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RESEARCH ARTICLE

Synthesis, Characterization and Evaluation the Biological activity for New Mesogenic 1, 3-oxazepine-4, 7-dione Derived from Trimesic Acid

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Abstract

In this work new liquid crystalline oxazepine compounds derived from trimestic acid were prepared. In the first step, 1, 3, 5-tris-[3-thiol-4-amino-1, 2, 4 triazole-5-yl] benzene [E] was synthesized through the preparation of 1, 3, 5-benzenetricarboxylic acid hydrazide [C]. The second step was the condensation reaction between different aldehydes: 4-hexyloxybenzaldehyde, 4-heptyloxybenzaldehyde and 4-octyloxybenzldehyde to yield new Schiff bases compounds [F1-F3] respectively. In the final step, oxazepine compounds [G1-G3] were prepared from reaction imines compounds [F1-F3] with succinic anhydride in dry benzene. All these derivatives were characterized via FTIR spectroscopy, elemental analysis and ^{1}H-NMR spectroscopy. Polarizing optical microscope and DSC were used to assessment the mesomorphic properties of the synthesized compounds. The synthesized compounds [G1-G3] were examined for antibacterial activity against *Staphylococcus aureous, Staphylococcus saprophyticus* (Gram-positive) and *Kelebsiella pneumonia, Escherichia Coli* (Gram-negative).

Keywords: 1*, 3-oxazepine-4, 7-dione, 3-mercapto-4-amino- 1, 2, 4- triazole, Liquid cystal, Antibacterial activity.*

Introduction

Heterocyclic compound support the development of life on the plant. They are commonly spread in nature and important to life, they have very important function in the metabolism of living cells [1]. In recent years heterocyclic compounds have more importance so it can be present in a huge number of compounds which exhibit biological activities [2]. Heterocyclic ring system that contains H, N and S hetero atoms have chemotherapeutic activity and another used. Five and six member heterocyclic rings have paying attention of pharmaceutical society over time because they have therapeutic values [3].

Heterocyclic compounds that contain more than one hetero atom called Polyfunctionalized. Heterocyclic compounds containing oxygen make essential roles in the medicine discovery [4]. There are many methods for preparation of Oxazepine seven membered heterocyclic ring, one of the method is the direct addition of malic anhydride and phthalic anhydride and succinic anhydride to the double bond (CH=N) for Schiff bases [5].

Experimental

General

All the chemicals (the reagents & the solvents) were supplied from Merck, BDH, Fluka and Alfa chemicals Co. and used as received. The infrared spectra of the prepared compounds were recorded using FT - IR 8300 Fourier transform infrared spectrophotometer of SHIMADZU Company, potassium bromide (KBr) discs; the wave's number ranges (4000-400) cm^{-1}, in Al-Nahrain University, Iraq. Uncorrected melting points were recorded on hot stage Gallen Kamp melting point device.

The ^{1}H NMR spectra were recorded on Brüker ACF 300 spectrometer at 300MHz, using DMSO as solvent with TMS as an internal standard, in the university of Exeter, England. Elemental analysis (CHNS-O) was carried out using EURO-EA elemental analyzer device. Transition temperatures and enthalpies were scanned by the differential scanning calorimeter LINSEIS DSC PT-1000 with a heating rate of

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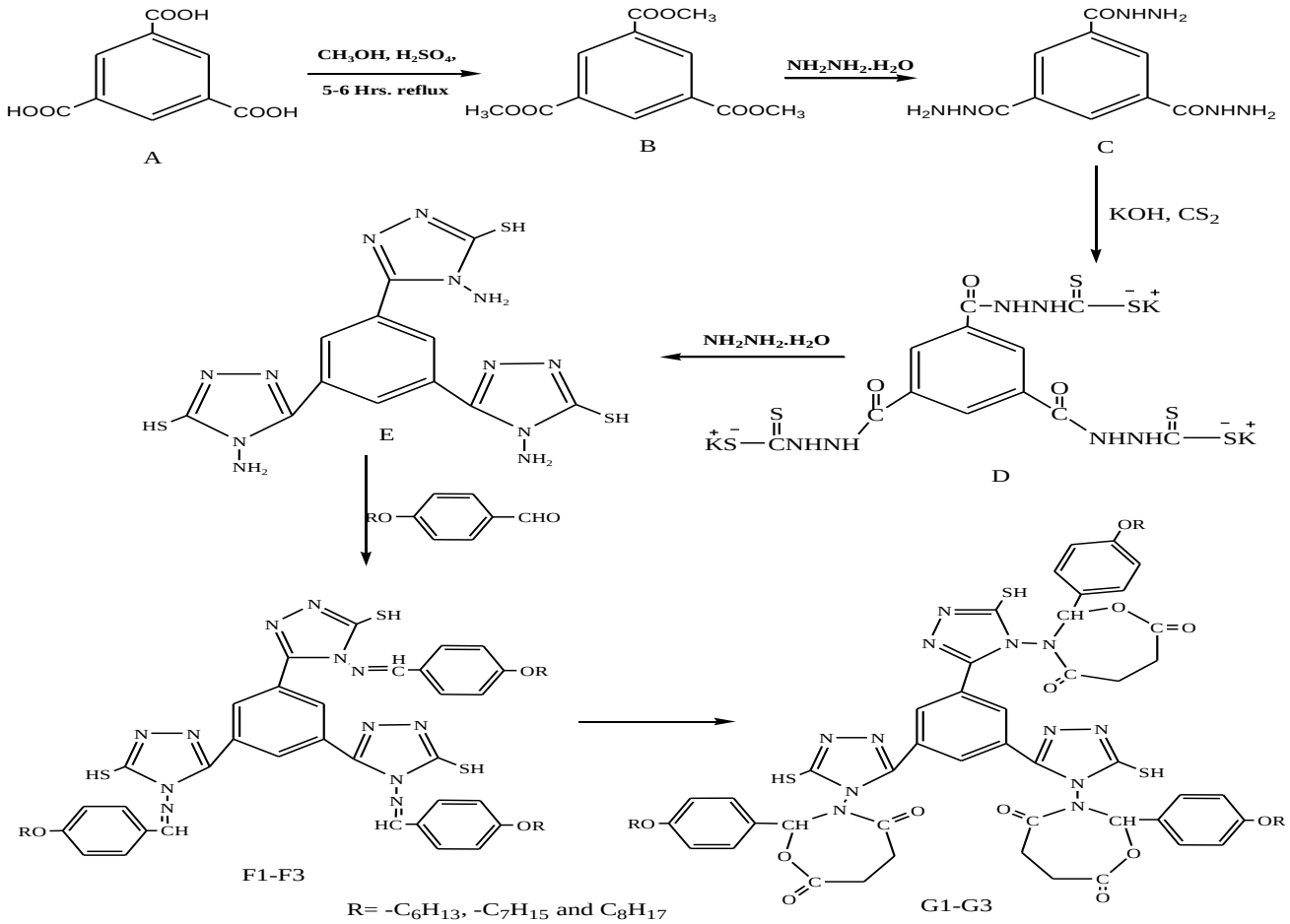
10.0 C / min in the air and calibrated with indium (156.6 C / g).

Liquid crystalline properties have been investigated using the polarizing optical microscope (Meiji MT9000) attached to the INSTEC hot stage. The compound texture was observed by means of polarized light with crossed polarizers and the sample was prepared as a thin film between a slide and over. A camera (Lumenera) has been installed on a polarizing microscope.



Scheme 1: Reaction sequence of 1, 3-oxazepine-4, 7-Dione

Synthesis and Characterization

Benzenetrimethylcarboxylate [B] [6]

A mixture of trimesic acid [A] (5 gm, 0.023 mole) and excess thionyl chloride (5 mL) for (2 hrs) was refluxed. Cold methanol (10 mL) was added almost readily after evaporating the excess thionyl chloride, and the desired product was given an instant reaction. The pure white crystals of the ester [B] that has been collected after filtration and washing with a cold solution of 10% $NaHCO_3$ then with cold water. Yield 81 %, m.p. 144-146°C, Lit; [6] m.p. 145-147°C.

Benzenetricarboxylic Acid Hydrazide [C]

A mixture of ester [B] (5.0 gm, 0.02 moles) and excess 98% hydrazine hydrate (10 mL) was refluxed for (hrs.), absolute ethanol (35 mL) was added and the reflux continued for another (24 hrs.). The crude product that was obtained after the excess ethanol had been distilled, cooled, filtered and washed with a little cold water. Yield 71%, m.p.> 341°C.

1, 3, 5-tris- phenyl thio carbazinate [D]

At 0°C, carbon disulphide (3.04 mL, 0.04 mole) was slowly added to a stirred solution of (2.5 gm, 0.01 mole) tri-acid hydrazide [C] in ethanol (10 mL) and potassium hydroxide (1.68 gm, 0.03 mole) until the yellow precipitate was obtained. To obtain the desired product, the solid product was filtered and dried [7]. Yield 54%, m.p. 212-214°C.

1, 3, 5-tris-[3-thiol-4-amino-1, 2, 4 triazole-5-yl] benzene [E]

To a stirred solution of 1, 3, 5-tris-phenyl thio carbazinate [D] (5.9 gm, 0.01 mole) in ethanol (10 mL), hydrazine hydrate (2.14 mL, 0.04 mole) was slowly added at 0°C and the mixture was refluxed for (24 hrs). Evaporated

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the solvent and dissolved the residue in water and acidified with diluted hydrochloric acid. Filtered and washed the precipitate with a little cold water. To give the desired product, the crude product has been recrystallized from ethanol. Yield 54%, m.p. 257-259°C.

1, 3, 5- tris- [3- thiol-4-*substitutedbenzeledineamino*-1, 2, 4-triazole-5-yl] benzene [F1-F3]

A mixture (0.03 mol) of appropriate 4-alkoxybenzaldehyde and (4.2 g, 0.01 mole) of 1, 3, 5-tris-[3-thiol-4-amino-1, 2, 4 triazole-5-yl] benzene [E] was dissolved in 10 ml absolute ethanol contain a drop of gla. Acetic acid then refluxed for 5hrs. The reaction mixture then set to cool to room temp. ,the solid then filtered and washed with (2 %) hydrochloric acid solution then with Distilled water then recrystallized from ethanol to get coloured crystals [8].

1, 3, 5-tris-[3-thiol-1, 2, 4-triazolo-2(-4`-alkoxyphenyl)-1, 3-Oxazepine-4, 7-Dione)-5-yl] benzene [G1-G3]

The mixture of the corresponding Schiff bases (0.001 mol) and (0.002 mol) of succinic anhydride was refluxed into dry benzene (30 ml) for (4 hours). The resulting solid was filtered, washed with a little cold water, dried to give the desired oxazepine.

Results and Discussion

It is well established that various derivatives of 1, 2, 4- triazoles exhibited interesting pharmacological and liquid crystalline properties. 1, 3, 5-tris-[3-thiol-4-amino-1, 2, 4 triazole-5-yl] benzene [E] was obtained by the reaction of compound [D] with hydrazine hydrate in ethanol. The structure of this compound was elucidated on the basis of its elemental analysis (C% Calc. 34.28, Found 34.25: H% Calc. 2.85, Found 2.81: N% Calc. 40.00, Found 40.08) and FTIR spectral data. The FTIR spectrum Figure 1 of this compound revealed N-H stretching bands at 3328 and 3225 cm^{-1}, a sulphohydryl absorption band (S – H) at 2743 cm^{-1}.

Also, the FTIR spectrum shows the typical absorption of the triazole ring at 1575 and 1081 cm^{-1} (endocyclic C = N, endocyclic C-N-C respectively). Evidence of the presence of 1,3,5-trisubstituted benzene ring was the presence of (C = C) aromatic stretching bands (1598 cm^{-1}) and also bands at (942 and 701 cm^{-1}) which were assigned to the in-plane and out-of-plane bending of C – H respectively for the 1,3,5-trisubstituted benzene ring.

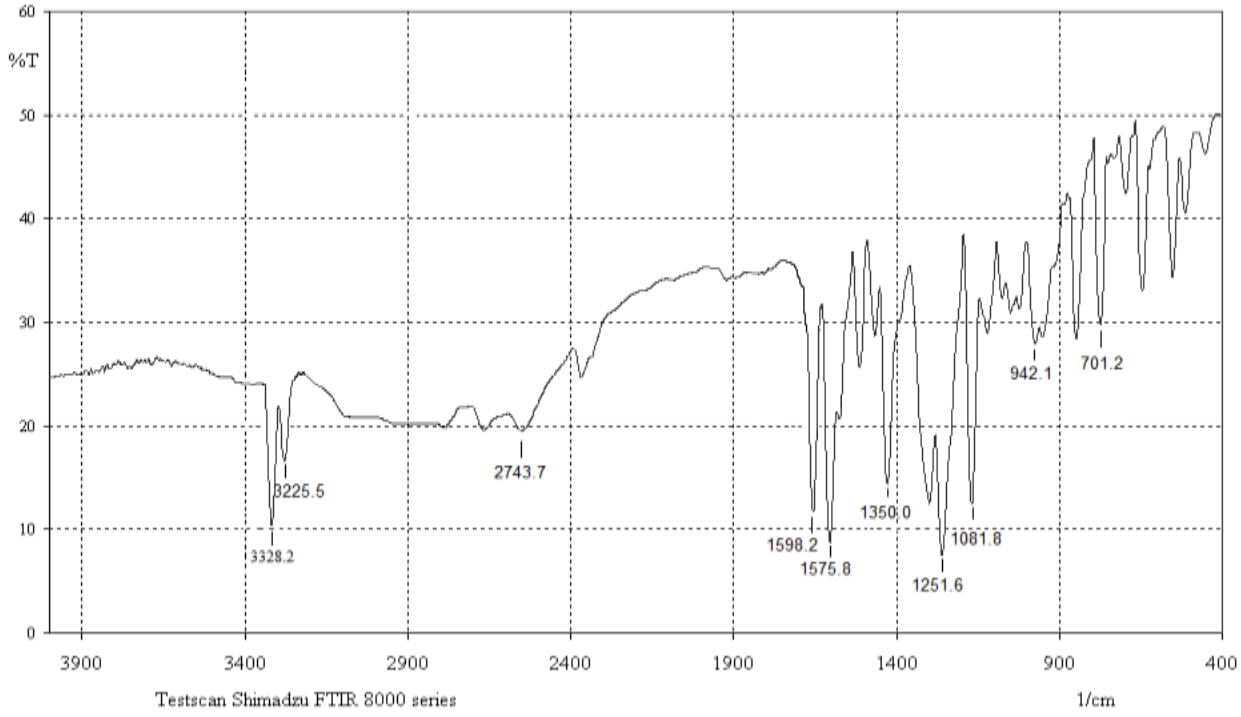

Figure 1: FTIR spectrum of 1, 3, 5-tris-[3-thiol-4-amino-1, 2, 4 triazole-5-yl] benzene [E]

Compounds [F1-F3] were synthesized through the reaction of 1,3,5-tris-[3-thiol-4-amino-1,2,4 triazole-5-yl]benzene [E] with 4-alkoxy benzaldehyde to achieved 1,3,5-tris-[3-thiol-4-*substitutedbenzeledineamino*-1,2,4-triazole-5-yl]benzene [F1-F3]. The structures of synthesized products were deduced using FT-IR and ^{1}H-NMR for some of them.

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All resulting spectral data matched expected values. Using an elemental analysis, the purities of compounds were confirmed. Table (1) lists the elemental analysis of compounds [F1-F3]. The observed values are consistent with the theoretical values that indicate the structure of the respective compounds.

Table 1: Elemental Analysis (CHNS-O) for compounds [F1-F3]

Comp. No.	Formula	%C		% H		% N		% S	
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
F1	$C_{51}H_{60}N_{12}O_3S_3$	62.19	62.13	6.09	5.98	17.07	17.11	9.75	9.66
F2	$C_{54}H_{66}N_{12}O_3S_3$	63.15	63.07	6.43	6.24	16.37	16.31	9.35	9.28
F3	$C_{57}H_{72}N_{12}O_3S_3$	64.04	63.97	6.74	6.58	15.73	15.63	8.98	8.74

The FTIR spectroscopic study of compound F1 is given in Figure (2), show the appearance of bands at 3121, 2964 & 2858, 2728, 1622, 1600 and 831.1 cm^{-1} that may be set to ν C – H of imines linkage, ν C-H aliphatic, ν S – H, ν C = N, ν C = C and out of plane bending of *para*- disustituted benzene ring.

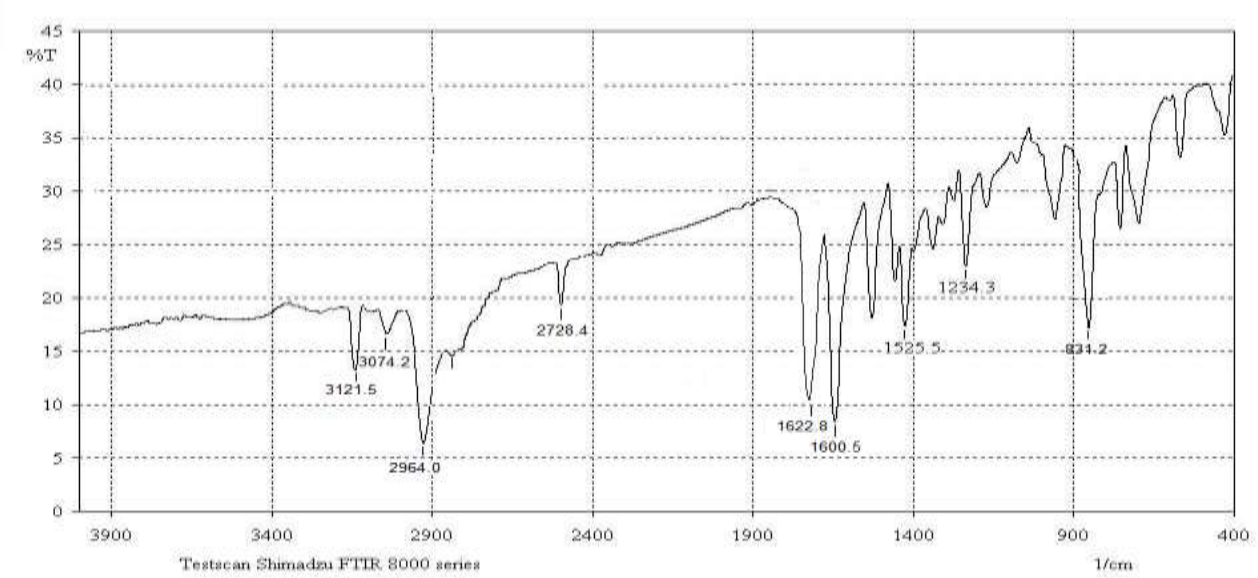

Figure 2: FTIR spectrum of 1, 3, 5-tris-[3-thiol-4-(4`-hexyloxy) benzeledineamino-1, 2, 4-triazole-5-yl] benzene [F1]

^{1}HNMR (DMSO-d_6), δ in ppm, compound F2 Figure (3): 7.59-6.52 (15H, arom. H), 8.17 (s, 3H, CH = N), 9.77(s, 3 H, SH), 4.52 (t, 6H, -OCH_2), 1.90 m, 30 H, $(CH_2)_{15}$), 0.90 (t, 9H, CH_3). Table (4) illustrates the FT-IR bands for synthesizes compounds.

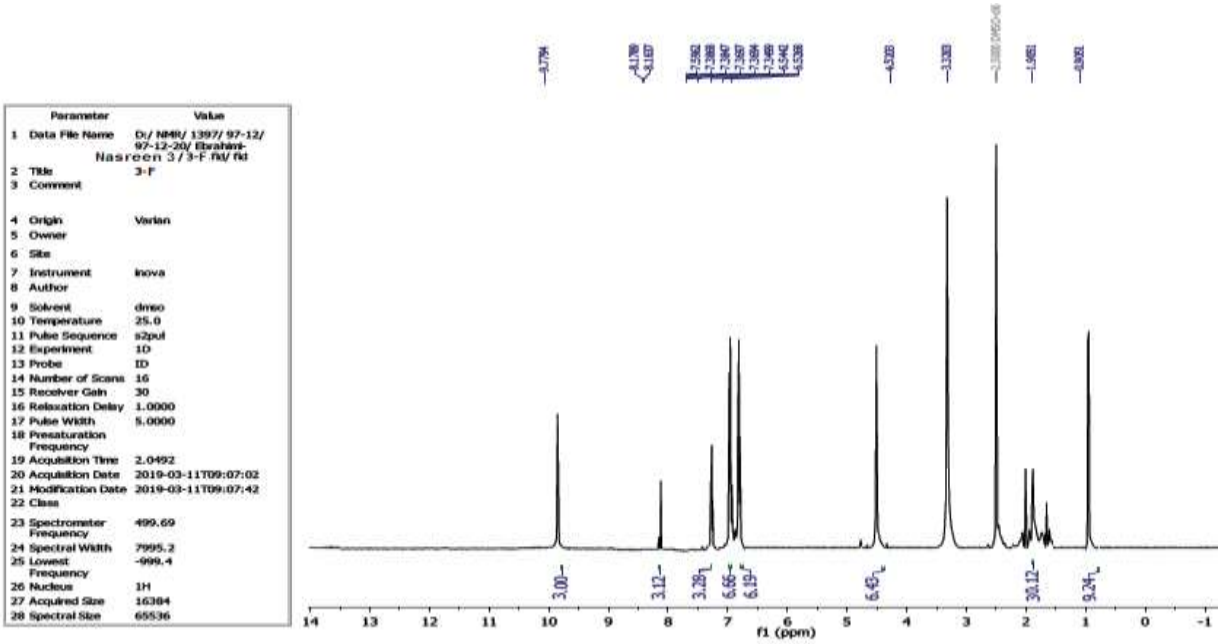

Figure 2: ^{1}HNMR spectrum of 1, 3, 5-tris-[3-thiol-4-(4`-heptyloxy) benzeledineamino-1, 2, 4-triazole-5-yl] benzene [F2]

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Table 2: Characteristic FTIR absorption bands of synthesizes compounds [F1-F3]

Comp. No.	R	νAr H	νC- H *Aliph.*	ν CH = N	ν C = N	ν C = C	γ *Para-Sub.*
F1	$-C_6H_{13}$	3074	2964 & 2858	3121	1622	1600	831
F2	$-C_7H_{15}$	3062	2971 & 2862	3118	1618	1602	839
F3	$-C_8H_{17}$	3053	2947 & 2878	3123	1620	1598	834

Synthesis of Substituted [1, 2, 4] triazolo [1, 3] Oxazepine-4, 7-dione [G1-G3]

Compounds [G1-G3] have been synthesized through the reaction of Schiff base compounds [F1-F3] with succinic anhydride in benzene. FT-IR and 1H-NMR were used to identify the structures of all products. Using an elemental analysis, the purities of compounds were confirmed. Table (3) lists the elementary analysis of compounds [G1-G3].

Table 3: Elemental Analysis (CHNS-O) for compounds [G1-G3]

Com. No.	Formula	%C		% H		% N		% S	
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
G1	$C_{63}H_{72}N_{12}O_{12}S_3$	58.87	58.82	5.60	5.54	13.08	13.11	7.47	7.61
G2	$C_{66}H_{78}N_{12}O_{12}S_3$	59.72	60.01	5.88	5.79	12.66	12.47	7.23	7.16
G3	$C_{69}H_{84}N_{12}O_{12}S_3$	60.52	60.24	6.14	6.08	12.28	12.09	7.01	6.97

For example, spectroscopic observation of (G2) is given: FT-IR (KBr, cm^{-1}) Figure (4): 1732 represent the carbonyl stretching of lactone ring, 1689 correspond to the carbonyl stretching of lactam ring [9], 3058 for aromatic C-H, 2967-2842 assigns to aliphatic C–H stretching, 1598 due to aromatic C = C stretching, 1251 for C-O stretching, 832 could be attributed to the out of plane bending of benzne ring replaced by para di substituted.

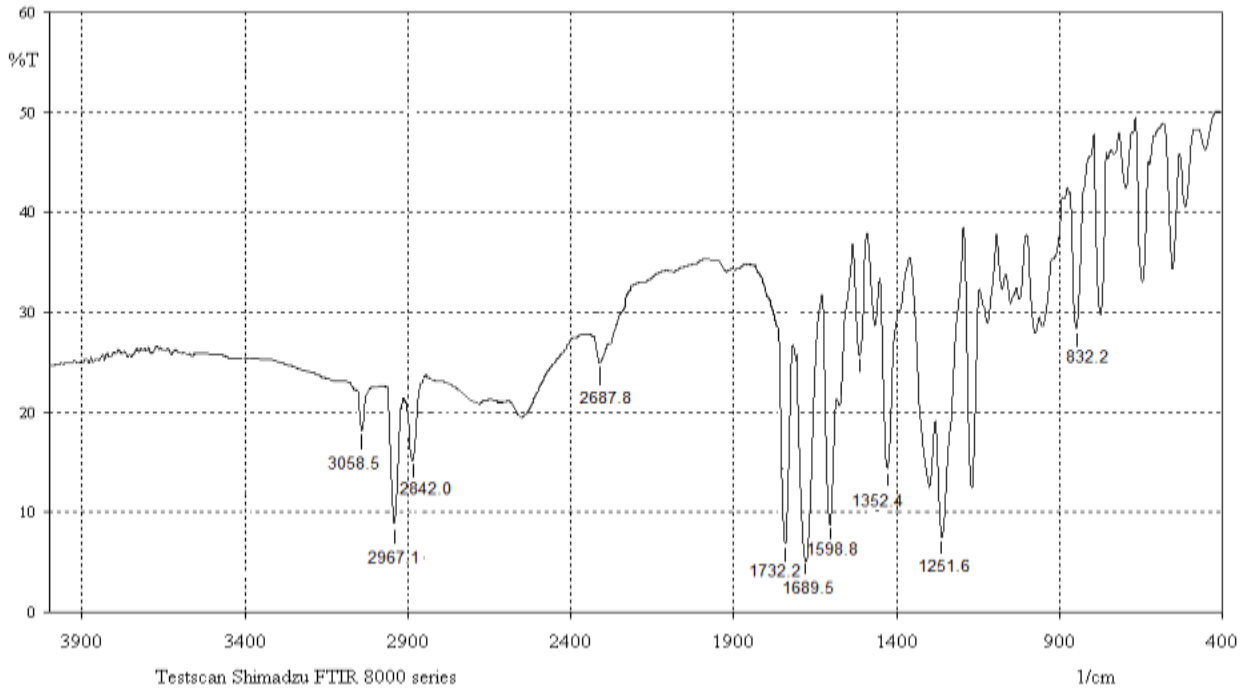

Figure 4: FTIR spectrum of 1,3,5-tris-[3-thiol-1,2,4-triazolo-2(-4`-heptyloxyphenyl)-1,3-Oxazepine-4,7-dione)-5-yl]benzene [G2]

^{1}HNMR spectrum of compound [G3] (DMSO-d_6, δ in ppm) figure (5) shows characteristic signals: 6.96 -7.48 (15H, arom. H), 6.46-6.55(s, 3H), 9.77 (s, 3H, SH) [10], 4.76-5.09 (s, 6 H, OCH_2), 1.90-2.4 m, 36 H, $(CH_2)_{18}$), 1.13-1.22 (t, 9H, CH_3).The FT-IR absorption bands for synthesizing compounds are shown in Table (4).

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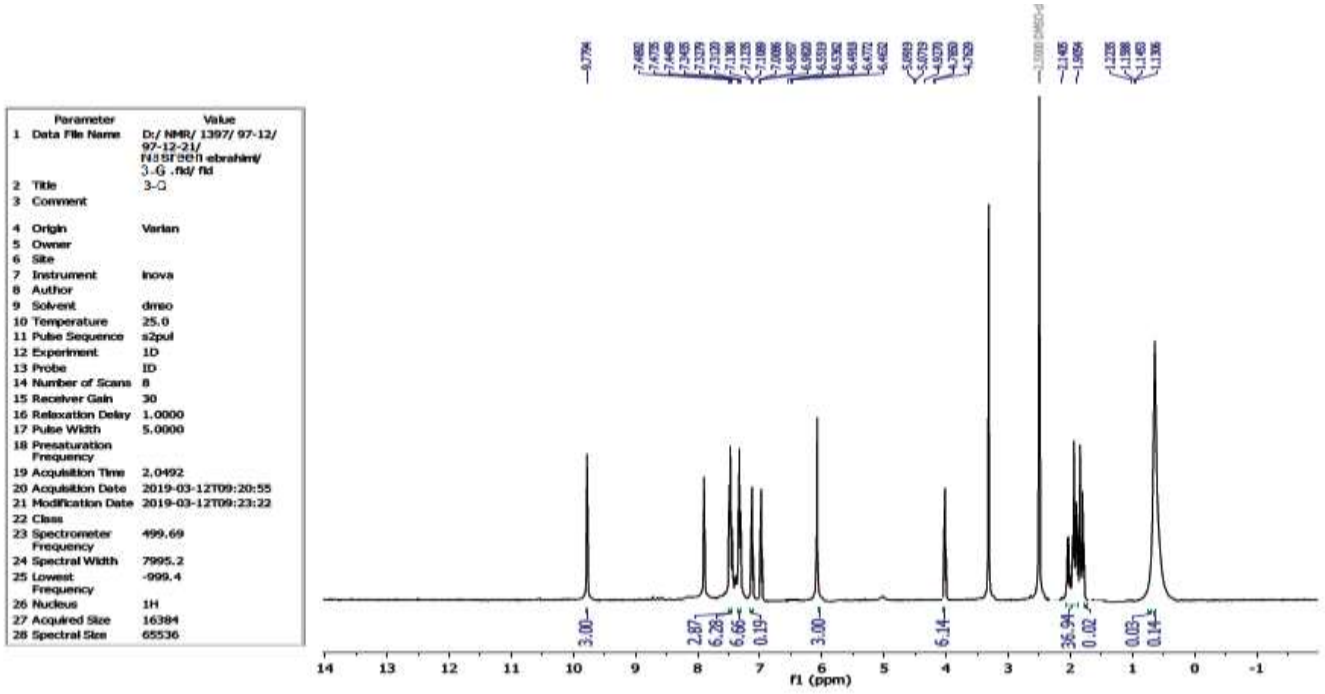

Figure 5: ^{1}HNMR spectrum 1,3,5-tris-[3-thiol-1,2,4-triazolo-2(-4`-octyloxyphenyl)-1,3-Oxazepine-4,7-dione)-5-yl]benzene [G3]

Table 4: Characteristic FTIR absorption bands of synthesizes compounds [G1-G3]

Comp. No.	R	νAr H	νC- H *Aliph.*	ν C = O lactam	ν C = O lactone	ν C = C	γ *para-Sub.*
G1	$-C_6H_{13}$	3061	2942 & 2861	1735	1674	1584	833
G2	$-C_7H_{15}$	3052	2966 & 2875	1727	1685	1600	834
G3	$-C_8H_{17}$	3058	2967 & 2842	1732	1689	1598	832

Liquid Crystalline Properties of the Synthesized Compounds

The liquid crystalline properties are examined by means of differential scanning calorimetric (DSC) and hot-stage polarizing microscopy.

The optical observations under the polarizing microscope of the three synthesized compounds [G1-G3] reveal the occurrence of liquid crystal texture with fan-shaped focal conic typical of a hexagonal column.

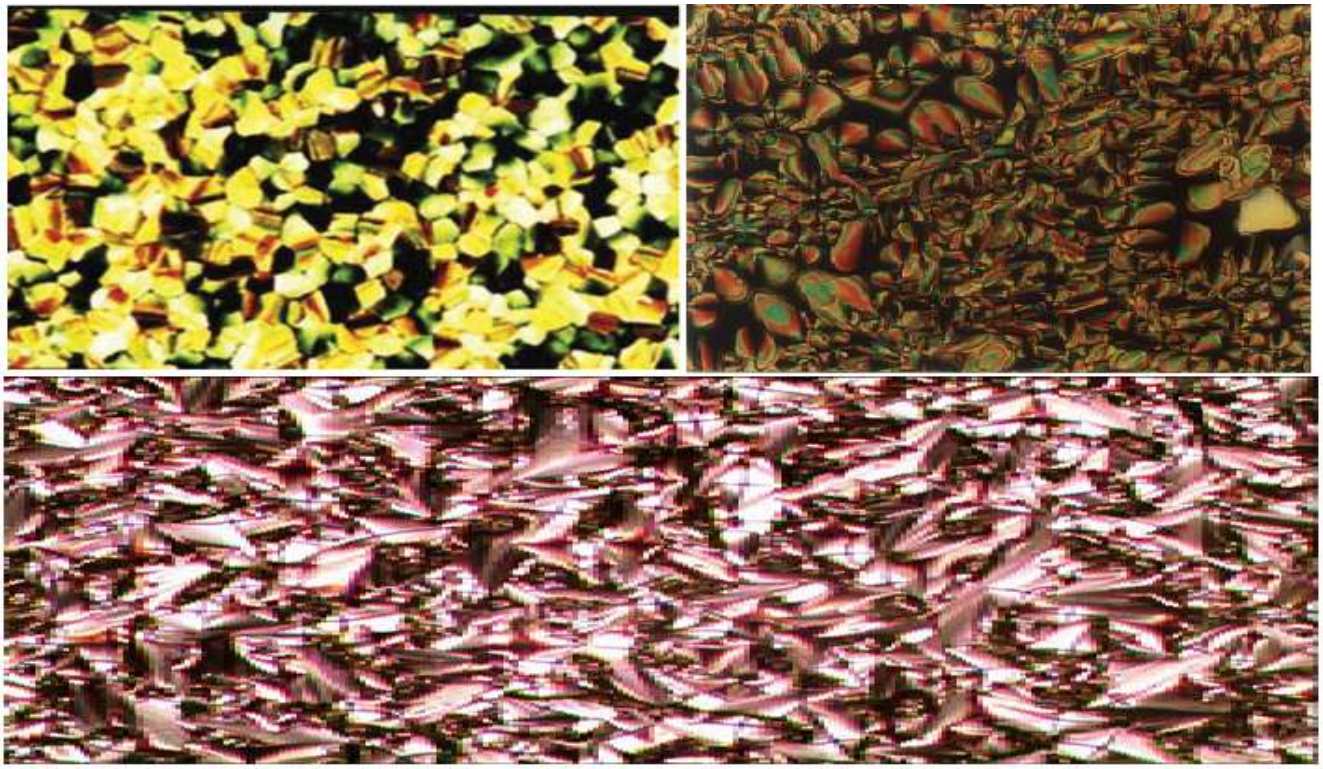

Figure 6: Discotic nematic texture of compounds G1-G3 at 206°C (magnification 10× 10)

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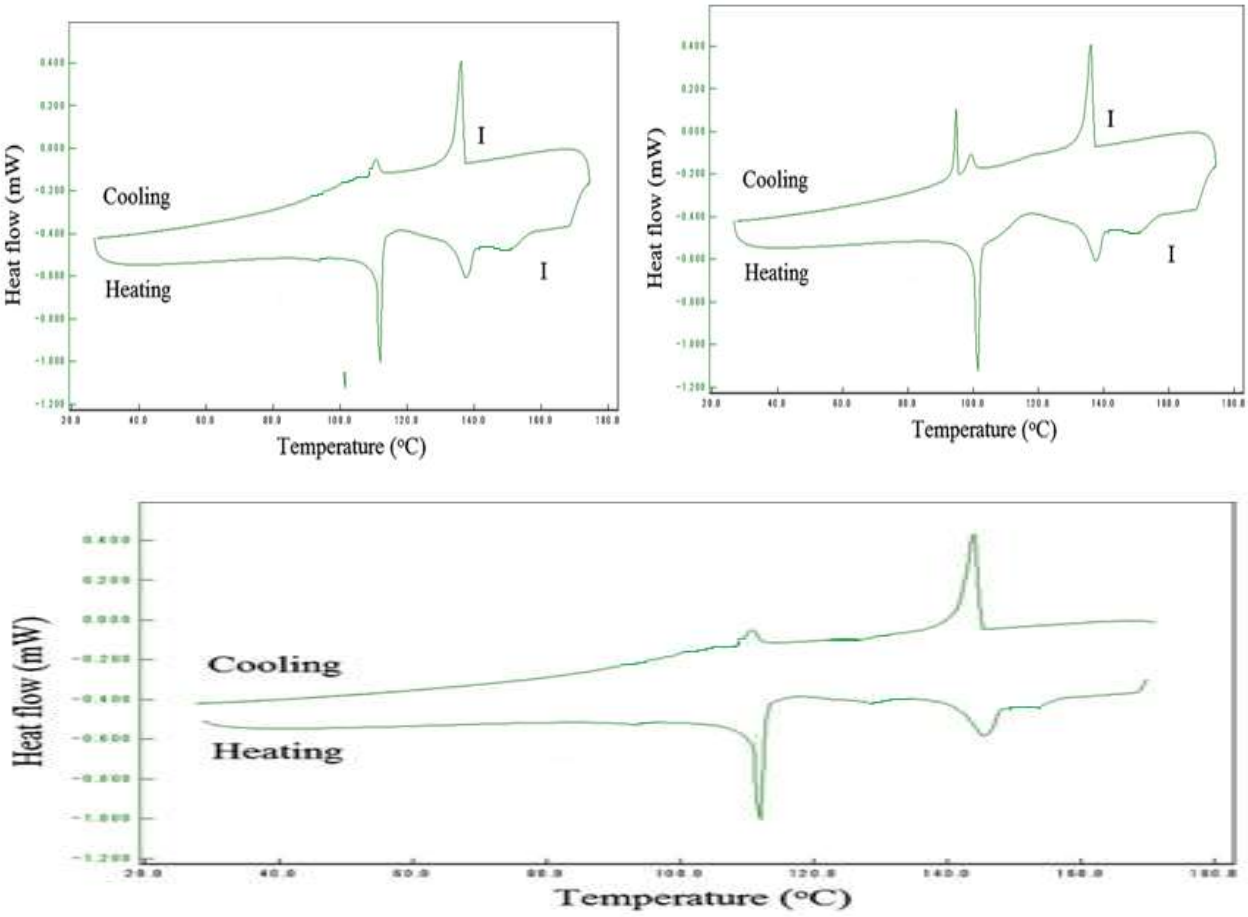

Figure 7: Differential scanning thermograms of compounds G1-G3 respectively as a function of temperature for the second heating and cooling cycles (at scan rate 10 °C min^{-1})

Biological Screening

The test was carried out using the method of disk diffusion. One strain of Gram +ve bacteria (Staphylococcus) and two strains of Geam -ve bacteria (Escherichia coli) and (Pseudo) were tested against the prepared compounds. The inhibition zones on the bacteria caused by the different compounds were examined. Table (5) lists the results of the preliminary screening test. From the data obtained in Table (5), it is clear that against these types of bacteria, all synthesized compounds were found to have higher activity.

Table 5: Antibacterial activity of the synthesized compounds

Compound No.	*Staphylococcus*	*Escherichia coli*	*Pseudo*
DMF (solvent)	-	-	-
G1	+	++	++
G2	++	+	++
G3	++	+	++

Conclusion

The main aim of the present study is to synthesize and investigate the mesomorphic properties and antibacterial activity of new heterocyclic derivatives containing, oxazepine ring. The mesomorphic properties were related to the presence of long chain alkoxy group as terminal group. The antibacterial activity was attributed to the presence of thiol group as well as the oxazepine ring.

Acknowledgments

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