Synthesis of steroid bearing heterocyclic derivatives and biological activity. Review 2014-2020

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Abstract. Steroidal building blocks have drawn research groups attention in many branches of science and technology, such as pharmacological and medical fields, supramolecular chemistry and compounds in nanotechnology. So the recent years have witnessed a wide focus of research directed towards preparing heterocyclic derivatives fused with steroid molecules as a result of the great biological activity these compounds. This review described an outline of the literature reports (2014-2020) of synthesis heterocyclic compounds for steroid molecules fused at rings-A or B or D of steroid skeleton or annealed. Also the review included the biological activity of steroid heterocyclic as anti breast cancer, anti prostate cancer, antioxidant and antimicrobial.

Keywords: steroid, heterocyclic, breast cancer, prostate cancer, antioxidant and antimicrobial

1. Introduction

Steroidal compounds are a class of bioactive substances that play a major role in living organisms they are widely existed in natural world. They have been recognized for more than a century because of Chevreul's isolation of cholesterol from gallstones (1815) and the explanation of its chemical formula by four fused rings, commonly one in five and three in six with a minimum of 17 carbon atoms from Windaus (1932). Steroids are one of the most significant secondary metabolites due to their large biological activity [1-3], steroids were used in a wide variety of ways. At first, it was thought that these adrenal gland isolates were only useful in patients with Addison disease [4]. Many steroidal compounds display a variety of biological activities, such as anti bacterium and hormone-like drugs, have been used as traditional medicines. The bulk of steroid drugs are semi-synthetic in addition to the naturally occurring substances [5] scientific have found that altering the steroidal molecule structure or adding other role groups in the steroidal skeleton may significantly change the bioactivity of these compounds and decrease side effects and even change pharmacodynamic properties [6,7], recent work has concentrated extensively on rational modification of steroid molecules for the last few decades, this is because such compounds are less toxic, less vulnerable to multi-drug resistance and highly bioavailable due to their ability to penetrate the cell wall and to be linked to nuclear and membrane receptors they draw researchers' attention automatically and help advanced pharmaceutical drug production [8,9], so there a number of manuscripts reporting the synthesis of the steroid molecules containing heterocyclic moieties, either annelated or spiro-coupled to ring A and D for example pyrazole, thiazole, oxazole, oxadiazole, 1pyridine or pyrimidine [10,11]. It has been found that many of these steroidal heterocycles have strong biological activities, such as anti-inflammatory, anti-estrogenic, anti-microbial, anabolic, hypotensive, and cardiovascular activities [12-14].
So many articles were worked to synthesize and identify substituted steroids have been carried out, various steroidal compounds have been synthesized and tested for their biological activities with unusual and interesting structures [15].

1-1 Steroid derivatives as anti-breast cancer

Breast cancer is the most common cancer among women worldwide, with over 1.5 million new cases identified annually, it is also the fifth-largest cause of death from cancer [16,17]. The tumor is demonstrated by the excess production of endogenous estrogens receptors that is similarly found in breast tissue pre- and post-menopausal [18]. The most common type of hormone-dependent malignancy is estrogenic steroids which support the growth and development of hormone-dependent breast cancer. Estrogens block potential for treating breast cancer [19]. Therapies that inhibit either estrogen synthesis or action for postmenopausal HR+ breast cancer are now recognized as first-line treatments for most postmenopausal women with active breast cancer with an estrogen receptor (ER+) [20]. Notwithstanding substantial progress in cancer treatment approaches, new highly efficient therapies and modern poly chemotherapy protocols remain urgently needed [21]. Natural products with a steroidal background have opened so many fields for medicinal chemistry and pharmacology. Steroids are a major natural product class and take a vital part of life. The investigation of alter steroid molecules condensed with the various heterocyclic cores has attracted considerable attention [22]. The essential component of the cell membrane is cholesterol, is a steroid serving as a complement to certain vitamins (D). Sometimes they play an important role alongside chemotherapy [23]. The development of high-power anticancer drugs with minimal side effects remains a general problem in the production of drugs [24,25]. Chemical steroid alteration provides means of altering the functional groups [26].

In 2014 Kovács, D et al. [27] were prepared novel classes of 17-exo-heterocycles in the androstene series bearing 1,3,4-oxadiazole moiety (4 a-c), the synthesized compounds were tested in vitro against four malignant cell lines (HeLa, MCF7, A2780 and A431), and showed the highest activity against HeLa cells as in scheme (1):

**Scheme 1.** explains prepared classes of androstene bearing 1,3,4-oxadiazole moiety

In 2015 and 2017 Dar, A. M et al. [28,29] synthesis new series of steroidal imidazolidine (6a-c) and pyrimidines (7a-c) derivatives after reacting steroidal thiosemicarbazones with chloro ethylacetate and (2-methyl) diethyl malonate respectively in ethanol as in scheme (2) and evaluation as anti-breast cancer by cell line MCF-7 as well as Cervical, Leukemia, Colon and Hepatic cancer cell lines:
Scheme 2. explains synthesis new series of steroidal imidazolidine and pyrimidines

In 2016 Elmegeed, G. A et al. [30] synthesis new class of triazolopyrimidino derivative (11) of steroid analogs by multi steps reaction as in scheme (3), the prepared compounds tested against human breast cancer cells (MCF-7):

Scheme 3. explains synthesis new class of triazolopyrimidino derivative of steroid analoge

In 2017 Lastly the Baji, Á. et al. [31] synthesis new derivatives of steroid bearing pyrazole moiety (14,15) in A ring of starting material and evaluation against three human breast malignant cell lines (MCF-7, T47D, MDA-MB-231) as follow in Scheme (4):
Scheme 4. Explains synthesis new derivatives of steroid bearing pyrazole moiety

In 2018 Amr, A et al. [32] synthesis new series of pyrazolines (18 a,b,19a,b) as follow in Scheme (5) the prepared compounds evaluation in vitro as anti-breast cell line MCF-7:

Scheme 5. Explains synthesis new series of pyrazolines for estrone

later in 2019 the same group [33] synthesis and designed new derivatives of pyrimidine (21,22a,b) of estrone by using estrone arylmethylenes as starting materials and evaluation as anti-breast cancer;
Scheme 6. Explains synthesis new series of pyrimidine for estrone

In 2020 Mótyán, G, et al. [34] synthesis new derivative of isoxazoline (26) by condensation dehydroepiandrosterone (DHEA) with ethyl formate the 16-formyl-DHEA were reacted with hydroxylamine to obtained the corresponding oxime [25] who was found to be more stable cyclic isoxazoline form as follow in Scheme (7), the synthesized compound tested against on human cancer cells in vitro, breast cancer cell (MCF-7) as well as (HeLa, PC-3, U2Os, and A549).

Scheme 7. Explains synthesis new derivative of isoxazoline for dehydroepiandrosterone

1-2. Steroid derivatives as anti-Prostate cancer

Prostate cancer is the most common disease among men worldwide, despite the enormous advancement in different scientific fields, prostate cancer remains a leading cause of death with age [35-37]. Androgens play an important role in the development and growth of prostate cancer [38-40], two of the most important androgens in this regard are testosterone and dihydrotestosterone [41,42]. Prostate cancer patients have been treated with various stages of treatment, In 1941 Huggins and et al introduced androgen deprivation as therapy for advanced prostate cancer [43] also the researchers suggested the treatment may be by inhibiting the formation of androgen [44] because the last step in the formation of androgen is stimulated by cytochrome P450 monooxygenase 17-hydroxylase 17,20-lyase (CYP17) [45], so researchers suggested that the treatment by inhibiting these enzymes via steroidal and non-steroidal compounds [46,47].

From the several studies have found can inhibition of the enzyme CYP17 by use hydrophobic molecules containing heterocycle in the outer part which can be coordinate as a sixth ligand with an iron atom.
present in the enzyme, comparable to a steroid molecule, and bear electronegative groups at its external positions \[48,49\]. So in 1996 the first steroid (27) was reported by Njar et al as an inhibitor for CYP17 containing the amidazole ring at site 17 \[50\]. Later in 2005 the galeterone (28) was prepared by the same group and used for the same purpose \[51\].

\[27\]
\[28\]

**Figure 1.** Anti prostate cancer

In 2014 Banday, A. H \[52\] was using pregnenolone as precursor for synthesis new derivatives of pyrazoline (31) and tested as inhibitor for 5α-reductase as follow in Scheme (8):

\[29\]
\[30\]
\[31\]

*Scheme 8. explains synthesis new derivative of pyrazoline for pregnenolone*

In 2015 Kovács, D et al. \[53\] synthesized new derivatives of 2,5 disubstituted oxadiazole (35 a-f) by multi step reactions from androstene and was studies effect inhibitors for C17,20-lyase on rat as in followed Scheme (9):

\[32\]
\[33\]
\[34 a-f\]

*Scheme 9. Explains synthesis new derivatives of oxadiazole*

In 2016 Fan, N. J et al. \[54\] used progesterone as the starting material for prepared a series of steroid derivatives possessing a D-ring substituted benzamidothiazole (39-44 a,b) as in Scheme (10) and evaluation against cell line PC-3 (prostate cancer) and SKOV-3 cell line (ovarian cancer):

\[35 a-f\]
Scheme 10. Explains synthesis new derivative of thiazole

In 2017 Nongthombam, G. S et al. [55] synthesized a novel series of substituted androst pyridines (pyridosterooids) (48 a-c) of the reaction from β-formyl enamides with alkynes as in Scheme (11), and evaluation against prostate cancer PC-3 cells with comparison normal cell line RWPE-1:

Scheme 11. Explains synthesis new derivative of pyridine

In 2018 Savić, M. P et al. [56] synthesized novel A-ring pyridine (50) fused androstanes , new derivatives were prepared by treatment of 4-en-3-one D-modified androstane compound with propargylamine catalyzed by Cu^{2+}, and tested as anticancer in vitro by different cell line including PC-3 cell line (prostate cancer):
In 2019 Mótyán, G et al. [57] used aldol condensation of DHT with acetaldehyde to obtained a 2-ethylidene derivative which was reacted with phenylhydrazines to synthesis of novel ring A-fused arylpyrazoline (54) of dihydrotestosterone, the 17-keto analogs of steroidal pyrazoles were synthesized by Jones oxidation, the last compounds tested in vitro as anti-prostate carcinoma cell lines and breast carcinoma cell lines (HeLa, MCF-7 and MDA-MB-231):

Scheme 12. Explains synthesis new derivative of pyridine arylpyrazoline of dihydrotestosterone.

In 2020 Latysheva, A. S et al. [58] synthesized new compounds of oxazoline (59,60) and benzoxazole (61) from 3β-acetoxyandrosta-5,16-dien-17-carboxylic as follow in Scheme (14), The synthesized derivatives tested as inhibitors for growth of prostate carcinoma cell line (LNCaP and PC-3):

Scheme 13. Explain synthesis new derivative of pyridine arylpyrazoline of dihydrotestosterone.
Scheme 14. Explains synthesis new derivative of benzoxazole and oxazoline

1-3: Steroid derivatives as anti-oxidant

Oxidative stress is identified by excess production of the species of reactive oxygen (ROS) which can cause damage to the mitochondria [59], (ROS) are radicals derived from oxygen and involve highly reactive superoxides (O$_2^•$), peroxy (RO$_2^•$), and hydroxyl (•OH) as well as nonradicals for instance peroxynitrite(ONOO$^-$) and hydrogen peroxyde (H$_2$O$_2$) [60,61], antioxidants any material that substantially retards or prevents the oxidation of that substrate when present at low concentrations compared to that of an oxidizable substrate [62,63]. Collection of amino steroids have been known as antioxidants and a growing array of evidence has verified these compounds ability to limit free radicalized cell injury, these agents may inhibit lipid peroxidation, prevents free arachidonic acid release from damaged cell membranes and, thus, mitigate the damage caused by the secondary wave of injury that follows any cell membrane insults [64,65].

So the number of papers dealt with prepared steroid bearing hetero cyclic and evaluation as anti-oxidant In 2014 Asif, M [66] synthesized new series of steroidal tetrazole derivatives (64a-c) and evaluation as anti-oxidant as well as anti proliferative has been obtained by convenient method in a two-step reactions as in following Scheme (15):
In 2015 Ali, A et al. [67] synthesized a new series of steroid heterocyclic molecules (70-72a-c) (oxazole, thiazole and imidazole) from cholesterol derivatives by multi-step reactions as in Scheme (16) and evaluation it as anti-oxidant as well as anti cancer.

More over in the same year Shamsuzzaman etal [68] synthesized new derivatives of steroidal 2Hpyrans (74a-c) by reacted (73a-c) with ethyl acetocacetate in presence chitosan as catalyst (as an eco-friendly heterogeneous) as in Scheme (17), the synthesized compounds were tested in vitro antioxidant activity.
by DPPH method as well as against two cancer cell lines [Jurkat (leukemia) and HeLa (cervical)], the compounds exhibited good antioxidant activity and moderate to good activity as anti-cancer.

Scheme 17. Explain synthesis new derivative of 2-Hpyran

In 2017 Asif, M et al. [69] synthesized steroidal compounds bearing a ring thiazole (75 a-c, 77) by the treatment of steroidal ketones with phenacyl bromide and thiosemicarbazide in ethyl alcohol under the microwave irradiation as in the following Scheme:

Scheme 18. Explain synthesis new derivative of oxazole, thiazole and imidazole

Later in the same year Ali, A et al. [70] synthesized new derivatives of steroidal heterocycles bearing pyrimidine (80 a-c) for cholesterol by multi step reaction as shown in Scheme (19), the prepared compounds evaluated as anti cancer by using different cell lines HeLa (human cervical carcinoma), MDAMB231 (breast carcinoma), HepG2 (hepatic carcinoma) and antioxidant activity.
Lastly in 2020 Popov, S. A et al. [71] synthesized novel compound of oxadiazole with mercapto substituents (80) possess a great potential for breast cancer and antioxidant as in the following Scheme (20):

**Scheme 19. explain synthesis new derivative of pyrimidine**

1.4. Steroid derivatives as antimicrobial

Antimicrobial resistance has gained renewed interest in the clinical arena in recent years and has raised serious public health issues since various microbial drug-resistant infections occur [72]. Bacteria are known to multiply very rapidly and can share genes with each other leading to resistance growth[73]. Enteric bacterial infections cause morbidity and mortality worldwide, mainly in developed countries and areas. For example the tropical part of Africa Indian sub-continent, and part of South
America [74], there is a strong need for new compounds with antibacterial activity to be discovered [75] incorporating heterocyclic rings to steroids often changes the physiological behavior [76] So the literature has shown that both steroids and heterocyclic compounds have therapeutic and biological activity [77,78], one of the steroids bearing heterocyclic as in (figure 2) use as antibacterial [79].

In 2014 Saikia, P et al. [80] synthesized cholesterol bearing heterocyclic (88 a-h) by multi step reactions, the last step involve reacted epoxy group with N-substituted heterocyclic under micro wave radiation as follow in Scheme (21), some of the compounds showed moderate inhibition against the growth of pathogenic *Staphylococcus aureus*, bacteria *Escherichia coli*, *Bacillus subtilis*, *Proteus vulgaris* and *Pseudomonas syringae*. 

In 2015 Lauro, F. V et al. [81] synthesized new derivative of diazolidine steroid (90) by the reaction of a testosterone molecule with thiourea in presence of hydrochloric acid as catalyst, the synthesized compound was evaluated on the Gram negative (*E coli* and *Vibrio cholerae*) and Gram positive (*Staphylococos aureus*) bacteria:

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**Figure 2.** antibacterial

**Scheme 21.** Explains synthesis new derivative of steroid bearing heterocyclic

**Scheme 22.** Explains synthesis new derivative of diazolidine

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In 2016 Khanam, H et al. [82] synthesized new derivatives of pyrazolines (91a-c) by reaction of the cholest-5-en-7-one (62a-c) with 2,4-diNirtophenylhydrazine as follow in Scheme (23). The synthesized compounds were tested in vitro as antimicrobial activity as well as anticancer, which compound (91c) showed potent antimicrobial behavior against *Staphylococcus epidermidis* and *Corynebacterium xerosis*.

![Scheme 23. Explain synthesis new derivative of pyrazolines](image)

In 2016 Sribalan, R et al. [83] synthesized new class of glycinate and carbonate derivatives of cholesterol bearing pyridine moiety (94) by multi step reactions as shown in Scheme (24) and evaluated for their *in vitro* antimicrobial activity against gram-negative bacteria and fungi.

![Scheme 24. Explain synthesis new derivative of pyrimidine](image)

In 2018 Ansari, A et al. [84] prepared a new series of derivatives of thiazole and oxazole(95a,c) employing thiosemicarbazide/semicarbazide hydrochloride and ethyl 2-chloroacetoacetate by one-pot multicomponent reaction pathway as shown in Scheme (25). The antimicrobial activity of newly compounds were evaluated against four bacterial strains namely Gram-positive bacteria (*Staphylococcus aureus* and *Listeria monocytogenes*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) as well as pathogenic fungi (*Candida albicans* and *Cryptococcus neoformans*).
Scheme 25. Explains synthesis new derivative of thiazole and oxazole

In 2019 Hryniewicka, A et al. [85] synthesized new derivatives of imidazole salts (99a,d) of lithocholic acid as shown in Scheme (26), the prepared compounds appears good activity as anti-microbial.

Scheme 26. Explains synthesis new derivative of imidazole salts

Alam, M et al. [86] designed and synthesized steroidal derivatives containing Phosphorus [101a,b] by reaction the hydroxyl group of (100 a,b) with phosphoryl tri chloride in presence ethylene di amine as basic catalyst as shown in Scheme (27), The prepared compounds studied as inhibitors for fungicidal and herbicidal, the compound (65 b) appear a good fungicidal activity against mycelium growth of fungi.

Scheme 27. Explains synthesis new derivative of steroidal containing Phosphorus
2. Conclusions
From the survey literature to the synthesis steroid heterocyclic has been found that some of derivatives have different biological activity and may be considered as potential for treatment breast and prostate cancer.

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