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Synthesis and Characterization of some β -lactam from substituted Malonic Ester

Entesar O. Al- Tamimi* and Hizoom M. Al- Mayiah*

Department of Chemistry, College of Science, Baghdad University, Baghdad, Iraq

ABSTRACT

Some new compounds were prepared containing β -lactam derivatives from substituted malonic acid with hydrazine hydrate to give hydrazide compounds, then reacted with chloroacetyl chloride in presence of ET_3N to obtain cycle β -lactam. The prepared compounds identified by FT-IR spectroscopy, physical properties including melting point, boiling point and some of them were identified by ^1H-NMR , $^{13}C-NMR$.

Keywords: FT-IR spectroscopy, β -lactam, ET_3N , ^1H-NMR , $^{13}C-NMR$

ARTICLE INFO

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*Corresponding Author

Hizoom M. Al- Mayiah
Department of Chemistry,
College of Science, Baghdad
University, Baghdad, Iraq
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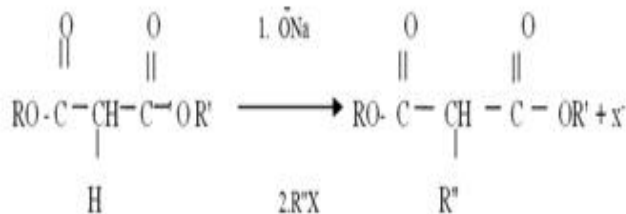
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1. Introduction

The starting material in this work is malonic acid also called Propanedioic Acid which is a white crystalline with melting point 135 -136 OC; readily soluble in water, alcohol and ether. Malonic acid itself is rather unstable and has few applications. Malonyl dichloride is a derivative of malonic acid which can be prepared from reaction of malonic acid with thionyl Chloride. Malonyl chloride has

two nucleophilic centers so that it can yield heterocycles [1]. In this work malonyl dichloride converted into diethyl malonate [2] which is more important commercially. It is colourless, fragrant liquid boiling at 199^o C. Malonic acid and its esters [3] contain active methylene groups which have relatively acidic alpha-protons due to H atoms adjacent to two carbonyl groups. β -hydrogen atom in

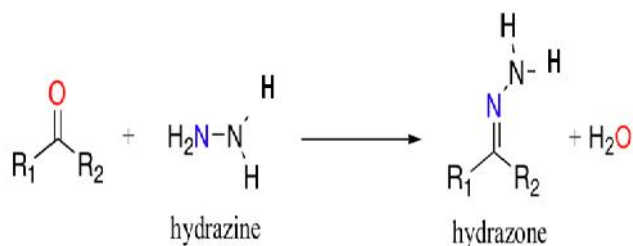
methylene group is removed by sodium alkoxide, which functions as a base and removes the acidic α -hydrogen giving the reactive enolate which is then alkylated by reaction with alkyl halide to form a diethyl 2-alkylmalonate as shown in equation (A) where R, is ethyl, isopropyl or benzyl.



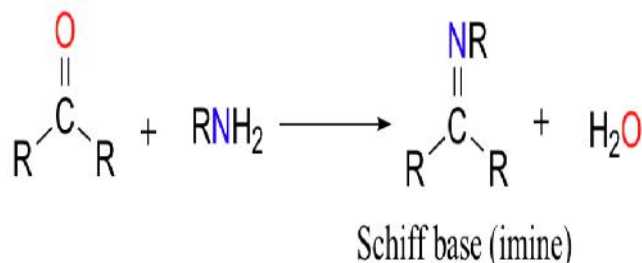
R, R', R''= alkyl or alkoxy

Equation (A): preparation of ethyl- 2- alkyl malonate

Malonic acid and its esters are characterized by the large number of condensation products. They are important intermediates in syntheses of vitamins B1 and B6, barbiturates, non-steroidal anti-inflammatory agents, other numerous pharmaceuticals, agrochemicals and flavors & fragrances compounds. Additionally is an important precursor in fatty acid biosynthesis along with acetyl CoA [4]. Diethyl malonate is useful because it has a relatively acidic α -proton so the enolate is readily formed with ethoxide ion, the enolate is good nucleophile and reacts with alkyl halide via SN2 type reactions to give substituted malonate which can be hydrolysed and decarboxylated to give substituted carboxylic acid [5]. Reaction of diethyl 2-alkyl malonates with hydrazine hydrate to give hydrazide derivatives which can be used for the synthesis of nitrogen heterocycles [6], so leading to the formation of some heterocyclic compounds. Dihydrazides derivatives (RCH-(CONHNH2)2 are highly useful starting materials and intermediates in the synthesis of heterocyclic molecules [7]. They can be synthesized by hydrazinolysis of amides, esters and thioesters [8]. The reaction of hydrazine with acyl chlorides or anhydrides is also well known [9]. Diacylation products predominate when hydrazine reacts with low molecular weight aliphatic acyl chlorides, which makes the reaction impractical for Preparatory purposes [10, 11]. Schiff base is a compound containing functional group (C = N-) with the nitrogen atom connected to an aryl or alkyl group [12]. Schiff bases in a broad sense have the general formula R1R2C=NR3.

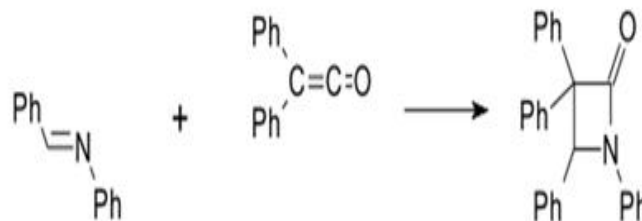


In this definition, Schiff base is synonymous with azomethine, thus with the general formula RCH=NR' [13]. Schiff bases can be synthesized from an aliphatic or aromatic primary amine and a carbonyl compound by nucleophilic addition, followed by a dehydration to generate an imine or Schiff base.



Where R is a phenyl or Aryl can be called aniline [14]. And R' is alkyl or aryl

Schiff base (imine) formation is a very important reaction in biological chemistry. Several modified methods for synthesis of Schiff bases have been reported in the literature in which Lewis acids were used as catalysts such as ZnCl2[15], TiCl4 [16], alumina[17], P2O5[18] also by using materials like Hydrotalcite [19]. P2O5/Al2O3[20] / CaO under microwave conditions has been also reported by Gopalakrishnan et al[21], cerium(III) [22] and by using UV chamber, sonicator and also by grinding method[23]. The first synthetic β -lactam was prepared by Hermann Staudinger in 1907 by reaction of the Schiff base of aniline and benzaldehyde with diphenylketene [24-25] in a [2+2] cyclo addition.



Up to 1970, most β -lactam research was concerned with the penicillin and cephalosporin groups, a wide variety of structures have been described [26]. Beta lactam derivatives are very important in medicinal and pharmaceutical fields because of their wide spectrum of biological activities. From the literature survey up to date, Synthesis and biological activity of Beta lactam derivatives have also been reported by different authors [27-41].

2. Materials and Methods

Instruments and chemicals:

A-instruments:

Uncorrected melting points were determined on Gallenkamp apparatus. Fourier transform infrared (FTIR) spectra were registered on a SHIMADZU (8300, Kyoto, Japan) infrared spectrophotometer, using KBr discs. The ¹H-NMR

spectra were measured on varian EM 60 and JEOL-90 MHz spectrometers with TMS as internal reference, chemical shifts were expressed in ppm.

B-chemicals: All chemicals in this work were supplied from BDH, Merk and Aldrich.

Preparation of malonyl chloride (2):

In round bottom flask was dissolved malonic acid (1) (0.02 mole) and thionyl chloride (0.04 mole) in 10 ml benzen heated under reflux for 3 hrs. at 62 °C with stirring to give pale yellow color of malonyl dichloride (2) (2.0 gm.72 % yield) , b.p 63-65 ° C. Physical properties of compound is listed in table(1) , infrared spectral data in table (2) and solubility of product in table (3).

Preparation of diethyl malonate (3):

In round bottom flask was placed Absolute ethanol (50 ml) and malonyl chloride (2) (0.1 mole) and the mixture is heated under reflux for 3 hrs. At 62 °C to give colorless liquid of diethyl malonate (3) is 12 gm (87 % yield), b.p 198- 200° C. Physical properties of compound listed in table (1), infrared spectral data in table (2) and solubility of product in table (3).

General Preparation of diethyl 2- alkyl malonate (4)

In round bottom flask Sodium metal (0.10 mole) was added to absolute ethanol (60 ml), then diethyl malonate (3) (0. 10 mole) was added to ethanolic sodium ethoxide, then added different alkyl halide (0.1 mole) (ethyl iodide ,isopropyl bromide,benzyl chloride) to mixture with triethyl amine. The resulting mixture was heated under reflux for 3 hrs.at 620C to obtain a colourless liquid, diethyl 2-alkyl malonate (4). Physical properties of compounds are listed in table (1),

infrared spectral data in table (2) and solubility of product in table (3).

Synthesis of 2-alkyl malonyl hydrazide derivatives:

In round bottom flask was dissolved diethyl 2-alkyl malonate (0.01 mole) and hydrazine hydrate (0.2 mole) in 10 ml benzen. The reaction mixture was refluxed for 3 hrs. With stirring. Precipitate obtained filtered, dried and recrystallized from THF. Physical properties of compounds (7,8,9) are listed in table(1) , infrared spectral data in table (2) and solubility of product in table (3).

General method for Preparation 2-alkyl malonyl hydrazone:

In round bottom flask was placed 2-alkyl malonyl hydrazide (1, 2, 3) (0.10 mole) and different carbonyl compound (propanal, benzaldehyde and aceto phenon) (0.20 mole) dissolved in 10 ml benzene. The reaction mixture was refluxed for 3 hrs. With stirring. Precipitate obtained filtered, dried and recrystallized from THF. Physical properties of compounds (10-18) are listed in table (1), infrared spectral data in table (2) and solubility of product in table (3).

General Procedure of beta-lactam derivatives:

Dissolved In round bottom flask 2-alkyl malonyl hydrazone (10, 11, 12) (0.01 mole), chloroacetylchloride (0.2 mole), and triethylamine (0.1 mole) in 10 ml benzene .The resultant mixture was refluxed for 3 hrs. at 40 °C , white Precipitate was formed, filtered, dried and recrystallized from THF to give bis- -lactam derivatives. Physical properties of compounds (19, 20, and 21) are listed in table (1), infrared spectral data in table (2) and solubility of product in table (3).

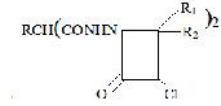
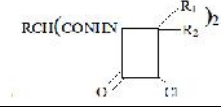
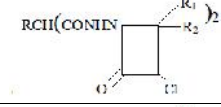
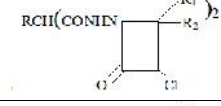
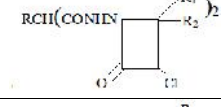
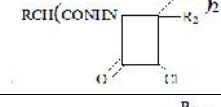
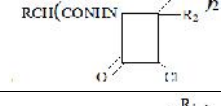
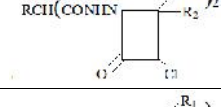
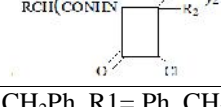
Table 1: Physical Properties of Prepared Compounds (2-9)

Comp. No.	Structure of Compound	Boiling point °C	Color	% Yield
2	Cl—CO—CH ₂ —CO—Cl	63	Pale Yellow	72 %
3	CH ₂ (COO C ₂ H ₅) ₂	200	Colorless	87 %
4	CH ₃ CH ₂ CH (COO C ₂ H ₅) ₂	104	Colorless	78 %
5	(CH ₃) ₂ CHCH (COO C ₂ H ₅) ₂	62	Colorless	75 %
6	ph CH ₂ CH (COO C ₂ H ₅) ₂	296	Colorless	65 %
7	CH ₃ CH ₂ CH (CONHNH ₂)	95	Gray black ppt	59 %
8	(CH ₃) ₂ CHCH (CONHNH ₂)	105	Gray black ppt	66 %
9	ph CH ₂ CH (CONHNH ₂) ₂	162	White ppt	60 %

Table 2: Physical Properties of Prepared Hydrazone Compounds

Comp. No.	Structure of Compound	Melting point °C	Color	% Yield
10	RCH (CO NH-N = C R ₁ R ₂) ₂	. 177	Pale White ppt	56 %
11	RCH (CO NH-N = C R ₁ R ₂) ₂	. 232	Yellow ppt	60 %
12	RCH (CO NH-N = C R ₁ R ₂) ₂	. 272	Pale Yellow ppt	55 %
13	RCH (CO NH-N = C R ₁ R ₂) ₂	. 260	Pale White ppt	48 %
14	RCH (CO NH-N = C R ₁ R ₂) ₂	. 263	Pale White ppt	56 %
15	RCH (CO NH-N = C R ₁ R ₂) ₂	. 293	White ppt	58 %
16	RCH (CO NH-N = C R ₁ R ₂) ₂	. 125	White ppt	78 %
17	RCH (CO NH-N = C R ₁ R ₂) ₂	. 205	White ppt	70 %
18	RCH (CO NH-N = C R ₁ R ₂) ₂	. 233	White ppt	54 %

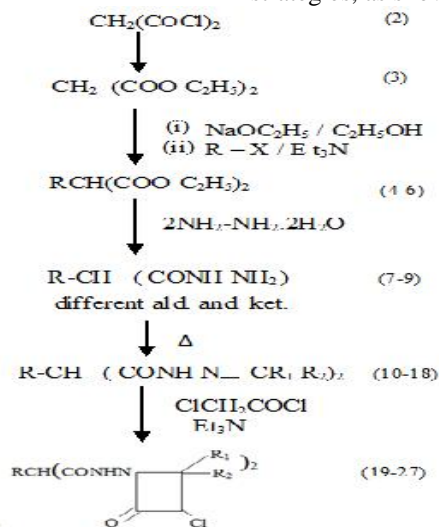
Table 3: Physical Properties of α -lactam

Comp. No.	Structure of Compound	Melting point °C	Color	% Yield
19		121	White ppt	81 %
20		135	White ppt	61 %
21		145	White ppt	62 %
22		78	White ppt	60%
23		122	White ppt	72 %
24		139	White ppt	56 %
25		140	White ppt	55 %
26		92	White ppt	60 %
27		167	White ppt	69%

R= CH₃ CH₂, (CH₃)₂CH, CH₂Ph, R₁= Ph, CH₃CH₂, R₃=H, H, CH₃.

3. Results and Discussion

Present work has been directed toward building new molecules containing active moieties via applying different strategies, as shown below



Scheme-1

R= CH₃ CH₂, (CH₃)₂CH, CH₂Ph, R₁= Ph, CH₃CH₂, Ph, R₃= H, H, CH₃.

FT-IR spectra of 2-Alkyl ethyl malonate absorption bands were show bands at 1745cm^{-1} , 773cm^{-1} due to (C=O) ester, (CH alip) and (C-Cl) respectively. 2-Alkyl malonyl hydrazide prepared by the reaction with hydrazine hydrate then to base-shiff formed by react with different aldehyde and keton. FT-IR of prepared shiff bases were show absorption band at $(1746-1739)\text{cm}^{-1}$, 1242cm^{-1} , 2977cm^{-1} , 1647cm^{-1} , 3419cm^{-1} and 3162cm^{-1} due to

(C=O)ester, (C-O ester), (CH alip), (C=O amide), (NH_2) and (NH) respectively. The last step including Preparation of schiff base (hydrazone) with chloro acetyl chloride to formed - lactam which shows absorption band at 1662cm^{-1} , 1730cm^{-1} , 1188cm^{-1} , 2960cm^{-1} , 3200cm^{-1} and 835cm^{-1} due to (C=O amide), (C=O lactam), (C-O), (CH alip), (NH) and (C-Cl) respectively.

Table 4: FT-IR Spectral data of synthesized compounds

Comp. No.	C=O	C=N	C-O-	-NH ₂	-NH	-CH alip.	C=C arom.	CH arom.	C-N	Other bond
2	1745	-	1228	-	-	2985	-	-	-	773 C-Cl
3	1746 ester	-	1220	-	-	2939	-	-	-	-
4	1739 ester	-	1242	-	-	2977	-	-	-	-
5	1730 ester	-	1238	-	-	2985	-	-	-	-
6	1662 amide	-	1238	-	-	2937	1662	3010	-	-
7	1733	-	1228	3589	3132	2937	-	-	1330	
8	1647 amide	-	1242	3419	3200	2923	-	-	1342	
9	1652 amide	-	1238	3446	3200		1600	3010	1390	
10	1695 amide	1627	1228	3400	3132	2960	-	3020	1320	
11	1645 amide	1627	1226	3400	3250	2960	-	3010	1360	
12	1645 amide	1470	1238	3400	3200	2960	1600	3010	1350	
13	1645	1627	1242	3400	3213	2960	-	3010	1330	
14	1645 amide	1627	1228	3400	3200	2960		3010	1325	
15	1645 amide	1627	1238	3400	3132	2960	1600	3020	1360	
16	1652 amide	1558	1228	3350	3200	-	1600	3020	1390	
17	1652 amide	1558	1188	3350	3200	-	1600	3010	1320	
18	1652 amide	1558	1228	3350	3200	-	1600	3010	1360	
19	1650 amide	-	1188	-	3325	2960	-	-	1310	1776 C=O Lactam 835 C-Cl
20	1650 amide	-	1200	-	3300	2960	-	-	1320	1776 C=O Lactam 830 C-Cl
21	1670 amide	-	1225	-	3325	2960	1600	3010	1330	1770 C=O Lactam 735 C-Cl

22	1698 amide	-	1188	-	3325	2960	-	-	1310	1773 C=O Lactam 770 C-Cl
23	1663 amide	-	1188	-	3300	2960	-	-	1320	1776 C=O Lactam 735 C-Cl
24	1650 amide	-	1238	-	3325	2960	1600	3010	1333	1766 C=O Lactam 820 C-Cl
25	1669 amide	-	1238	-	3350	2960	-	-	1316	1776 C=O Lactam 830 C-Cl
26	1650 amide	-	1188	-	3380	2960	-	-	1330	1775 C=O Lactam 810 C-Cl
27	1698 amide	-	1188	-	3350	2960	1600	3010	1340	1776 C=O Lactam 835 C-Cl

Table 5: ¹H NMR spectral data (ppm) for compounds (10,22,27)

Comop.No	¹ H NMR	¹³ C NMR
10	0.813 (t ,3H, CH ₃ – CH ₂ -CH-), 2.2 (p, 2H, CH ₃ – CH ₂ -CH-), 3.15 (t , 1H, CH ₃ -CH ₂ CH-),8. 4 (S, 1H , NH), 6.5 – 7.09 (m,5H, Ph).	39.7 (CH ₃ – CH ₂ - CH-), 40.3 (CH ₃ –CH ₂ - CH-), 40.6 (CH ₃ – CH ₂ - CH-), 161.8 (O=C-NH-), 133.7 (N= CHPh), 128- 132.7 (Ph),38.6 (C -N).
22	0.9 (d ,3H , CH- (CH ₃) ₂), 1.2 (m,1H, -CH-(CH ₃) ₂),1.64 (d ,1H , -CH- CO), 4.01 (d , 2H, -CHCl). 4.47 (m , 1H, N-HC), 1.9(p,2H,CH CH ₂ -CH ₃), 3.4 (s, 1H , NH).	38.9 (-CH-(CH ₃) ₂), – 38.6 (CH- CH ₃), 76 (-CH-CO), 90.3 (-CHCl), 168.5 (O=C NH), 38.6(-HC-CH ₂ - CH ₃).
27	2.5(d ,2H, CH ₂ - Ph), 3.38 (t,1H , -CH (CONH) ₂), 4.9 (s,1H , NH), 1.2 (s , 3H, -CH ₃ Ph), 7.1 – 7.7 (m ,5 H , -CH ₃ Ph), 3.4 (s , 1H, -CHCl) .	37.13 (CH ₂ - Ph), 126.1–128.01 (CH ₂ - Ph), 45 (-CH-(CONH) ₂), 36.59 (-CH ₃ Ph), 142 (-CH ₃ Ph), 79.8(CH C=O), 73.47 (CH-Cl), 148.4 (O=C-N).

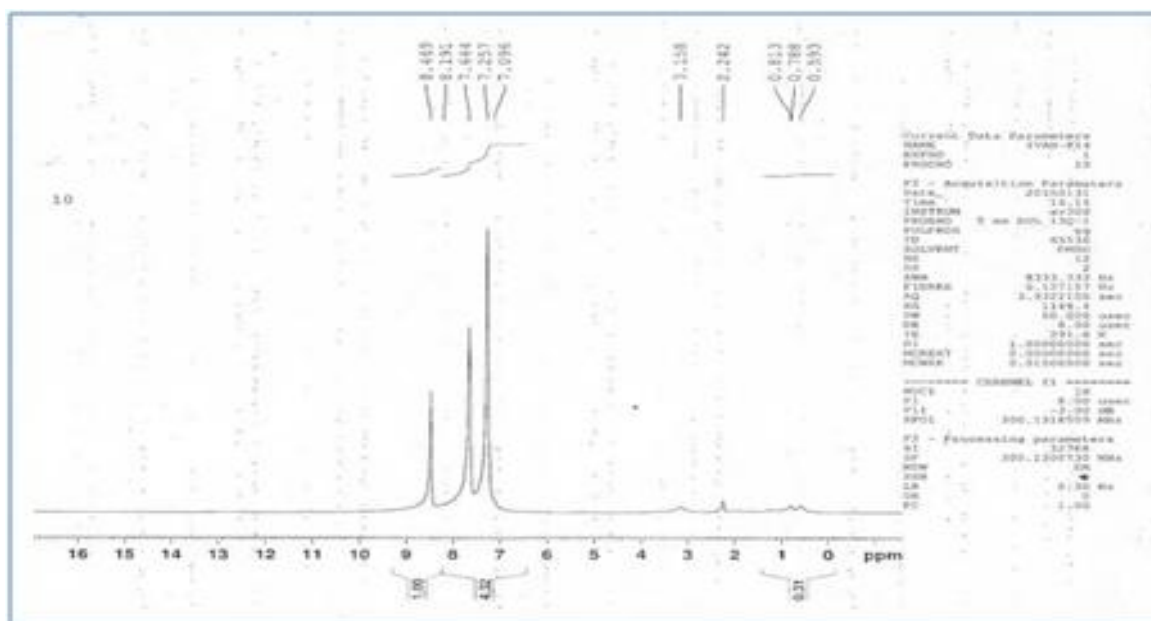


Figure 1: Compound No.10

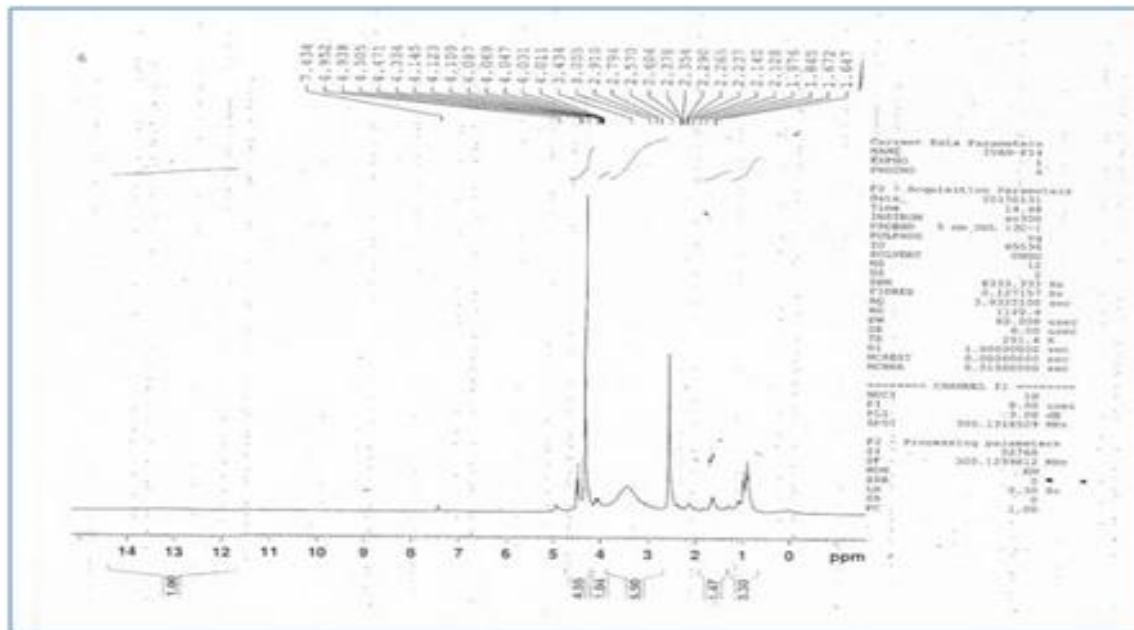


Figure 2: Compound No.22

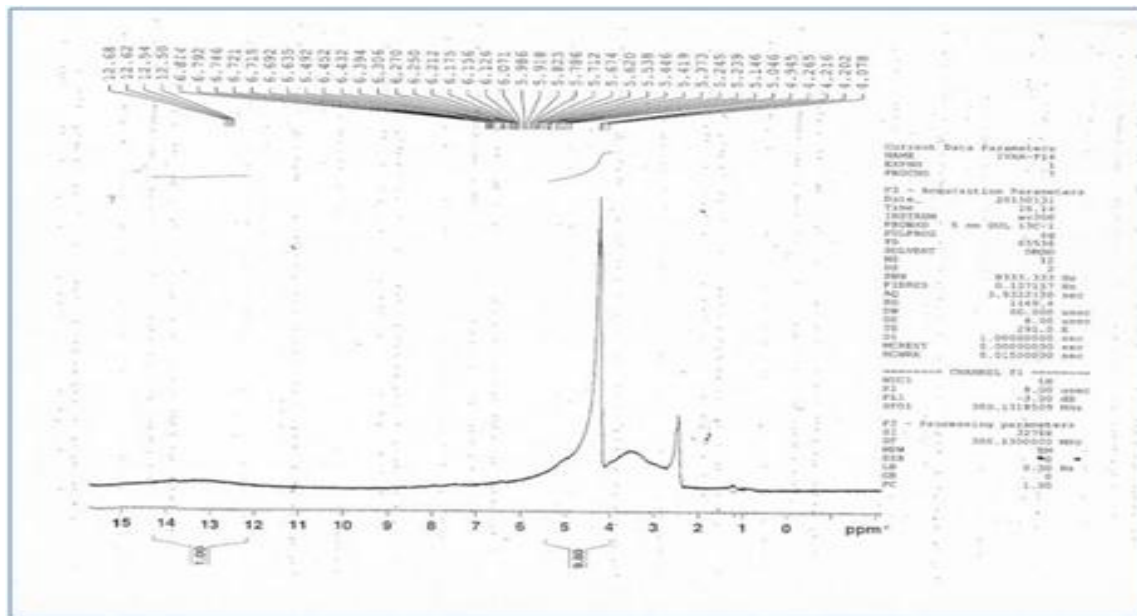


Figure 3: Compound No.27

Table 6: Solubility of Product

No.	Benzen	DMF	DMSO	THF	Water	CCl ₄	CHCl ₃	Aceton	EtOH
2	V.S	V.S	V.S	V.S	P.S	P.S	P.S	V.S	V.S
3	V.S	V.S	V.S	V.S	P.S	P.S	P.S	V.S	V.S
4	V.S	V.S	V.S	V.S	P.S	P.S	P.S	V.S	V.S
5	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
6	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
7	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
8	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
9	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
10	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
11	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
12	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
13	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S

14	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
15	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
16	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
17	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
18	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
19	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
20	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
21	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
22	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
23	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
24	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
25	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
26	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S
27	V.S	V.S	V.S	V.S	P.S	P.S	P.S	P.S	V.S

V .S =Very soluble, In.S = Insoluble, P.S = partial soluble

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