1. Derivatives of Z-bisdehydrodoisynolic acid provide a new description of the binding-activity paradox and selective estrogen receptor modulator activity

By Adler, Molly; Hou, Yuqing; Sandrock, Paul; Meyers, Cal Y.; Winters, Todd A.; Banz, William J.; Adler, Stuart
From Endocrinology (2006), 147(8), 3952-3960. Language: English, Database: CAPLUS, DOI:10.1210/en.2006-0316

Z-Bisdehydrodoisynolic acid [(±)-Z-BDDA], an estrogenic carboxylic acid, is highly active in vivo yet binds poorly to estrogen receptors (ERs). Studies of Z-BDDA and its enantiomers demonstrate therapeutic potential as selective ER modulators; however, the activity vs. binding paradox has remained. One possible explanation is that the carboxylic acid group of Z-BDDA may be modified in vivo to an ester or amide. Synthesis of these derivs. showed the relative binding affinity (RBA) of the Me ester for ERα and ERβ was increased approx. 14- and 20-fold, resp., relative to the parent compd. Yet, this increased affinity did not result in increased reporter gene expression. In contrast, the amide showed an unexpected approx. 4-fold decrease in RBA to both ERs compared with the parent. The relationship among the RBAs of ester, acid, and amide is consistent with their predicted polarity, suggesting the carboxylic acid, and not the carboxylate of BDDA, binds to ERs. Studies at pH 6.5, 7.4, and 8.0 were consistent with a simple acid-base equil. model, with BDDA binding as the undissociated acid and with affinity equal to or exceeding that of estradiol, consistent with high in vivo potency. Furthermore, the alc. BDD-OH also demonstrated high affinity and increased activity in gene expression assays. In addn. to suggesting a resoln. to the decades-old binding/activity paradox, these studies may provide a direction for definitive in vivo metabolic and pharmacokinetic studies and provide addnl. insight into the chem. and metabolic determinants of BBDA's unique tissue selectivity and selective ER modulator activities.

~4 Citings

2. Therapeutic applications of estrogenic carboxylic acids

By Adler, Stuart R.; Dandliker, Walter B.; Meyers, Cal Y.; Banz, William J.; Winters, Todd A.; Yuqing, Hou
From PCT Int. Appl. (1999), WO 9966915 A2 19991229, Language: English, Database: CAPLUS

Provided are methods of employing estrogenic compds. for repressing wt. gain or reducing wt. in male patients; treating or preventing prostate cancer and peri- or post-menopausal symptoms; treating estrogen-responsive conditions that no longer respond to treatment with conventional steroidal estrogens; treating or preventing estrogen-responsive uterine cancer, breast cancer, and ovarian follicle atresia; inducing ovulation to increase fertility; oral contraception; treating or preventing diseases or conditions caused or prolonged by free radicals; treating or preventing cardiovascular disease, hyperlipidemia or hypercholesterolemia, and hyperglycemia; improving body fat distribution; and treating or preventing Alzheimer's disease, osteoporosis, and pattern baldness. Also provided are methods for treating or preventing prostatic diseases including benign prostate hyperplasia and other related conditions, androgen-responsive pathol. conditions in males, and methods for male birth control and chem. castration, employing estrogenic carboxylic acids. The estrogenic carboxylic acids are selected from the group consisting of a doisynolic acid, an allenolic acid, a (hydroxy)phenylcyclohexenecarboxylic acid, a (hydroxy)phenylcyclohexanecarboxylic acid, and a (hydroxy)tetrahydroanthracenecarboxylic acid.

~6 Citings

3. Comparative effects of the selective estrogen receptor modulators (-)-, (+)-, and (±)-Z-bisdehydrodoisynolic acids on metabolic and reproductive parameters in male and female rats

By Banz, William J.; Winters, T. A.; Hou, Y.; Adler, S.; Meyers, C. Y.
From Hormone and Metabolic Research (1998), 30(12), 730-736. Language: English, Database: CAPLUS, DOI:10.1055/s-2007-978968

Doisynolic acids are non-steroidal estrogenic compds. originally obtained from alkali fusion of estrone and equilenin. Z-bisdehydrodoisynolic acids (Z-BDDA) exhibit a low binding affinity accompanied by a disproportionately high biol. activity. Two expts. were designed to investigate the chronic effects of (+)-, (-)-, and (±)-Z-BDDA and (+)-17β-estradiol (E2) in male and female rats. The (+)-, (-)-, and (±)-forms Z-BDDA were prepd. and injected, daily for 4-6 wk into male and female rats and changes in body wt., food intake, metabolic parameters, and reproductive parameters were investigated. Results from both expts. demonstrate that in male and female rats, (+)- and (±)-Z-BDDA had similar estrogenic effects on reproductive organ wt. Surprisingly, (-)-Z-BDDA did not induce the increase in uterine wt. obsd. with (+)- and (±)-Z-BDDA and E2, demonstrating selective estrogen receptor modulation (SERM). Beneficial metabolic effects, although compd.- and gender-specific, included a wt. repression, redn. in cholesterol, redn. in blood glucose, and pos. alterations in body fat distribution. Future research defining the optimal dosages of (-)-Z-BDDA that will maximize beneficial effects and minimize undesirable effects on reproductive tissues will lead to more efficacious treatment options for endocrine-responsive conditions in males and females.

~12 Citings

4. Transcriptional regulation of estrogen-responsive genes by non-steroidal estrogens: doisynolic and allenolic acids

By Meyers, Cal Y.; Lutfi, Hisham G.; Adler, Stuart
From Journal of Steroid Biochemistry and Molecular Biology (1997), 62(5/6), 477-489. Language: English, Database: CAPLUS, DOI:10.1016/S0960-0760(97)00063-0

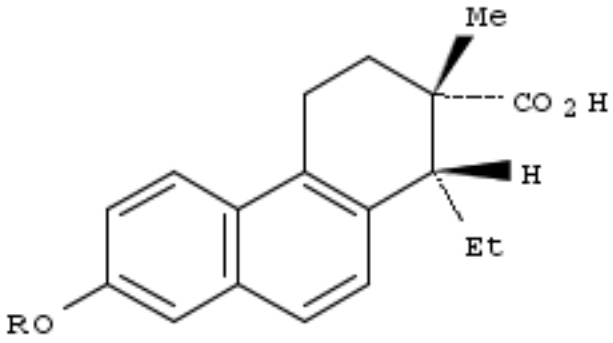
Estrogen receptor (ER), a member of the nuclear receptor superfamily, exerts prominent physiol. roles in both humans and other species by acting directly as a transcription factor, altering nuclear gene expression. One peculiarity of estrogenic regulation is that it is affected by a wide variety of non-steroidal compds. in addn. to the natural hormone, estradiol. Doisynolic and allenolic acid compds. are non-steroidal compds. that act as potent estrogens in animal studies, yet bind to ER extremely poorly in competitive binding assays, raising the possibility of alternative mol. mechanisms for the obsd. estrogenic effects. In this work we demonstrate that (±)-Z-bisdehydrodoisynolic acid, (±)-Z-bisdehydrodoisynolic acid 3-Me ether, and (-) allenolic acid can interact directly with ER. These compds. all serve as ligands for ER in mechanism-specific tissue culture-based reporter gene assays for both pos. and neg. gene regulation. We have also used a novel assay based on electromobility shift by ER for directly detg. relative binding affinities for ER. In addn., we show cell-type-specific activity differences for (±)-Z-bisdehydrodoisynolic acid 3-Me ether, supporting clin. observations indicating a higher potency of this compd. in female animals than in humans.

~14 Citings

5. Doisynolic acid type compounds as weight and appetite suppressing and control agents

By Meyers, Cal Y.
From U.S. (1995), US 5420161 A 19950530, Language: English, Database: CAPLUS

Compds. such as I (R = H or Me) are used in wt. and appetite suppression in an animal, including humans.



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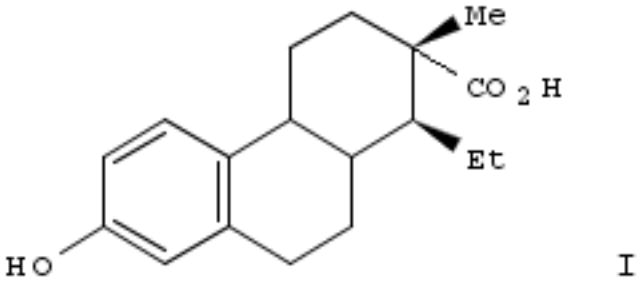
~7 Citings

6. Doisynolic-type acids - uterotropically potent estrogens which compete poorly with estradiol for cytosolic estradiol receptors

By Meyers, Cal Y.; Kolb, Vera M.; Gass, George H.; Rao, B. Ramanath; Roos, Conrad F.; Dandliker, Walter B.
From Journal of Steroid Biochemistry (1988), 31(4A), 393-404. Language: English, Database: CAPLUS, DOI:10.1016/0022-4731(88)90307-X

Derivs. of diosynolic acid (I), a class of seco-steroid acids some of which exhibit greater uterotropic estrogenicity than 17β-estradiol, are D-ring cleavage products of steroidal estrogens formed by fusion with KOH at >200°. Electron-transfer reactions between estrone or estradiol and CCl_4 or $CBrCl_3$ in KOH-tert-BuOH at 25° rapidly provide 16,16-dichloro- or -dibromodoisynolic acid, resp., the former approaching estradiol in uterotropic potency. Simple esters from these highly hindered tertiary carboxylic acids, easily prepd. via phase-transfer-catalyzed alkylations, also rival estradiol in uterotropic activity. Unlike natural steroidal estrogens or their commonly used artificial equivs. (DES, hexoestrol, ethynylestradiol, etc.) whose uterotropic activity is accompanied by substantial binding affinity for cytosolic estradiol receptors, these highly uterotropic doisynolic-type acids and esters exhibit binding affinities for this receptor of only ~1% that of 17β-estradiol as detd. by the usual competitive binding-inhibition studies with [^{3}H]estradiol. Other highly uterotropic carboxylic acids may exhibit similar characteristics. These unusual results leave open the possibilities that uterotropic seco-steroid and related carboxylic acids undergo some unknown metabolic activation, are exceptionally persistent estrogens, bind to a cytosolic receptor site other than the conventional (type I) estradiol site, or bind directly to type I or type II nuclear receptor sites. At dosages of 1000-fold those required for a uterotropic effect, the doisynolic-type acids (24 doses over an 8-wk period) were neither toxic nor carcinogenic.



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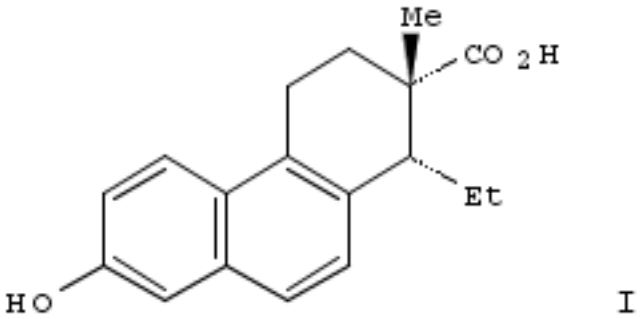
~19 Citings

7. Doisynolic acids: potent estrogens with very low affinity for estrogen receptors

By Meyers, Cal Y.; Kolb, Vera M.; Dandliker, Walter B.
From Research Communications in Chemical Pathology and Pharmacology (1982), 35(1), 165-8. Language: English, Database: CAPLUS

Doisynolic acids are alk. degrdn. products of steroidal estrogens. While these doisynolic acids are potent estrogens, some being more estrogenic than estradiol [50-28-2] itself, they bind to cytoplasmic estrogen receptors only feebly compared with estradiol. The binding activity of (±)-Z-bisdehydrodoisynolic acid (I) [15372-38-0], its Me ester [81269-73-0] and Et ester [36417-61-5], (+)-E-16,16-dichlorodoisynolic acid [81340-89-8], and (+)-E-16,16-dibromodoisynolic acid [81279-56-3] was investigated.



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~7 Citings

8. 1,2,3,4,9,12-Hexahydrophenanthrenes

By Dyson, Norman H.
From U.S. (1974), US 3846484 A 19741105, Language: English, Database: CAPLUS

1,2,3,4,9,12-Hexahydrophenanthrenes, useful as estrogenic and antifertility agents (no data), were prepd. by Li-liq. NH3 redn. of 1,2,3,4-tetrahydrophenanthrenes. Thus, 1α-ethyl-2α-carboxy-2β-methyl-7-hydroxy-1,2,3,4-tetrahydrophenanthrene was reduced with Li-liq. NH3 in THF at -78° for 11 hr to give the phenanthrene (I, R = OH, R1 = Me, R2 = CO2H, R3 = α-Et, R4 = H). About 8 more I (R = OH, acetoxy, cyclopentyloxy, OMe; R1 = Me, Et; R2 = CO2H, CH2OH, CHO; R3 = α-, β-Et; R4 = H, Me) were also prepd.

~0 Citings