judgment

DISTRICT COURT THE HAGUE

Team trade
Court seat The Hague

Judgment of 18 June 2025

in the case with case number / docket number: C/09/654970 / HA ZA 23-903 of

1. the legal entity
ACCORD HEALTHCARE LTD.,
based in North Harrow, Middlesex, United Kingdom,
2. the legal entity
ACCORD HEALTHCARE B.V.,
based in Utrecht,
claimants,
lawyer: mr. M.G.R. van Gardingen in Amsterdam,

against

1. the company under foreign law
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA,
based in Oakland, California, United States of America,
2. the company under foreign law
ASTELLAS PHARMA INC,
based in Tokyo, Japan,
defendants,
lawyer: mr. F.W.E. Eijsvogels in Amsterdam,

and in the case with case number / docket number C/09/654975 / HA ZA 23-904

of the company incorporated under foreign law
SANDOZ AG,
based in Basel, Switzerland,
claimant,
lawyer: mr. D.F. de Lange in Amsterdam,

against

1. the company under foreign law
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA,
based in Oakland, California, United States of America,
2. the company under foreign law
ASTELLAS PHARMA INC,
based in Tokyo, Japan,
defendants,
lawyer: mr. F.W.E. Eijsvogels in Amsterdam.

The parties will hereinafter be referred to separately as Accord Ltd, Accord NL (hereinafter collectively referred to as: Accord), Sandoz, The Regents and Astellas Inc. (hereinafter collectively referred to - also in the operative part - as: Astellas). For Accord and Sandoz (they will hereinafter jointly be referred to - also in the operative part - as: the generics), the substance of the case was handled by the aforementioned mr. Van Gardingen and mrs. B.J. Mooij and R. Rijpkema, lawyers in Amsterdam. Astellas was represented by the aforementioned lawyer and mrs. T.M. Blomme, D.W.R. Henderickx and I.M. ten Brink, lawyers in Amsterdam, assisted by dr. J.H.J. den Hartog, European Patent Attorney.

1. The proceedings in case 23-903

1.1. The course of the procedure is evidenced by:
- the order of the judge in preliminary proceedings of this court dated 9 June 2023 granting leave to Accord to proceed under the Accelerated Regime in Patent Cases;
- the writ of summons dated 16 June 2023;
- the deed of submitting exhibits dated 18 October 2023 with exhibits EP01 to EP22;
- the statement of defence dated 27 December 2023 with exhibits GP01 to GP15;
- Accord's deed of submitting further exhibits dated 1 May 2024 with exhibits EP23 to EP27;
- Astellas' deed of submitting further exhibits dated 1 May 2024 with exhibits GP16 to GP19;
- mr. Eijsvogels' letter of 2 May 2024, in which he objected on behalf of Astellas to exhibits EP23 and EP24, containing expert statements by Westwell and Hickson from the English proceedings, on the grounds that their scope would far exceed the word limit laid down in Article 6.2 of the Accelerated Regime in Patent Cases Regulations 2023;
- mr. Van Gardingen's response on behalf of Accord by letter of the same date;
- mr. Eijsvogels' letter of 3 May 2024 with a response to that again;
- the e-mail from the court clerk to Accord's lawyers dated 3 May 2024 giving them the opportunity to submit a final response to Astellas' letter of 3 May 2024 that afternoon, informing them that thereafter the objection will be decided (and no further responses are desired nor considered in the assessment);
- The response on behalf of Accord by letter dated 3 May 2024;
- mr. Eijsvogels' further response of 3 May 2024 18:05 hrs;
- the e-mail from the court to the parties dated 6 May 2024 informing the parties that, mindful of the instruction given earlier, mr. Eijsvogels' further response dated 3 May 2024 18:05 hrs will not be taken into consideration;
- the court's decision of 6 May 2024 to the effect that the objection was denied but that, in view of the size of the two statements and to that extent in derogation of 6.3 the Accelerated Regime in Patent Cases Regulations 2023, Astellas could respond to each statement with a statement of up to 1800 words instead of the usual 900 words;
- Accord's deed of submitting reactive exhibits of 29 May 2024 with exhibits EP28 to EP30;
- Accord's deed of submitting reactive exhibits dated 29 May 2024 with exhibits EP31 to EP33;
- Astellas' deed of submitting reactive exhibits dated 29 May 2024 with exhibits GP20 to GP22;

- Astellas' deed of submitting an additional exhibit dated 17 June 2024 with exhibit GP23;
- Accord/Sandoz's joint pleading notes;
- Astellas' pleading notes;
- Astellas' response to the Accord/Sandoz joint pleading.

1.2. On 28 June 2024, the oral hearing took place in hybrid format, with some of those present in the courtroom and some participating via video link (MCU). The court asked questions and then the parties replied and rejoined, Accord on the basis of a submitted written closing/reply, in which crossed out paragraph 2 except for the first paragraph, paragraphs 3-5, paragraph 7 last paragraph (except for the first sentence thereof), paragraph 10 last sentence, paragraphs 19 and 20, paragraphs 27 and 28, paragraph 31 except for the first two sentences, paragraph 36 except for the first three sentences, paragraph 38 where it concerns the “nota bene” comment, the citation in paragraph 47 and paragraph 56, which are not pleaded.

1.3. Judgment is further set for today.

2. The proceedings in case 23-904

2.1. The course of the procedure is evidenced by:

- The order of the judge in preliminary proceedings of this court dated 9 June 2023 granting leave to Sandoz to proceed under the Accelerated Regime in Patent Cases;
- the writ of summons dated 16 June 2023;
- the deed of submitting exhibits dated 18 October 2023 with exhibits EP01 to EP30;
- the statement of defence dated 27 December 2023 with exhibits GP01 to GP15;
- Sandoz' deed of submitting further exhibits dated 1 May 2024 with exhibits EP31 to EP36;
- Astellas' deed submitting further exhibits dated 1 May 2024 with exhibits GP16 to GP19;
- mr. Eijsvogels' letter of 2 May 2024 in which he objected on behalf of Astellas to exhibits EP31 and EP32, containing expert statements by Westwell and Hickson from the English proceedings, on the grounds that their scope would far exceed the word limit laid down in Article 6.2 of the Accelerated Regime in Patent Cases Regulations 2023;
- mr. Van Gardingen's response on behalf of Sandoz by letter of the same date;
- mr. Eijsvogels' letter of 3 May 2024 with a response to that again;
- the e-mail from the court clerk to Sandoz's lawyers dated 3 May 2024 giving them the opportunity to submit a final response to Astellas's letter of 3 May 2024 that afternoon, stating that thereafter the objection will be decided (and no further responses are desired nor included in the assessment);
- The response on behalf of Sandoz by letter dated 3 May 2024;
- mr. Eijsvogels' further response of 3 May 2024 18:05 hrs;
- the e-mail from the court to the parties dated 6 May 2024 informing the parties that, mindful of the instruction given earlier, mr. Eijsvogels' further response dated 3 May 2024 18:05 hrs will not be taken into consideration;

- the court's decision of 6 May 2024 to the effect that the objection was denied but that, in view of the size of the two statements and to that extent in derogation of 6.3 Accelerated Regime in Patent Cases Regulations, Astellas could respond to each statement with a statement of up to 1800 words instead of the usual 900 words;
- Sandoz' deed of submitting reactive exhibits dated 29 May 2024 with exhibits EP37 to EP39;
- Sandoz' deed of submitting reactive exhibits dated 29 May 2024 with exhibits EP40 to EP42;
- Astellas' deed of submitting reactive exhibits dated 29 May 2024 with exhibits GP20 to GP22;
- Astellas' deed of submitting an additional exhibit dated 17 June 2024 with exhibit GP23;
- Accord/Sandoz's joint pleading notes;
- Astellas' pleading notes;
- Astellas' response to the Accord/Sandoz joint pleading.

2.2. On 28 June 2024, the oral proceedings took place in hybrid format, with some of those present in the courtroom and some participating via video link (MCU). The court asked questions and the parties subsequently argued and rejoined, Sandoz on the basis of a written closing/reply, in which crossed out paragraph 2 except for the first paragraph, paragraphs 3-5, paragraph 7 last paragraph (except for the first sentence thereof), paragraph 10 last sentence, paragraphs 19 and 20, paragraphs 27 and 28, paragraph 31 except for the first two sentences, paragraph 36 except for the first three sentences, paragraph 38 with regard to the “nota bene” comment, the citation in paragraph 47 and paragraph 56, which were not pleaded.

2.3. Judgement is further set for today.

3. The facts in both cases

3.1. Accord Ltd is part of the Accord Healthcare group, which focuses on the development, production and distribution of generic drugs in particular. Accord NL supplies Accord products to the Dutch market.

3.2. Sandoz operates in the generic pharmaceutical industry. It is part of the Novartis group, a global group of companies active in both innovative and generic medicines.

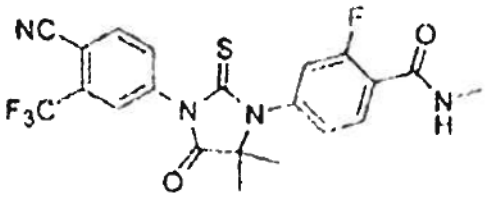
3.3. The Regents holds European patent 1 893 196 B2 (hereinafter also referred to as EP 196), entitled ‘*Diarylhydanoin compound’* (the Dutch translation of which reads ‘diarylhydantoïne verbindingen’) and its Supplementary Protection Certificate 300632 (hereinafter referred to as the SPC). EP 196 was granted on 18 January 2012 on an international application dated 29 March 2006, with number PCT/US2006/011417 (hereinafter: the (original) PCT application) published on 23 November 2006 as WO 2006/124118 A1 (hereinafter: WO 118). This included a claim of priority of US 680835 P dated 13 May 2005 (hereinafter P1), US 750351 P dated 15 December 2005 (hereinafter P2) and US 756552 P dated 6 January 2006 (hereinafter P3). EP 196 is the primary patent on (the use of) enzalutamide: it claims the compound enzalutamide as such, in addition to the medical use

thereof. The SPC, which takes effect on 29 March 2026, protects enzalutamide, in the form of a pharmaceutically acceptable salt thereof if desired, and expires on 24 June 2028.

3.4. EP 196's original application contained 52 claims, with claim 1 claiming a Markush formula. To address the Examing Division's objections, The Regents limited the claims to a specific compound, namely RD162' / enzalutamide. On the basis of that limitation, the patent was granted. Against the grant of the patent, opposition was filed. Shortly before the *oral hearings*, the opponent withdrew the request for an oral hearing. As a result, the hearing was cancelled and the opposition proceedings continued in writing. The patent was marginally amended in opposition. The only amendment was the removal of the term 'surgery' from claims 2 and 5, in response to an added matter objection by the Opposition Division. The Opposition Division's decision was not appealed. The prior art relied upon in these proceedings was not part of the opposition proceedings and thus was not previously included in the assessment of the validity of the patent.

3.5. EP 196 contains one independent claim (claim 1) and thereon dependent claims (2 to 18). In the original English language, these read as follows:

1. A compound having the formula



[RD162']

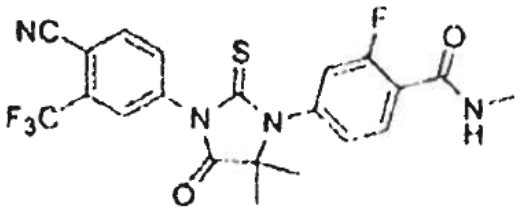
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof for use in the treatment of the human or animal body by therapy.
3. A compound according to claim 1 or a pharmaceutically acceptable salt thereof for use in a method of treating a hyperproliferative disorder.
4. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof. and a pharmaceutically acceptable carrier or diluent.
5. A pharmaceutical composition according to claim 4 for use in the treatment of the human or animal body by therapy.
6. A pharmaceutical composition according to claim 4. for use in a method for treating a hyperproliferative disorder.
7. The composition of claim 6. wherein the composition is administered at a dosage of the compound in the range of
(a) from about 0.00 1mg per kg body weight per day to about 100 mg per kg body weight per day. or
(b) from about 0.01 mg per kg body weight per day to about 1 00 mg per kg body weight per day. or
(c) from about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day.
8. The composition of claim 6. wherein the composition is administered at a dosage of the compound of about 1 mg per kg body weight per day.
9. The compound of claim 3 or a pharmaceutically acceptable salt thereof or the composition of claim 6. wherein the hyperproliferative disorder is hormone refractory prostate cancer.

10. The compound of claim 3 or a pharmaceutically acceptable salt thereof or the composition of claim 6. wherein the hyperproliferative disorder is prostate cancer.
11. The composition of claim 6. wherein the composition is administered by intravenous injection. by injection into tissue. intraperitoneally. orally. or nasally.
12. The composition of claim 6. wherein the composition has a form selected from the group consisting of a solution. dispersion. suspension. powder. capsule. tablet. pill. time release capsule. time release tablet. and time release pill.
13. A composition according to any one of claims 4 to 6. wherein the carrier is a liquid and the compound is dissolved in the liquid.
14. A composition according to any one of claims 4 to 6. wherein the carrier is a solvent.
15. Use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition as defined in any one of claims 4. 7. 8 or 11 to 14 in the manufacture of a medicament for use in a method of treating a hyperproliferative disorder.
16. Use according to claim 15. wherein the hyperproliferative disorder is prostate cancer.
17. Use according to claim 15. wherein the hyperproliferative disorder is hormone refractory prostate cancer.
18. Use according to claim 15. wherein the hyperproliferative disorder is hormone sensitive prostate cancer.

3.6. In the uncontested Dutch translation, the claims of EP 508 read as follows:

1. Verbinding met de formule



[RD162']

of een farmaceutisch aanvaardbaar zout daarvan.
2. Verbinding volgens conclusie 1 of een farmaceutisch aanvaardbaar zout daarvan voor gebruik bij de behandeling van het menselijke of dierlijke lichaam door middel van therapie.
3. Verbinding volgens conclusie 1 of een farmaceutisch aanvaardbaar zout daarvan voor gebruik in een werkwijze voor de behandeling van een hyperproliferatieve stoornis.
4. Farmaceutisch preparaat dat een therapeutisch effectieve hoeveelheid van een verbinding volgens conclusie 1 of een farmaceutisch aanvaardbaar zout daarvan en een farmaceutisch aanvaardbare drager of verdunningsmiddel omvat.
5. Farmaceutisch preparaat volgens conclusie 4 voor gebruik bij de behandeling van het menselijke of dierlijke lichaam door middel van therapie.
6. Farmaceutisch preparaat volgens conclusie 4 voor gebruik in een werkwijze voor de behandeling van een hyperproliferatieve stoornis.
7. Preparaat volgens conclusie 6. waarbij het preparaat wordt toegediend met een dosering van de verbinding in het traject van
(a) ongeveer 0.001 mg per kg lichaamsgewicht per dag tot ongeveer 100 mg per kg lichaamsgewicht per dag. of
(b) ongeveer 0.01 mg per kg lichaamsgewicht per dag tot ongeveer 100 mg per kg lichaamsgewicht per dag. of
(c) ongeveer 0.1 mg per kg lichaamsgewicht per dag tot ongeveer 10 mg per kg lichaamsgewicht per dag.
8. Preparaat volgens conclusie 6. waarbij het preparaat wordt toegediend met een dosering van de verbinding van ongeveer 1 mg per kg lichaamsgewicht per dag.
9. Verbinding volgens conclusie 3 of een farmaceutisch aanvaardbaar zout daarvan of preparaat volgens conclusie 6. waarbij de hyperproliferatieve stoornis hormoonresistente prostaatkanker is.
10. Verbinding volgens conclusie 3 of een farmaceutisch aanvaardbaar zout daarvan of preparaat volgens conclusie 6. waarbij de hyperproliferatieve stoornis prostaatkanker is.

11. Preparaat volgens conclusie 6. waarbij het preparaat door middel van intraveneuze injectie. door middel van injectie in weefsel. intraperitoneaal. oraal of nasaal wordt toegediend.
12. Preparaat volgens conclusie 6. waarbij het preparaat een vorm heeft gekozen uit de groep bestaande uit een oplossing. dispersie. suspensie. poeder. capsule. tablet. pil. capsule met vertraagde afgifte. tablet met vertraagde afgifte en pil met vertraagde afgifte.
13. Preparaat volgens een van de conclusies 4 tot 6. waarbij de drager een vloeistof is en de verbinding opgelost is in de vloeistof.
14. Preparaat volgens een van de conclusies 4 tot 6. waarbij de drager een oplosmiddel is.
15. Gebruik van een verbinding volgens conclusie 1 of een farmaceutisch aanvaardbaar zout daarvan of een farmaceutisch preparaat zoals gedefinieerd in een van de conclusies 4. 7. 8 of 11 tot 14 bij de bereiding van een geneesmiddel voor gebruik in een werkwijze voor de behandeling van een hyperproliferatieve stoornis.
16. Gebruik volgens conclusie 15. waarbij de hyperproliferatieve stoornis prostaatkanker is.
17. Gebruik volgens conclusie 15. waarbij de hyperproliferatieve stoornis hormoonresistente prostaatkanker is.
18. Gebruik volgens conclusie 15. waarbij de hyperproliferatieve stoornis hormoongevoelige prostaatkanker is.

3.7. The description of the patent - as far as relevant here - includes the following:

FIELD OF THE INVENTION

[0001] The present invention relates to a diarylhydantoin compound and methods for synthesizing them and using them in the treatment of hormone refractory prostate cancer.

BACKGROUND OF THE INVENTION

[0002] Prostate cancer is the most common incidence of cancer and the second leading cause of cancer death in Western men. When the cancer is confined locally. the disease can be cured by surgery or radiation. However. 30% of such cancer relapses with distant metastatic disease and others have advanced disease at diagnoses. Advanced disease is treated by castration and/or administration of antiandrogens. the so-called androgen deprivation therapy. Castration lowers the circulating levels of androgens and reduces the activity of androgen receptor (AR). Administration of antiandrogens blocks AR function by competing away androgen binding. therefore. reducing the AR activity. Although initially effective. these treatments quickly fail and the cancer becomes hormone refractory.

[0003] Recently. overexpression of AR has been identified and validated as a cause of hormone refractory prostate cancer. See Chen. C.D.. Welsbie. D.S.. Tran. C.. Baek. S.H.. Chen. R. Vessella. R. Rosenfeld. M.G.. and Sawyers. C.L.. Molecular determinants of resistance to antiandrogen therapy. Nat. Meal. 10: 33-39. 2004. Overexpression of AR is sufficient to cause progression from hormone sensitive to hormone refractory prostate cancer. suggesting that better AR inhibitors than the current drugs can slow the progression of prostate cancer. It was demonstrated that AR and its ligand binding are necessary for growth of hormone refractory prostate cancer. indicating that AR is still a target for this disease. It was also demonstrated that overexpression of AR converts anti-androgens from antagonists to agonists in hormone refractory prostate cancer (an AR antagonist inhabits AR activity and an AR agonist stimulates AR activity). Data from this work explains why castration and anti-androgens fail to prevent prostate cancer progression and reveals unrecognized properties of hormone refractory prostate cancer.

[0004] Bicalutamide (brand name: Casodex) is the most commonly used anti-androgen. While it has an inhibitory effect on AR in hormone sensitive prostate cancer. it fails to suppress AR when cancer becomes hormone refractory. Two weaknesses of current antiandrogens are blamed for the failure to prevent prostate cancer progression from the

hormone sensitive stage to the hormone refractory disease and to effectively treat hormone refractory prostate cancer. One is their weak antagonistic activities and the other is their strong agonistic activities when AR is overexpressed in hormone refractory prostate cancer. Therefore, better AR inhibitors with more potent antagonistic activities and minimal agonistic activities are needed to delay disease progression and to treat the fatal hormone refractory prostate cancer.

[0005] Nonsteroidal anti-androgens, such as bicalutamide, have been preferred over steroidal compounds for prostate cancer because they are more selective and have fewer side effects. This class of compounds has been described in many patents such as U.S. Patent Number 4,097,578, U.S. Pat. No. 5,411,981, U.S. Pat. No. 5,705,654, PCT International Applications WO 97/00071 and WO 00/17163, and U.S. Published Patent Application Number 2004/0009969.

[0006] U.S. Patent No. 5,434,176 includes broad claims which encompass a very large number of compounds, but synthetic routes are only presented for a small fraction of these compounds and pharmacological data are only presented for two of them, and one skilled in the art could not readily envision other specific compounds.

[0007] Because the mechanism of hormone refractory prostate cancer was not known, there was no biological system to test these compounds described in these patents for their effect on hormone refractory prostate cancer. Particularly, the ability of AR overexpression in hormone refractory prostate cancer to switch inhibitors from antagonist, to agonists was not recognized. Some new properties of hormone refractory prostate cancer are reported in PCT applications US04/42221 and US05/05529. PCT International Application US05/05529 presented a methodology for identifying androgen receptor antagonist and agonist characteristics of compounds. However, for each compound produced, the time consuming process of determining the antagonist and agonist characteristics of a compound must be determined. That is, there is no method to accurately predict characteristics relevant to treating prostate cancer from the chemical structure of a compound alone.

WO 2006/028226 describes imidazolidine derivatives that have a substituted alkyl group at a 3-position, which show an anti-androgen activity.

EP 0580459 describes substituted phenylimidazolidine compounds and their use as medicaments.

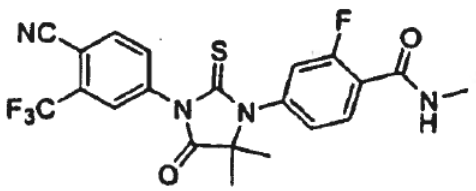
[0008] There is a need for new thiohydantoin compounds having desirable pharmacological properties, and synthetic pathways for preparing them. Because activities are sensitive to small structural changes, one compound may be effective in treating prostate cancer, whereas a second compound may be ineffective, even if it differs from the first compound only slightly, say by the replacement of a single substituent.

[0009] Identification of compounds which have high potency to antagonize the androgen activity, and which have minimal agonistic activity should overcome hormone refractory prostate cancer (HRPC) and avoid or slow down the progression of hormone sensitive prostate cancer (HSPC). Therefore, there is a need in the art for the identification of selective modulators of the androgen receptor, such as modulators which are non-steroidal, non-toxic, and tissue selective.

SUMMARY OF THE INVENTION

[0010] The invention provides a compound having strong antagonistic activity with minimal agonistic activity against AR. This compound inhibits the growth of hormone refractory prostate cancer.

[0011] The invention includes a compound having the formula



[RD162']

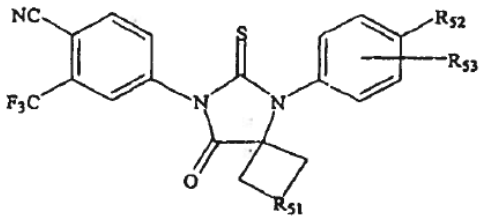
or a pharmaceutically acceptable salt thereof.

[0012] The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of the preceding compound or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

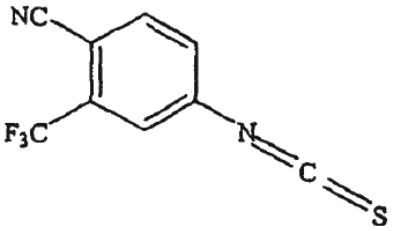
[0013] The invention encompasses the pharmaceutical composition for use in a method for treating a hyperproliferative disorder comprising administering such a pharmaceutical composition to a subject in need of such treatment, thereby treating the hyperproliferative disorder. The hyperproliferative disorder may be hormone refractory prostate cancer. The dosage may be in the range of from about 0.001 mg per kg body weight per day to about 100 mg per kg body weight per day, about 0.01 mg per kg body weight per day to about 100 mg per kg body weight per day, about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day, or about 1 mg per kg body weight per day.

[0014] The compound may be administered by intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally. The composition may have a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release pill.

[0015] Also described is a method of synthesizing a diaryl compound of formula:

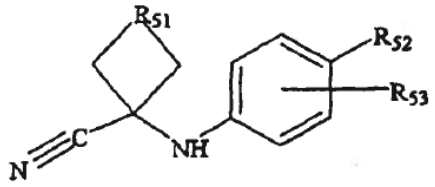


comprising mixing Compound I



Compound I

with Compound II



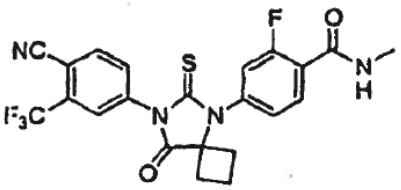
Compound II

in a first polar solvent to form a mixture, heating the mixture, adding a second polar solvent, the same as or different from the first polar solvent, and an aqueous acid to the mixture, refluxing the mixture, cooling the mixture and combining with water, and separating the diaryl compound from the mixture, wherein R51 comprises an alkyl chain of from 1 to 4 carbon atoms. R52 is selected &om the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl,

methoxycarbonyl. 3-cyano-4-truluoromethylphenylcarbamoyl. carbamoyl-substituted alkyl. carboxymethyl. methoxycarbonylmethyl. methanesulfonyl. 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl. carboxy-substitutedn alkyl.
4-methanesulfonyl-1-piperazinyl. piperazinyl. hydroxyethylcarbamoyl-substituted alkyl. and hydroxyethoxycarbonyl-substituted alkyl. and R53 is selected from the group consisting of F and H.

[0016] R51 may comprise an alkyl chain of from 1 to 2 carbon atoms. R52 may be selected From the group consisting of carbamoyl and methylcarbamoyl. and R53 may be F.

[0017] Methods of synthesizing a compound of formula are also described



[RD162]

comprising mixing 4-isothiocyanato-2-trifluoromethylbenzonihile and N-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide in dimethylformamide to form a first mixtures. heating the first mixture to form a second mixtiure. adding alcohol and acid to the second mixture to form a third mixture. refluxing the third mixture to form a fourth mixture. cooling the fourth mixture. combining the fourth mixture with water and extracting an organic layer. isolating the compound from the organic layer.

[0018] Likewise. a method of synthesizing RD162 is described comprising mixing N-Methyl-2-fluoro-4-(1.1-dimethylcyanomethyl) aminobenzamide and 4-Isothiocyanato-2-trifluoromethylbenzonitrile in DMF and heating to form a first mixture. and processing as above.

[0019] The compound of the invention has substantial androgen receptor antagonist activity and no substantial agonist activity on hormone refractory prostate cancer cells.

[0020] Also described herein is a method comprising providing the compound of the invention. measuring inhibition of androgen receptor activity for the compound and determining if the inhibition is above a first predetermined level. measuring stimulation of androgen receptor activity in hormone refractory cancer cells for the compound and determining if the stimulation is below a second predetermined level. and selecting the compound if the inhibition is above the first predetermined level and the stimulation is below the second predetermined level. The predetermined levels may be those of bicalutamide. The step of measuring inhibition may comprise measuring inhibitory concentration (IC50) in an AR response reporter system or a prostate specific antigen secreting system. The step of measuring stimulation may comprise measuring fold induction by increasing concentrations in an AR response reporter system or a prostate specific antigen secreting system. The method of measuring inhibition and/or stimulation may comprise measuring an effect of the compound on tumor growth in an animal.

BRIEF DESCRIPTION OF THE DRAWINGS

(...)

[0043] Figure 21 is a graph presenting PSA absorbance associated with LN-AR cells treated with various concentrations of RD 162. RD162', RD162", and RD170 and vehicle solution.

(...)

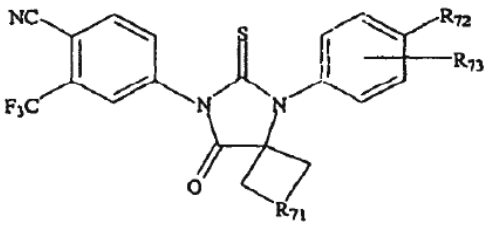
DETAILED DESCRIPTION

[0052] Embodiments of the invention are discussed in detail below. In describing embodiments. specific terminology is employed for the sake of clarity. However. the invention is not intended to be limited to the specific terminology so

selected.

Synthesis of Diarylhydantoin Compounds

[0053] The synthesis of diarylthiohydantoin compounds having the formula is described:



with R71 including an alkyl chain of from 1 to 4 carbon atoms. For example, R72 can be carbamoyl, e.g., -(CO)NH2, or methylcarbamoyl, e.g., -(CO)NHCH3. An amide group bonded at the carbon atom of the carbonyl to another structure is termed a carbamoyl substituent. For example, R73 can be a fluorine or a hydrogen atom. That is, a fluorine atom can be attached to any one of the carbons of the right-hand aryl ring which are not bonded to the R72 substituent or the nitrogen atom. Alternatively, no fluorine atom can be attached to the carbons of the right hand aryl ring which are not bonded to the R72 substituent or the nitrogen atom. For example, a hydrogen atom can be attached to each of the carbons of the right-hand aryl ring which are not bonded to the R72 substituent or the nitrogen atom

[0054] A list of several reference compounds is presented in Tables 5 - 11. The compound of the invention ([RD162']) is presented in Table 5. The compounds are grouped into tiers, with Tier 1 to Tier 3 compounds being expected to be superior to bicalutamide for the treatment of prostate cancer, Tier 4 compounds being comparable to bicalutamide in effectiveness, and Tier 5 and Tier 6 compounds being worse than bicalutamide for the treatment of prostate cancer. A more detained description of the protocol used to rank the compounds into tiers is presented below.

(...)

Example 52 [RD162]

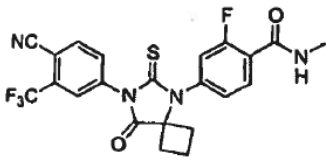
[0184] Thionyl chloride (2.38 g, 20 mmol) was added slowly to a solution of 2-fluoro-4-nitrobenzoic acid (2.97 g, 16 mmol) in DMF (50 ml) cooled at -5°C. The mixture was stirred for an additional 1 hour at -5°C. Methylamine (0.62 g, 20 mmol; freshly distilled from its 40% aqueous solution) was added to the reaction medium. The second mixture was stirred for an additional 1 hour. Ethyl acetate (300 ml) was added to the mixture, which was washed with brine (3 3 150 ml). The organic layer was dried over MgSO4, and concentrated to yield *N*-methyl-2-fluoro-4-nitrobenzamide (52a) (2.89 g, 14.6 mmol, 91%) as a yellow solid. 1H NMR (Acetone d6, 400 MHz) δ 3.05 (d, *J* = 4.3 Hz, 3H), 6.31 (dd, *J* = 13.5, 2.1 Hz, 1H), 6.40 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.64 (dd, *J* = 8.6, 8.6 Hz, 1H).

[0185] A mixture of *N*-methyl-2-fluoro-4-nitrobenzamide (52a) (2.89 g, 14.6 mmol) and iron (5.04 g, 90 mmol) in ethyl acetate (40 ml) and acetic acid (40 ml) was refluxed for 1 hour. The solid particles were filtered off. The filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over MgSO4, concentrated and chromatographed (dichloromethane:acetone, 95:5) to yield *N*-methyl-2-fluoro-4-aminobenzamide (52b) (2.3 g, 13.7 mmol, 94%) as an off-white solid. **1H** NMR (acetone-d6, 400 MHz) δ 2.86 (d, *J* = 4.3 Hz, 3H), 5.50 (bs, 2H), 6.37 (dd, *J1* = 14.7 Hz, *J2* = 2.1 Hz, 1H), 6.50 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.06 (bs, 1H), 7.68 (dd, *J* = 8.8 8.8 Hz, 1H); 13C NMR (acetone-d6, 100 MHz) δ 25.8, 99.6 (d, *J* = 13.8 Hz), 109.2 (d, *J* = 12.8 Hz), 110.0 (d, *J* = 1.6 Hz), 132.5 (d, *J* = 4.8 Hz), 153.5 (d, *J* = 12.6 Hz), 162.2 (d, *J* = 242.5 Hz), 164.0 (d, *J* = 3.1 Hz).

[0186] Sodium cyanide (1.47 g, 30 mmol) was added to a mixture of N-methyl-2-fluoro-4-aminobenzamide (52b) (1.68 g, 10 mmol) and cyclobutanone (1.4 g, 20 mmol) in 90% acetic acid (20 ml). The reaction mixture was stirred at 80 °C for 24 hours. The mixture was washed with water and extracted with ethyl acetate. The organic layer was dried over

magnesium sulfate and concentrated to dryness under vacuum. The solid was washed with a 50:50 mixture of ethyl ether and hexane (10 ml) to remove cyclobutanone cyanohydrin to afford after filtration *N*-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide (52c) (2.19 g. 8.87 mmol. 89%). 1H NMR (CDCl3. 400 MHz) δ 1.87-1.95 (m. 1H). 2.16-2.27 (m. 1H). 2.35-2.41 (m. 2H). 2.76-2.83 (m. 2H). 2.97 (d. *J* = 4.4 Hz. 3H). 4.68 (bs. 1H). 6.29 (dd. *J* = 14.3. 1.8 Hz. 1H). 6.48 (dd. *J* = 8.3. 1.8 Hz. 1H). 6.75 (q. *J* = 4.4 Hz. 1H). 7.90 (dd. *J* = 8.3. 8.3 Hz. 1H); 13C NMR (CDCl3. 100 MHz) δ 15.7. 26.7. 33.9. 49.4. 100.2 (d. *J* = 29.5 Hz). 110.6. 111.0 (d. *J* = 11.8 Hz). 133.1 (d. *J* = 4.2 Hz). 148.4 (d. *J* = 12.0 Hz). 162.0 (d. *J* = 244.1 Hz). 164.4 (d. *J* = 3 .6 Hz).

[0187] A mixture of 4-isothiocyanato-2-trifluoromethylbenzonitrile (1a) (2.16 g. 9.47 mmol) and *N*-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide (52c) (1.303 g. 5.27 mmol) in DMF (20 ml) was heated under microwave irradiation at 80°C for 16 hours. To this mixture was added methanol (50 ml) and aq. 2N HCl (20 ml). The second mixture was refluxed for 3 hours. After being cooled to room temperature. the reaction mixture was poured into cold water (100 ml) and extracted with ethyl acetate (150 ml). The organic layer was dried over MgSO4. concentrated and chromatographed (dichloromethane:acetone. 95:5) to yield *N*-methyl-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5.7-diazaspiro[3.4]oct-5-yl]-2-fluorobenzamide (52d) **[RD162]** (1.43 g. 3.0 mmol. 57%). the structure of which is illustrated in Formula 28. as a yellow powder.



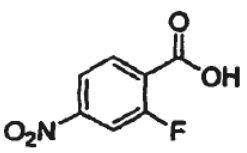
Formula 28

1H NMR (CDCl3. 400 MHz) δ 1.65-1.75 (m. 1H). 2.18-2.30 (m. 1H). 2.49-2.57 (m. 2H). 2.67-2.73 (m. 2H). 3.07 (d. *J* =4.4 Hz. 3H). 6.75 (q. *J* = 4.6 Hz. 1H). 7.17 (dd. *J* = 11.5. 1.9 Hz. 1H). 7.26 (dd. *J* = 8.3. 1.9 Hz. 1H). 7.83 (dd. *J* = 8.2. 2.0 Hz. 1H). 7.95 (d. *J* = 1.8 Hz. 1H). 7.97 (d. *J* = 8.3 Hz. 1H) 8.30 (dd. *J* = 8.3. 8.3 Hz. 1H); 13C NMR (CDCl3. 100 MHz) δ 13.6. 27.0. 31.7. 67.4. 110.3. 114.8. 118.2. 118.5. 121.9 (q. *J* = 272.7 Hz). 126.6. 127.0 (q. *J* = 4.8 Hz). 132.1. 133.3 (q. *J* = 33.2 Hz). 133.8. 135.3. 136.8. 139.1 (d. *J* = 10.9 Hz). 160.5 (d. *J* = 249.1 Hz). 162.7 (d. *J* = 3.3 Hz). 174.3. 179.8; 19F NMR (CDCl3. 100 MHz) δ -111.13. -62.58.

(...)

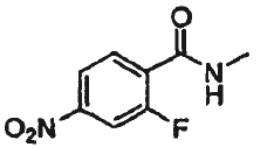
Example 56 [RD162']

[0195] In the following. air or moisture sensitive reactions were conducted under argon atmosphere using oven-dried glassware and standard syringe/septa techniques. The reactions were monitored with a SiO2 TLC plate under UV light (254 nm) followed by visualization with a *p*-anisaldehyde or ninhydrin staining solution. Column chromatography was performed on silica gel 60. 1H NMR spectra were measured at 400 MHz in CDCl3 unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS. 0.0 ppm): chemical shift (multiplicity. integration. coupling constant in Hz.).



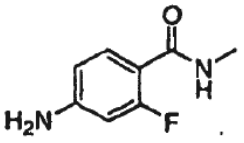
Formula 37

[0196] Periodic acid (1.69 g. 7.41 mmol) was dissolved in acetonitrile (25 mL) by vigorous stirring. and then chromium trioxide (0.16 g. 1.60 mmol) was dissolved into the solution. 2-Fluoro-4-nitrotoluene (0.33 g. 2.13 mmol) was added to the above solution with stirring. A white precipitate formed immediately with exothermic reaction. After 1 h of stirring. the supernatant liquid of the reaction mixture was decanted to a flask. and the solvent was removed by evaporation. The residues were extracted with methylene chloride (2x30 mL) and water (2330 mL). The organic layer was dried over MgSO4. and concentrated to give 2-Fluoro-4-nitrobenzoic acid (Formula 37) (0.32 mg. 81%) as a white solid. 1H NMR δ 8.06 (ddd. 1 H. *J*=9.9. 2.2 and 0.3). 8.13 (ddd. 1 H. *J*=8.6. 2.2 and 0.9). 8.25 (ddd. 1 H. *J*=8.6. 7.0 and 0.3).



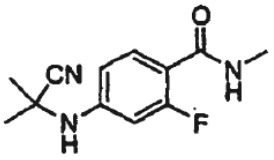
Formula 38

[0197] Thionyl chloride (0.15 g. 1.30 mmol) was added slowly to a solution of 2-fluoro-4-nitrobenzoic acid (Formula 37) (0.20 g. 1.10 mmol) in DMF (5 mL) cooled at -5 °C. The mixture was stirred for an additional 1 hour at -5 °C. Excess methylamine (freshly distilled from its 40% aqueous solution) was added to the reaction medium. The second mixture was stirred for an additional 1 hour. Ethyl acetate (50 mL) was added to the mixture. which was washed with brine (2 x 50 ml). The organic layer was dried over MgSO4. and concentrated to yield *N*-Methyl-2-fluoro-4-nitrobenzamide (Formula 38) (0.18 g. 85%) as a yellowish solid. 1H NMR (acetone-*d6*) δ 3.05 (d. 3 H. *J*=4.3). 6.31 (dd. 1 H. *J*=13.5 and 2.1). 6.40 (dd. 1H. *J*=8.6 and 2.1). 7.64 (dd. 1H. *J*= 8.6 and 8.6).



Formula 39

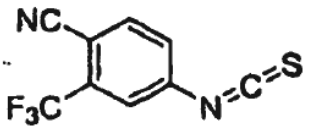
[0198] A mixture of *N*-Methyl-2-fluoro-4-nitrobenzamide (Formula 3 8) (0.18 g. 0.91 mmol) and iron (0.31 g. 5.60 mmol) in ethyl acetate (5 mL) and acetic acid (5 mL) was refluxed for 1 h. The solid particles were filtered off. The filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over MgSO4. concentrated and the residue was purified with SiO2 column chromatography (dichloromethane:acetone. 95:5) to give *N*-Methyl-2-fluoro-4-aminobenzamide (Formula 39) (0.14 g. 92%) as an off-white solid. 1H NMR (acetone-*d6*) δ 2.86 (d. 3 H. *J*=4.3). 5.50 (br s. 2 H). 6.37 (dd. 1 H. *J*=14.7 and 2.1). 6.50 (dd. 1H. *J*=8.6 and 2.1). 7.06 (br s. 1H). 7.68 (dd. 1H. *J*=8.8 and 8.8).



Formula 40

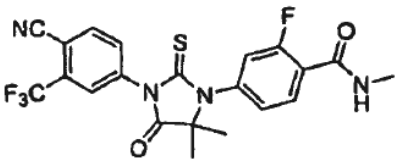
[0199] A mixture of *N*-Methyl-2-fluoro-4-aminobenzamide (Formula 39) (96 mg. 0.57 mmol). acetone cyanohydrin (0.3 mL. 3.14 mmol) and magnesium sulfate (50 mg) was heated to 80 °C and stirred for 12 h. To the medium was added ethyl acetate (25 mL) and then washed with water (2 3 25 mL). The organic layer was dried over MgSO4 and concentrated

and the residue was purified with SiO2 column chromatography (dichloromethane:acetone. 95:5) to give *N*-Methyl-2-fluoro-4-(1.1-dimethylcyanomethyl)-aminobenzamide (Formula 40) (101 mg. 75%) as a white solid. 1H NMR δ 1.74 (s. 6 H). 2.98 (dd. 3 H. *J*=4.8 and 1.1). 6.58 (dd. 1 H. *J*=14.6 and 2.3). 6.63 (dd. 1 H. *J*=8.7 and 2.3). 6.66 (br s. 1 H). 7.94 (dd. 1 H. *J*=8.7 and 8.7).



Formula 41

[0200] 4-Amino-2-trifluoromethylbenzonitrile (2.23 g. 12 mmol) was added portionwise over 15 min into a well-stirred heterogeneous mixture of thiophosgene (1 mL. 13 mmol) in water (22 mL) at room temperature. Stirring was continued for an additional 1 h. The reaction medium was extracted with chloroform (3 3 15 ml). The combined organic phase was dried over MgSO4 and evaporated to dryness under reduced pressure to yield desired product 4-Isothiocyanato-2-trifluoromethylbenzonitrile (Formula 41) as brownish solid and was used as such for the next step (2.72 g. 11.9 mmol. 99%). 1H NMR δ 7.49 (dd. 1 H. J=8.3 and 2.1). 7.59 (d. 1 H. J=2.1). 7.84 (d. 1 H. J=8.3).



RD162' (Formula 42)

56-1) RD162'

[0201] A mixture of *N*-Methyl-2-fluoro-4-(1.1-dimethyl-cyanomethyl)-aminobenzamide (Formula 40) (30 mg. 0.13 mmol) and 4-Isothiocyanato-2-trifluoromethylbenzonitrile (Formula 41) (58 mag. 0.26 mmol) in DMF (1 mL) was heated under microwave irradiation at 100 °C for 11 hours. To this mixture was added methanol (20 mL) and *aq.* 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature. the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over MgSO4. concentrated and the residue was purified with SiO2 column chromatography (dichloromethane acetone. 95:5) to give **RD162'** (Formula 42) (15 mg. 25%) as a colorless crystal. 1H NMR δ 1.61 (s. 6 H). 3.07 (d. 3 H. *J*=4.1). 6.71 (m. 1 H). 7.15 (dd. 1H. *J*=11.7 and 2.0). 7.24 (dd. 1H. *J*=8.4 and 2.0). 7.83 (dd. 1H. *J*=8.2 and 2.1). 7.95 (d. 1H. *J*=2.1). 7.99 (d. 1H. *J*=8.2). 8.28 (dd. 1H. *J*=8.4 and 8.4).

(...)

Pharmacological examination of the compounds

[0218] Compounds for which synthetic routes are described above were identified through screening on hormone refractory prostate cancer cells for antagonistic and agonistic activities against AR utilizing screening procedures similar to those in PCT applications US04/42221 and US05/05529. A number of compounds exhibited potent antagonistic activities with minimal agonistic activities for over expressed AR in hormone refractory prostate cancer.

(...)

Ranking of Compounds in Tiers

[0241] Tables 5 - 10 present diarylhydantoin compounds grouped into Tiers 1-6. Table 11 presents diarylhydantoin compounds which have not been placed into a tier. The placement of compounds into tiers was based on available data coupled with analytical judgment. Data considered included in vitro assays (AR response reporter system in LNCaP cell line. PSA level measurement. MTS mitochondrial assay) and in vivo experiments (tumor size measured directly or by emission induced by luciferase reporter gene. pharmacokinetic assays based on blood plasma levels). Not every compound was subjected to each assay. Not all data that was generated is shown. Judgment was applied in ranking compounds relative to each other for their utility in treating prostate cancer. in particular when ranking two compounds for which the same experiments were not performed. Characteristics considered in establishing the ranking include AR antagonism activity. lack of AR agonism in hormone refractory cells. prevention of tumor growth. tumor shrinkage. and pharmacokinetic behavior. with a longer residence time in blood being advantageous.

Tier 1

[0242] Generally. Tier 1 compounds are diarylthiohydantoins with a disubstituted left hand aryl ring that are disubstituted on the right hydantoin carbon. and have either an oxygen or N substituent on the left hydantoin carbon. It is expected that the amido substituent hydrolyzes to an oxygen in aqueous solutions such as encountered in biological systems. in vitro and in vivo. RD100 has good activity with an iodine instead of a CF3 substituent on the left hand aryl ring.

[0243] Tier 1 compounds (see Table 5) were judged to be much better than bicalutamide for treating prostate cancer. However. RD437[1] and RD131 were found to metabolize fast. that is. have a short residence time in blood. RD162 had desirable pharmacokinetics.

[0244] Figure 17 shows that under treatment with bicalutamide. PSA levels for LNCaP cells stayed the same or increased relative to treatment with vehicle solution. whereas under treatment with RD162. PSA levels decreased. Figure 18 illustrates that under treatment with vehicle solution. tumors continued to increase in size. By contrast. under treatment with RD162 at a dose of 1 mg per kg body weight per day. the rate of tumor increase decreased. and the size of the tumor appeared to be stabilizing after about 17 days. Under treatment with RD162 at a dose of 10 mg per kg body weight per day. tumor size decreased with time. Figure 19 illustrates that under treatment with RD162 at a dose of 10 mg per kg body weight per day. photon emission associated with luciferase activity decreased. Figure 20 shows that treatment with RD162 at this dose resulted in a decrease or stabilization of tumor size and a decrease in photon emission associated with luciferase activity.

[0245] Figure 21 shows that under treatment with RD162. RD162'. RD162". RD169. and RD170 at doses of 100. 200. 500. and 1000 nM. PSA levels of LN-AR cells decreased. Moreover. the higher the dose. the lower the PSA level. Figure 23 presents urogenital tract weight and rate of photon emission associated with luciferase activity initially and after 14 days of treatment with bicalutamide or with RD162 for intact and castrated mice. The weight and rate of photon emission increased for both intact and castrated mice. Treatment of castrated mice with RD162 resulted in a decrease in weight and photon emission with respect to the untreated castrated mice. as did treatment with bicalutamide.

[0246] Thus. Tier 1 compounds are particularly advantageous for use as AR antagonists. and as therapeutic agents for hormone refractory prostate cancer. They may be useful to treat other AR related diseases or conditions such as benign prostate hyperplasia. hair loss. and acne. These and related compounds may also be useful as modulators of other nuclear receptors. such as glucocorticoid receptor. estrogen receptor. and peroxisome proliferator-activated receptor. and as therapeutic agents for diseases in which nuclear receptors play a role. such as breast cancer. ovarian cancer. diabetes. cardiac diseases. and metabolism related diseases. They may be useful in assays e.g. as standards. or as intermediates or prodrugs.

[1] RD37 will be meant, DC.

(...)

Tier 2

[0247] Tier 2 compounds (see Table 6) were significantly better than bicalutamide for treating prostate cancer, although there were indications that RD54 could act as an agonist. (...)
(...)

Sensitivity of Anti-Cancer Activity of Compounds to Structural Differences

[0262] The inventors have determined that what might appear to be a small change in the structure of hydantoin compounds may result in a large change in that compound's performance in treating prostate cancer. For example, RD161 and RD162 differ only by a single fluorine substituent on an aryl ring, and RD 162 is in Tier 1, while RD161 is in Tier 2, both being better than bicalutamide for the treatment of prostate cancer, but RD162 being superior. (...)
(...)

3.8. The patent contains among others figures 21A and 21B:

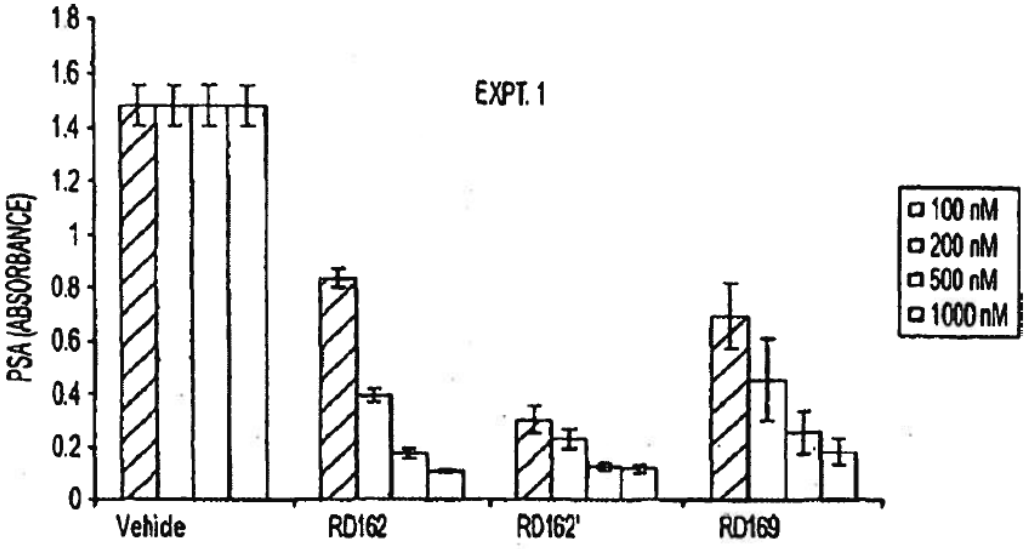


FIG. 21A

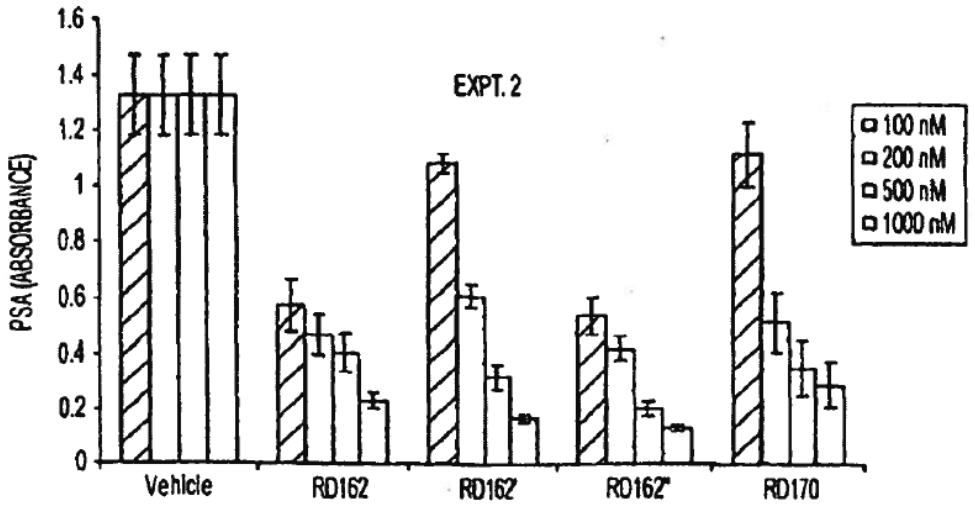


FIG. 21B

3.9. Enzalutamide was developed as part of a collaboration. The Regents, Astellas Inc. and a third party (Medivation, Inc.[2]) were involved in this development process. Medivation, Inc. obtained an exclusive licence from The Regents.

3.10. Astellas Inc. is a Japanese multinational pharmaceutical company. It has in turn obtained from Medivation, Inc. an exclusive sub-licence for the patent. Astellas Inc. has the right to enforce the patent and the SPC in the Netherlands. Astellas Inc. markets the drug Xtandi® which - in brief - is indicated for the treatment of adult men with (non-)metastatic castration resistant prostate cancer or metastatic, hormone sensitive prostate cancer. Xtandi® contains the active compound enzalutamide. Enzalutamide is also referred to as RD162' in the prior art.

3.11. The European market authorisation for Xtandi® was granted on 21 June 2013, and the 10-year market exclusivity period ended on 25 June 2024.

3.12. Accord intends to launch a generic version of Xtandi® after that date. Accord has asked The Regents to confirm that it will not act on the basis of EP 196 or the SPC, but The Regents has not provided such confirmation.

3.13. Sandoz obtained marketing authorisations for enzalutamide tablets on 16 December 2022. It has commercial interest in marketing a generic enzalutamide product. On 6 February 2023, Sandoz received a letter from The Regents' lawyers drawing its attention - in brief - to EP 196 and the formulation patent EP 3 725 778 B1 (see 3.15. below) and asking it to respect those rights until they expired. Sandoz responded on 17 February 2023 that it was willing to inform Astellas and The Regents two months before market entry,

[2] Medivation. Inc. was acquired by Pfizer in 2016.

in which it imposed two conditions to which The Regents' lawyers replied with their agreement on 8 March 2023.

3.14. In the UK, invalidity proceedings were brought by Accord and Sandoz before the High Court of England and Wales against the UK part of the patent. A *trial* took place in June 2024 before Mellor J. The court is ex officio aware of the High Court's decision of 4 October 2024 upholding the English part of EP 196 B2. The plea for lack of inventive step was dismissed.

3.15. Litigation was also conducted before this court between Synthon B.V., on the one hand, and Astellas Inc. and Medivation Prostate Therapeutics LLC. on the other, regarding the validity of formulation patent EP 3 725 778 B1 (hereinafter EP 778) granted on 18 August 2021 for 'Formulations of Enzalutamide'. By judgment of 22 January 2025[3] EP 778 was upheld in amended form (namely, according to the main request). Synthon's reliance on lack of inventive step was thereby dismissed.

3.16. Finally, the court is aware ex officio of the Bundespatentgericht's ruling of 8 April 2025 in the German parallel proceedings in which the German part of EP 196 B2 was also upheld.

4. The dispute

in the case 23-903

4.1. Accord seeks the annulment of the Dutch part of EP 196 and the annulment of the SPC, with an order that Astellas pay the costs of the proceedings to be assessed on the basis of Article 1019h DCCP[4], payable within 2 days of this judgment, failing which the amount due will be increased with interest, and that the judgment be declared provisionally enforceable insofar as the order to pay the costs of the proceedings is concerned.

4.2. Accord bases this, in summary, on the following. EP 196 wrongly invokes the priority of priority documents P1-P3 (see 3.3.). There is '*intervening prior art'* consisting of the Sawyers presentation (EP15/GP10) and the Ouk poster (EP18/GP14). This prior art was shown at a conference (see 5.14. et seq. below) in September/October 2005. That is after the priority date of P1 (13 May 2005), but before the priority date of P2 and P3 and therefore before the application date. The Sawyers presentation and the Ouk poster both disclose the compound RD162. EP 196 refers to the compound RD162' (enzalutamide). The only difference between the two compounds is the substitution pattern at the 5-position of the thiohydantoin ring (the middle ring): RD162' carries two methyl groups there while RD162 gives a cyclobutyl group. Any relevant technical effect cannot be attributed to this and does not follow from the patent. Based on the above, the objective technical problem can be formulated as providing an alternative/variant to RD162 with more or less the same efficacy. The skilled person would arrive at the claimed invention with a '*try and see'* approach without inventive thought. Even if there were no '*try and see'* situation, the

[3] District Court The Hague 22 January 2025 (Synthon v. Astellas Pharma Inc c.s.). ECLI:NL:RBDHA:2025:703
[4] Dutch Code of Civil Procedure

claimed subject matter is obvious. Claim 1 of EP 196 is therefore not inventive. The dependent claims 2 to 18 are also not inventive for that reason.

4.3. Astellas put forward a reasoned defence.

4.4. The parties' positions are discussed in more detail below, insofar as relevant.

in the case 23-904

4.5. Sandoz claims that the Dutch part of EP 196 and the SPC should be invalidated, and that Astellas should be ordered jointly and severally to pay the costs of the proceedings, to be assessed on the basis of Article 1019h DCCP, to be paid within two working days of this judgment, failing which the amount owed should be increased with interest, and that the judgment should be declared provisionally enforceable insofar as it concerns the order to pay the costs of the proceedings.

4.6. Sandoz bases this, in summary, on the following. EP 196 wrongly invokes the priority of priority documents P1-P3 (see 3.3.). There is '*intervening prior art'* consisting of the Sawyers presentation (EP15/GP10).[5] This prior art was shown at a congress (see 5.14. et seq. below) in September/October 2005. That is after the priority date of P1 (13 May 2005), but before the priority date of P2 and P3 and therefore before the application date. The Sawyers presentation discloses the compound RD162. The Sawyers presentation discloses the compound RD162. EP 196 looks at the compound RD162' (enzalutamide). The only difference between the two compounds is the substitution pattern at the 5-position of the thiohydantoin ring (the middle ring): RD162' carries two methyl groups there while RD162 gives a cyclobutyl group. Any relevant technical effect cannot be attributed to this and does not follow from the patent. The technical effect is to provide an alternative/variant to RD162 (for the treatment of hormone-resistant prostate cancer and hormone-sensitive prostate cancer). The skilled person would arrive at the claimed invention with a '*try and see'* approach without any inventive step. Even if there were no '*try and see'* situation, the claimed subject matter is obvious. EP 196 thus provides an obvious alternative. Claim 1 of EP 196 is thus not inventive. The dependent claims 2 to 18 are also not inventive for that reason.

4.7. Astellas put forward a reasoned defence.

4.8. The parties' contentions are discussed in more detail below, insofar as relevant.

5. The assessment

in both cases

jurisdiction

[5]Sandoz - unlike Accord - did not rely on the Ouk poster in its writ of summons. Astellas also addressed Accord's contentions in this regard in its statement of defence in the Sandoz case. Astellas' pleading notes no longer distinguish between the two cases either, so that the Court holds that Accord's views on the Ouk poster must be deemed to also underlie Sandoz' arguments (see also paragraph 5 in Astellas' pleading notes. including response to pleading note generics).

5.1. Based on Article 24(4) Brussels I bis-Regulation[6], the court has international jurisdiction and based on Article 80(1)(a) Dutch Patent Act 1995 in conjunction with Article 15(2) SPC Regulation[7], it also has relative jurisdiction to hear the claims.

technical background

5.2. Before assessing the generics' alleged objections to EP 196 on inventive step, the following is an undisputed technical background derived from the parties' submissions in relation to prostate cancer and anti-androgens.

5.3. Prostate cancer is the most common form of non-skin cancer in men. In this condition, malignant cells grow in the prostate, a small organ that is part of the male reproductive organs. This form of cancer usually grows slowly and causes few symptoms, especially in the beginning. Therefore, this form of cancer often goes undetected for a long time.

5.4. To work properly, the prostate depends on male sex hormones (so-called androgens), including testosterone and its metabolite dihydrotestosterone ('DHT'). The vast majority of androgen production takes place in the testes. A residual part of androgen production takes place in the adrenal glands. The blood then transports the androgens to other parts of the body, such as the prostate. If insufficient androgens circulate through the bloodstream, this leads to the death of prostate cells, including malignant (cancerous) cells when the disease is hormone-sensitive. This concept underlies hormonal prostate cancer treatments.

5.5. Male hormones/androgens exert their action by binding to a protein on tumour cells called the androgen receptor ('AR'). When androgens bind to an androgen receptor, the androgen receptor is 'activated'. Activation of the androgen receptor is commonly referred to as 'agonism'; prevention of activation as 'antagonism'. Androgen receptor antagonists block the action of androgens (including testosterone) by binding to the androgen receptors without activating them and thus compete with androgens for binding to the androgen receptors. The androgens are prevented from binding to the androgen receptors and thus their action is blocked. Androgen receptor antagonists are also called anti-androgens, androgen blockers or AR antagonists.

5.6. One of the genes wherefor the androgen receptor regulates expression codes for the protein PSA: prostate-specific antigen, a protein produced in the prostate. PSA is a well-known marker for prostate cancer. A small amount of this protein leaks from the prostate into the blood, and this amount can be measured with a PSA test. If the amount of PSA is above a certain value, it is an

[6] Regulation (EU) 1215/2012 of the European Parliament and of the Council of 12 December 2012 on jurisdiction. recognition and enforcement of judgments in civil and commercial matters

[7] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products

indication that that person may have prostate cancer. Further investigations, such as an ultrasound, biopsy or MRI scan, should determine this. An increased or rising PSA is associated with disease progression (that is, worsening), a decreasing PSA with disease inhibition (that is, improvement). When a drug is able to lower PSA, this is seen as a reflection of that drug's ability to lower the action of the androgen receptor.

5.7. Several treatments are available for prostate cancer. Prostate cancer that is localised - that is, confined to the prostate - can be treated surgically by removing the prostate or by radiotherapy. If curative treatment (surgery or radiotherapy) for localised disease is not (properly) possible, or if the cancer has already metastasised outside the prostate at diagnosis (metastasis), treatment of prostate cancer includes reducing the amount of male sex hormones (androgens - which can bind or interact with the androgen receptor) or preventing their interaction with the androgen receptor. Treatments aimed at reducing the (active) levels of androgen hormones or blocking the action of androgens in the body are referred to as *androgen deprivation therapy* (ADT), also known as hormone therapy. Hormone therapy can also be an adjunct to treatment in non-spread out (non-metastatic) prostate cancer to increase the chance of curing. First-generation anti-androgens that prevent androgens (e.g. testosterone) from binding to the androgen receptor include Flutamide (1989), Bicalutamide (1995 - known in the Netherlands as Casodex®) and Nilutamide (1996 - known in the Netherlands as Anandron®).

5.8. Even in prostate cancer patients treated with surgical or medical ADT in the above ways, disease progression could often eventually occur. Indeed, although hormone therapies are initially effective in blocking tumour growth, over time prostate cancer cells may lose their sensitivity to hormone therapy or hormone therapy may even exacerbate tumour growth because, over time, the antagonistic effect reverses and the drugs start showing agonistic activity. This stage, where patients show progression despite castration levels of testosterone, was initially called 'hormone-sensitive prostate cancer' (in English: '*hormone sensitive prostate cancer' - HSPC)* or 'hormone-resistant prostate cancer (in English: '*hormone-refractory prostate cancer'* or '*hormone-resistant prostate cancer'),* abbreviated to HRPC. Nowadays, this stage is commonly called '*castration-resistant prostate cancer'* (CRPC'). CRPC is incurable. Treatments are therefore mainly aimed at improving quality of life and prolonging life.

5.9. Bicalutamide and nilutamide were found to lose their antagonistic activity over time and show agonistic activity, especially with overexpression of the androgen receptor in CRPC. In this way, these agents stop reducing disease progression. None of these anti-androgens had shown to improve survival in CRPC. The chemotherapy docetaxel (Taxotere®) became (in combination with prednisone) the first treatment that proved capable of modestly prolonging the life of CRPC patients but could cause serious side effects.

5.10. Therefore, around the priority date, there was an urgent search for life-extending treatments that worked after docetaxel and for life-extending treatments with

fewer side effects. There were more than two hundred compounds in development for advanced prostate cancer at that time.[8]

priority

5.11. The generics have disputed that EP 196 is entitled to the priority claims of the priority documents mentioned in 3.3 because the compound RD 162' as claimed in EP 196 B2 is not disclosed therein. Astellas has not disputed this so that the filing date of 29 March 2006 is taken as the relevant date in these proceedings. Thereby, the Sawyer's presentation and the Ouk poster to be discussed below become relevant prior art.

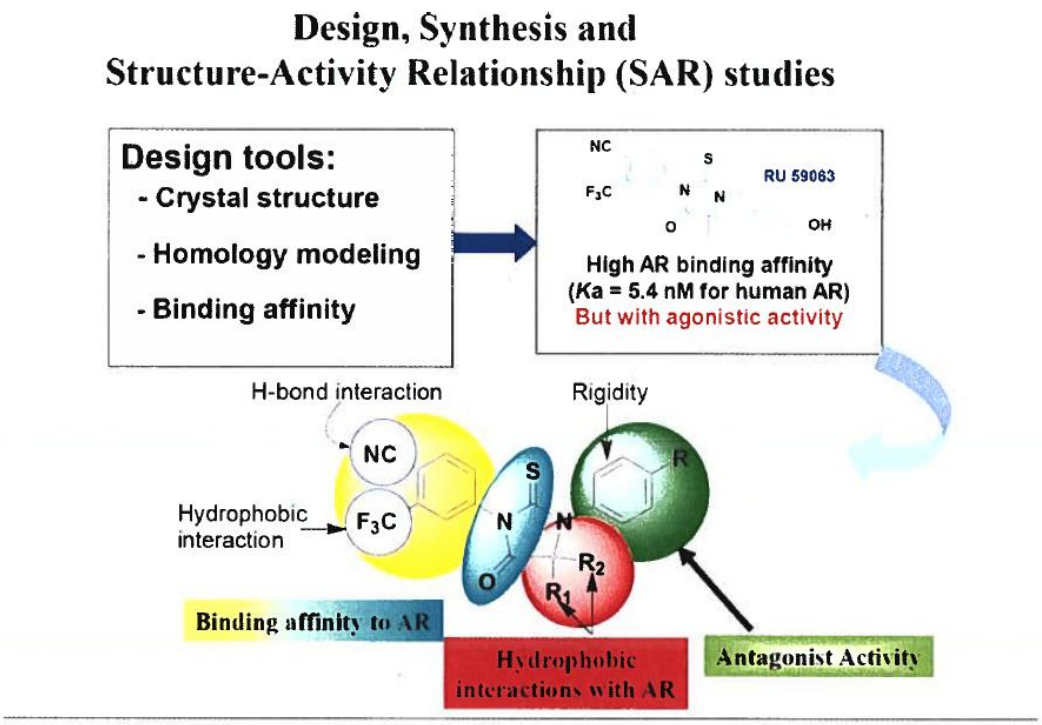
inventive step

5.12. From 29 September to 1 October 2005, the world's largest prostate cancer congress, the Prostate Cancer Foundation Scientific Retreat (the 'PCF Congress'), was held in Scottsdale, Arizona, USA. Two of the inventors of EP 196 B2, Charles Sawyers and Samedy Ouk (Michael Jung's research assistant), researchers affiliated with the Regents of the University of California, Los Angeles, presented at this congress their research results on potent antagonists for the treatment of *hormone-sensitive* and *hormone-refractory* prostate cancer, a study that Sawyers and Jung had started in early 2003 and among others included the RD series of molecules.

5.13. It was initially in dispute between the parties whether and, if so, to what extent, the content of the Sawyers (Powerpoint) presentation was publicly available on the relevant date, being the application date of 29 March 2006. Only in its (combined) written pleading notes did Astellas indicate its willingness to assume, solely for the purpose of procedural economy in these proceedings and without any admission or waiver, that the said presentation was publicly accessible on the relevant date. In view of this, the court assumes as fact in the present proceedings that the Sawyers presentation was publicly accessible on 29 March 2006. That the Ouk poster was displayed at the conference was not in dispute.

5.14. Sawyers' Powerpoint presentation includes the following two slides:

[8]Andre J. Armstrong and Michael A. Carducci. New Drugs in prostate cancer. Current Opinion in Urology 2006. 16: 138-145. exhibit GP05.



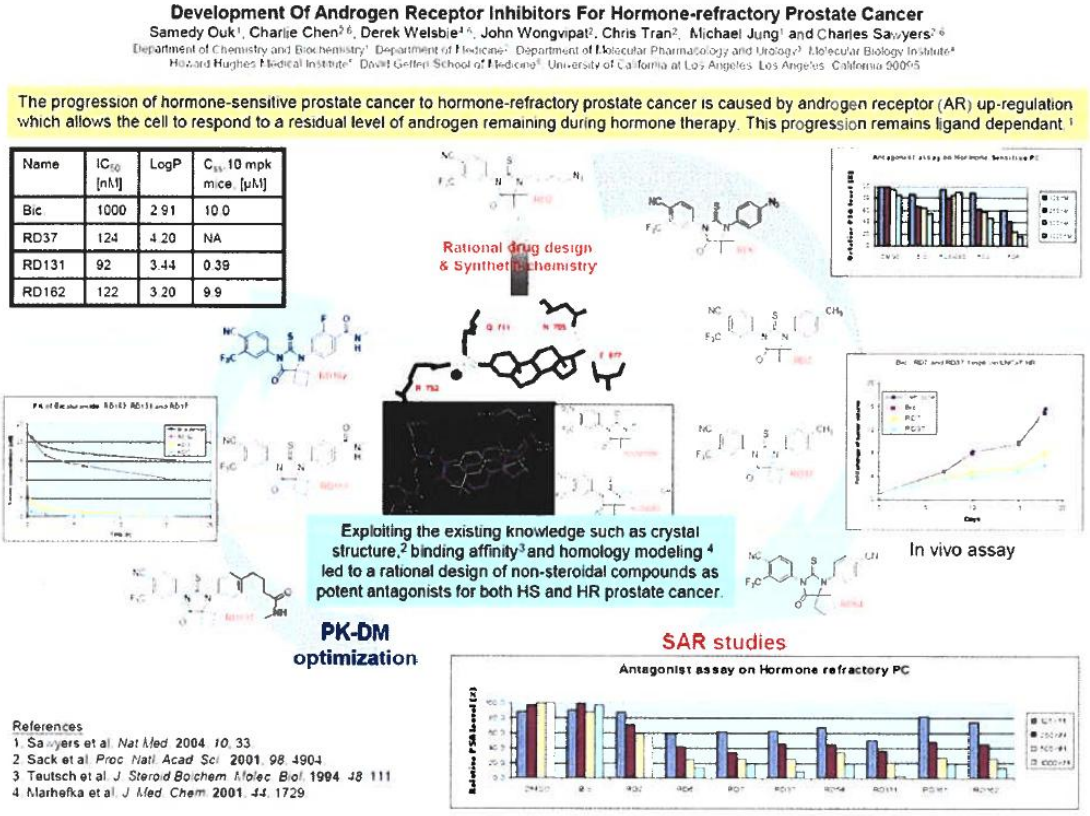
(slide 8)

Conclusions

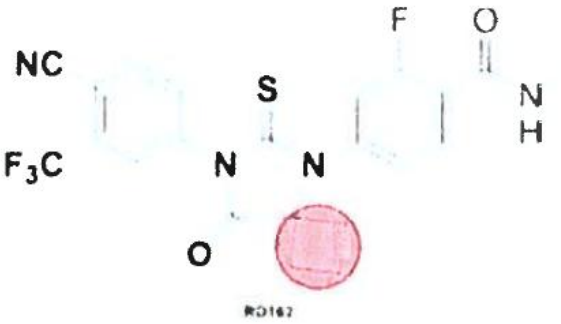
- Cell-based screens can be used to identify anti-androgens with greater potency than bicalumatide while avoiding the undesirable agonism side-effect
- SAR has defined a thiohydantoin imine derivative of the high affinity ligand RU59063 as an attractive lead
- Greater potency can be achieved in the absence of greater binding affinity, presumably through inducing altered AR conformation
- Further in vivo studies are in progress to define an optimal clinical candidate

(slide 18)

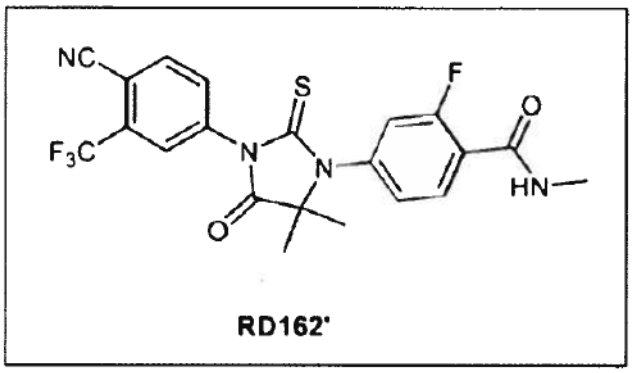
5.15. Ouk's poster looks as follows:



5.16. Sawyers and Ouk discussed the results of their own research at the PCF congress. Among other things, the presentation and poster show the structure of RD162, which is the structure shown in blue, at the top left of the page, at the end of the clockwise arrow. Below, the structure is shown separately, with the 5-position of the central thiohydantoin ring (the middle ring) highlighted in red. There is a cyclobutyl group at this position:



5.17. The compound claimed in EP 196 B2 enzalutamide, also referred to as RD162', differs from RD162 in that the cyclobutyl group (in molecular formula: C_3H_6) at the 5-position of the middle ring is replaced by a dimethyl group (in molecular formula: C_2H_6), shown in blue on the figure below:



RD162'

5.18. The central question in these proceedings is whether the disclosure of RD162 in Sawyers' and Ouk's presentations interfere with RD162's inventive step.

5.19. Both parties relied on the *problem-solution approach* in assessing inventiveness. However, they disagree on the technical effect of the distinguishing feature described above and therefore on how the objective technical problem should be formulated. Astellas argues that RD162' shows improved efficacy compared to RD162 in higher concentrations and formulates the objective technical problem as providing an improved prostate cancer treatment compared to treatment with RD162. In the alternative, Astellas invokes a less ambitious technical problem, consisting in providing an alternative prostate cancer treatment with at least comparable pharmacodynamics and pharmacokinetics to RD162, which it claims is inferable from the histograms of Figures 21A and 21B of the patent.

5.20. The generics believe that RD162' shows no distinctive technical effect compared to RD162. The patent itself classifies RD162 and RD162' both in Tier 1 (the identified compounds are classified in so-called '*Tiers',* of which Tier 1 concerns the category of substances that '*were judged to be much better than bicalutamide' (...) 'and particularly advantageous for use as AR antagonists, and as therapeutic agents for hormone refractory prostate cancer'* - cf. paragraphs [0054] and [0241] et seq. of the patent - see 3.7.) without noting any technical difference. Figures 21A and 21B still show experimental data of both compounds, but even there, according to the generics, no technically relevant difference is observable so that the objective technical problem can be no more than providing an alternative/variant to RD162 with more or less the same efficacy.

5.21. That RD162' however does (sec) show a technical effect (and thus enriches the state of the art), namely that it is at least[9] as good as RD162, has not been refuted by the generics (who assume this in their own objective technical problem as well).

[9] According to Astellas. which refers to Figures 21A and 21B of the patent for this. enzalutamide appears to work even better than RD162 at higher concentrations.

Therefore, for practical reasons, the court will assume the less ambitious definition of the problem because, as will be shown below, even if it is assumed that the average person skilled in the art will start from that problem, the invention provided in EP 196 B2 would still not be obvious. To this end, the reasoning is as follows.

5.22. The generics argued that starting from such a problem, the average skilled person will initially consult the structure-activity relationship as revealed in Sawyers to see where changes can be made to the molecule without compromising the pharmacological profile. The generics state that Sawyers teaches on slide 8 of the presentation that two parameters can be influenced: binding affinity with the androgen receptor (AR) and antagonistic activity. Slide 8 shows three residue (R) groups for this purpose. According to Sawyers' structure-activity relationship, the R_1 and the R_2 at the 5-position of the central thiohydantoin ring influence binding affinity with the AR, and the R on the right aryl ring influences antagonistic activity. The skilled person, who would adopt a ' *try and see'* approach, still according to generics, also knows from Saywers that the right aryl ring of RD 162 provides the strong antagonistic activity and stability in vivo, and would not focus on changing that part of the molecule, leaving only the binding activity with the AR (the R_1- and R_2- groups at the 5-position) according to them. The left ring would not be changed as it remained the same or optimised. The skilled person would thus by a process of negative elimination without any inventive thinking substitute the cyclobutyl group at the 5-position by a methyl group. Even if the average skilled person did not adopt a '*try and see'* approach, he would still have ended up with enzalutamide (RD 162') because the dimethyl group was already shown in the presentation or poster.

5.23. In the court's view, both approaches are based on *hindsight* and are rejected. Importantly, assessing inventive step using the '*could-would approach'* is not about whether the skilled person '**could** have carried out the invention, but whether he **would have done** so in the expectation of solving the underlying technical problem or in the expectation of some improvement or advantage.'[10] Furthermore, it is important to bear in mind that *'the technical disclosure in a prior art document should be considered in its entirety, as it would be done by a person skilled in the art and that it is not justified arbitrarily to isolate parts of such document from their context in order to derive from the technical information which would be distinct from the integral teaching of the document.*'[11] An ex post facto reading of the state of the art is hereby not allowed.[12]

5.24. Before discussing below how the average skilled person would read Sawyers' presentation and Ouk's poster and what that information would invite him/her to do, it is noted that, as the expert of the generics under reference to paragraph [0008] of the patent has acknowledged[13], apparently minor

[10] See Case Law book of the Boards of Appeal of the European Patent Office. I.D. 5.

[11] See Case Law book. t.a.p.. I.D. 9.5.

[12] See Case Law book. t.a.p. I.D. 6.

[13] First statement Prof Westwell. paragraph 12.6 (EP23): "*The second sentence of paragraph [0008] states: '[b]ecause activities are sensitive to small structural changes, one compound may be effective in prostate*

structural differences can have *'significant effects'* on the operation of a molecule. For example, it could lead to reduced efficacy or bioavailability[14] but also to a completely different effect[15]. This unpredictability would be strengthened for the skilled person by knowing that the then-standard treatment with biculatamide was often unable to inhibit prostate cancer growth and in some cases, by reversal of the antagonistic action causing hormone therapy drugs to show agonistic activity, was actually found to enhance disease progression.

the Sawyers presentation

5.25. As explained in Astellas' pleading notes at paragraphs 46 to 78, Sawyers' presentation shows the average skilled person - briefly and in summary form – the structure of the molecule RU59063 and a so-called pharmacophore, a model of the molecule that shows which parts of the molecule the researchers have been investigating in particular to achieve activity optimisation. With the expert of the generics, it can be assumed that RU59063 was '*the initial output or starting point'*. Slide 8 (cf. 5.14.) shows the said structure in the frame right above and notes that the compound has a high AR binding affinity but -and this in a red colour – '*But with agonistic activity',* which activity – also according to Prof Andrew D. Westwell and the generics' other expert, Prof Simon Paul MacKay, is undesirable.

5.26. The arrow pointing from molecule RU59063 in the top right frame to the pharmacophore indicates a connection. The skilled person will notice that relative to the starting compound RU59063, the pharmacophore has Residue (R) groups in three places, where the researchers apparently saw room for modifications. Those groups are positioned on the right side of the pharmacophore (the green part said to refer to rigidity and antagonistic activity) and in the red part, according to the text of slide 8 responsible for the hydrophobic interaction with the androgen receptor. At the same time, the skilled person would notice that the left and middle parts of the pharmacophore, the yellow and blue coloured parts (according to the accompanying text responsible for the binding affinity of the androgen receptor), are unchanged from RU59063, at least no R groups are placed there.

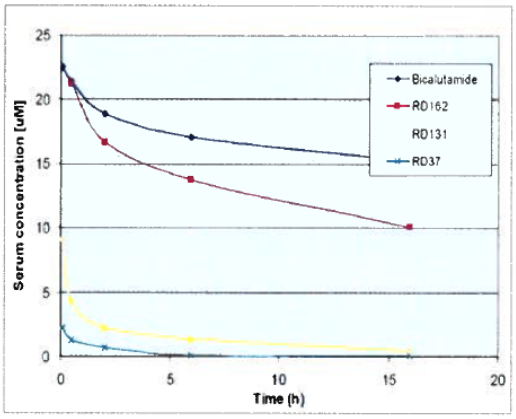
cancer, whereas a second compound may be ineffective, even if it differs from the first compound only slightly, say by the replacement of a single substituent'. The skilled medicinal chemist would agree with this statement as a matter of generality. Small structural changes can sometimes have significant effects, whereas sometimes they do not."

[14] Cf. paragraphs 0262]-[0266] of the patent: *"The inventors have determined that what might appear to be a small change in the structure of hydantoin compounds may result in a large change in that compound's performance in treating prostate cancer".* after which the example of the difference in efficacy between RD162 (Tier 1) and RD 161 (Tier 2) is given, among others: "*For example, RD161 and RD162 differ only by a single fluorine substituent on an aryl ring, and RD162 is in Tier 1, while RD161 is in Tier 2. both being better than bicalutamide for the treatment of prostate cancer, but RD162 being superior."*

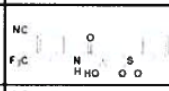
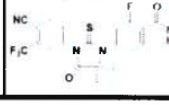
[15] Cf. Yin et al. Key Structural Features of Nonsteroidal Ligands for Binding and Activation of the Androgen Receptor. Molecular Pharmacology. pp. 211-223. 2003 (GP09): "The present functional activity data demonstrated that minor structural differences in these nonsteroidal molecules could greatly alter the nature of receptor-ligand interaction and lead to completely) different pharmacological responses (i.e. agonist or antagonist activities)."

5.27. By generalising the dimethyl group from RU59063 to groups R_1 and R_2 in the pharmacophore, the skilled person would realise that the researchers' intentions included changes to the location of the dimethyl group. This is reflected in the rest of the presentation. Indeed, the following slides, slides 9 to 15, discuss RD37, a molecule no longer equipped with a dimethyl group but with a cyclobutyl group. The data on the slides show the skilled person that RD37 has no agonist activity (slide 11: "*RD37: no agonism in hormone refractory LNCap/AR cells"),* has comparable binding affinity to bicalutamide but better antagonist activity (slide 13: *"RD37: comparable binding affinity to bicalutamide but greater antagonism in cell-based assays")* and is an effective tumour inhibitor (slide 14 - which contrasts RD37 with biculatamide, among others - says: "*RD37 slows the growth of LNCap/AR tumours in vivo").* However, slide 15 shows that RD37 has an unfavourable half-life, which is why, according to the opening words of slide 16, the researchers searched for derivatives of RD37 with at least improved pharmacokinetic properties.

Derivatives of RD37 have favorable PK that retain potent antagonism in LNCaP/AR cells



PK after IV dosing

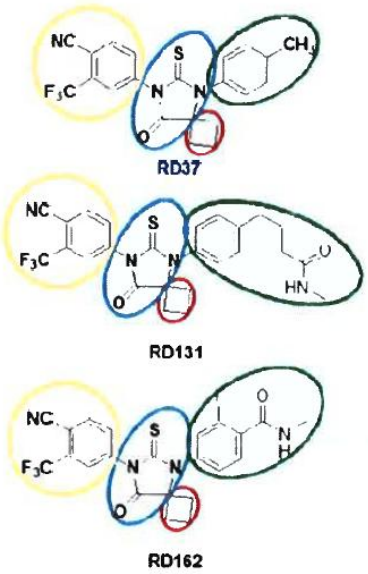
Name	Structure	IC_{50} [nM]	LogP	C_{ss}10mpk* [µM]
Bic.		1000	2.91	10.0
RD37		124	4.20	NA
RD131		92	3.44	0.39
RD162		122	3.20	9.9

*steady state concentration after 14 days of daily oral dosing

5.28. Besides RD37, the molecules RD131 and RD162 are shown on this slide. These molecules also have a cyclobutyl group at the 5-position. On slide 17, it is noted that RD131 and RD162 "*retain antagonist potency against hormone refractory LNCaP/AR cells".* The experts in these proceedings agree that of the shown molecules, RD162 possesses the best combination of properties and is the most promising.[16]

5.29. In Astellas' pleading notes, RD37, RD131 and RD162 are enlarged and colour-coded to correspond to the pharmacophore.

[16] For references. see footnote 41 pleadingnotes Astellas.



This figure emphasises that the research has focused on making modifications in only the (green) right-hand part of the pharmacophore, a conclusion also endorsed by the generics.[17] The yellow left aryl ring and the blue/red middle ring with a cyclobutyl group at the 5-position (in the red part) have always remained the same. The skilled person would see the consistent and continuous use of these molecule parts as the result of optimisation, at least realising that the researchers had made a positive selection.

the Ouk poster

5.30. The skilled person would have the same picture when taking note of the Ouk poster shown above. The poster sketchily shows the development pathway of a new potent anti-androgen and starts (from the centre of the poster) again from RU59063 (and nilutamide). The first step is taken from there to molecule RD2 and proceeds from there via a right-turning arrow from RD6 (where, compared to RD2, an activity enhancement can be seen by the insertion of an aromatic ring on the right side of the molecule) and RD7 to molecule RD37. The left group and thiohydantoin ring remain unchanged throughout. Almost all changes to the molecule are made in the right group, giving the molecule (enhanced) antagonistic activity. On the right-hand side of the poster, these steps are shown as '*SAR studies',* thus indicating that in that part of the development, they looked at how parts of the molecules studied affect their activity (SAR stands for structure-activity-relation). RU59063, nilutamide, RD2, RD6 and RD7 all have a dimethyl group at the 5-position. From molecule RD37, the development continues through RD54, and then from the bottom left of the poster RD131, RD161 to finally - shown in blue at the top left - RD162. From RD37 onwards, all compounds shown have a cyclobutyl group at the 5-position (except molecule RD54: it has a cyclopentyl group). As Prof Westwell also points out, the numbering of the RD molecules (RD2-

[17] Paragraph 44 written pleading (first term) generics

RD162) suggests that certainly more molecules were developed during the study than the 8 compounds shown on the poster.

5.31. On the right side of the poster, above and below *'antagonist assays'* are included for *hormone sensitive* prostate cancer and *hormone refractory* prostate cancer, respectively. These are *in vitro* (cell-based) *assays* that, by measuring PSA levels (as the equivalent of tumour growth), reflect the dose-response of each molecule. In the top assay with hormone-sensitive cells, for example, it shows that RD2 has activity similar to biculatamide but also shows that RD6 - where an aromatic ring is inserted on the right side in development - is clearly more potent. The *assay* on the bottom right compares the activity of a number of molecules in a hormone-resistant cell line. RD37 and RD131 are the most active compounds at high concentrations.

5.32. In the centre is an *in vivo* assay (mouse model) showing data on RD7 and RD37 and showing the change in tumour volume with respect to time. When compared with bicalutamide, the activity of RD7 and RD37 resulted in quite slower tumour growth. The activity of RD7 (with the dimethyl group at the 5 position) and RD37 (with the cyclobutyl group at the 5 position) was, the skilled person would understand from the *assay,* at least comparable. RD37 seems to perform slightly better than RD7 but, as Prof Brunsveld points out[18], there are no margins of error in the figure, making it difficult to draw firm conclusions.

5.33. The left-hand side of the poster is referred to as '*PK-DM optimisation'* (PK is the abbreviation for pharmacokinetics, DM for drug metabolism). Together, these roughly look at how a substance is absorbed and reacts in the human body *(in vivo)*. On this side of the poster are three more substances, the molecules RD131, RD161 and RD162. Here, only substituents on the aromatic ring on the right side of the molecule are modified, apparently to obtain better PK-DM properties. The graph also shown on slide 16 showing the improved PK properties of RD162 relative to RD37 and RD131 reappears here. It can be seen that the serum concentration of RD162 is retained longer, the half-life for RD37 and RD131 is much shorter than that of RD162. The results of the study are summarised in the table at the top left of the poster, which in turn corresponds to the data on slide 16 of the Sawyers presentation. Here the compound strength for receptor inhibition/blockade (shown as the concentration at which 50% of the inhibition effect is achieved by the antagonist; the IC_{50}-value[19)], the logP[20] and the steady-state concentration[21] are summarised. As Prof Westwell explains, based on this information, the skilled person would jointly understand that the RD molecules are better AR inhibitors than bicalutamide, with RD162 having '*better therapeutic potential'* than RD37 and RD131 based on its better 'PK-DM' properties,

[18] First statement Prof Brunsveld, para 26 (GP16 in Accord case)

[19] IC_{50} is a measure of the potency of a substance to inhibit a given process by 50% (the lower the value, the more potent the compound will be)

[20] The LOgP value is a measure of lipophilicity: the higher the value, the more lipophilic, the lower the value, the better the solubility in water. Less lipophilic drugs are more easily absorbed and bind more selectively to the target.

[21] After repeated administration of a drug, a 'steady state' is reached when the plasma concentration fluctuates around an average plateau value through absorption and excretion.

although Prof Brunsveld, who agrees with that conclusion based on Ouk per se, nuancing this by indicating that RD162 is numerically not the best candidate on each of the properties.[22]

teaching

5.34. Going back to the question of what the *teaching* is that the average skilled person learns from the information in the Sawyers presentation and the Ouk poster, the answer is that he/she will understand that RD162 may be a suitable candidate for the treatment of hormone-resistant prostate cancer, although the conclusion in Sawyers' slides indicates that further *in vivo* research is ongoing to find an optimal clinical candidate. Starting from the objective technical problem formulated above, the skilled person who would further synthesise the compounds to try to find a molecule with more or less equal antagonistic potency, it is logical - from molecule RD162 as a plausible starting point - to investigate modifications to the aromatic ring on the right side of the molecule.

5.35. In the presentation, the pharmacophore does not include a residue group in the left aryl ring structure, so it is not plausible that the skilled person, bearing in mind also that that structure in Ouk has remained unchanged from initial development from RU59063 to molecule RD162, would focus his attention on that part of the compound. The generics also agree with this. Of this ring, the generics' expert states that it '*has been optimised'* and that he '*would be hesitant to make changes here'*.[23] Prof Westwell also says so in paragraph 9.54 of his first statement (EP23): "*(...) based on the information in Ouk, the skilled medicinal chemist would not be confident that changes could be made to the left-hand side of RD162 (...) because that part of the structure has been kept fixed all the way from RU59063. It would therefore be uncertain, based on Ouk, as to whether changes to that part of the molecule are consistent with activity".*

5.36. However, it is difficult to reconcile this view with the fact that the skilled person would change the middle ring structure (with the cyclobutyl in the 5 position), which has been optimised to a far-reaching degree, during research into a potent antagonistic AR inhibitor. In this, therefore, the generics are not followed. From Ouk, the skilled person knows that from molecule RD37 onwards, the researchers had made a consistent choice for a cyclobutyl group at this position (had '*fixed'* it) and in developing good candidates thereafter only made changes to the right aryl ring of the pharmacophore and all compounds in the '*PK-DM optimisation'* have a cyclobutyl group. The Ouk poster shows that the dimethyl at the 5-position of the thiohydantoin ring in RD37 has been replaced by cyclobutyl. According to the Sawyers presentation, this will enhance the hydrophobic interaction with the AR. An attempt to move to cyclopentyl (RD54) has, the average skilled person - looking at Sawyers and Ouk - will believe, apparently not been sufficiently successful as shown by the PSA levels in the figure Antagonist Assange on HRPC. Subsequently, for PK-DM optimalisation, the return was made to the cyclobuthyl (RD131, RD161 and RD162). The skilled person would conclude that cyclobutyl is ' optimal' and see no reason to return to dimethyl at the 5-position. The Ouk poster therefore points away from the suggestion made by the generics of a dimethyl group on the

[22] First statement Prof Brunsveld. para 29 (GP16 in Accord case)

[23] First statement Prof MacKay. para 4.21 (EP25 in Accord case)

5-position. The skilled person would retain the structure of these parts of the molecule and not take steps backwards in the development process, especially since the generics themselves also indicate that these parts of the molecule are responsible for binding to the androgen receptor, which is ultimately needed to sufficiently inhibit the action of the androgen receptor. Therefore, the skilled person would not adopt a *'try-and-see'* attitude. Nor does the Sawyers presentation give any reason to change anything other than the upper-right ring in the compound, because all the new compounds shown on slide 16 of the presentation have a similar left and middle group, with a cyclobutyl group on the thiohydantoin ring. Of note here is that from both the SAR phase and the PK-DM phase until the very end - even when RD161 was changed to RD162, another fluorine was substituted on the aryl ring (bringing RD162 into Tier 1 and RD161 into Tier 2) - only the right ring has been modified.

5.37. That the modification of the dimethyl group of RU59063 to the cyclobutyl group had indeed been deliberately modified by the researchers as the result of an activity optimisation, the skilled person also learns from the last substantive slide of the presentation. Therein it is said that the Structure-Activity Relationship (SAR) studies revealed a derivative of RU59063 as an '*attractive lead'* and that - third bullet point – '*Greater potency can be achieved in the absence of greater binding affinity, presumably through inducing altered AR conformation'.* When the judge in *cross examination* in the English parallel proceedings asked the generics' expert whether this comment might be related to a hypothesis by the investigators that the modification on the R_1 and the R_2 group of the pharmacophore from dimethyl to cyclobutyl was advantageous for hydrophobic interaction of the molecule with the target (the androgen receptor) and thus - in short - resulted in improved activity and selectivity (potency), Prof Westwell replied in the affirmative. He said, "*Yes. Just to be clear, the major innovation is the introduction of the rigid phenyl ring. That is what has caused the switch to the agonist activity. The cyclobutyl, of course, is part of that. It has a role in binding. We have talked about whether there is a hydrophobic binding pocket and what that might look like. Yes, the take-home message, if you like, if I was reading this as a medical chemist, is actually in the top right. The cyclobutyl, yes, is the substituent, the R1/R2 substituent that they have chosen to base their series on, yes. But that does not mean that you would not consider other things."*

5.38. The skilled person would therefore conclude that the researchers had deliberately modified the dimethyl group for *drug design* reasons due to enhanced hydrophobic interaction with and 'fit' into the corresponding hydrophobic pocket of the androgen receptor. The strength of hydrophobic interactions is related to the number of carbon atoms within a molecule (or within the interaction region). Larger groups with more bulk, such as a cyclobutyl - which has one more carbon atom than a dimethyl, typically lead to more powerful hydrophobic interactions than smaller groups.[24] Therefore, from a technical point of view, it is unlikely that the skilled person would consider changes at the 5-position of the (middle) thiohydantoin ring in the further development of RD162, and certainly not that he would revert to the dimethyl structure of RU59063, which, according to the presentation and the poster, is inferior, especially when RD7 and RD37, which differ precisely in a dimethyl and a cyclobutyl group, show more or less similar effectiveness.

[24] Cf. Handbook Graham L. Patrick. An Introduction to Medicinal Chemistr). Third Edition. especially chapter 10 and figure 10.4 (EP25.3).

You can only reach that with knowledge of the invention, namely if there were a reason to investigate the size of the hydrophobic pocket of the androgen receptor to test whether another alkyl group would also be suitable for a 'fit' in the receptor. Finally, the generics then also overlook in their reasoning that the middle (red) thiohydantoin ring does not only see to binding affinity but also has an effect in antagonistic activity.

conclusion

5.39. With that, the curtain falls on the generics' statements. Their attack fails because with retrospective knowledge of the invention, the focus is wrongly placed solely on substituting the R_1 and R_2 groups at the 5-position of the (middle) thiohydantoin ring of a cyclobutyl into a dimethyl. It follows from the above that the average skilled person would have no reason to make changes at the 5-position of the (middle) thiohydantoin ring in the sense that he would *('would')* still change the '*fixed'* cyclobutyl into a dimethyl. That he could *('could')* do so, as indicated at the beginning of the reasonings, is not the test to be applied.

legal costs

5.40. The generics will be ordered to pay the costs of the proceedings as the unsuccessful party. Astellas claimed legal costs in accordance with Article 1019h DCCP. The parties have agreed that the total costs for the combined case including disbursements amount to € 200,000.-- and that Astellas is entitled to that full amount if the claims are dismissed. This amount will be awarded. In view of the agreement made (and in light of how the generics had claimed their costs order), the costs order will be awarded jointly and severally and declared provisionally enforceable, as claimed by Astellas.

6. The decision

The court

in cases 23-903 and 23-904

6.1. D i s m i s s e s the claims,

6.2. order the generics, whereby the one shall pay and the other shall be released, to pay the costs of the proceedings, so far estimated on the part of Astellas at € 200,000,

6.3. declares the costs order provisionally enforceable.

This judgment was rendered by mr. J.Th. van Walderveen, mr. H.F.R. van Heemstra and mr. dr. ir. C. Schüller and publicly pronounced on 18 June 2025.