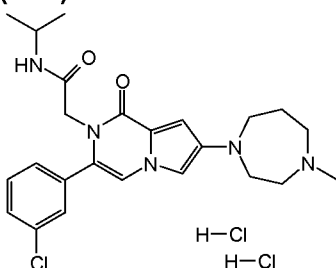


The title compound was prepared with an analogous procedure to that described in Example 50 in 6 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (100 mg, P63) and 1-methylhexahydro-1H-1,4-diazepine (73 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.45-7.37 (m, 4H); 6.82 (s, 1H); 6.61 (m, 1H); 6.65 (m, 1H); 5.98 (m, 1H); 4.32 (s, 2H); 4.08-4.01 (m, 1H); 3.52-3.48 (m, 2H); 3.41-3.38 (t, 2H); 2.83-2.75 (m, 2H); 2.72-2.63 (m, 2H); 2.44 (bs, 3H); 2.10-2.02 (m, 2H); 1.17-1.15 (d, 6H)..

MS (m/z): 456 [MH]⁺.

Example 55: 2-[3-(3-chlorophenyl)-7-(4-methylhexahydro-1H-1,4-diazepin-1-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide dihydrochloride (E55)

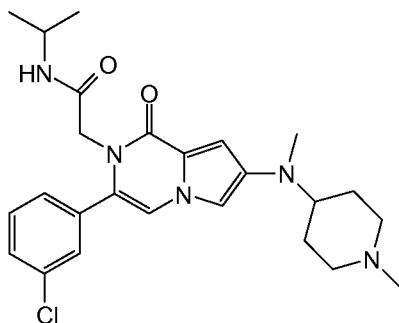


The title compound was prepared with an analogous procedure to that described in Example 53 in 7 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-(4-methylhexahydro-1H-1,4-diazepin-1-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (6 mg, E54).

¹H NMR (500 MHz, DMSO-d₆): δ 10.19 (br. s., 2 H) 7.76 (d, 1 H) 7.51 - 7.59 (m, 1 H) 7.44 - 7.51 (m, 2 H) 7.35 - 7.42 (m, 1 H) 7.21 (s, 1 H) 6.90 (d, 1 H) 6.55 (s, 1 H) 4.22 (br. s., 2 H) 3.71 - 3.78 (m, 1 H) 3.50 - 3.70 (m, 2 H) 3.27 - 3.49 (m, 4 H) 3.06 - 3.26 (m, 2 H) 2.81 (d, 3 H) 2.05 - 2.22 (m, 2 H) 0.96 (d, 6 H).

MS (m/z): 456 [MH]⁺.

Example 56: 2-[3-(3-chlorophenyl)-7-[methyl(1-methyl-4-piperidinyl)amino]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E56)

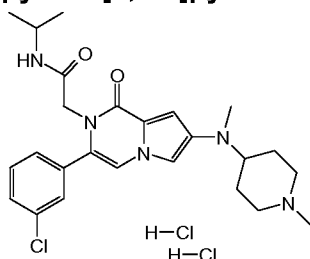


The title compound was prepared with an analogous procedure to that described in Example 50 in 5 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (100 mg, P63) and N,1-dimethyl-4-piperidinamine (82 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.46-7.36 (m, 4H); 6.84 (s, 1H); 6.79 (m, 1H); 6.68 (m, 1H); 5.95 (broad s, 1H); 4.32 (s, 2H); 4.1-4.01 (m, 1H); 3.43-3.33 (m, 1H); 3.22-3.10 (m, 2H); 2.72 (s, 3H); 2.52-2.42 (m, 3H); 2.37-2.20 (m, 2H); 2.10-1.95 (m, 2H); 1.88-1.77 (m, 2H); 1.17-1.15 (d, 6H).

MS (m/z): 470 [MH]⁺.

Example 57: 2-[3-(3-chlorophenyl)-7-[methyl(1-methyl-4-piperidiny)amino]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide dihydrochloride (E57)

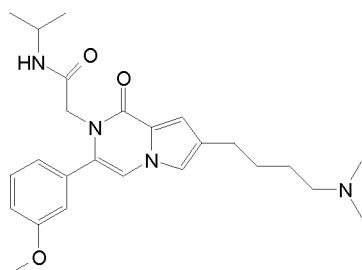


The title compound was prepared with an analogous procedure to that described in Example 53 in 5 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-[methyl(1-methyl-4-piperidiny)amino]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (5.7 mg, E56).

¹H NMR (400 MHz, DMSO-d₆): δ 10.02 (br. s., 1 H) 7.78 (d, 1 H) 7.46 - 7.59 (m, 3 H) 7.41 (m, 1 H) 7.28 (m, 1 H) 7.03 (m, 1 H) 6.7 (m, 1 H) 4.22 (br. s., 2 H) 3.6 - 3.8 (m, 3 H) 3.02 - 3.17 (m, 2 H) 2.6 - 2.8 (m, 5 H) 1.8 - 2.0 (m, 3 H) 0.96 (d, 6 H).

MS (m/z): 470 [MH]⁺.

Example 58: 2-[7-[4-(dimethylamino)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E58)

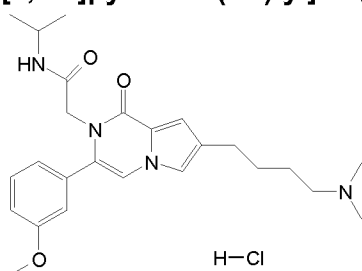


The title compound was prepared with an analogous procedure to that described in Example 11 in 10 mg yield as a white solid from 4-{2-[2-[(1-methylethyl)amino]-2-oxoethyl]-3-[3-(methyloxy)phenyl]-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl}butyl methanesulfonate (80 mg, prepared in analogy to P28) and dimethylamine (218 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.36 (t, 1 H) 7.05-7.00 (m, 4 H) 6.97 (s, 1 H) 6.89 (s, 1 H) 5.94 (m, 1 H) 4.33 (m, 2 H) 4.10-4.01 (m, 1 H) 3.85 (s, 3 H) 3.68-2.63 (m, 2 H) 2.49 - 2.40 (m, 2 H) 2.32 (m, 6 H) 1.75 - 1.59 (m, 4 H) 1.16 (m, 6 H).

MS (m/z): 439 [MH]⁺.

Example 59: 2-[7-[4-(dimethylamino)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo-[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E59)

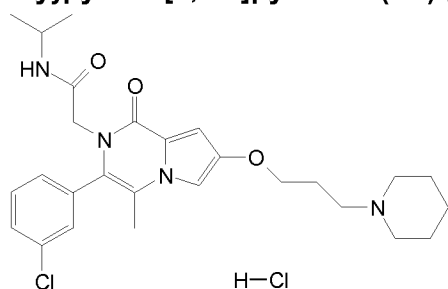


The title compound was prepared with an analogous procedure to that described in Example 2 in 9 mg yield from 2-[7-[4-(dimethylamino)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (10 mg, E58).

¹H NMR (500 MHz, DMSO-d₆): δ 9.55 (br. s., 1 H), 7.75 (d, 1 H), 7.38 (t, 1 H), 7.22 - 7.26 (m, 2 H), 6.96 - 7.09 (m, 3 H), 4.18 (m, 2 H), 3.7 - 3.8 (m, 3 H), 2.95 - 3.05 (m, 2 H), 2.65 - 2.75 (m, 6 H), 2.58 (m, 2 H), 1.55 - 1.70 (m, 4 H), 0.98 (d, 6 H).

MS (m/z): 439 [MH]⁺.

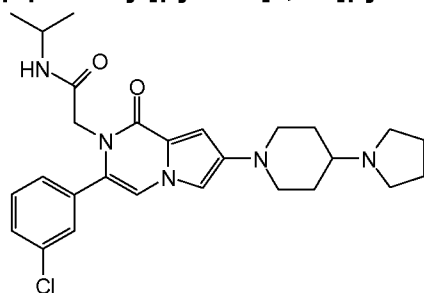
Example 60: 2-[3-(3-chlorophenyl)-4-methyl-1-oxo-7-{[3-(1-piperidinyl)propyl]-oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E60)



To a solution of 2-[3-(3-chlorophenyl)-7-hydroxy-4-methyl-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (90 mg, P67) in DMF (2 mL) potassium carbonate (133 mg) and 1-(3-chloropropyl)piperidine (58 mg) were added at rt and the mixture was heated at 100°C on. The mixture was cooled down to rt and portioned between EA and water. The organic layer was dried, filtered and concentrated under vacuum. The crude was purified by flash chromatography (eluent DCM:MeOH = 10:1) to give the title compound as free base. The free base was dissolved in DCM and hydrogen chloride (1 M solution in Et₂O) was added. The solvent was evaporated and the residue thus obtained triturated with dry diethyl ether. Then diethyl ether was removed and the resultant solid dried under vacuum to provide the title compound (36 mg) as a yellow solid.

¹H NMR (400 MHz, DMSO-d₆): δ 0.83 (6H, d), 1.35 (1H, m), 1.76 (5H, m), 1.97 (3H, s), 2.16 (2H, m), 2.85 (2H, m), 3.14 (2H, m), 3.42 (2H, m), 3.67~3.73 (1H, m), 3.98-4.24 (4H, m), 6.66 (1H, s), 7.22 (1H, s), 7.28 (1H, d), 7.37 (1H, s), 7.45-7.65 (3H, m), 10.04 (1H, br).
MS (m/z): 499 [MH]⁺.

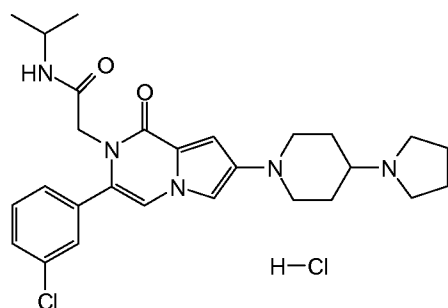
Example 61: 2-[3-(3-chlorophenyl)-1-oxo-7-[4-(1-pyrrolidinyl)-1-piperidinyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E61)



The title compound was prepared with an analogous procedure to that described in Example 50 in 13 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (50 mg, P63) and 4-(1-pyrrolidinyl)piperidine (164 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.45-7.36 (m, 4H); 6.82 (s, 1H); 6.78 (m, 1H); 6.68 (m, 1H); 5.97 (m, 1H); 4.31 (s, 2H); 4.08-4.01 (m, 1H); 3.53-3.48 (m, 2H); 2.72-2.64 (m, 6H); 2.20-2.15 (m, 1H); 2.05-1.98 (m, 2H); 1.85-1.80 (m, 4H); 1.80-1.70 (m, 2H); 1.17-1.15 (d, 6H).
MS (m/z): 497 [MH]⁺.

Example 62: 2-[3-(3-chlorophenyl)-1-oxo-7-[4-(1-pyrrolidinyl)-1-piperidinyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E62)

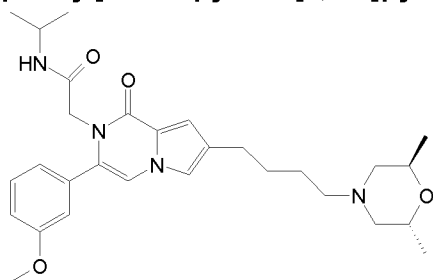


The title compound was prepared with an analogous procedure to that described in Example 2 in 13 mg yield as a white solid from 2-[3-(3-chlorophenyl)-1-oxo-7-[4-(1-pyrrolidinyl)-1-piperidinyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (13 mg, E61).

¹H NMR (500 MHz, DMSO-d₆): δ 9.42 (br. s., 1 H) 7.79 (d, 1 H) 7.61 (t, 1 H) 7.49 (t, 2 H) 7.42 - 7.45 (m, 1 H) 7.33 - 7.36 (m, 1 H) 7.25 - 7.29 (m, 1 H) 6.82 - 6.85 (m, 1 H) 4.22 (s, 2 H) 3.67 - 3.78 (m, 1 H) 3.39 (d, 2 H) 2.98 - 3.06 (m, 2 H) 2.75 - 2.87 (m, 2 H) 2.60 (t, 2 H) 1.74 - 1.83 (m, 2 H) 1.56 - 1.73 (m, 7 H) 1.31 - 1.42 (m, 1 H) 0.95 (d, 6 H).

MS (m/z): 497 [MH]⁺.

Example 63: 2-[7-{4-[meso-2,6-dimethyl-4-morpholinyl]butyl}-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E63)

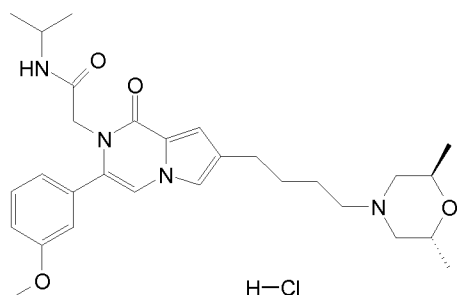


The title compound was prepared with an analogous procedure to that described in Example 19 in 16 mg yield as a white solid from 2-[7-(4-hydroxybutyl)-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (50 mg, P27) and 2,6-dimethylmorpholine (42 mg).

¹H NMR (500 MHz, CDCl₃): δ 7.35 (m, 1 H) 7.02 (m, 4 H) 6.95 (s, 1 H) 6.87 (s, 1 H) 5.9 (m, 1 H) 4.30 (s, 2 H) 4.05 (m, 1 H) 3.84 (s, 3H) 3.70 (m, 2H) 2.85 - 2.65 (m, 4 H) 2.32 (m, 2 H) 1.71 - 1.62 (m, 6 H) 1.10-1.20 (m, 12 H).

MS (m/z): 509 [MH]⁺.

Example 64: 2-[7-{4-[meso-2,6-dimethyl-4-morpholinyl]butyl}-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E64)

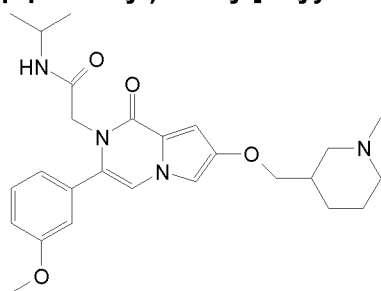


The title compound was prepared with an analogous procedure to that described in Example 2 in 16 mg yield from 2-[7-{4-[meso-2,6-dimethyl-4-morpholinyl]butyl}-3-[3-(methoxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (16 mg, E63).

¹H NMR (500 MHz, DMSO-d₆): δ 9.42 (br. s., 1 H) 7.79 (d, 1 H) 7.61 (t, 1 H) 7.49 (t, 2 H) 7.42 - 7.45 (m, 1 H) 7.33 - 7.36 (m, 1 H) 7.25 - 7.29 (m, 1 H) 6.82 - 6.85 (m, 1 H) 4.22 (s, 2 H) 3.67 - 3.78 (m, 1 H) 3.39 (d, 2 H) 2.98 - 3.06 (m, 2 H) 2.75 - 2.87 (m, 2 H) 2.60 (t, 2 H) 1.74 - 1.83 (m, 2 H) 1.56 - 1.73 (m, 7 H) 1.31 - 1.42 (m, 1 H) 0.95 (d, 6 H).

MS (m/z): 509 [MH]⁺.

Example 65: *N*-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-7-[[1-methyl-3-piperidinyl)methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E65)

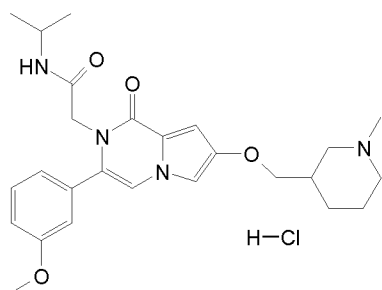


To a solution of 2-(3-(3-chlorophenyl)-7-hydroxy-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl)-N-isopropylacetamide (35mg, P71) in DMSO (0.8 mL) cesium carbonate (170 mg) and 3-(chloromethyl)-1-methylpiperidine hydrochloride (21.5 mg) were added at rt and the mixture was heated at 85 °C on. The mixture was cooled down to rt and loaded on an SCX cartridge. The column was washed with MeOH and the product eluted with NH₃ (2M in MeOH). The solvent was removed under reduced pressure to give the title compound (6.4 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.25-7.47 (m, 4H); 6.81 (s, 1H); 6.78 (m, 2H); 5.92 (m, 1H); 4.31 (s, 2H); 3.98-4.12 (m, 1H); 3.75-3.92 (m, 2H); 2.89-3.01 (m, 1H); 2.71-2.84 (m, 1H); 2.30 (s, 3H); 2.09-2.21 (m, 1H); 1.92-2.02 (m, 1H); 1.57-1.88 (m, 4H); 1.13-1.18 (m, 1H); 1.14-1.16 (d, 6H).

MS (m/z): 471 [MH]⁺.

Example 66: *N*-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-7-[[1-methyl-3-piperidinyl)methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E66)



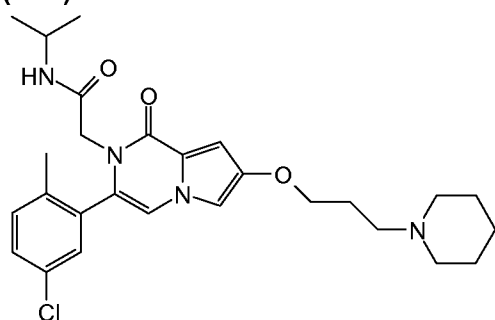
The title compound was prepared with an analogous procedure to that described in Example 2 in 6 mg yield from *N*-(1-methylethyl)-2-[3-[3-(methoxy)phenyl]-7-[[1-(methyl-3-piperidinyl)methyl]oxy]-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide (6.4 mg, E65).

- 5 **¹H NMR (500 MHz, DMSO-*d*₆):** δ 9.71 (br. s., 1 H) 7.76 (d, 1 H) 7.53 - 7.58 (m, 1 H) 7.46 - 7.52 (m, 2 H) 7.38 - 7.42 (m, 1 H) 7.25 - 7.29 (m, 1 H) 7.14 (d, 1 H) 6.62 (d, 1 H) 4.22 (s, 2 H) 3.93 - 3.99 (m, 1 H) 3.80 - 3.88 (m, 1 H) 3.69 - 3.78 (m, 1 H) 3.35 - 3.55 (m, 2 H) 2.72 - 2.89 (m, 5 H) 2.29 (br. s., 1 H) 1.59 - 1.92 (m, 3 H) 1.19 - 1.31 (m, 1 H) 0.97 (d, 6 H).

MS (m/z): 471 [MH]⁺.

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Example 67: 2-[3-(5-chloro-2-methylphenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide (E67)

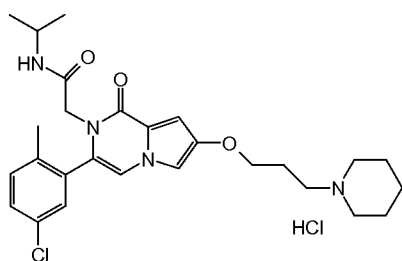


- 15 The title compound was prepared with an analogous procedure to that described in Example 19 in 21 mg yield from 2-[3-(5-chloro-2-methylphenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide (70 mg, P76) and piperidine (55 mg).

- 20 **¹H NMR (400 MHz, CDCl₃):** δ 7.30 - 7.38 (m, 2 H) 7.23 (d, 1 H) 6.75 - 6.82 (m, 3 H) 5.78 - 5.86 (m, 1 H) 4.51 - 4.60 (m, 1 H) 4.04 (t, 2 H) 3.93 - 4.01 (m, 1 H) 3.86 - 3.92 (m, 1 H) 2.45 - 2.51 (m, 2 H) 2.37 - 2.45 (m, 3 H) 2.20 (s, 3 H) 2.00 (d, 2 H) 1.69 (s, 1 H) 1.56 - 1.65 (m, 4 H) 1.41 - 1.50 (m, 2 H) 1.11 (dd, 6 H).

MS (m/z): 499 [MH]⁺.

- 25 **Example 68:** 2-[3-(5-chloro-2-methylphenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide hydrochloride (E68)

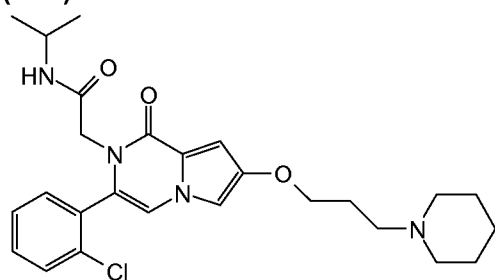


The title compound was prepared with an analogous procedure to that described in Example 2 in 21 mg yield as a white solid from 2-[3-(5-chloro-2-methylphenyl)-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (21 mg, E67).

¹H NMR (400 MHz, DMSO-d₆): δ 9.49 (br. s., 1 H) 7.65 (d, 1 H) 7.47 (dd, 1 H) 7.35 - 7.40 (m, 1 H) 7.26 (d, 1 H) 7.23 (s, 1 H) 7.13 (d, 1 H) 6.62 (d, 1 H) 4.59 (d, 1 H) 4.05 (t, 2 H) 3.58 - 3.75 (m, 2 H) 3.42 - 3.53 (m, 2 H) 3.12 - 3.23 (m, 2 H) 2.81 - 2.96 (m, 2 H) 2.17 (s, 3 H) 2.09 - 2.16 (m, 2 H) 1.59 - 1.88 (m, 5 H) 1.30 - 1.46 (m, 1 H) 0.94 (d, 3 H) 0.91 (d, 3 H).

MS (m/z): 499 [MH]⁺.

Example 69: 2-[3-(2-chlorophenyl)-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E69)

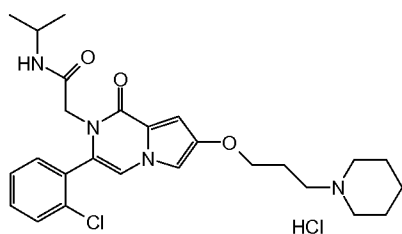


The title compound was prepared with an analogous procedure to that described in Example 19 in 27 mg yield from 2-[3-(2-chlorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (70 mg, P81) and piperidine (42 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.41 - 7.52 (m, 3 H) 7.37 (dd, 1 H) 6.77 - 6.83 (m, 3 H) 5.80 - 5.96 (m, 1 H) 4.72 (s, 1 H) 4.04 (t, 2 H) 3.89 - 4.00 (m, 1 H) 3.83 (d, 1 H) 2.46 - 2.52 (m, 2 H) 2.37 - 2.46 (m, 3 H) 1.93 - 2.04 (m, 2 H) 1.75 (s, 2 H) 1.56 - 1.65 (m, 3 H) 1.41 - 1.50 (m, 2 H) 1.03 - 1.14 (m, 6 H).

MS (m/z): 485 [MH]⁺.

Example 70: 2-[3-(2-chlorophenyl)-1-oxo-7-[[3-(1-piperidiny)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E70)

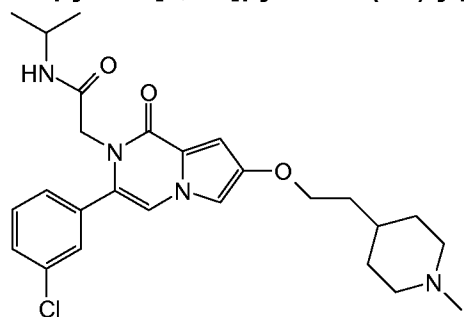


The title compound was prepared with an analogous procedure to that described in Example 2 in 27 mg yield as a white solid from 2-[3-(2-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (27 mg, E69).

¹H NMR (400 MHz, DMSO-d₆): δ 9.42 - 9.64 (m, 1 H) 7.59 - 7.69 (m, 2 H) 7.50 - 7.58 (m, 1 H) 7.36 - 7.47 (m, 2 H) 7.23 - 7.33 (m, 1 H) 7.12 - 7.23 (m, 1 H) 6.53 - 6.72 (m, 1 H) 4.79 - 4.92 (m, 1 H) 3.99 - 4.11 (m, 2 H) 3.57 - 3.71 (m, 1 H) 3.41 - 3.54 (m, 2 H) 3.11 - 3.24 (m, 2 H) 2.77 - 2.97 (m, 2 H) 2.06 - 2.20 (m, 2 H) 1.63 - 1.87 (m, 5 H) 1.32 - 1.45 (m, 1 H) 0.90 - 0.98 (m, 3 H) 0.76 - 0.88 (m, 3 H).

MS (m/z): 485 [MH]⁺.

Example 71: 2-[3-(3-chlorophenyl)-7-[[2-(1-methyl-4-piperidinyl)ethyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E71)

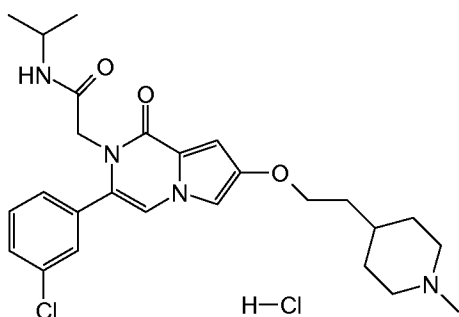


To a solution of 2-[3-(3-chlorophenyl)-1-oxo-7-[[2-(4-piperidinyl)ethyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (5 mg, P84) in THF (0.1 ml) and MeOH (0.1 ml), formaldehyde (1.835 μl) (37% aqueous solution) and sodium cyanoborohydride (1 mg) were subsequently added. After stirring the solution for 30 min at RT, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between DCM and water. The organic phase was separated, washed with water, brine, dried over Na₂SO₄ and the solvent removed under vacuum to give the title compound (3 mg).

¹H NMR (400 MHz, CDCl₃): δ 7.46 (d, 2 H) 7.38 (s, 2 H) 6.82 (d, 1 H) 6.78 (s, 2 H) 5.85 - 5.91 (m, 1 H) 4.29 - 4.33 (m, 2 H) 4.03 (s, 3 H) 2.85 - 2.95 (m, 2 H) 2.30 (s, 3 H) 1.93 - 2.04 (m, 3 H) 1.69 - 1.80 (m, 5 H) 1.33 - 1.43 (m, 1 H) 1.15 (d, 6 H)

MS (m/z): 485 [MH]⁺.

Example 72: 2-[3-(3-chlorophenyl)-7-[[2-(1-methyl-4-piperidinyl)ethyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E72)

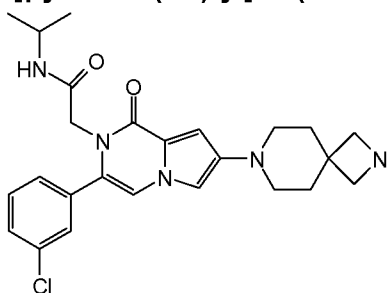


The title compound was prepared with an analogous procedure to that described in Example 2 in 2 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-[[2-(1-methyl-4-piperidiny)ethoxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (3 mg, E71).

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.42 (br. s., 1 H) 7.78 (d, 1 H) 7.56 (dt, 1 H) 7.46 - 7.52 (m, 2 H) 7.40 (dt, 1 H) 7.26 (s, 1 H) 7.12 (d, 1 H) 6.58 (d, 1 H) 4.22 (s, 2 H) 4.01 (t, 2 H) 3.69 - 3.79 (m, 1 H) 2.86 (br. s., 2 H) 2.66 - 2.73 (m, 2 H) 2.50 (s, 3 H) 1.83 - 1.93 (m, 2 H) 1.68 (br. s., 3 H) 1.39 (br. s., 2 H) 0.97 (d, 6 H).

MS (m/z): 485 [MH]⁺.

Example 73: 2-[3-(3-chlorophenyl)-7-(2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E73)

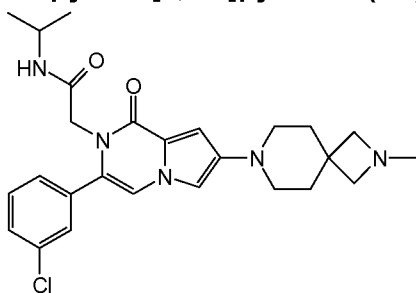


To a solution of 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (100 mg, prepared with an analogous procedure to that described in P63), potassium carbonate (23 mg), copper iodide (61 mg) and LD-proline (37 mg) in DMSO (2 mL) 1,1-dimethylethyl 2,7-diazaspiro[3.5]nonane-2-carboxylate (280 mg, commercially available) was added and the mixture stirred at 80 °C for 20h. Then one more portion of CuI (40 mg) was added and the mixture stirred at 80 °C for 3h more. The mixture was diluted with AcOEt and washed several times with a saturated solution of NH₄Cl. The organic phase was dried and evaporated. The residue was dissolved in dry DCM (1.5 ml) and TFA (1 ml, 12.98 mmol) was added at 0°. The mixture was stirred at RT for 1h. The solvent was evaporated and the crude purified by SCX cartridge (1g) eluting with NH₃ 2M in MeOH. The solvent was evaporated under reduced pressure to give the title compound (30 mg)

¹H NMR (400 MHz, CDCl₃): δ 7.33 - 7.49 (m, 4 H) 6.82 (s, 1 H) 6.76 (d, 1 H) 6.67 (d, 1 H) 5.96 - 6.10 (m, 1 H) 4.30 (s, 2 H) 3.96 - 4.12 (m, 1 H) 3.37 - 3.52 (m, 5 H) 2.93 - 3.05 (m, 2 H) 2.18 (br. s., 4 H) 1.89 - 1.99 (m, 2 H) 1.08 - 1.19 (m, 6 H).

MS (m/z): 468 [MH]⁺.

Example 74: 2-[3-(3-chlorophenyl)-7-(2-methyl-2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E74)

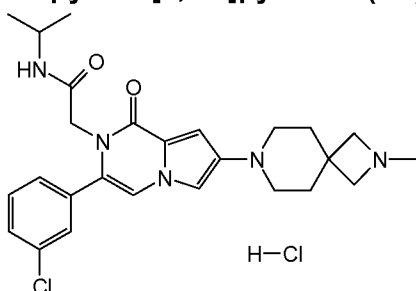


The title compound was prepared with an analogous procedure to that described in Example 71 in 8 mg yield from 2-[3-(3-chlorophenyl)-7-(2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (30 mg, E73).

¹H NMR (400 MHz, CDCl₃): δ 7.34 - 7.48 (m, 4 H) 6.82 (s, 1 H) 6.78 (d, 1 H) 6.67 (d, 1 H) 5.92 (d, 1 H) 4.31 (s, 2 H) 3.97 - 4.14 (m, 1 H) 3.08 (s, 4 H) 2.93 - 3.04 (m, 4 H) 2.38 (s, 3 H) 1.84 - 1.95 (m, 4 H) 1.15 (d, 6 H).

MS (m/z): 482 [MH]⁺.

Example 75: 2-[3-(3-chlorophenyl)-7-(2-methyl-2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E75)

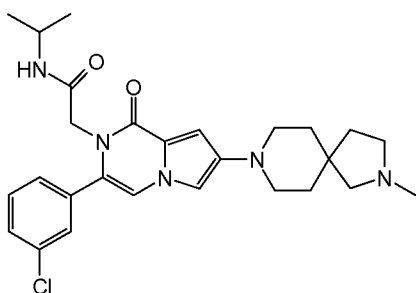


The title compound was prepared with an analogous procedure to that described in Example 2 in 8.5 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-(2-methyl-2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (8 mg, E74).

¹H NMR (500 MHz, DMSO-d₆): δ 10.28 (br. s., 1 H) 7.75 (d, 1 H) 7.34 - 7.59 (m, 4 H) 7.22 (s, 1 H) 7.00 (br. s., 1 H) 6.62 (br. s., 1 H) 4.20 (s, 2 H) 3.92 - 4.02 (m, 2 H) 3.68 - 3.83 (m, 3 H) 2.86 - 3.09 (m, 4 H) 2.83 (d, 3 H) 1.74 - 2.07 (m, 4 H) 0.96 (d, 6 H).

MS (m/z): 482 [MH]⁺.

Example 76: 2-[3-(3-chlorophenyl)-7-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E76)

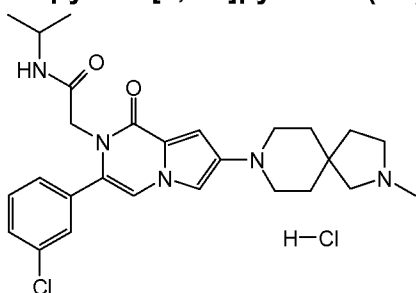


The title compound was prepared with an analogous procedure to that described in Example 71 in 9 mg yield from 2-[3-(3-chlorophenyl)-7-(2,8-diazaspiro[4.5]dec-8-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (29 mg, prepared with an analogous procedure to that described in P85).

¹H-NMR (DMSO-*d*₆): δ 10.34 (broad s, 1H); 7.77 (d, 1H); 7.59-7.37 (m, 4H); 7.26 (s, 1H); 7.09 (s, 1H); 6.70 (s, 1H); 4.21 (s, 2H); 3.80-3.69 (m, 1H); 3.62-3.48 (m, 2H); 3.18-2.98 (m, 5H); 2.90-2.84 (m, 1H); 2.82 (d, 3H); 2.04-1.95 (m, 1H); 1.92-1.67 (m, 5H); 0.97 (d, 6H).

MS (m/z): 496 [MH]⁺.

Example 77: 2-[3-(3-chlorophenyl)-7-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E77)

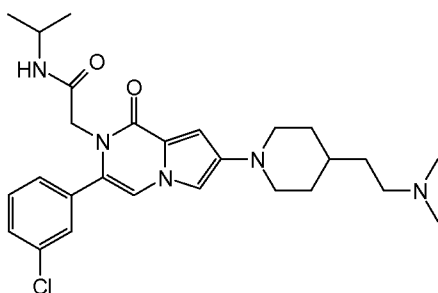


The title compound was prepared with an analogous procedure to that described in Example 2 in 9.5 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (9 mg, E76).

¹H-NMR (DMSO-*d*₆): δ 10.34 (broad s, 1H); 7.77 (d, 1H); 7.59-7.37 (m, 4H); 7.26 (s, 1H); 7.09 (s, 1H); 6.70 (s, 1H); 4.21 (s, 2H); 3.80-3.69 (m, 1H); 3.62-3.48 (m, 2H); 3.18-2.98 (m, 5H); 2.90-2.84 (m, 1H); 2.82 (d, 3H); 2.04-1.95 (m, 1H); 1.92-1.67 (m, 5H); 0.97 (d, 6H).

MS (m/z): 496 [MH]⁺.

Example 78: 2-[3-(3-chlorophenyl)-7-[4-[2-(dimethylamino)ethyl]-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E78)

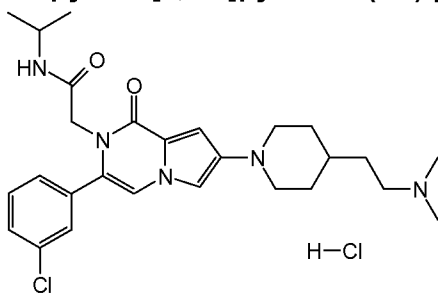


The title compound was prepared with an analogous procedure to that described in Example 50 in 7 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (100 mg, prepared with an analogous procedure to that described in P63) and N,N-dimethyl-2-(4-piperidiny)ethanamine (244 mg, commercially available).

¹H NMR (400 MHz, CDCl₃): δ 7.46-7.42 (m, 2H); 7.41-7.36 (m, 2H); 6.83 (s, 1H); 6.79 (d, 1H); 6.67 (d, 1H); 5.96 (broad s, 1H); 4.31 (broad s, 2H); 4.10-4.01 (m, 1H); 3.53-3.46 (m, 2H); 2.68-2.60 (m, 2H); 2.38-2.32 (m, 2H); 2.26 (s, 6H); 1.84-1.77 (m, 2H); 1.52-1.41 (m, 5H); 1.15 (d, 6H).

MS (m/z): 498 [MH]⁺.

Example 79: 2-[3-(3-chlorophenyl)-7-{4-[2-(dimethylamino)ethyl]-1-piperidinyl}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E79)

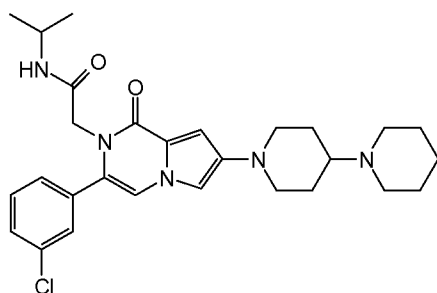


The title compound was prepared with an analogous procedure to that described in Example 2 in 7.5 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-{4-[2-(dimethylamino)ethyl]-1-piperidinyl}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (7 mg, E78).

¹H NMR (500 MHz, DMSO-d₆): δ 9.60 (broad s, 1H); 7.77 (d, 1H); 7.58-7.35 (m, 4H); 7.23 (s, 1H); 7.01 (broad s, 1H); 6.61 (broad s, 1H); 4.21 (s, 2H); 3.81-3.67 (m, 1H); 3.54-3.45 (m, 2H); 3.15-3.04 (m, 2H); 2.76 (d, 6H); 2.64-2.53 (m, 2H); 1.80-1.68 (m, 2H); 1.66-1.53 (m, 2H); 1.50-1.24 (m, 3H); 0.97 (d, 6H).

MS (m/z): 498 [MH]⁺.

Example 80: 2-[7-(1,4'-bipiperidin-1'-yl)-3-(3-chlorophenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E80)

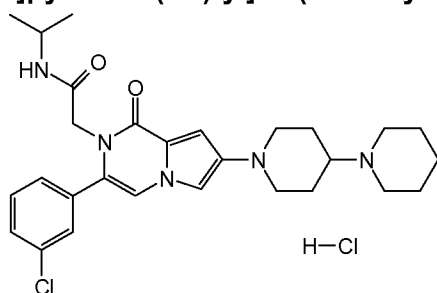


The title compound was prepared with an analogous procedure to that described in Example 50 in 22 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (100 mg, prepared with an analogous procedure to that described in P63) and 1,4'-bipiperidine (251 mg, commercially available).

¹H-NMR (CDCl₃): δ 7.46-7.36 (m, 4H); 6.82 (broad s, 1H); 6.77 (d, 1H); 6.66 (d, 1H); 5.96 (broad s, 1H); 4.31 (broad s, 2H); 4.09-4.00 (m, 1H); 3.62-3.53 (m, 2H); 2.70-2.61 (m, 2H); 2.60-2.54 (m, 4H); 2.49-2.39 (m, 1H); 1.96-1.88 (m, 2H); 1.83-1.70 (m, 2H); 1.67-1.59 (m, 4H); 1.52-1.43 (m, 2H); 1.15 (d, 6H).

MS (m/z): 510 [MH]⁺.

Example 81: 2-[7-(1,4'-bipiperidin-1'-yl)-3-(3-chlorophenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E81)

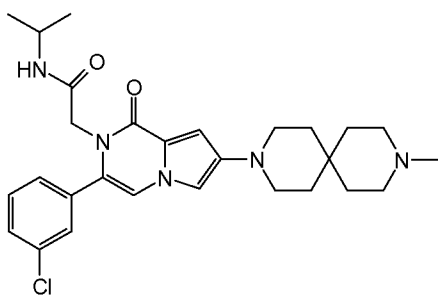


The title compound was prepared with an analogous procedure to that described in Example 2 in 23.5 mg yield as a white solid from 2-[7-(1,4'-bipiperidin-1'-yl)-3-(3-chlorophenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (22 mg, E80).

¹H-NMR (DMSO-d₆): δ 9.49 (broad s, 1H); 7.77 (d, 1H); 7.22 (s, 1H); 7.01 (d, 1H); 6.63 (d, 1H); 4.21 (s, 2H); 3.80-3.59 (m, 3H); 3.48-3.38 (m, 2H); 3.39-3.23 (m, 1H); 3.02-2.86 (m, 2H); 2.71-2.56 (m, 2H); 2.13-2.01 (m, 2H); 1.89-1.63 (m, 7H); 1.48-1.36 (m, 1H); 0.97 (d, 6H).

MS (m/z): 510 [MH]⁺.

Example 82: 2-[3-(3-chlorophenyl)-7-(9-methyl-3,9-diazaspiro[5.5]undec-3-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E82)

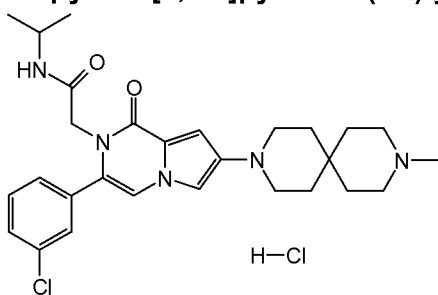


The title compound was prepared with an analogous procedure to that described in Example 71 in 6.6 mg yield from 2-[3-(3-chlorophenyl)-7-(3,9-diazaspiro[5.5]undec-3-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (35 mg, P86).

- 5 **¹H-NMR (CDCl₃):** δ 7.46-7.36 (m, 4H); 6.83 (s, 1H); 6.79 (d, 1H); 6.67 (d, 1H); 5.94 (broad s, 1H); 4.31 (broad s, 2H); 4.10-4.00 (m, 1H); 3.07-3.01 (m, 4H); 2.48-2.39 (m, 4H); 2.35-2.32 (s, 3H); 1.69-1.57 (m, 8H); 1.15 (d, 6H).

MS (m/z): 510 [MH]⁺.

- 10 **Example 83: 2-[3-(3-chlorophenyl)-7-(9-methyl-3,9-diazaspiro[5.5]undec-3-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E83)**

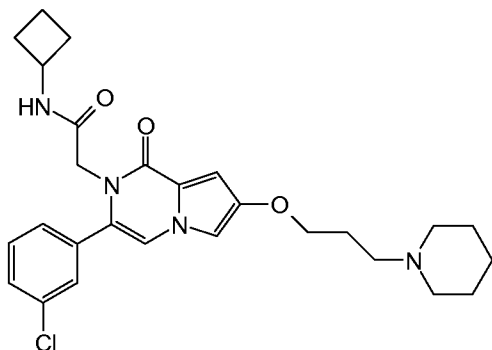


The title compound was prepared with an analogous procedure to that described in Example 2 in 7 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-(9-methyl-3,9-diazaspiro[5.5]undec-3-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (8 mg, E82).

- 15 **¹H-NMR (DMSO-d₆):** δ 9.54 (broad s, 1H); 7.76 (s, 1H); 7.58-7.35 (m, 4H); 7.26 (s, 1H); 7.07 (broad s, 1H); 6.70 (broad s, 1H); 4.22 (s, 2H); 3.79-3.69 (m, 1H); 3.28-2.96 (m, 8H); 2.74 (d, 3H); 1.93-1.43 (m, 8H); 0.96 (d, 6H).

- 20 **MS (m/z):** 510 [MH]⁺.

Example 84: 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-cyclobutylacetamide (E84)

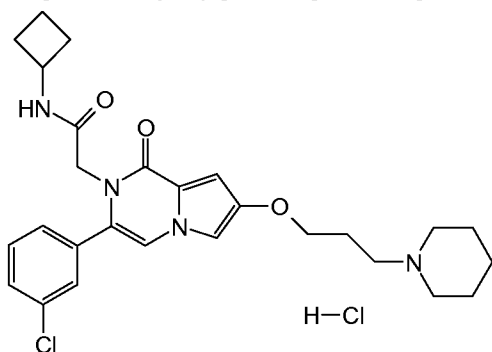


The title compound was prepared with an analogous procedure to that described in Example 19 in 11 mg yield from 2-[3-(3-chlorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-cyclobutylacetamide (30 mg, P90) and piperidine (419 mg).

¹H NMR (400 MHz, CDCl₃) δ 7.42 - 7.46 (m, 2 H) 7.35 - 7.39 (m, 2 H) 6.82 (d, 1 H) 6.80 (d, 1 H) 6.74 (dd, 1 H) 6.30 - 6.41 (m, 1 H) 4.31 (s, 3 H) 4.05 (t, 2 H) 2.67 - 2.90 (m, 4 H) 2.26 - 2.37 (m, 2 H) 2.15 - 2.26 (m, 2 H) 1.80 - 1.94 (m, 7 H) 1.65 - 1.76 (m, 3 H) 1.27 (d, 2 H).

MS (m/z): 497 [MH]⁺.

Example 85: 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-cyclobutylacetamide hydrochloride (E85)

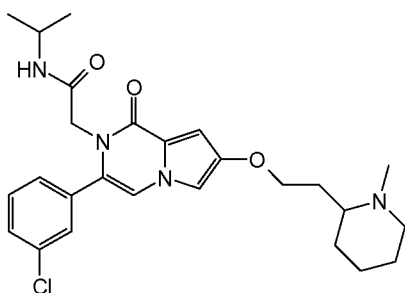


The title compound was prepared with an analogous procedure to that described in Example 2 in 5 mg yield as a white solid from 2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-cyclobutylacetamide (11 mg, E84).

¹H NMR (500 MHz, DMSO-d₆): δ 9.50 (br. s., 1 H) 8.16 (d, 1 H) 7.37 - 7.59 (m, 4 H) 7.28 (s, 1 H) 7.14 (d, 1 H) 6.61 (d, 1 H) 3.99 - 4.32 (m, 5 H) 3.41 - 3.50 (m, 2 H) 3.14 - 3.22 (m, 2 H) 2.83 - 2.96 (m, 2 H) 2.03 - 2.19 (m, 4 H) 1.52 - 1.88 (m, 9 H) 1.31 - 1.45 (m, 1 H).

MS (m/z): 497 [MH]⁺.

Example 86: 2-[3-(3-chlorophenyl)-7-[[2-(1-methyl-2-piperidinyl)ethyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E86)

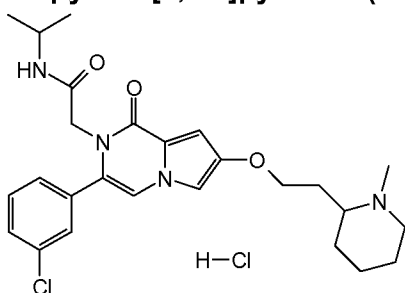


The title compound was prepared with an analogous procedure to that described in Example 71 in 36 mg yield from 2-[3-(3-chlorophenyl)-1-oxo-7-{2-(2-piperidinyloxy)ethyl}oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (48 mg, P93).

¹H NMR (400 MHz, CDCl₃): δ 7.46 (d, 2 H) 7.38 (s, 2 H) 6.82 (s, 1 H) 6.79 (s, 2 H) 5.82 - 5.93 (m, 1 H) 4.29 - 4.33 (m, 2 H) 4.02 - 4.09 (m, 3 H) 2.83 - 2.91 (m, 1 H) 2.32 (s, 3 H) 2.09 - 2.22 (m, 3 H) 1.83 - 1.94 (m, 1 H) 1.68 - 1.80 (m, 3 H) 1.58 - 1.62 (m, 1 H) 1.25 - 1.43 (m, 2 H) 1.16 (d, 6 H).

MS (m/z): 485 [MH]⁺.

Example 87: 2-[3-(3-chlorophenyl)-7-{[2-(1-methyl-2-piperidinyloxy)ethyl]oxy}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E87)

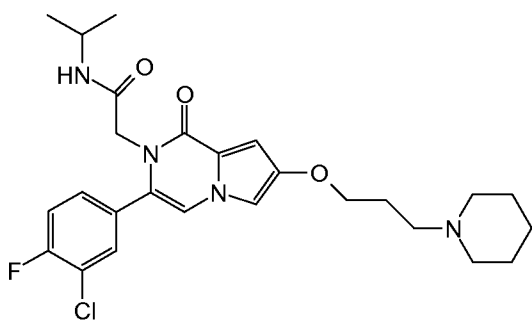


The title compound was prepared with an analogous procedure to that described in Example 2 in 36 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-{[2-(1-methyl-2-piperidinyloxy)ethyl]oxy}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (36 mg, E86).

¹H NMR (500 MHz, DMSO-d₆): δ 9.74 - 10.17 (m, 1 H) 7.73 - 7.82 (m, 1 H) 7.53 - 7.59 (m, 1 H) 7.45 - 7.52 (m, 2 H) 7.38 - 7.43 (m, 1 H) 7.21 - 7.33 (m, 1 H) 7.06 - 7.21 (m, 1 H) 6.54 - 6.69 (m, 1 H) 4.17 - 4.28 (m, 2 H) 3.99 - 4.13 (m, 2 H) 3.65 - 3.80 (m, 1 H) 3.36 - 3.55 (m, 0 H) 3.32 (s, 3 H) 3.09 - 3.25 (m, 0 H) 2.65 - 2.87 (m, 3 H) 1.85 - 2.05 (m, 2 H) 1.60 - 1.83 (m, 3 H) 1.37 - 1.61 (m, 2 H) 1.18 - 1.34 (m, 1 H) 0.97 (d, 6 H).

MS (m/z): 485 [MH]⁺.

Example 88: 2-[3-(3-chloro-4-fluorophenyl)-1-oxo-7-{[3-(1-piperidinyloxy)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E88)

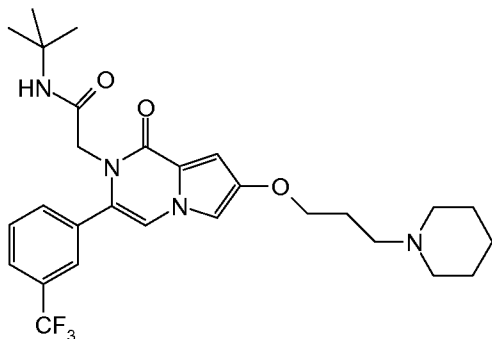


To a suspension of 2-[3-(3-chloro-4-fluorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (10 mg, P103), TEA (6.4 uL) in dry DCM (2 mL) at 0°C, methansulfonyl chloride (1.7 uL) was added dropwise, and the mixture was stirred at RT for 1h. The mixture was diluted with DCM and washed with water. The organic phase was dried and evaporated under vacuum. The crude obtained was dissolved in dry DMF (1.0 mL), potassium carbonate (14 mg) and piperidine (6 uL) were added and the mixture was stirred at 60°C for 3h. The mixture was cooled down, diluted with AcOEt and washed with ice and brine. The organic phase was dried and evaporated under vacuum and the crude purified by flash chromatography on silica column eluting with DCM:MeOH:NH₃_{acc} = 9:1:0.1 to give the title compound (1 mg).

¹H-NMR (CDCl₃): δ 7.54 (dd, 1H); 7.42-7.36 (m, 1H); 7.22 (t, 1H); 6.81-6.76 (m, 3H); 5.94 (d, 1H); 4.28 (s, 2H); 4.09-3.99 (m, 3H); 2.46 (t, 2H); 2.44-2.35 (m, 4H); 2.02-1.93 (m, 2H); 1.64-1.40 (m, 6H); 1.15 (d, 6H).

MS (m/z): 503 [MH]⁺.

Example 89: *N*-(1,1-dimethylethyl)-2-[1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E89)

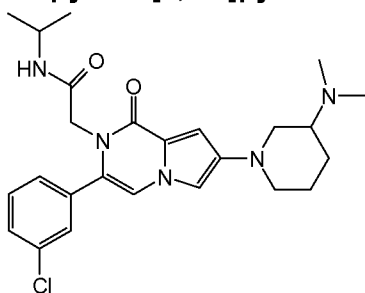


The title compound was prepared with an analogous procedure to that described in Example 88 in 1 mg yield from *N*-(1,1-dimethylethyl)-2-[7-[(3-hydroxypropyl)oxy]-1-oxo-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (25 mg, prepared with an analogous procedure to that described in P98) and piperidine (12 mg).

¹H-NMR (CDCl₃): δ 7.79-7.54 (m, 4H); 6.83-6.76 (m, 3H); 5.82 (broad s, 1H); 4.24 (s, 2H); 4.02 (t, 2H); 2.46 (t, 2H); 2.45-2.36 (m, 4H); 2.02-1.94 (m, 2H); 1.65-1.39 (m, 6H); 1.32 (s, 9H).

MS (m/z): 533 [MH]⁺.

Example 90: 2-[3-(3-chlorophenyl)-7-[3-(dimethylamino)-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E90)

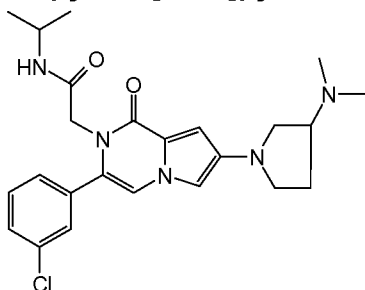


The title compound was prepared with an analogous procedure to that described in Example 50 in 13 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (100 mg, prepared with an analogous procedure to that described in P63) and N,N-dimethyl-3-piperidinamine (191 mg, commercially available).

¹H-NMR (CDCl₃): δ 7.47-7.36 (m, 4H); 6.84 (s, 1H); 6.80 (d, 1H); 6.69 (d, 1H); 5.98 (broad s, 1H); 4.32 (broad s, 2H); 4.10-4.01 (m, 1H); 3.64-3.59 (m, 1H); 3.44-3.37 (m, 1H); 2.64-2.52 (m, 3H); 2.39 (s, 6H); 2.05-1.85 (m, 2H); 1.78-1.69 (m, 1H); 1.42-1.32 (m, 1H); 1.16 (d, 6H).

MS (m/z): 470 [MH]⁺.

Example 91: 2-[3-(3-chlorophenyl)-7-[3-(dimethylamino)-1-pyrrolidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E91)

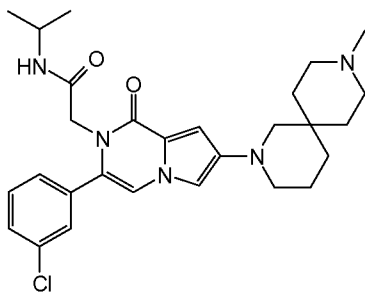


The title compound was prepared with an analogous procedure to that described in Example 50 in 25 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (100 mg, prepared with an analogous procedure to that described in P63) and N,N-dimethyl-3-pyrrolidinamine (170 mg, commercially available).

¹H-NMR (CDCl₃): δ 7.46-7.35 (m, 4H); 6.84 (s, 1H); 6.60 (d, 1H); 6.52 (d, 1H); 6.02 (broad s, 1H); 4.32 (broad s, 2H); 4.11-4.00 (m, 1H); 3.41-3.35 (m, 1H); 3.34-3.23 (m, 2H); 3.11-3.06 (m, 1H); 2.98-2.88 (m, 1H); 2.32 (s, 6H); 2.25-2.15 (m, 1H); 2.01-1.90 (m, 1H); 1.15 (d, 6H).

MS (m/z): 456 [MH]⁺.

Example 92: 2-[3-(3-chlorophenyl)-7-(9-methyl-2,9-diazaspiro[5.5]undec-2-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E92)

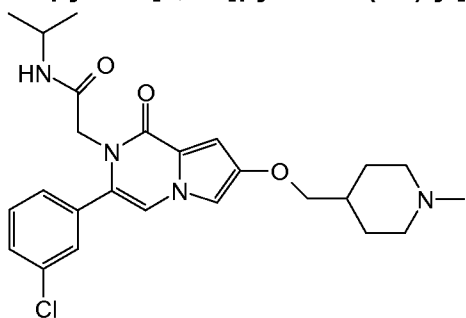


The title compound was prepared with an analogous procedure to that described in Example 71 in 1.1 mg yield from 2-[3-(3-chlorophenyl)-7-(2,9-diazaspiro[5.5]undec-2-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (25 mg, P103).

- 5 **¹H-NMR (CDCl₃):** δ 7.49-7.32 (m, 4H); 6.85-6.75 (m, 2H); 6.66 (s, 1H); 5.94 (d, 1H); 4.31 (d, 2H); 4.10-3.98 (m, 1H); 2.97 (t, 2H); 2.85 (s, 2H); 2.70-2.20 (m, 7H); 1.86-1.29 (m, 8H); 1.15 (d, 6H).

MS (m/z): 510 [MH]⁺.

- 10 **Example 93:** 2-[3-(3-chlorophenyl)-7-[(1-methyl-4-piperidiny)methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E93)



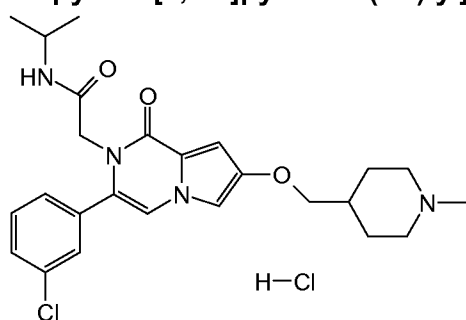
- To a stirred solution of 1,1-dimethylethyl 4-([3-(3-chlorophenyl)-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl]oxy)methyl-1-piperidinecarboxylate (42 mg, P106) in DMF (0.4 mL), at RT and under a nitrogen atmosphere, sodium hydride (5 mg) was added. After 10 min, NaI (15 mg) was added followed after 5 min by a solution of 2-chloro-N-(1-methylethyl)acetamide (17 mg) in DMF (0.1 mL). The reaction mixture was warmed to 65 °C and stirred for 5 h. The reaction mixture was allowed to reach RT and an additional amount of sodium hydride (3 mg) was added, followed after 5 min by 2-chloro-N-(1-methylethyl)acetamide (10 mg). The reaction mixture was heated to 60 °C and stirred overnight. Ether and water were added to the mixture at RT, the organic phase was washed with brine, dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude material was purified by flash chromatography (eluting with Cy/EA from 9/1 to 3/7) to give 17.7 mg of the secondary amine N-Boc intermediate. This material was dissolved in DCM (0.3 mL) and trifluoroacetic acid (50 μ L) was added at RT. After 2h the mixture was concentrated under reduced pressure and the residue was taken up with DCM and saturated NaHCO₃. The organic phase was washed with brine, dried over Na₂SO₄ and the solvent removed under vacuum to give 12 mg of the secondary amine intermediate. This material was dissolved in THF (0.05 mL) and MeOH (0.05 mL),

formaldehyde (1 μ l) and sodium cyanoborohydride (2.51 mg) were subsequently added at RT. After stirring for 30 min at RT, the reaction was quenched by adding 0.1 ml of saturated NaHCO_3 , the resulting mixture was concentrated under reduced pressure and the residue was partitioned between DCM and water. The organic phase was separated,
 5 washed with water, brine, dried over sodium sulphate and the solvent removed under vacuum to give the title compound (4 mg).

^1H NMR (400 MHz, CDCl_3): δ 7.46 (d, 2 H) 7.38 (s, 2 H) 6.82 (s, 1 H) 6.77 (s, 2 H) 5.82 - 5.94 (m, 1 H) 4.31 (s, 2 H) 4.00 - 4.10 (m, 1 H) 3.84 (d, 2 H) 3.11 - 3.24 (m, 2 H) 2.44 (s, 3 H) 2.15 - 2.30 (m, 2 H) 1.82 - 1.96 (m, 3 H) 1.51 - 1.67 (m, 2 H) 1.15 (d, 6 H).

MS (m/z): 471 $[\text{MH}]^+$.

Example 94: 2-[3-(3-chlorophenyl)-7-[[[(1-methyl-4-piperidiny)methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E94)

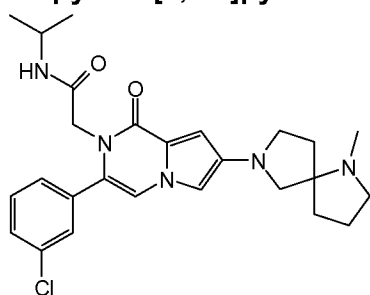


The title compound was prepared with an analogous procedure to that described in Example 2 in 4 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-[[[(1-methyl-4-piperidiny)methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (4 mg, E93).

^1H NMR (500 MHz, $\text{METHANOL}-d_4$): δ 7.80 - 7.88 (m, 0 H) 7.42 - 7.56 (m, 4 H) 7.35 - 7.43 (m, 1 H) 7.16 - 7.25 (m, 1 H) 7.05 - 7.13 (m, 1 H) 6.66 - 6.74 (m, 1 H) 4.32 - 4.46 (m, 2 H) 3.83 - 4.01 (m, 4 H) 3.52 - 3.62 (m, 1 H) 2.97 - 3.13 (m, 1 H) 2.80 - 2.94 (m, 3 H) 2.04 - 2.22 (m, 4 H) 1.54 - 1.76 (m, 2 H) 1.30 - 1.39 (m, 1 H) 1.02 - 1.11 (m, 6 H).

MS (m/z): 471 $[\text{MH}]^+$.

Example 95: 2-[3-(3-chlorophenyl)-7-(1-methyl-1,7-diazaspiro[4.4]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E95)



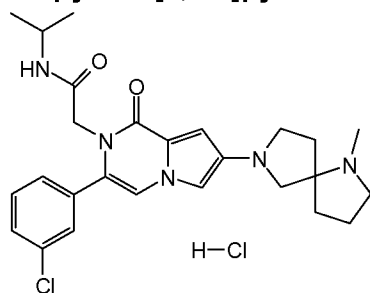
The title compound was prepared with an analogous procedure to that described in Example 50 in 6.3 mg yield from 2-[3-(3-chlorophenyl)-7-iodo-1-oxopyrrolo[1,2-a]pyrazin-

2(1H)-yl]-N-(1-methylethyl)acetamide (60 mg, prepared with an analogous procedure to that described in P63) and 1-methyl-1,7-diazaspiro[4.4]nonane (156 mg, P132).

¹H NMR (400 MHz, CDCl₃) δ 7.32-7.46 (m, 4H), 6.83 (s, 1H), 6.45-6.63 (m, 2H), 5.95-6.06 (m, 1H), 4.31 (s, 2H), 3.99-4.11 (m, 1H), 3.16-3.39 (m, 3H), 2.92 (d, 1H), 2.71-2.87 (m, 2H), 2.36 (s, 3H), 2.14-2.27 (m, 1H), 1.70-1.98 (m, 5H), 1.12-1.18 (d, 6H).

MS (m/z): 482 [MH]⁺.

Example 96: 2-[3-(3-chlorophenyl)-7-(1-methyl-1,7-diazaspiro[4.4]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E96)

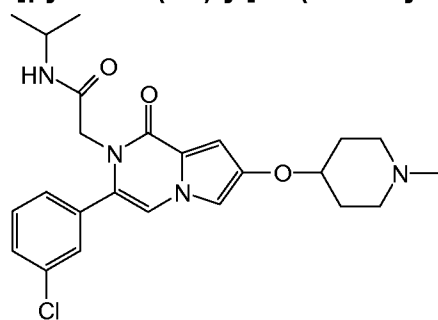


The title compound was prepared with an analogous procedure to that described in Example 5 in 6.3 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-(1-methyl-1,7-diazaspiro[4.4]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (5.9 mg, E95).

¹H NMR (400 MHz, DMSO) δ 10.33-10.53 (m, 1H), 7.75-7.82 (m, 1H), 7.45-7.57 (m, 3H), 7.37-7.43 (m, 1H), 7.27-7.31 (m, 1H), 6.84-6.89 (m, 1H), 6.42-6.55 (m, 1H), 4.19-4.29 (s, 2H), 3.68-3.78 (m, 1H), 3.51-3.68 (m, 2H), 2.9-3.25 (m, 2H), 2.69-2.79 (m, 3H), 2.51 (s, 3H), 1.92-2.3 (m, 5H), 0.92-1.11 (d, 6H).

MS (m/z): 482 [MH]⁺.

Example 97: 2-[3-(3-chlorophenyl)-7-[(1-methyl-4-piperidinyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E97)



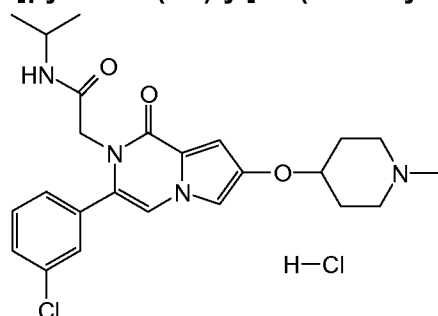
To a solution of 1,1-dimethylethyl 4-[(3-(3-chlorophenyl)-2-{2-[(1-methylethyl)amino]-2-oxoethyl}-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl)oxy]-1-piperidinecarboxylate (54 mg, P109) in DCM (0.4 mL), trifluoroacetic acid (0.1 mL) was added and the reaction mixture was stirred 2 h at RT. The mixture was concentrated under reduced pressure, the residue was taken up with DCM and saturated NaHCO₃, the organic phase was washed with brine, dried over Na₂SO₄ and the solvent removed under vacuum to give 35 mg of the

corresponding crude free base. This material was dissolved in THF (0.1 mL) and MeOH (0.1 mL), formaldehyde (9.10 μ l) (37% aqueous solution) and sodium cyanoborohydride (9.61 mg) were subsequently added. Then the solution was stirred for 30 min at RT. Saturated NaHCO_3 was added, the reaction mixture was concentrated under reduced pressure and the residue was partitioned between DCM and water. The organic phase was separated, washed with water, brine, dried over sodium sulphate and the solvent removed under vacuum. The residue was purified by FC on silica eluting with DCM/MeOH (from 100% to 85% of MeOH) to give the title compound (21 mg).

^1H NMR (400 MHz, CDCl_3): δ 7.42 - 7.47 (m, 2 H) 7.37 - 7.40 (m, 2 H) 6.82 (s, 1 H) 6.79 - 6.81 (m, 2 H) 5.82 - 5.93 (m, 1 H) 4.31 (s, 2 H) 4.14 (d, 1 H) 4.00 - 4.10 (m, 1 H) 2.66 - 2.78 (m, 2 H) 2.32 (s, 3 H) 2.21 - 2.31 (m, 2 H) 2.06 (s, 2 H) 1.80 - 1.92 (m, 2 H) 1.15 (d, 6 H).

MS (m/z): 457 $[\text{MH}]^+$.

Example 98: 2-[3-(3-chlorophenyl)-7-[(1-methyl-4-piperidinyloxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E98)

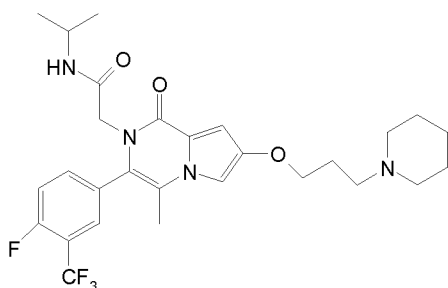


The title compound was prepared with an analogous procedure to that described in Example 2 in 21 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-[(1-methyl-4-piperidinyloxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (21 mg, E97).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.82 (br. s., 1 H) 7.78 (d, 1 H) 7.35 - 7.60 (m, 4 H) 7.14 - 7.33 (m, 2 H) 6.67 - 6.71 (m, 1 H) 4.28 - 4.65 (m, 1 H) 4.22 (s, 2 H) 3.67 - 3.82 (m, 1 H) 2.97 - 3.56 (m, 4 H) 2.78 (s, 3 H) 1.68 - 2.37 (m, 4 H) 0.97 (d, 6 H).

MS (m/z): 457 $[\text{MH}]^+$.

Example 99: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-{[3-(1-piperidinyloxy)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E99)

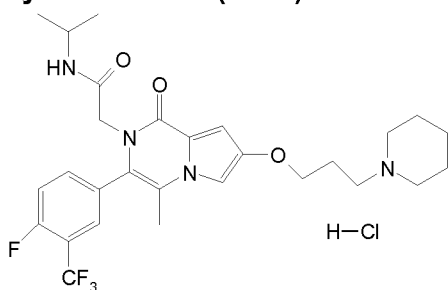


To a solution of 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-hydroxy-4-methyl-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (330 mg, P115) in dry DMF (3 mL), potassium carbonate (429 mg) and 1-(3-chloropropyl)piperidine hydrochloride (231 mg) were added at rt and the mixture was heated to 100°C and left stirring at that temperature overnight. The day after the mixture was diluted with AcOEt and washed with ice and brine. Organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude was purified first by scx cartridge eluting first with MeOH then with NH₃ 2M in MeOH, then by flash chromatography on SI column (eluent: DCM/(DCM:MeOH:NH₃(aq) = 9:1:0.1) from 100% to 0% of DCM) and at the end by flash chromatography on NH column (eluent: Cy/AcOEt from 0% to 100% of AcOEt) to give the title compound (186 mg).

¹H NMR (500 MHz, CDCl₃) δ 7.58-7.68 (m, 2H), 7.31-7.40 (m, 1H), 6.86-6.91 (d, 1H), 6.79-6.85 (d, 1H), 5.85-5.94 (m, 1H), 4.11-4.33 (m, 2H), 4.06 (t, 2H), 3.91-4.02 (m, 1H), 2.46-2.54 (m, 2H), 2.36-2.45 (m, 4H), 2.04 (s, 3H), 1.95-2.03 (m, 2H), 1.56-1.67 (m, 5H), 1.45-1.51 (m, 1H), 1.12 (d, 6H).

MS (m/z): 550 [MH]⁺.

Example 100: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E100)

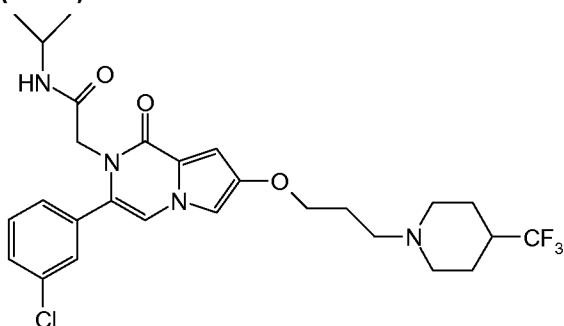


The title compound was prepared with an analogous procedure to that described in Example 5 in 189 mg yield from 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (186 mg, E99).

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.45 (br. S., 1H), 7.60-7.80 (m, 4H), 7.24 (d, 1H), 6.69 (d, 1H), 3.90-4.40 (m, 4H), 3.60-3.73 (m, 1H), 3.42-3.53 (m, 2H), 3.11-3.25 (m, 2H), 2.81-2.98 (m, 2H), 2.08-2.21 (m, 2H), 1.98 (s, 3H), 1.32-1.88 (m, 6H), 0.86-0.97 (m, 6H).

MS (m/z): 550 [MH]⁺.

Example 101: 2-[3-(3-chlorophenyl)-1-oxo-7-({3-[4-(trifluoromethyl)-1-piperidiny]propyl}oxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E101)

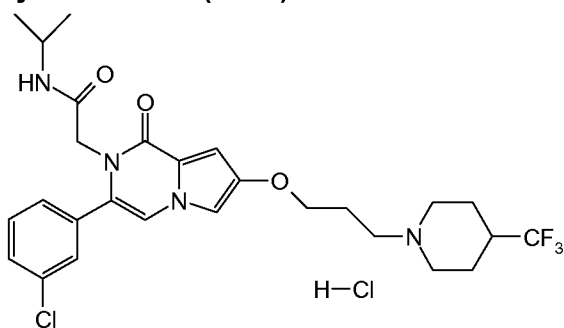


The title compound was prepared with an analogous procedure to that described in Example 19 in 20 mg yield from 2-[3-(2-chlorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (120 mg, P116) and 4-(trifluoromethyl)piperidine (137 mg).

¹H-NMR (CDCl₃): δ 7.46-7.36 (m, 4H); 6.82 (s, 1H); 6.81-6.78 (m, 2H); 5.85 (broad s, 1H); 4.31 (broad s, 2H); 4.11-4.00 (m, 3H); 3.08-3.00 (m, 2H); 2.55-2.50 (m, 2H); 2.04-1.83 (m, 7H); 1.72-1.62 (m, 2H); 1.16 (d, 6H).

MS (m/z): 553 [MH]⁺.

Example 102: 2-[3-(3-chlorophenyl)-1-oxo-7-({3-[4-(trifluoromethyl)-1-piperidiny]propyl}oxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E102)

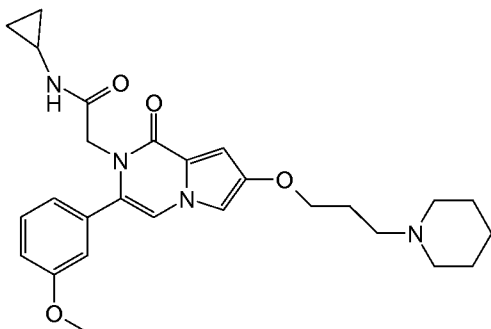


The title compound was prepared with an analogous procedure to that described in Example 5 in 20.8 mg yield from 2-[3-(3-chlorophenyl)-1-oxo-7-({3-[4-(trifluoromethyl)-1-piperidiny]propyl}oxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (20 mg, E101).

¹H-NMR (DMSO-d₆): δ 9.77 (broad s, 1H); 7.78 (d, 1H); 7.60-7.37 (m, 4H); 7.29 (s, 1H); 7.14 (d, 1H); 6.62 (d, 1H); 4.22 (s, 2H); 4.06 (t, 2H); 3.80-3.67 (m, 1H); 3.66-3.56 (m, 2H); 3.26-3.18 (m, 2H); 3.07-2.92 (m, 2H); 2.22-1.70 (m, 7H); 0.97 (d, 6H).

MS (m/z): 553 [MH]⁺.

Example 103: *N*-cyclopropyl-2-[3-[3-(methoxy)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide (**E103**)

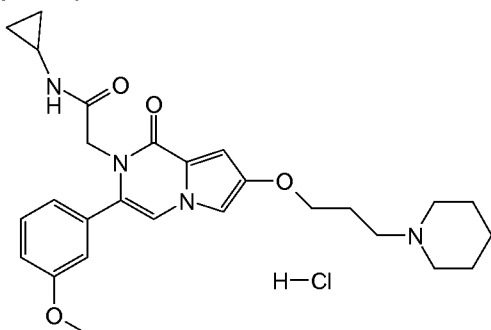


The title compound was prepared with an analogous procedure to that described in Example 15 in 12.9 mg yield from 3-(3-methoxyphenyl)-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (100 mg, P34) and 2-chloro-*N*-cyclopropylacetamide (38.5 mg, commercially available).

¹H NMR (400 MHz, CDCl₃): δ 7.33 - 7.39 (m, 1 H) 6.99 (s, 3 H) 6.85 (d, 1 H) 6.80 (s, 2 H) 6.32 - 6.46 (m, 1 H) 4.33 (s, 2 H) 4.10 - 4.20 (m, 1 H) 4.03 (s, 2 H) 3.86 (s, 3 H) 2.66 - 2.74 (m, 1 H) 2.46 - 2.52 (m, 3 H) 2.36 - 2.46 (m, 4 H) 1.93 - 2.05 (m, 2 H) 1.63 (br. s., 2 H) 1.41 - 1.51 (m, 2 H) 0.68 - 0.87 (m, 2 H) 0.40 - 0.61 (m, 2 H).

MS (m/z): 479 [MH]⁺.

Example 104: *N*-cyclopropyl-2-[3-[3-(methoxy)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide hydrochloride (**E104**)

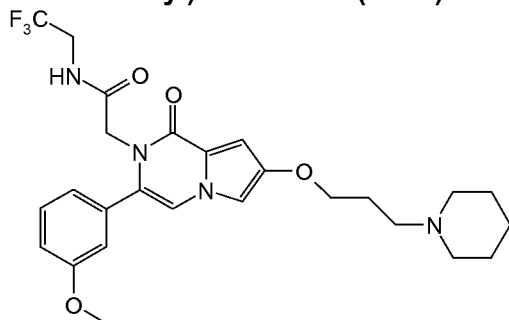


The title compound was prepared with an analogous procedure to that described in Example 5 in 13.1 mg yield from *N*-cyclopropyl-2-[3-[3-(methoxy)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]acetamide (12.9 mg, E103).

¹H NMR (500 MHz, DMSO-*d*₆): δ 9.34 (br. s., 1 H) 7.98 (d, 1 H) 7.37 (t, 1 H) 7.23 (s, 1 H) 7.15 (d, 1 H) 6.93 - 7.08 (m, 3 H) 6.55 - 6.63 (m, 1 H) 4.18 (s, 2 H) 3.98 - 4.08 (m, 2 H) 3.77 (s, 3 H) 3.42 - 3.52 (m, 2 H) 3.12 - 3.24 (m, 2 H) 2.80 - 2.96 (m, 2 H) 2.51 - 2.54 (m, 1 H) 2.07 - 2.19 (m, 2 H) 1.58 - 1.90 (m, 5 H) 1.31 - 1.45 (m, 1 H) 0.51 - 0.62 (m, 2 H) 0.24 - 0.33 (m, 2 H).

MS (m/z): 479 [MH]⁺.

Example 105: 2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(2,2,2-trifluoroethyl)acetamide (E105)

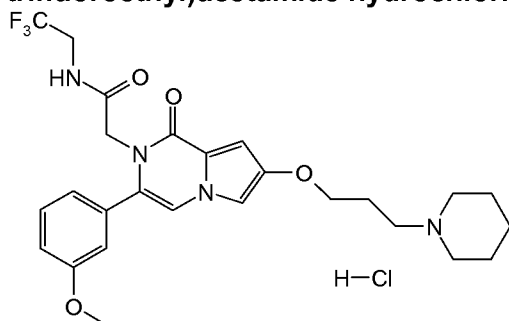


5 The title compound was prepared with an analogous procedure to that described in Example 15 in 12.8 mg yield from 3-(3-methyloxyphenyl)-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-1(2H)-one (100 mg, P34) and 2-chloro-N-(2,2,2-trifluoroethyl)acetamide (50.6 mg, commercially available)

10 ¹H NMR (400 MHz, CDCl₃): δ 7.34 - 7.40 (m, 1 H) 7.00 - 7.04 (m, 1 H) 6.95 - 6.99 (m, 2 H) 6.89 (d, 1 H) 6.82 (s, 1 H) 6.78 - 6.81 (m, 1 H) 4.43 (s, 2 H) 4.04 (s, 2 H) 3.87 - 4.00 (m, 2 H) 3.84 (s, 3 H) 2.35 - 2.54 (m, 5 H) 1.91 - 2.05 (m, 2 H) 1.63 (br. s., 6 H) 1.38 - 1.52 (m, 2 H).

MS (m/z): 521 [MH]⁺.

15 **Example 106:** 2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(2,2,2-trifluoroethyl)acetamide hydrochloride (E106)

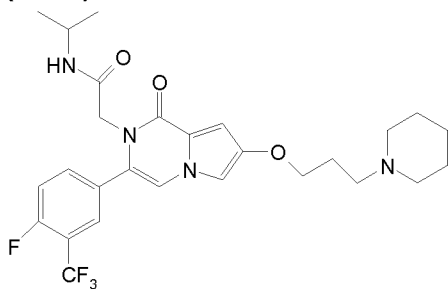


20 The title compound was prepared with an analogous procedure to that described in Example 5 in 12.8 mg yield from 2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(2,2,2-trifluoroethyl)acetamide (12.9 mg, E105).

25 ¹H NMR (500 MHz, DMSO-d₆): δ 9.37 (br. s., 1 H) 8.65 (t, 1 H) 7.36 (t, 1 H) 7.26 (s, 1 H) 7.16 (d, 1 H) 6.93 - 7.08 (m, 3 H) 6.57 - 6.62 (m, 1 H) 4.30 (s, 2 H) 3.98 - 4.08 (m, 2 H) 3.81 - 3.93 (m, 2 H) 3.75 (s, 3 H) 3.42 - 3.52 (m, 2 H) 3.13 - 3.23 (m, 2 H) 2.80 - 2.97 (m, 2 H) 2.05 - 2.22 (m, 2 H) 1.58 - 1.89 (m, 5 H) 1.31 - 1.47 (m, 1 H).

MS (m/z): 521 [MH]⁺.

Example 107: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E107)

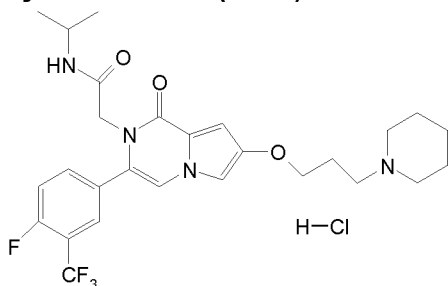


5 The title compound was prepared with an analogous procedure to that described in Example 99 in 8 mg yield from 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-hydroxy-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (30 mg, P121) and 1-(3-chloropropyl)piperidine hydrochloride (17 mg)

10 ¹H NMR (400 MHz, CDCl₃) δ 7.75 (s, 2 H) 7.29 - 7.36 (m, 1 H) 6.75 - 6.85 (m, 3 H) 5.99 - 6.10 (m, 1 H) 4.27 (s, 2 H) 4.03 (t, 3 H) 2.52 (s, 6 H) 1.96 - 2.08 (m, 2 H) 1.80 - 1.92 (m, 1 H) 1.59 - 1.70 (m, 4 H) 1.45 (s, 2 H) 1.15 (d, 6 H).

MS (m/z): 537 [MH]⁺.

15 **Example 108:** 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E108)

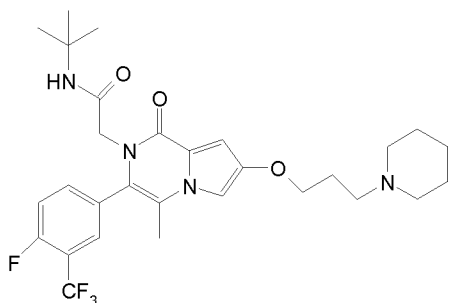


20 The title compound was prepared with an analogous procedure to that described in Example 5 in 8 mg yield from 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (8 mg, E107).

25 ¹H NMR (500 MHz, DMSO-d₆): δ 9.49 (br. s., 1 H) 7.73 - 7.88 (m, 3 H) 7.65 (t, 1 H) 7.31 (s, 1 H) 7.15 (d, 1 H) 6.63 (d, 1 H) 4.25 (br. s., 2 H) 4.04 (t, 2 H) 3.63 - 3.75 (m, 1 H) 3.46 (d, 2 H) 3.13 - 3.23 (m, 2 H) 2.79 - 2.97 (m, 2 H) 2.08 - 2.19 (m, 2 H) 1.81 (d, 2 H) 1.60 - 1.76 (m, 3 H) 1.30 - 1.46 (m, 1 H) 0.93 (d, 6 H).

MS (m/z): 537 [MH]⁺.

30 **Example 109:** N-(1,1-dimethylethyl)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (E109)

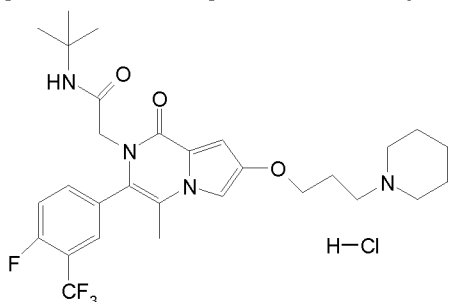


The title compound was prepared with an analogous procedure to that described in Example 99 in 39.5 mg yield from N-(1,1-dimethylethyl)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-hydroxy-4-methyl-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (65 mg, P123) and 1-(3-chloropropyl)piperidine hydrochloride (44.0 mg).

¹H NMR (400 MHz, CDCl₃) δ 7.63-7.68 (m, 1H), 7.58-7.63 (m, 1H), 7.34 (m, 1H), 6.86 (d, 1H), 6.83 (d, 1H), 5.81 (s, 1H), 4.15-4.23 (m, 2H), 4.07 (t, 2H), 2.43-2.69 (m, 6H), 2.05-2.15 (m, 2H), 2.04 (s, 3H), 1.60-1.79 (m, 4H), 1.46-1.57 (m, 2H), 1.30 (s, 9H).

MS (m/z): 565 [MH]⁺.

Example 110: N-(1,1-dimethylethyl)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide hydrochloride (E110)

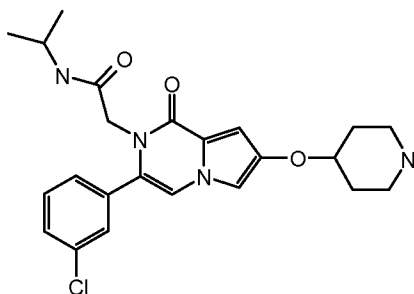


The title compound was prepared with an analogous procedure to that described in Example 2 in 39.5 mg yield from N-(1,1-dimethylethyl)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide (37.7 mg, E109).

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.47 (br. S., 1H), 7.71 (m, 3H), 7.42 (s, 1H), 7.24 (d, 1H), 6.68 (d, 1H), 4.34 (d, 1H), 4.09 (t, 2H), 3.95 (d, 1H), 3.45 (d, 2H), 3.19 (m, 2H), 2.88 (q, 2H), 2.14 (m, 2H), 1.97 (s, 3H), 1.75 (m, 5H), 1.40 (m, 1H), 1.11 (s, 9H).

MS (m/z): 565 [MH]⁺.

Example 111: 2-[3-(3-chlorophenyl)-1-oxo-7-(4-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E111)

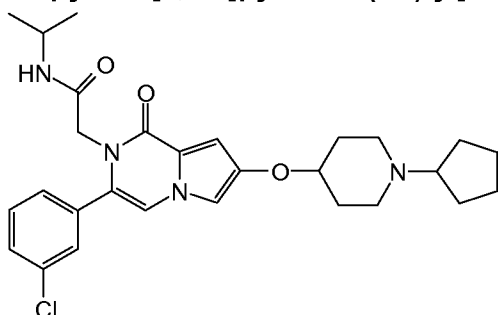


To a solution of 1,1-dimethylethyl 4-[(3-(3-chlorophenyl)-2-{2-[(1-methylethyl)amino]-2-oxoethyl}-1-oxo-1,2-dihydropyrrolo[1,2-a]pyrazin-7-yl)oxy]-1-piperidinecarboxylate (0.21 g, prepared with an analogous procedure to that described in P109) in DCM (4 mL) and trifluoroacetic acid (0.3 mL) was added at RT. After 1h the reaction mixture was concentrated under reduced pressure, the residue was dissolved in methanole and purified by SCX cartridge eluting with MeOH and 2N NH₃ /MeOH to give the title compound (53 mg).

¹H NMR (400 MHz, DMSO-*d*₆): δ 9.09 - 9.33 (m, 1 H) 7.71 - 7.92 (m, 1 H) 7.48 (d, 5 H) 7.23 (s, 1 H) 6.92 (s, 1 H) 6.36 (s, 1 H) 4.20 (br. s., 2 H) 3.66 - 3.84 (m, 1 H) 2.50 (br. s., 8 H) 0.97 (d, 6 H) .

MS (m/z): 443 [MH]⁺

Example 112: 2-[3-(3-chlorophenyl)-7-[(1-cyclopentyl-4-piperidinyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E112)

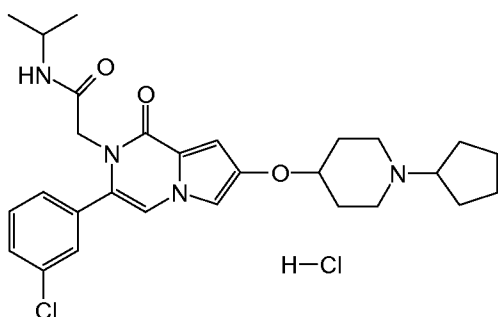


The title compound was prepared with an analogous procedure to that described in Example 71 in 8 mg yield from 2-[3-(3-chlorophenyl)-1-oxo-7-(4-piperidinyl)oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (25 mg, E111) and cyclopentanone (10 mg, commercially available).

¹H NMR (400 MHz, CDCl₃): δ 7.43 - 7.47 (m, 2 H) 7.37 - 7.41 (m, 2 H) 6.83 (s, 1 H) 6.81 (s, 2 H) 5.84 - 5.99 (m, 1 H) 4.31 (s, 2 H) 4.13 - 4.21 (m, 1 H) 4.01 - 4.10 (m, 1 H) 2.80 - 2.94 (m, 2 H) 2.52 - 2.64 (m, 1 H) 2.31 - 2.45 (m, 1 H) 2.03 - 2.17 (m, 2 H) 1.83 - 1.98 (m, 4 H) 1.65 - 1.82 (m, 4 H) 1.54 - 1.64 (m, 2 H) 1.40 - 1.54 (m, 1 H) 1.16 (d, 6 H).

MS (m/z): 511 [MH]⁺.

Example 113: 2-[3-(3-chlorophenyl)-7-[(1-cyclopentyl-4-piperidinyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E113)

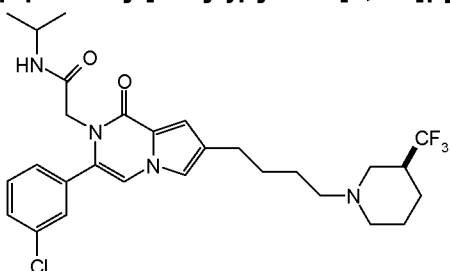


The title compound was prepared with an analogous procedure to that described in Example 2 in 8 mg yield as a white solid from 2-[3-(3-chlorophenyl)-7-[(1-cyclopentyl-4-piperidinyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (8 mg, E112).

¹H NMR (500 MHz, DMSO-d₆): δ 9.74 - 9.92 (m, 1 H) 7.72 - 7.82 (m, 1 H) 7.53 - 7.60 (m, 1 H) 7.46 - 7.52 (m, 2 H) 7.38 - 7.43 (m, 1 H) 7.24 - 7.32 (m, 1 H) 7.14 - 7.21 (m, 1 H) 6.68 - 6.74 (m, 1 H) 4.47 - 4.61 (m, 0 H) 4.33 - 4.46 (m, 0 H) 4.17 - 4.29 (m, 2 H) 3.67 - 3.84 (m, 2 H) 3.35 - 3.62 (m, 4 H) 2.96 - 3.21 (m, 2 H) 2.25 - 2.34 (m, 0 H) 1.95 - 2.18 (m, 4 H) 1.76 - 1.90 (m, 1 H) 1.65 - 1.80 (m, 3 H) 1.49 - 1.63 (m, 2 H) 1.19 - 1.29 (m, 1 H) 0.97 (d, 6 H).

MS (m/z): 511 [MH]⁺.

Example 114: 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S/3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E114)



The title compound was prepared with an analogous procedure to that described in Example 88 in 89 mg yield from mixture of 2-[3-(3-chlorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide and 2-[(3-(3-chlorophenyl)-7-[(3-hydroxypropyl)oxy]pyrrolo[1,2-a]pyrazin-1-yl)oxy]-N-(1-methylethyl)acetamide (100 mg, P116).

¹H-NMR (CDCl₃): δ 7.48-7.38 (m, 4H); 6.82 (s, 1H); 6.81-6.77 (m, 2H); 5.88 (broad s, 1H); 4.31 (broad s, 2H); 4.10-4.01 (m, 3H); 3.11-3.05 (m, 1H); 2.96-2.89 (m, 1H); 2.59-2.52 (m, 2H); 2.41-2.30 (m, 1H); 2.03-1.89 (m, 6H); 1.82-1.74 (m, 1H); 1.36-1.27 (m, 1H); 1.15 (d, 6H).

MS (m/z): 553[MH]⁺

2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S/3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (48mg) was submitted to preparative HPLC using a chiral column chiralpack AD-H, eluent A: n-

hexane; B: ethanol + 0.1% isopropylamine, gradient isocratic 40/60% v/v A/B, flow rate 13 mL/min, detection UV at 235 nm to give the separated enantiomers (retention times given were obtained using an analytical HPLC using a chiral column chiralpack AD-H, 25x0.46cm, eluent A: n-hexane; B: ethanol + 0.1% isopropylamine, gradient isocratic 40/60% v/v A/B, flow rate 0.8 mL/min, detection UV at 235 nm):

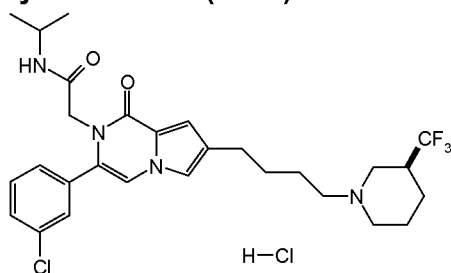
Example 115: 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E115)

Enantiomer 1 (Rt. = 14.13min) in 21 mg yield as white solid;

Example 116: 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E116)

Enantiomer 2 (Rt. = 19.88 min) in 16 mg yield as white solid.

Example 117: 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E117)

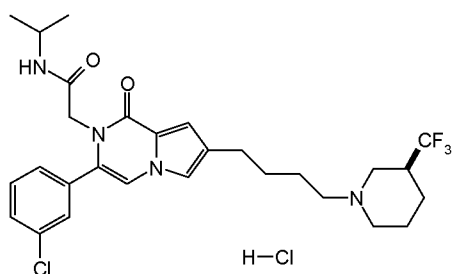


The title compound was prepared with an analogous procedure to that described in Example 5 in 22 mg yield from 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (21 mg, Enantiomer 1, E115).

¹H-NMR (DMSO-d₆): δ 9.96 (broad s, 1H); 7.78 (d, 1H); 7.61-7.37 (m, 4H); 7.28 (s, 1H); 7.14 (d, 1H); 6.62 (s, 1H); 4.22 (broad s, 2H); 4.05 (t, 2H); 3.80-3.63 (m, 2H); 3.62-3.52 (m, 1H); 3.30-3.20 (m, 2H); 3.14-22.81 (m, 3H); 2.26-2.13 (m, 2H); 2.04-1.41 (m, 4H); 0.97 (d, 6H).

MS (m/z): 553 [MH]⁺

Example 118: 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E118)



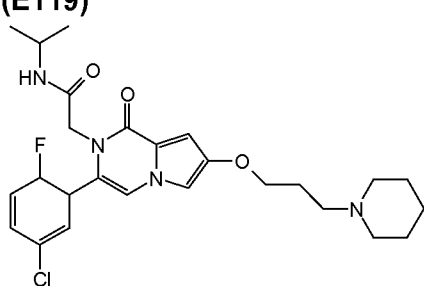
The title compound was prepared with an analogous procedure to that described in Example 5 in 17 mg yield from 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-

5 methylethyl)acetamide (16 mg, Enantiomer 2, E116).

¹H-NMR (DMSO-*d*₆): δ 9.96 (broad s, 1H); 7.78 (d, 1H); 7.61-7.37 (m, 4H); 7.28 (s, 1H); 7.14 (d, 1H); 6.62 (s, 1H); 4.22 (broad s, 2H); 4.05 (t, 2H); 3.80-3.63 (m, 2H); 3.62-3.52 (m, 1H); 3.30-3.20 (m, 2H); 3.14-22.81 (m, 3H); 2.26-2.13 (m, 2H); 2.04-1.41 (m, 4H); 0.97 (d, 6H).

10 **MS (*m/z*):** 553 [MH]⁺

Example 119: 2-[3-(3-chloro-6-fluoro-2,4-cyclohexadien-1-yl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E119)

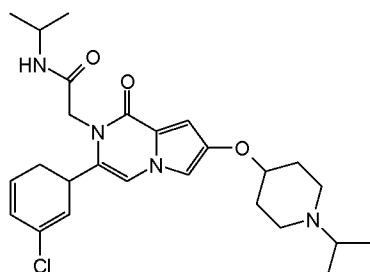


The title compound was prepared with an analogous procedure to that described in Example 19 in 1.5 mg yield from 2-[3-(5-chloro-2-fluorophenyl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (12 mg, P129).

¹H-NMR (400 MHz, CHLOROFORM-*d*): δ 7.40 - 7.49 (m, 2 H) 7.10 - 7.18 (m, 1 H) 6.87 (d, 1 H) 6.82 - 6.84 (m, 1 H) 6.81 (s, 1 H) 5.80 - 5.96 (m, 1 H) 3.94 - 4.08 (m, 3 H) 2.37 - 2.62 (m, 4 H) 1.96 - 2.12 (m, 2 H) 1.55 - 1.74 (m, 8 H) 1.43 - 1.54 (m, 2 H) 1.24 - 1.31 (m, 1 H) 1.06 - 1.19 (m, 6 H).

MS (*m/z*): 503 [MH]⁺

Example 120: 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-{[1-(1-methylethyl)-4-piperidinyl]oxy}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E120)

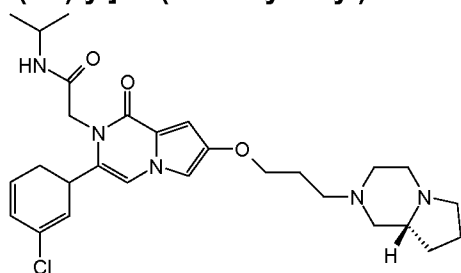


The title compound was prepared with an analogous procedure to that described in Preparation 82 in 3 mg yield from 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-hydroxy-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (30 mg, P131) and 1-(1-methylethyl)-4-piperidinol (21 mg, commercially available).

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.77 (d, 1 H) 7.54 - 7.59 (m, 1 H) 7.46 - 7.53 (m, 2 H) 7.39 - 7.44 (m, 1 H) 7.23 - 7.24 (m, 1 H) 7.15 (d, 1 H) 6.56 - 6.62 (m, 1 H) 4.23 (br. s., 2 H) 4.07 - 4.18 (m, 1 H) 3.62 - 3.85 (m, 1 H) 2.61 - 2.80 (m, 3 H) 2.26 - 2.38 (m, 2 H) 1.89 - 2.06 (m, 2 H) 1.49 - 1.68 (m, 2 H) 0.99 (d, 12 H).

MS (m/z): 485[MH]⁺

Example 121: 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-({3-[(8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl}oxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E121)

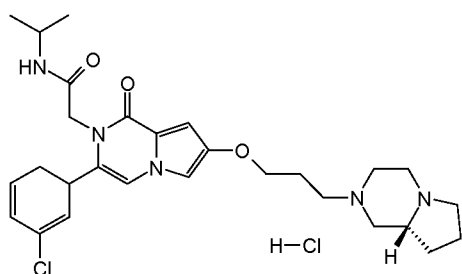


The title compound was prepared with an analogous procedure to that described in Example 19 in 14 mg yield from 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (80 mg, prepared with an analogous procedure to that described in P116) and (8aR)-octahydropyrrolo[1,2-a]pyrazine (152 mg, commercially available).

¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.33 - 7.54 (m, 4 H) 6.71 - 6.89 (m, 3 H) 5.94 (d, *J*=7.58 Hz, 1 H) 4.32 (s, 2 H) 3.94 - 4.14 (m, 3 H) 2.98 - 3.17 (m, 3 H) 2.89 (d, *J*=8.84 Hz, 1 H) 2.49 - 2.68 (m, 2 H) 2.30 (s, 4 H) 1.70 - 2.07 (m, 7 H) 1.15 (d, *J*=6.57 Hz, 6 H).

MS (m/z): 526[MH]⁺

Example 122: 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-({3-[(8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl}oxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E122)

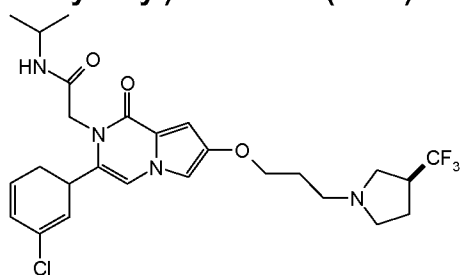


The title compound was prepared with an analogous procedure to that described in Example 2 in 14 mg yield from 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-({3-[(8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl}oxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (14 mg, E121).

¹H NMR (500 MHz, DMSO-d₆): δ 11.26 - 12.05 (m, 1 H) 7.74 - 7.84 (m, 1 H) 7.53 - 7.59 (m, 1 H) 7.49 (s, 2 H) 7.36 - 7.44 (m, 1 H) 7.28 (s, 1 H) 7.10 - 7.18 (m, 1 H) 6.57 - 6.65 (m, 1 H) 4.17 - 4.33 (m, 2 H) 4.00 - 4.11 (m, 2 H) 3.67 - 3.81 (m, 1 H) 3.40 (br. s., 8 H) 1.54 - 2.31 (m, 8 H) 1.18 - 1.34 (m, 2 H) 0.97 (d, 6 H).

MS (m/z): 526 [MH]⁺.

Example 123: 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-1-oxo-7-({3-[(3S/3R)-3-(trifluoromethyl)-1-pyrrolidiny]propyl}oxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E123)

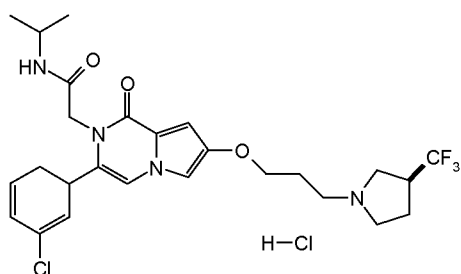


The title compound was prepared with an analogous procedure to that described in Example 19 in 5 mg yield from 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (51 mg, prepared with an analogous procedure to that described in P116) and (3S/3R)-3-(trifluoromethyl)pyrrolidine (22 mg, commercially available).

¹H NMR (400 MHz, CHLOROFORM-d) δ 7.33 - 7.51 (m, 4 H) 6.74 - 6.86 (m, 3 H) 5.90 (d, J=7.58 Hz, 1 H) 4.32 (s, 2 H) 3.99 - 4.12 (m, 3 H) 2.43 - 2.97 (m, 7 H) 1.86 - 2.17 (m, 4 H) 1.10 - 1.20 (m, 6 H).

MS (m/z): 539 [MH]⁺

Example 124: 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-1-oxo-7-({3-[(3S/3R)-3-(trifluoromethyl)-1-pyrrolidiny]propyl}oxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E124)

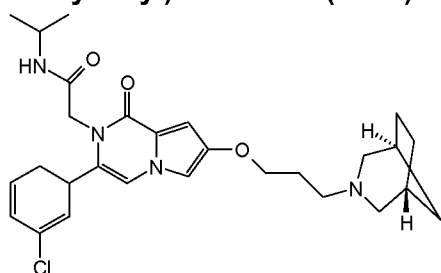


The title compound was prepared with an analogous procedure to that described in Example 2 in 5 mg yield from 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-1-oxo-7-({3-[(3S/3R)-3-(trifluoromethyl)-1-pyrrolidinyl]propyl}oxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (5 mg, E123).

¹H NMR (500 MHz, DMSO-d₆): δ 10.34 - 10.82 (m, 1 H) 7.74 - 7.82 (m, 1 H) 7.53 - 7.59 (m, 1 H) 7.46 - 7.52 (m, 2 H) 7.37 - 7.43 (m, 1 H) 7.25 - 7.31 (m, 1 H) 7.11 - 7.17 (m, 1 H) 6.55 - 6.69 (m, 1 H) 4.17 - 4.31 (m, 2 H) 3.98 - 4.10 (m, 2 H) 3.64 - 3.81 (m, 3 H) 3.09 - 3.24 (m, 1 H) 1.83 - 2.45 (m, 5 H) 1.17 - 1.31 (m, 2 H) 1.03 - 1.13 (m, 1 H) 0.97 (d, 6 H)

MS (m/z): 539 [MH]⁺.

Example 125: 2-[7-({3-[(1R,5S)-3-azabicyclo[3.2.1]oct-3-yl]propyl}oxy)-3-(3-chloro-2,4-cyclohexadien-1-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E125)

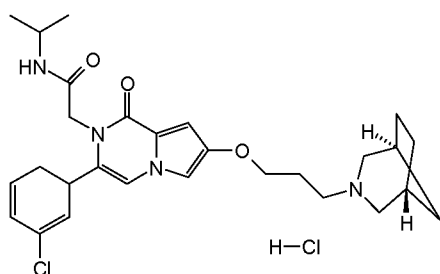


The title compound was prepared with an analogous procedure to that described in Example 19 in 26 mg yield from 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (70 mg, prepared with an analogous procedure to that described in P116) and (74 mg, commercially available).

¹H NMR (400 MHz, CHLOROFORM-d) δ 7.33 - 7.51 (m, 4 H) 6.74 - 6.88 (m, 3 H) 5.92 (d, J=7.33 Hz, 1 H) 4.32 (s, 2 H) 3.96 - 4.16 (m, 3 H) 2.71 (br. s., 2 H) 2.47 (br. s., 2 H) 2.14 (br. s., 2 H) 1.86 - 2.09 (m, 4 H) 1.43 - 1.76 (m, 6 H) 1.16 (d, J=6.57 Hz, 6 H).

MS (m/z): 511 [MH]⁺.

Example 126: 2-[7-({3-[(1R,5S)-3-azabicyclo[3.2.1]oct-3-yl]propyl}oxy)-3-(3-chloro-2,4-cyclohexadien-1-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E126)



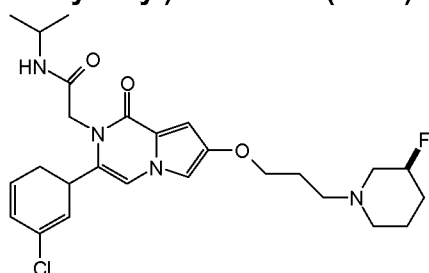
The title compound was prepared with an analogous procedure to that described in Example 2 in 26 mg yield from 2-[7-({3-[(1R,5S)-3-azabicyclo[3.2.1]oct-3-yl]propyl}oxy)-3-(3-chloro-2,4-cyclohexadien-1-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-

5 methylethyl)acetamide (26 mg, E125).

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.13 (br. s., 1 H) 7.79 (d, *J*=7.83 Hz, 1 H) 7.55 (dd, 1 H) 7.46 - 7.51 (m, 2 H) 7.40 (d, *J*=7.83 Hz, 1 H) 7.27 (s, 1 H) 7.14 (d, *J*=1.96 Hz, 1 H) 6.60 (d, 1 H) 4.22 (br. s., 2 H) 4.01 (t, *J*=5.87 Hz, 2 H) 3.68 - 3.78 (m, 1 H) 3.25 - 3.35 (m, 2 H) 3.11 - 3.18 (m, 2 H) 2.99 (t, *J*=10.76 Hz, 2 H) 2.34 (br. s., 2 H) 2.08 - 2.19 (m, 2 H) 1.79 - 1.87 (m, 2 H) 1.68 - 1.77 (m, 2 H) 1.66 (d, *J*=11.25 Hz, 1 H) 1.41 - 1.50 (m, 1 H) 0.96 (d, *J*=6.36 Hz, 6 H).

MS (*m/z*): 511 [MH]⁺.

Example 127: 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-({3-[(3S/3R)-3-fluoro-1-piperidinyl]propyl}oxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E127)

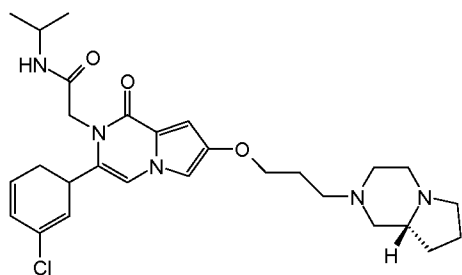


The title compound was prepared with an analogous procedure to that described in Example 19 in 26 mg yield from 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (80 mg, prepared with an analogous procedure to that described in P116) and (3S/3R)-3-fluoropiperidine (80 mg, commercially available).

¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.33 - 7.50 (m, 4 H) 6.72 - 6.87 (m, 3 H) 5.92 (br. s., 1 H) 4.52 - 4.81 (m, 1 H) 4.32 (s, 2 H) 3.97 - 4.19 (m, 3 H) 2.68 - 2.87 (m, 1 H) 2.25 - 2.64 (m, 4 H) 1.48 - 2.14 (m, 7 H) 1.16 (d, *J*=6.57 Hz, 6 H).

MS (*m/z*): 503 [MH]⁺.

Example 128: 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-({3-[(8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl}oxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E128)

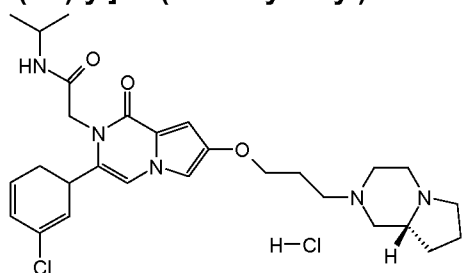


The title compound was prepared with an analogous procedure to that described in Example 19 in 12.5 mg yield from 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-[(3-hydroxypropyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (70 mg, prepared with an analogous procedure to that described in P116) and (8aS)-octahydropyrrolo[1,2-a]pyrazine (64 mg, commercially available).

¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.33 - 7.54 (m, 4 H) 6.71 - 6.89 (m, 3 H) 5.94 (d, *J*=7.58 Hz, 1 H) 4.32 (s, 2 H) 3.94 - 4.14 (m, 3 H) 2.98 - 3.17 (m, 3 H) 2.89 (d, *J*=8.84 Hz, 1 H) 2.49 - 2.68 (m, 2 H) 2.30 (s, 4 H) 1.70 - 2.07 (m, 7 H) 1.15 (d, *J*=6.57 Hz, 6 H).

MS (m/z): 526[MH]⁺

Example 129: 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-[(3-[(8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide hydrochloride (E129)

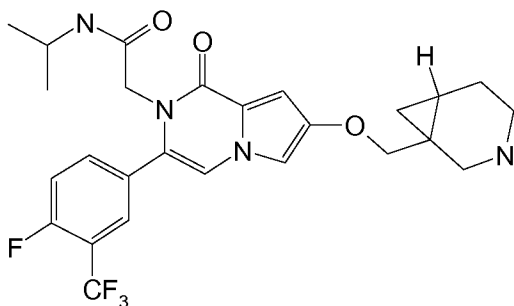


The title compound was prepared with an analogous procedure to that described in Example 2 in 13 mg yield from 2-[3-(3-chloro-2,4-cyclohexadien-1-yl)-7-[(3-[(8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl)oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (12.5 mg, E128).

¹H NMR (500 MHz, DMSO-*d*₆): δ 11.06 - 11.95 (m, 1 H) 7.76 - 7.83 (m, 1 H) 7.53 - 7.60 (m, 1 H) 7.45 - 7.52 (m, 2 H) 7.37 - 7.43 (m, 1 H) 7.25 - 7.31 (m, 1 H) 7.11 - 7.18 (m, 1 H) 6.58 - 6.65 (m, 1 H) 4.15 - 4.31 (m, 2 H) 3.98 - 4.13 (m, 2 H) 3.66 - 3.83 (m, 1 H) 3.36 (s, 8 H) 1.75 - 2.30 (m, 8 H) 1.53 - 1.75 (m, 1 H) 1.18 - 1.30 (m, 1 H) 0.97 (d, 6 H).

MS (m/z): 526 [MH]⁺.

Example 130: 2-[7-[(1R,6S/1S,6R))-3-azabicyclo[4.1.0]hept-1-ylmethyl]oxy]-3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (E130)



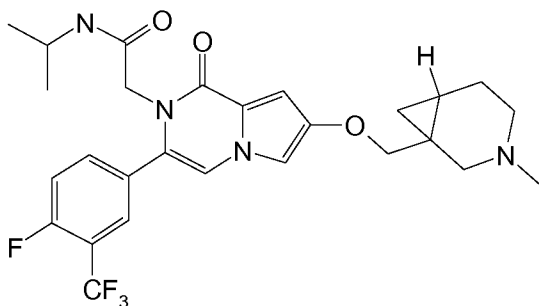
To a stirred solution of 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-hydroxy-1-oxopyrrolo[1,2-
 5 a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide (P121, 75 mg, 0.182 mmol), 1,1-
 dimethylethyl (1*R*,6*S*/1*S*,6*R*)-1-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate
 (P139, 65 mg, 0.286 mmol) and TPP (86 mg, 0.328 mmol) in DCM (2.4 mL), at 0 °C and
 under a nitrogen atmosphere, a solution of DEAD (59 mg, 0.339 mmol) in DCM (0.4 mL)
 was added. The ice-bath was removed and the reaction mixture was stirred at RT for 3h.

10 The reaction mixture was concentrated under reduced pressure and the crude material
 was purified by FC on silica (eluting with Cy/EA from 8/2 to 4/6) to give a mixture
 containing the required product and triphenylphosphine oxide.

This mixture was dissolved in DCM (1 mL) and trifluoroacetic acid (0.1 mL, 1.298 mmol)
 was added at RT. After 1h the reaction mixture was concentrated under reduced
 15 pressure, the residue was dissolved in methanol and passed through a SCX cartridge (2g)
 eluting with MeOH and 2*N* NH₃ /MeOH. The crude product obtained was purified by FC
 on silica (eluting with DCM/MeOH from 1/0 to 97/3) to give 31 mg of the title product.

NMR (¹H, DMSO): δ 7.75 (m, 2H), 7.31 (m, 1H), 6.78 (m, 3H), 6.08 (m, 1H), 4.26 (bs,
 2H), 4.02 (m, 1H), 3.83-3.69 (dd, 2H), 3.25-3.14 (dd, 2H), 2.60 (m, 2H), 1.92 (m, 1H), 1.65
 20 (m, 1H), 1.14 (dd, 6H), 1.06 (m, 1H), 0.73 (m, 1H), 0.62 (m, 1H); **MS(*m/z*):** 521.14 [MH]⁺.

**Example 131: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-({[(1*R*,6*S*/1*S*,6*R*)-3-methyl-
 3-azabicyclo[4.1.0]hept-1-yl]methyl}oxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-N-(1-
 methylethyl)acetamide (E131)**

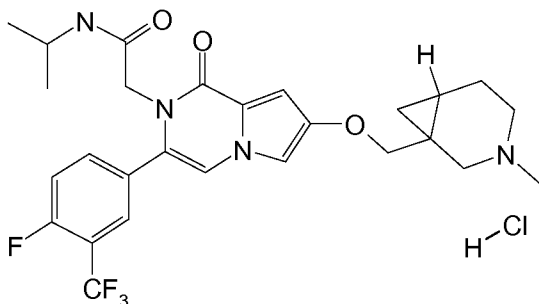


To a stirred solution of 2-[7-({[(1*R*,6*S*/1*S*,6*R*)-3-azabicyclo[4.1.0]hept-1-ylmethyl}oxy]-3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-

5 methylethyl)acetamide (E130, 31 mg, 0.060 mmol) in THF (0.1 ml) and Methanol (0.1 ml), at RT, aqueous 36% w/w formaldehyde (6 μ l, 0.078 mmol) was added, followed after 5 min by sodium triacetoxyborohydride (18 mg, 0.085 mmol) and the reaction mixture was stirred for 1h. 1% aqueous HCl was added up to pH ~5, the mixture was concentrated under reduced pressure. The residue was dissolved in methanol and the solution was passed through a SCX cartridge (1g), eluting with methanol and 2N NH₃/MeOH. The organic phase was concentrated under reduced pressure and the crude product was purified by FC on silica (eluting with DCM/MeOH from 1/0 to 97/3) to give 24 mg of the title product.

NMR (¹H, CDCl₃): δ 7.75 (m, 2H), 7.30 (d, 1H), 6.69(m, 3H), 5.99 (m, 1H), 4.26 (m, 2H), 4.02 (m, 1H), 3.92-3.68 (dd, 2H), 2.82-2.60 (dd, 2H), 2.24 (s, 3H), 2.07 (m, 2H), 1.30 (m, 2H), 1.15 (m, 6H), 1.00 (m, 1H), 0.69 (m, 2H). **MS(*m/z*):** 535.16 [MH]⁺.

Example 132: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-({[(1*R*,6*S*/1*S*,6*R*)-3-methyl-3-azabicyclo[4.1.0]hept-1-yl]methyl}oxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide hydrochloride (E132)



To a stirred solution of 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-({[(1*R*,6*S*/1*S*,6*R*)-3-methyl-3-azabicyclo[4.1.0]hept-1-yl]methyl}oxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-

methylethyl)acetamide (E131, 2 mg) in DCM (0.1 mL), at RT, 1M/ether HCl (4 µl) was added. The mixture was concentrated under *vacuum*, the solid was triturated with ethyl acetate to give 2 mg of the title compound as a pale orange solid.

NMR (¹H, DMSO-*d*₆): δ 9.50 (br. s., 1 H), 7.75 - 7.88 (m, 3 H), 7.59 - 7.68 (m, 1 H), 7.32 (s, 1 H), 7.12 (s, 1 H), 6.60 (s, 1 H), 4.24 (s, 2 H), 4.04 - 4.10 (m, 1 H), 3.53 - 3.88 (m, 3 H), 2.96 - 3.25 (m, 2 H), 2.65 - 2.87 (m, 4 H), 2.17 - 2.32 (m, 1 H), 1.77 - 1.91 (m, 1 H), 1.20 - 1.28 (m, 1 H), 0.77 - 0.96 (m, 8 H). **MS(*m/z*):** 535.16 [MH]⁺.

Example 133 and Example 134: 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-({[(1*S*,6*R* or 1*R*,6*S*)-3-methyl-3-azabicyclo[4.1.0]hept-1-yl]methyl}oxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide (E133, Enantiomer 1) and 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-({[(1*R*,6*S* or 1*S*,6*R*)-3-methyl-3-azabicyclo[4.1.0]hept-1-yl]methyl}oxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide (E134, Enantiomer 2)

2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-({[(1*R*,6*S*/1*S*,6*R*)-3-methyl-3-azabicyclo[4.1.0]hept-1-yl]methyl}oxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide (E131, 22 mg) was submitted to chiral preparative separation under the following Chromatographic conditions:

Column = Chiralpak AD-H

Mobile phase = *n*-Hexane/Ethanol +0.1% isopropylamine 50/50v/v

Flow rate = 0.8 ml/min

DAD= 210-340 nm

To give 4 mg of the title compound **E133**, Enantiomer 1 (RT 11.495 min)

NMR (¹H, CDCl₃): δ 7.68 - 7.81 (m, 2 H), 7.30 (t, 1 H), 6.76 - 6.83 (m, 3 H), 5.96 (d, 1 H), 4.25 (br. s., 2 H), 3.97 - 4.09 (m, 1 H), 3.90 (d, 1 H), 3.66 (d, 1 H), 2.78 (d, 1 H) 2.63 (d, 1 H), 2.23 (s, 3 H), 2.16 - 2.29 (m, 1 H), 2.01 - 2.15 (m, 2 H), 1.76 - 1.88 (m, 1 H), 1.15 (d, 6 H), 0.96 - 1.05 (m, 1 H), 0.68 - 0.76 (m, 1 H), 0.63 - 0.69 (m, 1 H). **MS(*m/z*):** 535.15 [MH]⁺.

and 4 mg of the title compound **E134**, Enantiomer 2 (RT 14.346 min)

MS(*m/z*): 535.15 [MH]⁺.

***In vitro* profile**

The *in vitro* assessment of the V1b antagonist compounds used a functional assay systems to determine the potency against the V1b receptor.

The functional activity of the compounds of the invention for the V1b receptor may be determined by the FLIPR/Ca²⁺ assay as described below. Such potency is typically calculated as an IC₅₀ value obtained in FLIPR experiments as the concentration of a compound necessary to decrease 50% of the calcium release following cells exposure to a concentration of AVP eliciting 80% response (i.e. EC80).

In the context of the present invention pIC₅₀ values (corresponding to the antilogarithm of IC₅₀) are used instead of IC₅₀; pIC₅₀ results are only estimated to be accurate to about 0.3-0.5.

Functional activity at recombinant human V1b receptor

The functional activity at the human V1b (h-V1b) receptor stably expressed in Chinese Hamster Ovary (CHO) cells was assessed using FLIPR/Ca²⁺ methodology.

AVP is an endogenous agonist and can activate the receptor, thereupon causing an increase in the level of calcium in the cells sensed by Fluo4-AM and measured by FLIPR. Antagonist effects are monitored by the blockade or decrease in calcium release once cells co-expressing h-V1b receptor are exposed to a concentration of AVP eliciting 80% response (i.e. EC80). A non-linear, 4 parameter logistic curve-fit of the data generated pIC₅₀ value.

Cells are cultured in DMEM/F12 supplemented with 10% FBS, 2mM Glutamine and 200µg/mL G418. The day before a FLIPR experiment, cells are plated out into 384-well Poly-D-Lysine coated FLIPR plates at a density of 400'000 cells/mL corrects to give 20'000 cells per 50µL per well using medium without antibiotics.

On the day of experiment, cells are washed with an assay buffer containing 20mM HEPES/NaOH, 145mM NaCl, 5mM KCl, 1mM MgCl₂, 2mM CaCl₂, 1g/L D-glucose and 2.5mM probenecid, pH 7.3 and loaded with 2µM Fluo-4 AM for 60 min at 37 °C and 5% CO₂. The excess of dye solution is removed by washing cells with buffer. Compound solutions, prepared by serially diluting compounds in neat DMSO and then a final 1:50 dilution step in assay buffer added with 0.05% pluronic acid, are added and incubated with the loaded cells for 10 min at 37 °C and 5% CO₂. The final concentration of DMSO in the assay was kept constant at 0.4%.

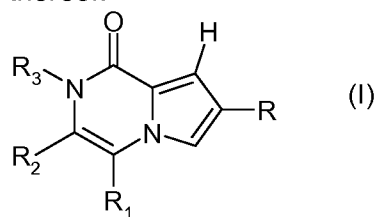
Cells are then put in the FLIPR for the stimulus addition corresponding to a concentration of AVP eliciting 80% of the response. The response of cells to the agonist is fast and measured for 2min after AVP addition.

All the compounds of formula (I) are believed to bind the V1b receptor.

Preferred examples show pIC₅₀ comprised between 6 and 10 towards V1b receptor.

Claims

1. A compounds of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



wherein

R is -X-[CH₂]_nCR₄R₅-Y; or a group G;

R₁ is H or C1-C4 alkyl;

R₂ is aryl, heteroaryl or C3-C7 cycloalkyl, which may be substituted with one or more: halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, -CN;

R₃ is -CH₂-C(=O)-NH-R₆;

X is -CR₇R₈-, -O-, -NR₉-, -S-;

Y is -NR₁₀R₁₁

R₄ is H or C1-C4 alkyl;

R₅ is H or C1-C4 alkyl;

R₆ is C1-C6 alkyl, C3-C6 cycloalkyl; C3-C6 cycloalkyl-(C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;

R₇ is H or C1-C4 alkyl;

R₈ is H or C1-C4 alkyl;

R₉ is H or C1-C4 alkyl;

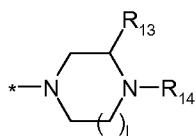
R₁₀ is H or C1-C4 alkyl, or together with R₁₁ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR₁₂; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;

R₁₁ is H or C1-C4 alkyl;

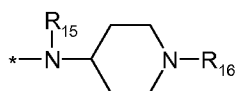
R₁₂ is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl-(C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;

G

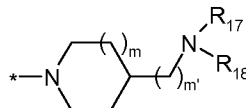
is one of the groups selected from the list consisting of G1, G2, G3, G4, G5, G6, G7, G8, G9, G10, G11 and G12:



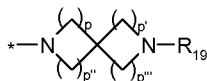
G1



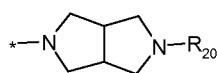
G2



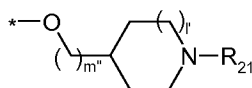
G3



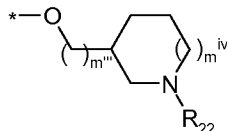
G4



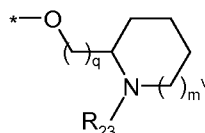
G5



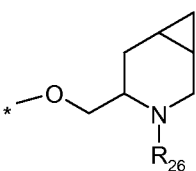
G6



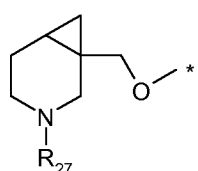
G7



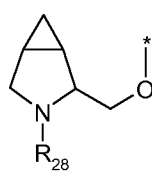
G8



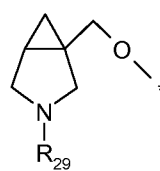
G9



G10



G11



G12

R₁₃

is H or C1-C4 alkyl, or together with R₁₄ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and -NR₂₄; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;

R₁₄, R₁₆

is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl-(C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;

R₁₅, R₁₇

correspond to H or C1-C4 alkyl and may assume different meanings;

5	R ₁₈	is H or C1-C4 alkyl, or together with R ₁₇ forms a 4-8 saturated or unsaturated heterocycle ring which may comprise a further heteroatom selected from O, S and –NR ₂₅ ; such heterocycle may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;
10	R ₁₉ , R ₂₀ , R ₂₁ , R ₂₂ , R ₂₃ , R ₂₄ , R ₂₅	is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl-(C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;
15	R ₂₆ , R ₂₇ , R ₂₈ , R ₂₉	is H, C1-C6 alkyl, C3-C7 cycloalkyl; C3-C6 cycloalkyl-(C1-C2 alkyl); which may be substituted by one or more halogen, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy;
	l, l'	correspond to 1 or 2 and may assume different meanings;
	m, m', m'', m''', m ^{iv} , m ^v	correspond to 0, 1 or 2 and may assume different meanings;
	n	is 1, 2 or 3;
20	q	is 1, 2 or 3;
	p, p', p'', p'''	correspond to 0, 1, 2 or 3 and may assume different meanings.

2. A compound of formula (I) according to claim 1, which is selected from the list consisting of:

- 25 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[5-(1-piperidiny)pentyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 30 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[1-methyl-4-(1-piperidiny)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[1-methyl-3-(1-piperidiny)propyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 35 N-(1-methylethyl)-2-[3-[4-(methyloxy)phenyl]-1-oxo-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[1-oxo-3-phenyl-7-[4-(1-piperidiny)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[3-(1-piperidiny)propyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 40 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{[3-(1-piperidiny)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;

- N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-(4-morpholinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S/2R)-2-methyl-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one;
- 5 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S or 2R)-2-methyl-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one;
- 2-{2-[(1-methylethyl)amino]-2-propen-1-yl}-3-[3-(methyloxy)phenyl]-7-{4-[(2S or 2R)-2-methyl-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-1(2H)-one;
- 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 10 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1,1-dimethylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(cyclopropylmethyl)acetamide;
- 15 2-[7-{4-[Meso -2,6-dimethyl-1-piperidinyl]butyl}-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidinyl)butyl]-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[7-[4-(4,4-difluoro-1-piperidinyl)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 20 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-[4-(4-methyl-1-piperazinyl)butyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[3-(3-methylphenyl)-1-oxo-7-[4-(1-piperidinyl)butyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 25 N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{4-[4-(trifluoromethyl)-1-piperidinyl]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-(1-methylethyl)-2-[3-[3-(methyloxy)phenyl]-7-{4-[4-(methyloxy)-1-piperidinyl]butyl}-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- N-ethyl-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 30 N-(1-methylethyl)-2-[1-oxo-7-[4-(1-piperidinyl)butyl]-3-{3-[(trifluoromethyl)oxy]phenyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[3-(3-fluorophenyl)-1-oxo-7-{[3-(1-piperidinyl)propyl]oxy}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 35 2-[3-(3-chlorophenyl)-7-(4-methyl-1-piperazinyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-[4-(dimethylamino)-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-(4-methylhexahydro-1H-1,4-diazepin-1-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 40 2-[3-(3-chlorophenyl)-7-[methyl(1-methyl-4-piperidinyl)amino]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

- 2-[7-[4-(dimethylamino)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-4-methyl-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
5 2-[3-(3-chlorophenyl)-1-oxo-7-[4-(1-pyrrolidinyl)-1-piperidinyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[7-[4-(2,6-dimethyl-4-morpholinyl)butyl]-3-[3-(methyloxy)phenyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-[(1-methyl-3-piperidinyl)methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
10 2-[3-(5-chloro-2-methylphenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(2-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
15 2-[3-(3-chlorophenyl)-7-[[2-(1-methyl-4-piperidinyl)ethyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-(2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-(2-methyl-2,7-diazaspiro[3.5]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
20 2-[3-(3-chlorophenyl)-7-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-[4-[2-(dimethylamino)ethyl]-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
25 2-[7-(1,4'-bipiperidin-1'-yl)-3-(3-chlorophenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-(9-methyl-3,9-diazaspiro[5.5]undec-3-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-cyclobutylacetamide;
30 2-[3-(3-chlorophenyl)-7-[[2-(1-methyl-2-piperidinyl)ethyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chloro-4-fluorophenyl)-1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
35 N-(1,1-dimethylethyl)-2-[1-oxo-7-[[3-(1-piperidinyl)propyl]oxy]-3-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
2-[3-(3-chlorophenyl)-7-[3-(dimethylamino)-1-piperidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
2-[3-(3-chlorophenyl)-7-[3-(dimethylamino)-1-pyrrolidinyl]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
40 2-[3-(3-chlorophenyl)-7-(9-methyl-2,9-diazaspiro[5.5]undec-2-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

- 2-[3-(3-chlorophenyl)-7-[[1-(1-methyl-4-piperidinyloxy)methyl]oxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-(1-methyl-1,7-diazaspiro[4.4]non-7-yl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 5 2-[3-(3-chlorophenyl)-7-[(1-methyl-4-piperidinyloxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-[[3-(1-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-((3-[4-(trifluoromethyl)-1-piperidinyloxy]propyl)oxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 10 N-cyclopropyl-2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[[3-(1-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[3-[3-(methyloxy)phenyl]-1-oxo-7-[[3-(1-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(2,2,2-trifluoroethyl)acetamide;
- 15 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxo-7-[[3-(1-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- N-(1,1-dimethylethyl)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-4-methyl-1-oxo-7-[[3-(1-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-(4-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 20 2-[3-(3-chlorophenyl)-7-[(1-cyclopentyl-4-piperidinyloxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S/3R)-3-(trifluoromethyl)-1-piperidinyloxy]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 25 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyloxy]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-1-oxo-7-{4-[(3S or 3R)-3-(trifluoromethyl)-1-piperidinyloxy]butyl}pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(5-chloro-2-fluorophenyl)-1-oxo-7-[[3-(1-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 30 2-[3-(3-chlorophenyl)-7-[[1-(1-methylethyl)-4-piperidinyloxy]-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-((3-[(8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl)oxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 35 2-[3-(3-chlorophenyl)-1-oxo-7-((3-[3-(trifluoromethyl)-1-pyrrolidinyloxy]propyl)oxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[7-((3-[(1R,5S)-3-azabicyclo[3.2.1]oct-3-yl]propyl)oxy)-3-(3-chlorophenyl)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 2-[3-(3-chlorophenyl)-7-[[3-(3-fluoro-1-piperidinyloxy)pyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;
- 40 2-[3-(3-chlorophenyl)-7-((3-[(8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]propyl)oxy)-1-oxopyrrolo[1,2-a]pyrazin-2(1H)-yl]-N-(1-methylethyl)acetamide;

2-[7-{{(1*R*,6*S*/1*S*,6*R*))-3-azabicyclo[4.1.0]hept-1-ylmethyl}oxy}-3-[4-fluoro-3-(trifluoromethyl)phenyl]-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide;

2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-{{(1*R*,6*S*/1*S*,6*R*))-3-methyl-3-azabicyclo[4.1.0]hept-1-yl}methyl}oxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-

5 methylethyl)acetamide;

2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-{{(1*S*,6*R* or 1*R*,6*S*))-3-methyl-3-azabicyclo[4.1.0]hept-1-yl}methyl}oxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-methylethyl)acetamide (Enantiomer 1);

2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-7-{{(1*R*,6*S* or 1*S*,6*R*))-3-methyl-3-azabicyclo[4.1.0]hept-1-yl}methyl}oxy)-1-oxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-*N*-(1-

10 methylethyl)acetamide (Enantiomer 2);
and pharmaceutically acceptable salts and solvate thereof.

3. A compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

4. A compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of depression.

5. A compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of anxiety.

6. Use of a compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of depression.

7. Use of a compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of anxiety.

8. Method of treating depression comprising administering to a human in need thereof a compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

9. Method of treating anxiety comprising administering to a human in need thereof a compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

10. A pharmaceutical composition comprising a compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/054777

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D519/00 C07D487/04 A61K31/4985 A61P25/22 A61P25/24

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 practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/033764 A (ORGANON NV [NL]; LETOURNEAU JEFFREY [US]; JOKIEL PATRICK [US]; NAPIER) 20 March 2008 (2008-03-20) Page 2, 2nd paragraph; page 142, 1st paragraph below table.claims 1-11; table 2	1-10
P,A	WO 2009/017236 A (TAISHO PHARMA CO LTD [JP]; KUWADA TAKESHI [JP]; NOZAWA DAI [JP]; ISHIZ) 5 February 2009 (2009-02-05) abstract	1-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

23 July 2009

Date of mailing of the international search report

29/07/2009

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/054777

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WO 2008033764 A	20-03-2008	AR 062731 A1	26-11-2008
		AU 2007296634 A1	20-03-2008
		CA 2663161 A1	20-03-2008
		EP 2069315 A2	17-06-2009
		US 2008090802 A1	17-04-2008
WO 2009017236 A	05-02-2009	NONE	