ZANCO Journal of Pure and Applied Sciences
The official scientific journal of Salahaddin University-Erbil
https://zancojournals.su.edu.krd/index.php/JPAS

ISSN (print):2218-0230**, ISSN (online):** 2412-3986**, DOI: http://dx.doi.org/10.21271/zjpas**

RESEARCH PAPER

Synthesis, biological and antioxidant activity of new diamides derived from sulfonamide drug and local anesthesia

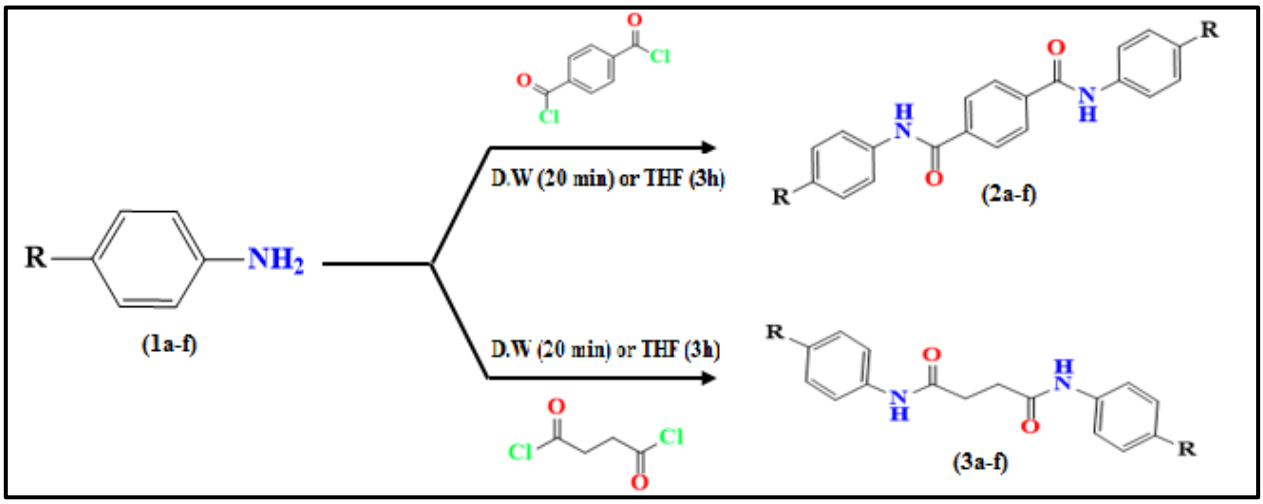
*Rebaz Jawhar Qadr[1], Lana H. Chawshli[1]

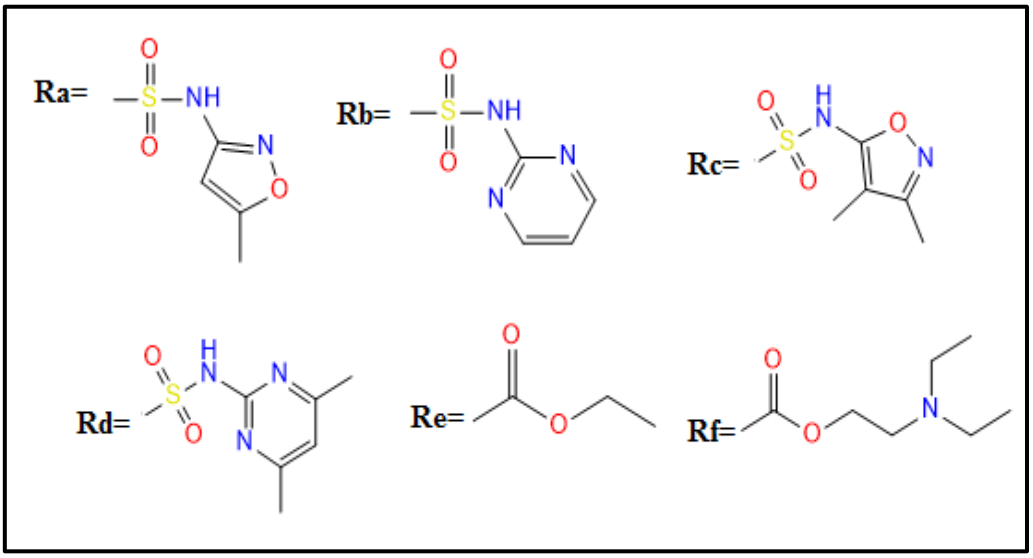
[1]Department of Chemistry- College of Education- Salahaddin University-Erbil, Erbil, Kurdistan Region, Iraq

A B S T R A C T:

A new series of sulfa drug diamides and local anesthesia diamides (2a-f) and (3a-f) have been prepared through the nucleophilic acyl substitution reaction. The pharmacological profile of all newly synthesized compounds was evaluated in vitro for their antibacterial and antifungal activities using the micro broth dilution assay method and antioxidant activity by the DPPH-radical scavenging method. It was revealed that synthesized compounds were exhibiting promising radical scavenging activity and pharmacological activities against both strains. The structures of synthesized diamides were expounded and elucidated on the bases of their FT-IR, ^{1}H- and ^{13}C –NMR spectral data.

KEY WORDS: Synthesis, diamide, sulfonamide drugs, local anesthesia, biological and antioxidant activity
DOI: http://dx.doi.org/10.21271/ZJPAS.35.4.21
ZJPAS (2023) , 35(4);210-229 .





*** Corresponding Author:**
Rebaz Jawhar Qadr
E-mail: rebaz.qadir@student.su.edu.krd
Article History:
Received: 25/10/2022
Accepted: 19/12/2022
Published: 30/08/2023

1. INTRODUCTION:

Sulfa drugs or sulfonamides were introduced in 1935 by the German physician Gerhard Domagk (1895-1964). Prontosil (sulfamidochrysoidine), was the first sulfa medication that had an extraordinary antibacterial action which was tested on diseased laboratory mice (Domagk, 1935). Several clinically relevant medications' biological responses are undergone by the sulfonamide subunits. Chemists' in the organic field are interested in sulfonamides as a result of their variety of biological functions, which include the suppression of carbonic anhydrase(Al-Rashida et al., 2014), antimicrobial (Genç et al., 2008), anticancer (Mun et al., 2012), anti-inflammatory (Borne et al., 1974), and antiviral agents as well as HIV protease inhibitors (Clercq, 2001). Local anesthetics (LA) are natural and synthetic chemicals that may produce reversible, temporary blocking/interruption of the excitability and conductivity of nerve receptors and conductors in direct contact with them. As a result, they cause a local loss of sensitivity and reduce the experience of pain, also known as pain sensitivity. Para aminobenzoic acid is the basic structure of current anesthetics. Local anesthetics such as benzocaine and procaine are widely used. They are active ingredients in a variety of drugs and medications. Procaine is utilized in local, infiltration, spinal, and therapeutic blockade anesthesia. The major use of Benzocaine is as a component of several free-sale formulations for topical use, such as skin creams, dry powder for skin ulcers, throat lozenges, and teething formulations for young children(Plotycya et al., 2018). Amide is an important functional group in organic chemistry because of its presence in peptide and non-peptide natural products, medicinal small compounds, and novel polymeric materials (Carey et al., 2006). Amides, including *N*-Methoxy-*N*-methylamides known as Weinreb amides(Nahm and Weinreb, 1981), morpholine amides(Sengupta et al., 1999), and pyrrolidine amides(Seki and Matsumoto, 1996), are helpful intermediates in the synthesis of aldehydes and ketones. There are several documented synthetic processes for synthesizing amides from different derivatives of carboxylic acid (Montalbetti and Falque, 2005). Due to the amide linkage having significant efficiency in medicine field for future study amides derived from sulfa drugs and local anesthesia may have further application as synthetic organic compounds for new pharmaceutical products.

2.Experimental

2.1Apparatus

Using the Electro Thermal Melting Point model 9100 Apparatus, melting points were recorded by (capillary method) and BIO Tek (800 TS) micro plate reader for antioxidant activity. The infrared spectra were recorded by FTIR (Shimadzu) spectrometer using KBr pellets as the background reference and as a carrier for the sample. ^{1}H-NMR, ^{13}C-NMR and ^{13}C-DEPT 135 NMR spectra were produced by Bruker Spetrometer (400 MHz) and using DMSO (Dimethylsulfixide) as a solvent for sample dissolving at Isfahan University, chemical shifts are displayed in ppm. All of the chemical reagents employed were of the analytical quality and were from commercial sources (Sigma Aldrich, Gleantham, Scharlau, Fluka).

3.General procedures for synthesis (2a-f) and (3a-f):

3.1Synthesis of diamides derived from N1,N4-bis(4-sulfamoylphenyl)terephthalamide (2a-d):

Sulfamethoxazole (2 mmol) were added to (15 mL) of distilled water, according to the procedure of (Samad and Hawaiz, 2019) with modification, (3 mmol) of NaOH (0.12 g)was added then cooled in an ice bath after that terphthaloyl chloride (1 mmol) (0.243 g) was added in three portions with continues stirring for about (20 min), finally, the precipitate filtered off, washed by distilled water and recrystallized with ethanol, and the same process was done for the (sulfadiazine, sulfisoxazole, sulfamethazine).

3.2Synthesis of diamides derived from N1,N4-bis(4-sulfamoylphenyl)succinamide (3a-d)

Sulfamethoxazole (2 mmol) were added to (15 mL) of distilled water, according to the same procedure of previous synthesis (Samad and Hawaiz, 2019) with modification, (3 mmol) of NaOH (0.12 g)was added then cooled in an ice bath after that succinyl chloride (1 mmol) (0.113 g) was added in three portions with continues stirring for (20 min), finally, the precipitate filtered off, washed by distilled water and recrystallized from ethanol, and the same process was done for the (sulfadiazine, sulfisoxazole, sulfamethazine).

3.3Route 2 synthesis of diamides derived from diethyl 4,4'-(terephthaloylbis(azanediyl))dibenzoate (2e & f):

According to the procedure of (Yasmeen et al., 2010) with modification Benzocaine or procaine (2 mmol) was added to (30 mL) THF, then (2 mmole) of K_2CO_3 was added to the solution of amine after that terphthaloyl chloride (1 mmol) (0.243 g) added, then stirred for (3h) at room temperature, then the precipitate filtrated off and recrystallized from ethanol.

3.4Synthesis of diamides derived from diethyl 4,4'-(succinylbis(azanediyl))dibenzoate (3 e & f)

According to the same procedure of (Yasmeen et al., 2010) with modification Benzocaine or procaine (2 mmol) was added to (30 mL) THF, then (2 mmol) of K_2CO_3 was added to the solution of amine after that succinyl chloride (1mmol) (0.113 g) added, then stirred for (3h) at room temperature, then the precipitate filtrated of and recrystallized from ethanol.

4.Biological Activity

The agar dilution(Wiegand et al., 2008) method was employed to evaluate the preliminary pharmacological profiles of the new Diamides against *E. coli* and *S. aureus* as anti-bacterial and *Candida albicans* as anti-fungal. Five different concentrations of 200, 400, 600, 800, and 1000 µg/mL were prepared from each synthesized compound by dissolved in dimethyl sulfoxide (DMSO) which was used as a negative control.

5.DPPH free radical scavenging assay

The antioxidant activity of synthesized diamides were resolved based on its scavenging ability to trap the stable free radical 2,2-diphenyl-2-picryl hydrazyl (DPPH). Free radical scavenging was determined according to the reported method (Saleh et al., 2019a) with some modifications. A stock solution of DPPH (4 mg/100 ml) was freshly prepared using methanol as a solvent and incubated for further use. The samples of diamide compounds (1000 ppm) were prepared by dissolving of the synthesized compounds in DMSO. The synthesized compound diluted to different concentrations (400,600, 800, and 1000 ppm) then 40 µL of diluted samples added to 160 µL of DPPH alcoholic solution. After incubation at 37 ^{0}C for half hour, the absorbance was recorded at 517 nm against a blank (DPPH 160 µL: methanol 40 µL) (El-Sayed et al., 2011) , where all measurements were made in triplicate and averaged. The percentage of inhibition of DPPH radical scavenging was calculated as follows (Kadhim et al., 2019):

$$\text{Radical scavenger activity } \% = \frac{A\ control - A\ sample}{A\ control} \text{ X } 100$$

6.Result and discussion

We used two synthetic routes for the synthesis of diamides. Comparing between them, fist route has some good points over second route. The first route uses water as solvent, which is safer and cheaper than THF. Moreover, the first route does not take as much time as the second.

The IR spectra were used to monitor the reaction by new carbonyl peak formation of amides group and the disappearing of primary amine peaks. Spectral data analysis such as (FT-IR, ^{1}H-NMR, and ^{13}C-NMR) of the synthesized compounds of (2a-f) and (3a-f) are shown in Table 1 and Table 2 respectively.

The IR spectrum of compound (2a) Figure (1) and Table (2) confirms the formation of amide linkage by showing only one new absorption band at 3269.34 cm^{-1} due to N-H stretching of amide group and as a compare with the starting material (amine) that has two peaks due to symmetric and asymmetric stretching, the infrared spectrum also displayed a characteristic band at 1666.50 cm^{-1} resulting from the carbonyl group of the amide moiety and it was shifted to lower frequency due to resonance while the acid chloride appeared at

1800 cm^{-1}. On the other hand, the ^{1}H-NMR spectrum has supported the infrared finding by showing two singlet signals at 10.41 and 10.57 ppm for both N-H of amide and sulfonamide groups respectively as shown in Figure(2). The ^{1}H-NMR spectrum has also been verified the projected structure by observing two characteristic singlet signals at 2.1 and 5.76 ppm the first related to the methyl group on the oxazole ring, second for C-H of oxazole, In addition, the (12) aromatic protons of the benzene ring resonated in the 7.6-8.09 ppm region.

In ^{13}C-NMR spectrum of synthesized compound (2a), carbonyl groups (C_{10} and C_{17}) of (2a) appeared at 165.58 and 164.92 ppm respectively because of having the same chemical environment, as shown in Figure (3). Peaks at 12.25 and 97.03 ppm appeared at DEPT-135 figure (4) confirming the presence of methyl group on (C_{26}) and CH group of (C_{25}) respectively in oxazole moiety. Moreover aromatic carbons were confirmed in the range of 119-128 ppm.

The IR spectrum conferred synthesized compound (3f) values at 1693.5 cm^{-1} confirms the presence of C=O group of amide linkage it was shifted to lower energy because the changing in dipolmoment as a result of resonance as while the acid chloride appear at 1800 cm^{-1} and 1703.14 cm^{-1} confirms the presence of C=O of ester group, the peak at 3356.14 cm^{-1} confirms the presence of N-H for amide group which shown in the Figure (5). From ^{1}H-NMR of synthesized compound (3f) showed signal at 10.56 ppm related to proton of N-H which confirms the formation of new amide group while the N-H of the starting material appeared at 5.5ppm because the protons are in deshielding region due to resonance of lone pair of nitrogen with the aromatic system, the aromatic protons are between 7.60-7.89 ppm that appeared in the Figure (6). From ^{13}C-NMR spectrum of compound (3f) peaks at 165.34 & 171.06 ppm again confirms the presence of carbonyl of amide and ester groups that depicted in Figure (7). The DEPT-135 NMR spectrum the compound showed, the peaks of carbon for methyl groups connected to (C_1 and C_2) both appeared at 12.05 ppm because of having the same chemical environment, C_{13}, C_1, C_3 and C_4 confirmed at 31.21, 47.05, 50.82 and 62.85 ppm respectively and the aromatic carbons appeared between 112-131 ppm that shown in Figure (8).

The antibacterial profile results described in table (5) and table (6) revealed that the tested compounds exhibited significant activity, according to the results, the tested compounds (2a-f) and (3a-f) displayed no significant difference between the potency of synthesized compounds and amines against *Escherichia coli gram-negative*, *Staphylococcus aureus gram-positive* and *Candida albicans Fungi*.

The capability of diamides to trap DPPH radicals is dependent on their capability to capture of pair and unpaired radicals(Gülşen et al., 2007). The decrease ability of DPPH radical is controlled by the lessening in its absorbance at 5l7 nm, initiated by anti-oxidants. The lessening in absorbance of DPPH radical is brought about by antioxidants, due to the reaction between diamides compounds and radicals of DPPH, advances, which results in the searching of the radical by hydrogen gift. It is outwardly recognizable as an adjustment in shading from purple to yellow. Thus, DPPH is generally utilized as a substrate to assess the anti-oxidative action(Ray et al., 2013).

Ascorbic acid has been employed as a standard compound for antioxidant activity. The results indicated in (µg/mL), the free radical scavenging capability of synthesized diamides shown in Table (7). Due to the absence of hydroxyl and electron-donating methoxy group, the synthesized showed moderate antioxidant activity with DPPH, but among the synthesized compounds (**2b**) has a highest and (**3f**) the least antioxidant activity%. The results compared with ascorbic acid as a control (Saleh et al., 2019b).

7.Conclusion

Some new diamides derived from sulfa drugs and local anesthesia were prepared with the goal of achieving good anti-fungal, antibacterial and antioxidant activities under available laboratory conditions. For this study we concluded that compounds containing bis-amides linkage have no significance difference in bacteriostatic and bactericidal effects against *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans* as a compare with drugs used for the preparation, but not at the same concentrations, and they have moderate antioxidant precedency against DPPH as

a compare with standard ascorbic acid (vitamin C). We concluded that the presence of amide linkage is important for antibacterial activity and the data recorded in this study may be a supportive guide for the medicinal chemists who are studying in this area.

Conflict of interest:

There is no Conflict of interest.

Table (1) Some Physical properties and significant IR peaks of for diamides (2a-f) and & (3a-f)

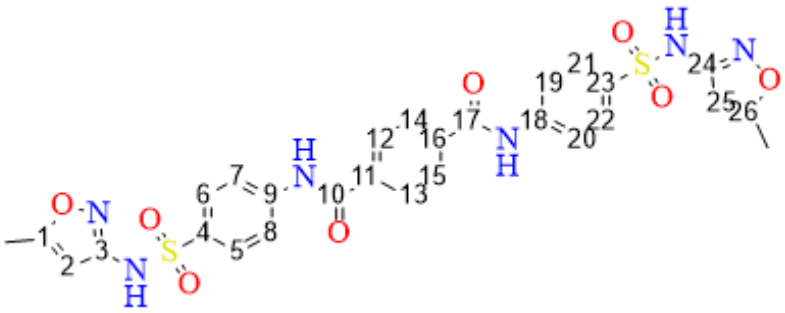
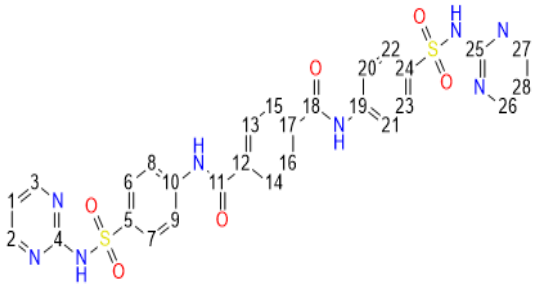
Compounds	*Molecular formula*	*M.wt g/mole*	*M.P Decomposed*	*Yield%*
1a	$C_{28}H_{24}O_8N_6S_2$	636.65	285 – 290 ^oC	70
1b	$C_{28}H_{22}O_6N_8S_2$	630.65	270 - 278 ^oC	73
1c	$C_{30}H_{28}O_8N_8S_2$	664.71	244 - 250 ^oC	88
1d	$C_{32}H_{30}O_6N_8S_2$	686.76	290 - 295 ^oC	82
1e	$C_{26}H_{24}O_6N_2$	460.49	262 - 268 ^oC	70
1f	$C_{34}H_{42}O_6N_4$	602.73	193 - 200 ^oC	95
2a	$C_{24}H_{24}O_6N_8S_2$	588.61	220 - 225 ^oC	65
2b	$C_{24}H_{22}O_6N_8S_2$	582.61	174 - 180 ^oC	75
2c	$C_{26}H_{28}O_8N_6S_2$	616.66	209 - 215 ^oC	65
2d	$C_{28}H_{30}O_6N_8S_2$	638.72	213 - 220 ^oC	60
2e	$C_{22}H_{24}O_6N_2$	412.44	269 - 276 ^oC	68
2f	$C_{30}H_{42}O_6N_4$	554.69	185 - 190 ^oC	60

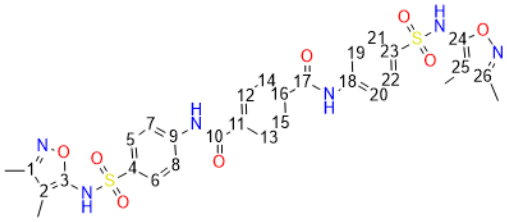
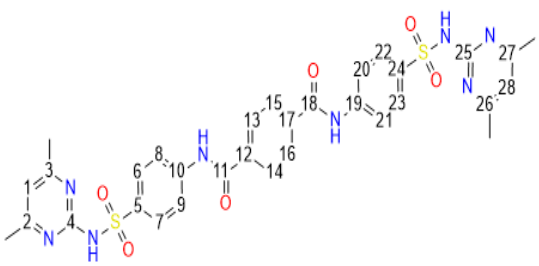
Table (2) some significant IR frequencies of* (cm^{-1}) *synthesized diamides (2a-f)&(3a-f)

Compounds	**N-H (sulfonamide)**	**N-H (amide)**	**C-H (aliphatic)**	**C=O (ester)**	**C=O (amide)**
2a	3354.21	3269.34	2337.72	-	1666.50
2b	3417.86	330.20	2950	-	1647.21
2c	3242.34	3107.32	2843.07	-	1647.21
2d	3304.06	3111.18	-	-	1658.78
2e	-	3360	2980	1697	1689.64
2f	-	3367.71	2968.45	1705	1662.64

Compounds	**N-H (sulfonamide)**	**N-H (amide)**	**C-H (aliphatic)**	**C=O (ester)**	**C=O (amide)**
3a	3375.43	3278.99	2950	-	1683.86
3b	3387	3242.34	2950	-	1691
3c	3228.84	3113.11	2850	-	1685.79
3d	3365.78	.109.25	2960	-	1699
3e	-	3360	2980	1700	1689.64
3f	-	3356.14	2970.38	1705	1693.5

Table (3) ^{1}H NMR and ^{13}C NMR assignment of diamides (2a-f)

	**N1,N4-bis(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)terephthalamide (2a):** $C_{28}H_{24}O_8N_6S_2$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 10.57(S, 2H, sulfonamide N-H), 10.41(S, 2H, amide N-H), (12H of Aromatic), 5.76(S, 2H, C_2 and C_{25}), 2.1(S, 6H, methyl of C_1 and C_{26}). **^{13}C-NMR (δ, ppm):** 165.98:C1 and C_{26} of oxazole, 164.92: C_{10} and C_{17} of C=O of amide, 142.6: C_3 and C_{24} of oxazole, 139.7: C_4 and C_{23}, 137.34: $C_{11}$and C_{16}, 140.01: C_9 and C_{18}, 128.9: C_5, C_6, C_{21} and C_{22}, 127.8: C_{12}, C_{13}, C_{14} and C_{15}, 119.39: C_7, C_8, C_{19} and C_{20}, 12.25: methyl of C_1 and C_{26}.
	**N1,N4-bis(4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)terephthalamide (2b):** $C_{28}H_{22}O_6N_8S_2$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 11.32(S, 2H, sulfonamide N-H), 10.20(S, 2H, amide N-H), 8.48(d, 4H): C-H of C_2, C_3, C_{26} and C_{27}, 8.18(S, 4H): C-H of C_{13}, C_{14}, C_{15} and C_{16}, 7.96(d, 4H): C-H C_8, C_9, C_{20} and C_{21}, 7.72(d, 4H): C-H of C5 and C_{24}, 7.02: C-H of C_1 and C_{28}. **^{13}C-NMR (δ, ppm):** 169.3: C_4 and C_{25}, 164.7: C_{11} and C_{18} of amide C=O, 157.9: C_2, C3, C_{26} and C_{27}, 157.9: C_2, C_3, C_{26} and C_{27}, 141.1: C_{10} and C_{19}, 135.3: C_5 and C_{24}, 134.2: C_{12} and C_{17}, 129.4: C_6, C_7, C_{22} and C_{23}, 127.6: C13, C14, C15 and C16, 118: C8,C9, C_{20}, C_{21}, 115.3: C_1 and C_{28}.

	**N1,N4-bis(4-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)phenyl)terephthalamide (2c):** $C_{30}H_{28}O_8N_8S_2$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 10.64(S, 2H, sulfonamide N-H), 10.20(S, 2H, amide N-H), 8.18(S, 4H) aromatic C-H of C_{12}, C_{13}, C_{14} and C_{15}, 7.96(d, 4H) aromatic C-H of C_7, C8, C_{19} and C_{20}, 7.72(d, 4H) aromatic C-H of C_5, C_6, C_{21} and C_{22}, 2.42(S, 12H) C-H of methyl groups of isoxazole. **^{13}C-NMR (δ, ppm):** 164.7: C_{10} and C_{17} of amide C=O, 159.9: C1 and C_{26} of isoxazole, 158.9: C_3 and C_{24} of isoxazole, 141.1: of C_9 and C_{18}, 135.3: of C_4 and C_{23}, 134.2: of C_{11} and C_{16}, 129.4: of C_5, C_6, C_{21} and C_{22}, 127.6: of C_{12}, C_{13}, C_{14} and C_{15}, 118: of C_7, C_8, C_{19} and C_{20}, 100.5: of C_2 and C_{25}, 10.5: of methyl groups of C_1 and C_{26}, 6.5: methyl groups of C_2 and C_{25}.
	**N1,N4-bis(4-(N-(4,6-dimethylpyrimidin-2-yl)sulfamoyl)phenyl)terephthalamide (2d):** $C_{32}H_{30}O_6N_8S_2$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 11.36(S, 2H, sulfonamide N-H), 10.20(S, 2H, amide N-H), 8.18(S, 4H) aromatic C-H of C_{13}, C_{14}, C_{15} and C_{16}, 7.96(d, 4H) aromatic C-H of C_8, C_9, C_{20} and C_{21}, 7.72(d, 4H) aromatic C-H of C_6, C_7, C_{22} and C_{23}, 6.74(S, 2H) C-H of C_1 and C_{28}, 2.25(S, 12H) of methyl groups of sulfadiazine. **^{13}C-NMR (δ, ppm):** 168.5: C_4 and C_{25}, 166.6: C_2, C_3, C_{26} and C_{27}, 164.7: C_{11} and C_{18} of amide C=O, 141.1: C_{10} and C_{19}, 135.3: C_5 and C_{24}, 134.2: C_{12} and C17, 129.4: C_6, C_7, C_{22} and C_{23}, 127.6: C_{13}, C_{14}, C_{15} and C_{16}, 118: C_8, C_9, C_{20} and C_{21}, 110: C_1 and C_{28}, 24.3: CH_3 of C_2, C_3, C_{26} and C_{27}.

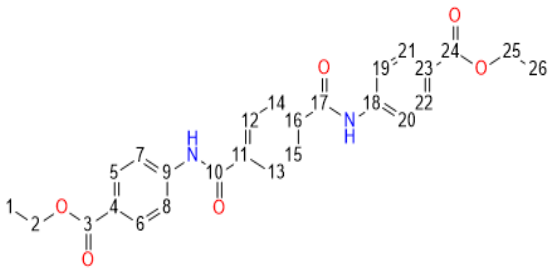
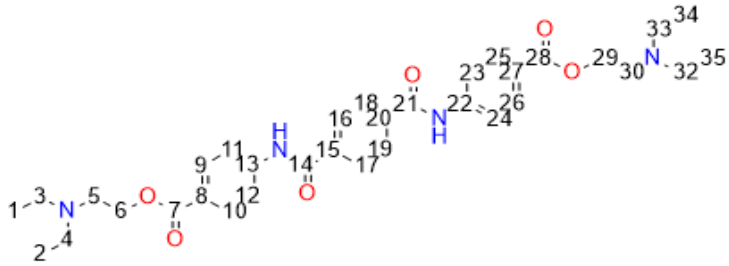
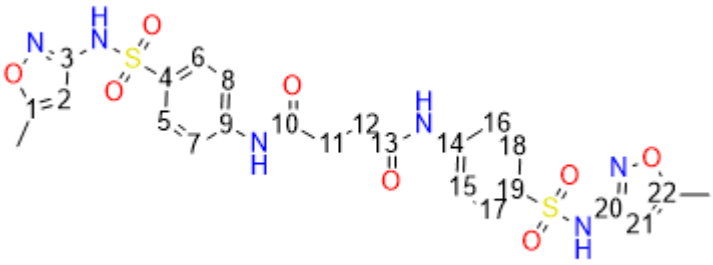
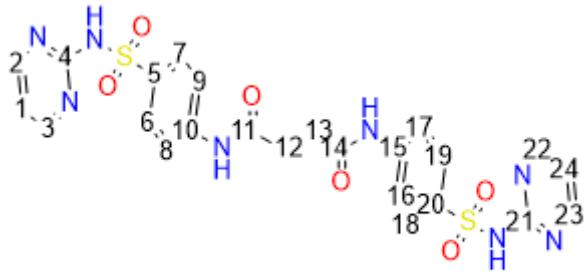
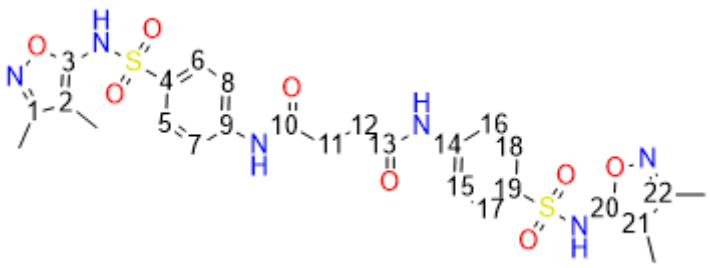
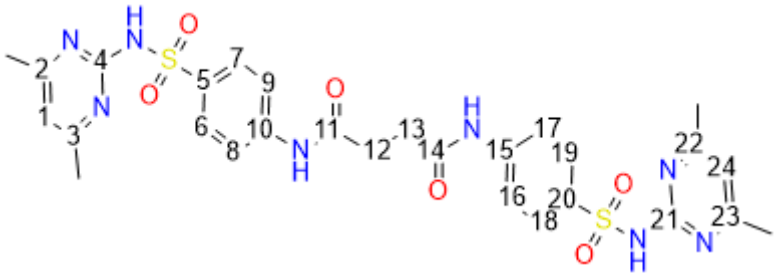
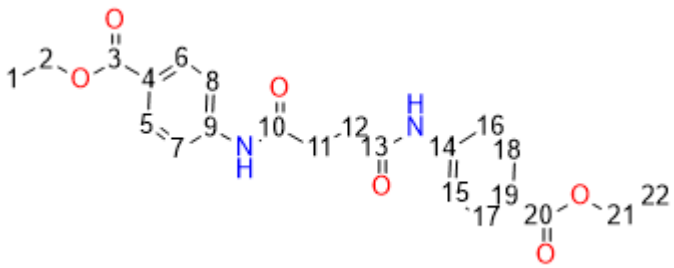
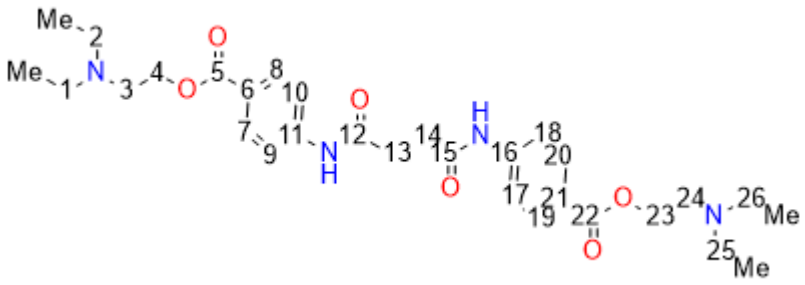
	**diethyl 4,4'-(terephthaloylbis(azanediyl))dibenzoate (2e):** $C_{26}H_{24}O_6N_2$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 10.73(S, 2H, amide N-H), (12H of Aromatic), 4.3(Q, 4H) C-H of C_2 and C_{25}, 1.3(T, 6H) of CH_3 groups of C_1 and C_{26}. **^{13}C-NMR (δ, ppm):** 165.9: C_3 and C_{24} of ester C=O, 164.7: C_{10} and C_{17} of amide C=O, 142.2: C_9 and C_{18}, 134.2: C_{11} and C_{16}, 130: C_5, C_6, C_{21} and C_{22}, 127.6: C_{12}, C_{13}, C_{14} and C_{15}, 125.7: C_4 and C_{23}, 118.7: C_7, C8, C_{19} and C_{20}, 60.9: C_2 and C25, 14: C_1 and C_{26}.
	**bis(2-(diethylamino)ethyl) 4,4'-(terephthaloylbis(azanediyl))dibenzoate (2f):** $C_{34}H_{42}O_6N_4$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 10.73(S, 2H, amide N-H), (12H of Aromatic), 4.30(t, 4H) CH_2 of C_6 and C_{29}, 2.89(q, 8H) CH_2 of C_3, C_4, C_{32} and C_{33}, 2.78(t, 4H) CH_2 of C5 and C_{30}, 1.14(t, 12H) CH_3 groups of C_1, C_2, C_{34}, C_{35}. **^{13}C-NMR (δ, ppm):** 165.9: C_7 and C_{28} of ester C=O, 164.7: C14 and C21 of amide C=O, 142: C_{13} and C_{22}, 134.2: C_{15} and C_{20}, 130.1: C_9, C_{10}, C_{25} and C_{26}, 127.6: C_{16}, C_{17}, C_{18} and C_{19}, 125.7: C_8 and C_{27}, 118.7: C_{11}, C_{12}, C_{23} and C_{24}, 63.2: C_6 and C_{29}, 54.2: C_5 and C_{30}, 49.6: C_3, C_4, C_{32} and C_{33}, 13.3: C_1, C_2, C_{34} and C_{35}.

Table (4) ^{1}H NMR and ^{13}C NMR assignment of diamides (3a-f)

	**N1,N4-bis(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)succinamide (3a):** $C_{24}H_{24}O_6N_8S_2$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 11.04(S, 2H, sulfonamide N-H), 10.16(S, 2H, amide N-H), (8H of Aromatic), 6.09(S, 2H) C-H of C_2 and C_{21}, 2.65(S, 4H) CH_2 of C_{11} and C_{12}, 2.29(S, 6H) of two CH_3 substituent. **^{13}C-NMR (δ, ppm):** 177.4: C_{10} and C_{13} of amide C=O, 169.6: C_1 and C_{22}, 150: C_3 and C_{20}, 141.7: C_9 and C_{14}, 135.3: C_4 and C_{19}, 129.4: C_5, C_6, C_{17} and C_{18}, 118: C_7, C_8, C_{15} and C_{16}, 95: C_2 and C_{21}, 31: C_{11} and C_{12}, 12 ppm: two CH_3 groups of C_1 and C_{22}.
	**N1,N4-bis(4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)succinamide (3b):** $C_{24}H_{22}O_6N_8S_2$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 11.32(S, 2H, sulfonamide N-H), 10.16(S, 2H, amide N-H), 8.48(d, 4H) C-H groups of C_2, C_3, C_{22} and C_{23}, (8H of Aromatic), 7.02(t, 2H) C-H of C_1 and C_{23}, 2.65(S, 4H) CH_2 C_{12} and C_{13}. **^{13}C-NMR (δ, ppm):** 177.4: C_{11} and C_{14} of amide C=O, 169.3: C_4 and C_{21}, 157.9: C_2, C_3, C_{22} and C_{23}, 141.7: C_{10} and C_{15}, 135.3: C_5 and C_{20}, 129.4: C_6, C_7, C_{18} and C_{19}, 118: C_8, C_9, C_{16} and C_{17}, 115.3: C_1 and C_{23}, 31.6: C_{12} and C_{13}.

	**N1,N4-bis(4-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)phenyl)succinamide (3c):** $C_{26}H_{28}O_8N_6S_2$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 10.54(S, 2H, sulfonamide N-H), 10.16(S, 2H, amide N-H), (8H of Aromatic), 2.65(S, 4H) CH_2 of C_{11} and C_{12}, 2.42(S, 12H) of methyl groups of C_1, C_2, C_{21} and C_{22}. **^{13}C-NMR (δ, ppm):** 177.4: C_{10} and C_{13} of amide C=O, 159.9: C1 and C_{22}, 158.9: C_3 and C_{20}, 141.7: C_9 and C_{14}, 135.3: C_4 and C_{19}, 129.4: C_5, C_6, C_{17} and C_{18}, 118: C_7, C_8, C_{15} and C_{16}, 110.5: C_2 and C_{21}, 31.6: C_{11} and C_{12}, 10.5: two methyl groups of C1 and C_{22}, 6.5: two methyl groups of C_2 and C_{21}.
	**N1,N4-bis(4-(N-(4,6-dimethylpyrimidin-2-yl)sulfamoyl)phenyl)succinamide (3d):** $C_{28}H_{30}O_6N_8S_2$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 11.36(S, 2H, sulfonamide N-H), 10.16(S, 2H, amide N-H), (8H of Aromatic), 6.74(S, 2H) C-H of C_1 and C_{24}, 2.65(S, 4H) CH_2 of C_{12} and C_{13}, 2.25(S, 12H) four methyl groups. **^{13}C-NMR (δ, ppm):** 177.4: C_{11} and C_{14} of amide C=O, 168.5: C_4 and C_{21}, 166.6: C_2, C_3, C_{22} and C_{23}, 141.7: C_{10} and C_{15}, 135.3: C_5 and C_{20}, 129.4: C_6, C_7, C_{18} and C_{19}, 118: C_8, C_9, C_{16} and C_{17}, 110: C_1 and C_{24}, 31.6: C_{12} and C_{13}, 24.6: methyl groups.
	Diethyl 4,4'-(succinylbis(azanediyl))dibenzoate **(3e):** $C_{22}H_{24}O_6N_2$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 9.97(S, 2H, amide N-H), (8H of Aromatic), 4.3:(q, 4H) CH_2 of C_2 and C_{21}, 2.65(S, 4H) CH_2 of C_{11} and C_{12}, 1.3(t, 6H) two methyl groups of C_1 and C_{22}. **^{13}C-NMR (δ, ppm):** 177.4: C_{10} and C_{13} of amide C=O, 165.9: C_3 and C_{20} of ester C=O, 142.8: C_9 and C_{14}, 130.1: C_5, C_6, C_1 and C_{16}, 125.7: C_4 and C_{14}, 118: C_7, C_8, C_{15} and C_{16}, 60.9: C_2 and C_{21}, 31.6: C_{11} and C_{12}, 14.6: C_1 and C_{22}.

	**bis(2-(diethylamino)ethyl) 4,4'-(succinylbis(azanediyl))dibenzoate (3f):** $C_{30}H_{42}O_6N_4$ **^{1}H-NMR** (δ, ppm) (400MHz DMSO): 10.56(S, 2H, amide N-H), (8H of Aromatic), 4.26(d, 4H) CH_2 of C_4 and C_{23}, 3.4(q, 8H) CH_2 of C_1, C_2, C_{25} and C_{26}, 2.76(t, 4H) CH_2 of C_3 and C_{24}, 2.53(S, 4H) CH_2 of C_{13} and C_{14}, 0.96(t, 12H) of four methyl groups. **^{13}C-NMR (δ, ppm):** 171: C_{12} and C_{15} of amide C=O, 165.3: C_5 and C_{22} of ester C=O, 143.7: C_{11} and C_{16}, 130.2: C_7, C_8, C_{19} and C_{20}, 123.8: C_6 and C_{21}, 118.2: C_9, C_{10}, C_{17} and C_{18}, 62.8: C_{23} and C_4, 50.8: C_3 and C_{24}, 47.06: C_1, C_2, C_{25} and C_{26}, 31.2: C_{13} and C_{14}, 12.05: four methyl groups.

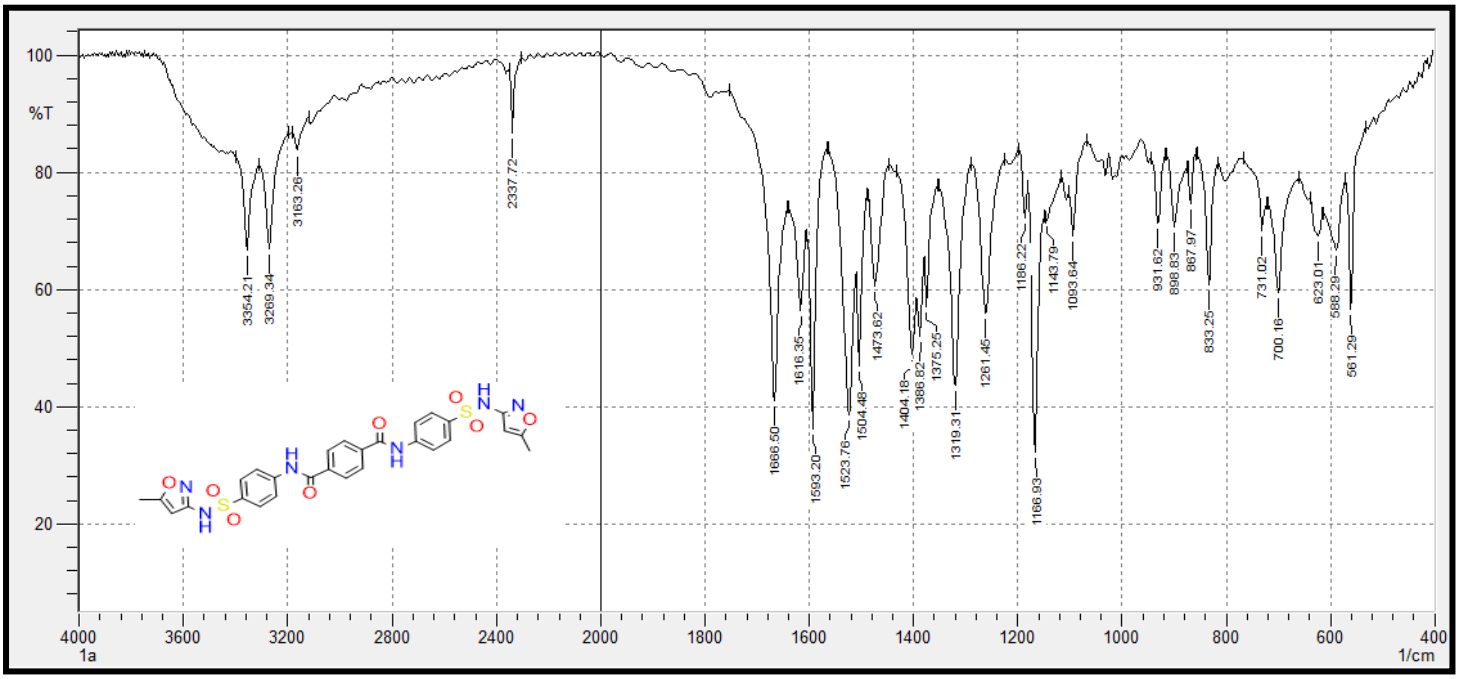


Figure (1) IR spectrum of compound N1,N4-bis(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)terephthalamide (2a)

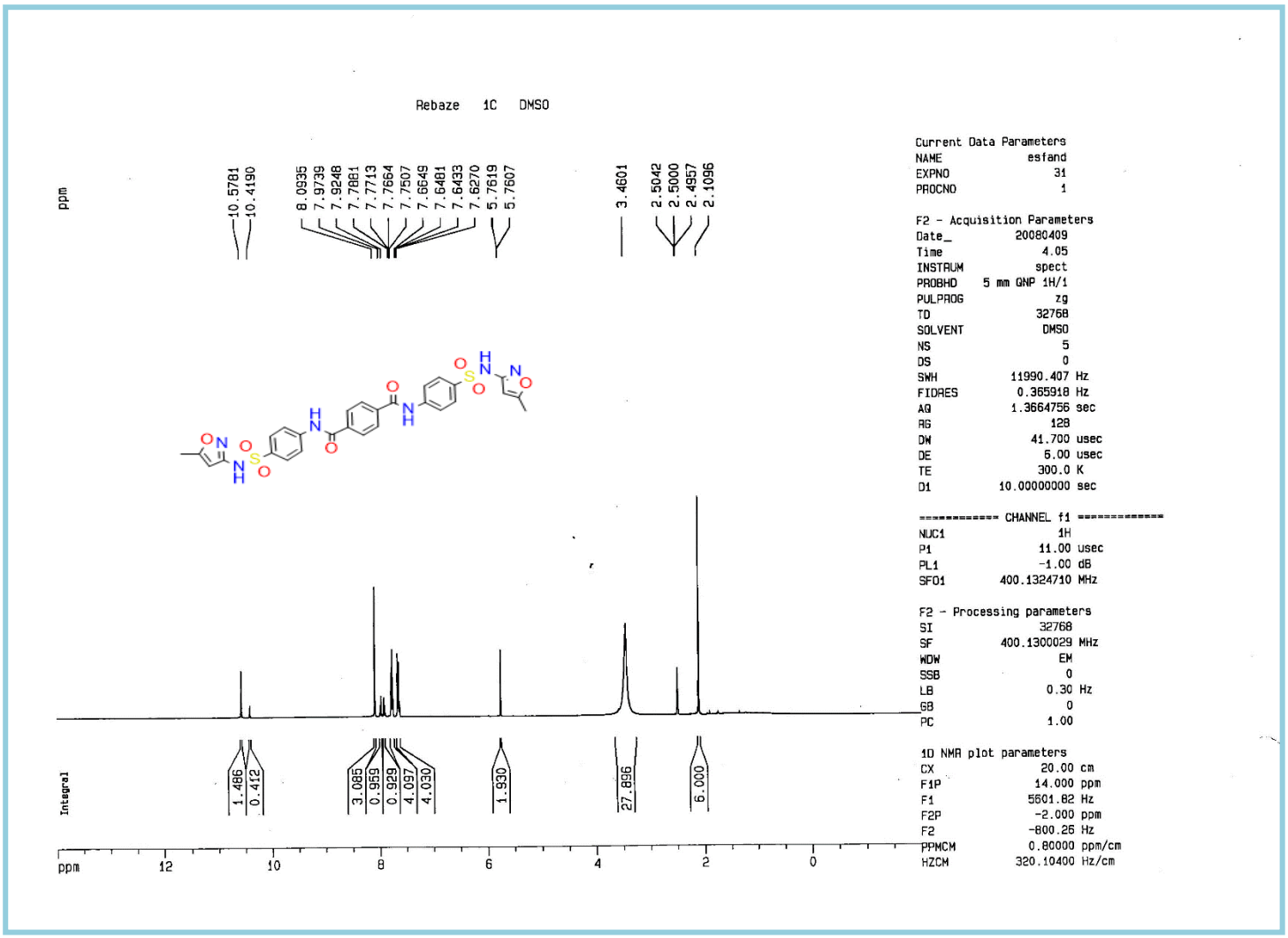


Figure (2) ^{1}H NMR of compound N1,N4-bis(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)terephthalamide (2a)

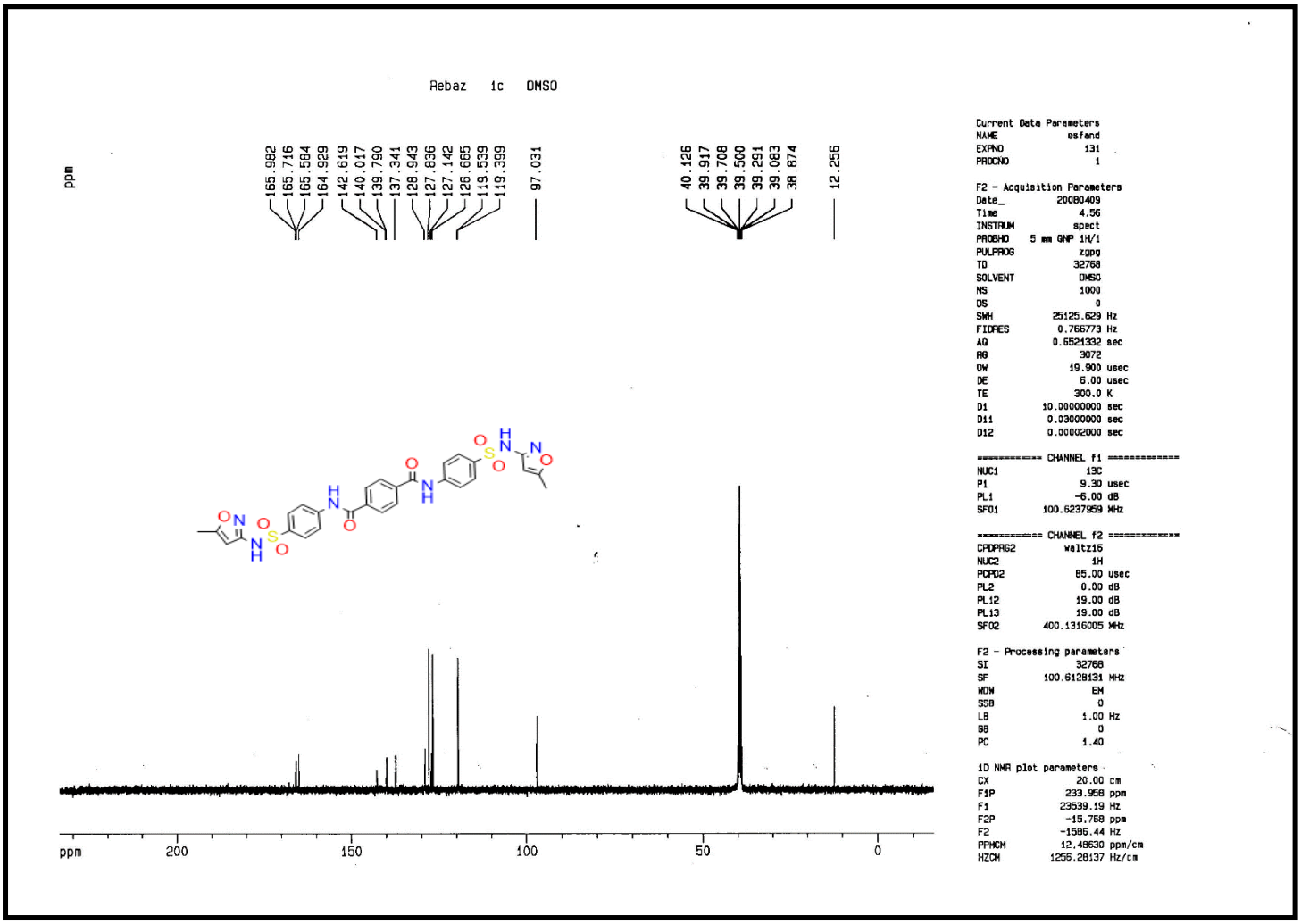


Figure (3) ^{13}C NMR of compound N1,N4-bis(4-(N-(5-methylisoxazol-3 yl)sulfamoyl)phenyl)terephthalamide (2a)

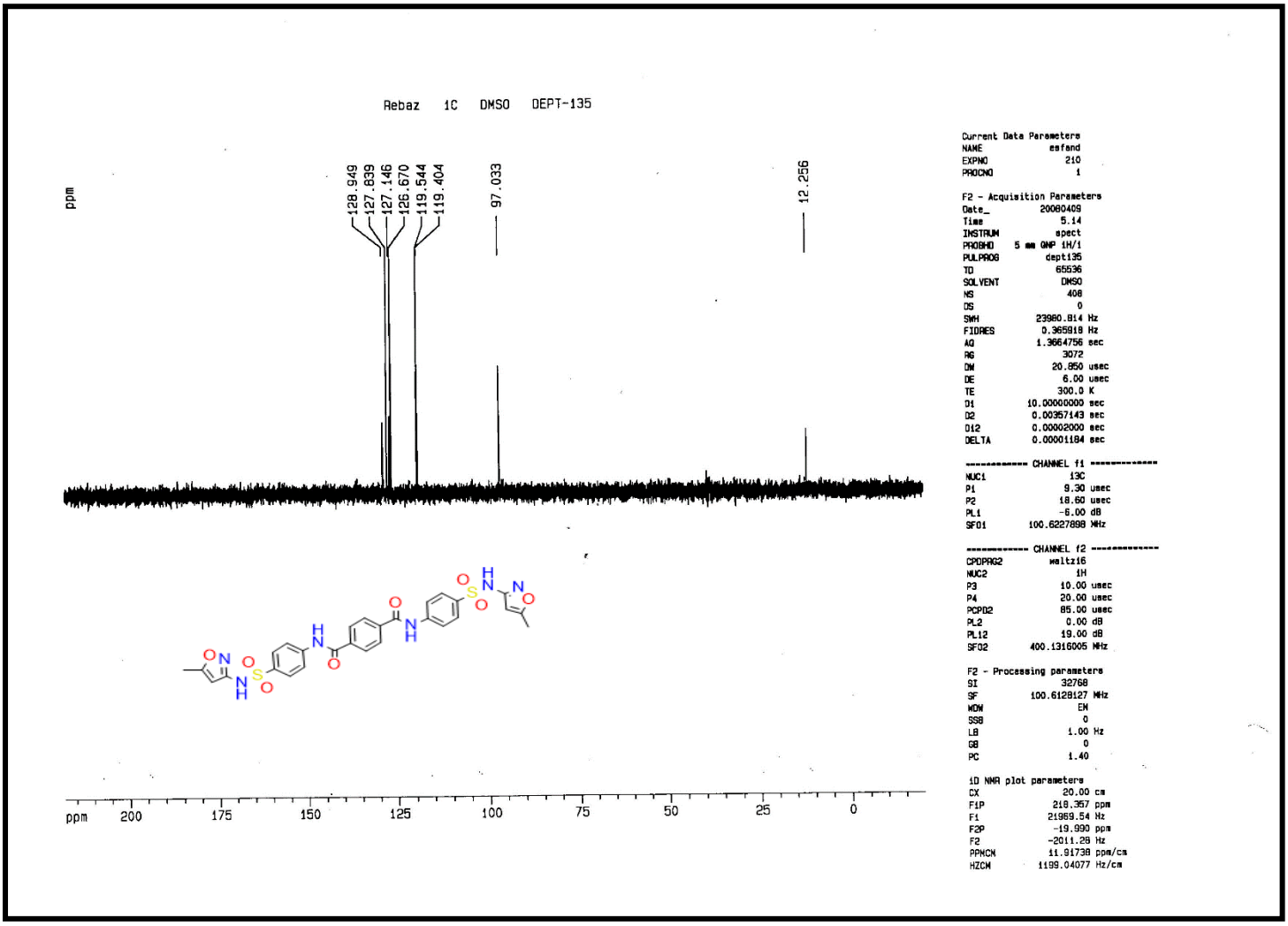


Figure (4) DEPT-135 NMR of compound N1,N4-bis(4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)terephthalamide (2a)

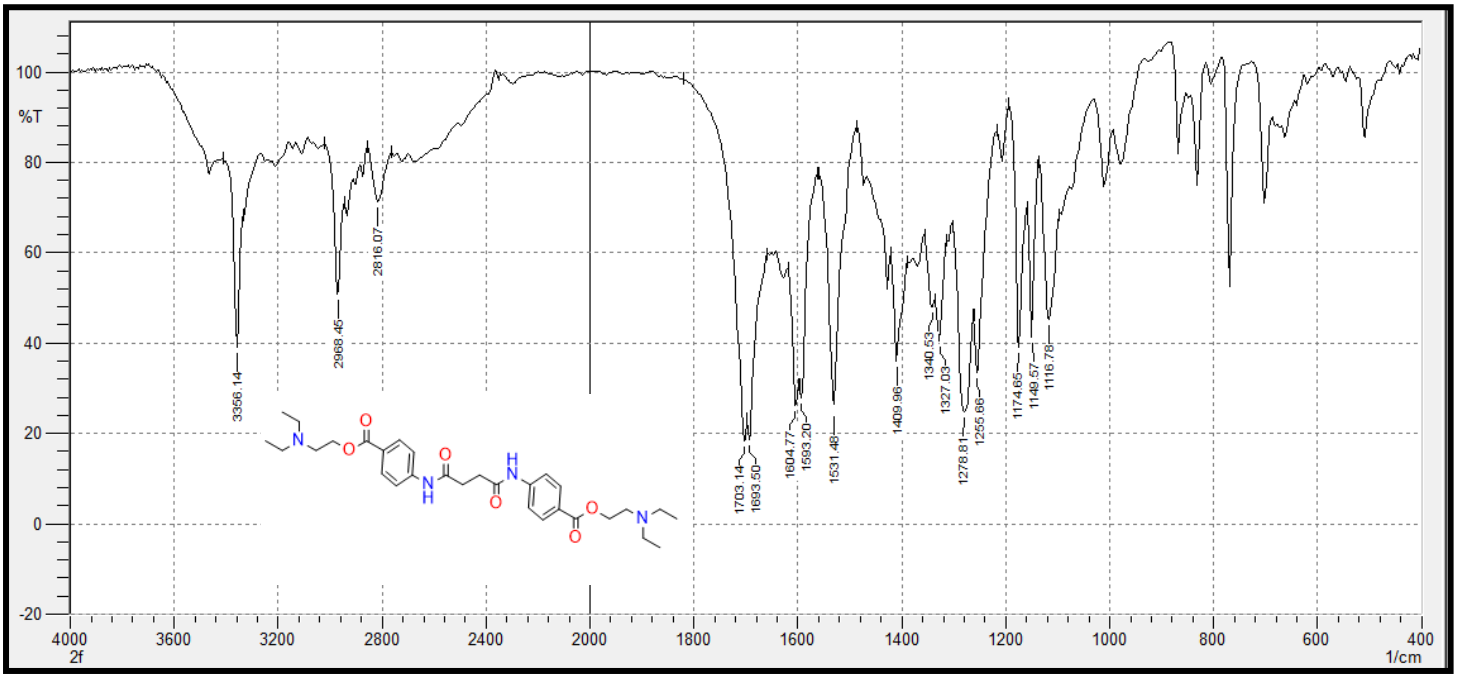


Figure (5) IR interpretation of compound bis(2-(diethylamino)ethyl) 4,4'-(succinylbis(azanediyl))dibenzoate (3f)

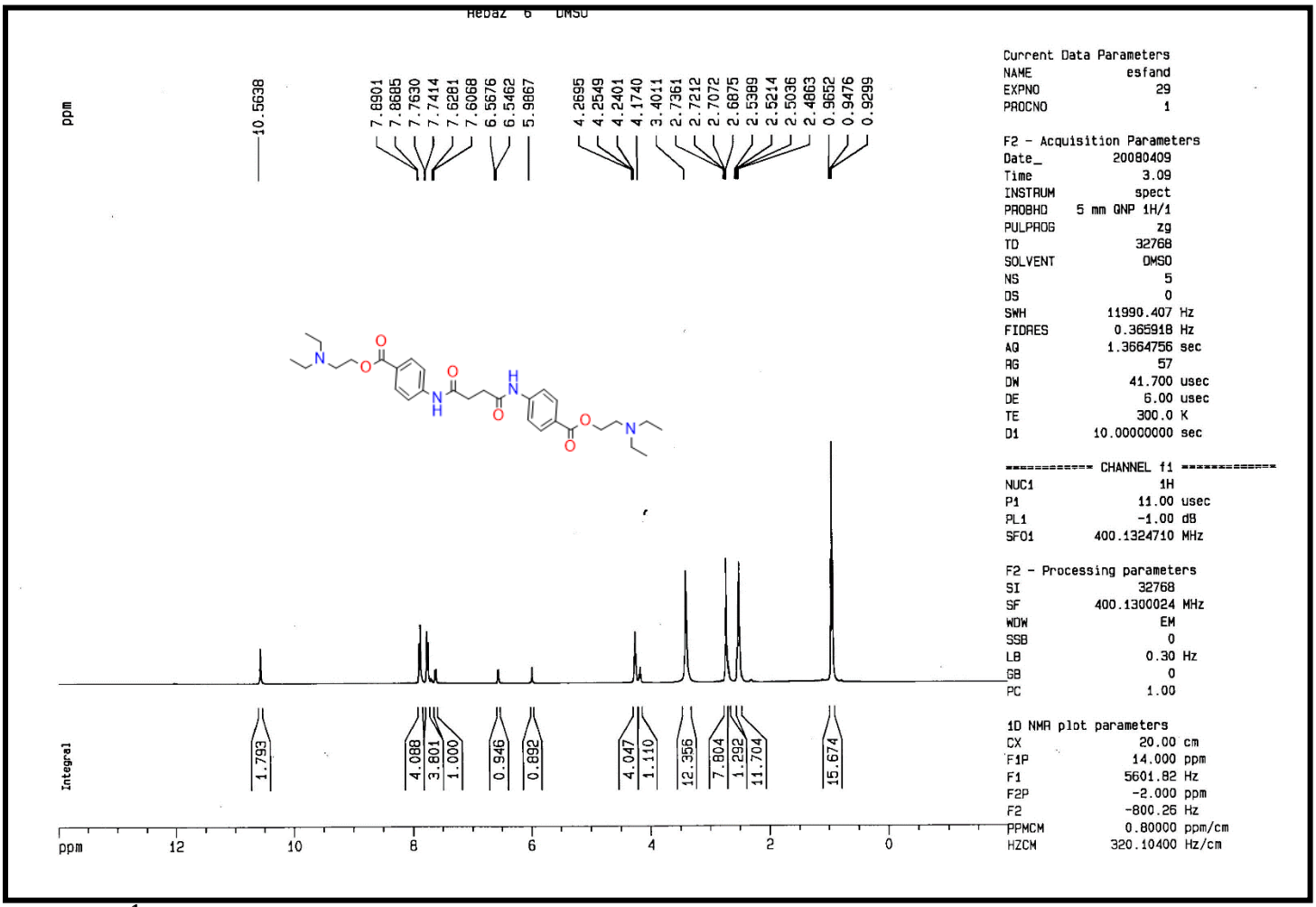


Figure (6) ^{1}H NMR of compound bis(2-(diethylamino)ethyl) 4,4'-(succinylbis(azanediyl))dibenzoate (3f)

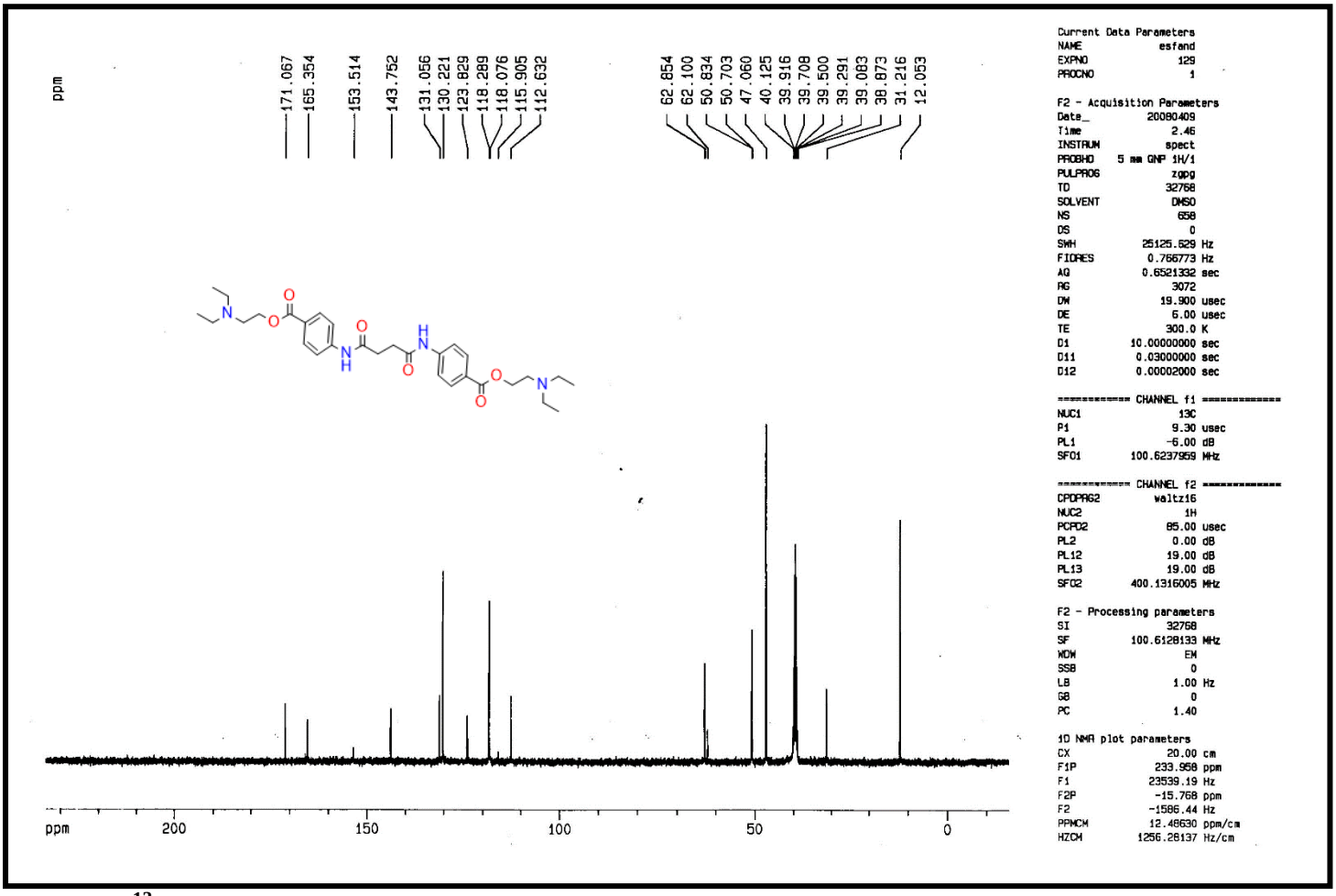


Figure (7) ^{13}C NMR of compound bis(2-(diethylamino)ethyl) 4,4'-(succinylbis(azanediyl))dibenzoate (3f)

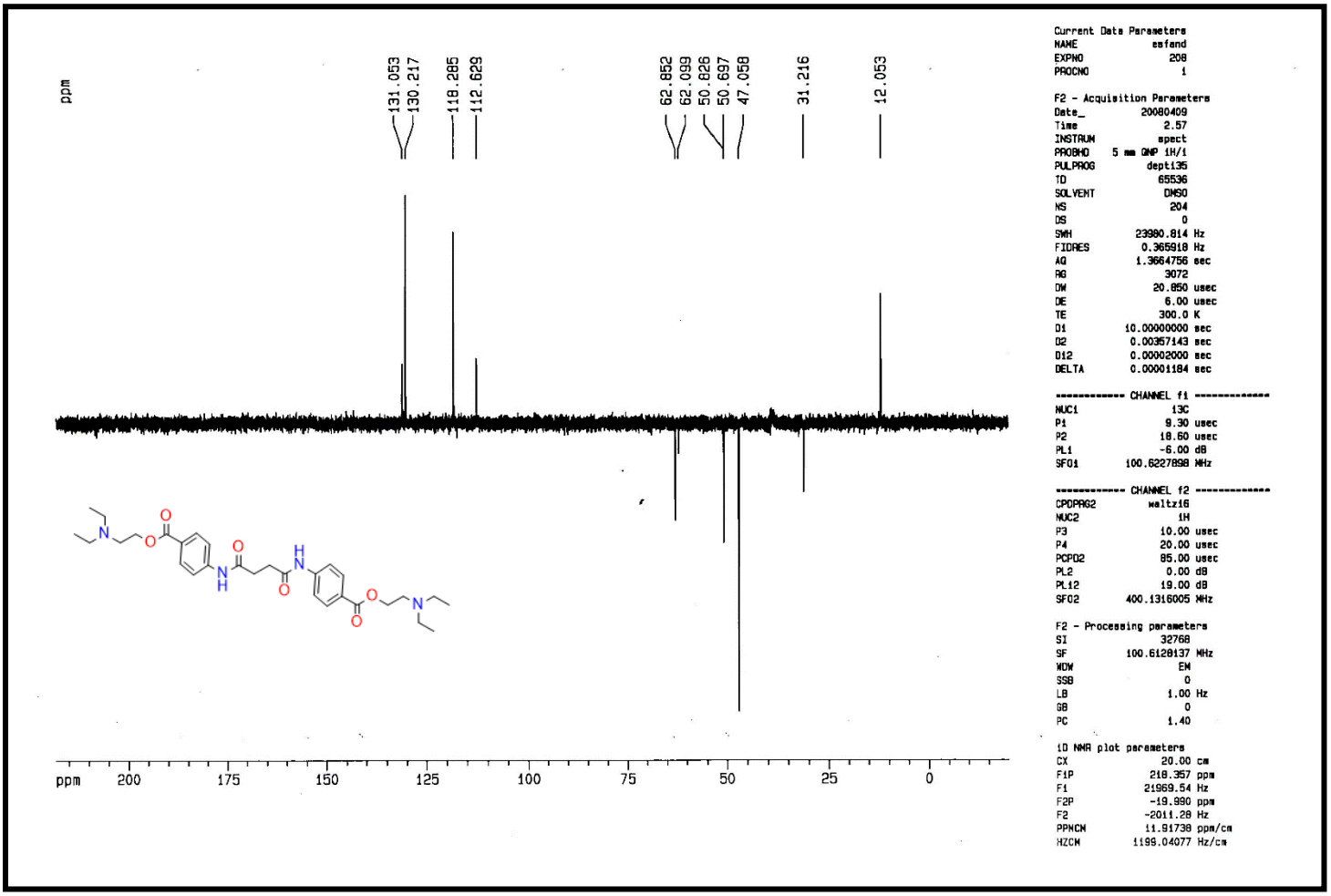


Figure (8) DEPT-135 NMR of compound bis(2-(diethylamino)ethyl) 4,4'-(succinylbis(azanediyl))dibenzoate (3f)

Table (5) Antibacterial activity (Zone of inhibition in mm) of compounds(2a-f) against human pathogens

		E. Coli Gram-Negative Bacteria				
Concentrations (ppm)		200	400	600	800	1000
Samples	**2a**	11	10.5	10	10.5	11
	2b	10	9	10.5	10.5	11
	2c	9	9	9	10	10
	2d	10	9.5	9.5	10.5	10.5
	2e	8.5	9	8.5	9	9
	2f	10	10	10.5	11	11
		S. Aureus Gram-Positive Bacteria				
Concentrations (ppm)		200	400	600	800	1000
Samples	**2a**	9	8.5	8.5	8	8.5
	2b	8.5	8	7.5	7.5	8
	2c	9	9	8	8.5	9.5
	2d	7.5	9	8.5	8.5	8
	2e	9	9.5	8	8	9
	2f	9	8.5	9	9	9.5
		C. albicans Fungi				

Concentrations (ppm)		200	400	600	800	1000
Samples	**2a**	11	10.5	10	10.5	11
	2b	10	9	10.5	10.5	11
	2c	8	9	8.5	9	9
	2d	9.5	10.5	9	10	11
	2e	9.5	9	8	9.5	9
	2f	10.5	11.5	10	10.5	11.5

Table (6) Antibacterial activity (Zone of inhibition in mm) of compounds (3a-f) against human pathogens

		E. Coli Gram-Negative Bacteria				
Concentrations (ppm)		200	400	600	800	1000
Samples	3a	10	10.5	10	9.5	11
	3b	8	9.5	9.5	10	10.5
	3c	9.5	10	9.5	9.5	8
	3d	9	9	9.5	9	9.5
	3e	9.5	10	9.5	8.5	9
	3f	10.5	10.5	11	10	11.5
		S. Aureus Gram-Positive Bacteria				
Concentrations (ppm)		200	400	600	800	1000
Samples	3a	8	9	7.5	8	8
	3b	8	8	8.5	9	9
	3c	9	9.5	9	8	8.5
	3d	8.5	8	8.5	9	9
	3e	8.5	9	8.5	8	9
	3f	7.5	9	8	8.5	8.5
		C. albicans Fungi				
Concentrations (ppm)		200	400	600	800	1000
Samples	**3a**	10	10	9	9.5	11
	3b	8.5	8	9.5	10	10
	3c	9	9	9.5	9	8.5
	3d	9.5	9.5	8.5	9	9
	3e	9	9	9	8.5	9
	3f	10	9.5	9	10	11

Table (7) Antioxidant activity of the synthesized diamides compounds (2a-f) (400ppm).

Samples	***Absorbance at 517nm***	***A control at 517nm***	***Antioxidant%***
2a	0.615	0.679	9.42
2b	0.458	0.679	32.5
2c	0.503	0.679	25.9

2d	0.589	0.679	13.2
2e	0.584	0.679	13.9
2f	0.530	0.679	21.9

Table (3) Antioxidant activity of the synthesized diamides compounds (3a-f) (400ppm).

Samples	*Absorbance at 517nm*	*A control at 517nm*	*Antioxidant%*
3a	0.506	0.679	25.4
3b	0.580	0.679	14.5
3c	0.519	0.679	23.5
3d	0.585	0.679	13.8
3e	0.614	0.679	9.5
3f	0.651	0.679	4.1

8.References:

AL-RASHIDA, M., HUSSAIN, S., HAMAYOUN, M., ALTAF, A. & IQBAL, J. 2014. Sulfa drugs as inhibitors of carbonic anhydrase: New targets for the old drugs. *BioMed Research International*, 2014.

BORNE, R. F., PEDEN, R. L., WATERS, I., WEINER, M., JORDAN, R. & COATS, E. A. J. J. O. P. S. 1974. Anti-inflammatory activity of para-substituted N-benzenesulfonyl derivatives of anthranilic acid. 63**,** 615-617.

CAREY, J. S., LAFFAN, D., THOMSON, C., WILLIAMS, M. T. J. O. & CHEMISTRY, B. 2006. Analysis of the reactions used for the preparation of drug candidate molecules. 4**,** 2337-2347.

CLERCQ, E. J. C. M. C. 2001. New developments in anti-HIV chemotherapy. 8**,** 1543-1572.

DOMAGK, G. 1935. Ein beitrag zur chemotherapie der bakteriellen infektionen. *DMW-Deutsche Medizinische Wochenschrift*, 61**,** 250-253.

EL-SAYED, M., MAHMOUD, M., HANAN, A., EL-TOUMY, S., EMAN, A. & GHAREEB, M. 2011. Chemical constituents, antischistosomal and antioxidant activities of the methanolic extract of Azadirachta indica. *Egypt J Chem*, 54**,** 99-113.

GENC, Y., ÖZKANCA, R., BEKDEMIR, Y. J. A. O. C. M. & ANTIMICROBIALS 2008. Antimicrobial activity of some sulfonamide derivatives on clinical isolates of Staphylococus aureus. 7**,** 1-6.

GULŞEN, A., MAKRIS, D. P. & KEFALAS, P. 2007. Biomimetic oxidation of quercetin: Isolation of a naturally occurring quercetin heterodimer and evaluation of its in vitro antioxidant properties. *Food Research International*, 40**,** 7-14.

KADHIM, N. J., AL-REKABY, L. S., REDHA, A. A. & CHAPPELL, J. Chemical composition and antioxidant capacity of Eggplant parts during vegetative and flowering stage. Journal of Physics: Conference Series, 2019. IOP Publishing, 092013.

MONTALBETTI, C. A. & FALQUE, V. 2005. Amide bond formation and peptide coupling. *Tetrahedron*, 61**,** 10827-10852.

MUN, J., JABBAR, A. A., DEVI, N. S., YIN, S., WANG, Y., TAN, C., CULVER, D., SNYDER, J. P., VAN MEIR, E. G. & GOODMAN, M. M. J. J. O. M. C. 2012. Design and in vitro activities of N-alkyl-N-[(8-R-2, 2-dimethyl-2 H-chromen-6-yl) methyl] heteroarylsulfonamides, novel, small-molecule hypoxia inducible factor-1 pathway inhibitors and anticancer agents. 55**,** 6738-6750.

NAHM, S. & WEINREB, S. M. 1981. N-Methoxy-N-methylamides as effective acylating agents. *Tetrahedron Letters*, 22**,** 3815-3818.

PLOTYCYA, S., STRONTSITSKA, O., PYSAREVSKA, S., BLAZHEYEVSKIY, M. & DUBENSKA, L. J. I. J. O. E. 2018. A new approach for the determination of benzocaine and procaine in pharmaceuticals by single-sweep polarography. 2018.

RAY, A., GUPTA, S. D. J. I. C. & PRODUCTS 2013. A panoptic study of antioxidant potential of foliar gel at different harvesting regimens of Aloe vera L. 51**,** 130-137.

SALEH, A., ELREFAIE, H., HASHEM, A., EL-MENOUFY, H., MANSOUR, N. & EL-BEIH, A. 2019a. Optimization studies and chemical investigations of Aspergillus terreus-18 Showing Antioxidant Activity. *Egyptian Journal of Chemistry*, 62**,** 215-230.

SALEH, A., ELREFAIE, H., HASHEM, A., EL-MENOUFY, H., MANSOUR, N. & EL-BEIH, A. J. E. J. O. C. 2019b. Optimization studies and chemical investigations of Aspergillus terreus-18 Showing Antioxidant Activity. 62**,** 215-230.

SAMAD, M. K. & HAWAIZ, F. E. 2019. Synthesis, characterization, antioxidant power and acute toxicity of some new azo-benzamide and azo-imidazolone derivatives with in vivo and in vitro

antimicrobial evaluation. *Bioorganic chemistry*, 85**,** 431-444.

SEKI, M. & MATSUMOTO, K. 1996. A novel approach to homochiral β-amino acids. *Tetrahedron letters*, 37**,** 3165-3168.

SENGUPTA, S., MONDAL, S. & DAS, D. 1999. Amino acid derived morpholine amides for nucleophilic α-amino acylation reactions: A new synthetic route to enantiopure α-amino ketones. *Tetrahedron letters*, 40**,** 4107-4110.

WIEGAND, I., HILPERT, K. & HANCOCK, R. E. J. N. P. 2008. Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances. 3**,** 163-175.

YASMEEN, S., MURTAZA, S., AKKURT, M., KHAN, I. U. & SHARIF, S. 2010. N-{4-[(5-Methylisoxazol-3-yl) sulfamoyl] phenyl} benzamide. *Acta Crystallographica Section E: Structure Reports Online*, 66**,** o2264-o2264.