

**Salt forms of a 6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene derivative,
process for their manufacture and pharmaceutical compositions
containing same**

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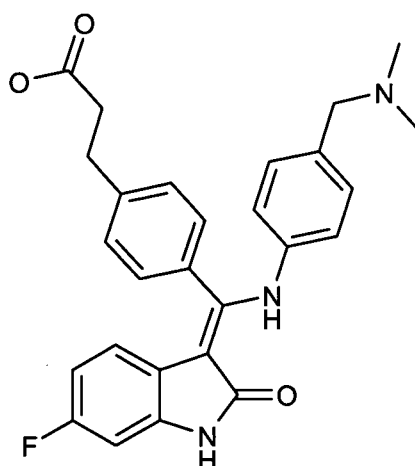
The present invention relates to the salt forms of a 6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene derivative, namely the 4-[(Z)-[[4-
10 [(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid, to a process for their manufacture and to pharmaceutical compositions containing these salts.

The compound 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-
15 dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid is depicted below as Formula I.

Formula I

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25



30 Background to the invention

A number of 2-indolinone derivatives are already known in the prior art. Thus,

for example, International Patent Applications WO 01/27081, WO 04/009546 and WO 04/009547 disclose 2-indolinone derivatives which have valuable pharmacological properties.

- 5 The compound of above formula I is disclosed in WO 04/009546 and WO 04/009547. In WO 04/009547, it is disclosed as example 10.1. A process for the manufacturing of this compound is disclosed in this patent application as well. This manufacturing process is described in WO 04/009547, under Example 10.1 and using the starting material of Example VI.22.

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Like the 2-indolinone derivatives mentioned in the prior art, the compound of above Formula I also has, in particular, an inhibiting effect on various kinases, particularly receptor tyrosine kinases such as VEGFR1, VEGFR2, VEGFR3, PDGFR α , PDGFR β , FGFR1, FGFR3, EGFR, HER2, c-Kit, IGF1R, Flt-3 and

- 15 HGFR, and on the proliferation of cultivated human cells, particularly endothelial cells, e.g. in angiogenesis, but also on the proliferation of other cells, particularly tumour cells.

- The pharmacologically valuable properties of the indolinone derivatives disclosed in the prior art and mentioned above constitute the basic prerequisite for an effective use of these compounds in pharmaceutical compositions. An active substance must in any case satisfy additional requirements in order to be accepted for use as a drug. These parameters are largely connected with the physicochemical nature of the active substance.

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Without being restrictive, examples of these parameters are the preservation of activity of the active substance under various environmental conditions, the stability during production of the pharmaceutical formulation and stability in the final compositions of the active substance or of the drug. The pharmaceutically active substance used to prepare the pharmaceutical compositions should therefore have great stability which is ensured even under all kinds of environmental conditions. This is absolutely essential to prevent pharmaceutical

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compositions being used which contain breakdown products, for example, in addition to the active substance itself. In such a case the content of active substance present in the pharmaceutical formulation might be lower than specified.

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The absorption of moisture reduces the content of pharmaceutically active substance as a result of the increased weight caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from moisture during storage, e.g. by the addition of suitable drying
10 agents or by storing the drug in an environment where it is protected from moisture. In addition, the uptake of moisture may reduce the content of pharmaceutically active substance during manufacture if the pharmaceutical substance is exposed to the environment without being protected from moisture in any way. Preferably, therefore, a pharmaceutically active substance should
15 be only slightly hygroscopic.

As the crystal stability of an active substance is an important factor for maintaining the content of active substance in a preparation stable, there is a need to clarify as far as possible any existing polymorphism of an active
20 substance present in crystalline form. If polymorphic modifications of an active substance occur under certain conditions, care must be taken to ensure that the crystalline modification of the substance does not change in the pharmaceutical preparation later produced from it. Otherwise, this could have a harmful effect on the reproducible potency of the drug. Generally, active substances
25 characterised by only slight polymorphism are thus preferred.

The problem underlying the present invention is thus the provision of a pharmaceutically active substance in an improved form which is not only characterised by high pharmacological potency but also satisfies the above-
30 mentioned physicochemical requirements.

Summary of the invention

This problem is solved by specific salt forms of the compound 4-[(Z)-[[4-
[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-
ylidene)methyl]-benzenepropanoic acid in accordance with the present
5 invention. These specific salt forms are the maleinate, fumarate, citrate,
succinate, tartrate, bromide, sulfate, sodium or chloride. Especially preferred
are the succinate, bromide and chloride salt forms. Most preferred is the
chloride salt form.

10 A first object of the present invention is thus a salt form of the compound 4-[(Z)-
[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-
3-ylidene)methyl]-benzenepropanoic acid, selected from the maleinate,
fumarate, citrate, succinate, tartrate, bromide, sulfate, sodium or chloride.

15 A further object of the present invention is a salt form of the compound 4-[(Z)-
[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-
3-ylidene)methyl]-benzenepropanoic acid, selected from the succinate, bromide
or chloride.

20 A further object of the present invention is the monohydrochloride salt form of
the compound 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-
dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid.

A further object of the present invention is the monohydrochloride crystalline
25 salt form of the compound 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-
fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid.

A further object of the present invention is a process for the manufacture of the
above mentioned salt forms of the compound 4-[(Z)-[[4-
30 [(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-
ylidene)methyl]-benzenepropanoic acid, process which is described hereafter in
the experimental section.

A further object of the present invention is a pharmaceutical composition containing a salt form of the compound 4-[(Z)-[[4-
[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid.

Brief description of the Figures

Figure 1 shows the thermoanalysis and determination of the melting point (DSC), and the determination of the weight loss (TG) of crystalline 4-[(Z)-[[4-
[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid, monohydrochloride.

Figure 2 shows the X-ray powder diffractogram of crystalline 4-[(Z)-[[4-
[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid, monohydrochloride.

Detailed description of the invention

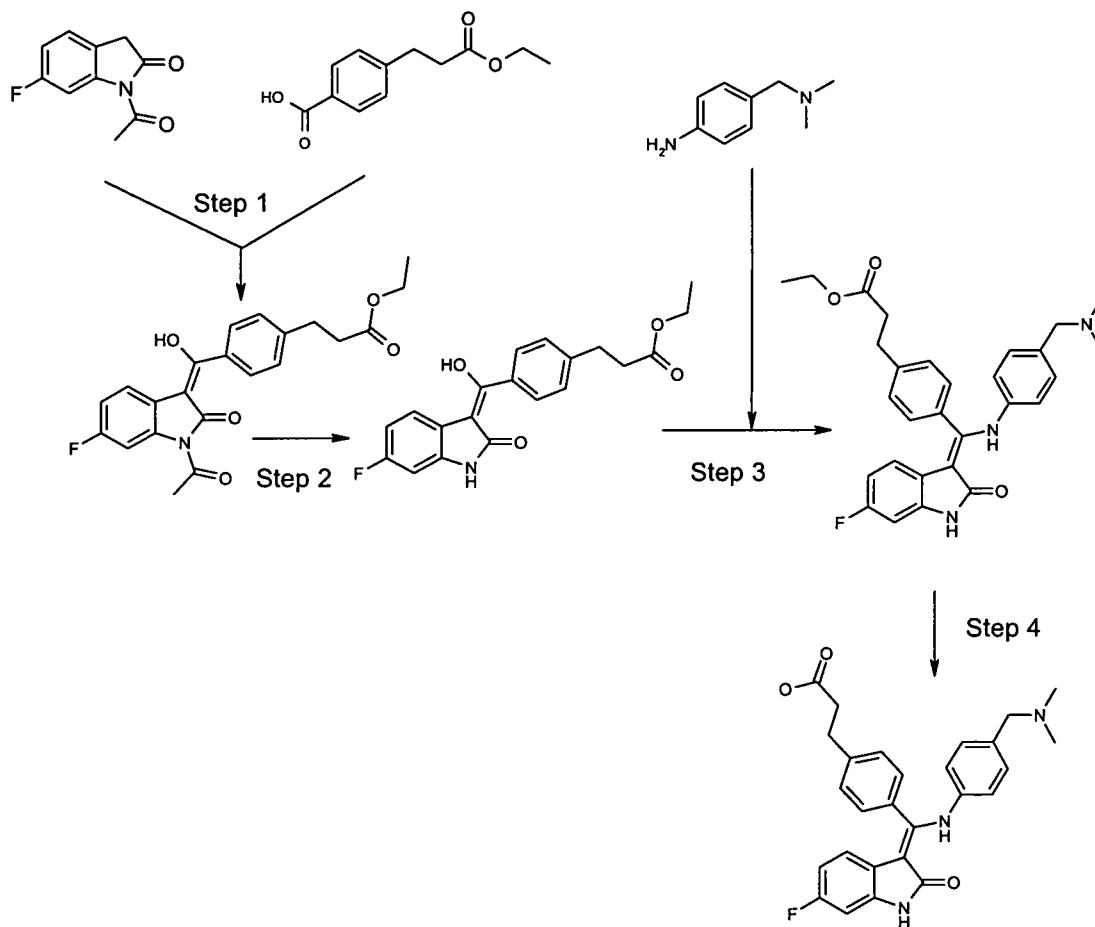
The compound 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid is described in WO 04/009547, however using a different nomenclature, namely 3-Z-[1-(4-dimethylaminomethyl)anilino]-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone. A process for the manufacture of this compound is also described in WO 04/009547, the content of which is incorporated herein by reference.

The manufacturing processes to obtain the compound 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid and the salts of this compound in accordance with the present invention are described in the following.

These processes are illustrative of the present invention and shall not represent

a limitation of the scope of the present invention.

Process for the synthesis of the compound 4-[(Z)-[[4-
 5 [(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-
 indol-3-ylidene)methyl]-benzenepropanoic acid



In the following, the experimental details of the synthesis are described.

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The starting compounds and reagents are all commercially available.

6-fluoro-oxindole (6-fluoro-2-indolinone), CAS 56341-39-0, is commercially available.

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2,5-difluoronitrobenzene, CAS 364-74-9, for the synthetic route described in WO 04/009547 in Examples I – IV, is commercially available.

4-carboxybenzaldehyde, CAS 619-66-9, used for the synthesis of 4-(2-ethoxycarbonylethyl)benzoic acid (preparation analogously to Tetrahedron **1997**, 53, 7335-7340), is commercially available.

5 4-amino-N,N-dimethyl-benzenemethanamine, CAS 6406-74-2, is commercially available.

Synthesis step 1

10 Synthesis of 4-[(E)-(1-acetyl- 6-fluoro-1,2-dihydro-2- oxo-3H-indol-3-ylidene) hydroxymethyl]-benzenepropanoic acid, ethyl ester

This synthesis step is described in WO 04/009547, under Example 10.1 and using the starting material of Example VI.22.

15 4-[(E)-(1-acetyl- 6-fluoro-1,2-dihydro-2- oxo-3H-indol-3-ylidene) hydroxymethyl]-benzenepropanoic acid, ethyl ester, or 1-acetyl-3-[1-hydroxy-1-(4-(2-ethoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone, is prepared from 1-acetyl-6-fluoro-2-indolinone (described in WO 04/009547, under Example V) and 4-(2-ethoxycarbonylethyl)benzoic acid (preparation analogously to Tetrahedron **1997**, 53, 7335-7340).

20

Synthesis step 2

25 Synthesis of 4-[(E)-(6-fluoro-1,2-dihydro-2- oxo-3H-indol-3-ylidene) hydroxymethyl]-benzenepropanoic acid, ethyl ester

25

1.62kg (4.077 mol) 4-[(E)-(1-acetyl-6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)hydroxymethyl]-benzenepropanoic acid, ethyl ester are suspended in 14 L methanol, and 220g (3.873mol) sodium-methoxide are added. After stirring for 1 hour under reflux the solution is cooled to 15°C. 340ml (4.079mol)
30 hydrochloride acid 37% in 3.7 L water is added at 15°C. The obtained precipitate is suction filtered, washed with 8 litres of water/methanol in proportion 1:1 and dried at 60°C.

Yield: 1.29 kg (89% of theory)
T_{m.p.} = 163 °C (DSC 10K/min)
Purity according to HPLC: 95.2% (column: Prontosil 120-3-C18, 3 µm)
5 Empirical formula: C₂₀H₁₈ FNO₄
ESI mass spectrum: m/z = 356 [M+H]⁺

Synthesis step 3

- 10 Synthesis of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid, ethyl ester

3.07kg (4.444 mol) 4-[(E)-(6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)hydroxymethyl]-benzenepropanoic acid, ethyl ester are suspended in
15 7.0 L dioxane. After addition of 1100ml (8.639mol) trimethylsilylchloride and 1.363kg (9.071) 4-amino-N,N-dimethyl-benzenemethanamine, the temperature is raised up to about 30°C. 3.65 L (17.278mol) hexamethyldisilazane and 4.2 L dioxane are added. The mixture is heated to about 100°C and stirred for about 60 hours. After cooling to about 60°C and carefully addition of 12 L ethanol the
20 solvents are evaporated under vacuum. The residue is dissolved in 10 L ethanol under reflux. The solution is cooled to about 8°C and the obtained precipitate is suction filtered, washed with 3.2 litres of ethanol and dried at 45°C under vacuum.

25 Yield: 3.355 kg (79.7% of theory)
T_{m.p.} = 159 °C (DSC 10K/min)
Purity according to HPLC: 99.1% (column: Prontosil 120-3-C18, 3 µm)
Empirical formula: C₂₉H₃₀ FN₃O₃
ESI mass spectrum: m/z = 488 [M+H]⁺

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Synthesis step 4

Synthesis of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid,

1055 g (2.164 mol) of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid, ethyl ester are suspended in 8.9 L of methanol. 4330 ml of 1 mol/l sodium hydroxide solution are added and the mixture is heated to about 70°C. After stirring for another two hours at about 70°C the solution is cooled to about 20°C. 2200ml of 1 mol/l hydrochloride acid is added, the yellow precipitate formed is suction filtered and washed with water. The substance is dried under vacuum at 55 °C.

Yield: 939 g (94.4% of theory),
T_{m.p.} = 176°C
Empirical formula: C₂₇H₂₆ FN₃O₃
ESI mass spectrum: m/z = 460 [M+H]⁺
Water content: 2.5% (KF) direct after drying
6-10% (KF) after equilibration on air

Process for the synthesis of the monohydrochloride salt form of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid

927 g (1.941 mol) of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid are suspended in 9 litres of acetone. 2020 ml (2.02 mol) of hydrochloride acid (1mol/L) are added. After one minute crystallisation sets in. 15 L ethylacetate are added and the obtained suspension is cooled to about -3°C. The yellow precipitate is suction filtered, washed with 2.5 litres of ethylacetate/acetone in proportion 1:1 and dried at 55°C under vacuum.

Yield: 851 g (88.4% of theory)
T_{m.p.} = 282 °C (DSC 10K/min)

Purity according to HPLC: 99.64% (column: Prontosil 120-3-C18, 3 μ m)

Empirical formula: $C_{27}H_{26}FN_3O_3 \times HCl$

ESI mass spectrum: $m/z = 460 [M+H]^+$

Water content: 2.1% (KF)

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Process for the synthesis of the succinate salt form of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid

- 10 2.4 g (5.0 mmol) of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid are suspended in 25 ml of acetone. A solution of 0.7g (5.0 mmol) of succinic acid in 10ml ethanol are added. The suspension is stirred at about 75°C for 1 hour. The suspension is cooled to about 20°C. The yellow precipitate is suction filtered
15 and dried at 40°C.

Yield: 2.6 g (50% of theory)

$T_{m.p.} = 242^\circ C$ (DSC 10K/min)

Empirical formula: $C_{27}H_{26}FN_3O_3 \times C_4H_6O_4$

- 20 ESI mass spectrum: $m/z = 460 [M+H]^+$

Process for the synthesis of the bromide salt form of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid

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- 2.4 g (5.0 mmol) of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid are suspended in 50 ml of acetone. A solution of 0.9 ml (5.0 mmol) of hydrobromide acid 33% diluted with 5ml water is added. After stirring at 50°C for 30 min, 50ml
30 ethylacetat is added and the yellow precipitate is suction filtered and dried at 40°C.

Yield: 2.1 g (78% of theory)
T_{m.p.} = 279 °C (DSC 10K/min)
Empirical formula: C₂₇H₂₆FN₃O₃ x HBr
ESI mass spectrum: m/z = 460 [M+H]⁺

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Process for the synthesis of the maleinate salt form of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid

- 10 5 g (10.5 mmol) of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid are suspended in 45 ml of ethanol. A solution of 1.2g (10.5 mmol) of maleinic acid in 5ml ethanol are added. A clear solution is obtained. After one minute crystallisation sets in. The suspension is stirred at about 20°C for 1 hour. The
- 15 yellow precipitate is suction filtered and dried at 40°C under vakuum.

- Yield: 5.1 g (85% of theory)
T_{m.p.} = 193 °C (DSC 10K/min)
Empirical formula: C₂₇H₂₆FN₃O₃ x C₄H₄O₄
- 20 ESI mass spectrum: m/z = 460 [M+H]⁺

Process for the synthesis of the fumarate salt form of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid

25

- 0.5 g (1.1 mmol) of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid are suspended in 4 ml of ethanol. The suspension was heated at about 75°C and a solution of 0.12g (1.1 mmol) of fumaric acid in 1ml ethanol are added. After
- 30 stirring at 50°C for 30 min the suspension is cooled to about 20°C. The yellow precipitate is suction filtered and dried at 50°C.

Yield: 0.5 g (83% of theory)
Empirical formula: $C_{27}H_{26}FN_3O_3 \times C_4H_4O_4$
ESI mass spectrum: $m/z = 460 [M+H]^+$

- 5 Process for the synthesis of the citrate salt form of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid

0.5 g (1.1 mmol) of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-
10 1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid are
suspended in 4 ml of ethanol. The suspension was heated at about 75°C and a
solution of 0.23g (1.1 mmol) of citric acid in 1ml ethanol are added. A clear
solution is obtained. After one minute crystallisation sets in. The suspension is
15 stirred at about 20°C for 1 hour. The yellow precipitate is suction filtered and
dried at 50°C.

Yield: 0.5 g (71% of theory)
 $T_{m.p.} = 176^\circ C$ (DSC 10K/min)
Empirical formula: $C_{27}H_{26}FN_3O_3 \times C_6H_8O_7$
20 ESI mass spectrum: $m/z = 460 [M+H]^+$

- 25 Process for the synthesis of the tartrate salt form of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid

2.4 g (5.0 mmol) of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-
1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid are
suspended in 25 ml of acetone. A solution of 0.75g (5.0 mmol) of L-tartaric acid
in 10ml ethanol are added. The suspension is stirred at about 55°C for 30 min.
30 The suspension is cooled to about 20°C. The yellow precipitate is suction
filtered and dried at 40°C.

Yield: 2.4 g (46% of theory)
Empirical formula: $C_{27}H_{26}FN_3O_3 \times C_4H_5O_5$
ESI mass spectrum: $m/z = 460 [M+H]^+$

- 5 Process for the synthesis of the sulfate salt form of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid

5 g (10.5 mmol) of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid are
10 suspended in 50 ml of methanol at 58°C. A solution of 1.4g (10.5 mmol) of sodium hydrogen sulphuric acid in 10ml water are added. A clear solution is obtained. After one minute crystallisation sets in. The suspension is stirred at about 20°C for 18 hours. The precipitate is suction filtered and dried at 40°C
15 under vacuum.

Yield: 5.5 g (91% of theory)
 $T_{m.p.} = 264^\circ C$ (DSC 10K/min)
Empirical formula: $C_{27}H_{26}FN_3O_3 \times NaHSO_4$
20 ESI mass spectrum: $m/z = 460 [M+H]^+$

- 25 Process for the synthesis of the sodium salt form of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid

2.4 g (5.0 mmol) of 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid are
suspended in 25 ml of acetone. 5.0ml (5.0 mmol) of sodium hydroxide solution (1mol/L) are added. The dark red suspension is stirred at about 20°C for 18
30 hours. The precipitate is suction filtered and dried at 40°C.

Yield: 2.2 g (91% of theory)

Empirical formula: $C_{27}H_{25}FN_3NaO_3$

ESI mass spectrum: $m/z = 460 [M+H]^+$

5 In the foregoing, the characteristics and properties of the salt forms in accordance with the present invention are discussed.

The monohydrochloride salt form of the compound according to the invention, namely 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid monohydrochloride, is a
10 yellow crystalline powder with irregular shaped crystals. No significant change in crystallinity is observed after intensive milling or compression. In addition it is slightly hygroscopic, but no change in crystal modification is observed.

The crystalline form of the monohydrochloride salt according to the invention is
15 characterised by a melting point of $285^{\circ}\text{C} \pm 5^{\circ}$, as determined by Differential Scanning Calorimetry (DSC; Peak maximum evaluation using a DSC 821 made by Mettler Toledo and a heating rate of $10^{\circ}\text{C}/\text{min}$). The DSC diagram is depicted in Figure 1.

20 The crystalline form of the monohydrochloride salt according to the invention is further characterised by a weight loss of ca. 1,6-1,8% water up to 130°C , as determined by Thermal Gravimetry (TG). Under standard conditions, the monohydrochloride salt form of the compound according to the invention is present in the form of the hemihydrate, from which water escapes at a
25 temperature of about 130°C . The TG diagram is also depicted in Figure 1.

Thus, the monohydrochloride salt form of the compound in accordance with the present invention is a crystalline salt form characterised by a melting point of $T_{m.p.} = 285 \pm 5^{\circ}\text{C}$ (Determined by DSC; Evaluation by peak maximum; Heating
30 rate: $10^{\circ}\text{C}/\text{min}$) and a weight loss of ca. 1,6- 1,8% water up to 130°C (Determined by TG).

The crystalline form of the monohydrochloride salt according to the invention can be further characterised by specific X-ray powder diffraction values. The X-ray powder diffractogram of the crystalline form recorded using a STOE - STADI P-diffractometer in transmission mode fitted with a location-sensitive detector (OED) and a Cu-anode as X-ray source (CuK α radiation, λ = 1,54056 Å , 40kV, 40mA) , is depicted in Figure 2. The following Table I contains the related diffraction values.

Table I

2 θ [°]	d-value [Å]	rel. Int. [%]
3.71	23.82	24
7.41	11.91	4
11.89	7.44	14
12.90	6.86	22
13.00	6.81	25
13.24	6.68	11
13.82	6.40	11
13.97	6.33	7
14.45	6.12	3
15.89	5.57	16
16.45	5.38	4
17.12	5.17	100
17.85	4.97	33
18.02	4.92	9
18.38	4.82	2
18.59	4.77	4
18.90	4.69	2
19.54	4.54	17
19.90	4.46	2
20.33	4.37	2

20.57	4.31	5
20.88	4.25	4
21.33	4.16	3
21.83	4.07	8
22.26	4.00	38
22.68	3.92	51
23.01	3.86	8
23.29	3.82	3
23.68	3.75	9
24.44	3.64	2
24.66	3.61	3
25.12	3.54	6
25.78	3.45	14
26.17	3.40	8
26.52	3.36	8
26.80	3.32	10
27.23	3.27	3
27.75	3.21	6
28.22	3.16	26
29.16	3.06	2
29.51	3.02	6
30.04	2.97	14

In the above Table I the value " 2θ [°]" denotes the angle of diffraction in degrees and the value " d_{hkl} [Å]" denotes the specified distances in Å between
5 the lattice planes.

According to the values shown in the above Table I, the crystalline form of the monohydrochloride salt in accordance with the present invention is crystalline 4-
[(Z)-[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-

indol-3-ylidene)methyl]-benzenepropanoic acid monohydrochloride, characterised by X-ray powder diagram values of $d = 6.81 \text{ \AA}$, $5.17 \text{ \AA}$, $4.92 \text{ \AA}$, $4.00 \text{ \AA}$, $3.92 \text{ \AA}$ and $3.16 \text{ \AA}$ having an intensity of more than 25%.

5 As can be seen from the above results, the monohydrochloride salt form of the compound in accordance with the present invention has unexpectedly good properties for pharmaceutical development and good stability properties, especially a high and sharp melting point, a slight hygroscopicity and a stable crystallinity in the form of an hemihydrate.

10

Although the other salts forms in accordance with the present invention, namely the maleinate, fumarate, citrate, succinate, tartrate, bromide, sulfate or sodium salt forms may as well be suitable for pharmaceutical development, these have less good properties, especially with respect to their crystalline stability and their
15 dissolution.

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For example, the sodium and tartrate salt forms have less good crystallinity properties, which affects the stability of the drug substance. As can be seen by differential scanning calorimetry (DSC), the sodium crystalline salt form shows a
20 dehydration/melting in a broad endothermal reaction up to 110°C and an exothermal recrystallization reaction at 212°C . The tartrate crystalline salt form shows three endothermal reactions at 65°C , 138°C and 167°C and two sharp endothermal reactions at 221°C and 232°C . In comparison, the monohydrochloride crystalline salt form shows a sharp melting point at 285°C ,
25 the succinate crystalline salt form shows a sharp melting point at 242°C and the bromide crystalline salt form shows a sharp melting point at 279°C . The monohydrochloride, the succinate and the bromide crystalline salt forms further show a loss of weight of, respectively, ca. 1.7%, ca. 1.5% and ca. 2.2% as measured by thermal gravimetry (TG), which is characteristic of a slight
30 hygroscopicity, whereas the sodium and tartrate salt forms show a loss of weight of, respectively, ca. 15% and ca. 4.3% as measured by thermal gravimetry (TG), which is characteristic of a strong hygroscopicity. Thus, the

chloride, succinate and bromide salt forms have unexpectedly better crystalline properties for pharmaceutical development than the sodium and tartrate salt forms.

- 5 Furthermore, although all the above mentioned salt forms are characterized by a low solubility over almost the whole pH range, the chloride salt form presents the advantage of a better dissolution rate. Hence, common to the chloride, succinate and bromide salt form is a rather low solubility in aqueous media over a wide pH-range. The succinate and bromide salt forms show in addition also a
10 very slow intrinsic dissolution rate, only the chloride form exhibits an acceptable fast intrinsic dissolution rate.

- Furthermore, the compounds in accordance with the present invention may be used on their own or in conjunction with other pharmacologically active
15 substances.

- Suitable preparations for the pharmaceutical compositions in accordance with the present invention include for example tablets, capsules, suppositories, solutions, elixirs, emulsions or dispersible powders. The proportion of the
20 pharmaceutically active compound(s) should be in the range from 0.01 to 90 wt.-%, preferably 0.1 to 50 wt.-% of the composition as a whole, i.e. in amounts which are sufficient to achieve the dosage necessary to achieve a therapeutic effect. If necessary the doses specified may be given several times a day.

- 25 Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as maize starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl
30 cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number or layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules. An especially suitable pharmaceutical formulation for the compounds in accordance with the present invention is soft gelatine capsules. Suitable soft gelatine capsules for the encapsulation of pharmaceutical compounds and the process for their preparation are described, for example, in GB patent No. 395546, US patent No. 2,720,463, US patent No. 2,870,062, US patent No.

4,829,057, and in the following publications: ANON (Verpack-Rundsch., Vol. 21, No. 1, Jan 1970, pp. 136-138), Lachman et al. (The Theory and Practice of Industrial Pharmacy, Chap. 13, published by Lea & Febiger, 1970), Ebert (Soft Gelatine Capsules: A Unique Dosage Form, reprint from Pharmaceutical Technology, Oct. 1977) and R. F. Jimerson (Soft Gelatine Capsule Update, Drug Development and Industrial Pharmacy, Vol. 12 (8 & 9), pp. 1133-1144, 1986).

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose) emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

The preparations are administered by the usual methods, preferably by oral route, by injection or transdermally. For oral administration the tablets may of course contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tableting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

For parenteral use, solutions of the active substances with suitable liquid carriers may be used.

The dosage for intravenous use is from 1 - 1000 mg per hour, preferably
5 between 5 and 500 mg per hour.

However, it may sometimes be necessary to depart from the amounts specified, depending on the body weight, the route of administration, the individual response to the drug, the nature of its formulation and the time or interval over
10 which the drug is administered. Thus, in some cases it may be sufficient to use less than the minimum dose given above, whereas in other cases the upper limit may have to be exceeded. When administering large amounts it may be advisable to divide them up into a number of smaller doses spread over the
15 day.

The following examples of formulations illustrate the present invention without restricting its scope.

20	A)	<u>Tablets</u>	<u>per tablet</u>
		active substance	100 mg
		lactose	140 mg
		maize starch	240 mg
		polyvinylpyrrolidone	15 mg
25		magnesium stearate	5 mg
			500 mg

The finely ground active substance, lactose and some of the maize starch are
30 mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed

together. The mixture is compressed to produce tablets of suitable shape and size.

B)	<u>Tablets</u>	<u>per tablet</u>
5	active substance	80 mg
	lactose	55 mg
	maize starch	190 mg
	microcrystalline cellulose	35 mg
10	polyvinylpyrrolidone	15 mg
	sodium-carboxymethyl starch	23 mg
	magnesium stearate	2 mg
		400 mg

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The finely ground active substance, some of the maize starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining maize starch and water to form a granulate which is dried and screened. The sodium carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

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Claims

1. Salt form of the compound 4-[(Z)-[[4-
5 [(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid selected from the maleinate, fumarate, citrate, succinate, tartrate, bromide, sulfate, sodium or chloride.
2. Salt form in accordance with claim 1, selected from the succinate,
10 bromide or chloride.
3. Salt form in accordance with claim 1 or 2, selected from the 4-[(Z)-[[4-
[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid, monohydrochloride.
15
4. 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid, monohydrochloride hemihydrate in crystalline form.
- 20 5. 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid, monohydrochloride hemihydrate in crystalline form in accordance with claim 4, characterised by a melting point of $T_{m.p.} = 285 \pm 5^{\circ}\text{C}$ (determined by Differential Scanning Calorimetry; evaluation using peak-maximum; heating rate: $10^{\circ}\text{C}/\text{min}$).
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6. 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid, monohydrochloride hemihydrate in crystalline form in accordance with claim 4, characterised by an X-Ray Powder Diagram showing the characteristic values $d = 6.81 \text{ \AA}$, $5.17 \text{ \AA}$,
30 $4.92 \text{ \AA}$, $4.00 \text{ \AA}$, $3.92 \text{ \AA}$ and $3.16 \text{ \AA}$ with an intensity of more than 25%.
7. Pharmaceutical composition containing the monohydrochloride salt of the

compound 4-[(Z)-[[4-[(dimethylamino)methyl]phenyl]amino](6-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-benzenepropanoic acid, and one or more inert carriers and/or diluents.