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### **ABSTRACT**

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The thesis entitled “**Design and Synthesis of Bile Acid Based Conjugates, Dimers, Oligomers and Their Pharmacological and Supramolecular Applications**” has been divided into three chapters.

Chapter 1: Synthesis of bile acid based dimers, oligomers to study their micelle like properties and studies towards the synthesis of cholaphanes.

Chapter 2: Synthesis of bile acid-fluconazole conjugates, new fluconazole analogues using click reaction, bile acid based amino alcohols and their bioevaluation.

Chapter 3: Stereoselective synthesis of steroidal side chain from 16-dehydropregalone acetate.

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**Chapter 1: Synthesis of bile acid based dimers, oligomers to study their micelle like properties and studies towards the synthesis of cholaphanes.**

#### **Introduction**

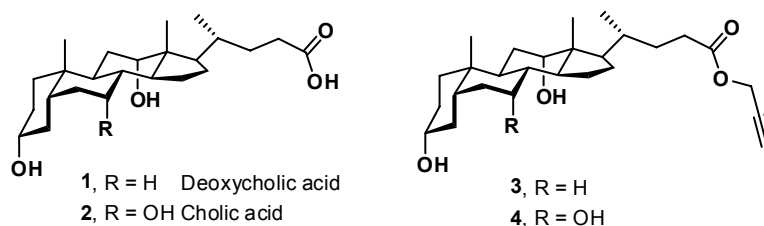
Bile acids are versatile building blocks for the design and synthesis of macrocyclic and open chain supramolecular hosts due to their large, rigid, and curved steroidal skeletons, chemically different hydroxy groups, enantiomeric purities, and their unique amphiphilicity, together with their availability and low cost.<sup>1</sup> Bile acids and their derivatives are also important compounds from the pharmaceutical point of view. In their

dimeric form, bile acids or their derivatives show inclusion of methanol, carbohydrate, perylene, and DNA. Such dimers also act as artificial ionophores and are found to be potential receptors for neutral molecules or metal cations.<sup>2</sup> The configuration of dendritic structures based on steroidal moieties may give rise to potential molecular assemblies with many interesting nano-scale applications, including organ-targeted drug carriers, artificial ion channels, organogelators and molecular switches.

In this chapter we present our studies on the synthesis of bile acid dimers and oligomers based on Cu (I) catalyzed 1,3 dipolar cycloaddition of terminal alkyne and azide (click reaction).<sup>3</sup> Their micelle like properties have been studied by encapsulation of hydrophilic dye (cresol red) in non polar solvent (chloroform) using solid liquid extraction protocol and efforts towards the synthesis of cholaphanes.

#### Synthesis of terminal alkynes:

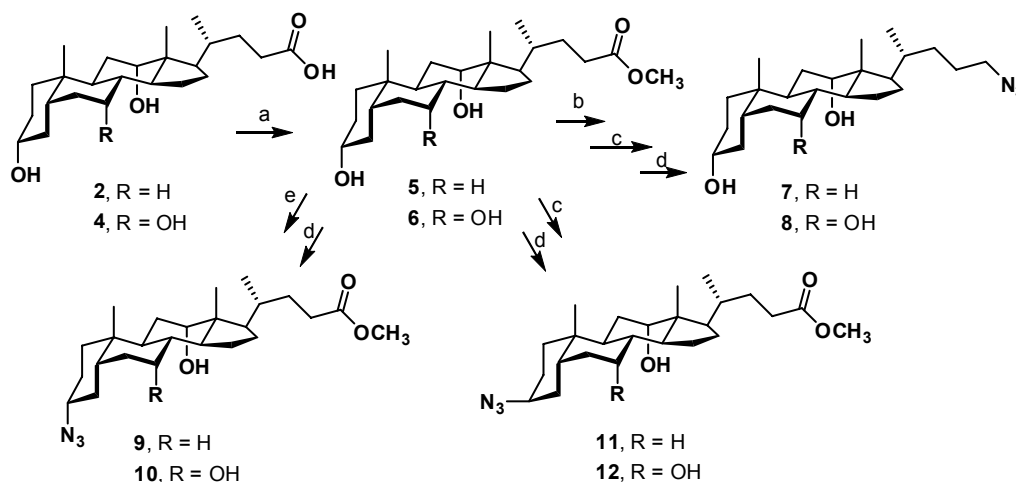
Terminal alkynes were synthesized by esterification of bile acids **1** and **2** using an excess of propargyl alcohol and a catalytic amount of *p*-TSA (*para*-toluenesulfonic acid) to get compounds **3** and **4** (Scheme 1).



**Scheme 1:** Reagents and Conditions: *p*-TSA (10 mol %), Propargyl alcohol, 55-60 °C, 7 h, **3** (96%), **4** (95%).

#### Synthesis of azides:

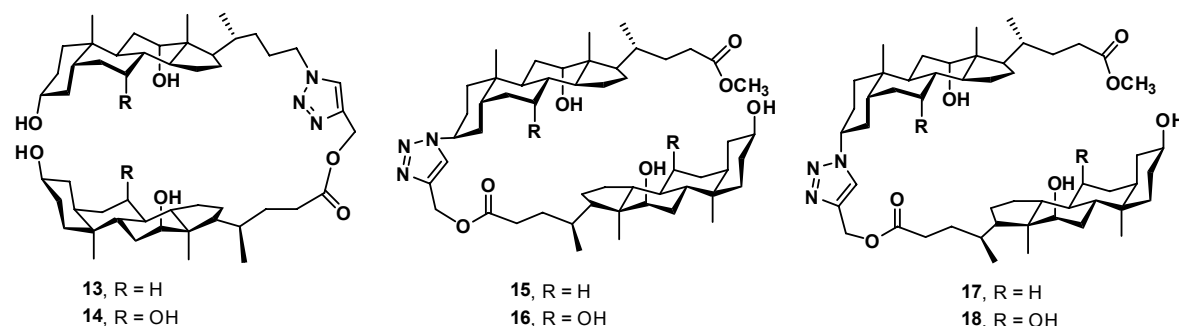
Azides at C-3 and C-24 positions of bile acids were synthesized (Scheme 2). Esterification of deoxycholic acid **1** and cholic acid **2** using excess methanol and catalytic amount of *p*-TSA afforded methyl esters **5** and **6**. These esters on reduction with LAH followed by selective mesylation and nucleophilic substitution of mesyl with sodium azide gave C-24 azido compounds **7** and **8**. C-3 $\alpha$ -azides **9** and **10** were synthesized using Mitsunobu reaction, while C-3 $\beta$ -azides **11** and **12** were synthesized by mesylation followed by nucleophilic substitution of mesyl with sodium azide from compounds **5** and **6**.



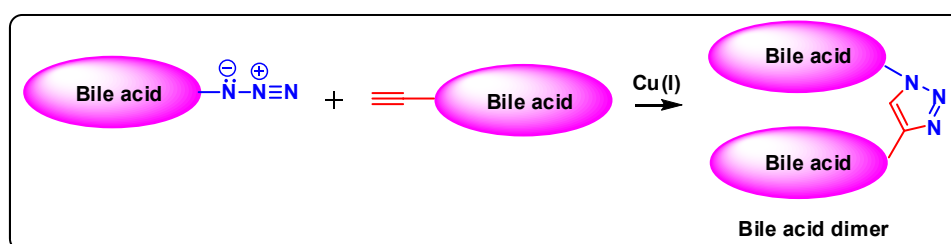
**Scheme 2:** Reagents and conditions: (a) *p*-TSA/MeOH, 25 °C, 24 h, 95-96%; (b) LAH/THF, 25 °C, 2 h, 93-97%; (c) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 10 min; (d) NaN<sub>3</sub>, DMF, 60 °C, 3 h, 93-94%; (e) Ph<sub>3</sub>P, Et<sub>3</sub>N, MeSO<sub>3</sub>H, DEAD, THF, 45 °C, 24 h.; 75-78 % (overall in 2 steps).

### Synthesis of Dimers:

Bile acid dimers **13-18** (Figure 1) linked with 1,2,3 triazole were synthesized on 1,3-dipolar cycloaddition of terminal alkynes **3** or **4** (Scheme 1) with terminal azides **7-12** (Scheme 2). General graphical representation is depicted in Scheme 3. In our earlier report<sup>4</sup> this reaction was carried out in *t*-BuOH/H<sub>2</sub>O using catalytic amount CuSO<sub>4</sub>·5H<sub>2</sub>O and sodium ascorbate at 60-65 °C for 3-12 h. Same reaction under microwave irradiation in DMF/H<sub>2</sub>O was completed in less reaction time (5-10 min).



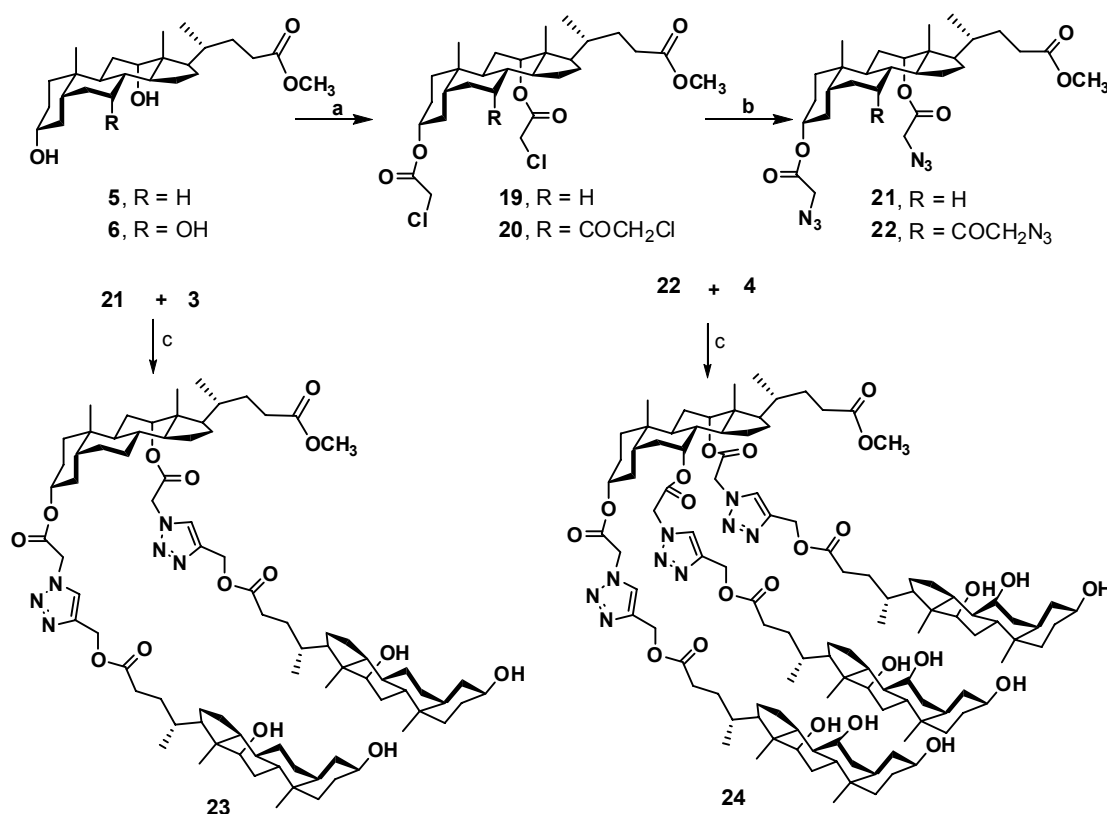
**Figure 1:** Bile acid dimers



**Scheme 3:** Reagents and conditions: CuSO<sub>4</sub>·5H<sub>2</sub>O (5 mol %), Sodium ascorbate (40 mol %), DMF:H<sub>2</sub>O (4:1), Microwave, 5 min, 90-96%.

### Synthesis of oligomers:

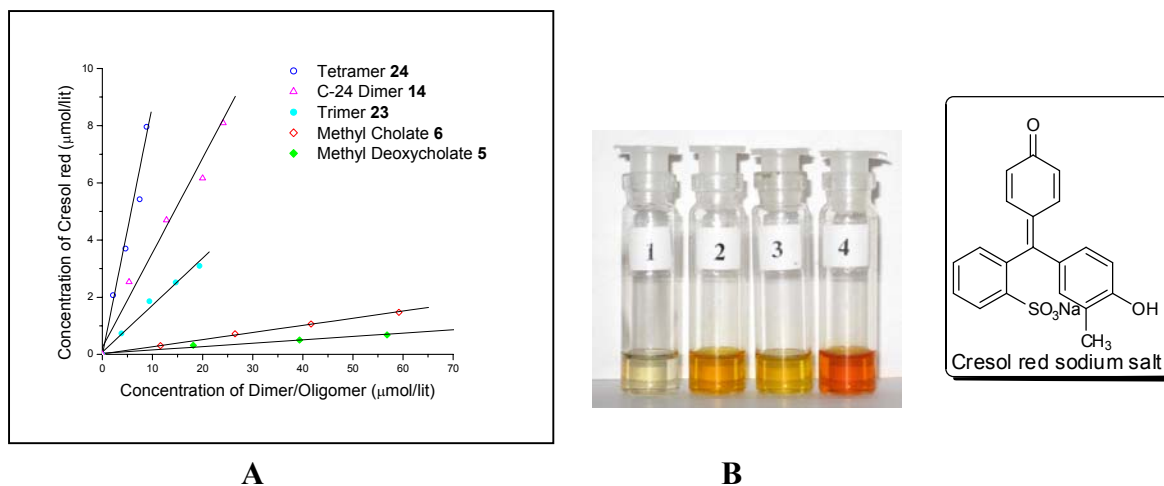
Hydroxyl groups of bile acids were esterified using chloroacetyl chloride (Scheme 4). Transformation of chloro functionality of compound **19** and **20** into azides **21** and **22** was carried out using sodium azide in DMF at 75 °C. These two azides on cycloaddition reaction with propargyl ester **3** and **4** afforded trimer **23** and tetramer **24** respectively.<sup>5</sup>



**Scheme 4:** Reagents and conditions: (a) CaH<sub>2</sub>, ClCH<sub>2</sub>COCl, TBAB, toluene (reflux), 3 h, 78-86%; (b) NaN<sub>3</sub>, DMF, 75 °C, 12 h, 79-82%; (c) CuSO<sub>4</sub>·5H<sub>2</sub>O (5 mol %), Sodium ascorbate (40 mol%), DMF:H<sub>2</sub>O (4:1), Microwave, 5 min, **23** (85%), **24** (82%).

### Dye solubilisation study:

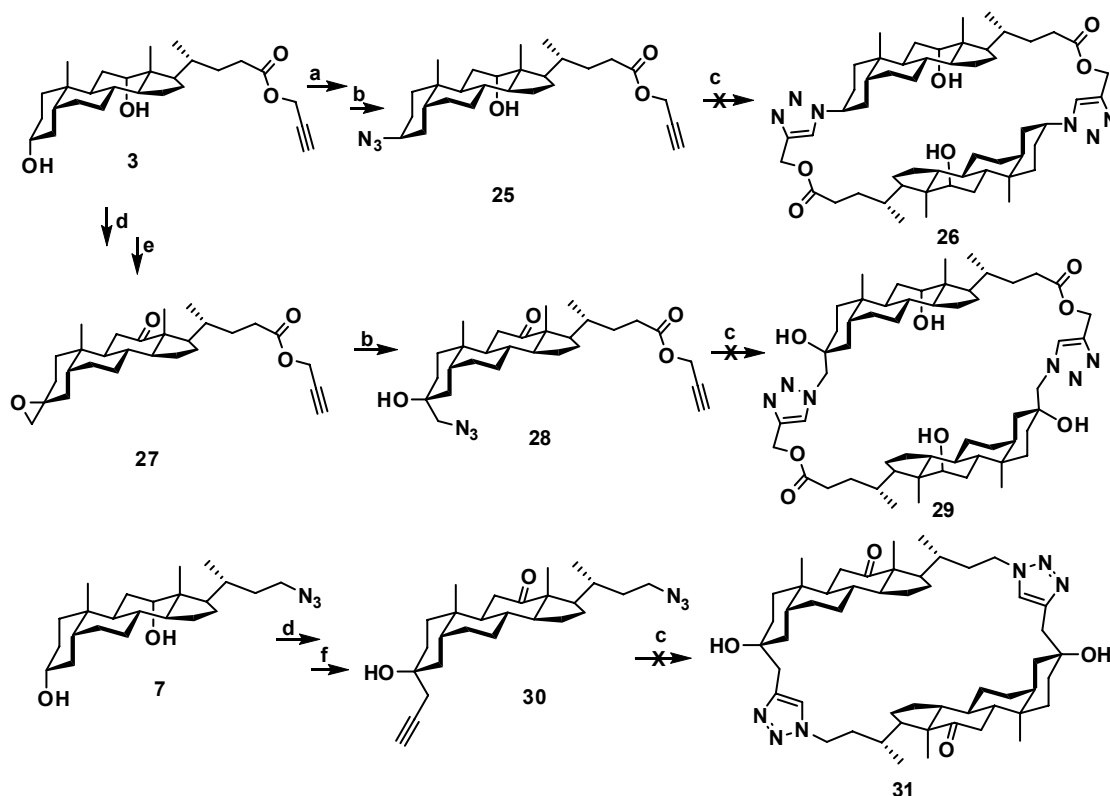
Bile acid dendrons can adopt a reverse micelle-like conformation in nonpolar solvent with the hydrophobic face turned outwards (towards the solvent).<sup>6</sup> In this chapter, the study of micellar properties of newly synthesized dimers **13-18** and oligomers **23** and **24** was carried out by solid liquid extraction protocol of the sodium salt of cresol red dye (hydrophilic dye) in nonpolar solvent, chloroform. We found that dimeric and oligomeric compounds of methyl cholate as well as methyl deoxycholate show linear increase in dye solubilisation with increasing concentrations of the dimer, trimer and tetramer (Figure 2).



**Figure 2:** Solubilisation of cresol red (CR) in chloroform tetramer **24**, C-24 dimer **14**, trimer **23**, and monomers **5**, **6**. Straight lines (**A**) are linear fit lines of experimental data; Cresol red sodium salt solubilisation in chloroform having a ratio of chloroform: cresol red: oligomer (1 mL : 5 mg : 5 mg) each sample was stirred for 12 h and filtered through 0.5 µ PTFE membrane. **vial 1** has no additive, **vial 2** has C-24 dimer **14**, **vial 3** has trimer **23** and **vial 4** has tetramer **24** (**B**).

### Synthesis of cholaphanes:

The design of novel macrocyclic synthetic receptors with molecular cavities is one of the most important fields in supramolecular chemistry. These host molecules can serve as model compounds for more complex biological systems and are important for molecular recognition of substrates in enzymatic processes. Typical macrocycles bind substrates in their defined cavity. The steroid nucleus can make unique contributions to this area owing to its size, chirality, and rigid polycyclic framework. The bile acids, such as cholic acid or deoxycholic acid, have proved especially useful, because of their availability and useful levels of functionalization. On one hand, the presence of functionality at both ends of these units suggests the construction of macrocyclic structures which may possess a high level of inward-directed polar functionality. On the other, the codirected hydroxyl groups present in most bile acids may be exploited (directly or indirectly) in podand-type receptors, linear dimeric hosts, or “facial amphiphiles”.<sup>7</sup> Here, we tried to synthesize cholaphanes using click chemistry approach. Starting from propargyl ester of deoxycholic acid **3**, we synthesized compounds **25**, **28** and **30** which contain both azide and acetylene groups in the same molecule (Scheme 5). 1,3-Dipolar cycloaddition of **25** under various conditions failed to give cholaphane **26**. This reaction led to uncharacterized solid material. In the next attempt, we increased the chain length at C-3 position.



**Scheme 5:** Reagents and conditions: (a) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub> 0 °C, 10 min.; (b) NaN<sub>3</sub>, DMF, 60-65 °C, 3 h, 90%; (c) CuSO<sub>4</sub>·5H<sub>2</sub>O (5 mol%), Sodium ascorbate (40 mol%), DMF:H<sub>2</sub>O (4:1), Microwave, 5 min. (d) Jones reagent, acetone, 5 min, 96%. (e) Trimethyl sulfoxoniumiodide, NaH, DMSO-THF, rt. 2 h, 91%; f) Propargyl bromide, Zn, DMF/THF 25 °C, 5 h.

Under cycloaddition reaction conditions these bifunctional compounds **28** and **30** again led to uncharacterized solid material instead of cholaphanes **29** and **31**. Efforts to synthesize cholaphane by changing the positions of alkyne and azide group as in **30** remained unsuccessful.

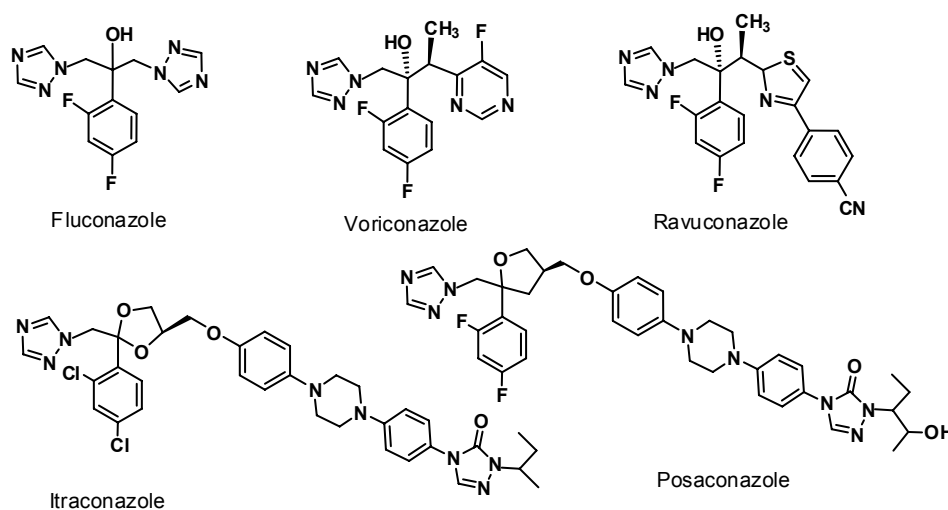
## Chapter 2: Synthesis of bile acid-fluconazole conjugate, new fluconazole analogues using click reaction, bile acid based amino alcohols and their bioevaluation.

### Section I: Synthesis of bile acid-fluconazole conjugates and new fluconazole analogues using click reaction and their bioevaluation.

#### Introduction

The incidence of life threatening fungal infections has tremendously increased in last two decades due to greater use of immunosuppressive drugs, prolonged use of broad-spectrum

antibiotics, wide-spread use of indwelling catheters and also in cancer and AIDS patients. The presently marketed antifungal drugs are either highly toxic (amphotericin-B) or are becoming ineffective due to appearance of resistant strains (flucytosine and azoles). Azole antifungals (Figure 3) are strong inhibitors of lanosterol  $14\alpha$ -demethylase, which is major component of fungal cell membrane.<sup>8</sup>



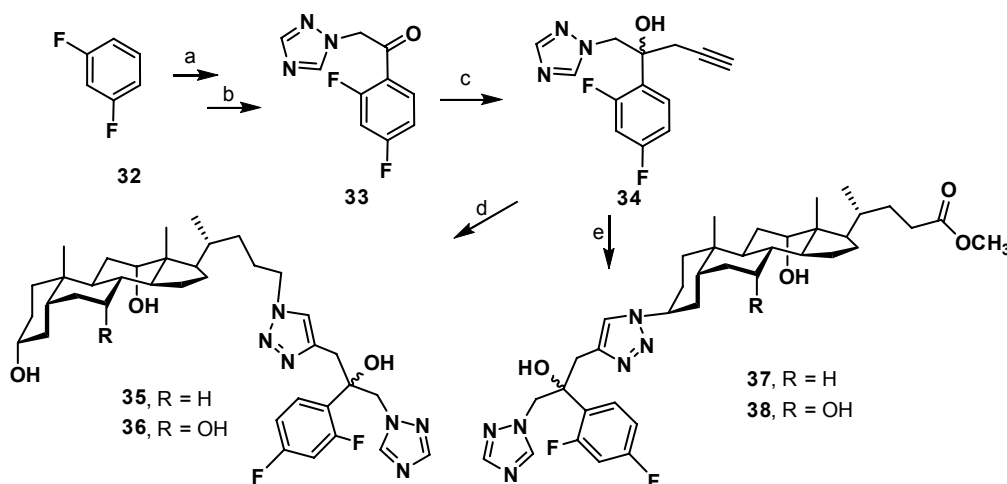
**Figure 3:** Azole based antifungal drugs.

Fluconazole is an orally effective, potent and safe triazole based antifungal drug, with favorable pharmacokinetic characteristics and low toxicity. Due to the emergence of new fungal pathogens, development of resistance to fluconazole, great efforts have been made to modify the chemical structure of fluconazole, in order to broaden its antifungal activity and increase its potency.<sup>9</sup>

Bile acid transporters have been shown to accept and carry a variety of drugs that are attached at different positions of bile acids. A common feature of bile acid derived antimicrobials is its potential to exhibit facially amphiphilic nature due to polar hydroxyl groups on one face and nonpolar hydrophobic methyl groups on the other face. Polyene macrolide amphotericin B, peptide antimicrobial agent polymixin B and squalamine in the cyclic form show such amphiphilicity and function as ionophores.<sup>10</sup>

Herein we designed bile acid- fluconazole conjugates (Scheme 6) in which one of the 1,2,4 triazole ring of fluconazole has been modified as substituted 1,2,3 triazole ring using click reaction.<sup>11</sup> In our approach to synthesize these new molecules **35-38** (Scheme 6) we considered performing click reaction to connect fluconazole part containing terminal alkyne **34** and bile acid containing azides **7, 8, 11, and 12** (Scheme 2).

Accordingly, we synthesized 2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)pent-4-yn-2-ol **34** by propargylation of the corresponding ketone **33** by using propargyl bromide and zinc dust to obtain racemic compound **34** (Scheme 6).



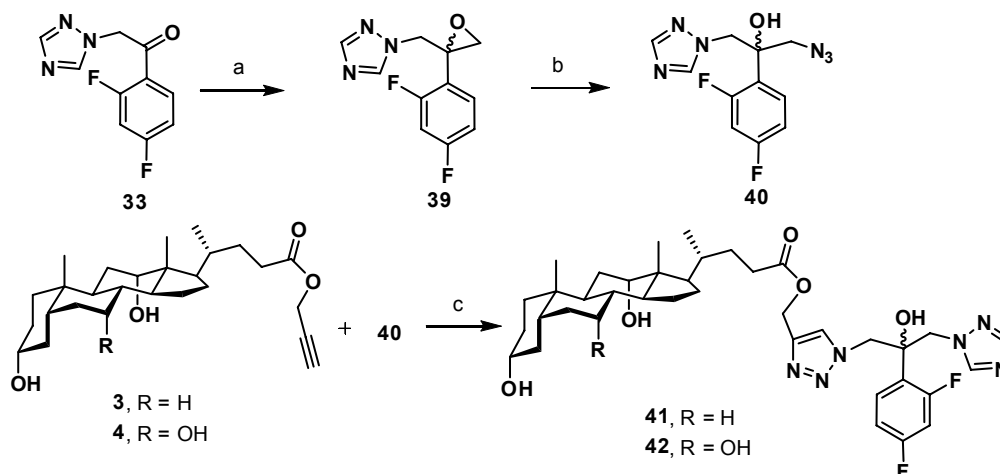
**Scheme 6:** Reagents and conditions: (a)  $\text{AlCl}_3$ , 1,2-dichloroethane, chloroacetyl chloride, 25 °C, 7 h; (b) 1,2,4-triazole,  $\text{NaHCO}_3$ , toluene, reflux, 4 h, (overall 55% in two steps); (c) Zn, Propargyl bromide, DMF/THF, 25 °C, 5 h, 95%; (d)  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (5 mol%), Sodium ascorbate (40 mol%), DMF:H<sub>2</sub>O (9:1), Microwave, 5 min, 90-95%.

Under microwave irradiation, compound **34** was reacted with C-24 azide **7** (Scheme 2) in DMF/H<sub>2</sub>O using catalytic amount of Cu(I) to give fluconazole-bile acid conjugate **35** as a diastereomeric mixture in 92% yield. We then extrapolated the ligation protocol successfully to other bile acid derived azides **8**, **11** and **12** (Scheme 2) and synthesized fluconazole-bile acid conjugates **36**, **37** and **38**.

The rationale for this drug design approach was based on the expectation that in these conjugates bile acid part would be useful to permeabilize the fungal cell membrane as well as transporter of the pharmacophore of fluconazole because of its amphiphilic nature and hence the conjugates were predicted to be more active than fluconazole itself. But all these fluconazole bile acid bioconjugates showed moderate antifungal activity against *Candida* species (MIC ranging from 3.12 to 6.25  $\mu\text{g/mL}$ ).

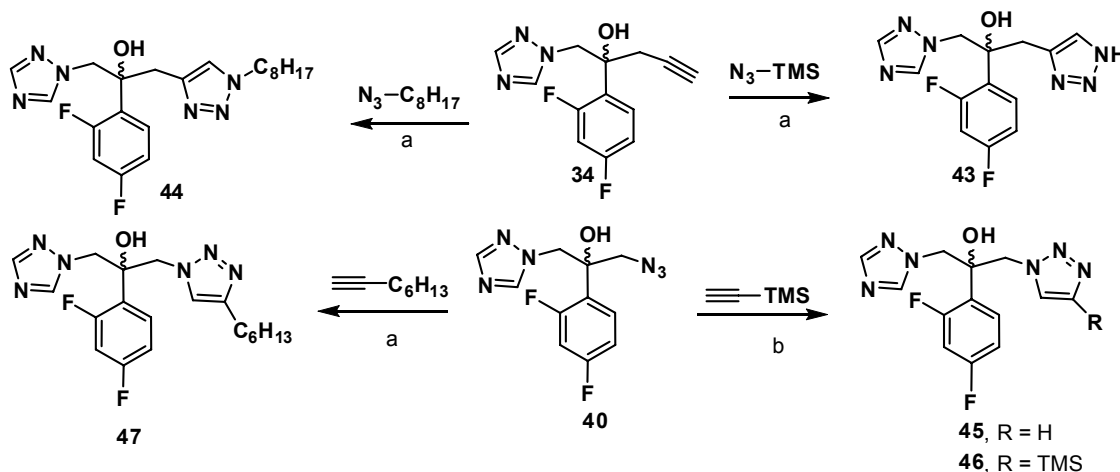
In order to find out the role of bile acid, we then synthesized two compounds **23** and **24** in which fluconazole part was attached with ester linkage. Accordingly, oxirane **39** was synthesized from the corresponding ketone **33** (Scheme 7). Opening of oxirane **39** with sodium azide gave racemic azido alcohol **40**. Microwave assisted copper catalyzed 1,3-dipolar cycloaddition of the azido alcohol **40** with propargyl esters **3** and **4** (Scheme 1), afforded diastereomeric mixture of compounds **41** and **42** in high yields. Compounds **41** and **42** showed much better antifungal activity against *Candida* species than

compounds **35-38**. We thought that ester functionality in these molecules may be hydrolyzing at physiological pH and the compounds having 1,4-substituted 1,2,3-triazole may be more active.



**Scheme 7:** Reagents and conditions: (a) Trimethylsulfoxonium iodide, NaH, DMSO-THF, rt, 2 h, 91%; (b) NaN<sub>3</sub>, DMF, 60-65 °C, 12 h, 75%; (c) CuSO<sub>4</sub>·5H<sub>2</sub>O (5 mol %), Sodium ascorbate (40 mol %), DMF:H<sub>2</sub>O (4:1), Microwave 10 min.

Encouraged by these biological results we synthesized fluconazole analogues containing monosubstituted (**43, 45**) and 1,4-disubstituted (**44, 46** and **47**) 1,2,3-triazoles from two common intermediates **34** and **40** as described in (Scheme 8) and studied their biological activity.



**Scheme 8:** Reagents and conditions: (a) CuSO<sub>4</sub>·5H<sub>2</sub>O (5 mol%), Sodium ascorbate (40 mol%), DMF:H<sub>2</sub>O (4:1), Microwave (245 W), 10 min; (b) CuSO<sub>4</sub>·5H<sub>2</sub>O (5 mol%), Sodium ascorbate (40 mol%), DMF:H<sub>2</sub>O (4:1), Microwave (175 W), 10 min.

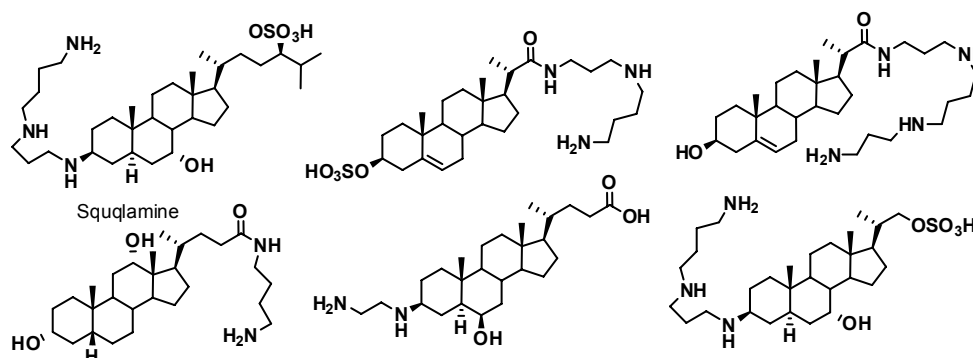
All these newly synthesized compounds were found to show good antifungal activity. From the biological data, it was observed that compounds **43** and **45** having monosubstituted 1,2,3-triazole ring which are isosteres of fluconazole and compound **46**

containing trimethylsilyl group, showed good *in vitro* antifungal activity against fungal pathogens *C. albicans*, *C. neoformans* and *S. schenckii*, which was comparable with fluconazole but these compounds were less active than amphotericin B and ketoconazole. 1,4-disubstituted 1,2,3-triazole compounds **44** and **47** with long alkyl chains showed very good antifungal activity against all the tested fungal pathogens. Compound **44** showed much better activity for *C. albicans* ( $IC_{50}$  0.001  $\mu\text{g/mL}$ ), *C. neoformans* ( $IC_{50}$  <0.006  $\mu\text{g/mL}$ ) and *C. parapsilosis* ( $IC_{50}$  0.002  $\mu\text{g/mL}$ ) as compared with fluconazole, amphotericin B and ketoconazole, while compound **47** was found to be less active than compound **44** but showed better activity against *C. albicans* ( $IC_{50}$  0.018  $\mu\text{g/mL}$ ), *C. neoformans* ( $IC_{50}$  <0.01  $\mu\text{g/mL}$ ) and *C. parapsilosis* ( $IC_{50}$  0.043  $\mu\text{g/mL}$ ) as compared with fluconazole and amphotericin B. Hence the lead compounds **44** and **47** were tested for *in vivo* activity against *C. albicans* intravenous challenge in Swiss mice. Antiproliferative activities of these molecules were tested against human hepatocellular carcinoma Hep 3B and human epithelial carcinoma A431 cell lines.

## Section II: Synthesis and bioevaluation of bile acid based amino alcohols.

### Introduction

The medicinal chemistry of steroids covers a large and interesting series of structures and biological activities.<sup>12</sup> Although the number of steroidal natural products is limited, millions of hybrids steroid conjugates can be prepared. This new approach seems to be very promising in the development of lead molecule. The sterol-polyamine conjugates as a new class of antibiotics have attracted much interest in recent years. Squalamine is the first sterol-polyamine conjugate having broad spectrum antimicrobial activity. Due to the low availability of squalamine from natural resources, several groups are working on the synthesis of squalamine and its analogs (Figure 4).

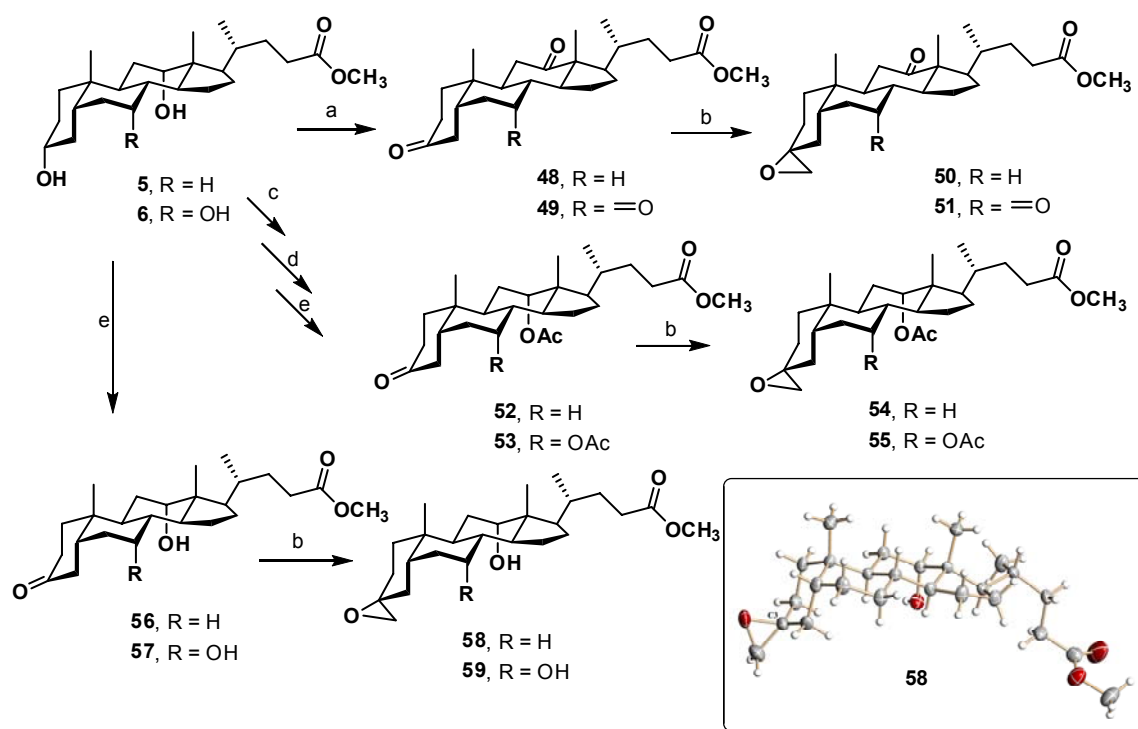


**Figure 4:** Sterol-polyamine conjugates.

Some of the analogues show better activity than squalamine.<sup>13</sup>

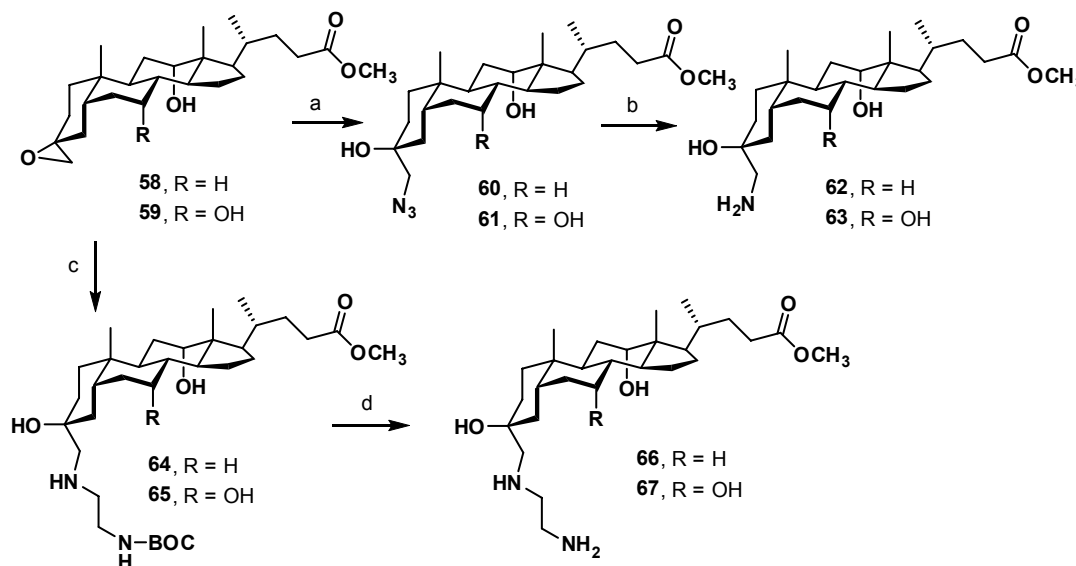
Variations in the structure of the analogues led to changes in the spectrum of activity against variety of bacteria and yeasts. From the literature studies it is observed that three common elements are required for their characteristic activity (i) long and rigid hydrophobic unit; (ii) a flexible hydrophilic chain which is linked to hydrophobic unit; (iii) a pendant polar head group. The precise structure of the polyamine is not important. The sulfate groups can be replaced by a carboxylate or hydroxyl or even removed altogether. The structure of the rigid hydrophobic unit i.e. steroid can also be varied.

In our approach we synthesized new steroidal amino alcohol having short linker at C-3 position of bile acids. For this synthesis C-3 oxiranes **50** and **51** were the key intermediates. These oxiranes were prepared from methyl esters **5** and **6** of bile acids (Scheme 2) by oxidation followed and regioselective epoxidation using dimethylsulfonium methylide to obtain oxiranes **50** and **51** (Scheme 9). Stereochemistry at C-3 was assigned by <sup>1</sup>H-NMR studies of oxiranes **50**, **51**, **54**, **55** and confirmed by single crystal X-ray of compound **58**.



**Scheme 9:** Reagents and conditions: (a) CrO<sub>3</sub>, H<sub>2</sub>SO<sub>4</sub>, acetone, 0-10 °C, 10 min; (b) Trimethyl sulphoxonium iodide, NaH, DMSO-THF, rt, 2 h; (c) Ac<sub>2</sub>O, DMAP, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 25-28 °C, 24 h; (d) K<sub>2</sub>CO<sub>3</sub>, MeOH, 3 h; (e) Ag<sub>2</sub>CO<sub>3</sub>, toluene, reflux, 5 h.

Opening of oxiranes **58** and **59** with sodium azide (Scheme 10) gave azido alcohols which on further hydrogenation on Pd-C gave amino alcohols **62** and **63**. Ethylene diamine derivatives **66** and **67** were synthesized by opening of oxiranes with N1-(Boc)-1,2-diaminoethane followed by deprotection. These new molecules containing amino alcohols with a small linker at C-3 are under biological evaluation.



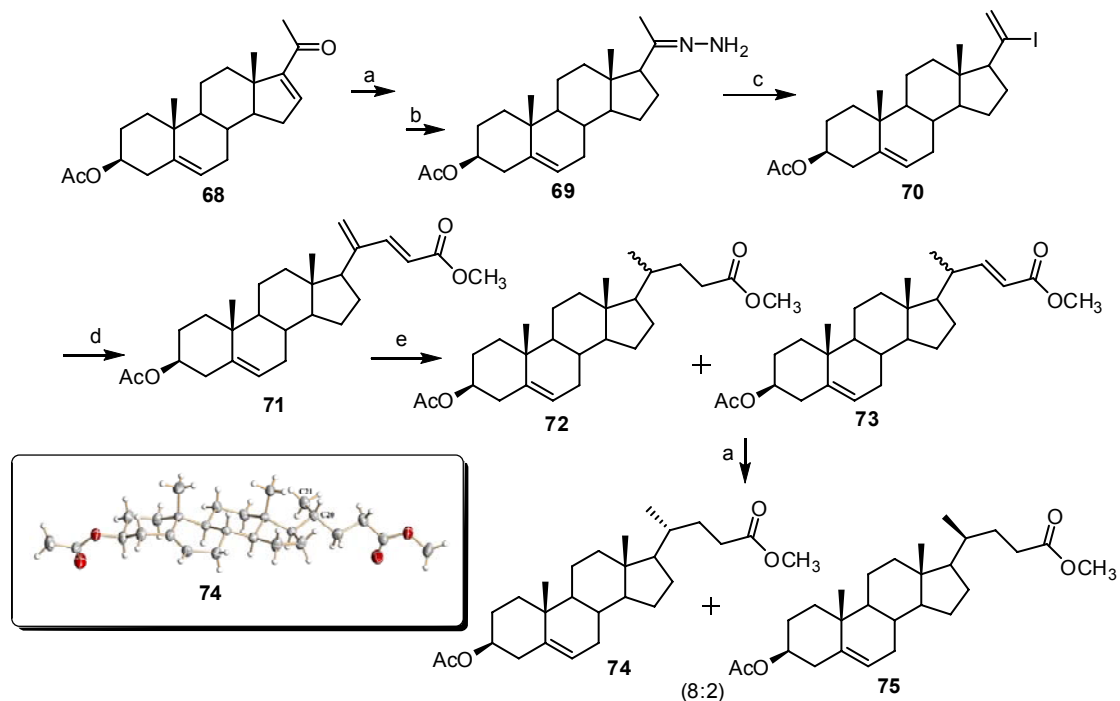
**Scheme 10:** Reagents and conditions: (a)  $\text{NaN}_3$ , DMF, 60-65 °C, 12 h; (b)  $\text{H}_2$  / Pd-C, MeOH; (c) N1-(Boc)-1,2-diaminoethane, MeOH reflux 2 h; (d) 50% TFA/ $\text{CH}_2\text{Cl}_2$ .

### Chapter 3: Stereoselective synthesis of steroidal side chain from 16-dehydropregalone acetate

#### Introduction

Steroid is a large class of natural products and widely distributed in animals and plants. A wide variety of steroids are known having modified side chains and is attached to the tetracyclic rigid unit at C-17 with both natural C-20(R) and unnatural C-20(S) stereochemistry.<sup>14</sup> The introduction of steroid side chain onto tetracyclic steroidal starting material to yield product with the natural C-20(R) configuration has been the subject of investigation by several research groups.<sup>15</sup> There are several reports for the stereoselective side chain synthesis at C-20 using ene reaction, catalytic hydrogenation, deoxygenation, Wittig rearrangement, aldol condensation, Michel addition, sigmatropic rearrangement and also using organometallic reagents such as organocopper, organoborane, organopalladium, organozirconium, organoruthenium reagent. In this chapter we report a short stereoselective synthesis of cholanic acid derivative starting from commercially available C-20 oxo steroid 16-dehydropregalone acetate (16-DPA) **68** (Scheme 11). Palladium catalyzed carbon-

carbon bond forming Heck reaction between C-20 vinyl iodide **70** with methyl acrylate to form unsaturated compound **71** and transfer hydrogenation with triethylsilane and Pd/C are the key steps for stereoselective side chain synthesis.



**Scheme 11:** Reagent and condition: (a) 10% Pd/C, H<sub>2</sub>, EtOAc, 45 psi, 25-30 °C, 12 h, 98%; (b) Hydrazine hydrate, NEt<sub>3</sub>, MeOH, 25-30 °C; (c) I<sub>2</sub>, NEt<sub>3</sub>, THF, 25-30 °C; (d) Pd(OAc)<sub>2</sub> (0.04%), K<sub>2</sub>CO<sub>3</sub>, methyl acrylate, DMF, 25-30 °C, 12 h; (e) 10-20% Pd-C (by weight), MeOH, triethylsilane (excess), 10-20 min.

Chemoselective catalytic hydrogenation of compound **68** with 10% Pd-C in ethyl acetate followed by reaction with hydrazine hydrate afforded C-20 hydrazone **69**. Oxidation of hydrazone **69** with iodine in the presence of organic base gave vinyl iodide **70** in good yield. Heck coupling of vinyl iodide **70** with methyl acrylate, afforded unsaturated carbonyl compound **71**. There are some reports for the reduction of C-20(21) or C-20(22) double bond by using different catalysts such as PtO<sub>2</sub>, (Ph<sub>3</sub>P)<sub>3</sub> RhCl with less selectivity at C-20. Pd-Carbon induced catalytic transfer hydrogenation with triethylsilane of compound **71** afforded compounds **72** and **73** as an epimeric mixture at C-20. Hydrogenation of this mixture using H<sub>2</sub>/Pd-C in ethylacetate gave a mixture of compounds **74** and **75** in 8:2 ratio. On crystallization in methanol:dichloromethane (9:1) gave pure cholanic acid derivative **74**. The stereochemistry of compound **74** at C-20(R) was confirmed by single crystal X-ray. Cholanic acid is a key intermediate for the synthesis of large number of biologically active steroids having natural C-20(R) configuration.

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