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Article

Synthesis of Heterosteroids and their Biological Evaluation: A Review

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ABSTRACT

Steroids are the compounds of prime importance due to being the fundamental class of biologically signaling molecules. Their profound biological activities are well validated. They can regulate a variety of biological processes and, thus, have the potential to act as drugs for the treatment of a number of diseases including breast cancer, prostate cancer, oxidation problems, and microbial infections. The diversity in the biological action might be due to the presence of different functional groups located around the tetracyclic core which serves as substrates for different targets. The advantage of employing hydrophobic steroid units is their ability to interact with cell membranes and thus pave the way for biological activity of such hybrid molecules. This review depicts not only the synthesis of different heterosteroids but also their biological behavior such as anticancer, antioxidant, antibacterial, and antifungal activity.

Key words: Heterosteroid, Breast cancer, Prostate cancer, Antioxidant and antimicrobial.

1. INTRODUCTION

Steroidal heterocycles are a class of biologically active molecules that play an important role in biological systems which are widely existed in natural world. They has been well recognized for more than a 100 years after the Chevreul's isolation of cholesterol from gallstones in 1815 and the explanation of its chemical formula by four fused rings, with a minimum of 17 carbon atoms from Windaus in 1932. Steroids are the one of the most significant secondary metabolites due to their large biological activity [1-3]. At first, it was thought that these adrenal gland isolates were only useful in patients with Addison disease [4], but, later, it was found that these heterosteroids display a variety of biological activities, such as antibacterial, antifungal and anticancer, and anti-human immunodeficiency virus. The majority of steroidal drugs are semi-synthetic compounds which are being prepared by appending a heterocyclic moiety to the steroid core [5]. Scientists studied that by altering the steroidal molecule or by adding other moiety in the steroidal skeleton may significantly change the bioactivity of these compounds and even change pharmacodynamic properties [6,7].

From the past decade, steroid molecules undergo on extensive rational modification which is due to their less toxic nature, less vulnerable to multidrug resistant, and more importantly being highly bioavailable due to their ability to penetrate the cell wall and get attached to the nuclear and membrane receptors [8,9]. Hence, there is a good amount of literature reporting the synthesis of the steroid molecules containing heterocyclic moieties, either annelated or *spiro*-coupled to ring A, B, and D, for example, pyrimidine, pyran, pyrazole, thiazole, oxazole, pyridine, or thiazine [10,11]. It has been found that many of these steroidal heterocycles have strong biological activities, such as anti-inflammatory, anti-microbial, anticancer, antioxidant, and cardiovascular activities [12-15].

2. HETEROSTEROIDS AS ANTI-BREAST CANCER AGENTS

Breast cancer is the fifth-largest cause of death from cancer and is the most common found in women worldwide, with over 1.5 million new cases identified annually [16,17]. In this type of tumor, there occurs excess production of endogenous estrogen receptors [18]. The most common type of hormone-dependent malignancy is due to the estrogenic steroids. Since estrogens block potential for treating breast cancer [19]; hence, therapies that inhibit either estrogen synthesis or action for postmenopausal HR+ breast cancer are now recognized as first-line treatments [20]. Since there had not been continuous, improved progress in cancer treatment approaches, hence, more efficient therapies or modern polychemotherapy protocols remain urgently needed [21]. Steroids are an important class of natural products and, hence, are the vital part of life, so the investigation to alter steroid molecules appended with the various heterocyclic moieties has attracted considerable attention [22]. The cyclopentanoperhydrophenanthrene being the essential component of the cell membrane, also play an important role in cancer chemotherapy [23]. Since steroid being non-metallic complex, their cytotoxicity is not as much efficient as in metallic complexes. Furthermore, the synthesis of efficient metallic anticancer drug with minimal side effects remained a general problem [24]; hence, there is a scope for the improvement which can be made either through core alteration or by changing the functional groups [25].

In 2013, Shamsuzzaman *et al.* [26] synthesized steroidal pyrimidines (**7-9**) by reacting steroidal thiosemicarbazones (**4-6**) with diethyl malonate. These compounds depicted potential toxicity against different cancer cell lines such as A545, MCF-7, HeLa, HL-60, SW480, HepG2, HT-29, and A549 (**Scheme 1**).

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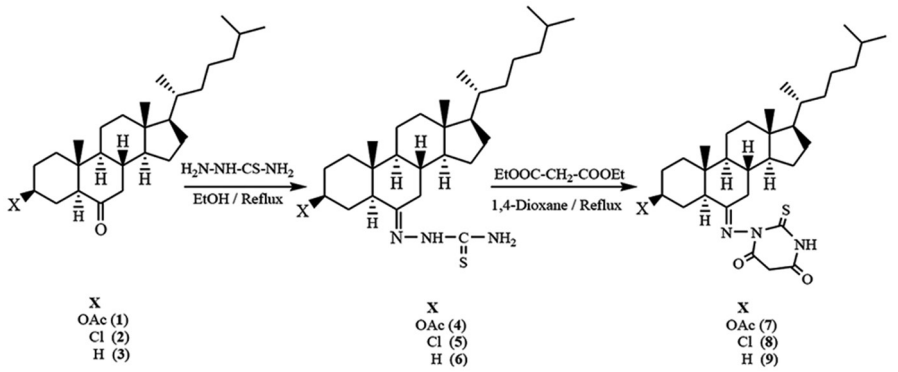
In 2013, Shamsuzzaman *et al.* [27] synthesized steroidal 1*H*-pyrimidines (**7-9**) by reacting steroidal thiosemicarbazones (**4-6**) with ethyl cyanoacetate. The MTT assay was carried out to check the toxicity of new compounds **7-9** against the different human cancer cell lines A545, MCF-7, HeLa, HL-60, SW480, HepG2, HT-29, and A549. It seemed to follow the mechanistic pathway involving the generation of singlet oxygen and a superoxide anion, which is responsible for initiating DNA strand scission (**Scheme 2**).

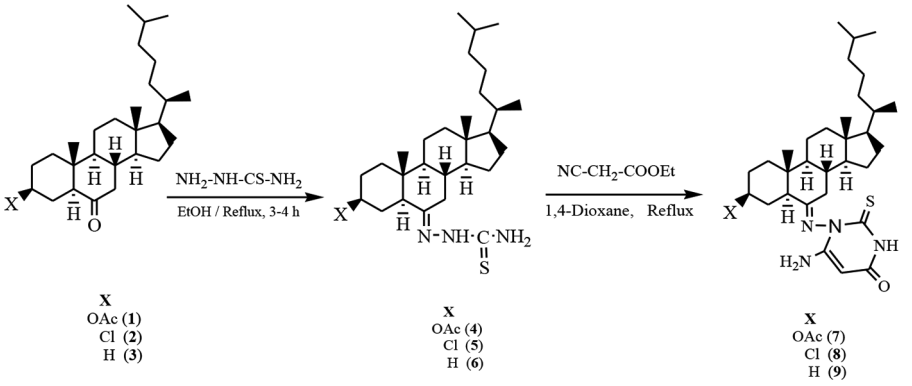
Kovacs *et al.,* in 2014 [28], synthesized new classes of 17-*exo*-androstene series bearing 1,3,4-oxadiazole moiety, the synthesized compounds were screened against different cancer cell lines (HeLa, MCF7, A2780, and A431) by MTT assay and depicted potential cytotoxicity (**Scheme 3**).

Dar *et al.,* in 2015 and 2017 [29,30], synthesis new series of steroidal imidazolidine (6a-c) and pyrimidines (7a-c) derivatives after reacting steroidal thiosemicarbazones with chloroethylacetate 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 4**).

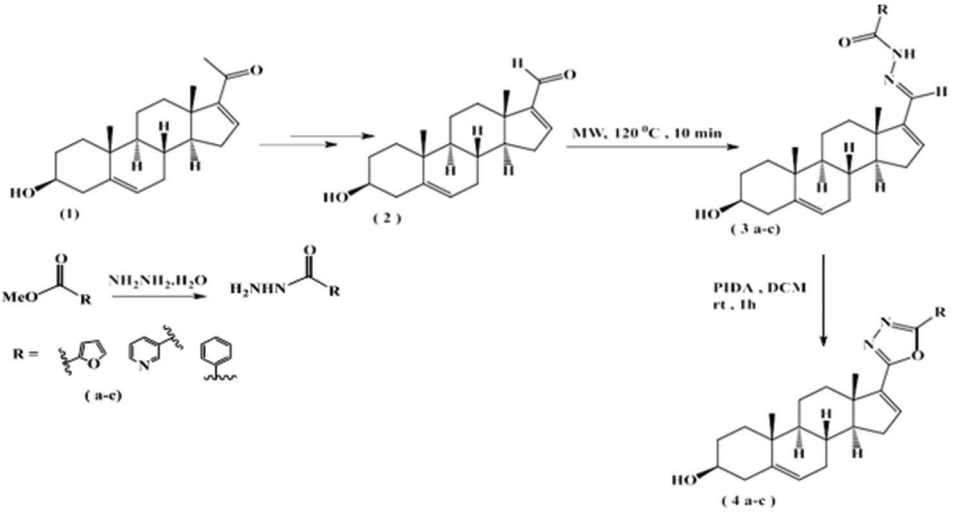
Elmegeed *et al.,* in 2016 [31], prepared new class of substituted steroidal triazolopyrimidines by multi steps reaction, as shown in **(Scheme 5)**, the compounds after characterization were later tested



Scheme 1: Pathways for the synthesis of steroidal pyrimidines.



Scheme 2: Pathways for the synthesis of steroidal 1*H*-pyrimidines.



Scheme 3: Synthesis of androstene bearing 1, 3, 4-oxadiazole moiety.

against human breast cancer cells (MCF-7) during which they showed potential activity:

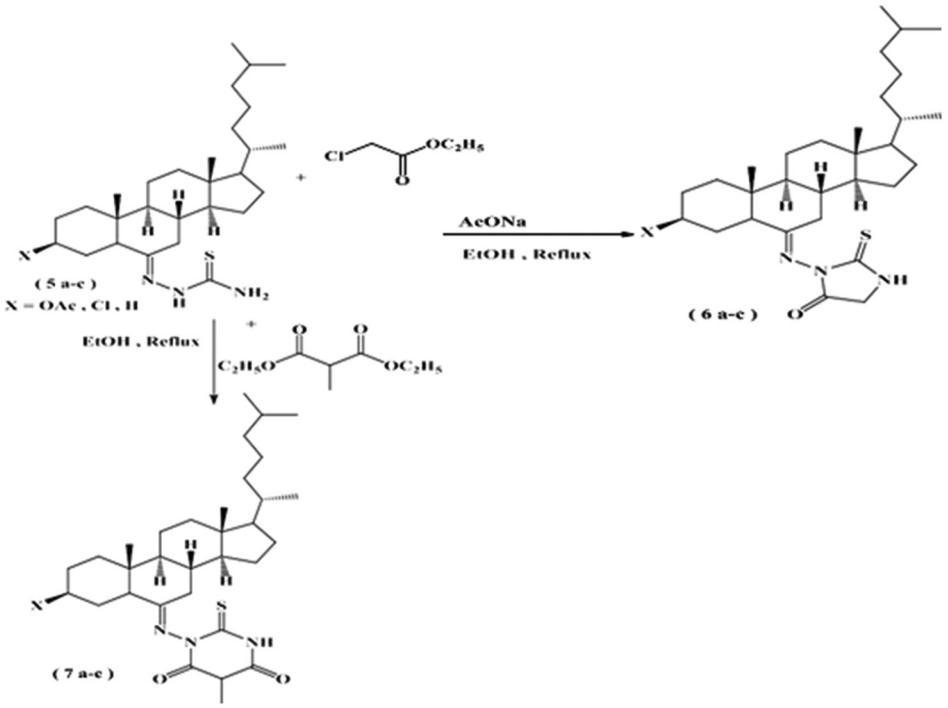
Baji *et al.,* in 2017 [32], synthesis new derivatives of steroidal pyrazoles (14,15) appended on ring A of starting steroid molecule (**Scheme 6**) and later these compounds were screened for anticancer activity against three human cancer cell lines (MCF-7, T47D, and MDA-MB-231), during which the compounds depicted potential cytotoxicity.

Amr *et al.,* in 2018 [33], synthesized a series of pyrazolines derivatives of estrone (18, 19) through Aldol type reaction (**Scheme 7**). The prepared compounds were screened for anticancer activity by means of MTT assay against breast cancer cell line MCF-7 during which the compounds depicted potential cytotoxic behavior.

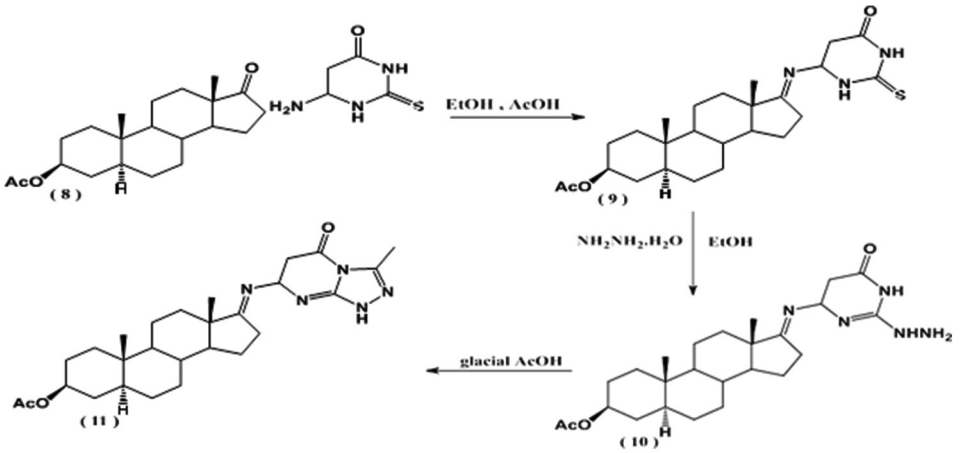
Also in 2019, the same group [34] synthesized and designed new pyrimidine derivatives of estrone (21, 22) of using estrone arylmethylenes as starting materials and in the report presented the anticancer evaluation against breast cancer line, during which the compounds depicted better anticancer activity (**Scheme 8**).

Motyan *et al.,* in 2020 [35], reported the scheme, in which the condensation of dehydroepiandrosterone (DHEA) (23) with ethyl formate was carried to yield 16-formyl dehydroepiandrosterone (24). The 16-formyldehydroepiandrosterone reacted with hydroxylamine to yield the corresponding oxime (25) which later on undergone cyclization and form more stable cyclic isoxazoline form **(Scheme 9)**. The new compounds were screened for *in vitro* anticancer activity against many human cancer cells such as MCF-7, HeLa, PC-3, and A549.

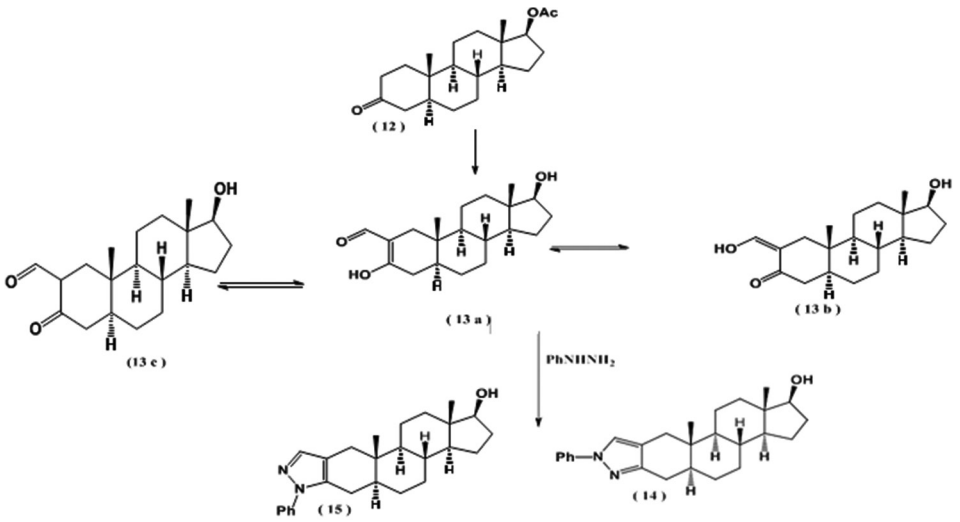
Ilovaisky and Terentev [36], in 2021, synthesized 13, 17-secoestra-1,3,5(10)-trien-17-oic acid hydrazides and their N'-(het)aryl methylene derivatives through a selective approach. The secosteroids were screened for cytotoxicity against hormone-dependent human breast



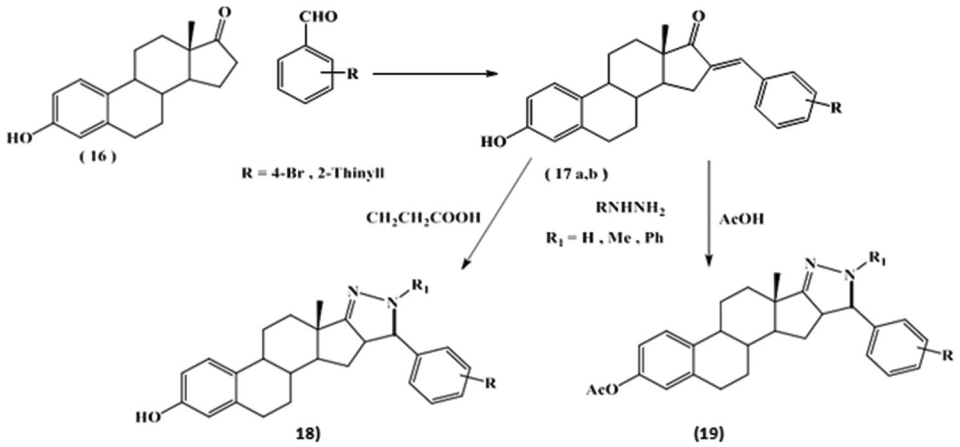
Scheme 4: The synthesis series of steroidal imidazolidine and pyrimidines.



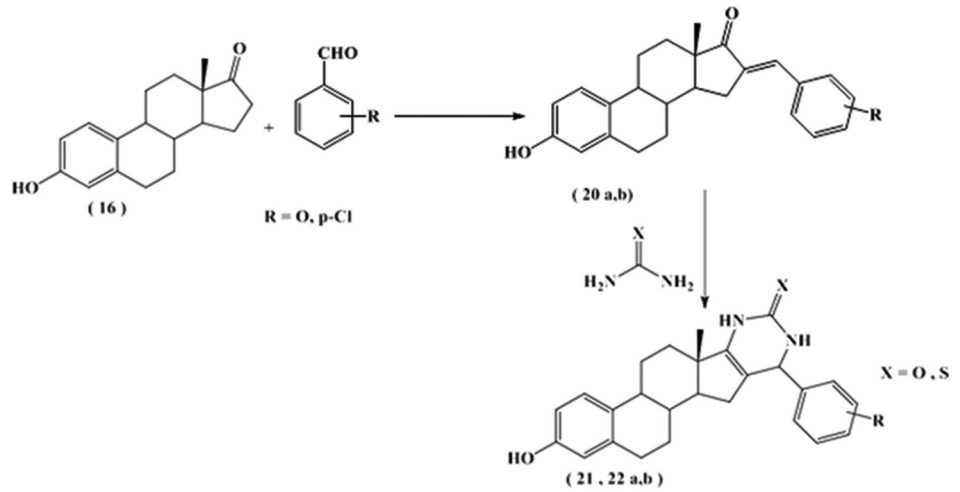
Scheme 5: The synthesis of steroidal triazolopyrimidine derivatives.



Scheme 6: Synthesis new derivatives of steroid bearing pyrazole moiety.



Scheme 7: The synthesis of pyrazolines derivatives of estrone.



Scheme 8: Synthesis of series of estrone pyrimidines.

cancer cell line MCF-7. A number of secosteroids showed significant anticancer activity even some depicted better cytotoxic behavior than the standard anticancer drug, cisplatin. One compound showed highest activity with the IC_{50} value of about 2 μM and is about 208 times more active than cisplatin (**Scheme 10**).

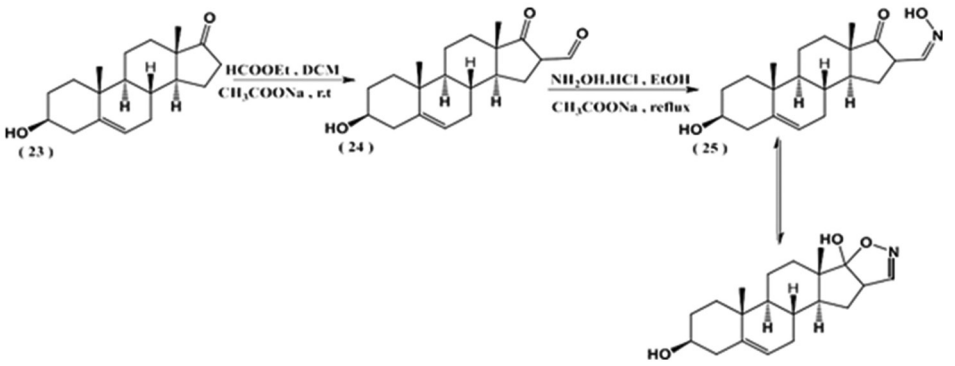
3. HETEROSTEROIDS AS ANTI-PROSTATE CANCER AGENTS

Despite of major advancement in cancer biology, prostate cancer still remained an unsolved problem, and hence due to this, innumerous

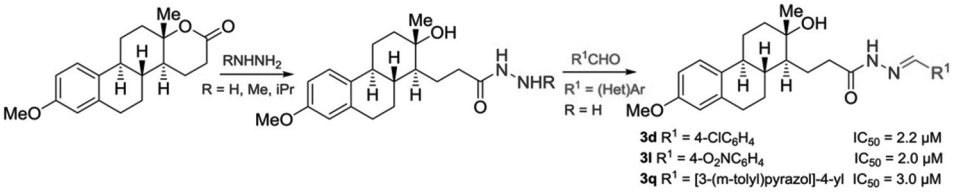
number of deaths had already occurred [37]. The main role played in the development of prostate cancer is Androgens [38-40], in which *testosterone* and *dihydrotestosterone* are two most important types [41,42]. There had been number of treatments in the treatment of prostate cancer starting from Huggins *et al.,* in 1941, who introduced androgen deprivation therapy for treatment of prostate cancer [43]. The other researchers suggested its treatment by inhibition of androgen formation [44], because the step in the androgen formation is activated by cytochromeP450-monooxygenase-17-hydroxylase-17,20-lyase (CYP17) enzyme[45], so scientists suggested the prostate cancer treatment by inhibition of enzyme through steroidal and non-steroidal compounds [46,47]. It has been found that inhibition of the enzyme CYP17 by these heterocycles is through the coordination of sixth ligand with an iron atom of the CYP17 enzyme with electronegative functional groups oriented toward outside [48,49]. The first CYP17 inhibitor which was first reported was steroidal imidazole derivative [50], and followed by another compound galeterone [51]. Both are the class of anti-androgen steroids later were where used for the treatment of prostate cancer **(Figure 1**).

Banday *et al.,* [52] in 2014, used pregnenolone as precursor for synthesis of new steroidal pyrazoline derivatives and successfully demonstrated them as 5α-reductase inhibitors. The compounds showed effective 5α-reductase inhibition, that is, compounds did an inhibition at very low concentration (**Scheme 11**).

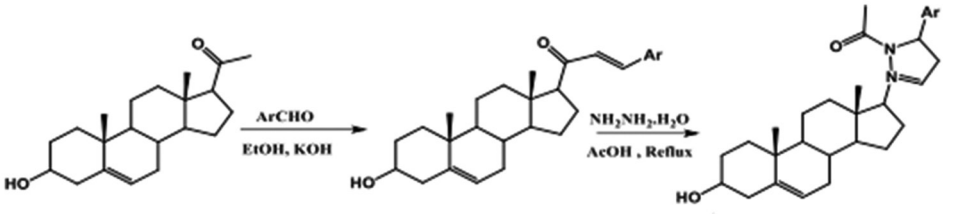
Kovacs *et al.,* [53] in 2015, prepared new series of disubstituted steroidal oxadiazole derivatives. The reaction started from androstene and after successful characterization, the compounds were screened for



Scheme 9: The synthesis of steroidal isoxazoline derivative.



Scheme 10: The synthesis of series of secosteroids.



Scheme 11: The synthesis of pyrazoline derivative of pregnenolone.

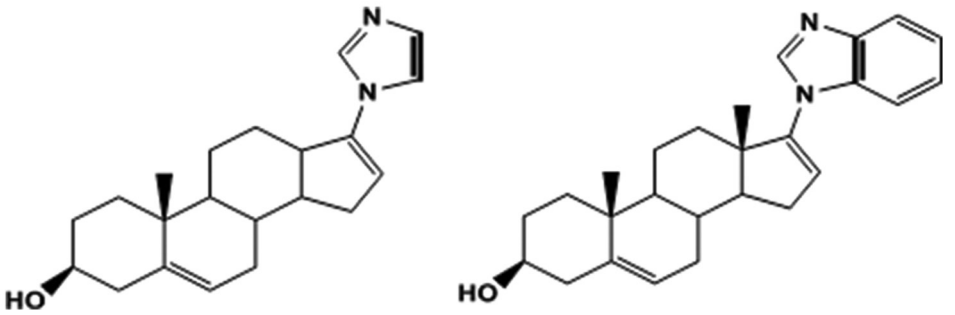


Figure 1: Steroidal imidazole derivatives as CYP17 inhibitor.

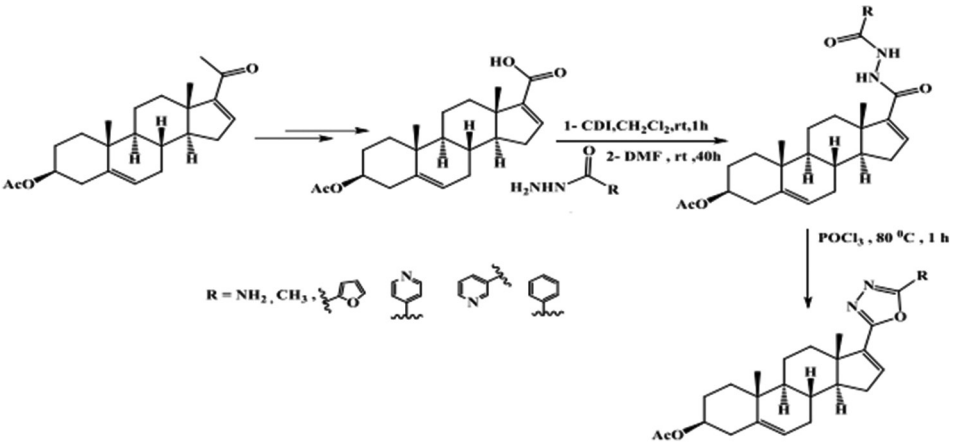
C17, 20-lyase inhibitors in rat. The compounds showed effective C17, 20-lyase inhibition, that is, compounds depicted lyase inhibition at minimum concentration which is dosable as per the health organization standards. The reaction **Scheme 12** is shown as follows:

Fan *et al.,* [54] in 2016, used progesterone as the starting material for preparation of a series of steroidal benzamidothiazoles. The compounds were characterized spectroscopically and later cytotoxic evaluation (MTT assay) was carried against PC-3 (prostate cancer cell line) and SKOV-3 (ovarian cancer cell line). The cell lines were incubated with the different concentrations of newly synthesized compounds for 24 h, 36 h, and 72 h. During the assay, the compounds showed concentration dependent toxicity and the compounds were toxic at very low inhibition count (**Scheme 13**).

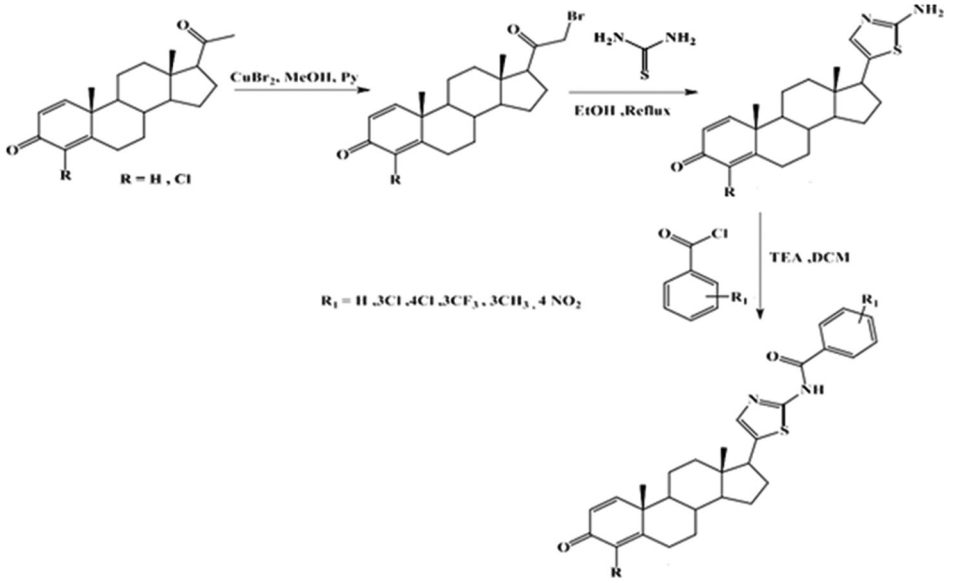
Nongthombam *et al.,* [55] in 2017, successfully prepared a new series of steroidal pyridines by the reaction of steroidal *β*-formyl enamides with alkynes. The steroidal *β*-formyl enamides were prepared from steroidal oxime under Vilsmeier–Haack conditions. The steroidal pyridines were screened for *in vitro* cytotoxicity against prostate cancer cell lines (PC-3 cells) during which compounds showed very low inhibition count. To check whether the compounds are generally toxic, MTT assay was carried for them against normal cell line (RWPE-1 cells), the compounds did not showed effective IC_{50} values (**Scheme 14**).

Savic *et al.,* [56] in 2018, synthesized novel androstane fused pyridine (A-ring) derivatives. The androstane underwent oxidation by Aluminum isopropoxide/cyclohexanone which yielded androstane 4-en-3-one derivative. The androstane 4-en-3-one derivative later reacted with propargylamine, catalyzed by Cu^{+2} in ethanol which yielded novel androstane fused pyridine (A-ring) derivatives. The new compounds were tested for *in vitro* anticancer activity against different cells (prostate cancer cells PC- 3), during which the compounds depicted potential anticancer behavior (**Scheme 15**).

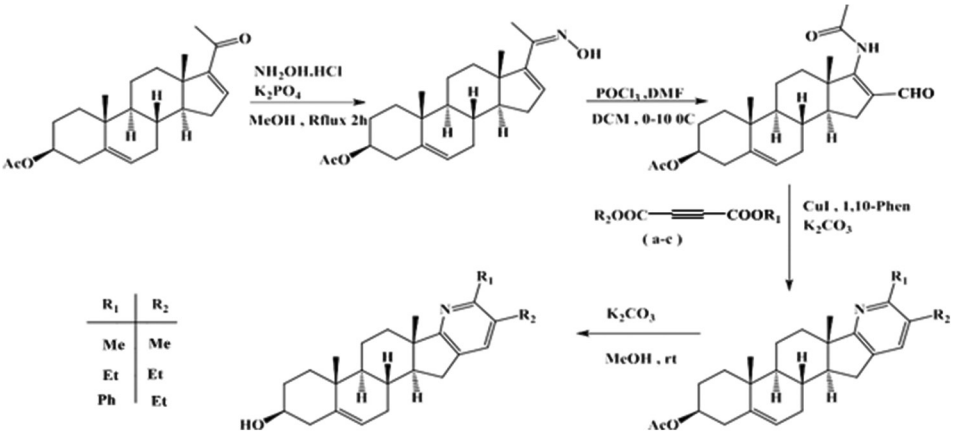
Motyan *et al.,* [57] in 2019, synthesized 2-ethylidene derivative by aldol condensation of dihydrotestosterone with acetaldehyde. The DHT reacted with phenylhydrazine to synthesize dihydrotestosterone fused with ring A-arylpyrazoline. The dihydrotestosterone with ring A- arylpyrazoline undergone the Jones oxidation and yielded the 17-keto analog of steroidal pyrazole. The final compound was screened for *in vitro* anticancer assay against prostate cancer cells and breast cancer cells (HeLa, MCF-7, and MDA-MB-231) during which the compound depicted effective IC_{50} (**Scheme 16**).



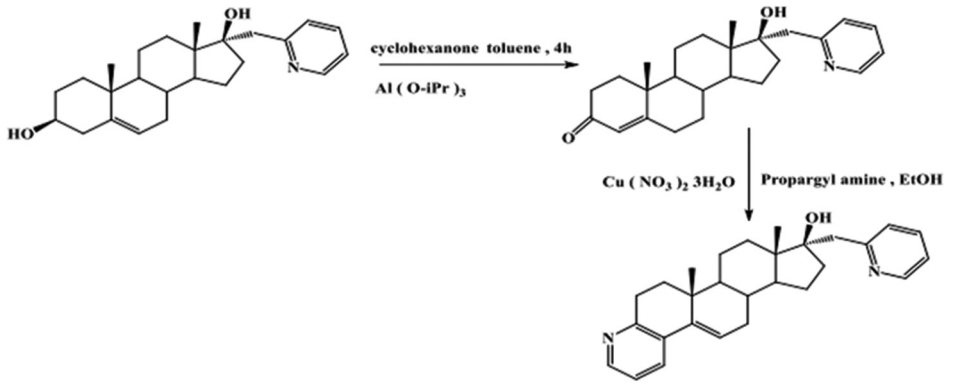
Scheme 12: The synthesis of new oxadiazole derivatives.



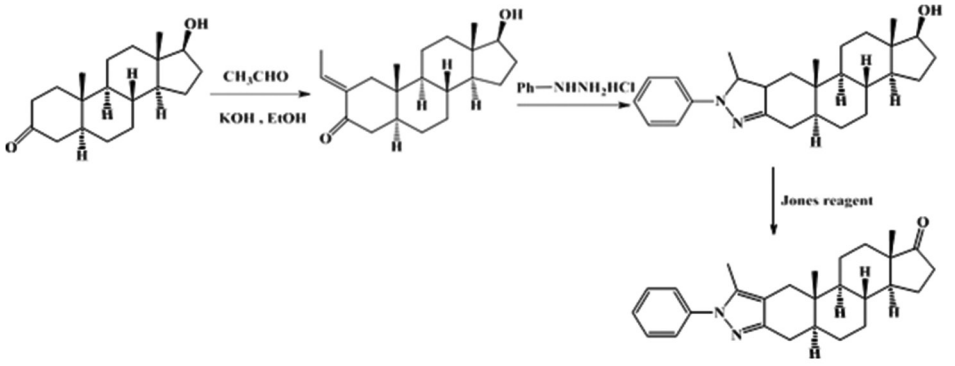
Scheme 13: Depicting the synthesis steroidal benzamidothiazole derivatives.



Scheme 14: The synthesis of disubstituted steroidal pyridines.



Scheme 15: The synthesis of androstane fused pyridine derivatives.



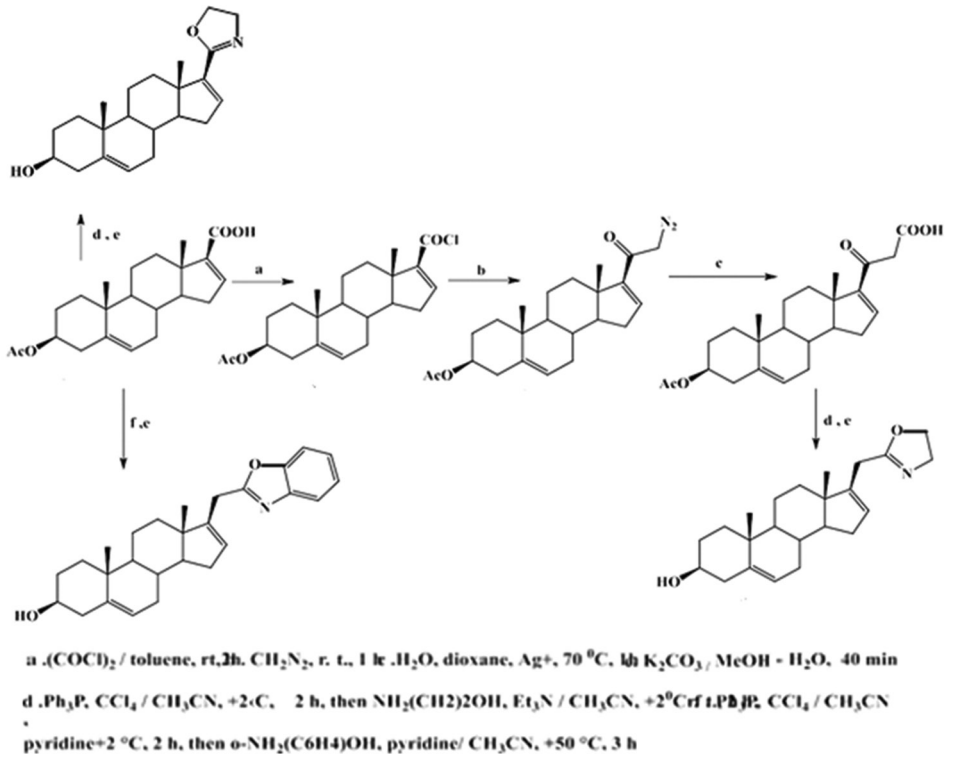
Scheme 16: The synthesis of steroidal pyrazole derivatives.

Latysheva *et al.,* [58] in 2020, performed the semi-synthesis of steroidal oxazoline and steroidal benzoxazole from 3β-acetoxyandrosta-5, 16-dien-17-carboxylic acid through the reaction cascade shown below. The reaction primarily converted acids into acid chlorides and later to the diazonium compounds. The compounds were screened for *in vitro* anticancer assay against as prostate carcinoma cells (LNCaP and PC-3) by MTT assay during which the compound depicted effective IC_{50} (**Scheme 17**).

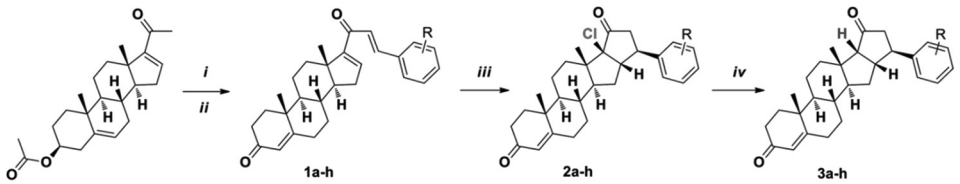
Vorontsova *et al.,* [59] in 2022, reported carbocyclic steroids *D*-annulated at 16α and 17α positions with a 5-membered ring E through Nazarov cyclization. Three steroid series have been structurally studied: chlorine-containing *D*-annulated pentacyclic steroids, their reduced derivatives, and their synthetic precursors – benzylidines of tetracyclic steroids. Selected steroids revealed antiproliferative potency and inhibited AR pathways in prostate cancer cells (22Rv1 cells), including down regulation in NKX3.1 and PSA expression. A combination of pentacyclic steroid with non-steroidal antiandrogen bicalutamide exhibited significant antiproliferative effects in 22Rv1 cells (**Scheme 18**).

4. HETEROSTEROID DERIVATIVES AS ANTI-OXIDANT ACTIVITY

Oxidative stress basically occurs when there is rigorous production of reactive oxygen species (ROS) that damages the DNA or mitochondria. The ROS is radical species generated from oxygen and involve highly reactive superoxides ($O_2^{\bullet-}$), peroxyl ($RO_2^{\bullet}$), and hydroxyl ($^{\bullet}OH$) as



Scheme 17: The synthesis of steroidal benzoxazole and oxazoline derivatives.



Scheme 18: The synthesis of carbocyclic steroids *D*-annulations with a 5-membered ring E through Nazarov cyclization.

well as non-radicals such as hydrogen peroxide (H_2O_2) and peroxy nitrite ($ONOO^-$) [60, 61]. The ROS disrupts DNA, causing oxidative cleavage and later leads to the apoptosis or simply cellular death. The antioxidant is any substance that prevents the peroxidation of the oxidizable substrate [62,63]. Among the steroid class, amino-steroids are well known antioxidants which stop the lipid peroxidation, prevent free release of arachidonic acid from damaged cell membranes, and, thus, overcome the damage [64,65].

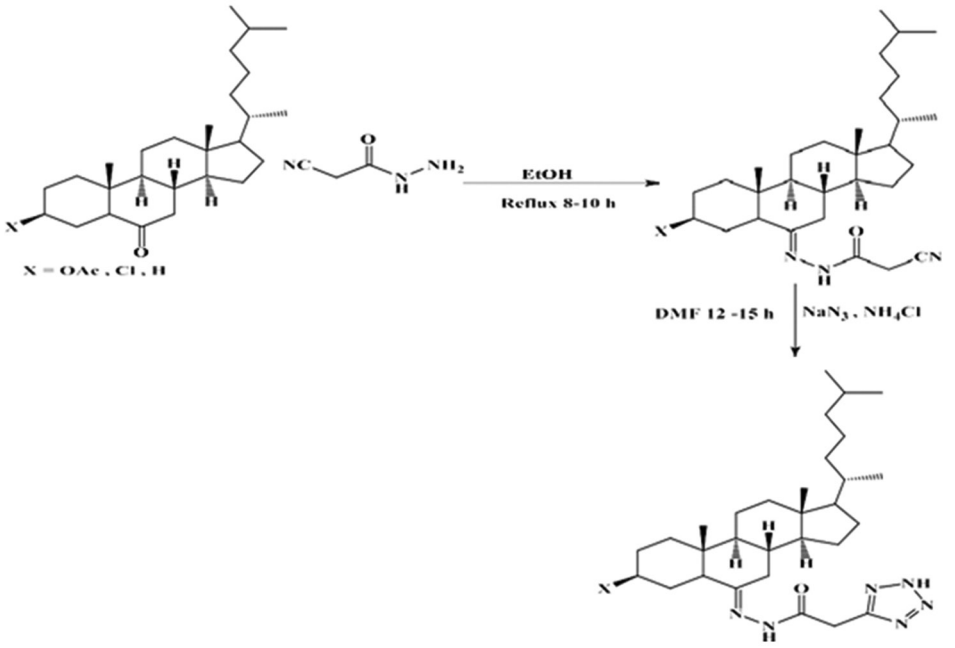
Asif [66], in 2014, reported the condensation of steroidal ketones with cyanoacetohydrazide which yielded cyanoacetohydrazone which later reacted cyclized with sodium azide and yielded new steroidal tetrazoles, as shown in **Scheme 19** below. Their evaluation as anti-oxidant as well as anti-proliferative agents was studied by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay and MTT assay during which compounds depicted effective behavior and has scope to act as both antioxidant and cytotoxic agents.

Ali *et al.,* [67] in 2015, described the nitration, reduction as well as condensation of cholesterol derivatives to yield nitrocholesterol, ketocholesterol, as well as hydrazone derivative of cholesterol through cascade of reactions. The hydrazone derivative reacts with 1, 2-benzenedicarboxaldehyde to yield another condensation product which further reacts with the 2-aminothiophenol and derivatives to yield steroidal oxazole, steroidal thiazole, and steroidal imidazole. The reaction **Scheme 20** is shown below.

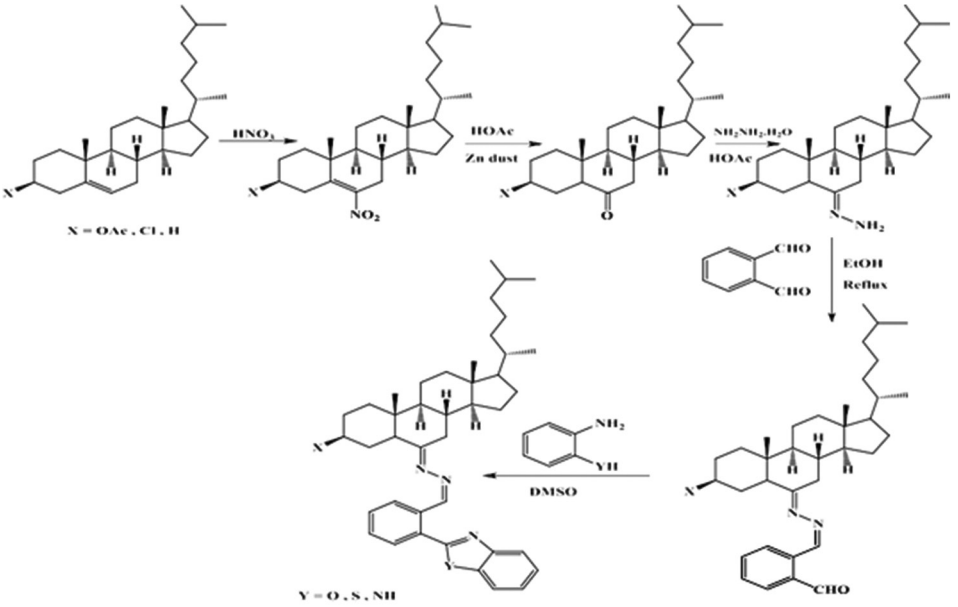
The compounds were later screened for antioxidant as well as anticancer activity. The antioxidant activity was checked by DPPH assay, while as the cytotoxicity was checked by MTT assay. During the screening the steroidal oxazole, steroidal thiazole and steroidal imidazole depicted the potential antioxidant as well as anticancer behavior.

Mashrai *et al.,* [22] again in 2015, synthesized new steroidal 2*H*-pyrans derivatives by reacting steroidal *α, β*-unsaturated ketone with ethyl acetoacetate in presence of chitosan as catalyst. The synthesized compounds were tested for *in vitro* antioxidant activity by DPPH method as well as for *in vitro* anticancer activity by MTT assay against two cancer cell lines [Jurkat (leukemia) and HeLa (cervical)], the compounds showed better antioxidant and anti-cancer activity (**Scheme 21**).

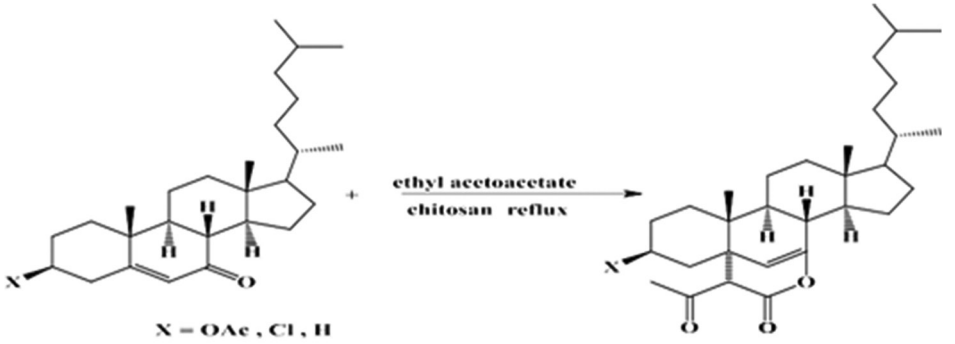
Asif *et al.,* [68] in 2017, prepared a procedure, in which the treatment of 3-substituted cholestan-6-one with phenacyl bromide and thiosemicarbazide was made under microwave conditions in one-pot manner, which leads to the formation of steroidal thiazoles. The synthesized compounds were screened for *in vitro* antioxidant activity



Scheme 19: Synthesis of steroidal tetrazole derivatives.



Scheme 20: Synthesis of steroidal tetrazole, oxazole, and thiazole derivatives.



Scheme 21: The synthesis of steroidal 2H-pyrans.

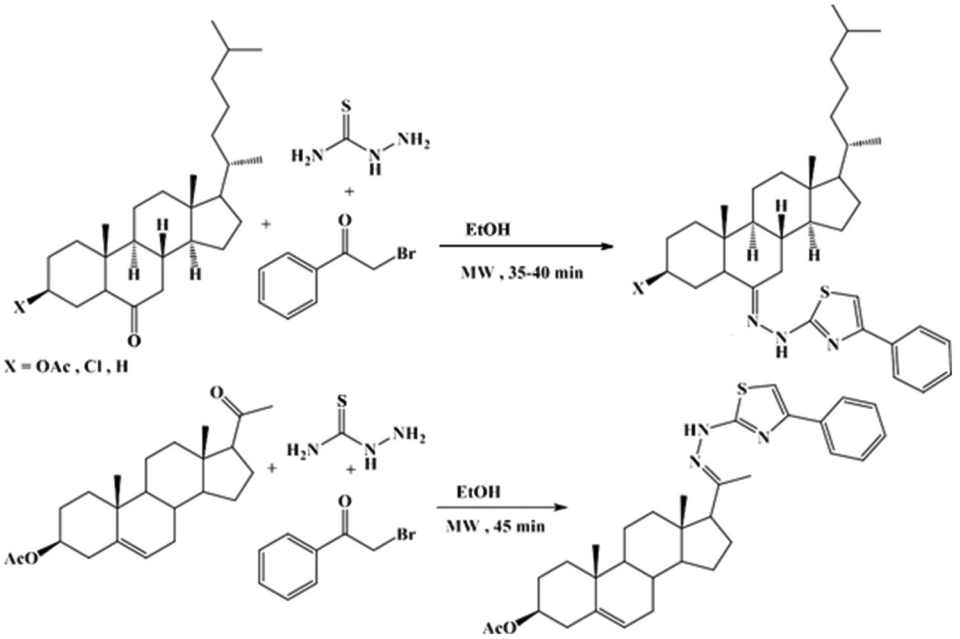
using DPPH method, in which the synthesized compounds depicted potential antioxidant activity. In addition to this, the compounds were also tested for pBR322 DNA cleavage activity, genotoxicity, reactive oxygen species (ROS) production, and RBC hemolysis. The compounds depicted better behavior in suppression of ROS production, potential cleavage activity, and proper genotoxic nature (**Scheme 22**).

Ali *et al.,* [69] in 2017, synthesized new derivatives of steroidal pyrimidine by the reaction of 3-substituted cholestan-6-one derivatives with urea and benzaldehyde in the presence of trimethylsilyl chloride. The new compounds were evaluated for anticancer activity against HeLa (human cervical carcinoma), MDAMB-231(breast carcinoma), and HepG2 (hepatic carcinoma) during which the compounds depicted potential cytotoxic nature. The compounds were also screened for *in vitro* antioxidant activity using DPPH assay during which the compounds depicted potential antioxidant activity (**Scheme 23**).

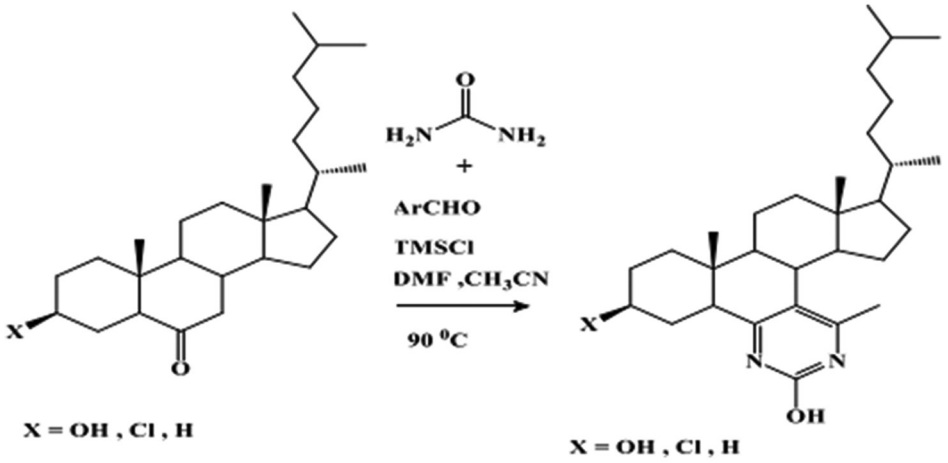
Popov *et al.,* [70] in 2020, prepared the protocol, in which the acetylation of steroid derivative was done, followed by reaction with hydrazine hydrate which finally on reaction with carbon disulfide yielded steroidal oxadiazole with mercapto substituent. The new compound was assessed for MTT assay during which the compound depicted potential breast cancer and antioxidant activity (**Scheme 24**).

5. HETEROSTEROID DERIVATIVES AS ANTIMICROBIAL AGENTS

Since in day to day life, different antibiotic drug-resistant infections occur hence bacterial infections have gained profound interest in the clinical microbiology in recent years [71], the reason being that the bacteria are known to grow very fast, multiply exponentially, and share genes with each other, leading to resistant growth [71]. Since the world is suffering due to the bacterial infections, as the entire morbidity and mortality occurring worldwide, particularly in developed countries and areas like the tropical part of Africa and Indian sub-continent, are due to these infections [72]. Hence, there is a strong urge to synthesize new compounds with antibacterial activity which can be made possible after incorporating the heterocyclic ring to steroid core which brings new biological activities of the hybrid molecule [73,74]. Since the literature reveals that both steroids and non-steroid compounds have therapeutic and biological properties [75,76], but, here, we restrict our study to the heterosteroid derivatives as antimicrobial agents.



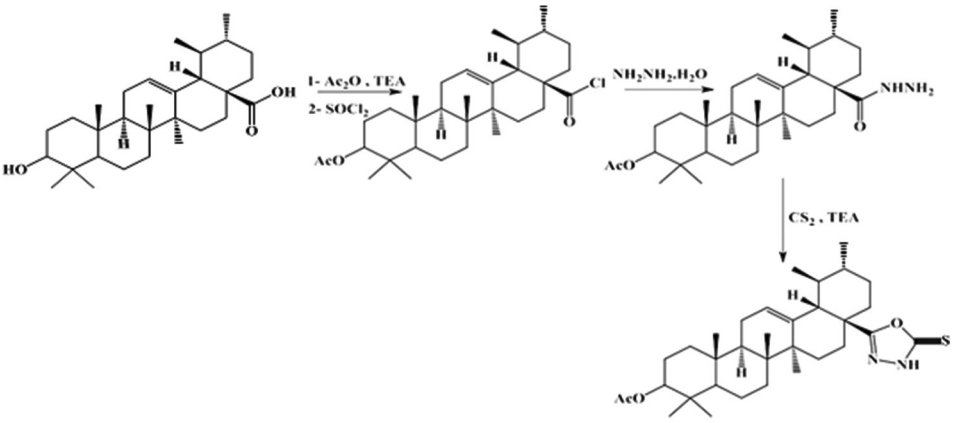
Scheme 22: The synthesis of new steroidal oxazole derivatives.



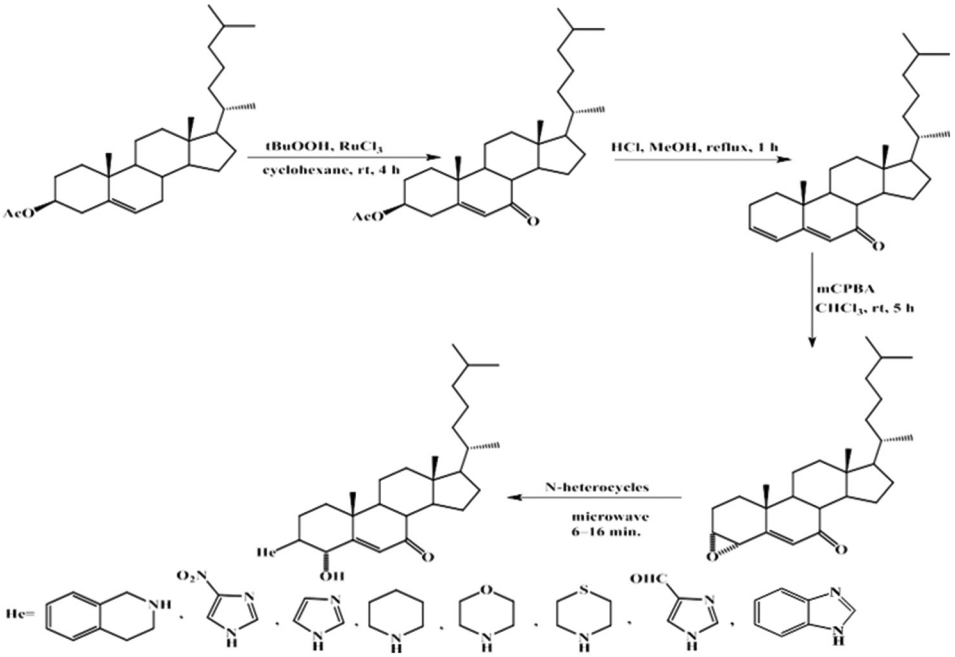
Scheme 23: Depicting the synthesis of steroidal pyrimidine derivatives.

Geetmani and Romesh [77], in 2019, synthesized steroid pyrido [2, 3-*d*] pyrimidine from steroidal formylenamides in the reaction cascade. The compound is shown below and can be used as antibacterial agent. The antibacterial activity was carried out by Disk Diffusion method during which the compound depicted effective zone of inhibition (**Figure 2**).

Saikia *et al.,* [78] in 2014, first synthesized cholest-3,5-dien-7-one which later yielded 3-epoxycholestane using *meta*-chloroperbenzoic acid. The last step involved reaction of epoxycholestane with *N*-substituted heterocycles under microwave conditions as shown below. The compounds were screened for antimicrobial activity against different strains such



Scheme 24: Schematic pathway for the synthesis of steroidal oxadiazoles.



Scheme 25: Pathway for the synthesis of 3-substituted-4-hydroxycholest-5-en-7-one.

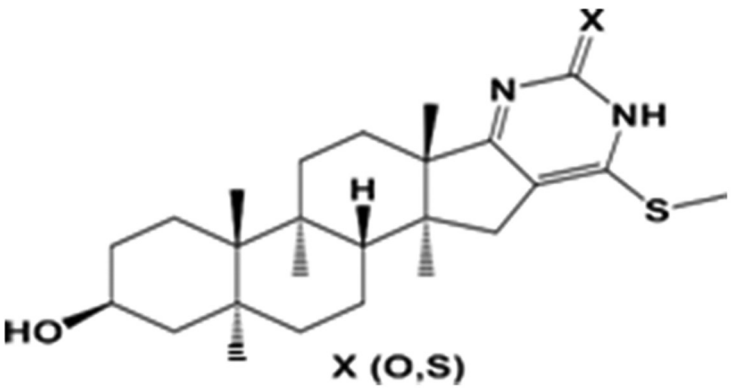


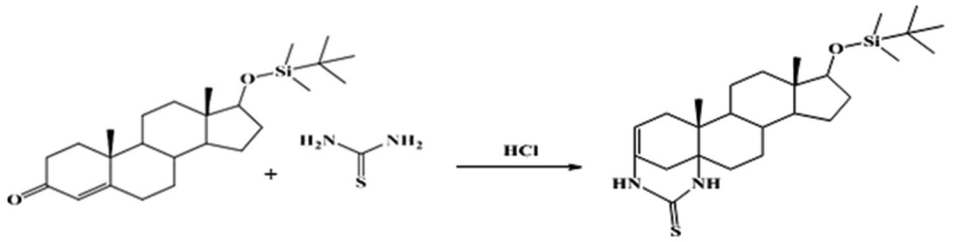
Figure 2: Steroid pyrido [2, 3-*d*] pyrimidine as antimicrobial agent.

as *Staphylococcus aureus*, *bacteria Escherichia coli, Bacillus subtilis, Proteus vulgaris,* and *Pseudomonas syringae* by Disk Diffusion Method during which they depicted moderate to effective inhibition (**Scheme 25**).

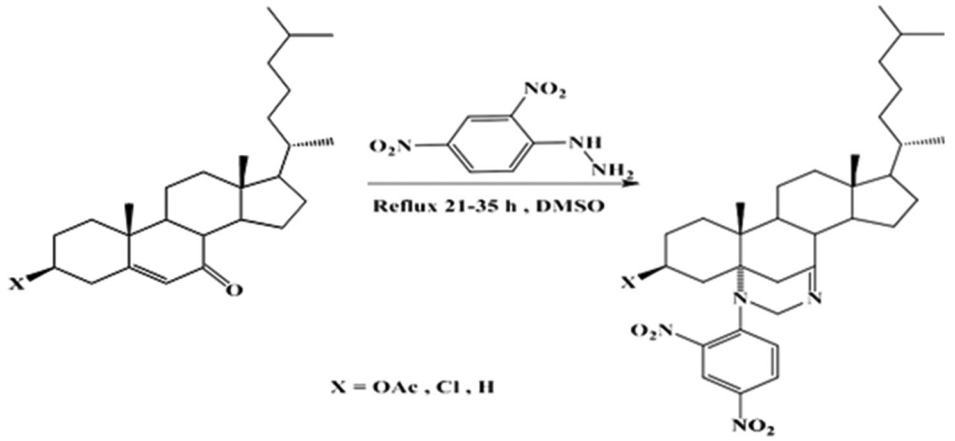
Lauro *et al.,* [79] in 2015, prepared new steroid diazolidine derivative by the reaction of testosterone with thiourea in presence of hydrochloric acid as catalyst, the synthesized compound was evaluated on the Gram negative (*E. coli and Vibrio cholerae*) and Gram-positive (*S. aureus*) bacteria during which the compounds depicted potential antibacterial activity (**Scheme 26**).

Shamsuzzaman *et al.,* [80] in 2016, prepared new pyrazoline derivatives by the reaction of cholest-5-en-7-one with 2,4-dinirtophenylhydrazine. The synthesized compounds were tested for *in vitro* antimicrobial activity by agar well method during which one of the compounds showed potent antimicrobial behavior by effective zone of inhibition against the strains of *S. epidermidis* and *C. xerosis.* The compound also showed least MBC (**Scheme 27**).

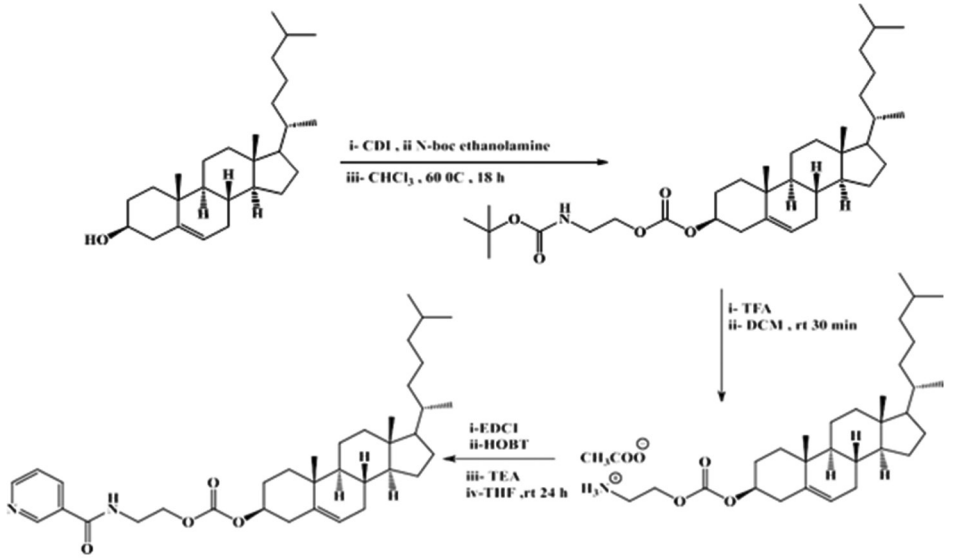
Sribalan *et al.,* [81] in 2016, prepared new glycinate and carbonate derivatives of cholesterol with pyridine moiety through different



Scheme 26: The synthesis of new steroid diazolidine.



Scheme 27: The synthesis of new steroidal pyrazolines.



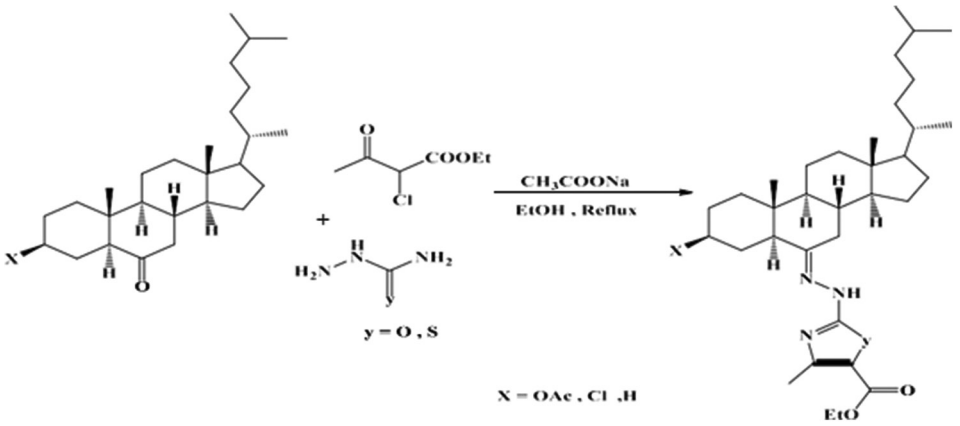
Scheme 28: Depicting synthesis of glycinate and carbonate derivatives of cholesteryl pyrimidine.

steps as shown below and evaluated them for *in vitro* antimicrobial activity against different strains of gram-negative bacteria and fungi. The compounds showed potent antimicrobial activity by showing effective zone of inhibition. The compound also showed least MIC (**Scheme 28**).

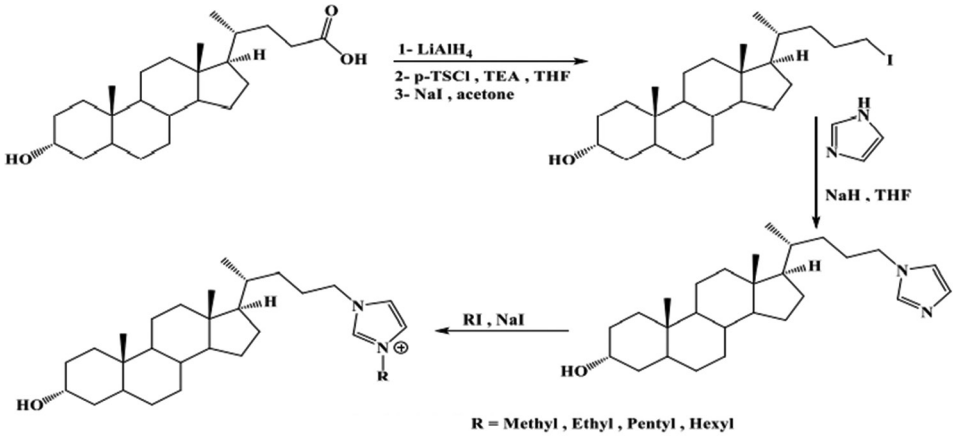
Ansari *et al.,* [82] in 2018, prepared a new series of derivatives of thiazole and oxazole employing thiosemicarbazide/semicarbazide and ethyl 2-chloroacetoacetate by one-pot manner as shown below. The antimicrobial activity of newly compounds was evaluated against four bacterial strains, namely, Gram-positive bacteria (*S. aureus* and *L. monocytogenes*) and Gram-negative (*E. coli* and *P. aeruginosa*) as well as pathogenic fungi (*C. albicans* and *C. neoformans*) (**Scheme 29**).

Hryniewicka *et al.,* [83] in 2019, synthesized new derivatives of imidazole salts of lithocholic acid through three reactions as shown below. The new compounds showed potential anti-microbial activity against different bacterial and fungal strains which are clear from MIC and zone of inhibition (**Scheme 30**).

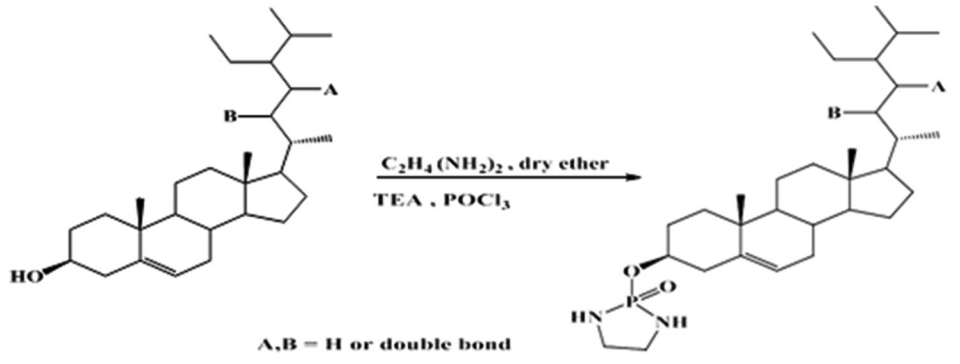
Alam *et al.,* [84] in 2019, designed and synthesized steroidal derivatives containing phosphorus by reaction the hydroxyl group of with phosphoryl trichloride in presence of ethylene diamine as basic catalyst as shown in below. The prepared compounds were screened for antifungal and herbicidal activity, the compound appear a good antifungal activity (**Scheme 31**).



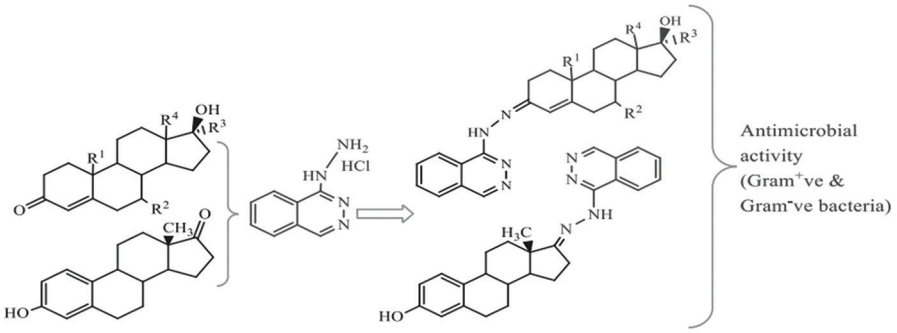
Scheme 29: Scheme showing the synthesis of steroidal thiazole and oxazole derivatives.



Scheme 30: The synthesis of steroidal imidazole salts.



Scheme 31: The synthesis of Phosphorus containing steroidal derivative.



Scheme 32: Synthesis of steroidal hydrazone, 4methyl nandrolone, and Δ^6-testosterone derivatives.

Mistry and Singh, [85] in 2022, synthesized new steroidal hydrazone, 4methyl nandrolone, Δ^6testosterone, and other steroidal derivatives as shown below. The new compounds were screened antifungal activity during which one of the Compounds (MIC = 580 µM) was found active against *C. albicans* as compare to griseofulvin (MIC = 1417 µM) and rest of the steroidal hydrazones exhibited less potency than standard antifungal drug nystatin and griseofulvin against *C. albicans*, *A. niger,* and *A. clavatus* (**Scheme 32**).

6. CONCLUSION

Development of facile, convenient, and efficient approach for the synthesis of new steroidal derivatives has been successful, as shown in the literature. The preparations were being carried out traditional methods such as stirring or refluxing or were carried out under modern methods such as microwave irradiation and sonication. From *in vitro* cytotoxicity screening data, it is clear that different steroidal derivatives such as steroidal pyrimidines, steroidal imidazolidines, steroidal oxadiazoles, steroidal pyrazoles, steroidal diazolidine, and steroidal thiazoles were found to be potential cytotoxic agents in comparison with different standard drugs such as Cisplatin, 5-flurouracil, and Doxorubicin. During the antioxidant screening by different assays like DPPH, the steroidal derivatives showed enhanced radical scavenging activity with respect to standards such as citric acid and hydrogen peroxide as depicted from antioxidant data. The steroidal derivatives showed potential antibacterial as well as antifungal activity with respect to the standard drugs such as nystatin and ciprofloxacin. Moreover, the compounds showed better zones of inhibition as well as minimum inhibitory concentration which correlates their behavior toward antimicrobial activity. The results revealed that these steroid derivatives have better prospectus to act as different chemotherapeutic candidates which warrant further *in vivo* anticancer, antioxidant, and antimicrobial investigations.

7. ACKNOWLEDGMENTS

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