

CHARLES UNIVERSITY IN PRAGUE
FACULTY OF PHARMACY IN HRADEC KRÁLOVÉ

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY
AND PHARMACEUTICAL ANALYSIS



**Current trends in the development of steroidal
hormone modulators**

Diploma Thesis

Hradec Králové 2015

Emmanouil Lioudakis

I declare that this thesis is my original copyrighted work. All literature and other resources I used while processing are listed in the bibliography and properly cited. The thesis was not misused for obtaining the same or different academic degree.

In Hradec Králové 22nd May 2015

Emmanouil Lioudakis

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ABSTRACT

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Title of Diploma Thesis: **Current trends in the development of steroidal hormone modulators**

Steroidal hormone modulators are considered to be both effective and vital agents concerning the treatment of various types of cancer, as well as playing a crucial role in the regulation of a wide range of physiological actions. Since the development of the very first modulators, a significant progress has been made regarding the development of new ones with limited adverse effects.

The current thesis provides information concerning older drugs and recent data about them. In addition, new drugs which are under clinical trials are described and their structures are referred.

New drugs have been developed in order to be safer and more efficient than older ones. A lot of promising agents which are considered as a successful alternative treatment and carry less risk are either already approved or will be accepted in the near future.

ABSTRAKT

Univerzita Karlova v Praze, Farmaceutická fakulta v Hradci Králové

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Název diplomové práce: **Současné trendy ve vývoji modulátorů steroidních hormonů**

Modulátory steroidních hormonů jsou považovány za účinné a život zachraňující léčiva pro léčbu různých typů rakoviny a hrají také zásadní úlohu v regulaci různých fyziologických funkcí. Od doby, kdy byly vyvinuty první modulátory, bylo dosaženo významného pokroku ve vývoji nových modulátorů s nižšími vedlejšími účinky

Tato diplomová práce přináší nové informace o starších léčivech a nově vyvíjených sloučeninách. Obsahuje také struktury popisovaných léčiv.

Nové sloučeniny jsou vyvíjeny za účelem získání bezpečnějších a účinnějších léčiv. Některé látky byly již schváleny jako alternativní a méně riziková léčba a lze očekávat, že další budou schváleny v blízké budoucnosti.

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Abbreviations

ACEIs	Angiotensin Converting Enzyme Inhibitors
ACTH	Adrenocorticotrophic Hormone
AIs	Aromatase Inhibitors
Akt	Serine/threonine kinase Akt (also known as protein kinase B, PKB)
ANP	Atrial Natriuretic Peptides
AR	Androgenic receptors
ARBs	Angiotensin Receptor Blockers
BMD	Bone Mineral Density
CAB	Calcium Channel Blockers
CaMKII	Ca ²⁺ /calmodulin-dependent protein kinase II
CRF	Corticotropin releasing factor
c-Src	Cytosolic Tyrosine Kinase c-Src
CVS	CardioVascular System
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DHT	Dihydrotestosterone
DRIs	Direct Renin Inhibitors
EGFR	Epidermal Growth Factor Receptor
ER	Estrogenic receptor
ERK	Extracellular-Signal-Regulated Kinase
GPR30	G-protein coupled receptor 30 (also known as G-protein-coupled estrogen receptor, GPER)
GR	Glucocorticoid Receptors
GREs	Glucocorticoid Response Elements
HRE	Hormone Response Elements
IGFR-1	Insulin-like Growth Factor 1 Receptor
LBM	Lean Body Mass
LH	Luteinizing Hormone
MPA	Medroxyprogesterone Acetate
MR	Mineralocorticoid Receptor
NCoR	Nuclear Receptor Corepressor
NFAT	Nuclear Factor of Activated T-cells

P300/GATA4	p300/GATA4 transcriptional factor complex
PAI-1	Plasminogen Activator Inhibitor-1
PI3K	Phosphatidyl-Inositol 3-Kinase
PKA	P21 Activated Kinase
PR	Progestogenic Receptors
RAAS	Renin Angiotensin Aldosterone System
REA	Repressor of Estrogen Action
ROS	Reactive Oxygen Species
SARMs	Selective Androgen Receptor Modulators
SEGRAs	Selective Glucocorticoid Receptor Agonists
SERDs	Selective Estrogen Receptor Downregulators
SERMs	Selective Estrogen Receptor Modulators
SMRT	Silencing Mediator of Retinoic acid and Thyroid hormone receptor
SNS	Sympathetic Nervous System
SPRMs	Selective Progesterone Receptor Modulators
SRC	Steroid Receptor Co-activators
TSEC	Tissue Selective Estrogen Complex

1. INTRODUCTION AND THE AIM OF THE STUDY

Steroid hormones include estrogens, androgens, progestogens, mineralocorticoids and glucocorticoids.

It is widely known that steroid hormones are secreted by a) adrenal cortex, b) testes, c) ovaries and d) placenta during pregnancy.

Adrenal glands produce over 50 different steroids, including precursors for other steroid hormones. The most important hormones produced by the adrenal cortex are mineralocorticoids and glucocorticoids. Mineralocorticoids, represented by aldosterone, maintain the balance between water and salts in the body and mainly exert their effects within the kidney. The primary glucocorticoid in humans is hydrocortisone (cortisol). The glucocorticoids play a key role in controlling carbohydrate, protein, and lipid metabolism. They also affect the cardiovascular and nervous system. They regulate growth hormone gene expression. Their anti-inflammatory and immunosuppressive effects result from complex mechanisms, and are important in treating rheumatoid arthritis and other immune diseases and preventing rejection of transplanted organs. Glucocorticoids stimulate formation of glucose from amino acids and fatty acids, and deposition of glycogen in the liver. They have a catabolic effect on muscle tissue. Lipid metabolism and synthesis increase significantly due to the action of glucocorticoids and other hormones or cofactors. [1]

Estrogens, progesterone and testosterone are biosynthesized in both males and females. Testosterone is one of the precursors of the estrogens. These hormones are important for reproduction, in controlling menstrual cycle, and they also give women and men their characteristic features. Estrogens and progesterone are produced in larger amounts in females. They have been used as hormonal contraceptives and in hormone replacement therapy (HRT), but they have also other therapeutic uses. Testosterone has two primary types of activities – androgenic and anabolic. The androgenic agents are mainly used in males. In women they can be used in certain sex organ cancers. [1]

In recent years, there has been significant progress in knowledge about mechanism of action of steroid hormones on the molecular level [2–8]. The new facts have been used for more effective and safe applications of these drugs in clinical practice as well as for design and development of new drugs [9–16]. The aim of the present thesis is to review current trends in the development of modulators of steroidal receptors from the medicinal chemistry point of view, with emphasis on structures of new drugs.

2. ESTROGENS

Estrogens are one type of female sex hormones. As mentioned before they are secreted predominantly by ovaries and in smaller amounts by adrenal glands. Estradiol is considered to be the most potent between the estrogens. Two metabolites of estradiol are much weaker agonists on estrogen receptors (ERs). Generally estrogens are vital for the development and maintenance of normal sexual and reproductive function. Furthermore, in both men and women, they have various biological effects in cardiovascular, central nervous, musculoskeletal as well as in immune system. [17]

2.1 Estrogenic receptors

Estrogen signaling is a balance between activation and inhibition of two receptors ($ER\alpha$ and $ER\beta$). Both ER belong to the nuclear receptor (NR) family of transcription factors and regulate tissue specific gene expression. ERs have distinct tissue distribution and can have different effects on the target genes. $ER\alpha$ occurs predominantly in the uterus, vagina, ovaries, breast, hypothalamus, endothelial cells, and vascular smooth muscle. $ER\beta$ is abundant in the ovaries and the prostate, but can be found also in the lungs, brain, and vasculature. [1]. These receptors can be selectively stimulated by subtype selective drugs and that constitutes promising therapeutic opportunities in hormone replacement, autoimmune diseases, breast and prostate cancer and depression. Of course ERs do not function by themselves but they need some regulatory proteins. [17] These protein are known as co-regulators. They interact with liganded or un-liganded ERs and modulate the transcriptions of the genes. Co-activators known also as steroid receptor co-activators (SRCs) promote the activation of transcription process play an important role in the pharmacological profile of selective estrogen receptor modulators (SERMs). SRC1 is abundant in uterine cells and are responsible for the agonistic activity of tamoxifen in the uterus. In breast cancer cells, with low SRC1 levels, tamoxifen acts as an estrogen antagonist. [18] Co-repressors repress the expression of genes. They interact with un-liganded and/or antagonist bound receptor. The two most extensively studied co-repressors are nuclear receptor corepressor (NCoR) and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT). [18] Another corepressor, known as repressor of estrogen action (REA) potentiates the inhibitory effects of anti-estrogens including 4-hydroxytamoxifen (a metabolite of tamoxifen). [18]

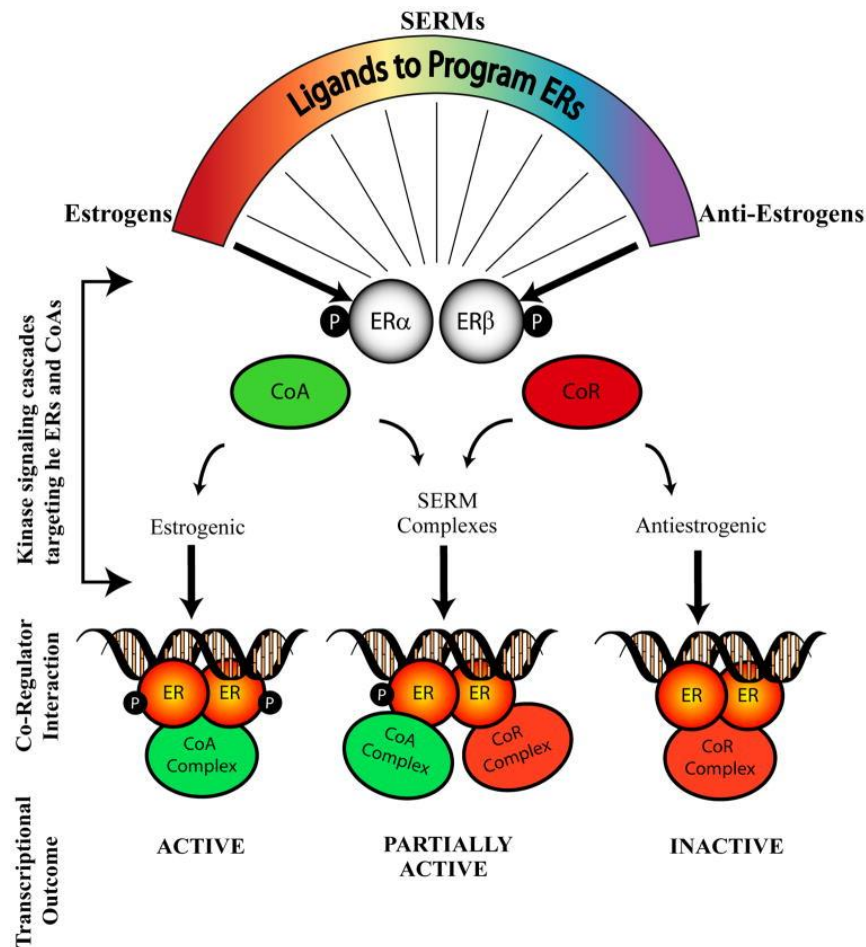


Fig. 1 Schematic representation of different liganded-ER complexes interacting with co-regulators and consequent transcriptional activities. ERs that bind to estrogenic ligands interact with co-activators (CoA) and activate transcription. Anti-estrogen liganded-ER complexes interact with co-repressors (CoR) and inactivate transcription of responsive genes. Selective estrogen receptor modulators (SERMs) bind to ERs and interact with either co-activator or co-repressor complexes eliciting partial transcriptional activity depending upon the cellular context. (Adopted from the ref. [18])

2.2 Selective estrogen receptor modulators (SERMs)

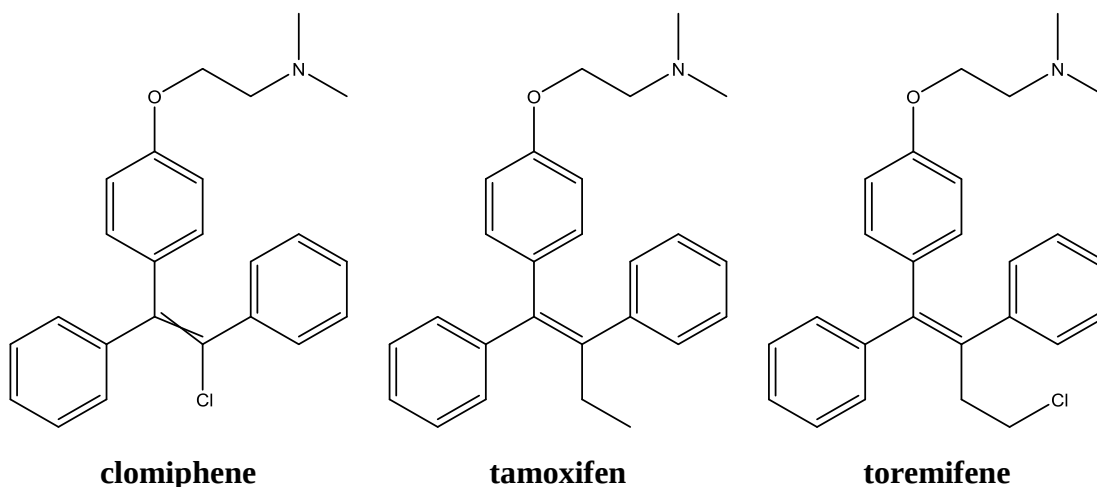
SERMs bind to ERs and have either agonist or antagonist responses which depends on the target tissue. They are used for conditions which are related to aging including

- hormone responsive cancer
- cardiovascular disease
- osteoporosis [12].

2.2.1 Clinically used SERMs

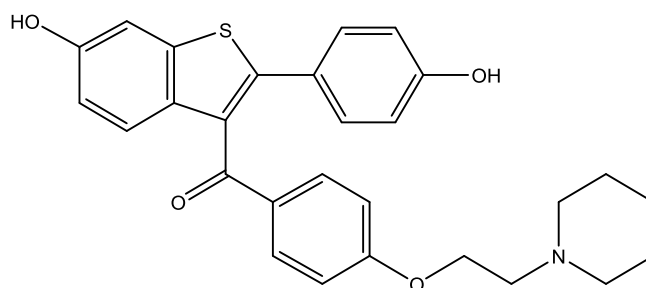
There are several structural types of SERMs. The first generation – triphenylethenes – include clomiphene, tamoxifen and toremifene. **Clomiphene** has been used for more than 50 years for the induction of ovulation. It is a mixture of *zuclomiphene* with estrogenic activity and its isomer *enclomiphene* with antiestrogenic activity. **Tamoxifen** is predominantly used for targeted therapy of ER positive breast cancers and is approved as the 1st chemopreventive agent for lowering breast cancer incidence in high risk women. However use of tamoxifen is associated with some undesirable side effects such as thromboembolic disorders and uterine cancer. The latter side effect is due to agonistic effect of tamoxifen in the uterus due to the abundance of SRC1. [12, 18].

Another clinically used drug is **toremifene**. It is a chlorinated tamoxifen analogue which has been approved in the US and several other countries for the treatment of metastatic breast cancer. Toremifene is as effective as tamoxifen in the treatment of ER-positive breast cancer but with the potential of fewer genotoxic effects, since it does not produce DNA adducts in rat liver and human endometrium. [18]



The second generation of SERMS is represented by **raloxifene** that is a derivative of benzothiophene indicated for the treatment and prevention of osteoporosis and the reduction of breast cancer incidence in high risk postmenopausal women. [12] Typical feature of raloxifene is a carbonyl group in the linking chain that is responsible for the different actions on the ERs. [1]. On contrary to tamoxifen, raloxifene does not recruit SRC1 in the uterine cells and lacks estrogenic activity in the uterus. [12, 18]. Another important difference is the length of action. Whilst tamoxifen is a long acting drug that is

metabolically converted to active metabolites, raloxifene is a very short acting drug that is rapidly conjugated and then excreted through the biliary tract. [12]



raloxifene

2.2.2 New SERMs

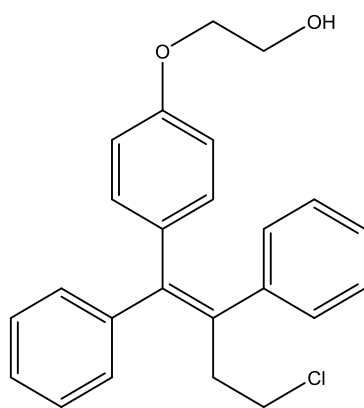
These compounds are also known as the third generation SERMs. [19, 20] They have been primarily developed for the therapy of osteoporosis [21, 22], but they have been studied for other indications as well. [19, 20, 23, 24]. Some of them form a constituent of tissue selective estrogen complex (TSEC) in which a SERM is combined with one or more estrogens. Such combinations are used to relieve various problems, such as vasomotor symptoms or vulvar-vaginal atrophy, in postmenopausal women. [23, 24] Structurally, these drugs are similar to tamoxifen, raloxifene or they have different structures.

2.2.2.1 Tamoxifen-like SERMs

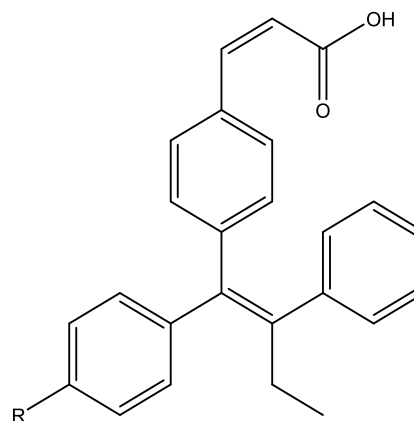
Ospemifene is a metabolite of toremifene. It is generally well tolerated and has a favorable safety profile. It does not induce DNA adducts in mice, rats and monkey. Ospemifene exerts a very weak estrogenic effect on endometrial histology, like raloxifene and decreases cholesterol. However, unlike tamoxifen or raloxifene, ospemifene has significant estrogenic effects on vaginal epithelium and is being developed for postmenopausal vaginal atrophy. Early results suggested that a 12 week course of ospemifene treatment significantly relieves symptoms of dryness in the vagina. [12,18] In 2013, FDA approved ospemifene for postmenopausal women experiencing pain during sex [25], and a year later it was approved in Europe for the treatment of moderate to severe symptomatic vulvar and vaginal atrophy in postmenopausal women. [26]

GW5638 is a full ER agonist in bones and the CVS and an antagonist in endometrial and breast system in rodent models. **GW7604** is the 4-hydroxy derivative of GW5638,

analogous to the major metabolite of tamoxifen, 4-hydroxytamoxifen. Although their structures are similar to that of tamoxifen they act in a different mechanism. Both compound can also be classified as selective estrogen receptor down-regulator (SERDs) because they induce ER α degradation. [18]



ospemifene



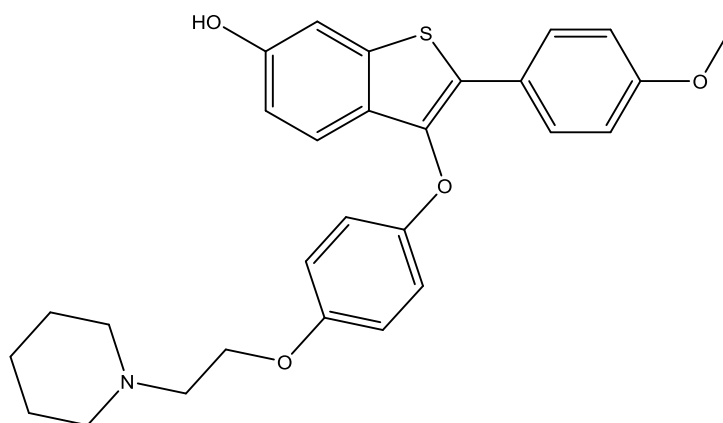
R = H: **GW5638**

R = OH: **GW7604**

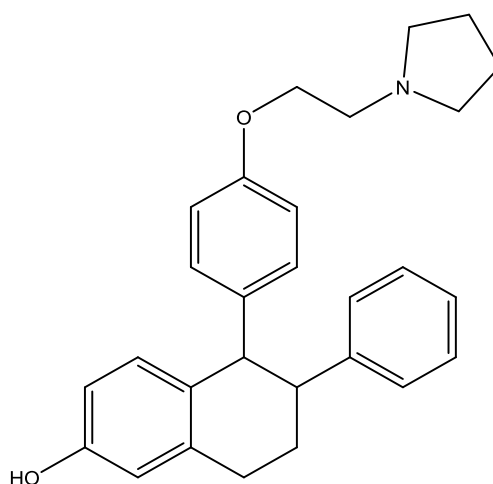
2.2.2.2 *Raloxifen-like SERMs*

Arzoxifene is a derivative of raloxifene. Instead of the ketone group there is an ether group and the hydroxy group is replaced by a methoxy group. These modifications have improved the pharmacokinetic properties. Arzoxifene has antiestrogenic effects on breast and endometrium but pro-estrogenic effects on bone and adipose tissue. [18] Arzoxifene was evaluated in phase 3 trials for postmenopausal osteoporosis and for the treatment of uterine malignancies, but its clinical development was discontinued. [13, 24]

Lasofoxifene has a naphthalene core structure which is different comparable to other SERMs that were discussed. Lasofoxifene has a strong binding to ER, similar with estradiol and higher than tamoxifen and raloxifene. It preserves bone density, lowers serum cholesterol and doesn't induce uterine hypertrophic effects. In addition to its effects on bone, lasofoxifene significantly improves symptoms of inflammation of vaginal walls. [12, 18, 24] Lasofoxifene was approved for use in the European Union but was never been launched or marketed despite the fact that clinical trials demonstrated a reduction in breast cancer, osteoporosis fracture, strokes, endometrial cancer and coronary heart disease. [27].

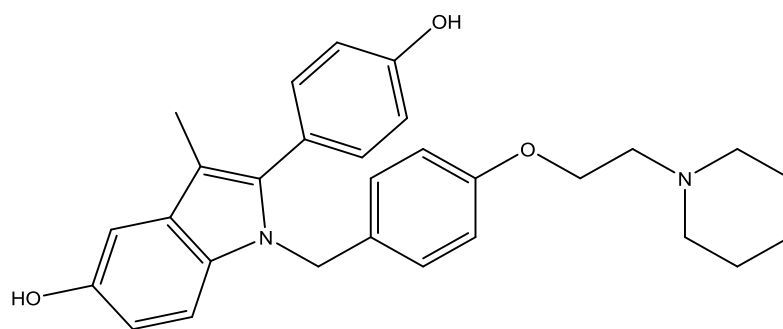


arzoxifene



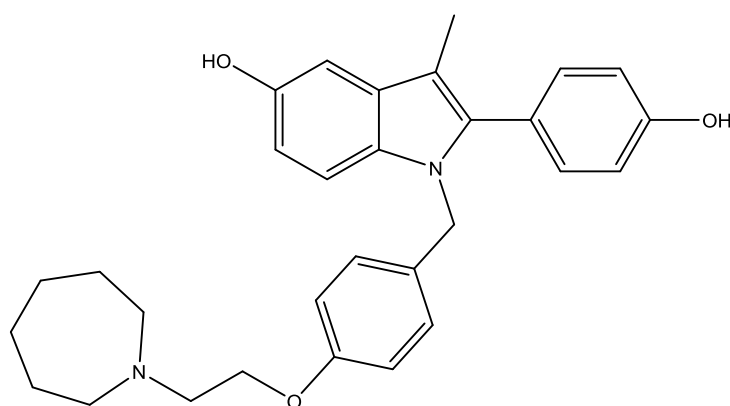
lasofoxifene

Pipendoxifene has indole core structure. It mimics the structure of raloxifene and is devoid of uterotrophic activities in immature rats and ovariectomized mice compared to raloxifene. It inhibits the growth of tamoxifen-sensitive and -resistant tumors in rats and mice and is under phase II clinical development for the treatment of tamoxifen-resistant metastatic breast cancer. [18]. In a recent study, a combination of pipendoxifene and temsirolimus, which is a mammalian target of rapamycin (mTOR) inhibitor, synergistically inhibited growth of MCF-7 cells and xenograft models even at suboptimal doses, primarily by causing G1 cell cycle arrest. This suggested that combination of a SERM and an mTOR inhibitor might be of clinic value as breast cancer treatments. [28]



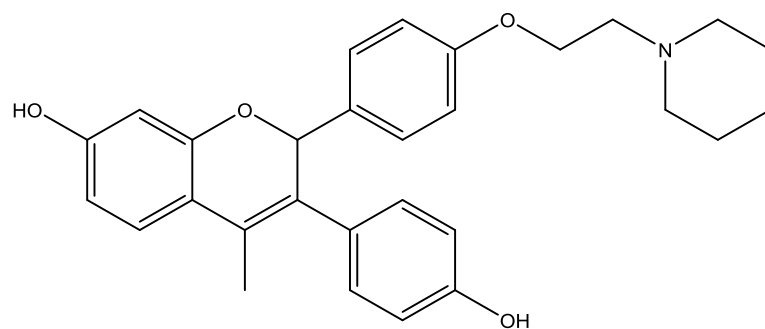
pipendoxifene

Bazedoxifene is indicated in treatment of postmenopausal osteoporosis with the potential to prevent breast cancer. [12, 18, 21, 22]. Bazedoxifene binds to $ER\alpha$ and $ER\beta$ with an affinity lower than raloxifene but is less selective for $ER\alpha$ [23]. In 2013, FDA approved a combination of bazedoxifene with estrogen for treatment of hot flashes associated with menopause and for the prevention of postmenopausal osteoporosis. Bazedoxifene reduces the risk of excessive growth of the uterus that can be caused by estrogen. [29]



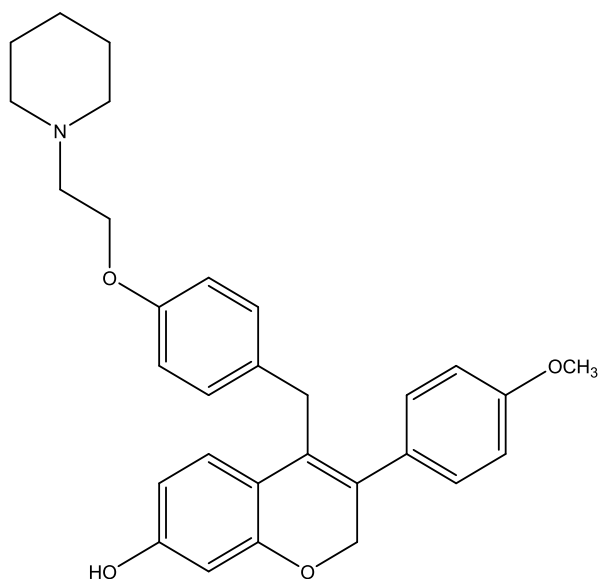
bazedoxifene

Acolbifene acts as antiestrogen in mammary and uterine tissues, but has estrogenic effects therefore it has a positive effect on bone and regulates lipid metabolism by lowering plasma cholesterol and triglyceride in rodent models. It is a promise agent against breast cancer as well as prevents thickness of endometrium. [18, 22]



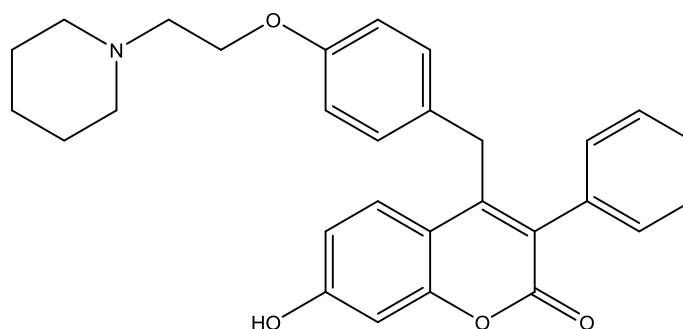
acolbifene

CHF4227 belongs to tissue selective benzopyran estrogens [30]. It binds both to ER α and ER β . It maintains bone mass and decreases serum cholesterol and fat mass. No negative effects in endometrium or fibrinolytic system have been observed. It does cause neither vaginal bleeding nor hot flashes. Therefore it can be studied further for treatment of osteoporosis and breast cancer. [18]



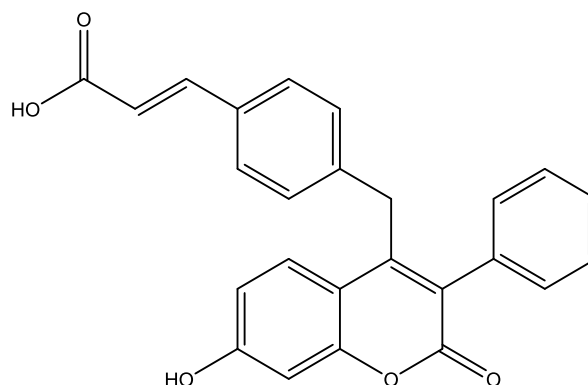
CHF-4227

SP500263 is an ER agonist in bone binding to both ER α and ER β . It inhibits growth of breast cancer, doesn't increase uterine weight and decreases osteoclasts in human bone cell. As a result it can be a possible treatment for osteoporosis and breast cancer but unfortunately its clinical value has not been determined yet. [18]



SP500263

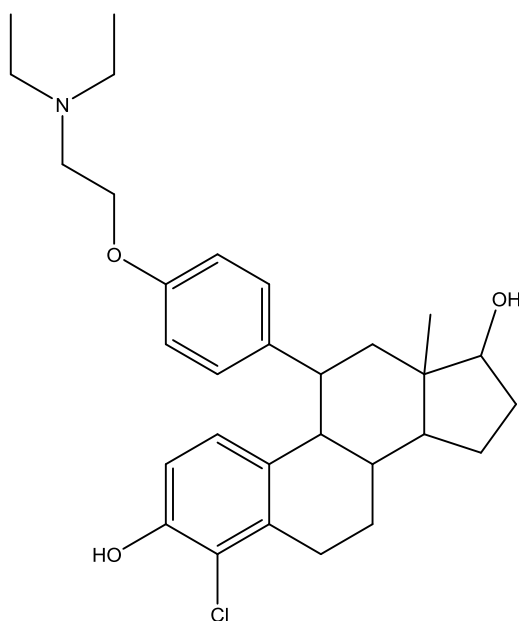
An analogue of SP500263 in which 2-(piperidin-1-yl)ethoxy moiety has been replaced with carboxypropenyl (**SS5020**) could be another safer antiestrogen alternative superior to tamoxifen and raloxifene [31].



SS5020

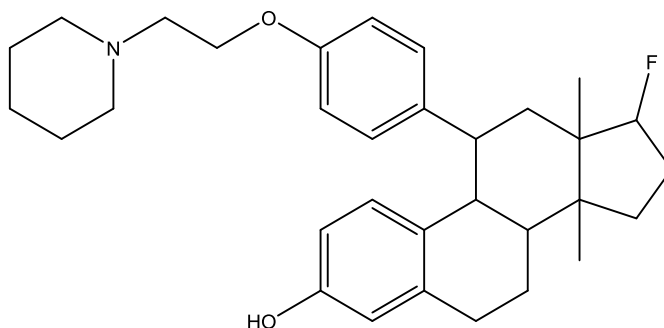
2.2.2.3 Steroidal SERMs

HMP3339 increases bone mineral density and is currently ongoing clinical investigation for the treatment of osteoporosis and CV diseases. On the other hand, it has not yet been proved that HMP3339 could be a cancer preventive agent. [18]



HMR3339

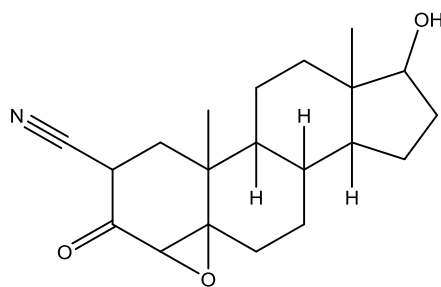
PSK3471 is another SERM. Reports say that it can prevent gonadectomy-induced bone loss and antagonizes estradiol. [18]



PSK3471

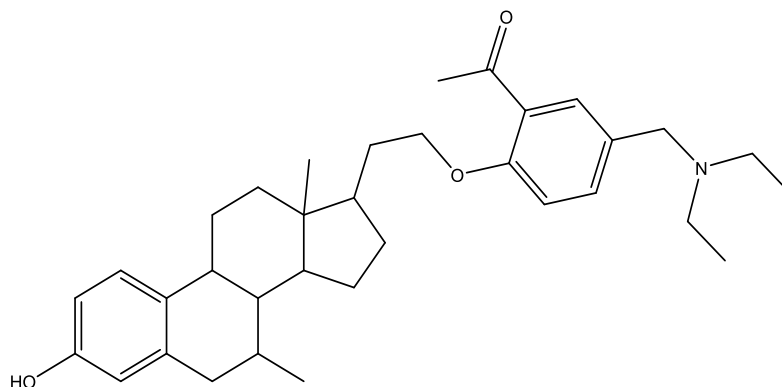
2.2.2.4 *ER subtype selective SERMs*

Trilostane is an inhibitor of 3 β -hydroxysteroid dehydrogenase, a critical enzyme in the conversion of dehydroepiandrosterone to estradiol in breast tumors. It has been used to treat advanced postmenopausal breast cancer after relapse to initial hormone therapy and is currently tested so that it can be used in prostate cancer and premenopausal breast cancer. [18]



trilostane

TAS-108 is an ER α antagonist but ER β partial agonist. It inhibits the growth of tamoxifen-resistant breast cancer cells and has no effects on thickness of endometrium according to trials in which vaginal-ultrasound took place. Since it has an agonistic effect on ER β it doesn't increase bone loss and is a promising breast cancer agent. [18]



TAS-108

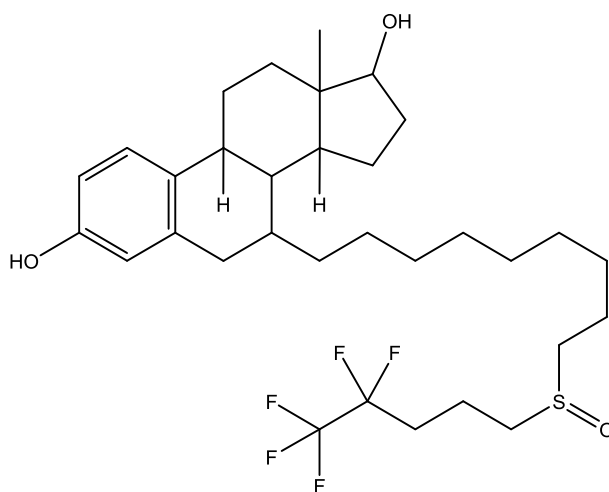
Since tamoxifen has estrogenic effects in some tissues such as bone and endometrium because of liganded estrogen receptor activating target genes, there was a need for the development of anti-estrogens that have reduced agonist activity on gynaecological tissues and able to overcome acquired endocrine resistance in breast cancer. Those anti-estrogenic compounds have potentially reduced toxicity and increased efficacy in comparison with tamoxifen. [18, 27, 33]

2.3 Selective estrogen receptors down regulators (SERDs)

These compounds are distinct from ER ligands such as tamoxifen and instead of acting like either agonists or antagonists, they only block ER.

Current SERDs, such as fulvestrant, have a more antagonistic profile than SERMs and are capable of inhibiting the growth of tamoxifen-resistant breast cancer cells. SERDs are currently used in the treatment of metastatic breast cancer, and their improved clinical activity is thought to derive from their ability to downregulate the ER protein as well as block ER action [32, 34]

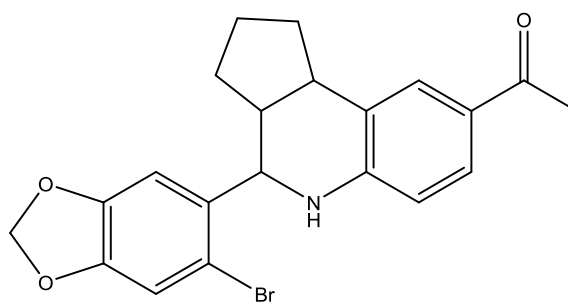
Of the SERDs, only **fulvestrant** has entered the clinic. Recently published phase III studies have shown fulvestrant to be at least as effective as anastrozole (aromatase inhibitor) in postmenopausal women with advanced breast cancer and it is well tolerated. [32–34]



fulvestrant

2.4 Modulators of G protein-coupled estrogen receptors

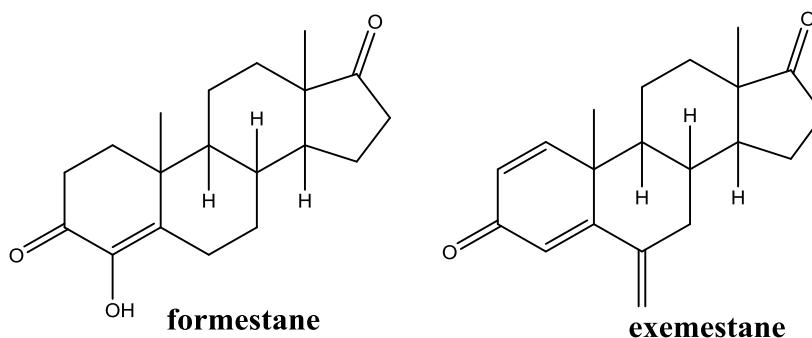
Apart from binding to ER α and ER β estradiol also mediates rapid signaling events through pathways that involve transmembrane ERs, such as G-protein coupled estrogen receptor (GPER). GPER plays an important role in reproductive, immune, nervous, cardiovascular, musculoskeletal, renal system as well as affects cancer growth and glucose metabolism. Recently, it was examined that their role in immunoregulation is crucial, since G-1 is important against inflammation of airways by reducing anti-IgE antibodies, thus it can be effective against asthma. [35, 36] Several other compounds are known to activate GPER including, genistein, nonylphenol, pesticides such as DDT and DDE, as well as bisphenol A, atrazine and equol. [35]



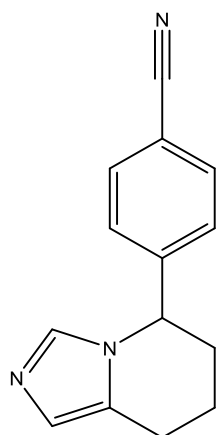
G-1

2.5 Aromatase inhibitors

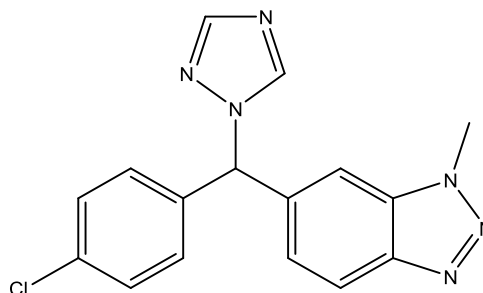
Aromatase is the enzyme which is present in various organs such as adipose tissue, breast tissue, skin, endometrium, bone blood vessels and brain. It is responsible for catalyzing the last step of biosynthesis of estrogen. Therefore inhibition of this enzyme is considered to be an effective therapy for breast cancer and it was essential since drugs like tamoxifen have some reverse estrogenic effect in uterus and vascular tissue. Aromatase inhibitors are used as 1st line therapy for postmenopausal women with hormone-sensitive breast cancer, 1st line therapy for metastatic disease and 2nd line therapy if tamoxifen resistance is presented. Aromatase inhibitors are divided into two types according to their structures. The first one is known as steroidal AIs and includes **formestane** and **exemestane**. [37]



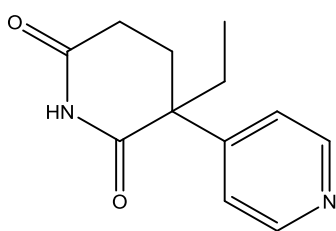
The second type a non-steroidal AIs to which **fadrozole**, **vorozole**, **rogletimide**, **letrozole**, and **anastrozole** belong. [37]



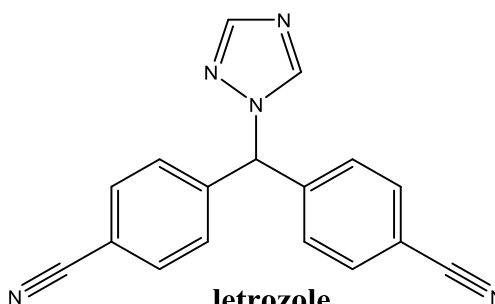
fadrozole



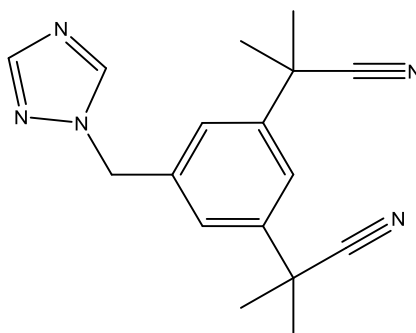
vorozole



rogletimide



letrozole



anastrozole

However, only letrozole, anastrozole and exemestane are clinically used since they have less adverse effects and better bioavailability. [37]

Letrozole is well-tolerated and effective in the treatment of metastatic breast cancer in postmenopausal women. Recently, its efficacy has been confirmed in neoadjuvant treatment in breast cancer, and it is more effective than tamoxifen in ER+ tumor proliferation according to these studies. [37, 38]

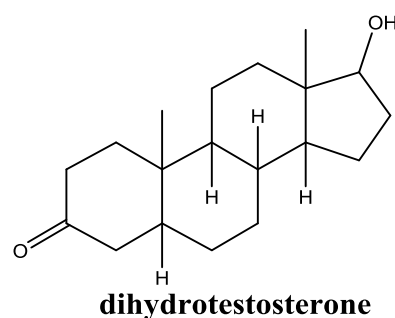
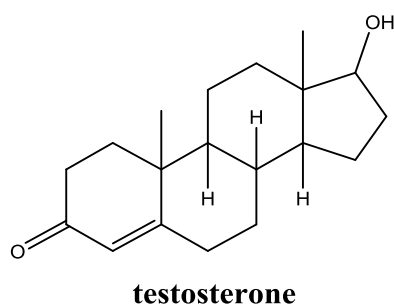
Anastrozole is also well tolerated but not as potent as letrozole. In long-term therapy anastrozole was more efficient than tamoxifen. Its side effects are the typical ones for

AIs, so there is just increased risk for bone fracture. However many patients discontinued therapy since the musculoskeletal pain was severe. [37, 39]

Exemestane has an androgen steroidal structure and it binds irreversibly to aromatase. Because of its structure, it behaves as a weak androgen in bone, thus it prevents resorptive effect of estrogen depletion. It is predominantly indicated for the treatment of both early-stage and advanced breast cancer in postmenopausal women. Despite the fact that it is well-tolerated, there is an increase risk of fracture risk. [37, 40]

3. ANDROGENS

Androgens (male sex hormones) are mainly produced by testes and in lesser amounts are produced by adrenal cortex (in women by ovaries). The principal androgens are testosterone and 5 α -dihydrotestosterone. Generally androgens are responsible for the reproductive function and the stimulation of secondary sex characteristics in male as well as initiation and maintenance of spermatogenesis. [41, 42]



3.1 Androgenic receptors

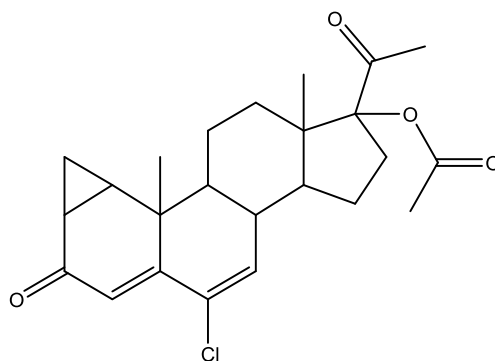
The androgenic receptor (AR) is vital for various processes either pathological or physiological. AR is important for mineralization of bones, muscle growth and it produces immune cells and helps them grow. The androgen receptors in hypothalamus and liver play a role in regulation of insulin sensitivity as well as homeostasis of glucose. Furthermore AR assists in wound healing and helps also in the treatment of CVS diseases. After controlled synthesis of testosterone by luteinizing hormone (LH), it binds to AR and eventually their complex after regulation transcription of genes, initiates spermatogenesis and development of mesonephric duct. [42, 43] Many AR ligands with different pharmacological properties have been identified in the last 40 years. [44]

3.2 Antiandrogens

3.2.1 Clinically used antiandrogens

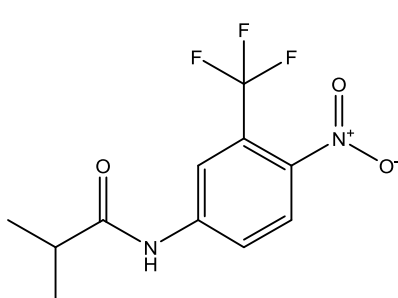
The first clinically used antiandrogen was steroidal **cypoterone-acetate**. It is a derivative of pregnane and was found within the studies aimed at hydroxyprogesterone derivatives without androgenic activity. It is used to treat prostate cancer and it has fewer side effects compared to standard therapy based on estrogenic estradiol undecylenate. It

is also an ingredient of contraceptive pills which shows beneficial effects on some acne types. [44]

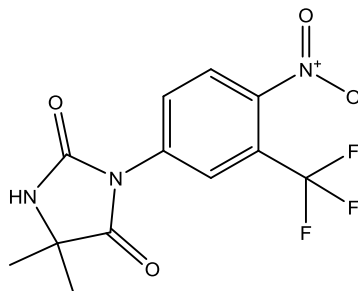


cyproterone acetate

Other antiandrogens are non-steroidal compounds known as arylpropionamides. **Flutamide** and **nilutamide** belong to the nitrotrifluorotoluene group. Flutamide is a prodrug which is metabolically converted to active hydroxyflutamide. **Nilutamide** has a longer half-life than flutamide. [44]

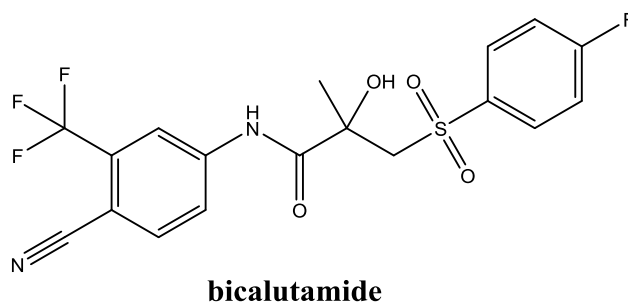


flutamide



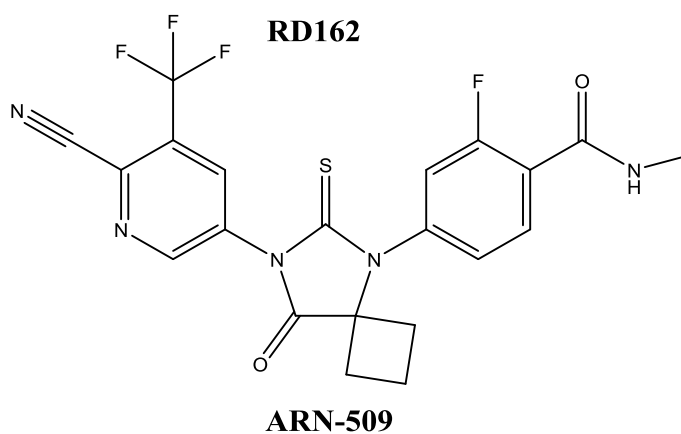
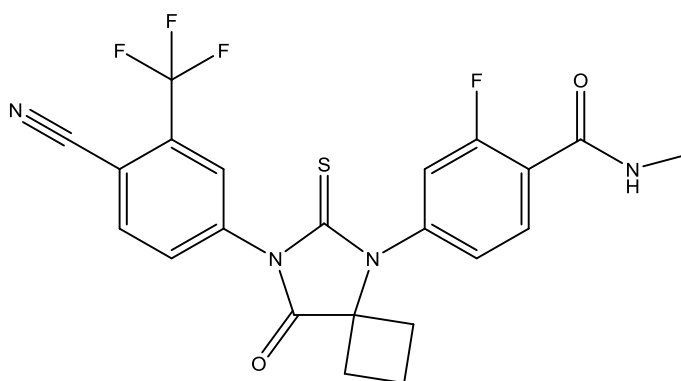
nilutamide

Bicalutamide has a larger molecule and contains sulfonyl group. It is currently used in its racemic form. Post-approval investigation revealed that the *R*-enantiomer is the active principle, whereas the *S*-enantiomer is inactive. Bicalutamide has better side-effect profile than other antiandrogens and has established itself as the current standard-of-care antiandrogen for prostate cancer treatment. [44] Structural modifications of bicalutamide have yielded selective androgen receptor modulators [45] that will be discussed later.

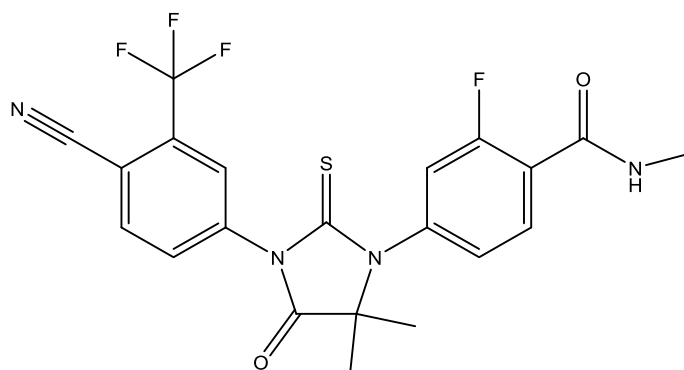


3.2.2 Antiandrogens under development

Unfortunately, many patients treated with antiandrogens develop resistance. Therefore the search for new drugs for the treatment of prostate cancer continues. The 2nd generation antiandrogens includes **RD162**, its pyridine congener **ARN-509**, and **MDV3100**. [44–47]



MDV3100 is currently marketed as **enzalutamide**. [48]



enzalutamide (MDV3100)

Other competitive androgen receptor antagonists are **BMS-641988**, **BMS-779333** and **CH5137291**. All of them have trifluoromethylbenzonitrile moiety in their structures. Non-competitive antagonist acting on the sites outside of the ligand-binding pocket, including the known drugs flufenamic acid and pyrvinium embonate, have been investigated. [44]

3.3 Selective androgen receptor modulators (SARMs)

SARMs bind to the AR but in comparison with other anabolic steroids they do not increase the size of prostate and other secondary sexual organs that much. They achieve tissue selectivity by differences in gene regulation, tissue distribution, and local interactions with aromatase and 5α -reductase, have myoanabolic and osteoanabolic activity, and have been used various diseases such as muscle wasting connected with aging, cancer, osteoporosis, burns, renal disease, hypogonadism, cachexia and sarcopenia. Due to the potential abuse in sport SARMs have been put on the list of prohibited substances by the International Olympic Committee in 2008. [44, 45, 49–52]

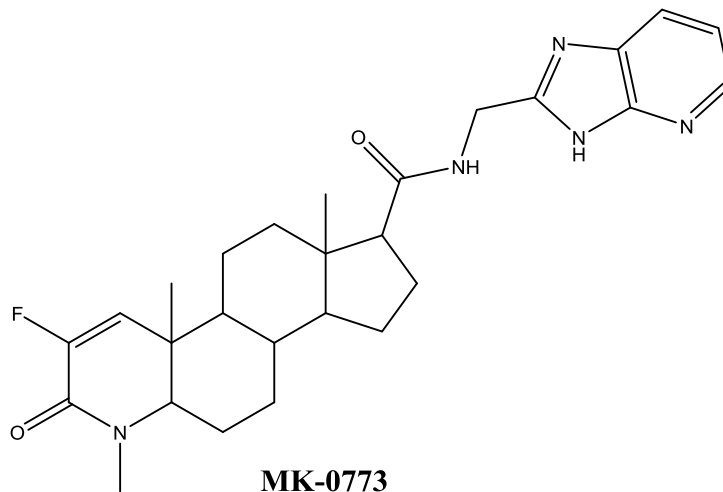
3.3.1 Clinically used SARMs

According Haendler and Cleve [44] 19-nortestosterone is a SARM as it is less susceptible to aromatization. It can be further modified by alkylation in position 7α which makes it less susceptible to 5α -reductase reduction. However, commonly these compounds are considered to be androgens.

3.3.2 SARMs under development

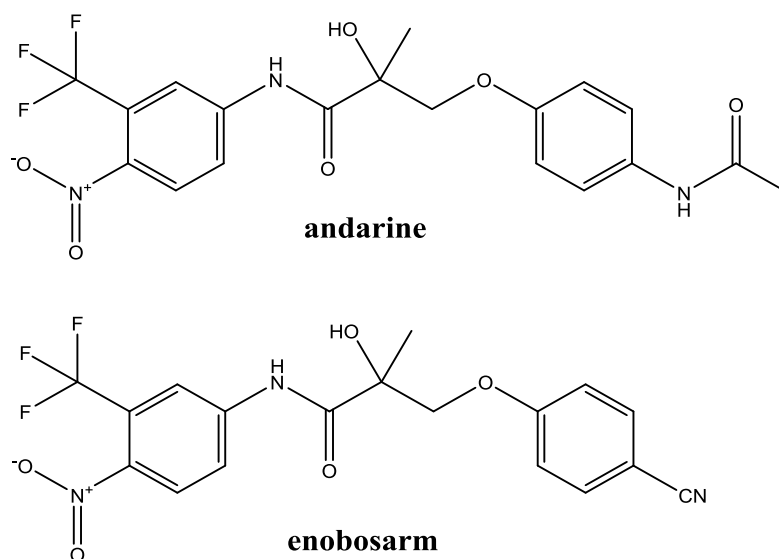
3.3.2.1 Steroidal SARMs

So far, only **MK-0773** from the class of 4-azasteroids has been tested clinically [44, 49].

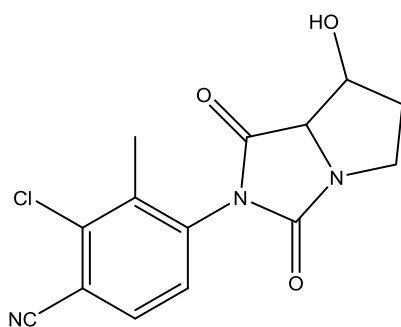


3.3.2.2 Non-steroidal SARMs

Some non-steroidal SARMs are structurally similar to antiandrogens of arylpropionamide type. **Andarine** (known also as S-4) is a potent SARM which after being tested in rats has shown that it is able to increase skeletal muscle strength, reduce body fat as well as increase lean body mass and also prevents bone loss. It is also an agent indicated in benign prostatic hyperplasia and male fertility. **Enobosarm** (S-22) undergoes clinical development as Ostarine[®]. [44, 49, 51, 52]

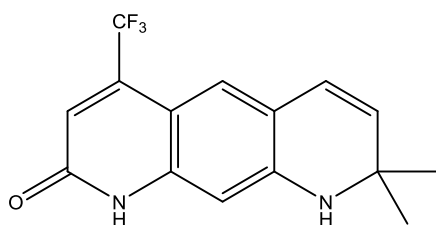


BMS-564929 is a derivative of hydantoin. It is a potent and hyperanabolic agonist compared to testosterone in skeletal muscle however it has a reducing stimulatory activity in prostate compared to testosterone. Nevertheless it suppresses LH which may cause adverse effects since endogenous testosterone is suppressed causing detrimental effects on multiple organ systems including pre-osteoporotic changes in bone. It was reported to be in Phase I clinical trials. [44]

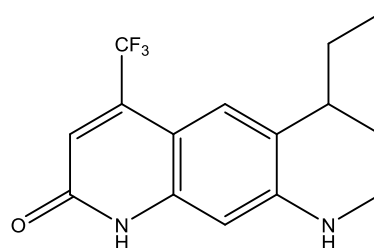


BMS-564929

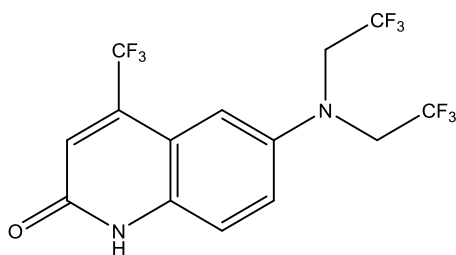
A large group of quinolin-2(1*H*)-one derivatives has been studied as potential SARMs. [44, 50, 51, 53]. Some examples are shown bellow.



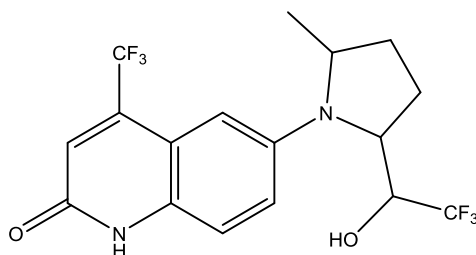
LG-120907



LGD121071



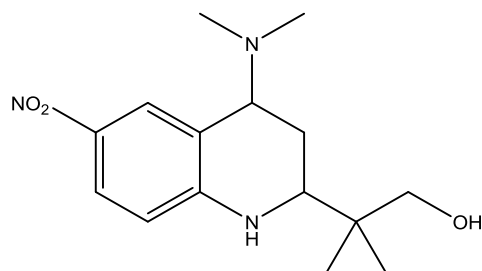
LGD-2226



LGD-2941

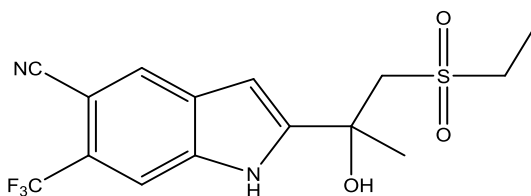
LGD2941 entered Phase I clinical trials for osteoporosis and frailty. It eventually demonstrated better bioavailability than LGD2226 and at the same time it maintained hypermyoanabolic and hyperosteoanabolic effect in both male and female. [44, 45, 50]

Tetrahydroquinoline derivative **S-40503** exerted androgenic effects, and partially restored the prostate back to a normal level when administered for 4 weeks to castrated rats beginning immediately after surgery. It also maintained BMD in males and it increased it in female ovariectomized rats. S-40503 has a high affinity for AR, with no measurable or a very feeble affinity for the PR, ER, GR and MR. In comparison with DHT it has a reducing effect in prostate enlargement. Eventually it did not advance to clinical trials. [45, 54]



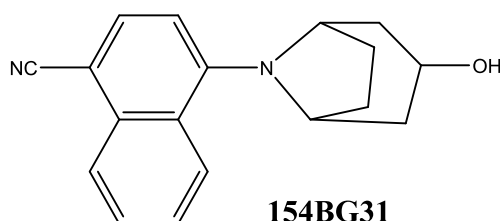
S-40503

JNJ26146900 retained levator ani weight, but reduces prostate weight in rats. It partially offsets castration-induced losses in BMD and LBM and blocks testosterone-induced prostate cancer growth. [45, 55]

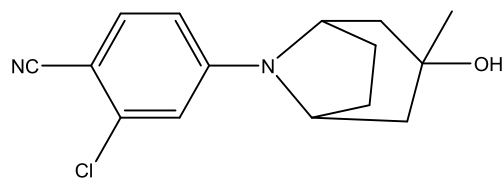


JNJ-26146900

154BG31 induces increase in ventral prostate, seminal vesicles and levator ani and suppresses LH. **198RL26** is a partial myoanabolic agonist. [45]



154BG31



198RL26

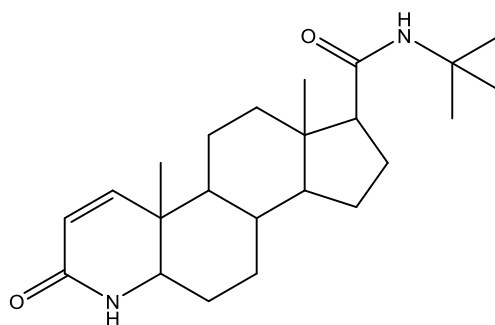
Promising clinical and preclinical SARMs should have hypermyoanabolic and

hyperosteoanabolic efficacy (hyper- defined as in excess of intact control) at doses associated with decreased prostate size and little to no suppression of pituitary gonadotropins. [45]

3.4 Inhibitors of 5 α -reductase

These agents are able to increase testosterone and decrease dihydrotestosterone levels by suppressing the action of 5 α -reductase enzyme which is responsible for the conversion of testosterone into dihydrotestosterone. They are used predominantly to treat BHP and androgenetic alopecia. [56]

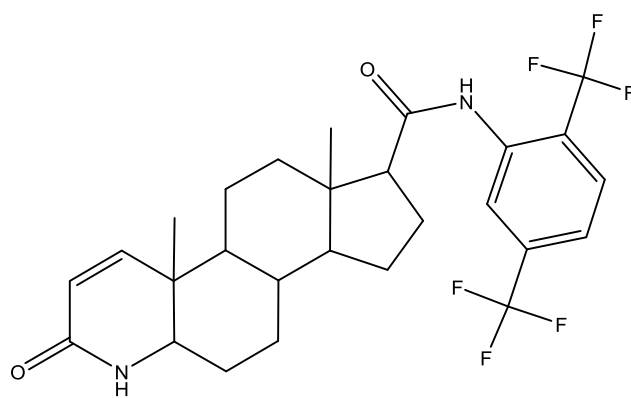
There are two isozymes of 5 α -reductase. **Finasteride** inhibits type 2 5 α -reductase which is located in the prostate. With this agent serum DHT concentration shows a decrease of 70%. Therefore finasteride is an efficient agent and is used successfully for the treatment of BHP, since if administered in long-term it doesn't induce any side effects in androgen responsive end points. Furthermore, trials in mice have shown that excessive amount of testosterone and DHT can have a negative effect in post-traumatic immune response. Therefore, finasteride with its inhibiting activity on 5 α -reductase can decrease this effect. [56, 57]



finasteride

Dutasteride inhibits both type 1 5 α -reductase (found in liver, skin and intestine) and type 2 5 α -reductase. As a result it decreases 95% serum DHT. This results in decrease of prostate volume, elimination of its symptoms as well as reduction of acute urinary retention. Dutasteride has some worth-mentioned effects in prostate specific antigen, bone, metabolism of lipoprotein and sexual function. If androgens are low, it can result to osteoporosis which means that decreased DHT is associated with decreased mineral bone density. Additionally evaluation of effect of dutasteride regarding its administration

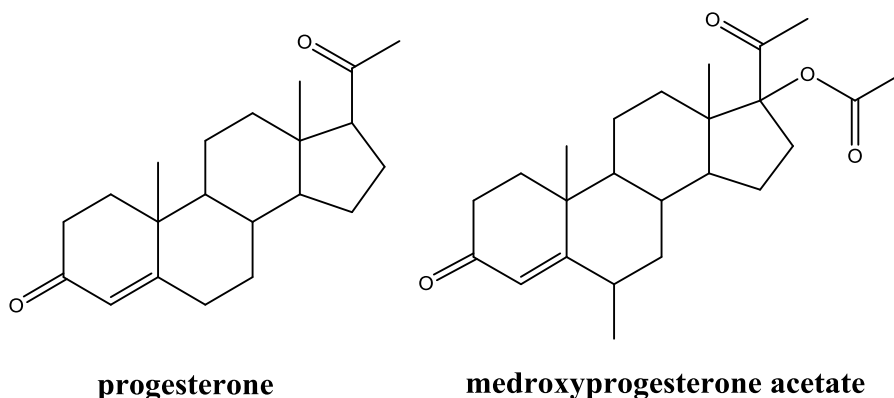
for 2 weeks before transurethral resection of prostate has taken place and the results had shown that dutasteride decreases bleeding during and after surgery. [56, 58]



dutasteride

4. PROGESTOGENS

The most important is progesterone. They are the other type of female sex hormones. Their name is derived by their role in pregnancy maintaining. To distinguish natural progesterone from synthetic progestogens, the latter are sometimes named progestins. Mainly progestins are used to protect endometrium against hyperplasia in postmenopausal women in combination with estrogen therapy. A well-know progestin which has been used is medroxyprogesterone acetate (MPA). Progestogens seem to have various beneficial affects in the CNS and CVS, but there is a lack of understanding of the differences between progestins and progesterone and between individual progestins differing in their effects on the CVS and CNS, the breast, and bone. Also their safety is controversial since recent results have shown that there is increased breast cancer risk if used in combination with estrogen but decreased risk if estrogen if used alone. [59]



4.1 Progestogenic receptors

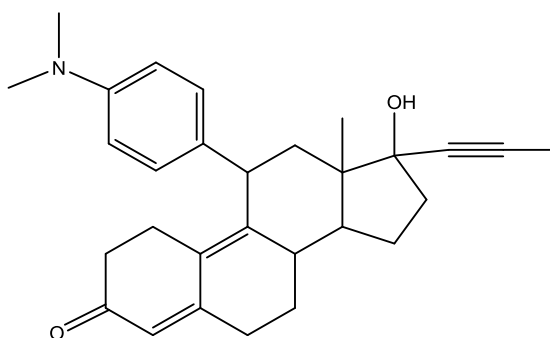
Progesterone and progesterone receptors (PRs) are necessary for the development and proper regulation of hormone-responsive tissues like breast and reproductive tract. In breast, progesterone acts in combination with estrogen in order to promote proliferative and pro-survival gene programs. On the other hand, progesterone inhibits estrogen-caused growth in the uterus and protects the ovary from neoplastic transformation, but if progesterone effect is inadequate then there is increased risk of endometrial cancer. Generally PRs and progesterone play a vital role as critical regulators of gynaecological cancers. This is mediated by two PR isoforms PR-A and PR-B. PR-A is important regarding ovulatory effects as well as enhancing the antiproliferative activity of

progesterone in uterus. PR-B is responsible for development and function of mammary gland. [60–62]

4.2 Antiprogestins

4.2.1 Clinically used antiprogestins

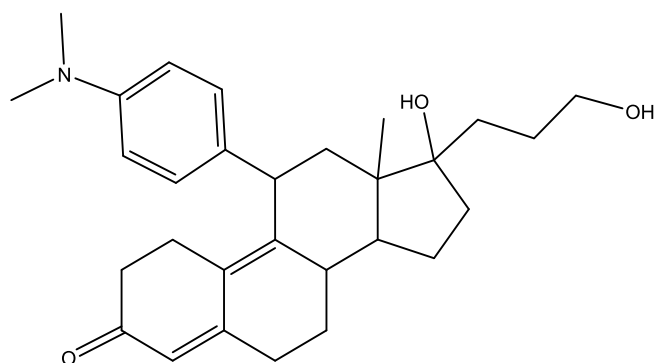
Mifepristone (also known as RU-482) has first reported in 1981. It is used to terminate pregnancy, and as such is commercially available in many countries. Its controversial image related to abortion limited further developments of progesterone antagonist. Mifepristone is also glucocorticoid antagonist. [63]. From the chemical point of view, mifepristone belongs to 17α -19-nortestosterone derived antiprogestins.



mifepristone

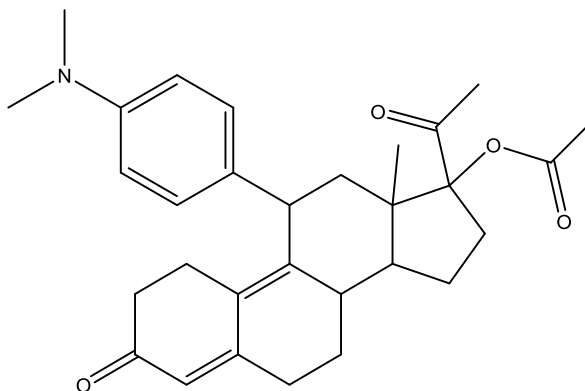
4.2.2. Antiprogestins under development

This class includes **onapristone** (ZK 98 299) and **CDB 2914** without antagonist properties and **Org 33628** acting mostly as antagonists [63]

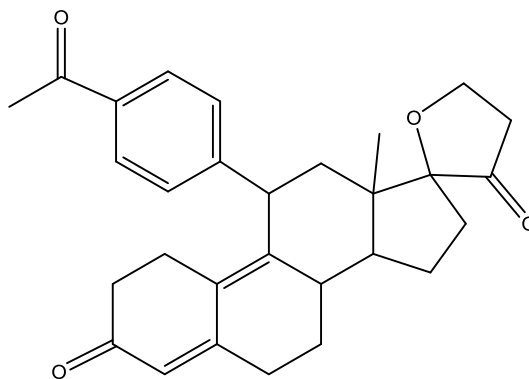


onapristone

CDB 2914 is similar to 17α -hydroxy-19-norprogesterone class of progestins, while **Org 33628** resembles aldosterone antagonist and on contrary to other antiprogestins has no basic amino group on the phenyl ring.



CDB 2914



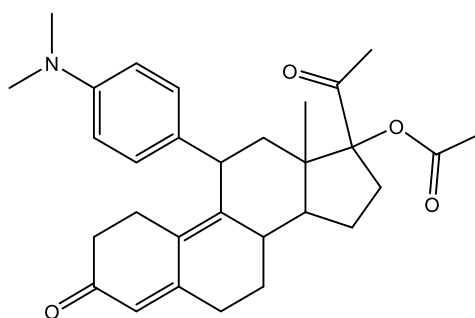
Org 33628

4.3 Selective progesterone receptor modulators (SPRMs)

SPRMs are a new class which exert tissue selective agonist, antagonist or mixed agonist-antagonist activity in target cells. These compounds are also known, progesterone receptor modulators (PRM), mesoprogestins or partial agonist-antagonists. While antiprogestins suppress late follicular development, block the LH surge and retard endometrial maturation, SPRMs are not as effective in blocking the LH elevation and appear to target the endometrium directly and produce amenorrhoea. Clinical data show that treatment with these compounds is not associated with hypo-estrogenism and bone loss. They could be used as emergency contraception, longterm estrogen-free contraception, and in the treatment of myomas and endometriosis. [63]

4.3.1. Clinically used SPRMs

Ulipristal acetate is efficient in treatment of uterine fibroids before surgery by decreasing uterine bleeding and leiomyoma volume and used generally in clinical management of pre-menopausal women. In addition recent studies have shown that it is even more effective than levonogestrel in preventing pregnancy. Its short-term administration is considered to be safe with minimal adverse effects such as headache and pain, discomfort and tenderness in breasts. However, its safety profile is not defined yet. Therefore clinical studies have to take place for its evaluation. [62, 64, 65]

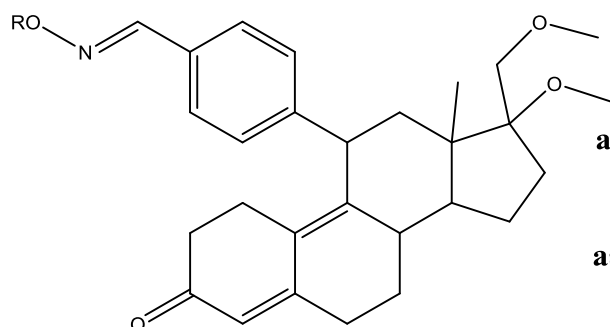


ulipristal acetate

4.3.2 SPRMs under development

4.3.2.1 Steroidal SPRMs

Asoprisnil exhibited mixed agonist–antagonists properties in the test aimed at determining the degree of endometrial proliferation and transformation in immature rabbits initially primed with estradiol. In another test it induced endometrial atrophy. Unlike mifepristone, the effects of asoprisnil on ovulation inhibition were inconsistent and lacked dose dependency. [63] Configuration on the oxime double bond is important for the receptor binding. Binding affinity of *E*-isomer is higher than that of *Z*-isomer. Carbonate and carbamate esters have been also studied. [66]

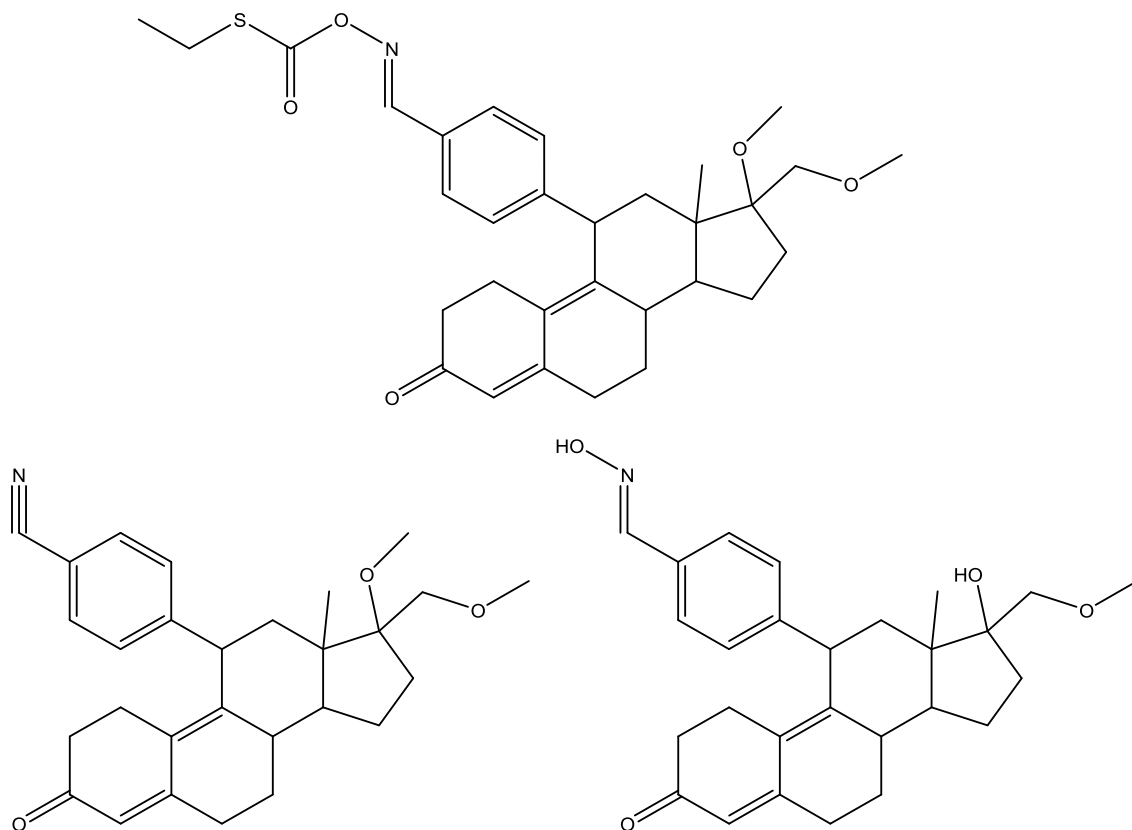


asoprisnil: R = H

asoprisnil carbonates: R = R¹-O-C(=O)-CH₃

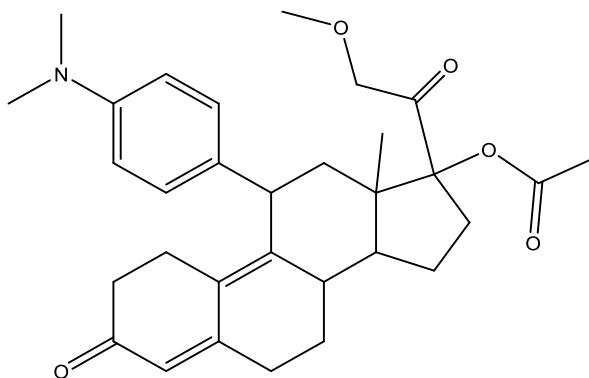
asoprisnil carbamates: R = R¹-NH-C(=O)-CH₃

Several analogues of asoprisnil have been reported as well. [66]



analogues of asoprisnil

Telapristone acetate (CDB 4124) undergoes clinical evaluation for the treatment of uterine fibroids and endometriosis as Proellex[®]. [67, 68]

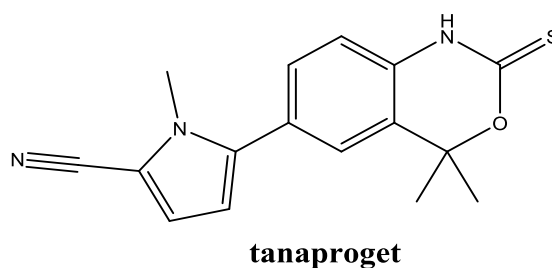


telapristone acetate

4.3.2.2 Non-steroidal SPRMs

Steroidal antiprogestins and SPRMs often display significant interactions with other steroid receptors. The search for non-steroidal compounds should result in the development of PR modulators with better specificity and less impact on other body systems. [66]

Tanaproget has high affinity and selectivity for PRs and was much more potent than the steroidal SPRMs in a variety of animal models. [F-18]fluorine-substituted tanaproget derivatives are studied as a progesterone receptor imaging agents for positron emission tomography. [66, 69]

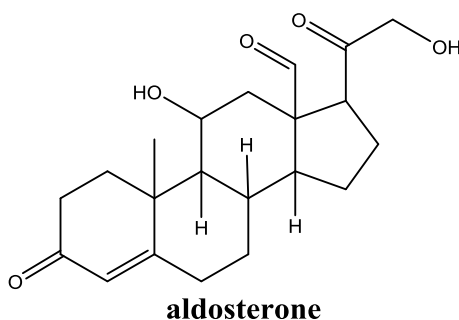


Many other non-steroidal SPRMs based on various skeletons, such as pyrazole, thiophene, diazepine, imidazole or carborane, have been recently reported. [66, 70, 71]

5. MINERALOCORTICOIDS

Mineralocorticoids are steroid hormones responsible for the retention of sodium and free water as well as the excretion of potassium. Any dearrangements in the production of mineralocorticoids could lead to several abnormalities such as hyponatremia, hyperkalemia and hypotension. On the contrary, in excess of mineralocorticoids the reverse effect can occur.

The primary mineralocorticoid is aldosterone which is synthesized in zona glomerulosa of the adrenal cortex and plays a vital role in electrolyte and fluid balance and thereby blood pressure. It acts by targeting epithelia in kidney and colon in order to regulate Na^+ absorption and K^+ secretion. Water follows the movement of sodium cations by osmosis establishing blood volume and therefore blood pressure. [9, 72, 73]



In addition to its main role in keeping body fluid and electrolyte balance, aldosterone affects many cell types where it regulates a variety of signal transduction mechanisms and cellular responses. [74]. It's effects can be divided into MR-dependent and MR-independent as shown in Fig 2.

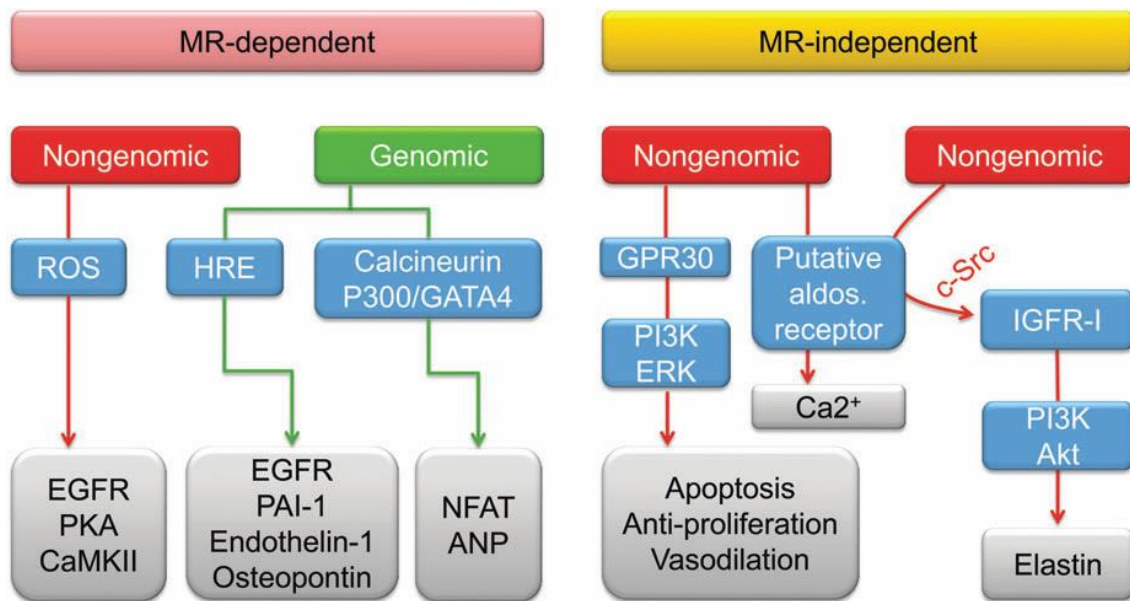


Fig. 2 MR-dependent and MR-independent effects of aldosterone. EGFR (Adopted from the ref. [75])

5.1 Mineralocorticoid receptors

Mineralocorticoid receptors bind both mineralocorticoids, and glucocorticoids with high affinity. They are found in kidney and colon as well as in nonepithelial tissues like heart and brain. In epithelial tissues, aldosterone has to compete for MR with cortisol that circulates in the body in much higher concentrations. Due to co-expression with the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD2) aldosterone is able to activate MR. This is achieved by conversion of cortisol to cortisone and NAD to NADH. In some transcription systems, NADH has been shown to be a potent inhibitor of transcriptional activation. Thus, 11 β HSD2 debulks the intracellular cortisol by 90% (still leaving a 10-fold higher level than that of aldosterone). However by generating NADH, it holds glucocorticoid-occupied MR transcriptionally inactive. When the enzyme is operating, most MR are occupied but not activated by cortisol. On the other hand, cortisol becomes an MR agonist, mimicking the effects of aldosterone, in the context of tissue damage, reactive oxygen species generation, and the consequent change in intracellular redox state. This particular effect of cortisol underlies the therapeutic efficacy of MR blockade in heart failure, hypertension, vascular inflammation and atherogenesis. [76, 77]

Mineralocorticoid receptors (MR) exist in many tissues, in which they mediate diverse functions crucial to normal physiology. However, inappropriate activation of MR within these tissues causes hypertension and pathological vascular, cardiac, and renal remodeling. [78, 79]

5.2 Renin angiotensin aldosterone system (RAAS)

Aldosterone secretion is regulated by angiotensin II (Ang II), potassium (K^+) and adrenocorticotropin (ACTH). Ang II influences aldosterone secretion mainly via the angiotensin II type 1 receptor (AT1R), whereas the angiotensin II type 2 receptor (AT2R) counteracts many of the AT1R mediated processes. [74, 80]

Ang II is the primary mediator of RAAS, but also renin and angiotensin converting enzyme play important roles. There are many RAAS modulators, including direct renin inhibitors (DRIs), angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), that affect secretion of aldosterone and are used in the treatment of hypertension and heart failure [79, 81–83].

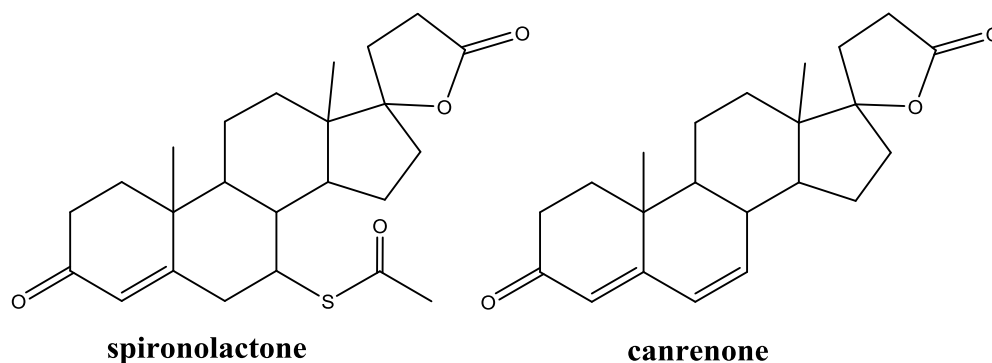
5.3 Mineralocorticoid receptor antagonists

Aldosterone antagonists or mineralocorticoid receptor blockers have a beneficial effect on patients with several clinical conditions such as primary aldosteronism, primary hypertension, heart failure and chronic kidney disease. According to studies in animals MR activation can exacerbate atherosclerosis and pulmonary hypertension; mineralocorticoid receptor antagonist can either eliminate or reduce these effects. [84–86]

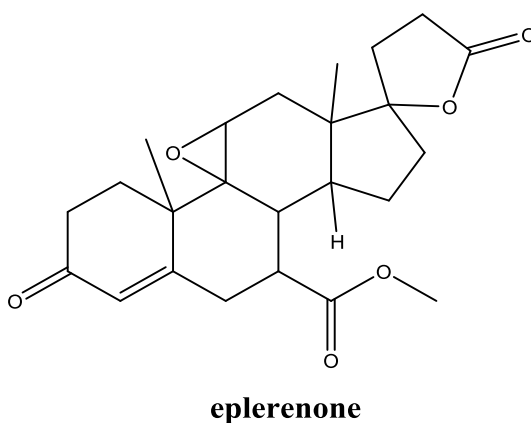
5.3.1 Clinically used MR antagonists

Spironalactone was developed as an antihypertensive agent in the 1950s and became commercially available in 1960. It is a competitive non-selective antagonist of MR. Despite the fact that it is an effective aldosterone antagonist it has some progestational and antiandrogenic adverse effects such as hyperkalemia, hyponatremia, impotence, gynecomastia, decreased libido, hirsutism. [84–87]

Canrenone is a spironalactone analogue with less androgenic effects that blocks all side effects of aldosterone. It improves diastolic function in primary hypertension without affecting blood pressure left ventricular mass regression, having a direct myocardial effect. It is used only in a few countries. [84, 86].



In order those side effects to be obviated **eplerenone** was developed. This drug was first marketed in the United States in 2002 and is ranked as second-generation MR antagonist. It is a competitive antagonist of MR having perfect selectivity compared with other steroid receptor, since 7 α -acetylsulfanyl group of spironolactone was replaced with a methoxycarbonyl group. Therefore eplerenone lacks many of the sexually-related adverse effects of spironolactone. [84, 85, 87]



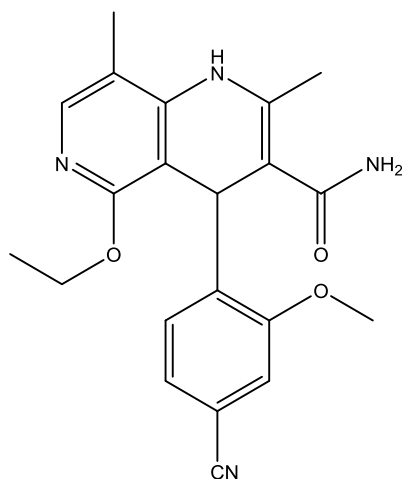
5.3.2. MR antagonists under development

Research for new MR antagonists had to take place because of known adverse effects of spironolactone. New MR antagonists are non-steroidal and designated as third- or fourth generation of MR antagonists. [87, 88]

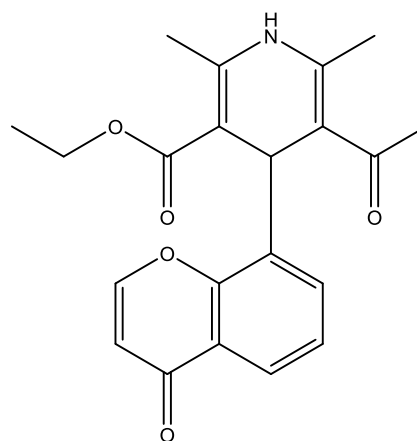
Finerenone (BAY 94-8862) was developed after it was found that dihydropyridines, which are L-type calcium channel blockers, act also as MR antagonists *in vitro* and *in vivo*. Finerenone may offer end-organ protection with a reduced risk of electrolyte disturbances. It is currently under investigation in clinical phase IIb studies in patients with worsening chronic heart failure with additional type 2 diabetes mellitus and/or

chronic kidney disease and in patients with type 2 diabetes mellitus and diabetic nephropathy. [87–90]

Another dihydropyridine derivative is **BR-4628**. It is a highly potent MR antagonist, with a low L-type calcium channel binding activity. 2-Methylchromenonyl substituent most probably drastically reduces calcium channel inhibitory activity, and it is responsible for high MR binding affinity. Biochemical studies demonstrated that BR-4628 forms complexes with MR that do not promote the recruitment of transcriptional co-regulators. It indicates that BR-4628 acts as a bulky-passive antagonist. Several *in vivo* investigations are underway to evaluate its end organ protective effects in preclinical animal models. [91]

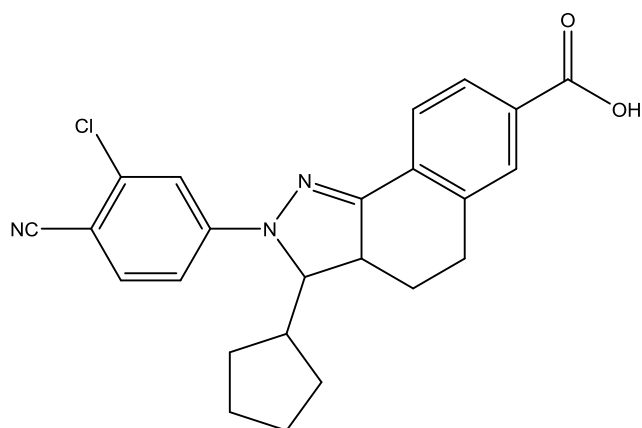


finerenone



BR-4628

Structurally different non-steroidal aldosterone antagonist **PF-03882845** is currently under clinical investigation. [92–94]



PF-03882845

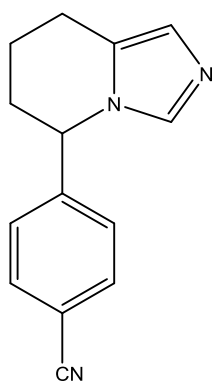
5.4 Aldosterone synthase inhibitors

CYP11B2, the aldosterone synthase, and CYP11B1, the cortisol synthase, are two highly homologous enzymes implicated in a range of cardiovascular and metabolic diseases. Cyp11B2, a mitochondrial cytochrome P450 enzyme responsible for the conversion of 11-deoxycorticosterone to aldosterone, has been identified as a potential therapeutic target. Cyp11B2 has 93% homology with Cyp11B1, and nonselective Cyp11B1/Cyp11B2 compounds could negatively influence cortisol synthesis, creating undesirable side effects in patients requiring treatment with an aldosterone synthesis inhibitor. Hence, compounds highly selective to CYP11B2 have intensively been searched for. [95–100]

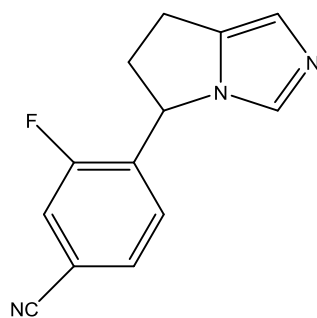
FAD286 – *R*-enantiomer of aromatase inhibitor fadrozole – is a powerful but non selective inhibitor of CYP11B2. [96, 99]

LCI699 has greater selectivity and is a first orally active aldosterone synthase inhibitor that has been tested in humans [98, 99].

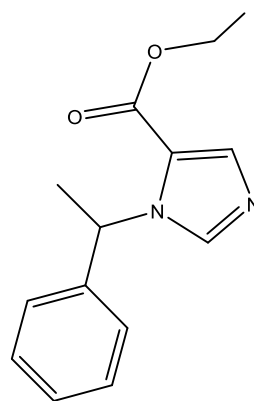
All compounds have been currently used as lead structure for further modifications. Also intravenous anesthetic *R*-etomidate is a lead structure for new aldosterone synthase inhibitors. [99, 100]



fadrozole



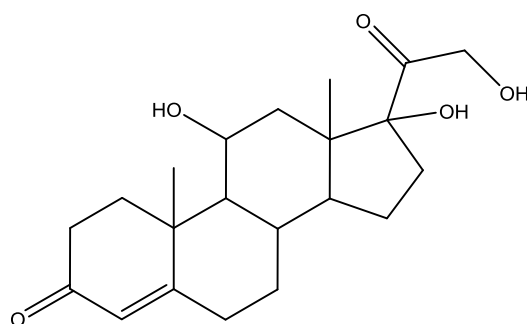
LCI699



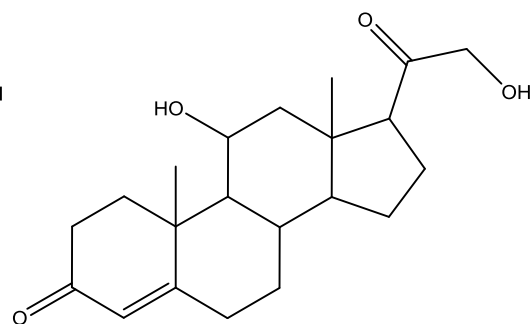
etomidate

6. GLUCOCORTICOIDS

They are cholesterol-derived steroid hormones which are secreted by zona fasciculata of the adrenal glands and are regulated in a circadian and stress-associated manner. When affected by stress glucocorticoids suppress the hypothalamic-pituitary-gonadal axis. They are responsible for various metabolic and haemostatic functions that are necessary for life. They are considered to be the most effective anti-inflammatory therapy for asthma, since they inhibit the multiple inflammatory genes which are activated in chronic inflammatory diseases, like asthma. This is achieved by reversing histone acetylation of activated inflammatory genes by binding to glucocorticoid receptor. Generally, availability of natural steroids in tissues is regulated by corticosteroid binding globulin in serum as well as by locally expressed 11β -hydroxysteroid dehydrogenase enzymes (11β -HSD). Those enzymes are catalysts for interconversion of active cortisol and corticosterone to cortisone and 11-dehydrocorticosterone. Imbalance in GCs levels can lead to Cushing syndrome or Addison disease. [11, 101–103]



cortisol



corticosterone

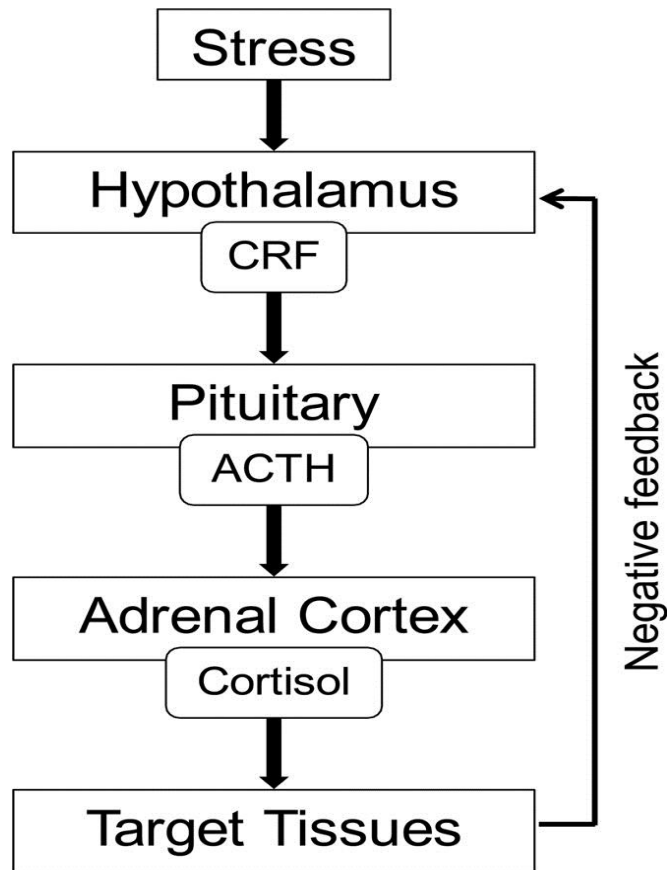


FIG. 3 BASIC HYPOTHALAMUS-PITUITARY-ADRENAL AXIS SUMMARY IN RESPONSE TO STRESS [104]

6.1 Glucocorticoid receptors

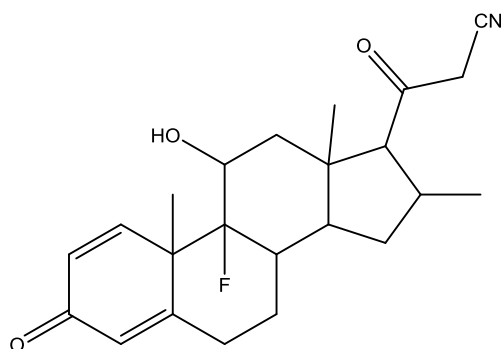
Corticosteroids diffuse through cell membrane and bind to glucocorticoid receptor in cytoplasm. GRs are activated upon ligand binding and they are released from chaperone proteins and then they rapidly translocate to the nucleus where they exert their molecular effects. The only form of GR that binds glucocorticoids is hGR α which functions as a ligand dependent transcription factor, and resides primarily in the cytoplasm until bound by ligand. Conversely, hGR β does not bind glucocorticoids but localizes to the nucleus where it functions as a dominant-negative inhibitor of the transcriptional activity. In the presence of GR antagonists, hGR β exerts its own transcriptional regulatory program. Depending on their relative expression, ligand availability, and activity, the presence of hGR α and/or hGR β contributes to the tissue-specific effects of glucocorticoids.

Positive regulation of the gene expression by the GR – *transactivation* – is mainly mediated by direct binding of receptor homodimers to specific sequences (glucocorticoid responsive elements – GREs) in promoter or enhancer regions of GC target genes.

Negative regulation by the GR – *transrepression* – proceeds via negative GREs that differ in structure and function from positive GREs. Only a few genes are regulated via these negative GREs. When GR are bound to other transcription factors they inhibit their activity. This mechanism is fully functional with dimerization-defective GR and is thought to occur through GR monomers. [11, 102–106]

It is assumed that the anti-inflammatory effects of GCs are largely mediated by GR transrepression mechanisms, while GR transactivation is a cause of most GC treatment-associated side effects. Actually, it is not so simple. It has indeed been shown that some side effects are predominantly mediated via transactivation (*e.g.* hyperglycemia and muscle wasting), but other side effects arise from transrepression (*e.g.* hypothalamic-pituitary-adrenal axis suppression), and still others (*e.g.* osteoporosis) are mediated by both transactivation and transrepression. Nevertheless, GR ligands which can selectively induce transrepression without significant transactivation exist.

Compounds that can activate specific GR mechanisms and thus alter GR-mediated gene expression profiles are referred to as dissociated compounds, selective glucocorticoid receptor agonists (SEGRAs) or modulators (SEGRMs). The term SEGRA was originally used, as these compounds historically were derived from a steroidal scaffold, such as RU 24858 and they often exhibited a partial agonistic effect on the transactivation mechanism of GR. The use of the term SEGRM was introduced to distinguish the newer, non-steroidal compounds from the older ones. [106]

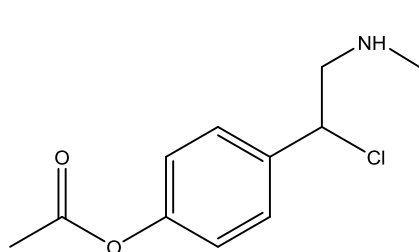


RU-24858

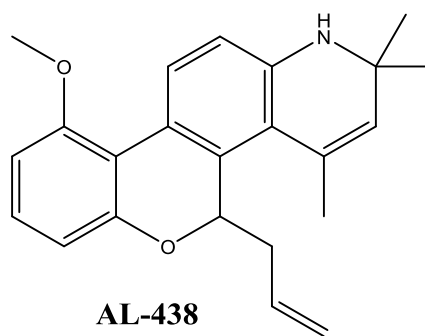
6.2 Selective glucocorticoid receptor modulators (SEGRMs)

It is commonly known that glucocorticoids are effective anti-inflammatory and immunosuppressive agents. However, their therapeutic effect is limited by several side effects such as osteoporosis, muscle atrophy, inhibition of wound healing and insulin resistance. New selective glucocorticoid receptor modulators are considered to be promising and alternative candidates for avoiding problems while maintaining completely their anti-inflammatory properties. [106, 107]

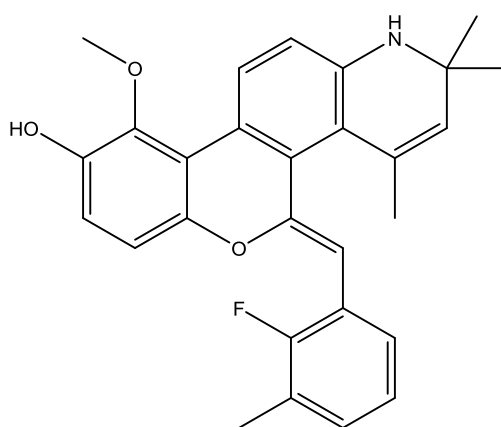
Compound A was the first SEGRM characterized in 2005. Although it is unstable and has a narrow therapeutic range, it remains an important tool for further research. Also **AL-438**, **LGD-5552** and **ZK-216348** are not promising drug candidates. [106–109]



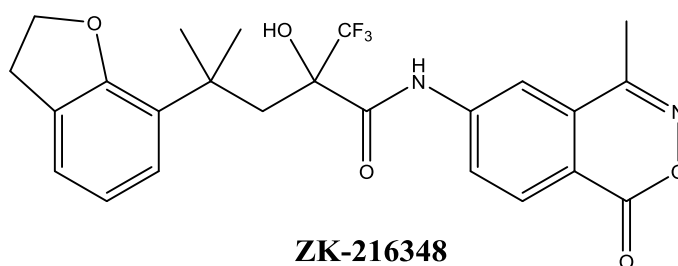
Compound A



AL-438

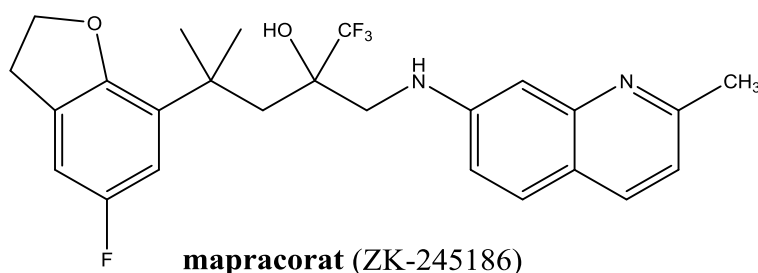


LGD-5552



ZK-216348

Structural modification of ZK-216348 resulted in ZK-245186 that undergoes clinical trials as **mapracorat**. When studied preclinically, it was shown that mapracorat suppresses the secretion of cytokines such as TNF- α and GM-CSF and prostaglandin E2, as well as T-cell proliferation. It has effective anti-allergic properties and is a promising agent for treatment of topical allergic eye disorders. [107, 110, 111]



6.3 Glucocorticoid antagonists

Acute high glucocorticoid levels are important for a variety of biological function. On the contrary, chronic elevated levels of GCs, *e.g.* Cushing's syndrome, can lead to muscle atrophy, increased insulin resistance, high risk for type II diabetes mellitus development. GR antagonists have become vital since they can manage unwanted metabolic effects of high levels of GCs. [112]

Mifepristone has already been mentioned as a PR antagonist. But it also acts as GR antagonist and is indicated for patients with hypercortisolemia or Cushing's syndrome associated with hyperglycemia, since mifepristone increases secretion of adiponectin – a hormone which decreases adipose tissue as well as reduces insulin resistance. It acts non-selectively by completely blocking GR, PR, but not MR. However, treatment with this agent demands consistent monitoring because it can induce some side effects such as hypokalemia, endometrial hypertrophy and aborted pregnancy. [112, 113]

C113176 is a selective GR antagonist which can decrease the effects induced by high levels of GCs. It enhances the response of β -cells, therefore it alleviates fasting hyperglycemia and insulin resistance. [112]

7. CONCLUSIONS

The predominant aim of my diploma thesis was to perform a research regarding the development of steroidal hormone modulators and write a review mentioning new drugs which are under clinical trials as well as referring to older drugs if necessary. Apparently novel drugs are both more efficient and less risky than the old ones. The main purpose of their development was to increase the quality of life by maximizing their effect as well as reducing their overall adverse effects.

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