

Synthesis and Characterization of Novel 4,4'-Methylenedianiline Derivatives: Evaluation of Their Biomedical and Liquid Crystalline Properties

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ABSTRACT

Background: Liquid crystalline compounds have gained significant attention due to their potential applications in biomedical sciences, pharmaceuticals, and material engineering. Among them, 4,4'-Methylenedianiline (MDA) derivatives have shown promise for their structural adaptability, mesophase behavior, and potential biomedical relevance. **Objective:** This study focuses on the synthesis, structural characterization, and evaluation of liquid crystalline properties of new derivatives of 4,4'-Methylenedianiline while exploring their biomedical applications, including biocompatibility and potential use in diagnostic or therapeutic materials. **Methods:** A series of 4,4'-Methylenedianiline-based derivatives were synthesized via condensation reactions with substituted benzaldehydes and other functionalized precursors. The chemical structures were confirmed through FT-IR, ¹H-NMR, and mass spectrometry. The mesophase characteristics were examined using differential scanning calorimetry (DSC) and polarized optical microscopy (POM) to identify nematic and smectic phases. Additionally, the biocompatibility of selected compounds was assessed using in vitro cytotoxicity assays to determine their potential biomedical applications. **Results:** The synthesized compounds exhibited nematic and smectic mesophases, with phase transition temperatures influenced by substituent groups. The thermal stability and molecular ordering were confirmed through DSC analysis, while POM observations revealed well-defined mesophase textures. Preliminary biocompatibility screening indicated low cytotoxicity, suggesting their potential suitability for medical or laboratory applications. **Conclusion:** The study successfully synthesized and characterized novel 4,4'-Methylenedianiline derivatives, demonstrating liquid crystalline properties with promising applications in biomedical research and material sciences. Future investigations will explore their potential in biosensing, controlled drug delivery, and tissue engineering.

Keywords: 4,4'-Methylenedianiline, Liquid Crystals, Acid Chloride.

INTRODUCTION

Liquid crystals are a distinct phase of matter that exhibits properties that lie between those of crystalline solids and isotropic liquids [1]. These materials have garnered significant attention in various scientific domains for their remarkable utility and intriguing applications. These include but are not limited to sunlight-driven polymer actuators [2], Pancharatnam-Berry (PB) microlenses [3], biosensors [4], organic field effect transistors (OFETs) [5], liquid crystal elastomers [6], photovoltaics [7], and telecommunications [8]. The task of developing and producing novel liquid crystalline materials that provide both thermal stability and a wide mesophase temperature range at a low cost is a perpetual endeavor. Chemically modifying the geometry has emerged as a very successful approach for the development of innovative and cost-effective liquid crystal (LC) materials with tailored characteristics. Amides hold significant importance as functional groups within the realm of organic chemistry, mostly owing to their involvement in many biological processes such as proteins and peptides. Furthermore, their presence may be observed in a wide range of bioactive compounds, further emphasizing their significance. The bioactivity and uses of these molecules are diverse, including a wide range of fields including medicines, insecticides, polymers, and adhesives [9].

EXPERIMENTAL PART

The compounds utilized in this study were procured from commercial suppliers and underwent purification by distillation or

recrystallization prior to their application. The melting points of all substances were obtained using electrothermal (Gallen Kamp) equipment, with the measurements being conducted in open capillary tubes.

It is important to note that the recorded melting values were not adjusted for any potential errors or factors. All reactions were monitored by using thin layer chromatography which coated aluminum plates and the purity was determined. The ¹H-NMR spectra were acquired using Bruker's 500 FT MHz NMR equipment in Iran. Dimethyl sulfoxide (DMSO) was employed as the solvent, while tetramethylsilane (TMS) served as the internal reference for chemical shifts, expressed in parts per million (ppm). The Shimadzu FTIR-8400S spectrophotometer, situated in Iraq, was utilized to get the Fourier-transform infrared (FT-IR) spectra.

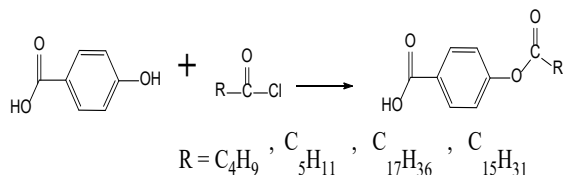
Synthesis of Acid Chloride [1a – 1d]

Carboxylic acid (7 ml), was mixed with (12 ml) of thionyl chloride with few drops of (DMF) and refluxed for 2 hours. Coold and the relevant solvent was evaporated [10].

Synthesis of Esters Derivatives (2a – 2d)

A solution was prepared by dissolving 0.001 mol of p-hydroxybenzoic acid in 15 ml of dry pyridine. To this solution, 0.001 mol of acid chloride was added while maintaining the reaction mixture in an ice bath. The solution was stirred at room temperature

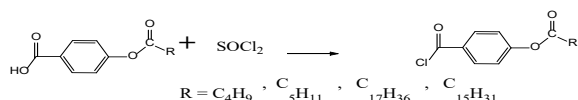
for a period of 24 hours. After the reaction was finished, the reaction mixture was treated with acidic iced water to aid in the removal of any leftover pyridine residue. Subsequently, the mixture was rinsed with distilled water [11].



Equation 1.2: Synthesis Pathway for the Compounds [2a, 2b, 2c, 2d].

Synthesis of Acid Chloride [3a – 3d]

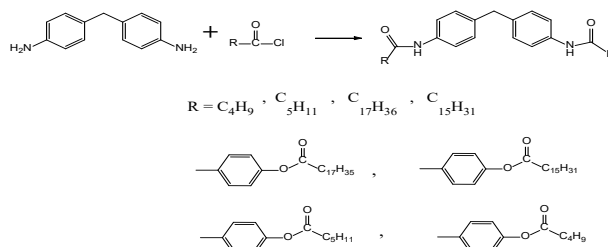
Ester's derivatives (2a – 2d) (0.5 g), was mixed with (12 ml) of thionyl chloride with few drops of (DMF) and refluxed for 2 hours. Coold and the relevant solvent was evaporated [10].



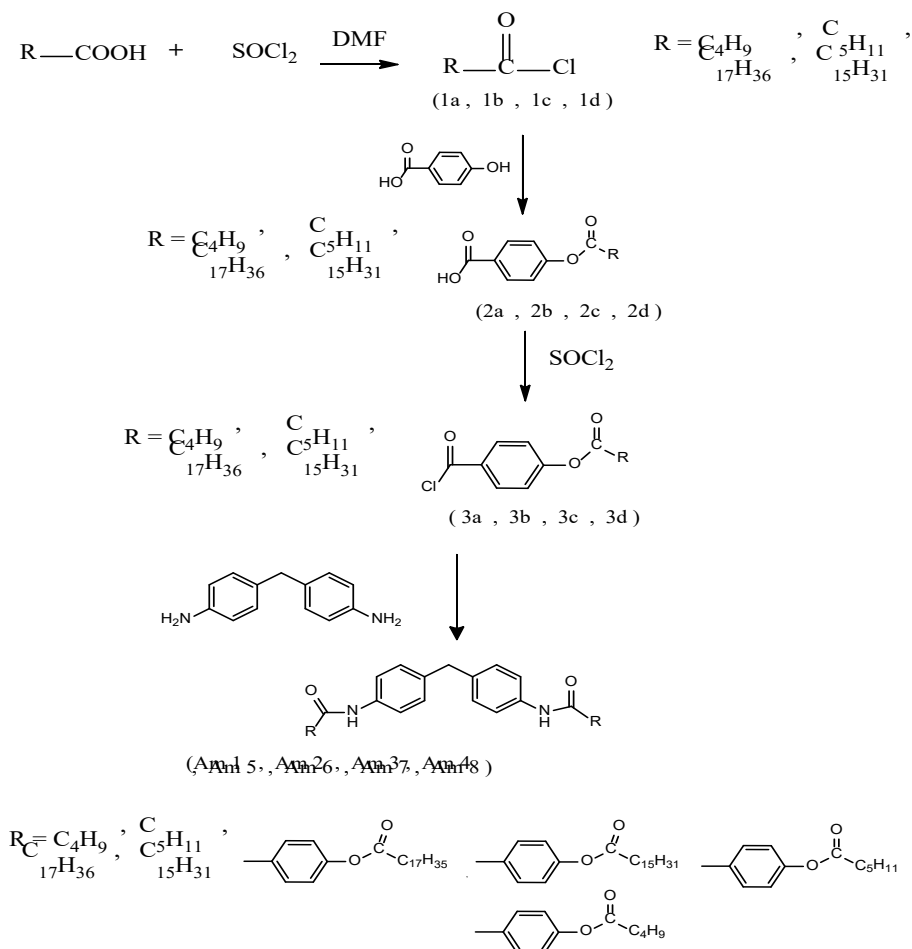
Equation 1.3: Synthesis Pathway for the Compounds [3a, 3b, 3c, 3d]

Synthesis of Acetamides Derivatives (Am1-Am8)

A solution was prepared by dissolving 0.001 mol of 4,4'-diaminodiphenyl methane in 15 ml of dry pyridine, with the addition of a few drops of dimethylformamide (DMF). To this solution, 0.002 mol of acid chloride was added while maintaining the reaction mixture in an ice bath. The solution was agitated at ambient temperature for a duration of 24 hours. Following the completion of the reaction, the reaction mixture was subjected to a process of pouring into acidic iced water, aiming to eliminate any remaining pyridine residue. Subsequently, the resulting mixture was washed with distilled water [9].



Equation 1.4: Synthesis Pathway for the Compounds [Am1-Am8].



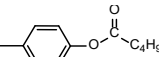
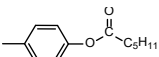
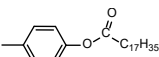
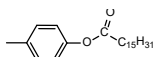
Scheme (1.1) Synthesis Pathway for the Compound [1-14]

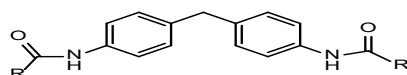
Results And Discussion

Table 1 displays the physical parameters of recently developed amide derivatives. The aforementioned compounds exhibit a notable degree of stability when exposed to arid atmospheric conditions, and

they possess the ability to dissolve readily in a wide range of organic solvents. The synthetic pathways leading to the desired molecules are outlined in Scheme 1. The identification of these compounds' structures was accomplished by the application of melting points and spectral data.

Table 1: Physical Properties and of Compounds Synthesized

Comp. No.	Ar	Nomenclature	M. Formula and M.Wt g/mol	Colour	M. P °C	Yield %	Rf
Am1	C ₆ H ₉	N,N'-(methylenebis(4,1-phenylene))dipentanamide	C ₂₃ H ₃₀ N ₂ O ₂ 366	White	140 – 170	95	0.87
Am2	C ₅ H ₁₁	N,N'-(methylenebis(4,1-phenylene))dihexanamide	C ₂₅ H ₃₄ N ₂ O ₂ 394	Gold	> 250	95	0.83
Am3	C ₁₇ H ₃₆	N,N'-(methylenebis(4,1-phenylene))distearamide	C ₄₆ H ₈₂ N ₂ O ₂ 731	Brown	180 – 200	82	0.85
Am4	C ₁₅ H ₃₁	N,N'-(methylenebis(4,1-phenylene))dipalmitamide	C ₄₅ H ₇₄ N ₂ O ₂ 675	Brown	120 – 150	55	0.76
Am5		(((methylenebis(4,1-phenylene))bis(azanediy))bis(carbonyl))bis(4,1-phenylene) dipentanoate	C ₃₇ H ₃₈ N ₂ O ₆ 606	Deep Brown	218-230	60	0.77
Am6		(((methylenebis(4,1-phenylene))bis(azanediy))bis(carbonyl))bis(4,1-phenylene) dihexanoate	C ₃₉ H ₄₂ N ₂ O ₆ 634	Gold	180 – 230	52	0.80
Am7		(((methylenebis(4,1-phenylene))bis(azanediy))bis(carbonyl))bis(4,1-phenylene) distearate	C ₆₃ H ₉₀ N ₂ O ₆ 971	Black	240 – 243	57	0.80
Am8		(((methylenebis(4,1-phenylene))bis(azanediy))bis(carbonyl))bis(4,1-phenylene) dipalmitate	C ₅₉ H ₈₂ N ₂ O ₆ 915	Brown	> 250	50	0.6
Comp. No.	Nomenclature		M. Formula and M.Wt g/mol	Colour	M. P °C	Yield %	R _f
2a	4-(pentanoyloxy)benzoic acid		C ₁₂ H ₁₈ O ₄ 222	Grey	149 – 151	83	0.83
2b	4-(hexanoyloxy)benzoic acid		C ₁₃ H ₁₈ O ₄ 236	Grey	122 - 125	89	0.93
2c	4-(stearoyloxy)benzoic acid		C ₂₅ H ₄₀ O ₄ 404	Mocha	114 - 118	95	0.94
2d	4-(palmitoyloxy)benzoic acid		C ₂₃ H ₃₆ O ₄ 376	Brown		65	0.80



Compound structure (Am1 – Am8)

FT-IR Spectra

The infrared spectra of all substances analyzed in this work were obtained in the solid state using the KBr disk method. Table 2 enumerates the prominently significant bands of produced compounds. The formation of benzoic acid (2a–2d) derivatives was indicated by their IR spectra through the manifestation of stretching bands of ester collection ($\text{—}\text{C}=\text{O}$) at $(1735 - 1750)\text{cm}^{-1}$, and stretching bands at $(1000 - 1320)\text{cm}^{-1}$ of $(\text{—}\text{C}=\text{O})$ groups [12, 13], besides the disappearance of absorption bands in the regions $(3200\text{--}3600)\text{cm}^{-1}$ corresponding to OH groups of (4-hydroxybenzoic acid) and at $(550\text{--}850)\text{cm}^{-1}$ for $(\text{C}=\text{Cl})$ group for acid chloride(C-Cl) (1a – 1d) [14]. While 4,4'-methylenedianiline derivatives (Am1 – Am8) confirmed by the appearance of absorption bands in the regions $(1600\text{--}1670)\text{cm}^{-1}$ due to $(\text{C}=\text{O})$ of amide groups [15-17] and the appearance of $(1735\text{--}1750)\text{cm}^{-1}$ due to $(\text{C}=\text{O})$ ester groups [18] and

also appearance of absorption bands in the regions $(3200\text{--}3400)\text{cm}^{-1}$ due to $(\text{N}=\text{H})$ groups [19], with the disappearance of absorption bands in the regions $(3200\text{--}3400)\text{cm}^{-1}$ corresponding to NH_2 group and $(550 - 800)\text{cm}^{-1}$ for $(\text{C}=\text{Cl})$ of acid chlorides group [20].

¹H-NMR Spectra:

¹H-NMR spectra of 4,4'-methylenedianiline derivatives (Am2) showed the appearance of the signals at $\delta(0.83\text{--}2.30)\text{ppm}$, $\delta(3.9)\text{ppm}$, $\delta(7.11\text{--}7.56)\text{ppm}$, $\delta(9.80)\text{ppm}$, which are related to C₅H₁₁ protons, CH₂ protons, aromatic protons and $(\text{H}=\text{N}=\text{C}=\text{O})$ protons, respectively [21], 4,4'-methylenedianiline derivatives (Am5) showed the appearance of the signals at $\delta(0.90\text{--}3.70)\text{ppm}$, $\delta(4.0)\text{ppm}$, $\delta(7.15\text{--}8.33)\text{ppm}$, $\delta(9.33)\text{ppm}$, which are related to C₄H₉ protons, CH₂ protons, aromatic protons and $(\text{H}=\text{N}=\text{C}=\text{O})$ protons, respectively. The 4,4'-methylenedianiline derivatives (Am6) showed the appearance of the signals at $\delta(0.87\text{--}2.30)\text{ppm}$, $\delta(3.88)\text{ppm}$, $\delta(6.86\text{--}8.06)\text{ppm}$, $\delta(9.75)\text{ppm}$, which are related to C₂H₅ protons, CH₂ protons, aromatic protons and $(\text{H}=\text{N}=\text{C}=\text{O})$ protons, respectively [22, 23].

Table 2(a): Major FT-IR Absorption Bands (cm^{-1}) of Synthesized Compounds.

Comp. No.	IR(KBr), cm^{-1}								
	V=C-H Aromatic	V-C-H Aliphatic	V N-H	C=C V Ar.	C=O V	V C-N	C-H V Out of plane	V C-O-C	Others
2a	3074	2960 2873	-	1490 1599	1737 1687	-	750 890	1209	O-H (carboxylic acid) V (3439)
2b	3074	2931 2870	-	1508 1604	1755 1739	-	763 860	1207	O-H (carboxylic acid) V (3001)
2c	3074	2920 2850	-	1504 1601	1755 1735	-	767 864	1207	O-H (carboxylic acid) V (3005)
2d	3078	2924 2854	-	1504 1604	1750 1737	-	756 887	1203	O-H (carboxylic acid) V (3456)
AM 1	3032	2958 2870	3298	1512 1600	1662	1207	775 813	-	-

Table 2(b): Major FT-IR Absorption Bands (cm^{-1}) of Synthesized Compounds

Comp. No.	IR(KBr), cm^{-1}								Others
	V=C-H Aromatic	V-C-H Aliphatic	V N-H	C=C V Ar.	C=O V	V C-N	C-H V Out of plane	V C-O-C	
AM 2	3039	2954	3298	1512	1668	1203	736	-	-
AM 3	3035	2924	3244	1508	1701	1242	721	-	-
		2854		1597			817		
AM 4	3082	2924	3235	1512	1701	1242	721	-	-
		2850		1620			860		
AM 5	3070	2958	3421	1508	1701	1261	725	1199	-
		2873		1600			856		
AM 6	3060	2956	3294	1512	1680	1255	730	1225	-
		2858		1602			874		
AM 7	3062	2924	3236	1508	1701	1238	763	1202	-
		2850		1600			865		
AM 8	3074	2924	3464	1508	1699	1261	759	1203	-
		2850		1600			887		

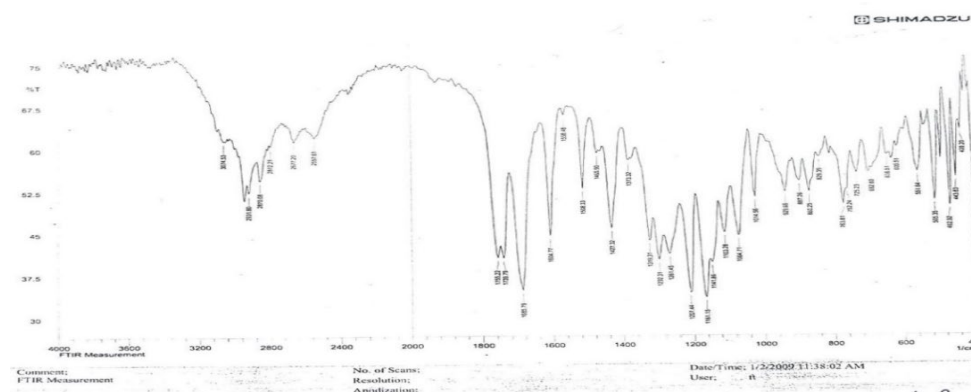
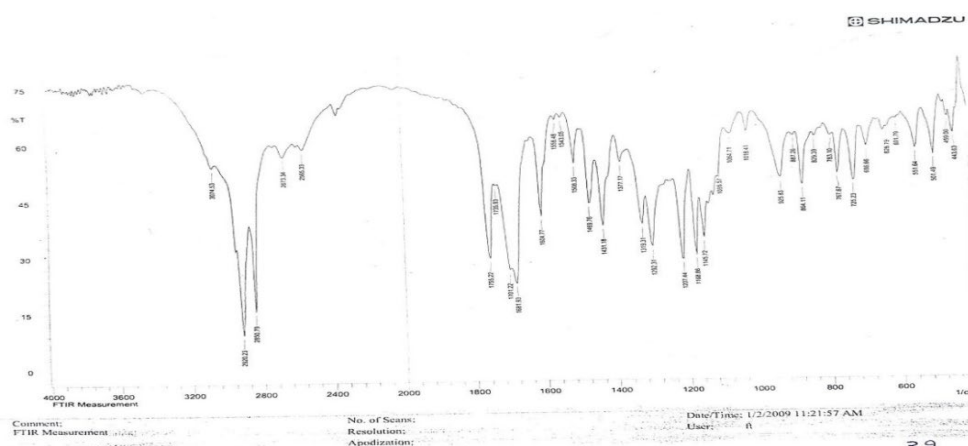
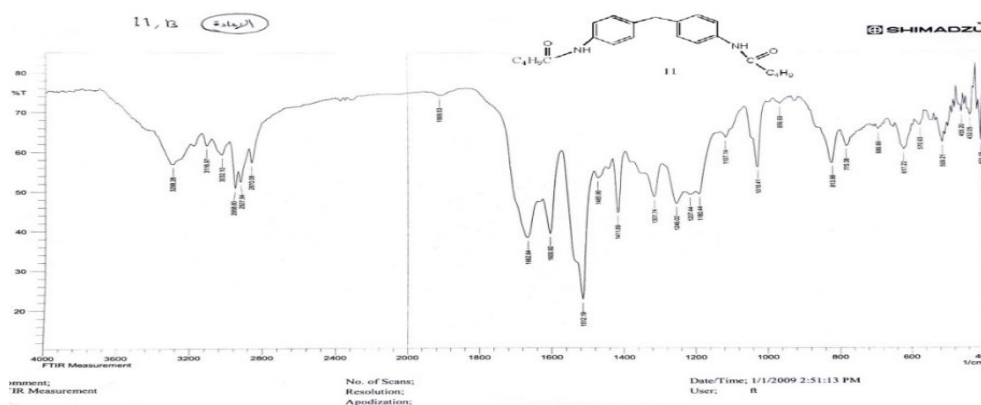
**Figure 1:** FTIR Spectrum for Compound [2a]**Figure 2:** FTIR Spectrum for Compound [2 c]

FIGURE 3: FTIR Spectrum for compound [Am 1]

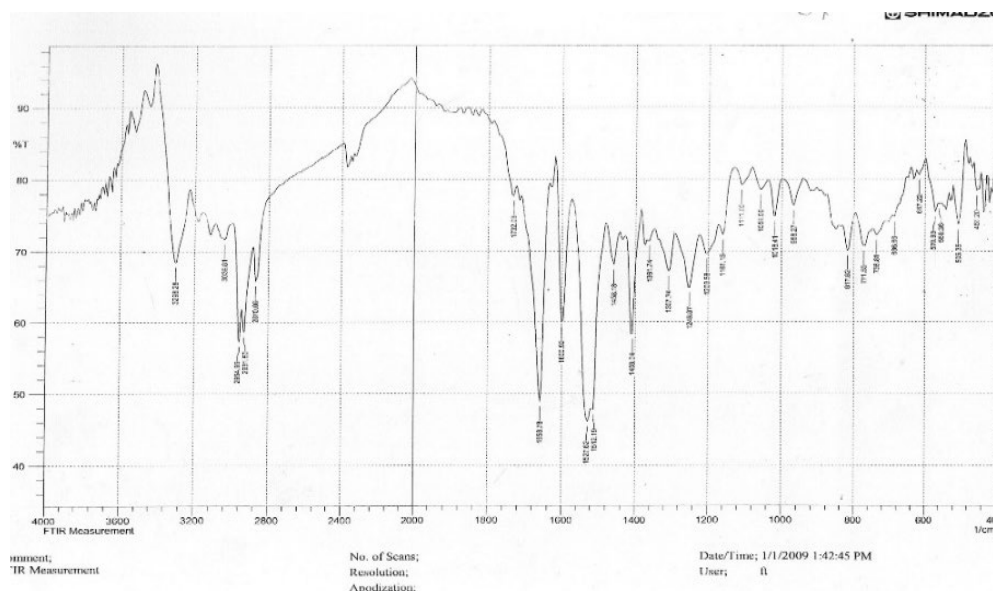


FIGURE 4: FTIR Spectrum for Compound [Am 2]

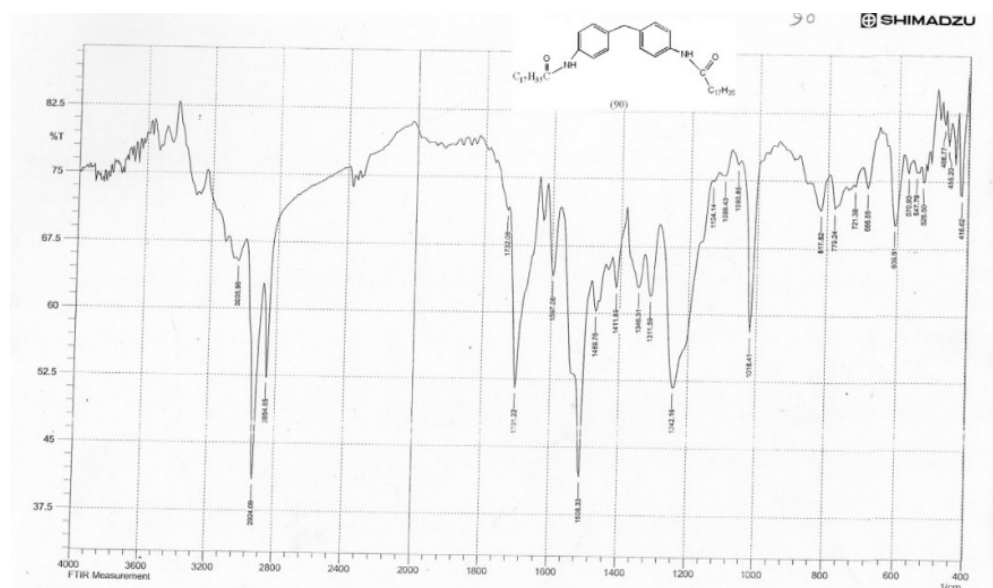


FIGURE 5: FTIR Spectrum for Compound [Am 3]

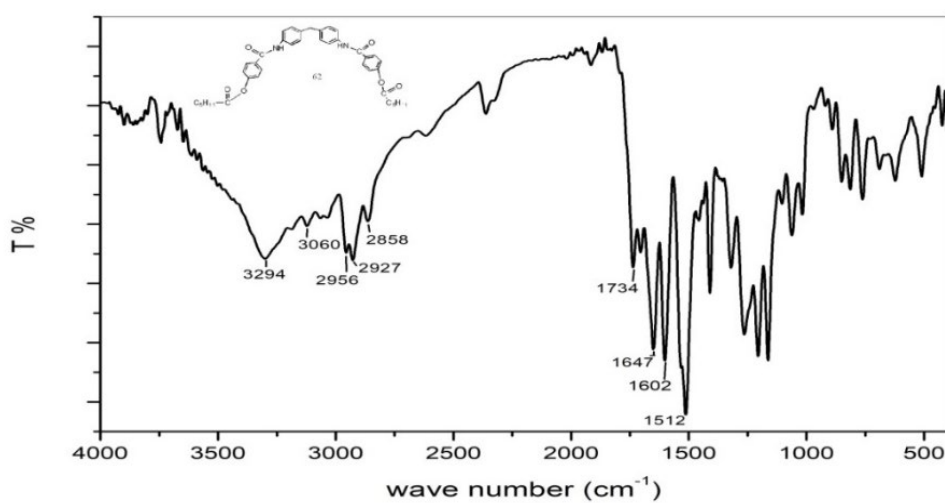


FIGURE 6: FTIR Spectrum for Compound [Am 6]

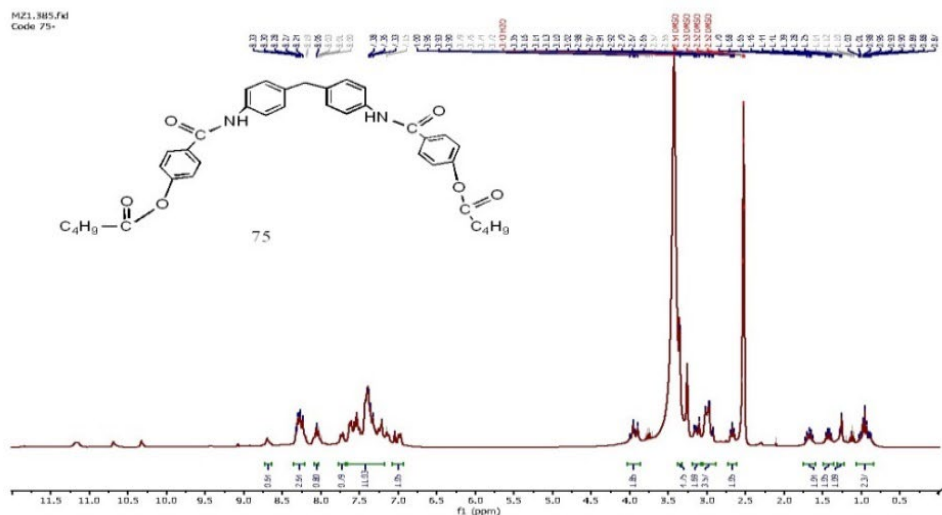


Figure 7: ^1H NMR Spectrum for Compound [Am 5]

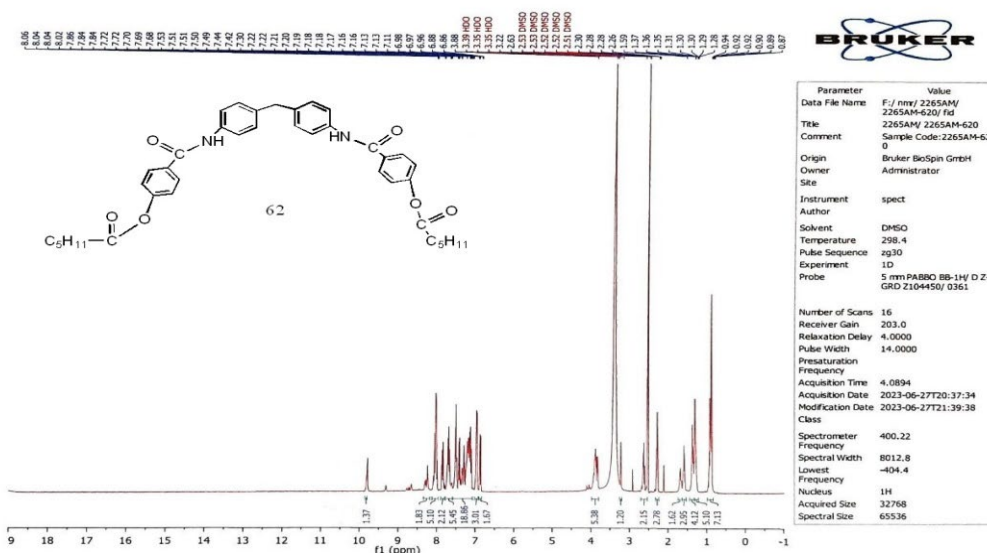


Figure 8: FTIR spectrum for Compound [Am6].

Mesomorphic Properties

The determination of the mesomorphic characteristics of the synthesized compounds was conducted using a polarizing optical microscope (POM) and differential scanning calorimetry (DSC) measurements.

Figure 9,10 displays the representative polarized optical micrograph of the obtained compounds (Am2 and Am3) during the liquid crystalline phase in the second heating and cooling cycle. The micrograph corresponds to compounds Am2 and Am3, as indicated [24].

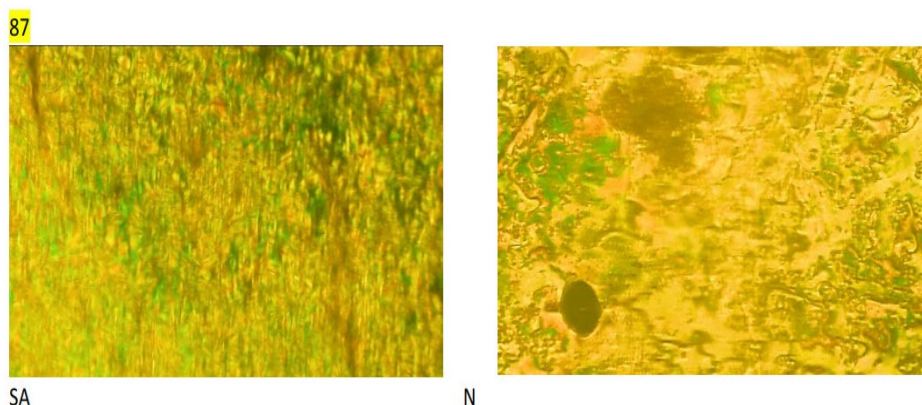


Figure 9: POM Textures of Bent-Core I, Liquid Crystal Phases [Am2 Compound]

2(a): SA phase during heating at 104 °C, 2(b): N phase during heating from 152 °C to isotropic.

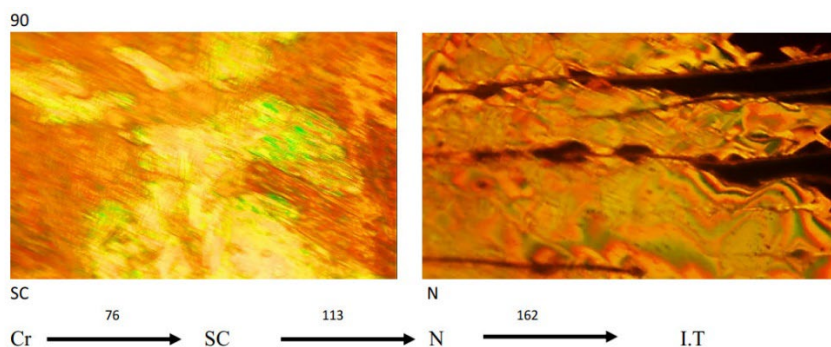


FIGURE 10: POM Textures of Bent-Core Liquid Crystal Phases [Am3 Compound]
 2(a): SC Phase During Heating at 113 °C, 2(b): N Phase During Heating from 162 °C to Isotropic.

Table 3: Transition Temperatures of Liquid Crystal Phases from Polarized Optical Microscope.

Comp. No.	Cry	S _A	S _C	N	ΔT_{S_A}	ΔT_{S_C}	ΔT_N
Am2	71	104	-	152	33	-	48
Am3	76	-	113	162	-	37	49

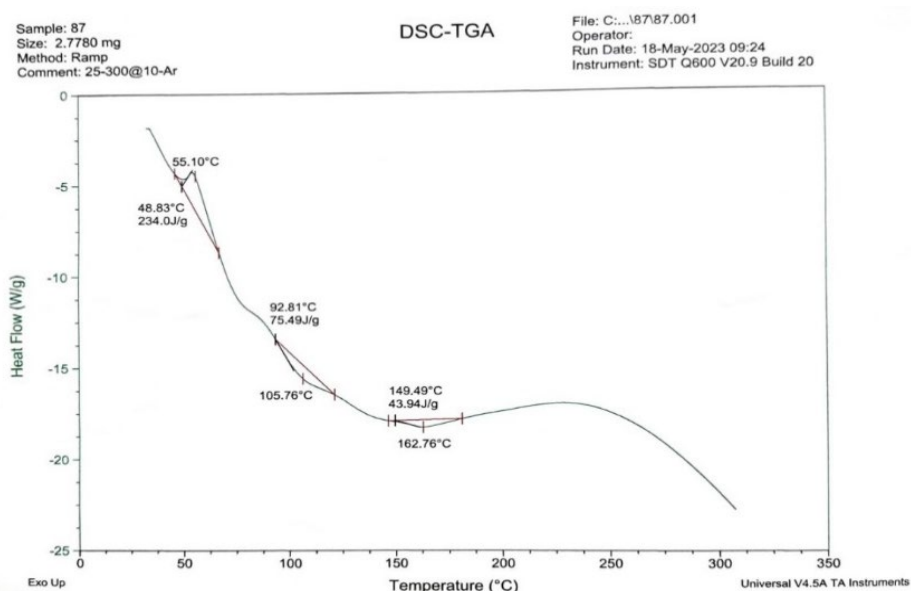


FIGURE 11: DSC Diagram of [Am2 compound].

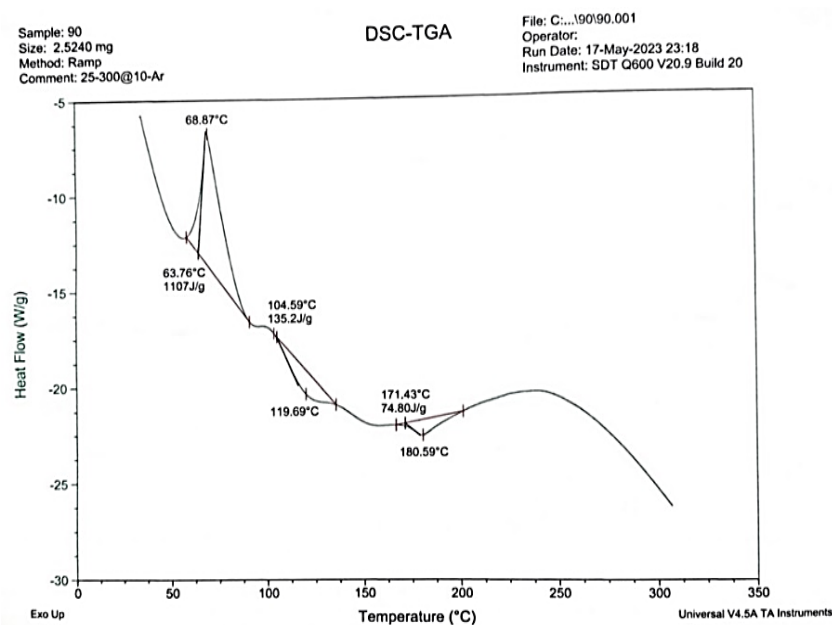


FIGURE 12: DSC Diagram of [Am3 Compound].

Docking Study

Docking is a technique utilized to validate the secure binding of a ligand to the target protein, hence facilitating the understanding of their interaction complexities [25, 26]. In order to investigate the antibacterial activity of newly synthesized Am2-Am1 derivatives, two

specific target proteins, namely THR159 and TYR331 from *E. coli*, as well as LEU317 and ARG161, were obtained from the Protein Data Bank (PDB) [18]. The synthesized compounds exhibited interactions and binding affinities with the target proteins in a simulated environment using MOE 2009 [27].

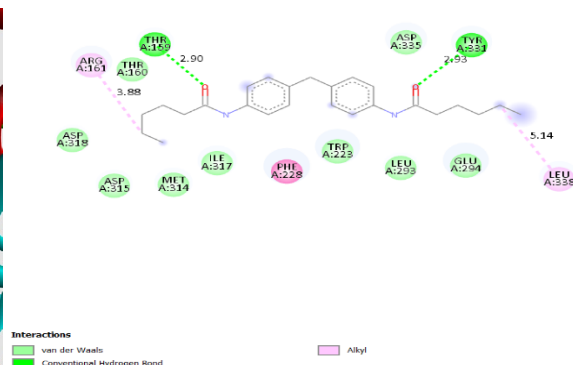
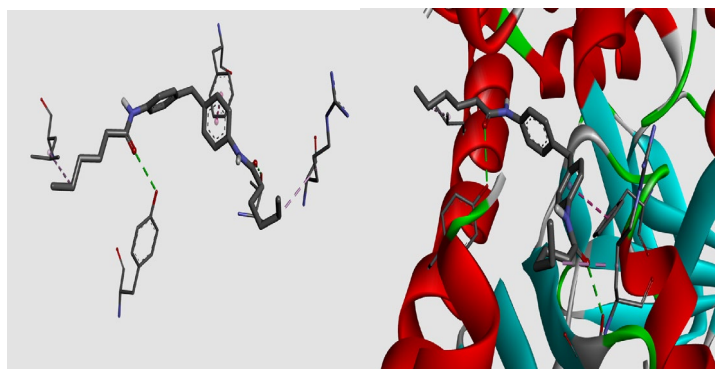


Figure 13: The Reactions between Compound Am2 with *Escherichia coli* in 3D,2D.

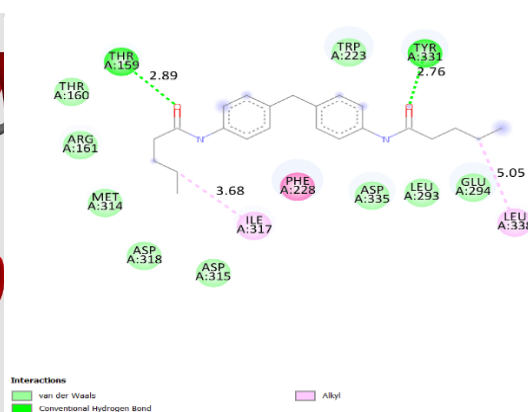
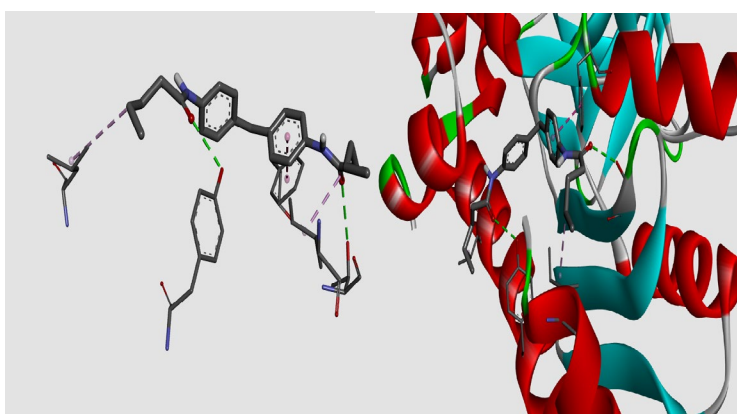


Figure 14: The Reactions between Compound Am1 with *Escherichia coli* in 3D,2D.

The study of molecular binding for organic derivatives gave the number and type of bonds that binds these prepared derivatives with the rest of amino acids in active site, so the study confirmed that the compound 11 reacts with the rest of amino acids that presents in active sites through formation of two types of bonds, two hydrogen bonding

binds between the rest of amino acids THR159, TYR331 with pair electrons of oxygen atom of amide.

Two bonds of pi-alkyl kind binds the rest amino ILE317, LEU338 that presents in the active sites with the terminal alkyl group of compound.

Table 4: Values of Binding Energies for the Prepared (Am1-Am2) Derivatives

Comp. Symb.	Enzyme (Protein)	RMSD	Docking Score
Am1	Escherichia coli	0.032	-7.4
Am2	Escherichia coli	0.021	-7.1
Am2	Staphylococci Aureus	0.038	-6.7

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