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(54) Title: THIOPHENEPYRIMIDINONES AS 17-BETA-HYDROXYSTEROID DEHYDROGENASE INHIBITORS

(57) Abstract: This invention relates to compounds useful in therapy, especially for use in the treatment and/or prevention of a steroid hormone dependent disorder, preferably a steroid hormone dependent disease or disorder requiring the inhibition of a 17 β -hydroxysteroid dehydrogenase (17 β -HSD) such as 17 β -HSD type 1, type 2 or type 3 enzyme.



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THIOPHENEPYRIMIDINONES AS 17-BETA-HYDROXYSTEROID
DEHYDROGENASE INHIBITORS

5

FIELD OF THE INVENTION

The present invention relates to novel thiophenepyrimidinone derivatives which represent
10 inhibitory compounds of the 17 β -hydroxysteroid dehydrogenase enzymes, preferably of the 17 β -
hydroxysteroid dehydrogenase type 1 (17 β -HSD1), type 2 (17 β -HSD2) or type 3 (17 β -HSD3)
enzyme, to their salts, to pharmaceutical preparations containing these compounds and to
processes for the preparation of these compounds. Furthermore, the invention concerns the
therapeutic use of said thiophenepyrimidinone derivatives, particularly their use in the treatment
15 or prevention of steroid hormone dependent diseases or disorders, such as steroid hormone
dependent diseases or disorders requiring the inhibition of 17 β -hydroxysteroid dehydrogenase
enzymes, in particular 17 β -HSD type I enzymes, and/or requiring the modulation of the endoge-
nous 17 β -estradiol and/or testosterone concentration.

20 BACKGROUND OF THE INVENTION

The publications and other materials used herein to illuminate the background of the invention,
and in particular, cases to provide additional details respecting the practice, are incorporated by
reference.

25

Mammalian 17 β -hydroxysteroid dehydrogenases (17 β -HSDs) are NAD(H) or NADP(H) depend-
ent enzymes which catalyze – besides other reactions – the final steps in male and female sex
hormone biosynthesis. These enzymes convert inactive 17-keto-steroids into their active 17 β -
hydroxy-forms or catalyze the oxidation of the 17 β -hydroxy-forms into the 17-keto-steroids.
30 Because both estrogens and androgens have the highest affinity for their receptors in the 17 β -
hydroxy form, 17 β -HSD enzymes play an essential role in the tissue-selective regulation of the
activity of sex steroid hormones.

At present, 10 human members of the 17 β -HSD enzyme family have been described (types 1-5,
35 7, 8, 10, 11 and 12). The human 17 β -HSD family members share less than 30% similarity in
their primary structure. The 17 β -HSDs are expressed in distinct, though in some cases, over-
lapping patterns. The different types of 17 β -HSDs also differ in their substrate and cofactor
specificities. In intact cells in culture, the 17 β -HSDs catalyze the reaction in a unidirectional way:

types 1, 3, 5 and 7 use NADP(H) as a cofactor and catalyze the reductive reaction (activation), while types 2, 4, 8 and 10 catalyze the oxidative reaction (inactivation) using NAD(H) as a cofactor. [see e.g. Labrie et al. (2000) Trends Endocrinol Metab., 11:421-7].

- 5 Due to their essential role in the tissue-selective regulation of the activity of sex steroid hormones 17 β -HSDs can be involved in the occurrence and development of estrogen-sensitive pathologies (f. ex. breast, ovarian, uterine and endometrium cancers etc.) and androgen-sensitive pathologies (f. ex. prostate cancer, benign prostatic hyperplasia, acne, hirsutism, etc). Furthermore, many types of 17 β -HSD have been shown to be involved in the pathogenesis of
- 10 particular human disorders. For example, 17 β -HSD3 is known to be involved in the development of pseudohermaphroditism, the 17 β -HSD8 plays a role in polycystic kidney disease and the 17 β -HSD4 is related to the occurrence of bifunctional enzyme deficiency. Therefore treatment of sex steroid-sensitive diseases by administration of specific inhibitors of the 17 β -HSDs enzymes have been suggested, optionally in combination with potent and specific antiestrogens and
- 15 antiandrogens [Labrie F et al. (1997) Steroids, 62:148-58].

- Due to the fact that each type of 17 β -HSD has a selective substrate affinity, directional (reductive or oxidative) activity in intact cells, and a particular tissue distribution, the selectivity of drug action could be achieved by targeting a particular 17 β -HSD isozyme. By individual modulation of
- 20 the particular 17 β -HSDs it is possible to influence or even control the local and paracrine concentration of estrogens and androgens in different target tissues.

- The best characterized member of the 17 β -HSD family is the type 1 17 β -HSD [EC 1.1.1.62]. This enzyme could be crystallized in different states of functionality (e.g. with and without ligand and/or co-factor). The 17 β -HSD1 catalyzes in vitro the reduction as well as the oxidation between estrone (E1) and estradiol (E2). However, under physiological in vivo conditions the enzyme only catalyzes the reductive reaction from the estrone (E1) to the estradiol (E2). The 17 β -HSD1 was found to be expressed in a variety of hormone-dependent tissues, e.g. placenta, mammary gland tissue or uterus and endometrium tissue, respectively. Estradiol itself is, especially in comparison to the significantly less active estrone, a very potent hormone, which regulates the expression of a variety of genes by binding to the nuclear estrogen receptor and plays an essential role in the proliferation and differentiation of the target cell. Physiological as well as pathological cell proliferations can be estradiol dependent. Especially many breast cancer cells are stimulated by a locally raised estradiol concentration. Furthermore, the occurrence or
- 30 course of benign pathologies such as endometriosis, uterine leiomyomas (fibroids or myomas), adenomyosis, menorrhagia, metrorrhagia and dysmenorrhea is dependent from the existence of significantly high estradiol levels.

Endometriosis is a well-known gynaecological disorder that affects 10 to 15% of women in the reproductive age. It is a benign disease defined as the presence of viable endometrial gland and stroma cells outside the uterine cavity. It is most frequently found in the pelvic area. In women developing endometriosis, the endometrial cells entering the peritoneal cavity by retro-grade menstruation (the most likely mechanism) have the capacity to adhere to and invade the peritoneal lining, and are then able to implant and grow. The implants respond to steroid hormones of the menstrual cycle in a similar way as the endometrium in the uterus. The infiltrating lesions and the blood from these lesions which are unable to leave the body cause inflammation of the surrounding tissue. The most common symptoms of endometriosis are dysmenorrhoea, dyspareunia and (chronic) abdominal pain. The occurrence of these symptoms is not related to the extent of the lesions. Some women with severe endometriosis are asymptomatic, while women with mild endometriosis may have severe pain. Endometriosis is found in up to 50% of the women with infertility. However, currently no causal relation has been proven between mild endometriosis and infertility. Moderate to severe endometriosis can cause tubal damage and adhesions leading to infertility. The aims of treatment of endometriosis are pain relief, resolution of the endometriotic tissue and restoration of fertility (if desired). The two common treatments are surgery or anti-inflammatory and/or hormonal therapy or a combination thereof.

Uterine leiomyomas (fibroids or myomas), benign clonal tumours, arise from smooth muscle cells of the human uterus. They are clinically apparent in up to 25% of women and are the single, most common indication for hysterectomy. They cause significant morbidity, including prolonged and heavy menstrual bleeding, pelvic pressure and pain, urinary problems, and, in rare cases, reproductive dysfunction. The pathophysiology of myomas is not well understood. Myomas are found submucosally (beneath the endometrium), intramurally (within the myometrium) and subserosally (projecting out of the serosal compartment of the uterus), but mostly are mixed forms of these 3 different types. The presence of estrogen receptors in leiomyoma cells has been studied by Tamaya et al. [Tamaya et al. (1985) *Acta Obstet Gynecol Scand.*, 64:307-9]. They have shown that the ratios of estrogen receptor compared to progesterone and androgen receptor levels were higher in leiomyomas than in the corresponding normal myometrium. Surgery has long been the main treatment for myomas. Furthermore, medical therapies that have been proposed to treat myomas include administration of a variety of steroids such as the androgenic steroids danazol or gestrinone, GnRH agonists and progestogens, whereby the administration is often associated a variety of serious side-effects.

Everything that has been said above in relation to the treatment of uterine leiomyomas and endometriosis equally applies to other benign gynaecological disorders, notably adenomyosis, functional menorrhagia and metrorrhagia. These benign gynaecological disorders are all estrogen sensitive and are treated in a comparable way as described herein before in relation to uterine leiomyomas and endometriosis. The available pharmaceutical treatments, however,

suffer from the same major drawbacks, i.e. they have to be discontinued once the side-effects become more serious than the symptoms to be treated and symptoms reappear after discontinuation of the therapy.

- 5 Since the aforementioned malign and benign pathologies are all 17β -estradiol dependent, a reduction of the endogenous 17β -estradiol concentration in the respective tissue will result in an impaired or reduced proliferation of 17β -estradiol cells in said tissues. Therefore, it may be concluded that selective inhibitors of the 17β -HSD1 enzyme are well suited for their use to impair endogenous productions of estrogens, in particular of 17β -estradiol, in myomas, endo-
- 10 metriotic, adenomyotic and endometrial tissue. The application of a compound acting as selective inhibitor on the 17β -HSD1 which preferentially catalyzes the reductive reaction will result in a lowered intracellular estradiol-concentration since the reductive conversion of the estrone into the active estradiol is reduced or suppressed. Therefore, reversible or even irreversible inhibitors of the 17β -HSD1 may play a significant role in the prophylaxis and/or treatment of steroid-
- 15 hormone, in particular 17β -estradiol, dependent disorders or diseases. Furthermore, the reversible or even irreversible inhibitors of the 17β -HSD1 should have no or only pure antagonistic binding activities to the estradiol receptor, in particular to the estrogen receptor α subtype, since agonistic binding of the estrogen receptor would lead to activation and therefore – by regulation of a variety of genes – to the proliferation and differentiation of the target cell. In contrast, an-
- 20 tagonists of the estrogen receptor, so called anti-estrogens, bind competitively to the specific receptor protein thus preventing access of endogenous estrogens to their specific binding site. At present it is described in the literature that several malignant disease as breast cancer, prostate carcinoma, ovarian cancer, uterine cancer, endometrial cancer and endometrial hyper-
- 25 plasia may be treated by the administration of a selective 17β -HSD1 inhibitor. Furthermore, a selective 17β -HSD1 inhibitor may be useful for the prevention of the aforementioned hormone-dependent cancers, especially breast cancer.

Several reversible or irreversible inhibitors of the 17β -HSD1 enzyme of steroidal and even non-steroidal origin are already known from the literature. The characteristics of these inhibitory

30 molecules, which mainly have a substrate or cofactor-like core structure, have been reported in the literature [reviewed in: Poirier D. (2003) *Curr Med Chem.* 10:453-77].

A further well characterized member of the 17β -HSD family is the 17β -HSD type 3 enzyme (17β -HSD3). The 17β -HSD3 has a distinct feature compared to other 17β -HSDs: it is found to be

35 expressed almost exclusively in the testis, whereas the other isoenzymes are expressed more widely in several tissues. 17β -HSD3 has a crucial role in androgen biosynthesis. It converts 4-androstene-3,17-one (A) to testosterone (T). The biological significance of the 17β -HSD3 is of undeniable physiological importance. Mutations in the gene for 17β -HSD3 have been found to lead to

decreased T formation in the fetal testis and consequently to a human intersex disorder termed male pseudohermaphroditism [Geissler WM et al. (1994) Nat Genet., 7:34-9].

With regard to the indication prostate cancer, the primary cancer cells mostly retain their responsiveness to androgens in their regulation of proliferation, differentiation, and programmed cell death for some period. At present, androgen deprivation is the only effective systemic hormonal therapy available for prostate cancer. The development of selective inhibitors against 17 β -HSD3 is a new therapeutic approach for the treatment of androgen dependent disease [Labrie et al. (2000) Trends Endocrinol Metab., 11:421-7]. Furthermore, Oefelein et al. reported that the depot GnRH analogue fails, in nearly 20% of cases, to achieve castrate levels of T in men [Oefelein MG & Cornum R (2000) J Urol.; 164:726-9]. In order to improve the response rate to endocrine therapy for men with prostate cancer it may be important to selectively inhibit testicular 17 β -HSD3 activity. Besides prostate cancer, many other androgen-sensitive diseases, i.e. diseases whose onset or progress is aided by androgenic activity, may be treated by selectively inhibiting 17 β -HSD3 activity. These diseases include but are not limited to benign prostatic hyperplasia, prostatitis, acne, seborrhea, hirsutism, androgenic alopecia, precocious puberty, adrenal hyperplasia, and polycystic ovarian syndrome. Furthermore, considering the fact that 17 β -HSD3 is found mainly in the testis, the development of potent inhibitors could be of interest for blocking spermatogenesis and as an anti-fertility agent for males.

Several reversible or irreversible inhibitors of the 17 β -HSD3 enzymes of steroidal and even non-steroidal origin are already known from the literature. The characteristics of these inhibitory molecules have been reported in the literature [reviewed in: Poirier D. (2003) Curr Med Chem. 10:453-77]. For example, US patent No. 6,541,463 discloses androsterone derived inhibitors for 17 β -HSD3. These derivatives have been synthesised by parallel solid- and liquid-phase chemistry and some of these compounds showed 2 to 18-fold higher inhibition activity than that of the natural substrate of the enzyme, A-dione, used itself as a inhibitor. Furthermore, the international patent application WO 01/42181 discloses benzyl-tetralins, the chemical structure of which is related to that of the phytoestrogen biochanin, as 17 β -HSD3 inhibitors. Furthermore, international patent applications WO 98/32724, WO 98/30556 and WO 99/12540 disclose tetralone, benzopyrane and benzofuranone derivatives, which have a 17 β -HSD inhibitory activity, for the treatment of hormone sensitive diseases.

Microsomal 17 β -hydroxysteroid dehydrogenase of human endometrium and placenta (designated 17 β -HSD type 2 or 17 β -HSD2) was cloned by expression cloning, and found to be equally active using androgens and estrogens as substrates for oxidation [Andersson S. (1995) J. Steroid Biochem. Molec. Biol., 55:533-534]. The recombinant 17 β -HSD2 converts the highly active 17 β -hydroxysteroids such as estradiol (E2), testosterone (T), and dehydrotestosterone

(DHT) to their inactive keto forms. In addition, the 17 β -HSD2 can, to a lesser extent, also convert 20 β -hydroxyprogesterone (20 β P) to progesterone (P). The broad tissue distribution together with the predominant oxidative activity of 17 β -HSD2 suggest that the enzyme may play an essential role in the inactivation of highly active 17 β -hydroxysteroids, resulting in diminished sex hormone action in target tissues. Dong and colleagues showed significant 17 β -HSD2 activity in cultured human osteoblasts and osteoblast-like osteosarcoma cells MG63 and TE85, but not in SaOS-2 [Dong Y et al. (1998) J. Bone Min. Res., 13:1539-1546]. The potential for interconversion of E1 to E2, T to A, and DHT to A by bone cells could therefore represent important mechanism for the local regulation of intracellular ligand supply for the estrogen and androgen receptors in the osteoblasts and other steroid sensitive cells. This modulation of steroid levels may be employed for a wide variety of indications, including the following: for the prevention and treatment of osteoporosis, for the treatment of ovarian cancer, for the treatment of breast cancer, for the treatment of endometrial cancer, for the treatment of endometriosis, for the treatment of prostate cancer and/or for the treatment of androgen-dependent hair-loss.

Several reversible or irreversible inhibitors of the 17 β -HSD2 enzymes of steroidal and even non-steroidal origin are already known from the literature. The characteristics of these inhibitory molecules have been reported in the literature [reviewed in: Poirier D. (2003) Curr Med Chem. 10:453-77]. In addition, the international patent application WO 02/26706 discloses 17 β -HSD2 inhibitors of non-steroidal origin.

Some thienopyrimidinones derivatives that are described as being useful in therapy have already been disclosed in the literature: The German patent application DE 2411273 (Schering AG) discloses compounds having anti-inflammatory activity. Manhas et al describe the synthesis and antiinflammatory activity of some substituted thienopyrimidinones [Manhas MS et al. (1972) J Med Chem. 15(1):106-7]. Kapustina et al. describe the synthesis and antibacterial and chemotherapeutic or antitubercular activity of some substituted thienopyrimidones [Kapustina MV et al. (1992) Khimiko-Farmatsevticheskii Zhurnal 26(1):56-7; and Kapustina MV et al (1991) Khimiko-Farmatsevticheskii Zhurnal 25(7): 38-9].

Furthermore, several other Thienopyrimidinones derivatives have been described but were not related to any medical use so far. For example, the compounds 1,2,7,8,9,10,11,13-octahydro-13-oxo-4-(phenylthio)-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-3-carboxaldehyde (CAS reg. no. 333774-42-8) and 1,2,7,8,9,10,11,13-octahydro-13-oxo-4-(chloro)-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-3-carboxaldehyde (CAS reg. no 299962-60-0) are commercially available. Further substituted thienopyrimidones have already been disclosed, e.g.: 1,2,7,8,9,10,11,13-octahydro-4-hydroxy-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepin-13(7H)-one (CA reg. no. 333774-26-8);

- 2,3,8,9,10,11-hexahydro-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-4,13(1H,7H)-dione (CA reg. no. 141581-80-8);
- 2,3,8,9-Tetrahydro[1]benzothieno[2,3-d]pyrrolo[1,2-a]pyrimidine-6,10(1H,7H)-dione (CA reg. no. 141581-81-9),
- 5 8,9,10,11-tetrahydro-4-hydroxy-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepin-13(7H)-one (CA reg. no. 333780-19-1);
- 3-Butyl-2,7-dimethyl-4b,5,6,7,8,8a-hexahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one (CA reg. no. 39625-80-4);
- 1,2,3,4,5,8,9,10,11,12-Decahydro-14H-cyclohepta[4',5']thieno[2',3':4,5]pyrimido-[1,2-a]azepin-
- 10 14-one-4-oxime (CA reg. no. 299962-59-7);
- 1,2,3,4,5,8,9,10,11,12-Decahydro-14H-cyclohepta[4',5']thieno[2',3':4,5]pyrimido-[1,2-a]azepin-14-one-3-oxime (CA reg. no. 296798-31-7);
- 1,2,3,4,7,9,10,12-Octahydro-12-oxo-8H-[1]benzothieno[2,3-d]pyrido[1,2-a]pyrimidine-7-carboxylic acid ethyl ester (CA reg no. 329059-69-0);
- 15 1,2,3,4-Tetrahydro-12H-[1]benzothieno[2,3-d]pyrido[1,2-a]pyrimidin-12-one (CA Reg. No. 60943-07-9), and
- 3-Methyl-2,3,4,7,8,9,10,11-octahydro-[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]azepin-13(1H)-one (CA Reg. No. 677320-14-8)

- 20 However, according to the inventors' knowledge none of the already known compounds described above has been described as useful in the treatment and/or prevention of a steroid hormone dependent disease or disorder, particularly a steroid hormone dependent disease or disorder requiring the inhibition of the 17 β -hydroxysteroid dehydrogenase (17HSD) type 1, type 2 or type 3 enzyme.

25

- There is a need for the development of compounds that are selectively inhibiting the 17 β -HSD1, 17 β -HSD3 and/or 17 β -HSD2 enzyme, while desirably failing to inhibit substantially other members of the 17 β -HSD protein family, or other catalysts of sex steroid degradation or activation. In particular, it is an aim of the present invention to develop selective inhibitors of the 17 β -HSD1
- 30 enzyme, whereby in addition the compounds have no or only pure antagonistic binding affinities to the estrogen receptor (both subtypes α and β).

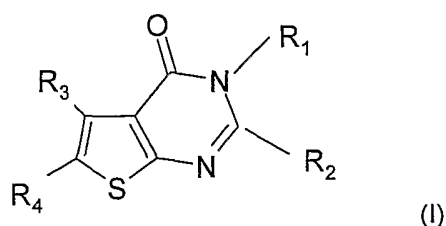
SUMMARY OF THE INVENTION

- 35 Therefore, it is an object of the present invention to develop novel inhibitors of the 17 β -HSD1 and 17 β -HSD2 enzyme, which have valuable pharmacological properties and which are suited for the treatment of estrogen dependent diseases and disorders. It is a further object of the present invention to develop novel inhibitors of the 17 β -HSD3 enzyme, which have valuable

pharmacological properties and which are suited for the treatment of androgen dependent diseases and disorders.

It has now been found that the thiophenepyrimidinone derivatives of the present invention would be valuable in therapy, especially in the treatment or prevention of steroid hormone dependent diseases or disorders, such as steroid hormone dependent diseases or disorders requiring the inhibition of 17β -hydroxysteroid dehydrogenase (HSD) enzymes. In particular, compounds of formula (I) represent potent inhibitors of the 17β -HSD1, 17β -HSD3 and/or 17β -HSD2 enzyme and possess valuable pharmacological properties for the treatment and/or prophylaxis of malignant steroid dependent diseases or disorders such as breast cancer, prostate carcinoma, ovarian cancer, uterine cancer, endometrial cancer and endometrial hyperplasia, but also for the treatment and/or prophylaxis of benign steroid dependent diseases or disorders such as endometriosis, uterine fibroids, uterine leiomyoma, adenomyosis, dysmenorrhea, menorrhagia, metrorrhagia, prostatic dysplasia, benign prostatic hyperplasia, prostatitis, acne, seborrhea, hirsutism, androgenic alopecia, precocious puberty, adrenal hyperplasia, polycystic ovarian syndrome, or urinary dysfunction. Further estrogen-dependent diseases which may be treated and/or prevented with an effective amount of a compound of the invention are multiple sclerosis, rheumatoid arthritis, Alzheimer's disease, colon cancer, tissue wounds, skin wrinkles and cataracts. Furthermore, compounds of formula (I) may be useful for the prevention and treatment of osteoporosis, and for blocking spermatogenesis and as an anti-fertility agent for males.

Accordingly, the present invention relates to the use of a compound having the structural formula (I)



wherein

- R_1 and R_2 represent the same or different alkyl, or one is alkyl and the other is H, or R_1 and R_2 form together with their binding sites a cyclic 5-, 6-, 7- or 8-membered ring system, which is saturated or contains one or more double bonds between the ring atoms, and which ring optionally contains up to two heteroatoms in addition to the nitrogen atom where R_1 is attached, the number of N atoms being 0-2 and the number of O or S atoms each being 0-1, wherein said ring is optionally substituted with up to three substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, or arylalkyl, whereby the aryl

group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, alkylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and amido;

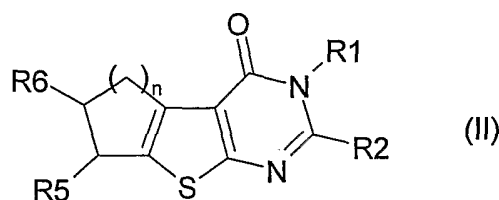
- 5 R₃ and R₄ form together with their binding sites a cyclic 5-, 6-, 7- or 8-membered hydrocarbon ringsystem, which is saturated or contains one or more double bonds between the carbon atoms, and

wherein said ring is optionally substituted with up to three substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl or arylalkyl, whereby the aryl
10 group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, alkylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and amido;

provided that said compound is not 1,2,7,8,9,10,11,13-octahydro-13-oxo-4-(phenylthio)-
15 [1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-3-carboxaldehyde;

for the manufacture of a medicament for the treatment and/or prevention of a steroid hormone dependent disease or disorder, preferably for a steroid hormone dependent disease or disorder requiring the inhibition of a 17 β -hydroxysteroid dehydrogenase (17 β -HSD) enzyme, most pref-
20 erably requiring the inhibition of the 17 β -HSD type 1, 17 β -HSD type 2 or 17 β -HSD type 3 enzyme.

According to another aspect, the invention concerns a compound of formula (II)



25 wherein

R₁ and R₂ represent the same or different C₁-C₈-alkyl, or one is C₁-C₈-alkyl and the other is H,
or

R₁ and R₂ form together with their binding sites a cyclic 5-, 6-, 7- or 8-membered ring system,
30 which is saturated or contains one or more double bonds between the ring atoms, and
which ring optionally contains up to two N-atoms in addition to the nitrogen atom where R₁ is attached,

wherein said ring is optionally substituted with up to two substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, or arylalkyl, whereby the aryl
35 group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, al-

kylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and amido;

the hydrocarbon chain $-C(R5)-C(R6)-(CH)_n-$ of the ring-system adjacent to the thiophen-ring is saturated or contains one or more double bonds between the carbon atoms;

n is an integer from 1 to 4, and

$R5$ and $R6$ are individually selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl or arylalkyl, whereby the aryl group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, alkylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and amido.

under the proviso that

in case n represents 1, 2 or 3, and $R1$ and $R2$ independently are selected from hydrogen or C_1 - C_4 alkyl or together form an unsubstituted alkylene group of 3 – 5 methylen groups or a iminoalkylene group of 2 – 4 methylen groups in the alkylene group, optionally substituted at the N-atom, then at least

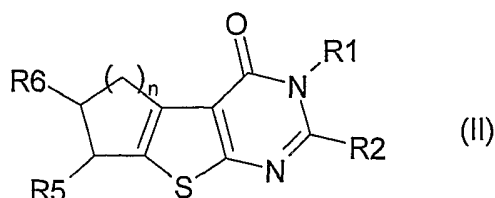
- (i) $R5$ or $R6$ has to be different from hydrogen, C_1 - C_4 alkyl or alkylcarboxyl, or
- (ii) the hydrocarbon chain $-C(R5)-C(R6)-(CH)_n-$ of the ring-system adjacent to the thiophen-ring has to be unsaturated or aromatic;

in case n represents 2, $R1$ - $R2$ form an unsubstituted alkylene group of 3 – 5 methylen groups and $R5$ represents a hydroxyl or oxo group, then $R6$ has to be different from bromo, di-bromo or phenylthio; or

in case n represents 2, $R1$ - $R2$ form an unsubstituted pentamethylen group, and $R6$ represents carbonyl, then $R5$ has to be different from phenylthio;

for use in therapy.

According to a third aspect, the invention concerns a novel compound of formula (II)



wherein

R_1 and R_2 represent the same or different C_1 - C_8 -alkyl, or one is C_1 - C_8 -alkyl and the other is H,
or

R_1 and R_2 form together with their binding sites a cyclic 5-, 6-, 7- or 8-membered ring system,
which is saturated or contains one or more double bonds between the ring atoms, and

5 which ring optionally contains up to two N-atoms in addition to the nitrogen atom where R_1 is
attached,

wherein said ring is optionally substituted with up to two substituents independently selected
from the group consisting of alkyl, substituted alkyl, aryl, or arylalkyl, whereby the aryl
group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, al-
10 kylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and
amido;

the hydrocarbon chain $-C(R_5)-C(R_6)-(CH)_n-$ of the ring-system adjacent to the thiophen-ring is
saturated or contains one or more double bonds between the carbon atoms;

15

n is an integer from 1 to 4, and

R_5 and R_6 are individually selected from the group consisting of hydrogen, alkyl, substituted
alkyl, aryl or arylalkyl, whereby the aryl group is optionally substituted, alkoxy, aryloxy,
20 acyloxy, arylthio, alkylthio, arylsulfonyl, alkylsulfonyl, hydroxyl, oxo, halogen, amino,
oxime, acyl, carboxyl, thiocarboxyl, and amido.

under the proviso that

in case n represents 1, 2 or 3, and R_1 and R_2 are independently selected from hydrogen or C_1 -
25 C_4 alkyl or form together an unsubstituted alkylene group of 3 – 5 methylene groups or a
iminoalkylene group with 2 – 4 methylene groups in the alkylene group, optionally substituted
at the N-atom, then

(i) at least R_5 or R_6 has to be different from hydrogen, C_1 - C_4 alkyl, alkylcar-
boxyl, or $=N-OH$, or
30 (ii) the hydrocarbon chain $-C(R_5)-C(R_6)-(CH)_n-$ of the ring-system adjacent to
the thiophen-ring has to be unsaturated or aromatic;

in case n represents 2, R_1 - R_2 form an unsubstituted alkylene group of 3 or 5 methylene groups,
and R_5 represents a hydroxyl or oxo group then R_6 has to be different from hydrogen,
bromo, dibromo or phenylthio;

35 in case n represents 2, R_1 - R_2 form an unsubstituted pentamethylene group, and R_6 represents
carbonyl, then R_5 has to be different from phenylthio or chloro;

in case n represents 2, the hydrocarbon chain $-C(R_5)-C(R_6)-(CH)_n-$ of the ring-system adjacent
the thiophene-ring is saturated and R_1 - R_2 together with their binding sites form an un-

substituted pyridine-ring, then at least one of R5 or R6 has to be different from hydrogen;
or

in case $-C(R5)-C(R6)-(CH)_n-$ represents an unsubstituted tetramethylen group, R1-R2 have to
be different from a tetramethylen group substituted with a carboxylethylester group.

5

According to a fourth aspect, the invention concerns a pharmaceutical composition comprising
as active agent a compound of formula (II) as defined herein, for which no use in therapy earlier
has been disclosed, and at least a pharmaceutically acceptable carrier.

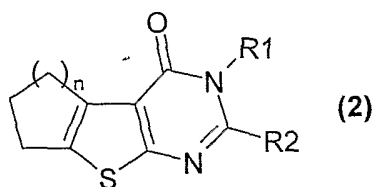
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According to a fifth aspect, the invention concerns the use of a compound of formula (I), more
preferably of formula (II), as defined herein, for the treatment or prevention of a steroid hormone
dependent disease or disorder. Preferably, the steroid hormone dependent disease or disorder
is a disease or disorder requiring the inhibition of a 17β -hydroxysteroid dehydrogenase enzyme,
preferably of the 17β -HSD type 1, 17β -HSD type 2 or 17β -HSD type 3.

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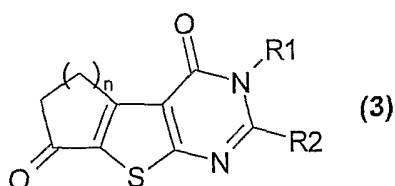
According to a sixth aspect the invention concerns a method for the preparation of the novel
compounds of formula (I) wherein

a) a compound of formula 2



20

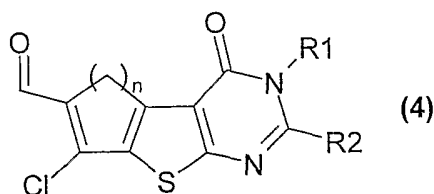
or a ring-substituted or ring-modified analogue thereof is oxidized, preferably by subject-
ing to PCC and celite, to give an oxo-substituted compound of formula 3 or an analogue
thereof,



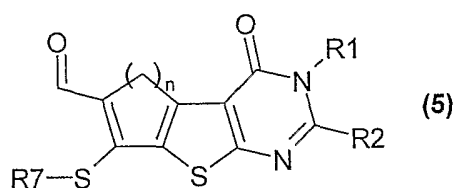
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b) the oxo-substituted compound obtained in step a) is optionally further subjected to Vils-
meier reaction, preferably by $POCl_3$ -DMF, to give a carbonylsubstituted compound of for-
mula 4 or an analogue thereof,

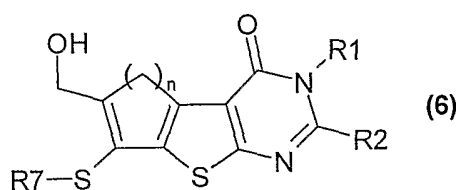
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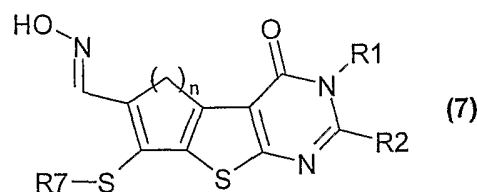
- c) the chlorosubstituent in the carbonylsubstituted compound obtained in step b) is optionally further replaced by an alkylthio or an arylthio group by subjecting to an appropriate thiol in the presence of a base to give an arylthio- or alkylthiosubstituted compound of formula 5 or an analogue thereof,



- d) the arylthio- or alkylthiosubstituted compound obtained in step c) is optionally further
- i) reduced to a compound of formula 6,



- or
- ii) reacted with NH_2OH to give a compound of formula 7,



- or
- e) the compound obtained in step b) is optionally further
 - i) reduced so as to replace the carbonyl group with hydroxyalkyl, or
 - ii) subjected to an appropriate thiol in the presence of a base and acetone, so as to replace the chloro substituent by a thiol group and to replace the carbonyl group with an oxosubstituted alkenyl.
- or
- f) the compound obtained in step a) is optionally further subjected to DMF acetal so as to introduce a dimethylaminomethylene substituent in the ring next to the oxo substituent.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

The following terms are used to describe various constituents of the chemical composition
5 useful in this invention. The terms are defined as follows:

As used herein, the terms "comprising" and "including" are used herein in their open, non-limiting sense.

10 The word "compound" shall here be understood to cover any and all isomers (e. g., enantiomers, stereoisomers, diastereomers, rotomers, and tautomers), racemates or any mixture of isomers, prodrugs, and any pharmaceutically acceptable salt of said compound.

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a
15 single compound, salt, or the like.

The term "substituted" means that the specified group or moiety bears one or more substituents. Where any group may carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not be the same. The term
20 "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents.

Any asymmetric carbon atoms may be present in the (R)-, (S)- or (R,S)-configuration, preferably
25 in the (R)- or (S)-configuration, whichever is most active. Substituents at a double bond or a ring may be present in cis- (=Z-) or trans (=E-) form.

The compounds of the present invention may contain asymmetric centers on the molecule, depending upon the nature of the various substituents. In certain instances, asymmetry may
30 also be present due to restricted rotation about the central bond adjoining the two aromatic rings of the specified compounds. It is intended that all isomers (including enantiomers and diastereomers), either by nature of asymmetric centers or by restricted rotation as described above, as separated, pure or partially purified isomers or racemic mixtures thereof, be included within the ambit of the instant invention.

35

The term "halogen" refers to fluorine (F, Fluoro-), bromine (Br, Bromo-), chlorine (Cl, Chloro), and iodine (I, Iodo-) atoms. Preferred in the context of the present invention are Br, Cl and F.

The terms "dihalogen", "trihalogen" and "perhalogen" refer to two, three and four substituents, respectively, each individually selected from the group consisting of fluorine, bromine, chlorine, and iodine atoms.

- 5 The term "hydroxyl" refers to the group -OH

The term "oxo" refers to the group =O

The term "thio" refers to the group =S

10

The term "thiol" refers to the group -SH

The term "sulfonyl" refers to the group $\text{-S(O)}_{1-2}\text{-}$

- 15 For the purpose of the present invention, the carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix $\text{C}_i\text{-C}_j$ defines the number of carbon atoms present from the integer "i" to the integer "j" inclusive. Thus $\text{C}_1\text{-C}_4$ -alkyl refers to alkyl of 1-4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl and isomeric forms thereof.

20

The term "alkyl" stands for a hydrocarbon radical which may be linear, cyclic or branched, with single or multiple branching, whereby the alkyl group comprises 1 to 12 carbon atoms. In one embodiment, the term "alkyl" stands for a linear or branched (with single or multiple branching) alkyl chain of 1 to 8 carbon atoms, exemplified by the term $(\text{C}_1\text{-C}_8)\text{alkyl}$, more preferably of 1 to 4 carbon atoms exemplified by the term $(\text{C}_1\text{-C}_4)\text{alkyl}$. The term $(\text{C}_1\text{-C}_8)\text{alkyl}$ is further exemplified by such groups as methyl; ethyl; n-propyl; isopropyl; n-butyl; sec-butyl; isobutyl; tert-butyl; n-pentyl; isopentyl; neopentyl; tert-pentyl; 2- or 3-methylpentyl; n-hexyl; isohexyl, and the like. The alkyl group may be partially unsaturated, forming such groups as, for example, methylenyl, ethenyl, ethylenyl, propenyl (allyl), methyl-propenyl, butenyl, pentenyl, pentinyl, hexenyl, octadienyl, and the like. The term "alkyl" further comprises cycloalkyl groups, preferably $\text{cyclo}(\text{C}_3\text{-C}_8)\text{alkyl}$ which refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and isomeric forms thereof such as methylcyclopropyl; 2- or 3-methylcyclobutyl; 2-, or 3-methylcyclopentyl, and the like. The cycloalkyl group may also be partly unsaturated, forming such groups as, for example, cyclohexenyl, cyclopentenyl, cyclooctadienyl, and the like. Furthermore, the term "alkyl" comprises a cycloalkyl-alkyl group comprising 4 to 12 carbon atoms, preferably "cyclo $(\text{C}_3\text{-C}_8)\text{alkyl}(\text{C}_1\text{-C}_4)\text{alkyl}$ " which refers to a alkyl group of 1 to 4 carbon atoms as described above substituted with a cyclo $(\text{C}_3\text{-C}_8)\text{alkyl}$ group as described above, forming such groups as for example cyclopropylmethyl, cyclohexylmethyl, cyclopentylethyl or cyclohexenylethyl.

35

The term "substituted alkyl" refers to alkyl as just described and substituted by up to five, more preferably by up to three, most preferably by one or two substituents independently selected from the group consisting of halogen, hydroxyl, thiol, nitro, nitrile, alkoxy, aryloxy, acyloxy, amino, imino, oxime, amido, acylamino, alkylthio, arylthio, acyl, carboxyl, sulfamoyl, sulfonamide, and alkylsulfonyl, as defined herein. These groups may be attached to any carbon atom of the alkyl moiety. Substituted alkyl is preferably substituted with hydroxyl, C₁-C₄-alkoxy, C₁-C₈-alkylthio, arylthio, preferably phenylthio, an alkylacyl group -CO-R'', a carboxyl group -(C=O)-OR'', an alkylamino group -NR''₂, an alkylimino group =N-R'', or an alkylloxime group =N-O-R'', wherein R'' represents hydrogen or C₁-C₄-alkyl. Preferably substituted alkyl refers to substituted C₁-C₄-alkyl, preferably methyl, substituted methylene and substituted C₂-C₄-alkenyl.

The term "alkoxy" refers to a group -OR, where R may be alkyl, arylalkyl, or substituted arylalkyl as defined herein, wherein the alkyl chain may be optionally further substituted as defined herein. Preferably, the term "alkoxy" refers to -O-(C₁-C₄)alkyl (or (C₁-C₄)alkoxy), with the (C₁-C₄)alkyl group as defined above, or to -O-(C₁-C₄)alkyl-phenyl, preferably benzoxy or phenethyloxy, optionally substituted in the aryl group with up to five independently selected substituents, in particular hydroxyl, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy; the number of said substituents being up to five for halogen, and up to three for any combination of said other substituents.

The term "aryloxy" refers to a group -OAr, where Ar may be aryl, or substituted aryl, as defined herein. Preferably, Ar represents aryl as defined herein, which is optionally substituted in the aryl group with up to five independently selected substituents, in particular hydroxyl, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy; the number of said substituents being up to five for halogen, and up to three for any combination of said other substituents. Preferably, aryloxy refers to phenoxy, optionally substituted as defined above.

The term "acyloxy" refers to a group -O-CO-R, where R may be alkyl, arylalkyl, substituted arylalkyl, aryl, or substituted aryl, as defined herein, wherein the alkyl chain may be optionally further substituted as defined herein.

The term "alkylacyloxy" represents a preferred selection of the term "acyloxy" and refers to the group -O-CO-C₁-C₁₂-alkyl, preferably to -O-CO-C₁-C₈-alkyl, and most preferably to -O-CO-C₁-C₄-alkyl.

The term "arylacyloxy" represents a preferred selection of the term "acyloxy" and refers to the group -O-CO-Ar, wherein Ar represents aryl as defined herein, preferably phenyl, which is optionally substituted in the aryl group with up to five independently selected substituents, in

particular hydroxyl, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy; the number of said substituents being up to five for halogen, and up to three for any combination of said other substituents

- 5 The term "acyl" refers to a group $-(C=O)-R$, where R may be hydrogen, alkyl, aryl or aryl-(C₁-C₄)-alkyl (both optionally substituted in the aryl group with independently selected substituents as defined herein), as defined herein. Preferably, the term "acyl" refers to a group $-(C=O)-R'$, where R' represents hydrogen, (C₁-C₄)-alkyl, phenyl, or phenyl-(C₁-C₄)-alkyl, preferably benzyl.

- 10 The term "carbonyl" represents a preferred selection of the term "acyl" and refers to the group $-CHO$.

The term "alkylacyl" represents a preferred selection of the term "acyl" and refers to a group $-(C=O)-alkyl$, preferably $-(C=O)-(C_1-C_4)alkyl$.

- 15 The term "arylacyl" represents a preferred selection of the term "acyl" and refers to the group $-CO-Ar$, wherein Ar represents aryl as defined herein, preferably phenyl, which is optionally substituted in the aryl group as defined herein.

- 20 The term "carboxyl" refers to a group $-(C=O)-OR$, where R may be hydrogen, alkyl, substituted alkyl, aryl or aryl-(C₁-C₄)-alkyl (both optionally substituted in the aryl group with independently selected substituents as defined herein), as defined herein. Preferably, the term "carboxyl" refers to a group $-(C=O)-OR'$, where R' represents hydrogen, (C₁-C₄)-alkyl, phenyl, or (C₁-C₄)-alkyl-phenyl, preferably benzyl; whereby the phenyl moiety may be optionally substituted with substituents independently selected from the group consisting of hydroxyl, halogen, (C₁-C₄)-alkoxy, and (C₁-C₄)-alkyl, the number of said substituents being up to five for halogen, and up to three for any combination of said other substituents.

- 30 The term "alkylcarboxyl" represents a preferred selection of the term "carboxyl" and refers to a group $-(C=O)-OR$, where R is hydrogen or C₁-C₄ alkyl.

- 35 The term "thio-carboxyl" refers to a group $-(C=S)-SR$, where R may be hydrogen, alkyl, substituted alkyl, aryl or aryl-(C₁-C₄)-alkyl (both optionally substituted in the aryl group with independently selected substituents as defined herein), as defined herein. Preferably, the term "thio-carboxyl" refers to a group $-(C=S)-OR'$, where R' represents hydrogen, (C₁-C₄)-alkyl, phenyl, or (C₁-C₄)-alkyl-phenyl, preferably benzyl; whereby the phenyl moiety may be optionally substituted with substituents independently selected from the group consisting of hydroxyl, halogen, (C₁-C₄)-alkoxy, and (C₁-C₄)-alkyl, the number of said substituents being up to five for halogen, and up to three for any combination of said other substituents.

The terms "alkylthio" ("alkylsulfanyl") and "alkylsulfonyl" refers to a group $-SR$ and $-S(O)_{n=1-2}-R$, respectively, where R may be alkyl, substituted alkyl, arylalkyl, or substituted arylalkyl, as defined herein. Preferably, the term "alkylthio" ("alkylsulfanyl") refers to a group $-SR'$ and the term "alkylsulfonyl" refers to a group $-S(O)_{n=1-2}-R'$, respectively, where R' represents (C₁-C₄)alkyl, or (C₁-C₄)alkyl-phenyl, preferably benzyl; optionally substituted in the alkyl chain with up to three substituents as defined herein, preferably hydroxyl, (C₁-C₄)-alkoxy or halogen.

The term "arylthio" ("arylsulfanyl") and "arylsulfonyl" refers to a group $-S-Ar$ and $-S(O)_{n=1-2}-Ar$, respectively, where Ar represents aryl, or substituted aryl, as defined herein. Preferably Ar represents aryl, which is optionally substituted in the aryl group with independently selected substituents as defined herein, in particular hydroxyl, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy, the number of said substituents being up to five for halogen, and up to three for any combination of said other substituents. Preferably, arylthio refers to phenylsulfanyl, optionally substituted as defined above.

The term "amino" refers to the group $-NRR'$, where R and R' may independently be hydrogen, alkyl (optionally substituted in the alkyl chain with up to five independently selected substituents as defined herein, in particular hydroxyl, halogen or (C₁-C₄)-alkoxy), aryl or aryl-(C₁-C₄)-alkyl (both optionally substituted in the aryl group with up to five independently selected substituents as defined herein, in particular hydroxyl, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy, the number of said substituents being up to five for halogen, and up to three for any combination of said other substituents), as defined herein.

The term "alkylamino" represents a preferred selection of the term "amino" and refers to the group $-NRR'$, where R and R' may independently be hydrogen or (C₁-C₄)alkyl.

The term "imino" refers to the group $=NR$, where R may be hydrogen, alkyl (optionally substituted in the alkyl chain with up to five independently selected substituents as defined herein, in particular hydroxyl, halogen or (C₁-C₄)-alkoxy), aryl or aryl-(C₁-C₄)-alkyl (both optionally substituted in the aryl group with up to five independently selected substituents as defined herein, in particular hydroxyl, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy, the number of said substituents being up to five for halogen, and up to three for any combination of said other substituents), as defined herein.

The term "alkylimino" represents a preferred selection of the term "imino" and refers to the group $=NR$, where R may be hydrogen or (C₁-C₄)alkyl.

The term "oxime" refers to the group $=N-OR$, where R may be hydrogen, alkyl (optionally substituted in the alkyl chain with up to five independently selected substituents as defined herein, in

particular hydroxyl, halogen or (C₁-C₄)-alkoxy), aryl or aryl-(C₁-C₄)-alkyl (both optionally substituted in the aryl group with up to five independently selected substituents as defined herein, in particular hydroxyl, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy, the number of said substituents being up to five for halogen, and up to three for any combination of said other substituents), as
5 defined herein.

The term "alkyl-oxime" represents a preferred selection of the term "oxime" and refers to the group =N-O-R, where R may be hydrogen or (C₁-C₄)alkyl.

10 The term "amido" refers to the group -(C=O)-NRR', where R and R' may independently be hydrogen, alkyl (optionally substituted in the alkyl chain with up to five independently selected substituents as defined herein, in particular hydroxyl, halogen or (C₁-C₄)-alkoxy), aryl or aryl-(C₁-C₄)-alkyl (both optionally substituted in the aryl group with independently selected substituents as defined herein, in particular hydroxyl, halogen, (C₁-C₄)-alkyl, or (C₁-C₄)-alkoxy, the
15 number of said substituents being up to five for halogen, and up to three for any combination of said other substituents), as defined herein.

The term "alkylamido" represents a preferred selection of the term "amido" and refers to the group -(C=O)-NRR', where R and R' may be independently selected from hydrogen or (C₁-C₄)alkyl.
20 C₄)alkyl.

The term "aryl" refers to an aromatic carbocyclic group comprising 6 to 14, more preferably 6 to 10, carbon atoms and having at least one aromatic ring or multiple condensed rings in which at least one ring is aromatic. Preferably, aryl is phenyl, naphthyl, indanyl, indenyl, fluorenyl,
25 1,2,3,4-tetrahydro-naphthalen-1-yl or even biphenyl.

The aryl group may optionally be substituted by substituents independently selected from the group consisting of halogen, hydroxyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyl, oxo, thiol, carboxyl, aryloxy or arylalkyloxy (both optionally substituted in the aryl moiety with independently selected substituents as defined herein), (C₁-C₆)alkylthio, arylthio or arylalkylthio (both optionally substituted in the aryl moiety with independently selected substituents as defined herein), amino, amido, acyl, and acylamino, as defined herein, the number of said substituents being up to five for halogen, and up to three for any combination of said other substituents.

35 Substituted aryl is preferably substituted by substituents selected from the group consisting of (C₁-C₆)alkoxy, preferably methoxy, hydroxyl, (C₁-C₄)alkyl, halogen, the number of said substituents being up to five for halogen, and up to four, preferably up to three, for any combination of said other substituents. Preferably substituted aryl is substituted phenyl.

The term "arylalkyl" refers to an alkyl group substituted with up to three independently selected aryl groups; preferably the term "arylalkyl" refers to "aryl-(C₁-C₄)-alkyl" or diaryl-(C₁-C₄)-alkyl, whereby the aryl is an aryl group as defined above. Arylalkyl is preferably benzyl (-CH₂-Phenyl) or phenethyl (-CH₂-CH₂-Phenyl).

5

The term "substituted arylalkyl" refers to an arylalkyl group as defined above, wherein the aryl group is substituted as defined above.

10 The term "pro-drug" as used herein, represents derivatives of the compounds of the invention that are drug precursors which, following administration to a patient, release the drug in vivo via a chemical or physiological process. In particular, pro-drugs are derivatives of the compounds of the invention in which functional groups carry additional substituents which may be cleaved under physiological conditions in vivo and thereby releasing the active principle of the compound (e. g., a pro-drug on being brought to a physiological pH or through an enzyme action is
15 converted to the desired drug form).

The term "pharmaceutically acceptable salts" refers to salt forms that are pharmacologically acceptable and substantially non-toxic to the subject being administered the compounds of the invention. Pharmaceutically acceptable salts of compounds of formula I include conventional
20 and stoichiometrical acid-addition salts or base-addition salts formed from suitable non-toxic organic or inorganic acids or inorganic bases. Acid addition salts, for example, from compounds of formula I with a basic nitrogen atom are formed preferably with organic or inorganic acids. Suitable inorganic acids are, for example, halogenic acids such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, or
25 sulfonic acids, for example acetic acid, propionic acid, glycolic acid, lactic acid, hydroxybutyric acid, malic acid, malonic acid, salicylic acid, fumaric acid, succinic acid, adipic acid, tartaric acid, citric acid, glutaric acid, 2- or 3-glycerophosphoric acid and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce a salt in the conventional
30 manner. Compounds containing acidic substituents may also form salts with inorganic or organic bases. Examples of suitable bases for salt formation include, but are not limited to, inorganic bases such as alkali or alkaline earth-metal (e.g., sodium, potassium, lithium, calcium, or magnesium) hydroxides, and those derived from ammonium hydroxides (e.g., a quaternary ammonium hydroxide such as tetramethylammonium hydroxide). Also contemplated are salts
35 formed with pharmaceutical acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine, benzylamines, piperidines, and pyrrolidines and the like. Certain compounds will be acidic in nature, e. g. those compounds which possess a carboxyl or phenolic hydroxyl group. Salts of phenols can be made by heating acidic compounds with any of the above mentioned bases according to procedures well known to those skilled in the art.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

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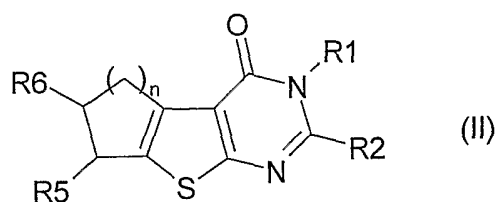
The phrase "effective amount" as used herein, means an amount of a compound or composition which is sufficient enough to significantly and positively modify the symptoms and/or conditions to be treated (e. g., provide a positive clinical response). The effective amount of an active ingredient for use in a pharmaceutical composition will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient(s) being employed, the particular pharmaceutically acceptable excipient(s)/carrier(s) utilized, and like factors within the knowledge and expertise of the attending physician.

10

15 Preferred Embodiments

According to a preferred embodiment of the present invention, the compound used for the for the manufacture of a medicament for the treatment and/or prevention of a steroid hormone dependent disease or disorder, preferably for a steroid hormone dependent disease or disorder requiring the inhibition of a 17 β -hydroxysteroid dehydrogenase (17 β -HSD) enzyme, most preferably requiring the inhibition of the 17 β -HSD type 1, 17 β -HSD type 2 or 17 β -HSD type 3 enzyme, is defined as follows: the compound has the formula (II)

20



25 wherein

R₁ and R₂ represent the same or different C₁-C₈-alkyl, or one is C₁-C₈-alkyl and the other is H,
or

R₁ and R₂ form together with their binding sites a cyclic 5-, 6-, 7- or 8-membered ring system,

30

which is saturated or contains one or more double bonds between the ring atoms, and

which ring optionally contains up to two N-atoms in addition to the nitrogen atom where R₁ is attached,

wherein said ring is optionally substituted with up to two substituents independently selected

from the group consisting of alkyl, substituted alkyl, aryl, or arylalkyl, whereby the aryl

35

group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, al-

kylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and amido;

the hydrocarbon chain $-C(R_5)-C(R_6)-(CH)_n-$ of the ring-system adjacent to the thiophen-ring is
 5 saturated or contains one or more double bonds between the carbon atoms;

n is an integer from 1 to 4, and

10 R₅ and R₆ are individually selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl or arylalkyl, whereby the aryl group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, alkylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and amido;

provided that said compound is not 1,2,7,8,9,10,11,13-octahydro-13-oxo-4-(phenylthio)-
 15 [1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-3-carboxaldehyde;

According to a preferable embodiment the compound of the formula (II) is characterized in that

the cyclic 5-, 6-, 7- or 8-membered ring system formed together by R₁ and R₂ is optionally
 20 substituted with up to two substituents independently selected from the group consisting of oxo, -CO-R, -CO-O-R, -O-R, -C₁-C₄-alkyl, optionally substituted with -O-R, -S-R or -N(R)₂;

25 R₅ and R₆ are individually selected from the group consisting of hydrogen, oxo, halogen, -O-R', -S-R', -SO-R', -CO-R, -CO-O-R, or -C₁-C₄-alkyl, -C₁-C₄-alkenyl or =C₁-C₄-alkylen, optionally substituted in the alkyl chain with -O-R, -S-R, -N(R)₂, -CO-R, or =N-O-R,

wherein R represents hydrogen or C₁-C₄-alkyl; and

30 wherein R' represents hydrogen, C₁-C₈-alkyl, which can be linear, cyclic or branched; aryl-C₁-C₄-alkyl, preferably benzyl; or aryl, preferably phenyl.

Especially preferable compounds are those wherein R₁ and R₂ form together with their binding sites an optionally substituted cyclic 5-, 6-, 7- or 8-membered ring system, which is saturated or
 35 contains one or more double bonds between the ring atoms, and which ring optionally contains up to two N-atoms in addition to the nitrogen atom where R₁ is attached.

Particularly preferable compounds of formula (II) are those wherein R5 is selected from the group consisting of hydrogen, oxo, halogen, -OH, -O-C₁-C₄-alkyl; -S-C₁-C₄-alkyl, -S-C₃-C₈-cycloalkyl, -S-phenyl, -SO-phenyl.

- 5 Further preferable compounds of formula (II) are those wherein R6 is selected from the group consisting of hydrogen, carbonyl, alkylcarboxyl, preferably -COOH, -C₁-C₄-alkyl, -C₁-C₄-alkenyl or =C₁-C₄-alkenyl, optionally substituted in the alkyl chain with -O-R, -N(R)₂, -CO-R, or =N-O-R, wherein R represents hydrogen or C₁-C₄-alkyl.
- 10 In a preferred embodiment, the invention relates to a compound selected from the group consisting of exemplary compounds
 - 2,3,8,9,10,11-Hexahydro[1]Benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-4,13(1*H*,7*H*)-dione;
 - 1,2,6,7,8,9,10-heptahydrocyclopenta[4',5']thieno[2',3':4,5]pyrimido[1,2-a]-azepin-3,12-dione;
 - 1,2,3,4,8,9,10,11,12-nonahydrocyclohepta[4',5']thieno[2',3':4,5]pyrimido-[1,2-a]azepine-
- 15 5(5*aH*),14-dione;
 - 1,2,7,8,9,10,11,12-octahydro[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]azocin-4,14(3*H*)-dione;
 - 1,2,3,4,7,8,9,10-Octahydro-12*H*-[1]benzothieno[2,3-d]pyrido[1,2-a]pyrimidin-12-one;
 - 5,6-Dihydro-2,3-dimethyl[1]benzothieno[2,3-d]pyrimidin-4,8(3*H*,7*H*)-dione;
 - 5,6-Dihydro-3-methyl[1]benzothieno[2,3-d]pyrimidin-4,8(3*H*,7*H*)-dione;
- 20 5,6-Dihydro-3-ethyl-2-methyl[1]benzothieno[2,3-d]pyrimidin-4,8(3*H*,7*H*)-dione;
 - 4-Chloro-1,2,3,7,8,9,10,11,12-octahydro[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]-azocin-14-one-4-carboxyaldehyde;
 - 1,2,3,4,5,8,9,10,11,12-Decahydro-14*H*-cyclohepta[4',5']thieno[2',3':4,5]-pyrimido[1,2-a]azepin-14-one;
- 25 8-Chloro-5,6-dihydro-3-methyl[1]benzothieno[2,3-d]pyrimidin-4(3*H*)-one-7-carboxyaldehyde;
 - 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(ethylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde;
 - 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(propylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde;
- 30 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(butylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde;
 - 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(isopropylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde;
 - 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(*t*-butylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-
- 35 a]azepine-3-carboxaldehyde;
 - 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(cyclopentylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde;
 - 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(cyclohexylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde;

- 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(phenylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-hydroxymethyl;
 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(cyclohexylthio)[1]benzothieno-[2',3':4,5]pyrimido [1,2-a]azepine-3-hydroxymethyl;
 5 Octahydro-13-oxo-4-(phenylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-oxime-methyl;
 4-Chloro-1,2,7,8,9,10,11,13-octahydro-13-oxo[1]benzothieno[2',3':4,5]-pyrimido[1,2-a]azepine-3-hydroxymethyl;
 3-N,N-Dimethylamino-methylen-2,3,8,9,10,11-hexahydro[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-4,13(1*H*,7*H*)-dione;
 10 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(propylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-(3-oxo)but-1-ene; and
 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(butylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-(3-oxo)but-1-ene,
 15 or a physiologically acceptable salt thereof.

Pharmaceutically acceptable salts of the compounds of the invention as well as commonly used pro-drugs and active metabolites of these compounds are also within the scope of the invention.

20

The invention also relates to pharmaceutical compositions comprising one or more of the compounds of the invention for which no use in therapy has been disclosed earlier, or their salts or pro-drugs, as active agent and at least one pharmaceutically acceptable carrier.

25

Furthermore, the invention relates to the use of an effective amount of a novel compound as defined herein for the treatment or prevention of a steroid hormone dependent disease or disorder in a mammal, in particular a human. Preferably the steroid hormone dependent disease or disorder is an estradiol or testosterone dependent disease or disorder.

30

In a preferred embodiment, the invention relates to the use of an effective amount of a novel compound as defined within the present invention for the treatment or prevention of a steroid hormone dependent disease or disorder in a mammal, whereby the steroid hormone dependent disease or disorder requires the inhibition of a 17 β -hydroxysteroid dehydrogenase (HSD) enzyme, preferably the human 17 β -hydroxysteroid dehydrogenase (HSD) enzyme type

35

1, type 2 or type 3.

In a further preferred embodiment of the invention the steroid hormone dependent disease or disorder to be treated and/or prevented requires the lowering of the endogenous 17 β -estradiol or testosterone concentration in a generalized and/or tissue specific manner.

The invention also relates to a method of treating a mammal such as a human having a condition related to 17 β -hydroxysteroid dehydrogenase (HSD) type 1, type 2 or type 3 activity, comprising administering to the mammal an amount of a compound of this invention, or a salt or a prodrug thereof, which amount is effective to treat the condition. Administration of compounds of this invention in combination with other pharmaceuticals used in treatment of the listed conditions is contemplated.

The conditions to be treated and/or prevented in the context of the present invention include but are not limited to breast cancer, prostate carcinoma, ovarian cancer, uterine cancer, endometrial cancer, endometrial hyperplasia, endometriosis, uterine fibroids, uterine leiomyoma, adenomyosis, dysmenorrhea, menorrhagia, metrorrhagia, prostatic hyperplasia, prostatitis, acne, seborrhea, hirsutism, androgenic alopecia, precocious puberty, adrenal hyperplasia, polycystic ovarian syndrome, and urinary dysfunction. A further condition to be treated and/or prevented in the context of the present invention includes osteoporosis.

Further estrogen-dependent diseases which may be treated and/or prevented with an effective amount of a compound of the invention are multiple sclerosis, rheumatoid arthritis, Alzheimer's disease, colon cancer, tissue wounds, skin wrinkles and cataracts.

In a preferred embodiment the invention relates to use of an effective amount of a compound of the invention for the treatment or prevention of one of the aforementioned disease or disorders in a mammal whereby the mammal is a human, preferably a female and most preferably a pre- or peri-menopausal female in the case of gynaecological disorders.

Furthermore, compounds of formula (I) may be useful for blocking spermatogenesis and as an anti-fertility agent for males.

The disclosed compounds are also useful as diagnostic agents (e.g. in diagnostic kits or for use in clinical laboratories) for screening for the presence or absence of 17 β -hydroxysteroid dehydrogenase (HSD) type 1, type 2 and/or type 3 activity.

It will be appreciated that the methods of the present invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent for the expert skilled in the field that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

Administration forms

The method of the invention is primarily intended for treatment in a mammal, preferably in humans and other primates, of steroid hormone dependent diseases or disorders, in particular estradiol dependent diseases or disorders, wherein the steroid hormone dependent disease or disorder preferably requires the inhibition of a 17β -hydroxysteroid dehydrogenase (HSD) enzyme, preferably the type 1 17β -hydroxysteroid dehydrogenase (HSD) enzyme [EC 1.1.1.62].

The compounds may be administered orally, dermally, parenterally, by injection, by pulmonal or nasal delivery, or sublingually, rectally or vaginally in dosage unit formulations. The term "administered by injection" includes intravenous, intraarticular, intramuscular (e.g. by depot injection where the active compounds are released slowly into the blood from the depot and carried from there to the target organs), intraperitoneal, intradermal, subcutaneous, and intrathecal injections, as well as use of infusion techniques. Dermal administration may include topical application or transdermal administration. One or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable auxiliaries such as excipients, adjuvants (e.g. buffers), carriers, inert solid diluents, suspending agents, preservatives, fillers, stabilizers, anti-oxidants, food additives, bioavailability enhancers, coating materials, granulating and disintegrating agents, binding agents etc., and, if desired, other active ingredients.

20

The pharmaceutical composition may be formulated for example as immediate release, sustained release, pulsatile release, two or more step release, depot or other kind of release formulations.

The manufacture of the pharmaceutical compositions according to the invention may be performed according to methods known in the art and will be explained in further detail below. Commonly known and used pharmaceutically acceptable auxiliaries as well as further suitable diluents, flavorings, sweetening agents, coloring agents etc. may be used, depending on the intended mode of administration as well as particular characteristics of the active compound to be used, such as solubility, bioavailability etc. Suitable auxiliaries and further ingredients may be such as recommended for pharmacy, cosmetics and related fields and which preferably are listed in the European Pharmacopoeia, FDA approved or cited in the "GRAS" list (FDA List of food additives that are 'generally recognized as safe' (GRAS)).

One mode of application of the compounds of general formula (I) or of pharmaceutical compositions comprising one or more of said compounds is oral application, e. g., by tablets, pills, dragees, hard and soft gel capsules, granules, pellets, aqueous, lipid, oily or other solutions, emulsions such as oil-in-water emulsions, liposomes, aqueous or oily suspensions, syrups, elixiers, solid emulsions, solid dispersions or dispersible powders. For the preparation of

pharmaceutical compositions for oral administration, the compounds suitable for the purposes of the present invention as defined above can be admixed with commonly known and used adjuvants and excipients such as for example, gum arabic, talcum, starch, sugars (such as, e. g., mannitolose, methyl cellulose, lactose), gelatin, surface-active agents, magnesium stearate, aqueous or non-aqueous solvents, paraffin derivatives, cross-linking agents, dispersants, emulsifiers, lubricants, conserving agents, flavoring agents (e. g., ethereal oils), solubility enhancers (e. g., benzyl benzoate or benzyl alcohol) or bioavailability enhancers (e.g. Gelucire™). In the pharmaceutical composition, the active ingredients may also be dispersed in a microparticle, e. g. a nanoparticulate, composition.

10

For parenteral administration, the active agents can be dissolved or suspended in a physiologically acceptable diluent, such as, e. g., water, buffer, oils with or without solubilizers, surface-active agents, dispersants or emulsifiers. As oils for example and without limitation, olive oil, peanut oil, cottonseed oil, soybean oil, castor oil and sesame oil may be used. More generally spoken, for parenteral administration the active agent can be in the form of an aqueous, lipid, oily or other kind of solution or suspension or even administered in the form of liposomes or nano-suspensions.

15

Transdermal application can be accomplished by suitable patches, as generally known in the art, specifically designed for the transdermal delivery of active agents, optionally in the presence of specific permeability enhancers. Furthermore, also emulsions, ointments, pastes, creams or gels may be used for transdermal delivery.

20

Another suitable mode of administration is via intravaginal devices (e. g. vaginal rings) or intrauterine systems (IUS) containing reservoirs for controlled release of active agents over extended periods of time. For rectal or vaginal administration of the drug the compounds may also be administered in the form of suppositories. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal or vaginal temperature and will therefore melt in the rectum or vagina to release the drug.

25

30

Another mode of application is by implantation of a depot implant comprising an inert carrier material, such as biologically degradable polymers or synthetic silicones such as e. g. silicone rubber. Such implants are designed to release the active agent in a controlled manner over an extended period of time (e. g., 3 to 5 years).

35

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics.

The actually required dosages of the agents of this invention for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the particular HSD type 1, type 2 or type 3 related condition being treated, the particular composition formulated, the mode of administration, time and duration of administration, route of administration and the particular site being treated, and furthermore the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, rate of excretion, drug combinations, and the severity of the condition undergoing therapy.

It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of Formula I or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests. Optimal dosages for a given set of conditions may be ascertained by those skilled in the art using conventional dosage-determination tests in view of the experimental data for a given compound. For oral administration, an exemplary daily dose generally employed will be from about 0.01 µg/kg to about 100 mg/kg of total body weight, whereby courses of treatment may be repeated at appropriate time intervals. Administration of pro-drugs may be dosed at weight levels that are chemically equivalent to the weight levels of the fully active compounds. The daily dosage for parenteral administration will generally be from about 0.01 µg/kg to about 100 mg/kg of total body weight. A daily rectal dosage regimen will generally be from about 0.01 µg/kg to about 200 mg/kg of total body weight. A daily vaginal dosage regimen will generally be from about 0.01 µg/kg to about 100 mg/kg of total body weight. The daily topical dosage regimen will generally be from about 0.1 µg to about 100 mg administered between one to four times daily. The transdermal concentration will generally be that required to maintain a daily dose of from 0.01 µg/kg to 100 mg/kg of total body weight.

Abbreviations and Acronyms

As employed herein, the following terms have the indicated meanings.

20βP	20β-hydroxyprogesterone
A	4-androstene-3,17-one
Ac	Acetyl
AcOH	acetic acid
HSD	hydroxysteroid dehydrogenase
DHT	dehydrotestosterone
DMF	N,N-dimethylformamide

	E1	estron
	E2	estradiol
	ER	estrogen receptor
	EtOAc	ethyl acetate
5	GnRH	Gonadotropin Releasing Hormone
	GRAS	generally recognized as safe
	MS	mass spectrometry
	NAD(P)[H]	nicotinamide-adenine-dinucleotide (phosphate) [reduced NAD(P)]
	NMR	nuclear magnetic resonance
10	P	progesterone
	PCC	pyridinium chlorochromate
	T	testosterone
	TBAB	Tetrabutylammonium Bromide
	THF	tetrahydrofuran
15	TOF	'Time-of-flight'

EXPERIMENTAL SECTION

20 General Preparative Methods

The compounds of the present invention may be prepared by use of known chemical reactions and procedures. Nevertheless, the following general preparative methods are presented to aid the reader in synthesizing the 17- β -hydroxysteroid dehydrogenase inhibitors with specific details provided below in the experimental section to illustrate working examples.

All variable groups of these methods are as described in the generic description if they are not specifically defined below.

30 It is recognized that compounds of the invention with each claimed optional functional group may not be prepared by each of the below-listed methods. Within the scope of each method, optional substituents may appear on reagents or intermediates which may act as protecting or otherwise non-participating groups. Utilizing methods well known to those skilled in the art, these groups are introduced and/or removed during the course of the synthetic schemes which provide the compounds of the present invention.

The compounds according to this invention can be prepared as shown in Schemes 2 to 6 described in the Experimental section. It is evident that otherwise ring-substituted or -modified

compounds as defined by formula (I) of the claims can be prepared analogously, e.g. by using ring-substituted or -modified analogues of the starting compound (2) in Scheme 1.

The invention will be illuminated by the following non-restrictive Experimental Section. In order to more fully illustrate the nature of the invention and the manner of practicing the same, the following examples are presented, but they should not be taken as limiting.

EXAMPLE 1

10 Scheme 1. Synthesis of compound classes 2-5

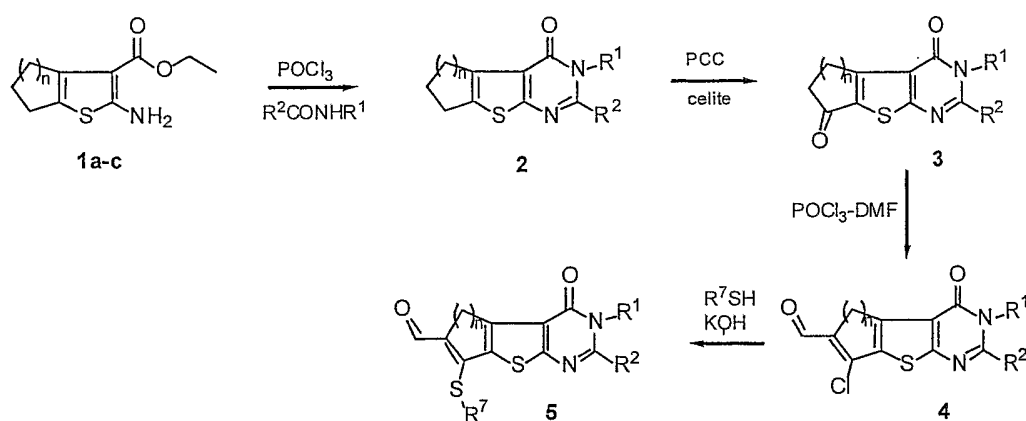


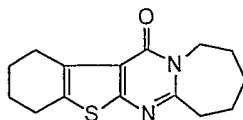
Table 1. Individual compounds of compound classes 2-4 prepared

compound	n	R ¹	R ²
2a	2		-(CH ₂) ₅ -
2b	1		-(CH ₂) ₅ -
2c	3		-(CH ₂) ₅ -
2d	2		-(CH ₂) ₆ -
2e	2		-(CH ₂) ₄ -
2f	2		-(CH ₂) ₃ -
2g	2	-CH ₃	-CH ₃
2h	2	-CH ₃	H
2i	2	-CH ₃	-CH ₂ CH ₃
3a	2		-(CH ₂) ₅ -
3b	1		-(CH ₂) ₅ -
3c	3		-(CH ₂) ₅ -
3d	2		-(CH ₂) ₆ -
3e	2		-(CH ₂) ₄ -
3f	2		-(CH ₂) ₃ -
3g	2	-CH ₃	-CH ₃
3h	2	-CH ₃	H
3i	2	-CH ₃	-CH ₂ CH ₃
4a	2		-(CH ₂) ₅ -
4b	2		-(CH ₂) ₆ -

compound	n	R ¹	R ²
4c	2	-(CH ₂) ₃ -	
4d	3	-(CH ₂) ₅ -	
4e	2	-CH ₃	H

General procedure for the synthesis of 2a-i:

- 5 **2a** 2,3,4,7,8,9,10,11-Octahydro[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]azepin-13(1*H*)-one:

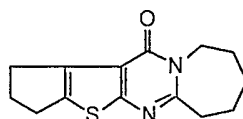


- To ethyl 2-amino-4,5,6,7-tetrahydrobenzo(b)thiophene-3-carboxylate **1b** (0.22mol) and ϵ -caprolactam (0.33mol) in dry dichloroethane (1500ml), POCl₃ (0.27mol) was added dropwise. The mixture was heated under reflux until no starting material was detected on TLC after which
 10 4/5 of the solvent was evaporated. Water (200ml) was added and the solution was made basic with 20% KOH. The solution was extracted with CH₂Cl₂, washed with brine and water and dried with Na₂SO₄. After filtration the solvent was evaporated. Recrystallisation from ethanol afforded **2a** as white crystals in 90% yield.

¹H NMR δ 1.85 (10H, m), 2.75 (2H, m), 3.00 (4H, m), 4.35 (2H, m)

15

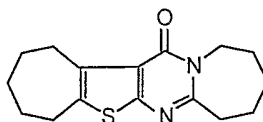
- 2b** 1,2,3,6,7,8,9,10-Octahydro-12*H*-cyclopenta[4',5']thieno[2',3':4,5]pyrimido[1,2-a]-azepin-12-one



- 2b** was synthesised as described above but ethyl 2-aminocyclopenta(b)-thiophene-3-carboxylate was used.
 20

¹H NMR δ 1.83 (8H, m), 2.45 (2H, qn), 3.00 (4H, m), 4.37 (2H, m)

- 2c** 1,2,3,4,5,8,9,10,11,12-Decahydro-14*H*-cyclohepta[4',5']thieno[2',3':4,5]pyrimido-[1,2-a]azepin-14-one

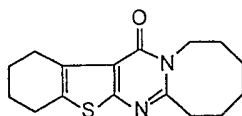


25

- 2c** was synthesised as described above but ethyl 2-aminocyclo-hepta(b)thiophene-3-carboxylate was used.

¹H NMR δ 1.77 (12H, m), 2.82 (2H, m), 3.01 (2H, m), 3.35 (2H, m), 4.36 (2H, m)

2d 2,3,4,7,8,9,10,11,12-Decahydro[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]azocin-14(1*H*)-one

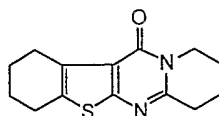


2d was synthesised as described above but 2-azacyclooctanone was used.

¹H NMR δ 1.40 (2H, m), 1.56 (2H, m), 1.89 (8H, m), 2.76 (2H, m), 2.99 (4H, m), 4.27 (2H, m)

5

2e 1,2,3,4,7,8,9,10-Octahydro-12*H*-[1]benzothieno[2,3-d]pyrido[1,2-a]pyrimidin-12-one

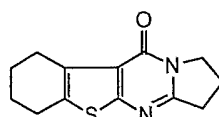


2e was synthesised as described above but γ -valerolactam was used.

¹H NMR δ 1.91 (8H, m), 2.75 (2H, m), 2.97 (4H, m), 4.02 (2H, t)

10

2f 2,3,6,7,8,9-Hexahydro[1]benzothieno[2,3-d]pyrrolo[1,2-a]pyrimidin-10(1*H*)-one

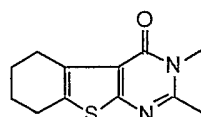


2f was synthesised as described above but 2-pyrrolidinone was used.

¹H NMR δ 1.86 (4H, m), 2.28 (2H, qn), 2.76 (2H, m), 3.00 (2H, m), 3.14 (2H, t), 4.16 (2H, t)

15

2g 5,6,7,8-Tetrahydro-2,3-dimethyl[1]benzothieno[2,3-d]pyrimidin-4(3*H*)-one

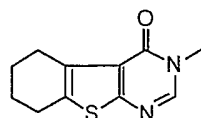


2g was synthesised as described above but *N*-methylacetamide was used.

¹H NMR δ 1.86 (4H, m), 2.58 (3H, s), 2.76 (2H, m), 3.00 (2H, m), 3.56 (3H, m)

20

2h 5,6,7,8-Tetrahydro-3-methyl[1]benzothieno[2,3-d]pyrimidin-4(3*H*)-one



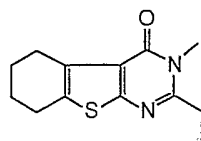
2h was synthesised as described above but acetamide was used.

¹H NMR δ 1.87 (4H, m), 2.78 (2H, m), 3.03 (2H, m), 3.56 (3H, s), 7.91 (1H, s)

25

2i 5,6,7,8-Tetrahydro-2-ethyl-3-methyl[1]benzothieno[2,3-d]pyrimidin-4(3*H*)-one

33



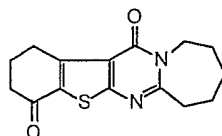
2i was synthesised as described above but *N*-methylpropanamide was used.

$^1\text{H NMR } \delta$ 1.36 (3H, t), 1.85 (4H, m), 2.78 (4H, m), 3.01 (2H, m), 3.57 (3H, s)

- 5 **General procedure for the synthesis of 3a-i:** PCC (37 mmol) , Celite (20g) and compound **2a** (7.3mmol) were mix into a fine powder and dry benzene (150ml) was added. The reaction mixture was heated under refluxed over night. The cooled slurry was filtrated through a pad of Celite and the solvent was evaporated. Recrystallisation from methanol afforded white powder in 50% yield.

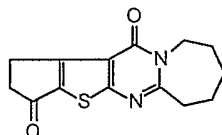
10

3a 2,3,8,9,10,11-Hexahydro[1]Benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-4,13(1*H*,7*H*)-dione



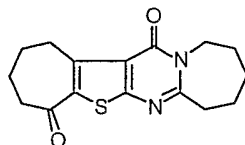
$^1\text{H NMR } \delta$ 1.58 (6H, m), 2.23 (2H, qn), 2.67 (2H, t), 3.07 (2H, m), 3.28 (2H, t), 4.36 (2H, m)

- 15 **3b** 1,2,6,7,8,9,10-heptahydrocyclopenta[4',5']thieno[2',3':4,5]pyrimido[1,2-a]-azepin-3,12-dione



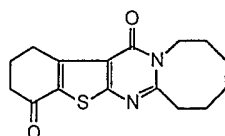
$^1\text{H NMR } \delta$ 1.88 (4H, m), 2.92 (2H, m), 3.09 (2H, m), 3.33 (2H, m), 4.39 (2H, m)

- 20 **3c** 1,2,3,4,8,9,10,11,12-nonahydrocyclohepta[4',5']thieno[2',3':4,5]pyrimido-[1,2-a]azepine-5(5*aH*),14-dione.



$^1\text{H NMR } \delta$ 1.90 (12H, m), 2.83 (2H, m), 3.05 (2H, m), 3.57 (2H, m), 4.36 (2H, m)

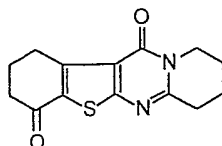
- 3d** 1,2,7,8,9,10,11,12-octahydro[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]azocin-4,14(3*H*)-dione



25

^1H NMR δ 1.45 (2H, m), 1.61 (2H, m), 1.97 (4H, m), 2.24 (2H, qn), 2.67 (2H, m), 3.02 (2H, m), 3.29 (2H, t), 4.31 (2H, m)

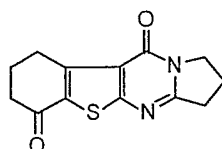
3e 1,2,3,4,7,8,9,10-Octahydro-12*H*-[1]benzothieno[2,3-*d*]pyrido[1,2-*a*]pyrimidin-12-one



5

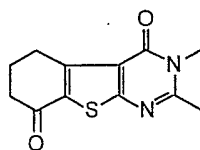
^1H NMR δ 1.99 (4H, m), 2.23 (2H, qt), 2.66 (2H, t), 3.01 (2H, t), 3.28 (2H, t), 4.03 (2H, t)

3f 2,3,8,9-Tetrahydro[1]benzothieno[2,3-*d*]pyrrolo[1,2-*a*]pyrimidine-6,10(1*H*,7*H*)-dione



10 ^1H NMR δ 2.29 (4H, m), 2.67 (2H, t), 3.24 (4H, m), 4.19 (2H, t)

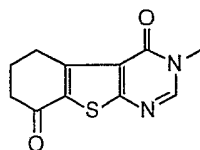
3g 5,6-Dihydro-2,3-dimethyl[1]benzothieno[2,3-*d*]pyrimidin-4,8(3*H*,7*H*)-dione



^1H NMR δ 2.24 (2H, qn), 2.63 (3H, s), 2.66 (2H, m), 3.28 (2H, t), 3.59 (3H, s)

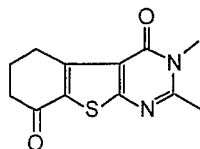
15

3h 5,6-Dihydro-3-methyl[1]benzothieno[2,3-*d*]pyrimidin-4,8(3*H*,7*H*)-dione



^1H NMR δ 2.25 (2H, qn), 2.69 (2H, t), 3.31 (2H, t), 3.60 (3H, s), 8.08 (1H, s)

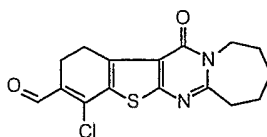
20 **3i** 5,6-Dihydro-3-ethyl-2-methyl[1]benzothieno[2,3-*d*]pyrimidin-4,8(3*H*,7*H*)-dione



^1H NMR δ 1.39 (3H, t), 2.23 (2H, qn), 2.67 (2H, m), 2.81 (2H, q), 3.29 (2H, t), 3.59 (3H, s)

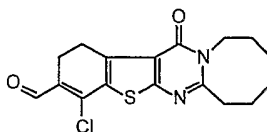
General procedure for the synthesis of 4a-4e: POCl₃ (135mmol) was added dropwise into DMF (170mmol) and CH₂Cl₂ (3ml) at 0 °C. After 30 minutes 3a (17mmol) in CH₂Cl₂ (15ml) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred for 48h. The reaction was quenched with saturated NaOAc, extracted with CH₂Cl₂, washed with brine and water, and dried with Na₂SO₄. After filtration the solvent was evaporated. The product was purified by flash chromatography using CH₂Cl₂-EtOAc 9:1 as an eluent. Recrystallisation from ethanol afforded **4a** as yellow crystals in 75% yield.

4a 4-Chloro-1,2,7,8,9,10,11,13-octahydro-13-oxo[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-3-carboxaldehyde



¹H NMR δ 1.86 (2H, m), 2.81 (2H, dt), 3.07 (2H, m), 3.28 (2H, dt), 4.37 (2H, m), 10.21 (1H, s)

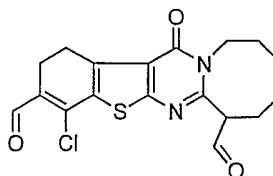
4b 4-Chloro-1,2,3,7,8,9,10,11,12-octahydro[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]-azocin-14-one-4-carboxyaldehyde:



Purification by flash chromatography afforded compound **4b** as a major product and compound **11** as a minor product.

¹H NMR δ 1.44 (2H, m), 1.60 (2H, m), 1.93 (4H, m), 2.76 (2H, m), 3.02 (2H, m), 3.28 (2H, m), 4.31 (2H, m), 10.21 (1H, s)

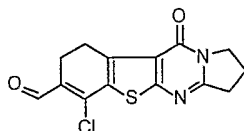
11 4-Chloro-1,2,7,9,10,11,12,14-octahydro-14-oxo-8*H*-[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]-azocine-3,7-dicarbaldehyde



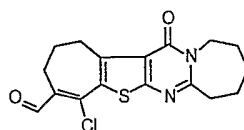
¹H NMR δ (CDCl₃) 1.31 (2H, m), 1.82 (5H, m), 2.43 (1H, m), 2.81 (2H, t), 3.29 (2H, m), 3.75 (2H, m), 4.93 (1H, m), 9.92 (1H, s), 10.21 (1H, s)

4c 8-Chloro-4-oxo-1,2,3,4,8,9-hexahydro[1]benzothieno[2,3-d]pyrrolo[1,2-a]pyrimidine-7-carbaldehyde

36


¹H NMR δ 2.33 (2H, m), 2.81 (2H, m), 3.25 (4H, m), 4.20 (2H, m), 10.20 (1H, s)

4d 1,2,3,4,5,8,9,10,11,12-Decahydro-14H-cyclohepta[4',5']thieno[2',3':4,5]-pyrimido[1,2-a]azepin-14-one


¹H NMR δ 2.82 (2H, m), 3.31 (2H, m), 3.60 (3H, s), 8.04 (1H, s), 10.22 (1H, s) ¹H NMR δ 2.82 (2H, m), 3.31 (2H, m), 3.60 (3H, s), 8.04 (1H, s), 10.22 (1H, s)

4e 8-Chloro-5,6-dihydro-3-methyl[1]benzothieno[2,3-d]pyrimidin-4(3H)-one-7-carboxyaldehyde

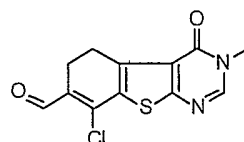

¹H NMR δ 2.81 (2H, m), 3.31 (2H, m), 3.59 (3H, s), 8.03 (1H, s), 10.22 (1H, s)

Table 2. Individual compounds of compound class 5 prepared.

compound	n	R ¹	R ²	R ³
5a	2	-(CH ₂) ₅ -		-Ph
5b	2	-(CH ₂) ₅ -		-CH ₂ CH ₃
5c	2	-(CH ₂) ₅ -		-CH ₂ CH ₂ CH ₃
5d	2	-(CH ₂) ₅ -		-CH ₂ CH ₂ CH ₂ CH ₃
5e	2	-(CH ₂) ₅ -		-CH(CH ₃) ₂
5f	2	-(CH ₂) ₅ -		-C(CH ₃) ₃
5g	2	-(CH ₂) ₅ -		cyclopentyl
5h	2	-(CH ₂) ₅ -		cyclohexyl
5i	2	-(CH ₂) ₆ -		-CH ₂ CH ₂ CH ₃

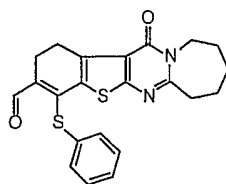
15

General procedure for the synthesis of 5a-5h: 4a (0.62mmol) in THF (20ml) followed by 1M NaOH (0.93ml) were added dropwise into thiophenol (1.06mmol) in THF (2ml) at -18 °C. The reaction mixture was allowed to reach room temperature and stirred until no starting material was detected on TLC. Reaction mixture was poured into large excess of water and stirred for 1h. The product was filtrated and recrystallisation afforded 5a as yellow crystals in 85% yield.

20

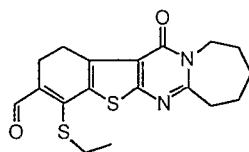
5a 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(phenylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde

37



^1H NMR δ 1.77 (6H, m), 2.82 (2H, m), 2.95 (2H, m), 3.25 (2H, m), 4.29 (2H, m), 7.23 (5H, m), 10.47 (1H, s)

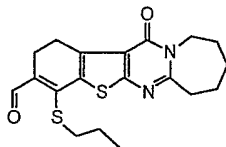
- 5 **5b** 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(ethylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde



5b was synthesised as described above but ethanethiol was used.

- 10 ^1H NMR δ 1.26 (3H, t), 1.85 (6H, m), 2.76 (2H, m), 2.91 (2H, q), 3.07 (2H, m), 3.22 (2H, m), 4.37 (2H, m), 10.48 (1H, s). M/z 360

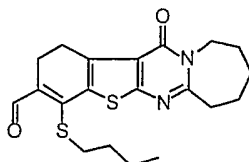
- 5c** 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(propylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde



- 15 **5c** was synthesised as described above but propanethiol was used.

^1H NMR δ 0.99 (3H, t), 1.63 (2H, m), 1.86 (6H, m), 2.76 (2H, m), 2.87 (2H, t), 3.06 (2H, m), 3.22 (2H, m), 4.37 (2H, m), 10.49 (1H, s). M/z 374

- 20 **5d** 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(butylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde

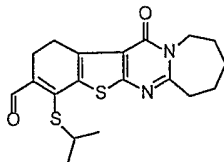


5d was synthesised as described above but butanethiol was used.

^1H NMR δ 0.89 (3H, t), 1.46 (4H, m), 1.86 (6H, m), 2.76 (2H, m), 2.89 (2H, t), 3.06 (2H, m), 3.22 (2H, m), 4.37 (2H, m), 10.48 (1H, s). M/z 388

25

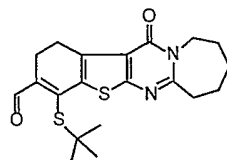
5e 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(isopropylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde



5e was synthesised as described above but 2-propanethiol was used.

5 ^1H NMR δ 1.31 (6H, d), 1.85 (6H, m), 2.77 (2H, m), 3.06 (2H, m), 3.23 (2H, m), 3.41 (1H, septet), 4.37 (2H, m), 10.47 (1H, m). M/z 374

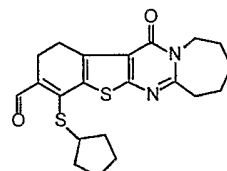
5f 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(*t*-butylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde



10

^1H NMR δ 1.37 (9H, s), 1.86 (6H, m), 2.80 (2H, t), 3.06 (2H, m), 4.37 (2H, m), 10.42 (1H, s)

5g 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(cyclopentylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde

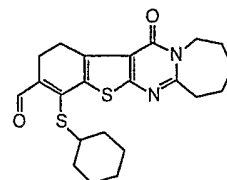


15

^1H NMR δ 1.60-1.85 (14H, m), 2.76 (2H, t), 3.22 (2H, t), 3.61 (1H, m), 4.37 (2H, m), 10.46 (1H, s)

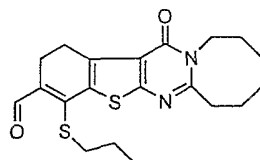
5h 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(cyclohexylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carboxaldehyde

20



^1H NMR δ ^1H NMR δ 1.25-1.99 (16H, m), 2.77 (2H, m), 3.06-3.27 (5H, m), 4.36 (2H, m), 10.47 (1H, s)

5i 1,2,7,9,10,11,12,14-octahydro-14-oxo-4-(propylthio)-8*H*-[1]benzothieno[2',3':4,5]pyrimido-[1,2-*a*]-azocine-3-carbaldehyde



Compound **5i** was synthesized as compound **5c** using **4b** as a starting material.

- 5** ^1H NMR (CDCl_3) δ 0.99 (3H, t), 1.44 (2H, m), 1.62 (4H, m), 1.93 (4H, m), 2.76 (2H, m), 2.87 (2H, m), 3.02 (2H, m), 3.22 (2H, m), 4.30 (2H, broad s), 10.49 (1H, s)

EXAMPLE 2

- 10** **Scheme 2.** Synthesis of compounds **6** and **7**.

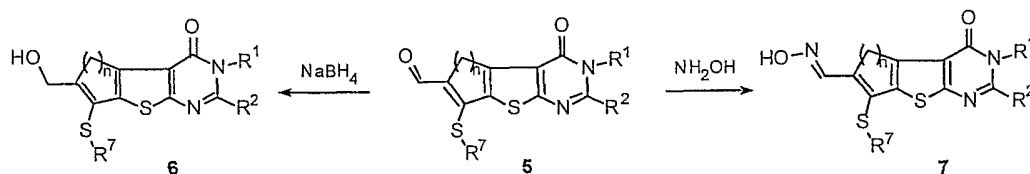
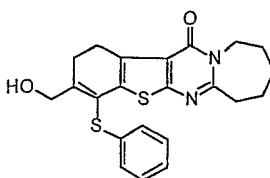


Table 3.

compound	n	R ¹	R ²	R ⁷
6a	2	-(CH ₂) ₅ -		-Ph
6b	2	-(CH ₂) ₅ -		cyclohexyl
6c	2	-(CH ₂) ₅ -		propyl
7	2	-(CH ₂) ₅ -		-Ph

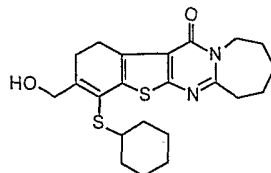
- 15** **General procedure for the synthesis of 6a-6b and 8:** NaBH₄ (0.66mmol) was added into **5a** (0.52mmol) in ethanol (300ml). After stirring for 20 minutes water (65ml) was added followed by acidification with HCl. Ethanol was evaporated and the product was filtered affording **6a** as pale yellow powder in 98% yield.

- 20** **6a** 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(phenylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-*a*]azepine-3-hydroxymethyl



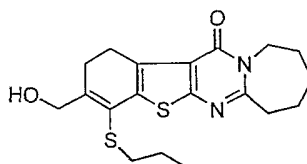
^1H NMR δ 1.80 (6H, m), 2.79 (2H, m), 2.99 (2H, m), 3.29 (2H, m), 4.33 (2H, m), 4.61 (2H, s), 7.17 (5H, m). M/z 410

6b 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(cyclohexylthio)[1]benzothieno-[2',3':4,5]pyrimido [1,2-a]azepine-3-hydroxymethyl



^1H NMR δ 1.22-1.92 (16H, m), 2.66 (2H, m), 2.9-3.1 (3H, m), 3.21 (2H, m), 4.36 (2H, m) 4.59 (2H, s)

6c 1,2,8,9,10,11 -Hexahydro-3-(hydroxymethyl)-4-(propylthio)-[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-13(7*H*)-one



10 Compound 6c was synthesised by the method described for 6a-b using compound 5c as a starting material.

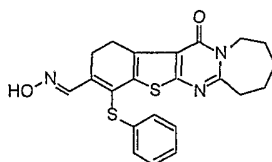
^1H NMR (D_6 -acetone) δ 0.96 (3H, t), 1.60 (2H, m), 1.84 (6H, m), 2.68 (4H, m), 3.10 (4H, m), 4.38 (2H, m), 4.57 (2H, broad s)

MS (m/z) 376

15

Synthesis of 7: NaOAc (0.50mmol) was added to $\text{NH}_2\text{OH}\cdot\text{HCl}$ (0.50mmol) in absolute ethanol (3ml) at 0°C , followed by addition of **5a** (0.26mmol) in dry THF (7ml). The reaction mixture was allowed to reach room temperature and stirred for over night. The reaction was quenched with water, extracted with CH_2Cl_2 , washed with brine and water, and dried with Na_2SO_4 . After filtration solvent was evaporated giving **7** in 95% yield. Recrystallisation from ethanol afforded pale yellow powder.

7 Octahydro-13-oxo-4-(phenylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-oxime-methyl

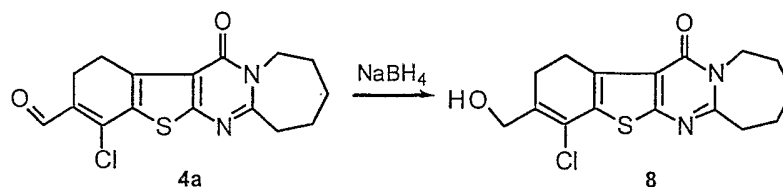


25

^1H NMR δ 1.81 (6H, m), 2.96 (4H, m), 3.30 (2H, m), 4.34 (2H, m), 7.18 (5H, m), 7.61 (1H, broad s), 8.76 (1H, s). M/z 423

EXAMPLE 3

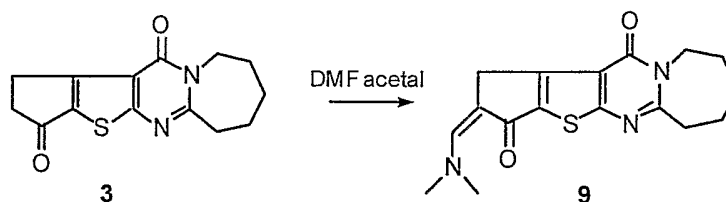
Scheme 3. Synthesis of compound 8



8 4-Chloro-1,2,7,8,9,10,11,13-octahydro-13-oxo[1]benzothieno[2',3':4,5]-pyrimido[1,2-a]azepine-
 5 3-hydroxymethyl
 ^1H NMR δ 1.84 (6H, m), 2.71 (2H, m), 3.05 (2H, m), 3.25 (2H, m), 4.36 (2H, m), 4.45 (2H, s).
 M/z 366

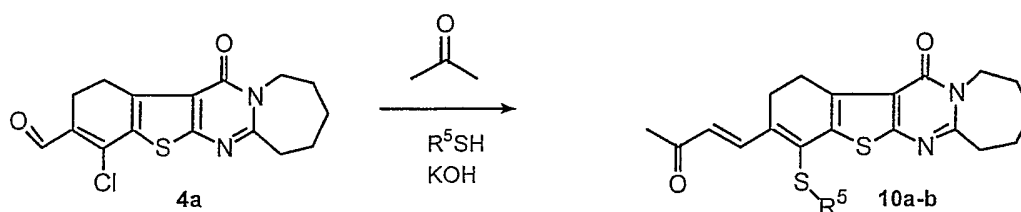
EXAMPLE 4

10 Scheme 4. Synthesis of compound 9



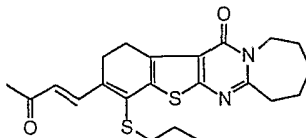
Synthesis of 9: Dry DMF (5ml), DMF acetal (1.56mmol) and **3b** (0.36mmol) were refluxed for 2 hours under a CaCl_2 -tube, after which DMF was distilled away and the crude product dried in a vacuum. Purification in a flash column using acetone as an eluent afforded **9** in 55% yield. ^1H
 15 NMR (CDCl_3) δ 1.86 (6H, m), 3.08 (2H, m), 3.17 (6H, s), 4.08 (2H, s), 4.40 (2H, m), 7.41 (1H, s).

EXAMPLE 5

Scheme 5. Synthesis of compound 10 (**10a** $R^7 = -\text{CH}_2\text{CH}_2\text{CH}_3$, **10b** $R^7 = -\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\text{H}$)

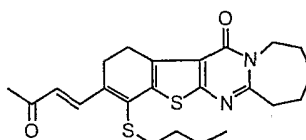
20 **General procedure for the synthesis of 10a-10b:** KOH (0.58mmol) and EtSH (0.59mmol) in EtOH (5ml) were stirred for 30 minutes, followed by addition of **4a** in acetone (40ml). After 30 minutes water (250ml) was added and the mixture stirred until the product precipitates. Filtration afforded **10a** as yellow powder in 86% yield.

10a 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(propylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-(3-oxo)but-1-ene



¹H NMR (CDCl₃) δ 1.00 (3H, t), 1.60 (2H, m), 1.85 (6H, m), 2.39 (3H, s), 2.75 (4H, m), 3.05 (2H, m), 3.27 (2H, m), 4.37 (2H, m), 6.35 (1H, d), 8.28 (1H, d)

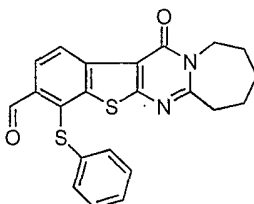
10b 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(butylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-(3-oxo)but-1-ene



¹H NMR (CDCl₃) δ 0.88 (3H, t), 1.46 (4H, m), 1.85 (6H, m), 2.38 (3H, s), 2.76 (4H, m), 3.05 (2H, m), 3.27 (2H, m), 4.37 (2H, m), 6.35 (1H, d), 8.27 (1H, d)

15 FURTHER EXAMPLES

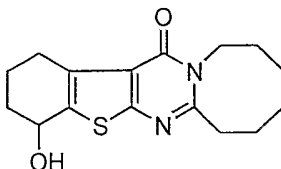
12 7,8,9,10,11,13-Hexahydro-13-oxo-4-(phenylthio)-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-3-carbaldehyde



Compound 5a (100 mg, 245 mmol) and DDQ (67 mg, 295 mmol) were refluxed over night in 15 ml of dry benzene. The reaction mixture was cooled to room temperature and filtered through a short column of silica gel. The solvent was evaporated. The product 12 was recrystallized from EtOH / petrol ether.

¹H NMR (CDCl₃) δ 1.86 (6H, m), 3.12 (2H, m), 4.47 (2H, m), 7.16 (5H, m), 8.16 (1H, d), 8.72 (1H, d), 10.78 (1H, s)

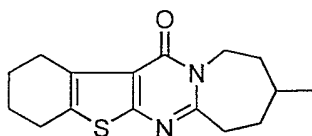
13 1,2,3,4,7,8,9,10,11,12-Decahydro-4-hydroxy-14*H*-[1]benzothieno[2',3':4,5]pyrimido[1,2-*a*]azocin-14-one



To compound 3d (200 mg, 0.66 mmol) in 5ml of THF and 15ml of EtOH, NaBH₄ (33 mg, 0.86 mmol) was added and the reaction mixture was stirred for 15 minutes. The reaction was quenched with water and extracted with CH₂Cl₂. The organic layer was washed with brine and dried with Na₂SO₂. After filtration the solvent was evaporated. The product was purified by flash chromatography using CH₂Cl₂/ EtOAc 1:1 as an eluent.

¹H NMR (CDCl₃) δ 1.42 (2H, m), 1.59 (2H, m), 1.95 (7H, m), 2.14 (2H, m), 3.05 (4H, m), 4.29 (2H, m), 4.87 (1H, m)

14 9-Methyl-2,3,4,7,8,9,10,11-octahydro-[1]benzothieno[2',3':4,5]pyrimido[1,2-*a*]azepin-13(1*H*)-one

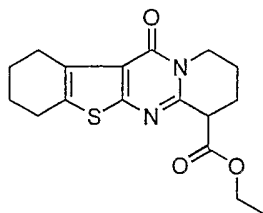


The compound was synthesized by the method described for 2a-i using 4-methyl-caprolactam as a starting material.

¹H NMR δ 0.98 (3H, d), 1.26 (2H, m), 1.84 (5H, m), 2.04 (2H, m), 2.74 (2H, m), 3.01 (4H, m), 3.51 (1H, m), 5.17 (1H, m)

MS (*m/z*) 288

15 1,2,3,4,7,9,10,12-Octahydro-12-oxo-8*H*-[1]benzothieno[2,3-*d*]pyrido[1,2-*a*]pyrimidine-7-carboxylic acid ethyl ester

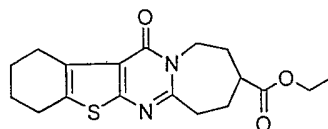


The compound was synthesized by the method described for 2a-i using 3-ethoxy-carbonyl-2-piperidone as a starting material.

¹H NMR δ 1.24 (3H, t), 1.99 (7H, m), 2.27 (1H, m), 2.74 (2H, m), 2.99 (2H, m), 4.01 (3H, m), 4.20 (2H, q)

MS (*m/z*) 332

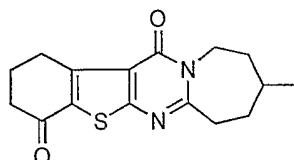
16 1,2,3,4,7,8,9,10,11,13-Decahydro-13-oxo-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-9-carboxylic acid ethyl ester



The compound was synthesized by the method described for 2a-i using ethyl 7-oxo-4-azepanecarboxylate as a starting material.

¹H NMR δ 1.23 (3H, t), 1.88 (6H, m), 2.15 (2H, m), 2.72 (3H, m), 3.03 (4H, m), 3.91 (1H, m), 4.13 (2H, q), 4.84 (1H, m)

17 2,3,8,9,10,11-Hexahydro-9-methyl-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-4,13(1H,7H)-dione

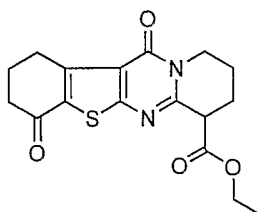


To compound 14 (4.0g, 13.9 mmol), potassium peroxodisulfate (11.3 g, 41.6 mmol) and CuSO₄·5H₂O, 250 ml of acetonitrile /water 1:1 were added. The reaction mixture was heated to reflux for 30 minutes. The reaction was quenched with water and extracted with CH₂Cl₂. The organic layer was washed with 10% sodium thiosulfate and brine, and dried over Na₂SO₄. After filtration the solvent was evaporated and the product purified by flash chromatography using CH₂Cl₂/ EtOAc 9:1 as an eluent.

¹H NMR (CDCl₃) δ 1.00 (3H, d), 1.28 (2H, m), 1.90 (1H, m), 2.08 (2H, m), 2.23 (2H, m), 2.66 (2H, m), 3.06 (2H, m), 3.28 (2H, m), 3.55 (1H, m), 5.16 (1H, m)

MS (*m/z*) 302

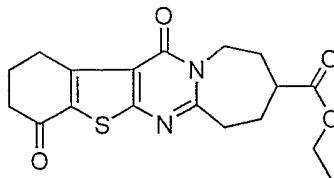
18 4,12-Dioxo -1,2,3,4,7,9,10,12-octahydro -8H-[1]benzothieno[2,3-d]pyrido[1,2-a]pyrimidine-7-carboxylic acid ethyl ester



Compound 18 was synthesized by the method described for compound 17 using compound 15 as a starting material.

¹H NMR (CDCl₃) δ 1.26 (3H, t), 1.80 (1H, m), 2.18 (4H, m), 2.62 (3H, m), 3.24 (3H, m), 3.81 (1H, m), 4.28 (3H, m)

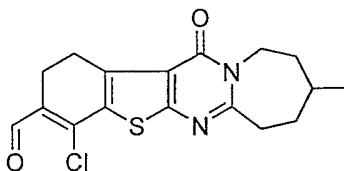
19 4,13-Dioxo-1,2,3,4,7,8,9,10,11,13-decahydro-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-9-carboxylic acid ethyl ester



Compound 19 was synthesized by the method described for compound 17 using compound 16 as a starting material.

^1H NMR (CDCl_3) δ 1.28 (3H, t), 1.97 (2H, m), 2.21 (4H, m), 2.66 (2H, m), 2.79 (1H, m), 3.03 (1H, m), 3.24 (3H, m), 4.01 (1H, m), 4.18 (2H, q), 4.84 (1H, m)

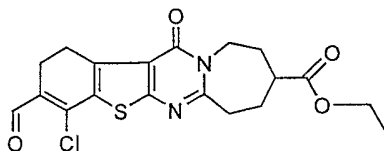
20 4-Chloro-9-methyl-1,2,7,8,9,10,11,13-octahydro-13-oxo-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-3-carbaldehyde



POCl_3 (2.91 mmol) was added dropwise into DMF (3.02 mmol) in CHCl_3 (2 ml) at 0 °C. After 30 minutes compound 17 (0.36 mmol) in CHCl_3 (6 ml) was added slowly dropwise. The reaction mixture was allowed to reach room temperature and stirred overnight after which the reaction mixture was heated to 50 °C for 12 hours. The reaction mixture was cooled to room temperature and quenched with saturated NaOAc, extracted with CH_2Cl_2 , washed with brine and water, and dried over Na_2SO_4 . After filtration the solvent was evaporated. The product was purified by flash chromatography using CH_2Cl_2 -EtOAc 9:1 as an eluent.

^1H NMR (CDCl_3) δ 1.00 (3H, d), 1.29 (2H, m), 1.90 (1H, m), 2.09 (2H, m), 2.80 (2H, m), 3.06 (2H, m), 3.27 (2H, m), 3.55 (1H, m), 5.15 (1H, m), 10.20 (1H, s)

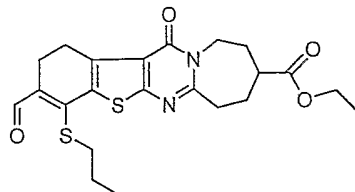
21 4-Chloro-3-formyl-1,2,7,8,9,10,11,13-octahydro-13-oxo-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-9-carboxylic acid ethyl ester



Compound 21 was synthesized by the method described for 4a using compound 19 as a starting material, with the exception that the reaction mixture was stirred for 8 days.

^1H NMR (CDCl_3) δ 1.28 (3H, t) 1.98 (2H, m), 2.22 (2H, m), 2.79 (3H, m), 3.03 (1H, m), 3.24 (3H, m), 4.01 (1H, m), 4.18 (2H, q), 4.85 (1H, m), 10.20 (1H, s)

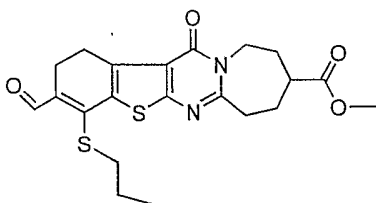
22 3-Formyl-1,2,7,8,9,10,11,13-octahydro-13-oxo-4-(propylthio)-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-9-carboxylic acid ethyl ester



Compound 22 was synthesized by the method described for 5c using compound 21 as a starting material.

^1H NMR (CDCl_3) δ 0.99 (3H, t), 1.27 (3H, t), 1.62 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 2.77 (3H, m), 2.86 (2H, t), 3.02 (1H, m), 3.21 (3H, m), 4.00 (1H, m), 4.17 (2H, q), 4.86 (1H, m), 10.49 (1H, s)

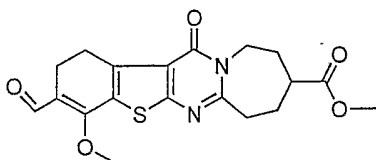
23 3-Formyl-1,2,7,8,9,10,11,13-octahydro-13-oxo-4-(propylthio)-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-9-carboxylic acid methyl ester



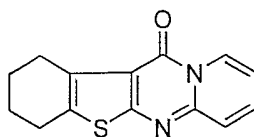
Compound 22 (80.37 mmol) was dissolved into MeOH (10 ml), and KOH (0.98 mmol) in MeOH (5 ml) was added. The reaction mixture was stirred for 2 hours in room temperature. The reaction mixture was poured into water, acidified with HCl and extracted with CH_2Cl_2 . Organic layer was washed with brine and dried with Na_2SO_4 . After filtration the solvent was evaporated. Purification by flash chromatography using CH_2Cl_2 -EtOAc 9:1 as an eluent afforded compound 23 as a major product and compound 24 as a minor product.

^1H NMR (CDCl_3) δ 0.99 (3H, t), 1.63 (2H, m), 1.98 (2H, m), 2.23 (2H, m), 2.77 (3H, m), 2.86 (2H, t), 3.02 (1H, m), 3.21 (3H, m), 3.73 (3H, s), 4.01 (1H, m), 4.84 (1H, m), 10.49 (1H, s)

24 3-Formyl-4-methoxy-1,2,7,8,9,10,11,13-octahydro-13-oxo-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-9-carboxylic acid methyl ester



^1H NMR (CDCl_3) 1.98 (2H, m), 2.20 (2H, m), 2.72 (2H, m), 2.80 (1H, m), 3.02 (1H, m), 3.21 (3H, m), 3.73 (3H, s), 4.04 (3H, s), 4.04 (1H, m), 4.84 (1H, m), 10.19 (1H, s)

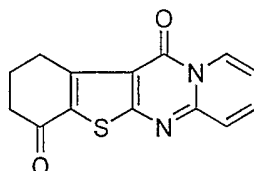
25 1,2,3,4-Tetrahydro-12*H*-[1]benzothieno[2,3-*d*]pyrido[1,2-*a*]pyrimidin-12-one

2-Bromopyridine and ethyl 2-amino-4,5,6,7-tetrahydrobenzo(b)thiophene-3-carboxylate 1b were heated to 165°C for three and half hours under argon. After cooling the solid material was crystallized from EtOH. The crystallised product was purified by flash chromatography using CH₂Cl₂/ EtOAc 9:1 as an eluent.

¹H NMR (CDCl₃) δ 1.92 (4H, m), 2.81 (2H, m), 3.14 (2H, m), 7.00 (1H, m), 7.57 (2H, m), 9.04 (1H, m)

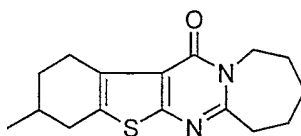
MS (*m/z*) 256

10

26 2,3-Dihydro-12*H*-[1]benzothieno[2,3-*d*]pyrido[1,2-*a*]pyrimidin-4,12(1*H*)-dione

Compound 26 was synthesized by the method described for compound 17 using compound 25 as a starting material.

¹H NMR (CDCl₃) δ 2.30 (2H, m) 2.71 (2H, m), 3.40 (2H, t), 7.12 (1H, m), 7.62 (1H, m), 7.76 (1H, m), 9.05 (1H, m)

27 3-Methyl-2,3,4,7,8,9,10,11-octahydro-[1]benzothieno[2',3':4,5]pyrimido-[1,2-*a*]azepin-13(1*H*)-one

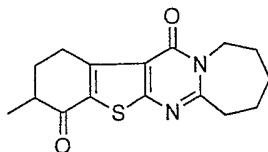
Compound 27 was synthesized by the method described for 2a-i using 2-amino-4,5,6,7-tetrahydro-6-methyl-benzo[b]thiophene-3-carboxylic acid ethyl ester as a starting material.

¹H NMR (CDCl₃) δ 1.09 (3H, d), 1.44 (1H, m), 1.89 (8H, m), 2.37 (1H, m), 2.85 (2H, m), 3.02 (2H, m), 3.21 (1H, m), 4.35 (2H, m)

MS (*m/z*) 288

30

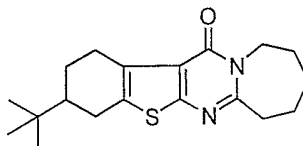
28 2,3,8,9,10,11-Hexahydro-3-methyl-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepin-4,13(1*H*,7*H*)-dione



Compound 28 was synthesized by the method described for compound 17 using compound 27 as a starting material.

¹H NMR (CDCl₃) δ 1.28 (3H, d), 1.85 (6H, m), 1.98 (1H, m), 2.29 (1H, m), 2.67 (1H, m), 3.06 (2H, m), 3.13 (1H, m), 3.50 (1H, m), 4.36 (2H, m)

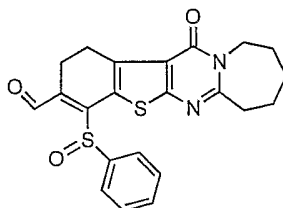
29 3-*t*-Butyl-2,3,4,7,8,9,10,11-octahydro-[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]azepin-13(1*H*)-one



Compound 29 was synthesized by the method described for 2a-i using 2-amino-4,5,6,7-tetrahydro-6-*t*-butylbenzo[b]thiophene-3-carboxylic acid ethyl ester as a starting material.

¹H NMR (CDCl₃) δ 0.95 (9H, s), 1.35 (1H, m), 1.55 (1H, m), 1.79 (6H, m), 2.06 (1H, m), 2.51 (1H, m), 2.76 (2H, m), 3.01 (2H, broad s), 3.32 (1H, m), 4.35 (2H, m)

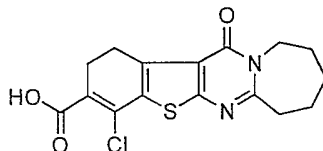
30 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(phenylsulfinyl)-[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-carbaldehyde



Compound 5a (100 mg, 0.25 mmol) and *m*-chloroperbenzoic acid (89mg, 0.52 mmol) in 25 ml dry CH₂Cl₂ were stirred for 3 days in room temperature. The reaction was quenched with water and extracted with CH₂Cl₂. The organic layer was washed with 10% sodium thiosulfate and brine and dried with Na₂SO₄. After filtration the solvent was evaporated and the product purified by flash chromatography using CH₂Cl₂/ EtOAc 8:2

¹H NMR (CDCl₃) δ 1.80 (6H, m), 2.71 (2H, m), 3.03 (2H, m), 3.06 (1H, m), 3.57 (1H, m), 4.31 (2H, m), 7.47 (3H, m), 7.69 (2H, m), 10.65 (1H, s)

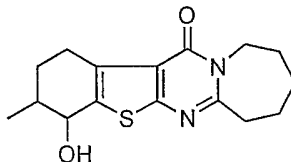
31 4-Chloro-1,2,7,8,9,10,11,13-octahydro-13-oxo-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-3-carboxylic acid



Compound 4a (335 mg, 1.00 mmol) and 2-methyl-2-butene (1.06 ml, 10.01 mmol) were dissolved into 50 ml THF. A freshly prepared solution of 80% NaClO₂ (339 mg, 3.00 mmol) and NaH₂PO₄·H₂O (414 mg, 3.00 mmol) in 55 ml of *t*-BuOH/H₂O 5:1 was added. The reaction mixture was stirred in room temperature for 6 hours. The reaction was quenched with water and extracted CH₂Cl₂. The organic phase was extracted with sat. NaHSO₄. The water phase was then made acidic with HCl and extracted with CH₂Cl₂. the organic layer was washed with brine and dried over Na₂SO₂. After filtration the solvent was evaporated and the product recrystallized from ethanol.

¹H NMR (D₆-DMSO) 1.71 (6H, m), 2.79 (2H, m), 3.06 (2H, m), 3.14 (2H, m), 4.31 (2H, m), 13.07 (1H, broad s)

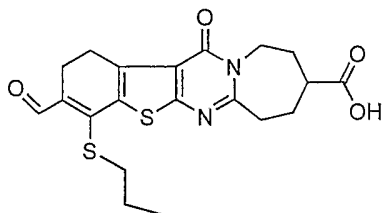
15 32 4-Hydroxy-3-methyl-2,3,4,7,8,9,10,11-octahydro [1]benzothieno[2',3':4,5]pyrimido-[1,2-a]azepin-13(1*H*)-one



Compound 32 was synthesized as mixture of diastereomers by the method described for compound 13 using compound 28 as a starting material.

20 ¹H NMR (CDCl₃) δ 1.14 (2H, d) 1.16 (2H, d), 1.58-2.04 (20H, m), 2.82 (1H, m), 2.95 (1H, m), 3.04 (4H, m), 3.13 (1H, m), 3.25 (1H, m), 3.75 (2H, m), 4.35 (4H, m), 4.42 (1H, m), 4.67 (1H, m)

33 3-Formyl-1,2,7,8,9,10,11,13-octahydro-13-oxo-4-(propylthio)-[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-9-carboxylic acid



25

Compound 22 (130 mg) in THF (2 ml) and 0.7 ml 10% KOH H₂O/MeOH (2:1) were stirred over night in room temperature. The reaction mixture was poured into water and washed with ether. The water phase was acidified with HCl and extracted with EtOAc. Organic phase was washed

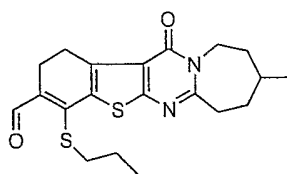
with brine and dried with Na₂SO₄. After filtration the solvent was evaporated and the product recrystallized from ethanol.

¹H NMR (D₆-DMSO) δ 0.93 (2H, t), 1.55 (2H, m), 1.71 (2H, m), 2.14 (2H, m), 2.65 (2H, t), 2.67 (2H, m), 2.91 (2H, m), 3.10 (2H, m), 3.12 (2H, m), 3.97 (1H, m), 4.74 (1H, m), 10.36 (1H, s),

5 12.37 (1H, broad s)

MS (*m/z*) 418

34 9-Methyl-1,2,7,8,9,10,11,13-octahydro-13-oxo-4-(propylthio)-[1]benzothieno[2',3':4,5]-pyrimido[1,2-*a*]azepine-3-carbaldehyde



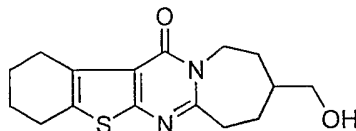
10

Compound 34 was synthesized by the method described for 5c using compound 21 as a starting material.

¹H NMR (CDCl₃) δ 0.99 (3H, t), 1.00 (3H, d), 1.28 (2H, m), 1.63 (2H, m), 1.89 (1H, m), 2.08 (2H, m), 2.75 (2H, m), 2.86 (2H, t), 3.06 (2H, m), 3.21 (2H, m), 3.55 (1H, m), 5.16 (1H, m), 10.49 (1H, s)

15 s)

35 9-(Hydroxymethyl)-2,3,4,7,8,9,10,11-octahydro-[1]benzothieno[2',3':4,5]pyrimido[1,2-*a*]azepin-13(1*H*)-one



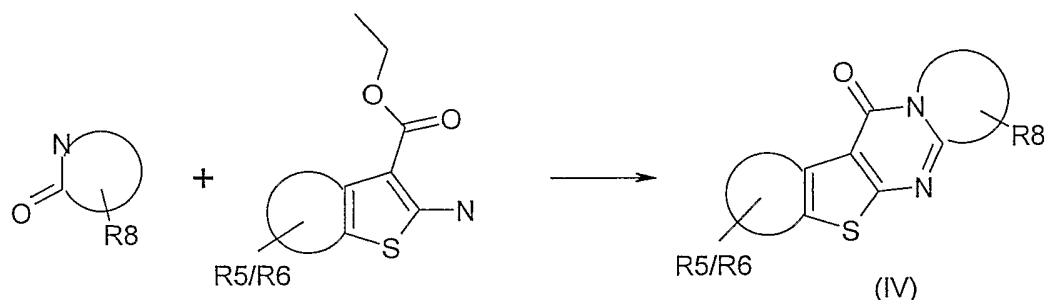
20 Compound 16 (0.72 mmol) in dry THF (6 ml) was added dropwise to LiAlH₄ (1.95 mmol) in THF (2 ml) under argon at 0° C. The reaction mixture was stirred for 20 minutes. The reaction was quenched with water and 10% NaOH was added, and extracted with ether. The organic layer was washed with brine and dried over Na₂SO₄. After filtration the solvent was evaporated and the product purified by flash chromatography using EtOAc as an eluent.

25 ¹H NMR (CDCl₃) δ 1.31 (2H, m), 1.80 (6H, m), 2.18 (2H, m), 2.75 (2H, m), 3.01 (3H, m), 3.11 (1H, m), 3.51 (3H, m), 5.25 (1H, m)

30 It is evident that otherwise ring-substituted or -modified compounds as defined by formula (I) of the claims can be prepared analogously, e.g. by using ring-substituted or -modified analogues of the starting compound (2) in Scheme 2.

Further compounds of general formula IV falling under the scope of general formula I can prepared by parallel chemistry using a reaction as shown in the following scheme 6:

Scheme 6: General procedure for the pyrimidinone synthesis of thiophene amino ester with lactames.



In a reaction vessel at room temperature are put together sequentially 0.25 M lactam, 0.25 M amino ester and 0.25 M POCl_3 . Of all reactants one equivalent is used as solution or suspension in chlorobenzene. After shaking for 80 hours at 100°C , the mixtures are cooled to room temperature, washed with 5% NaOAc and extracted with EtOAc. The organic layers are collected and concentrated to yield the desired compound. The obtained material of the formula IV was thereafter analyzed by LC-MS.

The LC-MS system consists of 2 Perkin Elmer series 200 micro-pumps. The pumps are connected to each other by a 50 μl tee mixer. The mixer is connected to the Gilson 215 auto-sampler. The LC method consists of the following steps:

Step	total time	flow (ul/min)	A(%)	B(%)
20	0	2300	95	5
1	1.8	2300	0	100
2	2.5	2300	0	100
3	2.7	2300	95	5
4	3.0	2300	95	5

25

Solution A= 100% Water with 0.025% HCOOH and 10mmol NH_4HCOO pH= +/- 3

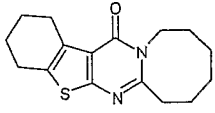
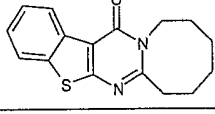
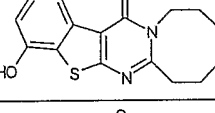
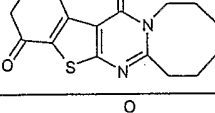
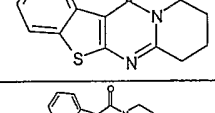
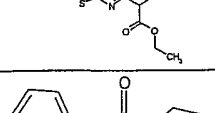
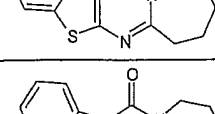
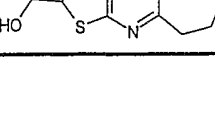
Solution B= 100% MeOH with 0.025% HCOOH

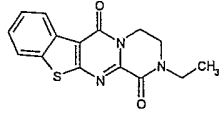
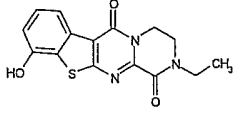
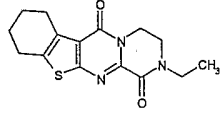
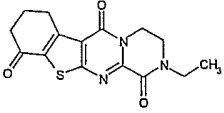
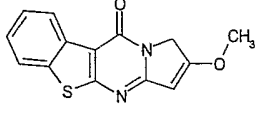
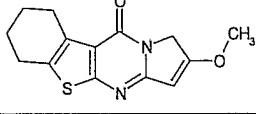
The auto sampler has a 2 μl injection loop. The auto sampler is connected to a Varian Polaris C18 A 30*4.6 mm column with 3 μm particles. The column is thermo stated in a Perkin Elmer series 200 column oven at 40°C . The column is connected to an Applied Biosystems ABI 785 UV meter with a 2.7 μl flowcel. The wavelength is set to 254 nm. The UVmeter is connected to a

Sciex API 150EX mass spectrometer having the following parameters (Scanrange:150-900 Amu, Polarity: positive, Scan mode: profile, Resolution Q1: UNIT, Step size: 0.10 amu, Time per scan: 0.500 sec, NEB: 10, CUR: 10, IS: 5200, TEM: 325, DF: 30, FP: 225, EP: 10). The light scattering detector is connected to the Sciex API 150. The light scattering detector is a Sedex 55 operating at 50°C and 3 bar N₂ pressure. The complete systems is controlled by a Dell optiplex GX400 computer operating under Windows NT.

The following table 4 lists compounds No. 41 to 53 of the general formula IV, which were prepared according to Scheme 6 starting with the lactams and the amino acid esters mentioned in the 2nd and 3rd row. In addition, the Molecular Weight and the Retention Time of the synthesized compounds determined by the LC-MS analysis are shown.

Table 4: Compounds No. 41 to 53 of the general formula IV:

No.	Structural Formula of final compound	Amino ester	Lactam	MH ⁺	RT
40		ETHYL 2-AMINO-4,5,6,7-TETRAHYDROBENZO[B]THIOPHENE-3-CARBOXYLATE	2-AZACYCLOOCTANONE	288,13	1,915
41		ETHYL 2-AMINO-BENZO[B]THIOPHENE-3-CARBOXYLATE	2-AZACYCLOOCTANONE	284,10	1,897
42		2-AMINO-7-HYDROXY-BENZO[B]THIOPHENE-3-CARBOXYLIC ACID ETHYL ESTER	2-AZACYCLOOCTANONE	300,09	1,700
43		ETHYL 2-AMINO-7-OXO-4,5,6,7-TETRAHYDRO-1-BENZOTHIOPHENE-3-CARBOXYLATE	2-AZACYCLOOCTANONE	302,11	1,684
44		ETHYL 2-AMINO-BENZO[B]THIOPHENE-3-CARBOXYLATE	DELTA-VALEROLACTAM	256,07	1,736
45		ETHYL 2-AMINO-BENZO[B]THIOPHENE-3-CARBOXYLATE	3-CARBETHOXY-2-PIPERIDONE	328,09	2,039
46		ETHYL 2-AMINO-BENZO[B]THIOPHENE-3-CARBOXYLATE	EPSILON-CAPROLACTAM	270,08	1,858
47		2-AMINO-7-HYDROXY-BENZO[B]THIOPHENE-3-CARBOXYLIC ACID ETHYL ESTER	EPSILON-CAPROLACTAM	286,08	1,645

No.	Structural Formula of final compound	Amino ester	Lactam	MH+	RT
48		ETHYL 2-AMINO-BENZO[B]THIOPHENE-3-CARBOXYLATE	N-ETHYL-2,3-DIKETOPIPERAZINE	299,07	1,509
49		2-AMINO-7-HYDROXY-BENZO[B]THIOPHENE-3-CARBOXYLIC ACID ETHYL ESTER	N-ETHYL-2,3-DIKETOPIPERAZINE	315,07	1,386
50		ETHYL 2-AMINO-4,5,6,7-TETRAHYDROBENZO[B]THIOPHENE-3-CARBOXYLATE	N-ETHYL-2,3-DIKETOPIPERAZINE	303,10	1,576
51		ETHYL 2-AMINO-7-OXO-4,5,6,7-TETRAHYDRO-1-BENZOTHIOPHENE-3-CARBOXYLATE	N-ETHYL-2,3-DIKETOPIPERAZINE	317,08	1,277
52		ETHYL 2-AMINO-BENZO[B]THIOPHENE-3-CARBOXYLATE	4-METHOXY-3-PYRROLIN-2-ONE	270,05	1,703
53		ETHYL 2-AMINO-4,5,6,7-TETRAHYDROBENZO[B]THIOPHENE-3-CARBOXYLATE	4-METHOXY-3-PYRROLIN-2-ONE	274,08	1,782

BIOLOGICAL TESTING MATERIALS AND METHODS

5 1. Inhibition of the 17 β -hydroxysteroid dehydrogenase type 1, type 2 and type 3 enzyme

The compounds were screened in respect of 17 β -HSD enzyme activity in vitro on established MCF-7 cell lines, each stably expressing one of the respective 17 β -HSD isoenzymes. The interconversion of substrate by each isoenzyme and the 17 β -HSD inhibiting activity of chemical compounds in these cell lines were detected by HPLC system.

Varying amounts of the test compounds were incubated in the growth medium of the 17 β -HSD expressing cells together tritium labeled substrate (2nM estrone for 17 β -HSD type 1; 2 nM estradiol for 17 β -HSD type 2; and 2 nM androstenedione for 17 β -HSD type 3). The medium samples were removed after exact incubation time and the reaction is stopped by trichloroacetic acid (TCA). The samples were analyzed by HPLC-coupled flow scintillation analysis.

For each enzyme type, the HSD-inhibiting activity of an individual test compound was calculated by comparing the conversion of a control sample without any test compound (re-

ferred to as "Negative Control") to the (reduced) conversion of the test sample containing the particular compound to be tested (referred to as "Test Sample").

Conversion in Negative Control – Conversion in Test Sample

$$5 \quad \% \text{ inhibition} = 100 \times \frac{\text{Conversion in Negative Control} - \text{Conversion in Test Sample}}{\text{Conversion in Negative Control}}$$

The obtained results are shown in Table 3 below. Two concentrations of each compound were used. The number of the compound refers to the numbers indicated in the Experimental Section.

Table 3: % Inhibition of the 17 β -HSD enzymes type 1, type 2 and type 3 by the compounds of the invention

Compound	HSD1		HSD2		HSD3	
	1 μ M	10 μ M	1 μ M	10 μ M	1 μ M	10 μ M
No. 2a	10.0	45.9	16.2	23.4	39.0	24.9
No. 2b	21.0	15.0	15.9	21.4	4.2	9.5
No. 2c	22.7	39.8	8.9	13.5	50.8	47.0
No. 2e	15.8	20.0	26.0	28.9	46.8	38.8
No. 2f	19.9	19.2	37	32.4	48.2	40.4
No. 2g	30.7	37.0	44.9	24.9	51.7	51.3
No. 2i	12.7	18.5	20.6	29.4	4.4	9.9
No. 3b	13.5	20.7	14.1	25.4	0.3	13.7
No. 3d	14.3/18.2 ^x	42.9/37.6 ^x	14.1	11.1	15.3/22.3 ^x	16.7/8.1 ^x
No. 3e	6.3	35.8	25.7	16.3	38.5	47.4
No. 3f	8.7	22.0	31.1	21.8	43.9	40.2
No. 4a	27.9	78.0	7.7	22.5	9.4	53.8
No. 4b	36.9/31.2 ^x	82.1/80.1 ^x	3.5	1.5	5.3/14.3 ^x	42.1/43.9 ^x
No. 4e	23.5/24.6 ^x	44.4/52.1 ^x	9.6	28.3	9.8/11.1 ^x	14.2/17.3 ^x
No. 5b	66.1	100.0	19.7	25.2	43.4	100.0
No. 5c	74.0	100.0	8.9	18.6	10.5	100.0
No. 5d	54.1	100.0	8.2	15.1	32.6	72.0
No. 5e	71.9	100.0	8.4	20.2	50.8	86.3
No. 5i	43.9	100.0	11.6	17.3	22.5	80.5
No. 6a	51.8	100.0	11.6	42.5	45.9	48.9
No. 6c	47.7	82.4	37.5	36.7	20.4	38.1
No. 11	4.7	51.1	16.7	28.3	7.3	31.7
No. 12	15.1	87.9	7.0	8.9	8.6	25.5
No. 13	5.0	20.0	1.7	18.6	-2.2	11.7
No. 14	12.8	19.6	5.9	14.9	27.6	34.2
No. 15	14.8	24.5	10.7	15.7	-0.3	13.5
No. 16	17.2	18.6	3.0	24.8	13.6	22.9
No. 17	18.4	39.4	15.2	20.1	21.6	32.4
No. 18	0.5	9.5	18.7	23.8	-3.0	21.3
No. 19	10.6	33.1	0.6	4.4	13.0	10.5
No. 20	10.4	45.7	11.2	6.2	32.0	100.0
No. 21	10.9	33.5	13.1	32.9	20.0	87.3

Compound	HSD1		HSD2		HSD3	
	1 μ M	10 μ M	1 μ M	10 μ M	1 μ M	10 μ M
No. 22	24.3	46.5	6.8	16.1	25.5	100.0
No. 23	17.4	64.7	9.7	17.7	19.5	89.5
No. 24	24.9	32.3	3.1	19.3	18.0	59.6
No. 25	6.2	8.7	14.0	33.6	-3.2	7.9
No. 26	6.4	-0.8	15.1	16.4	-2.1	0.3
No. 27	11.4	25.6	5.3	3.2	22.9	24.9
No. 28	14.3	15.3	18.2	18.7	7.8	9.5
No. 29	-1.0	1.3	13.1	10.1	14.9	25.8
No. 30	23.1	49.0	12.8	24.8	11.1	31.2
No. 31	2.1	6.8	-0.2	9.3	-6.4	-3.9
No. 32	19.7	22.5	14.0	-5.1	n.d.	n.d.
No. 33	15.3	22.6	5.0	-0.1	n.d.	n.d.
No. 34	14.9	48.1	13.0	-0.5	n.d.	n.d.
No. 35	4.8	22.4	15.8	27.7	16.2	23.4

x): two tests were run

n.d. = not determined

2. Estrogen Receptor Binding Assay

5

The binding affinity of the compounds of the invention to the estrogen receptor α and to the estrogen receptor β may be determined according to the in vitro ER binding assays described by Koffmann et al. [Koffmann B et al. (1991) J. Steroid. Biochem. Mol. Biol. 38:135]. Alternatively, an estrogen receptor binding assay may be performed according to international patent application PCT/US/17799 (published as WO 00/07996).

10

3. Estrogen Receptor Transactivation Assays

15

Compounds of the invention showing binding affinity towards the estrogen receptor may be further tested with regard to their individual estrogenic or anti-estrogenic potential (agonistic binding or antagonistic binding to the ER α or ER β). The determination of the estrogen receptor agonist activity may be performed according to an in vitro assay system using the MMTV-ERE-LUC reporter system which is for example described within US patent application No. 10/289079 (published as US 2003/0170292):

20

To assay estrogen receptor agonist activity, Hela cells are grown in 24-well microtiter plates and then transiently co-transfected with two plasmids using lipofectamine. The first plasmid comprises DNA encoding human estrogen receptor (either ER-alpha or ER-beta), and the second plasmid comprises an estrogen-driven reporter system comprising: a luciferase reporter gene (LUC) whose transcription is under the control of upstream regulatory elements

25

comprising 4 copies of the vitellogenin estrogen response element (ERE) cloned into the mouse mammary tumor virus (MMTV) promoter (the full name for the reporter system being "MMTV-ERE-LUC"). Cells are exposed to the compounds of the invention in RPMI 1640 medium, supplemented with 10% charcoal-treated fetal calf serum, 2 mM L-glutamine, 0.1 mM non-essential amino acids and 1 mM sodium pyruvate for 42-48 hours at 37°C in a 5% carbon dioxide incubator. Concurrently, cells exposed to estradiol (1 nM) serve as positive controls. Replicate wells exposed to the solvent in which the compounds of the invention are dissolved (i.e. ethanol or methanol) are used as negative controls. After the 42-48 hr incubation period, cells are rinsed with phosphate buffered saline (PBS), lysis buffer (Promega Corp) is added, and cell lysates are collected for measurement of luciferase activity with a luminometer. Estrogenic activity of the compounds of the invention is expressed as fold-increase in luciferase activity as compared to that observed in negative control cells.

Alternatively, the determination of the estrogen receptor transactivation activity (estrogenicity assay or agonist assay) and of the inhibitory potency of transactivation activity (anti-estrogenicity assay or antagonist assay) may be performed according to international patent application PCT/US/17799 (published as WO 00/07996).

It will be appreciated that the methods of the present invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent for the expert skilled in the field that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

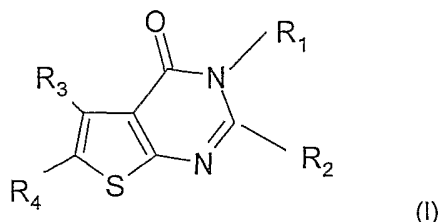
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- US 2003/0170292

CLAIMS

1. Use of a compound of formula (I)



5 wherein

R_1 and R_2 represent the same or different alkyl, or one is alkyl and the other is H, or
 R_1 and R_2 together with their binding sites form a cyclic 5-, 6-, 7- or 8-membered ring system,
 which is saturated or contains one or more double bonds between the ring atoms, and
 which ring optionally contains up to two heteroatoms in addition to the nitrogen atom where R_1
 10 is attached, the number of N atoms being 0-2 and the number of O or S atoms each being 0-1,

wherein said ring is optionally substituted with up to three substituents independently selected
 from the group consisting of alkyl, substituted alkyl, aryl, or arylalkyl, whereby the aryl
 group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, al-
 15 kylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and
 amido;

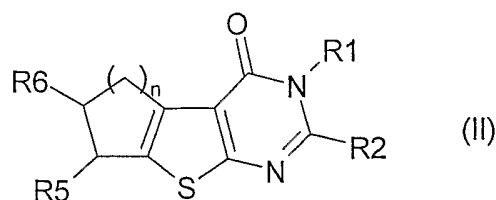
R_3 and R_4 together with their binding sites form a cyclic 5-, 6-, 7- or 8-membered hydrocarbon
 ringsystem, which is saturated or contains one or more double bonds between the carbon
 20 atoms, and

wherein said ring is optionally substituted with up to three substituents independently selected
 from the group consisting of alkyl, substituted alkyl, aryl or arylalkyl, whereby the aryl
 group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, al-
 kylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and
 25 amido;

provided that said compound is not 1,2,7,8,9,10,11,13-octahydro-13-oxo-4-(phenylthio)-
 [1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-3-carboxaldehyde;

30 for the manufacture of a medicament for the treatment and/or prevention of a steroid hormone
 dependent disease or disorder, preferably for a steroid hormone dependent disease or
 disorder requiring the inhibition of a 17β -hydroxysteroid dehydrogenase (17β -HSD) en-
 zyme, most preferably requiring the inhibition of the 17β -HSD type 1, 17β -HSD type 2 or
 17β -HSD type 3 enzyme.

2. Use of a compound according to claim 1, wherein the compound is of formula (II)



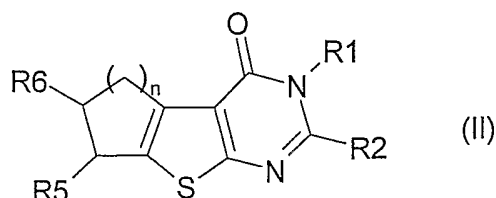
wherein

- 5 R_1 and R_2 represent the same or different C_1 - C_8 -alkyl, or one is C_1 - C_8 -alkyl and the other is H,
or
 R_1 and R_2 together with their binding sites form a cyclic 5-, 6-, 7- or 8-membered ring system,
which is saturated or contains one or more double bonds between the ring atoms, and
which ring optionally contains up to two N-atoms in addition to the nitrogen atom where R_1 is
10 attached,
wherein said ring is optionally substituted with up to two substituents independently selected from the group consisting of alkyl, substituted alkyl, aryl, or arylalkyl, whereby the aryl group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, alkylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and amido;
15 the hydrocarbon chain $-C(R_5)-C(R_6)-(CH)_n-$ of the ring-system adjacent to the thiophene-ring is saturated or contains one or more double bonds between the carbon atoms;

n is an integer from 1 to 4, and

20 R_5 and R_6 are individually selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl or arylalkyl, whereby the aryl group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, alkylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and amido.

3. A compound of formula (II)



30 wherein

R₁ and R₂ represent the same or different C₁-C₈-alkyl, or one is C₁-C₈-alkyl and the other is H,
or

R₁ and R₂ together with their binding sites form a cyclic 5-, 6-, 7- or 8-membered ring system,
which is saturated or contains one or more double bonds between the ring atoms, and

5 which ring optionally contains up to two N-atoms in addition to the nitrogen atom where R₁ is
attached,

wherein said ring is optionally substituted with up to two substituents independently selected
from the group consisting of alkyl, substituted alkyl, aryl, or arylalkyl, whereby the aryl
group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, al-
10 kylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and ami-
do;

the hydrocarbon chain -C(R5)-C(R6)-(CH)_n- of the ring-system adjacent to the thiophen-ring is
saturated or contains one or more double bonds between the carbon atoms;

15

n is an integer from 1 to 4, and

R5 and R6 are individually selected from the group consisting of hydrogen, alkyl, substituted
alkyl, aryl or arylalkyl, whereby the aryl group is optionally substituted, alkoxy, aryloxy,
20 acyloxy, arylthio, alkylthio, arylsulfonyl, alkylsulfonyl, hydroxyl, oxo, halogen, amino, oxi-
me, acyl, carboxyl, thiocarboxyl, and amido.

under the proviso that

25 in case n represents 1, 2 or 3, and R1 and R2 independently are selected from hydrogen
or C₁-C₄ alkyl or together form an unsubstituted alkylen group of 3 – 5 methylen groups or a
iminoalkylen group of 2 – 4 methylen groups in the alkylen group, optionally substituted at the
N-atom, then at least

(iii) R5 or R6 has to be different from hydrogen, C₁-C₄ alkyl or alkylcarboxyl, or

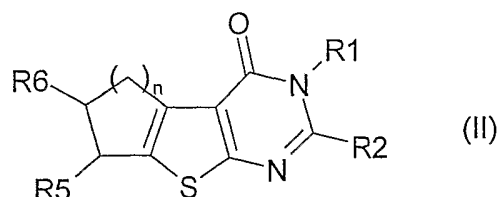
30 (iv) the hydrocarbon chain -C(R5)-C(R6)-(CH)_n- of the ring-system adjacent to
the thiophen-ring has to be unsaturated or aromatic;

in case n represents 2, R1-R2 form an unsubstituted alkylen group of 3 – 5 methylen
groups and R5 represents a hydroxyl or oxo group, then R6 has to be different from bromo,
dibromo or phenylthio; or

35 in case n represents 2, R1-R2 form an unsubstituted pentamethylen group, and R6
represents carbonyl, then R5 has to be different from phenylthio;

for use in therapy.

4. A novel compound of formula (II)



wherein

5 R_1 and R_2 represent the same or different C_1 - C_8 -alkyl, or one is C_1 - C_8 -alkyl and the other is H,
or

R_1 and R_2 together with their binding sites form a cyclic 5-, 6-, 7- or 8-membered ring system,
which is saturated or contains one or more double bonds between the ring atoms, and
which ring optionally contains up to two N-atoms in addition to the nitrogen atom where R_1 is
10 attached,

wherein said ring is optionally substituted with up to two substituents independently selected
from the group consisting of alkyl, substituted alkyl, aryl, or arylalkyl, whereby the aryl
group is optionally substituted, alkoxy, aryloxy, acyloxy, arylthio, alkylthio, arylsulfonyl, al-
kylsulfonyl, hydroxyl, oxo, halogen, amino, oxime, acyl, carboxyl, thiocarboxyl, and ami-
15 do;

the hydrocarbon chain $-C(R_5)-C(R_6)-(CH)_n-$ of the ring-system adjacent to the thiophen-ring is
saturated or contains one or more double bonds between the carbon atoms;

20 n is an integer from 1 to 4, and

R_5 and R_6 are individually selected from the group consisting of hydrogen, alkyl, substituted
alkyl, aryl or arylalkyl, whereby the aryl group is optionally substituted, alkoxy, aryloxy,
acyloxy, arylthio, alkylthio, arylsulfonyl, alkylsulfonyl, hydroxyl, oxo, halogen, amino, oxi-
25 me, acyl, carboxyl, thiocarboxyl, and amido.

under the proviso that

in case n represents 1, 2 or 3, and R_1 and R_2 are independently selected from hydrogen
or C_1 - C_4 alkyl or form together an unsubstituted alkylen group of 3 – 5 methylen groups or a
30 iminoalkylen group with 2 – 4 methylen groups in the alkylen group, optionally substituted at the
N-atom, then

(iii) at least R_5 or R_6 has to be different from hydrogen, C_1 - C_4 alkyl, alkylcar-
boxyl, or $=N-OH$, or

(iv) the hydrocarbon chain $-C(R_5)-C(R_6)-(CH)_n-$ of the ring-system adjacent to
the thiophen-ring has to be unsaturated or aromatic;

35

in case n represents 2, R₁-R₂ form an unsubstituted alkylen group of 3 or 5 methylen groups, and R₅ represents a hydroxyl or oxo group then R₆ has to be different from hydrogen, bromo, dibromo or phenylthio;

in case n represents 2, R₁-R₂ form an unsubstituted pentamethylen group, and R₆
5 represents carbonyl, then R₅ has to be different from phenylthio or chloro;

in case n represents 2, the hydrocarbon chain -C(R₅)-C(R₆)-(CH)_n- of the ring-system adjacent the thiophene-ring is saturated and R₁-R₂ together with their binding sites form an unsubstituted pyridine-ring, then at least one of R₅ or R₆ has to be different from hydrogen; or

in case -C(R₅)-C(R₆)-(CH)_n- represents an unsubstituted tetramethylen group, R₁-R₂
10 have to be different from a tetramethylen group substituted with a carboxylethylester group.

5. A novel compound of formula (II) according to claim 4, wherein

the cyclic 5-, 6-, 7- or 8-membered ring system formed together by R₁ and R₂ is optionally
15 substituted with up to two substituents independently selected from the group consisting of oxo, -CO-R, -CO-O-R, -O-R, -C₁-C₄-alkyl, optionally substituted with -O-R, -S-R or -N(R)₂;

R₅ and R₆ are individually selected from the group consisting of hydrogen, oxo, halogen, -O-R',
20 -S-R', -SO-R', -CO-R, -CO-O-R, or -C₁-C₄-alkyl, -C₁-C₄-alkenyl or =C₁-C₄-alkylen, optionally substituted in the alkyl chain with -O-R, -S-R, -N(R)₂, -CO-R, or =N-O-R,

wherein R represents hydrogen or C₁-C₄-alkyl; and

25 wherein R' represents hydrogen, C₁-C₈-alkyl, which can be linear, cyclic or branched; aryl-C₁-C₄-alkyl, preferably benzyl; or aryl, preferably phenyl.

6. A novel compound of formula (II) according to claim 4 or 5, wherein R₁ and R₂ together with their binding sites form an optionally substituted cyclic 5-, 6-, 7- or 8-membered ring system, which is saturated or contains one or more double bonds between the ring atoms, and which ring optionally contains up to two N-atoms in addition to the nitrogen atom where R₁ is attached.
30

7. A novel compound of formula (II) according to any of the preceding claims 4 to 6, wherein
35 R₅ is selected from the group consisting of hydrogen, oxo, halogen, -OH, -O-C₁-C₄-alkyl; -S-C₁-C₄-alkyl, -S-C₃-C₈-cycloalkyl, -S-phenyl, -SO-phenyl.

8. A novel compound of formula (II) according to any of the preceding claims 4 to 7, wherein R₆ is selected from the group consisting of hydrogen, carbonyl, alkylcarboxyl, preferably -

COOH, -C₁-C₄-alkyl, -C₁-C₄-alkenyl or =C₁-C₄-alkenyl, optionally substituted in the alkyl chain with -O-R, -N(R)₂, -CO-R, or =N-O-R, wherein R represents hydrogen or C₁-C₄-alkyl.

9. A novel compound of formula (II) according to claim 4 selected from:
- 5 2,3,8,9,10,11-Hexahydro[1]Benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-4,13(1*H*,7*H*)-dione;
1,2,6,7,8,9,10-heptahydrocyclopenta[4',5']thieno[2',3':4,5]pyrimido[1,2-a]-azepin-3,12-dione;
1,2,3,4,8,9,10,11,12-nonahydrocyclohepta[4',5']thieno[2',3':4,5]pyrimido-[1,2-a]azepine-
5(5*aH*),14-dione;
1,2,7,8,9,10,11,12-octahydro[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]azocin-4,14(3*H*)-dione;
 - 10 1,2,3,4,7,8,9,10-Octahydro-12*H*-[1]benzothieno[2,3-d]pyrido[1,2-a]pyrimidin-12-one;
5,6-Dihydro-2,3-dimethyl[1]benzothieno[2,3-d]pyrimidin-4,8(3*H*,7*H*)-dione;
5,6-Dihydro-3-methyl[1]benzothieno[2,3-d]pyrimidin-4,8(3*H*,7*H*)-dione;
5,6-Dihydro-3-ethyl-2-methyl[1]benzothieno[2,3-d]pyrimidin-4,8(3*H*,7*H*)-dione;
4-Chloro-1,2,3,7,8,9,10,11,12-octahydro[1]benzothieno[2',3':4,5]pyrimido-[1,2-a]-azocin-14-one-
 - 15 4-carboxyaldehyde;
1,2,3,4,5,8,9,10,11,12-Decahydro-14*H*-cyclohepta[4',5']thieno[2',3':4,5]-pyrimido[1,2-a]azepin-
14-one;
8-Chloro-5,6-dihydro-3-methyl[1]benzothieno[2,3-d]pyrimidin-4(3*H*)-one-7-carboxyaldehyde;
1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(ethylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-
 - 20 a]azepine-3-carboxyaldehyde;
1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(propylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-
a]azepine-3-carboxyaldehyde;
1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(butylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-
a]azepine-3-carboxyaldehyde;
 - 25 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(isopropylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-
a]azepine-3-carboxyaldehyde;
1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(*t*-butylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-
a]azepine-3-carboxyaldehyde;
1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(cyclopentylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-
 - 30 a]azepine-3-carboxyaldehyde;
1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(cyclohexylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-
a]azepine-3-carboxyaldehyde;
1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(phenylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-
a]azepine-3-hydroxymethyl;
 - 35 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(cyclohexylthio)[1]benzothieno-[2',3':4,5]pyrimido [1,2-
a]azepine-3-hydroxymethyl;
Octahydro-13-oxo-4-(phenylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-oxime-
methyl;

4-Chloro-1,2,7,8,9,10,11,13-octahydro-13-oxo[1]benzothieno[2',3':4,5]-pyrimido[1,2-a]azepine-3-hydroxymethyl;

3-N,N-Dimethylamino-methylen-2,3,8,9,10,11-hexahydro[1]benzothieno[2',3':4,5]pyrimido[1,2-a]azepine-4,13(1*H*,7*H*)-dione;

5 1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(propylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-(3-oxo)but-1-ene;

1,2,7,8,9,10,11,13-Octahydro-13-oxo-4-(butylthio)[1]benzothieno[2',3':4,5]-pyrimido-[1,2-a]azepine-3-(3-oxo)but-1-ene,

or a physiologically acceptable salt thereof.

10

10. A compound of formula (I) according to any of the preceding claims 4 to 9 for use in therapy.

11. Use of a compound of formula (I) as defined in any of the preceding claims 3 to 9 for the
15 treatment or prevention of a steroid hormone dependent disease or disorder.

12. Use according to claim 11, wherein the steroid hormone dependent disease or disorder is a disease or disorder requiring the inhibition of a 17 β -hydroxysteroid dehydrogenase enzyme, preferably of the 17 β -HSD type 1, 17 β -HSD type 2 or 17 β -HSD type 3.

20

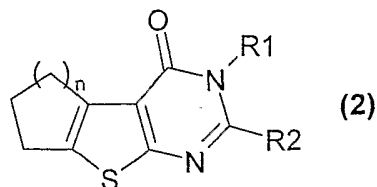
13. Use of a compound of formula (I) as defined in any of the preceding claims 2 to 9 for the manufacture of a medicament for the treatment and/or prevention of a steroid hormone dependent disease or disorder, preferably for a steroid hormone dependent disease or disorder requiring the inhibition of a 17 β -hydroxysteroid dehydrogenase enzyme, most preferably of the
25 17 β -HSD type 1, 17 β -HSD type 2 or 17 β -HSD type 3 enzyme.

14. Use according to claim 12 or 13, wherein the steroid hormone dependent disease or disorder is selected from the group consisting of breast cancer, prostate carcinoma, ovarian cancer, uterine cancer, endometrial cancer and endometrial hyperplasia, endometriosis, uterine
30 fibroids, uterine leiomyoma, adenomyosis, dysmenorrhea, menorrhagia, metrorrhagia, prosta-
dynia, benign prostatic hyperplasia, prostatitis, acne, seborrhea, hirsutism, androgenic alopecia, precocious puberty, adrenal hyperplasia, polycystic ovarian syndrome, urinary dysfunction, osteoporosis, multiple sclerosis, rheumatoid arthritis, Alzheimer's disease, colon cancer, tissue wounds, skin wrinkles and cataracts.

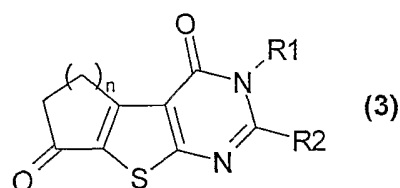
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15. A pharmaceutical composition comprising as active agent at least one of the compounds of formula (I) as defined in any of the preceding claims 2 to 9, and at least a pharmaceutically acceptable carrier.

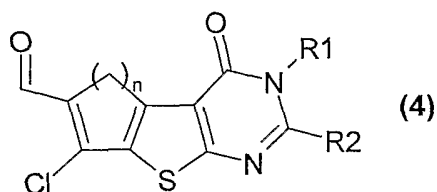
16. A method for the preparation of a compound of formula (I) as defined in claim 1 wherein
 g) a compound of formula 2



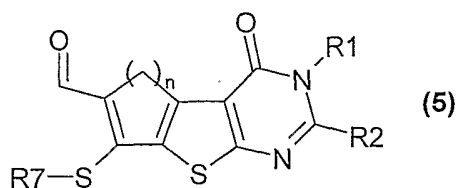
- 5 or a ring-substituted or ring-modified analogue thereof is oxidized, preferably by subject-
 ing to PCC and celite, to give an oxo-substituted compound of formula 3 or an analogue
 thereof,



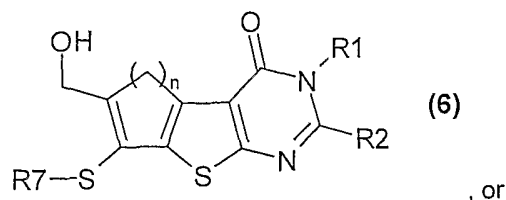
- h) the oxo-substituted compound obtained in step a) is optionally further subjected to Vils-
 meier reaction, preferably by POCl₃-DMF, to give a carbonylsubstituted compound of for-
 10 mula 4 or an analogue thereof,



- i) the chlorosubstituent in the carbonylsubstituted compound obtained in step b) is option-
 ally further replaced by an alkylthio or an arylthio group by subjecting to an appropriate
 thiol in the presence of a base to give an arylthio- or alkylthiosubstituted compound of
 15 formula 5 or an analogue thereof,

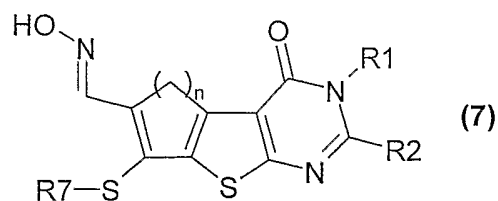


- j) the arylthio- or alkylthiosubstituted compound obtained in step c) is optionally further
 i) reduced to a compound of formula 6,



- 20 ii) reacted with NH₂OH to give a compound of formula 7,

66



or

k) the compound obtained in step b) is optionally further

- 5 i) reduced so as to replace the carbonyl group with hydroxyalkyl, or
 ii) subjected to an appropriate thiol in the presence of a base and acetone, so as to
 replace the chloro substituent by a thiol group and to replace the carbonyl group
 with an oxosubstituted alkenyl.

or

- 10 l) the compound obtained in step a) is optionally further subjected to DMF acetal so as to
 introduce a dimethylaminomethylene substituent in the ring next to the oxo substituent.

INTERNATIONAL SEARCH REPORT

National Application No

/EP2004/006231

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/55 C07D495/04 C07D495/14 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, INSPEC, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; FATHY, NAHED M. ET AL: "Synthesis of thienopyrimidotriazines, a new fused heterocyclic ring system" XP002299345 retrieved from STN Database accession no. 1997:778794 abstract & EGYPTIAN JOURNAL OF CHEMISTRY, 40(2), 117-128 CODEN: EGJCA3; ISSN: 0367-0422, 1997, ----- -/--	4



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
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Date of the actual completion of the international search

6 October 2004

Date of mailing of the international search report

20/10/2004

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INTERNATIONAL SEARCH REPORT

national Application No
 Γ/EP2004/006231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ARYA, V. P.: "Synthesis of new heterocycles. VI. Syntheses of certain novel condensed thiophenes" XP002299346 retrieved from STN Database accession no. 1973:124381 abstract & INDIAN JOURNAL OF CHEMISTRY , 10(12), 1141-50 CODEN: IJOCAP; ISSN: 0019-5103, 1972,	4
X	----- DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; EL-SHERBENY, M. A. ET AL: "Synthesis, antimicrobial and antiviral evaluation of certain thienopyrimidine derivatives" XP002299347 retrieved from STN Database accession no. 1995:656629 abstract & EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY , 30(5), 445-9 CODEN: EJMCA5; ISSN: 0223-5234, 1995,	3,4
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A	----- US 6 541 463 B1 (LUU-THE VAN ET AL) 1 April 2003 (2003-04-01) cited in the application abstract; claim 1	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

/EP2004/006231

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