

PUBLICATION PARTICULARS AND ABSTRACT

[Section 32(3)(a) - Regulation 22(1)(g) and 31]

21	01	Official Application No.:	2007 06061			DrG Ref.:	125926
22	Lodging date:		2007-07-17				
43	Acceptance date:		16.05.2008				
51	International Classification:		A61K; A61P				
		Not for publication.	WIPO				
		Classified by:					
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Earliest priority claimed		33	Country	31	Number	32	Date
			DE		10 2005 005 397.1		05 February 2005
54	Title of invention ISOLATION OF N-BUTYLBENZENESULFONAMIDE, SYNTHESIS OF BENZENESULFONAMIDE DERIVATIVES, AND USE OF N-BUTYLBENZENESULFONAMIDE AND BENZENESULFONAMIDE DERIVATIVES FOR THE TREATMENT OF BENIGN PROSTATE HYPERPLASIA AND/OR PROSTATE CARCINOMA						
57	Abstract See next page.						
Number of sheets		83					

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(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro



(43) Internationales Veröffentlichungsdatum
10. August 2006 (10.08.2006)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2006/081994 A2

(51) Internationale Patentklassifikation:

A61K 31/18 (2006.01) A61P 13/08 (2006.01)
A61K 36/00 (2006.01) A61P 35/00 (2006.01)

AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) Internationales Aktenzeichen: PCT/EP2006/000746

(22) Internationales Anmeldedatum:
28. Januar 2006 (28.01.2006)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
10 2005 005 397.1 5. Februar 2005 (05.02.2005) DE

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(81) Bestimmungsstaaten (soweit nicht anders angegeben, für jede verfügbare nationale Schutzrechtsart): AE, AG, AL,

(84) Bestimmungsstaaten (soweit nicht anders angegeben, für jede verfügbare regionale Schutzrechtsart): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Erklärungen gemäß Regel 4.17:

- hinsichtlich der Berechtigung des Anmelders, ein Patent zu beantragen und zu erhalten (Regel 4.17 Ziffer ii)
- Erfindererklärung (Regel 4.17 Ziffer iv)

Veröffentlicht:

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Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: ISOLATION OF N-BUTYLBENZENESULFONAMIDE, SYNTHESIS OF BENZENESULFONAMIDE DERIVATIVES, AND USE OF N-BUTYLBENZENESULFONAMIDE AND BENZENESULFONAMIDE DERIVATIVES FOR THE TREATMENT OF BENIGN PROSTATE HYPERPLASIA AND/OR PROSTATE CARCINOMA

(54) Bezeichnung: ISOLIERUNG VON N-BUTYLBENZOLSULFONAMID, SYNTHESE VON BENZOLSULFONAMID-DERIVATEN SOWIE VERWENDUNG VON N-BUTYLBENZOLSULFONAMID UND BENZOLSULFONAMID-DERIVATEN ZUR BEHANDLUNG DER BENIGNEN PROSTATAHYPERPLASIE UND/ODER DES PROSTATAKARZINOMS

(57) Abstract: The invention relates to a method for isolating N-butylbenzenesulfonamide (NBBS) from biological material, the chemical synthesis of benzenesulfonamide derivatives, and the use of NBBS and benzenesulfonamide derivatives for the treatment of or producing medicaments for the treatment of benign prostate hyperplasia and/or prostate carcinoma and as a basic substance for the development of agents used for treating said diseases.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft ein Verfahren zur Isolierung von N-Butylbenzolsulfonamid (NBBS) aus biologischem Material, die chemische Synthese von Benzolsulfonamid-Derivaten sowie die Verwendung von NBBS und Benzolsulfonamid-Derivaten zur Behandlung bzw. zur Herstellung von Arzneimitteln zur Behandlung der benignen Prostatahyperplasie und/oder des Prostatakarzinoms sowie als Leitsubstanz zur Entwicklung von Wirkstoffen zur Behandlung der vorgenannten Erkrankungen.

WO 2006/081994 A2

Isolation of *N*-butylbenzenesulfonamide, synthesis of benzenesulfonamide derivatives, and use of *N*-butylbenzenesulfonamide and benzenesulfonamide derivatives for treating benign prostatic hyperplasia and/or prostate carcinoma

Benign enlargement of the prostate, also called benign prostate syndrome (BPS) or benign prostatic hyperplasia (BPH), and prostate cancer (= prostate carcinoma) are among the most common diseases affecting males as they age.

About 50% of men over the age of 60 years are afflicted by a benign form of enlargement of the prostate.

Benign prostatic hyperplasia is closely related to the development of prostate cancer, which is the most common cancer affecting men in middle age in the western countries and the second most common cause of cancer death in men.

BPH and prostate cancer are characterized, inter alia, by the progressive enlargement of the prostate. Enlargement of the prostate causes increasing narrowing (= obstruction) of the urethra and obstruction of the bladder outlet, leading to problems when urinating. In the advanced stage the complete obstruction of the urethra, so-called anuria, leads to an emergency that requires immediate treatment.

The growth of the prostate is controlled by the male sex hormones, the androgens.

Several methods are available for the effective treatment of prostate carcinoma, amongst others, hormone therapy.

Once the cancer has disseminated, a cure of prostate cancer is no longer possible. This applies to as many as one third

of the patients at the time of the first diagnosis. In these cases, suppression of tumour growth and alleviation of the accompanying complaints are at the focus of the therapy. By suppressing the production of male sex hormones (testosterone) in order to counteract the transactivation function of the androgen receptor, it is possible to achieve temporary growth inhibition.

The major aim of the current therapies is to inactivate the androgen receptor (AR). The androgen receptor regulates male sex differentiation, is responsible for male fertility and promotes the growth of the normal prostate gland but also promotes the proliferation of cancer cells of the prostate. Therefore, the androgen receptor has become an important target for prostate carcinoma therapy.

However, the current therapies are clearly limited since a prostate carcinoma will eventually exhibit resistance to this therapy.

The AR induces the expression of AR-responsive genes when it is bound to androgens. The inactivation of the androgen receptor is achieved either by reducing androgen synthesis or by administering androgen antagonists. So far, bicalutamide, flutamide, hydroxyflutamide (OH-F), nilutamide and cyproterone acetate (CPA) are used for the treatment of prostate cancer. These substances are administered with the aim of inactivating the transactivation of human androgen receptor.

However, eventually during the therapy the prostate carcinoma starts to regrow exhibiting resistance to the hormone deficiency. It has been found that androgen receptors are

present and still remain active despite the treatment. The causes underlying this phenomenon remain largely unclear.

It is, however, apparent that there is a need for novel active substances for a successful treatment of BPH and/or prostate carcinoma.

Plant extracts for treating symptoms accompanying the enlargement of the prostate are traditionally wide-spread in many countries. The most commonly used extracts are those from the African plum tree (*Pygeum africanum*), which is also called *Prunus africana* (Hook. F.) Kalkm. according to more recent nomenclature, the Saw palmetto (*Serenoa repens*) and the pumpkin (*Cucurbita pepo*). The standardised lipophilic extracts from these plants contain sterols, saturated and unsaturated fatty acids as well as n-docosanol. The exact mechanism of action is yet unknown; it has been presumed, however, that the improvement of the symptoms associated with prostate enlargement is attributable to the sterol compound β -sitosterol, which is the quantitatively predominant component contained in the extracts.

Most of the clinical studies on the efficacy of extracts from the African plum tree were performed using chloroform extracts from its bark. This chloroform extract contains, inter alia, phytosterols, short-chain unsaturated fatty acids (lauric acid, myristic acid) and long-chain unsaturated fatty acids (oleic acid, linoleic acid. It is licensed under the designation Tadenan® in Italy, France and other European states, but not in Germany, for symptomatic treatment of BPH.

The placebo-controlled short-term studies using chloroform extracts from *P. africana* indeed showed a moderate clinical efficacy, but their concept was not even in accordance with the minimum requirements of the International Consultations on BPH. For this reason, a clear assessment of these studies is regrettably not possible.

The object of the present invention was to provide novel active substances for the treatment of benign or malignant prostate enlargement, i.e. benign prostatic hyperplasia and/or prostate carcinoma.

This object was achieved by isolating a substance having antiandrogenic activity from the bark of the African plum tree *P. africana*, and synthesising structural variants of these substances.

Surprisingly, the substance *N*-butylbenzenesulfonamide (NBBS) was isolated from the bark of *P. africana*, and it was found that this substance has a strong antiandrogenic activity. NBBS is even able to inhibit the growth of prostate cancer cells that do not respond to treatment with hydroxyflutamide.

NBBS is a lipophilic substance that is used as a plasticiser in the production of polyamides and copolyamides and is also used in the synthesis of sulfonyl carbamate herbicides. NBBS is practically insoluble in water but exhibits moderate solubility in alcohols and benzene. NBBS is very stable and persists in the environment. Thus, NBBS was previously found in ground water, river water, in wine and in snow in concentrations up to 100 µg/l. Therefore, when us-

ing NBBS as active substance in the treatment of BPH, there are hardly any toxicity problems to be expected.

However, on account of its antiandrogenic efficacy NBBS is a compound with which BPH and/or prostate cancer could be treated. NBBS may at least serve as a lead substance in the development of new active substances for the treatment of BPH and/or prostate carcinoma.

The object of providing novel antiandrogenic active substances for treating benign prostate hyperplasia and/or prostate carcinoma is also achieved by providing sulfonamide derivatives of NBBS wherein the butyl side chain and the benzene ring have been modified by substituents.

FIG. 1 shows the inhibition of the activity of an androgen by different extracts of *P. africana*.

FIG. 2 shows the antiandrogenic effect of fractions of the selective methylene chloride extract of *P. africana*.

FIG. 3 shows a comparison of the antiandrogenic effect of compounds contained in *P. africana*.

FIG. 4 illustrates the inhibition of the growth of human prostate carcinoma cells by NBBS.

FIG. 5 indicates the structural formula of the synthesised benzenesulfonamide derivatives.

FIG. 6 shows a diagram illustrating the antiandrogenic effect of the synthesised benzenesulfonamide derivatives.

To be able to identify the component or a component from the bark of *P. africana* that is effective in the treatment of BPH and/or prostate carcinoma, the bark was selectively extracted with various solvents and the extracts obtained were examined for antiandrogenic activity by measuring their potency for inhibiting the activity of the human, hormone-activated androgen receptor in a reporter gene-based test. The results of this test are shown in FIG. 1.

It was found that the water extract and the methanol extract of *P. africana* bark revealed no antiandrogenic activity in the test. The selective hexane extract only lead to approximately half of the androgen-induced luciferase activity compared to the controls, which were not treated with an extract.

The ethanol extract and the methylene chloride extract prevented androgen-induced luciferase activity in the tests almost completely. These two extracts showed the highest biological activity.

To further identify antiandrogenic active substances from *P. africana*, the selective methylene chloride extract was fractionated using silica gel chromatography. The resulting fractions were again tested for their antiandrogenic action in the reporter gene-based test. Part of the results of this test is shown in FIG. 2. Especially the fractions F7 and F8 showed an antiandrogenic effect in the cell culture test.

Both fractions were used for further analysis. By means of preparative HPLC, *N*-butylbenzenesulfonamide was isolated from fraction F8, as was shown by the analytical data.

N-butylbenzenesulfonamide inhibited the androgen-induced luciferase effect in the cell culture test (see FIG. 3). The activity of NBBS was compared with the effect of the compounds ursolic acid, oleanolic acid, ferulic acid, benzoic acid and β -sitosterol, which are also contained in *P. africana* and which are being discussed as being responsible, or which at least were possible candidates, for the efficacy of the known plant-derived drug (Tadenan[®]), which is extracted from *P. africana*. The results of this comparative test are shown in FIG. 3.

With the exception of β -sitosterol none of the comparison compounds had any significant influence on the androgen-induced reporter gene activity.

N-butylbenzenesulfonamide has an antiandrogenic activity that is higher than the antiandrogenic activity of the substances from *P. africana* that are taken into consideration as being the cause of the efficacy of the standardised chloroform extract from this plant species.

The present invention thus relates to the use of NBBS for treating benign prostate hyperplasia and for the manufacture of a medicament for treating benign prostate hyperplasia.

The growth of prostate cells and prostate cancer cells is originally dependent on androgens. To test whether the androgen antagonism of NBBS also affects cell growth, the human prostate cancer cell line LNCaP was used, whose growth is known to be androgen dependent. LNCaP cells were cultured in the presence of NBBS. FIG. 4 shows that already on

day 5 of treatment the cells treated with 100 μM NBBS exhibited a markedly slower proliferation than the untreated cells. This effect was even more prominent on day 8 of the treatment. In the presence of 10 μM NBBS, too, the LNCaP cells exhibited a reduced growth on day 8 of treatment, whereas the treatment with OH-F did not lead to reduction in cell proliferation. The latter may be due to LNCaP cells having a point mutation in the ligand binding domain of the human AR that prevents OH-F from acting as an antiandrogen in these cells.

These data show that the androgen antagonism of NBBS is also effective for a mutated human androgen receptor. Thus, NBBS is able to inhibit growth of LNCaP cells. Consequently, NBBS could also be used to treat prostate carcinomas that are resistant to known antiandrogenic active agents such as hydroxyflutamide.

The present invention thus also relates to the use of NBBS for treating prostate carcinoma and for the manufacture of a medicament for treating prostate carcinoma, particularly of prostate carcinomas that are resistant to any treatment with known androgen antagonists such as, for example, bicalutamide, flutamide, hydroxyflutamide, nilutamide or cyproterone acetate.

A further subject matter of the invention is the use of NBBS as a lead substance in the development of novel active substances for treating benign prostatic hyperplasia and/or prostate carcinoma.

The present invention further relates to a method of isolating NBBS from biological material, particularly from the bark of the African plum tree *P. africana*.

In the said method, the plant material is initially reduced to small pieces, then extracted with a solvent in which NBBS is soluble, and NBBS is purified from the resulting extract, for example by means of fractionation employing suitable chromatography methods and separating NBBS from the fractions containing that substance by removing the solvent.

Extraction is preferably performed as a selective extraction by means of a series of successive solvents with increasing polarity. The fractionation of the extract is preferably performed by means of gradient chromatography, with increasing polarity of the eluents. Isolation of NBBS may subsequently take place by preparative HPLC from the fractions containing NBBS.

In this way it was possible to isolate the antiandrogenic, lipophile substance NBBS from the selective methylene chloride extract. As was shown by analyses, NBBS was also contained in the ethanol extract, which likewise exhibited antiandrogenic action.

Solvents suitable for the extraction of NBBS from plant material are therefore the solvents selected from the group comprising univalent C_1 to C_4 alcohols (alcohols with one to four carbon atoms), and high-volatile, (partially) halogenated C_1 hydrocarbons, preferably methylene chloride and chloroform.

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The preferred chromatographic method is column chromatographic fractionation by means of silica gel, and preparative HPLC.

The object of providing novel active substances for treating benign prostatic hyperplasia and/or prostate carcinoma was also achieved by synthesizing further structural variants of this compound on the basis of NBBS isolated from *P. africana*.

The synthesis of structural variants of NBBS was started directly from arylsulfonic acid chloride and the primary aliphatic amine. The reaction of an acid chloride with the amine could take place without solvent, simply by mixing the two components in a mortar using a pestle. However, since in the case of the NBBS structural variants both starting compounds were mostly present in liquid form, a three-neck flask with a stirrer, reflux cooler, thermometer and dripping funnel were preferred. An excessive amount of amine was used, and the sulfonic acid chloride was slowly added in drops while stirring. The reaction is highly exothermic and takes place quantitatively. After cooling of the reaction mixture, water was added, and the reaction product was shaken out with dichloromethane. The progress of the reaction was monitored by thin-layer chromatography.

The ratio of amine:sulfonic acid chloride was 2:1 in the reactions; in the case of the gaseous amines methyl amine and ethyl amine, an aqueous solution was used and four times the equivalent of amine, compared to the acid chloride, was used.

In this reaction of a primary aliphatic amine with a sulfonic acid chloride, the free electron pair attacks as nucleophiles at the sulfur of the sulfonic acid chloride. Apart from the reaction product, this also produces hydrochloric acid, which protonates the excessive amine. The amine salt remains in the aqueous phase when the sulfonamide is shaken out with dichloromethane, and can thus be separated.

In this manner a series of *N*-monoalkylbenzenesulfonamides with different alkyl chains was prepared initially. The liquid benzenesulfonic acid chloride and the corresponding primary amine component were used as the starting materials. The structural formulas of the sulfonamides with variable alkyl chain are indicated in Figure 5. *N*-geranylbenzenesulfonamide (S4) is also shown there. This substance was synthesized because enhanced membrane permeability was hoped for on account of the terpenoid side chain.

The next series of synthesised sulfonamides comprises both the introduction of substituents at the aromatic (S5 and S6) and variation of the aminoalkyl chain with a terminal hydroxyl group (S7 and S8).

The compounds S5 and S6 were produced starting from 4-toluenesulfonic acid chloride and 4-fluorobenzenesulfonic acid chloride with *N*-butylamine in the same manner as the compounds S1 to S7, S9 and S12.

The synthesis of the compounds S7 and S8 could not be performed in this manner since here the hydroxyl group of the ethanolamine used competes with the amino group. Thus,

apart from the sulfonic acid amide there is also produced a certain amount of sulfonic acid ester.

However, the synthesis of S7 and S8 succeeded by initially treating one equivalent of benzenesulfonic acid chloride and 4-fluorobenzenesulfonic acid chloride, respectively, with 2.2 equivalents of ethanolamine in ortho-xylene for five hours under reflux. After completion of the reaction, a viscous liquid settled at the bottom; this liquid was separated. The liquid was the sulfonamide that on account of the excess of amine and its acidic character is present in deprotonated form and thus separates from the organic phase. By contrast, the sulfonic acid ester does not have acidic properties and remains dissolved in the xylene phase. Then, aqueous alkali was added to the separated sulfonamide until a clear solution was obtained. By acidifying with concentrated hydrochloric acid the sulfonamide settled again in purified form as yellow syrup. After separating the sulfonamide, acetone was added thereto. The sulfonamide was thereby dissolved, and the sodium chloride, which had formed in the acidifying step and had coprecipitated, remained as bottom sediment and could be removed by filtration. The acetone was removed in the rotary evaporator, and the purified product was obtained.

The third series of structural variants of NBBS was oriented on the structure of the antiandrogenic substance 2-hydroxyflutamide. 2-Hydroxyflutamide is the active metabolite of flutamide (Fugerel[®]).

Introducing a trifluoromethyl group at the meta-position enhances the lipophilicity of the molecule. This should en-

sure an improved ability to penetrate the cell membrane. The additional nitro group in S13 and S14 at the para-position results in a further improvement of the lipophilic properties. The geranyl side chain is to improve anchorage in biological membranes.

The synthesis of S10 to S14 was performed starting from 3-trifluoromethylbenzenesulfonamide and 4-nitro-3-trifluoromethylbenzenesulfonamide, respectively, and *N*-butylamine and *N*-geranylamine, respectively.

4-Nitro-3-trifluoromethylbenzenesulfonamide is solid at room temperature, so that dichloromethane had to be used as the solvent.

To examine the efficacy of the benzenesulfonamide derivatives with respect to an inhibition of the AR-mediated transactivation, each of the synthesized compounds was compared at a concentration of 10 μ M with the efficacy of NBBS (FIG. 6). A high concentration (3×10^{-8} M) of R1881 was used, at which 10 μ M of NBBS showed no specific inhibition of the AR-mediated transactivation.

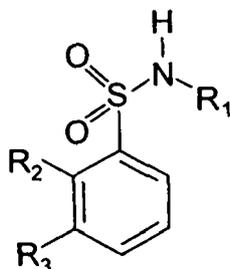
The compounds S1 to S3 and S5 to S8 at the concentration employed showed no significant antiandrogenic action that exceeded the antiandrogenic action of NBBS. The modifications of the compounds S1 to S3 and S5 to S8 included either shortening the butyl side chain (S1 to S3 and S7) or a substitution of the benzene ring at the para-position (S5, S6 and S8). The results on the antiandrogenic efficacy of these compounds reveal the importance of the length of the side chain and of the presence of a benzene ring that is

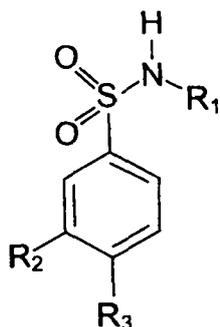
unsubstituted at the para-position for the antiandrogenic effect of benzenesulfonamide derivatives.

Surprisingly, lengthening the side chain by replacing the butyl side chain with a pentyl or a geranyl group (S4 and S9) enhanced the antiandrogenic activity indicating that a hydrophobic side chain is important for antiandrogenic activity. However, further extension of the side chain by introducing a lauryl group (S12) weakened the androgen antagonistic potency. Therefore, enhancing the hydrophobicity alone is not sufficient to enhance the antiandrogenic efficacy of NBBS.

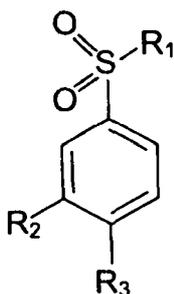
Surprisingly, also substitutions at the meta-position of the benzene ring enhanced antiandrogenic activity (S10, S11, S13 and S14), with an additional substitution at the benzene ring in para-position not significantly affecting the increased antiandrogenic activity of the compounds with a substitution at the meta-position, as demonstrated by a comparison of the antiandrogenic effects of substance S14 with S11, and S13 with S10.

The subject matter of the present invention is therefore a process for the production of benzenesulfonamide derivatives of the formula





wherein R_1 represents an aliphatic C_1 to C_{12} hydrocarbon, R_2 is hydrogen or a completely or partially halogenated C_1 residue; and R_3 is hydrogen or a nitro group, which process is characterized in that a benzenesulfonic acid derivative of the formula

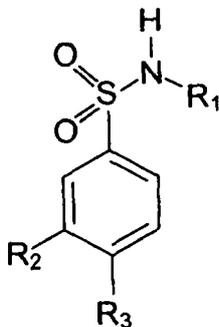


wherein R_1 represents halogen, R_2 hydrogen or a completely or partially halogenated C_1 -residue; and R_3 is hydrogen or a nitro group, is converted with a primary aliphatic amine, and the reaction product is shaken out with dichloromethane, with the primary aliphatic amine preferably being selected from the group comprising C_1 to C_{12} aliphatic hydrocarbons. Butylamine or geranylamine is used with particular preference as the primary aliphatic amine.

The reaction product can also be shaken out with ether to prevent the synthetic compounds from failing to gain drug approval because halogenated solvents were used.

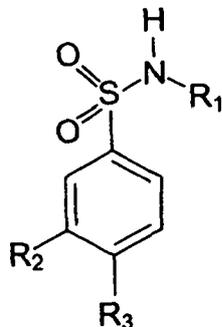
"Aliphatic" is to be understood to mean organic compounds whose carbon atoms are arranged in straight or branched chains and which may contain saturated and/or unsaturated C-C bonds and/or functional groups, but also organic compounds containing only one carbon atom.

A further subject matter of the present invention are therefore benzenesulfonamide derivatives for treating benign prostatic hyperplasia and/or prostate carcinoma that are characterized by the formula



wherein R_1 represents an aliphatic C_1 to C_{12} hydrocarbon, R_2 hydrogen or a completely or partially halogenated C_1 residue; and R_3 is hydrogen or a nitro group.

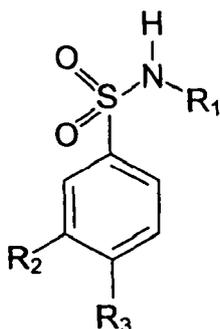
Insofar, the present invention also relates to the use of a benzenesulfonamide derivative of the formula



wherein R_1 represents an aliphatic C_1 to C_{12} hydrocarbon, R_2 hydrogen or a completely or partially halogenated C_1 residue; and R_3 is hydrogen or a nitro group, for the treatment of benign prostatic hyperplasia and/or prostate

carcinoma and for the production of a medicament for the treatment thereof, and as a lead substance for developing further/novel active substances for the treatment of benign prostatic hyperplasia and/or prostate carcinoma, especially for treating the prostate carcinoma that is resistant to a therapy with androgen antagonists.

A further subject matter of the invention are pharmaceutical preparations for the treatment of benign prostatic hyperplasia and/or prostate carcinoma that are characterized by containing at least one benzenesulfonamide derivative of the formula



wherein R_1 represents an aliphatic C_1 to C_{12} hydrocarbon, R_2 is hydrogen or a completely or partially halogenated C_1 residue; and R_3 is hydrogen or a nitro group.

Example 1: Extraction of the plant material

Dried bark of the African plum tree (*P. africanum*) was powdered, and 1.73 kg of the powdered bark were homogenized in 1 l *n*-hexane (ice-cooling) using an Ultra Turrax. The plant material was filled into a column (Merck Prepbar[®] 400 x 100 mm) and selectively extracted successively with 25.0 l of *n*-hexane, 26.0 l of methylene chloride, 25.0 l of methanol (MeOH) and 12.5 l of water at room temperature. The solvents of

For preparing an ethanolic extract, 300.00 g bark material of *P. africanum* was powdered and extracted three times, each time with 5.0 l ethanol (EtOH). After filtering the extract through filter paper of 0.7 μm pore size, the solvent was removed from the entire extract at 40 °C using a rotary evaporator. The dried mass of the resulting extract was 16.02 g.

Example 2: Fractionation of the methylene chloride extract

The selective methylene chloride extract of *Pygeum africanum* was fractionated with silica gel (Macherey - Nagel Si60, 15 - 25 μm). For this purpose the extract was dissolved in 2000 ml CH_2Cl_2 and filtered through filter paper with a pore size of 0.7 μm (Schleicher & Schüll). 25 g of silica gel (Merck Si60, 0.063 - 0.2 mm) was added to the extract and then the solvent was evaporated in vacuo at 40 °C. The thus-coated silica gel was placed on the top of a dry packed silica gel column (Merck Prepbar[®] 400 x 100 mm) and eluted, with a flow rate of 120 ml·min⁻¹, with a linear gradient of 0 min hexane (100:0), 50 min hexane (100:0), 350 min CH_2Cl_2 (100:0), 500 min CH_2Cl_2 (100:0), 700 min CH_2Cl_2 -MeOH (80:20), 750 min MeOH (100:0), 800 min MeOH (100:0), 850 min H_2O (100:0), 885 min H_2O (100:0). The chromatography gave 35 fractions which led to detection by UV light at a wavelength of 245 nm (Table 1).

Table 1: Fractionation of the selective methylene chloride extract of *P. africana*

Fraction	Min	Mass (mg)	Fraction	Min	Mass (mg)
F1	0-148	3	F19	615-630	799
F2	149-184	52	F20	631-638	292
F3	185-204	33	F21	639-659	1338
F4	205-229	63	F22	660-663	20
F5	230-238	14	F23	664-671	327
F6	239-261	61	F24	672-692	634
F7	262-266	30	F25	693-703	157
F8	267-293	243	F26	704-724	333
F9	294-331	380	F27	725-749	350
F10	332-338	17	F28	750-771	393
F11	339-356	164	F29	772-784	316
F12	357-369	119	F30	785-803	141
F13	370-373	38	F31	804-820	57
F14	374-375	71	F32	821-828	58
F15	376-562	110	F33	829-836	1
F16	563-581	44	F34	837-858	126
F17	582-592	24	F35	859-880	1
F18	593-614	1537			

Example 3: Isolation of *N*-butylbenzenesulfonamide

NBBS was isolated from fraction F8 by preparative HPLC (250 x 21 mm, 100-5 C18 HD Macherey - Nagel, 22 ml·min⁻¹, UV detection at 220 nm, Gradient: 0 min ACN-H₂O (with addition of 0.1% of TFA) ((20:80), 40 min ACN-H₂O (80:20), 45 min ACN (100:0)). NBBS was collected from min 12.6 to min 14.0. Its structure was elucidated on the basis of the ¹H and ¹³C NMR, EI-MS, HR-EI-MS, IR and UV spectra.

Example 4: Cell culture and luciferase assay

Monkey kidney cells, line CV1, lacking endogenous androgen receptor were cultured in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% (v/v) fetal calf serum, penicillin (100 IU/ml) and streptomycin (100 IU/ml) at 37°C and 5% CO₂.

For the transfection experiments, cells were seeded onto 6-well tissue culture plates (Nunc, Roskilde, Denmark) with a density of 1.2×10^5 cells per well and grown in DMEM medium supplemented with 10% (v/v) dextran-coated activated charcoal stripped serum. Six hours after seeding, the cells were transfected by using the Ca₃(PO₄)₂ method. The human androgen receptor (hAR) expression vector (0.2 µg) was co-transfected with 1 µg of the reporter plasmid MMTV-luc and 0.2 µg of the cytomegalovirus (CMV)-driven β-galactosidase expression virus, as internal control for transfection efficiency. After 14 hours the medium was replaced either without (white bars in Figures 1 to 3) or with the addition of methyltrienolone (R1881, 3×10^{-10} M final concentration; black bars in Figures 1 to 3) together with the indicated extracts (FIG. 1), fractions (FIG. 2) or substances (FIG. 3). After additional 48 hours cells were harvested and assayed for luciferase and β-galactosidase activity.

Luciferase activity was determined by injecting luciferin and measuring light emission at 562 nm and expressed as relative light units (RLU) by using the values of β-galactosidase activity for normalisation of the luciferase activity. All transfection assays shown were performed in duplicate and were repeated at least twice.

For determining antiandrogenic activity in the various extracts from the bark of *P. africanum*, the extracts were used at a concentration of 300 $\mu\text{g/ml}$. The results are shown in FIG. 1.

For determining the antiandrogenic activity in the fractions of the selective methylene chloride extracts, 2 μl of the respective fraction was used, corresponding to a final concentration of 30 $\mu\text{g/ml}$. Fractions F6 to F10 were additionally tested with 4 μl , corresponding to 60 $\mu\text{g/ml}$ final concentration. Active fractions F7 and F8 were used for the further tests. Part of the results is shown in FIG. 2.

For a comparison of antiandrogenic activity of compounds of *P. africanum*, cells were cultured in the presence of β -sitosterol, benzoic acid, NBBS, ferulic acid, oleanolic acid or ursolic acid at 10^{-5} M final concentration in the cell culture medium, and in the presence of or without methyltrienolone (3×10^{-10} M). The results are indicated in FIG. 3.

Example 5: Growth inhibition of human prostate carcinoma cells by NBBS

Human prostate carcinoma cells (cell line LNCaP) were cultured in RPMI-1640 medium, supplemented with 10% (v/v) fetal calf serum, penicillin (100 IU/ml) and streptomycin (100 IU/ml), 2 mM glutamine and 1 mM sodium pyruvate.

For the cell growth assays LNCaP cells were seeded onto a 24-well tissue culture plate at a density of 5×10^3 cells per well and cultured in RPMI-1640 medium containing 5% fetal calf serum. On day 2, the culture medium was replaced,

and ethanol/DMSO (control), NBBS (10 μM and 100 μM) or the known antiandrogen hydroxyflutamide (OH-F) (0.1 μM) was added to treat the cells. Every second day the medium and additives were replaced with fresh media together with freshly added compounds. The cells were trypsinized and counted using a counting cell chamber on the indicated days.

Example 6: Synthesis of methylbenzene sulfonamide (= S1)

IUPAC: *N*-Methylbenzenesulfonamide

Empirical formula: $\text{C}_7\text{H}_9\text{NO}_2\text{S}$ (MW = 171.04)

Synthesis:

17.662 g of benzenesulfonic acid chloride (0.1 mol) were added in drops to 31.06 g of an aqueous solution (40%) of methylamine (0.4 mol) while stirring. After cooling of the reaction mixture 20 ml of water were added, and the reaction product was shaken out with dichloromethane (3 x 20 ml). The combined organic phases were washed with water (2 x 20 ml) and narrowed down on the rotary evaporator at reduced pressure.

Appearance: colourless oil

Yield: 15.940 g (93%)

UV (MeOH) λ_{max} nm: 220, 265

IR (KBr) ν_{max} cm^{-1} : 3300, 3070, 2980, 1450, 1320, 1160

$^1\text{H-NMR}$ (500 MHz, CDCl_3), δ (ppm):

7.80 (2H, d, $^3\text{J} = 7.5$ Hz, C-2-H und C-6-H)

7.51 (1H, t, $^3\text{J} = 6.5$ Hz, C-4-H)

199 [M]⁺ (39), 170 (100), 141 (84), 77 (51)

High-accuracy mass determination (HR-EI-MS):

Calculated: 199.0667 for [M]⁺

Found: 199.0666

Example 9: Synthesis of geranylbenenesulfonamide (= S4)

IUPAC: N-[(2E)-3,7-Dimethylocta-2,6-diene-1-yl]benzenesulfonamide

Empirical formula: C₁₆H₂₃NO₂S (MW = 293.14)

Synthesis:

177 mg of benzenesulfonic acid chloride (1 mmol) were added in drops to 307 mg of geranylamine (2 mmol) while stirring. After cooling of the reaction mixture 10 ml of water were added, and the reaction product was shaken out with dichloromethane (3 x 10 ml). The combined organic phases were washed with 0.1 M of hydrochloric acid (3 x 5 ml) and narrowed down on the rotary evaporator at reduced pressure.

Appearance: brownish oil

Yield: 281 mg (96%)

UV (MeOH) λ_{max} nm: 205, 221, 264

IR (KBr) ν_{max} cm⁻¹: 3280, 2900, 1450, 1330, 1160

¹H-NMR (500 MHz, CDCl₃), δ (ppm):

7.82 (2H, d, ³J = 7.0 Hz, C-2-H und C-6-H)

7.51 (1H, t, ³J = 6.4 Hz, C-4-H)

7.45 (2H, t, ³J = 7.6 Hz, C-3-H und C-5-H)

4.95 (2H, m, $^3J = 7.0$ Hz, C-2'-H und C-6'-H)
 4.31 (1H, t, $^3J = 6.0$ Hz, N-H)
 3.52 (2H, q, $^3J = 6.5$ Hz, C-1'-H)
 1.90 (2H, q, $^3J = 8.0$ Hz, C-5'-H)
 1.84 (2H, t, $^3J = 8.0$ Hz, C-4'-H)
 1.60 (3H, s, C-3'-Me)
 1.50 (3H, s, C-7'-Me) 1.46 (3H, s, C-8')

^{13}C -NMR (125 MHz, CDCl_3), δ (ppm):

141.3 (C-3')	127.1 (C-2 und C-6)	26.2 (C-8')
140.1 (C-1)	123.6 (C-2')	25.6 (C-7'-Me)
132.6 (C-7')	118.5 (C-6')	17.7 (C-5')
131.9 (C-4)	41.0 (C-1')	16.2 (C-3'-Me)
129.0 (C-3 und C-5)	39.3 (C-4')	

EI-MS (70 eV): m/z (rel. int.):

293 $[\text{M}]^+$ (47), 210 (72), 170 (100), 152 (83), 141 (80), 77
 (46)

High-accuracy mass determination (HR-EI-MS):

Calculated: 293.1450 for $[\text{M}^+]$

Found: 293.1413

Example 10: Synthesis of butyltoluenesulfonamide (= S5)

IUPAC: *N*-butyl-4-methylbenzenesulfonamide

Empirical formula: $\text{C}_{11}\text{H}_{17}\text{NO}_2\text{S}$ (MW = 227.10)

Synthesis:

1.908 g of toluenesulfonic acid chloride (0.01 mol) were added in drops to 1.463 g of butylamine (0.02 mol) while stirring and heating. After cooling of the reaction mixture

Calculated: 227.0980 for $[M^+]$

Found: 227.0986

Example 11: Synthesis of butyl-4-fluorobenzenesulfonamide
(= S6)

IUPAC: *N*-Butyl-4-fluorobenzenesulfonamide

Empirical formula: $C_{10}H_{14}NO_2SF$ (MW = 231.07)

Synthesis:

0.973 g of 4-fluorobenzenesulfonic acid chloride (0.005 mol) were added in drops to 0.732 g of butylamine (0.01 mol) while stirring and heating. After cooling of the reaction mixture 10 ml of water were added, and the reaction product was shaken out with dichloromethane (3 x 10 ml). The combined organic phases were washed with water (2 x 5 ml) and narrowed down on the rotary evaporator at reduced pressure.

Appearance: light brown solid

Yield: 1.081 g (93%)

Melting point ($^{\circ}C$): 33

UV (MeOH) λ_{max} nm: 221, 260

IR (KBr) ν_{max} cm^{-1} : 1600, 1500, 1330, 1150

1H -NMR (500 MHz, $CDCl_3$), δ (ppm):

7.81 (2H, *dd*, 4J (H,F) = 5.0 Hz, 3J (H,H) = 8.3 Hz, C-2-H and C-6-H)

7.13 (2H, *t*, 3J (H,F) = 3J (H,H) = 8.3 Hz, C-3-H und C-5-H)

4.26 (1H, s, N-H)
 2.89 (2H, t, $^3J = 7.5$ Hz, C-1'-H)
 1.36 (2H, m, $^3J = 7.5$ Hz, C-2'-H)
 1.22 (2H, m, $^3J = 7.5$ Hz, C-3'-H)
 0.79 (3H, t, $^3J = 7.5$ Hz, C-4'-H)

^{13}C -NMR (125 MHz, CDCl_3), δ (ppm):

164.0 (C-4)	42.9 (C-1')
136.1 (C-1)	31.5 (C-2')
129.7 (C-2 und C-6)	19.7 (C-3')
116.2 (C-3 und C-5)	13.4 (C-4')

EI-MS (70 eV): m/z (rel. int.):

231 $[\text{M}]^+$ (20), 188 (100), 159 (86), 95 (44)

High-accuracy mass determination (HR-EI-MS):

Calculated: 231.0729 for $[\text{M}]^+$

Found: 231.0736

Example 12: Synthesis of hydroxyethyl benzenesulfonamide
(= S7)

IUPAC: *N*-(2-Hydroxyethyl)benzenesulfonamide

Empirical formula: $\text{C}_8\text{H}_{11}\text{NO}_3\text{S}$ (MW = 201.05)

Synthesis:

8.831 g of benzenesulfonic acid chloride (0.05 mol) and 6.720 g of ethanolamine were treated for 5 hours in 30 ml of *ortho*-xylene at 140 °C under reflux. After cooling, a viscous liquid settled at the bottom, this liquid was separated by means of a separating funnel. The viscous liquid was dissolved in 40 ml NaOH (10%). Then the product was

Calculated: 201.0460 for $[M^+]$

Found: 201.0460

Example 13: Synthesis of 4-fluoro-hydroxyethylbenzene-
sulfonamide (= S8)

IUPAC: 4-Fluoro-N-(2-hydroxyethyl)benzenesulfonamide

Empirical formula: $C_8H_{10}NO_3SF$ (MW = 219.04)

Synthesis:

9.731 g 4-fluorobenzenesulfonic acid chloride (0.05 mol) and 6.720 g ethanolamine were treated under reflux for 5 hours in 30 ml *ortho*-xylene at 140 °C. After cooling, a viscous liquid settled at the bottom, this liquid was separated by means of a separating funnel. The viscous liquid was dissolved in 40 ml NaOH (10%). Then the product was precipitated using concentrated hydrochloric acid and filtered off (0.7 μ m). The product was washed with water (3 x 5 ml).

Appearance: white powder

Yield: 3.656 g (33%)

Melting point (°C): 77

UV (MeOH) λ_{max} nm: 220, 270

IR (KBr) ν_{max} cm^{-1} : 3430, 1590, 1320, 1150

1H -NMR (500 MHz, $CDCl_3$), δ (ppm):

7.81 (2H, dd, 4J (H,F) = 5.2 Hz, 3J (H,H) = 8.3 Hz, C-2-H und C-6-H)

7.13 (2H, t, 3J (H,F) = 3J (H,H) = 8.3 Hz, C-3-H und C-5-H)

5.03 (1H, s, N-H)
3.66 (2H, t, $^3J = 6.2$ Hz, C-2'-H)
3.05 (2H, t, $^3J = 4.2$ Hz, C-1'-H)
1.96 (1H, s, O-H)

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3), δ (ppm):

164.1 (C-4)	61.2 (C-2')
135.8 (C-1)	45.1 (C-1')
129.9 (C-2 und C-6)	
116.4 (C-3 und C-5)	

EI-MS (70 eV): m/z (rel. int.):

219 $[\text{M}]^+$ (5), 188 (100), 159 (91), 95 (56)

High-accuracy mass determination (HR-EI-MS):

Calculated: 219.0365 for $[\text{M}^+]$

Found: 219.0367

Example 14: Synthesis of pentylbenzenesulfonamide (= S9)

IUPAC: N-Pentylbenzenesulfonamide

Empirical formula: $\text{C}_{11}\text{H}_{17}\text{NO}_2\text{S}$ (MW = 227.10)

Synthesis:

1.766 g of benzenesulfonic acid chloride (0.01 mol) were added in drops to 1.744 g of pentylamine (0.02 mol) while stirring. After cooling of the reaction mixture 10 ml of water were added, and the reaction product was shaken out with dichloromethane (3 x 10 ml). The combined organic phases were washed with water (3 x 5 ml) and narrowed down on the rotary evaporator at reduced pressure.

Example 15: Synthesis of butyl-3-trifluoromethylbenzene-sulfonamide (= S10)

IUPAC: *N*-Butyl-3-(trifluoromethyl)benzenesulfonamide

Empirical formula: $C_{11}H_{14}NO_2SF_3$ (MW = 281.07)

Synthesis:

978 mg of 3-trifluoromethylbenzenesulfonic acid chloride (4 mmol) were added in drops to 585 mg of butylamine (8 mmol) while stirring. After cooling of the reaction mixture 20 ml of water were added, and the reaction product was shaken out with dichloromethane (3 x 10 ml). The combined organic phases were washed with water (3 x 5 ml) and narrowed down on the rotary evaporator at reduced pressure.

Appearance: colourless oil

Yield: 1.112 g (99%)

UV (MeOH) λ_{max} nm: 205, 220, 265

IR (KBr) ν_{max} cm^{-1} : 3290, 2960, 2940, 1610, 1330, 1160

1H -NMR (500 MHz, $CDCl_3$), δ (ppm):

8.07 (1H, s, C-2-H)

7.99 (1H, d, $^3J = 7.5$ Hz, C-4-H)

7.77 (1H, d, $^3J = 8.0$ Hz, C-6-H)

7.62 (1H, t, $^3J = 8.0$ Hz, C-5-H)

2.93 (2H, t, $^3J = 7.0$ Hz, C-1'-H)

1.38 (2H, m, $^3J = 7.3$ Hz, C-2'-H)

1.24 (2H, m, $^3J = 7.3$ Hz, C-3'-H)

0.79 (3H, t, $^3J = 7.5$ Hz, C-4'-H)

¹³C-NMR (125 MHz, CDCl₃), δ (ppm):

140.4 (C-1)	128.2 (C-5)	30.5 (C-2')
130.6 (q, ² J (C,F) = 33 Hz, C-3)		123.1 (C-4)
18.7 (C-3')		
129.2 (C-2)	122.1 (q, ² J (C,F) = 220 Hz, CF ₃)	
128.9 (C-6)	42.0 (C-1')	12.5 (C-4')

EI-MS (70 eV): m/z (rel. int.):

281 [M]⁺ (8), 238 (100), 209 (84), 145 (58)

High-accuracy mass determination (HR-EI-MS):

Calculated: 281.0697 for [M⁺]

Found: 281.0705

Example 16: Synthesis of geranyl-3-trifluoromethylbenzenesulfonamide (= S11)

IUPAC: *N*-[(2*E*)-3,7-dimethylocta-2,6-diene-1-yl]-3-(trifluoromethyl)benzenesulfonamide

Empirical formula: C₁₇H₂₂NO₂SF₃ (MW = 361.13)

Synthesis:

1.233 g of 3-trifluoromethylbenzenesulfonic acid chloride (5 mmol) was dripped in 919 mg of geranylamine (6 mmol) in 40 ml of dichloromethane while stirring. After completion of the reaction the excess amine was shaken out with hydrochloric acid (0.1 M) (3 x 10 ml). Dichloromethane was removed on the rotary evaporator at reduced pressure and the product obtained.

Appearance: light brown oil

Yield: 1.770 g (98%)

UV (MeOH) λ_{\max} nm: 205, 220, 265

IR (KBr) ν_{\max} cm^{-1} : 3290, 2970, 2930, 1440, 1330, 1160

$^1\text{H-NMR}$ (500 MHz, CDCl_3), δ (ppm):

8.07 (1H, s, C-2-H)
 8.00 (1H, d, $^3\text{J} = 8.0$ Hz, C-4-H)
 7.77 (1H, d, $^3\text{J} = 8.0$ Hz, C-6-H)
 7.61 (1H, t, $^3\text{J} = 8.0$ Hz, C-5-H)
 4.95 (2H, m, $^3\text{J} = 7.0$ Hz, C-2'-H und C-6'-H)
 4.44 (1H, t, $^3\text{J} = 6.0$ Hz, N-H)
 3.57 (2H, q, $^3\text{J} = 6.5$ Hz, C-1'-H)
 1.89 (2H, q, $^3\text{J} = 8.0$ Hz, C-5'-H)
 1.83 (2H, t, $^3\text{J} = 8.0$ Hz, C-4'-H)
 1.59 (3H, s, C-3'-Me)
 1.49 (3H, s, C-7'-Me) 1.48 (3H, s, C-8')

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3), δ (ppm):

141.7 (C-3')	129.8 (C-6)	41.1 (C-1')	16.2 (C-3'-Me)
141.6 (C-1)	129.2 (C-5)	39.3 (C-4')	
131.9 (C-3)	124.2 (C-2')	26.1 (C-8')	
131.6 (C-7')	123.5 (C-4)	25.6 (C-7'-Me)	
130.3 (C-2)	118.1 (C-6')	17.6 (C-5')	

EI-MS (70 eV): m/z (rel. int.):

361 $[\text{M}]^+$ (39), 238 (100), 209 (67), 152 (75), 145 (58)

High-accuracy mass determination: (HR-EI-MS):

Calculated: 361.1323 for $[\text{M}^+]$

Found: 361.1333

Example 17: Synthesis of laurylsulfonamide (= S12)

IUPAC: N-Dodecylbenzenesulfonamide

Empirical formula: $C_{18}H_{31}NO_2S$ (MW = 325.21)

Synthesis:

177 g of benzenesulfonic acid chloride (1 mmol) were dripped in 370 mg of dodecylamine (2 mmol) in 10 ml of dichloromethane while stirring. After cooling of the reaction mixture 10 ml of water were added, and the reaction product was shaken out with dichloromethane (3 x 10 ml). The combined organic phases were washed with water (3 x 5 ml) and narrowed down on the rotary evaporator at reduced pressure.

Appearance: colourless crystals

Yield: 323 mg (99%)

Melting point (°C): 59-61

UV (MeOH) λ_{max} nm: 221, 265

IR (KBr) ν_{max} cm^{-1} : 3280, 2850, 1470, 1330, 1160

1H -NMR (500 MHz, $CDCl_3$), δ (ppm):

7.86 (2H, d, $^3J = 8.0$ Hz, C-2-H und C-6-H)

7.49 (1H, t, $^3J = 6.9$ Hz, C-4-H)

7.44 (2H, t, $^3J = 8.0$ Hz, C-3-H und C-5-H)

5.61 (1H, t, $^3J = 6.0$ Hz, N-H)

2.86 (2H, q, $^3J = 7.0$ Hz, C-1'-H)

1.39 (2H, m, $^3J = 7.1$ Hz, C-2'-H)

1.19 (18H, m, C-3'-H to C-11'-H)

0.82 (3H, t, $^3J = 6.8$ Hz, C-12'-H)

¹³C-NMR (125 MHz, CDCl₃), δ (ppm):

139.9 (C-1)	43.0 (C-1')	13.9 (C-12')
132.4 (C-4)	31.7 (C-2')	
128.7 (C-3 und C-5)	29.2 (7C, m, C-3' to C-10')	
126.8 (C-2 und C-6)	22.5 (C-11')	

EI-MS (70 eV): m/z (rel. int.):

325 [M]⁺ (9), 184 (88), 170 (100), 158 (58), 141 (64), 77 (21)

High-accuracy mass determination (HR-EI-MS):

Calculated: 325.2076 for [M⁺]

Found: 325.2080

Example 18: Synthesis of Butyl-4-nitro-3-trifluoromethylbenzenesulfonamide (= S13)

IUPAC: N-Butyl-4-nitro-3-(trifluoromethyl)benzenesulfonamide

Empirical formula: C₁₁H₁₃N₂O₄SF₃ (MW = 326.05)

Synthesis:

290 mg of 4-nitro-3-trifluoromethylbenzenesulfonic acid chloride (1 mmol) in 10 ml of dichloromethane were dripped in 146 mg of butylamine (2 mmol) while stirring. After cooling of the reaction mixture 20 ml of water were added, and the reaction product was shaken out with dichloromethane (3 x 10 ml). The combined organic phases were washed with water (3 x 5 ml) and narrowed down on the rotary evaporator at reduced pressure.

Appearance: white powder

Yield: 323 mg (99%)

Melting point (°C): 99

UV (MeOH) λ_{\max} nm: 205, 250

IR (KBr) ν_{\max} cm^{-1} : 3280, 2960, 1550, 1430, 1310, 1160, 1150

$^1\text{H-NMR}$ (500 MHz, CDCl_3), δ (ppm):

8.28 (1H, s, C-2-H)

8.19 (1H, d, $^3\text{J} = 8.3$ Hz, C-5-H)

7.98 (1H, d, $^3\text{J} = 8.3$ Hz, C-6-H)

4.62 (1H, s, N-H)

3.03 (2H, q, $^3\text{J} = 6.3$ Hz, C-1'-H)

1.49 (2H, m, $^3\text{J} = 7.3$ Hz, C-2'-H)

1.31 (2H, m, $^3\text{J} = 7.3$ Hz, C-3'-H)

0.87 (3H, t, $^3\text{J} = 7.3$ Hz, C-4'-H)

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3), δ (ppm):

149.9 (C-4) 126.8 (C-5) 31.7 (C-2')

144.9 (C-1) 125.0 (C-3) 19.6 (C-3')

131.8 (C-2) 123.5 (q, $^2\text{J}(\text{C},\text{F}) = 188$ Hz, CF_3)

126.9 (C-6) 43.2 (C-1') 13.4 (C-4')

EI-MS (70 eV): m/z (rel. int.):

326 $[\text{M}]^+$ (14), 285 (22), 283 (100), 254 (82), 190 (53), 55 (17)

High-accuracy mass determination (HR-EI-MS):

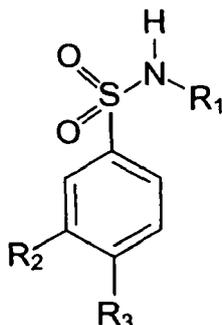
Calculated: 326.0548 for $[\text{M}]^+$

Found: 326.0553

Example 19: Synthesis of Geranyl-4-nitro-3-trifluoromethyl-benzenesulfonamide (= S14)

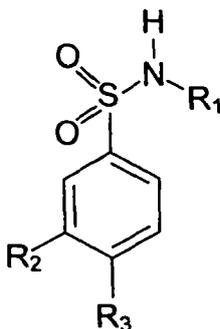
Amended Claims

1. Use of a benzenesulfonamide derivative of the formula



wherein R₁ represents an aliphatic C₁ to C₁₂ hydrocarbon, R₂ is hydrogen or a completely or partially halogenated C₁ residue; and R₃ is hydrogen or a nitro group, for the production of a medicament for treating benign prostatic hyperplasia and/or prostate carcinoma.

2. Use of a benzenesulfonamide derivative of the formula

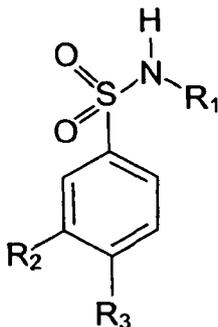


wherein R₁ represents an aliphatic C₁ to C₁₂ hydrocarbon, R₂ is hydrogen or a completely or partially halogenated C₁ residue; and R₃ is hydrogen or a nitro group, for treating benign prostatic hyperplasia and/or prostate carcinoma.

3. Use according to claim 1 or 2, characterised in that the said prostate carcinoma is resistant to a therapy with androgen antagonists.

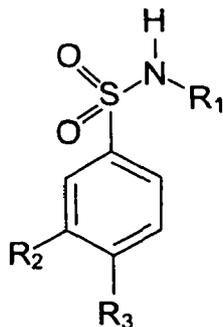
4. Use according to claim 3, characterised in that the said androgen antagonist is selected from the group comprising bicalutamide, flutamide, hydroxyflutamide, nilutamide and cyproterone acetate.

5. Use of a benzenesulfonamide derivative of the formula



wherein R_1 represents an aliphatic C_1 to C_{12} hydrocarbon, R_2 is hydrogen or a completely or partially halogenated C_1 residue; and R_3 is hydrogen or a nitro group, as a lead substance for developing active substances for treating benign prostatic hyperplasia and/or prostate carcinoma.

6. Pharmaceutical preparation for treating benign prostatic hyperplasia and/or prostate carcinoma, characterised in that said preparation contains at least one benzenesulfonamide derivative of the formula



wherein R_1 represents an aliphatic C_1 to C_{12} hydrocarbon, R_2 is a completely or partially halogenated C_1 residue and R_3 is hydrogen or a nitro group; or R_2 is hydrogen or a completely or partially halogenated C_1 residue and R_3 is a nitro group.

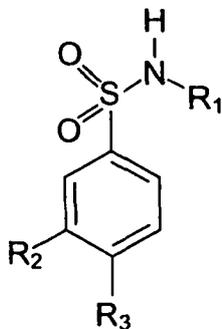
7. Process for isolating *N*-butylbenzenesulfonamide from biological material, comprising the steps:
- a. reducing the biological material to small pieces,
 - b. extracting the biological material with a solvent selected from the group comprising univalent C_1 to C_4 alcohols and high-volatile, (partially) halogenated C_1 hydrocarbons;
 - c. fractionating the extract,
 - d. isolation of *N*-butylbenzenesulfonamide from the fractions containing *N*-butylbenzenesulfonamide.
8. Process according to claim 7, characterised in that the said biological material is bark of the African plum tree *P. africana*.

9. Process according to claim 7 or 8, characterised in that said extraction is a selective extraction by means of a series of successive solvents of increasing polarity.

10. Process according to any one of claims 7 to 9, characterised in that said fractionation of the extract is performed using gradient extrography with increasing polarity of the eluents.

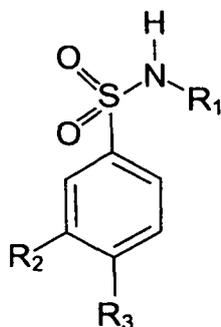
11. Process according to any one of claims 7 to 10, characterised in that isolation of *N*-butylbenzenesulfonamide from the fractions is performed by means of chromatography.

12. Benzenesulfonamide derivatives for treating benign prostatic hyperplasia and/or prostate carcinoma, characterised by the formula

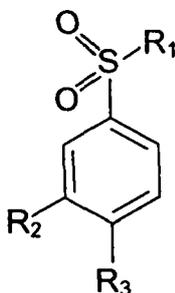


wherein R₁ represents an aliphatic C₁ to C₁₂ hydrocarbon, R₂ is a completely or partially halogenated C₁ residue and R₃ is hydrogen or a nitro group; or R₂ is hydrogen or a completely or partially halogenated C₁ residue and R₃ is a nitro group.

13. Process for the production of benzenesulfonamide derivatives of the formula



wherein R_1 represents an aliphatic C_1 to C_{12} hydrocarbon, R_2 is hydrogen or a completely or partially halogenated C_1 residue; and R_3 is hydrogen or a nitro group, characterised in that a benzenesulfonic acid derivative of the formula



wherein R_1 represents halogen, R_2 hydrogen or a completely or partially halogenated C_1 -residue; and R_3 is hydrogen or a nitro group, is converted with a primary aliphatic amine and the reaction product is shaken out with dichloromethane or ether.

14. Process according to claim 13, characterised in that said primary aliphatic amine is selected from the group comprising C_1 to C_{12} aliphatic hydrocarbons and, preferably, butylamine or geranylamine.

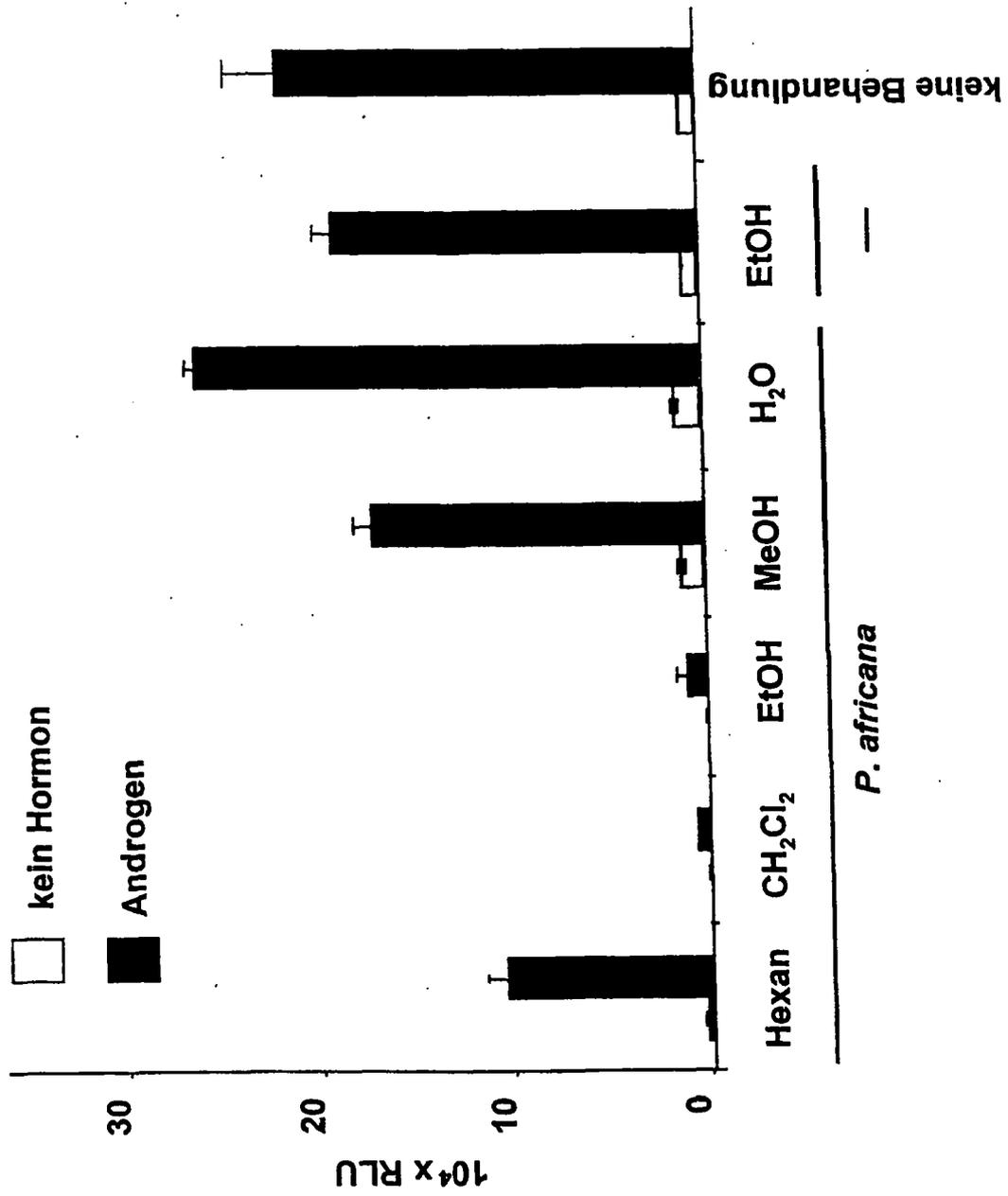


FIG. 1

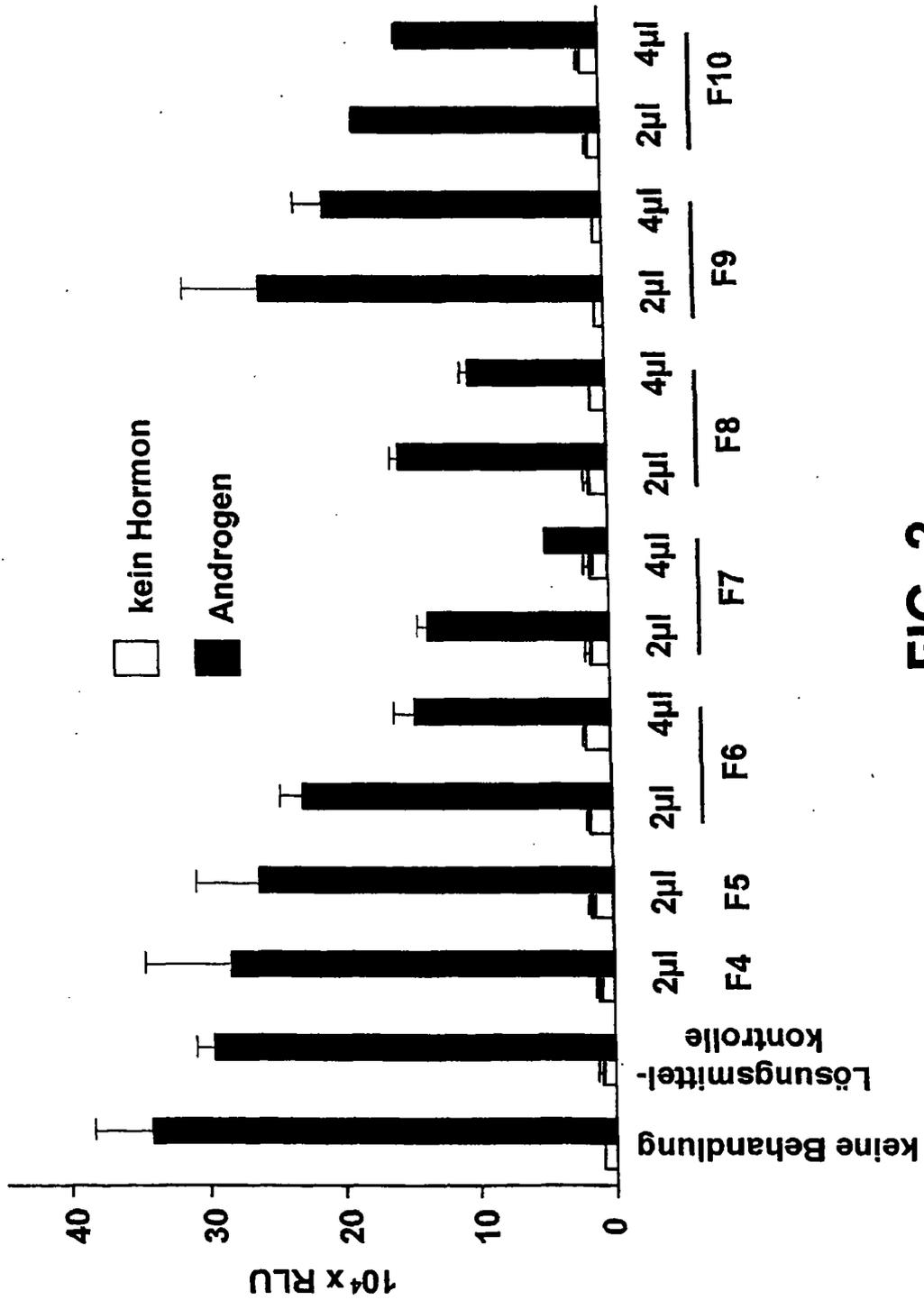
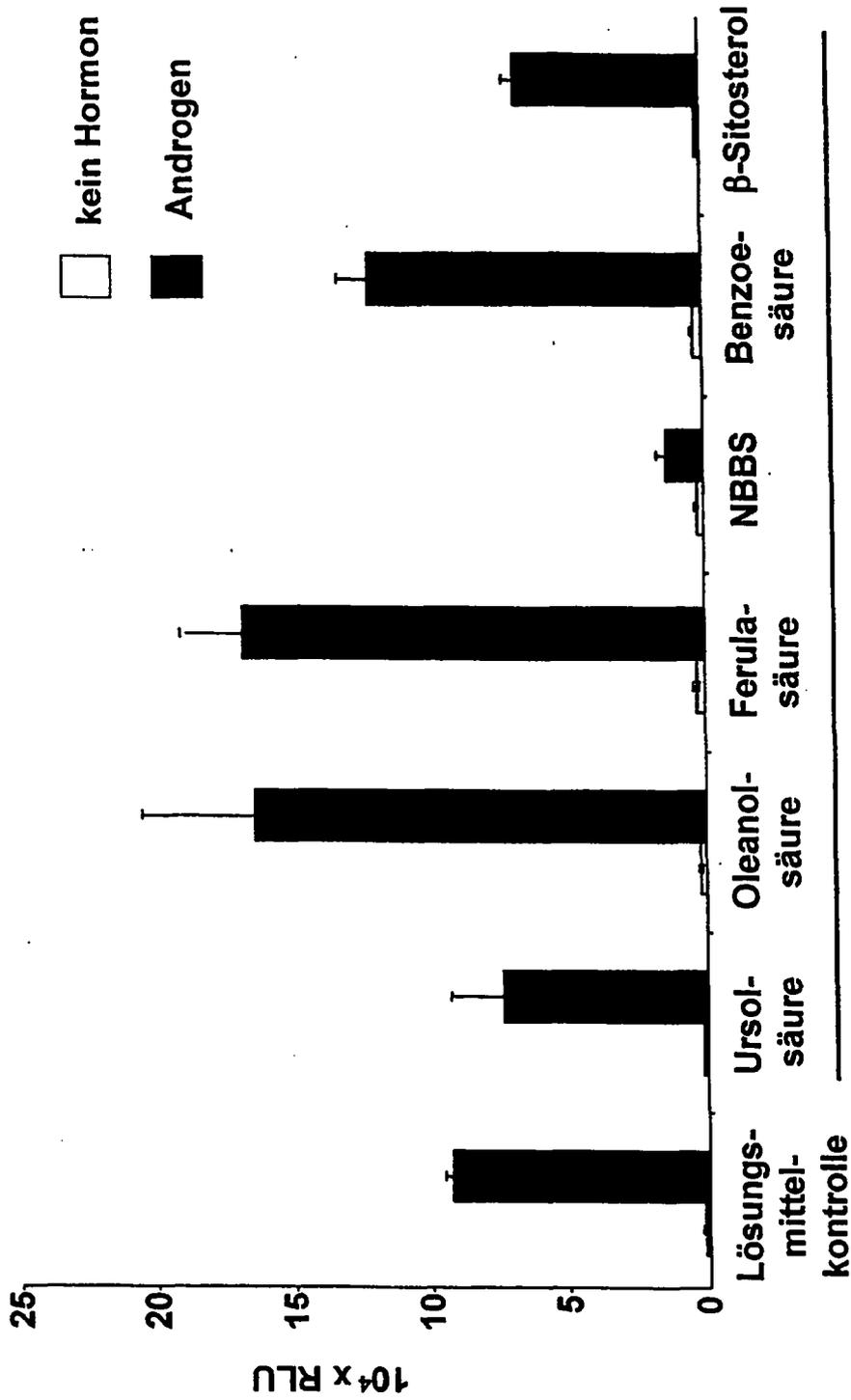


FIG. 2



Verbindungen, isoliert aus *P. africana*

FIG. 3

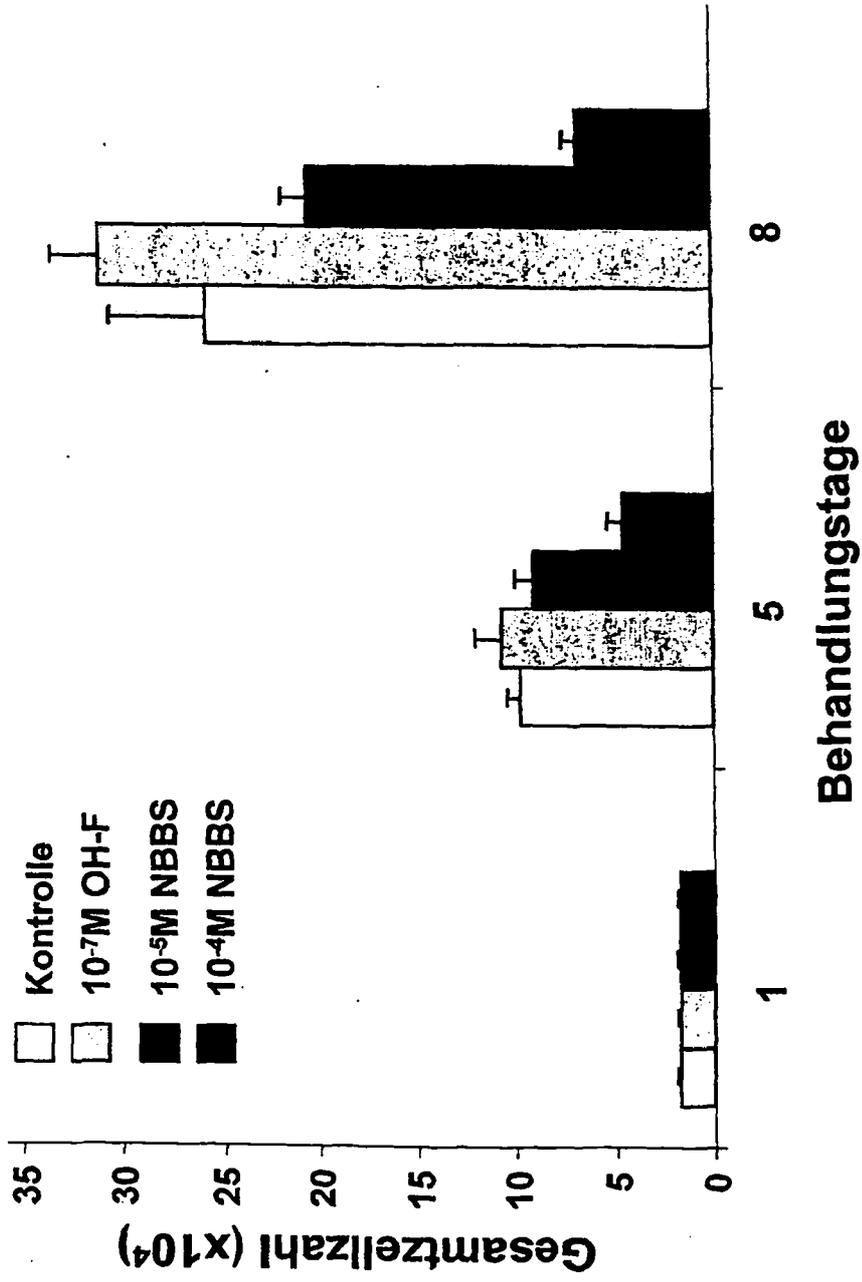


FIG. 4

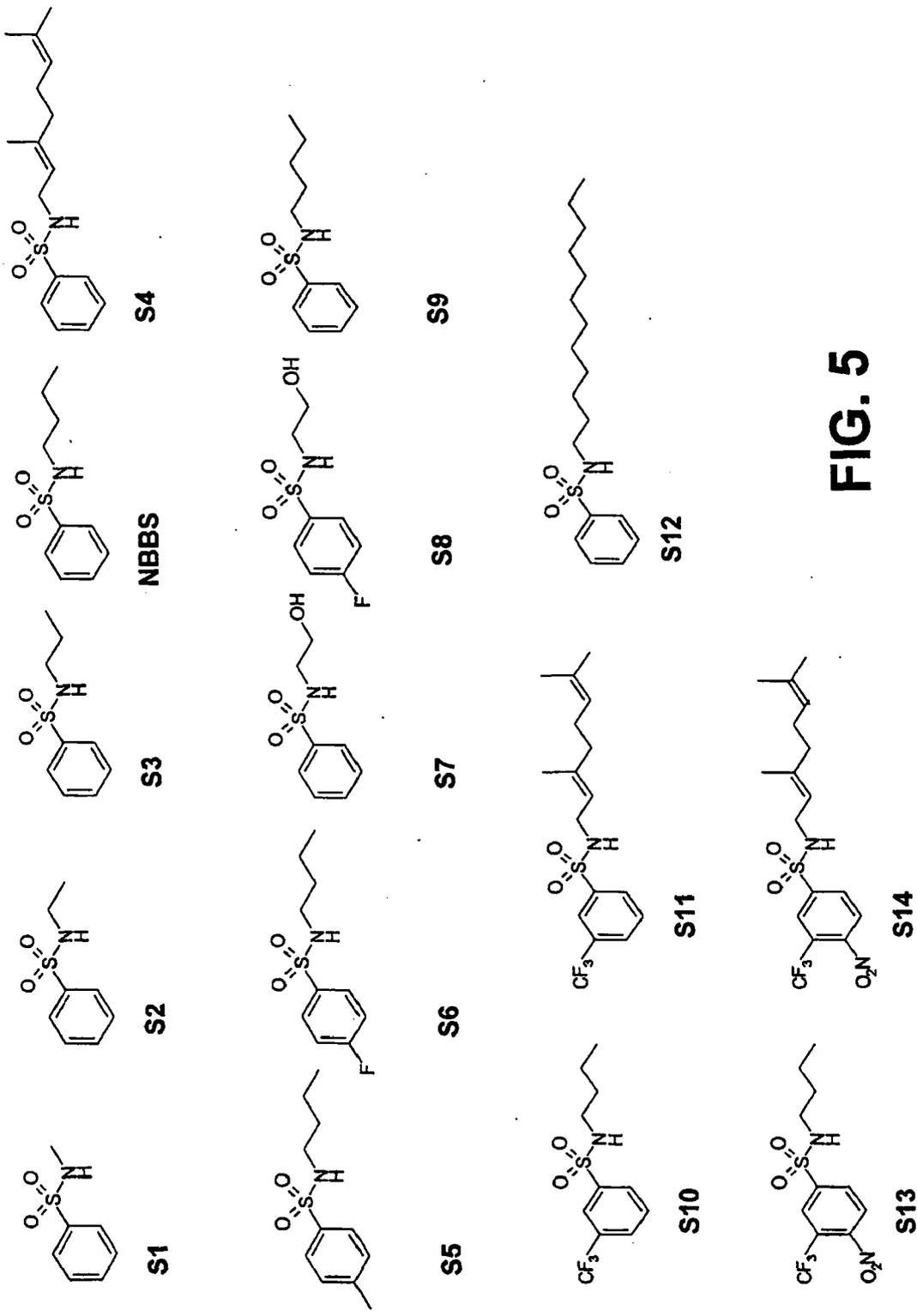


FIG. 5

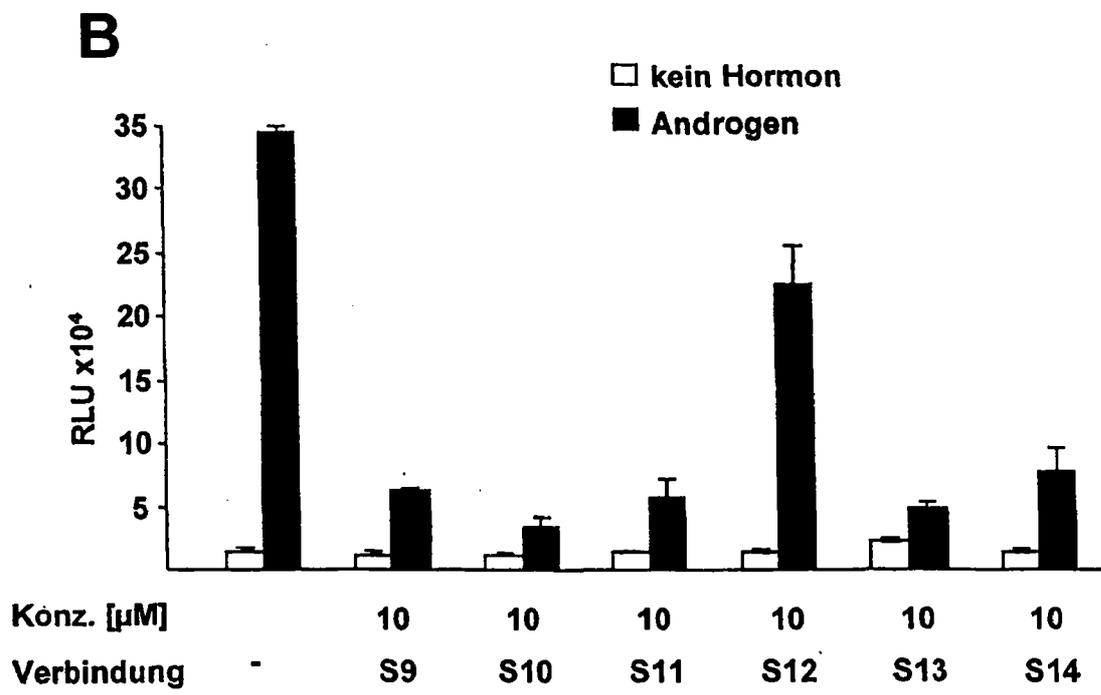
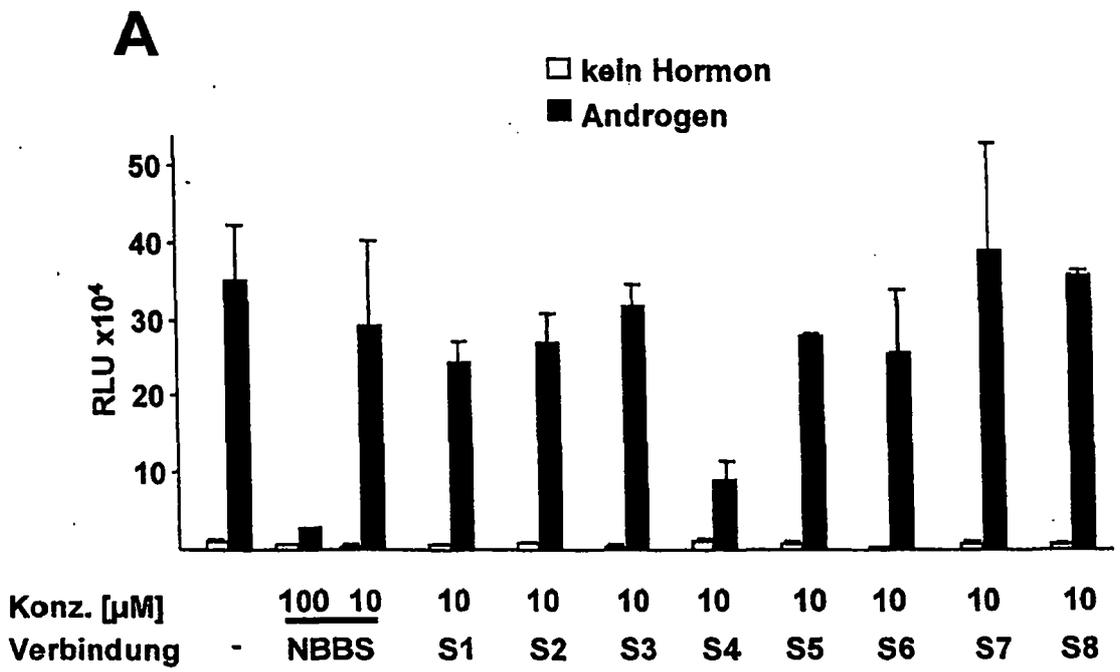


FIG. 6