USE OF SELECTIVE LIGANDS FOR TREATMENT OF DISEASE STATES RESPONSIVE TO STEROID OR STEROID-LIKE HORMONES

VERWENDUNG VON SELEKTIVEN LIGANDEN ZUR BEHANDLUNG VON HORMONANSPRECHENDEIN KANKHEIZZUSTÄNDEM

EMPLOI DE LIGANDS SELECTIFS DANS LE TRAITEMENT D’ETATS PATHOLOGIQUES SENSIBLES AUX HORMONES STEROIDES OU ANALOGUES

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FIELD OF THE INVENTION

[0001] The present invention relates to therapeutic uses of a compound which function as steroid hormone or steroid-like hormone. In a particular aspect, the present invention relates to the use of a compound which selectively or preferentially interacts with a single subtype of a given steroid hormone or steroid-like hormone receptor class.

BACKGROUND OF THE INVENTION

[0002] Many disease states are consistently associated with the occurrence of karyotypic change, e.g., a chromosomal translocation. For example, when the gene encoding PML (for "promyelocytes") undergoes a translocation with the retinoic acid receptor-α (RAR-α) (i.e., translocation between chromosomes 15 and 17 at the RAR-α and PML loci), the translocation is manifested as a form of leukemia, acute promyelocytic leukemia (APL).

[0003] It is possible, and even likely in many cases, that when translocation occurs, a gene product not normally subject to hormone expression control (e.g., PML) may be placed under the control of a hormone responsive sequence (e.g., RAR-α). Thus a gene such as PML may fall under the control of a hormone responsive sequence (such as RAR-α) as a result of a translocation event.

[0004] It has recently been discovered that APL can be effectively controlled by treatment with retinoic acid. Unfortunately, since several different receptors (and subtypes thereof) are known which respond to retinoic acid (e.g., RAR-α, RAR-β, RAR-γ, RXR-α, RXR-β, RXR-γ), administration of retinoic acid as a treatment for APL has the potential to cause many undesirable side-reactions for the patient.

[0005] There are numerous other disease states which have also been found to be responsive to treatment with hormones and/or hormone-like compounds. For example, Vitamin D-dependent Ricketts is responsive to treatment with Vitamin D, acne is responsive to treatment with retinoic acid, and the like. While available hormone or hormone-like compounds are effective for the treatment of such disease states, there is always the competing concern of undesirable side effects of such hormone treatments.

[0006] Accordingly, such disease states can potentially be much more effectively treated by using ligands which are selective for the specific receptor subtype which is involved in the disease state. Indeed, in view of the potential for the use of hormone therapy in the treatment of many disease states, it would be desirable to have the ability to selectively treat subjects with compounds which selectively interact as ligands with the specific receptor subtype involved in the disease state.


BRIEF DESCRIPTION OF THE INVENTION

[0014] In accordance with the present invention, we have discovered a compound

![Formula I](image)
which selectively interacts with a single receptor subtype, to a much greater extent than do other subtypes of the same receptor class.

[0015] This compound is useful for the selective treatment of hormone responsive disease states, thereby minimizing the occurrence of side effects caused by the activation of hormone responsive pathways not directly associated with the disease state being treated.

**BRIEF DESCRIPTION OF THE FIGURES**

[0016] Figure 1 is a dose response curve showing the response of RAR-α, RAR-β, RAR-γ, and RXR-α to increasing concentrations of retinoic acid.

[0017] Figure 2 is a dose response curve showing the response of RAR-α, RAR-β, RAR-γ, and RXR-α to increasing concentrations of the phenyl-naphthyl derivative referred to herein as Compound I.

**DETAILED DESCRIPTION OF THE INVENTION**

[0018] In accordance with the present invention, there are provided uses of an effective amount of the compound of formula I which, at a given concentration, selectively interacts with the receptor subfamily or subtype associated with a steroid or steroid-like hormone-responsive disease state to a significantly greater extent than with other subfamilies or subtypes of the same receptor class for the preparation of a medicament for the treatment of said steroid or steroid-like hormone-responsive disease state.

[0019] As employed herein, the phrase "steroid or steroid-like hormone-responsive disease state" refers to:

(i) any disease state wherein a gene product (or a portion of a gene product) not normally subject to steroid or steroid-like hormone expression control is placed, by translocation, under the control of a steroid or steroid-like hormone responsive sequence, or

(ii) any disease state wherein a first gene product (or a portion of a gene product) subject to steroid or steroid-like hormone expression control by a first steroid or steroid-like hormone is placed, by translocation, under the control of a second steroid or steroid-like hormone responsive sequence, or

(iii) any disease state which correlates with the expression of abnormal gene product, wherein said gene product (or a portion of said gene product) is normally subject to steroid or steroid-like hormone expression control, or

(iv) any disease state which correlates with an abnormal level of expression of gene product, the expression of which is normally maintained under steroid or steroid-like hormone expression control, or

(v) any disease state which correlates with an abnormal level of receptor, the presence of which is normally maintained under steroid or steroid-like hormone expression control, or

(vi) any disease state which correlates with an abnormal level of ligand, the presence of which is normally maintained under steroid or steroid-like hormone expression control.

[0020] As employed herein, the phrase "ligand which selectively interacts with the receptor subtype associated with said steroid or steroid-like hormone responsive disease state to a significantly greater extent than with other subtypes of the same receptor class" refers to compounds which are preferentially selective for one receptor subtype in modulating the transcription activation properties thereof. The terminology "significantly greater extent", as applied to interaction between ligand and a specific receptor subtype, refers to ligands which have a significantly higher therapeutic index (i.e., the ratio of efficacy to toxicity) for treatment of the target disease state than for activation of pathways mediated by other subtypes of the same receptor class. The toxicity of therapeutic compounds frequently arises from the non-selective interaction of the therapeutic compound with receptor subtypes other than the desired receptor subtype. Thus, the present invention provides a means to dramatically reduce the incidence of side-reactions commonly associated with hormone therapy. See, for example, the selectivity demonstrated in Figure 2.

[0021] It is useful to distinguish the terms receptor "subtype" and receptor "class". For example, retinoid responsive receptors comprise a "class" of receptors, all of which are responsive to retinoid compounds. Similarly, thyroid hormone receptors comprise a "class" of receptors which are responsive to thyroid hormone. Each class can be divided into various subtypes, i.e., specific members of the class which have different tissue distributions, different affinities for the native ligand, different activation properties when contacted with the native ligand, and so on.

[0022] Some classes of receptors include sub-families of distinctly different types of receptors. Thus, for example, while the retinoid class of receptors includes both the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs), these two different sub-families are clearly distinct. For example, each member of the RAR sub-family is responsive to a defined first hormone response element (HRE), and each member of the RXR sub-family is responsive to a defined second HRE (which is distinctly different from the first HRE). Accordingly, in accordance with the present invention, there are provided compounds which distinguish between the various sub-families of a receptor, and/or
A ligand contemplated for use in the practice of the present invention is the phenyl-naphthyl derivative having the structure:

![structure](image)

distinguished between the various subtypes thereof.

A ligand contemplated for use in the practice of the present invention is the phenyl-naphthyl derivative having the structure:

![structure](image)

referred to herein as Compound I, which selectively interacts with the retinoic acid receptor-β and retinoic acid receptor-γ (see, for example, FIG. 2).

The above-described ligand, in suitable form (employing suitable vehicle for delivery, such as, for example, gelatin capsule(s) or compressed tablet(s) where oral administration is contemplated; in an appropriate base where topical administration is contemplated; in a suitable infusion medium where injection or other means of delivery are contemplated; and the like), can be administered to a subject employing standard methods, such as, for example, orally, topically (e.g., transdermal mode of administration), by intraperitoneal, intramuscular, intravenous, or subcutaneous injection or implant, and the like. One of skill in the art can readily determine appropriate dosage(s), treatment regimens, etc., depending on the mode of administration employed.

For example, for oral administration, dosages in the range of about 1 up to 500 mg/kg body weight per day, depending on the disease state being treated, will be employed. Active compound can be administered in a sustained release form, or in divided doses throughout the day. For topical delivery, in the range of about 0.05 mg up to 10 mg/kg body weight per day, depending on the disease state being treated, will be employed. For injection modes of delivery, in the range of about 10 μg up to 2 mg/kg body weight per day, depending on the disease state being treated, will be employed. It should be emphasized, however, that dosage requirements are variable and are typically individualized on the basis of the disease under treatment and the response of the patient. After a favorable response is noted, the proper maintenance dosage can be determined by decreasing the initial drug dosage in small increments at appropriate time intervals until the lowest drug dosage which will maintain an adequate clinical response is reached. Those of skill in the art recognize that constant monitoring of the patient's condition is desirable in regards to drug dosage.

Ultimately, physicians will determine the particular dosage of the selective ligand which is most suitable. The selected dosage will vary depending upon the mode of administration employed, the particular compound administered, the patient under treatment, and the particular disease being treated.

The use of the invention can be applied to the selective treatment of skin disorders such as acne, psoriasis, photodamage, and the like.

It can be readily seen, therefore, that the invention is useful in the treatment of a wide variety of disease states.

The invention will now be described in greater detail by reference to the following non-limiting examples.

**EXAMPLES**

A series of dose response curves were generated to determine the response of retinoic acid receptor-α, retinoic acid receptor-β, retinoic acid receptor-γ and retinoid X receptor-α upon exposure to retinoic acid or Compound I (i.e., the phenyl-naphthyl derivative).

Response to the various compounds was measured employing the "cis/trans assay" as described by Evans et al., in USSN 108,471 (filed November 30, 1988, now issued as U.S. Patent No. 5,071,773, issued December 10, 1991).

All assays were carried out employing CV-1 host cells co-transformed with vectors encoding a receptor selected from RAR-α, RAR-β, RAR-γ, or RXR-α and a reporter vector.

The retinoic acid receptor-α was encoded by vector pRSrRAR-alpha (see US Patent No. 4,981,784, issued January 1, 1991), retinoic acid receptor-β was encoded by vector pRSrRAR-beta (see Brand et al. in Nature 332:850 (1988) and Benbrook et al. in Nature 333:669 (1988)), retinoic acid receptor-γ was encoded by vector pRSrRAR-gamma (see USSN 370,407, filed June 22, 1989, now issued as U.S. Patent No. 5,260,432, issued November 9, 1993) and retinoid X receptor-α was encoded by vector pRSrRXR-alpha (see USSN 478,071, filed February 9, 1990, continuation-in-part thereof issued as U.S. Patent No. 5,723,329, issued March 3, 1998).

The reporter vector used in all experiments was TREp-ΔMTV-LUC, as described by Umesono et al. in Nature
EXAMPLE I

RETINOIC ACID DOSE RESPONSE CURVE

[0035] Figure 1 presents the results of a dose response study carried out with retinoic acid as the ligand for each of
the receptors: RAR-α, RAR-β, RAR-γ, and RXR-α.

[0036] At very low concentrations of retinoic acid (i.e., concentrations below about 1x10^-9), each of the retinoid re-
ceptor subtypes is activated to approximately the same extent. Similarly, at concentrations above about 1x10^-6, each
of the retinoid receptor subtypes is activated to approximately the same extent. Although, in the concentration range
of about 1x10^-9 - 1x10^-6, there is a readily discerned rank order potency as follows:

\[ \text{RAR-γ} > \text{RAR-β} > \text{RAR-α} > \text{RXR-α}, \]

retinoic acid is seen to exert a substantial effect on each of the retinoid receptors tested. Administration of retinoic acid
as a therapeutic agent is, therefore, likely to induce many hormone mediated pathways, not just the pathway involved
in the disease state to be treated.

EXAMPLE II

DOSE RESPONSE CURVE FOR COMPOUND I

[0037] Figure 2 presents the results of a dose response study carried out with Compound I (phenyl-naphthyl deriv-
ative) as the ligand for each of the receptors: RAR-α, RAR-β, RAR-γ, and RXR-α.

[0038] At very low concentrations of Compound I (i.e., concentrations below about 1x10^-8), each of the retinoid re-
ceptor subtypes is activated to approximately the same extent. However, at concentrations above about 1x10^-8, there
is a readily discerned rank order potency as follows:

\[ \text{RAR-γ} = \text{RAR-β} >> \text{RAR-α} = \text{RXR-α}. \]

[0039] Thus, Compound I could be used for the treatment of a disease state which involves RAR-γ and/or RAR-β,
without perturbing pathways which are responsive to RAR-α or the retinoid X receptor.

Claims

1. The use of an effective amount of the compound of formula I:

   ![Compound I](image)

   which, at a given concentration, selectively interacts with the receptor subfamily or subtype associated with a
   steroid or steroid-like hormone-responsive skin disorder to a significantly greater extent than with other subfamilies
   or subtypes of the same receptor class for the preparation of a medicament for the treatment of said steroid or
   steroid-like hormone-responsive skin disorder.

2. The use according to claim 1 wherein said skin disorder is retinoid responsive.

3. The use according to claim 2 wherein the compound of formula I is selective for retinoic acid receptor-mediated
processes, relative to retinoid X mediated processes.

4. The use according to claim 2 wherein the compound of formula I is selective for retinoid X receptor-mediated processes, relative to retinoic acid mediated processes.

5. The use according to claim 1 wherein said steroid or steroid-like hormone-responsive skin disorder is the result of translocation of a portion of a gene encoding a member of the steroid/thyroid superfamily of receptors and a portion of a second gene; wherein the expression of said second gene is not ordinarily subject to regulation by the steroid or steroid-like hormone which binds to said member of the steroid/thyroid superfamily of receptors.

6. A pharmaceutical composition comprising the compound of formula I:

![Chemical Structure]

**Patentansprüche**

1. Verwendung einer wirksamen Menge der Verbindung der Formel (I):

![Chemical Structure]

die, in einer gegebenen Konzentration, selektiv mit der Rezeptorunterfamilie oder dem -subtyp, die bzw. der mit Hautfunktionsstörungen verbunden ist, die auf Steroid- oder steroidartige Hormone reagieren, in einem wesentlich stärkeren Ausmass als andere Subfamilien oder Subtypen derselben Rezeptorklasse wechselwirkt, für die Herstellung eines Medikaments zur Behandlung der Hautfunktionsstörungen, die auf Steroid- oder steroidartige Hormone reagieren.

2. Verwendung gemäss Anspruch 1, wobei die Hautfunktionsstörung auf Retinoide reagiert.

3. Verwendung gemäss Anspruch 2, wobei die Verbindung der Formel (I) selektiv für Retinsäurereszeptorvermittelte Prozesse relativ zu Retinoid X-vermittelten Prozessen ist.

4. Verwendung gemäss Anspruch 2, wobei die Verbindung der Formel (I) selektiv für Retinoid X-Rezeptorvermittelte Prozesse relativ zu Retinsäureremittelten Prozessen ist.

5. Verwendung gemäss Anspruch 1, wobei die Hautfunktionsstörung, die auf Steroid- oder steroidartige Hormone reagiert, das Ergebnis einer Translokation eines Teils eines Gens, das ein Mitglied der Steroid/Thyroid-Superfamilie von Rezeptoren codiert, und eines Teils eines zweiten Gens ist; wobei die Expression des zweiten Gens normalerweise nicht der Regulierung durch das Steroid oder steroidartige Hormon, das an das Mitglied der Steroid/Thyroid-Superfamilie von Rezeptoren bindet, unterliegt.

6. Pharmazeutische Zusammensetzung, umfassend die Verbindung der Formel (I):
Revendications

1. Utilisation, en une quantité efficace, du composé de formule (I):

qui, à une concentration donnée, interagit sélectivement avec des récepteurs d'une sous-famille ou d'un sous-type associé à une affection cutanée répondant à une hormone stéroïde ou similaire, à un degré significativement plus grand qu'avec des récepteurs appartenant à la même classe, mais à d'autres sous-familles ou sous-types, pour la préparation d'un médicament destiné au traitement de ladite affection cutanée répondant à une hormone stéroïde ou similaire.

2. Utilisation conforme à la revendication 1, dans laquelle ladite affection cutanée répond à un rétinoïde.

3. Utilisation conforme à la revendication 2, dans laquelle le composé de formule I est sélectif pour les processus à médiation par récepteur de l'acide rétinoïque, par rapport aux processus à médiation par rétinoïde X.

4. Utilisation conforme à la revendication 2, dans laquelle le composé de formule I est sélectif pour les processus à médiation par récepteur de rétinoïde X, par rapport aux processus à médiation par acide rétinolique.

5. Utilisation conforme à la revendication 1, dans laquelle ladite affection cutanée répondant à une hormone stéroïde ou similaire est le résultat de la translocation d'un fragment d'un gène codant un membre de la superfamille des récepteurs d'hormones stéroïdes/thyroïdiennes et d'un fragment d'un second gène, l'expression de ce second gène n'étant pas ordinairement assujettie à une régulation par l'hormone stéroïde ou similaire qui se lie audit membre de la superfamille des récepteurs d'hormones stéroïdes/thyroïdiennes.

6. Composition pharmaceutique qui contient du composé de formule I:
FIG. 1
FIG. 2