Steroidal lactams: a review

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Abstract

Steroidal lactams are also a class of steroid derivatives that were synthesized and modified to increase the biological activity of steroids. Their synthesis is a stimulating challenge to the scientist, often claiming the development of new and generally useful reactions. Some of them have been tested successfully as anticancer drugs against different types of leukemia. Recent developments in the syntheses of steroidal lactams are described herein. The biological activities of those steroidal derivatives for which data are available are given.

Keywords: Steroid, oxime, lactam moiety, Beckmann rearrangement
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1. Introduction

Steroids constitute an extensive and important class of biologically active polycyclic compounds that are widely used for therapeutic purposes.\textsuperscript{1-27} Even after decades of research, the total synthesis of steroid nuclei by improved strategies continues to receive considerable attention. Numerous methods\textsuperscript{28-34} have been exploited for the total synthesis of steroids which are widely distributed in nature, and which possess practical medical importance. Research into steroid total synthesis continues to this day.\textsuperscript{35-38}

The introduction of heteroatom or replacement of one or more carbon atoms in a steroidal molecule by a heteroatom affects the chemical properties of that particular steroid and often results in alterations of its biological activities, which sometimes may be useful. Azasteroids especially express numerous biological activities. Studies of steroidal lactams revealed that the presence of the characteristic group (-NH-CO-) in theaza-steroid molecule is important in lowering the acute toxicity and improving the anticancer activity of the compounds.\textsuperscript{39}

Moreover, steroidal lactams have attracted much interest, as many as 4-azalactams exhibiting strong inhibition of human steroid 5α-reductase, making them potential drugs for the treatment of benign prostatic hyperplasia (BPH), acne, male pattern baldness, and alopecia.\textsuperscript{40} Finasteride and turosteride are two commercial drugs belonging to this class.\textsuperscript{41-42} Finasteride was the first 5α-reductase inhibitor clinically approved in 1992 in the U.S. for the treatment of BPH. The 5α-reductase inhibitory activity of these steroids is considered to be attributed to the lactam in ring A of the steroidal nucleus that mimics the intermediate transition state.\textsuperscript{43}

This article provides an overview of the various synthetic strategies, which have been employed to synthesize steroidal lactams along with their biological properties, if provided, from the years 2011 to 2021. Although a previous review by Panda et al. has appeared in 2013 for heterocyclic steroids, some reports were missing from their compilation regarding steroidal lactams.\textsuperscript{44} Thus, we have chosen to cover the aforementioned period on steroidal lactams.

2. Synthesis of Steroidal Lactams

In 2011, Zhou and coworkers\textsuperscript{45} reported the synthesis of some steroidal lactams functionalized at the 6-position of the steroidal skeleton, using cholesterol as starting material. A series of 6-substituted-3-aza-A-homo-3-oxocholestanes and 6-substituted-4-aza-A-homo-3-oxocholestanes were prepared using the Beckman rearrangement as the key step. The oxime 4 was isolated by four steps in 66.5% yield as depicted in Scheme 1.\textsuperscript{46} The diketone 1 was selectively reduced to yield the crude alcohol 2, which was directly oxidized to generate 3,6-diketone 3. In the last step,
treatment of this derivative with hydroxylamine hydrochloride (1:1.1) in ethanol in the presence of sodium acetate led to compound 4.

A Beckmann rearrangement of 4 with SOCl₂/THF at 0 °C led to steroidal lactams 5 and 6 with moderate yields. The major product was the 4-aza derivative 5 which was isolated in 45% yield (Scheme 2).

The steroidal lactams 7 and 11 were prepared by reduction using the reductant NaBH₄ in methanol. The oximation of compounds 5 and 6 led to steroidal derivatives 8 and 12, respectively, as depicted in Schemes 3.
and 4. In the same way, the steroidal derivatives 9 and 10 were synthesized by treatment of compound 5 with thiosemicarbazide or semicarbazide adding a few drops of glacial acetic acid as a catalyst (Scheme 3).


Reagents: a- NaBH₄/MeOH, r.t.; b- H₂NOH.HCl/Na₂Ac.3H₂O/EtOH, reflux; c- H₂NC(S)NHNH₂/EtOH, 60 °C; d- H₂NC(O)NHNH₂/EtOH.

These steroidal lactams showed distinct cytotoxicity against HeLa, MGC 7901, and SMMC 7404 cancer cells. Moreover, these results showed the importance of the functional groups in the C-6 position of the steroid skeleton for the IC50 value of these derivatives. Moreover, the authors do not observe any notable difference between the 3-aza and the 4-aza steroids. In particular, compounds 9, 11, 12 (IC50 6: 6.5 μmol/L; 8: 7.7 μmol/L; 9: 5.6 μmol/L) showed even higher cytotoxicity than cisplatin for HeLa cells (positive contrast, 10.1 μmol/L).

In 2012, these authors reported that 6-hydroxyl-4-aza-A-homocholest-3-one 7 and 6-hydroximino-4-aza-A-homo-cholest-3-one 8, displayed antiproliferative activity against some cancer cells through inducing cancer cell apoptosis by activation of the intrinsic pathway. Furthermore, the compound 8 was able to inhibit tumor growth in an athymic mouse model.

In 2014, the same authors reported the synthesis of a series of steroidal lactams derivatives possessing different substituted groups at the C-3 position of the steroidal skeleton.

The 3-hydroximino steroidal derivative 18 was synthesized as depicted in Scheme 5. The synthesis of the steroid derivative 14 was already published, from compound 13, by the same group in 2009. 3-Acetoxy-7-aza-B-homocholest-4-en-6-one 15 was obtained by Beckman rearrangement of 14 with SOCl2 in THF. Deacetylation of compound 15 in K2CO3 aqueous solution (13%) gave steroidal lactam 16, which on oxidation with Jones' reagent gave 7-aza-B-homocholest-4-ene-3,6-dione 17. Finally, the reaction of the latter with hydroxylamine hydrochloride in ethanol in the presence of NaOAc gave the steroidal lactam oxime 18 with a yield of 42%.

Similarly, steroidal lactams 23-26 exhibiting the 3-substituted-6-aza-B-homocholest-7-one key motif in their structures were prepared in 8 steps using cholesterol as starting material (Figure 6). The steroid derivative 19 was obtained using the procedure described in the literature.\textsuperscript{50} The 3-keto steroid 22 was synthesized by oxidation of the alcohol 21 by Jones' reagent. Finally, the corresponding steroidal lactams 23-26 were isolated by reaction of compound 22 with HONH\textsubscript{2}·HCl, CH\textsubscript{3}ONH\textsubscript{2}·HCl, PhCH\textsubscript{2}ONH\textsubscript{2}·HCl, or thiosemicarbazide.
Finally, the authors were interested in the synthesis of compounds 28-32 having the structure of 7α-aza-B-homocholest-4(or 5)-ene to identify whether the aza position effects on the cytotoxicity of compounds (Scheme 7). Thus, the 3-acetoxy-7α-aza-B-homocholest-5-ene-7-one compound 28 was obtained by Beckman rearrangement of 27. In addition, after oxidation by Jones reagent of compound 29, migration of its 5,6 double bond into the more stable 4,5 double bond of compound 30 is observed. Then, the reaction of the α,β-unsaturated derivative 30 with HONH₂.HCl or thiosemicarbazide led to the steroidal lactams 31 and 32 respectively.

The authors studied the antiproliferative activity of the various synthesized compounds against HeLa, SGC-7901, GNE 2, Bel-7404, Tu 686, and SPC-A cell lines. They observed remarkable cytotoxic activity for steroidal lactams possessing 3-hydroximin, 3-hydroxyl, and 3-thiosemicarbazone groups. The derivatives which have proved to be the most potent anticancer agents are the steroids 16, 21, 23, 26, and 29 which, moreover, have an antiproliferative activity similar to that of cisplatin. In addition, by the annexin V staining test, the authors showed that compound 26 was able to effectively induce tumor cell apoptosis.
In 2015, Cui and coworkers\textsuperscript{51} reported the synthesis of a series of 3-substituted-6-aza-B-homo-5α-stigmastan-7-one and 3-substituted-6-aza-B-homo-5α-sitostan-7-one derivatives using stigmasterol and sitosterol as starting materials.

Scheme 8 outlines the synthetic procedures of compounds 34a-42a, 34b-41b and 43b. Compounds 33a and 33b were prepared as reported previously.\textsuperscript{50} The synthesis of compounds 34a and 34b was carried out by Beckmann rearrangement of 33a and 33b with SOCl\textsubscript{2}/THF at 0 °C, and the acetylation of compounds 34a and 34b gave compounds 35a and 35b. Next, compounds 34a-34b were converted to corresponding 3-carbonyl derivatives (36a-36b) via oxidation with PCC. The reaction of compounds 36a and 36b with CH\textsubscript{3}ONH\textsubscript{2}.HCl, PhCH\textsubscript{2}ONH\textsubscript{2}.HCl or HONH\textsubscript{2}.HCl afforded the corresponding products 37a-39a and 37b-39b. The (E)- and (Z)-stereoisomer were obtained in preparation of 37a-38a and 37b-38b, respectively. Similarly, compounds 36a and 36b reacted with different 4-alkyl-3-thiosemicarbazide or 4-phenyl-3-thiosemicarbazide gave the 6-aza-7-oxo-B-homo-5α-stigmastan-3-{alkyl}thiosemicarbazone derivatives 40a-42a and 6-aza-7-oxo-B-homo-5α-sitostan-3-alkyl(or phenyl)thiosemicarbazone derivatives 40b-41b and 43b.

Reagents: a-SOCl\textsubscript{2}/THF, 0 °C; b-K\textsubscript{2}CO\textsubscript{3}/MeOH, reflux, 4h; c-Jones reagent/acetone, r.t., 2h; d-NH\textsubscript{2}OH.HCl, Na\textsubscript{2}Ac.3H\textsubscript{2}O, EtOH, reflux; e-H\textsubscript{2}NC(S)NHNH\textsubscript{2}.HCl, EtOH, 60 °C.
Their antiproliferative activities against SGC 7901 (human gastric carcinoma), CNE (nasopharyngeal carcinoma), Bel 7404 (human liver carcinoma) and HeLa (human cervical carcinoma) cancer cells were assayed. The results showed that compounds with the side chain of sitosterol had better antiproliferative activity than compounds with the side chain of stigmasterol. The compound 40b with 3-thiosemicarbazone and 41b with 3-(40-methyl)thiosemicarbazone group displayed an excellent antiproliferative activity against Bel-7404 cells owning an IC\textsubscript{50} value of 3.9 and 5.6 \textmu M, respectively (compared with cisplatin, IC\textsubscript{50}: 23 \textmu M).

\[ \text{Scheme 8. Synthesis of steroidal lactams 34-43.} \]

Reagents: a-SOCl\textsubscript{2}/THF, 0 °C; b- Ac\textsubscript{2}O/Pyridine; c- PCC, CH\textsubscript{2}C\textsubscript{10}H\textsubscript{12}; d- NH\textsubscript{2}OCH\textsubscript{3}.HCl 95%, NaOAc.3H\textsubscript{2}O, EtOH; e- PhCH\textsubscript{2}ONH\textsubscript{2}.HCl 95%, EtOH, NaOAc.3H\textsubscript{2}O; f- NH\textsubscript{2}OH.HCl 95%, NaOAc.3H\textsubscript{2}O, EtOH; g- H\textsubscript{2}NC(S)NHNH\textsubscript{2}.HCl, EtOH, AcOH; h- H\textsubscript{2}NC(S)NHNHCH\textsubscript{3}.HCl, EtOH, AcOH; i- H\textsubscript{2}NC(S)NHNHCH\textsubscript{2}CH\textsubscript{3}.HCl, EtOH, AcOH; j- H\textsubscript{2}NC(S)NHNHPh.HCl, EtOH, AcOH.
In 2016, Sarli and coworkers reported the evaluation and the synthesis of novel steroidal lactam derivatives, which are conjugated with 3-(4-(bis(2-chloroethyl)amino)phenoxy)propanoic acid (POPAM) hoping to improve its biological activity. Four novel steroidal lactams related to POPAM have been synthesized.

The first conjugate was prepared using testosterone as starting material according to the known procedure of Camoutsis and Catsoulacos (Scheme 9). Acetylation of testosterone with acetic anhydride in pyridine led to the corresponding acetate which was condensed with hydroxylamine to provide the Z- and E-oximes. In a second step, a Beckman rearrangement of the mixture of oximes with SOCl₂ in dioxane was realized and as predicted by previously described results, a single lactam was obtained in a moderate yield (63%) most likely due to Z/E isomerization before alkyl migration. Next, the acetyl moiety was deprotected under basic conditions with excellent yield (92%) and in a final step, the hydroxyl group at C-17 of the steroidal skeleton was esterified by POPAM in the presence of DMAP and DCC in CH₂Cl₂ to provide, with a quantitative yield, the desired conjugate ENGA-L06E.

Reagents: a- 1- Ac₂O, DMAP, pyridine, 100%; 2- NH₃HCl, pyridine, 74%; b- SOCl₂, dioxane, 63%; c- POPAM, DCC, DMAP, CH₂Cl₂, 99%.

Scheme 9. Synthesis of ENGA-L06E.
The second conjugate, ENGA-L08E 51 was isolated using estrone 49 as starting material as depicted in Scheme 10. The methodology of Liao and coworkers\textsuperscript{55} was used to synthesize the 17α-aza-D-homoestrone derivative 50. Then, esterification of lactam 50 with POPAM 47 in DMF in the presence of DCC and DMAP led to the corresponding ester 51 in good yield.

\textbf{Scheme 10. Synthesis of ENGA-L08E 51.}

The other two steroidal lactams 57 and 61 were prepared via the novel monolactam 56 and dilactam 60 using adrenosterone as starting material.

The monolactam 56 was prepared as depicted in Scheme 11. Firstly, according to Morreal\textsuperscript{56-58}, a regioselective reduction of the 17-keto group of the D-ring of adrenosterone was done with NaBH\textsubscript{4}/MeOH to provide the corresponding alcohol, which was used without further purification in the next step. Next, the hydroxyl group at C-17 was protected into its corresponding acetate 53 in a yield of 90%. The treatment of this latter with NH\textsubscript{2}OH.HCl in pyridine led selectively to the desired oximes 54, which by Beckman rearrangement provided the steroidal monolactam 55. Finally, the C-17 position of compound 55 was deprotected followed by esterification with POPAM 47 to afford a yield of 96%, the desired conjugate ENGA-L07E 57.
A similar way was used to synthesize the bislactam alkylator 61, as depicted in Scheme 12. A Beckmann rearrangement of oximes 58 led to the desired bislactam 59 in a 75% yield.

It is interesting to note that all new synthesized steroidal lactams with POPAM 47 performed relatively very low acute toxicities, together with important antileukemic activity in vitro and in vivo, producing a high therapeutic ratio.

In 2017, Montiel-Smith et al.\textsuperscript{59} reported the synthesis of steroidal lactams starting from the easily available cholesterol and pregnenolone. A new procedure for the synthesis of a $6\alpha$-aza-$B$-homo steroidal lactam analog of vespertilin, starting from diosgenin, was also described.

The synthesis of derivative 62 has been previously reported\textsuperscript{60} from cholesterol by a synthetic route of five steps and polluting oxidants were used. Herein the formation of compound 62 was accomplished, in just one step, as depicted in Scheme 13 and the best yield of 65% was observed using 8 equivalents of BF$_3$·OEt$_2$ and NaNO$_2$ and a 3:1 (v/v) Ac$_2$O-AcOH ratio.


Reagents: a- NH₂OH.HCl, pyridine, 50%; b- SOCl₂, dioxane, 75%;
c- LiOH, MeOH, 93%; d- POPAM 47, DCC, DMAP, CH₂Cl₂, 70%.

Scheme 13. Synthesis of steroidal lactam 64.

Reagents: a- NaNO₂, BF₃·Et₂O, AcOH; b- Na₂CO₃, CH₂Cl₂/Methanol, reflux; c- SOCl₂, dioxane.
The new protocol described above for cholesterol was applied with pregnenolone 65 possessing a ketone at C-20, as reported in Scheme 14. Using the same conditions, the steroidal derivative 66 was isolated without alteration of the carbonyl group in a 77% yield. In the next step, the (Z)-oxime 67 was obtained by treatment of compound 66 with sodium carbonate Na₂CO₃. Finally, the Beckmann rearrangement of steroidal oxime 67 was successfully performed using SOCl₂ in dioxane and the desired B-homo steroidal lactam 68 was isolated in only 3 steps, with an overall yield of 27%.

![Scheme 14](image)

Reagents: a- NaNO₂, BF₃·Et₂O, AcOH; b- Na₂CO₃, CH₂Cl₂/MeOH, reflux; c- SOCl₂, dioxane.

**Scheme 14.** Synthesis of steroidal lactam 68.

Then, the authors used the same conditions to afford steroidal lactam 64 from oxime 63, as depicted in Scheme 15.

Firstly, the nitroimino derivative 70a was synthesized in a poor yield (22% yield) by a nitrosation reaction of diosgenin acetate 69a using the conditions described by Iglesias. Indeed, three side products were also obtained. The reaction was performed in AcOH with NaNO₂ (10 equiv.) and BF₃·OEt₂ (10 equiv.) and the temperature (15–20 °C) was controlled over 4 h. No purification of the crude products was done to prevent the degradation of the side chain promoted by the silica gel and alumina. A treatment of the mixture of compounds 70a and 71a was performed with NH₂OH·HCl and NaOAc in refluxing ethanol to convert the ketone group and the nitroimino moieties of the main compounds into oximes. The same treatment was applied to the mixture of derivatives 70b and 71b. The dioxime 72a or 72b was thus isolated without affecting the other functionalities (Scheme 14). In the next step, 72a or 72b was submitted under protic acidic conditions to a second-order Beckmann rearrangement to give in both cases vespertiline oxime 73. The use of the mixture CF₃COOH, Ac₂O, BF₃·OEt₂ at room temperature led to the best results in a very short reaction time (20 min.) and to the acetylation of the hydroxyl group at C-3 in compound 72b. Next, treatment of compound 73 with Na₂CO₃ in a 1:1 MeOH/CH₂Cl₂ refluxing solution led to the (Z)-oxime 74 without the ester group at C-5. In a final step,
the desired lactam 75 was isolated in a good yield of 70% using the same conditions described above for the synthesis of B-homo steroidal lactams 64 and 68.

A panel of six human solid tumor cell lines was used to test the antiproliferative activity of these compounds. The authors observed that the most potent of all the derivatives assayed was compound 61a, displaying slightly better GI50 values against WiDr and T-47D cancer cells when compared to cisplatin. A moderate activity in the cell lines screened was determined for the steroidal lactams 68 and 75.

Reagents: a- NaNO2, BF3·Et2O, AcOH; b- NH2OH·HCl, EtOH, reflux; c- CF3COOH, Ac2O, BF3·Et2O; d- Na2CO3, CH2Cl2/MeOH, reflux; e- SOCl2, dioxane.

Scheme 15. Synthesis of steroidal lactam 75.
In 2020, Liu et al.\textsuperscript{63} reported the synthesis of biologically relevant steroidal spirolactams from dienamides through the cascade 4-endo $N$-cyclization/aerobic oxidation sequence.

The synthetic pathway is depicted in Scheme 16. Dienamides 77 were prepared from $\alpha,\alpha$-dicyanoalkene 76, and aldehydes through the cascade reactions under mild conditions.\textsuperscript{64} Then, treatment of compound 66 in the presence of NaH in THF at 0 °C under air atmosphere led exclusively to the unexpected steroidal spirolactam 78 within 1 h. Surprisingly, an additional hydroxyl group was also introduced at the $\alpha$ position of the $\beta$-lactam ring via the base-promoted aerobic oxidation. The above reactions proceeded selectively through the 4-endo $N$-cyclization in the presence of NaH, followed by the base-mediated aerobic oxidation under air. No 6-endo $N$-cyclization products, namely 2-piperidinones were observed. This approach has several advantages such as short reaction time and mild reaction conditions.

**Scheme 16.** Synthesis of steroidal $\beta$-lactam 78 from dienamide 77.

In 2021, Hernandez-Linares et al.\textsuperscript{65} reported the synthesis of new steroidal lactams 82 and 87 from diosgenin 79 (Scheme 17 and 18).

In the case of the steroidal derivative 71, the synthetic pathway is depicted in Scheme 17. Firstly, oxidation of diosgenin with PCC and calcium carbonate in dichloromethane led to the $\alpha,\beta$-unsaturated compound 80 with a slightly improved yield (90%) compared to that described.\textsuperscript{66} In the next step, this latter was oxidized using the oxidant reagent potassium permanganate-sodium periodate.\textsuperscript{67} Thus, the use of permanganate provided the formation of 1,2-diol, which carbon-carbon bond was then cleaved to give a carboxylic acid group and a ketone, without degradation, leading to the desired derivative 81.
In the final step, two techniques for the ring closure were used to obtain the targeted steroidal derivative 82. In the first case, following the methodology reported by Jiang, a conventional N source, ammonium sulfate in refluxing glacial acetic acid for 4 h, was attempted and the overall yield was improved from 39% to 63%. In the second case, focused microwave irradiation (FMWI) was tried with ammonium acetate as a reagent, for 3 min, leading to a much higher yield of 75%, than that reported in previous works of 19%. Finally, the authors succeeded in increasing the yield to 94%, using 1 eq. of compound 70 with 3.8 eq. of ammonium acetate in acetic acid. The use of DMF instead of acetic acid decreased the yield to 71% and no reaction can be observed with ammonium hydroxide as an N source.

Scheme 1. Synthesis of steroidal lactam 82.

An oxidation reaction was tested with CrO₃ to obtain the lactam moiety in ring B, but the yield was low. The best yield of the allylic oxidation reaction was observed starting with diosgenin acetate as substrate and using the Collins reagent. Thus, using compound 84, which contains a ketone group, as a precursor, a ring expansion was done leading to the intermediary oxime 86. In the next step, a Beckmann rearrangement was performed with SOCl₂ in THF, to provide the targeted 7-azasteroid 87 as depicted in Scheme 18.

Moreover, the by-product 85 with a carboxylic group, was isolated in addition to 84. The treatment of enone 84 with NH₂OH.HCl under reflux in an ethanol and sodium acetate solution for two hours led to the corresponding oxime with a yield of 91%. One equivalent of the enone for 1.5 eq. of NH₂OH.HCl was used to obtain the best yield. Finally, the reaction of derivative 86 with a solution of thionyl chloride in THF for 4 h at 0 °C provided the steroidal lactam-type enamide 87.
A specificity to different types of cellular receptors in cancer cell lines tested, as well as significant antiproliferative activities, were observed for some of the synthesized compounds, depending on the structure and conformation. The steroidal lactam 82 inhibits cancer cell lines with the PR and ERα without showing cytotoxicity for lymphocytes of PHB; however, the derivative seco-ketoacid 81 does not inhibit cells with the receptors ERα, ERβ, and PR.

Moreover, it was observed that the steroidal lactam 87 inhibits the proliferation in MDA-MB-231 cell lines that do not express ERα, PR, or HER2 receptors, with IC50 values lower than 0.093 μg/mL, showing that the route through which that bind to cells is different.

Reagents: a- Ac₂O, DMAP, reflux, 1 h, 85%; b- Method A: CrO₃, AcOH/H₂O, 0 °C, 3 h; Method B: Collins reagent, CH₂Cl₂, r.t., 12 h, 71%; c- NH₂OH.HCl, AcONa, EtOH, reflux, 2 h, 91%; d- SOCl₂, THF, 0 °C, 4 h, 52%.

3. Conclusions

The lactam moiety and the steroid nucleus are prevalent in drug molecules and natural products, the derivatives possessing such fragments always present diverse and interesting biological profiles. Presented here is up-to-date literature on the syntheses of steroid lactams reported during the last years. Several of these syntheses may be useful, and in most cases reporting the cytotoxicity of the tested compounds, there seems to be a link with the presence of the lactam moiety in the steroid skeleton. Currently, interest in steroids and related molecules continues because of the emerging bioactivity and structural diversity inherent in this class of compounds.

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