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(54) **Title:** PYRIDONE AND PYRIDAZINONE DERIVATIVES AS MCH ANTAGONISTS

(57) **Abstract:** The present invention relates to pyridone and pyridazinone derivatives as listed in claim 1 including their salts. Moreover the invention relates to pharmaceutical compositions containing at least one compound according to the invention. By virtue of their MCH- receptor antagonistic activity the pharmaceutical compositions according to the invention are suitable for the treatment of metabolic disorders and/or eating disorders, particularly obesity, bulimia, anorexia, hyperphagia and diabetes.



WO 2009/103478 A1

PYRIDONE AND PYRIDAZINONE DERIVATIVES AS MCH ANTAGONISTS

The present invention relates to pyridone and pyridazinone derivatives, the physiologically acceptable salts thereof as well as their use as MCH antagonists and their use in preparing a pharmaceutical preparation which is suitable for the prevention and/or treatment of symptoms and/or diseases caused by MCH or causally connected with MCH in some other way. The invention also relates to the use of a compound according to the invention for influencing eating behaviour and for reducing body weight and/or for preventing any increase in body weight in a mammal. It further relates to compositions and medicaments containing a compound according to the invention and processes for preparing them.

Background to the Invention

The intake of food and its conversion in the body is an essential part of life for all living creatures. Therefore, deviations in the intake and conversion of food generally lead to problems and also illness. The changes in the lifestyle and nutrition of humans, particularly in industrialised countries, have promoted morbid overweight (also known as corpulence or obesity) in recent decades. In affected people, obesity leads directly to restricted mobility and a reduction in the quality of life. There is the additional factor that obesity often leads to other diseases such as, for example, diabetes, dyslipidaemia, high blood pressure, arteriosclerosis and coronary heart disease. Moreover, high body weight alone puts an increased strain on the support and mobility apparatus, which can lead to chronic pain and diseases such as arthritis or osteoarthritis. Thus, obesity is a serious health problem for society.

The term obesity means an excess of adipose tissue in the body. In this connection, obesity is fundamentally to be seen as the increased level of fatness which leads to a health risk. There is no sharp distinction between normal individuals and those suffering from obesity, but the health risk accompanying obesity is presumed to rise continuously as the level of fatness increases. For simplicity's sake, in the present invention, individuals with a Body Mass Index (BMI), which is defined as the body weight measured in kilograms divided by the height (in metres) squared, above a value of 25 and more particularly above 30, are preferably regarded as suffering from obesity.

Apart from physical activity and a change in nutrition, there is currently no convincing treatment option for effectively reducing body weight. However, as obesity is a major risk

factor in the development of serious and even life-threatening diseases, it is all the more important to have access to pharmaceutical active substances for the prevention and/or treatment of obesity. One approach which has been proposed recently is the therapeutic use of MCH antagonists (cf. *inter alia* WO 01/21577, WO 01/82925).

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Melanin-concentrating hormone (MCH) is a cyclic neuropeptide consisting of 19 amino acids. It is synthesised predominantly in the hypothalamus in mammals and from there travels to other parts of the brain by the projections of hypothalamic neurones. Its biological activity is mediated in humans through two different G-protein-coupled receptors (GPCRs) from the family of rhodopsin-related GPCRs, namely the MCH receptors 1 and 2 (MCH-1R, MCH-2R).

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Investigations into the function of MCH in animal models have provided good indications for a role of the peptide in regulating the energy balance, i.e. changing metabolic activity and food intake [1,2]. For example, after intraventricular administration of MCH in rats, food intake was increased compared with control animals. Additionally, transgenic rats which produce more MCH than control animals, when given a high-fat diet, responded by gaining significantly more weight than animals without an experimentally altered MCH level. It was also found that there is a positive correlation between phases of increased desire for food and the quantity of MCH mRNA in the hypothalamus of rats. However, experiments with MCH knock-out mice are particularly important in showing the function of MCH. Loss of the neuropeptide results in lean animals with a reduced fat mass, which take in significantly less food than control animals.

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The anorectic effects of MCH are presumably mediated in rodents through the $G_{\alpha s}$ -coupled MCH-1R [3-6], as, unlike primates, ferrets and dogs, no second MCH receptor subtype has hitherto been found in rodents. After losing the MCH-1R, knock-out mice have a lower fat mass, an increased energy conversion and, when fed on a high fat diet, do not put on weight, compared with control animals. Another indication of the importance of the MCH system in regulating the energy balance results from experiments with a receptor antagonist (SNAP-7941) [3]. In long term trials the animals treated with the antagonist lose significant amounts of weight.

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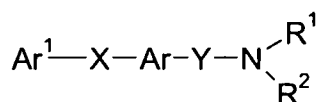
In addition to its anorectic effect, the MCH-1R antagonist SNAP-7941 also achieves additional anxiolytic and antidepressant effects in behavioural experiments on rats [3]. Thus, there are clear indications that the MCH-MCH-1R system is involved not only in regulating the energy balance but also in affectivity.

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Literature:

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- 15 6. Takekawa, S., et al., T-226296: A novel, orally active and selective melanin-concentrating hormone receptor antagonist. Eur J Pharmacol, 2002. **438**(3): p. 129-35.

In the patent literature (WO 01/21577, WO 01/82925) amine compounds of the general formula



are proposed as MCH antagonists for the treatment of obesity.

Further patent publication related to amine compounds with MCH antagonistic activity are for example: WO 04/024702, WO 04/039780, WO 04/039764, WO 05/063239, WO 05/085221, WO 05/103031, WO 05/103032, WO 05/103029, WO 05/100285, WO 05/103002, WO 05/85200, WO 2007/048802.

In the WO 03/068230, WO 2005/018557 (Pharmacia Corp.) substituted pyridinones are described. The WO 2004/087677 (Pharmacia Corp.) is related to pyrimidone derivatives and the WO 03/059891 as well as the WO 2005/007632 (Pharmacia Corp.) refer to pyridazinone derivatives. These compounds are described as modulators of p38 MAP kinase.

In the EP 1741703 A1, EP 1916239 A1, EP1939194, EP 1921065 A1 and WO 2007/142217 (Banyu Pharmaceuticals) pyridone derivatives are described as antagonists of the MCH receptor.

In the WO 2008/022979 (Boehringer Ingelheim), published 28.02.2008, pyridone derivatives with MCH antagonistic activity are described.

5 Aim of the invention

The aim of the present invention is to identify compounds which are especially effective as MCH antagonists. Another aim of this invention is to provide compounds which are effective as MCH antagonists and which possess advantageous pharmacokinetic properties. The invention also sets out to provide compounds which can be used to influence the eating
10 habits of mammals and achieve a reduction in body weight, particularly in mammals, and/or prevent an increase in body weight.

The present invention further sets out to provide new pharmaceutical compositions which are suitable for the prevention and/or treatment of symptoms and/or diseases caused by MCH or
15 otherwise causally connected to MCH. In particular, the aim of this invention is to provide pharmaceutical compositions for the treatment of metabolic disorders such as obesity and/or diabetes as well as diseases and/or disorders which are associated with obesity and diabetes. Other objectives of the present invention are concerned with demonstrating advantageous uses of the compounds according to the invention. The invention also sets out
20 to provide a process for preparing the compounds according to the invention. Other aims of the present invention will be immediately apparent to the skilled man from the foregoing remarks and those that follow.

Object of the invention

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In a first aspect the present invention relates to one or more compounds selected from the group consisting of the following pyridone and pyridazinone derivatives

1.1	4-Benzyloxy-1-{2-[4-(4-methoxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.2	4-Benzyloxy-1-{2-[4-(4-hydroxy-4-trifluoromethyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.3	4-Benzyloxy-1-{2-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.4	4-Benzyloxy-1-{2-[4-[(2-hydroxy-ethylamino)-methyl]-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one

1.5	4-Benzyloxy-1-{2-[4-(tert-butylamino-methyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.6	4-Benzyloxy-1-{2-[4-(isopropylamino-methyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.7	4-Benzyloxy-1-{2-[4-[(1-hydroxy-cyclopropylmethyl)-amino]-methyl]-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.8	4-Benzyloxy-1-(2-{4-[(tert-butyl-methyl-amino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.9	4-Benzyloxy-1-[2-(4-cyclopropylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
1.10	4-Benzyloxy-1-[2-(4-[(2-hydroxy-ethyl)-methyl-amino]-methyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
1.11	4-Benzyloxy-1-(2-{4-[(isopropyl-methyl-amino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.12	(S)-4-Benzyloxy-1-{2-[4-(3-fluoro-pyrrolidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.13	(R)-4-Benzyloxy-1-{2-[4-(3-fluoro-pyrrolidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.14	4-Benzyloxy-1-(2-oxo-2-{4-[(3,3,3-trifluoro-propylamino)-methyl]-phenyl}-ethyl)-1H-pyridin-2-one
1.15	4-Benzyloxy-1-(2-{4-[(2,2-dimethyl-propylamino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.16	1-{4-[2-(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-acetyl]-benzyl}-piperidine-4-carbonitrile
1.17	4-Benzyloxy-1-[2-oxo-2-(4-thiomorpholin-4-ylmethyl-phenyl)-ethyl]-1H-pyridin-2-one
1.18	4-Benzyloxy-1-{2-oxo-2-[4-(1-oxo-thiomorpholin-4-ylmethyl)-phenyl]-ethyl}-1H-pyridin-2-one
1.19	4-Benzyloxy-1-(2-{4-[(2,2-difluoro-ethylamino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.20	4-Benzyloxy-1-[2-(4-[(2,2-difluoro-ethyl)-methyl-amino]-methyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
1.21	4-Benzyloxy-1-(2-{4-[(cyclopropyl-methyl-amino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.22	4-Benzyloxy-1-[2-(4-[(1-hydroxy-cyclopropylmethyl)-methyl-amino]-methyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one

2.1	5-Benzyloxy-2-{2-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one
2.2	5-Benzyloxy-2-{2-[4-(4-hydroxy-4-trifluoromethyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one
2.3	5-Benzyloxy-2-[2-(4-cyclopentylaminomethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
2.4	5-Benzyloxy-2-[2-(4-ethylaminomethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
2.5	5-Benzyloxy-2-{2-[4-(isopropylamino-methyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one
2.6	5-Benzyloxy-2-[2-(4-methylaminomethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
2.7	5-Benzyloxy-2-[2-oxo-2-(4-propylaminomethyl-phenyl)-ethyl]-2H-pyridazin-3-one
3.1	4-Benzyloxy-1-{2-[4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-3-methoxy-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
3.2	4-Benzyloxy-1-[2-(4-dimethylaminomethyl-3-methoxy-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
3.3	4-Benzyloxy-1-{2-[4-(4-hydroxy-piperidin-1-ylmethyl)-3-methoxy-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
4.1	4-Benzyloxy-1-[2-(4-dimethylaminomethyl-2-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
4.2	4-Benzyloxy-1-{2-[2-fluoro-4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
5.1	4-Benzyloxy-1-[2-(4-dimethylaminomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
5.2	4-Benzyloxy-1-[2-(3-fluoro-4-methylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
5.3	4-Benzyloxy-1-[2-(4-ethylaminomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
5.4	4-Benzyloxy-1-[2-(4-diethylaminomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
5.5	4-Benzyloxy-1-(2-{4-[(ethyl-methyl-amino)-methyl]-3-fluoro-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
5.6	4-Benzyloxy-1-[2-[3-fluoro-4-(isopropylamino-methyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
5.7	4-Benzyloxy-1-{2-[3-fluoro-4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one

6.1	5-Benzyloxy-2-{2-[3-fluoro-4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one
6.2	5-Benzyloxy-2-[2-(4-dimethylaminomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
6.3	5-Benzyloxy-2-{2-[3-fluoro-4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one
7.1	4-Benzyloxy-1-[2-(5-diethylaminomethyl-pyridin-2-yl)-2-oxo-ethyl]-1H-pyridin-2-one
7.2	4-Benzyloxy-1-[2-(5-dimethylaminomethyl-pyridin-2-yl)-2-oxo-ethyl]-1H-pyridin-2-one
7.3	4-Benzyloxy-1-[2-(5-ethylaminomethyl-pyridin-2-yl)-2-oxo-ethyl]-1H-pyridin-2-one
7.4	4-Benzyloxy-1-{2-[5-(4-hydroxy-piperidin-1-ylmethyl)-pyridin-2-yl]-2-oxo-ethyl}-1H-pyridin-2-one
7.5	4-Benzyloxy-1-{2-[5-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-2-oxo-ethyl}-1H-pyridin-2-one
8.1	4-(4-Fluoro-benzyloxy)-1-(2-{4-[1-(4-hydroxy-4-methyl-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
8.2	4-(4-Fluoro-benzyloxy)-1-(2-{4-[1-(4-hydroxy-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
8.3	4-(4-Chloro-benzyloxy)-1-(2-{4-[1-(4-hydroxy-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
8.4	4-(4-Chloro-benzyloxy)-1-(2-{4-[1-(4-hydroxy-4-methyl-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
8.5	1-(2-{4-[1-(4-Hydroxy-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-4-(4-methoxy-benzyloxy)-1H-pyridin-2-one
8.6	1-(2-{4-[1-(4-Hydroxy-4-methyl-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-4-(4-methoxy-benzyloxy)-1H-pyridin-2-one
9.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-{2-[4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
9.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(4-dimethylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
9.3	4-(5-Chloro-pyridin-2-ylmethoxy)-1-{2-[4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
9.4	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(4-pyrrolidin-1-ylmethyl-phenyl)-ethyl]-1H-pyridin-2-one

9.5	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(4-methylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
9.6	4-(5-Chloro-pyridin-2-ylmethoxy)-1-(2-{4-[(ethyl-methyl-amino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
9.7	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(4-diethylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
9.8	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(4-piperidin-1-ylmethyl-phenyl)-ethyl]-1H-pyridin-2-one
10.1	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-{4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl}-2-oxo-ethyl]-2H-pyridazin-3-one
10.2	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-{4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-phenyl}-2-oxo-ethyl]-2H-pyridazin-3-one
11.1	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(4-piperidin-1-ylmethyl-phenyl)-ethyl]-1H-pyridin-2-one
11.2	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(4-dimethylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
12.1	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-oxo-2-(4-piperidin-1-ylmethyl-phenyl)-ethyl]-2H-pyridazin-3-one
12.2	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(4-dimethylaminomethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
13.1	4-Benzoyloxy-1-{2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-1H-pyridin-2-one
13.2	1-[2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-benzyloxy-1H-pyridin-2-one
14.1	4-Benzoyloxy-1-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-1H-pyridin-2-one
14.2	4-Benzoyloxy-1-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
15.1	5-Benzoyloxy-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
15.2	5-Benzoyloxy-2-[2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl]-2H-pyridazin-3-one
16.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
16.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one

16.3	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
16.4	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
16.5	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
17.1	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
17.2	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-oxo-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
17.3	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
18.1	4-Benzoyloxy-1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
18.2	4-Benzoyloxy-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
19.1	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
19.2	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
20.1	5-Benzoyloxy-2-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
20.2	5-Benzoyloxy-2-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
21.1	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
21.2	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
21.3	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
21.4	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-[2-(2-hydroxy-ethyl)-2,3-dihydro-1H-isoindol-5-yl]-ethyl]-2H-pyridazin-3-one
21.5	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
22.1	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
22.2	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one

23	4-Benzyloxy-1-[2-[4-(1-dimethylaminomethyl-cyclopropyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
24.1	4-Benzyloxy-1-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
24.2	4-Benzyloxy-1-[2-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
25.1	5-Benzyloxy-2-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
25.2	5-Benzyloxy-2-[2-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
26.1	4-Benzyloxy-1-[2-oxo-2-(5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)-ethyl]-1H-pyridin-2-one
26.2	4-Benzyloxy-1-[2-(6-methyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)-2-oxo-ethyl]-1H-pyridin-2-one
27.1	5-Benzyloxy-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
27.2	5-Benzyloxy-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
28.1	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
28.2	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
29.1	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
29.2	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
30	5-Benzyloxy-2-(2-[4-[2-(4-hydroxy-4-methyl-piperidin-1-yl)-ethyl]-phenyl]-2-oxo-ethyl)-2H-pyridazin-3-one
31.1	1-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-(4-fluoro-benzyloxy)-1H-pyridin-2-one
31.2	4-(4-Fluoro-benzyloxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
32.1	2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-5-(4-fluoro-benzyloxy)-2H-pyridazin-3-one
32.2	5-(4-Fluoro-benzyloxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one

33.1	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
33.2	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
34	1-[2-Oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-4-(5-trifluoromethyl-pyridin-2-ylmethoxy)-1H-pyridin-2-one
35.1	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
35.2	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
35.3	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
35.4	5-(5-Bromo-pyridin-2-ylmethoxy)-2-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-2H-pyridazin-3-one
35.5	5-(5-Bromo-pyridin-2-ylmethoxy)-2-{2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-2H-pyridazin-3-one
35.6	5-(5-Bromo-pyridin-2-ylmethoxy)-2-{2-[2-(2-fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-2H-pyridazin-3-one
35.7	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-cyclopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
36.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
36.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
36.3	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
36.4	4-(5-Chloro-pyridin-2-ylmethoxy)-1-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-1H-pyridin-2-one
36.5	4-(5-Chloro-pyridin-2-ylmethoxy)-1-{2-[2-(2-fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-1H-pyridin-2-one
37.1	2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-5-(5-fluoro-pyridin-2-ylmethoxy)-2H-pyridazin-3-one
37.2	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
37.3	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-2H-pyridazin-3-one

38.1	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
38.2	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
38.3	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
38.4	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-1H-pyridin-2-one
38.5	1-{2-[2-(2-Fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-4-(5-fluoro-pyridin-2-ylmethoxy)-1H-pyridin-2-one
39.1	4-(4-Fluoro-benzyloxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
39.2	4-(4-Fluoro-benzyloxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
40.1	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
40.2	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
40.3	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
41.1	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-oxo-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
41.2	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
42.1	4-(4-Fluoro-benzyloxy)-1-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-1H-pyridin-2-one
42.2	4-(4-Fluoro-benzyloxy)-1-{2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-1H-pyridin-2-one
43.1	5-(4-Fluoro-benzyloxy)-2-{2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-2H-pyridazin-3-one
44.1	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
44.2	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-1H-pyridin-2-one
45.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one

45.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-1H-pyridin-2-one
46.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
46.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
47.1	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
47.2	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
48	4-Benzoyloxy-1-[2-hydroxy-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
49.1	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-[2-(2-hydroxy-ethyl)-2,3-dihydro-1H-isoindol-5-yl]-ethyl]-1H-pyridin-2-one
49.2	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-[2-(2-fluoro-ethyl)-2,3-dihydro-1H-isoindol-5-yl]-ethyl]-1H-pyridin-2-one
49.3	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-ethyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
49.4	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-[2-(3-hydroxy-1-methyl-propyl)-2,3-dihydro-1H-isoindol-5-yl]-ethyl]-1H-pyridin-2-one
50.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
50.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
51.1	1-[2-(2,3-Dihydro-1H-isoindol-5-yl)-ethyl]-4-(5-fluoro-pyridin-2-ylmethoxy)-1H-pyridin-2-one
51.2	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
52	4-Benzoyloxy-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-allyl]-1H-pyridin-2-one
53	4-Benzoyloxy-1-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-1H-pyridin-2-one
54	5-Benzoyloxy-2-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-2H-pyridazin-3-one
55	4-Benzoyloxy-1-[2-[4-(1-methyl-piperidin-2-yl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
56	5-Benzoyloxy-2-[2-[4-(1-methyl-piperidin-2-yl)-phenyl]-2-oxo-ethyl]-2H-pyridazin-3-one

57	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
58	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
59	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
60	4-Benzyloxy-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
61	4-Benzyloxy-1-[2,2-difluoro-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
62	4-Benzyloxy-1-[2-(4-imidazol-1-ylmethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
63	4-Benzyloxy-1-[2-(4-imidazol-1-ylmethyl-phenyl)-ethyl]-1H-pyridin-2-one
64	4-Benzyloxy-1-[2-[4-(2-oxo-2H-pyridin-1-ylmethyl)-phenyl]-ethyl]-1H-pyridin-2-one
65	2-[2-(2,3-Dihydro-1H-isoindol-5-yl)-ethyl]-5-(5-fluoro-pyridin-2-ylmethoxy)-2H-pyridazin-3-one
66	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
67	4-(5-Methyl-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
68	4-(5-Methyl-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
69	1-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-(5-methyl-pyridin-2-ylmethoxy)-1H-pyridin-2-one
70	1-{2-[2-(2-Fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-4-(5-methyl-pyridin-2-ylmethoxy)-1H-pyridin-2-one
71	5-(5-Methyl-pyridin-2-ylmethoxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
72	5-(5-Methyl-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
73	2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-5-(5-methyl-pyridin-2-ylmethoxy)-2H-pyridazin-3-one
74	2-{2-[2-(2-Fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-5-(5-methyl-pyridin-2-ylmethoxy)-2H-pyridazin-3-one
75	4-Benzyloxy-1-[2-oxo-2-[4-(1-piperidin-1-yl-cyclopropyl)-phenyl]-ethyl]-1H-pyridin-2-one

76	4-Benzyloxy-1-[2-oxo-2-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)-ethyl]-1H-pyridin-2-one
77	4-Benzyloxy-1-[2-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)-2-oxo-ethyl]-1H-pyridin-2-one
78	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
79	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one

while in each of the above-mentioned compounds one or more C atoms may additionally be mono- or polysubstituted by F, and in each case one or two C atoms independently of one another may additionally have a substituent selected from the group Cl, Br, cyano, C₁₋₄-alkyl, C₁₋₄-alkoxy, difluoromethyl, trifluoromethyl, hydroxy, acetylamino, aminocarbonyl, difluoromethoxy, and trifluoromethoxy, and

an H atom bound to an N atom may in each case be replaced by a group which can be cleaved *in vivo*,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

The invention also relates to the compounds in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the tautomers and in the form of the free bases or corresponding acid addition salts with pharmacologically acceptable acids. The subject of the invention also includes the compounds according to the invention, including their salts, wherein one or more hydrogen atoms are replaced by deuterium.

This invention also includes the physiologically acceptable salts of the compounds according to the invention as described above and hereinafter.

Also covered by this invention are compositions containing at least one compound according to the invention and/ or a salt according to the invention optionally together with one or more physiologically acceptable excipients.

Also covered by this invention are pharmaceutical compositions containing at least one compound according to the invention and/ or a salt according to the invention optionally together with one or more inert carriers and/or diluents.

This invention also relates to the use of at least one compound according to the invention and/or a salt according to the invention, for influencing the eating behaviour of a mammal.

- 5 The invention further relates to the use of at least one compound according to the invention and/or a salt according to the invention, for reducing the body weight and/ or for preventing an increase in the body weight of a mammal.

- 10 The invention also relates to the use of at least one compound according to the invention and/or a salt according to the invention, for preparing a pharmaceutical composition with an MCH receptor-antagonistic activity, particularly with an MCH-1 receptor-antagonistic activity.

- 15 This invention also relates to the use of at least one compound according to the invention and/or a salt according to the invention, for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

- 20 A further object of this invention is the use of at least one compound according to the invention and/or a salt according to the invention, for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of metabolic disorders and/or eating disorders, particularly obesity, bulimia, bulimia nervosa, cachexia, anorexia, anorexia nervosa and hyperphagia.

- 25 The invention also relates to the use of at least one compound according to the invention and/or a salt according to the invention, for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of diseases and/or disorders associated with obesity, particularly diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, pathological glucose tolerance, encephalorrhagia, cardiac insufficiency, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.
- 30

- In addition the present invention relates to the use of at least one compound according to the invention and/or a salt according to the invention, for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of hyperlipidaemia, cellulitis, fat accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affective
- 35

disorders, depression, anxiety, sleep disorders, reproductive disorders, sexual disorders, memory disorders, epilepsy, forms of dementia and hormonal disorders.

5 The invention also relates to the use of at least one compound according to the invention and/or a salt according to the invention, for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of urinary problems, such as for example urinary incontinence, overactive bladder, urgency, nycturia and enuresis.

10 The invention further relates to the use of at least one compound according to the invention and/or a salt according to the invention, for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of dependencies and/or withdrawal symptoms.

15 The invention also relates to a pharmaceutical composition containing a first active substance which is selected from the compounds according to the invention and/or the corresponding salts, as well as a second active substance which is selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, preferably other than MCH antagonists, active substances for the treatment of high blood pressure, active substances for the treatment of dyslipidaemia or hyperlipidaemia, including arteriosclerosis, 20 active substances for the treatment of arthritis, active substances for the treatment of anxiety states and active substances for the treatment of depression, optionally together with one or more inert carriers and/or diluents.

25 The starting materials and intermediate products used in the synthesis of one or more of the compounds according to the invention are also a subject of this invention.

Detailed description of the invention

30 The compounds listed in the experimental section, including the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, are preferred according to the invention.

According a preferred first embodiment the invention relates to one or more of the compounds comprising an 2-oxoethyl-spacer linked to the pyridinone or pyridazinone group wherein said compounds are selected from the group consisting of 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 35 1.7, 1.8, 1.9, 1.10, 1.11, 1.12, 1.13, 1.14, 1.15, 1.16, 1.17, 1.18, 1.19, 1.20, 1.21, 1.22, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 3.1, 3.2, 3.3, 4.1, 4.2, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 6.1, 6.2, 6.3,

7.1, 7.2, 7.3, 7.4, 7.5, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 10.1, 10.2, 11.1, 11.2, 12.1, 12.2, 13.1, 13.2, 14.1, 14.2, 15.1, 15.2, 16.1, 16.2, 16.3, 16.4, 16.5, 17.1, 17.2, 17.3, 23, 24.1, 24.2, 25.1, 25.2, 26.1, 26.2, 27.1, 27.2, 30, 31.1, 31.2, 32.1, 32.2, 34, 40.1, 40.2, 40.3, 41.1, 41.2, 42.1, 42.2, 43.1, 44.1, 44.2, 45.1, 45.2, 53, 54, 55, 56, and
5 62, including the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

According to said first embodiment a preferred subset relates to one or more of the compounds comprising an amino-group which is not part of an azabicyclic moiety wherein
10 said compounds are selected from the group consisting of 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, 1.12, 1.13, 1.14, 1.15, 1.16, 1.17, 1.18, 1.19, 1.20, 1.21, 1.22, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 3.1, 3.2, 3.3, 4.1, 4.2, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 6.1, 6.2, 6.3, 7.1, 7.2, 7.3, 7.4, 7.5, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 10.1, 10.2, 11.1, 11.2, 12.1, 12.2, 23, 30, 53, 54, 55, 56, and 62 including the tautomers, the diastereomers,
15 the enantiomers, the mixtures thereof and the salts thereof.

According to said first embodiment another preferred subset relates to one or more of the compounds comprising an azabicyclic moiety wherein the compounds are selected from the group consisting of 13.1, 13.2, 14.1, 14.2, 15.1, 15.2, 16.1, 16.2, 16.3, 16.4, 16.5, 17.1, 17.2,
20 17.3, 24.1, 24.2, 25.1, 25.2, 26.1, 26.2, 27.1, 27.2, 31.1, 31.2, 32.1, 32.2, 34, 40.1, 40.2, 40.3, 41.1, 41.2, 42.1, 42.2, 43.1, 44.1, 44.2, 45.1, and 45.2, including the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

According a preferred second embodiment the invention relates to one or more of the
25 compounds comprising an azabicyclic moiety which is linked to the pyridinone or pyridazinone group via an optionally substituted ethylene spacer wherein said compounds are selected from the group consisting of 18.1, 18.2, 19.1, 19.2, 20.1, 20.2, 21.1, 21.2, 21.3, 21.4, 21.5, 22.1, 22.2, 28.1, 28.2, 29.1, 29.2, 33.1, 33.2, 35.1, 35.2, 35.3, 35.4, 35.5, 35.6, 35.7, 36.1, 36.2, 36.3, 36.4, 36.5, 37.1, 37.2, 37.3, 38.1, 38.2, 38.3, 38.4, 38.5, 39.1, 39.2,
30 46.1, 46.2, 47.1, 47.2, 48, 49.1, 49.2, 49.3, 49.4, 50.1, 50.2, 51.1, 51.2, 57, 58, 59, 60, 61, 63, 64, 65, 66, 78, and 79, including the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

According to said second embodiment a preferred subset relates to one or more of the
35 compounds comprising an azabicyclic moiety which is linked to the pyridinone or pyridazinone group via a not further substituted ethylene spacer wherein said compounds are

selected from the group consisting of 18.1, 18.2, 19.1, 19.2, 20.1, 20.2, 21.1, 21.2, 21.3, 21.4, 21.5, 22.1, 22.2, 28.1, 28.2, 29.1, 29.2, 33.1, 33.2, 35.1, 35.2, 35.3, 35.4, 35.5, 35.6, 35.7, 36.1, 36.2, 36.3, 36.4, 36.5, 37.1, 37.2, 37.3, 38.1, 38.2, 38.3, 38.4, 38.5, 39.1, 39.2, 46.1, 46.2, 47.1, 47.2, 49.1, 49.2, 49.3, 49.4, 50.1, 50.2, 51.1, 51.2, 65, 66, 78, and 79, including
5 the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

According to said second embodiment another preferred subset relates to one or more of the compounds comprising an azabicyclic moiety which is linked to the pyridinone or pyridazinone group via an 1,1-difluoroethylene spacer wherein said compounds are selected
10 from the group consisting of 57, 58, 59, 60, 61, including the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

The compounds according to the invention as described hereinbefore and hereinafter may optionally be substituted. In case a compound of the invention is additionally substituted one
15 or more C atoms are additionally mono- or polysubstituted by F, and/or one or two C atoms independently of one another additionally have a substituent selected from the group Cl, Br, cyano, C₁₋₄-alkyl, C₁₋₄-alkoxy, difluoromethyl, trifluoromethyl, hydroxy, acetamino, aminocarbonyl, difluoromethoxy, and trifluoromethoxy. Preferred substituents are F, Cl, cyano, methyl, ethyl, methoxy, ethoxy, difluoromethyl, trifluoromethyl, hydroxy, acetamino,
20 aminocarbonyl, difluoromethoxy, and trifluoromethoxy, most preferably F, Cl, cyano, methyl, methoxy, difluoromethyl, trifluoromethyl, and hydroxy,

Most preferably the compounds according to the invention do not possess any additional substituents.

25 Some expressions used hereinbefore and below to describe the compounds according to the invention will now be defined more fully.

The term "optionally substituted" used in this application indicates that the group thus
30 designated is either unsubstituted or mono- or polysubstituted by the substituents specified. If the group in question is polysubstituted, the substituents may be identical or different.

The H atom bound to an N atom (imino or amino group) may in each case be replaced by a group which can be cleaved in vivo. By a group which can be cleaved in vivo from an N atom
35 is meant, for example, a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C₁₋₁₆-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or

hexanoyl group, an allyloxycarbonyl group, a C₁₋₁₆-alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C₁₋₆-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C₁₋₃-alkylsulphonyl-C₂₋₄-alkoxycarbonyl, C₁₋₃-alkoxy-C₂₋₄-alkoxy-C₂₋₄-alkoxycarbonyl or R_eCO-O-(R_fCR_g)-O-CO- group wherein

R_e denotes a C₁₋₈-alkyl, C₅₋₇-cycloalkyl, phenyl or phenyl- C₁₋₃-alkyl group,

R_f denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl or phenyl group and

R_g denotes a hydrogen atom, a C₁₋₃-alkyl or R_eCO-O-(R_fCR_h)-O group wherein R_e and R_f are as hereinbefore defined and R_h is a hydrogen atom or a C₁₋₃-alkyl group,

while the phthalimido group is an additional possibility for an amino group.

The residues and substituents described above may be mono- or polysubstituted by fluorine as described. Preferred fluorinated alkyl groups are fluoromethyl, difluoromethyl and trifluoromethyl. Preferred fluorinated alkoxy groups are fluoromethoxy, difluoromethoxy and trifluoromethoxy. Preferred fluorinated alkylsulphonyl and alkylsulphonyl groups are trifluoromethylsulphonyl and trifluoromethylsulphonyl.

The compounds according to the invention may have basic groups such as e.g. amino functions. The compounds according to the invention may therefore be present as internal salts, as salts with pharmaceutically useable inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids (such as for example maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid) *inter alia*.

The compounds according to the invention may be obtained using methods of synthesis which are known to the one skilled in the art and described in the literature of organic synthesis. Preferably the compounds are obtained as described in the experimental section.

Stereoisomeric compounds according to the invention may chiefly be separated by conventional methods. The diastereomers are separated on the basis of their different physico-chemical properties, e.g. by fractional crystallisation from suitable solvents, by high

pressure liquid or column chromatography, using chiral or preferably non-chiral stationary phases.

Racemates of compounds according to the invention may be separated for example by HPLC on suitable chiral stationary phases (e.g. Chiral AGP, Chiralpak AD). Racemates which contain a basic or acidic function can also be separated via the diastereomeric, optically active salts which are produced on reacting with an optically active acid, for example (+) or (-)-tartaric acid, (+) or (-)-diacetyl tartaric acid, (+) or (-)-monomethyl tartrate or (+)-camphorsulphonic acid, or an optically active base, for example with (R)-(+)-1-phenylethylamine, (S)-(-)-1-phenylethylamine or (S)-brucine.

According to a conventional method of separating isomers, the racemate of a compound according to the invention is reacted with one of the above-mentioned optically active acids or bases in equimolar amounts in a solvent and the resulting crystalline, diastereomeric, optically active salts thereof are separated using their different solubilities. This reaction may be carried out in any type of solvent provided that it is sufficiently different in terms of the solubility of the salts. Preferably, methanol, ethanol or mixtures thereof, for example in a ratio by volume of 50:50, are used. Then each of the optically active salts is dissolved in water, carefully neutralised with a base such as sodium carbonate or potassium carbonate, or with a suitable acid, e.g. with dilute hydrochloric acid or aqueous methanesulphonic acid and in this way the corresponding free compound is obtained in the (+) or (-) form.

The (R) or (S) enantiomer alone or a mixture of two optically active diastereomeric compounds according to the invention may also be obtained by performing the syntheses described above with a suitable reaction component in the (R) or (S) configuration.

As already mentioned, the compounds according to the invention may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically and pharmacologically acceptable salts thereof. These salts may be present on the one hand as physiologically and pharmacologically acceptable acid addition salts of the compounds according to the invention with inorganic or organic acids. The acid addition salts may be prepared, for example, using hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. Moreover, mixtures of the above mentioned acids may be used.

The compounds according to the present invention, including the physiologically acceptable salts, are effective as antagonists of the MCH receptor, particularly the MCH-1 receptor, and exhibit good affinity in MCH receptor binding studies. Pharmacological test systems for MCH-antagonistic properties are described in the following experimental section.

5

As antagonists of the MCH receptor the compounds according to the invention are advantageously suitable as pharmaceutical active substances for the prevention and/or treatment of symptoms and/or diseases caused by MCH or causally connected with MCH in some other way. Generally the compounds according to the invention have low toxicity, they are well absorbed by oral route and have good intracerebral transitivity, particularly brain accessibility. Compounds of the invention predominantly have a good to excellent efficacy on body weight reduction in preclinical models of obesity and/or have advantageous pharmacokinetic properties, in particular AUC (plasma) (AUC = area under the curve), AUC (brain), brain to plasma ratio which can be expressed as AUC (brain)/AUC (plasma), cerebrospinal fluid (CSF) levels, clearance, half life ($t_{1/2}$), in each case in particular in preclinical species such as for example rat, monkey, dog, pig, etc.. The procedures to determine said pharmacokinetic properties are well known to the one skilled in the art and are described in textbooks and literature.

Compounds and pharmaceutical compositions according to this invention can be tested for their efficacy on body weight reduction in rats with diet-induced obesity. To this end, obesity is induced in female HanWistar rats by feeding them a cafeteria diet in addition to their standard diet for 4 to 8 weeks. The cafeteria diet consists of a mixture of palatable commercially available supermarket foods to stimulate energy intake. The rats with diet-induced obesity are treated once or twice daily for for example 2 to 4 weeks by oral administration of either one or more compound according to this invention or vehicle which is usually 0.5% aqueous hydroxyethylcellulose. Prior to start of treatment, the animals are randomized for body weight and the cafeteria diet feeding is continued throughout the study. At the end of the study, the body weight of animals treated with compounds according to this invention is compared to vehicle treatment.

Therefore, MCH antagonists which contain at least one compound according to the invention are particularly suitable in mammals, such as for example rats, mice, guinea pigs, hares, dogs, cats, sheep, horses, pigs, cattle, monkeys and humans, for the treatment and/or prevention of symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

Diseases caused by MCH or otherwise causally connected with MCH are particularly metabolic disorders, such as for example obesity, and eating disorders, such as for example bulimia, including bulimia nervosa. The indication obesity includes in particular exogenic
5 obesity, hyperinsulinaemic obesity, hyperplasmic obesity, hyperphyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, central obesity. This range of indications also includes cachexia, anorexia and hyperphagia.

- 10 Compounds according to the invention may be particularly suitable for reducing hunger, curbing appetite, controlling eating behaviour and/or inducing a feeling of satiation.

In addition, the diseases caused by MCH or otherwise causally connected with MCH also include hyperlipidaemia, cellulitis, fatty accumulation, malignant mastocytosis, systemic
15 mastocytosis, emotional disorders, affectivity disorders, depression, anxiety states, reproductive disorders, sexual disorders, memory disorders, epilepsy, forms of dementia and hormonal disorders.

Compounds according to the invention are also suitable as active substances for the
20 prevention and/or treatment of other illnesses and/or disorders, particularly those which accompany obesity, such as for example diabetes, diabetes mellitus, particularly type II diabetes, hyperglycaemia, particularly chronic hyperglycaemia, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, etc., insulin resistance, pathological glucose tolerance, encephalorrhagia, cardiac insufficiency,
25 cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.

MCH antagonists and formulations according to the invention may advantageously be used in combination with a dietary therapy, such as for example a dietary diabetes treatment, and
30 exercise.

Another range of indications for which the compounds according to the invention are advantageously suitable is the prevention and/or treatment of micturition disorders, such as for example urinary incontinence, hyperactive bladder, urgency, nycturia, enuresis, while the
35 hyperactive bladder and urgency may or may not be connected with benign prostatic hyperplasia.

Generally speaking, the compounds according to the invention are potentially suitable for preventing and/or treating dependencies, such as for example alcohol and/or nicotine dependency, and/or withdrawal symptoms, such as for example weight gain in smokers coming off nicotine. By "dependency" is generally meant here an irresistible urge to take an
5 addictive substance and/or to perform certain actions, particularly in order to either achieve a feeling of wellbeing or to eliminate negative emotions. In particular, the term "dependency" is used here to denote a dependency on an addictive substance. By "withdrawal symptoms" are meant here, in general, symptoms which occur or may occur when addictive substances are
10 withdrawn from patients dependent on one or more such substances. The compounds according to the invention are potentially suitable particularly as active substances for reducing or ending tobacco consumption, for the treatment or prevention of a nicotine dependency and/or for the treatment or prevention of nicotine withdrawal symptoms, for reducing the craving for tobacco and/or nicotine and generally as an anti-smoking agent. The
15 compounds according to the invention may also be useful for preventing or at least reducing the weight gain typically seen when smokers are coming off nicotine. The substances may also be suitable as active substances which prevent or at least reduce the craving for and/or relapse into a dependency on addictive substances. The term addictive substances refers particularly but not exclusively to substances with a psycho-motor activity, such as narcotics
20 or drugs, particularly alcohol, nicotine, cocaine, amphetamine, opiates, benzodiazepines and barbiturates.

The dosage required to achieve such an effect is conveniently, by intravenous or sub-cutaneous route, 0.001 to 30 mg/kg of body weight, preferably 0.01 to 5 mg/kg of body
25 weight, and by oral or nasal route or by inhalation, 0.01 to 50 mg/kg of body weight, preferably 0.1 to 30 mg/kg of body weight, in each case 1 to 3 x daily.

For this purpose, the compounds prepared according to the invention may be formulated, optionally in conjunction with other active substances as described hereinafter, together with
30 one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or
35 coated tablets, capsules, lozenges, powders, granules, solutions, emulsions, syrups, aerosols for inhalation, ointments or suppositories.

In addition to pharmaceutical compositions the invention also includes compositions containing at least one compound according to the invention and/ or a salt according to the invention optionally together with one or more physiologically acceptable excipients. Such compositions may also be for example foodstuffs which may be solid or liquid, in which the compound according to the invention is incorporated.

For the above mentioned combinations it is possible to use as additional active substances particularly those which for example potentiate the therapeutic effect of an MCH antagonist according to the invention in terms of one of the indications mentioned above and/or which make it possible to reduce the dosage of an MCH antagonist according to the invention. Preferably one or more additional active substances are selected from among

- active substances for the treatment of diabetes,
- active substances for the treatment of diabetic complications,
- 15 - active substances for the treatment of obesity, preferably other than MCH antagonists,
- active substances for the treatment of high blood pressure,
- active substances for the treatment of hyperlipidaemia, including arteriosclerosis,
- active substances for the treatment of dyslipidaemia, including arteriosclerosis,
- active substances for the treatment of arthritis,
- 20 - active substances for the treatment of anxiety states,
- active substances for the treatment of depression.

The above mentioned categories of active substances will now be explained in more detail by means of examples.

25

Examples of active substances for the treatment of diabetes are insulin sensitisers, insulin secretion accelerators, biguanides, insulins, α -glucosidase inhibitors, β 3 adreno-receptor agonists.

30 Insulin sensitisers include glitazones, particularly pioglitazone and its salts (preferably hydrochloride), troglitazone, rosiglitazone and its salts (preferably maleate), JTT-501, GI-262570, MCC-555, YM-440, DRF-2593, BM-13-1258, KRP-297, R-119702 and GW-1929.

35 Insulin secretion accelerators include sulphonylureas, such as for example tolbutamide, chloropropamide, tolazamide, acetohexamide, glycopyramide and its ammonium salts,

glibenclamide, gliclazide, glimepiride. Further examples of insulin secretion accelerators are repaglinide, nateglinide, mitiglinide (KAD-1229) and JTT-608.

Biguanides include metformin, buformin and phenformin.

5

Insulins include those obtained from animals, particularly cattle or pigs, semisynthetic human insulins which are synthesised enzymatically from insulin obtained from animals, human insulin obtained by genetic engineering, e.g. from *Escherichia coli* or yeasts. Moreover, the term insulin also includes insulin-zinc (containing 0.45 to 0.9 percent by weight of zinc) and protamine-insulin-zinc obtainable from zinc chloride, protamine sulphate and insulin. Insulin may also be obtained from insulin fragments or derivatives (for example INS-1, etc.).

10

Insulin may also include different kinds, e.g. with regard to the onset time and duration of effect ("ultra immediate action type", "immediate action type", "two phase type", "intermediate type", "prolonged action type", etc.), which are selected depending on the pathological condition of the patient.

15

α -Glucosidase inhibitors include acarbose, voglibose, miglitol, emiglitate.

20

β_3 Adreno receptor agonists include AJ-9677, BMS-196085, SB-226552, AZ40140.

Active substances for the treatment of diabetes other than those mentioned above include ergoset, pramlintide, leptin, BAY-27-9955 as well as glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, protein tyrosine phosphatase 1B inhibitors, dipeptidyl protease inhibitors, glipazide, glyburide.

25

Active substances for the treatment of diabetes or diabetic complications furthermore include for example aldose reductase inhibitors, glycation inhibitors and protein kinase C inhibitors, DPPIV blockers, GLP-1 or GLP-2 analogues and SGLT-2 inhibitors.

30

Aldose reductase inhibitors are for example tolrestat, epalrestat, imirestat, zenarestat, SNK-860, zopolrestat, ARI-50i, AS-3201.

35

An example of a glycation inhibitor is pimagedine.

Protein Kinase C inhibitors are for example NGF, LY-333531.

DPPIV blockers are for example LAF237 (Novartis), MK431 (Merck) as well as 815541, 823093 and 825964 (all GlaxoSmithkline).

5

GLP-1 analogues are for example Liraglutide (NN2211) (NovoNordisk), CJC1131 (Conjuchem), Exenatide (Amylin).

10

SGLT-2 inhibitors are for example AVE-2268 (Aventis) and T-1095 (Tanabe, Johnson&Johnson).

Active substances other than those mentioned above for the treatment of diabetic complications include alprostadil, thiapride hydrochloride, cilostazol, mexiletine hydrochloride, ethyl eicosapentate, memantine, pimagedine (ALT-711).

15

Active substances for the treatment of obesity, preferably other than MCH antagonists, include lipase inhibitors and anorectics.

A preferred example of a lipase inhibitor is orlistat.

20

Examples of preferred anorectics are phentermine, mazindol, dexfenfluramine, fluoxetine, sibutramine, baiamine, (S)-sibutramine, SR-141716, NGD-95-1.

Active substances other than those mentioned above for the treatment of obesity include lipstatin.

25

Moreover, for the purposes of this application, the active substance group of anti-obesity active substances also includes the anorectics, of which the β_3 agonists, thyromimetic active substances and NPY antagonists should be emphasised. The range of substances which may be considered as preferred anti-obesity or anorectic active substances is indicated by the following additional list, by way of example: phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A (hereinafter referred to as CCK-A) agonist, a monoamine reuptake inhibitor (such as for example sibutramine), a sympathomimetic active substance, a serotonergic active substance (such as for example dexfenfluramine, fenfluramine, a 5-HT_{2C} agonist such as BVT.933 or APD356, or duloxetine), a dopamine antagonist (such as for example

35

bromocriptine or pramipexol), a melanocyte-stimulating hormone receptor agonist or mimetic, an analogue of melanocyte-stimulating hormone, a cannabinoid receptor antagonist (Rimonabant, ACOMPLIA TM), an MCH antagonist, the OB protein (hereinafter referred to as leptin), a leptin analogue, a fatty acid synthase (FAS) antagonist, a leptin receptor agonist, a galanine antagonist, a GI lipase inhibitor or reducer (such as for example orlistat). Other anorectics include bombesin agonists, dehydroepiandrosterone or its analogues, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists, urocortin binding protein antagonists, agonists of the Glucagon-like Peptide-1 receptor, such as for example exendin, AC 2993, CJC-1131, ZP10 or GRT0203Y, DPPIV inhibitors and ciliary neurotrophic factors, such as for example axokines. In this context mention should also be made of the forms of therapy which produce weight loss by increasing the fatty acid oxidation in the peripheral tissue, such as for example inhibitors of acetyl-CoA carboxylase.

Active substances for the treatment of high blood pressure include inhibitors of angiotensin converting enzyme, calcium antagonists, potassium channel openers and angiotensin II antagonists.

Inhibitors of angiotensin converting enzyme include captopril, enalapril, alacepril, delapril (hydrochloride), lisinopril, imidapril, benazepril, cilazapril, temocapril,trandolapril, manidipine (hydrochloride).

Examples of calcium antagonists are nifedipine, amlodipine, efonidipine, nicardipine.

Potassium channel openers include levcromakalim, L-27152, AL0671, NIP-121.

Angiotensin II antagonists include telmisartan, losartan, candesartan cilexetil, valsartan, irbesartan, CS-866, E4177.

Active substances for the treatment of hyperlipidaemia, including arteriosclerosis, include HMG-CoA reductase inhibitors, fibrate compounds.

HMG-CoA reductase inhibitors include pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, itavastatin, ZD-4522 and their salts.

Fibrate compounds include fenofibrate, bezafibrate, clinofibrate, clofibrate and simfibrate.

Active substances for the treatment of dyslipidaemia, including arteriosclerosis, include e.g.
5 medicaments which raise the HDL level, such as e.g. nicotinic acid and derivatives and preparations thereof, such as e.g. niaspan, as well as agonists of the nicotinic acid receptor.

Active substances for the treatment of arthritis include NSAIDs (non-steroidal antiinflammatory drugs), particularly COX2 inhibitors, such as for example meloxicam or
10 ibuprofen.

Active substances for the treatment of anxiety states include chlordiazepoxide, diazepam, oxazolam, medazepam, cloxazolam, bromazepam, lorazepam, alprazolam, fludiazepam.

15 Active substances for the treatment of depression include fluoxetine, fluvoxamine, imipramine, paroxetine, sertraline.

The dosage for these active substances is conveniently 1/5 of the lowest normal recommended dose up to 1/1 of the normal recommended dose.

20 4

In another embodiment the invention also relates to the use of at least one compound according to the invention and/ or a salt according to the invention for influencing the eating behaviour of a mammal. This use is particularly based on the fact that compounds according to the invention may be suitable for reducing hunger, curbing appetite, controlling eating
25 behaviour and/or inducing a feeling of satiety. The eating behaviour is advantageously influenced so as to reduce food intake. Therefore, the compounds according to the invention are advantageously used for reducing body weight. Another use according to the invention is the prevention of increases in body weight, for example in people who had previously taken steps to lose weight and are interested in maintaining their lower body weight. A further use
30 may be the prevention of weight gain in a co-medication with a substance generally causing weight gain (such a glitazones). According to this embodiment it is preferably a non-therapeutic use. Such a non-therapeutic use might be a cosmetic use, for example to alter the external appearance, or an application to improve general health. The compounds according to the invention are preferably used non-therapeutically for mammals, particularly humans,
35 not suffering from any diagnosed eating disorders, no diagnosed obesity, bulimia, diabetes and/or no diagnosed micturition disorders, particularly urinary incontinence. Preferably, the

compounds according to the invention are suitable for non-therapeutic use in people whose BMI (body mass index), defined as their body weight in kilograms divided by their height (in metres) squared, is below a level of 30, particularly below 25.

- 5 Other features and advantages of the present invention will become apparent from the following more detailed examples which illustrate, by way of example, the principles of the invention.

Preliminary remarks:

- 10 As a rule, ¹H-NMR and/or mass spectra have been obtained for the compounds prepared. The R_f values are determined using ready-made silica gel 60 TLC plates F₂₅₄ (E. Merck, Darmstadt, Item no. 1.05714) without chamber saturation or using ready-made aluminium oxide 60 F₂₅₄ TLC plates (E. Merck, Darmstadt, Item no. 1.05713) without chamber saturation. The ratios given for the eluents relate to units by volume of the solvent in question.
- 15 The units by volume for NH₃ relate to a concentrated solution of NH₃ in water. Silica gel made by Millipore (MATREXTM, 35-70 my) is used for chromatographic purification. Alox (E. Merck, Darmstadt, aluminium oxide 90 standardised, 63-200 µm, Item no. 1.01097.9050) is used for chromatographic purification. Purity data given for compounds are based on ¹H-NMR.
- 20 The HPLC data given are measured under the following parameters:

mobile phase A: water:formic acid 99.9:0.1
 mobile phase B: acetonitrile:formic acid 99.9:0.1
 mobile phase C: water:NH₄OH 99.9:0.1
 25 mobile phase D: acetonitrile: NH₄OH 99.9:0.1

method A: analytical column: Zorbax column (Agilent Technologies), SB (Zorbax stable bond) - C18; 3.5 µm; 4.6 mm x 75 mm; column temperature: RT

gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
4.50	10.0	90.0	1.60
5.00	10.0	90.0	1.60
5.50	95.0	5.00	1.60

method B: analytical column: Zorbax column (Agilent Technologies), Bonus-RP - C14; 3.5 µm; 4.6 mm x 75 mm; column temperature: RT

gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
4.00	50.0	50.0	1.60
4.50	10.00	90.00	1.60
5.00	10.00	90.00	1.60
5.50	95.0	5.0	1.60

5 **method C:** analytical column: Waters Symmetry - C18; 3.5 µm; 4.6 mm x 75 mm; column temperature: RT

gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
4.00	50.0	50.0	1.60
4.50	10.00	90.00	1.60
5.00	10.00	90.00	1.60
5.50	95.0	5.0	1.60

10 **method D:** analytical column: Waters SunFire - C18; 3.5 µm; 4.6 mm x 75 mm; column temperature: RT

gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
4.00	50.0	50.0	1.60
4.50	10.0	90.0	1.60
5.00	10.0	90.0	1.60
5.50	95.0	5.0	1.60

method E: analytical column: Zorbax column (Agilent Technologies), SB (Zorbax stable bond) - C18; 3.5 µm; 4.6 mm x 75 mm; column temperature: RT

15 gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
2.00	10.0	90.0	1.60

32

5.00	10.0	90.0	1.60
5.50	95.0	5.0	1.60

method F: analytical column: Zorbax column (Agilent Technologies), SB (Zorbax stable bond) - C18; 3.5 µm; 4.6 mm x 75 mm; column temperature: RT

5

gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
4.00	50.0	50.0	1.60
4.50	10.0	90.0	1.60
5.00	10.0	90.0	1.60
5.50	95.0	5.0	1.60

method G: analytical column: Waters SunFire - C18; 3.5 µm; 4.6 mm x 75 mm; column temperature: RT

gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
4.50	10.0	90.0	1.60
5.00	10.0	90.0	1.60
5.50	95.0	5.00	1.60

10

method H: analytical column: Waters Symmetry - C18; 3.5 µm; 4.6 mm x 75 mm; column temperature: RT

gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
4.50	10.0	90.0	1.60
5.00	10.0	90.0	1.60
5.50	95.0	5.00	1.60

15 **method I:** analytical column: Waters XBridge - C18; 3.5 µm; 4.6 mm x 75 mm; column temperature: RT

gradient:

time in min	%C	%D	flow rate in ml/min
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33

0.00	95.0	5.0	1.60
4.50	10.0	90.0	1.60
5.00	10.0	90.0	1.60
5.50	95.0	5.00	1.60

method J: analytical column: Zorbax column (Agilent Technologies), SB (Zorbax stable bond) - C18; 1.8 μ m; 3.0 mm x 30 mm; column temperature: RT
gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
0.10	95.0	5.00	1.60
1.75	5.0	95.0	1.60
1.90	5.0	95.0	1.60
1.95	95.0	5.0	1.60
2.00	95.0	5.0	1.60

5

method K: analytical column: Waters XBridge - C18; 2.5 μ m; 3.0 mm x 30 mm; column temperature: RT
gradient:

time in min	%C	%D	flow rate in ml/min
0.00	95.0	5.0	1.40
1.80	10.0	90.0	1.40
2.00	10.0	90.0	1.40
2.20	95.0	5.00	1.40

10 **method L:** analytical column: Zorbax column (Agilent Technologies), SB (Zorbax stable bond) - C18; 1.8 μ m; 3.0 mm x 30 mm; column temperature: RT
gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
1.00	10.0	90.0	1.60
2.50	10.0	90.0	1.60
2.75	95.0	5.0	1.60

method M: analytical column: Waters XBridge - C18; 2.5 μ m; 3.0 mm x 30 mm; column temperature: RT

15

34

gradient:

time in min	%C	%D	flow rate in ml/min
0.00	95.0	5.0	1.40
0.80	10.0	90.0	1.40
2.00	10.0	90.0	1.40
2.20	95.0	5.00	1.40

method N: analytical column: Gemini - C18; 3.0 μ m; 3.0 mm x 30 mm; column temperature: RT

5

gradient:

time in min	%C	%D	flow rate in ml/min
0.00	95.0	5.0	1.40
1.80	10.0	90.0	1.40
2.00	10.0	90.0	1.40
2.20	95.0	5.00	1.40

method O: analytical column: XBridge C18; 3.0 μ m; 4.6 mm x 75 mm; column temperature: RT

gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.60
1.00	10.0	90.0	1.60
2.50	10.0	90.0	1.60
2.75	95.0	5.0	1.60

10

method P: analytical column: Water X-terra MS C18; 2.5 μ m; 4.6 mm x 30 mm; column temperature: RT

gradient:

time in min	%A	%B	flow rate in ml/min
0.00	95.0	5.0	1.00
0.10	95.0	5.0	1.00
3.10	2.00	98.0	1.00
4.50	2.00	98.0	1.00
5.00	95.0	5.0	1.00

15

The following abbreviations for the eluent mixtures are used hereinafter when giving the R_f values:

- (A): silica gel, DCM/MeOH/ammonia (9:1:0.1)
- (B): silica gel, DCM/ MeOH /ammonia (9.5:0.5:0.05)
- 5 (C): silica gel, PE/EtOAc (8:2)
- (D) silica gel, DCM/MeOH (9:1)
- (E) silica gel, PE/EtOAc (1:1)
- (F): silica gel, Cyclohexane/EtOAc (8:2)
- (G): silica gel, EtOAc/ MeOH /ammonia (8:2:0.2)
- 10 (H): silica gel, Chloroform/MeOH/ammonia (9:1:0.1)
- (I): silica gel, PE/EtOAc (6:4)
- (J): silica gel, Cyclohexane/EtOAc (6:4)

The following abbreviations are used above and hereinafter:

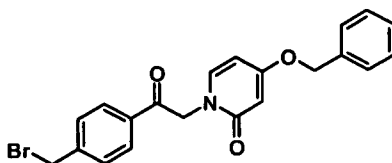
- 15 BOC *tert*-Butylcarbonate
- cal. Calculated
- CDI 1,1'-Carbonyl-di-imidazole#
- CO Carbon monoxide
- 20 DCM Dichloromethane
- DMAP Dimethyl-pyridin-4-yl-amine
- DMF *N,N*-Dimethylformamide
- DMSO Dimethylsulfoxide
- EII Electron impact ionisation
- 25 ESI Electron spray ionisation
- EtOAc Ethyl acetate
- h Hour
- HCl Hydrochloric acid
- Hg Mercury
- 30 hPa hecto Pascale
- HPLC High pressure liquid chromatography
- KHSO₄ Potassium hydrogen sulfate
- MeOH Methanol
- MgSO₄ Magnesium sulfate
- 35 min Minutes
- Na₂CO₃ Sodium carbonate

NaHCO ₃	Sodiumhydrogencarbonate
NH ₄ OH	Ammonium hydroxide
OMe	Methoxy
Pd/C	Palladium on charcoal
5 PE	Petrolether
RT	Ambient temperature (approx. 20°C)
TFA	Trifluoro acidic acid
THF	Tetrahydrofuran

10 **Preparation of starting materials:**

Preparation 1:

4-Benzyloxy-1-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one



15 1a 2-Bromo-1-(4-hydroxymethyl-phenyl)-ethanone

To 7.00 g (46.6 mmol) 1-(4-hydroxymethyl-phenyl)-ethanone in 100 mL THF is added 22.5 g (46.6 mmol) tetrabutylammonium-tribromide dissolved in MeOH/THF. The reaction mixture is stirred 1 h at RT and the solvent is evaporated. The residue is dissolved with water and *tert*-butylmethylether. The organic phase is washed eight times with water. The combined organic phase is dried over MgSO₄, filtered and the solvent is evaporated. The residue is elutriated with diisopropylether and the precipitate is collected and dried.

Yield: 8.10 g (76% of theory); ESI Mass spectrum: [M+H]⁺ = 229/231

R_F-value: 0.2 (silica gel, mixture I).

25 1b 4-Benzyloxy-1-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one

To 3.29 g (16.4 mmol) 4-benzyloxy-1H-pyridin-2-one in 16 mL DMF is added 13.3 g (40.9 mmol) cesium carbonate and the mixture is stirred 15 min at RT. Then 3.75 g (16.4 mmol) 2-bromo-1-(4-hydroxymethyl-phenyl)-ethanone (preparation 1a) is added and is stirred 2 h at RT. Water is added, the precipitate is collected, washed with water and dried.

30 Yield: 5.30 g (93% of theory); ESI Mass spectrum: [M+H]⁺ = 350

Retention time HPLC: 3.0 min (method A).

1c 4-Benzyloxy-1-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one

To 3.00 g (8.59 mmol) 4-benzyloxy-1-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one (preparation 1b) in 20 mL of DCM and 20 mL THF is added 0.81 mL (8.59 mmol) phosphorus tribromide at 0°C. The cooling bath is removed and the mixture is stirred 1 h at RT in an ultrasound bath.

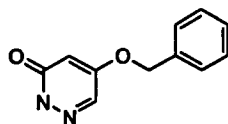
- 5 The precipitate is collected, washed with diisopropylether and water and is dried.

Yield: 3.40 g (96% of theory); ESI Mass spectrum: $[M+H]^+ = 412/414$

Retention time HPLC: 4.0 min (method H).

Preparation 2:

- 10 5-Benzyloxy-2*H*-pyridazin-3-one



2a 5-Hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one

- To 14.3 g (62.0 mmol) 4-chloro-5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one in 200 mL MeOH and 8.71 mL (62.0 mmol) triethylamine is added 5.00 g 10% Pd/C. The reaction mixture is stirred under a hydrogen atmosphere of 1700 hPa at RT for 16 h. The catalyst is removed by filtration and the solvent is evaporated. 200 mL water is added to the residue, the precipitate is collected, washed with water and dried (fraction A, 7.80 g). The aqueous phase is concentrated and the residue is directly added to a reverse HPLC for purification (Waters xbridge; water (0.15% NH₄OH)/acetonitril 95:5 to 10:90) to afford fraction B (4.2 g) which is combined with fraction A.

Yield: 12.0 g (99% of theory); ESI Mass spectrum: $[M-H]^- = 195$

Retention time HPLC: 2.4 min (method A).

2b 5-Benzyloxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one

- 25 To 500 mg (2.55 mmol) 5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (preparation 2a) in THF is added at 0°C subsequently 315 mg (2.80 mmol) potassium-*tert*-butylate, 47 mg (0.13 mmol) tetra-butylammonium-iodide and 0.45 mL (3.82 mmol) benzylbromide. The reaction mixture is stirred overnight at RT and is diluted with EtOAc and 1M aqueous sodium hydroxide solution. The organic phase is separated, washed with water and dried over MgSO₄. After filtration, the solvent is evaporated and the residue is elutriated in *tert*-butylmethylether. The precipitate is collected and dried.

Yield: 500 mg (69% of theory); ESI Mass spectrum: $[M+H]^+ = 287$

Retention time HPLC: 4.0 min (method A).

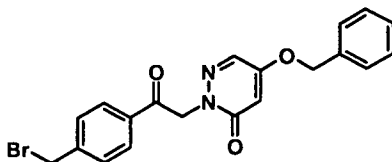
2c 5-Benzyloxy-2*H*-pyridazin-3-one

To 500 mg (1.75 mmol) 5-benzyloxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (preparation 2b) in 10 mL MeOH is added 8.73 mL (8.73 mmol) 1M aqueous HCl solution and the reaction mixture is stirred overnight at RT and 10 h at reflux. MeOH is evaporated, to the residual aqueous phase is added saturated aqueous NaHCO₃-solution until the solution is basic. The aqueous phase is extracted with EtOAc, the combined organic phase is washed with water, dried over MgSO₄, filtered and evaporated to afford the product.

Yield: 200 mg (57% of theory); ESI Mass spectrum: [M+H]⁺ = 203

Retention time HPLC: 3.2 min (method G).

Preparation 3:

5-Benzyloxy-2-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-2*H*-pyridazin-3-one3a 5-Benzyloxy-2-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-2*H*-pyridazin-3-one

5-Benzyloxy-2-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-2*H*-pyridazin-3-one is prepared following preparation 1b from 5.20 g (25.7 mmol) 5-benzyloxy-2*H*-pyridazin-3-one (preparation 2) and 7.70 g (28.6 mmol) 2-bromo-1-(4-hydroxymethyl-phenyl)-ethanone (preparation 1a) using DMSO as solvent.

Yield: 9.40 g (94% of theory); ESI Mass spectrum: [M+H]⁺ = 351

Retention time HPLC: 0.9 min (method L).

3b 5-Benzyloxy-2-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-2*H*-pyridazin-3-one

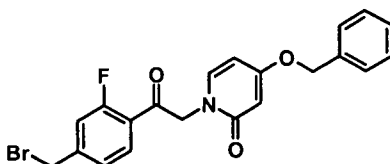
5-Benzyloxy-2-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-2*H*-pyridazin-3-one is prepared following preparation 1c from 9.40 g (26.8 mmol) 5-benzyloxy-2-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-2*H*-pyridazin-3-one (preparation 3a) and 2.52 mL (26.8 mmol) phosphorus tribromide.

Yield: 10.0 g (90% of theory); ESI Mass spectrum: [M+H]⁺ = 413/415

Retention time HPLC: 1.6 min (method J).

Preparation 4:

4-Benzyloxy-1-[2-(4-bromomethyl-2-fluoro-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one



4a 1-(4-Bromomethyl-2-fluoro-phenyl)-ethanone

A solution of 2-fluoro-4-methylacetophenone (17.6 g, 112 mmol) and N-bromosuccinimide (21.6 g, 178 mmol) in tetrachloromethane (150 mL) is refluxed for 2 h while irradiating with a Hg lamp. After filtration, the reaction mixture is adsorbed onto silica gel and purified chromatographically (silica gel, 10% ethyl acetate in hexanes).
Yield: 15.7 g (59% of theory); ESI Mass spectrum: $[M+H]^+ = 231/233$.

4b Acetic acid 4-acetyl-3-fluoro-benzyl ester

A mixture of 1-(4-Bromomethyl-2-fluoro-phenyl)-ethanone (preparation 4a, 15.7 g, 68 mmol) and sodium acetate (22.3 g, 200 mmol) in acetic acid (150 mL) is heated at reflux for 4 h. The reaction mixture is poured into ice water and extracted with *tert*-butylmethylether. The organic layer is washed with aqueous sodium carbonate solution and water, dried over $MgSO_4$ and evaporated in vacuo.
Yield: 13.1 g (92% of theory); ESI Mass spectrum: $[M+H]^+ = 211$.

4c 1-(2-Fluoro-4-hydroxymethyl-phenyl)-ethanone

A solution of acetic acid 4-acetyl-3-fluoro-benzyl ester (preparation 4b, 13.1 g, 62 mmol) in methanol (100 mL) and 4N aqueous sodium hydroxide solution (31.2 mL, 125 mmol) is heated at reflux for 2h. After cooling, the reaction mixture is poured into ice water and extracted several times with *tert*-butylmethylether. The organic layer is washed with water, dried over $MgSO_4$ and evaporated in vacuo.
Yield: 10.1 g (96% of theory); ESI Mass spectrum: $[M+H]^+ = 169$.

4d 2-Bromo-1-(2-fluoro-4-hydroxymethyl-phenyl)-ethanone

To 10.1 g (60 mmol) 1-(2-fluoro-4-hydroxymethyl-phenyl)-ethanone (preparation 4c) in 100 mL DCM and 10 mL MeOH is added 29.0 g (60 mmol) tetrabutylammonium-tribromide. The reaction mixture is stirred 2 h at RT and the solvent is evaporated. The remaining residue is treated with water and extracted several times with DCM. The combined organic layer is dried over $MgSO_4$ and evaporated in vacuo. The remaining oil is adsorbed onto silica gel and purified chromatographically (silica gel, 30% ethyl acetate in hexanes).
Yield: 10.4 g (70% of theory); ESI Mass spectrum: $[M+H]^+ = 245/247$.

4e 4-Benzyloxy-1-[2-(2-fluoro-4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one

To 1.00 g (4.97 mmol) 4-benzyloxy-1*H*-pyridin-2-one in 5 mL DMSO is added 4.05 g (12.4 mmol) cesium carbonate and the mixture is stirred 15 min at RT. Then 1.23 g (4.97 mmol) 2-bromo-1-(2-fluoro-4-hydroxymethyl-phenyl)-ethanone (preparation 4d) is added and the
5 reaction mixture is stirred 2 h at RT. Water is added, the precipitate is collected, washed with water and dried.

Yield: 1.40 g (77% of theory); ESI Mass spectrum: $[M+H]^+ = 368$

Retention time HPLC: 1.41 min (method J).

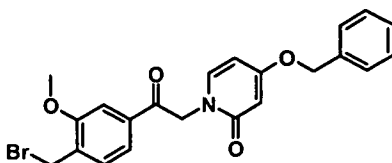
10 4f 4-Benzyloxy-1-[2-(4-bromomethyl-2-fluoro-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one

To a solution of 1.40 g (2.86 mmol) 4-benzyloxy-1-[2-(2-fluoro-4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one (preparation 4e) in 20 mL of DCM is added 0.54 mL (5.72 mmol) phosphorus tribromide at 0°C. The cooling bath is removed and the mixture is stirred 5 h at RT. Under cooling, the reaction mixture is quenched by addition of sodium bicarbonate
15 solution and extracted with dichloromethane. The organic layer is washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The remaining solid is purified by preparative reverse phase HPLC (Gilson, Waters Symmetry C18, 7 μ m, gradient from 10% to 95% acetonitrile in water + 0.1% HCOOH, 120 mL/min).

Yield: 0.60 g (49% of theory); ESI Mass spectrum: $[M+H]^+ = 430/432$

20 Retention time HPLC: 1.57 min (method J).

Preparation 5:

4-Benzyloxy-1-[2-(4-bromomethyl-3-methoxy-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one

25 5a 4-Hydroxymethyl-3-methoxy-benzoic acid

A solution of methyl 4-bromomethyl-3-methoxy-benzoate (Trans World Chemicals, 5.18 g, 20 mmol) in 50 mL dioxane, 15 mL water and 50 mL 1N aqueous sodium hydroxide is heated at reflux for 6 h. The reaction mixture is neutralized with 50 mL 1N hydrochloric acid and extracted several times with ethyl acetate. The organic layer is washed with water, dried over
30 $MgSO_4$ and evaporated under reduced pressure.

Yield: 3.40 g (93 % of theory); ESI Mass spectrum: $[M-H]^- = 181$

Retention time HPLC: 0.81 min (method J).

5b 4-Hydroxymethyl-3,N-dimethoxy-N-methyl-benzamide (Weinreb amide of 5a)

A solution of 4-hydroxymethyl-3-methoxy-benzoic acid (preparation 5a, 3.30 g, 18.1 mmol), N,O-dimethylhydroxylamine hydrochloride (2.12 g, 21.7 mmol) and 4-methylmorpholine (3.99 mL, 36.2 mmol) is stirred for 10 min at RT. Then, 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride hydrate (Acros, 5.51 g, 19.9 mmol) is added and the reaction mixture is stirred for 3 h at ambient temperature. The reaction mixture is concentrated in vacuo and purified by preparative HPLC (Gilson, Waters XBridge C18, 5 μ m, gradient from 10% to 95% acetonitrile in water + 0.3% NH_4OH , 120 mL/min).

Yield: 2.80 g (69 % of theory); ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 226$

Retention time HPLC: 1.10 min (method K).

5c 1-(4-Hydroxymethyl-3-methoxy-phenyl)-ethanone

At 0°C, methylmagnesium bromide (12 mL of a 3M solution in diethyl ether, 36 mmol) is added to a solution of Weinreb amide 5b (4-Hydroxymethyl-3,N-dimethoxy-N-methyl-benzamide, 2.70 g, 12.0 mmol) in anhydrous THF (50 mL). After stirring for 1.5 h at 0°C, another 2 equivalents of methylmagnesium bromide (8 mL) are added to the reaction mixture. After 30 min, the reaction mixture is carefully poured into saturated aqueous ammonium chloride solution and extracted several times with *tert*-butylmethylether. The combined organic layer is washed with water, dried over MgSO_4 and evaporated in vacuo. The resulting oil is purified chromatographically (silica gel, gradient from 10% to 30% MeOH in DCM).

Yield: 1.60 g (76 % of theory); ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 181$

R_f value = 0.64 (silica gel, mixture D).

5d 2-Bromo-1-(4-hydroxymethyl-3-methoxy-phenyl)-ethanone

To 400 mg (2.2 mmol) 1-(4-hydroxymethyl-3-methoxy-phenyl)-ethanone (preparation 5c) in 8 mL dioxane is added at 35°C a solution of 0.12 mL bromine (2.3 mmol) in 2 mL DCM. After 10 min, the reaction mixture is quenched with aqueous sodium thiosulfate solution and extracted several times with DCM. The combined organic layer is dried over MgSO_4 and evaporated in vacuo. The resulting oil is purified by preparative HPLC (Gilson, Zorbax Stablebond C18, 7 μ m, gradient from 10% to 95% acetonitrile in water + 0.1% HCOOH , 120 mL/min).

Yield: 150 mg (26% of theory); ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 259/261$

Retention time HPLC: 1.12 min (method J).

5e 4-Benzyloxy-1-[2-(4-hydroxymethyl-3-methoxy-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one

To 117 mg (0.58 mmol) 4-benzyloxy-1*H*-pyridin-2-one in 3 mL DMSO is added 472 mg (1.45 mmol) cesium carbonate and the mixture is stirred 15 min at RT. Then 150 mg (0.5 mmol) 2-bromo-1-(4-hydroxymethyl-3-methoxy-phenyl)-ethanone (preparation 5d) is added and the reaction mixture is stirred for 2 h at RT. Water is added, the precipitate is collected, washed with water and dried.

Yield: 160 mg (73% of theory); ESI Mass spectrum: $[M+H]^+ = 380$

Retention time HPLC: 1.26 min (method J).

5f 4-Benzyloxy-1-[2-(4-bromomethyl-3-methoxy-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one

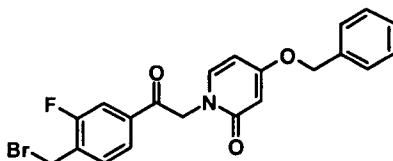
To 160 mg (0.42 mmol) 4-benzyloxy-1-[2-(4-hydroxymethyl-3-methoxy-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one (preparation 5e) in 5 mL of DCM is added 28 μ L (0.3 mmol) phosphorus tribromide at 0°C. The cooling bath is removed and the mixture is stirred 2 h at RT. Under cooling, the reaction mixture is quenched by addition of sodium bicarbonate solution and extracted with dichloromethane. The organic layer is washed with water, dried over $MgSO_4$ and evaporated under reduced pressure.

Yield: 140 mg (75% of theory); ESI Mass spectrum: $[M+H]^+ = 442/444$

Retention time HPLC: 2.77 min (method E).

Preparation 6:

4-Benzyloxy-1-[2-(4-bromomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one



6a (4-Bromo-2-fluoro-benzyloxy)-*tert*-butyl-dimethyl-silane

To 5.10 g (24.9 mmol) (4-bromo-2-fluoro-phenyl)-methanol in 30 mL DMF is added subsequently 4.06 g (26.1 mmol) *tert*-butyl-chloro-dimethyl silane, 2.57 g (37.3 mmol) imidazole and 456 mg (3.73 mmol) DMAP. The reaction mixture is stirred overnight at RT and the solvent is evaporated. The residue is diluted with EtOAc, washed five times with water and the combined organic phase is dried over $MgSO_4$, filtered and the solvent is evaporated. Yield: 7.70 g (97% of theory); R_f -value: 0.9 (silica gel, mixture C).

6b *tert*-Butyl-(2-fluoro-4-iodo-benzyloxy)-dimethyl-silane

To 7.70 g (24.1 mmol) (4-bromo-2-fluoro-benzyloxy)-*tert*-butyl-dimethyl-silane (preparation 6a) in 8 mL 1,4-dioxane is added 937 mg (4.82 mmol) Cu(I)-iodide. The reaction mixture is flushed with argon and 7.23 g (48.2 mmol) sodium iodide and 1.03 mL (9.65 mmol) N,N-

dimethylethylen-diamine are added. The mixture is stirred at 120°C for 7 h in a sealed tube. The reaction mixture is diluted at RT with 5% aqueous NH₃-solution and the aqueous phase is extracted with EtOAc. The combined organic phase is washed a few times with water, dried over MgSO₄, filtered and the solvent is evaporated.

5 Yield: 7.80 g (88% of theory); Retention time HPLC: 4.2 min (method E).

6c 4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-fluoro-benzoic acid methyl ester

To 3.00 g (8.19 mmol) *tert*-butyl-(2-fluoro-4-iodo-benzyloxy)-dimethyl-silane (preparation 6b) in 20 mL MeOH and 20 mL DMF is added 455 mg (0.82 mmol) 1,1-bis-(diphenylphosphino)-ferrocene, 184 mg (0.82 mmol) Pd(II)-acetate and 2.27 mL (16.3 mmol) triethylamine. The reaction mixture is stirred under a CO atmosphere (4000 hPa) at 50°C for 24 h. The solvent is evaporated, the residue is dissolved in DMF and is purified by HPLC (Zorbax stable bond, C18; water (0.15% formic acid)/acetonitrile 85:5 to 0:100).

Yield: 1.46 g (60% of theory); Retention time HPLC: 3.8 min (method E).

15

6d 4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-fluoro-benzoic acid

To 2.20 g (7.37 mmol) 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-fluoro-benzoic acid methyl ester (preparation 6c) in 30 mL EtOH is added 12 mL 1 M aqueous NaOH-solution. The mixture is stirred 1 h at RT, additional 4 mL 1 M aqueous NaOH-solution are added and the reaction mixture is stirred an additional hour. The solvent is evaporated, the residue is acidified with 1 M aqueous HCl-solution. The precipitate is collected and dried.

Yield: 540 mg (26% of theory); ESI Mass spectrum: [M-H]⁻ = 283

Retention time HPLC: 4.9 min (method A).

25 6e 1-[4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-fluoro-phenyl]-ethanone

A solution of 540 mg (1.90 mmol) 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-fluoro-benzoic acid (preparation 6d) in 20 mL THF is degassed and cooled to -30°C. 3.56 mL (5.67 mmol) 1.6 M methyl-lithium solution in diethylether is added, the mixture is stirred 2 h at -30°C and 3.12 mL (24.7 mmol) trimethyl-chloro-silane is added. The mixture is stirred 2 min and is transferred to a pH 7 buffer solution (0°C). The aqueous phase is extracted with EtOAc and diethylether. The combined organic phase is washed with water, dried over MgSO₄, filtered and the solvent is evaporated. The residue is purified by silica gel column chromatography with PE/EtOAc (9:1) as eluent.

Yield: 280 mg (52% of theory); ESI Mass spectrum: (M+H)⁺ = 283

35 R_F-value: 0.5 (silica gel, mixture C).

6f 2-Bromo-1-(3-fluoro-4-hydroxymethyl-phenyl)-ethanone

2-Bromo-1-(3-fluoro-4-hydroxymethyl-phenyl)-ethanone is prepared following preparation 1a from 280 mg (0.99 mmol) 1-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-fluoro-phenyl]-ethanone (preparation 6e) and 478 mg (0.99 mmol) tetrabutylammonium-tribromide.

5 Yield: 230 mg (94% of theory); R_f -value: 0.3 (silica gel, mixture J).

6g 4-Benzyloxy-1-[2-(3-fluoro-4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one

4-Benzyloxy-1-[2-(3-fluoro-4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one is prepared following preparation 1b from 193 mg (0.93 mmol) 4-benzyloxy-1H-pyridin-2-one and 230 mg
10 (0.93 mmol) 2-bromo-1-(3-fluoro-4-hydroxymethyl-phenyl)-ethanone (preparation 6f).

Yield: 240 mg (70% of theory); ESI Mass spectrum: $(M+H)^+ = 368$

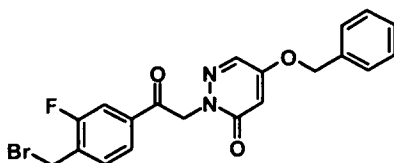
Retention time HPLC: 3.2 min (method A).

6h 4-Benzyloxy-1-[2-(4-bromomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one

15 4-Benzyloxy-1-[2-(4-bromomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one is prepared following preparation 1c from 240 mg (0.65 mmol) 4-benzyloxy-1-[2-(3-fluoro-4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one (preparation 6g) and 0.43 mL (4.57 mmol) phosphorus tribromide.

Yield: 210 mg (75% of theory); ESI Mass spectrum: $(M+H)^+ = 430/432$

20 Retention time HPLC: 2.4 min (method E).

Preparation 7:**5-Benzyloxy-2-[2-(4-bromomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one**

25

7a 5-Benzyloxy-2-[2-(3-fluoro-4-hydroxymethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one

5-Benzyloxy-2-[2-(3-fluoro-4-hydroxymethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one is prepared following preparation 1b from 1.64 g (8.1 mmol) 5-benzyloxy-2H-pyridazin-3-one (preparation 2) and 2.00 g (8.1 mmol) 2-bromo-1-(3-fluoro-4-hydroxymethyl-phenyl)-ethanone (preparation 6f).
30

Yield: 1.40 g (47% of theory); ESI Mass spectrum: $(M+H)^+ = 369$

Retention time HPLC: 1.34 min (method J).

7b 5-Benzyloxy-2-[2-(4-bromomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one

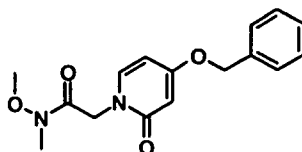
5-Benzyloxy-2-[2-(4-bromomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one is prepared following preparation 1c from 1.40 g (3.80 mmol) 5-benzyloxy-2-[2-(3-fluoro-4-hydroxymethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one (preparation 7a) and 0.71 mL (7.60 mmol) phosphorus tribromide.

Yield: 1.40 g (85% of theory); ESI Mass spectrum: $(M+H)^+ = 431/433$

Retention time HPLC: 1.58 min (method J).

Preparation 8

10 2-(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-N-methoxy-N-methyl-acetamide



8a (4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-acetic acid methyl ester

(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-acetic acid methyl ester is prepared following preparation 1b from 10.0 g (49.7 mmol) 4-benzyloxy-1H-pyridin-2-one and 4.96 mL (52.2 mmol) methyl bromoacetate, employing DMSO as the solvent.

Yield: 12.7 g (94% of theory); ESI Mass spectrum: $(M+H)^+ = 274$

Retention time HPLC: 1.12 min (method J).

8b (4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-acetic acid

20 A solution of (4-benzyloxy-2-oxo-2H-pyridin-1-yl)-acetic acid methyl ester (preparation 8a, 12.0 g, 43 mmol) in 150 mL ethanol and 22 mL 4N aqueous sodium hydroxide solution is stirred for 18 h at room temperature. The reaction mixture is diluted with water and acidified with 4N aqueous HCl. The formed precipitate is filtered off, washed with hot acetonitrile and *tert*-butylmethylether and dried in vacuo.

25 Yield: 9.30 g (82 % of theory); ESI Mass spectrum: $[M+H]^+ = 260$

Retention time HPLC: 1.13 min (method J).

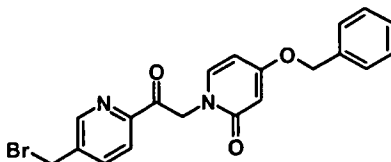
8c 2-(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-N-methoxy-N-methyl-acetamide

30 2-(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-N-methoxy-N-methyl-acetamide is prepared following preparation 5b from (4-benzyloxy-2-oxo-2H-pyridin-1-yl)-acetic acid (preparation 8b, 5.19 g, 20 mmol).

Yield: 4.60 g (76 % of theory); ESI Mass spectrum: $[M+H]^+ = 303$

Retention time HPLC: 1.16 min (method J).

Preparation 9

4-Benzyloxy-1-[2-(5-bromomethyl-pyridin-2-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one9a 5-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-iodo-pyridine

- 5 To a solution of 2-bromo-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-pyridine (1.51 g, 5.00 mmol, preparation according to J. Org. Chem. 69 (2), 250-262, 2004) in dioxane (5 mL) is added CuI (98 mg, 0.5 mmol), sodium iodide (1.5 g, 10 mmol) and N,N'-dimethyl ethylenediamine (0.11 mL, 1.0 mmol). The reaction mixture is heated for 3 h at 100°C. After cooling, the reaction mixture is poured into 5% aqueous ammonia solution and extracted with *tert*-butylmethylether. The organic layer is washed with water, dried over MgSO₄ and evaporated
- 10 under reduced pressure. The remaining oil is adsorbed onto silica gel and purified chromatographically (silica gel, gradient from 0% to 20% ethyl acetate in cyclohexane).

Yield: 1.50 g (86% of theory); ESI Mass spectrum: [M+H]⁺ = 350

R_F-value: 0.75 (silica gel, mixture F).

15

9b 4-Benzyloxy-1-[2-(5-hydroxymethyl-pyridin-2-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one

- To a solution of 5-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-iodo-pyridine (preparation 9a, 1.22 g, 3.50 mmol) in anhydrous THF (20 mL) is added at -20°C a solution of isopropylmagnesium chloride and lithium chloride ("Turbo Grignard", 2.69 mL of 14% solution in THF). After 10
- 20 min, the Grignard solution is added to a suspension of the Weinreb amide 2-(4-benzyloxy-2-oxo-2*H*-pyridin-1-yl)-N-methoxy-N-methyl-acetamide (preparation 8, 1.06 g, 3.50 mmol) in THF (20 mL), while keeping the temperature below 0°C. After stirring for 5 h at room temperature, the reaction mixture is poured into 1N aqueous HCl, *tert*-butylmethylether is added and the mixture is stirred for 2 h at room temperature. The formed precipitate is filtered
- 25 off, washed with *tert*-butylmethylether and dried in vacuo.

Yield: 250 mg (20 % of theory); ESI Mass spectrum: [M+H]⁺ = 351

Retention time HPLC: 1.19 min (method J).

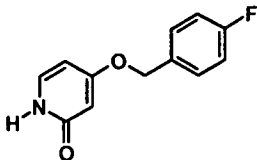
9c 4-Benzyloxy-1-[2-(5-bromomethyl-pyridin-2-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one

- 30 4-Benzyloxy-1-[2-(5-bromomethyl-pyridin-2-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one is prepared following preparation 1c from 300 mg (0.86 mmol) 4-benzyloxy-1-[2-(5-hydroxymethyl-pyridin-2-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one (preparation 9b) and 41 μL (0.43 mmol) phosphorus tribromide.

Yield: 250 mg (71% of theory).

Preparation 10.1

4-(4-Fluoro-benzyloxy)-1*H*-pyridin-2-one



5

To 1.40 g (7.41 mmol) 1-bromomethyl-4-fluoro-benzene in 20 mL acetonitrile is added 822 mg (7.40 mmol) 2,4-dihydroxy pyridine and 2.05 g (14.8 mmol) potassium carbonate. The reaction mixture is stirred overnight at RT. 5 mL of DMF is added and the reaction is stirred overnight. After filtration and evaporation of the solvent, is the residue purified by HPLC (Zorbax stable bond, C18; water (0.15% formic acid)/acetonitrile 95:5 to 5:95).

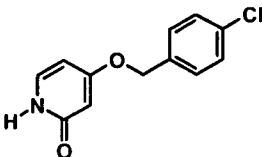
10

Yield: 600 mg (37% of theory); ESI Mass spectrum: $[M+H]^+ = 220$

Retention time HPLC: 2.8 min (method A).

Preparation 10.2

4-(4-Chloro-benzyloxy)-1*H*-pyridin-2-one



15

4-(4-Chloro-benzyloxy)-1*H*-pyridin-2-one is prepared as described for preparation 10.1, employing 1-bromomethyl-4-chloro-benzene as the alkylating agent.

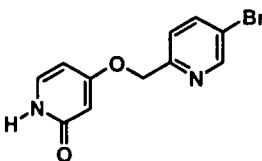
Yield: 43% of theory; ESI Mass spectrum: $[M+H]^+ = 236/238$

20

Retention time HPLC: 1.1 min (method K).

Preparation 10.3

4-(5-Bromo-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one



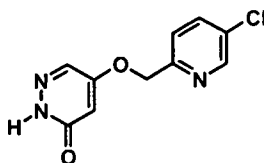
25

4-(5-Bromo-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one is prepared as described for preparation 10.1, employing 2-Bromomethyl-5-bromo-pyridine as the alkylating agent.

Yield: 46% of theory; ESI Mass spectrum: $[M+H]^+ = 281/283$

Retention time HPLC: 2.5 min (method A).

Preparation 10.4

5-(5-Chloro-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one5 10.4a 5-(5-Chloro-pyridin-2-ylmethoxy)-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one

To 5.00 g (25.5 mmol) 5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (see preparation 2a) and 4.03 g (28.0 mmol) (5-chloro-pyridin-2-yl)-methanol in 25 mL THF and 15 mL DCM is added molecular sieve and then 12.7 g (38.2 mmol) of polymer bound triphenylphosphane (3 mmol/g). The reaction mixture is cooled to 0°C and 7.53 mL (38.2 mmol) diisopropyl azodicarboxylate is added. The mixture is stirred 10 min at 0°C and 30 min at RT. The reaction mixture is filtered and the solvent is evaporated. The residue is purified via reverse HPLC chromatography (Zorbax stable bond, C18; water (0.1 % formic acid)/acetonitrile (0.1 % formic acid) 95:5 to 10:90).

Yield: 5.50 g (67% of theory); ESI Mass spectrum: $[M+H]^+ = 322/324$

15 Retention time HPLC: 3.3 min (method A).

10.4b 5-(5-Chloro-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one

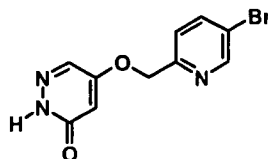
To 5.50 g (17.1 mmol) 5-(5-chloro-pyridin-2-ylmethoxy)-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (preparation 10.4a) in 50 mL MeOH is added 7.1 mL conc. HCl and the reaction mixture is refluxed for 2 h. The solvent is evaporated, the precipitate collected and added to 50 mL of water. The mixture is neutralized with saturated aqueous NaHCO₃-solution. The precipitate is collected, washed with water and dried.

Yield: 3.00 g (74% of theory); ESI Mass spectrum: $[M+H]^+ = 238/240$

Retention time HPLC: 1.0 min (method J).

25

Preparation 10.5

5-(5-Bromo-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one10.5a 5-(5-Bromo-pyridin-2-ylmethoxy)-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one

30 To 3.29 g (16.7 mmol) 5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (preparation 2a) in acetonitrile is added at RT subsequently 4.63 g (33.4 mmol) potassium-carbonate and

4.20 g (16.7 mmol) 5-bromo-2-bromomethyl-pyridine. The reaction mixture is stirred 3 h at RT and 5 mL DMF is added. The reaction mixture is stirred overnight and the solvent is evaporated. To the residue water and *tert*-butylmethylether is added. The precipitate is collected and dried.

- 5 Yield: 5.30 g (86% of theory); ESI Mass spectrum: $[M+H]^+ = 366/368$
Retention time HPLC: 3.7 min (method A).

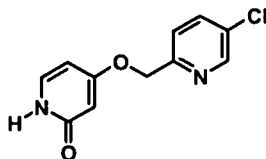
10.5b 5-(5-Bromo-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one

- 5-(5-Bromo-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one is prepared following preparation 10.4b
10 from 5.30 g (14.5 mmol) 5-(5-bromo-pyridin-2-ylmethoxy)-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (preparation 10.5a).

Yield: 4.20 g (103% of theory); ESI Mass spectrum: $[M+H]^+ = 282/284$
Retention time HPLC: 2.8 min (method A).

15 Preparation 10.6

4-(5-Chloro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one

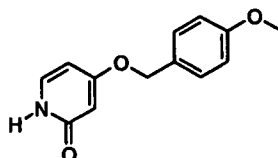


4-(5-Chloro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one is prepared following preparation 10.1, employing 2-bromomethyl-5-chloro-pyridine as the alkylating agent.

- 20 Yield: 39% of theory; ESI Mass spectrum: $[M+H]^+ = 237/239$
Retention time HPLC: 1.05 min (method J).

Preparation 10.7

4-(4-Methoxy-benzyloxy)-1*H*-pyridin-2-one



- 25 4-(4-Methoxy-benzyloxy)-1*H*-pyridin-2-one is prepared as described for preparation 10.1, employing 4-methoxybenzyl chloride as the alkylating agent and DMSO as solvent. The reaction mixture is poured into water under vigorous stirring, the formed precipitate is filtered off, washed with *tert*-butylmethylether and dried. The solid is triturated with acetonitrile,
30 collected and dried.

Yield: 24% of theory; ESI Mass spectrum: $[M+H]^+ = 232$

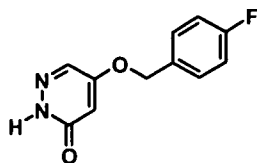
50

Retention time HPLC: 1.07 min (method K).

Preparation 10.8

5-(4-Fluoro-benzyloxy)-2*H*-pyridazin-3-one

5



10.8a 5-(4-Fluoro-benzyloxy)-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one

5-(4-Fluoro-benzyloxy)-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one is prepared following preparation 10.5a from 8.00 g (40.8 mmol) 5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (preparation 2a) and 5.4 mL (44.9 mmol) 1-chloromethyl-4-fluoro-benzene.

10

Yield: 10.5 g (85% of theory); ESI Mass spectrum: $[M+H]^+ = 305$

Retention time HPLC: 3.6 min (method A).

10.8b 5-(4-Fluoro-benzyloxy)-2*H*-pyridazin-3-one

5-(4-Fluoro-benzyloxy)-2*H*-pyridazin-3-one is prepared following preparation 10.4b from 10.5 g (34.5 mmol) 5-(4-fluoro-benzyloxy)-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (preparation 10.8a).

15

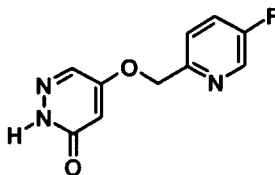
Yield: 7.30 g (96% of theory); ESI Mass spectrum: $[M+H]^+ = 221$

Retention time HPLC: 2.7 min (method A).

20

Preparation 10.9

5-(5-Fluoro-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one



25

10.9a 5-(5-Fluoro-pyridin-2-ylmethoxy)-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one

5-(5-Fluoro-pyridin-2-ylmethoxy)-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one is prepared following preparation 10.4a from 2.40g (12.2 mmol) 5-hydroxy-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one (preparation 2a) and 1.56 g (12.2 mmol) (5-fluoro-pyridin-2-yl)-methanol

30

Yield: 800 mg (21% of theory); ESI Mass spectrum: $(M+H)^+ = 306$

Retention time HPLC: 3.0 min (method A).

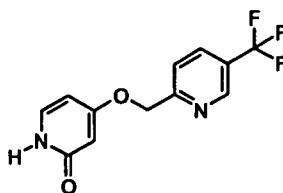
10.9b 5-(5-Fluoro-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one

5-(5-Fluoro-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one is prepared following preparation 10.4b from 800 mg (2.62 mmol) 5-(5-fluoro-pyridin-2-ylmethoxy)-2-(tetrahydro-pyran-2-yl)-2*H*-pyridazin-3-one.

Yield: 350 mg (60% of theory); ESI Mass spectrum: $[M+H]^+ = 222$

Retention time HPLC: 2.0 min (method A).

Preparation 10.10

10 4-(5-Trifluoromethyl-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one

10.10a 2-Bromomethyl-5-trifluoromethyl-pyridine

To an ice-cooled solution of (5-trifluoromethyl-pyridin-2-yl)-methanol (300 mg, 1.69 mmol) in DCM (10 mL) is added phosphorus tribromide (96 μ L, 1.02 mmol) and the reaction mixture is stirred for 2 h at room temperature. The reaction mixture is quenched with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer is dried over $MgSO_4$ and evaporated under reduced pressure.

Yield: 350 mg (86% of theory); ESI Mass spectrum: $[M+H]^+ = 239$

Retention time HPLC: 1.37 min (method J).

20

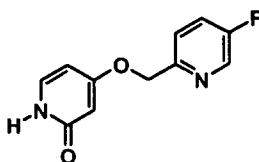
10.10b 4-(5-Trifluoromethyl-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one

4-(5-Trifluoromethyl-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one is prepared following preparation 10.1, employing 2-bromomethyl-5-trifluoromethyl-pyridine as the alkylating agent.

Yield: 14% of theory; ESI Mass spectrum: $[M+H]^+ = 271$

25 Retention time HPLC: 1.17 min (method J).

Preparation 10.11

4-(5-Fluoro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one30 10.11a 4-Benzyloxy-1-(tetrahydro-pyran-2-yl)-1*H*-pyridin-2-one

To 45.2 g (225 mmol) 4-benzyloxy-1*H*-pyridin-2-one in 200 mL THF is added 63.4 mL (84.1 mmol) 3,4-dihydro-2*H*-pyran and 4.27 g (22.5 mmol) toluene-4-sulfonic acid mono hydrate. The reaction mixture is stirred 2 h at reflux and additional 4.00 mL (5.30 mmol) 3,4-dihydro-2*H*-pyran is added. After 2 h at reflux, additional 4.00 mL (5.30 mmol) 3,4-dihydro-2*H*-pyran is added and the reaction mixture is stirred 2 h at reflux and then overnight at RT. The reaction mixture is concentrated in vacuo and the residue is diluted with EtOAc. The organic phase is washed with an aqueous sodium hydroxide solution (1M). The organic phase is washed with water, dried over MgSO₄ and evaporated in vacuo. The residue is purified chromatographically (silica gel, PE:EtOAc 1:1 to EtOAc).

Yield: 73% of theory; ESI Mass spectrum: $[M+H]^+ = 286$
Retention time HPLC: 1.10 min (method L).

10.11b 4-Hydroxy-1-(tetrahydro-pyran-2-yl)-1*H*-pyridin-2-one

To 47.0 g (165 mmol) 4-benzyloxy-1-(tetrahydro-pyran-2-yl)-1*H*-pyridin-2-one in 700 mL ethanol and 30.1 mL (214 mmol) triethylamine is added 5.00 g 10% Pd/C. The reaction mixture is stirred under a hydrogen atmosphere at 40°C for 1.5 h. The catalyst is removed by filtration and the solvent is evaporated. 200 mL water and pH 5 buffer solution is added to the residue. The precipitate is collected, washed with water and dried at 50°C.

Yield: 30.4 g (95% of theory); ESI Mass spectrum: $[M+H]^+ = 196$

Retention time HPLC: 0.98 min (method J).

10.11c 4-(5-Fluoro-pyridin-2-ylmethoxy)-1-(tetrahydro-pyran-2-yl)-1*H*-pyridin-2-one

4-(5-Fluoro-pyridin-2-ylmethoxy)-1-(tetrahydro-pyran-2-yl)-1*H*-pyridin-2-one is prepared following preparation 10.4a from 4.61 g (23.6 mmol) 4-hydroxy-1-(tetrahydro-pyran-2-yl)-1*H*-pyridin-2-one (preparation 10.11b) and 3.00 g (23.6 mmol) (5-fluoro-pyridin-2-yl)-methanol.

Yield: 2.90 g (40% of theory); ESI Mass spectrum: $[M+H]^+ = 305$

Retention time HPLC: 1.46 min (method K).

10.11d 4-(5-Fluoro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one

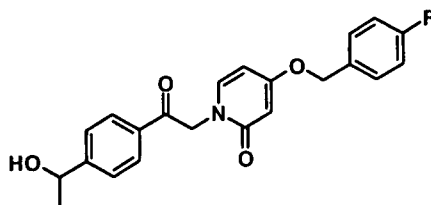
4-(5-Fluoro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one is prepared following preparation 10.4b from 2.90 g (9.53 mmol) 4-(5-fluoro-pyridin-2-ylmethoxy)-1-(tetrahydro-pyran-2-yl)-1*H*-pyridin-2-one (preparation 10.11c).

Yield: 2.20 g (105% of theory); ESI Mass spectrum: $[M+H]^+ = 221$

Retention time HPLC: 1.10 min (method K).

Preparation 11.1

4-(4-Fluoro-benzyloxy)-1-{2-[4-(1-hydroxy-ethyl)-phenyl]-2-oxo-ethyl}-1*H*-pyridin-2-one



11.1a 2-Bromo-1-[4-(1-hydroxy-ethyl)-phenyl]-ethanone

2-Bromo-1-[4-(1-hydroxy-ethyl)-phenyl]-ethanone is prepared following preparation 1a from

5 600 mg (3.65 mmol) 1-[4-(1-hydroxy-ethyl)-phenyl]-ethanone.

Yield: 750 mg (84% of theory); ESI Mass spectrum: $[M+H]^+ = 243/245$

R_f -value: 0.5 (silica gel, mixture E).

11.1b 4-(4-Fluoro-benzyloxy)-1-{2-[4-(1-hydroxy-ethyl)-phenyl]-2-oxo-ethyl}-1*H*-pyridin-2-one

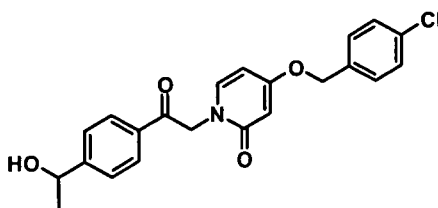
10 4-(4-Fluoro-benzyloxy)-1-{2-[4-(1-hydroxy-ethyl)-phenyl]-2-oxo-ethyl}-1*H*-pyridin-2-one is prepared following preparation 1b (DMSO as solvent) from 400 mg (1.83 mmol) 4-(4-fluoro-benzyloxy)-1*H*-pyridin-2-one (preparation 10.1) and 626 mg (2.19 mmol) 2-bromo-1-[4-(1-hydroxy-ethyl)-phenyl]-ethanone (preparation 11.1a).

Yield: 415 mg (60% of theory); ESI Mass spectrum: $[M+H]^+ = 382$

15 Retention time HPLC: 1.62 min (method K).

Preparation 11.2

4-(4-Chloro-benzyloxy)-1-{2-[4-(1-hydroxy-ethyl)-phenyl]-2-oxo-ethyl}-1*H*-pyridin-2-one



20 4-(4-Chloro-benzyloxy)-1-{2-[4-(1-hydroxy-ethyl)-phenyl]-2-oxo-ethyl}-1*H*-pyridin-2-one is prepared as described for preparation 11.1b starting from 4-(4-chloro-benzyloxy)-1*H*-pyridin-2-one (preparation 10.2, 319 mg, 1.15 mmol).

Yield: 0.50 g (48% of theory); ESI Mass spectrum: $[M+H]^+ = 398$

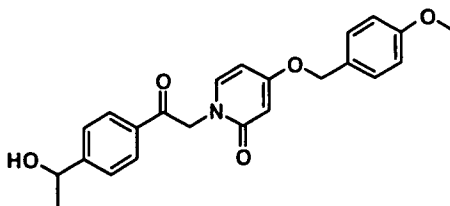
Retention time HPLC: 1.71 min (method K).

25

Preparation 11.3

1-{2-[4-(1-Hydroxy-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-methoxy-benzyloxy)-1*H*-pyridin-2-one

54

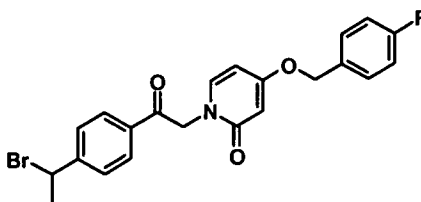


1-{2-[4-(1-Hydroxy-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-methoxy-benzyloxy)-1*H*-pyridin-2-one is prepared as described for preparation 11.1b starting from 4-(4-methoxy-benzyloxy)-1*H*-pyridin-2-one (preparation 10.7, 400 mg, 1.73 mmol).

- 5 Yield: 0.47 g (69% of theory); ESI Mass spectrum: $[M+H]^+ = 394$
Retention time HPLC: 1.61 min (method K).

Preparation 12.1

1-{2-[4-(1-Bromo-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-fluoro-benzyloxy)-1*H*-pyridin-2-one



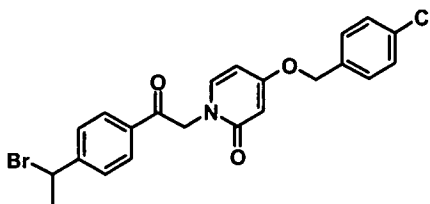
10

1-{2-[4-(1-Bromo-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-fluoro-benzyloxy)-1*H*-pyridin-2-one is prepared following preparation 1c from 415 mg (1.09 mmol) 4-(4-fluoro-benzyloxy)-1-{2-[4-(1-hydroxy-ethyl)-phenyl]-2-oxo-ethyl}-1*H*-pyridin-2-one (preparation 11.1) and 72 μ L phosphorus tribromide (0.76 mmol).

- 15 Yield: 328 mg (68% of theory); ESI Mass spectrum: $[M+H]^+ = 444/446$
Retention time HPLC: 1.57 min (method J).

Preparation 12.2

1-{2-[4-(1-Bromo-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-chloro-benzyloxy)-1*H*-pyridin-2-one



20

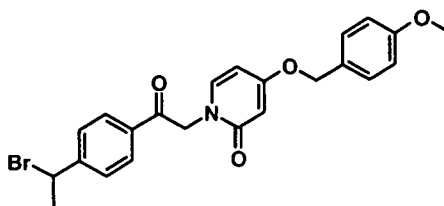
1-{2-[4-(1-Bromo-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-chloro-benzyloxy)-1*H*-pyridin-2-one is prepared following preparation 1c from 216 mg (0.54 mmol) 4-(4-chloro-benzyloxy)-1-{2-[4-(1-hydroxy-ethyl)-phenyl]-2-oxo-ethyl}-1*H*-pyridin-2-one (preparation 11.2) and 36 μ L phosphorus tribromide (0.38 mmol).

- 25 Yield: 110 mg (44% of theory; 85% purity); ESI Mass spectrum: $[M+H]^+ = 460/462/464$

Retention time HPLC: 1.63 min (method J).

Preparation 12.3

1-{2-[4-(1-Bromo-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-methoxy-benzyloxy)-1*H*-pyridin-2-one



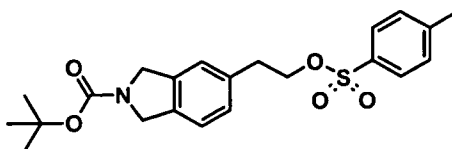
5

1-{1-[2-[4-(1-Bromo-ethyl)-phenyl]-2-oxo-ethyl]-4-(4-methoxy-benzyloxy)-1*H*-pyridin-2-one is prepared following preparation 1c from 472 mg (1.20 mmol) 1-{2-[4-(1-hydroxy-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-methoxy-benzyloxy)-1*H*-pyridin-2-one (preparation 11.3) and 79 μ L phosphorus tribromide (0.84 mmol).

10 Yield: 241 mg (26% of theory; 60% purity); ESI Mass spectrum: $[M+H]^+ = 456/458$
Retention time HPLC: 1.56 min (method J).

Preparation 13

5-[2-(Toluene-4-sulfonyloxy)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester



15

13a 5-(2-Hydroxy-ethyl)-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

To a solution of di-prop-2-ynyl-carbamic acid *tert*-butyl ester (1.91 g, 9.84 mmol) and 3-buten-1-ol (3.00 mL, 39.5 mmol) in anhydrous EtOH is added chloro tris(triphenylphosphin) rhodium (I) (Wilkinson catalyst). Caution: In larger scale preparations (> 10 g) strong exothermia is observed. The reaction mixture is heated to reflux shortly. After cooling, the reaction mixture is purified by preparative HPLC (Gilson, Waters XBridge C18, 5 μ m, gradient from 10% to 95% acetonitrile in water + 0.1% HCOOH, 120 mL/min).

20 Yield: 1.47 g (56% of theory); ESI Mass spectrum: $[M+H]^+ = 264$
Retention time HPLC: 1.39 min (method J).

25

13b 5-[2-(Toluene-4-sulfonyloxy)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

At 0°C, a solution of 4-methylbenzenesulfonyl chloride (1.17 g, 6.14 mmol) in DCM (5 mL) is added dropwise to a stirred solution of 5-(2-hydroxy-ethyl)-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 13a, 1.47 g, 5.58 mmol) in DCM (15 mL) and pyridine (0.66 mL). The reaction mixture is stirred for 3 h at RT. An additional 0.12 g 4-

30

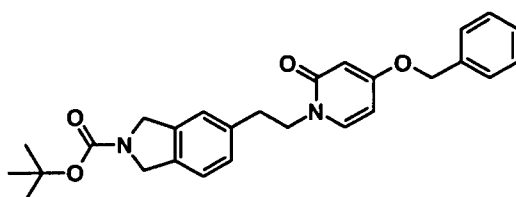
methylbenzenesulfonyl chloride plus 0.07 mL pyridine is added and the reaction mixture is stirred overnight. The reaction mixture is poured into ice water and extracted with dichloromethane. The organic layer is dried over MgSO_4 and evaporated in vacuo. The remaining residue is purified chromatographically (silica gel, gradient from 20% to 50% ethyl acetate in cyclohexane).

Yield: 770 mg (33% of theory); ESI Mass spectrum: $[\text{M}+\text{NH}_4]^+ = 435$

Retention time HPLC: 2.05 min (method K).

Preparation 14

5-[2-(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester



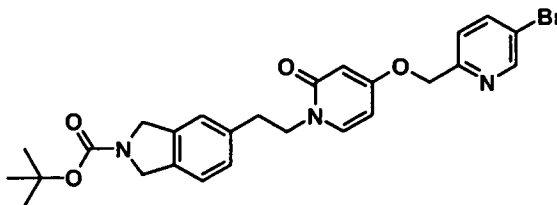
5-[2-(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 174 mg (0.86 mmol) 4-benzyloxy-1H-pyridin-2-one and 360 mg (0.86 mmol) 5-[2-(toluene-4-sulfonyloxy)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 13).

Yield: 350 mg (91% of theory); ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 447$

Retention time HPLC: 1.92 min (method K).

Preparation 15

5-{2-[4-(5-Bromo-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-ethyl}-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester



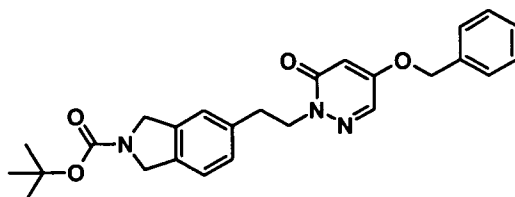
5-{2-[4-(5-Bromo-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-ethyl}-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 242 mg (0.86 mmol) 4-(5-bromo-pyridin-2-ylmethoxy)-1H-pyridin-2-one (preparation 10.3) and 360 mg (0.86 mmol) 5-[2-(toluene-4-sulfonyloxy)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 13).

Yield: 120 mg (26% of theory); ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 526/528$

Retention time HPLC: 1.87 min (method K).

Preparation 16

5-[2-(4-Benzyloxy-6-oxo-6*H*-pyridazin-1-yl)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester



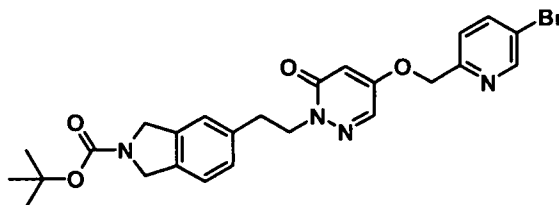
5-[2-(4-Benzyloxy-6-oxo-6*H*-pyridazin-1-yl)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 174 mg (0.86 mmol) 5-benzyloxy-2*H*-pyridazin-3-one (preparation 2) and 360 mg (0.86 mmol) 5-[2-(toluene-4-sulfonyloxy)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 13).

Yield: 360 mg (70% of theory); ESI Mass spectrum: $[M+H]^+ = 448$

Retention time HPLC: 2.01 min (method K).

Preparation 17

5-[2-[4-(5-Bromo-pyridin-2-ylmethoxy)-6-oxo-6*H*-pyridazin-1-yl]-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester



5-[2-[4-(5-Bromo-pyridin-2-ylmethoxy)-6-oxo-6*H*-pyridazin-1-yl]-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 243 mg (0.86 mmol) 5-(5-bromo-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one (preparation 10.3) and 360 mg (0.86 mmol) 5-[2-(toluene-4-sulfonyloxy)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 13).

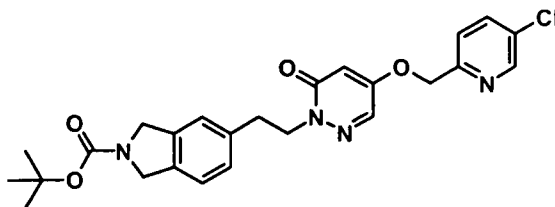
Yield: 180 mg (40% of theory); ESI Mass spectrum: $[M+H]^+ = 527/529$

Retention time HPLC: 1.95 min (method K).

Preparation 18

5-[2-[4-(5-Chloro-pyridin-2-ylmethoxy)-6-oxo-6*H*-pyridazin-1-yl]-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

58



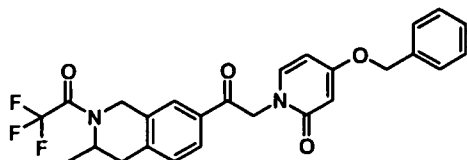
5-[2-[4-(5-chloro-pyridin-2-ylmethoxy)-6-oxo-6H-pyridazin-1-yl]-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 205 mg (0.86 mmol) 5-(5-chloro-pyridin-2-ylmethoxy)-2H-pyridazin-3-one (preparation 10.4) and 360 mg (0.86 mmol) 5-[2-(toluene-4-sulfonyloxy)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 13).

Yield: 360 mg (87% of theory); ESI Mass spectrum: $[M+H]^+ = 483/485$

Retention time HPLC: 1.93 min (method K).

10 Preparation 19

4-Benzyloxy-1-{2-[3-methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-1H-pyridin-2-one



19a N-[2-(4-Bromo-phenyl)-1-methyl-ethyl]-2,2,2-trifluoro-acetamide

15 To an ice-cooled solution of 2-(4-bromo-phenyl)-1-methyl-ethylamine (0.80 g, 3.74 mmol) in DCM (5 mL) is added trifluoroacetic acid anhydride (0.57 mL, 4.11 mmol) and the reaction mixture is stirred for 1 h at RT. The reaction mixture is quenched with aqueous sodium bicarbonate solution and extracted twice with DCM. The organic layer is dried over $MgSO_4$ and evaporated in vacuo.

20 Yield: 1.2 g (quantitative); ESI Mass spectrum: $[M+H]^+ = 310/312$

Retention time HPLC: 0.92 min (method J).

19b 1-(7-Bromo-3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone

25 Under cooling, sulphuric acid (15 mL) is added to glacial acetic acid (23 mL). The mixture is allowed to warm to room temperature and N-[2-(4-bromo-phenyl)-1-methyl-ethyl]-2,2,2-trifluoro-acetamide (preparation 19a, 9.00 g, 29 mmol) is added. After 10 min, paraformaldehyde (1.50 g) is added and the reaction mixture is stirred for 18 h at 40°C. Another portion of paraformaldehyde (1.50 g) is added and the reaction mixture is stirred for an additional 2 h at 40°C. The reaction mixture is poured into ice water and extracted twice

with ethyl acetate. The organic layer is dried over MgSO_4 and evaporated in vacuo. The resulting residue is purified chromatographically (silica gel, 20% ethyl acetate in hexanes).

Yield: 6.7 g (72% of theory); ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 322/324$

Retention time HPLC: 1.72 min (method J).

5

19c 1-(7-Iodo-3-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone

1-(7-Iodo-3-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone is prepared following preparation 9a from 1.00 g 1-(7-bromo-3-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone (preparation 19b, 3.10 mmol).

10 Yield: 0.86 g (75% of theory); ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 370$

Retention time HPLC: 1.80 min (method J).

19d 1-[7-(2-Chloro-acetyl)-3-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone

15 To a solution of 1-(7-iodo-3-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone (preparation 19c, 860 mg, 2.33 mmol) in anhydrous THF (20 mL) is added at -20°C a solution of isopropylmagnesium chloride and lithium chloride ("Turbo Grignard", 1.79 mL of 14% solution in THF). After 10 min, the Grignard solution is added to a solution of 2-chloro-*N*-methoxy-*N*-methylacetamid (320 mg, 2.33 mmol) in THF (20 mL), keeping the temperature below 0°C . After stirring for 30 min (temperature increases to 5°C), the reaction mixture is
20 poured into pH 7 buffer and extracted with *tert*-butylmethylether. The organic layer is washed with water, dried over MgSO_4 and concentrated in vacuo.

Yield: 550 mg (74 % of theory); R_f value: 0.29 (silica gel, 30% ethyl acetate in hexanes).

25 19e 4-Benzyloxy-1-{2-[3-methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-1*H*-pyridin-2-one

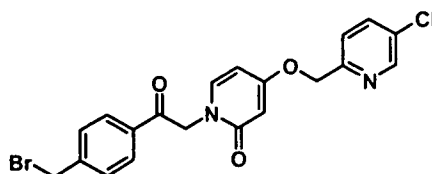
4-Benzyloxy-1-{2-[3-methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-1*H*-pyridin-2-one is prepared following preparation 1b from 350 mg (1.72 mmol) 4-benzyloxy-1*H*-pyridin-2-one and 550 mg (1.72 mmol) 1-[7-(2-chloro-acetyl)-3-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (preparation 19d), employing DMSO as
30 solvent.

Yield: 80 mg (10% of theory); Retention time HPLC: 1.58 min (method J).

Preparation 20:

1-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-4-(5-chloro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one

60



20a 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one

To 2.50 g (10.6 mmol) 4-(5-chloro-pyridin-2-ylmethoxy)-1H-pyridin-2-one (preparation 10.6) in 11 mL DMSO is added 8.6 g (26.4 mmol) cesium carbonate and the mixture is stirred 15 min at RT. Then, 3.75 g (16.4 mmol) 2-bromo-1-(4-hydroxymethyl-phenyl)-ethanone (preparation 1a) is added and the reaction mixture is stirred for 2 h at RT. Water is added, the precipitate is collected, washed with water and dried.

Yield: 3.30 g (81% of theory); ESI Mass spectrum: $[M+H]^+ = 385/387$

Retention time HPLC: 1.18 min (method J).

20b 1-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-4-(5-chloro-pyridin-2-ylmethoxy)-1H-pyridin-2-one

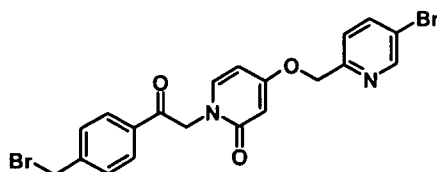
1-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-4-(5-chloro-pyridin-2-ylmethoxy)-1H-pyridin-2-one is prepared following preparation 1c from 4-(5-chloro-pyridin-2-ylmethoxy)-1-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one (preparation 20a, 3.10 g, 8.06 mmol). After cooling, the reaction mixture is quenched with aqueous sodium bicarbonate solution. The organic layer is washed with water and dried over $MgSO_4$. The volatiles are removed in vacuo and the resulting residue is purified via preparative reverse HPLC chromatography (Gilson, Stable Bond C18, 7 μ m, gradient from 10% to 95% acetonitrile in water + 0.1% HCOOH, 120 mL/min).

Yield: 1.30 g (36% of theory); ESI Mass spectrum: $[M+H]^+ = 447/449/451$

Retention time HPLC: 1.08 min (method L).

Preparation 21:

1-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-4-(5-bromo-pyridin-2-ylmethoxy)-1H-pyridin-2-one



21a 4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one

To 1.00 g (3.56 mmol) 4-(5-bromo-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one (preparation 10.3) in 4 mL DMSO is added 2.90 g (8.90 mmol) cesium carbonate and the mixture is stirred 15 min at RT. Then 0.82 g (3.60 mmol) 2-bromo-1-(4-hydroxymethyl-phenyl)-ethanone (preparation 1a) is added and the reaction mixture is stirred 2 h at RT. Water is added, the precipitate is collected, washed with water and dried.

Yield: 1.30 g (64% of theory); ESI Mass spectrum: $[M+H]^+ = 429/431$

Retention time HPLC: 1.32 min (method J).

21b 1-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-4-(5-bromo-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one

1-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-4-(5-bromo-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one is prepared following preparation 1c from 4-(5-bromo-pyridin-2-ylmethoxy)-1-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one (preparation 21a, 1.30 g, 2.27 mmol).

After cooling, the reaction mixture is quenched with aqueous sodium bicarbonate solution.

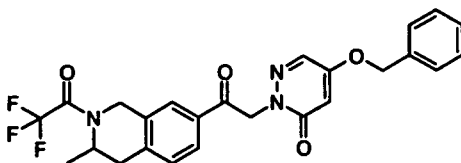
The organic layer is washed with water, dried over $MgSO_4$ and concentrated in vacuo. The resulting solid is triturated with acetonitrile, the precipitate is filtered off and dried.

Yield: 670 mg (60% of theory); ESI Mass spectrum: $[M+H]^+ = 491/493/495$

Retention time HPLC: 1.49 min (method J).

Preparation 22

5-Benzyloxy-2-{2-[3-methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-2*H*-pyridazin-3-one

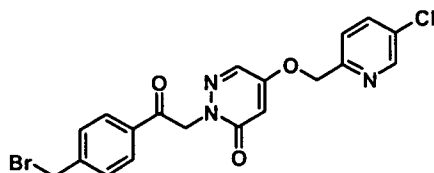


5-Benzyloxy-2-{2-[3-methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-2*H*-pyridazin-3-one is prepared following preparation 1b from 126 mg 5-benzyloxy-2*H*-pyridazin-3-one (preparation 2, 0.63 mmol) and 200 mg (0.63 mmol) 1-[7-(2-chloro-acetyl)-3-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (preparation 19d), employing DMSO as solvent.

Yield: 60 mg (20% of theory); Retention time HPLC: 1.63 min (method J).

Preparation 23

2-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-5-(5-chloro-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one



23a 5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one

To 4.20 g (17.7 mmol) 5-(5-chloro-pyridin-2-ylmethoxy)-2H-pyridazin-3-one (preparation 10.4) in 20 mL DMSO is added 14.4 g (44.2 mmol) cesium carbonate and the mixture is stirred 15 min at RT. Then 4.45 g (19.4 mmol) 2-bromo-1-(4-hydroxymethyl-phenyl)-ethanone (preparation 1a) is added and the reaction mixture is stirred for 2 h at RT. Water is added, the precipitate is collected, washed with water and dried.

Yield: 6.80 g (100% of theory); ESI Mass spectrum: $[M+H]^+ = 386$

Retention time HPLC: 1.18 min (method J).

23b 2-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-5-(5-chloro-pyridin-2-ylmethoxy)-2H-pyridazin-3-one

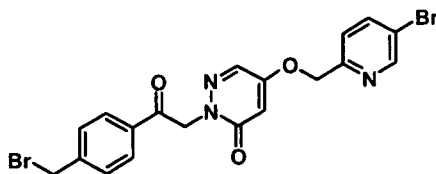
2-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-5-(5-chloro-pyridin-2-ylmethoxy)-2H-pyridazin-3-one is prepared following preparation 1c from 5-(5-chloro-pyridin-2-ylmethoxy)-2-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one (preparation 23a, 6.80 g, 17.6 mmol). After cooling, the reaction mixture is treated with diisopropyl ether. The formed precipitate is filtered off and dried. The solid is dissolved in DCM and small amounts of MeOH, filtered over aluminium oxide and the filtrate is concentrated in vacuo.

Yield: 5.50 g (70% of theory); ESI Mass spectrum: $[M+H]^+ = 448/450/452$

Retention time HPLC: 1.08 min (method L).

Preparation 24

2-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-5-(5-bromo-pyridin-2-ylmethoxy)-2H-pyridazin-3-one



24a 5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one

To 500 mg (1.77 mmol) 5-(5-bromo-pyridin-2-ylmethoxy)-2H-pyridazin-3-one (preparation 10.5) in 2 mL DMSO is added 1.44 g (4.42 mmol) cesium carbonate and the mixture is stirred

15 min at RT. Then 406 mg (1.77 mmol) 2-bromo-1-(4-hydroxymethyl-phenyl)-ethanone (preparation 1a) is added and the reaction mixture is stirred for 2 h at RT. Water is added, the precipitate is collected, washed with water and dried.

Yield: 600 mg (71% of theory); ESI Mass spectrum: $[M+H]^+ = 430/432$

5 Retention time HPLC: 1.36 min (method J).

24b 2-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-5-(5-bromo-pyridin-2-ylmethoxy)-2H-pyridazin-3-one

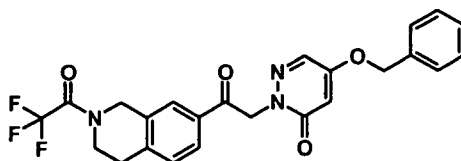
2-[2-(4-Bromomethyl-phenyl)-2-oxo-ethyl]-5-(5-bromo-pyridin-2-ylmethoxy)-2H-pyridazin-3-one is prepared following preparation 1c from 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(4-hydroxymethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one (preparation 24a, 600 mg, 1.40 mmol). After cooling, the reaction mixture is quenched with aqueous sodium bicarbonate solution. The organic layer is washed with water, dried over $MgSO_4$ and concentrated in vacuo. The resulting solid is triturated with acetonitrile, the precipitate is filtered off and dried.

15 Yield: 688 mg (73% of theory); ESI Mass spectrum: $[M+H]^+ = 492/494/496$

Retention time HPLC: 1.56 min (method J).

Preparation 25

5-Benzyloxy-2-{2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-2H-pyridazin-3-one



5-Benzyloxy-2-{2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-2H-pyridazin-3-one is prepared following preparation 1b (DMSO as solvent) from 2.02 g (10.0 mmol) 5-benzyloxy-2H-pyridazin-3-one (preparation 2) and 3.21 g (10.0 mmol) 1-[7-(2-chloro-acetyl)-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (prepared according to WO2005/66165). Water is added to the reaction mixture and the formed precipitate is filtered off. The crude material is purified via reverse HPLC chromatography (Gilson; Stablebond C18; water (0.15% formic acid) / acetonitrile (0.15% formic acid) 95:5 to 5:95; 120 mL/min).

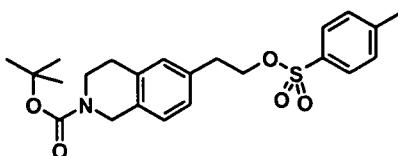
25 Yield: 2.50 g (53% of theory); ESI Mass spectrum: $[M+H]^+ = 472$

30 Retention time HPLC: 1.56 min (method J).

Preparation 26:

6-[2-(Toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

64



26a 6-Iodo-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

- To 13.0 g (41.6 mmol) 6-bromo-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester in 42 mL 1,4-dioxane is added 817 mg (4.21 mmol) copper(I)-iodide under argon. After flushing with argon, 0.89 mL (8.33 mmol) *N,N*-dimethylethylen-diamine and 12.5 g (83.3 mmol) sodium iodide is added at RT. The reaction mixture is stirred 14 h at 110°C, is cooled to RT and is diluted with 5% aqueous ammonia-solution. The layers are separated and the aqueous phase is extracted with EtOAc. The combined organic phase is washed with water and is dried over MgSO₄, filtered and the solvent is evaporated to give the product.
- Yield: 14.0 g (94% of theory); EI Mass spectrum: [M]⁺ = 359
- R_F-value: 0.8 (silica gel, mixture C).

26b 6-(2-Hydroxy-ethyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

- To 1.80 g (5.00 mmol) 6-iodo-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 26a) in 5.0 mL THF at -20°C is added 6.34 g (5.50 mmol) of a THF-solution of 14% isopropylmagnesium-chloride*lithiumchloride under argon. The mixture is warmed to 0°C and stirred 1 h at 0°C. The reaction mixture is cooled to -60°C and 0.88 g (20.0 mmol) oxirane in 2.0 mL THF is added. The cooling bath is removed and the reaction is warmed to RT. The reaction mixture is poured into 50 mL aqueous ammonium chloride solution and the aqueous phase is extracted with EtOAc. The combined organic phase is washed with water, dried over MgSO₄. After filtration and evaporation of the solvent, the residue is purified *via* reverse HPLC chromatography (Zorbax stable bond, C18; water (0.15% formic acid)/acetonitrile 95:5 to 5:95).
- Yield: 47% of theory; R_F-value: 0.4 (silica gel, mixture D).

26c 6-[2-(Toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

- To 1.60 g (5.76 mmol) 6-(2-hydroxy-ethyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 26b) in 20 mL DCM is added at 0°C subsequently 0.68 mL (8.66 mmol) pyridine and 1.21 g (6.34 mmol) 4-methyl-benzenesulfonyl chloride in 10.0 mL DCM. The reaction mixture is warmed to RT and is stirred 5 h at RT. Additional 0.68 mL (8.66 mmol) pyridine and 1.21 g (6.34 mmol) 4-methyl-benzenesulfonyl chloride in 5.0 mL DCM are added and the mixture is stirred overnight. The reaction mixture is poured into ice-water and the organic phase is separated, washed with aqueous KHSO₄-solution and aqueous

NaHCO₃-solution, dried over MgSO₄. After evaporation of the solvent, the residue is purified via chromatography (silica gel; cyclohexane/EtOAc 8:2 to 1:1).

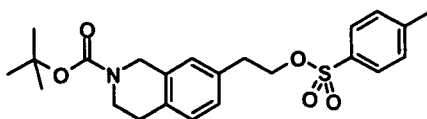
Yield: 1.30 g (52% of theory); ESI Mass spectrum: [M+NH₄]⁺ = 449

R_F-value: 0.4 (silica gel, mixture C).

5

Preparation 27

7-[2-(Toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester



10

27a 7-Bromo-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

To 10.0 g (40.2 mmol) 7-bromo-1,2,3,4-tetrahydro-isoquinoline hydrochloride in 250 mL DCM and 50 mL (101 mmol) 2M aqueous Na₂CO₃-solution is added a solution of 9.27 g (42.5 mmol) BOC-anhydride in DCM. The reaction is stirred 1 h at RT and is diluted with 100 mL water. The organic phase is washed with water, dried over MgSO₄, filtered and the solvent is evaporated. To the residue is added PE and the mixture is cooled to -30°C. The precipitate is collected, washed with cold PE and dried.

15

Yield: 10.3 g (82% of theory); ESI Mass spectrum: [M+H]⁺ = 312/314

R_F-value: 0.5 (silica gel, mixture C).

20

27b 7-Iodo-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

To 11.0 g (35.2 mmol) 7-bromo-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 27a) in 35 mL 1,4-dioxane is added 692 mg (3.56 mmol) copper(I)-iodide under argon. After flushing with argon, 0.75 mL (7.05 mmol) *N,N*-dimethylethylen-diamine and 10.6 g (70.5 mmol) sodium-iodide is added at RT. The reaction mixture is stirred 14 h at 110°C, cooled to RT and diluted with 5% aqueous ammonia-solution. The aqueous phase is extracted with EtOAc and the combined organic phase is washed with water, dried over MgSO₄. After filtration and evaporation of the solvent, the residue is purified via chromatography (silica gel; Cyclohexane/EtOAc 85/15).

25

Yield: 10.8 g (purity 75% (contains compound 27a), 78% of theory)

30

ESI Mass spectrum: [M+H]⁺ = 360; R_F-value: 0.6 (silica gel, mixture F).

27c 7-(2-Hydroxy-ethyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

To 1.80 g (5.00 mmol) 7-iodo-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 27b) in 5.0 mL THF at -20°C is added 6.34 g (5.50 mmol) of a THF-solution of 14% isopropylmagnesium-chloride*lithiumchloride under argon. The mixture is warmed to 0°C and stirred 1 h at 0°C. The reaction mixture is cooled to -60°C and 0.88 g (20.0 mmol) oxirane in 2.0 mL THF is added. The cooling bath is removed and the reaction is warmed to RT. The reaction mixture is poured into 50 mL aqueous ammonium chloride solution and the aqueous phase is extracted with EtOAc. The combined organic phase is washed with water, dried over MgSO₄. After filtration and evaporation of the solvent, the residue is purified *via* reverse HPLC chromatography (Zorbax stable bond, C18; water (0.15% formic acid)/acetonitrile 95:5 to 5:95).

Yield: 800 mg (58% of theory); ESI Mass spectrum: [M+H]⁺ = 278

Retention time HPLC: 2.6 min (method E).

27d 7-[2-(Toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

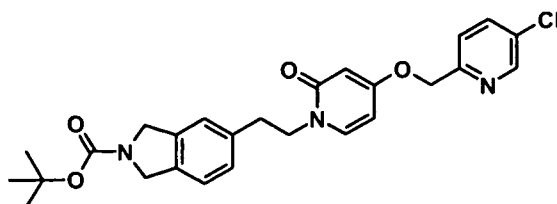
To 800 mg (2.88 mmol) 7-(2-hydroxy-ethyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 27c) in 10 mL DCM is added at 0°C subsequently 0.34 mL (4.33 mmol) pyridine and 605 mg (3.17 mmol) 4-methyl-benzenesulfonyl chloride in 5.0 mL DCM. The reaction mixture is warmed to RT and is stirred 5 h at RT. Additional 0.34 mL (4.33 mmol) pyridine and 605 mg (3.17 mmol) 4-methyl-benzenesulfonyl chloride in 5.0 mL DCM are added and the mixture is stirred over night. The reaction mixture is poured into ice-water and the organic phase is separated, washed with aqueous KHSO₄-solution and aqueous NaHCO₃-solution, dried over MgSO₄. After evaporation of the solvent, the residue is purified *via* chromatography (silica gel; cyclohexane/EtOAc 8:2 to 1:1).

Yield: 1.10 g (88% of theory); ESI Mass spectrum: [M+H]⁺ = 432

R_f-value: 0.4 (silica gel, method F).

Preparation 28

5-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester



5-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from

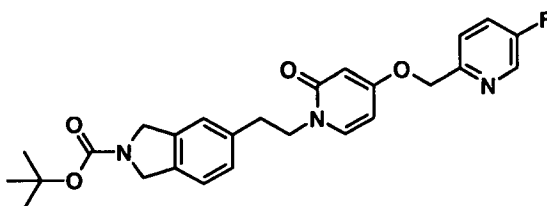
400 mg (1.69 mmol) 4-(5-chloro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one (preparation 10.6) and 706 mg (1.69 mmol) 5-[2-(toluene-4-sulfonyloxy)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 13).

Yield: 460 mg (57% of theory); ESI Mass spectrum: $[M+H]^+ = 482/484$

5 Retention time HPLC: 1.84 min (method K).

Preparation 29

5-[2-[4-(5-Fluoro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester



10

5-[2-[4-(5-Fluoro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 300 mg (1.36 mmol) 4-(5-fluoro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one (preparation 10.11) and 569 mg (1.36 mmol) 5-[2-(toluene-4-sulfonyloxy)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 13).

15

Yield: 340 mg (54% of theory); ESI Mass spectrum: $[M+H]^+ = 466$

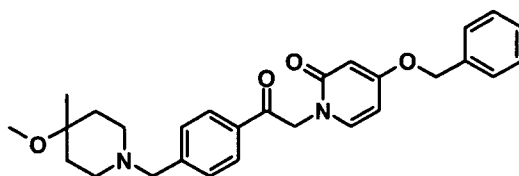
Retention time HPLC: 1.57 min (method J).

Preparation of example compounds of the invention:

20

Example 1.1

4-Benzyloxy-1-[2-[4-(4-methoxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl]-1*H*-pyridin-2-one



25

To 247 mg (0.60 mmol) 4-benzyloxy-1-[2-(4-bromomethyl-phenyl)-ethyl]-1*H*-pyridin-2-one (preparation 1) in 2.00 mL of DMF is added 194 mg (1.50 mmol) 4-methoxy-4-methyl-piperidine. The reaction mixture is stirred for 18 h at RT and is directly purified by HPLC (Stable Bond C18; 7 μ m; water (0.1% formic acid) / acetonitrile (0.1% formic acid) 95:5 to 10:90).

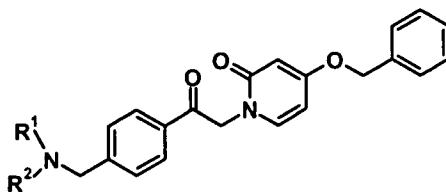
30

Yield: 105 mg (38% of theory)

ESI Mass spectrum: $[M+H]^+ = 461$

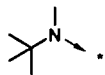
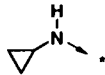
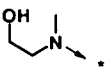
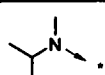
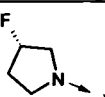
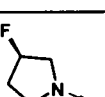
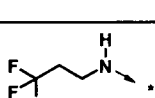
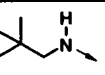
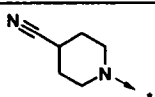
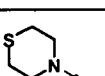
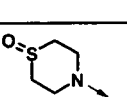
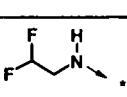
Retention time HPLC: 1.77 min (method K).

- The following examples are prepared as described for Example 1.1. For the preparation of example 1.7, 4 equivalents of triethylamine are added to the reaction mixture. For the preparation of example 1.12 and 1.13, the hydrochloride salt of the amine reagent plus 5 equivalents of Hünig's base (N-ethyl-diisopropylamine) are employed.



10

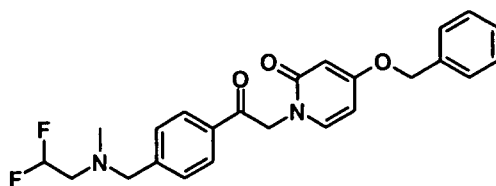
Example	R ¹ R ² N-	Yield (%)	Formula	MS	Retention time HPLC in min (method)
1.2		48	C ₂₇ H ₂₇ F ₃ N ₂ O ₄	501 [M+H] ⁺	2.31 (H)
1.3		61	C ₂₇ H ₃₁ N ₃ O ₃	446 [M+H] ⁺	1.15 (J)
1.4		43	C ₂₃ H ₂₄ N ₂ O ₄	393 [M+H] ⁺	1.51 (K)
1.5		70	C ₂₅ H ₂₈ N ₂ O ₃	405 [M+H] ⁺	1.80 (K)
1.6		68	C ₂₄ H ₂₆ N ₂ O ₃	391 [M+H] ⁺	1.70 (K)
1.7		9	C ₂₅ H ₂₆ N ₂ O ₄	419 [M+H] ⁺	3.1 (A)

1.8		64	C ₂₆ H ₃₀ N ₂ O ₃	419 [M+H] ⁺	1.96 (K)
1.9		64	C ₂₄ H ₂₄ N ₂ O ₃	389 [M+H] ⁺	1.08 (J)
1.10		82	C ₂₄ H ₂₆ N ₂ O ₄	407 [M+H] ⁺	1.01 (J)
1.11		66	C ₂₅ H ₂₈ N ₂ O ₃	405 [M+H] ⁺	1.07 (J)
1.12		38	C ₂₅ H ₂₅ FN ₂ O ₃	421 [M+H] ⁺	1.15 (J)
1.13		38	C ₂₅ H ₂₅ FN ₂ O ₃	421 [M+H] ⁺	2.92 (C)
1.14		21	C ₂₄ H ₂₃ F ₃ N ₂ O ₃	445 [M+H] ⁺	3.16 (C)
1.15		36	C ₂₆ H ₃₀ N ₂ O ₃	419 [M+H] ⁺	1.23 (J)
1.16		41	C ₂₇ H ₂₇ N ₃ O ₃	442 [M+H] ⁺	1.56 (J)
1.17		41	C ₂₅ H ₂₆ N ₂ O ₃ S	435 [M+H] ⁺	1.16 (J)
1.18		41	C ₂₅ H ₂₆ N ₂ O ₄ S	451 [M+H] ⁺	1.08 (J)
1.19		36	C ₂₃ H ₂₂ F ₂ N ₂ O ₃	413 [M+H] ⁺	1.11 (J)

Example 1.20

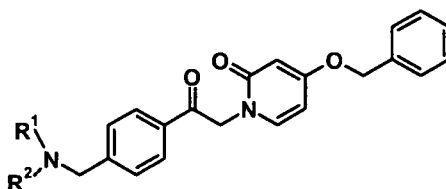
4-Benzyloxy-1-[2-(4-[(2,2-difluoro-ethyl)-methyl-amino]-methyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one

70



- To 100 mg (0.24 mmol) 4-benzyloxy-1-(2-{4-[(2,2-difluoro-ethylamino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one (example 1.19) in 5 mL THF is added 79 μ L (0.97 mmol) 37% aqueous formaldehyde solution and 103 mg (0.49 mmol) sodium triacetoxy-borohydride. The mixture is acidified with pH 5 buffer solution (1 mL) and stirred for 48 h at RT. The reaction mixture is quenched with aqueous sodium bicarbonate solution and extracted twice with ethyl acetate. The organic layer is dried over MgSO_4 and concentrated in vacuo. The resulting residue is purified *via* preparative reverse HPLC chromatography (Zorbax Stable Bond C18, 7 μ m, gradient from 10% to 95% acetonitrile in water + 0.1% HCOOH , 120 mL/min).
- Yield: 50 mg (48% of theory)
- ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 427$
- Retention time HPLC: 1.26 min (method J).

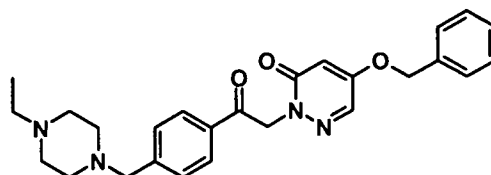
- Examples 1.21 and 1.22 are prepared as described for Example 1.20, starting from examples 1.9 and 1.7, respectively.



Example	$\text{R}^1\text{R}^2\text{N}-$	Yield (%)	Formula	MS	Retention time HPLC in min (method)
1.21		70	$\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_3$	403 $[\text{M}+\text{H}]^+$	1.82 (K)
1.22		48	$\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_4$	433 $[\text{M}+\text{H}]^+$	1.19 (J)

Example 2.1

5-Benzyloxy-2-{2-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one



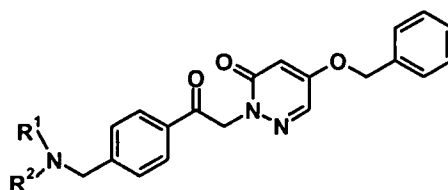
To 500 mg (1.21 mmol) 5-benzyloxy-2-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-2*H*-pyridazin-3-one (preparation 3) in 10 mL of DMF is added 415 mg (3.63 mmol) 1-ethylpiperazine. The reaction mixture is stirred for 18 h at RT and is directly purified by HPLC (Waters Symmetry C18; 7 μ m; water (0.1% formic acid) / acetonitrile (0.1% formic acid) 95:5 to 10:90).

Yield: 280 mg (52% of theory)

ESI Mass spectrum: $[M+H]^+ = 447$

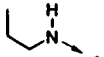
Retention time HPLC: 2.90 min (method C).

10 The following examples are prepared as described for Example 2.1.

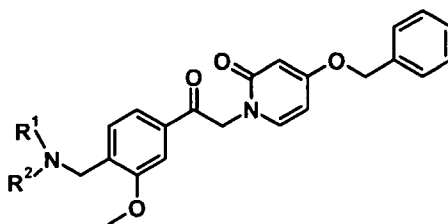


Example	R ¹ R ² N-	Yield (%)	Formula	MS	Retention time HPLC in min (method)
2.2		46	C ₂₆ H ₂₆ F ₃ N ₃ O ₄	502 [M+H] ⁺	1.79 (K)
2.3		51	C ₂₅ H ₂₇ N ₃ O ₃	418 [M+H] ⁺	1.18 (J)
2.4		79	C ₂₂ H ₂₃ N ₃ O ₃	378 [M+H] ⁺	2.18 (H)
2.5		72	C ₂₃ H ₂₅ N ₃ O ₃	392 [M+H] ⁺	1.74 (K)

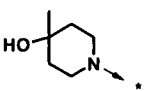
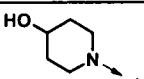
72

2.6		47	C ₂₁ H ₂₁ N ₃ O ₃	364 [M+H] ⁺	1.61 (K)
2.7		59	C ₂₃ H ₂₅ N ₃ O ₃	392 [M+H] ⁺	3.04 (C)

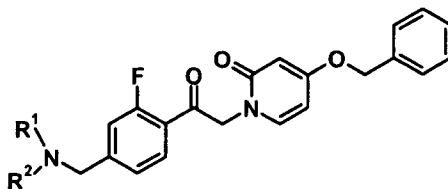
The following examples are prepared as described for Example 1.1 starting from 4-benzyloxy-1-[2-(4-bromomethyl-3-methoxy-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one (preparation 5).



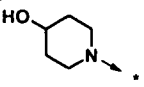
5

Example	R ¹ R ² N-	Yield (%)	Formula	MS	Retention time HPLC in min (method)
3.1		71	C ₂₈ H ₃₂ N ₂ O ₅	477 [M+H] ⁺	3.28 (A)
3.2		60	C ₂₄ H ₂₆ N ₂ O ₄	407 [M+H] ⁺	3.26 (A)
3.3		52	C ₂₇ H ₃₀ N ₂ O ₅	463 [M+H] ⁺	3.16 (A)

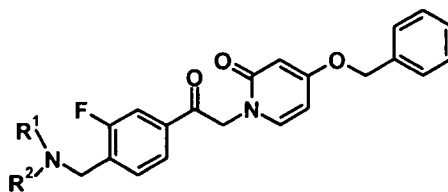
The following examples are prepared as described for Example 1.1 starting from 4-benzyloxy-1-[2-(4-bromomethyl-2-fluoro-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one (preparation 4).



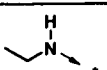
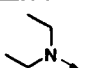
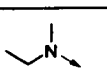
10

Example	R ¹ R ² N-	Yield (%)	Formula	MS	Retention time HPLC in min (method)
4.1		74	C ₂₃ H ₂₃ FN ₂ O ₃	395 [M+H] ⁺	1.67 (J)
4.2		66	C ₂₆ H ₂₇ FN ₂ O ₄	451 [M+H] ⁺	1.56 (J)

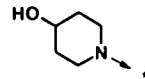
The following examples are prepared as described for Example 1.1 starting from 4-benzyloxy-1-[2-(4-bromomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one (preparation 6).



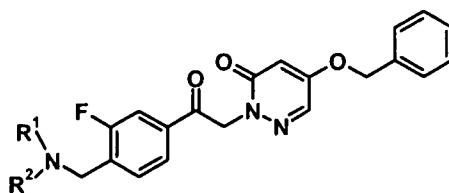
5

Example	R ¹ R ² N-	Yield (%)	Formula	MS	Retention time HPLC in min (method)
5.1		40	C ₂₃ H ₂₃ FN ₂ O ₃	395 [M+H] ⁺	2.87 (C)
5.2		41	C ₂₂ H ₂₁ FN ₂ O ₃	379 [M-H] ⁺	2.07 (H)
5.3		51	C ₂₃ H ₂₃ FN ₂ O ₃	395 [M+H] ⁺	1.06 (J)
5.4		69	C ₂₅ H ₂₇ FN ₂ O ₃	423 [M+H] ⁺	1.06 (J)
5.5		70	C ₂₄ H ₂₅ FN ₂ O ₃	409 [M+H] ⁺	1.06 (J)

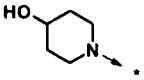
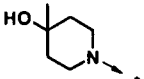
74

5.6		57	C ₂₄ H ₂₅ FN ₂ O ₃	409 [M+H] ⁺	1.18 (J)
5.7		31	C ₂₆ H ₂₇ FN ₂ O ₄	451 [M+H] ⁺	1.14 (J)

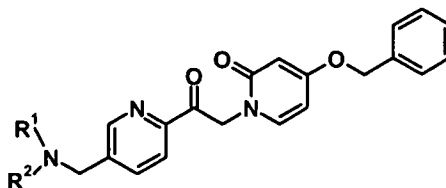
The following examples are prepared as described for Example 2.1 starting from 5-benzyloxy-2-[2-(4-bromomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one (preparation 7).



5

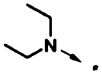
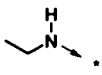
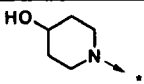
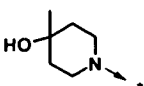
Example	R ¹ R ² N-	Yield (%)	Formula	MS	Retention time HPLC in min (method)
6.1		53	C ₂₅ H ₂₆ FN ₃ O ₄	452 [M+H] ⁺	1.60 (K)
6.2		65	C ₂₂ H ₂₂ FN ₃ O ₃	396 [M+H] ⁺	1.73 (K)
6.3		79	C ₂₆ H ₂₈ FN ₃ O ₄	466 [M+H] ⁺	1.64 (K)

The following examples are prepared as described for Example 1.1 starting from 4-benzyloxy-1-[2-(5-bromomethyl-pyridin-2-yl)-2-oxo-ethyl]-1H-pyridin-2-one (preparation 9).

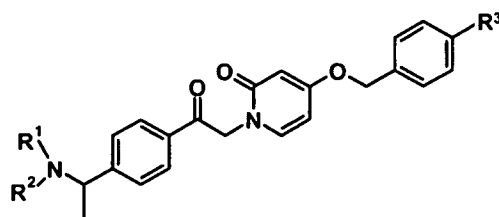


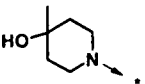
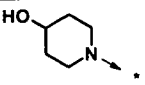
10

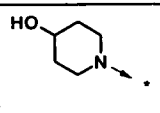
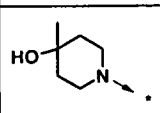
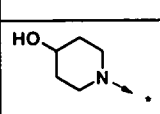
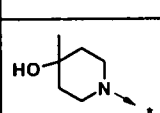
Example	R ¹ R ² N-	Yield	Formula	MS	Retention time
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		(%)			HPLC in min (method)
7.1		54	C ₂₄ H ₂₇ N ₃ O ₃	406 [M+H] ⁺	1.21 (J)
7.2		71	C ₂₂ H ₂₃ N ₃ O ₃	378 [M+H] ⁺	1.17 (J)
7.3		69	C ₂₂ H ₂₃ N ₃ O ₃	378 [M+H] ⁺	1.20 (J)
7.4		83	C ₂₅ H ₂₇ N ₃ O ₄	434 [M+H] ⁺	1.17 (J)
7.5		26	C ₂₆ H ₂₉ N ₃ O ₄	448 [M+H] ⁺	1.12 (K)

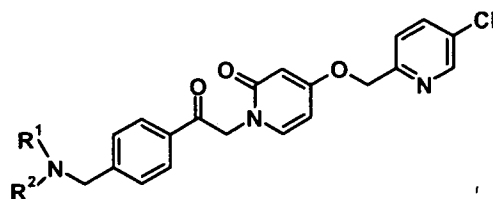
The following examples are prepared as described for Example 1.1 starting from 1-{2-[4-(1-bromo-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-fluoro-benzyloxy)-1*H*-pyridin-2-one (preparation 12.1, R³ = F), 1-{2-[4-(1-bromo-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-chloro-benzyloxy)-1*H*-pyridin-2-one (preparation 12.2, R³ = Cl) and 1-{2-[4-(1-bromo-ethyl)-phenyl]-2-oxo-ethyl}-4-(4-methoxy-benzyloxy)-1*H*-pyridin-2-one (preparation 12.3, R³ = MeO).



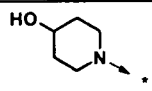
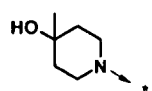
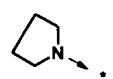
Example	R ¹ R ² N-	R ³	Yield (%)	Formula	MS	Retention time HPLC in min (method)
8.1		F	75	C ₂₈ H ₃₁ FN ₂ O ₄	479 [M+H] ⁺	1.65 (K)
8.2		F	38	C ₂₇ H ₂₉ FN ₂ O ₄	465 [M+H] ⁺	1.63 (K)

8.3		Cl	52	C ₂₇ H ₂₉ ClN ₂ O ₄	481/483 [M+H] ⁺	1.69 (K)
8.4		Cl	42	C ₂₈ H ₃₁ ClN ₂ O ₄	495/497 [M+H] ⁺	1.73 (K)
8.5		OMe	53	C ₂₈ H ₃₂ N ₂ O ₅	477 [M+H] ⁺	1.08 (J)
8.6		OMe	69	C ₂₉ H ₃₄ N ₂ O ₅	491 [M+H] ⁺	1.11 (J)

The following examples are prepared as described for Example 1.1 starting from 1-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-4-(5-chloro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one (preparation 20).

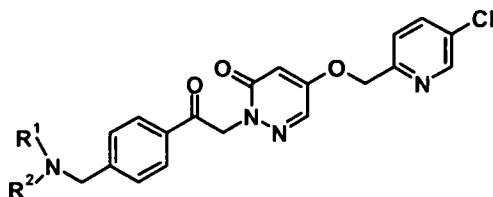


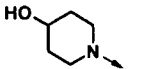
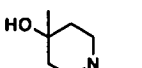
5

Example	R ¹ R ² N-	Yield (%)	Formula	MS	Retention time HPLC in min (method)
9.1		84	C ₂₅ H ₂₆ ClN ₃ O ₄	468/470 [M+H] ⁺	1.43 (K)
9.2		16	C ₂₂ H ₂₂ ClN ₃ O ₃	412/414 [M+H] ⁺	1.53 (K)
9.3		76	C ₂₆ H ₂₈ ClN ₃ O ₄	482/484 [M+H] ⁺	1.46 (K)
9.4		65	C ₂₄ H ₂₄ ClN ₃ O ₃	438/440 [M+H] ⁺	1.63 (K)

9.5		47	C ₂₁ H ₂₀ CIN ₃ O ₃	398/400 [M+H] ⁺	1.46 (K)
9.6		74	C ₂₃ H ₂₄ CIN ₃ O ₃	426/428 [M+H] ⁺	1.61 (K)
9.7		75	C ₂₄ H ₂₆ CIN ₃ O ₃	440/442 [M+H] ⁺	1.72 (K)
9.8		57	C ₂₅ H ₂₆ CIN ₃ O ₃	452/454 [M+H] ⁺	1.73 (K)

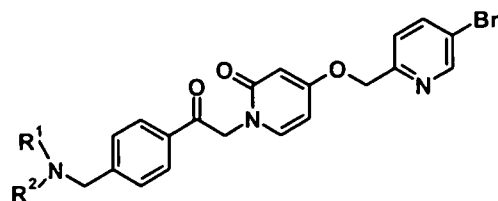
The following examples are prepared as described for Example 1.1 starting from 2-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-5-(5-chloro-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one
 5 (preparation 23).



Example	R ¹ R ² N-	Yield (%)	Formula	MS	Retention time HPLC in min (method)
10.1		65	C ₂₄ H ₂₅ CIN ₄ O ₄	469/471 [M+H] ⁺	1.51 (K)
10.2		77	C ₂₅ H ₂₇ CIN ₄ O ₄	483/485 [M+H] ⁺	1.51 (K)

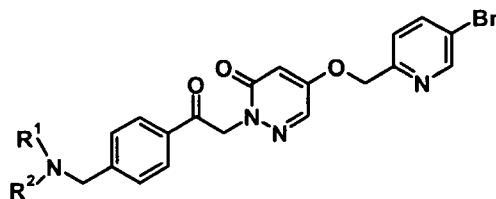
The following examples are prepared as described for Example 1.1 starting from 1-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-4-(5-bromo-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one
 10 (preparation 21).

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Example	R ¹ R ² N-	Yield (%)	Formula	MS	Retention time HPLC in min (method)
11.1		51	C ₂₅ H ₂₆ BrN ₃ O ₃	496/498 [M+H] ⁺	1.76 (K)
11.2		59	C ₂₂ H ₂₂ BrN ₃ O ₃	456/458 [M+H] ⁺	1.55 (K)

The following examples are prepared as described for Example 1.1 starting from 2-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-5-(5-bromo-pyridin-2-ylmethoxy)-2H-pyridazin-3-one (preparation 24).

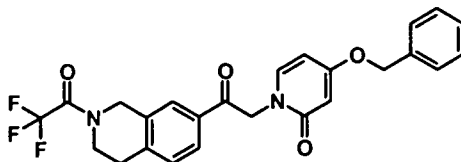


Example	R ¹ R ² N-	Yield (%)	Formula	MS	Retention time HPLC in min (method)
12.1		60	C ₂₄ H ₂₅ BrN ₄ O ₃	497/499 [M+H] ⁺	1.86 (K)
12.2		61	C ₂₁ H ₂₁ BrN ₄ O ₃	457/459 [M+H] ⁺	1.62 (K)

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Example 13.1:

4-Benzyloxy-1-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-1H-pyridin-2-one



To 600 mg (2.98 mmol) 4-benzyloxy-1H-pyridin-2-one in 6 mL THF is added at 0°C 368 mg (3.28 mmol) potassium *tert*-butylate and 55 mg (0.15 mmol) *tert*-butylammonium iodide. After 5 min 1.00 g (3.28 mmol) 1-[7-(2-chloro-acetyl)-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (prepared according to WO2005/66165) is added. After 2 h additional 600 mg (1.97 mmol) 1-[7-(2-chloro-acetyl)-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone is added and the mixture is stirred an additional hour. The reaction mixture is diluted with EtOAc and the organic phase is washed with water, filtered, dried over MgSO₄ and the solvent is evaporated. The residue is purified *via* reverse HPLC chromatography (Zorbax stable bond; water (0.15% formic acid)/acetonitrile (0.15% formic acid) 95:5 to 5:95).

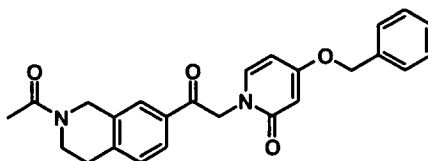
Yield: 600 mg (43% of theory)

ESI Mass spectrum: [M+H]⁺ = 471

Retention time HPLC: 3.9 min (method A).

Example 13.2

1-[2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-benzyloxy-1H-pyridin-2-one



13.2a 4-Benzyloxy-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one

To 600 mg (1.28 mmol) 4-benzyloxy-1-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-1H-pyridin-2-one (example 13.1) in 20 mL MeOH is added 10.6 mL (10.6 mmol) aqueous 1 M sodium hydroxide solution. The reaction mixture is stirred 3 h at RT. The solvent is evaporated and the residue is triturated with a small amount of water. The formed precipitate is filtered off, washed with water and dried in vacuo.

Yield: 220 mg (46% of theory)

ESI Mass spectrum: [M+H]⁺ = 375

Retention time HPLC: 1.04 min (method J).

13.2b 1-[2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-benzyloxy-1H-pyridin-2-one

To a solution of 4-benzyloxy-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 13.2a, 75 mg, 0.20 mmol) in acetic acid (1 mL) is added acetic anhydride (47 μ L, 0.50 mmol). After stirring for 1 h at room temperature, the reaction mixture is quenched with water and adjusted to basic pH with concentrated aqueous ammonia solution. The mixture is extracted with DCM, the organic layer is dried over MgSO_4 and concentrated in vacuo.

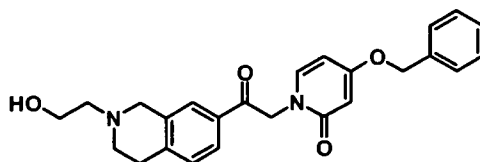
Yield: 62 mg (74% of theory)

ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 417$

Retention time HPLC: 1.27 min (method J).

Example 14.1

4-Benzyloxy-1-[2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl]-1*H*-pyridin-2-one



To a solution of 4-benzyloxy-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 13.2a, 780 mg, 2.08 mmol) in ethanol is added potassium carbonate (575 mg, 4.00 mmol) and the mixture is stirred for 10 min at 60°C. Then chloroethanol (168 μ L, 2.00 mmol) is added and the reaction mixture is stirred at 60°C. After 2 h and 4 h, more chloroethanol (168 μ L, 2.00 mmol) is added and the reaction mixture is left stirring overnight at 50°C. The reaction mixture is concentrated under reduced pressure, triturated with DCM and filtered. The filtrate is concentrated in vacuo and purified chromatographically (silica gel, 10% MeOH in DCM).

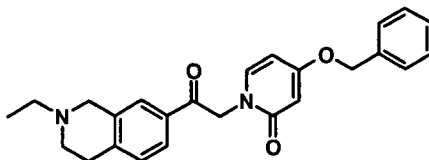
Yield: 330mg (38% of theory)

ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 419$

Retention time HPLC: 1.10 min (method J).

Example 14.2

4-Benzyloxy-1-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one



To 2.00 g (5.34 mmol) 4-benzyloxy-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 13.2a) in 25 mL THF is added 332 μ L (5.88 mmol) acetaldehyde and

1.36 g (6.41 mmol) sodium triacetoxo-borohydride. The mixture is acidified with pH 5 buffer solution (10 mL) and stirred 48 h at RT. The reaction mixture is quenched with aqueous sodium bicarbonate solution and extracted twice with ethyl acetate. The organic layer is dried over MgSO_4 and concentrated in vacuo. The resulting residue is purified via preparative reverse HPLC chromatography (Zorbax Stable Bond C18, 7 μm , gradient from 10% to 95% acetonitrile in water + 0.1% HCOOH , 120 mL/min).

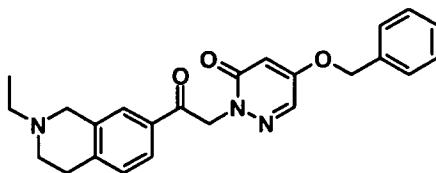
Yield: 1.30 g (61% of theory)

ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 403$

Retention time HPLC: 1.10 min (method J).

Example 15.1

5-Benzyloxy-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one



15.1a 5-Benzyloxy-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one

5-Benzyloxy-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one is prepared following example 13.2a from 5-benzyloxy-2-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-2H-pyridazin-3-one (preparation 25, 1.40 g, 2.97 mmol).

Yield: 550 mg (49% of theory)

ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 376$

Retention time HPLC: 1.05 min (method J).

15.1b 5-Benzyloxy-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one

5-Benzyloxy-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one is prepared following example 14.2 from 5-benzyloxy-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (example 15.1a, 187 mg, 0.50 mmol).

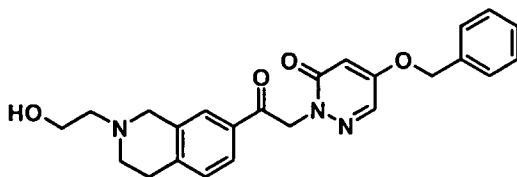
Yield: 50 mg (25% of theory)

ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 404$

Retention time HPLC: 1.13 min (method J).

Example 15.2

5-Benzyloxy-2-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-2H-pyridazin-3-one

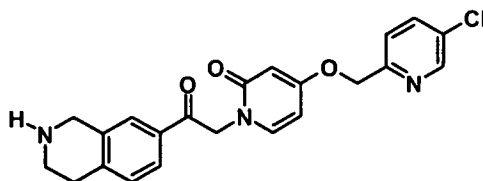


5-Benzyloxy-2-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-2H-pyridazin-3-one is prepared following the procedure for the preparation of example 14.1 from 5-benzyloxy-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (example 15.1a, 113 mg, 0.30 mmol). The crude product is purified *via* preparative reversed phase HPLC (Zorbax Stable Bond C18, 7 μ m, gradient from 10% to 95% acetonitrile in water + 0.1% HCOOH, 120 mL/min).

- Yield: 55 mg (44% of theory)
ESI Mass spectrum: $[M+H]^+ = 420$
Retention time HPLC: 1.65 min (method J).

Example 16.1

- 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one



16.1a 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-1H-pyridin-2-one

- 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-1H-pyridin-2-one is prepared following preparation 1b from 700 mg (2.96 mmol) 4-(5-chloro-pyridin-2-ylmethoxy)-1H-pyridin-2-one (preparation 10.6) and 904 mg (2.96 mmol) 1-[7-(2-chloro-acetyl)-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone, employing DMSO as solvent.

- Yield: 1.2 g (80% of theory)
ESI Mass spectrum: $[M+H]^+ = 506/508$
Retention time HPLC: 1.46 min (method J).

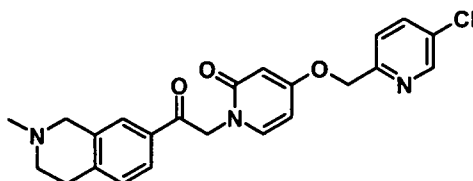
- 16.1b 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 13.2a from 4-(5-chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-1*H*-pyridin-2-one (example 16.1a, 1.20 g, 2.37 mmol).

- 5 Yield: 800 mg (82% of theory)
ESI Mass spectrum: $[M+H]^+ = 410/412$
Retention time HPLC: 1.07 min (method J).

Example 16.2

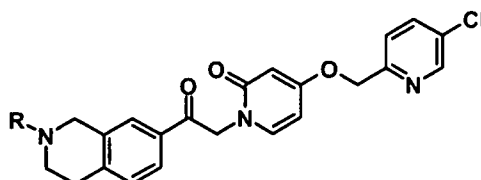
- 10 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one



- 15 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one is prepared following example 14.2 from 4-(5-chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 16.1a, 200 mg, 0.49 mmol) and 79 μ L 37% aqueous formaldehyde solution instead of acetaldehyde.

- Yield: 130 mg (63% of theory)
ESI Mass spectrum: $[M+H]^+ = 424/426$
20 Retention time HPLC: 1.53 min (method K).

- The following examples are prepared as described for Example 16.2 starting from 4-(5-chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 16.1a), employing the corresponding aldehyde in the reductive amination step.
25

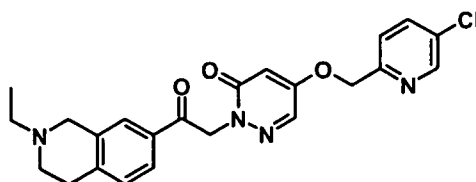


Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
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16.3	CH ₂ CH ₃	35	C ₂₄ H ₂₄ ClN ₃ O ₃	438/440 [M+H] ⁺	1.59 (K)
16.4	CH ₂ CH ₂ CH ₃	47	C ₂₅ H ₂₆ ClN ₃ O ₃	452/454 [M+H] ⁺	1.69 (K)
16.5	i-Pr	35	C ₂₅ H ₂₆ ClN ₃ O ₃	452/454 [M+H] ⁺	2.66 (C)

Example 17.1

5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one



5

17.1a 5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-2H-pyridazin-3-one

10 5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-2H-pyridazin-3-one is prepared following preparation 1b from 700 mg (2.95 mmol) 5-(5-chloro-pyridin-2-ylmethoxy)-2H-pyridazin-3-one (preparation 10.4) and 900 mg (2.95 mmol) 1-[7-(2-chloro-acetyl)-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone, employing DMSO as solvent.

Yield: 1.40 g (94% of theory)

15 ESI Mass spectrum: [M+H]⁺ = 507/509

Retention time HPLC: 1.52 min (method J).

17.1b 5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one

20 5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one is prepared following example 13.2a from 5-(5-chloro-pyridin-2-ylmethoxy)-2-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-2H-pyridazin-3-one (example 17.1a, 1.40 g, 2.76 mmol).

Yield: 800 mg (71% of theory)

25 ESI Mass spectrum: [M+H]⁺ = 411/413

Retention time HPLC: 1.09 min (method J).

17.1c 5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one

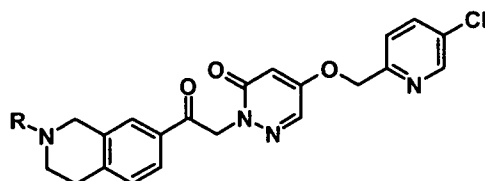
5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one is prepared following example 14.2 from 5-(5-chloro-pyridin-2-ylmethoxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (example 17.1b, 200 mg, 0.49 mmol).

Yield: 80 mg (37% of theory)

ESI Mass spectrum: $[M+H]^+ = 439/441$

Retention time HPLC: 1.65 min (method K).

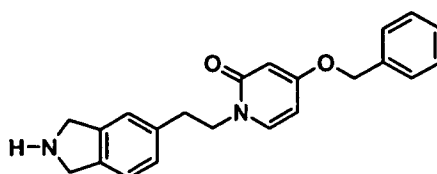
The following examples are prepared as described for Example 17.1 starting from 5-(5-chloro-pyridin-2-ylmethoxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (example 17.1b), employing 1-propanal (R = *n*-propyl) or acetone (R = *i*-propyl) instead of acetaldehyde in the reductive amination step.



Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
17.2	CH ₂ CH ₂ CH ₃	48	C ₂₄ H ₂₅ ClN ₄ O ₃	453/455 [M+H] ⁺	1.78 (K)
17.3	CH(CH ₃) ₂	71	C ₂₄ H ₂₅ ClN ₄ O ₃	453/455 [M+H] ⁺	1.74 (K)

Example 18.1

20 4-Benzyloxy-1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one



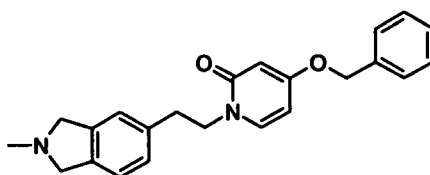
To a stirred solution of 5-[2-(4-benzyloxy-2-oxo-2H-pyridin-1-yl)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 14, 180 mg, 0.40 mmol) in DCM (10 mL) is added

TFA (0.31 mL, 4.03 mmol). After stirring for 5 h at 40°C, the volatiles are removed in vacuo. The resulting residue is purified via preparative reverse HPLC chromatography (Gilson, Waters XBridge C18, 5 µm, gradient from 10% to 95% acetonitrile in water + 0.1% HCOOH, 120 mL/min).

- 5 Yield: 105 mg (75% of theory)
ESI Mass spectrum: $[M+H]^+ = 347$
Retention time HPLC: 1.61 min (method K).

Example 18.2

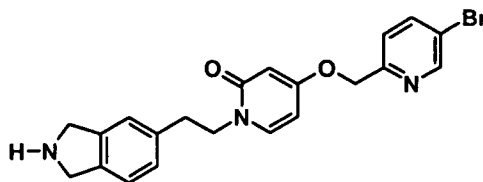
- 10 4-Benzyloxy-1-[2-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-1*H*-pyridin-2-one



- To 90 mg (0.26 mmol) 4-benzyloxy-1-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-1*H*-pyridin-2-one (example 18.1) in 5 mL THF is added 31 µL 37% aqueous formaldehyde solution (0.39 mmol) and 83 mg (0.39 mmol) sodium triacetoxy-borohydride. The mixture is acidified with pH 5
15 buffer solution (2 mL) and stirred 48 h at RT. The reaction mixture is concentrated under reduced pressure and the resulting residue is purified via preparative reverse HPLC chromatography (Gilson; basisch; XBridge; Standard; 120 mL/min).
Yield: 71 mg (76% of theory)
ESI Mass spectrum: $[M+H]^+ = 361$
20 Retention time HPLC: 1.65 min (method K).

Example 19.1

- 4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-1*H*-pyridin-2-one



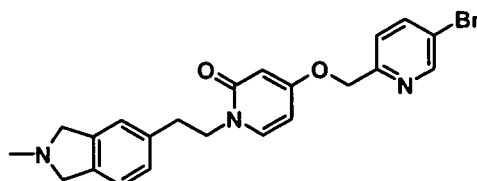
- 25 4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 18.1 from 5-{2-[4-(5-bromo-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 15, 120 mg, 0.23 mmol).
Yield: 80 mg (82% of theory)
30 ESI Mass spectrum: $[M+H]^+ = 426/428$

Retention time HPLC: 1.55 min (method K).

Example 19.2

4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-

5 pyridin-2-one



4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one is prepared following example 18.2 from 4-(5-bromo-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one (example 19.1, 60 mg, 0.14 mmol).

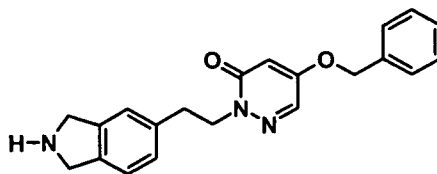
Yield: 23 mg (37% of theory)

ESI Mass spectrum: $[M+H]^+ = 440/442$

Retention time HPLC: 1.58 min (method K).

Example 20.1

5-Benzyloxy-2-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one



5-Benzyloxy-2-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one is prepared following example 18.1 from 5-[2-(4-benzyloxy-6-oxo-6H-pyridazin-1-yl)-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

(preparation 16, 360 mg, 0.60 mmol).

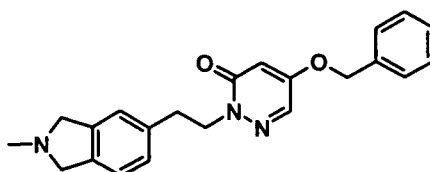
Yield: 140 mg (67% of theory)

ESI Mass spectrum: $[M+H]^+ = 348$

Retention time HPLC: 2.11 min (method H).

Example 20.2

5-Benzyloxy-2-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one



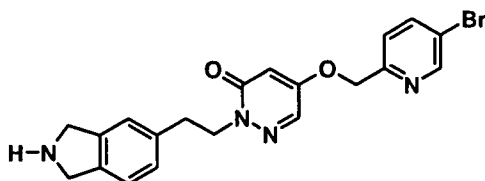
5-Benzyloxy-2-[2-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following the procedure for the preparation of example 18.2 from 5-benzyloxy-2-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one (example 20.1, 100 mg, 0.29 mmol).

Yield: 46 mg (44% of theory)

- 5 ESI Mass spectrum: $[M+H]^+ = 362$
Retention time HPLC: 1.73 min (method K).

Example 21.1

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one



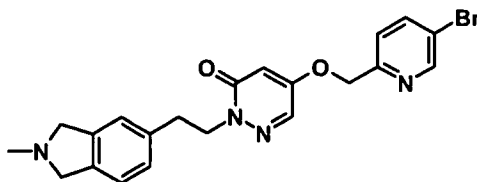
10

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following example 18.1 from 5-{2-[4-(5-bromo-pyridin-2-ylmethoxy)-6-oxo-6*H*-pyridazin-1-yl]-ethyl}-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 17, 180 mg, 0.34 mmol).

- 15 Yield: 130 mg (89% of theory)
ESI Mass spectrum: $[M+H]^+ = 427/429$
Retention time HPLC: 1.61 min (method K).

Example 21.2

- 20 5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one



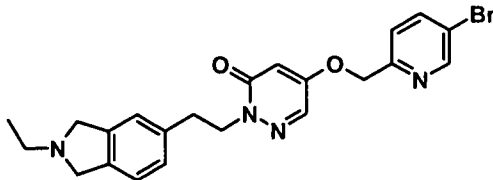
- 25 5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following example 18.2 from 5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one (example 21.1, 100 mg, 0.23 mmol).

Yield: 72 mg (70% of theory)
ESI Mass spectrum: $[M+H]^+ = 441/443$
Retention time HPLC: 1.65 min (method K).

30

Example 21.3

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one



- 5 5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following example 18.2 from 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one (example 21.1, 136 mg, 0.32 mmol) and acetaldehyde (27 μ L, 0.48 mmol).

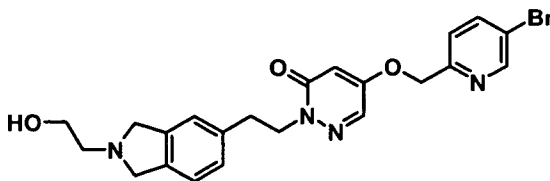
Yield: 13 mg (9% of theory)

- 10 ESI Mass spectrum: $[M+H]^+ = 455/457$

Retention time HPLC: 1.73 min (method K).

Example 21.4

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-[2-(2-hydroxy-ethyl)-2,3-dihydro-1*H*-isoindol-5-yl]-ethyl]-2*H*-pyridazin-3-one



- 15 5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-[2-(2-hydroxy-ethyl)-2,3-dihydro-1*H*-isoindol-5-yl]-ethyl]-2*H*-pyridazin-3-one is prepared following the procedure for the preparation of example 14.1 from 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one (example 21.1, 136 mg, 0.32 mmol).

Yield: 30 mg (20% of theory)

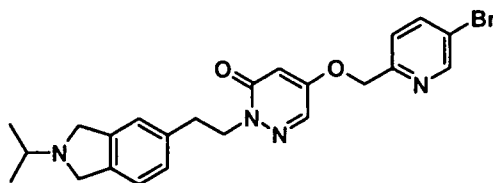
ESI Mass spectrum: $[M+H]^+ = 471/473$

Retention time HPLC: 2.64 min (method C).

- 25 Example 21.5

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one

90



5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following the procedure for the preparation of example 14.1 (acetonitrile as solvent instead of ethanol) from 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one (example 21.1, 136 mg, 0.32 mmol) and isopropyl bromide (60 μ L, 0.64 mmol) as alkylating agent instead of chloroethanol.

Yield: 5 mg (5% of theory)

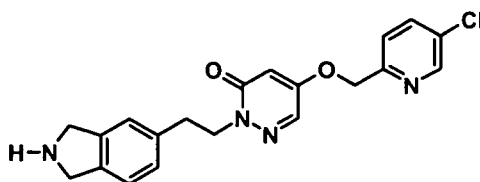
ESI Mass spectrum: $[M+H]^+ = 469/471$

Retention time HPLC: 2.80 min (method C).

10

Example 22.1

5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one



5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following example 18.1 from 5-[2-[4-(5-chloro-pyridin-2-ylmethoxy)-6-oxo-6*H*-pyridazin-1-yl]-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 18, 360 mg, 0.75 mmol).

Yield: 190 mg (67% of theory)

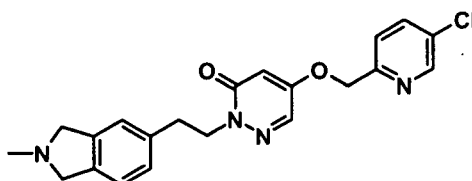
ESI Mass spectrum: $[M+H]^+ = 383/385$

Retention time HPLC: 1.58 min (method K).

20

Example 22.2

5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one



25

5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following example 18.2 from 5-(5-chloro-pyridin-2-ylmethoxy)-2-

[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-2*H*-pyridazin-3-one (example 22.1, 140 mg, 0.37 mmol).

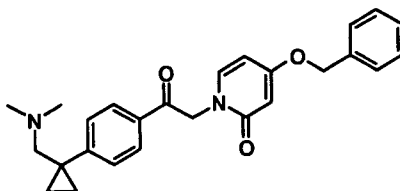
Yield: 100 mg (69% of theory)

ESI Mass spectrum: $[M+H]^+ = 397/399$

5 Retention time HPLC: 1.63 min (method K).

Example 23

4-Benzyloxy-1-{2-[4-(1-dimethylaminomethyl-cyclopropyl)-phenyl]-2-oxo-ethyl}-1*H*-pyridin-2-one



10

23a 1-(4-Bromo-phenyl)-cyclopropanecarbaldehyde

A solution of 1-(4-bromo-phenyl)-cyclopropanecarbonitrile (500 mg) in diethyl ether (15 mL) is cooled to -10°C. Then, a solution of DIBAL (1.2 M in toluene, 2.44 mL, 2.93 mmol) is added in dropwise fashion. The reaction mixture is stirred for 2 h between -10°C and 5°C, quenched by
15 addition of 1 N aqueous HCl (6 mL) and extracted twice with ethyl acetate. The combined organic layer is washed with water, dried over MgSO₄ and concentrated under reduced pressure.

Yield: 450 mg (89% of theory)

ESI Mass spectrum: $[M+H]^+ = 224/226$

20 Retention time HPLC: 1.52 min (method J).

23b [1-(4-Bromo-phenyl)-cyclopropylmethyl]-dimethyl-amine

To a solution of 450 mg (2.00 mmol) 1-(4-bromo-phenyl)-cyclopropanecarbaldehyde (example 23a) in 15 mL THF is added 1.2 mL of a solution of dimethylamine in THF (2M, 2.40 mmol), 137 µL glacial acetic acid (137 µL, 2.40 mmol) and sodium triacetoxyborohydride (508 mg, 2.40 mmol). The mixture is stirred for 48 h at RT, quenched with aqueous sodium bicarbonate solution and extracted twice with ethyl acetate. The organic layer is dried over MgSO₄ and concentrated in vacuo. The resulting residue is purified *via* preparative reverse
25 HPLC chromatography (Waters XBridge C18, 5 µm, gradient from 10% to 95% acetonitrile in water + 0.3% NH₄OH, 120 mL/min).

30

Yield: 250 mg (49% of theory)

ESI Mass spectrum: $[M+H]^+ = 254/256$

Retention time HPLC: 2.00 min (method K).

23c [1-(4-iodo-phenyl)-cyclopropylmethyl]-dimethyl-amine

3[1-(4-iodo-phenyl)-cyclopropylmethyl]-dimethyl-amine is prepared following preparation 9a from 250 mg (0.98 mmol) [1-(4-bromo-phenyl)-cyclopropylmethyl]-dimethyl-amine (example 23b).

Yield: 300 mg (quantitative)

ESI Mass spectrum: $[M+H]^+ = 302$

Retention time HPLC: 2.07 min (method K).

23d 4-Benzyloxy-1-[2-[4-(1-dimethylaminomethyl-cyclopropyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one

4-Benzyloxy-1-[2-[4-(1-dimethylaminomethyl-cyclopropyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one is prepared following preparation 9b from 300 mg (1.00 mmol) [1-(4-iodo-phenyl)-cyclopropylmethyl]-dimethyl-amine.

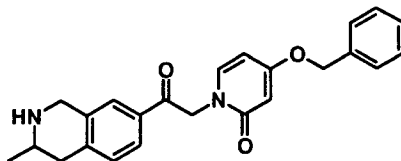
Yield: 7 mg (2% of theory)

ESI Mass spectrum: $[M+H]^+ = 417$

Retention time HPLC: 2.22 min (method H).

Example 24.1

4-Benzyloxy-1-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one



4-Benzyloxy-1-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one is prepared following example 13.2a from 4-benzyloxy-1-[2-[3-methyl-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl]-1H-pyridin-2-one (preparation 19, 80 mg, 0.17 mmol).

Yield: 40 mg (62% of theory)

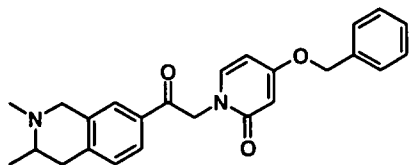
ESI Mass spectrum: $[M+H]^+ = 389$

Retention time HPLC: 2.10 min (method H).

30

Example 24.2

4-Benzyloxy-1-[2-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one



4-Benzyloxy-1-[2-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one is prepared following example 18.2 from 4-benzyloxy-1-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one (example 24.1, 40 mg, 0.103 mmol) and 12.5 μ L 37% aqueous formaldehyde solution (0.154 mmol).

Yield: 33 mg (80% of theory)

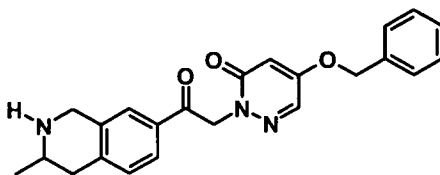
ESI Mass spectrum: $[M+H]^+ = 403$

Retention time HPLC: 1.65 min (method K).

10

Example 25.1

5-Benzyloxy-2-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one



15 25.1a 5-Benzyloxy-2-[2-[3-methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl]-2H-pyridazin-3-one

5-Benzyloxy-2-[2-[3-methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl]-2H-pyridazin-3-one is prepared following preparation 1b from 127 mg (0.63 mmol) 5-benzyloxy-2H-pyridazin-3-one (preparation 2) and 200 mg (0.63 mmol) 1-[7-(2-chloro-acetyl)-3-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (preparation 19d), employing DMSO as solvent.

20

Yield: 60 mg (20% of theory)

Retention time HPLC: 1.63 min (method J).

25 25.1b 5-Benzyloxy-2-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one

5-Benzyloxy-2-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one is prepared following example 13.2a from 5-benzyloxy-2-[2-[3-methyl-2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl]-2H-pyridazin-3-one (example 25.1a, 60 mg, 0.124 mmol).

30

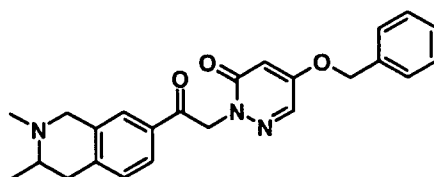
Yield: 32 mg (67% of theory)

ESI Mass spectrum: $[M+H]^+ = 390$

Retention time HPLC: 1.65 min (method K).

5 Example 25.2

5-Benzyloxy-2-[2-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one



10 5-Benzyloxy-2-[2-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one is prepared following example 18.2 from 5-benzyloxy-2-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one (example 25.1, 88 mg, 0.23 mmol) and 37% aqueous formaldehyde solution (28 μ L, 0.34 mmol).

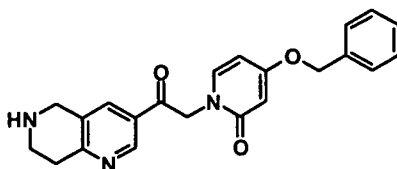
Yield: 60 mg (66% of theory)

ESI Mass spectrum: $[M+H]^+ = 404$

15 Retention time HPLC: 1.65 min (method K).

Example 26.1

4-Benzyloxy-1-[2-oxo-2-(5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)-ethyl]-1H-pyridin-2-one



20 26.1a 3-Iodo-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid *tert*-butyl ester

3-Iodo-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid *tert*-butyl ester is prepared following preparation 9a from 3-bromo-7,8-dihydro-5H-[1,6]naphthyridine-6-carboxylic acid *tert*-butyl ester (7.00 g, 22.4 mmol).

Yield: 7.80 g (97% of theory)

25 ESI Mass spectrum: $[M+H]^+ = 361$

Retention time HPLC: 1.56 min (method J).

26.1b 4-Benzyloxy-1-[2-oxo-2-(5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)-ethyl]-1H-pyridin-2-one

4-Benzyloxy-1-[2-oxo-2-(5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)-ethyl]-1*H*-pyridin-2-one is prepared following preparation 9b from 3-iodo-7,8-dihydro-5*H*-[1,6]naphthyridine-6-carboxylic acid *tert*-butyl ester (example 26.1a, 1.00 g, 2.78 mmol).

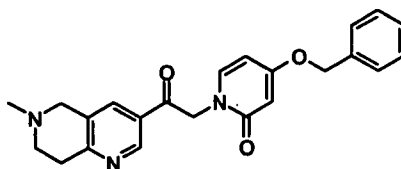
Yield: 36 mg (4% of theory)

5 ESI Mass spectrum: $[M+H]^+ = 376$

Retention time HPLC: 2.09 min (method H).

Example 26.2

4-Benzyloxy-1-[2-(6-methyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one



4-Benzyloxy-1-[2-(6-methyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one is prepared following example 18.2 from 4-benzyloxy-1-[2-oxo-2-(5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)-ethyl]-1*H*-pyridin-2-one (example 26.1, 60 mg, 0.160 mmol) and 37% aqueous formaldehyde solution (19.5 μ L, 0.24 mmol).

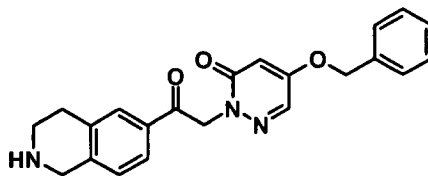
Yield: 53 mg (85% of theory)

ESI Mass spectrum: $[M+H]^+ = 390$

Retention time HPLC: 1.45 min (method K).

20 Example 27.1

5-Benzyloxy-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2*H*-pyridazin-3-one



27.1a 6-(Methoxy-methyl-carbamoyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

25 6-(Methoxy-methyl-carbamoyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 5b from 3,4-dihydro-1*H*-isoquinoline-2,6-dicarboxylic acid 2-*tert*-butyl ester (2.80 g, 10.1 mmol).

Yield: 2.20 g (68% of theory)

ESI Mass spectrum: $[M+H]^+ = 321$

30 Retention time HPLC: 1.42 min (method J).

27.1b 6-Acetyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

6-Acetyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 5c from Weinreb amide 6-(methoxy-methyl-carbamoyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 27.1a, 2.20 g, 6.87 mmol).

Yield: 1.50 g (79% of theory)

ESI Mass spectrum: $[M+H]^+ = 276$

Retention time HPLC: 1.52 min (method J).

27.1c 6-(2-Bromo-acetyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

6-(2-Bromo-acetyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 4d (mixture of 20% MeOH in THF as solvent) from 6-acetyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 27.1b, 1.50 g, 5.45 mmol).

Yield: 1.00 g (44% of theory)

ESI Mass spectrum: $[M+H]^+ = 354/356$

Retention time HPLC: 1.91 min (method K).

27.1d 6-[2-(4-Benzyloxy-6-oxo-6*H*-pyridazin-1-yl)-acetyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

6-[2-(4-Benzyloxy-2-oxo-2*H*-pyridin-1-yl)-acetyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 6-(2-bromo-acetyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 27.1c, 1.00 g, 2.82 mmol) and 5-Benzyloxy-2*H*-pyridazin-3-one (570 mg, 2.82 mmol).

Yield: 700 mg (52% of theory)

ESI Mass spectrum: $[M+H]^+ = 476$

Retention time HPLC: 1.96 min (method K).

27.1e 5-Benzyloxy-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2*H*-pyridazin-3-one

6-[2-(4-Benzyloxy-6-oxo-6*H*-pyridazin-1-yl)-acetyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 27.1d, 700 mg, 1.47 mmol) is dissolved in DCM (10 mL) and TFA (1.13 mL) is added. The reaction is stirred for 18 h at room temperature. The volatiles are removed in vacuo and the resulting residue is purified via preparative reverse HPLC chromatography (Gilson, XBridge C18, 5 μ m, gradient from 10% to 95% acetonitrile in water + 0.3% NH_4OH , 120 mL/min).

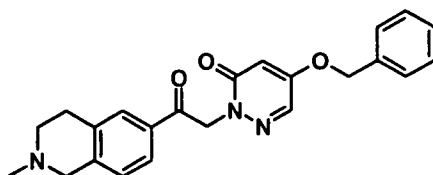
Yield: 500 mg (91% of theory)

ESI Mass spectrum: $[M+H]^+ = 376$

Retention time HPLC: 1.59 min (method K).

Example 27.2

5-Benzyloxy-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-2H-pyridazin-3-one



5-Benzyloxy-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-2H-pyridazin-3-one is prepared following example 18.2 from 5-benzyloxy-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one (example 27.1, 350, 0.932 mmol) and 105 μ L 37% aqueous formaldehyde solution (0.24 mmol).

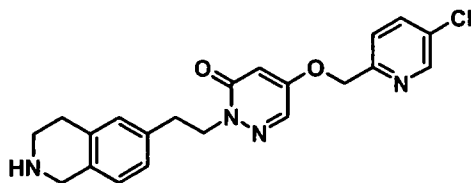
Yield: 322 mg (89% of theory)

ESI Mass spectrum: $[M+H]^+ = 390$

Retention time HPLC: 2.80 min (method C).

Example 28.1

5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one



28.1a 6-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-6-oxo-6H-pyridazin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

6-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-6-oxo-6H-pyridazin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b from 5-(5-chloro-pyridin-2-ylmethoxy)-2H-pyridazin-3-one (preparation 10.4, 238 mg, 1.00 mmol) and 6-[2-(toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 26, 432 mg, 1.00 mmol).

Yield: 175 mg (35% of theory)

ESI Mass spectrum: $[M+H]^+ = 497/499$

Retention time HPLC: 1.71 min (method J).

28.1b 5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one

5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one is prepared following example 18.1 from 6-{2-[4-(5-chloro-pyridin-2-ylmethoxy)-6-oxo-6H-pyridazin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 28.1a, 175 mg, 0.35 mmol).

Yield: 100 mg (62% of theory)

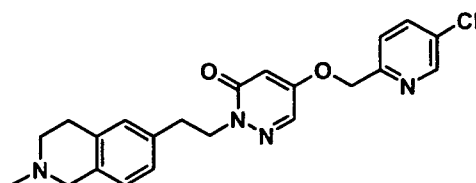
ESI Mass spectrum: $[M+H]^+ = 397/399$

Retention time HPLC: 1.05 min (method J).

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Example 28.2

5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one



15 5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one is following example 18.2 from 5-(5-chloro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one (example 28.1, 70 mg, 0.18 mmol).

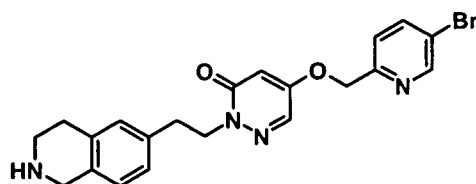
Yield: 23 mg (29% of theory)

ESI Mass spectrum: $[M+H]^+ = 411/413$

20 Retention time HPLC: 1.15 min (method J).

Example 29.1

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one



25

29.1a 6-{2-[4-(5-Bromo-pyridin-2-ylmethoxy)-6-oxo-6H-pyridazin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

6-{2-[4-(5-Bromo-pyridin-2-ylmethoxy)-6-oxo-6H-pyridazin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b from 5-(5-bromo-pyridin-2-ylmethoxy)-2H-pyridazin-3-one (preparation 10.5, 282 mg, 1.00 mmol) and 6-

30

[2-(toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 26, 432 mg, 1.00 mmol).

Yield: 140 mg (26% of theory)

ESI Mass spectrum: $[M+H]^+ = 541/543$

5 Retention time HPLC: 1.52 min (method J).

29.1b 5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2*H*-pyridazin-3-one

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following the preparation of example 18.1 from 6-{2-[4-(5-bromo-pyridin-2-ylmethoxy)-6-oxo-6*H*-pyridazin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 28.1a, 140 mg, 0.26 mmol).

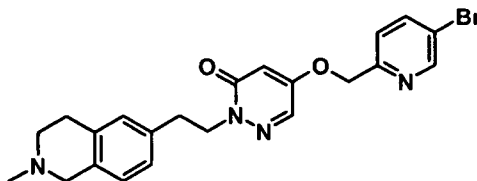
Yield: 90 mg (68% of theory)

ESI Mass spectrum: $[M+H]^+ = 441/443$

15 Retention time HPLC: 1.10 min (method J).

Example 29.2

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2*H*-pyridazin-3-one



20

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2*H*-pyridazin-3-one is following example 18.2 from 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2*H*-pyridazin-3-one (example 29.1, 60 mg, 0.14 mmol).

Yield: 20 mg (29% of theory)

25 ESI Mass spectrum: $[M+H]^+ = 455/457$

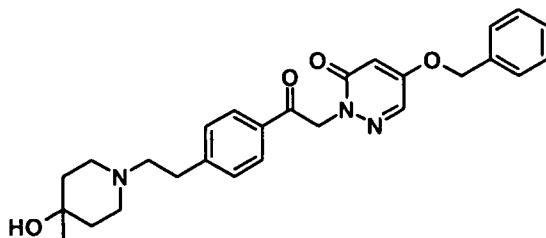
Retention time HPLC: 1.17 min (method J).

Example 30

5-Benzyloxy-2-(2-[4-[2-(4-hydroxy-4-methyl-piperidin-1-yl)-ethyl]-phenyl]-2-oxo-ethyl)-2*H*-pyridazin-3-one

30

100



30a 5-Benzyloxy-2-{2-[4-(2-chloro-ethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one

5-Benzyloxy-2-{2-[4-(2-chloro-ethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one is prepared following preparation 1b (DMSO as solvent) from 1.00 g (3.82 mmol) 2-bromo-1-[4-(2-chloro-ethyl)-phenyl]-ethanone (preparation according to J. Med. Chem. 34, 6, 1991, 1860-1866) and 0.773 g (3.82 mmol) 5-benzyloxy-2H-pyridazin-3-one (preparation 2).

Yield: 570 mg (32% of theory, 80% purity)

ESI Mass spectrum: $[M+H]^+ = 383/385$

10

30b 5-Benzyloxy-2-(2-{4-[2-(4-hydroxy-4-methyl-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-2H-pyridazin-3-one

To a solution of 5-benzyloxy-2-{2-[4-(2-chloro-ethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one (example 30a, 110 mg, 0.29 mmol) in DMF (2 mL) is added 4-hydroxy-4-methyl-piperidine (66 mg, 0.58 mmol) and tetrabutylammonium iodide (106 mg, 0.29 mmol). The reaction mixture is heated for 5 min to 120°C in the microwave. The crude reaction mixture is purified via preparative reverse phase HPLC (Waters XBridge C18, 5 μ m, gradient from 10% to 95% acetonitrile in water + 0.3% NH_4OH , 120 mL/min).

Yield: 5 mg (4% of theory)

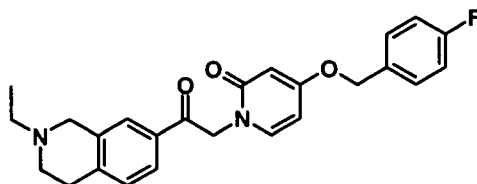
20 ESI Mass spectrum: $[M+H]^+ = 462$

Retention time HPLC: 1.70 min (method J).

Example 31.1

1-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-(4-fluoro-benzyloxy)-1H-pyridin-2-one

25



31.1a 4-(4-Fluoro-benzyloxy)-1-{2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-1H-pyridin-2-one

4-(4-Fluoro-benzyloxy)-1-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-1*H*-pyridin-2-one is prepared following preparation 1b from 330 mg (1.51 mmol) 4-(4-fluoro-benzyloxy)-1*H*-pyridin-2-one (preparation 10.1) and 460 mg (1.51 mmol) 1-[7-(2-chloro-acetyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone, employing DMSO as
5 solvent.

Yield: 0.40 g (54% of theory)

ESI Mass spectrum: $[M+H]^+ = 489$

Retention time HPLC: 1.52 min (method J).

10 31.1b 4-(4-Fluoro-benzyloxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one

4-(4-Fluoro-benzyloxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 13.2a from 4-(4-fluoro-benzyloxy)-1-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-1*H*-pyridin-2-one (example 31.1a, 0.40 g,
15 0.82 mmol).

Yield: 0.28 g (87% of theory)

ESI Mass spectrum: $[M+H]^+ = 393$

Retention time HPLC: 1.11 min (method J).

20 31.1c 1-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-(4-fluoro-benzyloxy)-1*H*-pyridin-2-one

1-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-(4-fluoro-benzyloxy)-1*H*-pyridin-2-one is prepared following example 14.2 from 4-(4-fluoro-benzyloxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 31.1b, 70 mg, 0.18
25 mmol) and 11 μ L acetaldehyde.

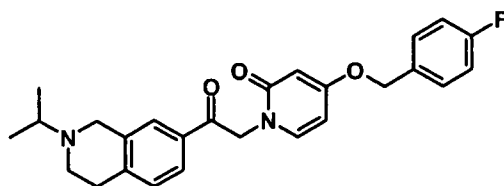
Yield: 35 mg (75% of theory)

ESI Mass spectrum: $[M+H]^+ = 421$

Retention time HPLC: 1.15 min (method J).

30 Example 31.2

4-(4-Fluoro-benzyloxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one



4-(4-Fluoro-benzyloxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one is prepared following example 14.2 from 4-(4-fluoro-benzyloxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 31.1b, 70 mg, 0.18 mmol) and 14 μ L acetone instead of acetaldehyde.

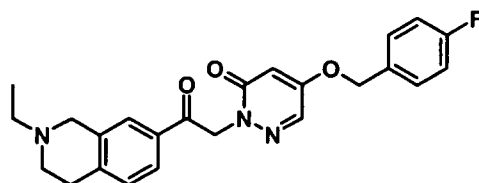
5 Yield: 6 mg (8% of theory)

ESI Mass spectrum: $[M+H]^+ = 435$

Retention time HPLC: 1.19 min (method J).

Example 32.1

10 2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-5-(4-fluoro-benzyloxy)-2*H*-pyridazin-3-one



32.1a 5-(4-Fluoro-benzyloxy)-2-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-2*H*-pyridazin-3-one

15 5-(4-Fluoro-benzyloxy)-2-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-2*H*-pyridazin-3-one is prepared following preparation 1b from 660 mg (3.00 mmol) 5-(4-fluoro-benzyloxy)-2*H*-pyridazin-3-one (preparation 10.8) and 917 mg (3.00 mmol) 1-[7-(2-chloro-acetyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone, employing DMSO as

20 solvent.

Yield: 1.35 g (92% of theory)

ESI Mass spectrum: $[M+H]^+ = 490$

Retention time HPLC: 1.57 min (method J).

25 32.1b 5-(4-Fluoro-benzyloxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one

5-(4-Fluoro-benzyloxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following example 13.2a from 5-(4-fluoro-benzyloxy)-2-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-2*H*-pyridazin-3-one (example 32.1a,

30 1.30 g, 2.66 mmol).

Yield: 1.03 g (99% of theory)

ESI Mass spectrum: $[M+H]^+ = 394$

Retention time HPLC: 1.12 min (method J).

32.1c 2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-5-(4-fluoro-benzyloxy)-2*H*-pyridazin-3-one

2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-5-(4-fluoro-benzyloxy)-2*H*-

5 pyridazin-3-one is prepared following example 14.2 from 5-(4-fluoro-benzyloxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one (example 32.1b, 100 mg, 0.25 mmol) and 16 μ L acetaldehyde.

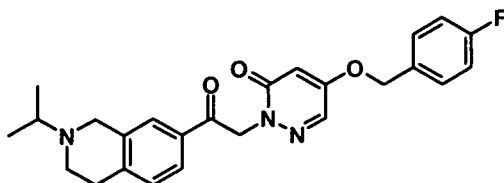
Yield: 30 mg (28% of theory)

ESI Mass spectrum: $[M+H]^+ = 422$

10 Retention time HPLC: 1.16 min (method J).

Example 32.2

5-(4-Fluoro-benzyloxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2*H*-pyridazin-3-one



15

5-(4-Fluoro-benzyloxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2*H*-pyridazin-3-one is prepared following example 14.2 from 5-(4-fluoro-benzyloxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one (example 32.1b, 100 mg, 0.25 mmol) and 21 μ L acetone instead of acetaldehyde.

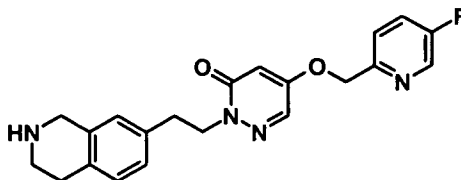
20 Yield: 20 mg (18% of theory)

ESI Mass spectrum: $[M+H]^+ = 436$

Retention time HPLC: 1.20 min (method J).

Example 33.1

25 5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one



33.1a 7-[2-[4-(5-Fluoro-pyridin-2-ylmethoxy)-6-oxo-6*H*-pyridazin-1-yl]-ethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

7-{2-[4-(5-Fluoro-pyridin-2-ylmethoxy)-6-oxo-6*H*-pyridazin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b from 5-(5-fluoro-pyridin-2-ylmethoxy)-2*H*-pyridazin-3-one (preparation 10.9, 80 mg, 0.36 mmol) and 7-[2-(toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 27, 156 mg, 0.36 mmol).

Yield: 160 mg (92% of theory)

ESI Mass spectrum: $[M+H]^+ = 481$

Retention time HPLC: 1.89 min (method K).

33.1b 5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one

5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following example 18.1 from 7-{2-[4-(5-fluoro-pyridin-2-ylmethoxy)-6-oxo-6*H*-pyridazin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 33.1a, 160 mg, 0.33 mmol).

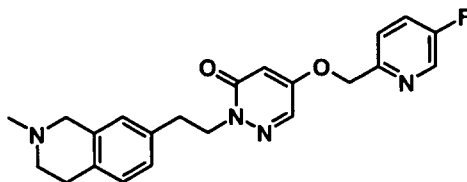
Yield: 160 mg

ESI Mass spectrum: $[M+H]^+ = 381$

Retention time HPLC: 1.53 min (method K).

Example 33.2

5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one



5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one is prepared following example 18.2 from 5-(5-fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one (example 33.1, 30 mg, 0.08 mmol).

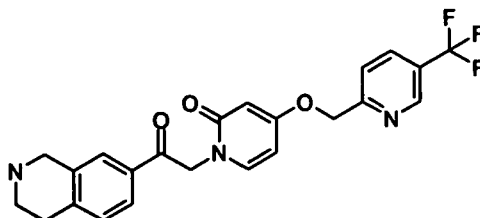
Yield: 27 mg (87% of theory)

ESI Mass spectrum: $[M+H]^+ = 395$

Retention time HPLC: 1.58 min (method K).

Example 34

1-[2-Oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-4-(5-trifluoromethyl-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one



5

34a 1-[2-Oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-4-(5-trifluoromethyl-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one

1-[2-Oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-4-(5-trifluoromethyl-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one is prepared following preparation 1b
 10 from 110 mg (0.41 mmol) 4-(5-trifluoromethyl-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one (preparation 10.10) and 137 mg (0.45 mmol) 1-[7-(2-chloro-acetyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone, employing DMSO as solvent.

Yield: 0.30 g (ca. 70% pure, ca. 96% of theory)

ESI Mass spectrum: $[M+H]^+ = 540$

15 Retention time HPLC: 1.53 min (method J).

34b 1-[2-Oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-4-(5-trifluoromethyl-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one

1-[2-Oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-4-(5-trifluoromethyl-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one is prepared following example 13.2a from 1-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-4-(5-trifluoromethyl-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one (example 34a, 0.30 g, 70% pure, 0.39 mmol).
 20

Yield: 7 mg (4% of theory)

ESI Mass spectrum: $[M+H]^+ = 444$

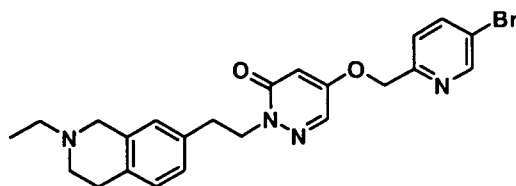
25 Retention time HPLC: 1.23 min (method J).

Example 35.1

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2*H*-pyridazin-3-one

30

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5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one is prepared following example 14.2 from 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (for preparation see WO 08/022979; 150 mg, 0.34 mmol) and acetaldehyde (30 mg, 0.68 mmol).

Yield: 21 mg (13% of theory)

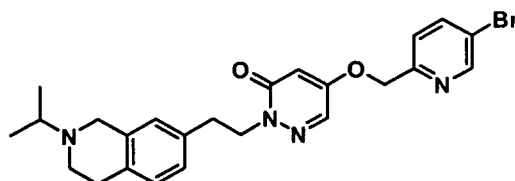
ESI Mass spectrum: $[M+H]^+ = 469/471$

Retention time HPLC: 1.79 min (method K).

10

Example 35.2

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one



15

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one is prepared following example 14.2 from 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (for preparation see WO 08/022979; 1.90 g, 4.31 mmol) and acetone (0.63 mL, 8.61 mmol).

20

Yield: 1.00 g (48% of theory)

ESI Mass spectrum: $[M+H]^+ = 483/485$

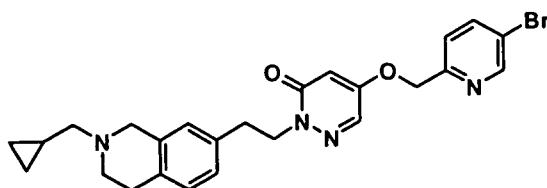
Retention time HPLC: 1.90 min (method K).

25

Example 35.3

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one

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5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one is prepared following example 14.2 from 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (for preparation see WO 08/022979; 150 mg, 0.34 mmol) and cyclopropanecarbaldehyde (48 mg, 0.68 mmol).

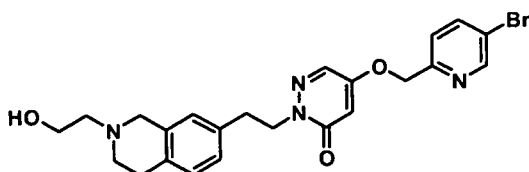
Yield: 70 mg (42% of theory)

ESI Mass spectrum: $[M+H]^+ = 495/497$

Retention time HPLC: 1.91 min (method K).

Example 35.4

5-(5-Bromo-pyridin-2-ylmethoxy)-2-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-2H-pyridazin-3-one



To a solution of 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (for preparation see WO 08/022979, 130 mg, 0.30 mmol) in 4.0 mL THF is added potassium carbonate (103 mg, 0.74 mmol) and bromoethanol (25 μ L, 0.35 mmol). The reaction mixture is stirred overnight at 60°C, diluted with MeOH and after filtration directly subjected to preparative reverse HPLC chromatography (Waters XBridge 5 μ m, gradient from 10% to 100% acetonitrile in water + 0.3% NH_4OH).

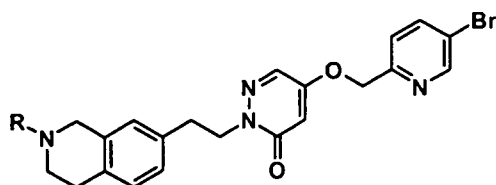
Yield: 76 mg (53% of theory)

ESI Mass spectrum: $[M+H]^+ = 485/487$

Retention time HPLC: 1.57 min (method K).

The following examples are prepared as described for Example 35.4 starting from 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (for preparation see WO 08/022979).

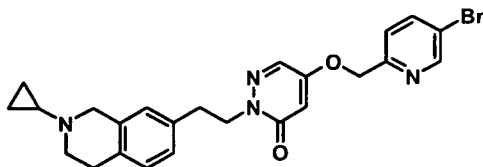
108



Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
35.5		25	C ₂₄ H ₂₇ BrN ₄ O ₃	499/501 [M+H] ⁺	1.72 (K)
35.6		36	C ₂₃ H ₂₄ BrFN ₄ O ₂	487/489 [M+H] ⁺	1.75 (K)

5 Example 35.7

5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-cyclopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one



- 10 To a solution of 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (for preparation see WO 08/022979, 300 mg, 0.54 mmol) in 5.0 mL MeOH is added (1-ethoxy-cyclopropoxy)-trimethyl-silane (0.12 mL, 0.60 mmol). The reaction mixture is stirred 40 min at RT and sodium cyano-borohydride (41 mg, 0.65 mmol) is added. After stirring overnight at 80°C, aqueous half saturated NaHCO₃-solution is added. The
- 15 aqueous phase is extracted two times with DCM, the combined organic phase is dried over MgSO₄ and evaporated in vacuo. The residue is purified *via* preparative reversed HPLC chromatography (Waters XBridge 5 μm, gradient from 10% to 100% acetonitrile in water + 0.3% NH₄OH).

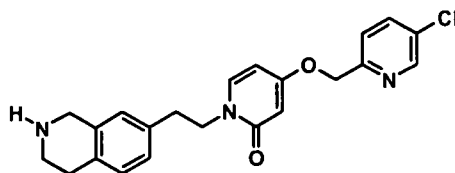
Yield: 27 mg (10% of theory)

- 20 ESI Mass spectrum: [M+H]⁺ = 481/483

Retention time HPLC: 1.92 min (method K).

Example 36.1

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one



5

36.1a 7-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

7-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 7-[2-(toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 27, 4.32 g, 10.0 mmol) and 4-(5-chloro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one (preparation 10.6, 2.37 g, 10.0 mmol).

10

Yield: 2.00 g (40% of theory)

ESI Mass spectrum: $[M+H]^+ = 496/498$

15

Retention time HPLC: 1.92 min (method K).

36.1b 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 18.1 from 7-{2-[4-(5-chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 36.1a, 340 mg, 0.69 mmol).

20

Yield: 230 mg (85% of theory)

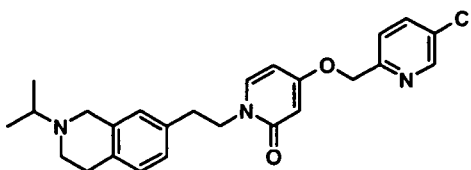
ESI Mass spectrum: $[M+H]^+ = 396/398$

25

Retention time HPLC: 1.52 min (method K).

Example 36.2

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one



30

To 250 mg (0.63 mmol) 4-(5-chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 36.1) in 10 mL MeOH is added 110 mg (1.90 mmol) acetone and 401 mg (1.90 mmol) sodium triacetoxy-borohydride. After 1 h stirring at RT, the mixture is acidified with acetic acid and stirred overnight at RT. The mixture is directly purified
5 via preparative reverse HPLC chromatography (Waters XBridge 5 μ m, gradient from 10% to 100% acetonitrile in water + 0.3% NH_4OH).

Yield: 260 mg (94% of theory)

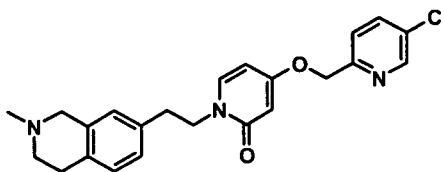
ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 438/440$

Retention time HPLC: 1.76 min (method K).

10

Example 36.3

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one



15

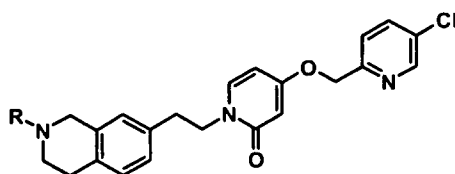
4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 14.2 from 4-(5-chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 36.1; 100 mg, 0.25
20 mmol) and 37% aqueous formaldehyde solution (31 μ L, 0.38 mmol).

Yield: 80 mg (77% of theory)

ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 410/412$

Retention time HPLC: 1.59 min (method K).

25 The following examples are prepared as described for Example 35.4 starting from 4-(5-chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 36.1).

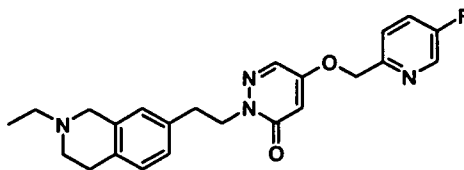


Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
36.4		72	C ₂₄ H ₂₆ ClN ₃ O ₃	440/442 [M+H] ⁺	1.47 (K)
36.5		18	C ₂₄ H ₂₅ ClFN ₃ O ₂	442/444 [M+H] ⁺	1.64 (K)

Example 37.1

2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-5-(5-fluoro-pyridin-2-ylmethoxy)-2H-

5 pyridazin-3-one



2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-5-(5-fluoro-pyridin-2-ylmethoxy)-2H-

10 pyridazin-3-one is prepared following example 14.2 from 5-(5-fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (example 33.1; 150 mg, 0.39 mmol) and acetaldehyde (25 μ L, 0.43 mmol).

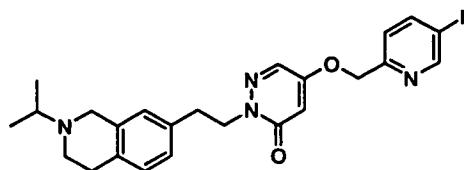
Yield: 90 mg (56% of theory)

ESI Mass spectrum: [M+H]⁺ = 409

15 Retention time HPLC: 1.7 min (method K).

Example 37.2

5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one



To 150 mg (0.39 mmol) 5-(5-fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (example 33.1) in 6.0 mL THF is added 145 μ L (1.97 mmol) acetone and after 10 min stirring 209 mg (0.99 mmol) sodium triacetoxo-borohydride. After 4 h stirring at RT, the mixture is directly purified *via* preparative reverse HPLC chromatography (Waters XBridge 5 μ m, gradient from 10% to 100% acetonitrile in water + 0.3% NH_4OH).

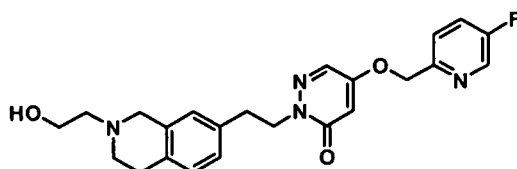
Yield: 129 mg (77% of theory)

ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 423$

Retention time HPLC: 1.8 min (method K).

Example 37.3

5-(5-Fluoro-pyridin-2-ylmethoxy)-2-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-2H-pyridazin-3-one



15

5-(5-Fluoro-pyridin-2-ylmethoxy)-2-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-2H-pyridazin-3-one is prepared following example 35.4 (EtOH as solvent) from 5-(5-fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (example 33.1; 1.00 g, 2.63 mmol) and bromoethanol (187 μ L, 2.63 mmol).

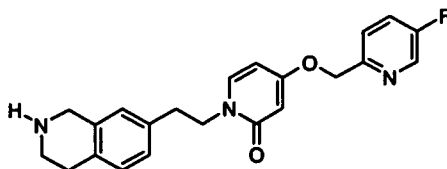
20 Yield: 580 mg (52% of theory)

ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 425$

Retention time HPLC: 1.50 min (method K).

Example 38.1

25 4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one



30 38.1a 7-[2-[4-(5-Fluoro-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

7-{2-[4-(5-Fluoro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 7-[2-(toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 27, 1.96 g, 4.54 mmol) and 4-(5-fluoro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one (preparation 10.11, 1.00 g, 4.54 mmol).

Yield: 1.00 g (46% of theory)

ESI Mass spectrum: $[M+H]^+ = 480$

Retention time HPLC: 1.72 min (method J).

- 38.1b 4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one
4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 18.1 from 7-{2-[4-(5-fluoro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 38.1a, 120 mg, 0.25 mmol).

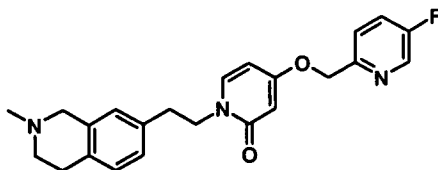
Yield: 77 mg (81% of theory)

ESI Mass spectrum: $[M+H]^+ = 380$

Retention time HPLC: 0.99 min (method J).

Example 38.2

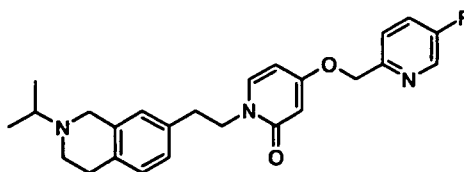
4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one



- 4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 14.2 from 4-(5-fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 38.1; 400 mg, 1.05 mmol) and 37% aqueous formaldehyde solution (128 μ L, 1.58 mmol).
Yield: 220 mg (53% of theory)
ESI Mass spectrum: $[M+H]^+ = 394$
Retention time HPLC: 1.10 min (method K).

Example 38.3

4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one



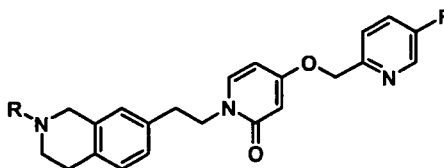
- 5 4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 37.2 from 4-(5-fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 38.1; 200 mg, 0.53 mmol) and acetone (194 μ L, 2.64 mmol).

Yield: 100 mg (45% of theory)

- 10 ESI Mass spectrum: $[M+H]^+ = 422$
Retention time HPLC: 1.69 min (method K).

The following examples are prepared as described for Example 35.4 (for example 38.4 EtOH is used as the solvent) starting from 4-(5-fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 38.1).

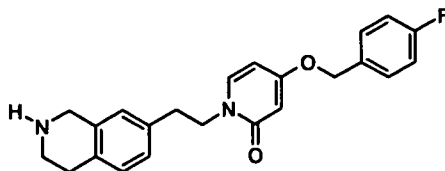
- 15



Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
38.4		47	C ₂₄ H ₂₆ FN ₃ O ₃	424 [M+H] ⁺	1.4 (K)
38.5		67	C ₂₄ H ₂₅ F ₂ N ₃ O ₂	426 [M+H] ⁺	1.53 (K)

- 20 Example 39.1
4-(4-Fluoro-benzyloxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one

115



39.1a 7-{2-[4-(4-fluoro-benzyloxy)-2-oxo-2H-pyridin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

5 7-{2-[4-(4-fluoro-benzyloxy)-2-oxo-2H-pyridin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 7-[2-(toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 27, 2.94 g, 6.81 mmol) and 4-(4-fluoro-benzyloxy)-1H-pyridin-2-one (preparation 10.1, 1.50 g, 6.84 mmol).

10 Yield: 1.50 g (46% of theory)

ESI Mass spectrum: $[M+H]^+ = 479$

R_f -value: 0.2 (silica gel, mixture E).

39.1b 4-(4-Fluoro-benzyloxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one

15 4-(4-Fluoro-benzyloxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one is prepared following example 18.1 from 7-{2-[4-(4-fluoro-benzyloxy)-2-oxo-2H-pyridin-1-yl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 39.1a, 1.50 g, 3.13 mmol).

Yield: 400 mg (34% of theory)

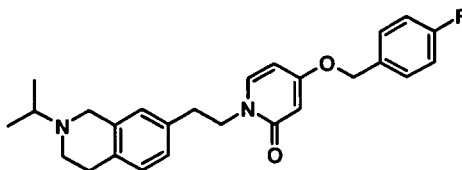
20 ESI Mass spectrum: $[M+H]^+ = 379$

Retention time HPLC: 1.67 min (method K).

Example 39.2

4-(4-Fluoro-benzyloxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one

25 2-one



4-(4-Fluoro-benzyloxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one is prepared following example 37.2 from 4-(4-fluoro-benzyloxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one (example 39.1; 600 mg, 1.59 mmol) and acetone (582 μ L, 7.93 mmol).

30

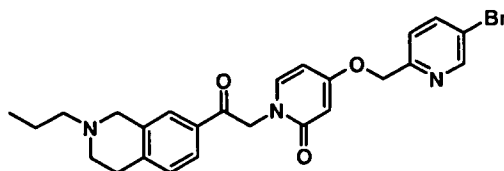
Yield: 280 mg (42% of theory)

ESI Mass spectrum: $[M+H]^+ = 421$

Retention time HPLC: 1.86 min (method K).

5 Example 40.1

4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one



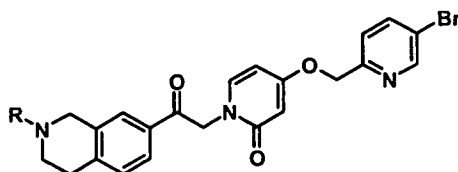
- 10 To 70 mg (0.15 mmol) 4-(5-bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one (for preparation see WO 08/022979) in 2.0 mL THF is added 10 mg (0.17 mmol) propionaldehyde and 39 mg (0.19 mmol) sodium triacetoxyborohydride. The mixture is acidified with acetic acid and stirred 2h at RT. The mixture is directly purified via preparative reverse HPLC chromatography (Waters XBridge 5 μ m, gradient from 5% to 95% acetonitrile in water + 0.3% NH_4OH).

Yield: 25 mg (33% of theory)

ESI Mass spectrum: $[M+H]^+ = 496/498$

Retention time HPLC: 1.84 min (method N).

- 20 The following examples are prepared as described for Example 40.1 starting from 4-(5-bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one (for preparation see WO 08/022979).

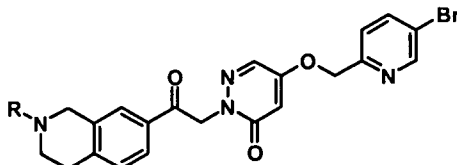


Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
40.2		64	C ₂₅ H ₂₆ BrN ₃ O ₃	496/498 [M+H] ⁺	1.74 (K)

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40.3		20	C ₂₄ H ₂₄ BrN ₃ O ₃	482/484 [M+H] ⁺	1.74 (N)
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The following examples are prepared as described for Example 40.1 starting from 5-(5-bromo-pyridin-2-ylmethoxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (for preparation see WO 08/022979).

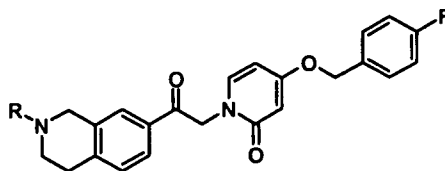


5

Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
41.1		69	C ₂₄ H ₂₅ BrN ₄ O ₃	497/499 [M+H] ⁺	1.84 (K)
41.2		49	C ₂₃ H ₂₃ BrN ₄ O ₃	483/485 [M+H] ⁺	1.72 (K)

The following examples are prepared as described for Example 35.4 (for example 42.2 EtOH is used as the solvent) starting from 4-(4-fluoro-benzyloxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one (for preparation see WO 08/022979).

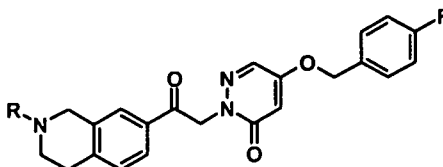
10



Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
42.1		58	C ₂₅ H ₂₅ FN ₂ O ₄	437 [M+H] ⁺	1.56 (K)

42.2		23	C ₂₆ H ₂₇ FN ₂ O ₄	451 [M+H] ⁺	1.68 (K)
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The following example is prepared as described for Example 35.4 starting from 5-(4-fluorobenzyloxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one (for preparation see WO 08/022979).



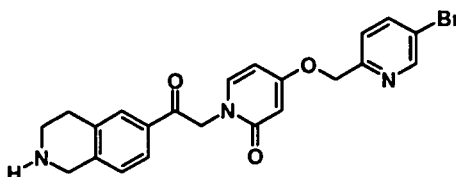
5

Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
43.1		47	C ₂₅ H ₂₆ FN ₃ O ₄	452 [M+H] ⁺	1.72 (K)

Example 44.1

4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one

10



44.1a 6-{2-[4-(5-Bromo-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-acetyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

15

6-{2-[4-(5-Bromo-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-acetyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 6-(2-bromo-acetyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (for preparation see WO08/022979, 1.30 g, 3.67 mmol) and 4-(5-bromo-pyridin-2-ylmethoxy)-1H-pyridin-2-one (preparation 10.3, 1.03 g, 3.67 mmol).

20

Yield: 2.10 g (103% of theory)

ESI Mass spectrum: [M+H]⁺ = 554/556

Retention time HPLC: 1.86 min (method K).

44.1b 4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one

4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-

pyridin-2-one is prepared following example 18.1 from 6-{2-[4-(5-bromo-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-acetyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 44.1a, 2.00 g, 3.61 mmol).

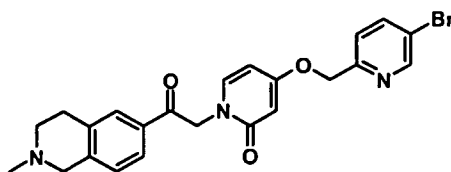
Yield: 650 mg (40% of theory)

ESI Mass spectrum: $[M+H]^+ = 454/456$

Retention time HPLC: 1.50 min (method K).

Example 44.2

4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-1H-pyridin-2-one



4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-1H-pyridin-2-one is prepared following example 40.1 from 4-(5-bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one (example

44.1, 550 mg, 1.21 mmol) and 37% aqueous formaldehyde solution (99 μ L, 1.33 mmol).

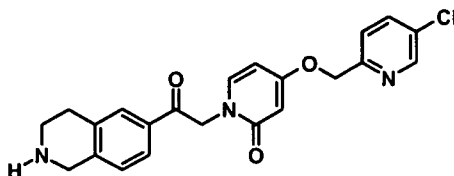
Yield: 360 mg (64% of theory)

ESI Mass spectrum: $[M+H]^+ = 468/470$

Retention time HPLC: 1.58 min (method K).

Example 45.1

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one



45.1a 6-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-acetyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

6-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-acetyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b (DMSO as solvent) from 6-(2-bromo-acetyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (for preparation see WO08/022979, 700 mg, 1.48 mmol) and 4-(5-chloro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one (preparation 10.6, 468 mg, 1.98 mmol).

Yield: 140 mg (19% of theory)

ESI Mass spectrum: $[M+H]^+ = 510/512$

Retention time HPLC: 1.84 min (method K).

45.1b 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1*H*-pyridin-2-one

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 18.1 from 6-{2-[4-(5-chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-acetyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 45.1a, 140 mg, 0.28 mmol).

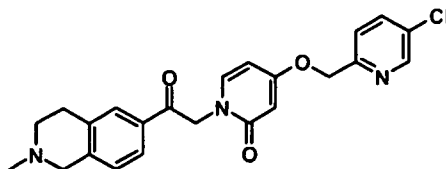
Yield: 70 mg (62% of theory)

ESI Mass spectrum: $[M+H]^+ = 410/412$

Retention time HPLC: 1.48 min (method K).

Example 45.2

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one



4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-1*H*-pyridin-2-one is prepared following example 40.1 from 4-(5-chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1*H*-pyridin-2-one (example

45.1, 750 mg, 1.83 mmol) and 37% aqueous formaldehyde solution (150 μ L, 2.01 mmol).

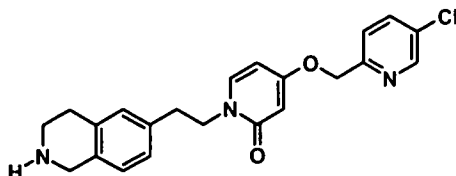
Yield: 450 mg (58% of theory)

ESI Mass spectrum: $[M+H]^+ = 424/426$

Retention time HPLC: 1.56 min (method K).

Example 46.1

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1*H*-pyridin-2-one



5

46.1a 6-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

6-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-3,4-dihydro-1*H*-

10 isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b from 6-[2-(toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 26, 1.51 g, 3.50 mmol) and 4-(5-chloro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one (preparation 10.6, 828 mg, 3.50 mmol).

Yield: 420 mg (24% of theory)

15 ESI Mass spectrum: $[M+H]^+ = 496/498$

Retention time HPLC: 1.92 min (method K).

46.1b 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1*H*-pyridin-2-one

20 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 18.1 from 6-{2-[4-(5-chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 46.1a, 420 mg, 0.63 mmol).

Yield: 250 mg (75% of theory)

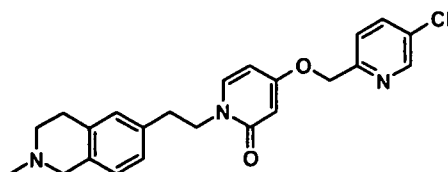
25 ESI Mass spectrum: $[M+H]^+ = 396/398$

Retention time HPLC: 1.54 min (method K).

Example 46.2

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1*H*-
30 pyridin-2-one

122



4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one is prepared following example 40.1 from 4-(5-chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one (example 46.1, 220 mg, 0.56 mmol) and 37% aqueous formaldehyde solution (46 μ L, 0.61 mmol).

Yield: 180 mg (79% of theory)

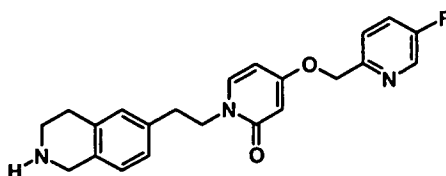
ESI Mass spectrum: $[M+H]^+ = 410/412$

Retention time HPLC: 1.24 min (method J).

10

Example 47.1

4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one



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47.1a 6-[2-[4-(5-Fluoro-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

6-[2-[4-(5-Fluoro-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following preparation 1b from 6-[2-(toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 26, 650 mg, 1.51 mmol) and 4-(5-fluoro-pyridin-2-ylmethoxy)-1H-pyridin-2-one (preparation 10.11, 330 mg, 1.50 mmol).

20

Yield: 130 mg (18% of theory)

ESI Mass spectrum: $[M+H]^+ = 480$

25

Retention time HPLC: 1.84 min (method K).

47.1b 4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one

4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one is prepared following example 18.1 from 6-[2-[4-(5-fluoro-pyridin-2-ylmethoxy)-2-oxo-2H-

30

pyridin-1-yl]-ethyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 47.1a, 130 mg, 0.27 mmol).

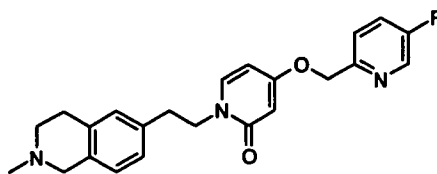
Yield: 65 mg (63% of theory)

ESI Mass spectrum: $[M+H]^+ = 380$

5 Retention time HPLC: 1.46 min (method K).

Example 47.2

4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1*H*-pyridin-2-one



10

4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 40.1 from 4-(5-fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1*H*-pyridin-2-one (example 47.1, 40 mg, 0.11 mmol) and 37% aqueous formaldehyde solution (9 μ L, 0.12 mmol).

15

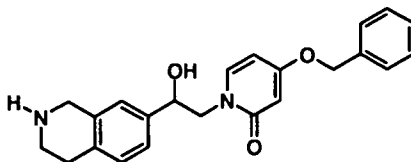
Yield: 25 mg (60% of theory)

ESI Mass spectrum: $[M+H]^+ = 394$

Retention time HPLC: 1.60 min (method K).

20 Example 48

4-Benzyloxy-1-[2-hydroxy-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one



To 8.70 g (18.5 mmol) 4-benzyloxy-1-[2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-1*H*-pyridin-2-one (example 13.1) in 150 mL isopropanol is added at RT 350 mg (9.25 mmol) sodium borohydride. The reaction mixture is stirred 2h at RT and is added to a pH 5 buffer-solution. After 1h the reaction mixture is filtered and the filtrate is concentrated in vacuo. The residue is purified via reversed HPLC chromatography (Gemini-C18 10 μ M; gradient from 5% to 95% acetonitrile in water + 0.15% HCOOH).

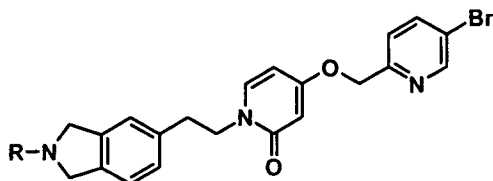
25

Yield: 2.10 g (30% of theory)

30 ESI Mass spectrum: $[M+H]^+ = 377$

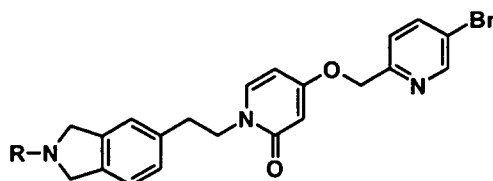
Retention time HPLC: 0.74 min (method O).

The following examples are prepared as described for Example 35.4 (for example 49.1 DMF is used as the solvent) starting from 4-(5-bromo-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one (example 19.1).



Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
49.1		68	C ₂₃ H ₂₄ BrN ₃ O ₃	470/472 [M+H] ⁺	1.45 (K)
49.2		32	C ₂₃ H ₂₃ BrFN ₃ O ₂	472/474 [M+H] ⁺	1.62 (K)

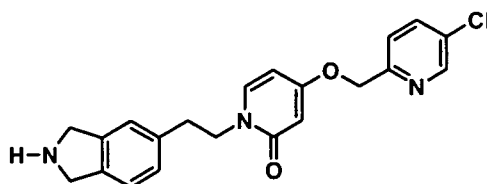
The following examples are prepared as described for Example 14.2 starting from 4-(5-bromo-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one (example 19.1). For example 49.3 1.0 eq. acetaldehyde and for example 49.4 2.0 eq acetaldehyde is used.



Example	R	Yield (%)	Formula	MS	Retention time HPLC in min (method)
49.3		19	C ₂₃ H ₂₄ BrN ₃ O ₂	454/456 [M+H] ⁺	1.66 (K)
49.4		9	C ₂₅ H ₂₈ BrN ₃ O ₃	498/500 [M+H] ⁺	Not determined

Example 50.1

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-1*H*-pyridin-2-one



5

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 18.1 from 5-[2-[4-(5-chloro-pyridin-2-ylmethoxy)-2-oxo-2*H*-pyridin-1-yl]-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 28, 460 mg, 0.95 mmol).

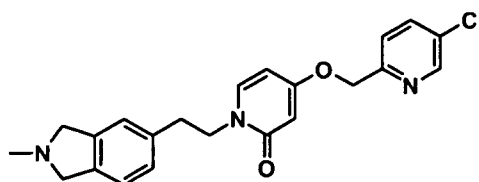
10 Yield: 140 mg (38% of theory)

ESI Mass spectrum: $[M+H]^+ = 382/384$

Retention time HPLC: 1.47 min (method K).

Example 50.2

15 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-1*H*-pyridin-2-one



20 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 14.2 from 4-(5-chloro-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1*H*-isoindol-5-yl)-ethyl]-1*H*-pyridin-2-one (example 50.1, 100 mg, 0.26 mmol) and 37% aqueous formaldehyde solution (32 μ L, 0.39 mmol).

Yield: 95 mg (92% of theory)

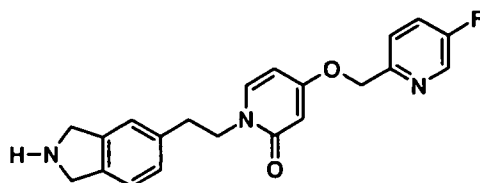
ESI Mass spectrum: $[M+H]^+ = 396/398$

25 Retention time HPLC: 1.55 min (method K).

Example 51.1

1-[2-(2,3-Dihydro-1*H*-isoindol-5-yl)-ethyl]-4-(5-fluoro-pyridin-2-ylmethoxy)-1*H*-pyridin-2-one

126



1-[2-(2,3-Dihydro-1H-isoindol-5-yl)-ethyl]-4-(5-fluoro-pyridin-2-ylmethoxy)-1H-pyridin-2-one is prepared following example 18.1 from 5-[2-[4-(5-fluoro-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-ethyl]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (preparation 29, 340 mg, 0.73 mmol).

Yield: 190 mg (71% of theory)

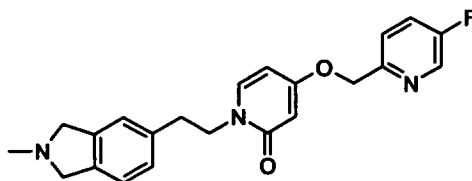
ESI Mass spectrum: $[M+H]^+ = 366$

Retention time HPLC: 0.92 min (method J).

10

Example 51.2

4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one



15

4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one is prepared following example 14.2 from 1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-4-(5-fluoro-pyridin-2-ylmethoxy)-1H-pyridin-2-one (example 51.1, 140 mg, 0.38 mmol) and 37% aqueous formaldehyde solution (47 μ L, 0.58 mmol).

Yield: 55 mg (38% of theory)

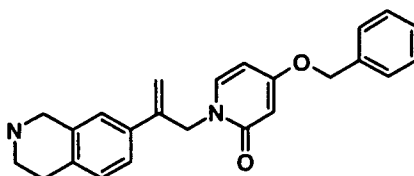
ESI Mass spectrum: $[M+H]^+ = 380$

Retention time HPLC: 1.46 min (method K).

20

Example 52

4-Benzyloxy-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-allyl]-1H-pyridin-2-one



25

52a 7-[2-(4-Benzoyloxy-2-oxo-2H-pyridin-1-yl)-acetyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of 4-benzoyloxy-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one (1.50 g, 4.01 mmol; preparation according to WO 2008022979) and triethylamine (0.85 mL, 6.02 mmol) in 40 mL THF is added Boc-anhydride (0.92 g, 4.21 mmol) and the mixture is stirred for 30 min at ambient temperature. The reaction mixture is poured into water and the resulting precipitate is filtered off, washed with water and dried *in vacuo*.

Yield: 1.71 g (90% of theory)

ESI Mass spectrum: $[M+H]^+ = 475$.

52b 7-[1-(4-Benzoyloxy-2-oxo-2H-pyridin-1-yl)methyl]-vinyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of 7-[2-(4-benzoyloxy-2-oxo-2H-pyridin-1-yl)-acetyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 52a, 0.20 g, 0.42 mmol) in 5.0 mL THF is added a solution of the Tebbe-Reagent (0.84 mL, 0.5 M in toluene, 0.42 mmol) and the reaction mixture is stirred for 18 h at RT. The mixture is quenched with water and extracted with ethyl acetate. The combined organic layer is washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The remaining residue is purified by flash chromatography (silica gel, 10% MeOH in dichloromethane).

Yield: 0.02 g (10% of theory)

ESI Mass spectrum: $[M+H]^+ = 473$.

52c 4-Benzoyloxy-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-allyl]-1H-pyridin-2-one

A solution of 7-[1-(4-benzoyloxy-2-oxo-2H-pyridin-1-yl)methyl]-vinyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 52b, 0.10 g, 0.42 mmol) in 10 mL 4N HCl in dioxane is stirred for 1 hr at RT. The volatiles are removed under reduced pressure, the residue is triturated with diisopropyl ether, filtered off and dried *in vacuo*.

Yield: 0.055 g (64% of theory)

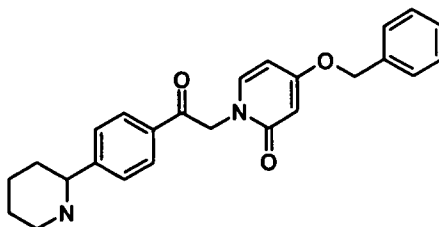
ESI Mass spectrum: $[M+H]^+ = 373$

Retention time HPLC: 2.07 min (method P).

Example 53

4-Benzoyloxy-1-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-1H-pyridin-2-one

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**53a 4-Piperidin-2-yl-benzoic acid, acetate salt**

To a solution of 4-pyridin-2-yl-benzoic acid (5.00 g, 25 mmol) in 72 mL glacial acetic acid is added palladium on charcoal (10%, 2.00 g) and the mixture is hydrogenated in an autoclave (3 days, 3 bar hydrogen, RT). The catalyst is filtered off, the filtrate is concentrated under reduced pressure and the residue is dried *in vacuo*. The remaining solid is triturated with acetonitrile, filtered off and dried.

Yield: 4.4 g (66% of theory)

ESI Mass spectrum: $[M+H]^+ = 206$

Retention time HPLC: 0.67 min (method J).

53b 4-[1-(2,2,2-Trifluoro-acetyl)-piperidin-2-yl]-benzoic acid

To an ice-cooled solution of 4-piperidin-2-yl-benzoic acid, acetate salt (example 53a, 4.40 g, 16.6 mmol) and triethylamine (6.93 mL, 49.8 mmol) in 100 mL dichloromethane is added trifluoroacetic anhydride (4.61 mL, 33.2 mmol). After warming to RT., the reaction mixture is stirred for another hour. The volatiles are removed *in vacuo*, the residue is dissolved in a small volume of MeOH and purified by preparative HPLC (Gilson, StableBond C18, gradient from 5% to 95% acetonitrile in water + 0.15% HCOOH, 120 mL/min).

Yield: 1.60 g (32% of theory)

ESI Mass spectrum: $[M-H]^+ = 300$.

53c N-Methoxy-N-methyl-4-[1-(2,2,2-trifluoro-acetyl)-piperidin-2-yl]-benzamide (Weinreb amide of 53b)

A solution of 4-[1-(2,2,2-trifluoro-acetyl)-piperidin-2-yl]-benzoic acid (example 53b, 1.60 g, 5.31 mmol), N,O-dimethylhydroxylamine hydrochloride (0.62 g, 6.37 mmol) and 4-methylmorpholine (1.17 mL, 10.6 mmol) in 40 mL MeOH is stirred for 10 min at RT. Then, 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride hydrate (1.54 g, 5.58 mmol) is added and the reaction mixture is stirred for 18 h at ambient temperature. The reaction mixture is concentrated *in vacuo* and purified by preparative HPLC (Gilson, Waters XBridge

C18, 5 μ m, gradient from 10% to 95% acetonitrile in water + 0.3% NH_4OH , 120 mL/min).

Yield: 1.50 g (82 % of theory)

ESI Mass spectrum: $[M+H]^+ = 345$

Retention time HPLC: 1.41 min (method J).

53d 1-(4-Piperidin-2-yl-phenyl)-ethanone

At 0°C, methylmagnesium bromide (2.9 mL of a 3M solution in diethyl ether, 8.7 mmol) is added to a solution of Weinreb amide 53c (N-methoxy-N-methyl-4-[1-(2,2,2-trifluoro-acetyl)-piperidin-2-yl]-benzamide, 1.50 g, 4.36 mmol) in anhydrous THF (50 mL). After stirring for 1 h at -5°C, another 2 equivalents of methylmagnesium bromide (2.9 mL) are added to the reaction mixture. After an additional 1 h at -5°C, the reaction mixture is carefully poured into ice-cold 1N aqueous HCl. The volatiles are removed under reduced pressure and the remaining residue is dissolved in water and purified by preparative HPLC (Gilson, Waters XBridge C18, 5 µm, gradient from 10% to 95% acetonitrile in water + 0.3% NH₄OH, 120 mL/min).

Yield: 0.74 g (84 % of theory)

ESI Mass spectrum: [M+H]⁺ = 204

Retention time HPLC: 1.44 min (method K).

53e 1-[2-(4-Acetyl-phenyl)-piperidin-1-yl]-2,2,2-trifluoro-ethanone

To an ice-cooled solution of 1-(4-piperidin-2-yl-phenyl)-ethanone (example 53d, 0.60 g, 2.95 mmol) in 10 mL dichloromethane is added trifluoroacetic anhydride (0.45 mL, 3.25 mmol). After warming to RT, the reaction mixture is stirred for 18 h. The volatiles are removed *in vacuo*, the residue is dissolved in a small volume of MeOH and purified by preparative HPLC (Gilson, StableBond C18, gradient from 5% to 95% acetonitrile in water + 0.15% HCOOH, 120 mL/min).

Yield: 0.50 g (57% of theory)

ESI Mass spectrum: [M+H]⁺ = 300

Retention time HPLC: 1.52 min (method J).

53f 1-{2-[4-(2-Bromo-acetyl)-phenyl]-piperidin-1-yl}-2,2,2-trifluoro-ethanone

To a solution of 1-[2-(4-acetyl-phenyl)-piperidin-1-yl]-2,2,2-trifluoro-ethanone (example 53e; 0.50 g, 1.67 mmol) in 10 mL THF is added tetrabutylammonium-tribromide (0.81 g, 1.67 mmol) dissolved in MeOH/THF. After stirring for 30 min at RT, the volatiles are removed *in vacuo*. The residue is stirred with 1N aqueous HCl and extracted with *tert*-butylmethylether. The organic phase is washed with 1N aqueous HCl and water, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography (silica gel, 30% ethyl acetate in hexanes).

Yield: 0.56 g (89% of theory)

ESI Mass spectrum: $[M+H]^+ = 378/380$.

53g 4-Benzyloxy-1-(2-oxo-2-{4-[1-(2,2,2-trifluoro-acetyl)-piperidin-2-yl]-phenyl}-ethyl)-1H-pyridin-2-one

- 5 To a solution of 4-benzyloxy-1H-pyridin-2-one (149 mg, 0.74 mmol) in 2.0 mL DMSO is added cesium carbonate (0.60 g, 1.85 mmol) and the mixture is stirred for 15 min at RT. Then, 1-{2-[4-(2-bromo-acetyl)-phenyl]-piperidin-1-yl}-2,2,2-trifluoro-ethanone (example 53f, 280 mg, 0.74 mmol) is added and the reaction mixture is stirred for 1 h at RT. Water is added, the precipitate is collected, washed with water and dried.

- 10 Yield: 340 mg (92% of theory)

ESI Mass spectrum: $[M+H]^+ = 499$

Retention time HPLC: 1.63 min (method J).

53h 4-Benzyloxy-1-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-1H-pyridin-2-one

- 15 To a solution of 4-benzyloxy-1-(2-oxo-2-{4-[1-(2,2,2-trifluoro-acetyl)-piperidin-2-yl]-phenyl}-ethyl)-1H-pyridin-2-one (example 53g, 340 mg, 0.68 mmol) in 10 mL THF and 2.0 mL MeOH is added 1N aqueous NaOH solution (3.4 mL) and the reaction mixture is stirred for 1 h at RT. The volatiles are removed *in vacuo*, the residue is dissolved in a small volume of DMF and MeOH and purified by preparative HPLC (Gilson, Waters XBridge C18, 5 μ m, gradient from 10% to 95% acetonitrile in water + 0.3% NH_4OH , 120 mL/min).

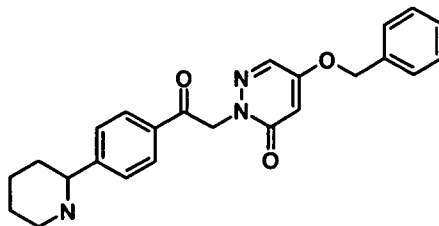
Yield: 180 mg (66% of theory)

ESI Mass spectrum: $[M+H]^+ = 403$

Retention time HPLC: 1.69 min (method K).

- 25 Example 54

5-Benzyloxy-2-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-2H-pyridazin-3-one



- 54a 5-Benzyloxy-2-(2-oxo-2-{4-[1-(2,2,2-trifluoro-acetyl)-piperidin-2-yl]-phenyl}-ethyl)-2H-pyridazin-3-one

- 30 5-Benzyloxy-2-(2-oxo-2-{4-[1-(2,2,2-trifluoro-acetyl)-piperidin-2-yl]-phenyl}-ethyl)-2H-

pyridazin-3-one is prepared following example 53g from 5-benzyloxy-2H-pyridazin-3-one (150

mg, 0.74 mmol) and 1-[2-[4-(2-bromo-acetyl)-phenyl]-piperidin-1-yl]-2,2,2-trifluoro-ethanone (example 53f, 280 mg, 0.74 mmol).

Yield: 300 mg (81% of theory)

ESI Mass spectrum: $[M+H]^+ = 500$

5 Retention time HPLC: 1.70 min (method J).

54b 5-Benzyloxy-2-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-2H-pyridazin-3-one

5-Benzyloxy-2-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-2H-pyridazin-3-one is prepared

following example 53h from 5-benzyloxy-2-(2-oxo-2-{4-[1-(2,2,2-trifluoro-acetyl)-piperidin-2-

10 yl]-phenyl)-ethyl)-2H-pyridazin-3-one (example 54a, 300 mg, 0.60 mmol).

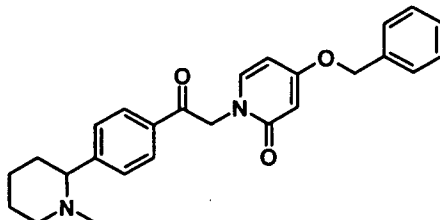
Yield: 150 mg (62% of theory)

ESI Mass spectrum: $[M+H]^+ = 404$

Retention time HPLC: 1.75 min (method K).

15 Example 55

4-Benzyloxy-1-[2-[4-(1-methyl-piperidin-2-yl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one



To a solution of 4-benzyloxy-1-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-1H-pyridin-2-one (example 53, 120 mg, 0.30 mmol) in THF (5.0 mL), formaldehyde (36 μ M of 37% aqueous solution, 0.45 mmol) and aqueous buffer pH 5 (2.0 mL) is added sodium triacetoxyborohydride (95 mg, 0.45 mmol) and the reaction mixture is stirred for 18 h at RT. The volatiles are removed *in vacuo*, the residue is dissolved in a small volume of MeOH and purified by preparative HPLC (Gilson, Waters XBridge C18, 5 μ m, gradient from 10% to 95% acetonitrile in water + 0.3% NH_4OH , 120 mL/min).

25 Yield: 122 mg (98% of theory)

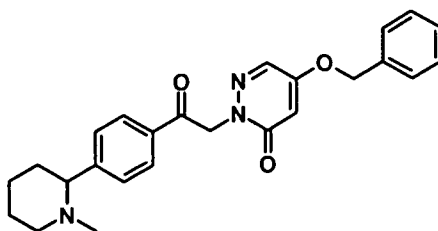
ESI Mass spectrum: $[M+H]^+ = 417$

Retention time HPLC: 1.76 min (method K).

Example 56

30 5-Benzyloxy-2-[2-[4-(1-methyl-piperidin-2-yl)-phenyl]-2-oxo-ethyl]-2H-pyridazin-3-one

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5-Benzyloxy-2-{2-[4-(1-methyl-piperidin-2-yl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one is prepared following example 55 from 5-benzyloxy-2-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-2H-pyridazin-3-one (example 54, 110 mg, 0.27 mmol).

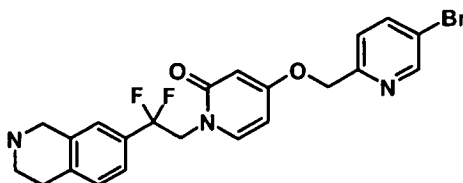
5 Yield: 75 mg (66% of theory)

ESI Mass spectrum: $[M+H]^+ = 418$

Retention time HPLC: 1.85 min (method K).

Example 57

10 4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one



15 57a 7-(Ethoxycarbonyl-difluoro-methyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of 7-iodo-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 27b, 10.0 g, 27.8 mmol) and ethyl difluoroiodoacetate (8.2 mL, 56 mmol) in 40 mL DMSO is added copper powder (Aldrich, "nano powder", 100 nm, 7.1 g, 111 mmol) and the mixture is stirred for 18 h at RT. Another 4.0 mL of ethyl difluoroiodoacetate is added and the reaction mixture is stirred for an additional 24 h. The mixture is filtered over a pad of silica gel, washed with DCM/MeOH, concentrated under reduced pressure and purified by preparative HPLC (Agilent, Zorbax Stablebond C18, 7 μ m, gradient from 5% to 95% acetonitrile in water + 0.15% HCOOH).

Yield: 4.10 g (41% of theory)

25 ESI Mass spectrum: $[M+NH_4]^+ = 373$

Retention time HPLC: 1.88 min (method J).

57b 7-(1,1-Difluoro-2-hydroxy-ethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

To an ice-cooled solution of 7-(ethoxycarbonyl-difluoro-methyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 57a, 4.00 g, 11.3 mmol) in 250 mL MeOH is added sodium borohydride (2.24 g, 56 mmol). The reaction mixture is stirred for 18 h at RT, poured into brine and concentrated under reduced pressure. The aqueous phase is extracted with EtOAc, the organic layer is dried over MgSO₄, evaporated *in vacuo* and purified by preparative HPLC (Gilson, Waters XBridge C18, 5 µm, gradient from 5% to 95% acetonitrile in water + 0.3% NH₄OH, 120 mL/min).

Yield: 1.54 g (44% of theory)

ESI Mass spectrum: [M+NH₄]⁺ = 314

Retention time HPLC: 1.77 min (method K).

57c 7-[1,1-Difluoro-2-(toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of 7-(1,1-difluoro-2-hydroxy-ethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 57b, 1.50 g, 4.79 mmol), triethylamine (0.81 mL, 5.8 mmol), DMAP (58 mg, 0.48 mmol) in 30 mL dichloromethane is added p-toluenesulfonyl chloride (1.10 g, 5.75 mmol). After stirring for 1 h at RT, the reaction mixture is poured into 20 mL ice water and extracted with DCM. The combined organic layer is washed with water, dried over MgSO₄ and evaporated under reduced pressure.

Yield: 2.20 g (98% of theory)

ESI Mass spectrum: [M+H]⁺ = 468

Retention time HPLC: 1.38 min (method L).

57d 7-{2-[4-(5-Bromo-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-1,1-difluoro-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of 4-(5-bromo-pyridin-2-ylmethoxy)-1H-pyridin-2-one (722 mg, 2.57 mmol, preparation 10.3) in 3.0 mL DMSO is added cesium carbonate (2.09 g, 6.42 mmol) and the mixture is stirred for 15 min at RT. Then, 7-[1,1-difluoro-2-(toluene-4-sulfonyloxy)-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 57c, 1200 mg, 2.57 mmol) is added and the reaction mixture is stirred for 4 h at 80°C. The reaction mixture is filtered and purified by preparative HPLC (Gilson, Waters XBridge C18, 5 µm, gradient from 5% to 95% acetonitrile in water + 0.3% NH₄OH, 120 mL/min).

Yield: 230 mg (16% of theory)

ESI Mass spectrum: [M+H]⁺ = 576/578

Retention time HPLC: 1.99 min (method K).

57e 4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one

To a solution of 7-{2-[4-(5-bromo-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-1,1-difluoro-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 57d, 230 mg, 0.40 mmol) in 5.0 mL dichloromethane is added 1.5 mL trifluoroacetic acid. After stirring for 1 h at RT, the reaction mixture is evaporated *in vacuo* and the remaining residue is purified by preparative HPLC (Gilson, Waters XBridge C18, 5 μ m, gradient from 5% to 95% acetonitrile in water + 0.3% NH₄OH, 120 mL/min).

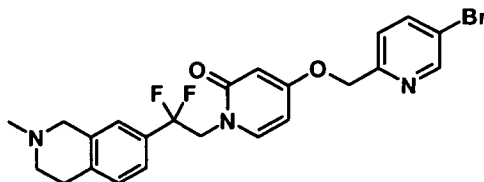
Yield: 120 mg (63% of theory)

ESI Mass spectrum: [M+H]⁺ = 476/478

Retention time HPLC: 1.64 min (method K).

Example 58

4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one



4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one is prepared following example 55 from 4-(5-bromo-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one

(example 57, 70 mg, 0.15 mmol).

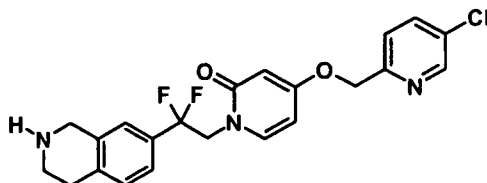
Yield: 50 mg (69% of theory)

ESI Mass spectrum: [M+H]⁺ = 490/492

Retention time HPLC: 1.72 min (method K).

Example 59

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one



59a 7-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-1,1-difluoro-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

7-{2-[4-(5-Chloro-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-1,1-difluoro-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following example 57d from

5 4-(5-chloro-pyridin-2-ylmethoxy)-1H-pyridin-2-one (278 mg, 1.18 mmol, preparation 10.6).

Yield: 160 mg (26% of theory)

ESI Mass spectrum: $[M+H]^+ = 532/534$

Retention time HPLC: 1.19 min (method O).

10 59b 4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one

4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one is prepared following example 57e from 7-{2-[4-(5-chloro-pyridin-2-ylmethoxy)-2-oxo-2H-pyridin-1-yl]-1,1-difluoro-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (preparation 59a, 150 mg, 0.28 mmol).

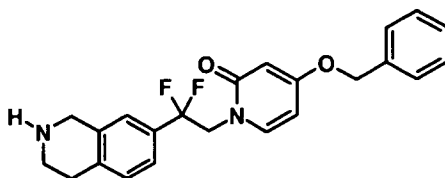
15 Yield: 120 mg (99% of theory)

ESI Mass spectrum: $[M+H]^+ = 432/434$

Retention time HPLC: 0.76 min (method O).

20 Example 60

4-Benzyloxy-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one



60a 7-[2-(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-1,1-difluoro-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

25 7-[2-(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-1,1-difluoro-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester is prepared following example 57d from 4-benzyloxy-1H-pyridin-2-one (166 mg, 0.82 mmol).

Yield: 75 mg (20% of theory)

30 ESI Mass spectrum: $[M+H]^+ = 497$.

60b 4-Benzyloxy-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one

4-Benzyloxy-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 57e from 7-[2-(4-benzyloxy-2-oxo-2*H*-pyridin-1-yl)-1,1-difluoro-ethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (example 60a, 75 mg, 0.15 mmol).

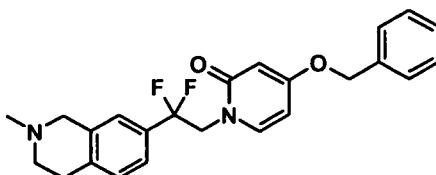
5 Yield: 60 mg (100% of theory)

ESI Mass spectrum: $[M+H]^+ = 397$

Retention time HPLC: 0.92 min (method L).

Example 61

10 4-Benzyloxy-1-[2,2-difluoro-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one



4-Benzyloxy-1-[2,2-difluoro-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one is prepared following example 55 from 4-benzyloxy-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1*H*-pyridin-2-one (example 60, 35 mg, 0.09 mmol).

15 Yield: 25 mg (69% of theory)

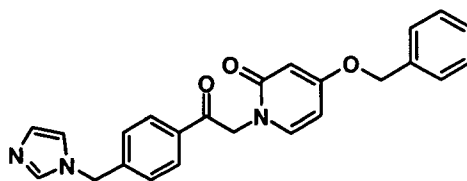
Yield: 25 mg (69% of theory)

ESI Mass spectrum: $[M+H]^+ = 411$

Retention time HPLC: 1.78 min (method K).

20 Example 62

4-Benzyloxy-1-[2-(4-imidazol-1-ylmethyl-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one



A solution of 4-benzyloxy-1-[2-(4-bromomethyl-phenyl)-2-oxo-ethyl]-1*H*-pyridin-2-one (preparation 1, 250 mg, 0.61 mmol) and imidazole (124 mg, 1.82 mmol) in DMF (2.0 mL) is stirred for 2 h at RT. The reaction mixture is diluted with water, the formed precipitate is filtered off and purified by preparative HPLC (Gilson, StableBond C18, gradient from 5% to 95% acetonitrile in water + 0.15% HCOOH, 120 mL/min).

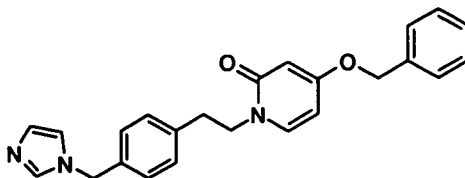
25 Yield: 27 mg (11% of theory)

Yield: 27 mg (11% of theory)

ESI Mass spectrum: $[M+H]^+ = 400$

30 Retention time HPLC: 2.5 min (method A).

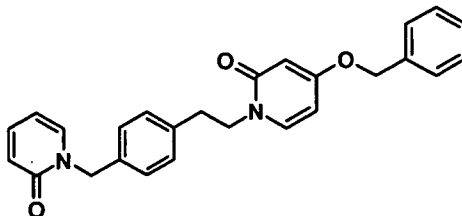
Example 63

4-Benzyloxy-1-[2-(4-imidazol-1-ylmethyl-phenyl)-ethyl]-1*H*-pyridin-2-one

- 5 A solution of 4-benzyloxy-1-[2-(4-bromomethyl-phenyl)-ethyl]-1*H*-pyridin-2-one (preparation according to WO2008022979, 239 mg, 0.60 mmol) and imidazole (163 mg, 2.40 mmol) in DMF (2.0 mL) is stirred for 2 h at RT. The reaction mixture is purified by preparative HPLC (Gilson, Waters XBridge C18, 5 μ m, gradient from 10% to 95% acetonitrile in water + 0.3% NH_4OH , 120 mL/min).
- 10 Yield: 157 mg (68% of theory)
ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 386$
Retention time HPLC: 1.60 min (method K).

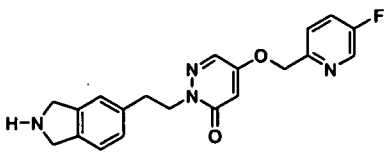
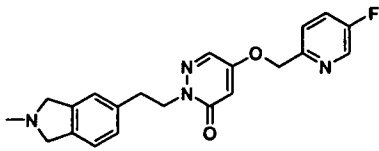
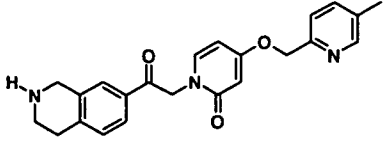
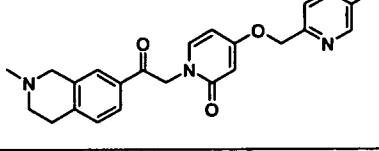
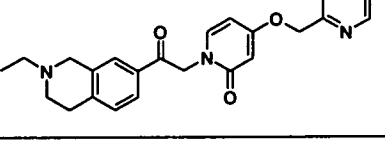
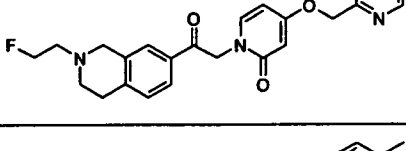
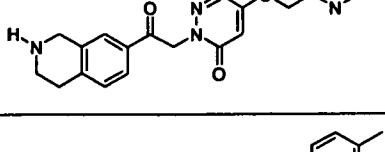
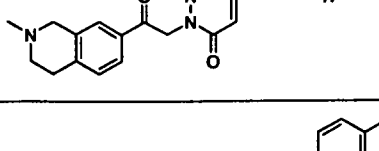
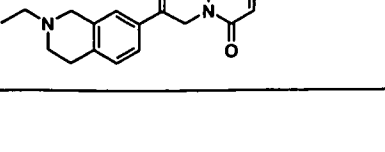
Example 64

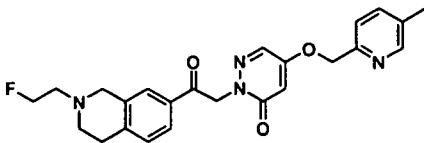
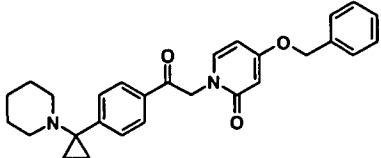
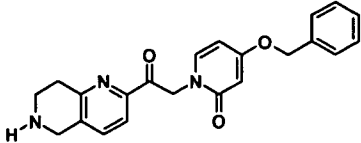
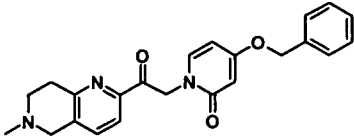
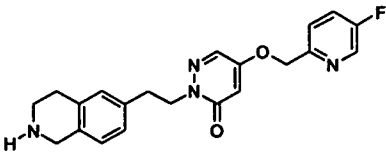
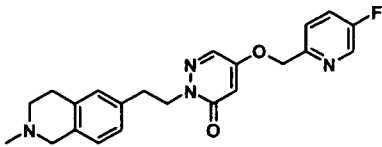
- 15 4-Benzyloxy-1-[2-[4-(2-oxo-2*H*-pyridin-1-ylmethyl)-phenyl]-ethyl]-1*H*-pyridin-2-one



- To a solution of 2-hydroxypyridine (19 mg, 0.20 mmol) in 3.0 mL THF is added potassium *tert*-butoxide (24 mg, 0.21 mmol) and the mixture is stirred for 20 min at RT. Then, 4-benzyloxy-1-[2-(4-bromomethyl-phenyl)-ethyl]-1*H*-pyridin-2-one (preparation according to
- 20 WO2008022979, 50 mg, 0.13 mmol) is added and the reaction mixture is stirred for 2 h at 50°C. The reaction mixture is concentrated under reduced pressure and purified by preparative HPLC (XTerra MS C18, gradient from 5% to 95% acetonitrile in water + 0.15% HCOOH , 120 mL/min).
- Yield: 23 mg (44% of theory)
- 25 ESI Mass spectrum: $[\text{M}+\text{H}]^+ = 413$
Retention time HPLC: 2.81 min (method P).

The following examples can be prepared following the above described procedures:

Example	Structure
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Some test methods for determining an MCH-receptor antagonistic activity will now be described. In addition, other test methods known to the skilled man may be used, e.g. by

5 inhibiting the MCH-receptor-mediated inhibition of cAMP production, as described by Hoogduijn M et al. in "Melanin-concentrating hormone and its receptor are expressed and functional in human skin", *Biochem. Biophys. Res Commun.* 296 (2002) 698-701 and by biosensory measurement of the binding of MCH to the MCH receptor in the presence of

antagonistic substances by plasmon resonance, as described by Karlsson OP and Lofas S. in

10 "Flow-Mediated On-Surface Reconstitution of G-Protein Coupled Receptors for Applications in Surface Plasmon Resonance Biosensors", *Anal. Biochem.* 300 (2002), 132-138. Other methods of testing antagonistic activity to MCH receptors are contained in the references and patent documents mentioned hereinbefore, and the description of the test methods used is hereby incorporated in this application.

MCH-1 receptor binding test

Method: MCH binding to hMCH-1R transfected cells

Species: Human

5 Test cell: hMCH-1R stably transfected into CHO/Galpha16 cells

Results: IC50 values

Membranes from CHO/Galpha16 cells stably transfected with human hMCH-1R are resuspended using a syringe (needle 0.6 x 25 mm) and diluted in test buffer (50 mM HEPES, 10 mM MgCl₂, 2 mM EGTA, pH 7.00; 0.1 % bovine serum albumin (protease-free), 0.021 % bacitracin, 1 µg/ml aprotinin, 1 µg/ml leupeptin and 1 µM phosphoramidone) to a concentration of 5 to 15 µg/ml.

200 microlitres of this membrane fraction (contains 1 to 3 µg of protein) are incubated for 60 minutes at ambient temperature with 100 pM of ¹²⁵I-tyrosyl melanin concentrating hormone (¹²⁵I-MCH commercially obtainable from NEN) and increasing concentrations of the test compound in a final volume of 250 microlitres. After the incubation the reaction is filtered using a cell harvester through 0.5% PEI treated fibreglass filters (GF/B, Unifilter Packard). The membrane-bound radioactivity retained on the filter is then determined after the addition of scintillator substance (Packard Microscint 20) in a measuring device (TopCount of Packard).

20 The non-specific binding is defined as bound radioactivity in the presence of 1 micromolar MCH during the incubation period.

The analysis of the concentration binding curve is carried out on the assumption of one receptor binding site.

Standard:

25 Non-labelled MCH competes with labelled ¹²⁵I-MCH for the receptor binding with an IC50 value of between 0.06 and 0.15 nM.

The KD value of the radioligand is 0.156 nM.

Relative binding of MCH (as a radioligand) at a concentration of 10⁻⁷ M of a respective compound according to this invention is expressed as %CTL and is calculated from the whole concentration curve whereas total specific binding of ligand without a compound according to this invention is set 100%. Values are the mean of two separately performed experiments.

MCH-1 receptor-coupled Ca²⁺ mobilisation test

Method: Calcium mobilisation test with human MCH (FLIPR³⁸⁴)

35 Species: Human

Test cells: CHO/ Galpha 16 cells stably transfected with hMCH-R1

Results: 1st measurement: % stimulation of the reference (MCH 10^{-6} M)
 2nd measurement: pKB value

Reagents:	HBSS (10x)	(GIBCO)
	HEPES buffer (1M)	(GIBCO)
	Pluronic F-127	(Molecular Probes)
	Fluo-4	(Molecular Probes)
	Probenecid	(Sigma)
	MCH	(Bachem)
	bovine serum albumin (protease-free)	(Serva)
	DMSO	(Serva)
	Ham's F12	(BioWhittaker)
	FCS	(BioWhittaker)
	L-Glutamine	(GIBCO)
	Hygromycin B	(GIBCO)
	PENStrep	(BioWhittaker)
	Zeocin	(Invitrogen)

- 5 Clonal CHO/Galpha16 hMCH-R1 cells are cultivated in Ham's F12 cell culture medium (with L-glutamine; BioWhittaker; Cat.No.: BE12-615F). This contains per 500 ml 10% FCS, 1% PENStrep, 5 ml L-glutamine (200 mM stock solution), 3 ml hygromycin B (50 mg/ml in PBS) and 1.25 ml zeocin (100 µg/ml stock solution). One day before the experiment the cells are
- 10 plated on a 384-well microtitre plate (black-walled with a transparent base, made by Costar) in a density of 2500 cells per cavity and cultivated in the above medium overnight at 37°C, 5% CO₂ and 95% relative humidity. On the day of the experiment the cells are incubated with cell culture medium to which 2 mM Fluo-4 and 4.6 mM Probenecid have been added, at 37°C for 45 minutes. After charging with fluorescent dye the cells are washed four times with Hanks buffer solution (1 x HBSS, 20 mM HEPES), which has been combined with 0.07% Probenecid.
- 15 The test substances are diluted in Hanks buffer solution, combined with 2.5% DMSO. The background fluorescence of non-stimulated cells is measured in the presence of substance in the 384-well microtitre plate five minutes after the last washing step in the FLIPR³⁸⁴ apparatus (Molecular Devices; excitation wavelength: 488 nm; emission wavelength: bandpass 510 to 570 nm). To stimulate the cells MCH is diluted in Hanks buffer with 0.1% BSA, pipetted into
- 20 the 384-well cell culture plate 35 minutes after the last washing step and the MCH-stimulated fluorescence is then measured in the FLIPR³⁸⁴ apparatus.

Data analysis:

1st measurement: The cellular Ca^{2+} mobilisation is measured as the peak of the relative fluorescence minus the background and is expressed as the percentage of the maximum signal of the reference (MCH 10^{-6}M). This measurement serves to identify any possible agonistic effect of a test substance.

2nd measurement: The cellular Ca^{2+} mobilisation is measured as the peak of the relative fluorescence minus the background and is expressed as the percentage of the maximum signal of the reference (MCH 10^{-6}M , signal is standardised to 100%). The EC_{50} values of the MCH dosage activity curve with and without test substance (defined concentration) are determined graphically by the GraphPad Prism 2.01 curve program. MCH antagonists cause the MCH stimulation curve to shift to the right in the graph plotted.

The inhibition is expressed as a pKB value:

$$\text{pKB} = \log(\text{EC}_{50}(\text{testsubstance} + \text{MCH}) / \text{EC}_{50}(\text{MCH}) - 1) - \log C(\text{testsubstance})$$

The compounds according to the invention, including their salts, exhibit an excellent MCH-receptor antagonistic activity in the tests mentioned above. Using the MCH-1 receptor binding test described hereinbefore the compounds according to this invention predominantly have IC_{50} values below 100 nM, in particular below 50 nM.

In order to illustrate that compounds according to the invention with different structural elements possess an excellent MCH-1 receptor antagonistic activity, the %CTL values of the compounds are provided in the following table wherein "Ex. No." means the compound according to the respective example number and "%CTL" means the relative binding of MCH at a concentration of 100 nM of said compound. The measurement of %CTL is described hereinbefore.

Table 1

Ex. No.	%CTL	Ex. No.	%CTL	Ex. No.	%CTL
1.1	11.3	1.2	9.6	1.3	19.2
1.4	6.6	1.5	15.9	1.6	6.6
1.7	4.3	1.8	11.2	1.9	7.7
1.10	7.7	1.11	5.8	1.12	20.4
1.13	22.6	1.14	16.0	1.15	14.3
1.16	26.3	1.17	23.9	1.18	51.8

1.19	47.1
1.22	5.3
2.3	8.6
2.6	12.7
3.2	33.9
4.2	22.6
5.3	13.6
5.6	15.3
6.2	10.3
7.2	39.3
7.5	16.4
8.3	6.9
8.6	6.2
9.3	26.6
9.6	32.5
10.1	29.9
11.2	21.6
13.1	31.6
14.2	15.4
16.1	30.9
16.4	21.7
17.2	21.5
18.2	7.6
20.1	30.7
21.2	8.7
21.5	10.8
23	39.5
25.1	17.5
26.2	77.3
28.1	22.2
29.2	13.7
31.2	23.2
33.1	21.0

1.20	44.7
2.1	17.6
2.4	13.8
2.7	8.1
3.3	39.7
5.1	13.1
5.4	15.6
5.7	17.3
6.3	12.3
7.3	35.1
8.1	15.6
8.4	6.3
9.1	34.2
9.4	23.2
9.7	26.5
10.2	25.3
12.1	16.1
13.2	40.0
15.1	10.6
16.2	33.1
16.5	23.6
17.3	37.7
19.1	4.6
20.2	19.1
21.3	7.8
22.1	16.6
24.1	20.1
25.2	18.3
27.1	25.8
28.2	17.3
30	13.7
32.1	20.6
33.2	15.3

1.21	12.8
2.2	9.4
2.5	17.2
3.1	30.0
4.1	15.5
5.2	11.3
5.5	11.6
6.1	13.6
7.1	24.9
7.4	40.8
8.2	13.6
8.5	9.7
9.2	29.0
9.5	29.4
9.8	21.0
11.1	15.5
12.2	17.9
14.1	21.9
15.2	16.1
16.3	28.0
17.1	30.1
18.1	7.0
19.2	5.8
21.1	12.0
21.4	12.6
22.2	10.9
24.2	19.1
26.1	66.0
27.2	24.4
29.1	13.6
31.1	29.4
32.2	25.5
34	41.6

35.1	12.8	35.2	8.8	35.3	10.5
35.4	8.8	35.5	8.1	35.6	20.9
35.7	16.1	36.1	6.7	36.2	10.2
36.3	8.0	36.4	10.8	36.5	17.0
37.1	14.7	37.2	22.4	37.3	20.7
38.1	16.3	38.2	16.0	38.3	22.0
38.4	15.3	38.5	24.5	39.1	4.6
39.2	6.7	40.1	16.3	40.2	26.8
40.3	26.8	41.1	21.1	41.2	29.6
42.1	27.1	42.2	19.0	43.1	20.9
44.1	17.6	44.2	8.5	45.1	37.2
45.2	27.5	46.1	10.1	46.2	33.3
47.1	36.0	47.2	32.0	48	25.6
49.1	4.8	49.2	14.1	49.3	6.6
49.4	8.7	50.1	7.0	50.2	7.0
51.1	23.6	51.2	21.2	52	12.0
53	22.7	54	18.4	55	19.9
56	14.1	57	20.8	58	29.4
59	28.6	60	25.5	61	30.1
62	26.1	63	8.1	64	22.1

Some examples of formulations will be described hereinafter, wherein the term "active substance" denotes one or more compounds according to the invention, including their salts.

In the case of one of the combinations with one or more active substances described, the term "active substance" also includes the additional active substances.

Example A

Tablets containing 20 mg of active substance

Composition:

10	active substance	20 mg
	lactose	120 mg
	maize starch	40 mg
	magnesium stearate	2 mg
	Povidone K 25	18 mg

15 Preparation:

Active substance, lactose and maize starch are homogeneously mixed; granulated with an aqueous solution of Povidone; mixed with magnesium stearate; compressed in a tablet press; weight of tablet 200 mg.

5

Example BCapsules containing 20 mg active substance

Composition:

	active substance	20 mg
10	maize starch	80 mg
	highly dispersed silica	5 mg
	magnesium stearate	2.5 mg

Preparation:

- 15 Active substance, maize starch and silica are homogeneously mixed; mixed with magnesium stearate; the mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

Example CSuppositories containing 50 mg of active substance

20 Composition:

	active substance	50 mg
	hard fat (Adeps solidus) q.s. ad	1700 mg

Preparation:

- 25 Hard fat is melted at about 38°C; ground active substance is homogeneously dispersed in the molten hard fat; after cooling to about 35°C it is poured into chilled moulds.

Example DInjectable solution containing 5 mg of active substance per 5 ml

30 Composition:

	active substance	5 mg
	glucose	250 mg
	human serum albumin	10 mg
	glycofurol	250 mg
35	water for injections ad	5 ml

Preparation:

Glycofurol and glucose are dissolved in water for injections (Wfi); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfi; transferred into ampoules under nitrogen gas.

5

Example EInjectable solution containing 10 mg of active substance per 1 ml

Composition:

	active substance	10 mg
10	mannitol	50 mg
	human serum albumin	10 mg
	water for injections ad	1 ml

Preparation:

- 15 Mannitol is dissolved in water for injections (Wfi); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfi; transferred into ampoules under nitrogen gas.

Patent Claims

1. A compound selected from the group consisting of

1.1	4-Benzyloxy-1-{2-[4-(4-methoxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.2	4-Benzyloxy-1-{2-[4-(4-hydroxy-4-trifluoromethyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.3	4-Benzyloxy-1-{2-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.4	4-Benzyloxy-1-(2-{4-[(2-hydroxy-ethylamino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.5	4-Benzyloxy-1-{2-[4-(tert-butylamino-methyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.6	4-Benzyloxy-1-{2-[4-(isopropylamino-methyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.7	4-Benzyloxy-1-[2-(4-[(1-hydroxy-cyclopropylmethyl)-amino]-methyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
1.8	4-Benzyloxy-1-(2-{4-[(tert-butyl-methyl-amino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.9	4-Benzyloxy-1-[2-(4-cyclopropylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
1.10	4-Benzyloxy-1-[2-(4-[(2-hydroxy-ethyl)-methyl-amino]-methyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
1.11	4-Benzyloxy-1-(2-{4-[(isopropyl-methyl-amino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.12	(S)-4-Benzyloxy-1-{2-[4-(3-fluoro-pyrrolidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.13	(R)-4-Benzyloxy-1-{2-[4-(3-fluoro-pyrrolidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
1.14	4-Benzyloxy-1-(2-oxo-2-{4-[(3,3,3-trifluoro-propylamino)-methyl]-phenyl}-ethyl)-1H-pyridin-2-one
1.15	4-Benzyloxy-1-(2-{4-[(2,2-dimethyl-propylamino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.16	1-{4-[2-(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-acetyl]-benzyl}-piperidine-4-carbonitrile

1.17	4-Benzyloxy-1-[2-oxo-2-(4-thiomorpholin-4-ylmethyl-phenyl)-ethyl]-1H-pyridin-2-one
1.18	4-Benzyloxy-1-{2-oxo-2-[4-(1-oxo-thiomorpholin-4-ylmethyl)-phenyl]-ethyl}-1H-pyridin-2-one
1.19	4-Benzyloxy-1-(2-{4-[(2,2-difluoro-ethylamino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.20	4-Benzyloxy-1-[2-(4-[(2,2-difluoro-ethyl)-methyl-amino]-methyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
1.21	4-Benzyloxy-1-(2-{4-[(cyclopropyl-methyl-amino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
1.22	4-Benzyloxy-1-[2-(4-[(1-hydroxy-cyclopropylmethyl)-methyl-amino]-methyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
2.1	5-Benzyloxy-2-{2-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one
2.2	5-Benzyloxy-2-{2-[4-(4-hydroxy-4-trifluoromethyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one
2.3	5-Benzyloxy-2-[2-(4-cyclopentylaminomethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
2.4	5-Benzyloxy-2-[2-(4-ethylaminomethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
2.5	5-Benzyloxy-2-{2-[4-(isopropylamino-methyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one
2.6	5-Benzyloxy-2-[2-(4-methylaminomethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
2.7	5-Benzyloxy-2-[2-oxo-2-(4-propylaminomethyl-phenyl)-ethyl]-2H-pyridazin-3-one
3.1	4-Benzyloxy-1-{2-[4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-3-methoxy-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
3.2	4-Benzyloxy-1-[2-(4-dimethylaminomethyl-3-methoxy-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
3.3	4-Benzyloxy-1-{2-[4-(4-hydroxy-piperidin-1-ylmethyl)-3-methoxy-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
4.1	4-Benzyloxy-1-[2-(4-dimethylaminomethyl-2-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
4.2	4-Benzyloxy-1-{2-[2-fluoro-4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one

5.1	4-Benzyloxy-1-[2-(4-dimethylaminomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
5.2	4-Benzyloxy-1-[2-(3-fluoro-4-methylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
5.3	4-Benzyloxy-1-[2-(4-ethylaminomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
5.4	4-Benzyloxy-1-[2-(4-diethylaminomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
5.5	4-Benzyloxy-1-[2-(4-[(ethyl-methyl-amino)-methyl]-3-fluoro-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
5.6	4-Benzyloxy-1-[2-(3-fluoro-4-(isopropylamino-methyl)-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
5.7	4-Benzyloxy-1-[2-(3-fluoro-4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
6.1	5-Benzyloxy-2-[2-(3-fluoro-4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
6.2	5-Benzyloxy-2-[2-(4-dimethylaminomethyl-3-fluoro-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
6.3	5-Benzyloxy-2-[2-(3-fluoro-4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
7.1	4-Benzyloxy-1-[2-(5-diethylaminomethyl-pyridin-2-yl)-2-oxo-ethyl]-1H-pyridin-2-one
7.2	4-Benzyloxy-1-[2-(5-dimethylaminomethyl-pyridin-2-yl)-2-oxo-ethyl]-1H-pyridin-2-one
7.3	4-Benzyloxy-1-[2-(5-ethylaminomethyl-pyridin-2-yl)-2-oxo-ethyl]-1H-pyridin-2-one
7.4	4-Benzyloxy-1-[2-[5-(4-hydroxy-piperidin-1-ylmethyl)-pyridin-2-yl]-2-oxo-ethyl]-1H-pyridin-2-one
7.5	4-Benzyloxy-1-[2-[5-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-2-oxo-ethyl]-1H-pyridin-2-one
8.1	4-(4-Fluoro-benzyloxy)-1-[2-(4-[1-(4-hydroxy-4-methyl-piperidin-1-yl)-ethyl]-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
8.2	4-(4-Fluoro-benzyloxy)-1-[2-(4-[1-(4-hydroxy-piperidin-1-yl)-ethyl]-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
8.3	4-(4-Chloro-benzyloxy)-1-[2-(4-[1-(4-hydroxy-piperidin-1-yl)-ethyl]-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one

8.4	4-(4-Chloro-benzyloxy)-1-(2-{4-[1-(4-hydroxy-4-methyl-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
8.5	1-(2-{4-[1-(4-Hydroxy-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-4-(4-methoxy-benzyloxy)-1H-pyridin-2-one
8.6	1-(2-{4-[1-(4-Hydroxy-4-methyl-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-4-(4-methoxy-benzyloxy)-1H-pyridin-2-one
9.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-{2-[4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
9.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(4-dimethylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
9.3	4-(5-Chloro-pyridin-2-ylmethoxy)-1-{2-[4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-1H-pyridin-2-one
9.4	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(4-pyrrolidin-1-ylmethyl-phenyl)-ethyl]-1H-pyridin-2-one
9.5	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(4-methylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
9.6	4-(5-Chloro-pyridin-2-ylmethoxy)-1-(2-{4-[(ethyl-methyl-amino)-methyl]-phenyl}-2-oxo-ethyl)-1H-pyridin-2-one
9.7	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(4-diethylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
9.8	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(4-piperidin-1-ylmethyl-phenyl)-ethyl]-1H-pyridin-2-one
10.1	5-(5-Chloro-pyridin-2-ylmethoxy)-2-{2-[4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one
10.2	5-(5-Chloro-pyridin-2-ylmethoxy)-2-{2-[4-(4-hydroxy-4-methyl-piperidin-1-ylmethyl)-phenyl]-2-oxo-ethyl}-2H-pyridazin-3-one
11.1	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(4-piperidin-1-ylmethyl-phenyl)-ethyl]-1H-pyridin-2-one
11.2	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(4-dimethylaminomethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
12.1	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-oxo-2-(4-piperidin-1-ylmethyl-phenyl)-ethyl]-2H-pyridazin-3-one
12.2	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(4-dimethylaminomethyl-phenyl)-2-oxo-ethyl]-2H-pyridazin-3-one
13.1	4-Benzyloxy-1-{2-oxo-2-[2-(2,2,2-trifluoro-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-1H-pyridin-2-one

13.2	1-[2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-benzyloxy-1H-pyridin-2-one
14.1	4-Benzyloxy-1-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-1H-pyridin-2-one
14.2	4-Benzyloxy-1-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
15.1	5-Benzyloxy-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
15.2	5-Benzyloxy-2-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-2H-pyridazin-3-one
16.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
16.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
16.3	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
16.4	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
16.5	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
17.1	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
17.2	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-oxo-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
17.3	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
18.1	4-Benzyloxy-1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
18.2	4-Benzyloxy-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
19.1	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
19.2	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
20.1	5-Benzyloxy-2-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
20.2	5-Benzyloxy-2-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-

	3-one
21.1	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
21.2	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
21.3	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
21.4	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-[2-(2-hydroxy-ethyl)-2,3-dihydro-1H-isoindol-5-yl]-ethyl]-2H-pyridazin-3-one
21.5	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
22.1	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
22.2	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
23	4-Benzyloxy-1-[2-[4-(1-dimethylaminomethyl-cyclopropyl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
24.1	4-Benzyloxy-1-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
24.2	4-Benzyloxy-1-[2-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
25.1	5-Benzyloxy-2-[2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
25.2	5-Benzyloxy-2-[2-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
26.1	4-Benzyloxy-1-[2-oxo-2-(5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)-ethyl]-1H-pyridin-2-one
26.2	4-Benzyloxy-1-[2-(6-methyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-3-yl)-2-oxo-ethyl]-1H-pyridin-2-one
27.1	5-Benzyloxy-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
27.2	5-Benzyloxy-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
28.1	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one

28.2	5-(5-Chloro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
29.1	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
29.2	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
30	5-Benzyloxy-2-(2-{4-[2-(4-hydroxy-4-methyl-piperidin-1-yl)-ethyl]-phenyl}-2-oxo-ethyl)-2H-pyridazin-3-one
31.1	1-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-(4-fluoro-benzyloxy)-1H-pyridin-2-one
31.2	4-(4-Fluoro-benzyloxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
32.1	2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-5-(4-fluoro-benzyloxy)-2H-pyridazin-3-one
32.2	5-(4-Fluoro-benzyloxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
33.1	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
33.2	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
34	1-[2-Oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-4-(5-trifluoromethyl-pyridin-2-ylmethoxy)-1H-pyridin-2-one
35.1	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
35.2	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
35.3	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
35.4	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-2H-pyridazin-3-one
35.5	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-2H-pyridazin-3-one
35.6	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-[2-(2-fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl]-2H-pyridazin-3-one
35.7	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-cyclopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one

36.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
36.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
36.3	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
36.4	4-(5-Chloro-pyridin-2-ylmethoxy)-1-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-1H-pyridin-2-one
36.5	4-(5-Chloro-pyridin-2-ylmethoxy)-1-{2-[2-(2-fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-1H-pyridin-2-one
37.1	2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-5-(5-fluoro-pyridin-2-ylmethoxy)-2H-pyridazin-3-one
37.2	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
37.3	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-2H-pyridazin-3-one
38.1	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
38.2	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
38.3	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
38.4	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-1H-pyridin-2-one
38.5	1-{2-[2-(2-Fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-ethyl}-4-(5-fluoro-pyridin-2-ylmethoxy)-1H-pyridin-2-one
39.1	4-(4-Fluoro-benzyloxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
39.2	4-(4-Fluoro-benzyloxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
40.1	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
40.2	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
40.3	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one

41.1	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-oxo-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
41.2	5-(5-Bromo-pyridin-2-ylmethoxy)-2-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
42.1	4-(4-Fluoro-benzyloxy)-1-{2-[2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-1H-pyridin-2-one
42.2	4-(4-Fluoro-benzyloxy)-1-{2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl}-1H-pyridin-2-one
43.1	5-(4-Fluoro-benzyloxy)-2-[2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl]-2H-pyridazin-3-one
44.1	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
44.2	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-1H-pyridin-2-one
45.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
45.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-oxo-ethyl]-1H-pyridin-2-one
46.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
46.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
47.1	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
47.2	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-1H-pyridin-2-one
48	4-Benzyloxy-1-[2-hydroxy-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
49.1	4-(5-Bromo-pyridin-2-ylmethoxy)-1-{2-[2-(2-hydroxy-ethyl)-2,3-dihydro-1H-isoindol-5-yl]-ethyl}-1H-pyridin-2-one
49.2	4-(5-Bromo-pyridin-2-ylmethoxy)-1-{2-[2-(2-fluoro-ethyl)-2,3-dihydro-1H-isoindol-5-yl]-ethyl}-1H-pyridin-2-one
49.3	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2-(2-ethyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
49.4	4-(5-Bromo-pyridin-2-ylmethoxy)-1-{2-[2-(3-hydroxy-1-methyl-propyl)-2,3-dihydro-1H-isoindol-5-yl]-ethyl}-1H-pyridin-2-one

50.1	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
50.2	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
51.1	1-[2-(2,3-Dihydro-1H-isoindol-5-yl)-ethyl]-4-(5-fluoro-pyridin-2-ylmethoxy)-1H-pyridin-2-one
51.2	4-(5-Fluoro-pyridin-2-ylmethoxy)-1-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-1H-pyridin-2-one
52	4-Benzylloxy-1-[2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-allyl]-1H-pyridin-2-one
53	4-Benzylloxy-1-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-1H-pyridin-2-one
54	5-Benzylloxy-2-[2-oxo-2-(4-piperidin-2-yl-phenyl)-ethyl]-2H-pyridazin-3-one
55	4-Benzylloxy-1-[2-[4-(1-methyl-piperidin-2-yl)-phenyl]-2-oxo-ethyl]-1H-pyridin-2-one
56	5-Benzylloxy-2-[2-[4-(1-methyl-piperidin-2-yl)-phenyl]-2-oxo-ethyl]-2H-pyridazin-3-one
57	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
58	4-(5-Bromo-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
59	4-(5-Chloro-pyridin-2-ylmethoxy)-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
60	4-Benzylloxy-1-[2,2-difluoro-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
61	4-Benzylloxy-1-[2,2-difluoro-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one
62	4-Benzylloxy-1-[2-(4-imidazol-1-ylmethyl-phenyl)-2-oxo-ethyl]-1H-pyridin-2-one
63	4-Benzylloxy-1-[2-(4-imidazol-1-ylmethyl-phenyl)-ethyl]-1H-pyridin-2-one
64	4-Benzylloxy-1-[2-[4-(2-oxo-2H-pyridin-1-ylmethyl)-phenyl]-ethyl]-1H-pyridin-2-one
65	2-[2-(2,3-Dihydro-1H-isoindol-5-yl)-ethyl]-5-(5-fluoro-pyridin-2-ylmethoxy)-2H-pyridazin-3-one
66	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-2H-pyridazin-3-one
67	4-(5-Methyl-pyridin-2-ylmethoxy)-1-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-1H-pyridin-2-one

68	4-(5-Methyl-pyridin-2-ylmethoxy)-1-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-1H-pyridin-2-one
69	1-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-4-(5-methyl-pyridin-2-ylmethoxy)-1H-pyridin-2-one
70	1-[2-[2-(2-Fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl]-4-(5-methyl-pyridin-2-ylmethoxy)-1H-pyridin-2-one
71	5-(5-Methyl-pyridin-2-ylmethoxy)-2-[2-oxo-2-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-ethyl]-2H-pyridazin-3-one
72	5-(5-Methyl-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-2H-pyridazin-3-one
73	2-[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-oxo-ethyl]-5-(5-methyl-pyridin-2-ylmethoxy)-2H-pyridazin-3-one
74	2-[2-[2-(2-Fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-2-oxo-ethyl]-5-(5-methyl-pyridin-2-ylmethoxy)-2H-pyridazin-3-one
75	4-Benzyloxy-1-[2-oxo-2-[4-(1-piperidin-1-yl-cyclopropyl)-phenyl]-ethyl]-1H-pyridin-2-one
76	4-Benzyloxy-1-[2-oxo-2-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)-ethyl]-1H-pyridin-2-one
77	4-Benzyloxy-1-[2-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)-2-oxo-ethyl]-1H-pyridin-2-one
78	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one
79	5-(5-Fluoro-pyridin-2-ylmethoxy)-2-[2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-ethyl]-2H-pyridazin-3-one

while in each of the above-mentioned compounds one or more C atoms may additionally be mono- or polysubstituted by F, and in each case one or two C atoms independently of one another may additionally have a substituent selected from the group Cl, Br, cyano, C₁₋₄-alkyl, C₁₋₄-alkoxy, difluoromethyl, trifluoromethyl, hydroxy, acetylamino, aminocarbonyl, difluoromethoxy, and trifluoromethoxy, and

an H atom bound to an N atom may in each case be replaced by a group which can be cleaved *in vivo*,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

2. Physiologically acceptable salts of one or more compounds according to the claim 1.
- 5 3. Composition, containing at least one compound according to claim 1 and/ or a salt according to claim 2, optionally together with one or more physiologically acceptable excipients.
- 10 4. Pharmaceutical compositions, containing at least one compound according to claim 1 and/ or a salt according to claim 2, optionally together with one or more inert carriers and/or diluents.
- 15 5. Use of at least one compound according to claim 1 and/ or a salt according to claim 2, for influencing the eating behaviour of a mammal.
- 20 6. Use of at least one compound according to claim 1 and/or a salt according to claim 2, for reducing the body weight and/ or for preventing an increase in the body weight of a mammal.
- 25 7. Use of at least one compound according to claim 1 and/or a salt according to claim 2, for preparing a pharmaceutical composition with an MCH-receptor-antagonistic activity.
- 30 8. Use of at least one compound according to claim 1 and/or a salt according to claim 2, for preparing a pharmaceutical composition which is suitable for preventing and/or treating symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

9. Use of at least one compound according to claim 1 and/or a salt according to claim 2, for preparing a pharmaceutical composition which is suitable for preventing and/or treating metabolic disorders and/or eating disorders, particularly obesity, bulimia, bulimia nervosa, cachexia, anorexia, anorexia nervosa and hyperphagia.
- 5
10. Use of at least one compound according to claim 1 and/or a salt according to claim 2, for preparing a pharmaceutical composition which is suitable for preventing and/or treating diseases and/or disorders associated with obesity, particularly diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, pathological glucose tolerance, encephalorrhagia, cardiac insufficiency, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.
- 10
11. Use of at least one compound according to claim 1 and/or a salt according to claim 2, for preparing a pharmaceutical composition which is suitable for preventing and/or treating hyperlipidaemia, cellulitis, fat accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affective disorders, depression, anxiety, sleep disorders, reproductive disorders, sexual disorders, memory disorders, epilepsy, forms of dementia and hormonal disorders.
- 15
12. Use of at least one compound according to claim 1 and/or a salt according to claim 2, for preparing a pharmaceutical composition which is suitable for preventing and/or treating micturition disorders, such as for example urinary incontinence, hyperactive urinary bladder, urgency, nycturia and enuresis.
- 20
13. Use of at least one compound according to claim 1 and/or a salt according to claim 2, for preparing a pharmaceutical composition which is suitable for preventing and/or treating dependencies and/or withdrawal symptoms.
- 25
14. Pharmaceutical composition, containing
- 30
- 35 a first active substance which is selected from the compounds according to claim 1

and/or a salt according to claim 2, and

a second active substance selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, preferably other than MCH antagonists, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis, active substances for the treatment of arthritis, active substances for the treatment of anxiety states and active substances for the treatment of depression,

optionally together with one or more inert carriers and/or diluents.

INTERNATIONAL SEARCH REPORT

CORRECTED VERSION

International application No

PCT/EP2009/001081

A. CLASSIFICATION OF SUBJECT MATTER		
INV. C07D213/64	C07D213/69	C07D237/14
C07D401/14	C07D401/12	C07D471/04
A61K31/495		A61K31/435
		A61K31/47
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 A61K		
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, 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.
X	WO 2007/018248 A (BANYU PHARMA CO LTD [JP]; ANDO MAKOTO [JP]; SEKINO ETSUKO [JP]; HAGA Y) 15 February 2007 (2007-02-15) abstract; claim 1	1-14
P,X	WO 2008/022979 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; STENK) 28 February 2008 (2008-02-28) cited in the application abstract; claim 1	1-14
☐ 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 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "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		Date of mailing of the international search report
19 May 2009		- 3 JUN 2009
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Fritz, Martin

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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WO 2007018248	A	15-02-2007	AU 2006277253 A1	15-02-2007
			CA 2618112 A1	15-02-2007
			EP 1916239 A1	30-04-2008

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			AU 2007287601 A1	28-02-2008
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			US 2008255083 A1	16-10-2008
