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Synthesis of cholest-5-en-3-ol(3β)-3-[4-(2,2,2-trifluoroacetamido) benzoate] (ChTfAB) a thermotropic liquid crystalline material

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The synthesis of cholest-5-en-3-ol(3β)-3-[4-(2,2,2-trifluoroacetamido)benzoate] (ChTfAB) is carried out by esterification of cholesterol and *p*-nitrobenzoic acid using DCC, DMAP, followed by reduction of nitro group using $SnCl_2$. The so formed amino group is further N-acylated using trifluoroacetic anhydride. The newly synthesized compound is characterized using IR and ^{1}H NMR spectroscopic techniques. Its mesomorphic properties have been investigated using Differential Scanning Colorimetry (DSC) and Polarising Optical Microscopy (POM). The thermal and phase behaviour studies reveal the synthesized compound to be an enantiotropic, thermotropic liquid crystal. This synthesized compound overcomes the problem of degrading at the melting temperature associated with one of the previously synthesized and reported steroidal compound.

Keywords: DCC, DMAP, DSC, POM, Thermotropic, Cholesteric, Liquid Crystal

The Australian botanist, Friedrich Reinitzer, in 1888, while confirming the structure of cholesterol by preparing its benzoate derivatives, observed two distinct melting points for cholesteryl benzoate[1,2]. This phenomenon was further studied by Otto Lehmann in 1889 and he coined the term "Liquid Crystal"[3]. Liquid crystals are known as the fourth state of matter that exhibit phases, which has the intermediate properties of those between the crystalline solid and liquid. The molecules in solid state are highly ordered. However, in liquid state this ordering is lost. Liquid crystals can be compared to have order similar to solids and the fluid like nature of liquids. As they possess characteristic of both crystal and liquid, they are termed as liquid crystal.

Thermotropic liquid crystals are temperature dependent liquid crystals; they exhibit variety of phases with the change in temperature. At high temperature, the thermal motion destroys the ordering of the liquid crystal phase and transforms the solid into an isotropic liquid phase. For a liquid crystalline compound, the liquid crystal phase is displayed either by cooling an isotropic liquid below its clearing point or by heating a solid crystal above its melting point. The thermotropic liquid crystals are of two types namely, Enantiotropic and Monotropic. If the liquid crystalline phase is achieved reversibly either by heating or cooling, it is termed as Enantiotropic. The Monotropic phase is irreversibly achieved only while cooling the isotropic liquid[4,5]. These liquid crystalline compounds may exhibit one of the Nematic, Smectic, Cholesteric, *etc*., phase or it might exhibit more than one phases. The cholesteric phases are observed by cholesterol based compounds. The term cholesteric phase refers to chiral nematic phases. Out of these known phases theNematic (N) phase is simplest thermotropic mesogenic phase. In this type of phases the molecules looses the positional order but maintains an orientational[6,7]. Originally, the research in this area was motivated by the desire to understand the behavior of this interesting state of matter. Moreover, the recent research is motivated by

applications of these materials which have led to significant invention and technological developments. Mesogenic materials are largely influencing the recent advance technology due to their magnificent phase transformations[8,9].

The recent developments are also extended towards the interface of nanomaterial chirality and mesogenic compound[10]. Today, even after over a century from its discovery the interesting state of matter is able to keep researchers attracted and interested in its investigation. This interest is mainly due to its varied known and some yet to be known applications. T. Thiemann and V. Vill in1997, highlighted the importance of the steroids as source for generation of chiral mesophases. They provided exhaustive list of steroidal derivatives with their melting behavior and mesomorphic properties[11]. Selective cholesteric ester with varying functional groups at different positions have been analyzed for their thermal stability[12]. Synthesis and mesomorphic properties of similar compounds like cholesteryl-4-(alkanoyl-amino) benzoates are been reported[13]. Steroid based series of fluorine containing liquid crystalline compounds were synthesized and their mesomorphic properties wereknown to be investigated. The Cholesteryl esters having fluorinated terminal chains are been synthesized and reported to exhibit mesomorphism[14]. Series of aromatic cholesteryl derivatives ranging from ethers, esters, phenyl carbonates and benzyl carbonates were prepared and investigated for liquid crystalline phases including the cholesteric phase[15]. The mesomorphic properties of compounds derived from bioactive natural sterols have also been reported[16]. The physiochemical properties of fluorine based mesogenic compounds, and the effect of position and the number of fluorine atom as substituent have been reported by Shiyan Li *et al.*[17] Literature studies revealed that presence of fluorine tends to increase the probability of the compound to exhibit liquid crystalline phase. Some parameters of commonly used substituents like fluorine are been highlighted[18-20]. Mesomorphism of fluoro substituted organic compound can be attributed to the various advantageous properties of fluorine[21–30]. Some of the fascinating and interesting properties of organofluorine compounds are been discussed in detail by M. Hird in 2007. Wherein, incorporation of fluorine into previously known liquid crystalline molecules is known to have some subtle, yet significant, influence to their physical properties including melting point. This is mainly due to strength of the carbon-fluorine bond that provides increased stability to the molecule[31].

Apreutesei *et al*., in 2006, investigated thermostability of certain cholesteric ester. Out of these the Cholesteryl 4-amino benzoate synthesized although liquid crystalline was found to undergo degradation at melting temperature[12]. Taking clue from the above reports and the comparative studies based on the measurable parameters like polarity and size[18-20]. It has prompted to consider the advantageous strategy to incorporate fluorine and synthesis the steroid based organofluorine compound. The synthesis of compound (V) (ChTfAB) was planned by incorporating fluorine atom in the form of 2,2,2trifluoroacetamido group in steroidal moiety. As this group contained three fluorine atoms, makes it ideal candidate to be used for generating mesomorphic properties. Furthermore, this synthesis might also overcome the decomposition problem associated with cholesteryl 4-amino benzoate. Fluorinated compounds are known for exerting control over mesomorphism and thermal stability of liquid crystalline materials. Now, as it is clear that fluorine containing group play significant role in formation of liquid crystalline material. This fact has been explored and it has led to the benefit of synthesizing fluorinated steroidal compound *i.e*., synthesis of (ChTfAB).

Experimental Section

Materials and Methods

All the required chemicals and solvents were procured from Sigma-Aldrich India and used as received without any purification. Dichloromethane (DCM) was dried using calcium hydride. All reactions were carried out using hot air dried glassware and under inert atmosphere unless otherwise specified. ^{1}H NMR (300 MHz)spectrums were recorded on Bruker AVANCE spectrometer (Bruker BioSpin AG, Fällanden, Switzerland; 300 MHz) using $CDCl_3$ (δ 7.26 for 1H) as solvent and TMS as an internal standard. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The peak multiplicities were given as follows s = singlet; d = doublet; dd = doublet of doublet; t = triplet; m = multiplet. Silica gel of commercial source (60–120mesh) was used in column chromatography. Infrared spectra were recorded on a Perkin Elmer (Model – Frontier) spectrometer (Waltham, MA, USA). Transition temperatures were

investigated by DSC analysis (Mettler-Toledo AG Analytical, Schwerzenbach, Switzerland) under a nitrogen atmosphere, with samples measured in closed-lid aluminium pans and POM using Mettler Toledo FP90 heating stage containing temperature control unit in conjunction with a Carl Zeiss polarizing optical microscope (Carl Zeiss MicroImaging GmbH, Koenigsallee, Goettingen, Germany). The mesophase type was assigned by visual comparison (under the microscope) with known standardmesogenic phases.

Synthesis of cholest-5-en-3-ol(3β)-3-[4-(2,2,2-trifluoroacetamido) benzoate] (ChTfAB)

Synthesis of cholest-5-en-3-ol(3β)-3-[4-(2,2,2-trifluoroacetamido) benzoate] (ChTfAB) is depicted in Scheme 1.

Preparation of cholest-5-en-3-ol(3β)-3-(4-nitrobenzoate)

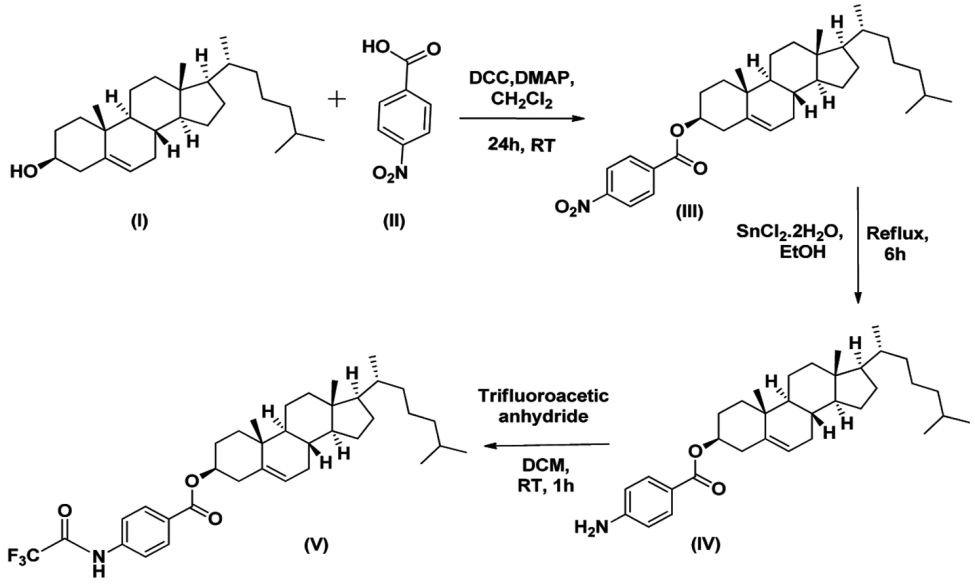
4-nitrobenzoic acid (5.0 g, 29.94 mmol) and cholesterol (11.57 g, 29.94 mmol) were added in anhydrous CH_2Cl_2 (100 mL). Add DMAP in catalytic amount, along with DCC (6.79g, 32.93 mmol) under constant stirring. DCU was filtered off after 24h and the solution was concentrated. The solid residue was purified on silica gel (60-120mesh) using column chromatography to yield pure cholest-5-en-3-ol (3β)-3-(4-nitrobenzoate) as white solid. (12.67 g, yield: 79%), m.p. (liquid crystal 179°C (K/Ch); 264°C (Ch/I))[12]. liquid crystal 179°C(K/Ch); 264°C(Ch/I)). The IR, ^{1}H NMR spectral data of this compound was also in agreement with the reported data.

Preparation of cholest-5-en-3-ol(3β)-3-(4-aminobenzoate)

In 100 mL ethanol, (2.0 g, 3.73 mmol) Cholest-5-en-3-ol (3β)-, 3-(4-nitrobenzoate) and (6.73g, 29.84 mmol) of $SnCl_2.2H_2O$ were refluxed for 6 h. After cooling, the mixture was poured into crushed ice. By using a 5% NaOH solution the *p*H of mixture was adjusted between 7-8 solution. The reaction mixture was extracted using dichloromethane (DCM), washed several times with water and dried over anhydrous $MgSO_4$. After solvent removal, the white solid was purified by column chromarography (silica gel (60-120) 3:1 dichloromethane: hexane) to afford Cholest-5-en-3-ol (3β)-3-(4-aminobenzoate).(12.67g, yield: 79%), m.p. (liquid crystal 241°C (K/Ch), this product undergoes decomposition when heated till melting temperature[12]. The IR, ^{1}H NMR spectral data of this compound was also in agreement with the reported data.

Synthesis of (ChTfAB)

Cholest-5-en-3-ol(3β)-3-(4-aminobenzoate). was acylated by treating the reduction product obtained in step two with trifluoroacetic anhydride in dichloromethane at RT for 1 hour. After the completion of reaction the acid was neutralized by adding sat. $NaHCO_3$ solution. The mixture was extracted with dichloromethane, washed several times with water and dried over anhydrous $MgSO_4$. After removal of solvent, the solid obtained was purified by column chromarography (Silica 60-120, hexane) to afford white solid of (ChTfAB) (yield: 79%), m.p. 225°C.



Scheme 1 — Synthesis of Cholest-5-en-3-ol(3β)-3- [4-(2,2,2-trifluoroacetamido) benzoate](ChTfAB)

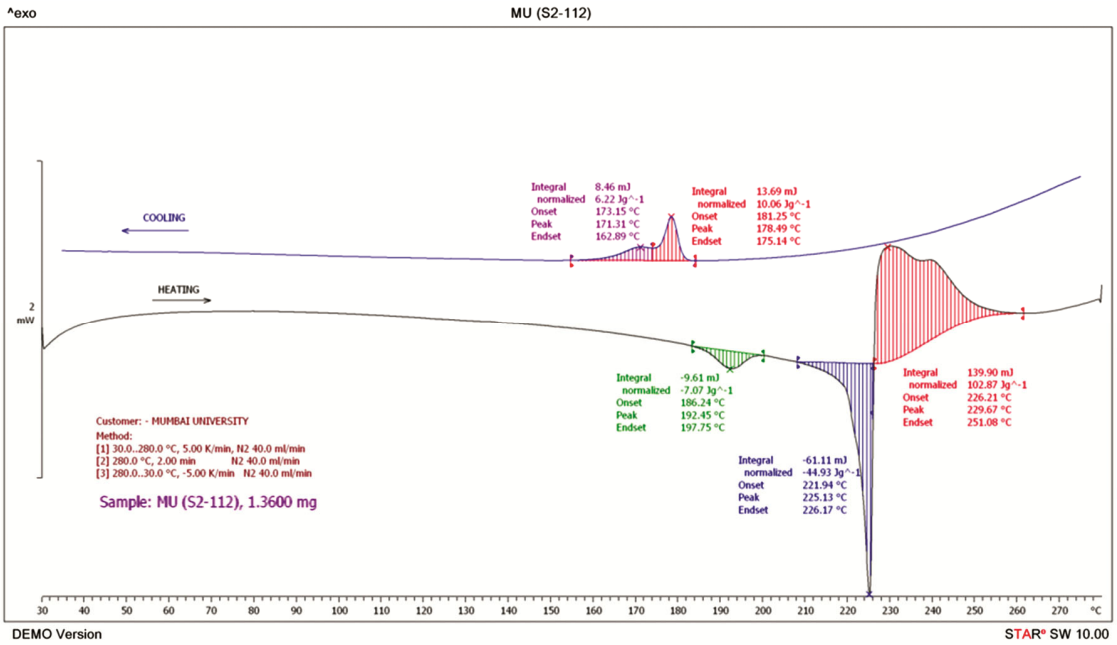


Fig. 1 — DSC Thermogram of compound (V) (ChTfAB

Characterization

Elemental analysis of this compound agreed with the molecular formula required for the compound (V)(ChTfAB). Further characterization was carried out by recording the spectral data. The spectral data for the above compound V:

IR: 3321.16 (N-H of amide), 2845.08 (C-H), 2678.52 (C-H),1713.48 (C=O of ester), 1682.65 (C=O of amide), 1600.59, 1542.99 (C=C), 1186.49 cm^{-1} (C-O ester); ^1H NMR ($CDCl_3$): δ 8.203 (bs, 1H, -NH), 8.096-7.665 (dd, 4H, Ar-H), 5.425 (d, 1H, *J* = 3.0 Hz, olefinic-H), 4.882 (m, 1H, O-CH proton), 2.479-0.886 (m, 43H, -aliphatic protons).

Thermal investigation (Liquid crystalline properties and Phase Behavior)

The thermal and phase behavior property of the compound (V)was investigated by using Polarizing Optical Microscopy (POM)and Differential Scanning Calorimetry (DSC) (Fig. 1). Both DSC and POM study confirmed the mesomorphic nature of compound (V). POM study confirmed the formation of Cholesteric phase for compound (V) during heating (Fig. 2). and during cooling (Fig. 3). The details of the transition temperature data, phase behavior along with enthalpy change ΔH (J g^{-1}) compound (V) is displayed in Table 1.

Results and Discussion

Elemental analysis of this compound agreed with the molecular formula required for the compound and based on the spectroscopic evidences, the compound with m.p. (Liquid Crystal Cr/N 192°C, N/I 225°C) was assigned the structure as Cholest-5-en-3-ol(3β)-3-[4-(2,2,2-trifluoroacetamido)benzoate]. The results obtained after the investigation of liquid crystalline properties revealed that the newly synthesized compound not only was stable at isotropic temperature but also had lower melting temperature compared to compound (IV). Enantiotropic, thermotropic liquid crystalline behavior was confirmed by DSC and POM.

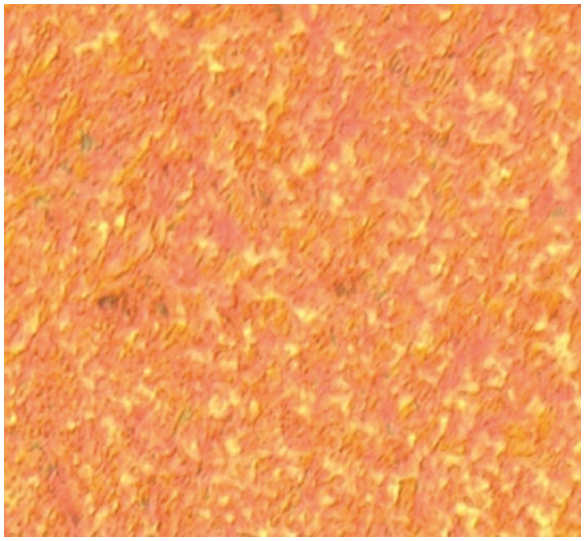


Fig. 2 — Thermal optical micrographof the texture(Cholesteric phase) displayed by compound (V) (ChTfAB)captured at 195°C while heating

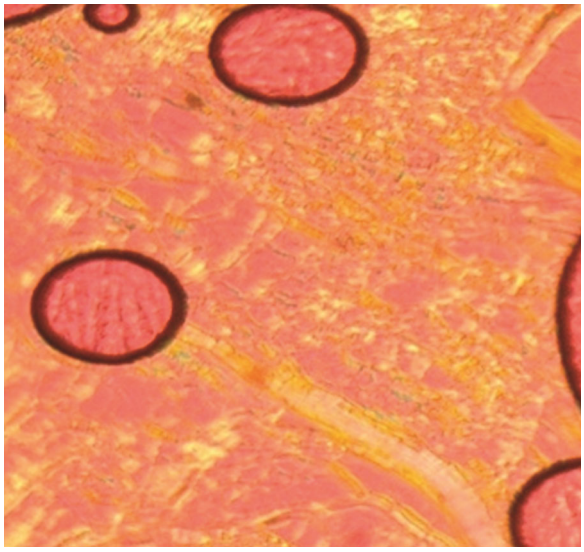


Fig. 3 — Thermal optical micrograph of the texture (Cholesteric phase)displayed by compound (V)(ChTfAB)captured at 177°C while cooling

Table 1 — Transition temperature data of compound (V)(ChTfAB)

Compd V	Transition	Temperature (°C)	ΔH (J g^{-1})
(ChTfAB)	Cr→N*	192	6.22
	N*→I	225	20.06

Cr = Crystal, N*= Cholesteric phase, I = Isotropic liquid

Conclusion

Incorporation of fluorine in the form of 2,2,2-trifluoroacetamide on the cholesterol benzoate derivative led to successful synthesis of (ChTfAB)as aliquid crystalline compound. Though, the liquid crystalline properties and phase behavior analysis of compound (IV) were previously reported. The compound (IV) had demerit of under going decomposition at isotropic temperature. Due to that the use and the characterization of liquid crystalline property while cooling cycle was not possible. The compound (V) (ChTfAB) is synthesized by trifluoro acylation of compound (IV) and it was found to stable as it did not decompose even when heated to or beyond the isotropic temperature. Furthermore the newly synthesized compound had help in lowering of the melting point compared to compound (IV). This newly synthesized compound on thermal analysis and phase behavior investigation revealed it to be enantiotropic, thermotropic liquid crystalline material. This newly synthesized (ChTfAB) have stable cholesteric phase as commonly exhibited by cholesterol derivatives. Thus, the synthesis of (ChTfAB) and its mesomorphic studies has again highlighted the importance of incorporating fluorine for generation of the necesssarymesogenic characteristics into the organic compounds.

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Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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