

Steroidal chalcones and derivatives: A review

Malika Ibrahim-Ouali,^{*a} and Frédéric Dumur^b

^aAix Marseille Univ, CNRS, Centrale Marseille, iSm2, F-13397 Marseille, France

^bAix Marseille Univ, CNRS, ICR, UMR 7273, F-13397 Marseille, France

Email: malika.ibrahim@univ-amu.fr

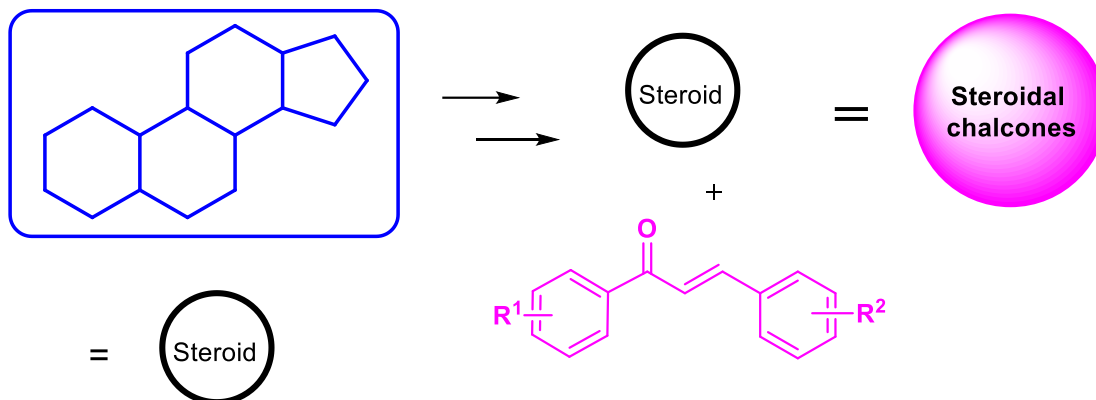
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Abstract

It was observed that the presence of heterocycles to steroids often leads to a change in their physiological activity and the appearance of new interesting biological precursors. Recent developments in the syntheses of steroidal chalcones and their derivatives are described herein. The biological activities of those steroidal derivatives for which data are available are given. The chalcone moiety shows great promise to allow us to develop novel molecules with characteristic functions.



Keywords: chalcones; steroids; enones; pregnenolone.

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1. Introduction

Steroids represent a large and important class of biologically active polycyclic molecules that are widely used in medicinal chemistry.¹⁻³ Even today, the total synthesis of steroids by new and more elaborate strategies continues to interest chemists. Thus, many total syntheses of biologically active steroids have been developed in recent decades. Interest in the total synthesis of such molecules continues to this day.^{4,5}

Chalcones (1,3-diphenyl-2-propen-1-one) are well known for their interesting biological properties. It is thus known that chalcones exhibit biological activities, such as anticancer, antioxidant, anti-inflammatory,^{6,7} and antimicrobial activities.^{8,9} Two phenyl rings and a α, β -unsaturated carbonyl system that connects them constitutes the structural base of chalcone. It has been shown that the nature of the substituents on the phenyl rings and their conformation in the central structure is at the origin of their biological activities. Some work has shown that reactions causing conformational changes, such as substitution on the double bond or epoxidation, can lead to a decrease in bioactivity.¹⁰

The synthesis of hybrid compounds from the coupling of two or more natural products is at the origin of an inexhaustible new class of molecules with many structures. The objective of such syntheses is to combine the pharmacological properties of two or more biologically active molecules to increase or modulate these activities to obtain derivatives exhibiting new properties.^{11,12} Previous works of literature have been reported that such structures as steroidal chalcones have been shown to bear a lot of different biological activities such as antimicrobial, anti-inflammatory, anticancer, antioxidant, and hypotensive activities.¹³⁻¹⁶

This review presents the various syntheses of steroidal chalcones and their derivatives along with interesting biological activities, which have appeared in the literature in recent years. To the best of our knowledge and much to our surprise, there are no reports on this subject.

2. Synthesis of Steroidal Chalcones and Derivatives

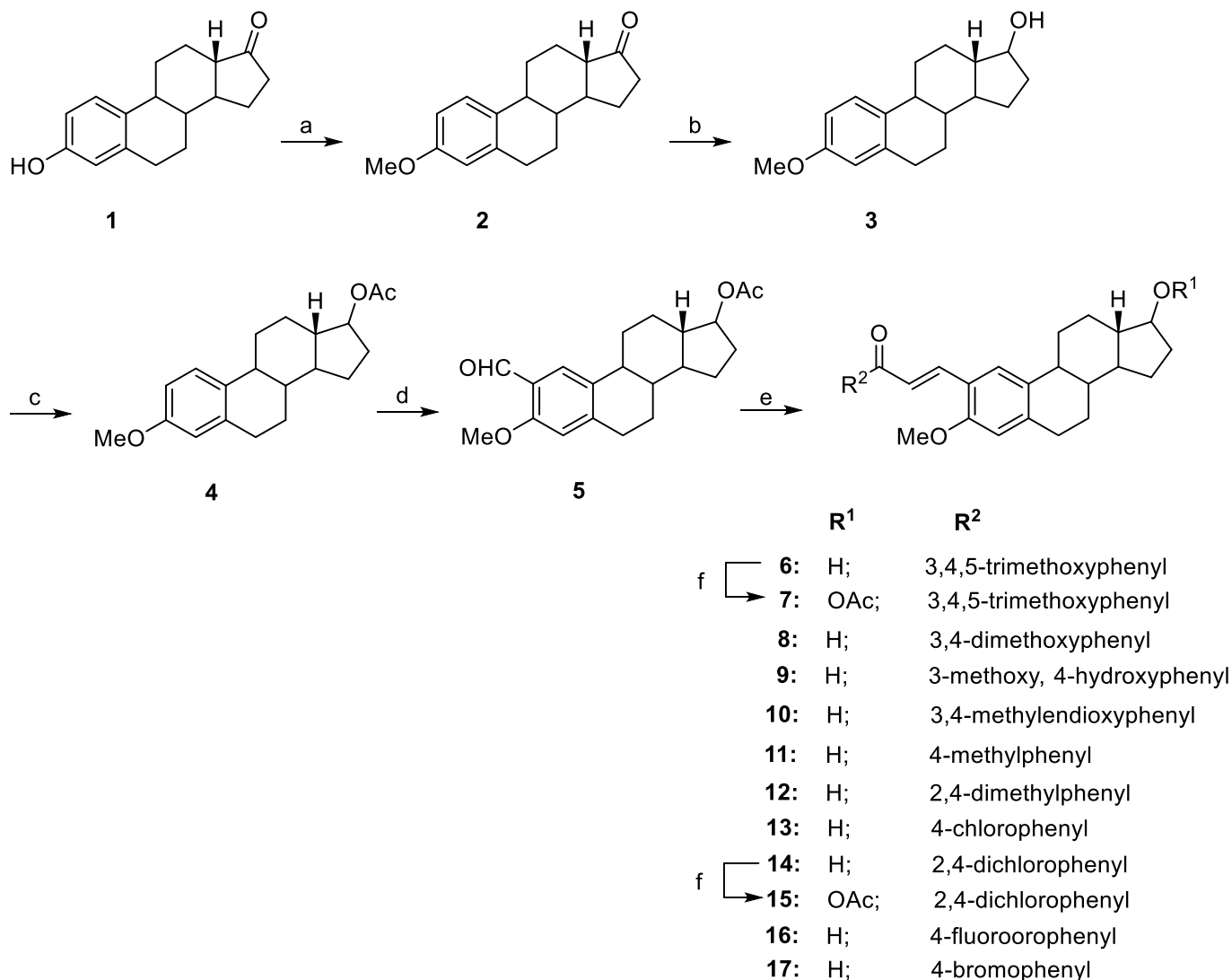
In 2007, Negi et al.¹⁷ reported the synthesis of steroidal chalcones from estradiol. Some of these compounds have significant anticancer activity against certain human cancer cell lines.

Estrone **1** was chosen as the starting aldehyde substrate to carry out the synthesis (Scheme 1).

Thus, to prepare the aldehyde derivative **5**, a protection reaction by methylation of the phenolic hydroxyl of **1** was first carried out using dimethyl sulfate and anhydrous potassium carbonate in anhydrous acetone under reflux. Protected estrone **2** was isolated with a yield of 91%. After a reaction of reduction using sodium borohydride in a mixture of methanol-chloroform (2: 1), the ketone of derivative **2** led to the corresponding alcohol **3** in a yield of 94% and an acetylation reaction using acetic anhydride in dry pyridine of this latter,

provided the steroidal derivative 17-acetate **4** in a very good yield. A Vilsmeier formylation reaction,¹⁸ using dimethylformamide and phosphorus oxychloride at 80 °C resulted in the aldehydic substrate **5**.

The desired steroidal chalcones deprotected at the C-17 position were obtained by reacting the substrate **5** with various acetophenone derivatives in a solution of hydroalcoholic potassium hydroxide at 7%. Chalcones **6** and **14** were then acetylated with acetic anhydride to give the corresponding acetylated derivatives **7** and **15**.

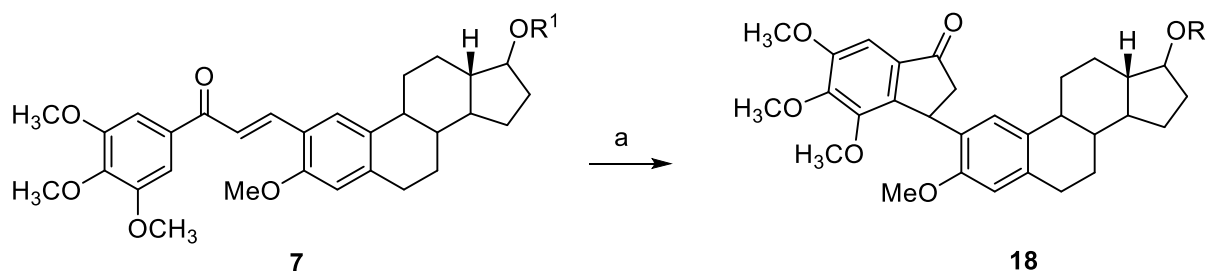


Reagents : a- dimethyl sulfate, K₂CO₃, acetone-DCM, reflux, 5h, 91%; b- NaBH₄, MeOH-DCM, 50 °C, 1h, 94%; c- pyridine, acetic anhydride, r.t., 24h, 93%; d- DMF, POCl₃, 0-10 °C for 1h then heat 80 °C for 3h, 36%; e- acetophenones as per R², 7% KOH solution in EtOH, at 10 °C, 24h, 34-86%; f- substrate, acetic anhydride, pyridine, r.t., 24h.

Scheme 1. Synthesis of steroidal chalcones **6-17**.

One of the chalcone derivatives was further modified to the corresponding 1-indanone derivative **18** using the trifluoroacetic acid-catalyzed Nazarov cyclization reaction (Scheme 2). Indanone **18** was prepared in a yield of 23% by treatment in a sealed tube of chalcone **7** with trifluoroacetic acid for 4 h.¹⁹

Some of these chalcones show significant anticancer activity against certain human cancer cell lines. This is the case with derivatives **9** and **18** which exhibit real activity against MCF-7, a hormone-dependent breast cancer cell line. Indanone **18** showed better activity than the parent chalcone against the MCF-7 breast cancer cell line. Using the erythrocyte as a model system, the most active chalcones were also tested for osmotic hemolysis. It has thus been shown that the fragility of erythrocytes is not modified by these biologically active chalcones. We can therefore consider these chalcones as non-toxic for normal cells.



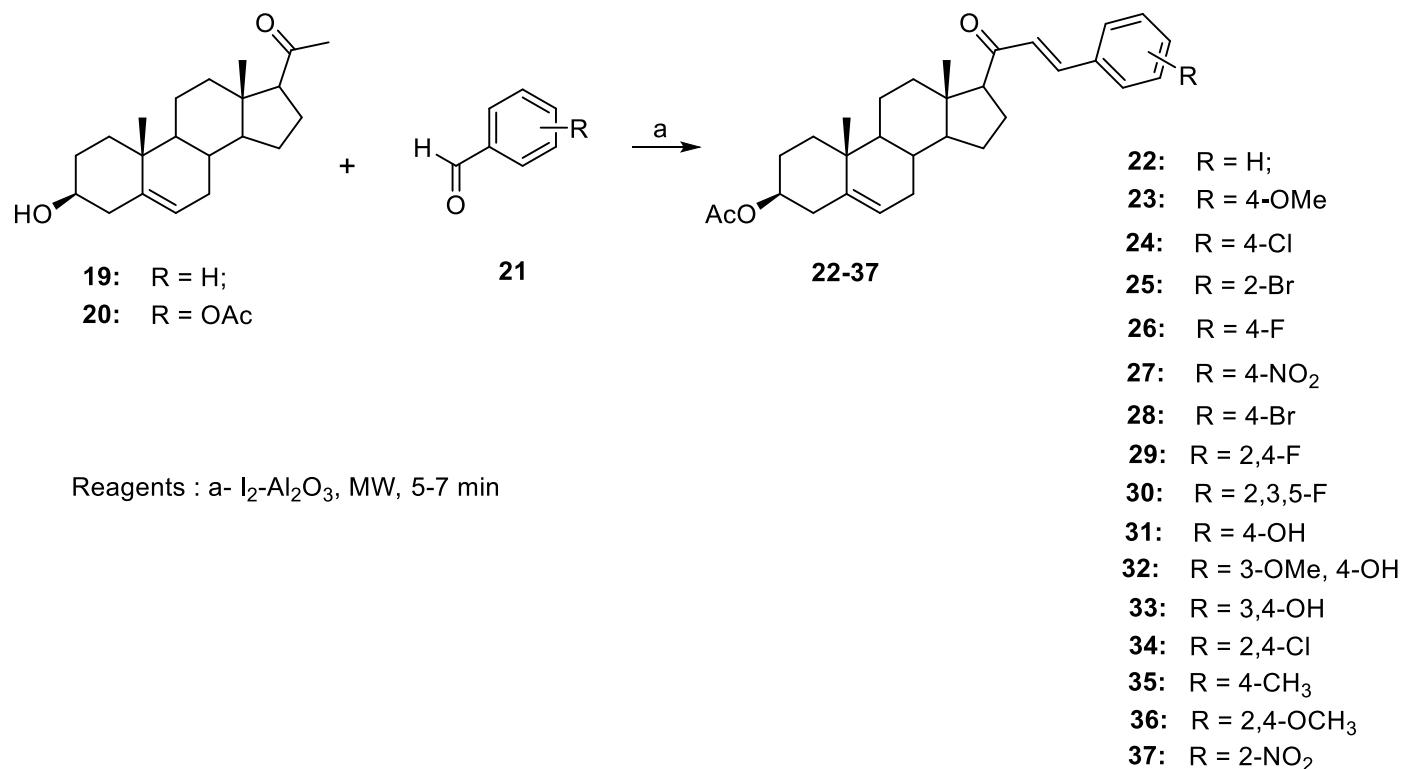
Reagents : a- trifluoroacetic acid, sealed tube, 120 °C, 4h, 23%.

Scheme 2. Synthesis of the steroidal indanone **18** from chalcone **7**.

In 2013, Sarma et al.²⁰ reported the synthesis of a new class of chalconoyl pregnenolones based on a Claisen-Schmidt reaction without solvent and under microwave activation conditions.

Cortisone, estrogen, testosterone, and progesterone among others are natural hormones biosynthesized from pregnenolone, a neurosteroid derived from cholesterol by biosynthesis in the adrenal gland and the central nervous system.^{21,22}

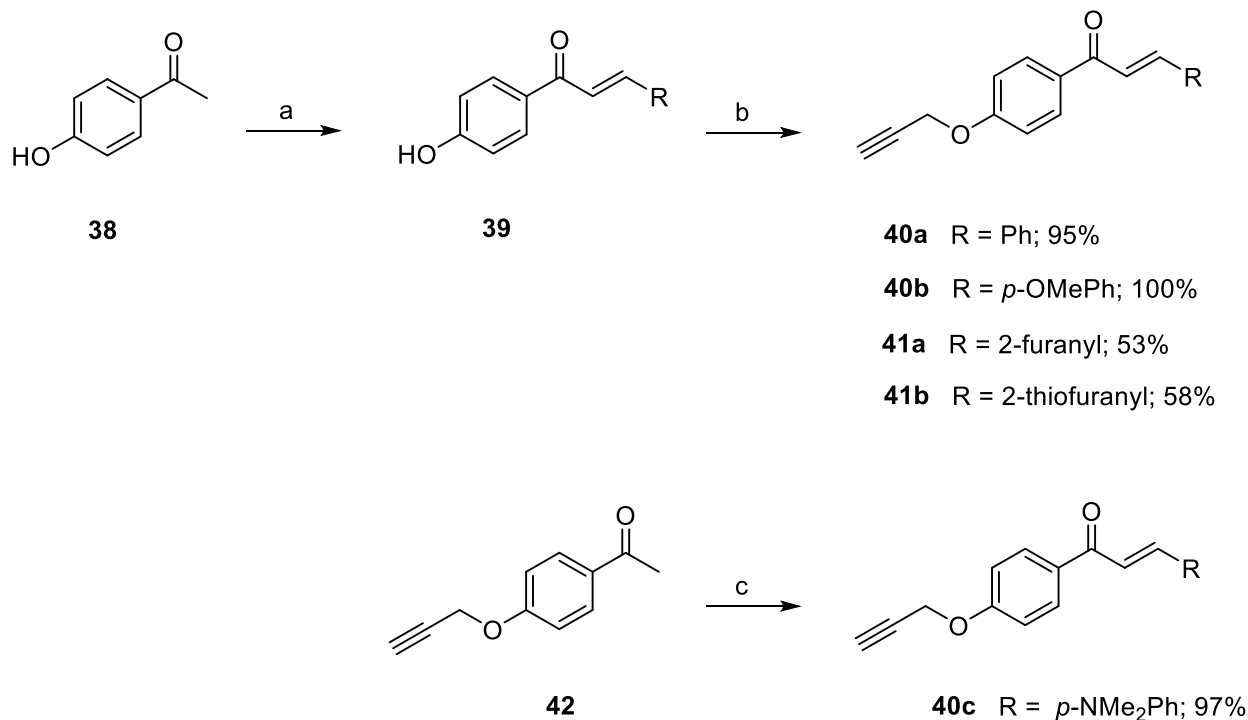
The condensation between the acetate derivative of pregnenolone **20** and the benzaldehyde **21** carried out without solvent and by microwave activation using 20 mol% of the catalyst, $I_2-Al_2O_3$ led to the desired compound with a good yield of 86% after only 6 min of reaction at 250 W of microwave power. The authors were thus able to prepare sixteen new steroidal chalcones by condensation of compound **20** with different substituted benzaldehydes (Scheme 3). Furthermore, no by-product was observed, these clean reactions led to the desired chalcones with good yields of between 79 and 86%. Longer reaction times or an increase in the percentage of catalysts resulted in the decomposition of the desired product. In addition, the nature of the substituents on the aromatic ring of benzaldehyde does not affect the yield of the desired product.



Scheme 3. Synthesis of steroidal chalcones **22-37**.

Two fungal strains *Aspergillus niger* and *Candida albicans* and two bacterial strains *Bacillus subtilis* and *Escherichia coli* were used to test the synthesized derivatives **22-37**. Some have interesting inhibitory activity. Furthermore, it has been observed that this activity is considerably reduced if the double bond is epoxidized. The presence of the unsaturated chalcone moiety, therefore, plays a significant role in this inhibitory activity.

In 2015, El Sayed Aly et al.²³ described the synthesis of steroidal chalcones from cholesterol in good yield. The starting chalcones were synthesized as described in Scheme 4. Intermediates **40a-b** and **41a-b** were prepared in average yields at room temperature by propargylation of chalcones **39** using propargyl bromide and the potassium carbonate as the base. The chalcone **40c** was prepared by the Claisen-Schmidt condensation reaction of intermediate **42**, previously propargylated as described above, in the presence of *p*-dimethylaminobenzaldehyde. In doing so, the extinction of propargyl bromide as a quaternary ammonium salt by the dimethylamino group is prevented which would not have been the case if the chalcone engaged had been propargylated as described previously for compounds **40a-b** and **41a-b**.



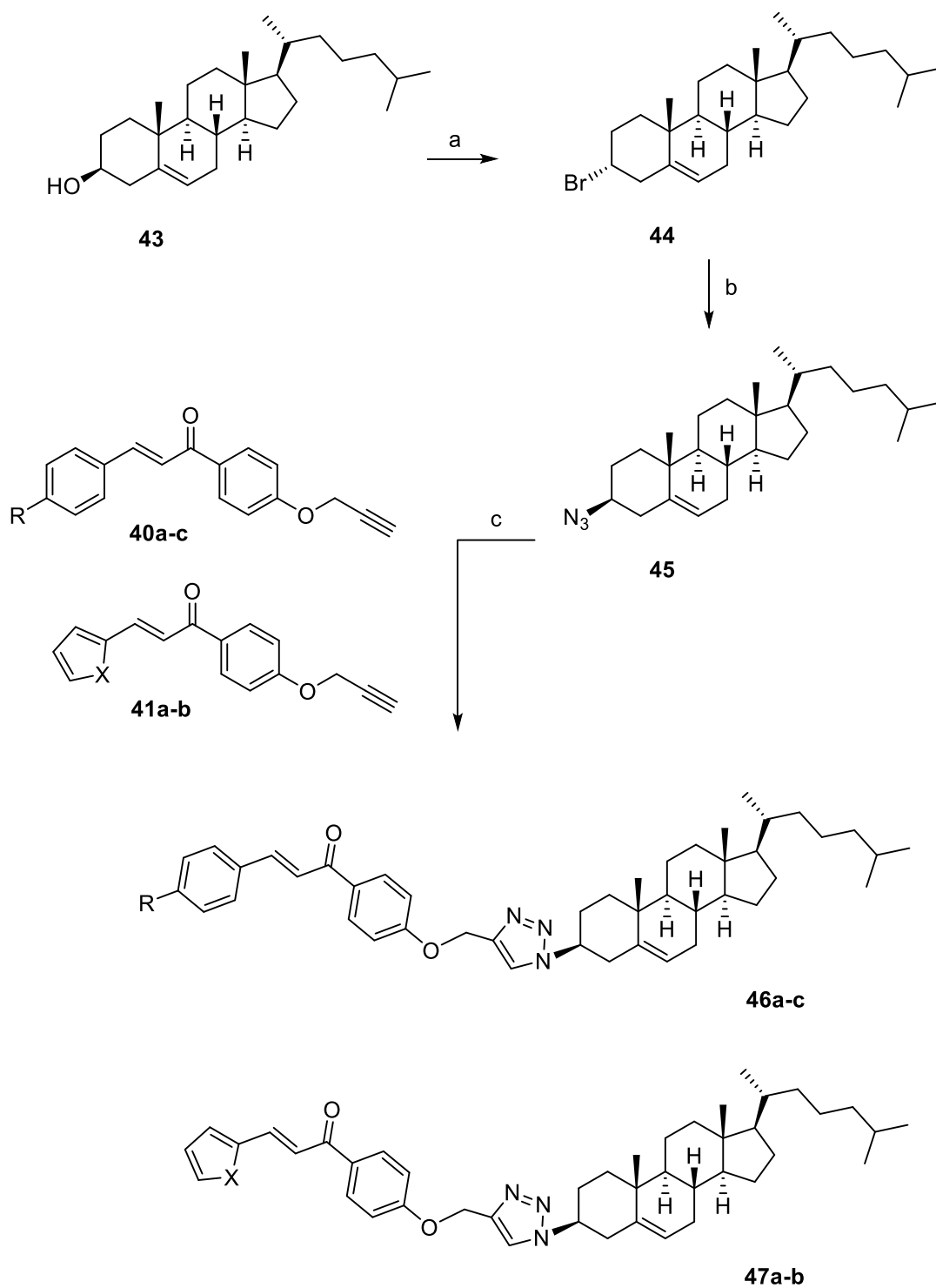
Reagents :a- R-CHO, NaOH aq., EtOH; b- propargyl bromide, K₂CO₃, DMF, r.t.
 c- *p*-dimethylaminobenzaldehyde, NaOH aq., EtOH, r.t.

Scheme 4. Synthesis of chalcones derivatives **40a-c** and **41a-b**.

Cholest-5-en-3 β -ol **43** was activated as bromide in very good yield under Appel conditions,²⁵ which means treatment with CBr₄/PPh₃ to afford 3 α -bromocholest-5-ene **44** due to inversion of the configuration at the C-3 carbon (Scheme 5). An S_N2 substitution of the bromine atom of compound **44** with the N₃ group was ensured by refluxing with NaN₃ in dry DMF to afford 3 β -azidocholest-5-ene **45** after inversion of the configuration again at the C-3 carbon. The product was isolated in good yield.

The target cholesterol–chalcone conjugates **46a-c** and **47a-b** were prepared by reacting 3 β -azidocholest-5-ene **45** with propargylated chalcones **40a-c** and **41a-b** under CuAAC conditions.²⁶ The reactions proceeded fairly in gently refluxing THF/H₂O mixture containing L-ascorbic acid as a reducing agent and a catalytic amount of CuSO₄·5H₂O.

The chalcone modified cholesterol derivatives **46a, c**, and **47b** were active against *E. coli*. They were as active as ampicillin. Thus, the chalcones possessing unsubstituted phenyl, and *p*-dimethylaminophenyl, as well as 2-thienyl alternatives were more active than other congeners against *E. coli*. The chalcone derivative **46c** emerged as the most promising antimicrobial probe. It was as active as the controls against *E. coli*, *S. aureus*, and *C. albicans*.

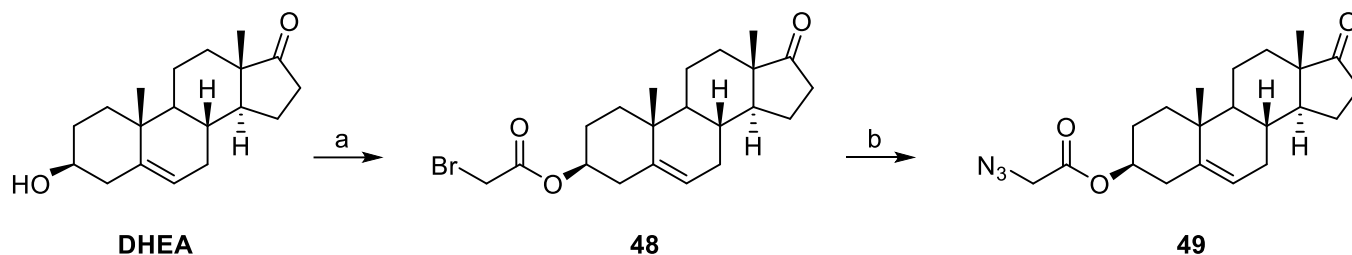


Reagents : a- CBr_4 , PPh_3 , DCM (74%); b- NaN_3 , DMF, 100 °C, (63%);
 $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, L-ascorbic acid (L-AsAc), THF/ H_2O , (**46a**, R = H (40%);
46b, R = OMe (41%); **46c**, R = NMe_2 (68%); **47a**, X = O (47%); **47b**, X = S (60%).

Scheme 5. Synthesis of derivatives **46a-c** and **47a-b**.

In 2016, Liu et al.²⁷ described the synthesis of steroidal chalcones using the molecular hybridization approach.

The target molecules can be synthesized from the corresponding alkynes and steroidal azide **49** through click chemistry. The synthesis of the steroidal azide **49** is shown in Scheme 6. Bromoacetylation of DHEA under Schotten-Baumann conditions²⁸ afforded the corresponding bromide **1** in 87% yield, which then reacted with NaN₃ in DMSO to give the steroidal azide **49** in 85% yield.

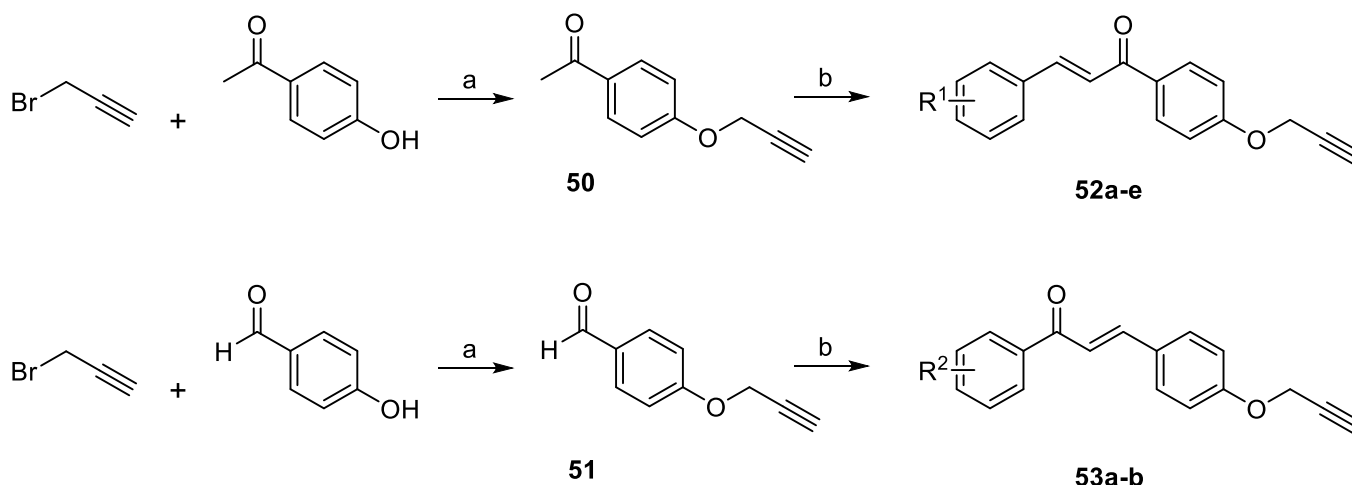


Reagents : a- bromoacetyl bromide, NaHCO₃, DCM/H₂O (1/1), r.t.; b- NaN₃, DMSO, r.t., - 50 °C.

Scheme 6. Synthesis of the steroidal azide **49**.

The steroidal azide **49** was used directly for the next step after a simple aqueous work-up procedure. In the first step, a two-phase solvent system (DCM/H₂O) was used; the base NaHCO₃ in the aqueous phase neutralized the generated HBr, while the starting materials and the product were in the organic phase. Besides, this condition avoided unwanted side reactions of bromide **48** with H₂O.

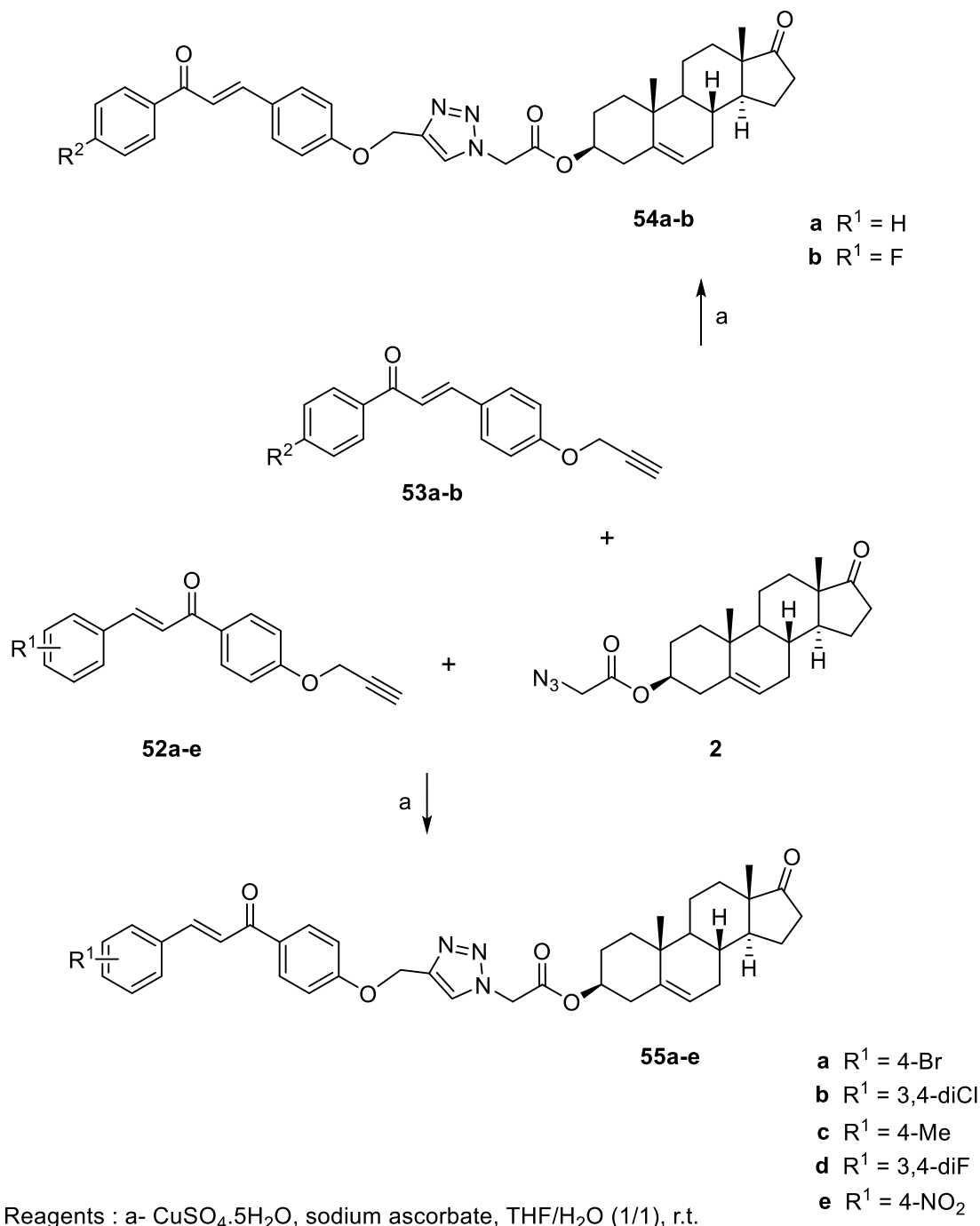
The synthesis of alkyne building blocks is shown in Scheme 7. Treatment of 4-hydroxy acetophenone and 4-hydroxybenzaldehyde with propargyl bromide in the presence of K₂CO₃ gave compounds **50** and **51**, respectively, which then underwent the KF/Al₂O₃-catalyzed Claisen-Schmidt condensations with aromatic aldehydes and acetophenones, affording substituted chalcones **52a-e** and **53a-b**.



Reagents : a- K₂CO₃, DMF, r.t.; b- Al₂O₃/KF, EtOH, 50 °C.

Scheme 7. Synthesis of alkyne building blocks **52** and **53**.

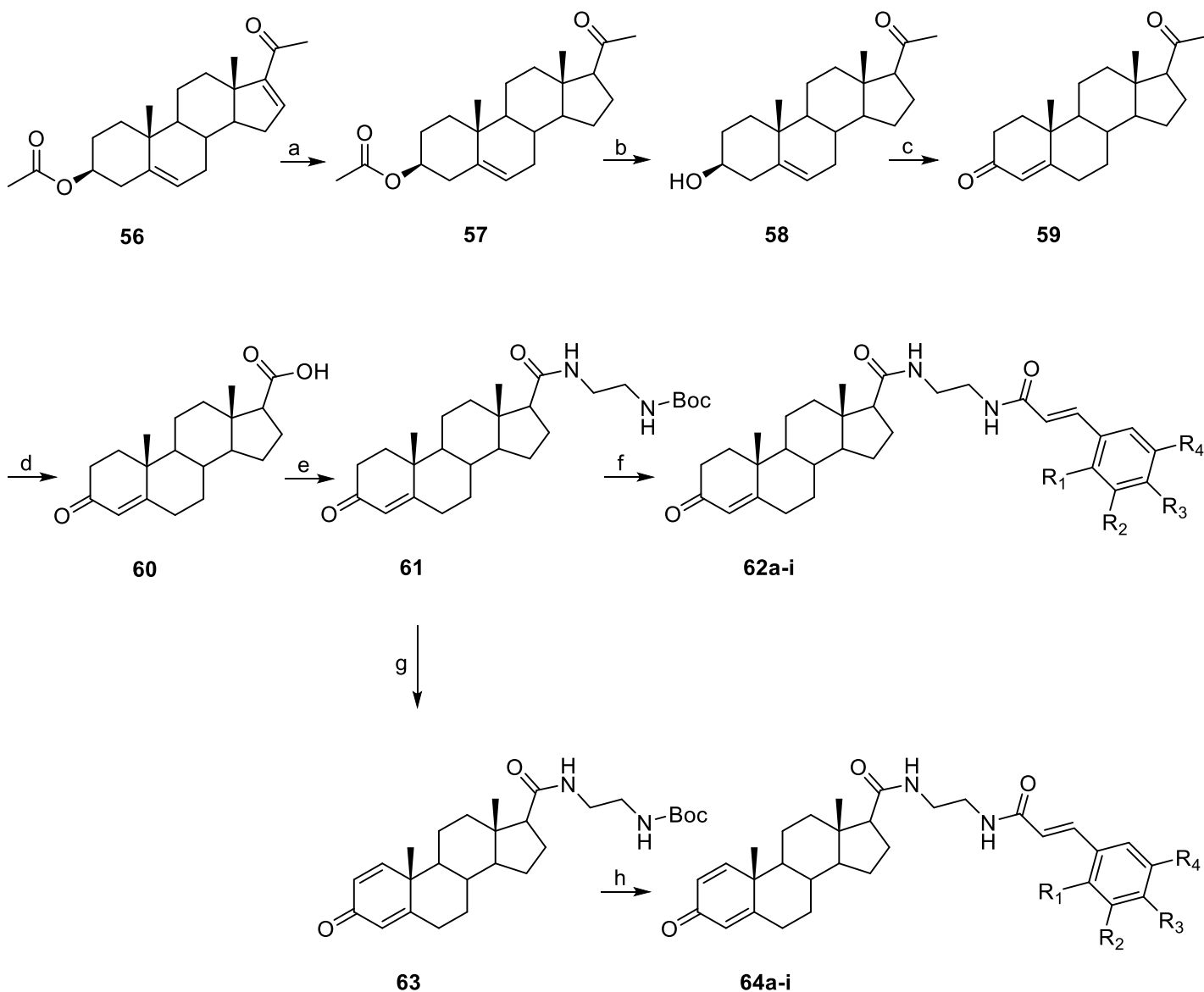
With the azide and alkyne building blocks in hand, the steroidal chalcones **54** and **55** were efficiently synthesized through the standard CuAAC reactions in moderate to good yields (Scheme 8). These compounds showed moderate but remarkably decreased inhibitory activity against SH-SY5Y cells with IC₅₀ values more than 36.64 μ M. They exerted weak or no activity toward other cancer cell lines regardless of their substituent patterns and the nature of substituents.



Scheme 8. Synthesis of steroidal chalcones **54** and **55**.

In 2020, Xiang et al.²⁹ reported the synthesis of a series of novel steroidal-chalcone derivatives based on the molecular hybridization strategy.

The starting material was inexpensive pregnenolone acetate which was reduced by H₂ to obtain compound **57**. The intermediate **58** was acquired via a hydrolysis reaction. Subsequently, compound **58** was oxidized to yield the progesterone **59**, whose acetyl group was then oxidized to generate the key intermediate **60**. The compound **60** reacted with *N*-Boc-ethylenediamine to afford **61**. The compound **61** was first deprotected and then reacted with various carboxylic acids to offer the final productions **62a-i** (Scheme 9). The synthesis of target compounds **64** began from the intermediate **61** that was dehydrogenized by DDQ to form the intermediate **63**. Then, the final compounds **64a-i** were obtained through deprotection and condensation reaction.



R₁ = H or OMe; R₂ = H, OMe or NO₂; R₃ = H, OMe, Cl, CF₃ or NO₂; R₄ = H or OMe.

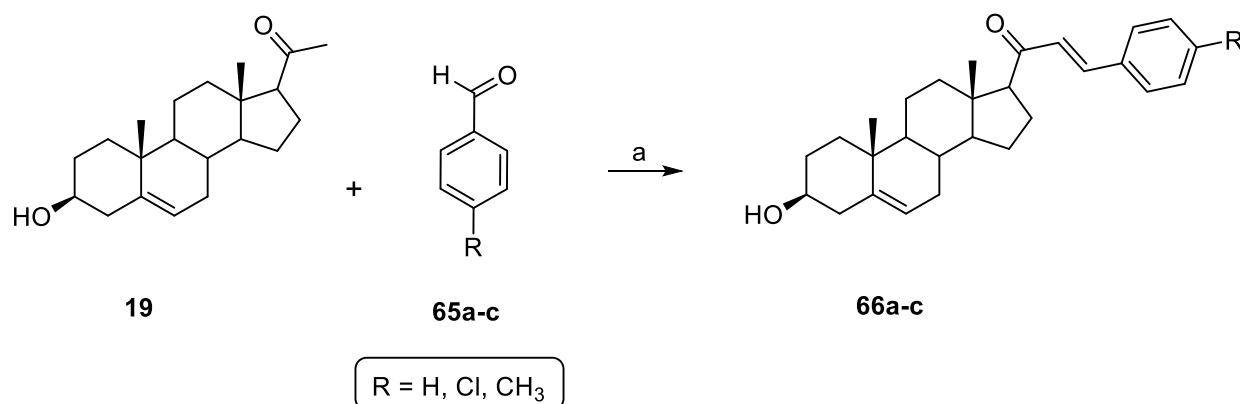
Reagents : a- Pd/C, H₂, 30 °C, r.t., 6h; b- NaOH, CH₃OH, 1,4-dioxane, r.t., 30 min; c- cyclohexanone, aluminium isopropoxide, toluene, reflux, 7h; d- NaOH, Br₂, 1,4-dioxane, 0 °C, 1.5h; e- HATu, DIPEA, DMF, r.t., overnight; f- 1) CF₃COOH, CH₂Cl₂, 0 °C, 30 min, 2) HATu, DIPEA, DMF, r.t., overnight; g- DDQ, TBDMSCl, 1,4-dioxane, 2h; h- 1) CF₃COOH, CH₂Cl₂, 0 °C, 30 min, 2) HATu, DIPEA, DMF, r.t., overnight.

Scheme 9. Synthesis of steroidal chalcones **62** and **64**.

A preliminary biological activity evaluation was carried out. The antiproliferative results showed that most compounds exerted weak activity against human colon cancer cells HT-29 and lung cancer cells A549. In contrast, most compounds showed excellent growth inhibitory activity against human TNBC cells MDA-MB-231. Among these compounds, compounds **62c** (with $R_1 = \text{OMe}$ and $R_2 = R_3 = R_4 = \text{H}$) demonstrated the most potent activities with the IC_{50} values of $0.42 \mu\text{M}$. Moreover, compound **62c** could accumulate the ROS levels in MDA-MB-231 cells and induced cell apoptosis. Western Blot analysis documented that compound **62c** could down-regulate anti-apoptotic Bcl-2 but up-regulate pro-apoptotic Bax expression. Additionally, compound **62c** could also activate the caspase-3 signaling pathway, which accelerated the apoptosis of MDA-MB-231 cells.

In 2021, Rashid et al.³⁰ described the synthesis of chalcone derivatives of pregnenolone *via* base-catalyzed Claisen-Schmidt condensation reaction.

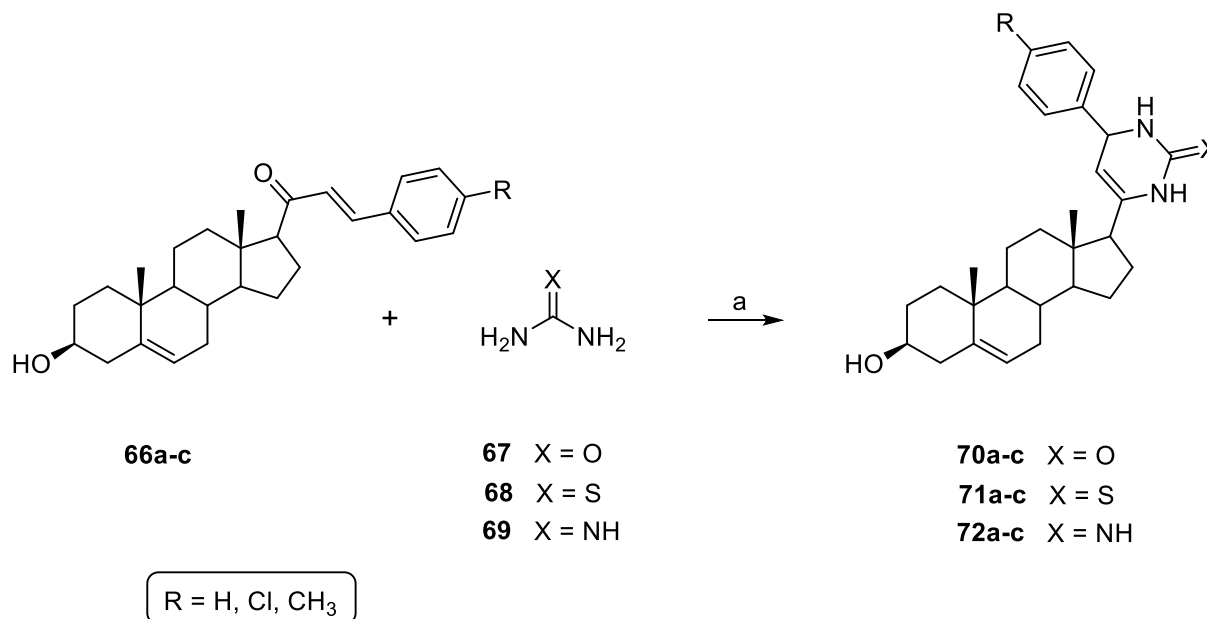
The synthesis of compounds **66a-c** was carried out in ethanolic potassium hydroxide by treating Pregnenolone **19** with a series of both the substituted and non-substituted aromatic aldehydes **65a-c**. The synthetic process is outlined in Scheme 10.



Reagents : a- KOH/MeOH, r.t., 18-20 h.

Scheme 10. Synthesis of chalcone derivatives of pregnenolone.

Subsequently, the syntheses of 3,4-dihydropyrimidin-2(1H)-one **70a-c** and 3,4-dihydropyrimidin-2(1H) - thione **71a-c** and 2-amino-3,4-dihydropyrimidine **72a-c** derivatives of pregnenolone-chalcones were carried out in ethanolic potassium hydroxide by treating chalcone derivatives of pregnenolone **66a-c** with urea **67**/thiourea **68**/guanidine HCl **69**. The process of synthesis is outlined in Scheme 11.



Reagents : a- KOH/EtOH, reflux, 8-10 h.

Scheme 11. syntheses of 3,4-dihydropyrimidin-2(1H)-one **70a-c** and 3,4-dihydropyrimidin-2(1H)-thione **71a-c** and 2-amino-3,4-dihydropyrimidine **72a-c** derivatives of pregnenolone-chalcones.

Cell viability test of synthesized steroidal chalcones and their pyrimidine and thiopyrimidine derivatives against human breast (MCF-7), human lung (A549), and human prostate (PC-3) cancer cell lines was done using MTT ((4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), assay. Compounds were further evaluated for their inhibition potential against recombinant human DHFR (rhDHFR). All compounds showed activity from the low micromolar to the submicromolar range. Compound **72b** with an IC₅₀ value of 180 nM emerged as the most potent compound against rhDHFR. Interaction of the newly synthesized pregnenolone derivatives with hDHFR and estrogen receptor alpha (ER α) was also explored via docking simulations. The overall results of hDHFR inhibition have shown that these analogs can be further optimized and developed as potent anticancer agents.

3. Conclusions

The present review offers up-to-date literature on the syntheses of steroidal chalcones and derivatives reported during the last years. An almost infinite quantity of new molecules with various structures can be obtained by coupling two or more natural compounds. The objective of such syntheses is to combine the pharmacological properties of two or more biologically active molecules to increase or modulate these activities to obtain derivatives exhibiting new properties. In general, it has been observed that the unsaturated chalcone moiety in the synthesized compounds is at the origin of the activity of steroidal chalcones. Generally speaking, it is observed that the steroids and the resulting derivatives continue to be of interest to researchers, given the biological potential inherent in this family of molecules.

4. Acknowledgements

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Authors' Biographies



Malika Ibrahim-Ouali carried out her Ph.D. under the supervision of Professor Gramain in Clermont-Ferrand (France) in 1996. The work was focused on the synthesis of alkaloids. She was a postdoctoral fellow with Prof. Knochel (Humboldt fellowship) in 1996 in Germany where she got her first training in organometallic chemistry. In 1997, she joined Professor H. P Husson's group at the ICSN (Paris) as a postdoctoral researcher. Since 1998, she is currently an Associate Professor at Aix-Marseille University and her field of interest remains the total synthesis of natural compounds.



Frédéric Dumur received his Ph.D. 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 300 publications and 5 book chapters.

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