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(54) **Ciklikus n,n'-diariltiokarbamidok és n,n'-diarilkarbamidok mint androgén receptor antagonisták, rákellenes szerek, ezek előállítására szolgáló eljárás és alkalmazásuk**

Az európai szabadalom ellen, megadásának az Európai Szabadalmi Közlönyben való meghirdetésétől számított kilenc hónapon belül, felszólalást lehet benyújtani az Európai Szabadalmi Hivatalnál. (Európai Szabadalmi Egyezmény 99. cikk(1))

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**A61K 9/08** (2006.01) **A61P 35/00** (2006.01)

(54) **Cyclic n,n'-diarylthioureas and n,n'-diarylureas as androgen receptor antagonists, anti-cancer agent, method for producing and using same**

Zyklische N,N'-Diarylthioharnstoffe und N,N'-Diarylharnstoffe als Androgenrezeptorantagonisten, Antikrebsmittel damit sowie Verfahren zu ihrer Herstellung und Verwendung

Cycliques de N,N'-diarylthioureas et N,N'-diarylureas comme antagonistes du récepteur d'androgènes, agent anticancéreux, procédé de production et d'utilisation de celui-ci

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(56) References cited:  
**WO-A1-2006/124118 WO-A2-2007/127010 FR-A1- 2 715 402**

• **CHRIS TRAN ET AL: "Development of a second-generation antiandrogen for treatment of advanced prostate cancer", SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, US, vol. 324, no. 5928, 8 May 2009 (2009-05-08), pages 787-790, XP002696684, ISSN: 1095-9203, DOI: 10.1126/SCIENCE.1168175 [retrieved on 2009-04-09]**

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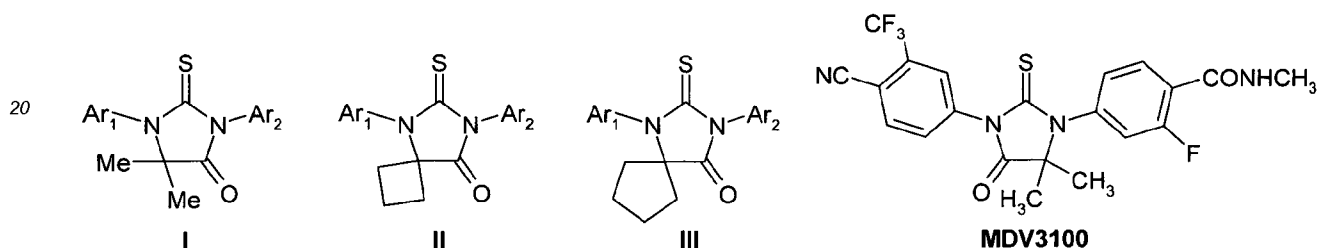
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**Description****Field of the invention**

5 **[0001]** The invention relates to novel cyclic N,N'-diarylthioureas and N,N'-diarylhureas - androgen receptor antagonists, anticancer agent, pharmaceutical composition, and medicament for treatment of cancer including prostate cancer.

**Prior art**

10 **[0002]** There are known androgen receptor antagonists which are -1,3-diaryl-5,5-dimethyl-2-thioxoimidazolidin-4-ones **I**, 5,7-diaryl-6-thioxo-5,7-diazaspiro[3,4]octan-8-ones **II** and 1,3-diaryl-2-thioxo-1,3-diazaspiro[4,4]nonan-4-ones **III** exhibiting anticancer activity [WO2006124118, WO2007127010]. Amongst these compounds the most promoted is 4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]-2-fluoro-N-methylbenzamide **MDV3100** (androgen receptor antagonist with IC<sub>50</sub> = 36 nM), which is now in the III phase of clinical trials as medicament for prostate cancer treatment [Drug Data Rep., 2009, 31(6), 609].



30 **[0003]** Searching for highly effective anticancer medicaments exhibiting enhanced activity and reduced toxicity, is still one of the main directions in the development of novel pharmacological remedies for cancer treatment, including prostate cancer. In this context the development of novel anticancer active agents, pharmaceutical compositions and medicaments, and also methods for their preparation and use is of essential importance.

**Disclosure of the invention**

35 **[0004]** In the context of the invention, the terms are generally defined as follows: "**Azaheterocycle**" means an aromatic or non aromatic mono- or poly- cyclic system, comprising at least one nitrogen atom in the cycle. Azaheterocycle may have one or more "cyclic system" substituents.

**[0005]** "**Active component**" (drug-substance) means a physiologically active compound of synthetic or other origin (biotechnological, vegetable, animal, microbe and so on), exhibiting pharmacological activity and being an active component of pharmaceutical composition, employing in production and preparation of medicaments.

40 **[0006]** "**Alkyl**" means an aliphatic hydrocarbon straight or branched chain with 1-12 carbon atoms. Branched means an alkyl chain with one or more "lower alkyl" substituents. Alkyl group may have one or more substituents of the same or different structure ("alkyl substituent") including halogen, alkenyloxy, cycloalkyl, aryl, heteroaryl, heterocyclyl, aroyl, cyano, hydroxy, alkoxy, carboxy, alkynyloxy, aralkoxy, aryloxy, aryloxycarbonyl, alkylthio, heteroarylthio, aralkylthio, arylsulfonyl, alkylsulfonylheteroaralkyloxy and so on.

45 **[0007]** "**Antagonists**" mean ligands which being bound to definite receptors not cause active cellular responses. Antagonists prevent linkage between agonists and receptors and by that block specific receptor signal transmission.

**[0008]** "**Aryl**" means aromatic mono- or poly- cyclic system with 6 - 14 carbon atoms, predominantly 6-10 carbon atoms. Aryl may have one or more "cyclic system substituents" of the same or different structure. Phenyl, substituted phenyl, naphthyl, or substituted naphthyl are the representatives of aryl groups. Aryl could be annelated with nonaromatic cyclic system or heterocycle.

50 **[0009]** "**Heterocyclyl**" means aromatic or saturated mono- or polycyclic system with 3 - 10 carbon atoms, preferably from 5 to 6, wherein one or more carbon atoms are substituted by one or more heteroatoms, such as N, S or O. Prefix "aza", "oxa" or "thia" before "heterocyclyl" means that N, O or S atoms are introduced in the cycle, respectively. Heterocyclyl may have one or more "cyclic system substituents" of the same or different structure. N- and S- atoms of heterocyclyl cycle could be oxidized to N-oxide, S-oxide or S-dioxide. Piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxane-2-yl, tetrahydrofuranyl, tetrahydrothiophenyl and others are examples of heterocyclyl.

55 **[0010]** "Hydrate" means stoichiometric or nonstoichiometric compositions of compounds or their salts with water.

**[0011]** "**Substituent**" means a chemical radical attached to scaffold (fragment), for example, "alkyl substituent", "amino group substituent", "carbamoyl substituent", and "cyclic system substituent", the meanings of which are defined in this

section. "**Medicament**" - is a compound (or mixture of compounds in the form of pharmaceutical composition) in the form of tablets, capsules, injections, ointments and other ready forms intended for restoration, improvement or modification of physiological functions at humans and animals, and also for treatment and prophylaxis of diseases, diagnostics, anesthesia, contraception, cosmetology and others.

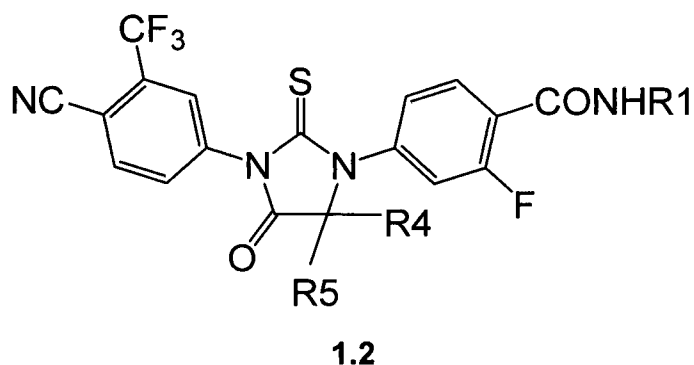
5 **[0012]** "**Lower alkyl**" means a straight or branched alkyl with 1-4 carbon atoms. "**Pharmaceutical composition**" means a composition comprising a compound of general formula **1** and at least one of components selected from the group consisting of pharmaceutically acceptable and pharmacologically compatible fillers, solvents, diluents, auxiliary, distributing and sensing agents, delivery agents, such as preservatives, stabilizers, disintegrators, moisteners, emulsifiers, suspending agents, thickeners, sweeteners, flavouring agents, aromatizing agents, antibacterial agents, fungicides, lubricants, and prolonged delivery controllers, the choice and suitable proportions of which depend on the nature and way of administration and dosage. Examples of suitable suspending agents are ethoxylated isostearyl alcohol, polyox-

10 **[0013]** tragacant and their mixtures as well. Protection against the action of microorganisms can be provided by various antibacterial and antifungal agents, such as, for example, parabens, chlorobutanol, sorbic acid, and similar compounds. Composition may also contain isotonic agents, such as, for example, sugar, sodium chloride, and similar compounds. Prolonged effect of composition may be achieved by agents slowing down absorption of active ingredient, for example, aluminum monostearate and gelatine. Examples of suitable carriers, solvents, diluents and delivery agents include water, ethanol, polyalcohols and their mixtures, natural oils (such as olive oil) and organic esters (such as ethyl oleate) for injections. Examples of fillers are lactose, milk-sugar, sodium citrate, calcium carbonate, calcium phosphate and the like. Examples of disintegrators and distributors are starch, alginic acid and its salts, and silicates. Examples of suitable lubricants are magnesium stearate, sodium lauryl sulfate, talc and polyethylene glycol of high molecular weight. Pharmaceutical composition for peroral, sublingual, transdermal, intramuscular, intravenous, subcutaneous, local or rectal administration of active ingredient, alone or in combination with another active compound may be administered to humans and animals in standard administration form, or in mixture with traditional pharmaceutical carriers. Suitable standard administration forms include peroral forms such as tablets, gelatin capsules, pills, powders, granules, chewing-gums and peroral solutions or suspensions, sublingual and transbuccal administration forms; aerosols; implants; local, transdermal, subcutaneous, intramuscular, intravenous, intranasal or intraocular forms of introduction and rectal administration forms. Pharmaceutical compositions are usually prepared by means of standard procedures by mixing an active compound with liquid or overgrounded solid carrier.

25 **[0014]** "**Pharmaceutically acceptable salt**" means a relatively nontoxic both organic and inorganic salts of acids and bases disclosed in this invention. Salts could be prepared **in situ** in processes of synthesis, isolation or purification of compounds or be prepared specially. In particular, bases salts could be prepared starting from purified base of disclosed compound and suitable organic or mineral acid.

30 **[0015]** Examples of salts prepared in this manner include hydrochlorides, hydrobromides, sulfates, bisulfates, phosphates, nitrates, acetates, oxalates, valerates, oleates, palmitates, stearates, laurates, borates, benzoates, lactates, p-toluenesulfonates, citrates, maleates, fumarates, succinates, tartrates, methane sulphonates, malonates, salicylates, propionates, ethane sulphonates, benzene sulfonates, sulfamates and the like (Detailed description of properties of such salts is given in: Berge S.M., et al., "Pharmaceutical Salts" J.Pharm.Sci., 1977, 66: 1-19). Salts of disclosed acids may be also prepared by reaction of purified acids specifically with suitable base; moreover, metal salts and amine salts may be synthesized too. Metal salts are salts of sodium, potassium, calcium, barium, magnesium, zink, lithium and aluminum, sodium and potassium salts being preferred. Suitable inorganic bases from which metal salts can be prepared are sodium hydroxide, carbonate, bicarbonate and hydride; potassium hydroxide, carbonate and bicarbonate, lithium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide. Organic bases suitable for preparation of disclosed acid salts are amines and amino acids of sufficient basicity to produce stable salt suitable for medical purposes use (in particular, they are to have low toxicity). Such amines include ammonia, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, benzylamine, dibenzylamine, dicyclohexylamine, piperazine, ethylpiperidine, tris(hydroxymethyl)aminomethane and the like. Besides, salts can be prepared using some tetraalkylammonium hydroxides, such as holine, tetramethylammonium, tetraethylammonium, and the like. Aminoacids may be selected among main aminoacids - lysine, ornithine and agrinine.

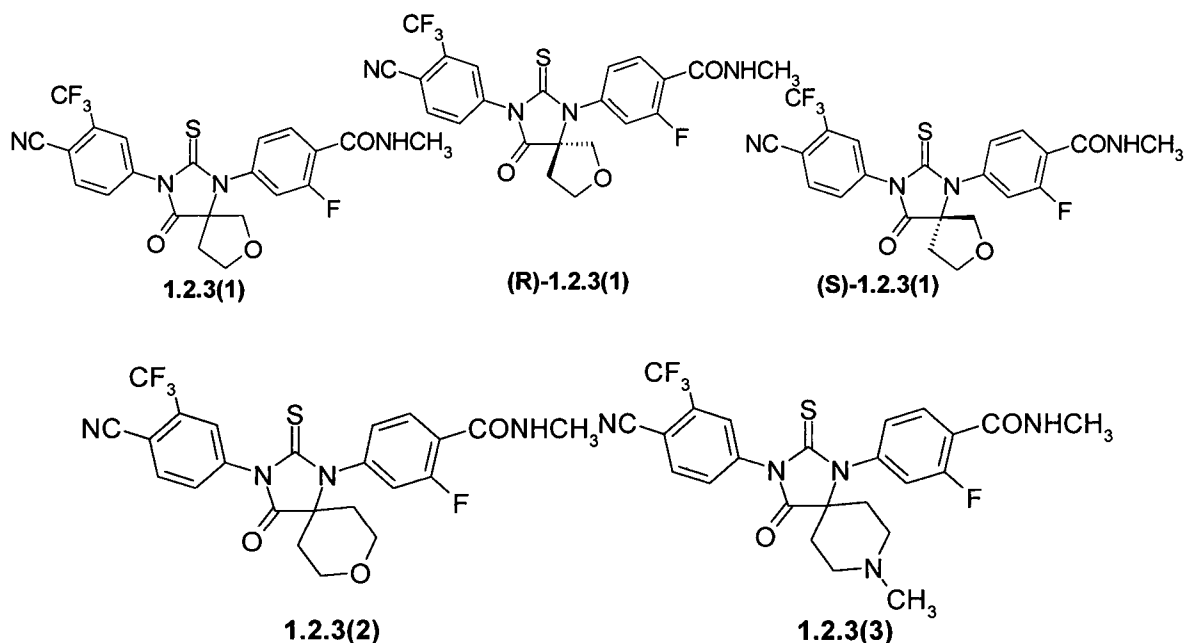
45 **[0016]** The authors have disclosed novel cyclic N,N'-diarylthioureas and N,N'-diarylureas of the general formula **1.2**, optical (R)- and (S)- isomers and pharmaceutically acceptable salts thereof which are androgen receptor antagonists:



wherein:

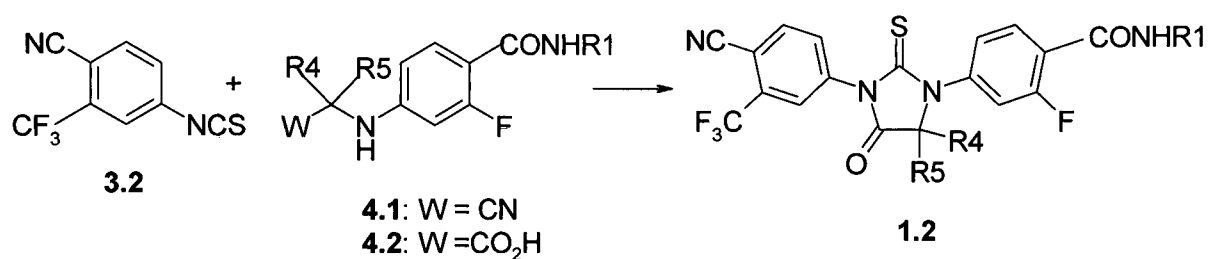
15 **R5** and **R4** together with the C-atom to which they are attached form a 5- or 6-membered heterocycle comprising at least one oxygen atom or nitrogen atom optionally substituted with methyl.

20 **[0017]** The preferred compounds are compounds of formulas **1.2.3(1)**, **1.2.3(2)** and **1.2.3(3)**, their optical (R)-isomers - (R)- **1.2.3(1)**, and (S)-isomers - (S)-**1.2.3(1)**, or a pharmaceutically acceptable salt thereof,



45 **[0018]** Subject of the present invention is also a method for preparation of compounds of the general formula **1.2** and optical (R)- and (S)- isomers thereof.

**[0019]** 1,3-Diarylhydantoines of the general formula **1.2** are prepared by interaction of isothiocyanate **3.2** with the corresponding 4-(cyanomethyl)aminobenzamides **4.1** or (4-carbamoylphenylamino) acetic acids **4.2** according to scheme 1.





**[0028]** According to the present invention the carriers used in pharmaceutical compositions represent carriers which are applied in the sphere of pharmaceuticals for preparation of commonly used forms including: binding agents, greasing agents, disintegrators, solvents, diluents, stabilizers, suspending agents, colorless agents, taste flavors are used for peroral forms; antiseptic agents, solubilizers, stabilizers are used in the forms for injections; base materials, diluents, greasing agents, antiseptic agents are used in local forms.

**[0029]** The pharmaceutical compositions according to the invention can be prepared by mixing novel anti-cancer agent with an inert excipient and/or solvent, the distinctive feature of which consists in utilization as anticancer agent, at least, one cyclic N,N'-diarylthiourea or N,N'-diarylurea of the general formula 1, its optically active isomer or pharmaceutically acceptable salt.

The subject of the present invention is also a medicament in the form of tablets, sheaths or injections including novel anticancer agent or a novel pharmaceutical composition intended for cancer treatment.

**[0030]** The preferred medicament including novel anticancer agent or novel pharmaceutical composition is a medicament intended for use in the treatment of prostate cancer.

**[0031]** Thus, the compounds of the present invention are suitable for use as a medicament, for use in treating cancer, preferably prostate cancer.

**[0032]** Therapeutic cocktails for treatment of cancer diseases, among them prostate cancer, may include as one of the components the novel medicament or the novel pharmaceutical composition, comprising as active component at least one cyclic N,N'-diarylthiourea or N,N'-diarylurea of the general formula 1.2, its optically active isomer or pharmaceutically acceptable salt.

**[0033]** Therapeutic cocktails for treatment of prostate cancer, along with the medicament disclosed in the invention, may include other known drug substances intended for treatment cancer diseases.

**[0034]** Treatment of oncologic diseases, among them, prostate cancer, at humans and warm-blooded animals consists in introduction to human or warm-blooded animal of the novel medicament, the novel pharmaceutical composition or the novel therapeutic cocktail.

**[0035]** Medicaments could be administered perorally or parenterally, for example, intravenously, subcutaneously, intraperitoneally or locally. The clinical dosage of the active component of the general formula 1.2 could be corrected depending on: therapeutic efficiency and bioavailability of the active ingredients in organism, rate of their exchange and deducing from organism, and also depending on the age, sex and the severity of the patient's symptoms; the daily dosage for adults falls within the range of about 10 to about 500 mg of the active ingredient, preferably of about 50 to about 300 mg. Therefore, according to the present invention in the process of preparation of a medicament from the pharmaceutical composition as units of dosage it is necessary to keep in mind the above effective dosage, so that each unit of dosage should contain of about 10 to about 500 mg of the compound of the general formula 1.2, preferably 50 ~ 300 mg. In accordance with the recommendation of physician or pharmacist the above dosage can be taken several times during the definite time intervals (preferably - from one to six times).

### Best Embodiment of the invention

**[0036]** The invention is illustrated by the following drawings.

**Fig.1.** Weight change of male mice at peroral introduction of compound **1.2.2(1)** (not according to the invention).

**Fig.2.** Weight change of male mice at peroral introduction of compound **MDV3100**. The examples given below describe synthesis of N,N'-diarylthioureas and N,N'-diarylureas and data of their biological investigation, which illustrate but not limit the scope of the invention.

### Example 1

**[0037]** Synthesis of *N*-methyl-4-{4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-hydantoin-1-yl}-2-fluorobenzamides **1.2.3** (general method). Solution of the corresponding *N*-methyl-2-fluoro-4-[(1-cyanomethyl)amino]benzamide **4.1** (0.75 mmol) and 4-isothiocyanato-2-(trifluoromethyl)benzonitrile **3.2** (342 mg, 1.5 mmol) in DMF (3 ml) was stirred at 110 °C for 12 h in microwave oven. The reaction mixture was dissolved in MeOH (30 ml), 1N HCl (7.5 ml) was added and the resultant mixture was boiled for 1.5 h. The solution was evaporated in *vacuo*, treated with water, the solid was filtered off, washed with water and dried in *vacuo*. The product was isolated by HPLC method. It gave:

*N*-methyl-4-{4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-7-oxa-1,3-diazaspiro[4.4]non-1-yl}-2-fluorobenzamide **1.2.3(1)**,  $K_i^{1.2.3(1)} = 33.9$  nM. LCMS (M+H)<sup>+</sup> 493. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): 8.30 (t, *J* = 8.4 Hz, 1 H), 8.02 (d, *J* = 8.4 Hz, 1 H), 7.98 (d, *J* = 1.6 Hz, 1 H), 7.85 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 7.34 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 7.25 (dd, *J*<sub>1</sub> = 11.8 Hz, *J*<sub>2</sub> = 1.6 Hz, 1 H), 6.78 (q, *J* = 4.4 Hz, 1 H), 4.43 (d, *J* = 10.0 Hz, 1 H), 4.16 (d, *J* = 10.0 Hz, 1H), 3.96 (m, 1 H), 3.75 (m, 1 H), 3.09 (d, *J* = 4.4 Hz, 3H), 2.74 (m, 1 H), 2.48 (m, 1 H);

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*N*-methyl-4-{4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-8-oxa-1,3-diazaspiro[4.5]dec-1-yl}-2-fluorobenzamide **1.2.3(2)**. LCMS (M+H)<sup>+</sup> 507. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): 8.32 (t, *J* = 8.4 Hz, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.95 (s, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.20 (d, *J* = 8.4 Hz, 1 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 6.73 (br. m, 1 H), 4.18 (m, 2H), 3.94 (m, 2H), 3.09 (d, *J* = 4.4 Hz, 3H), 2.07 (m, 4H);

*N*-methyl-4-{8-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-1,3,8-triazaspiro[4.5]dec-1-yl}-2-fluorobenzamide **1.2.3(3)**.  $K_i^{1.2.3(3)} = 39.2$  nM,  $IC_{50} = 170$  nM. LCMS (M+H)<sup>+</sup> 520. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): 10.09 (br. s, 1H), 8.48 (q, *J* = 4.4 Hz, 1 H), 8.43 (d, *J* = 8.4 Hz, 1 H), 8.29 (s, 1 H), 8.11 (d, *J* = 8.4 Hz, 1 H), 7.84 (t, *J* = 8.0 Hz, 1 H), 7.42 (d, *J* = 10.4 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 3.50 (m, 4H), 2.80 (d, *J* = 4.4 Hz, 3H), 2.78 (s, 3H), 2.72 (d, *J* = 14.0 Hz, 1 H), 2.16 (m, 2H).

### Example 2

**[0038]** Determination of antagonistic activity of cyclic *N,N'*-diarylthioureas and *N,N'*-diarylureas of the general formula **1** and their analog **MDV3100** towards androgen receptors. The ability of novel cyclic *N,N'*-diarylthioureas and *N,N'*-diarylureas of the general formula **1.2** and **MDV3100** agent to block androgen receptors was determined by their effectiveness of inhibition of dihydrotestosterone stimulated expression of prostate specific antigen (PSA) in cancer cells of human prostrate LNCap, derived from the American Tissue Culture Collection (ATCC, USA). These cells are sensitive towards 5- $\alpha$ -dihydrotestosterone (DHT) and in its presence produce cancer markers (PSA). The cells were cultured in RPMI 1640 medium (Invitrogen, USA) containing 10% calf serum (Hyclone, USA), 1% antibacterial/antifungal mixture (Sigma, USA) and 4,5% glucose. Before the experiment the cells were washed and suspended in the same medium in which, however, instead of calf serum the serum which had been treated with charcoal for removal of hormone traces was used. The cells were embedded into wells of 96-well plates by 100  $\mu$ l per cell (10 000 cells) and left for 4 days in incubator at 37°C (100% humidity) in atmosphere of 95% air/5% CO<sub>2</sub>. After incubation cyclic *N,N'*-diarylthioureas or *N,N'*-diarylureas of the general formula **1.2** were added to the cells in various concentrations, and then - 20nM DHT (concentration corresponding to 80-90% of maximum stimulation). The cells were left for 5 days for additional incubation under the same conditions. After that the samples of supracellular medium were taken on analysis for PSA content. The test was carried out according to the protocol, recommended by manufacturer of the kit for determination of PSA (Alpha Diagnostic International, USA). After wetting the wells containing PSA antibodies attached to their bottom to each well 25  $\mu$ l of the tested compounds and 100  $\mu$ l of PSA antibodies conjugated previously with horseradish peroxidase were added successively.

**[0039]** After incubation at room temperature for 30 minutes, the contents of the wells were removed, the wells were washed several times, and then 100  $\mu$ l of chromogenic substrate of peroxidase was added to each well. Plates were held for 15 min. at room temperature, after that 50  $\mu$ l of stop solution was added to every well; at that a dye is formed the absorption intensity of which was measured at 450 nM; the value obtained is proportional to PSA concentration in the sample. Based on the dependence of lowering of PSA synthesis, caused by dihydrotestosterone (DHT), on the concentration of the tested compounds, dose-response curves were plotted, from which  $IC_{50}$  values were determined. They were used for calculation of the values of apparent inhibition constants ( $K_i$ ) for the compounds of the general formula **1** according to Cheng-Prusoff equation. [Cheng, Y., Prusoff, W. H. "Relationship between the inhibition constant ( $K_i$ ) and the concentration of inhibitor which causes 50 per cent inhibition ( $IC_{50}$ ) of an enzymatic reaction". *Biochem Pharmacol.* (1973) 22, 3099-3108];

$$K_i = IC_{50}/(1+L/K_D),$$

wherein L - agonist concentration (DHT),  $K_D$  - receptor activation constant, numerically equal to  $EC_{50}$  value, which is determined in every experiment according to dependence of stimulation of PSA synthesis on DHT concentration.

**[0040]** The data obtained given in the corresponding examples testify that novel androgen receptor antagonists, in some cases, are more active than MDV3100, tested under the same conditions as a compound for comparison, for which  $K_i^{MDV3100} = 79.5$  nM.

### Example 3

**[0041]** Determination of maximum tolerated dose of novel antagonists **1.2.2(1)** (not according to the invention), and **1.2.3(3)** and its analog **MDV3100**. Maximum tolerated dose (MTD) of novel antagonists **1.2.2(1)** (not according to the invention) and **1.2.3(3)** and its analog **MDV3100** were determined in experiments on male mice of CD1 line at peroral administration 1 time a day within 5 days in doses 10, 30 and 100 mg/kg. The compound was dissolved in sterile water with addition of Twin-80. Sterile water with Twin-80 was introduced to control animals (Placebo group). Body weight

was appreciated, and also animals' mortality rate. Statistical comparison of groups was carried out according to non-parametric test ANOVA, with the use of Statistica programme.

[0042] At the introduction of compounds **1.2.2(1)** (not according to the invention) or **1.2.3(3)** in dose up to 100 mg/kg mice death was not observed. On the 3rd - 4th day body weight of mice in the group, received the tested compound in dose 100 mg/kg was less in comparison with the body weight of control animals, however, statistical significance at this was not observed (fig. 1). The data show that compound **1.2.2(1)** (not according to the invention) and **1.2.3(3)** has MTD > 100 mg/kg.

At the introduction of **MDV3100** in doses 10 and 30 mg/kg mice death was not observed. In the group of mice to which the tested compound was introduced in dose 100 mg/kg, the body weight began to lower on the 3<sup>rd</sup> day. On the 5<sup>th</sup> day body weight of this group of animals statistically differed from body weight of animals from Placebo group (p=0,002, fig. 2). One animal died. The data show that compound **MDV3100** has MTD ~ 30 mg/kg.).

**Example 4** (not according to the invention)

[0043] Preparation of medicament in the form of tablets. Starch (1600 mg), grained lactose (1600 mg), talcum (400 mg) and *N*-methyl-4-[5-methyl-5-(methoxymethyl)-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-imidazolidin-1-yl]-2-fluorobenzamide (**R**)-**1.2.2(1)** (1000 mg) mixed together and pressed in a brick. Prepared brick was crushed to granules and riddled through sieves, gathering granules of 14-16 mesh size. The obtained granules were pelletised in tablets of suitable form of 560 mg by weight each.

**Example 5** (not according to the invention)

[0044] Preparation of medicament in the form of capsules. *N*-Methyl-4-[5-methyl-5-(methoxymethyl)-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-imidazolidin-1-yl]-2-fluorobenzamide (**R**)-**1.2.2(1)** was carefully mixed with lactose powder in ratio 2 : 1. The prepared pharmaceutical composition was packed on 300 mg into gelatinous capsules of suitable size.

**Example 6** (not according to the invention)

[0045] Preparation of medicament in the form of compositions for intramuscular, intraperitoneal or hypodermic injections. *N*-Methyl-4-[5-methyl-5-(methoxymethyl)-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-imidazolidin-1-yl]-2-fluorobenzamide (**R**)-**1.2.2(1)** (500 mg) was dissolved in the mixture of chlorobutanol (300 mg), propylene glycol (2 ml), and water for injections (100 ml). The prepared solution was filtered and placed in 1 ml ampoules which were sealed up and sterilized in an autoclave.

### Industrial applicability

[0046] The present invention could be used in medicine, veterinary, biochemistry.

### Example 1

[0047] Synthesis of *N*-methyl-4-[4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl]-2-fluorobenzamide **1.2(1)**. Glycine (80 mg, 1.07 mmol) and K<sub>2</sub>CO<sub>3</sub> (207 mg, 1.5 mmol) were added to solution of 4-iodo-*N*-methyl-2-fluorobenzamide (279 mg, 1 mmol) in DMF (3 ml). The reaction mixture was stirred at 140°C for 18 min. in microwave oven, cooled, diluted with AcOEt (10 ml) and water (10 ml), neutralized with HCl to pH 2-3, organic layer was separated, water layer was extracted with AcOEt (5 x 20 ml). The combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in *vacuo*. The product was isolated by column chromatography on SiO<sub>2</sub>. It gave *N*-(4-methylcarbamoyl-2-fluorophenyl)glycine **4.2(1)** (R1=CH<sub>3</sub>, R4=R5=H). A solution of *N*-(4-methylcarbamoyl-2-fluorophenyl)glycine **4.2(1)** (113 mg, 0.5 mmol) and 4-isothiocyanato-2-(trifluoromethyl)benzimidazole **3.2** (174 mg, 1.0 mmol) in DMF (2 ml) was stirred at 90°C for 12 h. The reaction mixture was evaporated in *vacuo*, and *N*-methyl-4-[4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-imidazolidin-1-yl]-2-fluorobenzamide **1.2(1)**, was isolated by HPLC method, LCMS (M+H)<sup>+</sup> 437.

### Example 2

[0048] General method for synthesis of *N*-methyl-4-[5-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl]-2-fluorobenzamide **1.2(2)**, *N*-methyl-4-[(S)-5-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl]-2-fluorobenzamide (**S**)-**1.2(2)** and *N*-methyl-4-[(R)-5-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl]-2-fluorobenzamide (**R**)-**1.2(2)**.

(D,L)-, (D)- or (L)-Alanine (347 mg, 7.8 mmol) and  $\text{Cs}_2\text{CO}_3$  (2.54 g, 7.8 mmol) were added to the solution of *N*-methyl-2,4-difluorobenzamide (667 mg, 3.9 mmol) in DMSO (3 ml). The reaction mixture was stirred in closed vial at 90°C for 18 h. Cooled mixture was diluted with isopropanol, neutralized with HCl (1.36 ml, 15.6 mmol), filtered, evaporated in *vacuo*, and by HPLC method *N*-(4-methylcarbamoyl-3-fluorophenyl)alanine **4.2(2)** ( $\text{R}1=\text{CH}_3$ ,  $\text{R}4=\text{H}$ ,  $\text{R}5=\text{CH}_3$ ), (**S**)-*N*-(4-methylcarbamoyl-3-fluorophenyl)alanine (**S**)-**4.2(2)** or (**R**)-*N*-(4-methylcarbamoyl-3-fluorophenyl)alanine (**R**)-**4.2(2)** were isolated. LCMS ( $\text{M}+\text{H}$ )<sup>+</sup> 241. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): 12.66 (br. s, 1 H), 7.62 (m, 1 H), 7.45 (t,  $J = 8.8$  Hz, 1 H), 6.67 (br. d,  $J = 7.2$  Hz, 1 H), 6.42 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 6.29 (dd,  $J_1 = 14.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 4.03 (m, 1 H), 2.73 (d,  $J = 4.4$  Hz, 3H), 1.37 (d,  $J = 7.2$  Hz, 3H). Solution of amine **4.2(2)**, (**S**)-**4.2(2)** or (**R**)-**4.2(2)** (110 mg, 0.46 mmol) and 4-isothiocyanato-2-(trifluoromethyl)-benzonitrile **3.2** (144 mg, 0.55 mmol) in DMF (2 ml) was stirred at 90°C for 12 h in microwave oven, then additional portion of 4-isothiocyanato-2-(trifluoromethyl)-benzonitrile **3.2** (50 mg, 0.19 mmol) was added and stirring was continued for another 12 h. The reaction mixture was evaporated in *vacuo*, and by HPLC method *N*-methyl-4-{5-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl}-2-fluorobenzamide **1.2(2)**, or *N*-methyl-4-[(S)-5-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl]-2-fluorobenzamide (**S**)-**1.2(2)** or *N*-methyl-4-[(R)-5-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl]-2-fluorobenzamide (**R**)-**1.2(2)** were isolated, respectively. The apparent inhibition constant of androgen receptors ( $K_i$ ) for these compounds are:  $K_i^{1.2(2)} = 140.2$  nM,  $K_i^{(S)-1.2(2)} = 106.7$  nM and  $K_i^{(R)-1.2(2)} = 73.6$  nM, respectively. LCMS ( $\text{M}+\text{H}$ )<sup>+</sup> 451. <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 400 MHz): 8.28 (t,  $J = 8.6$  Hz, 1 H), 8.01 (d,  $J = 8.0$  Hz, 1 H), 7.94 (d,  $J = 1.2$  Hz, 1H), 7.81 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.2$  Hz, 1 H), 7.48 (dd,  $J_1 = 12.4$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.36 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 1.6$  Hz, 1 H), 6.72 (br. m, 1 H), 4.83 (q,  $J = 7.2$  Hz, 1 H), 3.08 (d,  $J = 4.8$  Hz, 3H), 1.60 (d,  $J = 7.2$  Hz, 3H).

### Example 3

**[0049]** Synthesis of *N*-methyl-4-{2-thio-3-[3-(trifluoromethyl)-4-cyanophenyl]-hydantoin-1-yl}-2-fluorobenzamides **1.2.2** and **1.2.3** (general method). Solution of the corresponding *N*-methyl-2-fluoro-4-[(1-cyanomethyl)amino]benzamide **4.1** (0.75 mmol) and 4-isothiocyanato-2-(trifluoromethyl)benzonitrile **3.2** (342 mg, 1.5 mmol) in DMF (3 ml) was stirred at 110 °C for 12 h in microwave oven. The reaction mixture was dissolved in MeOH (30 ml), 1N HCl (7.5 ml) was added and the resultant mixture was boiled for 1.5 h. The solution was evaporated in *vacuo*, treated with water, the solid was filtered off, washed with water and dried in *vacuo*. The product was isolated by HPLC method. It gave: *N*-methyl-4-[5-methyl-5-(methoxymethyl)-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl]-2-fluorobenzamide **1.2.2(1)**,  $K_i^{1.2.2(1)} = 115.9$  nM, which was separated to enantiomers by means of high pressure liquid chromatography on Chiralpak HD-H 25x1 cm (Chiral Technologies Inc., USA). Mixture of 80% *n*-hexane, 20% 2-propanol and 0.02% triethylamine was used as eluent. Flowrate was 4 ml/min. It gave optically pure isomers (**R**)-**1.2.2(1)** and (**S**)-**1.2.2(1)**,  $K_i^{(R)-1.2.2(1)} = 53.3$  nM,  $K_i^{(S)-1.2.2(1)} = 721.5$  nM. LCMS ( $\text{M}+\text{H}$ )<sup>+</sup> 495. <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 400 MHz): 8.28 (t,  $J = 8.4$  Hz, 1 H), 7.99 (d,  $J = 8.0$  Hz, 1 H), 7.92 (s, 1 H), 7.80 (d,  $J = 8.0$  Hz, 1 H), 7.29 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 1.2$  Hz, 1 H), 7.21 (dd,  $J_1 = 11.6$  Hz,  $J_2 = 1.2$  Hz, 1 H), 6.72 (q,  $J = 4.4$  Hz, 1 H), 3.71 (d,  $J = 10.0$  Hz, 1 H), 3.43 (s, 3H), 3.35 (d,  $J = 10.0$  Hz, 1 H), 3.09 (d,  $J = 4.4$  Hz, 3H), 1.52 (s, 3H); *N*-methyl-4-{5-[(benzyloxy)methyl]-5-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl}-2-fluorobenzamide **1.2.2(2)**. LCMS ( $\text{M}+\text{H}$ )<sup>+</sup> 571. <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 400 MHz): 8.22 (t,  $J = 8.4$  Hz, 1 H), 7.96 (d,  $J = 8.0$  Hz, 1 H), 7.86 (s, 1 H), 7.70 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.2$  Hz, 1 H), 7.39 (m, 3H), 7.29 (m, 2H), 7.25 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.18 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 1.6$  Hz, 1 H), 6.71 (q,  $J = 4.8$  Hz, 1 H), 4.59 (m, 2H), 3.79 (d,  $J = 10.2$  Hz, 1 H), 3.45 (d,  $J = 10.2$  Hz, 1 H), 3.08 (d,  $J = 4.8$  Hz, 3H), 1.51 (s, 3H);

ethyl {4-methyl-3-(4-methylcarbamoyl-3-fluorophenyl)-5-oxo-2-thioxo-1-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-4-yl}acetate **1.2.2(4)** ( $\text{R}1=\text{CH}_3$ ,

$\text{R}4=\text{CH}_3$ ,  $\text{R}5=\text{CH}_2\text{COOC}_2\text{H}_5$ ). LCMS ( $\text{M}+\text{H}$ )<sup>+</sup> 536. <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 400 MHz): 8.26 (t,  $J = 8.4$  Hz, 1 H), 8.01 (d,  $J = 8.0$  Hz, 1 H), 8.00 (s, 1 H), 7.90 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.18 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.10 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.6$  Hz, 1 H), 6.78 (q,  $J = 4.8$  Hz, 1 H), 4.26 (m, 1 H), 3.13 (d,  $J = 18.0$  Hz, 1 H), 3.09 (d,  $J = 4.8$  Hz, 3H), 2.64 (d,  $J = 18.0$  Hz, 1 H), 1.67 (s, 3H), 1.31 (t,  $J = 7.0$  Hz, 3H); *N*-methyl-4-{4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-7-oxa-1,3-diazaspiro[4.4]non-1-yl}-2-fluorobenzamide **1.2.3(1)**,  $K_i^{1.2.3(1)} = 33.9$  nM. LCMS ( $\text{M}+\text{H}$ )<sup>+</sup> 493. <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 400 MHz): 8.30 (t,  $J = 8.4$  Hz, 1 H), 8.02 (d,  $J = 8.4$  Hz, 1 H), 7.98 (d,  $J = 1.6$  Hz, 1 H), 7.85 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.34 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.25 (dd,  $J_1 = 11.8$  Hz,  $J_2 = 1.6$  Hz, 1 H), 6.78 (q,  $J = 4.4$  Hz, 1H), 4.43 (d,  $J = 10.0$  Hz, 1H), 4.16 (d,  $J = 10.0$  Hz, 1H), 3.96 (m, 1H), 3.75 (m, 1 H), 3.09 (d,  $J = 4.4$  Hz, 3H), 2.74 (m, 1 H), 2.48 (m, 1 H); *N*-methyl-4-{4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-8-oxa-1,3-diazaspiro[4.5]dec-1-yl}-2-fluorobenzamide **1.2.3(2)**. LCMS ( $\text{M}+\text{H}$ )<sup>+</sup> 507. <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 400 MHz): 8.32 (t,  $J = 8.4$  Hz, 1 H), 8.01 (d,  $J = 8.0$  Hz, 1 H), 7.95 (s, 1 H), 7.83 (d,  $J = 8.0$  Hz, 1 H), 7.20 (d,  $J = 8.4$  Hz, 1 H), 7.10 (d,  $J = 8.0$  Hz, 1 H), 6.73 (br. m, 1 H), 4.18 (m, 2H), 3.94 (m, 2H), 3.09 (d,  $J = 4.4$  Hz, 3H), 2.07 (m, 4H); *N*-methyl-4-{8-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-1,3,8-triazaspiro[4.5]dec-1-yl}-2-fluorobenzamide **1.2.3(3)**.  $K_i^{1.2.3(3)} = 39.2$  nM,  $\text{IC}_{50} = 170$ nM. LCMS ( $\text{M}+\text{H}$ )<sup>+</sup> 520. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): 10.09 (br. s, 1H), 8.48 (q,  $J = 4.4$  Hz, 1 H), 8.43

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(d,  $J = 8.4$  Hz, 1 H), 8.29 (s, 1 H), 8.11 (d,  $J = 8.4$  Hz, 1 H), 7.84 (t,  $J = 8.0$  Hz, 1 H), 7.42 (d,  $J = 10.4$  Hz, 1 H), 7.30 (d,  $J = 8.0$  Hz, 1 H), 3.50 (m, 4H), 2.80 (d,  $J = 4.4$  Hz, 3H), 2.78 (s, 3H), 2.72 (d,  $J = 14.0$  Hz, 1 H), 2.16 (m, 2H).

### Example 4

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**[0050]** Synthesis of *N*-methyl-4-[5-(hydroxymethyl)-5-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl]-2-fluorobenzamide **1.2.2(3)**.  $\text{BBr}_3$  (53 mkl, 0.55 mmol) was added dropwise to solution of *N*-methyl-4-[5-methyl-5-(methoxymethyl)-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl]-2-fluorobenzamide (55 mg, 0.11 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.5 ml) in argon atmosphere at  $-78^\circ\text{C}$ . The reaction mixture was stirred at  $-78^\circ\text{C}$  for 3 h and then for another 3 h at room temperature. After the reaction was completed the excess of  $\text{BBr}_3$  was neutralized by addition of 5%  $\text{Na}_2\text{CO}_3$  solution (10 ml), the product was extracted with AcOEt, dried over  $\text{Na}_2\text{SO}_4$ , evaporated in *vacuo*, and by HPLC method *N*-methyl-4-[5-(hydroxymethyl)-5-methyl-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-1-yl]-2-fluorobenzamide **1.2.2(3)** was isolated,  $K_1^{1.2.2(3)} = 46.3$  nM,  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ , 400 MHz): 8.43 (br. m, 1 H), 8.39 (d,  $J = 8.4$  Hz, 1 H), 8.13 (s, 1 H), 7.98 (d,  $J = 8.4$  Hz, 1H), 7.78 (t,  $J = 8.0$  Hz, 1 H), 7.42 (d,  $J = 10.8$  Hz, 1 H), 7.37 (d,  $J = 8.0$  Hz, 1 H), 5.93 (t,  $J = 4.4$  Hz, 1 H), 3.81 (dd,  $J_1 = 11.6$  Hz,  $J_2 = 4.4$  Hz, 1 H), 3.45 (dd,  $J_1 = 11.6$  Hz,  $J_2 = 5.0$  Hz, 1 H), 2.79 (d,  $J = 4.0$  Hz, 3H), 1.38 (s, 3H).

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### Example 5

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**[0051]** Synthesis of {4-methyl-3-(4-methylcarbamoyl-3-fluorophenyl)-5-oxo-2-thioxo-1-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-4-yl}acetic acid **1.2.2(5)** ( $\text{R}_1 = \text{CH}_3$ ,  $\text{R}_4 = \text{CH}_3$ ,  $\text{R}_5 = \text{CH}_2\text{COOH}$ ). Solution of NaOH (7 mg, 0.172 mmol) in water (0.5 ml) was added to the solution of ester (46 mg, 0.086 mmol) **1.2.2(4)** in alcohol (2 ml), and the reaction mixture was stirred for 12 h (LCMS control). The solvent was evaporated, isopropanol (2 ml) and HCl (15 mkl, 0.172 mmol) were added, filtered and evaporated again in *vacuo*. {4-Methyl-3-(4-methylcarbamoyl-3-fluorophenyl)-5-oxo-2-thioxo-1-[3-(trifluoromethyl)-4-cyanophenyl]imidazolidin-4-yl}acetic acid **1.2.2(5)** was isolated by HPLC method. LCMS ( $\text{M} + \text{H}$ )<sup>+</sup> 469.  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ , 400 MHz): 13.31 (br. s, 1 H), 8.44 (m, 2H), 8.10 (s, 1 H), 7.95 (d,  $J = 7.6$  Hz, 1 H), 7.81 (t,  $J = 8.0$  Hz, 1 H), 7.25 (d,  $J = 10.8$  Hz, 1 H), 7.19 (d,  $J = 8.0$  Hz, 1 H), 3.16 (d,  $J = 17.6$  Hz, 1 H), 2.79 (d,  $J = 3.6$  Hz, 3H), 2.70 (d,  $J = 17.6$  Hz, 1 H), 1.59 (s, 3H).

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### Example 6

**[0052]** Synthesis of 4-[3-[3-(trifluoromethyl)-4-cyanophenyl]-2-oxo-tetrahydro-pyrimidin-1(2*H*)-yl]-*N*-methyl-2-fluorobenzamide **1.3.1**.  $\text{K}_2\text{CO}_3$  (109 mg, 0.79 mmol) and 1,3-dibromopropane (32 mkl, 0.32 mmol) were added to a solution of 4-[4-cyano-3-(trifluoromethyl)-phenylcarbamoylamino]-*N*-methyl-2-fluorobenzamide (100 mg, 0.26 mmol) **2** in DMF (2 ml). Mixture was stirred at  $90^\circ\text{C}$ . In 18 h another portion of  $\text{K}_2\text{CO}_3$  (109 mg) and 1,3-dibromopropane (32 mkl) were added and stirring was continued at the same temperature. Addition was repeated by 2 more times. After the reaction was completed the mixture was evaporated in *vacuo*, the residue was dissolved in chloroform, washed with water, dried over  $\text{Na}_2\text{SO}_4$ , the solvent was evaporated. The product was isolated by column chromatography on  $\text{SiO}_2$  (eluent - AcOEt). LCMS ( $\text{M} + \text{H}$ )<sup>+</sup> 421.  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ , 400 MHz): 8.17 (br. m, 1 H), 8.13 (d,  $J = 8.4$  Hz, 1 H), 8.07 (d,  $J = 2.0$  Hz, 1 H), 7.83 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.62 (t,  $J = 8.4$  Hz, 1 H), 7.38 (dd,  $J_1 = 12.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.29 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.0$  Hz, 1 H), 3.90 (t,  $J = 5.8$  Hz, 2H), 3.81 (t,  $J = 5.8$  Hz, 2H), 2.77 (d,  $J = 4.8$  Hz, 3H), 2.21 (m, 2H).

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### Example 7

**[0053]** Synthesis of *N*-methyl-4-[[3-(trifluoromethyl)-4-cyanophenyl]-2,4-dioxo-tetrahydropyrimidin-1(2*H*)-yl]benzamide **1.3.2(1)**, ( $\text{X} = \text{O}$ ,  $\text{R}_1 = \text{CH}_3$ ). Ethyl acrylate (8 g, 80 mmol) and DBU (0.81 g, 5.4 mmol) were added to a solution of 4-amino-*N*-methyl-2-fluorobenzamide (9 g, 53.6 mmol) in DMSO (90 ml) and stirring was continued for 24 h at  $70^\circ\text{C}$  (LCMS control). The reaction mixture was subjected to lyophilization, the residue was recrystallized from aqueous alcohol. It gave ethyl *N*-[4-(methylcarbamoyl)-3-fluorophenyl]- $\beta$ -alaninate **5**. LCMS ( $\text{M} + \text{H}$ )<sup>+</sup> 269.  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  7.57 (br. s, 1 H), 7.48 (t,  $J = 8.8$  Hz, 1H), 6.47 (br. s, 1 H), 6.42 (d,  $J = 8.8$  Hz, 1 H), 6.33 (d,  $J = 14.8$  Hz, 1 H), 4.07 (q,  $J = 7.2$  Hz, 2H), 3.32 (br. m, 2H), 2.73 (d,  $J = 4.4$  Hz, 3H), 2.55 (t,  $J = 6.4$  Hz, 2H), 1.18 (t,  $J = 7.2$  Hz, 3H). The solution of 4-isocyanato-2-(trifluoromethyl)benzonitrile (425 mg, 1.87 mmol) **3.1** and ethyl *N*-[4-(methylcarbamoyl)-3-fluorophenyl]- $\beta$ -alaninate (500 mg, 1.87 mmol) **5** ( $\text{R}_1 = \text{CH}_3$ ) in  $\text{CH}_2\text{Cl}_2$  (10 ml) was stirred for 5 h. The reaction mixture was evaporated in *vacuo*, and the product was isolated by column chromatography on  $\text{SiO}_2$  (eluent - *n*-hexane : AcOEt :  $\text{Et}_3\text{N} = 1:1:0.03$ ). It gave ethyl *N*-[4-(methylcabamoyl)-3-fluorophenyl]-*N*-[[3-(trifluoromethyl)-4-cyanophenyl]-carbamoyl]- $\beta$ -alaninate **6(1)** ( $\text{R}_1 = \text{CH}_3$ ,  $\text{X} = \text{O}$ ). LCMS ( $\text{M} + \text{H}$ )<sup>+</sup> 481. HCl (2.5 ml) was added to the solution of ethyl *N*-[4-(methylcabamoyl)-3-fluorophenyl]-*N*-[[3-(trifluoromethyl)-4-cyanophenyl]-carbamoyl]- $\beta$ -alaninate (500 mg, 1.04 mmol) **6(1)** in AcOH (5 ml) and the resultant mixture was stirred for 15 h. The reaction mixture was poured into water, the product was

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extracted with EtOAc. Organic layer was dried over  $\text{Na}_2\text{SO}_4$ , evaporated in *vacuo* and by means of column chromatography on  $\text{SiO}_2$  (eluent - n-hexane : AcOEt = 1:1) *N*-methyl-4-[[3-(trifluoromethyl)-4-cyanophenyl]-2,4-dioxo-tetrahydropyrimidin-1(2*H*)-yl]benzamide **1.3.2**, (X=O, R1=CH<sub>3</sub>) was isolated;  $K_1^{1.3.2(1)} = 85.6$  nM, LCMS (M+H)<sup>+</sup> 435. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta$  8.29 (d,  $J = 7.6$  Hz, 1 H), 8.23 (br. m, 1H), 8.11 (s, 1 H), 7.89 (d,  $J = 2.0$  Hz, 1 H), 7.67 (t,  $J = 8.4$  Hz, 1 H), 7.39 (d,  $J = 12.4$  Hz, 1 H), 7.33 (d,  $J = 8.4$  Hz, 1 H), 4.02 (t,  $J = 6.4$  Hz, 2H), 3.03 (t,  $J = 6.4$  Hz, 2H), 2.77 (d,  $J = 4.4$  Hz, 3H).

### Example 8

**[0054]** Synthesis of *N*-methyl-4-[[3-(trifluoromethyl)-4-cyanophenyl]-4-oxo-2-thioxo-tetrahydropyrimidin-1(2*H*)-yl]benzamide **1.3.2(2)**, (X=S, R1=CH<sub>3</sub>). A solution of 4-isothiocyanato-2-(trifluoromethyl)benzonitrile (320 mg, 1.51 mmol) **3.2** and ethyl *N*-[4-(methylcarbamoyl)-3-fluorophenyl]- $\beta$ -alaninate (404 mg, 1.51 mmol) **5** (R1=CH<sub>3</sub>) in DMF (8 ml) was heated at 60°C in microwave stove for 8 h. The reaction mixture was evaporated in *vacuo*, and by means of column chromatography on  $\text{SiO}_2$  (eluent - n-hexane : AcOEt = 1:2) ethyl *N*-[4-(methylcarbamoyl)-3-fluorophenyl]-*N*-[[3-(trifluoromethyl)-4-cyanophenyl]thiocarbamoyl]- $\beta$ -alaninate **6(2)** (R1=CH<sub>3</sub>, X=S) was isolated. LCMS (M+H)<sup>+</sup> 497. A solution of NaOH (32 mg, 0.8 mmol) in water (0.25 ml) was added to a solution of ester (200 mg, 0.4 mmol) **6(2)** in alcohol (1 ml), and the resultant mixture was stirred at 80°C for 2 h (LCMS control), cooled and neutralized with HCl (69 mkl, 0.8 mmol), evaporated in *vacuo*, the residue was extracted with hot isopropanol and evaporated in *vacuo* again. It gave *N*-[4-(methylcarbamoyl)-3-fluorophenyl]-*N*-[[3-(trifluoromethyl)-4-cyanophenyl]thiocarbamoyl]- $\beta$ -alanine **6(3)** (R1=CH<sub>3</sub>, X=S). LCMS (M+H)<sup>+</sup> 469. TBTU (86 mg, 0.36 mmol) and diisopropylethylamine (110 mg, 0.84 mmol) were added to the solution of the prepared acid (114 mg, 0.24 mmol) **6(3)** in DMF (1.5 ml). The reaction mixture was stirred at 45°C for 15 h. When the reaction was completed (LCMS control) the solution was poured into water and extracted with EtOAc. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , evaporated in *vacuo* and by HPLC method *N*-methyl-4-[[3-(trifluoromethyl)-4-cyanophenyl]-4-oxo-2-thioxo-tetrahydropyrimidin-1(2*H*)-yl]-2-fluorobenzamide **1.3.2(2)** (R1=CH<sub>3</sub>, X=S) was isolated;  $K_1^{1.3.2(2)} = 95.2$  nM. LCMS (M+H)<sup>+</sup> 451. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): 8.35 (q,  $J = 4.4$  Hz, 1 H), 8.27 (d,  $J = 8.0$  Hz, 1 H), 8.06 (d,  $J = 1.6$  Hz, 1 H), 7.83 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.71 (t,  $J = 8.2$  Hz, 1 H), 7.42 (dd,  $J_1 = 11.0$  Hz,  $J_2 = 1.8$  Hz, 1 H), 7.33 (dd,  $J_1 = 8.2$  Hz,  $J_2 = 1.8$  Hz, 1 H), 4.13 (t,  $J = 6.8$  Hz, 2H), 3.17 (t,  $J = 6.8$  Hz, 2H), 2.78 (d,  $J = 4.4$  Hz, 3H).

### Example 9

**[0055]** Synthesis of *N*-methyl-2-fluoro-4-[4-[3-(trifluoromethyl)-4-cyanophenyl]-3,5-dioxo-1,2,4-triazolidin-1-yl]benzamide **1.4** (R1=CH<sub>3</sub>). 2.5M Solution of  $\text{NaNO}_2$  (2.38 ml) was added dropwise to a solution of 4-amino-*N*-methyl-2-fluorobenzamide (1 g, 5.95 mmol) in B 5N HCl (3.1 ml), so that the temperature of the reaction mixture did not exceed 5°C. The mixture was stirred for additional 30 min at the same temperature, after that the prepared solution was added drop by drop to a suspension of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (4.03 g, 17.9 mmol) in HCl (4.2 ml) at 0°C, and stirring was continued for 2 h at the same temperature. Precipitated solid was filtered off, dissolved in water (40 ml) and NaOH was added to strongly basic reaction. The mixture was extracted with ether (3\*100 ml), dried over  $\text{MgSO}_4$  and evaporated in *vacuo*. It gave 4-hydrazino-*N*-methyl-2-fluorobenzamide **7** (R1=CH<sub>3</sub>). LCMS (M+H)<sup>+</sup> 184. <sup>1</sup>H NMR ( $\text{CDCl}_3$ , 400 MHz): 7.96 (t,  $J = 8.4$  Hz, 1 H), 6.64 (br. m, 1 H), 6.60 (t,  $J = 1.6$  Hz, 1 H), 6.57 (dd,  $J_1 = 7.2$  Hz,  $J_2 = 2.0$  Hz, 1 H), 5.60 (br. s, 1 H), 3.66 (br. s, 2H), 3.00 (dd,  $J_1 = 4.8$  Hz,  $J_2 = 1.2$  Hz, 1 H). The solution of 4-isocyanato-2-(trifluoromethyl)benzonitrile (59 mg, 0.27 mmol) **3.1** in dioxane (2 ml) was added to a solution of 4-hydrazino-*N*-methyl-2-fluorobenzamide (54 mg, 0.29 mmol) **7** in dioxane (3 ml), and the resultant mixture was stirred for 2 h. Then dioxane was distilled in *vacuo*, the residue was crumbled with ether, filtered off and dried in *vacuo*. It gave 2-[[4-(methylcarbamoyl)-3-fluorophenyl]-*N*-[3-(trifluoromethyl)-4-cyanophenyl]-hydrazine carboxamide **8(1)** (R1=CH<sub>3</sub>). LCMS (M+H)<sup>+</sup> 405. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): 9.65 (br. s, 1 H), 8.72 (br. s, 1 H), 8.37 (s, 1 H), 8.25 (br. s, 1 H), 8.03 (br. m, 1 H), 7.88 (d,  $J = 8.8$  Hz, 1 H), 7.58 (m, 2H), 6.63 (d,  $J = 8.4$  Hz, 1 H), 6.48 (d,  $J = 14.0$  Hz, 1 H), 2.77 (d,  $J = 4.4$  Hz, 3H). Triethylamine (56 mkl, 0.4 mmol) and diphosgene (27 mkl, 0.22 mmol) were added one after another to 2-[[4-(methylcarbamoyl)-3-fluorophenyl]-*N*-[3-(trifluoromethyl)-4-cyanophenyl]-hydrazine carboxamide (80 mg, 0.2 mmol) **8(1)** in dichloroethane (2 ml). The reaction mixture was stirred in a closed vial at 80 °C for 15 h. The solvent was evaporated in *vacuo* and the residue was subjected to chromatography on  $\text{SiO}_2$  (eluent -  $\text{CH}_2\text{Cl}_2$ : MeOH, gradient from 100:1 till 20:1). It gave *N*-methyl-2-fluoro-4-[4-[3-(trifluoromethyl)-4-cyanophenyl]-3,5-dioxo-1,2,4-triazolidin-1-yl]benzamide **1.4** (R1=CH<sub>3</sub>).  $K_1^{1.4} = 55.2$  nM, LCMS (M+H)<sup>+</sup> 422. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): 11.53 (s, 1 H), 8.22 (br. m, 1 H), 8.16 (d,  $J = 8.8$  Hz, 1 H), 7.99 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 1.6$  Hz, 1 H), 7.95 (d,  $J = 1.6$  Hz, 1 H), 7.81 (t,  $J = 8.4$  Hz, 1 H), 7.69 (dd,  $J_1 = 8.8$  Hz,  $J_2 = 2.0$  Hz, 1 H), 7.62 (dd,  $J_1 = 12.0$  Hz,  $J_2 = 2.0$  Hz, 1 H), 2.79 (d,  $J = 4.4$  Hz, 3H).

**Example 10**

**[0056]** Determination of antagonistic activity of cyclic N,N'-diarylthioureas and N,N'-diarylureas of the general formula **1** and their analog **MDV3100** towards androgen receptors. The ability of novel cyclic N,N'-diarylthioureas and N,N'-diarylureas of the general formula **1** and **MDV3100** agent to block androgen receptors was determined by their effectiveness of inhibition of dihydrotestosterone stimulated expression of prostate specific antigen (PSA) in cancer cells of human prostate LNCap, derived from the American Tissue Culture Collection (ATCC, USA). These cells are sensitive towards 5- $\alpha$ -dihydrotestosterone (DHT) and in its presence produce cancer markers (PSA). The cells were cultured in RPMI 1640 medium (Invitrogen, USA) containing 10% calf serum (Hyclone, USA), 1% antibacterial/antifungal mixture (Sigma, USA) and 4,5% glucose. Before the experiment the cells were washed and suspended in the same medium in which, however, instead of calf serum the serum which had been treated with charcoal for removal of hormone traces was used. The cells were embedded into wells of 96-well plates by 100  $\mu$ l per cell (10 000 cells) and left for 4 days in incubator at 37°C (100% humidity) in atmosphere of 95% air/5% CO<sub>2</sub>. After incubation cyclic N,N'-diarylthioureas or N,N'-diarylureas of the general formula **1** were added to the cells in various concentrations, and then - 20nM DHT (concentration corresponding to 80-90% of maximum stimulation). The cells were left for 5 days for additional incubation under the same conditions. After that the samples of supracellular medium were taken on analysis for PSA content. The test was carried out according to the protocol, recommended by manufacturer of the kit for determination of PSA (Alpha Diagnostic International, USA). After wetting the wells containing PSA antibodies attached to their bottom to each well 25  $\mu$ l of the tested compounds and 100  $\mu$ l of PSA antibodies conjugated previously with horseradish peroxidase were added successively.

**[0057]** After incubation at room temperature for 30 minutes, the contents of the wells were removed, the wells were washed several times, and then 100  $\mu$ l of chromogenic substrate of peroxidase was added to each well. Plates were held for 15 min. at room temperature, after that 50  $\mu$ l of stop solution was added to every well; at that a dye is formed the absorption intensity of which was measured at 450 nM; the value obtained is proportional to PSA concentration in the sample. Based on the dependence of lowering of PSA synthesis, caused by dihydrotestosterone (DHT), on the concentration of the tested compounds, dose-response curves were plotted, from which IC<sub>50</sub> values were determined. They were used for calculation of the values of apparent inhibition constants (K<sub>i</sub>) for the compounds of the general formula **1** according to Cheng-Prusoff equation. [Cheng, Y., Prusoff, W. H. "Relationship between the inhibition constant (K<sub>i</sub>) and the concentration of inhibitor which causes 50 per cent inhibition (IC<sub>50</sub>) of an enzymatic reaction". Biochem Pharmacol. (1973) 22, 3099-3108]:

$$K_i = IC_{50} / (1 + L / K_D),$$

wherein L - agonist concentration (DHT), K<sub>D</sub> - receptor activation constant, numerically equal to EC<sub>50</sub> value, which is determined in every experiment according to dependence of stimulation of PSA synthesis on DHT concentration.

**[0058]** The data obtained given in the corresponding examples testify that novel androgen receptor antagonists, in some cases, are more active than MDV3100, tested under the same conditions as a compound for comparison, for which K<sub>i</sub><sup>MDV3100</sup> = 79.5 nM.

**Example 11**

**[0059]** Determination of maximum tolerated dose of novel antagonists **1.2.2(1)**, and **1.2.3(3)** and its analog **MDV3100**. Maximum tolerated dose (MTD) of novel antagonists **1.2.2(1)** and **1.2.3(3)** and its analog **MDV3100** were determined in experiments on male mice of CD1 line at peroral administration 1 time a day within 5 days in doses 10, 30 and 100 mg/kg. The compound was dissolved in sterile water with addition of Twin-80. Sterile water with Twin-80 was introduced to control animals (Placebo group). Body weight was appreciated, and also animals' mortality rate. Statistical comparison of groups was carried out according to non-parametric test ANOVA, with the use of Statistica programme.

**[0060]** At the introduction of compounds in dose up to 100 mg/kg mice death was not observed. On the 3rd - 4th day body weight of mice in the group, received the tested compound in dose 100 mg/kg was less in comparison with the body weight of control animals, however, statistical significance at this was not observed (fig. 1). The data show that compound has MTD > 100 mg/kg.

**[0061]** At the introduction of **MDV3100** in doses 10 and 30 mg/kg mice death was not observed. In the group of mice to which the tested compound was introduced in dose 100 mg/kg, the body weight began to lower on the 3<sup>rd</sup> day. On the 5<sup>th</sup> day body weight of this group of animals statistically differed from body weight of animals from Placebo group (p=0,002, fig. 2). One animal died. The data show that compound **MDV3100** has MTD ~ 30 mg/kg.).

**Example 12**

[0062] Preparation of medicament in the form of tablets. Starch (1600 mg), grained lactose (1600 mg), talcum (400 mg) and N-methyl-4-[5-methyl-5-(methoxymethyl)-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-imidazolidin-1-yl]-2-fluorobenzamide (**(R)**-1.2.2(1)) (1000 mg) mixed together and pressed in a brick. Prepared brick was crushed to granules and riddled through sieves, gathering granules of 14-16 mesh size. The obtained granules were pelletised in tablets of suitable form of 560 mg by weight each.

**Example 13**

[0063] Preparation of medicament in the form of capsules. N-Methyl-4-[5-methyl-5-(methoxymethyl)-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-imidazolidin-1-yl]-2-fluorobenzamide (**(R)**-1.2.2(1)) was carefully mixed with lactose powder in ratio 2 : 1. The prepared pharmaceutical composition was packed on 300 mg into gelatinous capsules of suitable size.

**Example 16**

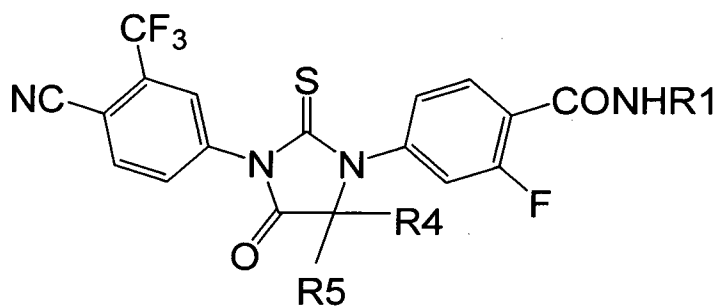
[0064] Preparation of medicament in the form of compositions for intramuscular, intraperitoneal or hypodermic injections. N-Methyl-4-[5-methyl-5-(methoxymethyl)-4-oxo-2-thioxo-3-[3-(trifluoromethyl)-4-cyanophenyl]-imidazolidin-1-yl]-2-fluorobenzamide (**(R)**-1.2.2(1)) (500 mg) was dissolved in the mixture of chlorobutanol (300 mg), propylene glycol (2 ml), and water for injections (100 ml). The prepared solution was filtered and placed in 1 ml ampoules which were sealed up and sterilized in an autoclave.

**Industrial applicability**

[0065] The present invention could be used in medicine, veterinary, biochemistry.

**Claims**

1. Compounds being cyclic *N,N'*-diarylthioureas and *N,N'*-diarylureas of general formula 1.2, their optical (R)- and (S)-isomers, and their pharmaceutically acceptable salts,

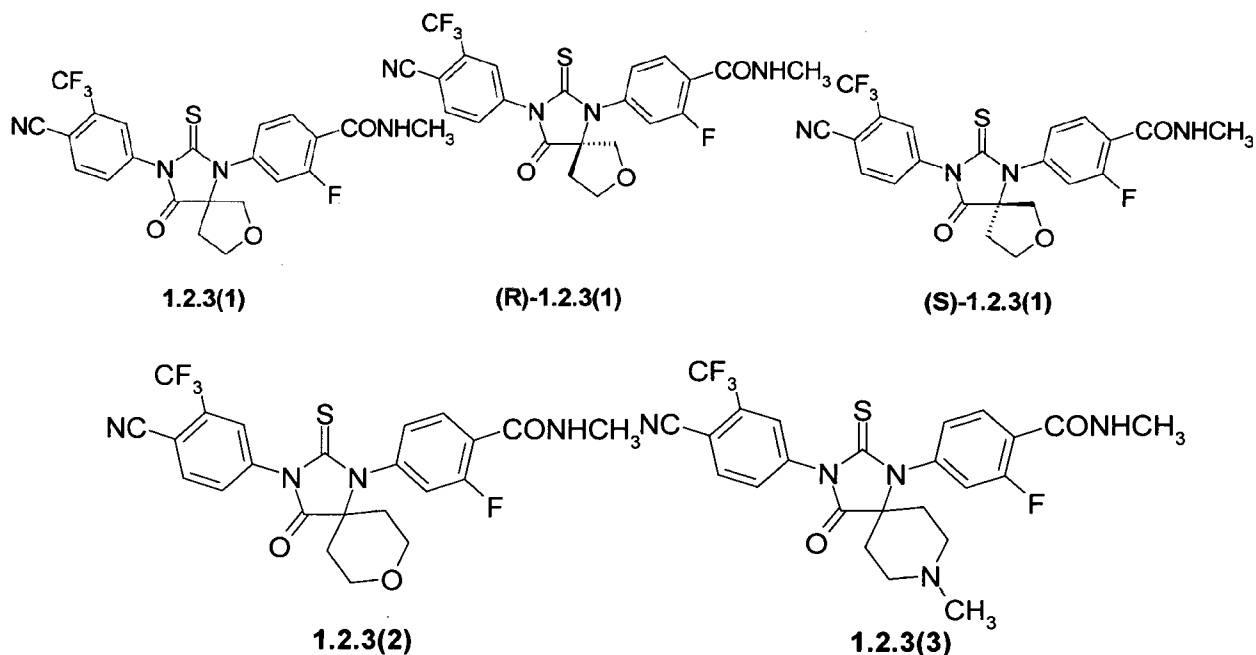
**1.2**

wherein:

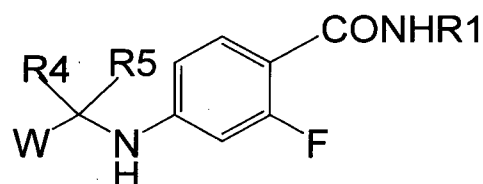
**R1** - represents  $C_1$ - $C_3$ alkyl;

**R5** and **R4** together with the C-atom to which they are attached form a 5- or 6-membered heterocycle comprising at least one oxygen atom or nitrogen atom optionally substituted with methyl.

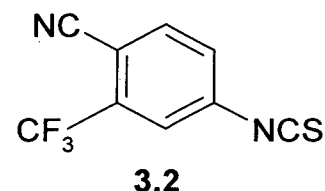
2. The compounds of claim 1 being compounds of formulae 1.2.3(1), 1.2.3(2) and 1.2.3(3), and optical (R)-isomers - (**(R)**-1.2.3(1), and (S)-isomers - (**(S)**-1.2.3(1),



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- The compounds of any of claims 1 to 2 for use as a medicament.
  - The compounds of any of claims 1 to 3 for use in treating cancer.
  - The compounds for use of claim 4 wherein the cancer is prostate cancer.
  - Method for the preparation of compounds of the general formula **1.2** and their optical **(R)**- and **(S)**- isomers thereof according to any of claims 1-5 by interaction of the corresponding 4-(cyanomethyl)amino-benzamides **4.1** or (4-carbamoylphenylamino)-acetic acids **4.2** or their optical **(R)**- and **(S)**-isomers thereof with isothiocyanate **3.2**.



**4.1:** W = CN  
**4.2:** W = CO<sub>2</sub>H



wherein:

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**R1** - represents C<sub>1</sub>-C<sub>3</sub>alkyl;  
**R5** and **R4** together with the C-atom to which they are attached form a 5- or 6-membered heterocycle comprising at least one oxygen atom or nitrogen atom optionally substituted with methyl.

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- A pharmaceutical composition comprising as active component a compound of any of claims 1 to 5.
  - The pharmaceutical composition according to claim 7 for use as an androgen receptor antagonist.
  - The pharmaceutical composition according to claim 7 or the pharmaceutical composition according to claim 8 additionally comprising an inert filler and/or solvent.
  - The pharmaceutical composition according to any of claims 7 or the pharmaceutical composition according to claims 8 to 9 additionally comprising an agent for treating cancerous diseases, said agent being different from the compounds

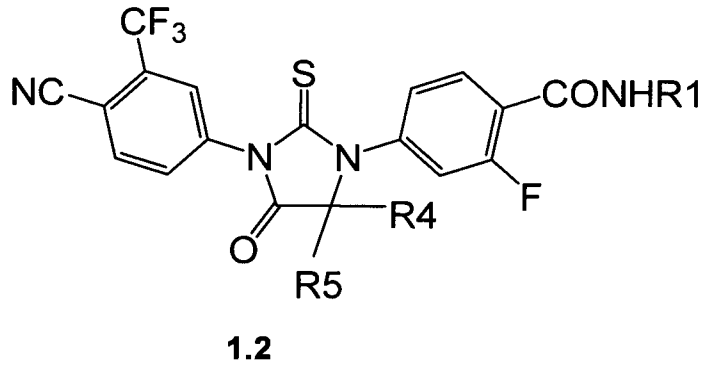
of any of claims 1 to 5.

11. A medicament in the form of tablets, capsules or injections for the treatment of cancerous diseases comprising a compound according to any of claims 1 to 5 or a pharmaceutical composition according to any of claims 7 to 9.

12. The medicament according to claim 11 for use in the treatment of prostate cancer.

Patentansprüche

1. Verbindungen, die cyclische *N,N'*-Diarylthioharnstoffe und *N,N'*-Diarylharnstoffe der allgemeinen Formel 1.2 sind, deren optische (R)- und (S)- Isomere, und deren pharmazeutisch akzeptable Salze,

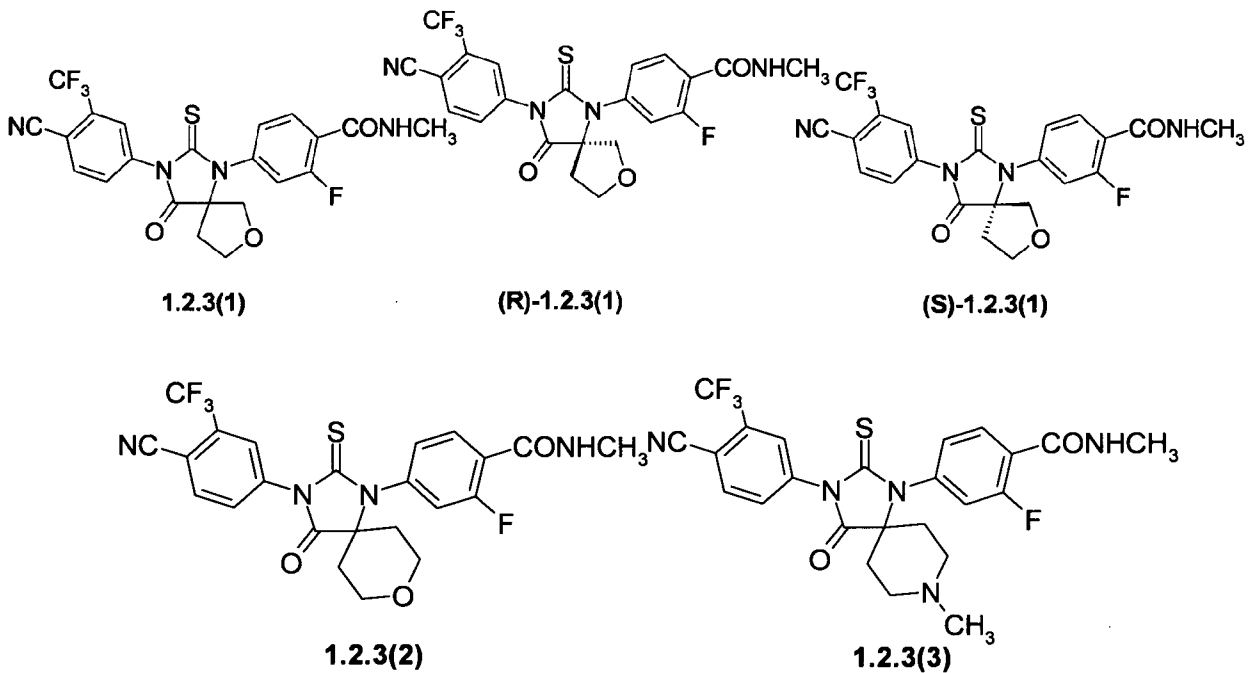


worin:

**R1** für C<sub>1</sub>-C<sub>3</sub>-Alkyl steht;

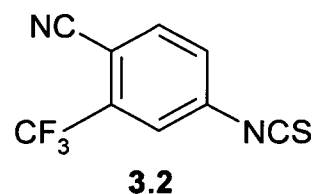
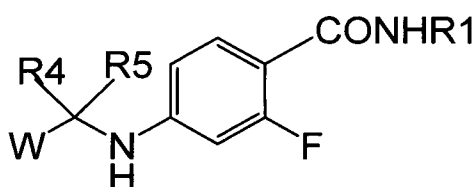
**R5** und **R4** zusammen mit dem C-Atom, an das sie gebunden sind, einen 5- oder 6-gliedrigen Heterocyclus bilden, der mindestens ein Sauerstoffatom oder Stickstoffatom, optional substituiert mit Methyl, umfasst.

2. Verbindungen nach Anspruch 1, die Verbindungen der Formeln 1.2.3(1), 1.2.3(2) und 1.2.3(3) sind, und optische (R)-Isomere - (R)-1.2.3(1), und (S)-Isomere - (S)-1.2.3(1),



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3. Verbindungen nach einem der Ansprüche 1 bis 2 zur Verwendung als Medikament.
4. Verbindungen nach einem der Ansprüche 1 bis 3 zur Verwendung bei der Behandlung von Krebs.
5. Verbindungen zur Verwendung nach Anspruch 4, wobei der Krebs Prostatakrebs ist.
6. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel **1.2** und deren optischen (**R**)- und (**S**)-Isomeren nach einem der Ansprüche 1-5 durch Wechselwirkung der korrespondierenden 4-(Cyanomethyl)amino-benzamide **4.1** oder (4-Carbamoyl-phenylamino)-Essigsäuren **4.2** oder deren optischen (**R**)- und (**S**)-Isomeren mit Isothiocyanat **3.2**



**4.1:** W = CN

**4.2:** W = CO<sub>2</sub>H

worin:

**R1** - für C<sub>1</sub>-C<sub>3</sub>-Alkyl steht;

**R5** und **R4** zusammen mit dem C-Atom, an das sie gebunden sind, einen 5- oder 6-gliedrigen Heterocyclus bilden, der mindestens ein Sauerstoffatom oder Stickstoffatom, optional substituiert mit Methyl, umfasst.

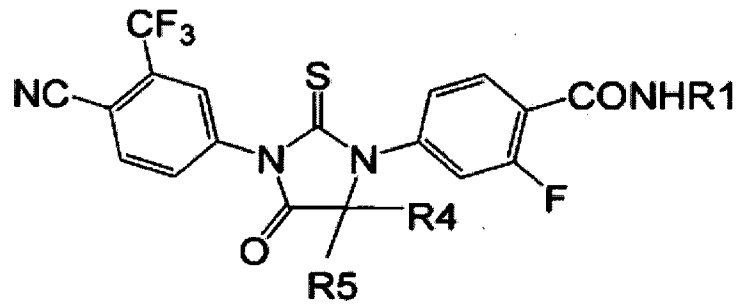
7. Pharmazeutische Zusammensetzung umfassend eine Verbindung nach einem der Ansprüche 1 bis 5 als aktive Komponente.
8. Pharmazeutische Zusammensetzung nach Anspruch 7 zur Verwendung als ein Androgen-Rezeptor-Antagonist.
9. Pharmazeutische Zusammensetzung nach Anspruch 7 oder pharmazeutische Zusammensetzung nach Anspruch 8 zusätzlich umfassend einen inerten Füllstoff und/oder Lösungsmittel.
10. Pharmazeutische Zusammensetzung nach einem der Ansprüche 7 oder pharmazeutische Zusammensetzung nach den Ansprüchen 8 bis 9 zusätzlich umfassend einen Wirkstoff zur Behandlung von Krebserkrankungen, der von den Verbindungen nach einem der Ansprüche 1 bis 5 verschieden ist.
11. Arzneimittel in Form von Tabletten, Kapseln oder Injektionen für die Behandlung von Krebserkrankungen, umfassend eine Verbindung nach einem der Ansprüche 1 bis 5 oder eine pharmazeutische Zusammensetzung nach einem der Ansprüche 7 bis 9.
12. Arzneimittel gemäß Anspruch 11 zur Verwendung bei der Behandlung von Prostatakrebs.

### Revendications

1. Composés, à savoir des *N,N'*-diarylthiourées et des *N,N'*-diarylurées cycliques répondant à la formule générale **1.2**, leurs isomères optiques (**R**) et (**S**), et leurs sels pharmaceutiquement acceptables,

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**1.2**

dans laquelle

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**R1** représente un groupe alkyle en C<sub>1</sub>-C<sub>3</sub> ;

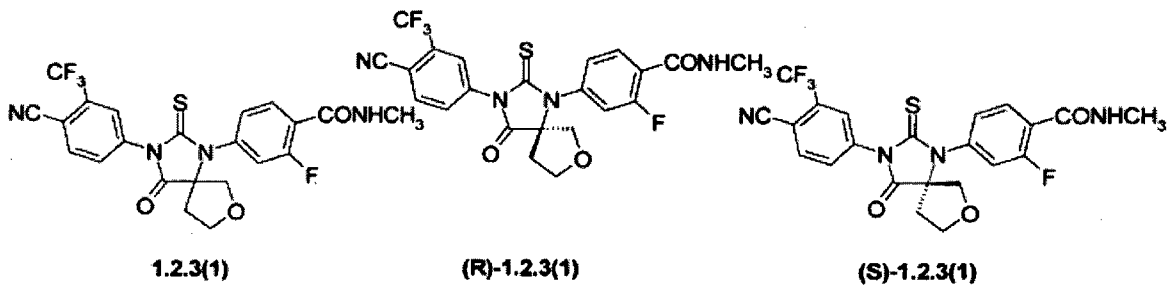
**R5** et **R4**, conjointement avec l'atome de carbone auquel ils sont fixés, forment un hétérocycle à 5 ou 6 membres comprenant au moins un atome d'oxygène ou un atome d'azote substitué de manière facultative avec un groupe méthyle.

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2. Composés selon la revendication 1, à savoir les composés répondant aux formules **1.2.3(1)**, **1.2.3(2)** et **1.2.3(3)**, et les isomères (R) - (R)-**1.2.3(1)** et les isomères (S) - (S)-**1.2.3(1)**:

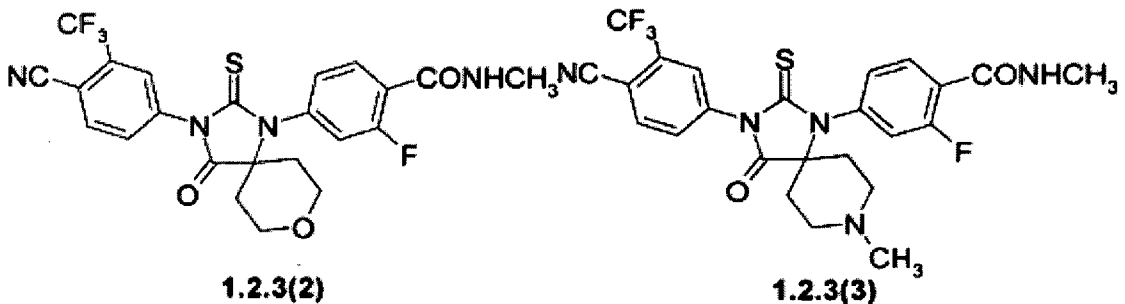
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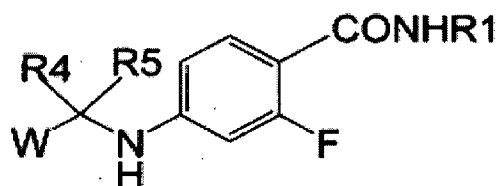
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3. Composés selon l'une quelconque des revendications 1 à 2, pour leur utilisation comme médicament.
4. Composés selon l'une quelconque des revendications 1 à 3, pour leur utilisation dans le traitement du cancer.
5. Composés pour leur utilisation selon la revendication 4, dans lesquels le cancer est un cancer de la prostate.
6. Procédé pour la préparation de composés répondant à la formule générale **1.2** et de leurs isomères optiques (R) et (S) selon l'une quelconque des revendications 1 à 5, par interaction des 4-(cyanométhyl)amino-benzylamides **4.1** ou des acides (4-carbamoyl-phénylamino)-acétiques **4.2** correspondants ou de leurs isomères optiques (R) et (S) avec l'isothiocyanate **3.2**.

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4.1: W = CN

4.2: W = CO<sub>2</sub>H

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dans lesquels

R1 représente un groupe alkyle en C<sub>1</sub>-C<sub>3</sub> ;

R5 et R4, conjointement avec l'atome de carbone auquel ils sont fixés, forment un hétérocycle à 5 ou 6 membres comprenant au moins un atome d'oxygène ou un atome d'azote substitué de manière facultative avec un groupe méthyle.

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7. Composition pharmaceutique comprenant, à titre de composant actif, un composé selon l'une quelconque des revendications 1 à 5.

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8. Composition pharmaceutique selon la revendication 7, pour son utilisation à titre d'antagoniste du récepteur androgénique.

9. Composition pharmaceutique selon la revendication 7 ou composition pharmaceutique selon la revendication 8 comprenant en outre une matière de charge inerte et/ou un solvant.

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10. Composition pharmaceutique selon la revendication 7 ou composition pharmaceutique selon l'une quelconque des revendications 8 à 9 comprenant en outre un agent pour traiter des maladies cancéreuses, ledit agent étant différent des composés selon l'une quelconque des revendications 1 à 5.

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11. Médicament sous la forme de comprimés, de capsules ou d'injections pour le traitement de maladies cancéreuses, comprenant un composé selon l'une quelconque des revendications 1 à 5 ou une composition pharmaceutique selon l'une quelconque des revendications 7 à 9.

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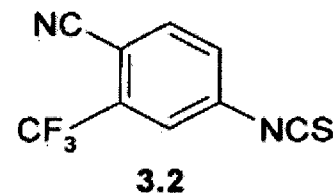
12. Médicament selon la revendication 11, pour son utilisation dans le traitement du cancer de la prostate.

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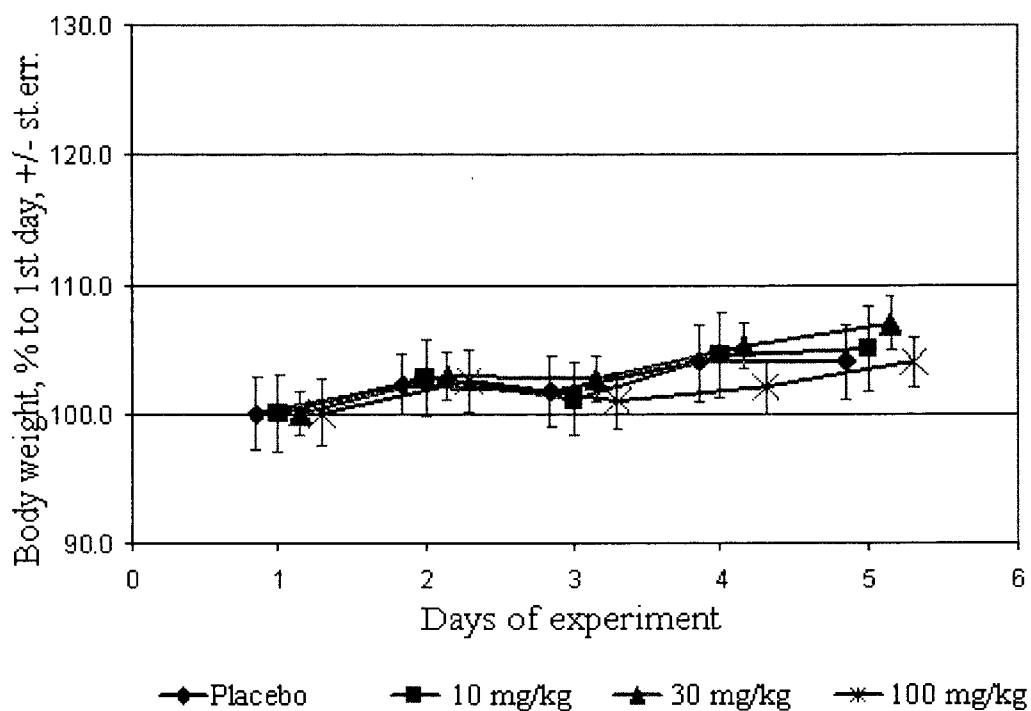


Fig. 1.

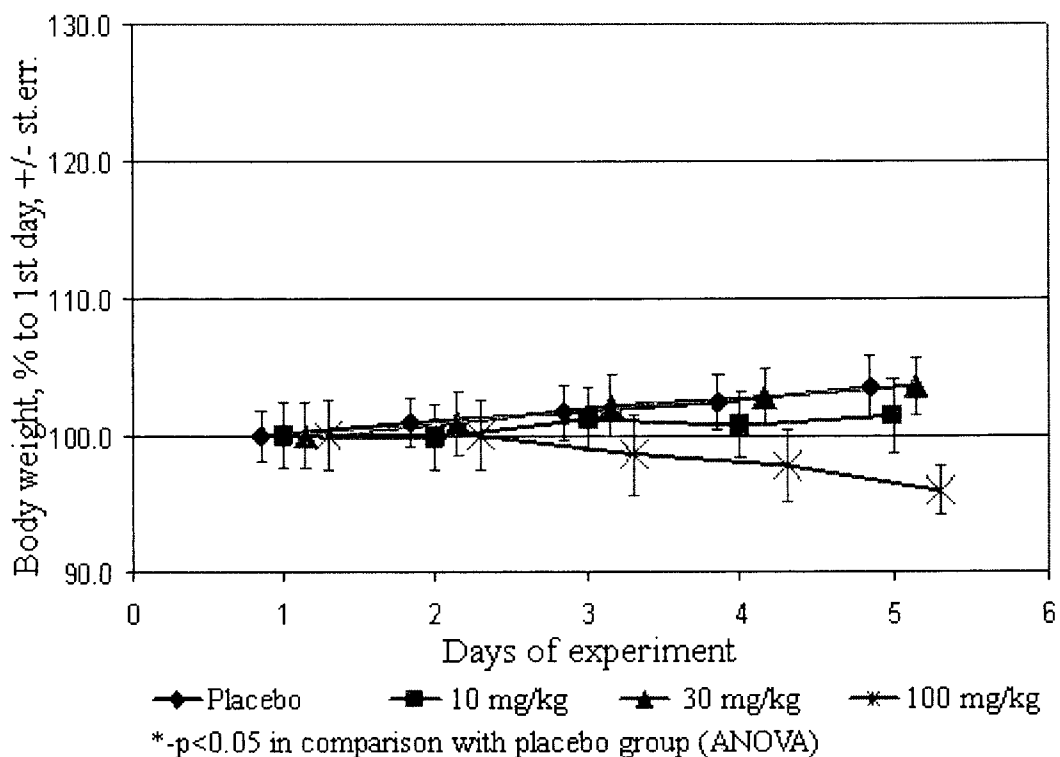


Fig. 2.

**REFERENCES CITED IN THE DESCRIPTION**

*This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.*

**Patent documents cited in the description**

- WO 2006124118 A [0002] [0022]
- WO 2007127010 A [0002] [0022]

**Non-patent literature cited in the description**

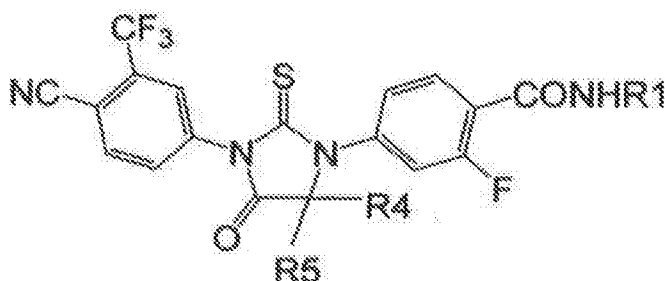
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- **BERGE S.M. et al.** Pharmaceutical Salts. *J.Pharm.Sci.*, 1977, vol. 66, 1-19 [0015]
- *Drug Data Rep.*, 2009, vol. 31 (6), 609 [0022]
- **CHENG, Y. ; PRUSOFF, W. H.** Relationship between the inhibition constant (Ki) and the concentration of inhibitor which causes 50 per cent inhibition (IC50) of an enzymatic reaction. *Biochem Pharmacol.*, 1973, vol. 22, 3099-3108 [0039] [0057]



Ciklikus *n,n'*-diariltiokarbamidok és *n,n'*-diarilkarbamidok mint androgén receptor antagonisták, rákellenes szerek, ezek előállítására szolgáló eljárás és alkalmazásuk.

Szabadalmi igénypontok:

1. Az 1.2 általános képlet szerinti ciklikus *N,N'*-diariltiokarbamid és *N,N'*-diarilkarbamid vegyületek, optikai (R)- és (S)-izomerjeik, és gyógyszerészetileg elfogadható sóik,



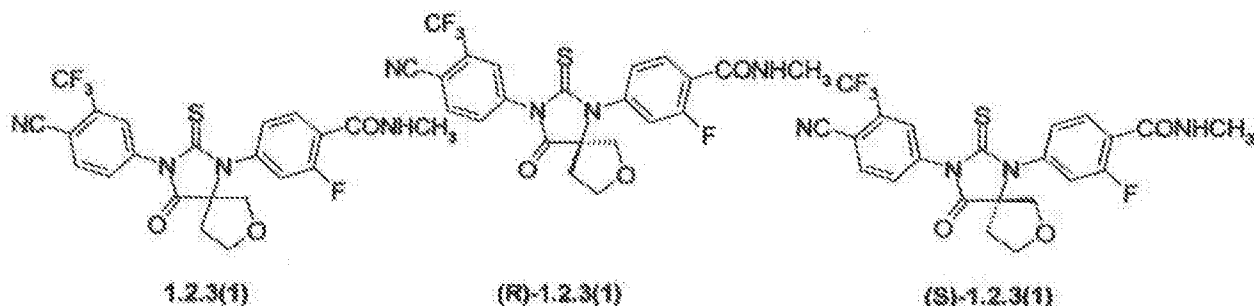
1.2

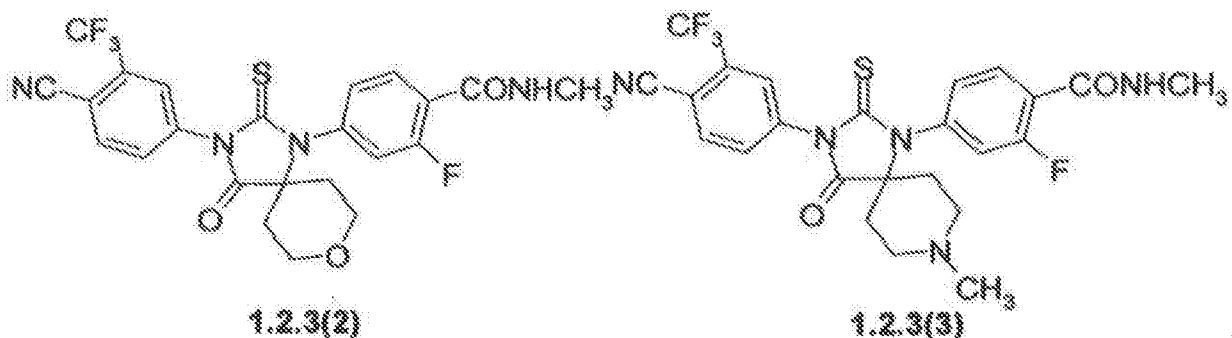
ahol:

R1 jelentése C<sub>1</sub>-C<sub>3</sub> alkil;

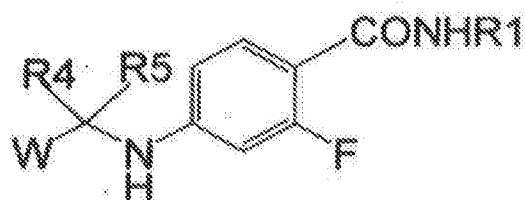
R5 és R4 együttesen a C-atommal, amihez kapcsolódnak egy 5- vagy 6-tagú olyan heterociklust alkotnak, amely legalább egy oxigénatomot vagy nitrogénatomot tartalmaz, amely adott esetben metillett szubsztituált.

2. Az 1. igénypont szerinti vegyületek, amely vegyületek az 1.2.3(1), 1.2.3(2) és 1.2.3(3) képlet szerinti vegyületek, és optikai (R)-izomerjeik - (R)-1.2.3(1), és (S)-izomerjeik - (S)-1.2.3(1),

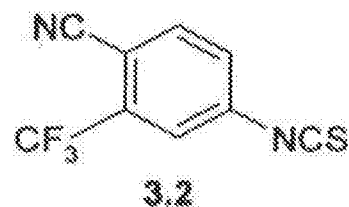




3. Az 1. - 2. igénypontok bármelyike szerinti vegyületek gyógyszerként történő alkalmazására.
4. Az 1. - 3. igénypontok bármelyike szerinti vegyületek rák kezelésében történő alkalmazására.
5. A 4. igénypont szerinti alkalmazásra szolgáló vegyületek, ahol a rák a prosztata rák.
6. Eljárás az 1. - 5. igénypontok bármelyike szerinti 1.2 általános képletű vegyületek és optikai (R)- és (S)-izomerjeik előállítására, ahol a megfelelő 4.1 4-(cianometil)amino-benzamidokat vagy a 4.2 (4-karbamoyl-fenilamino)-ecetsavakat vagy ezek optikai (R)- és (S)-izomerjeit 3.2 izotiocianáttal hozzuk köleszönbatásba



**4.1:** W = CN  
**4.2:** W = CO<sub>2</sub>H



ahol:

R1 jelentése C<sub>1</sub>-C<sub>3</sub> alkil;

R5 és R4 együttesen a C atommal, amihez kapcsolódnak egy 5- vagy 6- tagú olyan heterociklust alkotnak, amely legalább egy oxigénatomot vagy nitrogénatomot tartalmaz, amely adott esetben metilrel szubsztituált.

7. Gyógyszerészeti kompozíció, amely hatóanyagként az 1. - 5. igénypontok bármelyike szerinti vegyületet tartalmazza.
8. A 7. igénypont szerinti gyógyszerészeti kompozíció androgén receptor antagonistaként történő alkalmazásra.

9. A 7. igénypont szerinti gyógyszerészeti kompozíció vagy a 8. igénypont szerinti gyógyszerészeti kompozíció, amely tartalmaz továbbá inert töltőanyagot és/vagy oldószert.
10. A 7. igénypont vagy a 8. - 9. igénypontok bármelyike szerinti gyógyszerészeti kompozíció, amely tartalmaz továbbá rákos betegségek kezelésére szolgáló szert, nevezett szer különbözik az 1. - 5. igénypontok bármelyike szerinti vegyületektől.
11. Gyógyszer tabletták, kapszulák vagy injekciók formájában rákos betegségek kezelésére, amely az 1. - 5. igénypontok bármelyike szerinti vegyületet vagy a 7. - 9. igénypontok bármelyike szerinti gyógyszerészeti készítményt tartalmazza.
12. A 11. igénypont szerinti gyógyszer prosztata rák kezelésében történő alkalmazásra.