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Synthesis and Mesomorphic Properties of 3, 5-disubstituted -4,5-dihydroisoxazole Derivatives

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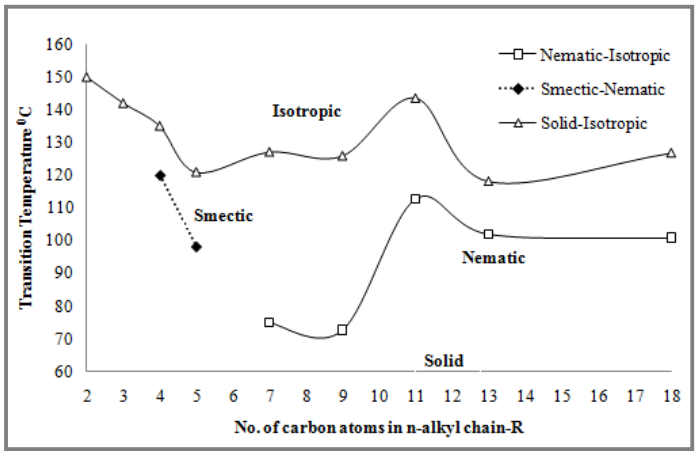
ABSTRACT

It reported that the synthesis and evaluation of thermal behavior of a new homologous series of 4,5-dihydroisoxazole based liquid crystalline compounds. The flexibility in these systems is provided by attaching straight chain saturated aliphatic carboxylic acids, RCOOH ($R=C_nH_{2n+1}$) where, n=2-5, 7, 9, 11, 13, 17. The synthesized compounds were analyzed on the basis of mass, IR and NMR spectroscopy. The melting points, transition temperatures and mesophase morphologies were determined mainly by polarizing optical microscopy (POM) in conjunction with a hot stage and by differential scanning calorimetry (DSC).

Graphical Abstract



Plot of transition temperature against the number of carbon atoms in the n-alkoxy chains for **3(a-i)**

Keywords: Mesophases, Heterocycles, Enantiotropy, Chalcone.

INTRODUCTION

In the field of materials, the construction of isoxazoline rings forms an important class of molecular platform for the synthesis of smart molecules. Daniel Vorlander used isoxazoline as a structural molecular element of liquid crystals (LCs) nearly a century ago [**1**]. Further isoxazoline derivatives exhibit a wide spectrum of pharmacological activities [**2-4**] and are key precursors for different natural products [**5-6**]. A wide variety of mesogenic compounds containing five-membered heterocycles have been synthesized to date [**7-10**]. Among them 3,5-diaryl isoxazoles forms an important class of liquid crystalline materials [**11-15**]. Cyclocondensation of chalcone with hydroxyl amine hydrochloride offer a simple one-step route for the synthesis of isoxazolines which forms a synthetically versatile intermediates which readily undergo transformations such as dehydrogenation to isoxazoles, alkylation and reductive cleavage to functionalities such as α,β-unsaturated ketones, β-hydroxy ketones, β-amino acids or γ-amino alcohols.

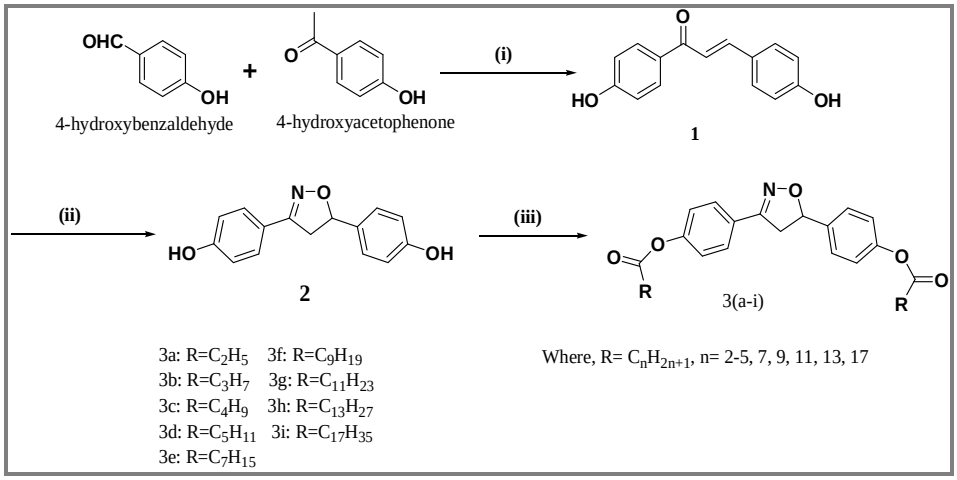
Literature studies showed that the introduction of an isoxazoline ring flanked by aromatic rings at C_3 and C_5 positions in the heterocyclic ring can exhibit LC properties and their study is an excellent opportunity to establish the relationship between molecular structure and mesomorphic behavior and as useful intermediates in the field of LC [**16**]. Further the molecular topology of the isoxazoline ring can guide liquid-crystalline parameters as a template for materials with potential technological applications. Based upon the considerations discussed above, herein, we describe the preparation of a new homologous series of 3,5-disubstituted isoxazoline derivatives by a convenient and simple practical route for the study of their liquid crystalline behavior. Synthesis involves the condensation of chalcone and hydroxylamine hydrochloride to form isoxazoline derivative which was carried for esterification further with different saturated fatty acids using *N,N′*-Dicyclohexylcarbodiimide which overall involves simple and easy work up procedures to synthesize a low molar mass and non-polymer liquid crystalline materials.

MATERIALS AND METHODS

(a) Procedure for the synthesis of (E)-1,3-bis(4-hydroxyphenyl)prop-2-en-1-one (1): The most common procedure to synthesize α, β-unsaturated ketone is the classic Claisen-Schimdt reaction by a well established method [**17**]. Synthesis involves the condensation of 4 hydroxybenzaldehyde (1 mmol) with an 4-hydroxyacetophenone (1 mmol) in ethanol and the reaction mixture was maintained in a cold water bath. 10 mL of 50% NaOH solution was added dropwise and the whole reaction mixture was stirred for 14 h at 60-70°C. After the completion of the reaction, the whole reaction mixture was cooled, water was added and the mixture was neutralized with 10% HCl. The crude residue was extracted with ethyl acetate and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The product 1,3-bis(4-hydroxyphenyl) prop-2-en-1-one (1), a chalcone obtained was purified by column chromatography using silica gel (60-120 mesh)**.** Yield**:** 55%.

Procedure for the synthesis of 4,4'-(4,5-dihydroisoxazole-3,5-diyl)diphenol (2): Mixture of the synthesized chalcone **1** (1 mmol), hydroxylamine hydrochloride (3 mmol) and sodium acetate (3 mmol) in methanol was refluxed at 50-55°C for 8 h. The crude product obtained was purified by column chromatography using silica gel (60-120 mesh) to get the 4,5 dihydroisoxazole (**2**). Yield: 72%

General procedure for esterification (3a-3i): Mixture of synthesized isoxazoline (1 mmol), *N, N′*-Dicyclohexylcarbodiimide (2 mmol) and fatty acids (2 mmol) in dichloromethane was stirred at room temperature for 5h to obtain a long chain esters (Scheme 1). All the synthesized compounds were purified by column chromatography using silica gel (60-120 mesh) until constant transition temperature was obtained to get the **3a-3i** series. Yield: 70-83%.



Reagents and conditions: **i)** NaOH, EtOH, 14hr 60-70°C **ii)** $NH_2OH.HCl$, CH_3COONa, MeOH, 8h, 50-55ºC **iii)** DCC, RCOOH, DCM, rt, 5 h

Scheme 1. Procedure for esterification.

Synthetic route for 3,5-disubstituted-4,5-dihydroisoxazole derivatives

Characterization: All the common reagents procured from commercial supplies were used as such without any purification. The solvents were of analytical grade and were used without further purification. All the reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 (Merck 60F254, 0.25 mm thickness) and visualization under UV light. Melting points were recorded on SELACO melting point apparatus. For few representative compounds, IR spectra in the spectral range of 400-4000 cm^{-1} were recorded on Shimadzu FT-IR model 8300 spectrophotometers, ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) was recorded using Agilent-NMR using $CDCl_3$ and the chemical shifts are recorded in ppm relative to TMS as an internal standard. Mass spectral analysis was registered in a mass spectrometer of Synapt G2 HDMS. The liquid crystalline properties, melting temperatures and transition temperatures were determined by using optical polarizing microscope in conjunction with LTS 420 Lincam hot stage of Olympus BX51 model. The mesophase type was determined by comparing the observed texture with the corresponding standards [**18**]. Samples were prepared as thin films between a glass slide and a glass cover slip. Transition temperatures and associated enthalpies were determined by differential scanning calorimetry (DSC), using DSC Mettler TA 4000 at a scanning rate of 10ºC min^{-1} with a controlled cooling accessory. The purity of the compounds was further confirmed by elemental analysis using Perkin CHN analyzer.

Spectral data

4,5-dihydroisoxazol-3,5-diylbis(4,1-phenylene)dipropionate (3a): ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.87(t, $-CH_3$, 6H), 1.39(m, $-CH_2$, 4H), 1.44 (m, $-CH_2$, 4H), 3.28(dd, 1H), 3.75(dd, 1H), 5.75 (dd, 1H), 7.06(d,ArH,2H), 7.13(d,ArH, 2H), 7.39(d, ArH, 2H), 7.69(d, ArH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 9.4, 27.3, 42.0, 84.8, 121.7, 126.5, 127.1, 128.3, 139.2, 150.0, 156.5, 172.3. LCMS: 368.31 $[M+H]^+$. Elemental Analysis (%): Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81 found C, 68.60; H, 5.69; N, 3.78. Yield: 89%.

4,5-dihydroisoxazol-3,5-diylbis(4,1-phenylene)dibutyrate (3b): ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.88(t, $-CH_3$, 6H), 1.68(m, $-CH_2$, 4H), 2.52 (m, $-CH_2$, 4H), 3.24(dd, 1H), 3.73 (dd,1H), 5.72 (dd, 1H), 7.06 (d, ArH, 2H), 7.13(d, ArH,2H), 7.43(d, ArH, 2H), 7.87(d,ArH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.5, 18.4, 35.7, 84.8, 121.7, 127.2, 139.2, 150.1, 156.0, 172.4. LCMS: 396.54 $[M+H]^+$. Elemental Analysis (%): Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54 found C, 69.90; H, 6.40; N, 3.51. Yield: 85%.

4,5-dihydroisoxazol-3,5-diylbis(4,1-phenylene) dipentanoate (3c): ^{1}H NMR ($CDCl_3$,400 MHz) δ: 0.88(t, 6H), 1.39(m, -CH_2, 8H), 1.74 (m, -CH_2, 4H), 3.28(dd, 1H), 3.75(dd, 1H), 5.75(dd, 1H), 7.06(d, ArH, 2H), 7.13(d, ArH, 2H), 7.39(d, ArH, 2H), 7.69(d, ArH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 22.1, 27.2, 33.2, 42.0, 84.0, 121.8, 126.4, 127.2, 139.2, 150.0, 156.2, 172.3. LCMS: 424.54 $[M+H]^+$. Elemental Analysis (%): Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31 found C, 70.92; H, 6.40; N, 3.38. Yield: 84%.

4,5-dihydroisoxazol-3,5-diylbis(4,1-phenylene) dihexanoate (3d): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88(t, 6H), 1.29(m, -CH_2, 8H), 1.52 (m, -CH_2, 4H), 2.30 (m, -CH_2, 4H), 3.28 (dd, 1H), 3.75 (dd, 1H), 5.75(dd, 1H), 7.06(d, ArH, 2H), 7.13(d, ArH, 2H), 7.39(d, ArH2H), 7.69 (d, ArH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 22.4, 24.7, 33.5, 42.1, 84.8, 121.8, 126.4, 127.1, 128.1, 139.2, 150.0, 156.5, 172.3. LCMS: 452.55 $[M+H]^+$. Elemental Analysis (%): Calcd for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10 found C, 71.85; H, 7.35; N, 3.18. Yield: 84%.

4,5-dihydroisoxazol-3,5-diylbis(4,1-phenylene) dioctanoate (3e): ^{1}H NMR($CDCl_3$, 400 MHz) δ: 0.88(t, 6H), 1.29(m, -CH_2, 16H), 1.52 (m, -CH_2, 4H), 2.30 (m, -CH_2, 4H), 3.27(dd, 1H), 3.70 (dd, 1H), 5.68(dd, 1H), 7.04(d, ArH, 2H), 7.17(d,ArH,2H), 7.42(d, ArH, 2H), 7.72 (d, ArH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 22.7, 24.7, 25.0, 29.0, 31.8, 33.5, 42.1, 84.8, 121.8, 126.4, 127.1, 128.1, 139.2, 150.0, 156.5, 172.3. LCMS: 508.74 $[M+H]^+$. Elemental Analysis (%): Calcd for $C_{31}H_{41}NO_5$: C, 73.34; H, 8.14; N, 2.76 found C, 73.38; H, 8.10; N, 2.68. Yield: 80%.

4,5-dihydroisoxazol-3,5-diylbis(4,1-phenylene) bis(decanoate) (3f): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88(t, 6H), 1.29 (m, -CH_2, 16H), 1.52 (m, -CH_2, 4H), 2.30 (m, -CH_2, 4H), 3.27(dd, 1H), 3.70 (dd, 1H), 5.68(dd, 1H), 7.04(d, ArH, 2H), 7.17(d, ArH, 2H), 7.42(d, ArH, 2H), 7.72(d, ArH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 22.7, 24.7, 25.0, 29.0, 31.8, 33.5, 42.1, 84.8, 121.8, 126.4, 127.1, 128.1, 139.2, 150.0, 156.5, 172.3. LCMS: 564.67 $[M+H]^+$. Elemental Analysis (%): Calcd for $C_{35}H_{49}NO_5$: C, 74.57; H, 8.76; N, 2.48 found C, 74.67; H, 8.66; N, 2.35. Yield: 78%.

4,5-dihydroisoxazol-3,5-diylbis(4,1-phenylene) didodecanoate (3g): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88(t, 6H), 1.29(m, -CH_2, 28H), 1.76 (m, -CH_2, 4H), 2.16(m, -CH_2, 4H), 3.27(dd, 1H), 3.70 (dd, 1H), 5.68(dd, 1H), 7.04(d, ArH, 2H), 7.17(d, ArH, 2H), 7.42(d, ArH2H), 7.72(d, ArH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 22.7, 24.7, 25.0, 29.0, 31.8, 33.5, 42.1, 84.8, 121.8, 126.4, 127.1, 128.1, 139.2, 150.0, 156.5, 172.3. LCMS: 620. 54 $[M+H]^+$. Elemental Analysis (%): Calcd for $C_{39}H_{57}NO_5$: C, 75.57; H, 9.27; N, 2.26 found C, 75.51; H, 9.34; N, 2.21. Yield: 75%.

4,5-dihydroisoxazol-3,5-diylbis(4,1-phenylene) ditetradecanoate (3h): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88(t, 6H), 1.29(m, -CH_2, 36H), 1.76 (m, -CH_2, 4H), 2.16(m, -CH_2, 4H), 3.27(dd, 1H), 3.70 (dd, 1H), 5.68(dd, 1H), 7.04(d, ArH, 2H), 7.17(d, ArH, 2H), 7.42(d, ArH, 2H), 7.72(d, ArH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 22.7, 24.7, 25.0, 29.0, 31.8, 33.5, 42.1, 84.8, 121.8, 126.4, 127.1, 128.1, 139.2, 150.0, 156.5, 172.3. LCMS: 676.50 $[M+H]^+$. Elemental Analysis (%): Calcd for $C_{43}H_{65}NO_5$: C, 76.40; H, 9.69; N, 2.07 found C, 76.30; H, 9.73; N, 2.00. Yield: 74%.

4,5-dihydroisoxazol-3,5-diylbis(4,1-phenylene) distearate (3i): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88(t, 6H), 1.39(m, -CH_2, 50), 1.76 (m, -CH_2, 10H), 2.57(m, -CH_2, 4H), 3.27 (dd, 1H), 3.70(dd, 1H), 5.68(dd, 1H), 7.04(d, ArH, 2H), 7.17(d, ArH,2H), 7.42(d, ArH,2H), 7.72(d, ArH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 22.7, 24.7, 25.0, 29.0, 31.8, 33.5, 42.1, 84.8, 121.8, 126.4, 127.1, 128.1, 139.2, 150.0, 156.5, 172.3. LCMS: 789.12$[M+H]^+$. Elemental Analysis (%): Calcd for $C_{51}H_{81}NO_5$: C, 77.72; H, 10.36; N, 1.78 found C, 77.74; H, 10.38; N, 1.81. Yield: 72%.

RESULTS AND DISCUSSION

Thermal behavior: To investigate the thermotropic properties of the isoxazoline derivatives, polarized optical microscopic observation was carried where the sample was sandwiched between two

glass plates as the temperature was changed at a rate of 0.5°C min^{-1}. The mesomorphic behavior of all the synthesized compounds has been evaluated mainly by optical studies. However, for some representative compounds, the phase transition temperatures have been confirmed by DSC studies. Compounds exhibited both nematic and /or smectic phases. To understand the molecular structure-liquid crystal property relationship, the compounds 3(a-i) possess isoxazoline ring as central core armed with two phenyl aromatic rings attached by terminal chains of -$OCOC_nH_{2n+1}$ where *n* ranges from *n*=2-5, 7, 9 11, 13, 17 was studied. A new series of compounds were synthesized from a simple condensation and esterification method. Except for **3a** and **3b** all the compounds exhibited good liquid crystalline profile. The transition temperature and the phase sequence of the compounds synthesized in this investigation are presented in table 1.

Table 1. Transition temperatures of 3(a-i) in°C

Compound No.	R=C_nH_{2n+1}	Smectic (Sm)	Nematic (N)	Isotropic
3a	2	--	--	150.00
3b	3	--	--	142.00
3c	4	120.00	--	135.00
3d	5	98.00	--	120.80
3e	7	--	75.00	127.00
3f	9	--	72.56	125.80
3g	11	--	112.80	143.50
3h	13	--	102.00	118.00
3i	18	--	100.8	126.70

Investigation revealed that all the synthesized compounds exhibited smectic and nematic phases with a middle ordered melting point. Lower homologous with short alkyl chains have exhibited smectic phase while the higher homologous with long alkyl chains have exhibited nematic phase. Liquid crystalline transitions vary with different magnitudes of phase lengths including smectic and nematic lengths. Non-mesomorphic behavior of compounds **3a** and **3b** derivatives is attributed to their high crystallizing tendency, as the molecules are unable to resist exposed thermal vibrations, which results in the sudden breaking of the crystal structure and converts the substance sharply into the isotropic liquid state from the solid state without exhibition of a liquid crystalline mesophase. A plot of the transition temperature versus the number of carbon atoms present in n-alkyl terminal chain consists of three transition curves, smectic-nematic, nematic-isotropic and solid-isotropic/ mesomorphic transition curve was plotted which is represented in figure 1.

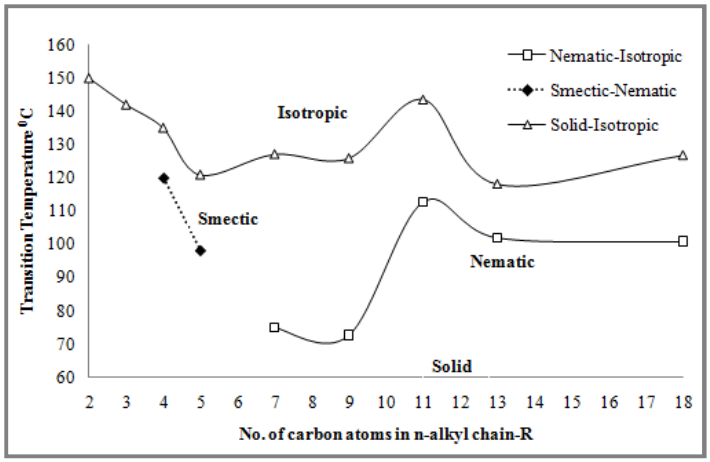


Figure 1. Plot of transition temperature against the number of carbon atoms in the n-alkoxy chains for **3(a-i).**

The solid-isotropic or mesomorphic transition curve rises and falls as the series is ascended in a zig-zag manner and it is also observed that isotropic curve and smectic-nematic curve has descended gradually with the increase in the chain length thus exhibiting enhanced liquid crystalline nature. The characteristic optical texture images procured from POM are represented in figure 2. Figure 2(a) shows the photomicrograph of the smectic phase (at 120.0°C) for butyl derivative **3c**, figure 2(b) shows the texture of nematic phase (at 75.0°C) for heptyl derivative **3e**, figure 2(c) shows the texture of nematic phase (at 112.80°C) for undecyl derivative **3g**, figure 2(d) shows the texture of smectic phase (98.0°C) for pentyl derivative **3d** and figure 2(e) shows the texture of nematic phase (100.0°C) for octadecyl derivative.

Mesomorphic properties obtained can be attributed to the changes in the molecular orientations and in the symmetries of the molecule observed in thermotropic LC's when they are heated or cooled. Further, the presence of isoxazoline at the core owing to their ability to impart lateral and/or longitudinal dipoles combined with changes in the molecular shape as most of the heteroatoms (N,O and S) are more polarizable than carbon are also responsible for the thermal behavior of the synthesized isoxazoline series [**19**].

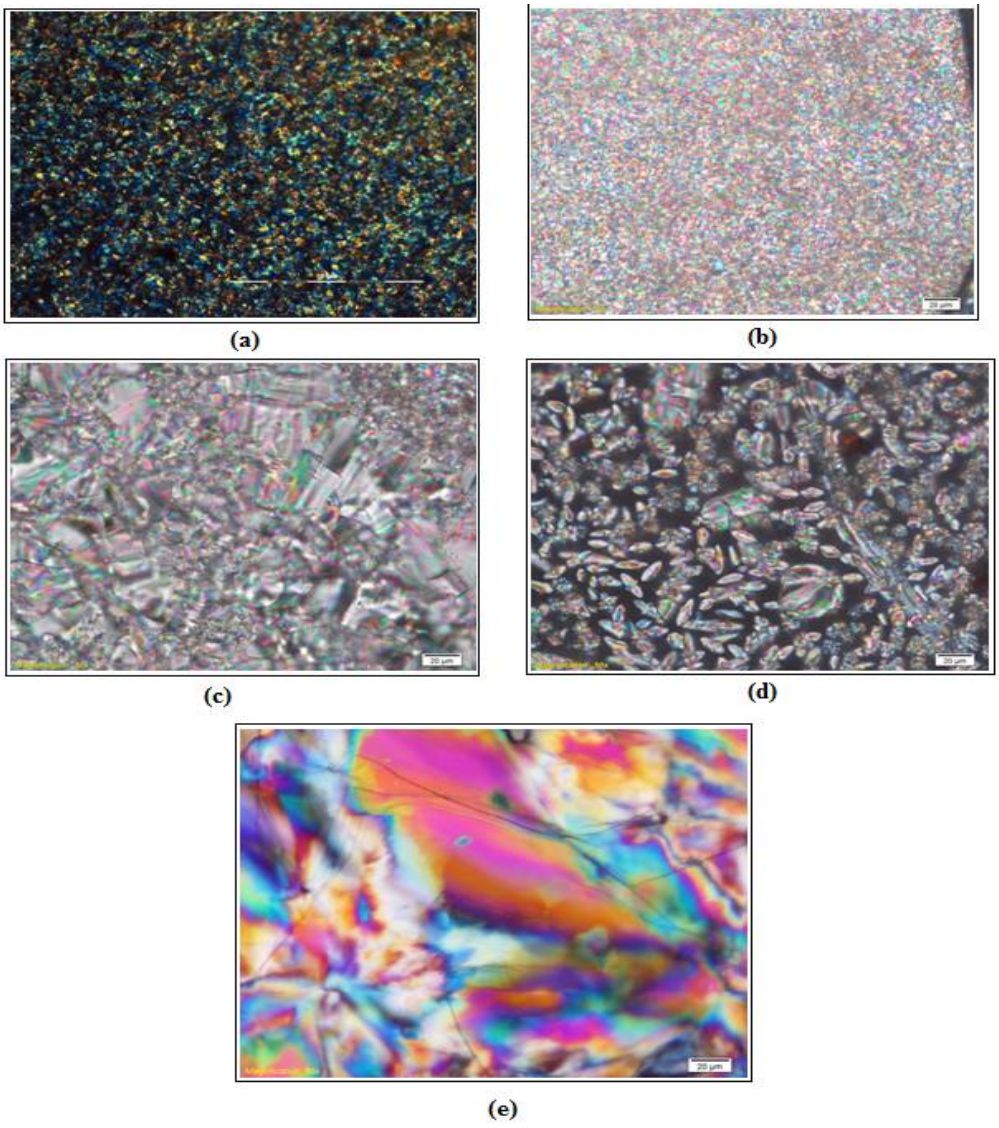


Figure 2. Characteristic optical textures of (a) the Sm phase observed for **3c** (b) the N phase observed for **3e** (c) the N phase observed for **3g** (d) the Sm phase seen for the compound **3d** (e) the N phase seen for **3i**..

All the mesogenic members of the series are enantiotropic in nature. The exhibition of mesogenic properties from the butyl to the hexadecyl homologous is attributed to the suitable magnitudes of anisotropic intermolecular forces of attraction caused by the favorable molecular polarity and polarizability, aromatic, electronic-electronic interactions, length-to-breadth ratio and the ratio of the polarity to polarizability as a consequence of the resultant molecular rigidity and flexibility [**20**].

APPLICATION

The synthesis of isoxazoline derivatives for the characterization of their liquid crystalline property has advantages such as benign reaction conditions and good product yield.

CONCLUSION

Simple and convenient procedures were employed to obtain all the isoxazoline derivatives in moderate to good yields from a simple chalcogen to study their mesomorphic behavior by POM and DSC. The present investigation revealed that except for ethyl and methyl derivatives all the compounds exhibited liquid crystalline nature with smectic and nematic phases in 3,5-disubstituted-4,5-dihydroisoxazole derivatives. To understand the structure-property relationships side chains have been varied on both the terminal ends. Further, variations in the liquid crystalline profile can be attributed to central group, molecular shape and linking group.

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