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Recent syntheses of steroidal derivatives containing heterocycles

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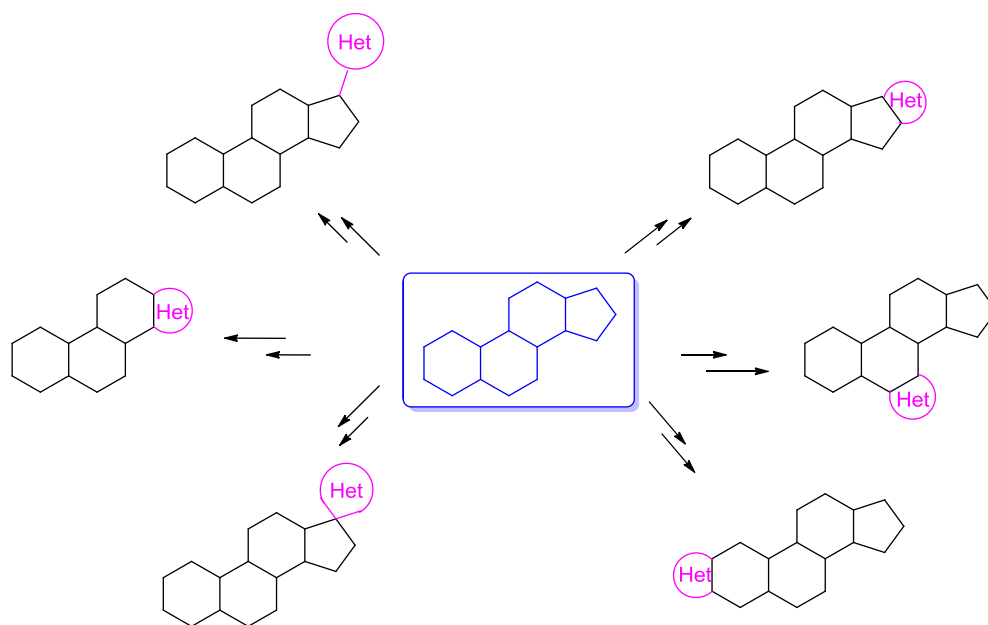
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Abstract

It was found that the introduction of a heterocycle or replacement by a heteroatom of one or more carbon atoms in the steroidal moiety could have a significant biological impact, and there has been much progress in the field of steroidal derivatives since. Recent developments in the syntheses of steroidal derivatives containing heterocycles are described herein.



Keywords: Heterocycles, steroids, pyridines, thiazoles

Table of Contents

1. Introduction
 2. Synthesis of Steroidal Heterocycles
 - 2.1 A-Ring fused steroidal heterocycles
 - 2.2 B-Ring fused steroidal heterocycles
 - 2.3 D-Ring fused steroidal heterocycles
 3. Synthesis of Steroidal Derivatives Containing Heterocyclic Side-chains
 4. Synthesis of Steroidal Spiro-heterocycles
 5. Synthesis of Heterocyclic Steroidal Analogues
 6. Conclusions
- Acknowledgements
- References

1. Introduction

Steroids constitute an extensive and important class of biologically active polycyclic compounds that are widely used for therapeutic purposes.¹⁻³ Even after decades of research, the total synthesis of steroid nuclei by improved strategies continues to receive considerable attention. Numerous methods 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.^{4,5}

Heterocycles are widespread in drug molecules because they possess hydrogen bond donors and acceptors in a rigid framework, and they can therefore effectively interact with target enzymes and receptors via hydrogen bond interactions. They can enhance binding affinity and improve *in vitro* potency. Heterocycles can modulate the lipophilicity of the drug molecules or improve aqueous solubility of the compounds, thus providing desired pharmacokinetic and pharmacodynamic properties.⁶ Heterocyclic compounds are therefore widely applied in pharmaceutical and agrochemical research.

It was found that introducing heterocycles into steroids,⁷⁻¹² by modification of the steroidal side chain or substitution of the steroidal skeleton, introducing a heteroatom or replacing one or more carbon atoms in steroidal molecule with a heteroatom, can result in a change in its biological activities.¹³⁻¹⁷ Steroids containing heteroatoms have been widely researched and reported.¹⁸ Literature reports have suggested that such compounds can display distinct cytotoxicity against cancer cell lines.¹⁹⁻²²

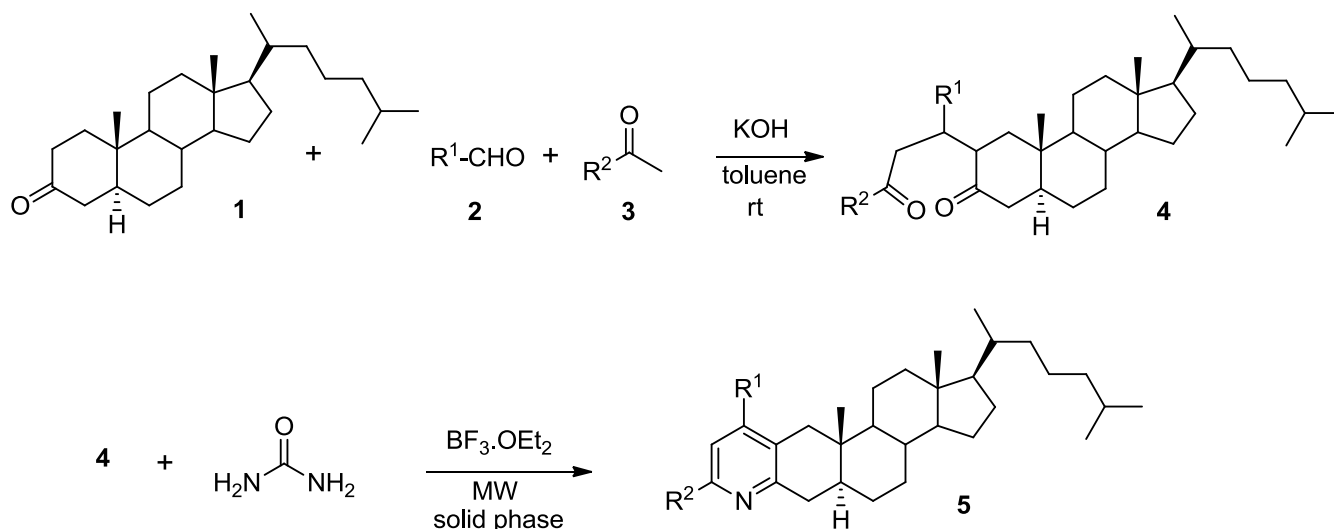
This article provides an overview of the various synthetic strategies which have been employed to synthesize steroidal derivatives containing heterocycles along with interesting biological activities, from the years 2013-2019.

2. Synthesis of Steroidal Heterocycles

2.1 A-Ring fused steroidal heterocycles

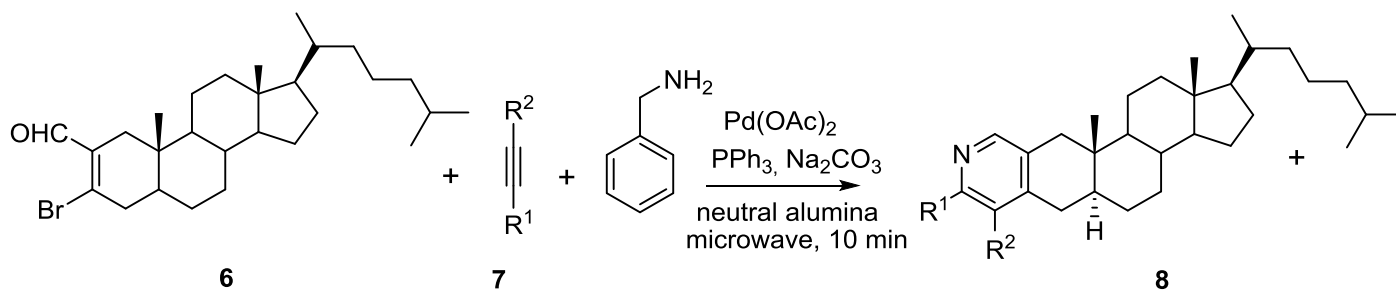
In 2013, Dutta *et al.*²³ developed a solventless one-pot reaction of a steroidal 1,5-diketo compound with urea employing BF₃.OEt₂ as the catalyst, for the synthesis of steroidal A- and D-ring fused 4,6-diarylpyridines under microwave irradiation. The intermediate steroidal 1,5-diketo compounds were synthesized by Michael addition reaction of steroidal ketones with enones *in situ*-generated from aromatic ketones and aldehydes (Scheme 1). The reaction of steroidal ketone **1** with a variety of aromatic aldehydes and aryl ketones including

both electron-deficient and electron-rich groups was investigated. The 1,5-dicarbonyl compounds were obtained in excellent yields in all cases and no undesired side reactions were observed. In the next step, the cyclization reaction of the diketones **4** afforded steroidal pyridines **5** in excellent yields.



Scheme 1. Synthesis of 4',6'-diaryl-cholest[3,2-*b*]pyridine derivatives **5**.

In 2013, the same authors developed a solvent-free multi-component reaction condition for the synthesis of steroidal A-ring fused 5,6-disubstituted pyridines using $\text{Pd}(\text{OAc})_2$ as the catalyst under microwave irradiation.²⁴ A wide variety of alkyl-, aryl- and ester-substituted alkynes undergo this highly regioselective reaction to give good yields of pyridine derivatives. The starting material, the steroidal 5-bromovinyl aldehyde **6**, was synthesized from commercially available 5-cholestan-3-one by reaction with Vilsmeier reagent in refluxing chloroform.²⁵ A mixture of steroidal 5-bromovinyl aldehyde **6**, benzylamine, alkyne **7**, palladium acetate (5 mol%), triphenylphosphine, Na_2CO_3 and neutral alumina was then irradiated in a closed vessel in a Synthos 3000 microwave reactor at 600 Watts for 10 min, affording A-ring fused 5,6-disubstituted pyridines **8** (Scheme 2) in good yields. Instead of benzylamine, other amines such as *tert*-butylamine were tried, but a decreased yield of compound **8** was obtained, which could be due to the lower boiling point of *tert*-butylamine. They also observed that reducing the quantity of $\text{Pd}(\text{OAc})_2$ decreased the yield of **8** while increase of catalyst loading to 10 mol% did not affect the yield of **8** at all.



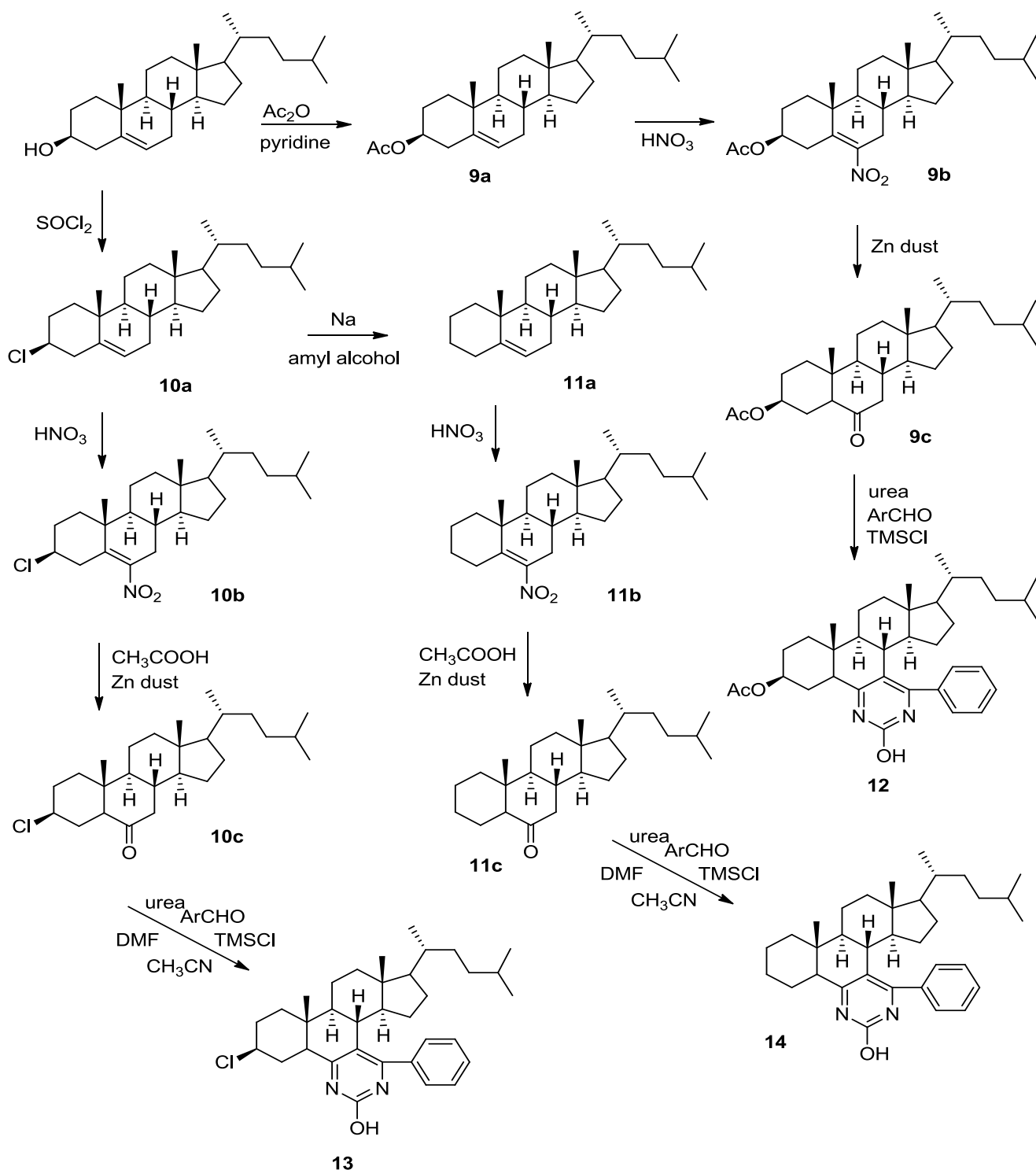
$\text{R}^1 = \text{H}, \text{COOMe}, \text{Me}, \text{Pr}, \text{Si}(\text{CH}_3)_3$

$\text{R}^2 = \text{H}, \text{Ph}, \text{F-Ph}$

Scheme 2. Synthesis of steroidal A-ring fused substituted pyridines.

2.2 B-Ring fused steroidal heterocycles

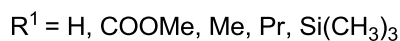
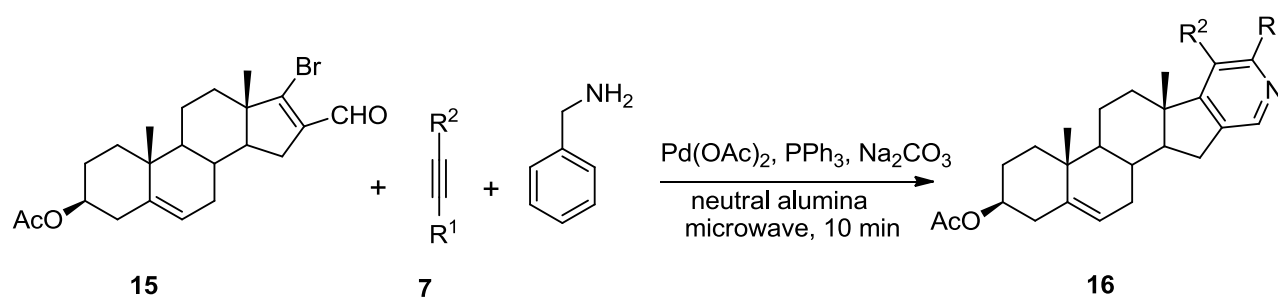
In 2017, Ali *et al.*²⁶ prepared a series of novel steroidal pyrimidine derivatives via a multicomponent domino process. For the synthesis of steroidal pyrimidines **12-14**, 3 β -acetoxycholestan-6-one **9c**, 3 β -chlorocholestan-6-one **10c**, and 5 β -cholestan-6-one **11c** were synthesized by literature methods,²⁷ and these were treated with urea and benzaldehyde in DMF/CH₃CN in the presence of TMSCl (used as promoter) under air; the reaction mixture was initially maintained at room temperature, and then warmed to 90 °C under reflux conditions (Scheme 3). The compounds **12-14** showed different cytotoxicity against three cancer cell lines.



Scheme 3. Synthetic pathway for the formation of B-ring fused steroidal pyrimidines **12-14**.

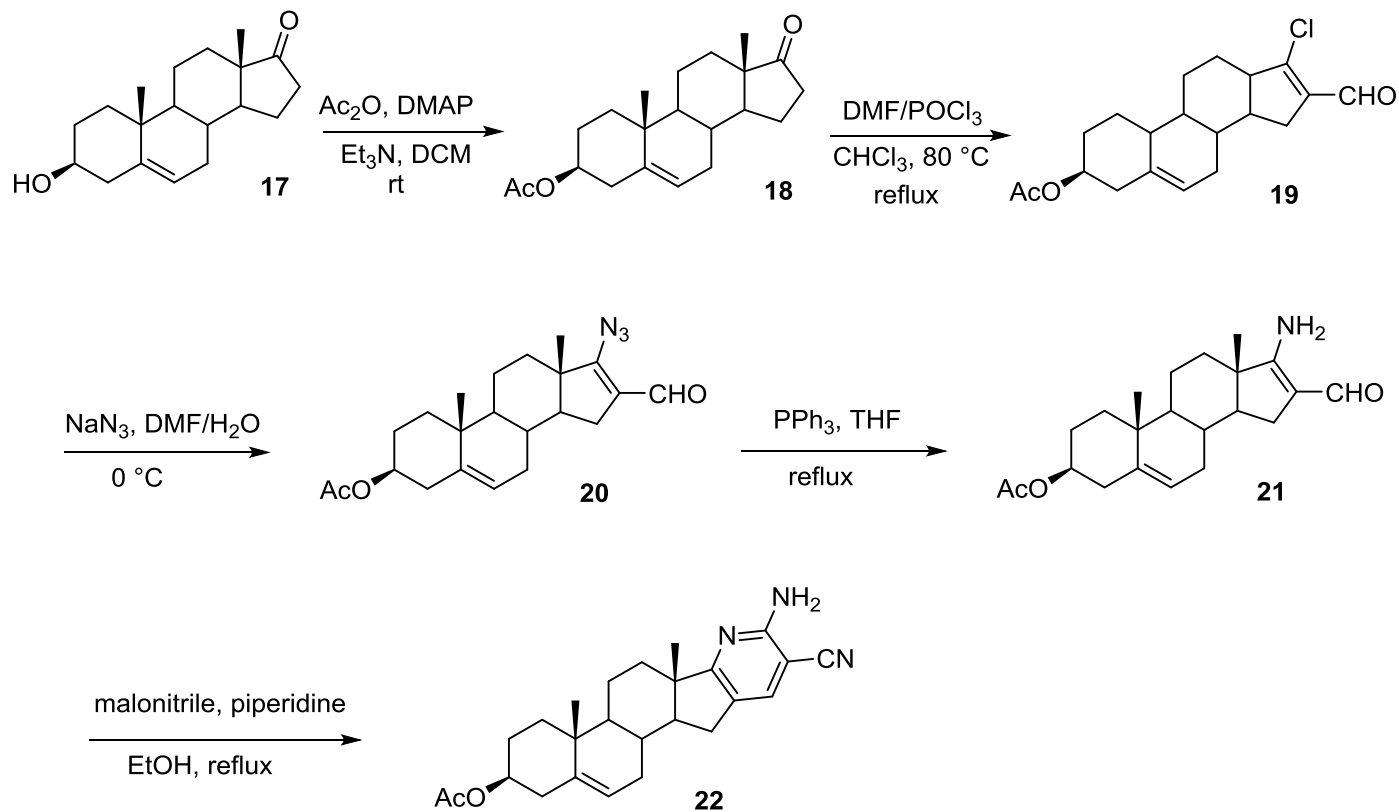
2.3 D-Ring fused steroidal heterocycles

As described in Section 2.1, Dutta *et al.*²⁴ developed a solvent free multi-component reaction process for the synthesis of steroidal A-ring fused 5,6-disubstituted pyridines. The same method was used for the synthesis of steroidal D-ring fused 5,6-disubstituted pyridines using Pd(OAc)₂ as the catalyst under microwave irradiation. A steroidal α -bromovinyl aldehyde **15** was synthesized starting commercially available 3-acetoxyandrost-5-en-17-one by treatment with Vilsmeier reagent prepared from PBr₃ and DMF.²⁵ Similarly, microwave reactions of steroidal α -bromovinyl aldehyde **15** with alkynes **7** afforded steroidal D-ring fused substituted pyridines **16** in high yields (Scheme 4). In all of the reactions of α -bromovinyl aldehydes with substituted alkynes and benzylamine under the reaction conditions described above (see 2.1), only one regioisomer of the pyridine derivative was obtained.



Scheme 4. Synthesis of steroidal D-ring fused pyridines.

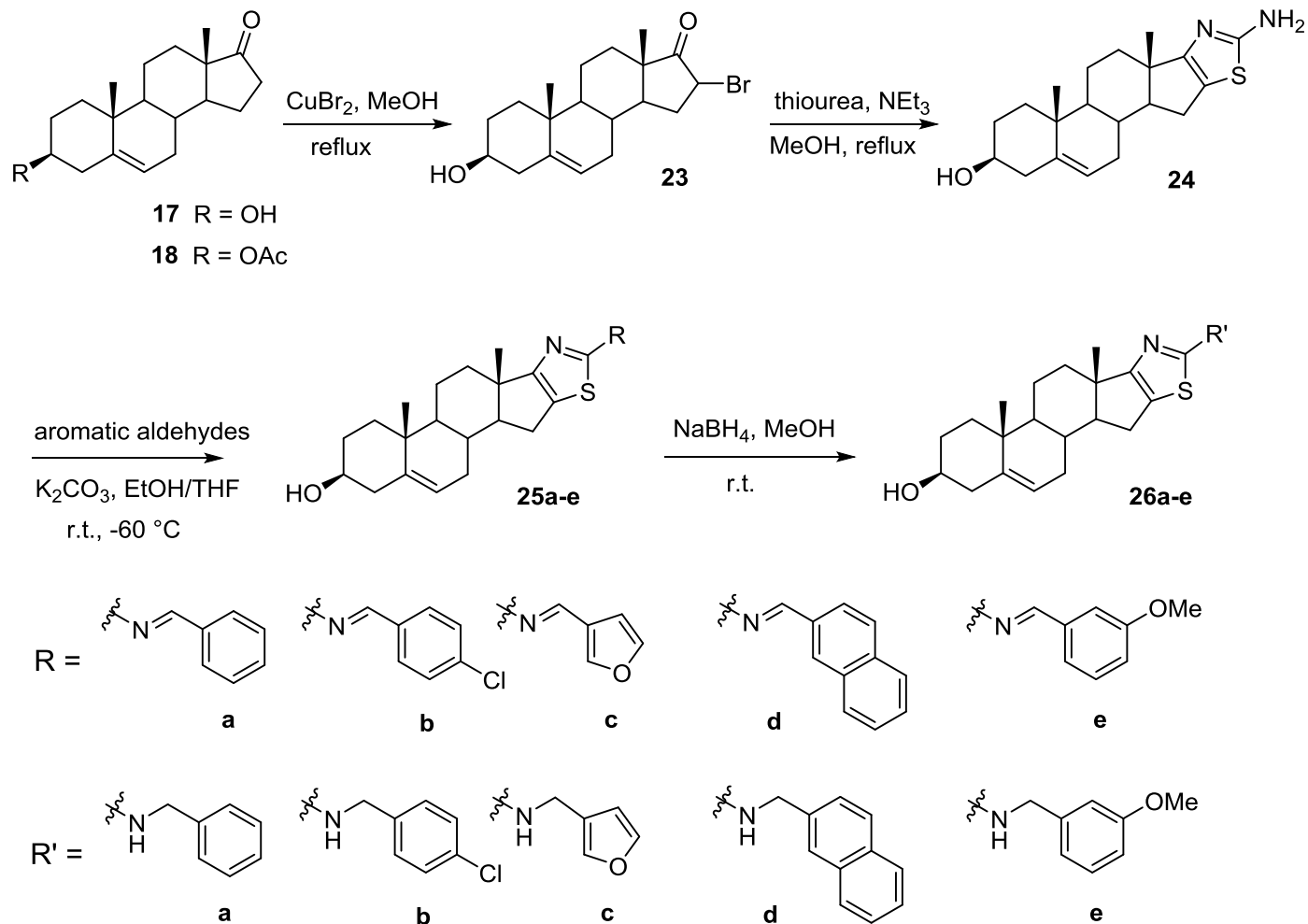
In the same year, Zhang *et al.*²⁸ developed a convenient synthesis of pure, air-stable steroidal D-ring fused pyridine compound **22**, D-ring fused thiazole imines and reductive products **25a-e** and **26a-e**, and D-ring fused imidazo[2,1-*b*]thiazole product **27** from readily available starting material dehydroepiandrosterone (DHEA) **17** (Schemes 5-7). This provided a simple strategy to synthesize steroids combined at the D-ring with heterocycles, extending the categories of heterosteroids. The strategy can be applied to diverse 3- or 17-ketosteroids and the steroidal thiazole-imines may allow further modification on the steroidal skeleton. They synthesized a series of D-ring fused pyridines with **17** as the starting material by the means of a Friedländer reaction (Scheme 5). Compound **18** was prepared by a standard procedure, by treating **17** with acetic anhydride catalyzed by DMAP with a good yield. Compound **19** was synthesized by a Vilsmeier reaction²⁹ and compound **21** was also synthesized according to Staudinger's procedure by treating **20** with Ph₃P in THF/H₂O (9:1). The yield was not very good (under 50%). Compound **20** was synthesized by treating **19** with NaN₃ in DMF/H₂O. In the synthesis process of **22**, when the base was replaced by NaOH, only the deacetylation product was detected. When they tried to expand the series of **22** with various reactive methylene species, such as acetophenone, 4-methoxyacetophenone, ethyl cyanoacetate, ethyl chloroacetate, ethyl acetoacetate, or ethyl 4-chloroacetoacetate, no product was obtained with any of them.



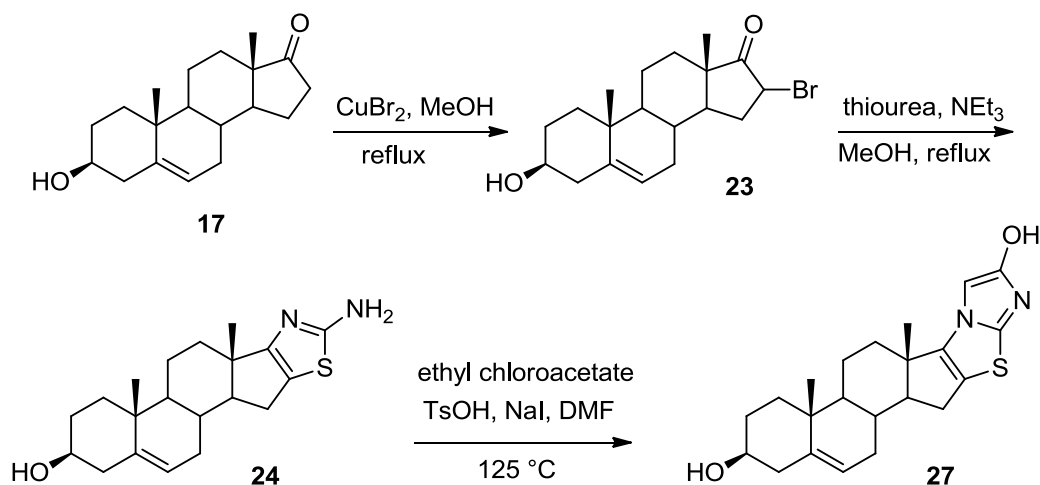
Scheme 5. Synthesis of steroidal D-ring fused pyridines **22**.

In 2011, Elmegeed³⁰ reported that the first step can be done by using 3 β -acetoxy-5 α -androstan-17-one, which is similar to **18**, as the starting material without losing the acetyl group under the same condition, followed by the next cyclization step in THF, and catalyzed by piperidine with a yield of 50%. Their procedure here was carrying out this step in EtOH by using triethylamine as a catalyst with a yield over 50%. With **24** in hand, they selected a benzaldehyde without an electron-withdrawing or electron-donating group as the first aldehyde, to carry out the next step to generate thiazolyl imines. Compounds **25a-e** were purified by column chromatography and then treated with NaBH₄ in MeOH to generate **26a-e** (Scheme 6).

Scheme 7 outlines the synthetic procedures of compound **27**;²⁸ the measures to prepare **24** were identical to the ways of synthesizing D-ring fused thiazole imine and reductive products. **27** was synthesized by treating compound **24** with ethyl chloroacetate in DMF; it was characterized by 1D- and 2D-NMR spectroscopy.

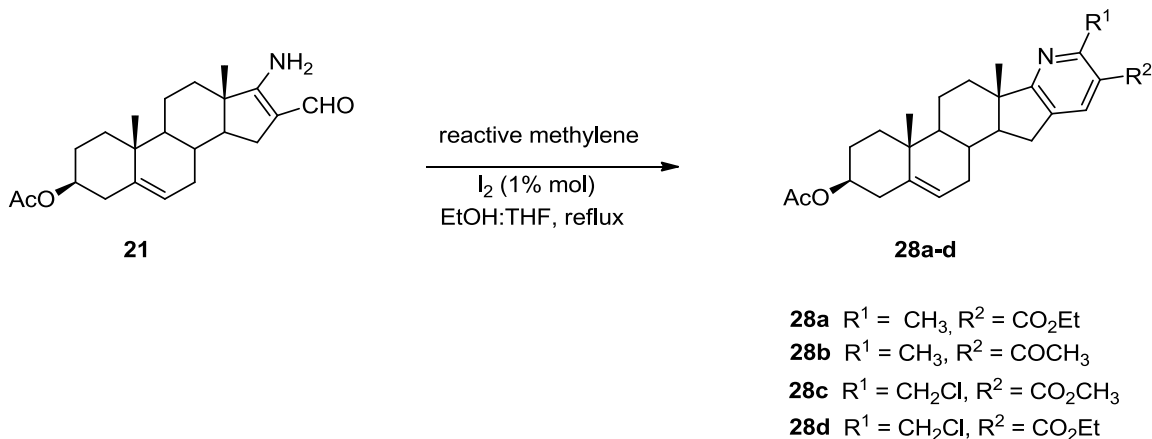


Scheme 6. Synthesis of steroidal D-ring fused thiazole imine and reductive products.



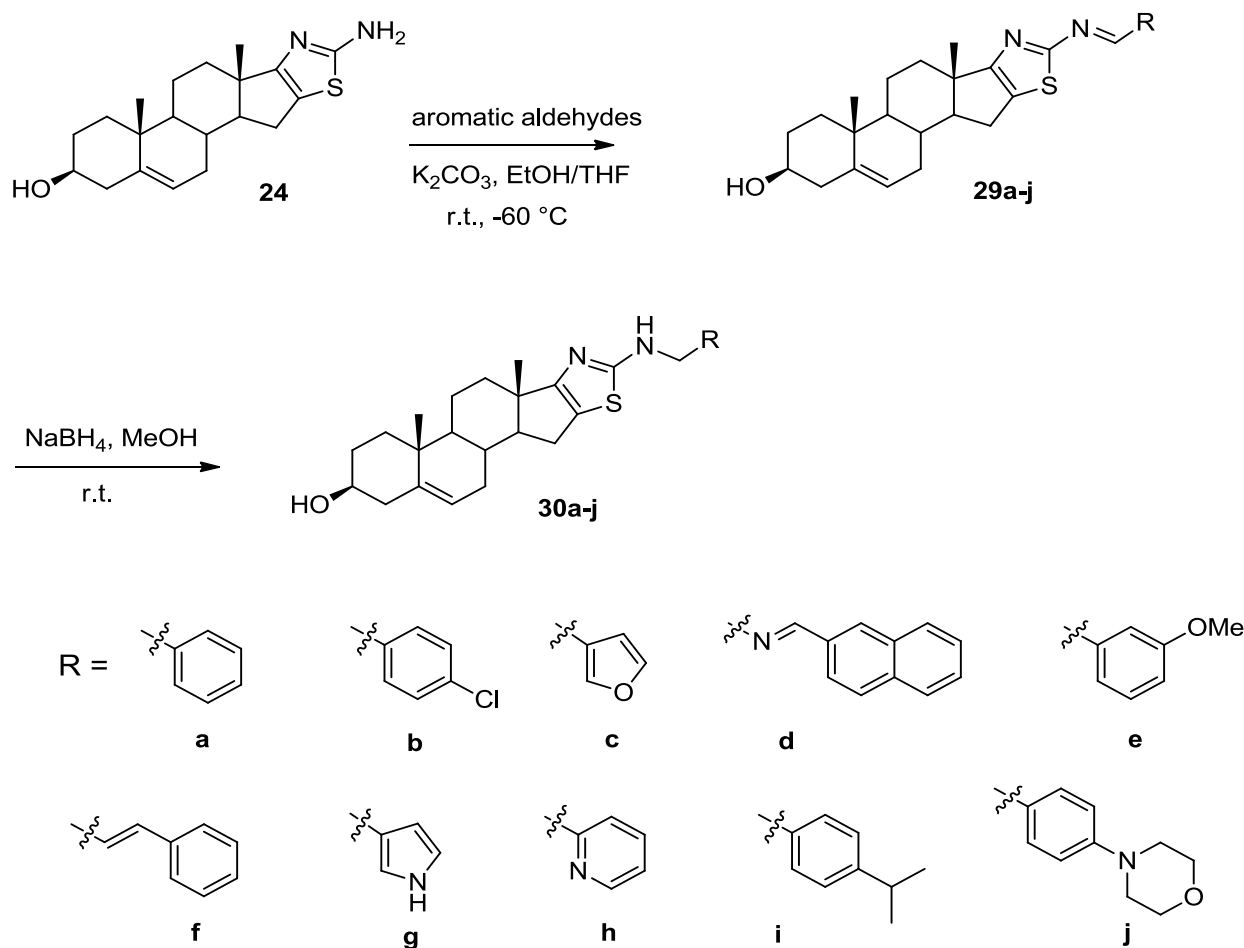
Scheme 7. Synthesis of steroidal D-ring fused imidazo[2,1-*b*]thiazole products.

In 2014, Zhang *et al.*³¹ developed convenient syntheses of steroidal [1,2-*b*]pyridine, [17,16-*d*]thiazole and [17,16-*d*]thiazolo[2,1-*b*]imidazole ring-fused analogues. After further exploration of the reaction conditions and reference to Wu's work,³² they completed the synthesis of compounds **28a-d** (Scheme 8).

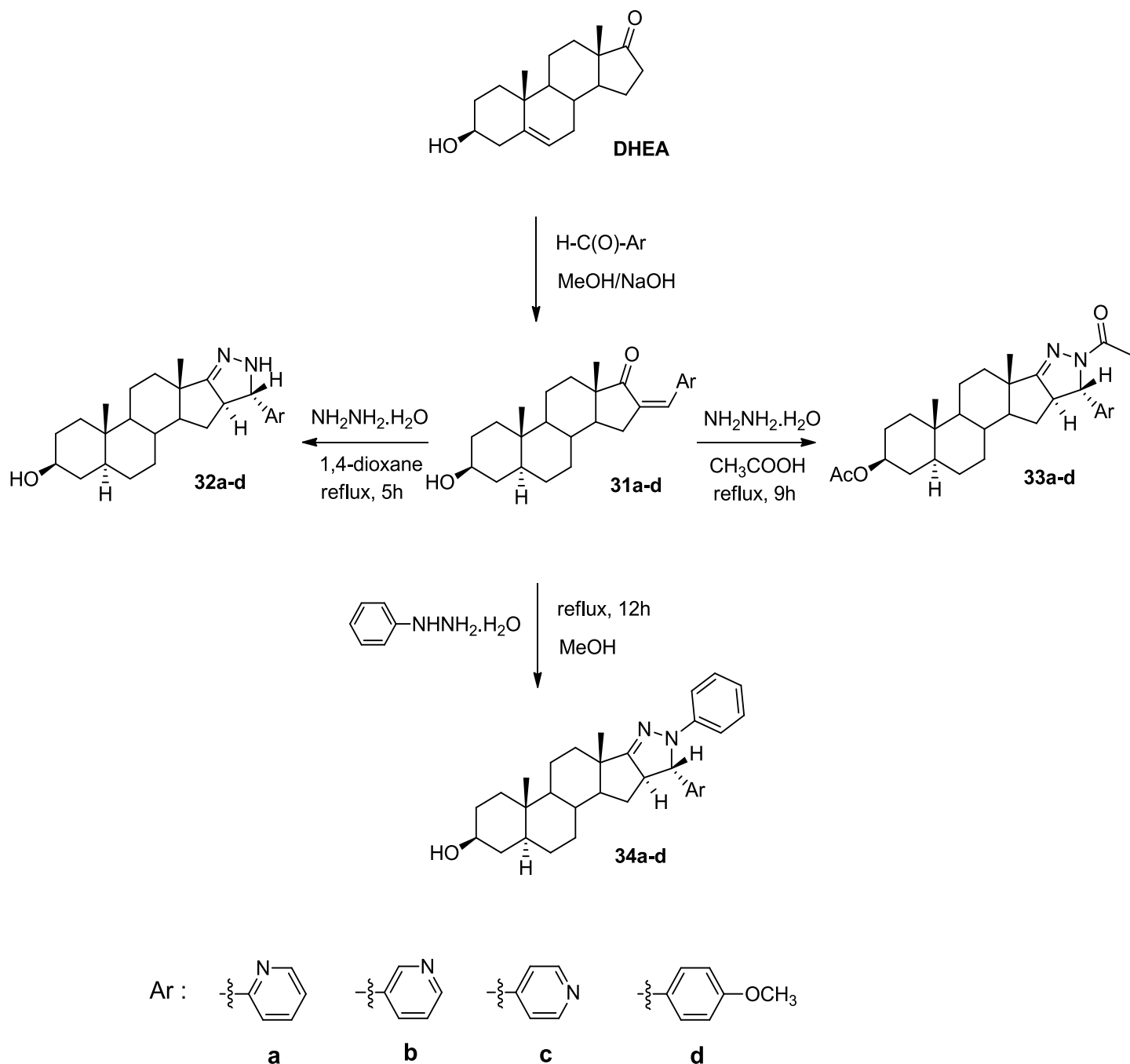


Scheme 8. Synthesis of steroidal D-ring fused pyridines **28a-d**.

The authors applied their protocol to the preparation of several new substituted aryl derivatives **29** and **30** (Scheme 9). These compounds were evaluated for their antiproliferation activity *in vitro* against EC109 (human esophageal carcinoma), EC9706 (human esophageal carcinoma) and MGC803 (human gastric carcinoma) cell lines. Bioactivity test results showed that compound **30** series have a relatively good activity against the three cell lines, especially the EC109 line. Both the synthesized compounds **28b-d**, **29a-j** and **30a-j** are reported to have a good activity against the MGC803 cell line.



Scheme 9. Synthesis of steroidal thiazole imines and corresponding reduction products.

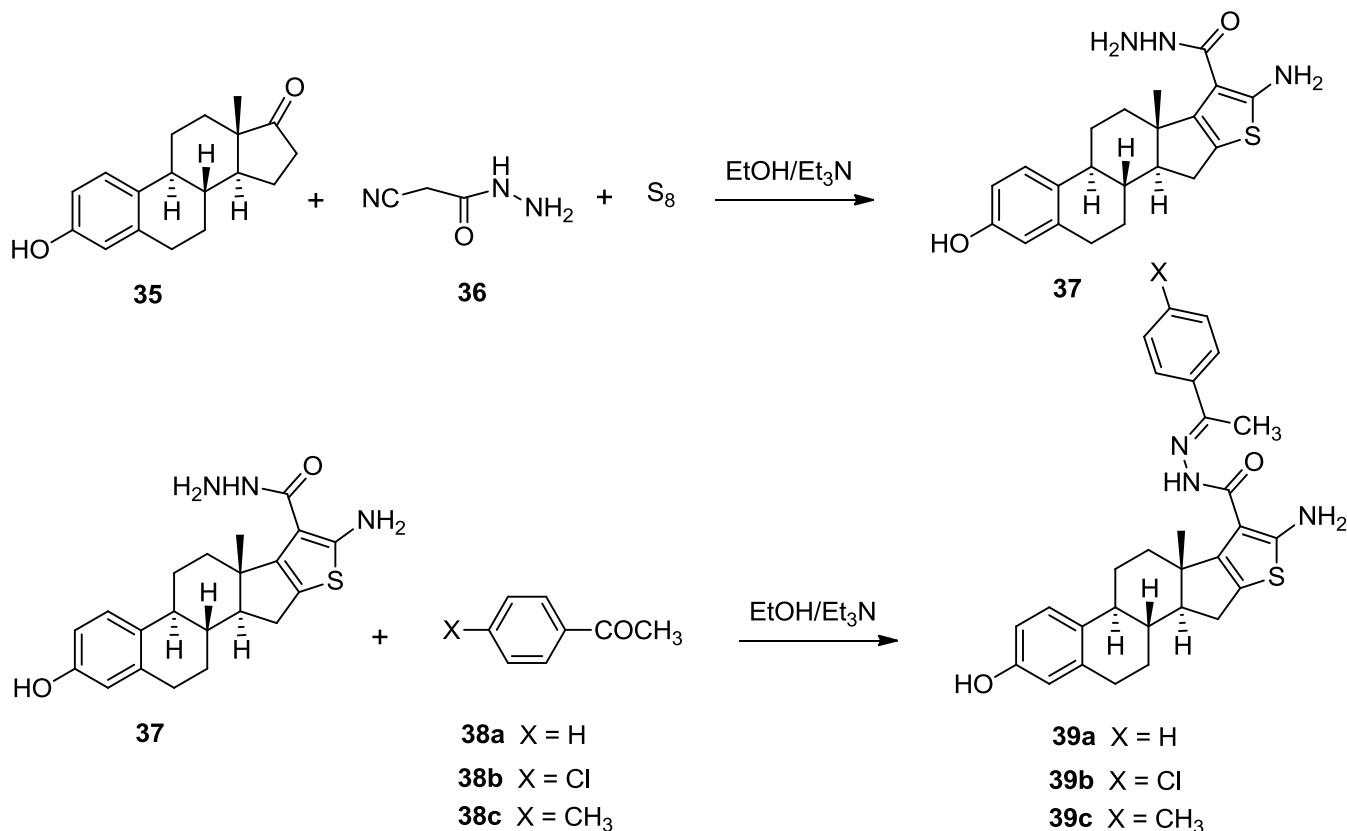


Scheme 10. Synthetic route to the formation of various 16,17-pyrazolo-steroids.

Anhydrous 1,4 dioxane and anhydrous methanol were found to be the most suitable solvents for the synthesis of pyrazolo-steroids. The compounds were purified by automated flash chromatography as they decompose while crystallizing in most solvents. Treatment with the pyrazoline substituted steroids considerably improved the LPS- induced learning, memory and movement deficits in animal models. Suppression of biochemical parameters of oxidative and nitrosative stress, acetylcholine esterase activity, and $\text{TNF-}\alpha$ levels was also observed. 16,17-Pyrazolo-steroids **32-34c** substituted with a 4-pyridyl moiety at the 5-position of the heterocyclic ring were found to be the most potent agents and produced neuroprotective effects better than standard drugs celecoxib and dexamethasone. Of these pyrazoline-substituted steroids,

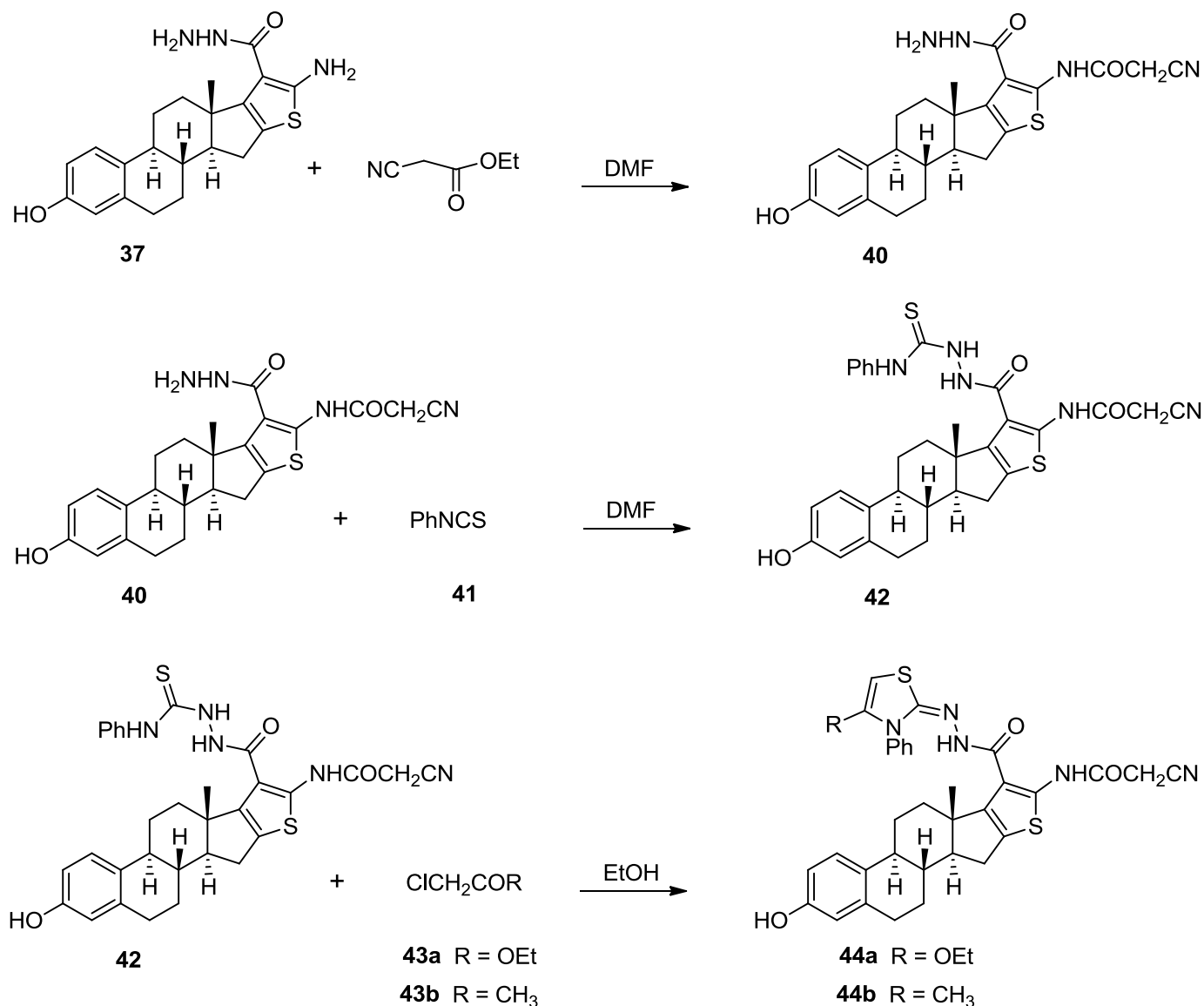
1 the *N*-acetyl analogue **33c** displayed better neuroprotective effects than *N*-phenyl **34c**, which in turn showed a
 2 higher potency than the *N*-unsubstituted analogue **32**.

3 In 2019, Mohareb *et al.*³⁶ synthesized a series of heterocyclic estrone derivatives. They investigated the
 4 Gewald reaction³⁷ of estrone **35** with cyanoacetylhydrazine **36** in ethanol and triethylamine which gave the
 5 thiophene derivative **37**. The hydrazide group present in compound **37** reacted with acetophenone **38a**, 4-
 6 chloroacetophenone **38b** or 4-methylacetophenone **38c** to give the hydrazide-hydrazone derivatives **39a-c**,
 7 respectively (Scheme 11).
 8



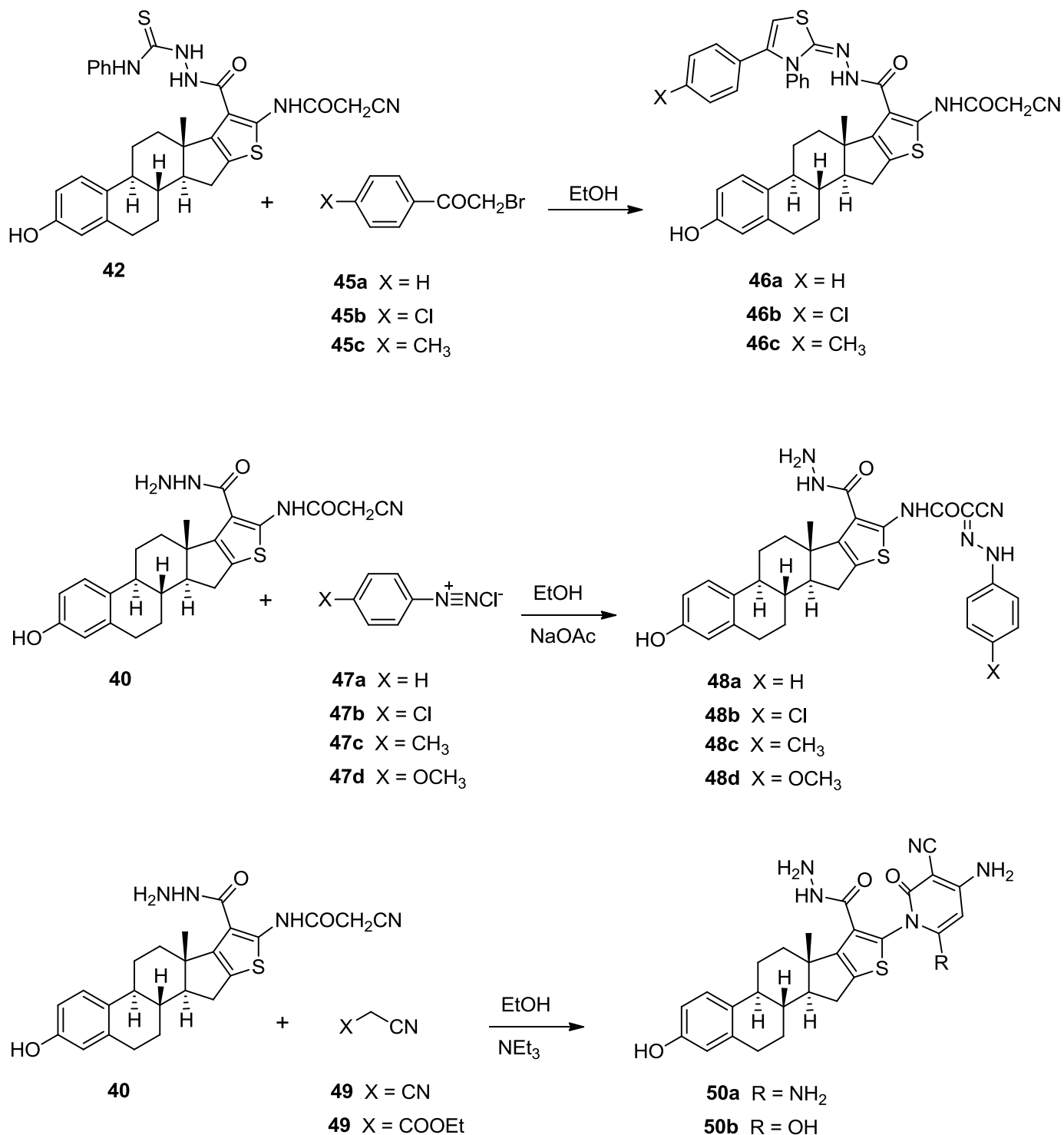
9
 10
 11 **Scheme 11.** Synthesis of compounds **37** and **39a-c**.
 12

13 The 2-amino group present in compound **37** is capable of amide formation. Thus, compound **37** reacted
 14 with ethyl cyanoacetate in dimethylformamide to afford the 2-cyanoacetamide derivative **40**. Compound **40**
 15 reacted with phenyl isothiocyanate **41** to give the *N*-phenylthiosemicarbazide derivative **42**. Compound **42**
 16 reacted with either of ethyl chloroacetate **43a** or α -chloroacetone **43b** to give the thiazole derivatives **44a** and
 17 **44b**, respectively (Scheme 12).



Scheme 12. Synthesis of compounds **40**, **42** and **44a,b**.

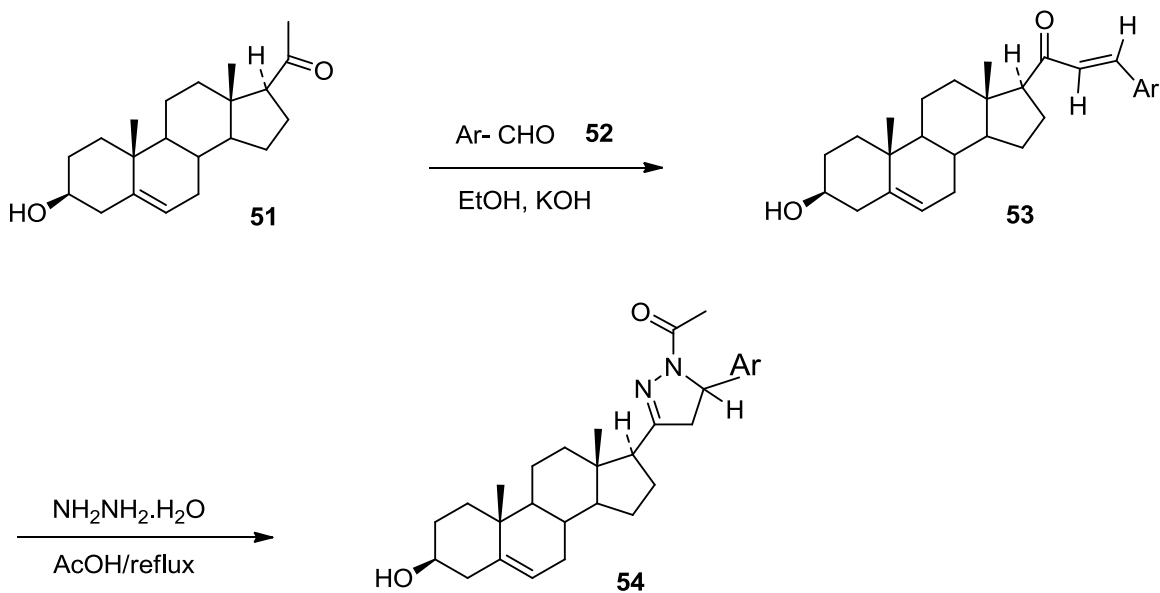
The reaction of compound **42** with ω -bromoacetophenone **45a**, 4-methyl- ω -bromoacetophenone **45b** or 4-chloro- ω -bromoacetophenone **45c** gave the thiazole derivatives **46a-c**, respectively. Compound **40** reacted with any of benzenediazonium chloride **47a**, 4-methylbenzenediazonium chloride **47b**, 4-chlorobenzenediazonium chloride **47c** or 4-methoxybenzenediazonium chloride **47d** to give the arylhydrazone derivatives **48a-d**, respectively. On the other hand, the reaction of compound **40** with either of malononitrile **49a** or ethyl cyanoacetate **49b** in refluxing ethanol containing triethylamine gave the pyridine derivatives **50a** and **50b**, respectively (Scheme 13). The nine compounds **39**, **39c**, **44a**, **46c**, **48b**, **48c**, **48d**, **50a** and **50b** showed the highest potency against c-Met kinase and six cancer cell lines. These compounds were investigated against the five tyrosine kinases c-Kit, Flt-3, VEGFR-2, EGFR, and PDGFR where compound **50b** showed the highest inhibitory effect. Compounds **39b**, **48d**, **50a** and **50b** were selected to examine their Pim-1 kinase inhibition activity where compounds **48d** and **48b** were the most active compounds. The toxicity against shrimp larvae revealed that compounds **39b**, **46c**, **48c**, **48d** and **50a** were non-toxic against the tested organisms.

Scheme 13. Synthesis of compounds **46a-c**, **48a-c** and **50a,b**.

3. Synthesis of Steroidal Derivatives Containing Heterocyclic Side-chains

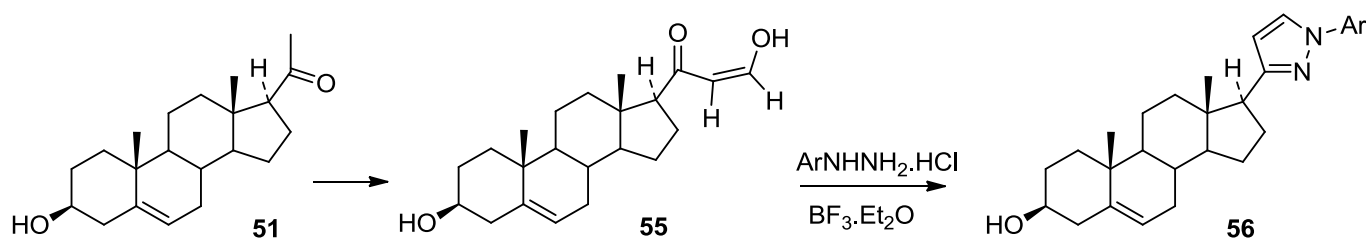
In 2014, a series of D-ring substituted pyrazolonyl pregnenolone (**54**) and pyrazolyl pregnenolone (**56**) derivatives were synthesized and screened for their 5 α -reductase inhibitory activity by Banday *et al.*³⁸ To a solution of pregnenolone **51** in ethanol was added a solution of KOH. Then aldehyde **52** was added to the

1 reaction mixture to get the corresponding benzylidene derivative **53**. The condensation product **53** was
 2 refluxed in acetic acid in the presence of hydrazine to yield the desired *N*-acetylpyrazolines (Scheme 14).
 3



4
 5 **Scheme 14.** Synthesis of D-ring substituted pyrazolinyl-pregnenolones.
 6

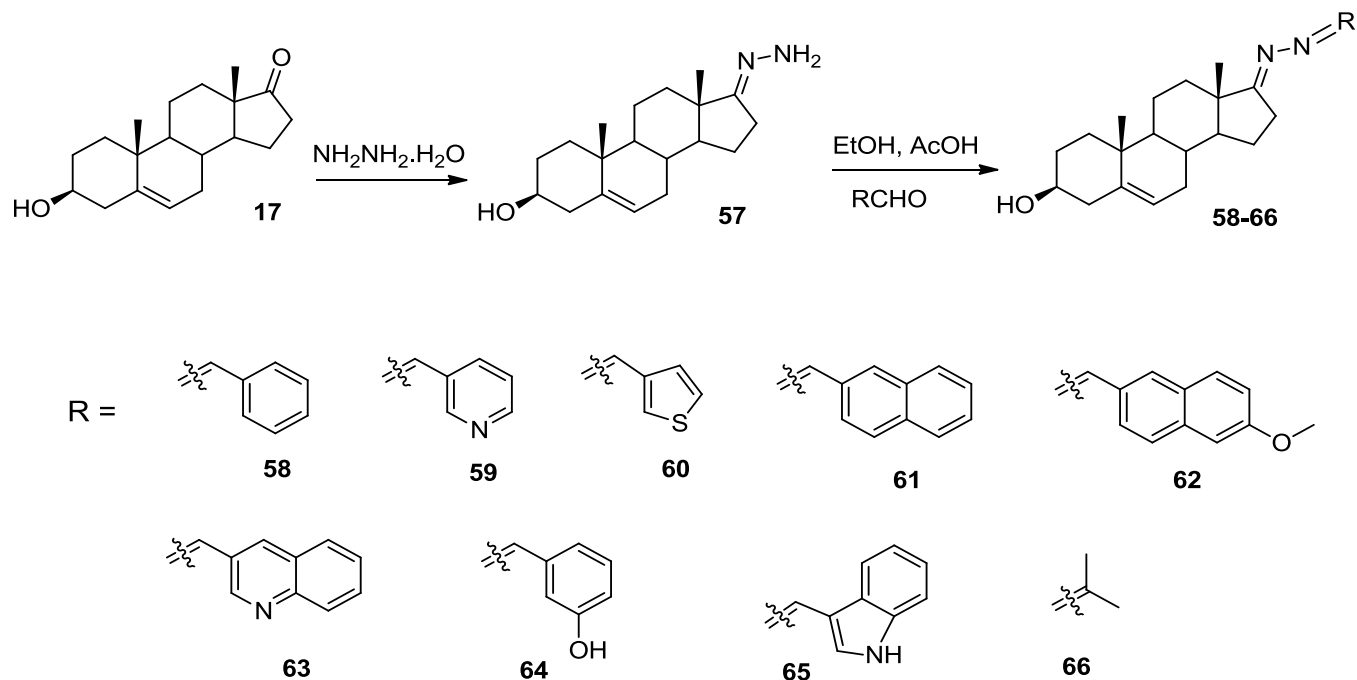
7 All the pyrazolyl pregnenolone derivatives were prepared by known literature methods.³⁹ The route
 8 described by Ivany *et al.*³⁹ involves the cyclization of 3 β -hydroxy-21-hydroxymethylenepregn-5-en-20-one
 9 **55**⁴⁰ with phenylhydrazine or its *p*-substituted derivatives (Scheme 15). All the compounds exhibited promising
 10 inhibitory activity especially against type I human steroid-5 β -reductase.
 11



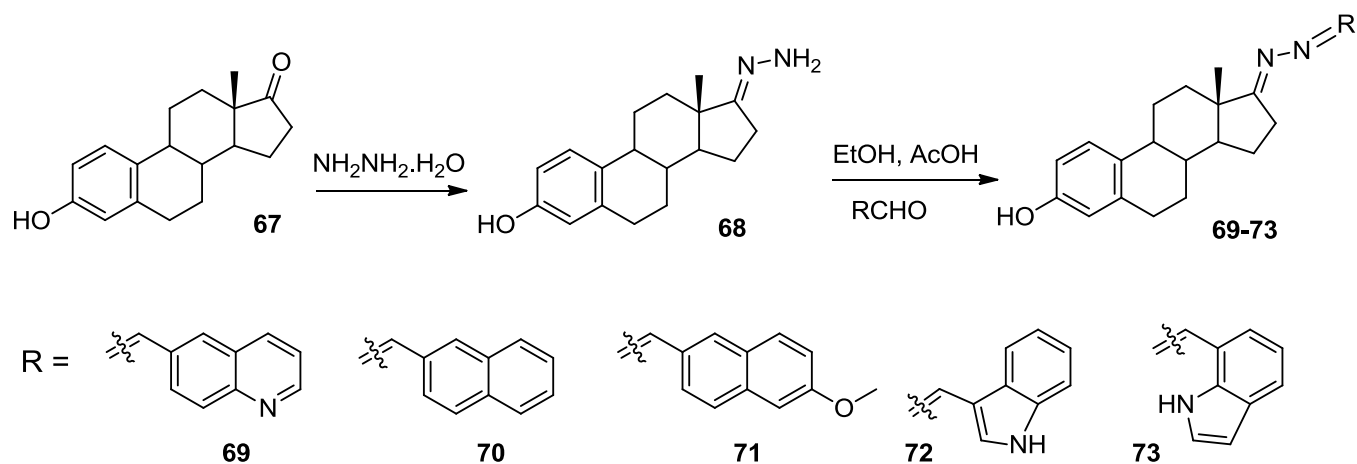
12
 13
 14 **Scheme 15.** Synthesis of D-ring substituted pyrazolyl-pregnenolones.
 15

16 Cui *et al.*⁴¹ synthesized a series of dehydroepiandrosterone-17-hydrazone and estrone-17-hydrazone
 17 derivatives possessing various aromatic heterocyclic structures at C-17 of their steroidal nucleus. Scheme 16
 18 outlines the synthetic procedures of compounds **58-66**. First, the dehydroepiandrosterone was converted into
 19 the corresponding dehydroepiandrosterone-17-hydrazone **57** via reaction with hydrazine hydrate in
 20 anhydrous ethanol. After crystallization, reaction of the pure steroidal hydrazone with aromatic aldehydes
 21 gave steroidal hydrazone derivatives **58-66**.

22 To determine the effect of the A-ring structure in the steroidal nucleus on the cytotoxicity, they also
 23 synthesized compounds **69-73** (Scheme 17). Compounds **69-73** were prepared similarly as the procedures for
 24 the synthesis of compounds **58-66**.
 25

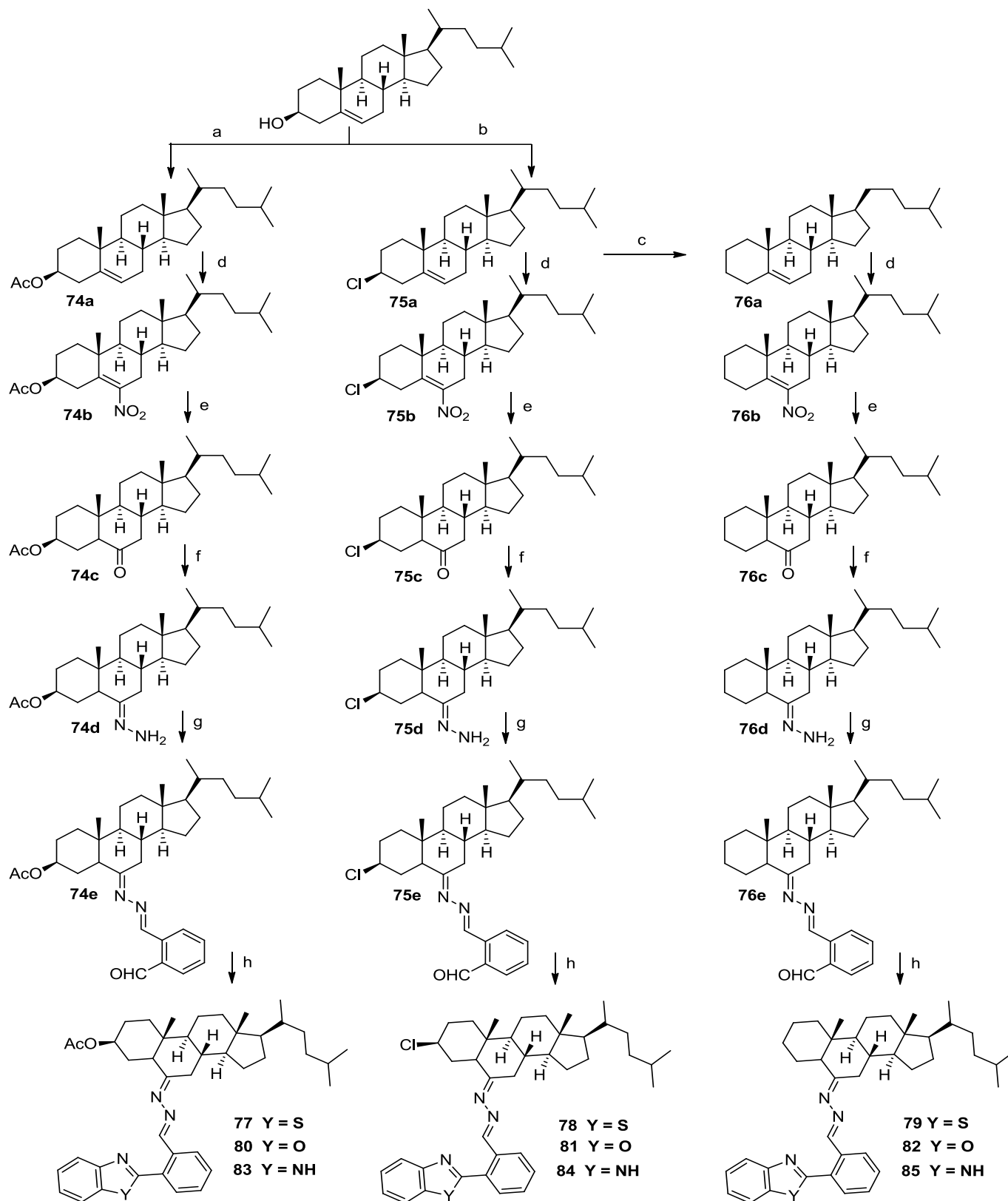


Scheme 16. Synthesis of compounds **58-66**.



Scheme 17. Synthesis of compounds **69-73**.

In 2015, a series of new steroidal heterocyclic compounds with significant anti-tumor and antioxidant activities was successfully synthesized by Abad *et al.*⁴² All the compounds (Scheme 18) were prepared by refluxing compounds **74e-76e** with *o*-aminothiophenol/ *o*-aminophenol/ *o*-phenylenediamine in DMSO. Their anti-tumor activity *in vitro* was evaluated against Hep3B (human hepatocellular carcinoma), MCF7 (human breast adenocarcinoma), HeLa (human cervical carcinoma) cancer cell lines and on normal PBMCs (peripheral blood mononuclear cells). The results demonstrated that most of the synthesized derivatives showed significant anti-tumor activity; however compounds **78**, **79**, **81**, **82** and **85** exhibited excellent activity with IC₅₀ < 19 μM against all the cancer cell lines. In addition, compounds **83-85** were found to be good antioxidants. Nonenzymatic degradation of DNA has also been investigated. The application of compounds **79** as DNA gene

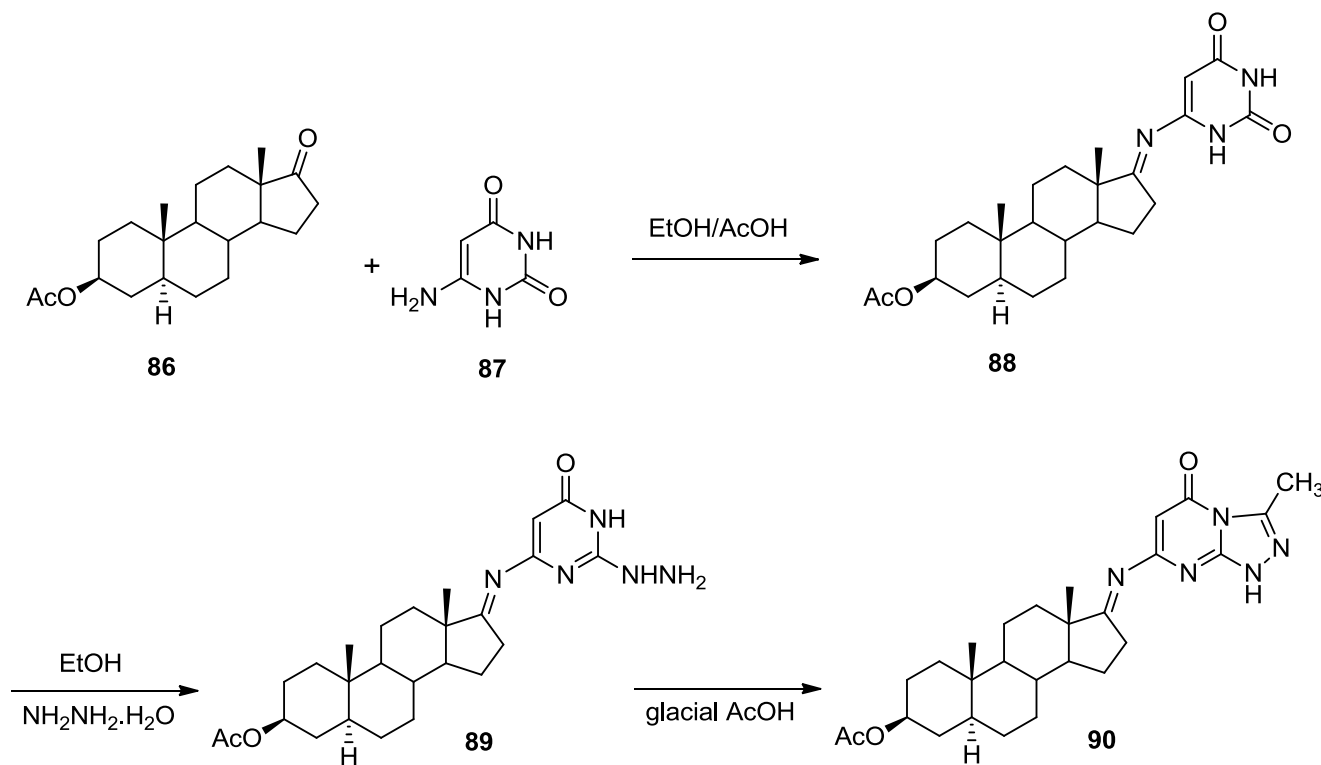


Reagents : a- pyridine; b- SOCl_2 ; c- Na, amyl alcohol; d- HNO_3 ; e- acetic acid, Zn dust; f- $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, CH_3COOH , ethanol, reflux; g- ethanol, reflux; h- DMSO.

Scheme 18. Synthetic pathways for the formation of steroidal compounds **77-85**.

1 transporter was evaluated by DNA condensation and ascertained by employing TEM and AFM, which
 2 illustrated that the compound **79** induces the condensation of CT-DNA. Lipinski's 'Rule of Five' analysis
 3 predicted good oral absorption of the synthesized compounds. Moreover, the acetylcholinesterase (AChE)
 4 inhibitor activities of the steroidal derivatives were also evaluated using Ellman's method. From the results
 5 obtained they deduced that compound **77**, **80** and **83** exhibited significant inhibition on AChE among all the
 6 synthesized compounds.

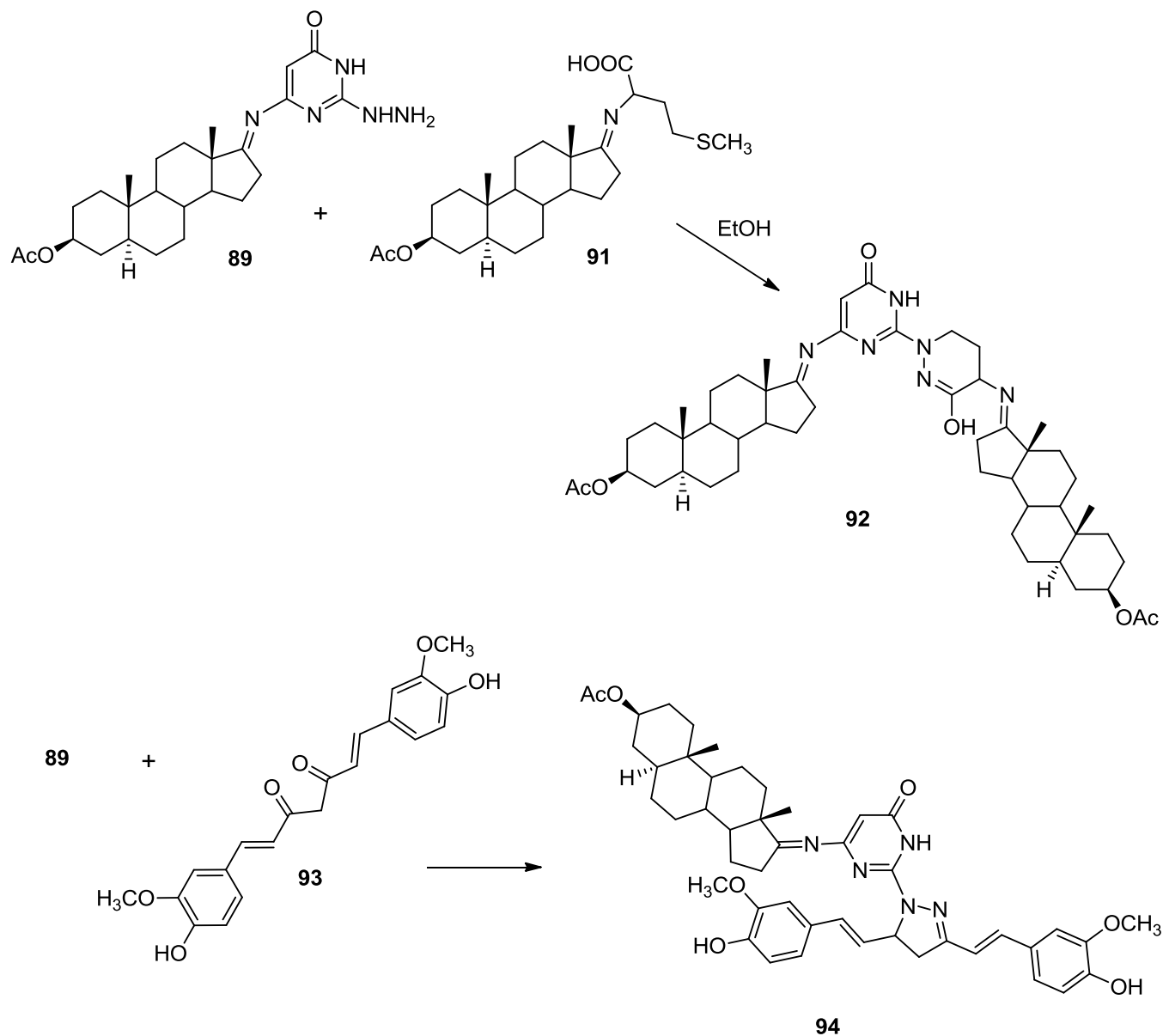
7 Elmegeed *et al.*⁴³ synthesized new hetero-steroids with promising anticancer effects. The reaction of
 8 compound **86** with 4-amino-2-thiouracil **87** in ethanolic solution containing acetic acid afforded the
 9 corresponding thioxypyrimidinyl androstane derivative **88** in 75% yield. Compound **88** reacted with hydrazine
 10 hydrate in boiling ethanol to give the hydrazinyloxypyrimidinyl androstane derivative **89** in 58% yield.
 11 Treatment of compound **89** with glacial acetic acid gave the triazolopyrimidinyl androstane derivative **90** in
 12 64% yield (Scheme 19).
 13



14
 15
 16 **Scheme 19.** Synthesis of compounds **88**, **89** and **90**.

17
 18 Reaction of compound **91**³⁰ with compound **89** in ethanol gave the corresponding hydroxypyridazinyl-
 19 pyrimidinyl androstane derivative **92**. The structure of compound **92** was confirmed based on the analytical
 20 and spectral data.

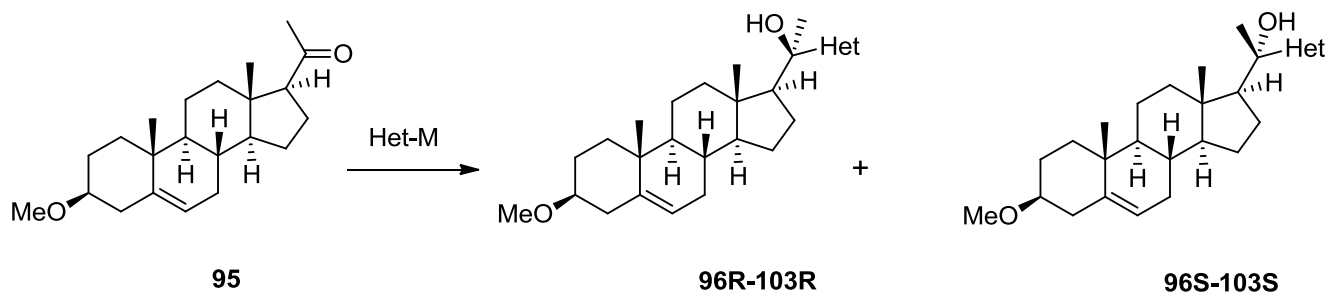
21 The reaction of compound **89** with curcumin **93** in glacial acetic acid containing sodium acetate afforded
 22 pyrazolo-curcumin-pyrimidinyl androstane derivative **94** in 75% yield (Scheme 19). Compound **88**, **90**, **92**, **94**,
 23 showed significant cytotoxic effect on breast cancer cells. This study clarified that the compounds **88**, **90**, **92**,
 24 **94** are the most promising as pro-apoptotic factors. Compounds **88**, **94**, act through the downregulation of
 25 CCND1, survivin, BCL-2 and CDC2 gene expression, while compounds **90** and **92** activate the P53/P21 pathway,
 26 resulting in tumor suppression and increased apoptosis.



Scheme 20. Synthesis of compounds **92** and **94**.

In 2016, Vitellozzi *et al.*⁴⁴ prepared a range of novel steroid analogues bearing a C-17 side-chain containing a 20*R*-hydroxyl group and a variety of heterocyclic substituents by organometallic additions to 3-methoxy-pregnenolone. This methodology was extended, by use of the Achmatowicz rearrangement and ring-closing metathesis approaches, to prepare pyrandione and δ -lactone steroidal analogues reminiscent of the withanolide natural products. The addition of simple lithiated heterocycles to the C-20 ketone of steroid **95** were studied first. Thus, 3 β -methoxypregnenolone **95** was added to a solution of 2-lithiothiazole, and a chromatographically inseparable mixture of adducts **96R** and **96S** (84%, 9:1) was obtained; however, recrystallisation of the mixture from methanol gave the required *R*-diastereomeric adduct **96R** in 48% isolated yield. The addition of other lithiated five-membered heterocycles onto ketone **95** was also investigated. Using thiophene, furan and TBS-protected furfural, lithiation was aided by the addition of TMEDA, although the isolated yields of adducts **97–99** were depressed by the ease with which the products, particularly **97**, underwent dehydration. Nevertheless, the reactions proceeded with complete diastereoselectivity, giving **97R–99R** with no sign of the corresponding *S*-isomers. They next examined the addition of lithiated

1 benzothiophene, benzofuran and *N*-methylindole (Scheme 21); organometallic addition of such reagents to
 2 20-ketosteroids was not previously reported. All additions proceeded diastereoselectively, although the yields
 3 of the adducts were modest (**101R**, 47%; **102R**, 56%) or low (**103R**, 12%). In each of these examples, *n*-
 4 butyllithium was used for the metallation reactions.

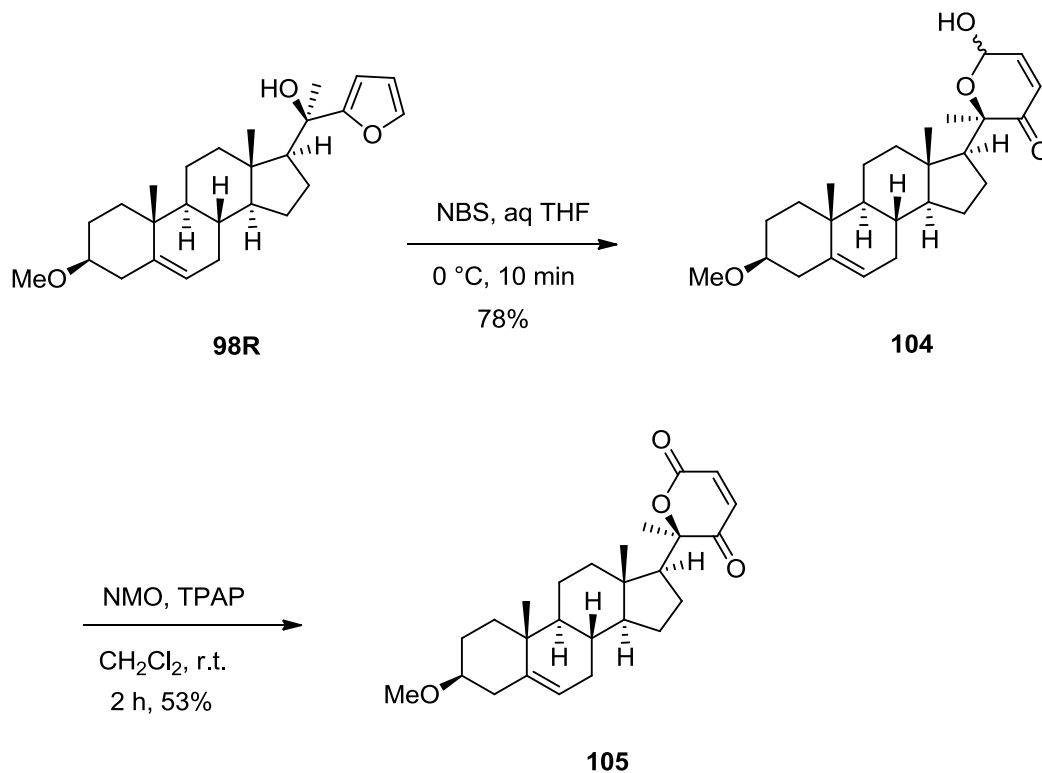
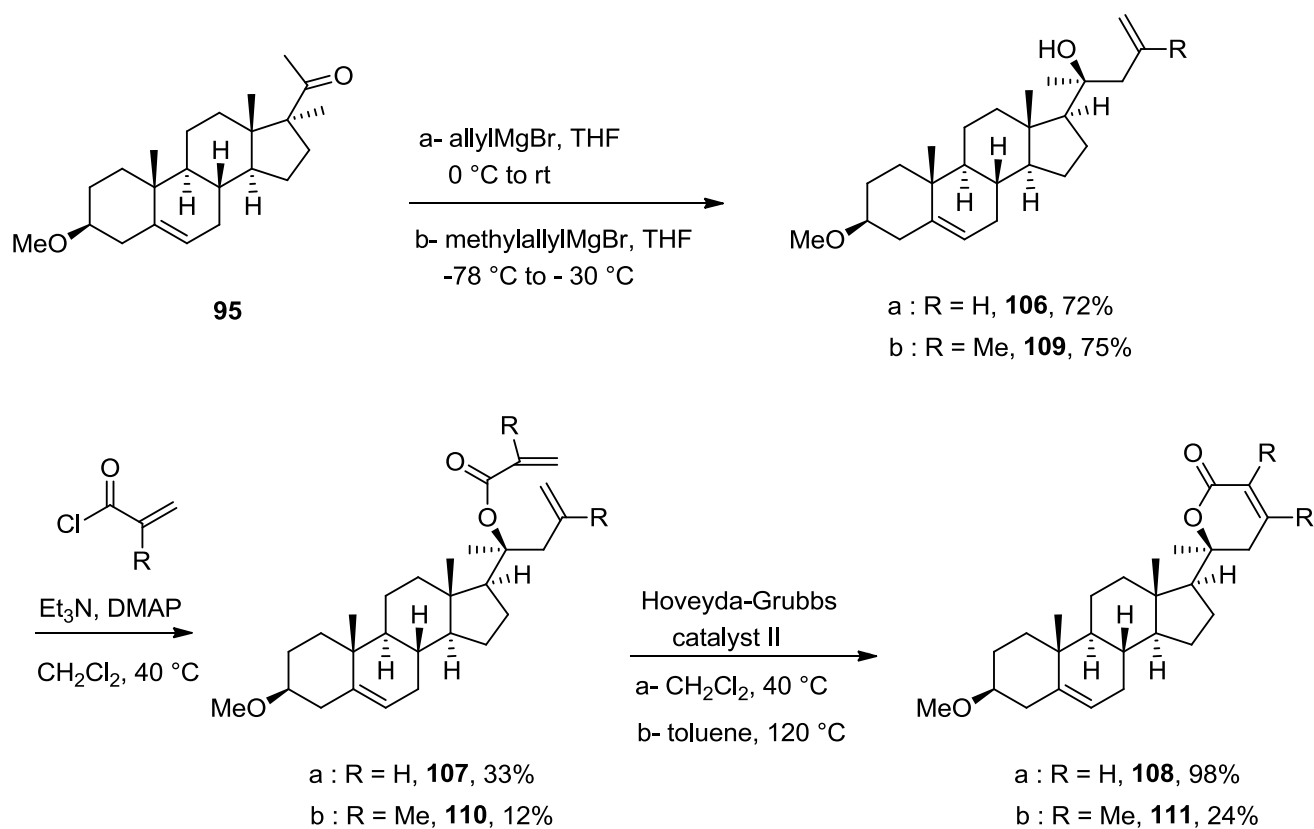


Entry	Het-Li	Entry	Het-Li	Product	yield (%)
1		5		96 from entry 1	84; R/S : 9/1
2		6		97 from entry 2	51; R/S : 98/2
3		7		98 from entry 3	84; R/S : 98/2
4		8		99 from entry 4	75; R/S : 98/2
				100 from entry 5	68; R/S : 9/1
				101 from entry 6	47; R/S : 98/2
				102 from entry 7	56; R/S : 98/2
				103 from entry 8	12; R/S : 98/2

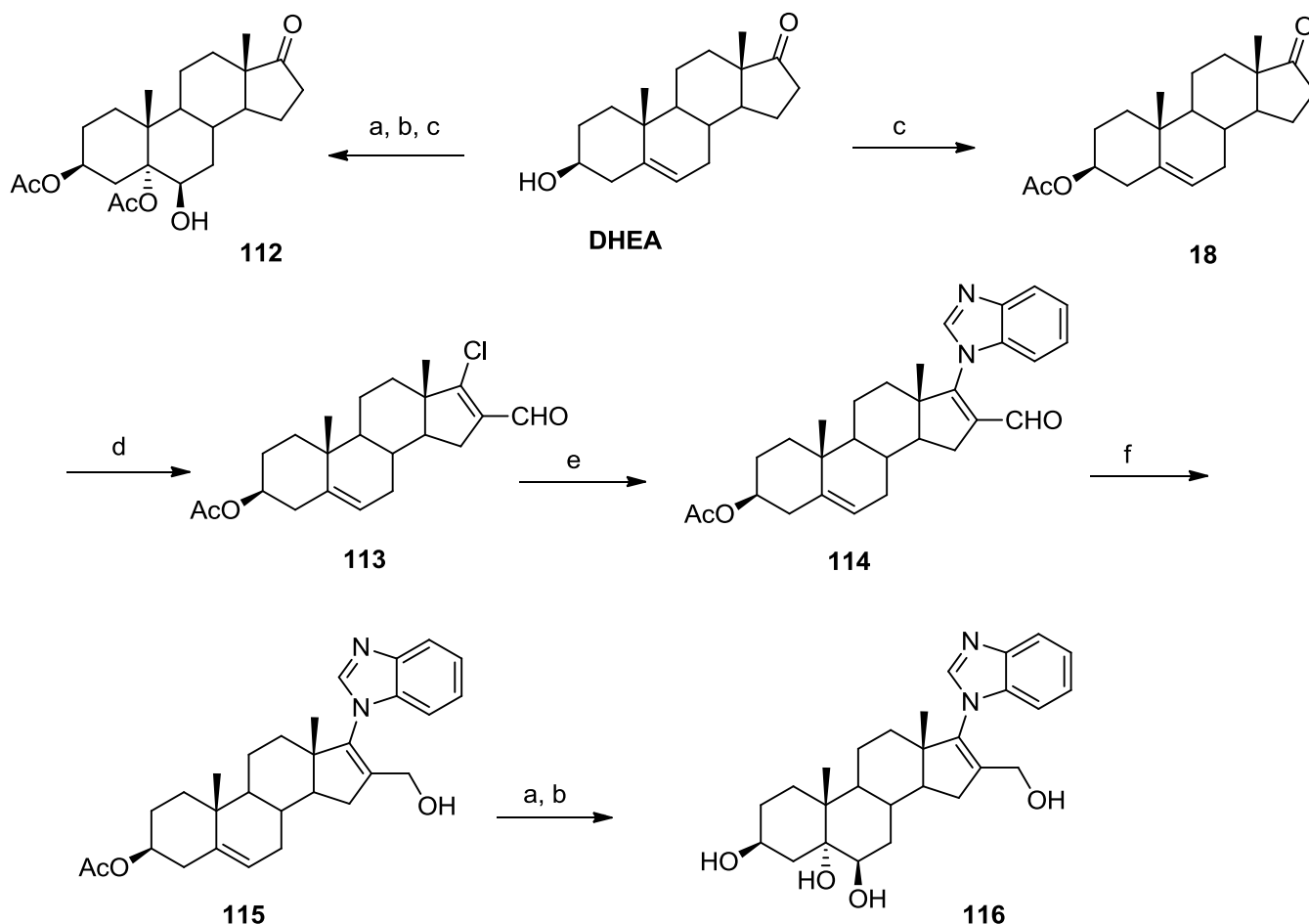
6
7
8 **Scheme 21.** Organometallic additions to ketone **95**.

9
10 The authors then explored routes to systems containing a pyrandione or lactone ring in the side-chain to
 11 mimic the withanolide (and bufadienolide) natural products. The pyrandione analogue **105** was readily
 12 obtained from furan **98R** using the Achmatowicz rearrangement⁴⁵ in the key step (Scheme 22). This sequence,
 13 originally developed by Kametani *et al.*⁴⁶ on a closely related system, proceeded efficiently using *N*-
 14 bromosuccinimide for the furan ring elaboration, and tetrapropylammonium perruthenate (TPAP)/ *N*-
 15 methylmorpholine *N*-oxide for the oxidation of the lactol **104** to lactone **105**.

16 Following recent research on the use of ring-closing metathesis (MCR) for δ -lactone formation,⁴⁷ 3-
 17 methoxypregnenolone **95** was treated with allylmagnesium bromide to generate exclusively the 20S-alcohol
 18 **106** in 72% yield (Scheme 23). Subsequent esterification of the sterically hindered tertiary alcohol in **106** with
 19 acryloyl chloride afforded ester **107** in 33% yield. The use of second-generation Hoveyda–Grubbs catalyst then
 20 gave the desired α,β -unsaturated lactone **108** in near quantitative yield. The organometallic addition to
 21 generate alcohol **106** occurred with complete Felkin–Anh control. Finally, the authors wanted to investigate
 22 whether similar reaction conditions could be applied to the synthesis of the α,β -dimethyl- α,β -unsaturated C-
 23 20- δ -lactone **111**, that is, possessing a substituted lactone moiety typical of withanolide A. Thus, addition of 2-
 24 methylallylmagnesium chloride to ketone **95** gave the β -alcohol **109** in 75% yield (Scheme 23). Diene **110** was
 25 isolated in 12% unoptimised yield along with recovered starting material. Treatment with the second-
 26 generation Hoveyda–Grubbs catalyst gave dimethyl- α,β -unsaturated lactone **111** in 24% yield.⁴⁴

Scheme 22. Preparation of the pyran lactone **105**.Scheme 23. Synthesis of the dihydropyrone **108**, **111** by RCM reactions

In 2018, polyhydroxy steroids bearing the $3\beta,5\alpha,6\beta$ -trihydroxy pattern were synthesized by Mohammed Kolo *et al.*⁴⁸ from different heterocyclic-substituted unsaturated steroids by a simple and easy method with high yields. 3β -Acetoxyandrost-5-en-17-one **18** was synthesized from the acylation reaction of DHEA with acetic anhydride in order to protect the hydroxyl group at C-3 from given a side reaction. 3β -Acetoxy-17-chloro-16-formylandrosta-5,16-diene **112** was synthesized with high efficiency by the Vilsmeier–Haack reaction of compound **18**. 3β -Acetoxy-17-(1*H*-benzimidazol-1-yl)-16-formylandrosta-5,16-diene **114** was obtained from the reaction of compound **112** with benzimidazole in basic medium. The formyl group on compound **114** was reduced to the corresponding 3β -acetoxy-17-(1*H*-benzimidazol-1-yl)-16-(hydroxymethyl)androsta-5,16-diene **115**. 17-(1*H*-Benzimidazol-1-yl)- $3\beta,5\alpha,6\beta$ -trihydroxy-16-(hydroxymethyl)-16-androstene **116** was synthesized with good efficiency from the reaction of compound **115** with *m*-CPBA and methanolic KOH (Scheme 24).

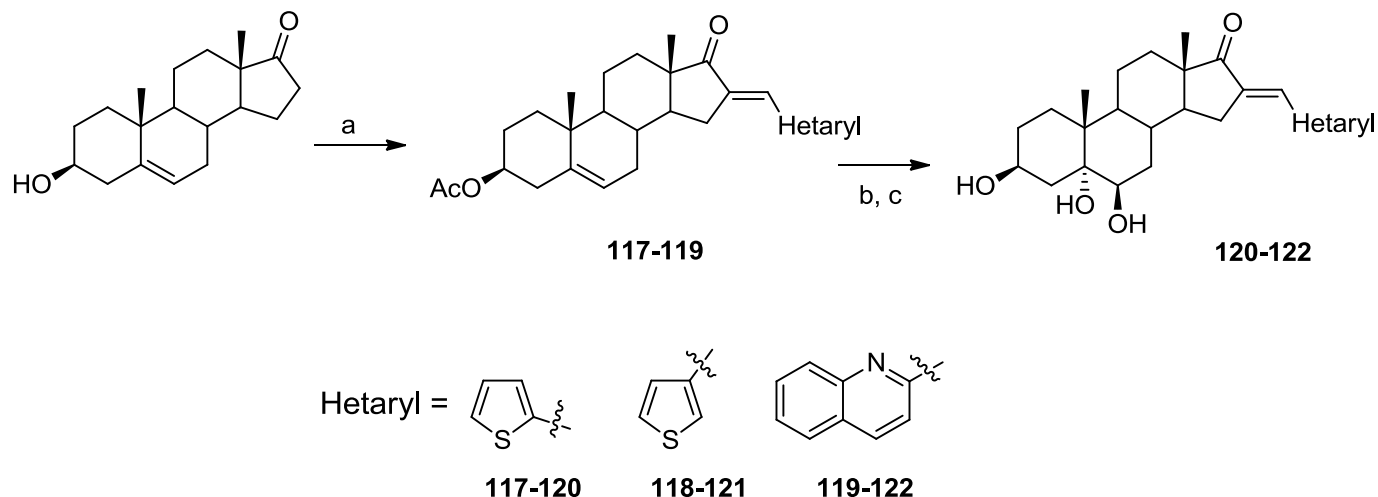


Reagents and conditions: a- *m*-chloroperoxybenzoic acid, 25 °C, 15 h; b- 5% methanolic KOH, 25 °C, 24 h; c- acetic anhydride, pyridine, 25 °C, 2h; d- POCl₃, dimethylformamide, 80 °C, 5h; benzimidazole, K₂CO₃, 80 °C, 2h; e- NaBH₄, 25 °C, 16h, DHEA, *trans*-dehydroandrosterone.

Scheme 24. Synthesis of 17-benzimidazolyl-16-(hydroxymethyl)androst-16-ene-3,5,6-triol.

16*E*-Arylidene steroidal derivatives **117-119** were synthesized from the base-catalyzed condensation reaction of DHEA with the heteroaromatic aldehydes such as thiophene-2-carboxaldehyde, thiophene-3-carboxaldehyde, and quinoline-2-carboxaldehyde (Scheme 25). In the structure of compounds **117-119**, the new exocyclic double bond (Δ^{16}) was a consequence of the condensation reaction. Different heteroaryl-

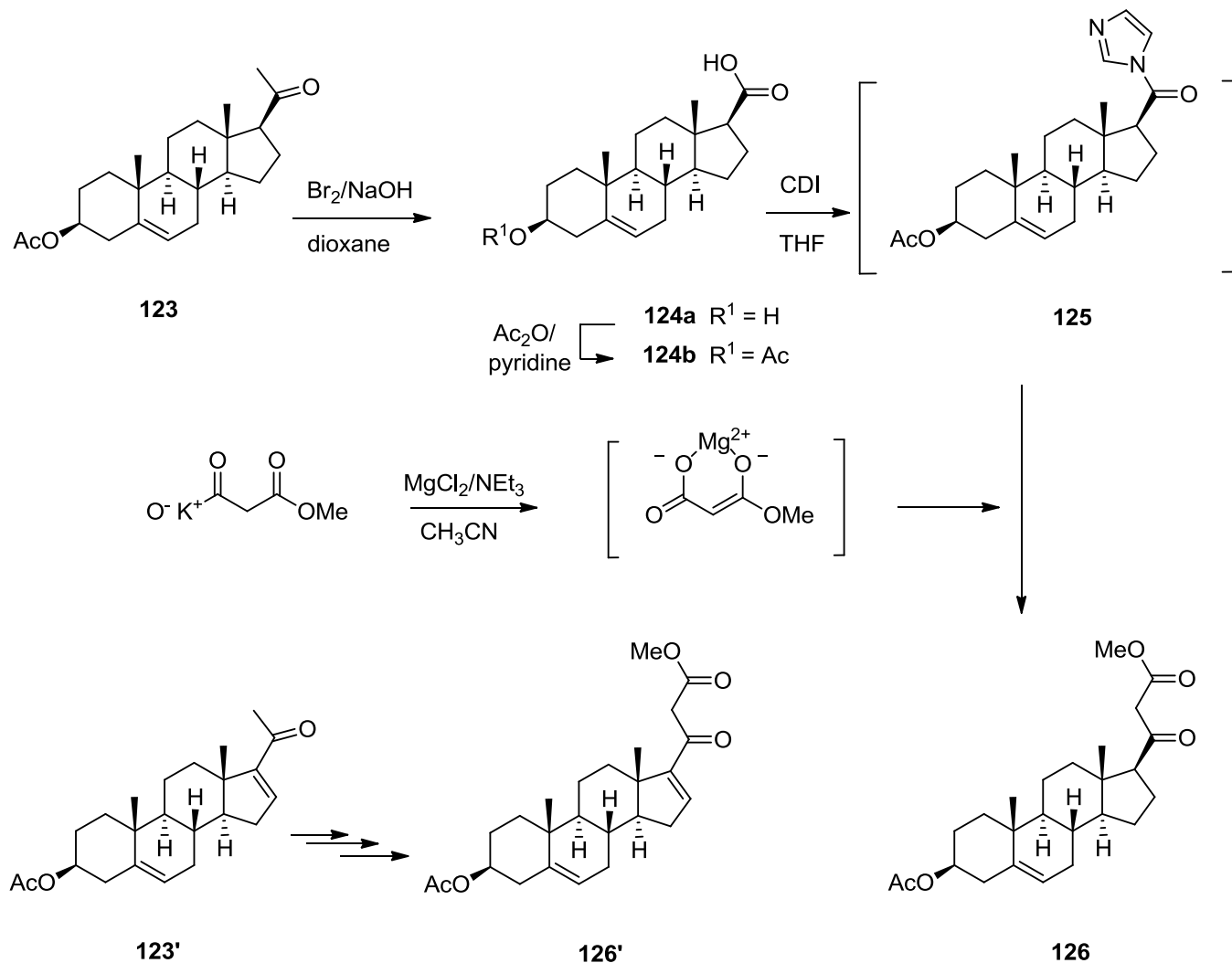
1 substituted new trihydroxyandrosterone derivatives **120-122** were synthesized from the reaction of α,β -
 2 unsaturated heterocyclic-substituted steroids **117-119** with *m*-CPBA in dichloromethane and methanolic KOH.
 3 *m*-CPBA converts only the endocyclic double bond of compounds **117-119** to *trans*-diaxial diol derivatives with
 4 both regioselective and stereoselective reaction. *In situ* reaction, firstly, the endocyclic double bond
 5 transforms to epoxides and then resulting in the *trans*-dihydroxylation by opening the ring with the *anti*-attack
 6 of the hydroxyl nucleophile. DHEA and the compounds **115** and **117-119** were converted into the compounds
 7 **116** and **120-122** by this method.
 8



9 Reagents and conditions: a- NaOH, requisite aldehyde, 25 °C, 3h; b- *m*-chloroperoxybenzoic acid, 25 °C, 15 h;
 10 c- 5% methanolic KOH, 25 °C, 24 h.

11 **Scheme 25.** Synthesis of 16-(heteroaryl)methyleneandrosterone-17-ones **120-122**.
 12

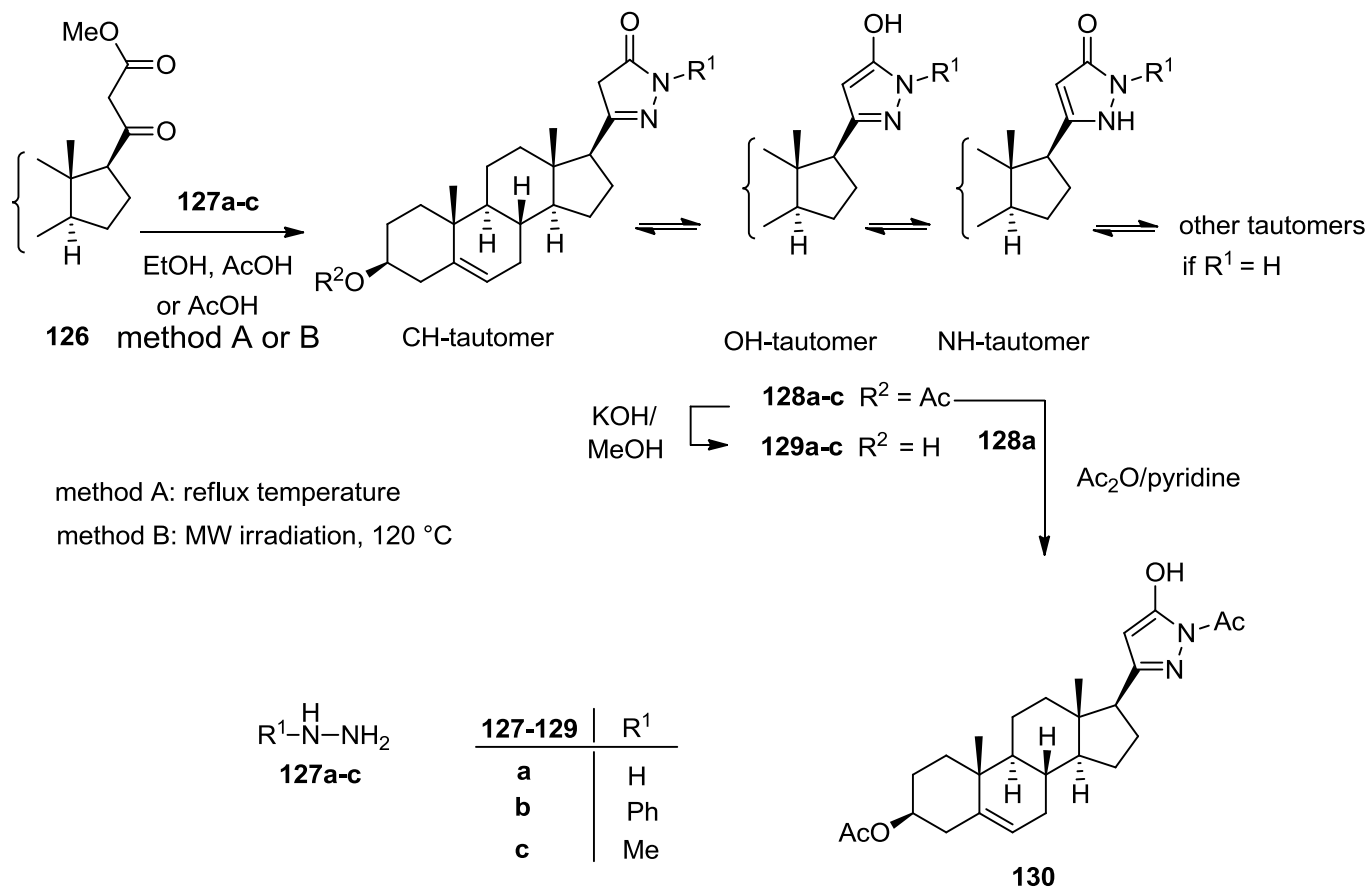
13 Motyan *et al.*⁴⁹ developed a microwave-assisted one-pot method for the facile and efficient synthesis of
 14 novel steroidal 17-*exo*-pyrazol-5'-ones from a β -ketoester precursor with arylhydrazine hydrochlorides. The
 15 steroidal β -ketoester precursor **126**, suitable for the attempted heterocyclization reaction with hydrazines,
 16 was synthesized from commercially available pregnenolone acetate **123** via a multistep sequence (Scheme
 17 26). First compound **123** was converted to the 17 β -carboxylic acid **124b** by the bromoform reaction and
 18 subsequent acetylation according to well-known literature procedures.⁵⁰ After the activation of **124b** with
 19 1,1'-carbonyldiimidazole (CDI) as coupling reagent in THF, the magnesium enolate of malonic acid half ester
 20 prepared *in situ* was added. The acylation of magnesium methyl malonate by the preformed imidazole **125** led
 21 to the desired bifunctional starting material **126** in good yield (79%). Analogously, β -ketoester **126'** could be
 22 obtained from pregnadienolone acetate **123'** through a $\Delta^{5,16}$ -carboxylic acid intermediate under identical
 23 conditions albeit in disappointing low yield (33%) which is presumably caused by the decreased propensity of
 24 the conjugated carbonyl compound to react with the magnesium enolate.



Scheme 26. Multistep synthesis of steroidal β -ketoesters **126** and **126'** from pregnenolone acetate **123** and pregnadienolone acetate **123'**

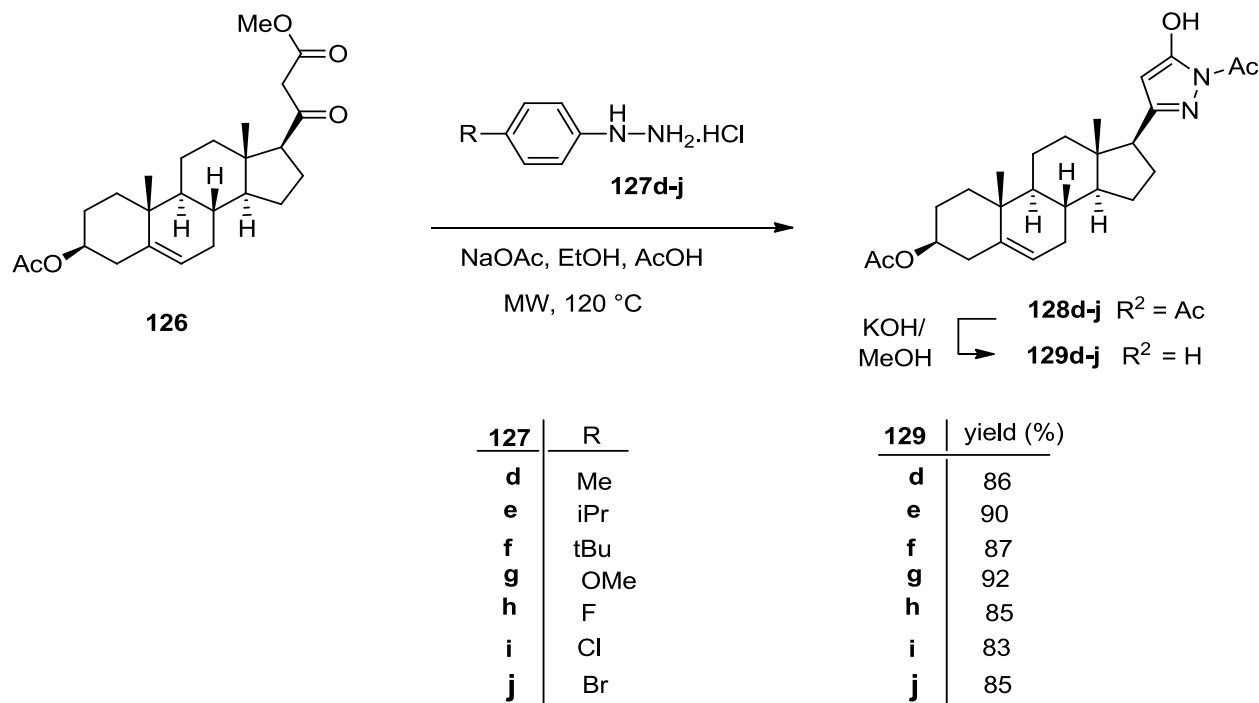
The ring-closure reactions of **126** with unsubstituted and monosubstituted hydrazines as binucleophilic reagents were investigated next. First, compound **126** was reacted with hydrazine hydrate **127a** in refluxing ethanol containing a catalytic amount of AcOH (Scheme 27). Full conversion of **126** within 4 h reaction time afforded a fairly polar product insoluble or only slightly soluble in all commonly used NMR solvents. However, a subsequent derivatization with acetic anhydride in pyridine to afford **130**, allowed its structure verification indirectly. This derivatization did not only improve the solubility of the compound, but also eliminated the possibility of prototropic tautomerism through acetylation of both the amino and hydroxy groups present in the heterocyclic ring in **128a**. The reaction with phenylhydrazine **127b** was completed within 7 h in refluxing EtOH in the presence of an acid catalyst. A reduction of the reaction time to 3 h could be achieved by changing the solvent to AcOH affording the desired product **128b** in high yield (86%, Scheme 27). On the other hand, the reaction of **126** with methylhydrazine **127c** required a longer reaction time in refluxing AcOH to furnish the purified product **128c** in a diminished yield (61%). This may be attributed to the weaker nucleophilic character of the external N compared to the internal one in **127c**,⁵¹ in contrast to phenylhydrazine **127b**, making the first condensation step more difficult. The regioselectivity of the reactions with monosubstituted hydrazines is controlled by the higher reactivity of the ketone moiety over the ester towards nucleophiles, and the least

1 hindered terminal nitrogen atom of the binucleophiles. Both reactions were repeated in AcOH under
 2 microwave conditions at 120 °C furnishing products **128b** and **128c** within a shorter time (20 min and 40 min),
 3 however, without substantial improvement in the yields.



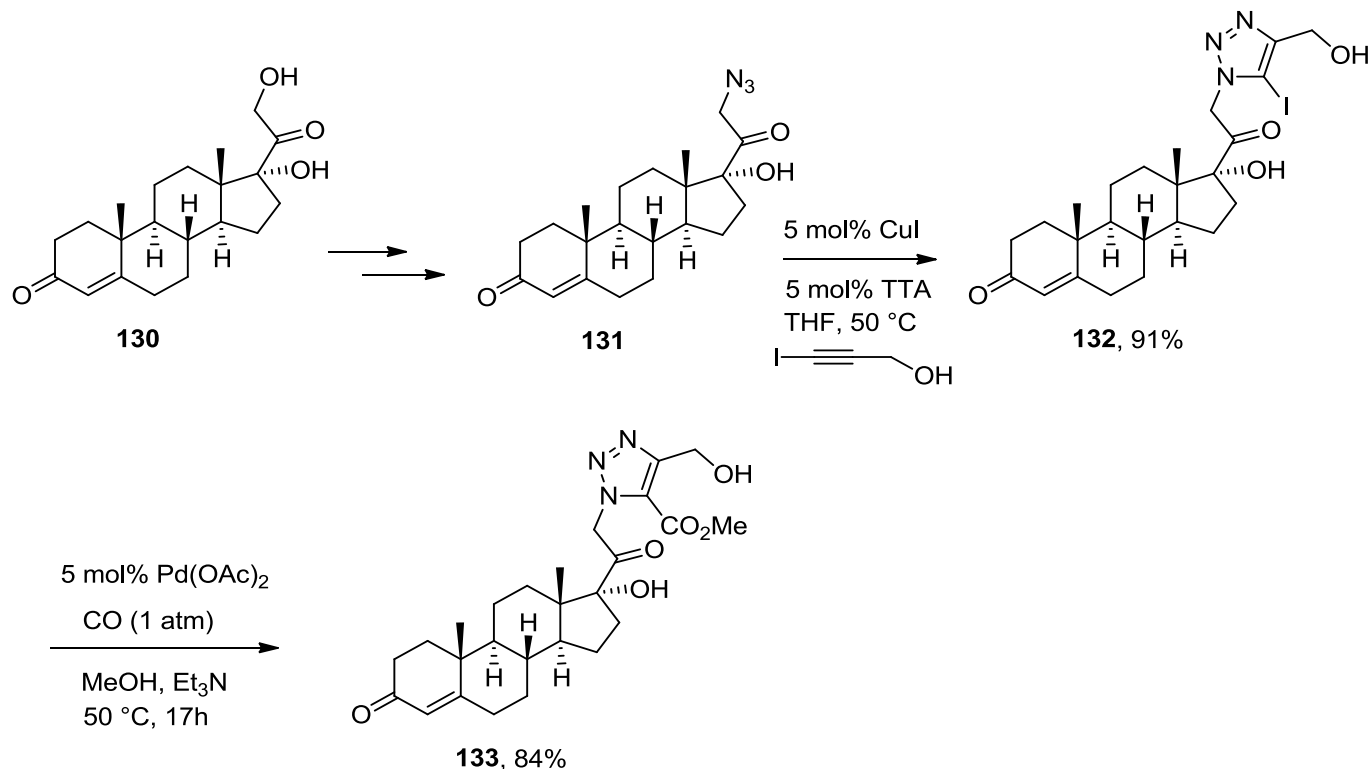
5
 6
 7 **Scheme 27.** Cyclization of compound **126** with hydrazine hydrate **127a**, phenylhydrazine **127b** and
 8 methylhydrazine **127c**.

9
 10 After optimizing the conditions for the MW-assisted synthesis of **128b** from **126** with **127**·HCl, analogous
 11 heterocyclization reactions were carried out with different substituted phenylhydrazine hydrochlorides **127d–**
 12 **j**. All reactions furnished the corresponding 17-*exo*-heterocycles **129d–j** in good to excellent yields (83–92%,
 13 Scheme 28). Some of these compounds (**128h**, **129f**, **129i** and **129j**) exerted considerable antiproliferative
 14 activity with promising cancer selectivity on a panel of human breast cancer cell lines. This indicates that the
 15 pyrazolone heterocyclic ring at the 17 β position is a promising scaffold for the design of anticancer agents of
 16 the Δ^5 -androstene series.



Scheme 28. Synthesis of steroidal *N*(1')-aryl-substituted pyrazol-5'-ones.

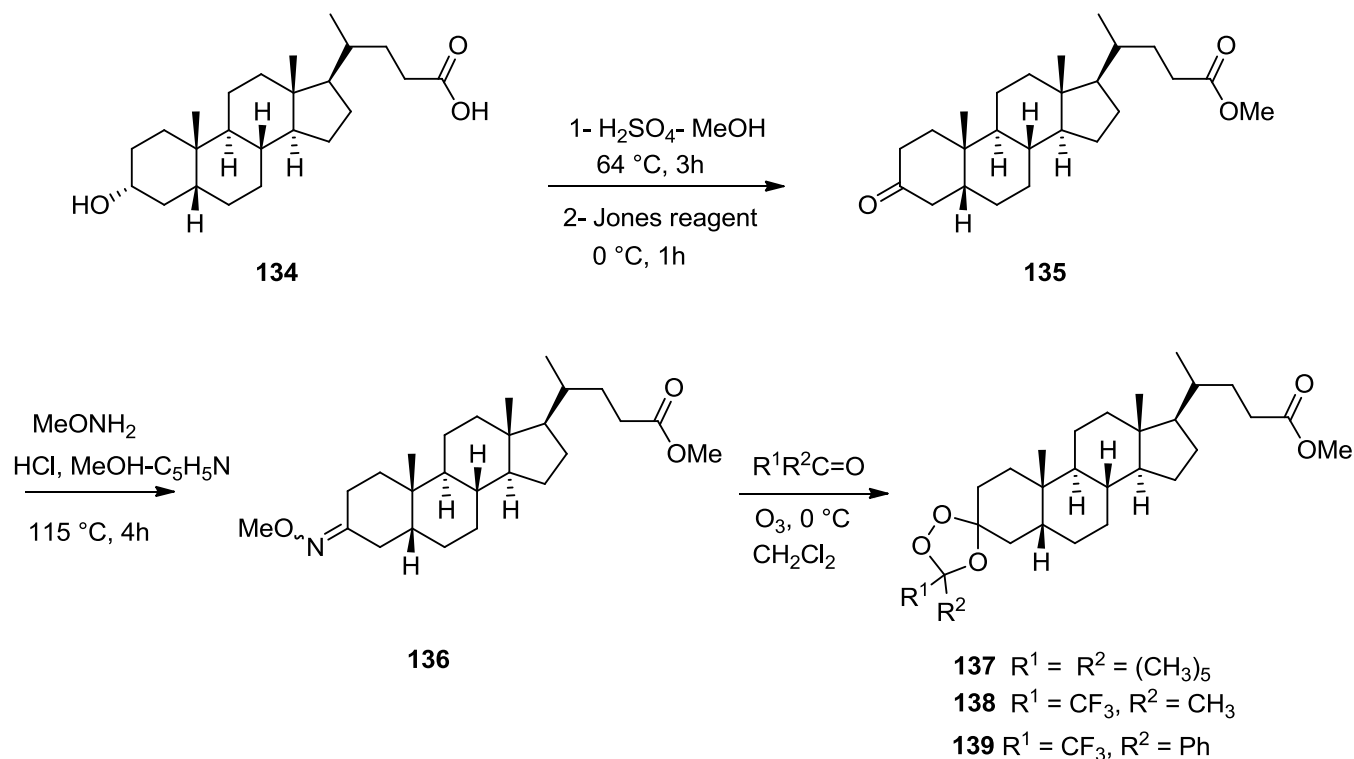
Kotovshchikov *et al.*⁵² developed a regioselective approach to 5-carboxy-1,2,3-triazoles based on the Cu-catalyzed synthesis of 5-iodo-1,2,3-triazoles and subsequent Pd-catalyzed carbonylation. To demonstrate the applicability of their protocol for the derivatization of complex natural products, they introduced an azido group to cortisolone **130**, an important steroidal hormone (Scheme 29). Azide **131** was subsequently transformed into iodotriazole **132** and the corresponding methyl ester **133**, in high yields for both steps (91 and 84%, respectively).



Scheme 29. Modification of cortisolone.

4. Synthesis of Steroidal Spiro-heterocycles

In 2014, Yamansarov *et al.*⁵³ synthesized for the first time steroidal 1,2,4-trioxolanes by ozonolysis of methyl 3-(methoxyimino)-5 β -cholan-24-oate with ketones. As starting compound they used methyl 3-oxo-5 β -cholan-24-oate **135** which was prepared from commercially available lithocholic acid **134** according to standard procedures. The reaction of **135** with a slight excess of *O*-methylhydroxylamine hydrochloride in boiling methanol–pyridine gave 93% of *O*-methyl ketone oxime **136** which was isolated as a mixture of two isomers at a ratio of 1 : 1 (Scheme 30). Methyl 3-(methoxyimino)-5 β -cholan-24-oate **136** was ozonolysed in the presence of ketones (cyclohexanone, methyl trifluoromethylketone, phenyl trifluoromethyl ketone) in a mixture of methylene chloride with cyclohexane. Compounds **137–139** were isolated in 53–82% yield.

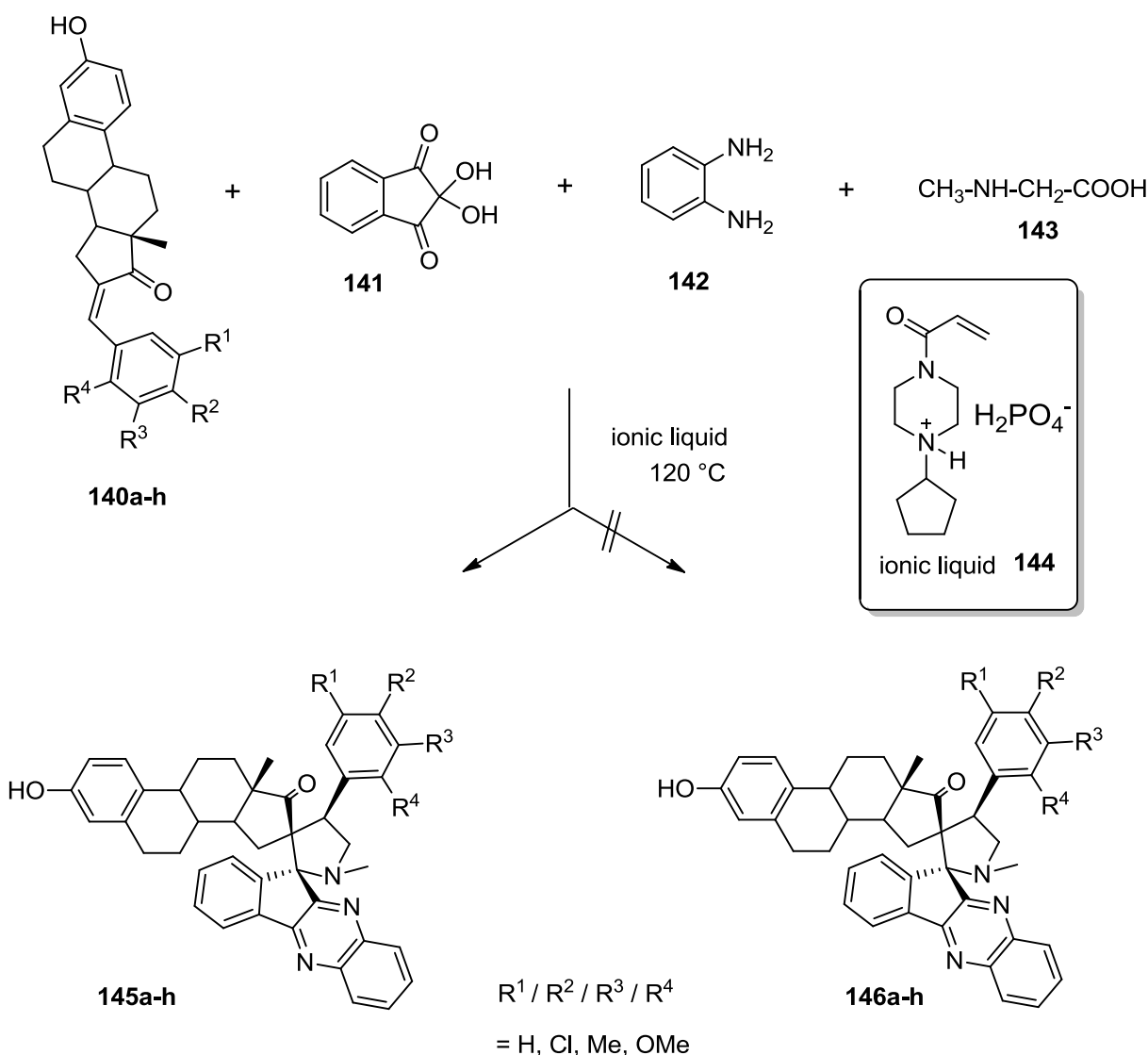


Scheme 30. Synthesis of steroidal 1,2,4-trioxolanes.

In 2016, a facile one-pot synthesis of novel steroidal dispiro-indenoquininoxaline pyrrolidines via multi-component-[3+2]-cycloaddition of azomethine ylides in ionic liquid was described by Gavaskar *et al.*⁵⁴ They reported a mild and expeditious one-pot sequential four-component synthesis of novel steroidal dispiro-pyrrolidine heterocycles through 1,3-dipolar cycloaddition of azomethine ylide generated from 1,2-phenylenediamine, ninhydrin and sarcosine with various unusual estrone-derived dipolarophiles in the ionic liquid *N*-(1-acryloyl)-*N*-(4-cyclopentyl)-piperazinium phosphate synthesized by them⁵⁵ recently (Scheme 31).

Initially, they investigated the one-pot sequential four-component reaction involving ninhydrin **141**, 1,2-phenylenediamine **142**, sarcosine **143** and estrone-derived dipolarophiles **140a–h** which proceeded well in the ionic liquid **144** to give a series of novel steroidal dispiroindenoquininoxaline pyrrolidines **145a–h** as the only products in good yield (76–85%). The formation of the hybrid steroidal heterocyclic scaffold **145** involved a multistep sequence. This method of sequential assembly of steroid grafted spiro-pyrrolidines in ionic liquid medium offers several advantages including its simplicity with a one-pot four-component approach, mild

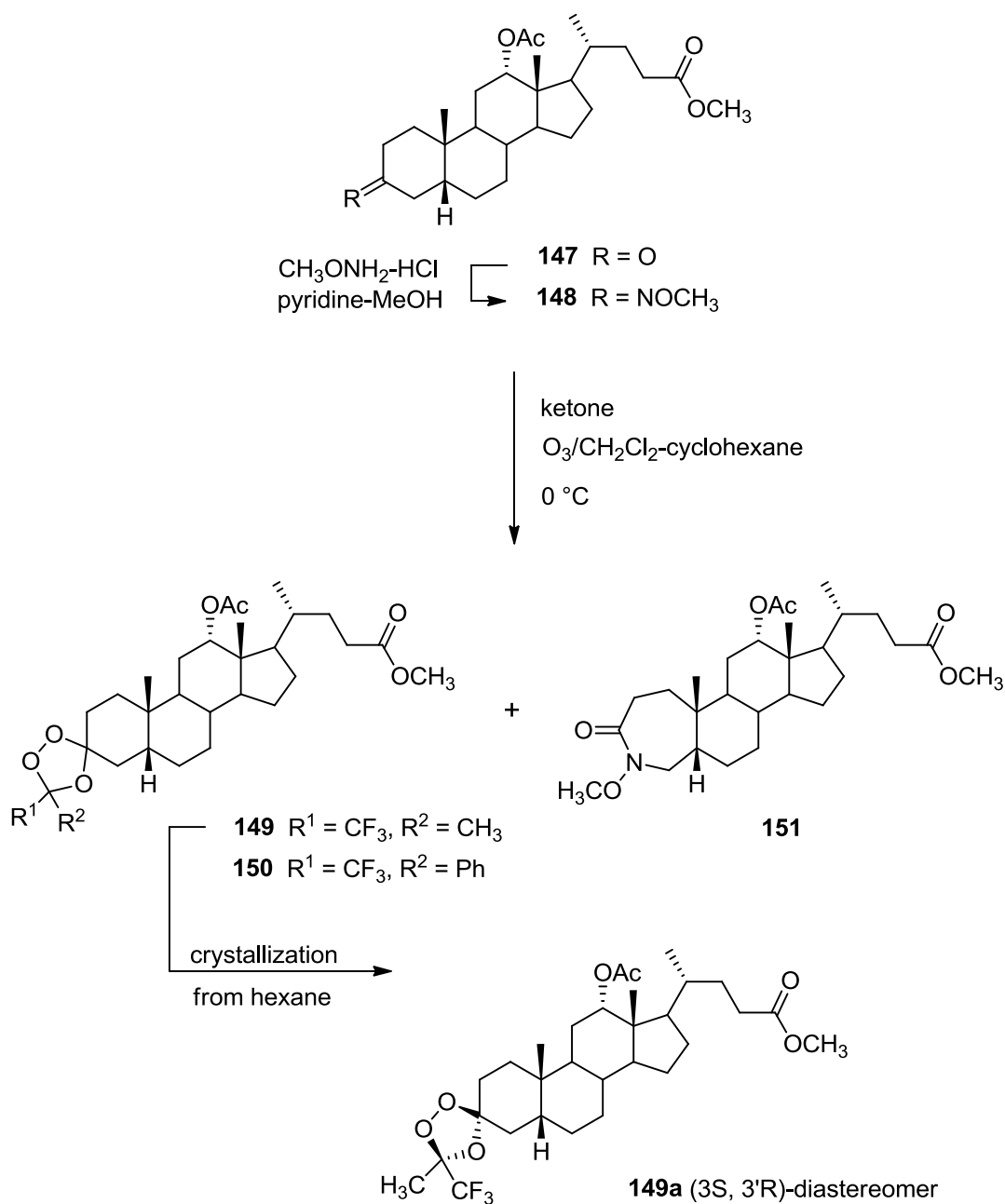
1 reaction conditions, easy workup, affording the desired products in good yield from readily and cheaply
 2 available starting materials in a single step. This method is general and is applicable for the synthesis of a
 3 variety of unusual complex highly substituted pyrrolidines containing steroidal and spiro-indenoquinoline
 4 moiety of biological significance.



6
7
8 **Scheme 31.** Synthesis of steroidal spiro-indenoquinoline-pyrrolidines **145a-h**.

9
10 In 2018, Yamansarova *et al.*⁵⁶ reported the synthesis of 1,2,4-trioxolanes of deoxycholic acid by the
 11 Griesbaum co-ozonolysis and compared their antimalarial activity with 1,2,4,5-tetraoxanes obtained by acid-
 12 catalyzed peroxycondensation. They used deoxycholic acid as an available starting material to synthesize
 13 steroidal peroxides. The required ketone **147** was obtained according to the procedure previously described.⁵⁷
 14 The next step included high-yield selective preparation of *O*-methyl oxime **148** (90%) as a mixture of *syn*-/*anti*-
 15 isomers in a ratio of 1:1 (Scheme 32). Thus, they introduced the unsaturated C=N double bond into the
 16 structure of the initial substrate. In the subsequent synthesis intermediate **148** was applied as a mixture of
 17 oximes. The Griesbaum co-ozonolysis⁵⁸ of **148** in the presence of fluorinated ketones $\text{CF}_3\text{C(O)CH}_3$ or $\text{CF}_3\text{C(O)Ph}$
 18 gave 1,2,4-trioxolanes **149** and **150** in yields of 50% and 38%, respectively. A byproduct of these reactions was
 19 the expected lactam **151** isolated in yields of 14% and 10%, respectively. Surprisingly, the ozonolysis of **148**

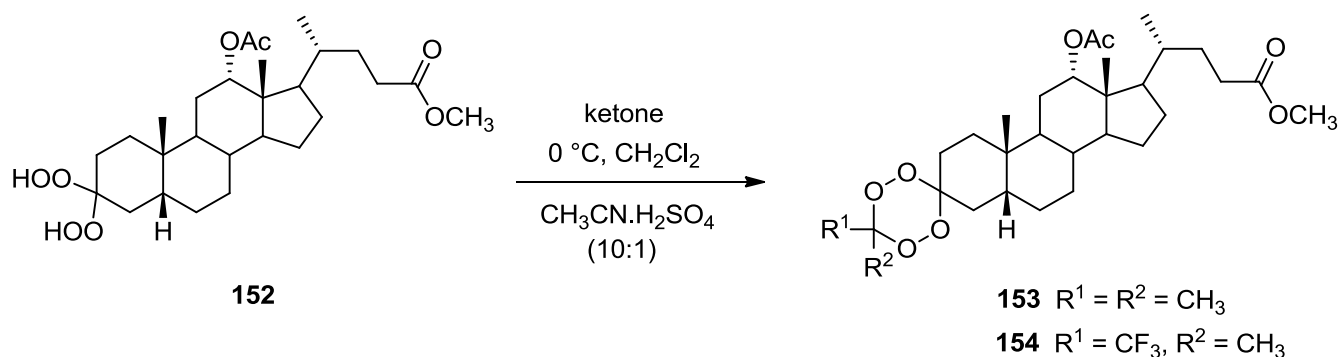
1 without the presence of ketones gave the lactam **151** as the major reaction product (52%). It was noted that
 2 the Griesbaum co-ozonolysis of **148** in the presence of acetone gave no 1,2,4-trioxolanes, perhaps due to its
 3 low dipolarophilicity. The ozonolysis reactions were carried out in cyclohexane-CH₂Cl₂ solvent mixture at 0 °C
 4 and the ozonides obtained were isolated as the mixtures of achiral diastereomers. For compound **149**, the
 5 only major diastereomer **149a** was separated from hexane by crystallization of a stereoisomeric mixture and
 6 individually characterized. A (3*S*,3'*R*)-configuration was assigned based on X-ray crystallographic analysis.
 7



8
 9
 10 **Scheme 32.** Preparation of the ozonide **149a**.

11
 12 It was found that 1,2,4-trioxolane and 1,2,4,5-tetraoxane show a similar pharmacology profile against
 13 malarial parasites.⁵⁹ In order to compare the antimalarial potency of different steroidal peroxides *in vitro*
 14 against *P. falciparum*, they carried out the synthesis of 1,2,4,5-tetraoxanes **153** and **154** via acid-catalyzed

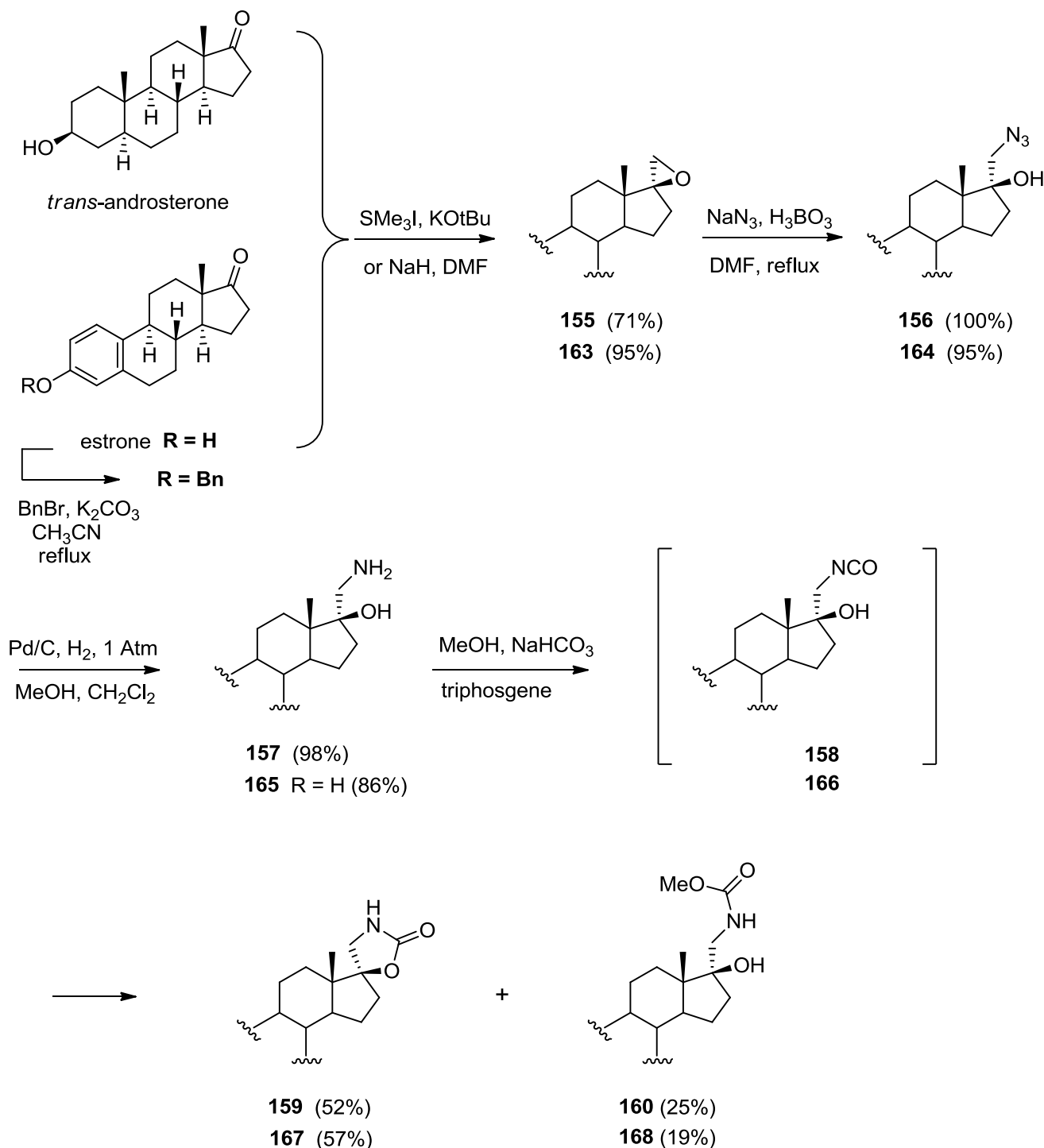
1 condensation of **152** with acetone and $\text{CF}_3\text{C}(\text{O})\text{CH}_3$ (Scheme 33). The yields were 37% and 44%, respectively.
 2 Trifluoromethylated 1,2,4,5-tetroxane showed good results against the chloroquine-resistant CQR-strain K1
 3 of *P. falciparum*, comparable to chloroquine, while the 1,2,4-trioxolane was better against the chloroquine-
 4 sensitive CQS-strain T96.



6
7
8 **Scheme 33.** Synthesis of tetroxanes **153**, **154**.

9
10 In 2018, Romero-Hernandez *et al.*⁶⁰ reported the straightforward preparation of novel conformationally-
 11 restricted steroids from *trans*-androsterone and estrone with spirocyclic oxazolidin-2-one or 2-aminooxazoline
 12 motifs at C-17 as potential antiproliferative agents. The key step to synthesize these heterocycles on the
 13 steroidal backbone was access to an aminomethyl alcohol on C-17 and its transformation into transient
 14 isocyanates and thioureas. The synthesis of the aminoalcohol was accomplished in three steps from *trans*-
 15 androsterone and four steps from estrone (Scheme 34).

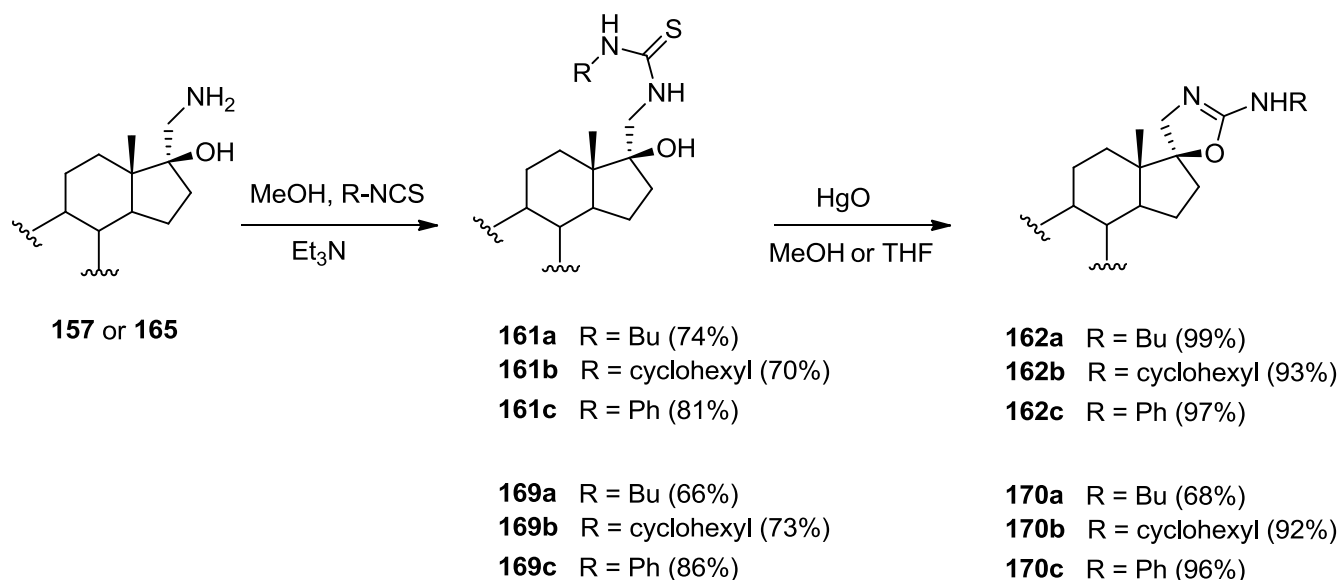
16 Trans-androsterone was treated with trimethylsulfonium iodide under basic conditions to obtain epoxide
 17 **155** in a total stereoselective fashion via a Corey-Chaykovsky reaction.⁶¹ Nucleophilic opening of epoxide **155**
 18 was carried out using sodium azide in the presence of boric acid to form the azide **156** in quantitative yield;
 19 the absolute configuration of the new chiral carbon was assigned for compound **156** as the (*S*)-diastereomer.
 20 Azide **156** was reduced by catalytic hydrogenation to get the aminomethylalcohol **157**, which in turn was
 21 treated with triphosgene, as a safe alternative to hazardous phosgene, in a $\text{MeOH}-\text{CH}_2\text{Cl}_2$ mixture to obtain
 22 the transient isocyanate **158**; this compound underwent a spontaneous cyclization involving the nucleophilic
 23 attack of the free OH to the heterocumulene, affording the spirooxazolidin-2-one (spirocarbamate) **159** (52%);
 24 the use of MeOH as solvent led also to carbamate **160** as a by-product (25%). The same reaction sequence was
 25 applied to form the estrone derived spirocarbamate **167**; changing the nature of the A-ring (aromatic for
 26 estrone) might modify the biological properties and thus afford valuable structure-activity relationships. For
 27 this purpose, the free OH on C-3 was first protected as its benzyl ether, and then, the functionalization of the
 28 C-17 was accomplished. Epoxide **163** was obtained in a stereoselective fashion, using KOtBu to form the sulfur
 29 ylid. The nucleophilic opening of **163** was carried out using sodium azide in DMF. The structure of azide **164**
 30 obtained by single crystal X-ray diffraction showed the configuration of C-17 as (*S*). Reduction of azide **164**
 31 under catalytic hydrogenation conditions also eliminated the benzyl group at C-3, giving amine **165** in a 77%
 32 yield after four steps. Reaction between **165** and triphosgene gave isocyanate **166**, which was not isolated and
 33 spontaneously gave the final compound **167** and the by-product **168** in a 3:1 ratio (Scheme 34).



Scheme 34. Synthesis of oxazolidin-2-ones **159-167** from *trans*-androsterone and estrone.

Aminoalcohols from *trans*-androsterone and estrone were also used to obtain 2-aminoxazolines. Derivatives **157** and **165** were treated with different isothiocyanates (butyl, cyclohexyl and phenyl) under basic conditions, giving thioureas **161** and **169**. The cyclodesulfurization reaction of thioureas promoted by yellow HgO afforded 2-aminoxazolines **162** and **170** with good to excellent yields (Scheme 35). Compounds **156-162** and **164-170** were tested as potential antiproliferative agents, and the order of activity was found to be amino oxazoline > spiro carbamate > thiourea. The lead compounds, bearing a spiranic amino oxazoline motif on an estrone backbone, exhibited GI_{50} values in the low micromolar to submicromolar range (0.34-1.5 μM),

with particular increase in activity against drug-resistant cell lines compared to other steroidal chemotherapeutic agents (Abiraterone and Galeterone).

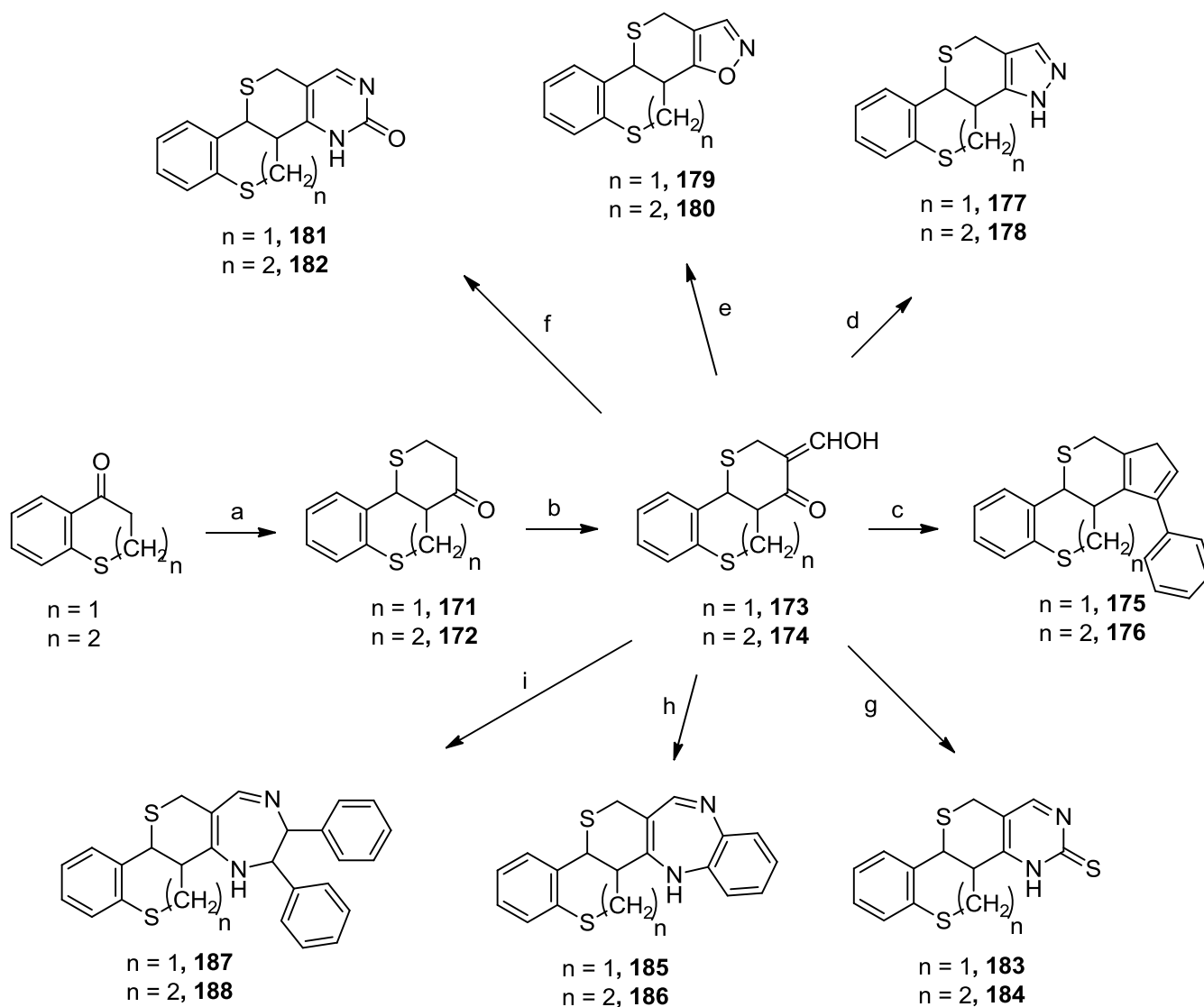


Scheme 35. Synthesis of 2-aminoxazolines **162**, **170** from *trans*-androsterone and estrone.

4. Synthesis of Heterocyclic Steroidal Analogues

In 2015, Palanisamy *et al.*⁶² synthesized and investigated the antimicrobial, antituberculosis, and antitumor activity of some new pyrazole-, isoxazole-, pyrimidine- and benzodiazepine derivatives containing 3-(hydroxymethylene)-2,3-dihydrothiopyrano[3,2-*c*]thiochromen-4(5*H*)-one (**173**) and 2,3,5,6-tetrahydro-3-(hydroxymethylene) 4*H*-thiopyrano [3,2-*d*][1]benzothiepin-4-one (**174**) moieties. Preparation of the pyrazole, isoxazole, pyrimidine, and benzodiazepine derivatives was performed following the synthetic route described in Scheme 36.

The starting ketones **171** and **172** were prepared following the reported method.⁶³ The starting key intermediates 3-(hydroxymethylene)-2,3-dihydrothiopyrano[3,2-*c*]thiochroman-4(5*H*)-one **173** and 2,3,5,6-tetrahydro-3-(hydroxymethylene)4*H*-thiopyrano[3,2-*d*][1]benzothiepin-4-one **174** were obtained reacting ethyl formate with **171** and **172**. Condensation of compounds **173** and **174** with phenylhydrazine hydrochloride, hydrazine hydrochloride, hydroxylamine hydrochloride, urea, thiourea, *o*-phenylenediamine, and 1,2-diphenylethane-1,2-diamine afforded the target series **175-188** (Scheme 36). The results obtained clearly revealed that the 1,2-diphenylene-1,2-diamine substituted 2,3-dihydrothiopyrano[3,2-*c*]thiochromen-4(5*H*)-one **187** and 2,3,5,6-tetrahydro-4*H*-thiopyrano[3,2-*d*][1]benzothiepin-4-one derivatives **188** exhibited better antimicrobial activity than their counterparts. Similarly compounds **185** and **188** displayed more antimicrobial, antituberculosis, antitumor, and DNA cleavage activity compared to the other derivatives. In general, the benzodiazepine analogues **185-188** exhibited higher activity than the pyrazole, isoxazole, and pyrimidine analogues.



Reaction conditions : (a) $\text{ClCH}_2\text{CH}_2\text{COOH}/\text{NaOH}$, PPA; (b) NaOEt , dry toluene, HCOOC_2H_5 ;
 (c) $\text{C}_6\text{H}_5\text{NHNH}_2\cdot\text{HCl}$, EtOH; (d) $\text{NH}_2\text{NH}_2\cdot\text{HCl}$, EtOH; (e) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH; (f) urea, CH_3COOH ;
 (h) *o*-phenylenediamine, CH_3COOH ; (i) 1,2-diphenylethane-1,2-diamine, CH_3COOH .

Scheme 36. Synthesis of heterocyclic steroidal analogues.

6. Conclusions

The present review offers an up-to-date literature on the latest syntheses of steroidal derivatives containing heterocycles 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 to the incorporation of heterocyclic ring into the steroid moiety. In addition, some reports verified the importance of the presence of heterocyclic moieties as pharmacophores for the activity against cancer cell lines.

Overall, the interest in steroids and related compounds continue to expand given the diversity of structure and emerging bioactivity inherent in this compound class.

Acknowledgements

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References

1. Zeelen, J.F. *Medicinal chemistry of steroids*; Elsevier: Amsterdam, Netherlands, 1990.
2. Trager, L. F. *Steroidhormone*; Springer: Berlin, **1977**.
3. Biellmann, J. F. *Chem. Rev.* **2003**, *103*, 2019.
<http://doi.org/10.1021/cr020071b>
4. Nising, C. F.; Bräse, S. *Ang. Chem. Int. Ed.* **2008**, *47*, 9389.
<https://doi.org/10.1002/anie.200803720>
5. Hanson, J. R. *Nat. Prod. Reports* **2010**, *27*, 887.
<https://doi.org/10.1039/C001262A>
6. Lewis, D. F. V.; Jacobs, M.; Dickins, M. *Drug Discov. Today* **2004**, *9*, 530.
[https://doi.org/10.1016/S1359-6446\(04\)03115-0](https://doi.org/10.1016/S1359-6446(04)03115-0)
7. Imtiyaz, H. L.; Khaliqz, Z. K.; Bharat, I. F.; Fida, H. *Steroids* **2013**, *78*, 945.
<https://doi.org/10.1016/j.steroids.2013.05.015>
8. Zhungietu, G. I.; Dorofeenko, G. N. *Russ. Chem. Rev.* **1967**, *36*, 24.3
<https://doi.org/10.1070/RC1967v036n01ABEH001581>
9. Li, Y.; Huang, J.; Liu, J.L.; Yan, P. Y.; Liu, H.; Sun, Q. *Steroids* **2011**, *76*, 1615.
<https://doi.org/10.1016/j.steroids.2011.10.003>
10. Rafat, M. M.; Wagnat, W. W.; Gamal, A. E.; Rehab, M. S. A. *Steroids* **2012**, *77*, 1560.
<https://doi.org/10.1016/j.steroids.2012.09.004>
11. Dwipen, K.; Rupak, K. S.; Ratul, S.; Nabin, C. B.; Jadab, C. S. *Steroids* **2013**, *78*, 321.
<https://doi.org/10.1016/j.steroids.2012.12.003>
12. Ranju, B.; Pratap, C. A. *Steroids* **2012**, *77*, 552.
<https://doi.org/10.1016/j.steroids.2012.01.020>
13. Duha, C. Y.; Loa, I. W.; Wang, S. K.; Dai, C. F. *Steroids* **2007**, *72*, 573.
<https://doi.org/10.1016/j.steroids.2007.03.010>
14. Ibrahim-Ouali, M.; Santelli M. *Steroids* **2006**, *71*, 1025.
<https://doi.org/10.1016/j.steroids.2006.09.006>
15. Hanson, J. R. Steroids: partial synthesis in medicinal chemistry. *Nat. Prod. Rep.* **2006**, *23*, 100.
<https://doi.org/10.1039/B512848J>
16. Chen, S. J.; Cui, J. G.; Li, Y.; Fan, L. H. *Chin. J. Org. Chem.* **2011**, 187.
http://sioc-journal.cn/Jwk_yjhx/EN/Y2011/V31/I02/187
17. Zhang, X. J.; Cui, J. G.; Li, Y.; Chen, S. J. *Chin. J. Org. Chem.* **2010**, *30*, 655.
http://sioc-journal.cn/Jwk_yjhx/EN/Y2010/V30/I05/655
18. Stulov, S. V.; Misharin A. Y. *Chem. Heterocycl. Compd.* **2013**, *48*, 1431.
<https://doi.org/10.1007/s10593-013-1158-8>
19. Ma, B.; Xiao, Z. Y.; Chen, Y. J.; Lei, M.; Meng, Y. H.; Guo, D. A. *Steroids* **2013**, *78*, 508.
<https://doi.org/10.1016/j.steroids.2013.02.007>

- 1 20. Guo, H.; Zhang, G. L.; Zhang, T.; He, X. R.; Wu, Z. Y.; Xiao, Y. L.; Pan, Y.; Qiu, G.; Liu, P.; Hu, X. *Eur. J. Med.*
2 *Chem.* **2011**, *46*, 3662.
3 <https://doi.org/10.1016/j.ejmech.2011.05.030>
- 4 21. Huang, L. H.; Zheng, Y. F.; Lu, Y. Z.; Song, C. J.; Wang, Y. G.; Yu, B.; Liu, H. M. *Steroids* **2012**, *77*, 710.
5 <https://doi.org/10.1016/j.steroids.2012.03.002>
- 6 22. Kovács, D.; Mótyán, G.; Wölfling, J.; Kovács, I.; Zupkó, I.; Frank, É. *Bioorg. Med. Chem. Lett.* **2014**, *24*,
7 1265.
8 <https://doi.org/10.1016/j.bmcl.2014.01.069>
- 9 23. Dutta, M.; Saikia, P.; Gogoi, S.; Boruah, C. R. *Steroids* **2013**, *78*, 387.
10 <https://doi.org/10.1016/j.steroids.2013.01.006>
- 11 24. Shekarrao, K.; Nath, D.; Kaishap, P. P.; Gogoi, S.; Boruah, C. R. *Steroids* **2013**, *78*, 1126.
12 <https://doi.org/10.1016/j.steroids.2013.08.002>
- 13 25. Shekarrao, K.; Duarah, A.; Bora, T. C.; Gogoi, S.; Boruah, C. R. *Steroids* **2012**, *77*, 1438.
14 <https://doi.org/10.1016/j.steroids.2012.08.008>
- 15 26. Abad, Ali; Mohd, A.; Parvez, A.; Mohammad, J. A.; Mohd, A. S.; Rizwan, H. K.; Shabbir Ahmad, S. *J. Bioorg.*
16 *Chem.* **2017**, *73*, 83.
17 <http://dx.doi.org/10.1016/j.bioorg.2017.06.001>
- 18 27. Callow, R.K.; James, V.H.T. *J. Chem. Soc.* **1956**, 927, 4744.
19 <https://doi.org/10.1039/JR9560004744>
- 20 28. Zhang, B. L.; Zhang, E.; Pang, L. P.; Song, L. X.; Li, Y. F.; Yu B.; Liu, H. M. *Steroids* **2013**, *78*, 1200.
21 <https://doi.org/10.1016/j.steroids.2013.07.006>
- 22 29. Siddiqui, A. U.; Rao, V. U. M.; Maimirani, M.; Siddiqui, A. H. *J. Heterocycl. Chem.* **1995**, *32*, 353.
23 <https://doi.org/10.1002/jhet.5570320159>
- 24 30. Elmegeed, G. A.; Khalil, W. K. B.; Mohareb, R. M.; Ahmed, H. H.; Abd-Elhalim, M. M.; Elsayed, G.H. *Biorg.*
25 *Med. Chem.* **2011**, *19*, 6860.
26 <https://doi.org/10.1016/j.bmc.2011.09.033>
- 27 31. Zhang, B. L.; Song, L. X.; Li, Y. F.; Zhang, E.; Guo, Y. Z.; Liu, H. M. *Steroids* **2014**, *80*, 92.
28 <https://doi.org/10.1016/j.steroids.2013.12.003>
- 29 32. Wu, J.; Xia, H. G.; Gao, K. *Org. Biomol. Chem.* **2006**, *4*, 126.
30 <https://doi.org/10.1039/B514635F>
- 31 33. Singh, R.; Thota, S.; Bansal, R. *ACS Chem. Neurosci.* **2018**, *9*, 272.
32 <https://doi.org/10.1021/acscchemneuro.7b00303>
- 33 34. Singh, R.; Bansal, R. *ACS Chem. Neurosci.* **2017**, *8*, 186.
34 <https://doi.org/10.1021/acscchemneuro.6b00313>
- 35 35. Banday, A. H.; Mir, B. P.; Lone, I. H.; Suri, K. A.; Kumar, H. M. *Steroids* **2010**, *75*, 805.
36 <https://doi.org/10.1016/j.steroids.2010.02.014>
- 37 36. Mohareb, R. M.; Samir, E. M.; Halim P. A. *Bioorg. Chem.* **2019**, *83*, 402.
38 <https://doi.org/10.1016/j.bioorg.2018.10.067>
- 39 37. Han, Y.; Tang, W. Q.; Yan, C. G. *Tetrahedron Lett.* **2014**, *55*, 1441.
40 <https://doi.org/10.1016/j.tetlet.2014.01.043>
- 41 38. Banday, A. H.; Shameem, S. A.; Jeelani, S. *Steroids* **2014**, *92*, 13.
42 <https://doi.org/10.1016/j.steroids.2014.09.004>
- 43 39. Ivany, Z.; Wolfing, J.; Gorbe, T.; Szecsi, M.; Wittmann, T.; Schneider, G. *Steroids* **2010**, *75*, 450.
44 <https://doi.org/10.1016/j.steroids.2010.02.013>

- 1 40. Wölfling, J.; Oravec, E. A.; Ondré, D.; Mernyák, E.; Schneider, G.; Tóth, I. *Steroids* **2006**, *71*, 809.
2 <https://doi.org/10.1016/j.steroids.2006.05.011>
- 3 41. Cui, J.; Liu, L.; Zhao, D.; Gan, C.; Huang, X.; Xiao, Q.; Qi, B.; Yang, L.; Huang, Y. *Steroids* **2015**, *95*, 32.
4 <https://doi.org/10.1016/j.steroids.2015.01.002>
- 5 42. Abad, A.; Mohd, A.; Hena, K.; Ashraf, M.; Mohd, A. S.; Mohamma, O.; Shamsuzzaman. *RSC Adv.*, **2015**, *5*,
6 75964.
7 <https://doi.org/10.1039/C5RA11049A>
- 8 43. Elmegeed, G. A.; Yahya, S. M.M.; Abd-Elhalim, M. M.; Mohamed, M. S.; Mohareb, R. M.; Elsayed, G. H.
9 *Steroids* **2016**, *115*, 80.
10 <https://doi.org/10.1016/j.steroids.2016.08.014>
- 11 44. Vitellozzi, L.; McAllister, G. D.; Genski, T.; Taylor, R. J. K. *Synthesis* **2016**, *48*, 48.
12 <https://doi.org/10.1055/s-0035-1560353>
- 13 45. Achmatowicz, O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*,
14 1973.
15 [https://doi.org/10.1016/S0040-4020\(01\)98229-8](https://doi.org/10.1016/S0040-4020(01)98229-8)
- 16 46. Kametani, T.; Tsubuki, M.; Furuyama, H.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 557.
17 <https://doi.org/10.1039/P19850000557>
- 18 47. Matsuya, Y.; Yamakawa, Y.-i.; Tohda, C.; Teshigawara, K.; Yamada, M.; Nemoto, H. *Org. Lett.* **2009**, *11*,
19 3970.
20 <https://doi.org/10.1021/ol901553w>
- 21 48. Mohammed Kolo, A.; İpek, E.; Çapan, İ.; Servi, S. *J. Het. Chem.* **2018**, *55*, 492.
22 <https://doi.org/10.1002/jhet.3070>
- 23 49. Mótyán, G.; Mérai, L.; Kiss, M. A.; Schelz, Z.; Sinka, I.; Zupkó, I.; Frank, É. *Beilstein J. Org. Chem.* **2018**, *14*,
24 2589–2596.
25 <https://doi.org/10.3762/bjoc.14.236>
- 26 50. Kovács, D.; Wölfling, J.; Szabó, N.; Szécsi, M.; Minorics, R.; Zupkó, I.; Frank, É. *Eur. J. Med. Chem.* **2015**,
27 *98*, 13–29.
28 <https://doi.org/10.1016/j.eimech.2015.05.010>
- 29 51. Mótyán, G.; Kovács, F.; Wölfling, J.; Gyovai, A.; Zupkó, I.; Frank, É. *Steroids* **2016**, *112*, 36.
30 <https://doi.org/10.1016/j.steroids.2016.04.014>
- 31 52. Kotovshchikov, Y. N.; Latyshev, G. V.; Beletskaya, I. P.; Lukashev N. V. *Synthesis* **2018**, *50*, 1926.
32 <https://doi.org/10.1055/s-0036-1591896>
- 33 53. Yamansarov, E. Yu.; Kazakova, O. B.; Medvedeva, N. I.; Kazakov, D. V.; Kukovinets, O. S.; Tolstikov, G. A.
34 *Russian J. Org. Chem.* **2014**, *50*, 1043.
35 <https://doi.org/10.1134/S1070428014070197>
- 36 54. Gavaskar, D.; Suresh Babu, A. R.; Raghunathan, R.; Dharani, M.; Balasubramanian, S. *Steroids* **2016**, *109*,
37 1.
38 <https://doi.org/10.1016/j.steroids.2016.02.010>
- 39 55. Gavaskar, D.; Suresh Babu, A. R.; Raghunathan, R.; Dharani, M.; Balasubramanian, S.; *J. Organomet.*
40 *Chem.* **2014**, *768*, 128.
41 <https://doi.org/10.1016/j.iorganchem.2014.06.015>
- 42 56. Yamansarova, E. Y.; Kazakova, D. V.; Medvedeva, N. I.; Khusnutdinova, E. F.; Kazakova, O. B.; Legostaeva,
43 Y. V.; Ishmuratova, G. Y.; Huong, L. M.; Hong Ha, T. T.; Huong, D. T.; Suponitsky, K. Y. *Steroids* **2018**, *129*,
44 17.

- 1 <https://doi.org/10.1016/j.steroids.2017.11.008>
- 2 57. Opsenica, D.; Pocsfalvi, G.; Jurani, Z.; Tinant, B.; Declercq, J. P.; Kyle, D. E.; Milhous, W. K.; Šolaj B. A. *J.*
- 3 *Med. Chem.* **2000**, *43*, 3274.
- 4 <http://doi.org/10.1021/jm000952f>
- 5 58. Griesbaum, K.; Liu, X.; Kassiaris, A.; Scherer M. *Liebigs Ann.* **1997**, 1381.
- 6 <https://doi.org/10.1002/jlac.199719970715>
- 7 59. Bousejra-El Garah, F.; Wong, M.H.-L.; Amewu, R. K.; Muangnoicharoen, S.; Maggs, J. L.; Stigliani, J. L.;
- 8 Park, B.K.; Chadwick, J.; Ward, S.A.; O'Neill, P.M. *J. Med. Chem.* **2011**, *54*, 6443.
- 9 <http://doi.org/10.1021/jm200768h>
- 10 60. Romero-Hernandez, L. L.; Merino-Montiel, P.; Meza-Reyes, S.; Vega-Baez, J. L.; Lopez, O.; Padron, J. M.;
- 11 Montiel-Smith, S. *Eur. J. Med. Chem.* **2018**, *143*, 21.
- 12 <https://doi.org/10.1016/j.ejmech.2017.10.063>
- 13 61. Maltais, R.; Tremblay, M.R.; Poirier, D. *J. Comb. Chem.* **2000**, *2*, 604.
- 14 <https://doi.org/10.1021/cc0000242>
- 15 62. Palanisamy, P.; Sudhakar, S.; Kumaresan, S. *World J. Pharm. Sci.* **2015**, 2321. <http://www.wjpsonline.org/>
- 16 63. Kumaresan, S.; Ramadas, S. R. *Sulfur Lett.*, **1984**, *2*, 31.
- 17 <https://doi.org/10.1080/03086648408077592>
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Authors' Biographies



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Frédéric Dumur received his PhD in chemistry in 2002 from the University of Angers (France) under the supervision of Professor Pietrick Hudhomme. After Post-Doctoral studies at the University of Groningen (The Netherlands), Reims Champagne-Ardennes (France) and Versailles Saint-Quentin-en-Yvelines (France), he joined the Faculty of Sciences at Aix-Marseille University in 2008, where he is currently working as an Associate Professor. His research interests include the synthesis of phosphorescent dopants for OLEDs and photoinitiators of polymerization. He co-authored about 225 publications and 5 book chapters.

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