An-Najah National University

Faculty of Graduate Studies

Cur Cumin Based Herero Cycles With Possible Dual Action Antibacterial Activity

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DEDICATION

To my great father, my mother, my beloved husband Hani, and my lovely son Omar.

And

To all of my Friends

ACKNOWLEDGMENT

Praise and thanks to Allah, for helping and directing me to the right path. Special thanks are due to my direct research supervisor Dr. Othman Hamed, for the opportunity to work with him in his research group. I am deeply grateful to him for his constant presence, his willingness to help at any time and his encouragement throughout this research project. I thank also the second research supervisor Dr. ShehdeJodeh, for his assistance and supervision during the course of this work.

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الإقرار

أنا الموقع أدناه مقدم الرسالة التي تحت عنوان

Curcumin Based Heterocycles With Possible Dual Action Antibacterial Activity

أقر بأن ما اشتملت عليه هذه الرسالة إنما هي من نتاج جهدي الخاص باستثناء ما تمت الإشارة إليه حيثما ورد، وأن هذه الرسالة ككل، أو أي جزء منها لم يقدم من قبل لنيل أية درجة علمية أو بحث علمي أو بحثي لدى مؤسسة تعليمية أو بحثية أخرى

Declaration

The work provided in this thesis, unless otherwise referenced, is my own research work and has not been submitted elsewhere for any other degree or qualification.

Student's name: **اسم الطالب:** شيماء عبد القادر حامد خليل

Date: **التاريخ:** ٢٠١٥/١٠/٢٠

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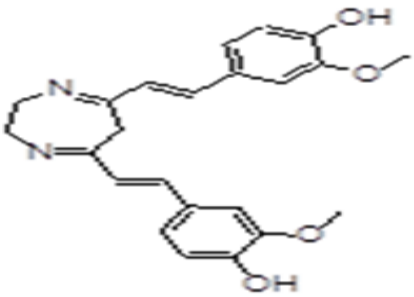
Abstract

A new series of curcumin and tetrahydrocurcumin (THC) based diazepines were synthesized. Tetrahydrocurcumin was prepared by hydrogenation of curcumin using Pd/C as a catalyst. Synthesis of the diazepines was carried out by a new method. In this method, curcumin or tetrahydrocuccumin is dissolved in ethanol then reacted with various aromatic diamino compounds in presence of catalytic amount of concentrated sulfuric acid. The prepared diazepines were purified by Flash chromatography or crystallization in water-Ethanol solution. Then were characterized by various spectroscopic techniques such as MS, FT-IR, ^{13}C and ^{1}H NMR spectroscopy.

The prepared diazepinesare expected to have excellent antibacterial activity since, in a previous study, it has been shown that diazepine (figure below) made from curcumin and ethylene diamine exhibitedremarkablepotencyagainstGrampositive bacteria*S. aureus.* The antibacterial activity of the prepared diazepinesagainst four different types of bacteria *Staphylococcus aureus*, *Escherichia coli*,

Proteus mirabilis and *Pseudomonas aeruginosa* will be evaluated in a future work.



CHAPTER ONE

INTRODUCTION

1.1 Background

Pathogenic bacteria has inflected diseases upon human, for along time. Advances in research has helped limit the suffering by the introduction of antibacterial agents. Since this time, a multitude of antibacterial agents have been developed and used in a clinical setting. However, almost as quickly as the antibacterial agents have been developed, resistance to them was also observed.[1] As we entered the 21st century the prospect for "superbugs" which are resistance to all antibacterial agent becoming more of a reality. Therefore, mankind being is in a great need to develop new and innovative antibacterial agents to regain the dominance over the pathogenic bacteria.

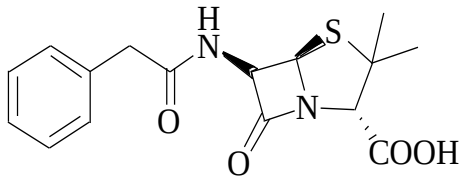


Fig 1.1: Penicillin

After the first antibacterial agent Penicillin (Fig.1) discovered in 1928 by Alexander Flemming, several other antibacterial agents were discovered. In 1994 Australian pathologist Howard Flory and his German collaborator discovered penicilin I. Since this time the golden age of antibacterial agents and antibiotic agents has started and the bacteria seemed to be under control.

1.1.1 Type of Antimicrobials

Antimicrobials can be both natural products and synthetic chemicals, which are designed to inhibit or destroy the growth and reproduction of pathogenic microorganisms, such as bacteria, fungi, protozoa, and viruses.While antibiotics and antibacterial both attack bacteria, these terms have evolved over the years to mean two different things. Antibacterial unlike antibiotics they are used to disinfect surfaces and eliminate potentially harmful bacteria. For this reason they are used in lots of products such as soaps, detergents, health and skincare products and household cleaners.

1.1.2 Types of Antibacterial agents

Antibacterial may be divided into two groups according to their speed of action and residue production:

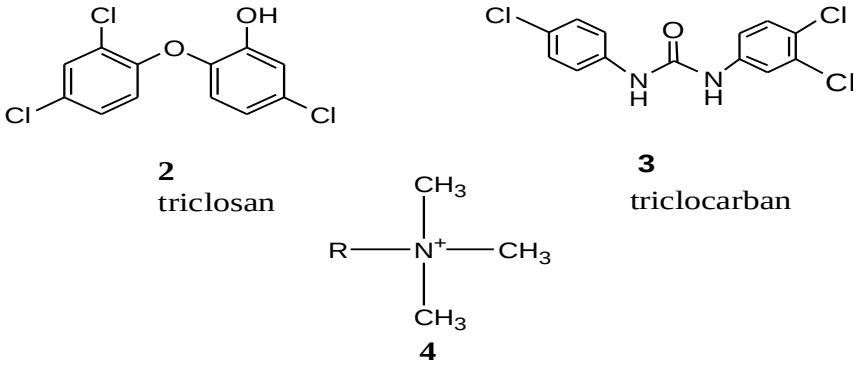
1.1.2.1 Fast acting antibacterial agents

The first group contains those that act rapidly to destroy bacteria, but quickly disappear (by evaporation or breakdown) and leave no active residue behind (referred to as *non-residue-producing*). Examples of this type are the alcohols, chlorine, and peroxides.

1.1.2.2 Long lasting antibacterial agenst

The second group consists mostly of newer compounds that leave long-acting residues on the surface to be disinfected and thus have a prolonged

action (referred to as *residue-producing*). Common examples of this group are triclosan (2), triclocarban (3), and benzalkonium chloride (4). Among the most widely used antibacterial agents are triclosan, triclocarban and quaternary ammonium compounds (Scheme 1). [2]



Scheme 1: examples on Long lasting antibacterial agenst

A recent survey reported that 76% of liquid soaps from 10 states in the US contained triclosan and approximately 30% of bar soaps contained triclocarban.[2] Many cleaning compounds contain quaternary ammonium compounds. Because these compounds have very long chemical names, they are often not easily recognized as antibacterial agents on packaging labels. More recently, triclosan has been bonded into the surface of many different products with which humans come into contact, such as plastic kitchen tools, cutting boards, highchairs, toys, bedding and other fabrics. The prolonged use of the antibacterial may cause undesirable side effects on the body. Furthermore, resistance of bacteria to these agents was also observed.[3] Therefore, there is a pressing need to develop new and

innovative antimicrobial agents able to evade microbial resistance mechanisms.

1.1.3 Cellular targets for antibacterial agents

There are three main cellular targets for antibacterial agents: inhibition of bacterial cell wall biosynthesis, inhibition of bacterial proteins, and inhibition of DNA synthesis, replication or repair. Bacterial cell walls are essential for the survival of any bacterium as they maintain cell integrity and the high osmotic pressure necessary for cellular function. Consequently, inhibition of bacterial cell wall biosynthesis is quite an effective method of killing bacteria. The β-lactam amoxicillin **5** (Fig.1.2) is an example of clinically used antibacterial agents which act on the cell wall of bacteria bacterial target.[4]

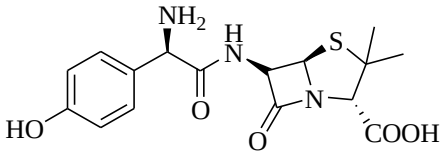


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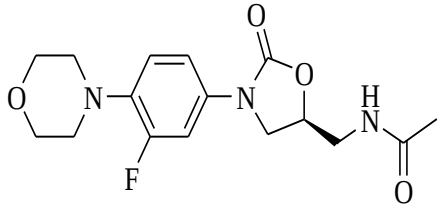
Fig 1.2: The β-lactam amoxicillin

An example on clinically used antibacterial agents that targets both RNA and DNA of bacteria is oxazolidinone linezolid **6**[3] (Fig.1.3).



6

Fig 1.3: oxazolidinone linezolid

DNA synthesis, replication and repair are essential processes for the survival of bacterial cells, so compounds which interfere with these processes can be effective antibacterials. Examples on such compounds are quinolones, like ciprofloxacin **7**, which targets the replication process. Sulfonamides, such as the dual drug Bactrim® (which contains a 1:5 mixture of trimethoprim **8** and sulfamethoxazole **9** (Fig.1.4), also fall into this category by indirectly inhibiting nucleic acid synthesis.[2]

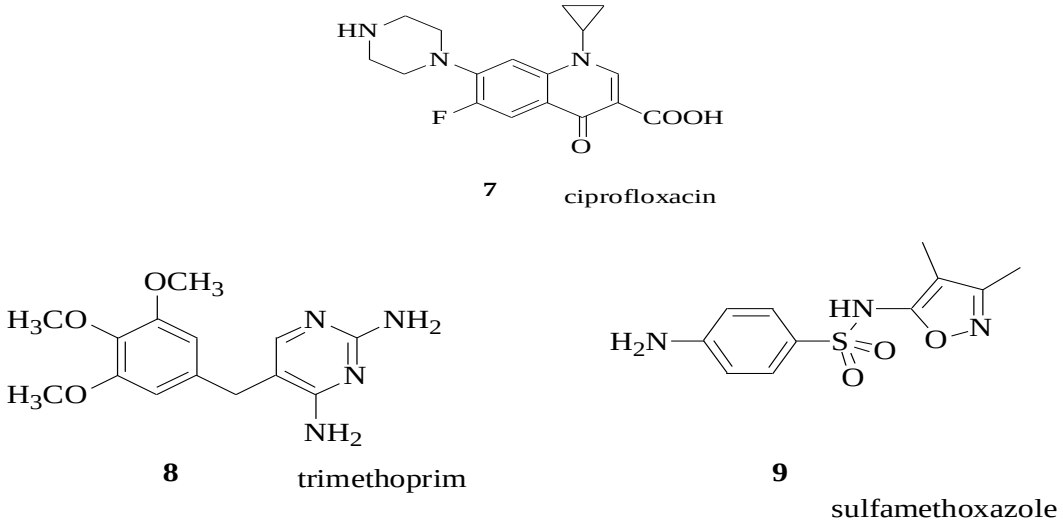


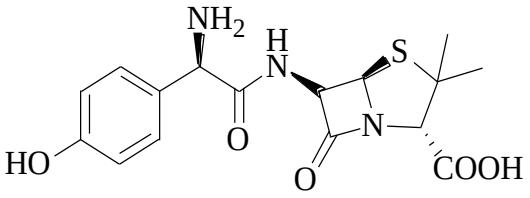
Fig 1.4: Ciprofloxacin, Trimethoprim and Sulfamethoxazole

1.1.4 Resistance of bacteria to antibacterial agents

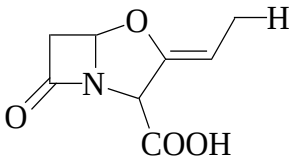
Synthetic antibacterial agent as well as excessive use of these agents has resulted in bacteria developing various adaptive strategies in order to resist these antibacterial drugs. There are three main mechanisms by which bacteria confer resistance to antibacterial agents, namely antibiotic inactivation, target alteration, and decreased intracellular drug concentration.[5,6]

A promising strategy to tackle the resistance problem is that of employing two reagents with dual biological actions. These "dual action" concepts of drug are divided in the literature into two main categories: dual drugs, cross-linked dual action drugs.

Dual drugs are drugs which are administered in a tablet for oral administration. A prototypical example of these is Augmentin®, which contains a combination of a penicillin antibiotic, amoxicillin **5**, and the β-lactamase inhibitor clavulanic acid **10**. With this combination, clavulanic acid inhibits the β-lactamase enzyme, which preserves the integrity of amoxicillin **5** allowing it to exert its own antibacterial activity. Augmentin® is used to treat infections resulting from Augmentin®-sensitive, β-lactamase producing bacterial strains, such as skin infections (caused by S. aureus).[7]



5 amoxicillin

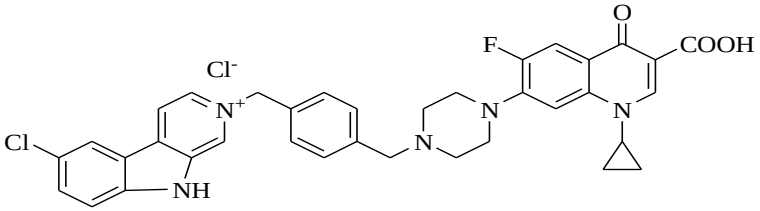


10 clavulanic acid

Fig 1.5: Amoxicillin and Clavulanic acid.

The second type of dual action drug is chemically cross-linked by a non-cleavable linkage, or via a cleavable linkage. A prototype of the cross-linked by a non-cleavable linkage is the incorporation cross-linking of the algicidal natural product nostocarboline with ciprofloxacin **7** via a 1,4-dimethylbenzene linker. The cross-linked hybrid showed a minimum

inhibitor cocentration (MIC) value of about 2- orders of magnitude greater than those for ciprofloxacin itself.[8]

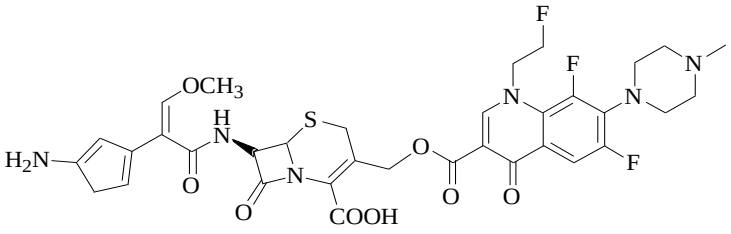


11
nostocarboline

7
ciprofloxacin

Fig 1.6: Nostocarboline and Ciprofloxacin

A prototype of the cross-linked by a cleavable linkage is the ester-linked derivative **12** which incorporated a third-generation cephalosporin (desacetylcefotaxime) linked to a third-generation quinolone (fleroxacin). It showed excellent in vitro and in vivo activity against a variety of Gram-positive (e.g. a minimum inhibitor concentration [MIC] of 1.0 µg/mL against S. aureus) and Gram-negative (e.g. an MIC of 0.125 µg/mL against E. coli) strains.[9,10]



12
desacetylcefotaxime linked to fleroxacin

Fig 1.7: ester-linked derivative

Unfortunately, some of the new dual drug likes quinupristin-dalfopristin (Synercid)^{TM}, a new drug that has activity against S. aureus and has been introduced into hospital use, does not control E. faecalis.[11,12]

Clearly, new drugs are urgently needed to overcome the serious multidrug resistance problem in pathogenic bacteria.

1.2 Heterocyclics

As shown in (Fig.1.7) most of the antibacterial agent listed are heterocyclics. Heterocyclic compounds, in general, are very important class of organic compounds, making up more than half of all known organic compounds. Heterocycles are present in a wide variety of [13] drugs, most vitamins, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents. Also, they have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals. Most of the heterocycles possess important applications in materials science such as dyestuff, fluorescent sensor, brightening agents, information storage, plastics, and analytical reagents. In addition, they have applications in supra molecular and polymer chemistry, especially in conjugated polymers. Moreover, they act as organic conductors, semiconductors, molecular wires, photovoltaic cells, and organic light-emitting diodes (OLEDs), light harvesting systems, optical data carriers, chemically controllable switches, and liquid crystalline compounds. Heterocycles are also of considerable interest because of their synthetic utility as synthetic intermediates, protecting groups, chiral auxiliaries, organ catalysts, and metal ligands in asymmetric catalysts inorganic

synthesis. Therefore, substantial attention has been paid to develop efficient new methods to synthesize heterocycles. In this study, two new groups of heterocycles have been synthesized using curcumin natural product as a starting material.

1.3 Aims of the Study

The present study will focus on synthesizing a new family of heterocycles with possible antibacterial activities with the aim to overcome the serious multidrug resistance problem in pathogenic bacteria.

Natural product curcumin **(13)** was chosen as a starting material in this study. The advantages of using curcumin as starting material in this study come from several factors, among these are:

1. Clinical trials have shown curcumin to be safe, even when consumed at a daily dose of 12 g for 3 months.[14]

2. It has been utilized for centuries in Eastern medicine as a topical treatment for wounds, inflammation, and tumors. It showed several activities as an anti-inflammatory, anti-oxidant, anti-viral, wound healing, hypocholesterolemic -effects in diabetic patients. Curcumin also has been shown to suppress carcinogenesis of the skin, liver, lung, colon, stomach and breast.[15,16]

3. It has a unique structure, it incorporates several functional groups. The aromatic rings which are methoxylated phenols,the two carbonyl groups

form a diketone, the enol of the heptadiene-3,5-diketone , and unsaturated carbonyls.

4. The diketone functional group in curcumin is very useful in organic synthesis it could be converted to several other functional groups, among these alcohol, imine, and amine.

Curcumin is an orange–yellow crystalline powder practically insoluble in water and ether but soluble in ethanol, dimethylsulfoxide, and acetone.

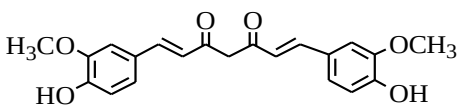
Curcumin was first isolated in 1815 by Vogel,[17] and in 1870 it was isolated in crystalline form and identified as 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E) or diferuloylmethane. The feruloylmethane skeleton of curcumin was confirmed in 1910 by the initial work and synthesis by Lampe.[18] Curcumin has a melting point of 183°C; its molecular formula is $C_{21}H_{20}O_6$ and molecular weight 368.37g/mol. Besides curcumin, turmeric contains other chemical constituents known as the curcuminoids (scheme 3).[19] The curcuminoids impart the characteristic yellow color to turmeric. The major curcuminoids present in turmeric are: demethoxycurcumin, bisdemethoxycurcumin, and the recently identified cyclocurcumin.[20] Commercial curcumin contains about 77% curcumin, 17% demethoxycurcumin, and 3% bis-demethoxycurcumin as its major components is curcumin .

Curcuminis the major constituent of the yellow pigments isolated from rhizome of *Curcuma longa* (turmeric). The root of this plant has been used

in India as preservative, colorant, flavoring in meals (curry) and as a traditional medicine.

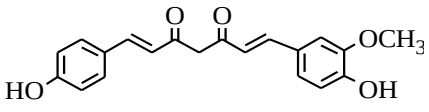
Several studies in recent years have shown that curcumin has antioxidant, anti-inflammatory, anti-microbial, anti-parasitic, anti-mutagen and anticancer properties.[21]

Curcumin shows a variety of physiological and pharmacological effects, and several studies indicate curcumin to be anticarcinogenc [22] and anti-inflammatoy.[23] Curcumin acts as a superoxide radical scavenger.[24]



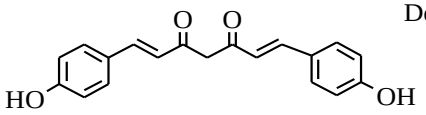
13

Curcumin I



Curcumin II

Demethoxycurcumin



Curcumin III
Bis-demethoxycurcumin

Scheme 2: structures of various curcumins

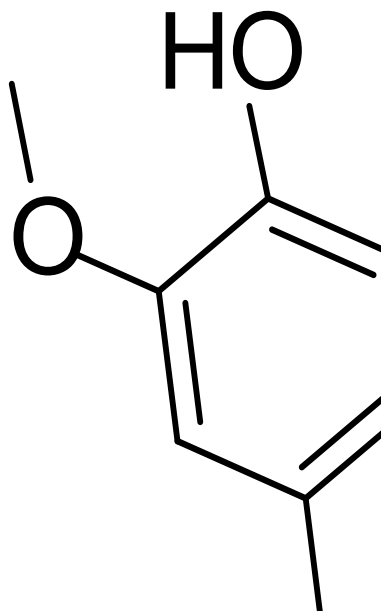
Curcumin was tested for its antimicrobial potential against two Gram-positive (*B. cereus* and *S. aureus*) and two Gram-negative bacteria (*E. coli* and *Y. enterocolitica*). MIC of the compounds is presented in Table 1 which shows the inhibition of bacteria at different concentrations of curcumin.

Table 1: Minimum inhibitory concentration (µM) of curcumin (MIC)

Bacteria	MIC of Curcumin (µM)
Bacillus cereus	0.135
Staphylococcus aureus	0.081
Escherichia coli	0.611
Yersinia enterocolitica	0.679

Previous study [25] that was carried out at our laboratory, a numberofcurcumin based pyrazoles,isoxazoles,andadiazepine 14 (Scheme 3)have been synthesized and evaluated fortheirantibacterialactivities. The chemical structures ofthenewly synthesized compounds were verified on the basis of spectral data and elemental analyses. Investigation of antimi crobi al activity of the compounds was done bydiscdiffusion method using Gram-positive (*S. aureus*)and Gram-negative (*E. coli, P. mirabilis* ,and *P. aeruginosa*) bacteria . All prepared compounds exhibited good antibacterialactivitiesagainst Grampositive bacteria.

Among all tested compounds, derivative **13** (Scheme3) exhibitedremarkablepotencyagainst Gram positive bacteria *S. aureus.*



Scheme 3: Some curcumin derevatives

In order to optimize the antibacterial activity of diazepine it is necessary to extend the previous study and synthesize various tetrahydro-based curcumin **16** and curcumin based diazepines **17**. The structures of the diazepines that will be synthesized and investigated in this study are shown in Scheme 4.

The curcumin based heterocycles after preparation will be subjected to purification by various chromatographic techniques and to analysis by NMR and elemental analysis to determine their purities. For future work the diazepines will be evaluated for antibacterial activities. The antibacterial activities will be carried out by collaboration with the Biology Department at An-Najah National University.

Scheme 4: The structures of the diazepines that will be synthesized and investigated in this study.

CHAPTER TWO

EXPERIMENTAL

2.1 General Experimental

All chemicals were purchased from Aldrich Chemical Company and used without any further purification unless otherwise specified. All prepared compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, elemental analysis. Nuclear Magnetic Resonance spectra were recorded on Varian Gemini 2000, 300 MHz instrument (Loyola University at Chicago, Chicago, IL), and on Bruker DPX-300 MHz instruments (Hashemite University, City of Zarqa, Jordan). Infrared spectra were recorded in KBr on a Shimadzu 820 PC FT-IR spectrometer (Loyola University at Chicago, Chicago, IL). All ^{1}H-NMR experiments were reported in δ units, parts per million (ppm) downfield from tetramethylsilane (TMS). All ^{13}C NMR spectra were reported in ppm relative to deuterochloroform (77.0 ppm).

At least two measurements were carried out for each compound. Elemental analyses were carried out with ElementarVario EL III elemental analyzer (Hashemite University, City of Zarqa, Jordan). TLC analysis was performed on silica gel plates pre-coated with Merck Kieselgel 60 F254 (obtained from Aldrich Chemical Company), and visualization was done using UV lamp. Sample purifications were performed by crystallization.

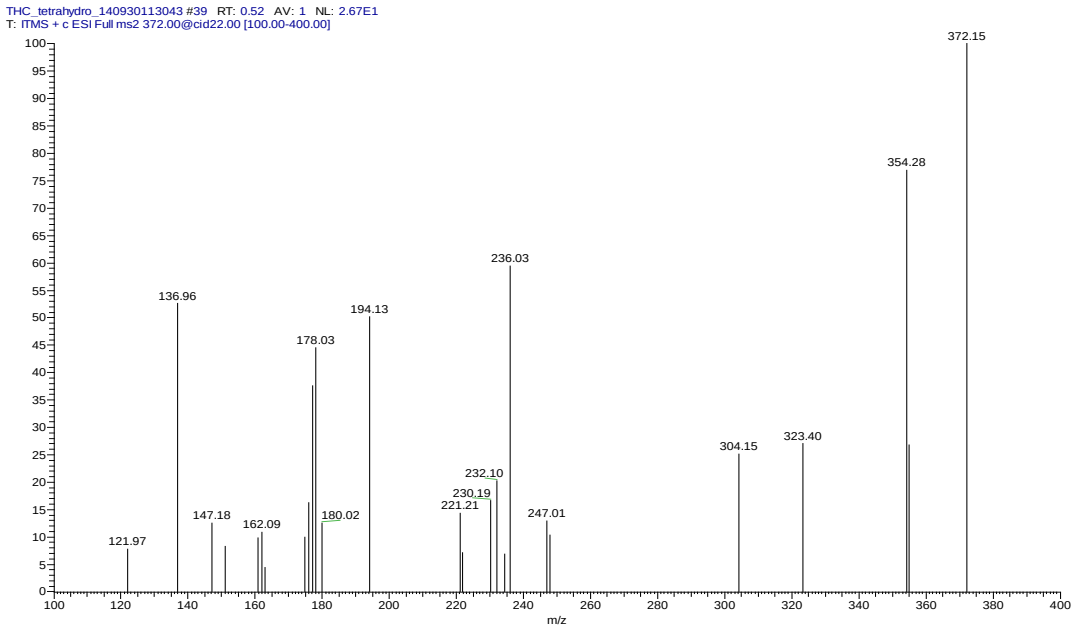
2.2 Preparation of Tetrahydrocurcuminoids (THC) 15

A low pressure reaction bottle was charged with a solution of 5.0g(13.44 mmol) of curcuminoids **13** in 100 ml absolute ethanol. To the suspension was added Pd/C catalyst (0.3 g). The bottle was attached to the low pressure hydrogenation apparatus and evacuated, and then hydrogen was admitted to a pressure slightly above 3 atm. The contents of the flask were shaken until absorption of hydrogen stopped (about 4 hrs). The catalyst was removed by filtration and ethanol was removed under vacuum to afford 4.6 g (91.8%) of pale yellow gummy material. The gummy material was purified by flash chromatography using hexane: EtOAC (8 : 2)). The products THC **15, 15a** were analyzed by ^{1}H NMR and ^{13}C NMR. ^{1}H NMR (300 MHz) ($CDCl_3$): δ: 6.8 (d, J = 8.24, 2H), 6.62 (d, J = 8.42 =2H), 6.6 (s, 2H), 5.6 (br, 2H, OH), 5.4 (s, 0.75 H, vinylic), 3.90 (s, 0.5H, diketone), 3.85 (s, 6H, OCH_3), 2.9 (t, J = 7.97, 3H), 2.6 (t, J = 7.14, 3H). ^{13}C NMR ($CDCl_3$ d6) δ: 193.2 (Cc and Ce), 144.5 (C4'), 143.9 (C3'), 132.5 (C1'), 120.7 (C6'), 114.3 (C2'), 110.9 (C5'), 99.8 (Cd), 55.8 (OMe), 40.4 (Cb, Cf), 31.1 (Ca, Cg).LC/MS [M + 1] for $C_{21}H_{24}O_4$Calculated 371.45, found: 372.0. A

15

Tetrahydrocurcuminoids

THC



Fig(2.1): Mass spectrum of tetrahydrocurcuminoids (**15)**.

2.3 Preparation of Heterocyclic based curcumin compounds

2.3.1 Preparation of 4,4'-((3,6-dihydro-2*H*-1,4-diazepine 5,7-diyl)bis (ethane-2,1-diyl))bis(2-methoxyphenol) (16a)

In a round bottomed flask equipped with a magnetic stirring bar and a condenser, tetrahydrocurcuminoids (1.0g, 2.7mmol) was dissolved in 15 ml ethanol. Ethylenediamine (0.18 g, 0.2 mL, 3.0 mmol) was added to the curcumin solution in ethanol followed with 0.5 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo*. The residue was washed with an aqueous solution of sodium carbonate (5%), filtered, washed with water and dried in an 80 ^{o} C oven. The solid product was

purified by flash chromatography (hexane: EtOAC (4 : 6)) to afford 0.91 g (85.0%) of a yellow solid.

The product was analyzed by FT-IR: $V_{max}cm^{-1}$3605 (-C-OH), 3020, 1640 (-C=N), 1600, 1080 (C-O ether). ^{1}H NMR (400 MHz, DMSO-d6) δ: 1.92 (t, 2H, CH_2), 2.76 (t, 2H, CH_2) 3.16 (s, 2H, CH_2), 3.65 (s, 4H, CH_2CH_2); 3.72 (s, 6H, OCH_3), 5.70 (s, 2H, OH), 6.65 (m, 2H), 6.71 (d, 2H, J = 15.2 Hz), 7.03 (d, 2H), 7.16 (s, 2H), 7.35- 7.54 (m, 2H). 13C-NMR (400 MHz, DMSO-d6) δ: 24.50, 28.7,36.3, 48.30, 56.40, 112.90, 116.30, 122.40, 127.80, 148.20, 149.30, 165.80. LC/MS [M+1] for $C_{23}H_{28}N_2O_4$:Calculated 396.45, [found: 397.0. Anal.] Calculated for $C_{23}H_{28}N_2O_4$: C 69.61, H 7.06, N 7.07. Found: C 70.41, H 6.98, N 7.17.

2.3.2 Preparation of 4,4'-((1*E*,1'*E*)-(3,6-dihydro-2H-1,4-diazepine 5,7-diyl)bis (ethene-2,1-diyl))bis(2-methoxyphenol) (17a)

In a round bottomed flask equipped with magnetic stirring bar and a condenser, curcumin (1.0g, 2.8 mmole) was dissolved in 15.0ml ethanol. Ethylenediamine (0.18 g, 0.2 mL, 3.0 mmol) was added to the curcumin

solution in ethanol followed with 0.5 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo*. The residue was washed with an aqueous solution of sodium carbonate (5%), filtred, washed with water and dried in an 80 ^{o} C oven. The solid product was purified by flash chromatography (hexane: EtOAc (4 : 6)) to afford 0.76 g (64.4%) of a yellow solid.

FT-IR: $V_{max}cm^{-1}$ 3605 (-C-OH), 3020 (=C-H), 1640 (-C=N), 1600 (C=C), 1080 (C-O ether). ^{1}H NMR (400 MHz, DMSO-d6) δ: 3.16 (s, 2H, CH2), 3.764 (s, 4H, CH_2CH_2); 3.78 (s, 6H, OCH_3), 5.72 (s, 2H, OH), 6.85 (m, 2H), 6.91 (d, 2H, J = 15.2 Hz), 7.05 (d, 2H, J = 12.1 Hz), 7.20 (s, 2H), 7.40- 7.60 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d6) δ: 24.50, 48.30, 56.40, 112.90, 116.30, 120.60, 122.40, 127.80, 129.30, 148.20, 149.30, 165.80. LC/MS [M+1] for $C_{23}H_{24}N_2O_4$: Calculated 393.0, found: 394.0. Anal. Calculated for $C_{23}H_{24}N_2O_4$: C 70.39, H 6.16, N 7.14. Found: C 70.33, H 6.21, N 7.19. The differences in the [M+1] values could be due to the protonation of compound 4 during LC/MS analysis, since mobile phase used in the analysis was an acidic solution of aqueous methanol.

2.3.3 Preparation of 4,4'-((3H-benzo[b] [1,4-diazepine-2,4-diyl) bis (ethane-2,1-diyl)) bis (2-methoxyphenol) (16b).

In a round bottomed flask equipped with a magnetic stirring bar and a condenser, tetrahydrocurcuminoids (1.0g, 2.7mmol) was dissolved in 15.0 ml ethanol. 1,2-diaminobenzene (0.324 g, 3.0 mmol) was added to the curcumin solution in ethanol followed with 0.5 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo*. The residue was washed with an aqueous solution of sodium carbonate (5%), filtered, washed with water and dried in an 80 ^{o} C oven. The produced solid was purified by recrystallization from EtOH/water solution to afford 1.17 g (97.5%) of a brown solid.

IR: ν_{max} cm^{-1} 3350 (-C-OH), 3020 (=C-H), 1640 (-C=N), 1600 (C=C), 1180 (C-O ether), 1220 (C-N). ^{1}H NMR (400 MHz, DMSO-d6) δ: 1.86 (t, 4H,

CH_2), 2.52 (s, 2H, CH_2), 2.59 (t, 4H, CH_2); 3.88 (s, 3H, OCH_3), 5.42 (s, 1H, OH), 6.65-6.81 (m, 3H), 7.35 (dd, 1H, J = 12.3 Hz), 7.37 (dd, 1H, J = 12.3 Hz). ^{13}C NMR (400 MHz, DMSO-d6) δ: 28.9, 33.8, 45.1, 56.40, 113.9, 121.3, 125.2, 130.1, 132.9,140.3, 144.7, 147.8, 165.3. LC/MS [M + 1] for $C_{27}H_{28}N_2O_4$ Calculated 444.52, found: 445.25. Anal. Calculated for $C_{27}H_{28}N_2O_4$: C 72.95, H 6.35, N 6.30. Found: C 71.33, H 6.45, N 7.43.

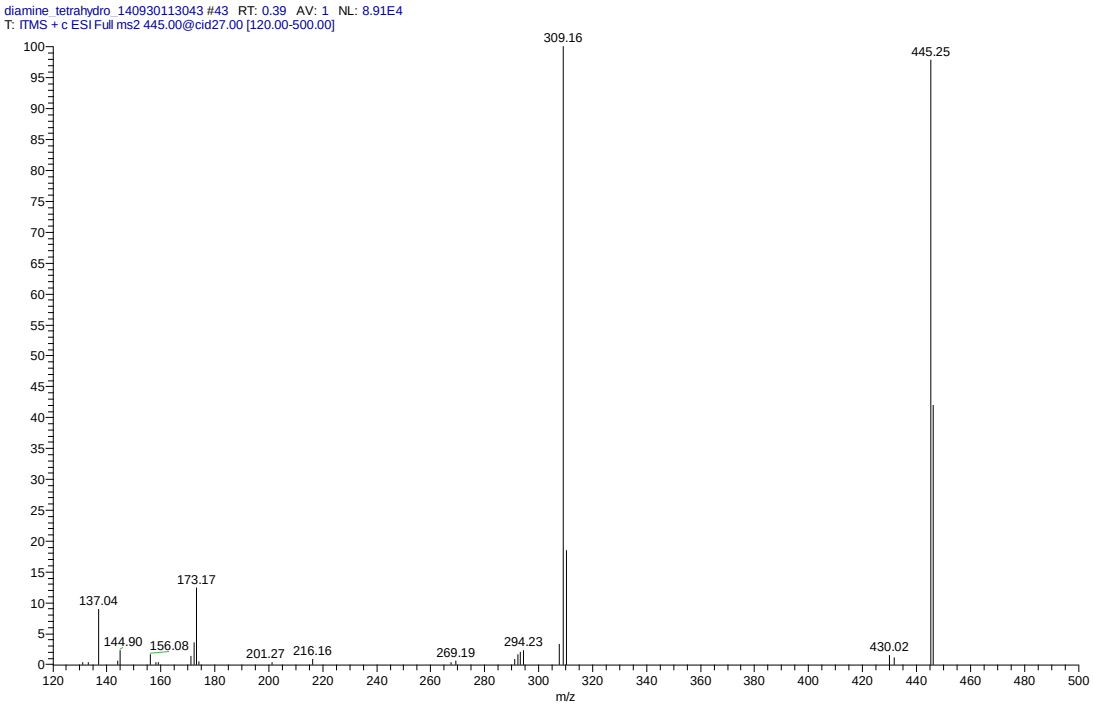


Figure 2.2: Mass spectrum of 4,4'-((3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethane-2,1-diyl))bis(2-methoxyphenol) (**17b**)

2.3.4 Preparation of 4,4'-((1*E*,1'*E*)-(3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (18b)

In a round bottomed flask equipped with a magnetic stirring bar and a condenser, curcumin(1.0g, 2.8 mmol) was dissolved in 15.0 ml ethanol. 1,2-diaminobenzene (0.324 g, 3.0 mmol) was added to the curcumin solution in ethanol followed with 0.5 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo*. The residue was washed with an aqueous solution of sodium carbonate (5%), filtered, washed with water and dried in an 80 ^{o} C oven. The produced solid was purified by recrystallization form EtOH/water solution to afford 1.22 g (93.8%) of a brown solid.

IR: V_{max} cm^{-1} 3405 (-C-OH), 3020, 1640 (-C=N), 1600 (C=C, aliphatic), 1580 (C=C, aromatic), 1220 (C-N), 1180 (C-O ether) and 1080 (C-O alcohol). ^{1}H NMR (400 MHz, DMSO-d6) δ: 2.61 (s, 2H, CH_2); 3.88 (s, 3H, OCH_3), 5.42 (s, 1H, OH), 6.65-6.81 (m, 3H), 7.01 (d, 1H, J = 15.3); 7.35 (dd, 1H, J = 12.3 Hz), 7.37 (dd, 1H, J = 12.3 Hz), 7.64 (d, 1H, J = 15.3). ^{13}C NMR (400 MHz, DMSO-d6) δ: 28.9, 33.8, 45.1, 56.40, 113.9, 121.3, 125.2, 130.1, 132.9,140.3, 144.7, 147.8, 165.3.LC/MS [M+1] for $C_{27}H_{24}N_2O_4$ Calculated 440.17, found: 441.24. Elemental analysis calculated: C, 73.62; H, 5.49; N, 6.36. Found: C, 73.51; H, 5.59; N, 6.49.

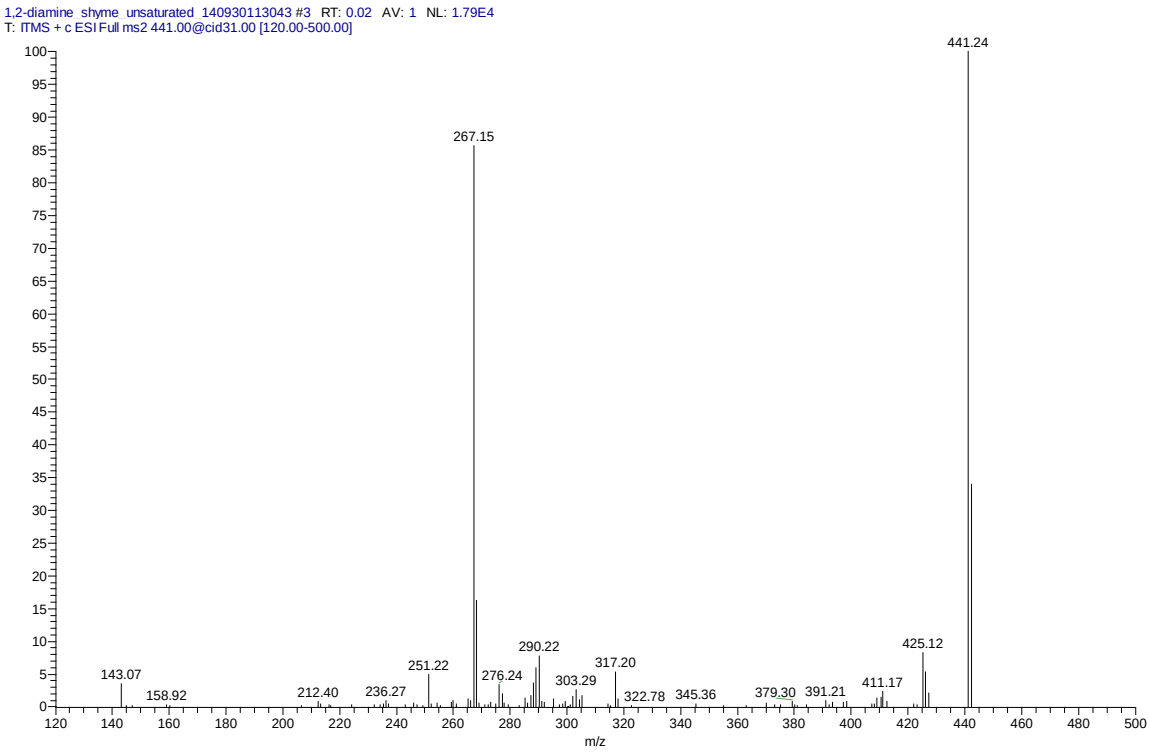


Figure 2.3: Mass spectrum of 4,4'-((1E,1'E)-(3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (**18b**)

2.3.5 Preparation of 4,4'- ((7-chloro-3H-benzo[b] [1,4-diazepine-2,4-diyl) bis (ethane-2,1-diyl)) bis (2-methoxyphenol) (17C).

In a round bottomed flask equipped with a magnetic stirring bar and a condenser tetrahydrocurcuminoids (1.0g, 2.7 mmol) was dissolved in 30.0 ml ethanol. 4-chloro-o-pheneylenediamine (0.385 mg, 3.0 mmol) was added to the solution of curcumin in ethanol followed with 0.5 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo*. The residue was washed with an aqueous solution of sodium carbonate (5%), filtered, washed with water and dried in an 80 ^{o} C oven. The produced solid was purified by recrystallization from EtOH/water solution to afford 1.24 g (96.1%) of a brown solid.

IR:ν_{max} cm^{-1} 3405 (-C-OH), 3020, 1640 (-C=N), 1580 (C=C, aromatic), 1220 (C-N), 1180 (C-O ether) and 1080 (C-O alcohol), 870 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d6) δ: 1.88 (t, 4H, CH_2), 2.58 (s, 2H, CH_2), 2.72 (t, 4H, CH_2); 3.67 (s, 6H, OCH_3), 5.38 (s, 2H, OH), 6.74-6.83 (m, 6H), 7.02 (dd, 1H, J = 3.4 &12.7 Hz), 7.67 (d, 1H, J = 12.7 Hz), 7.82 (d, 1H, J = 3.4 Hz). ^{13}C NMR (400 MHz, DMSO-d6) δ: 28.7, 34.8, 45.3, 56.40, 113.7, 116.1, 121.8, 122.1, 125.4, 127.1, 131.6, 132.9, 142.2, 144.7, 165.5. LC/MS [M+1] for $C_{27}H_{27}ClN_2O_4$ Calculated: 478.17, found: 479.08. Anal. Calculated: C 67.71, H 5.68, Cl 7.40 N 5.85. Found: C 67.01, H 5.72, Cl 7.48 N 5.96.

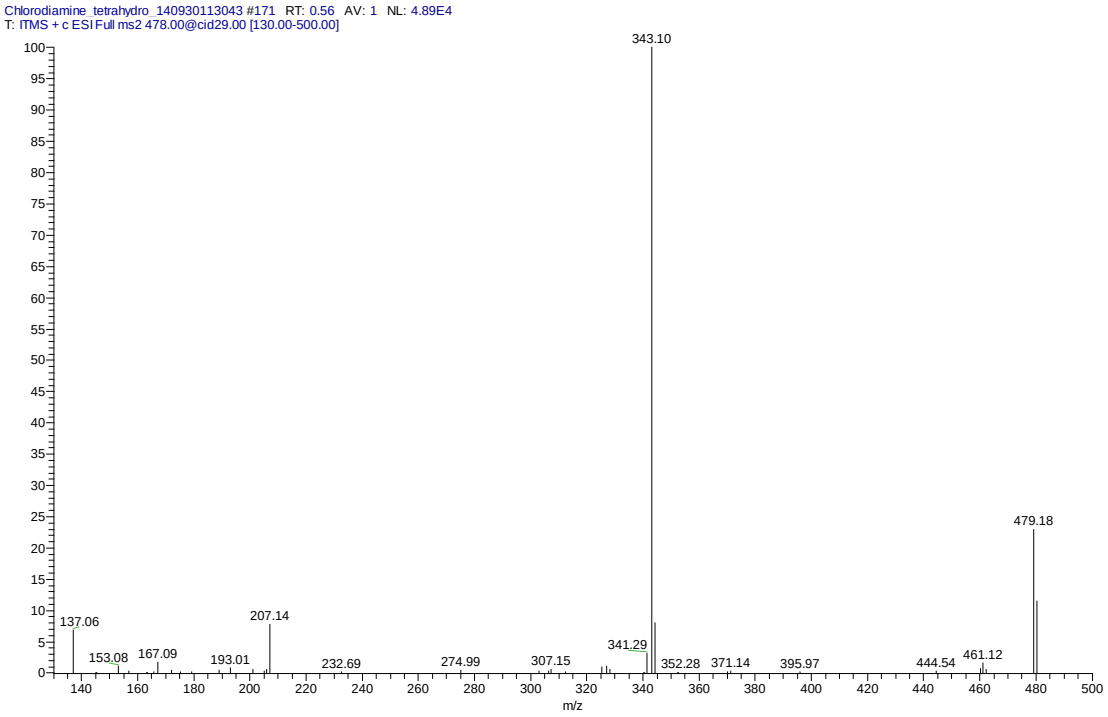


Figure 2.4: Mass spectrum of 4,4'-((7-chloro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethane-2,1-diyl))bis(2-methoxyphenol) (**17C**)

2.3.6 Preparation of 4, 4'- ((1*E*,1'*E*) - (7-chloro-3*H*-benzo[b] [1,4-diazepine-2,4-diyl) bis (ethene-2,1-diyl)) bis (2-methoxyphenol) (18C)

In a round bottomed flask equipped with a magnetic stirring bar and a condenser, curcumin (1.0g, 2.8 mmol) was suspended in ethanol (30.0 mL). 4-chloro-o-pheneylenediamine (0.385 mg, 3.0 mmol) was added to the solution of curcumin. To the mixture was added 0.2 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo. The residue was washed sequentially* with saturated solution of $NaHCO_3$ and water. The produced solid dried in an oven at about 70 ^{o}C then purified by recrystallization form EtOH/water solution to afford 1.26 g (95.3%) of bright green crystals.

IR:V_{max} cm^{-1} 3405 (-C-OH), 3020, 1640 (-C=N), 1600 (C=C, aliphatic), 1580 (C=C, aromatic), 1220 (C-N), 1180 (C-O ether) and 1080 (C-O alcohol), 870 (C-Cl).

^{1}H NMR (400 MHz, DMSO-d6) δ: 2.61 (s, 2H, CH_2); 3.69 (s, 6H, OCH_3), 5.34 (s, 2H, OH), 6.94-6.99 (m, 8H), 7.22 (dd, 1H, 3.4 & 12.5); 7.68 (d, 1H, J = 15.3), 7.80 (d, 1H, J = 12.5 Hz), 7.82 (d, 1H, J = 3.4 Hz). ^{13}C NMR (400 MHz, DMSO-d6) δ: 56.50, 112.1, 117.8, 120.8, 122.1, 124.8, 127.6, 127.5, 130.1, 131.9, 140.1, 141.7, 148.6, 150.3, 163.9. LC/MS [M + 1] for $C_{27}H_{23}ClN_2O_4$ Calculated 474.94, found: 475.0. Elemental analysis calculated: C, 68.28; H, 4.88; Cl, 7.46, N, 5.90; O, 13.48. Found: C, 67.78; H, 4.79; Cl, 7.58, N, 6.01; O, 13.39.

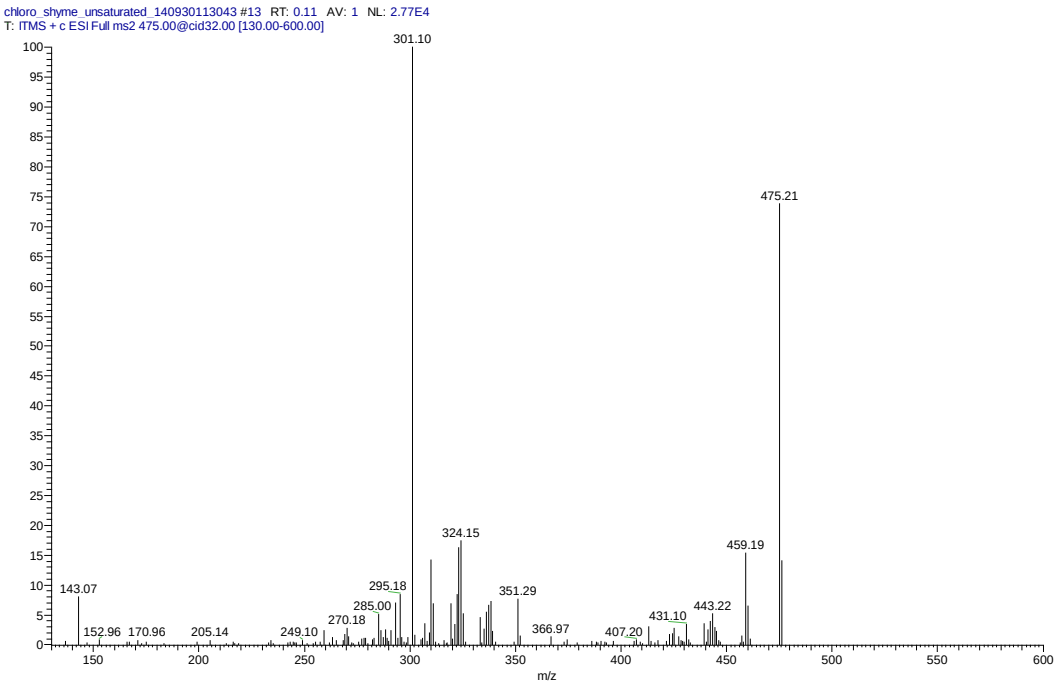


Figure 2.5: Mass spectrum of 4,4'-((1*E*,1'*E*)-(7-chloro-3*H*-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (**18C**)

2.3.7 Preparation of 4, 4'- ((7-bromo-3*H*-benzo[b] [1,4-diazepine-2,4-diyl) bis (ethane-2,1-diyl)) bis (2-methoxyphenol (17D)

In a round bottomed flask equipped with a magnetic stirring bar and a condenser tetrahydrocurcuminoids (1.0g, 2.7 mmol) was dissolved in ethanol (30.0 mL). 4-bromo-1,2-diaminobenzene (0.561 g, 3.0 mmol) was added to the solution of curcumin in ethanol followed with 0.5 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo*. The residue was washed with an aqueous solution of sodium carbonate (5%), filtered, washed with water and dried in an 80 ^{o} C oven. The produced solid was purified by recrystallization from EtOH/water solution to afford 1.28 g (90.7%) of a brown solid.

IR:V_{max} cm^{-1} 3405 (-C-OH), 3020, 1640 (-C=N), 1580 (C=C, aromatic), 1220 (C-N), 1180 (C-O ether) and 1080 (C-O alcohol), 870 (C-Br). ^{1}H NMR (400 MHz, DMSO-d6) δ: 1.88 (t, 4H, CH_2), 2.58 (s, 2H, CH_2), 2.72 (t, 4H, CH_2); 3.67 (s, 6H, OCH_3), 5.38 (s, 2H, OH), 6.74-6.83 (m, 6H), 7.02 (dd, 1H, J = 3.4 &12.7 Hz), 7.67 (d, 1H, J = 12.7 Hz), 7.82 (d, 1H, J = 3.4 Hz). ^{13}C NMR (400 MHz, DMSO-d6) δ: 28.7, 34.8, 45.3, 56.40, 113.7, 116.1, 121.8, 122.1, 125.4, 127.1, 131.6, 132.9, 142.2, 144.7, 165.5. LC/MS [M + 1] for $C_{27}H_{27}BrN_2O_4$ Calculated 523.42, found: 523.13. Anal. Calculated: C, 61.96; H, 5.20; Br, 15.27, N, 5.35;Found:C, 61.87; H, 5.29; Br, 15.42, N, 5.51.

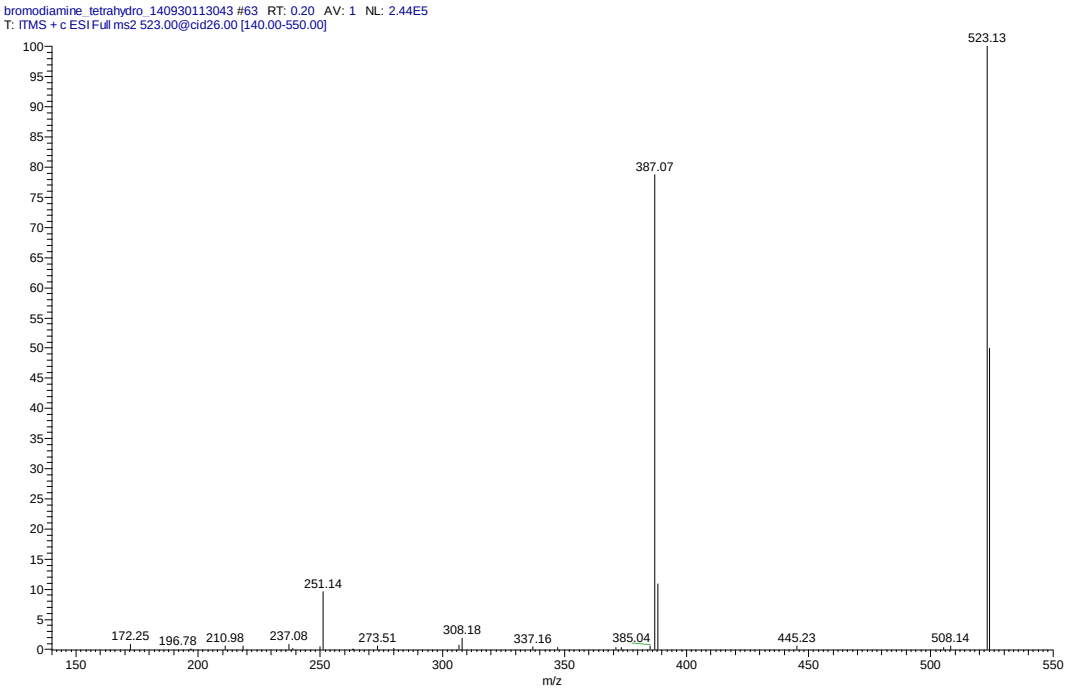


Figure 2. 6: MS of 4,4'- ((7-bromo-3H-benzo[b] [1,4-diazepine-2,4-diyl) bis (ethane-2,1-diyl)) bis (2-methoxyphenol) (1**7D**)

2.3.8 Preparation of 4, 4'-((1*E*,1'*E*) - (7-bromo-3*H*-benzo [b] [1,4-diazepine-2,4-diyl) bis (ethene-2,1-diyl)) bis (2-methoxyphenol) (18D).

In a round bottomed flask equipped with a magnetic stirring bar and a condenser, curcumin (1.0g, 2.8 mmol) was suspended in ethanol (30.0 mL). 4-bromo-1,2-diaminobenzene (0.561 g, 3.0 mmol) was added to the suspension of curcumin. To the mixture was added 0.2 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo. The residue was washed sequentially* with saturated solution of $NaHCO_3$ and water. The produced solid dried in an oven at about 70 ^{o}C then purified by

by recrystallization form EtOH/water solution to afford 1.29 g (83.2%) of a brown solid.

IR:V_{max} cm^{-1} 3405 (-C-OH), 3020, 1640 (-C=N), 1600 (C=C, aliphatic), 1580 (C=C, aromatic), 1220 (C-N), 1180 (C-O ether) and 1080 (C-O alcohol), 870 (C-Br).

^{1}H NMR (400 MHz, DMSO-d6) δ: 1.48 (s, 2H, CH_2); 3.89 (s, 6H, OCH_3), 5.23 (s, 2H, OH), 6.96-7.01 (m, 8H), 7.20 (dd, 1H, 3.4 & 12.5); 7.72 (d, 1H, J = 15.3), 7.82 (d, 1H, J = 12.5 Hz), 7.85 (d, 1H, J = 3.4 Hz). ^{13}C NMR (400 MHz, DMSO-d6) δ: 56.50, 111.9, 116.8, 121.6, 122.0, 124.4, 127.3, 127.8, 129.1, 130.8, 140.5, 141.4, 148.5, 150.1, 163.3. LC/MS [M + 1] for $C_{27}H_{23}BrN_2O_4$ Calculated 518.08, found: 518.52. Anal. Calculated: C, 62.44; H, 4.46; Br, 15.38, N, 5.39; Found: C, 62.30; H, 4.56; Br, 15.48, N, 5.51.

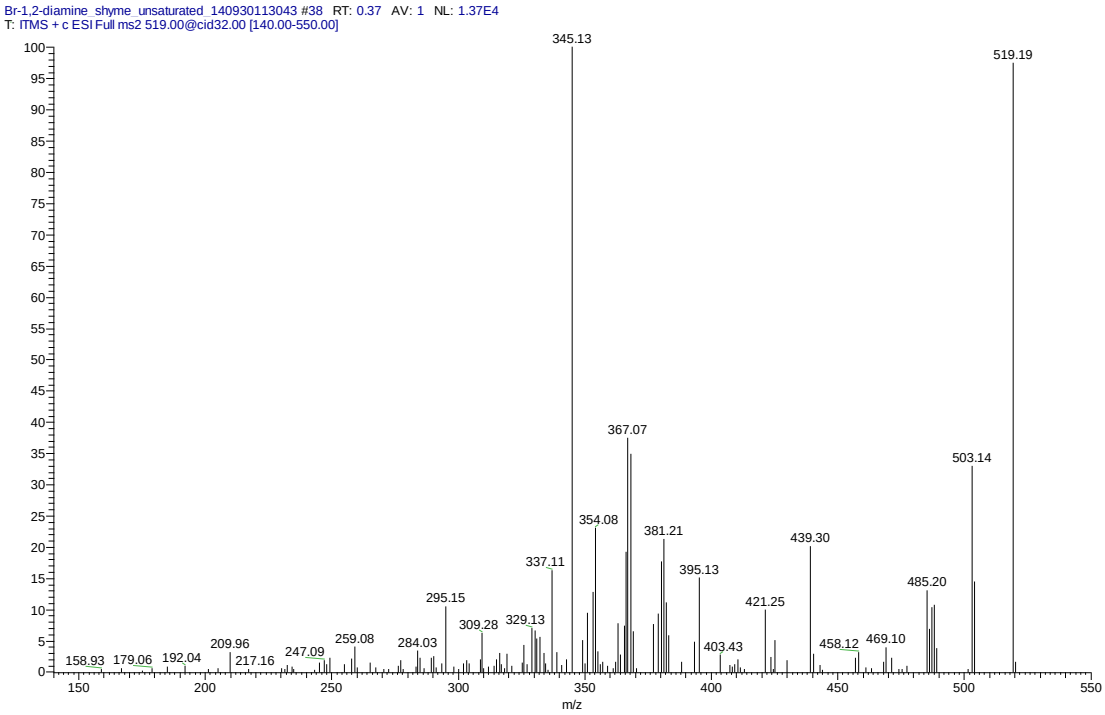


Figure 2.7: MS of 4,4'-((1E,1'E)-(7-bromo-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (**18D**)

2.3.9 Preparation of 4, 4'-((1*E*,1'*E*) - (7-flouro-3*H*-benzo [b] [1,4-diazepine-2,4-diyl) bis (ethene-2,1-diyl)) bis (2-methoxyphenol) (17E)

In a round bottomed flask equipped with a magnetic stirring bar and a condenser tetrahydrocurcuminoids (1.0g, 2.7 mmol) was dissolved in 30.0 ml ethanol. 4-flouro-1,2-diaminobenzene (0.378 g, 3.0 mmol) was added to the solution of tetrahydrocurcuminoids in ethanol followed with 0.5 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo*. The residue was washed with an aqueous solution of sodium carbonate (5%), filtered, washed with water and dried in an 80 ^{o} C oven. The produced solid was purified by recrystallization from EtOH/water solution to afford 1.11 g (88.8%) of a brown solid.

IR:V_{max} cm^{-1} 3405 (-C-OH), 3020, 1640 (-C=N), 1580 (C=C, aromatic), 1220 (C-N), 1180 (C-O ether) and 1080 (C-O alcohol), 850 (C-F).

^{1}H NMR (400 MHz, DMSO-d6) δ: 1.84 (t, 4H, CH_2), 2.55 (s, 2H, CH_2), 2.70 (t, 4H, CH_2); 3.63 (s, 6H, OCH_3), 5.35 (s, 2H, OH), 6.72-6.80 (m, 6H), 7.01(dd, 1H, J = 3.4 &12.7 Hz), 7.63 (d, 1H, J = 12.7 Hz), 7.80 (d, 1H, J = 3.4 Hz). ^{13}C NMR (400 MHz, DMSO-d6) δ: 28.5, 34.4, 45.1, 56.43, 113.6, 116.5, 121.4, 122.3, 125.9, 126.9, 131.8, 132.7, 142.0, 144.5, 165.1. LC/MS [M + 1] for $C_{27}H_{27}FN_2O_4$ Calculated 462.5, found: 463.3. Anal. Calculated: C, 70.11; H, 5.88; F, 4.11, N, 6.06; Found: C, 69.65; H, 5.93; F, 4.22, N, 6.26.

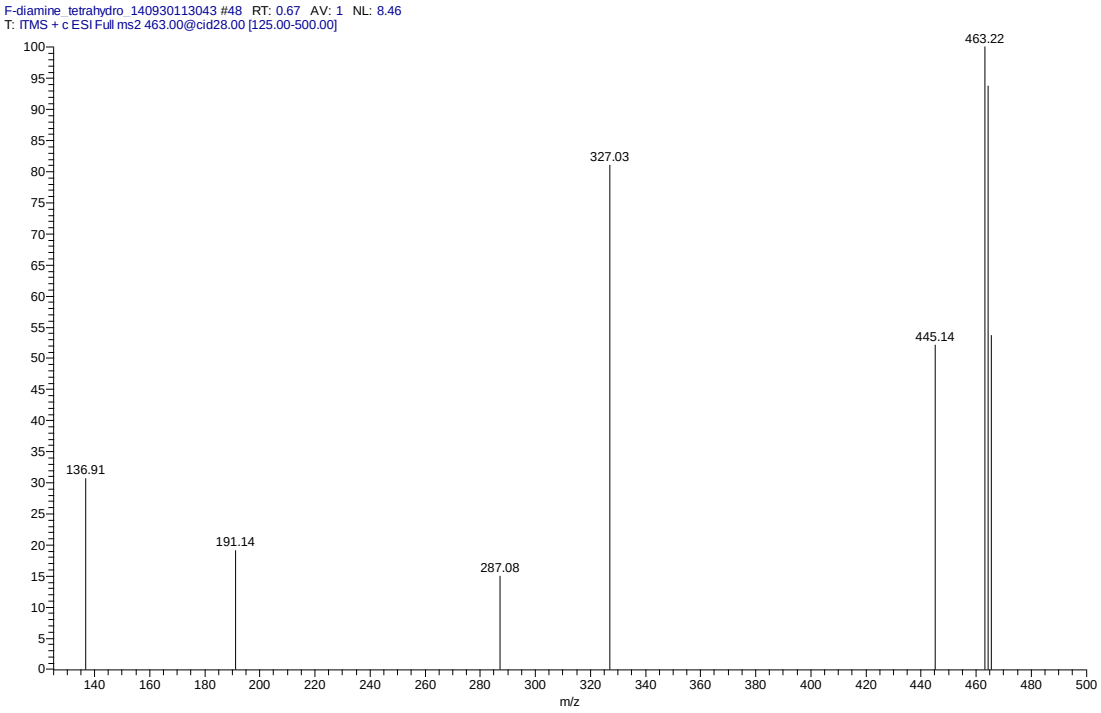


Figure 2.8: Mass spectrum **of 4,4'-((1E,1'E)-(7-flouro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (17E)**

2.3.10 Preparation of 4, 4'-((7-flouro-3*H*-benzo[b] [1,4-diazepine-2,4-diyl) bis (ethane-2,1-diyl)) bis (2-methoxyphenol) (18E).

In a round bottomed flask equipped with a magnetic stirring bar and a condenser, curcumin (1.0g, 2.8 mmol) was suspended in 30.0 ml ethanol. 4-flouro-1,2-diaminobenzene (0.378 g, 3.0 mmol) was added to the suspension of curcumin. To the mixture was added 0.2 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo.* The residue was washed sequentially with saturated solution of $NaHCO_3$ and water. The produced solid dried in an oven at about 70 ^{o}C then purified

by recrystallization from EtOH/water solution to afford 1.23 g (89.78%) of a brown solid.

IR:V_{max} cm^{-1} 3405 (-C-OH), 3020, 1640 (-C=N), 1600 (C=C, aliphatic), 1580 (C=C, aromatic), 1220 (C-N), 1180 (C-O ether) and 1080 (C-O alcohol), 860 (C-F).

^{1}H NMR (400 MHz, DMSO-d6) δ: 2.59 (s, 2H, CH_2); 3.71 (s, 6H, OCH_3), 5.36 (s, 2H, OH), 6.95-6.99 (m, 8H), 7.23 (dd, 1H, 3.4 & 12.5); 7.70 (d, 1H, J = 15.3), 7.82 (d, 1H, J = 12.5 Hz), 7.85 (d, 1H, J = 3.4 Hz). ^{13}C NMR (400 MHz, DMSO-d6) δ: 56.52, 112.3, 117.6, 120.9, 122.0, 124.5, 127.4, 127.3, 130.3, 131.8, 140.5, 141.9, 148.8, 150.1, 163.6. LC/MS [M + 1] for $C_{27}H_{23}FN_2O_4$ Calculated 458.16, found: 458.31. Anal. Calculated: C, 70.73; H, 5.06; F, 4.14, N, 6.11; Found: C, 70.42; H, 5.21; F, 4.27, N, 6.31.

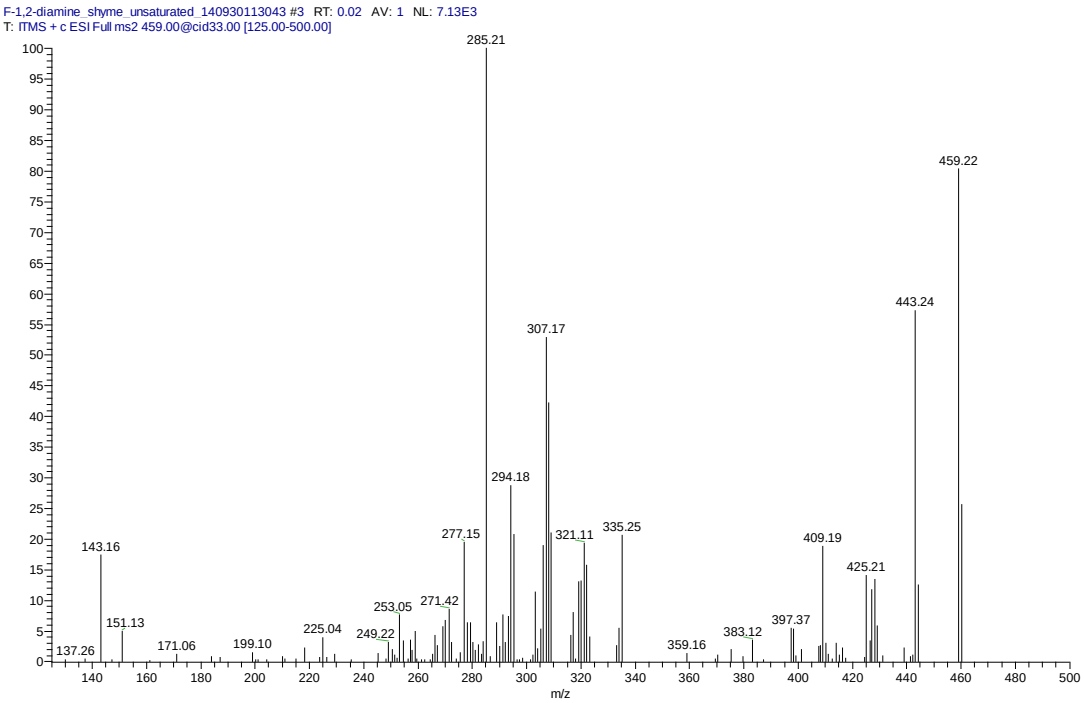


Figure 2.9: Mass spectrum of 4, 4'- ((7-flouro-3*H*-benzo[b] [1,4-diazepine-2,4-diyl) bis (ethane-2,1-diyl))bis(2-methoxyphenol) (**18E**)

2.3.11 Preparation of 4,4'- ((7,8-dichloro-3H-benzo[b] [1,4-diazepine-2,4-diyl) bis (ethane-2,1-diyl)) bis (2-methoxyphenol) (19)

In a round bottomed flask equipped with a magnetic stirring bar and a condensertetrahydrocurcuminoids (1.0g, 2.7 mmole) was dissolved in ethanol (30.0 mL). 4,5-dichloro-o-pheneylenediamine (0.531 mg, 3.0 mmol) was added to the solution of curcumin in ethanol followed with 0.5 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo*. The residue was washed with an aqueous solution of sodium carbonate (5%), filtered, washed with water and dried in an 80 ^{o} C oven. The produced solid was purified by recrystallization from EtOH/water solution to afford 1.24 g (96.1%) of a brown solid.

IR:V_{max} cm^{-1} 3405 (-C-OH), 3020, 1640 (-C=N), 1600 (C=C, aromatic), 1220 (C-N), 1180 (C-O ether) and 1080 (C-O alcohol), 870 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d6) δ: 1.83 (t, 4H, CH_2), 2.62 (t, 4H, CH_2), 2.70 (s, 2H, CH_2); 3.77 (s, 6H, OCH_3), 5.24 (s, 2H, OH), 6.70-6.74 (m, 4H), 6.92 (dd, 2H, J = 3.3 &12.5 Hz), 7.43 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d6) δ: 29.3, 35.4, 45.7, 56.30, 115.8, 122.8, 125.6, 129.1, 133.3, 140.0, 142.3, 145.7, 164.9. LC/MS [M + 1] for $C_{27}H_{26}Cl_2N_2O_4$Calculated 512.67, found: 513.0. Anal. Calculated: C 63.16, H 5.10, Cl 13.81, N 5.46. Found: C 62.91, H 5.32, Cl13.95 N 5.54.

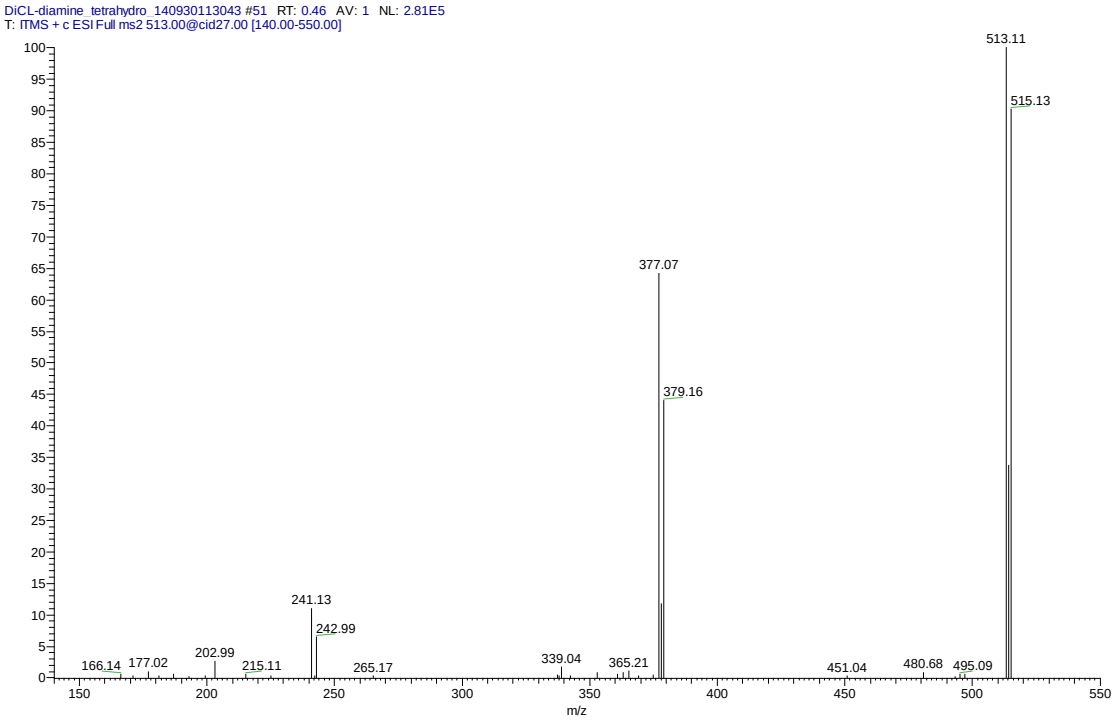


Figure 2.10: Mass spectrum of 4,4'-((7,8-dichloro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethane-2,1-diyl))bis(2-methoxyphenol) (**19**)

2.3.12 Preparation of 4,4'- ((1*E*,1'*E*) - (7,8-dichloro-3*H*-benzo [b] [1,4-diazepine-2,4-diyl) bis (ethene-2,1-diyl)) bis (2-methoxyphenol) (20).

In a round bottomed flask equipped with a magnetic stirring bar and a condenser, curcumin (1.0g, 2.8 mmol) was suspended in 30.0 ml ethanol. 4,5-dichloro-o-pheneylenediamine (0.531 mg, 3.0 mmol) was added to the solution of curcumin. To the mixture was added 0.2 mL of concentrated sulfuric acid. The produced solution was refluxed for 2 hr. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was cooled down to room temperature, concentrated *in-vacuo. The residue was washed sequentially* with saturated solution of $NaHCO_3$ and water. The produced solid dried in an oven at about 70 ^{o}C then purified by recrystallization from EtOH/water solution to afford 1.26 g (95.3%) of brown solid.

IR:V_{max} cm^{-1} 3405 (-C-OH), 3020, 1640 (-C=N), 1600 (C=C, aliphatic), 1580 (C=C, aromatic), 1220 (C-N), 1180 (C-O ether) and 1080 (C-O alcohol), 870 (C-Cl).

^{1}H NMR (400 MHz, DMSO-d6) δ: 2.66 (s, 2H, CH_2); 3.89 (s, 6H, OCH_3), 5.94 (s, 2H, OH), 6.73-6.98 (m, 6H), 7.12 (dd, 2H, 3.5 & 12.5); 7.37 (d, 2H, J = 15.1). ^{13}C NMR (400 MHz, DMSO-d6) δ: 26.40, 56.3, 112.2, 116.9, 120.5, 122.7, 125.1, 126.8, 127.6, 129.4, 140.3, 144.9, 149.1, 164.8. LC/MS [M + 1] for $C_{27}H_{22}Cl_2N_2O_4$ Calculated 509.4, found: 475.0. Elemental analysis calculated: C, 63.66; H, 4.35; Cl, 13.92, N, 5.50. Found: C, 63.38; H, 4.82; Cl, 7.65, N, 6.23.

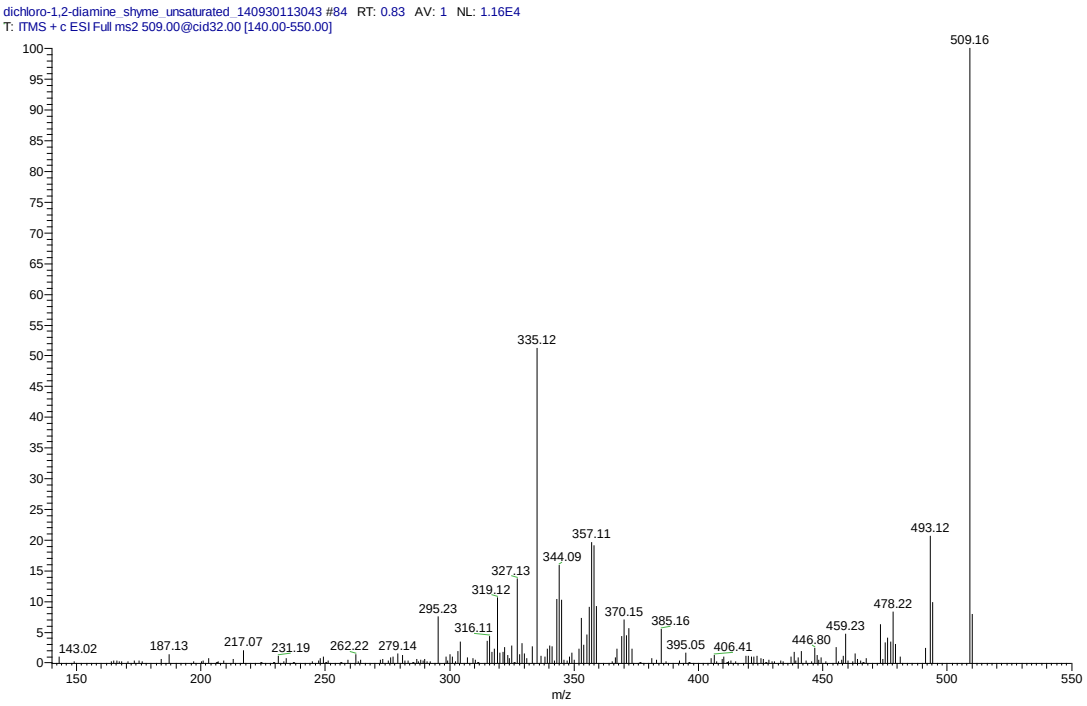


Figure 2.11: Mass spectrum of4,4'-((1*E*,1'*E*)-(7,8-dichloro-3*H*-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) **(20).**

CHAPTER THREE

RESULTS AND DISCUSSION

The main goal of this work is to design and prepare novel curcumin based heterocyclic compounds with antibacterial activities that exceeds current antibacterial reagents and less toxic.

Curcumin **13** was chosen as the base of the heterocyclic derivatives due to several reasons among which mentioned earlier in the introduction. Curcumin and hydrogenated curcumin **14** were derivatized with diamino aromatic compounds to form various diazepines heterocyclic aromatic compounds. As shown in the introduction (chapter I) heterocycles have a large number of medical applications.

3.1 Preparation of Tetrahydrocurcuminoids (THC):

Tetrahydrocurcuminoids (14) was prepared as shown in equation 1 from hydrogenation of curcumin catalyzed with Pd/C. The hydrogenation was performed in ethanol under H_2 pressure of about 2 psi.The apparatus used in the hydrogenation are shown in Figure 3.1, the balloon was used as hydrogen reservoir. The yield was quantitative, the structure of the product was identified by ^{1}H NMR, IR and MS as shown in the experimental part. ^{1}H NMR shows the presence of two triplet at about 2.9 (t, J = 7.97, 3H), 2.6 (t, J = 7.14, 3H) which belong to the methylene groups adjacent to carbonyl and aromatic groups. The prepared tetrahydrocurcuminoids (14) was used as a starting material for making heterocycles diazepines. It was chosen to determine the effect of the two double

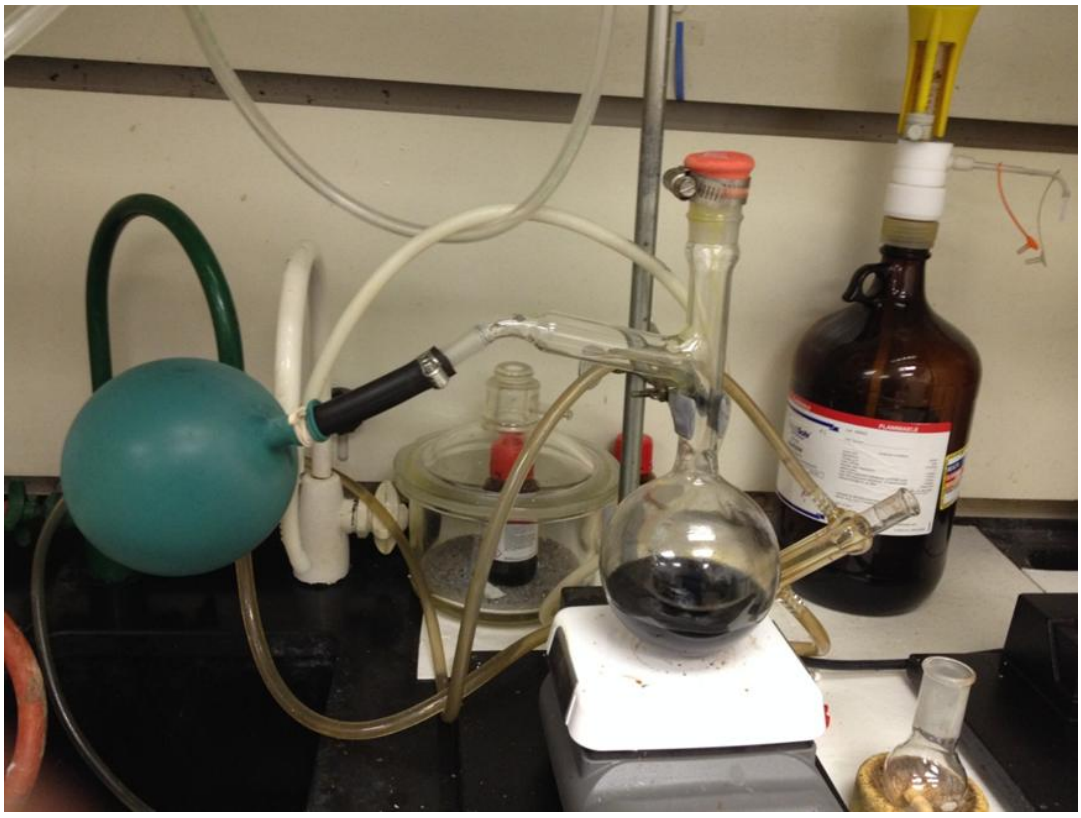
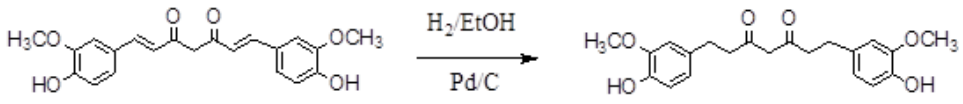


Fig 3.1: The apparatus used in the hydrogenation of curcumin

bonds in the curcumin molecule on its bioactivity. [Since the doubles have great effect on curcumin geometry]. A 3D representative structure of both curcumin and THC are shown in Figure 3.2, Curcumin has a rigid structure while THC is flexible. The rigidity of curcumin could be considered as an important factor in its bioactivity.



13 14 **Eq. 1**

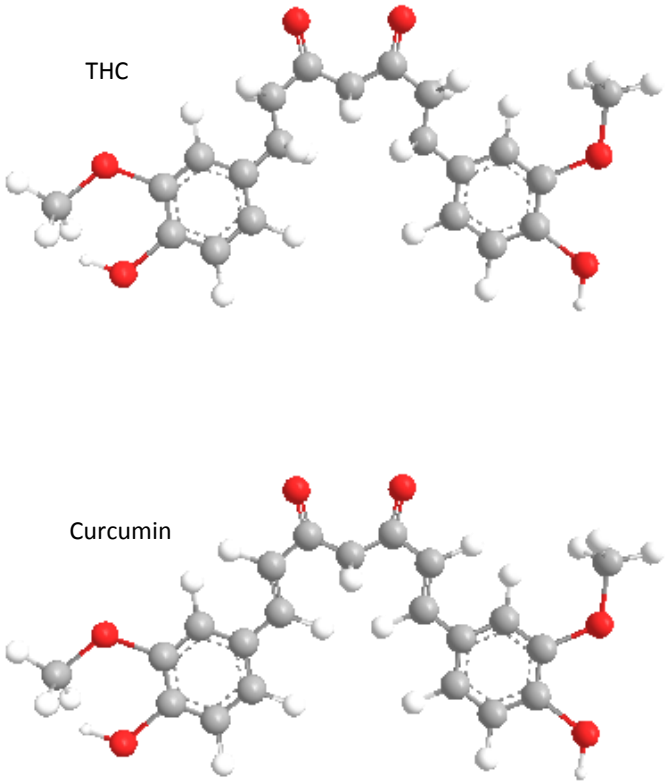


Figure 3.2: 3D structure of curcumin and THC

3.2 Preparation of tetrahydrocurcuminoids (THC) based diazepines (17)

Diazepine compounds (17) were prepared with a new developed procedure. In this procedure, tetrahydrocurcuminoids was stirred with various aromatic and aliphatic diamino compounds in the presence of catalytic amount of sulfuric acid. The reaction needed some heat for completion.The progress of the reaction was monitored by TLC. Some reactions required heating time longer than others. In all cases about 2 hour reaction period was optimum time for the completion of the reaction and obtaining an excellent yield.

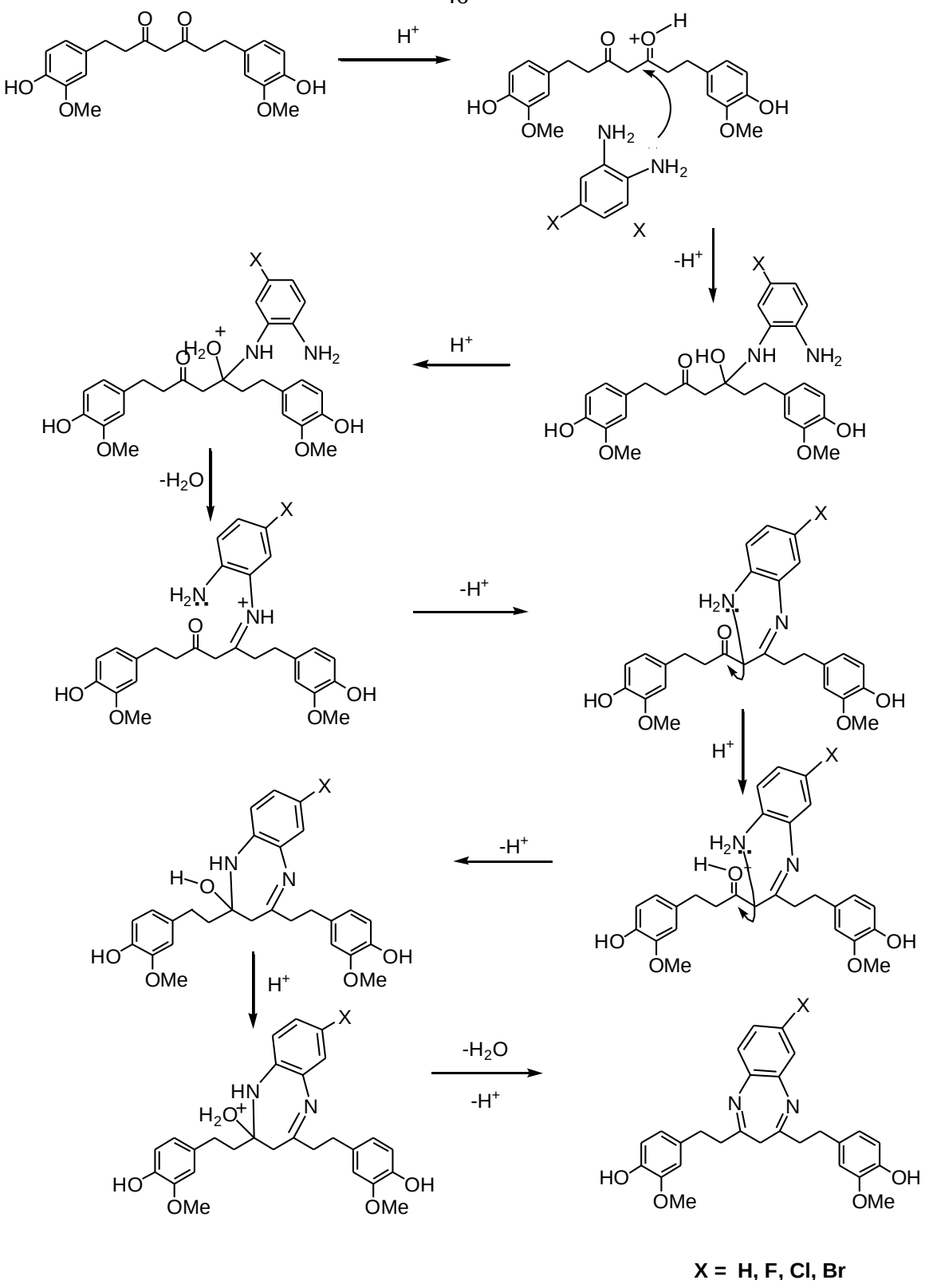
The followed procedure produced only the expected product, no side products were observed but some starting materials were also observed because an excess of starting material was used. Purification of the products were performed by recrystallization from a mixture of two solvents ethanol and water. Purification of the crude products of all reactions by recrystallization gave only one major fraction which were characterized through by various spectroscopic techniques, such as; FT-IR, NMR, LC/MS and elemental analysis. In all cases the results are consistent with the expected structures. All compounds were obtained in excellent yield (over 85.0%).

3.2.1 Mechanism for formation of tetrahydrocurcuminoids (THC) based diazepines (17)

General reaction equation for the preparation of tetrahydrocurcuminoids (THC) based diazepines is shown in equation 2. Tetrahydrocurcuminoids and diamines were reacted in 1:1 mole ratio using sulfuric acid as a catalyst.

Running the reaction in acetic acid alone for more than 24 hr showed only the presence of starting material with no diazepine. Running the reaction in ethanol in the presence of a ctalystic amount of acetic acid also didn't give any product. Strong acid such as sulfuric acid was needed to catalyze the condensation reaction between THC (14) and various diamine compounds.

Mechanistically, the coupling between tetrahydrocurcuminoids (14) and diamino compounds is expected to proceed as shown in scheme 3.1. An amino group of diamino compounds makes a nucleophilic attack on one of the tetrahydrocurcuminoids carbonyl groups, which are protonated, followed by loss of a water molecule. Nucleophilic attack by the second amino group on the intermediate **22** followed with a loss of water results on the formation of the diazepine.



Scheme 3.1 : Mechanism of coupling between THC and aromatic amines

3.2.2 FT-IR of Tetrahydrocurcuminoids (THC) Based Diazepines

The structure of the prepared diazepines were confirmed by IR and NMR spectroscopy. In the IR spectrum. All diazepine compounds showed some similarities in their FT-IR spectra, several bands showed up at same frequencies as shown in Figure 3.3, these bands are at about 1700 cm^{-1} which represents the C=N vibrational stretching, the band 1080 cm^{-1} is characteristic for (C-O ether) of methoxy group. Bands at 3100 and 1600 cm^{-1} are for =C-H and C=C in aromatic, respectively. Another broad band showed at about 3300 cm^{-1} that is a characteristic O-H phenolic group. Regarding the band that represents the halogens on aromatic ring these showed at different frequencies (=C-X, X = Cl, Br, F). FT-IR spectra of all prepared compound are shown in the index.

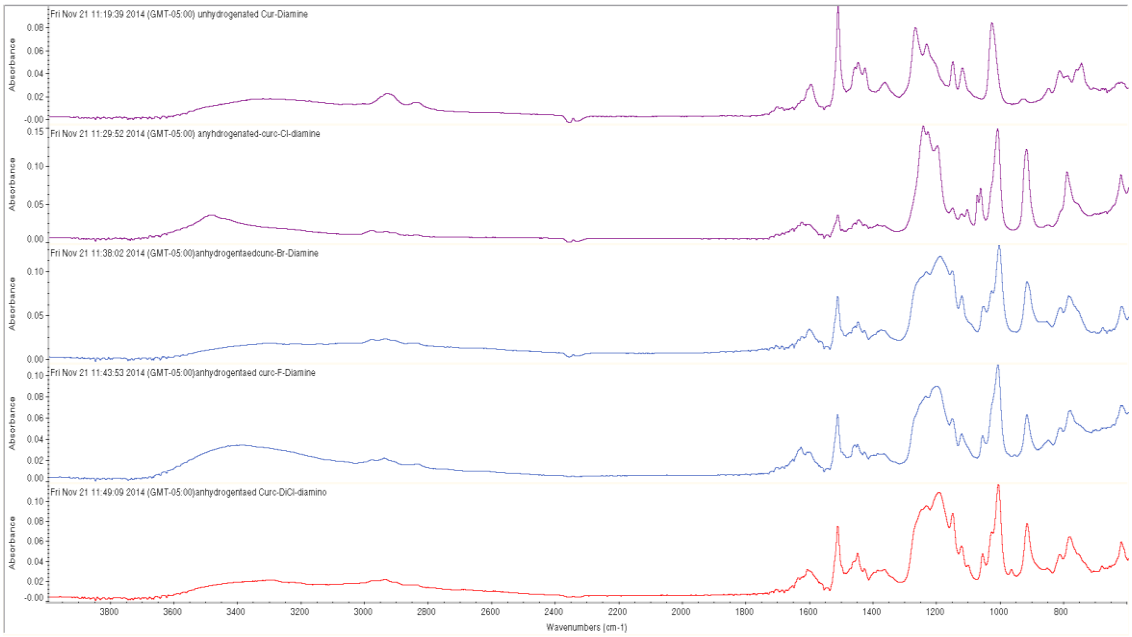


Figure3.3: Overlaid FT-IR spectra of Tetrahydrocurcuminoids (THC) Based Diazepines (**17**)

3.2.3 NMR of Tetrahydrocurcuminoids (THC) Based Diazepines (17)

All derivatives showed in their ^{1}H NMR spectrum the aromatic rings protons in the region δ 6.9-7.9 ppm, which appeared as multiplets. The most de-shielded protons among all other aromatic protons one at the para position form the N of the diazipen ring. A singlet signal attributed to OCH_3 attached to the ring appeared at δ 3.70, the aliphatic protons of C1, C2, C4, C-6, and C-7 appeared at in the range of δ 1.8 and δ 2.6.

Figure 3.4: The chemical shifts of the diazepines based THC in proton NMR spectroscopy.

The compounds showed similarities in their ^{13}C NMR spectra. Imine carbon (-C=N) appeared at about 164 ppm. The aromatic carbon bond to halogen (=C-X) appear at about 121ppm. The other aromatic carbons on the diazepines ring showed in the range (125.0 to 143.0 ppm), =C-N carbon of the diazepine ring showed the lowest frequency (143 ppm) among the other aromatic rings. While the curcumin aromatic carbon showed up in the range of 113 to 147 ppm, the most de-shielded one is the one bonded to

the methoxy groups. The carbon of the methoxy group appear at about 56.0 ppm in all compounds.

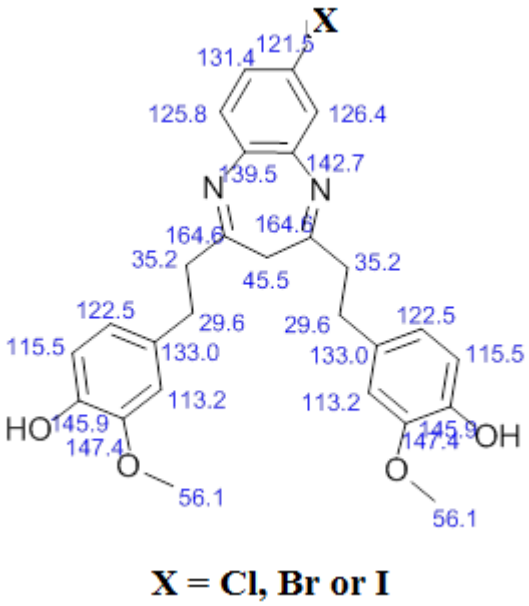


Figure 3.5: The chemical shifts of the diazepines based THC (17) in the C-13 NMR spectroscopy.

3.2.4 Mass spectroscopy of diazepines based THC (17)

Mass spectroscopy was performed on all samples, solutions of all samples were prepared in Nano scale concentration using a multi dilution procedure. The LCQ Fleet ion trap mass spectrometer was operated in positive electrospray mode. The electrospray voltage was 5 kV.The capillary temperature was 290°C and the sheath gas flow was 30 units. An isolation width of 2 Da was used with a 20 msec activation time for MS experiments. All scan events were acquired with a 250 ms maximum ionization time. As demonstrated in MS **Figure 2.3,** shown in the experimental part, 4,4'-((1E,1'E) - (3H – benzo [b] [1,4 – diazepine - 2,4 - diyl) bis(ethene-2,1-diyl))bis(2-methoxyphenol) **17B** shows in addition to

the molecular ion a base peak at m/z 309. Compound 4,4'-((7-chloro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethane-2,1-diyl))bis(2-methoxyphenol) **17C** shows a base peak at m/z 343. Diazepine 4,4'-((7-bromo-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethane-2,1-diyl))bis(2-methoxyphenol) **17D** shows a base peak at about m/z 387. Compound 4,4'-((1E,1'E)-(7-flouro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) **17E** shows a base peak at about m/z 327, and compound 4,4'-((7,8-dichloro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethane-2,1-diyl))bis(2-methoxyphenol) **20** showed a base peak of m/z 377. As shown in Figure 3.6 and Figure 3.7, all diazepines based THC have the same structure for the base peak considering different halogens on the aromatic rings.

Figure 3.6: Structure of fragments represent the base peaks in MS spectra of THC based diazepines (17B to D).

Figure 3.7: Structure of fragments represent the base peaks in MS spectra of THC based diazepines (17E and 20).

3.3 Preparation of curcumin based diazepines(18)

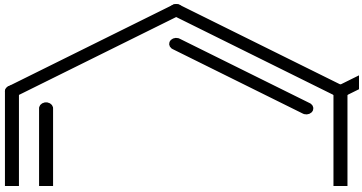
Diazepine curcumin based compounds were prepared with the developed procedure mentioned above. In this procedure, curcumin was stirred with various aromatic and aliphatic diamino compounds in the presence of catalytic amount of sulfuric acid. The reaction needed to be refluxed due to the lower reactivity of cunrcumin compared to THC, since the carbonyl groups are conjugated with double bonds. The progress of the reaction was monitored by TLC. In all cases, about 2hour reaction period with reflux

was optimum time for the completion of the reaction and obtaining excellent yield.

The followed procedure produced only the expected product, no side products were observed but some starting materials were also observed because excess of curcumin was used. Purification of the products were performed by recrystallization from a mixture of two solvents ethanol and water solvents. Purification of the crude products of all reaction by recrystallization gave only one major fraction which characterized by various spectroscopic techniques, such as; FT-IR, NMR, LC/MS and elemental analysis. In all cases results are consistent with the expected structures. All compounds were obtained in excellent yield (over 85.0%).

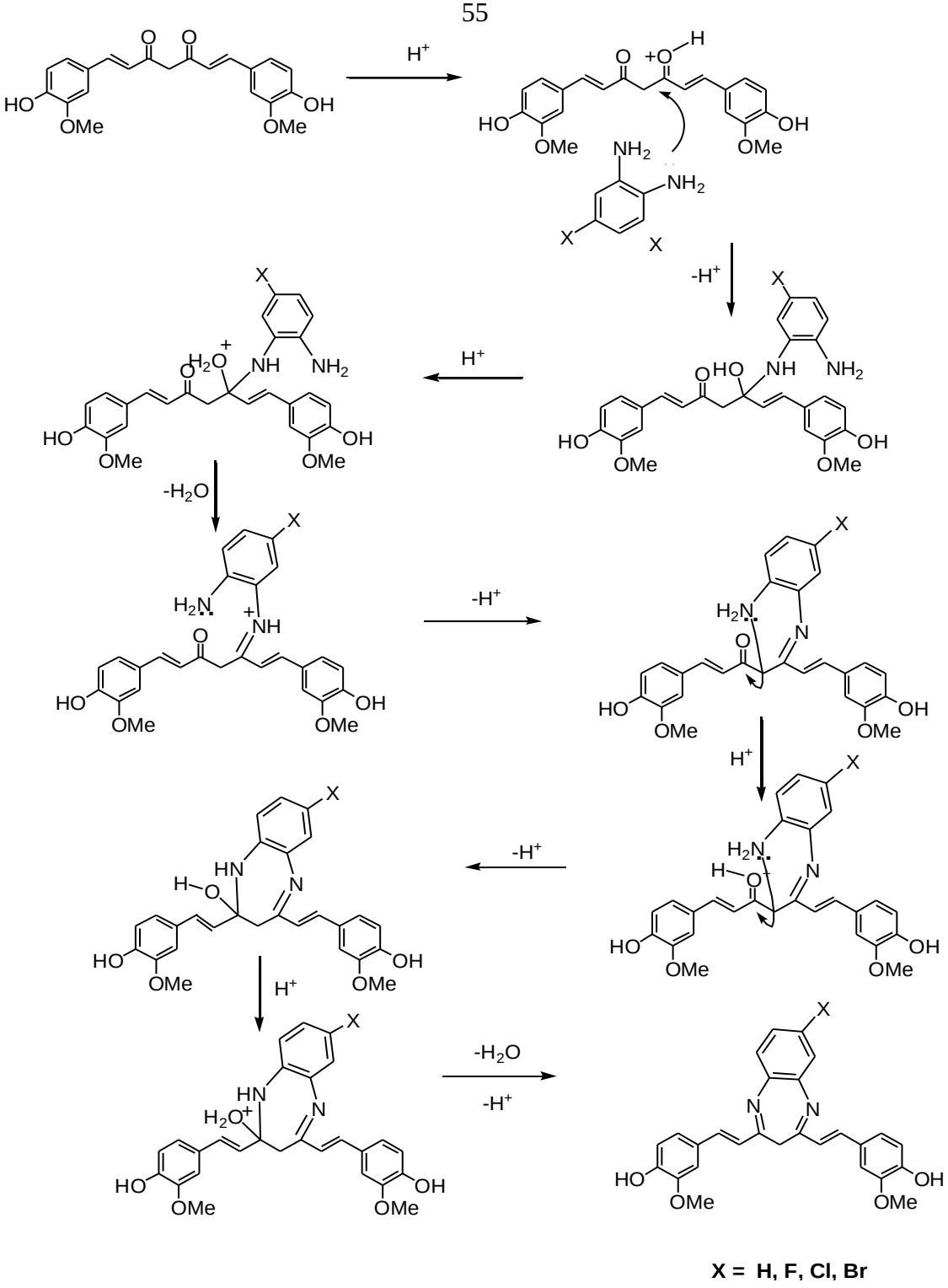
3.3.1 Mechanism for formation of curcumin based diazepines (18)

General reaction equation for the preparation of curcumin based diazepines is shown in equation 2. Tetrahydrocurcuminoids and diamines were reacted in 1:1 mole ratio using sulfuric as a catalyst



Several reaction conditions and reagent were tried to make the curcumin based diazepines. Carrying the reaction in acetic acid alone with reflux for more than 24 hr showed only starting material. Running the reaction in ethanol in the presence of a catalytic amount of acetic acid also didn't give any product. Strong acid such as sulfuric acid was needed to catalyze the condensation reaction between curcumin **13** and various aromatic and aliphatic diamine compounds.

The condensation reaction between curcumin **13** and diamino compounds**10** is expected to proceed as shown in scheme (3.2). An amino group of diamino compounds makes a nucleophilic attack on one of the tetrahydrocurcuminoids carbonyl groups followed by loss of a water molecules. Nucleophilic attack by the second amino group on the intermediate **12** followed with a loss of a second molecule of water results on the formation of the diazepine.



Scheme 3.2 : Mechanism of coupling between curcumin and aromatic amines

3.3.2 FT-IR of Tetrahydrocurcuminoids (THC) Based Diazepines (18)

The structure of the prepared curcumin based diazepines (18) were confirmed by FT-IR. In the FT-IR spectrum. All diazepine compounds showed similarities in most of the peaks present in their FT-IR spectra, several bands showed up at same frequencies as shown in Figure 3.8. These bands are less than 1700 cm^{-1} which represents the C=N vibrational stretching, the band 1080 cm^{-1} ischaracteristic for (C-O ether) of methoxy group. Bands at 3100 and 1600 cm^{-1} are for =C-H and C=C in aromatic, respectively. Another broad band showed at 3300 cm^{-1} that is a characteristic O-H phenolic group. Regarding the band that represents the halogens on aromatic ring these showed at different frequencies (=C-X, X = Cl, Br, F). FT-IR spectra of all prepared compound are shown in the index.

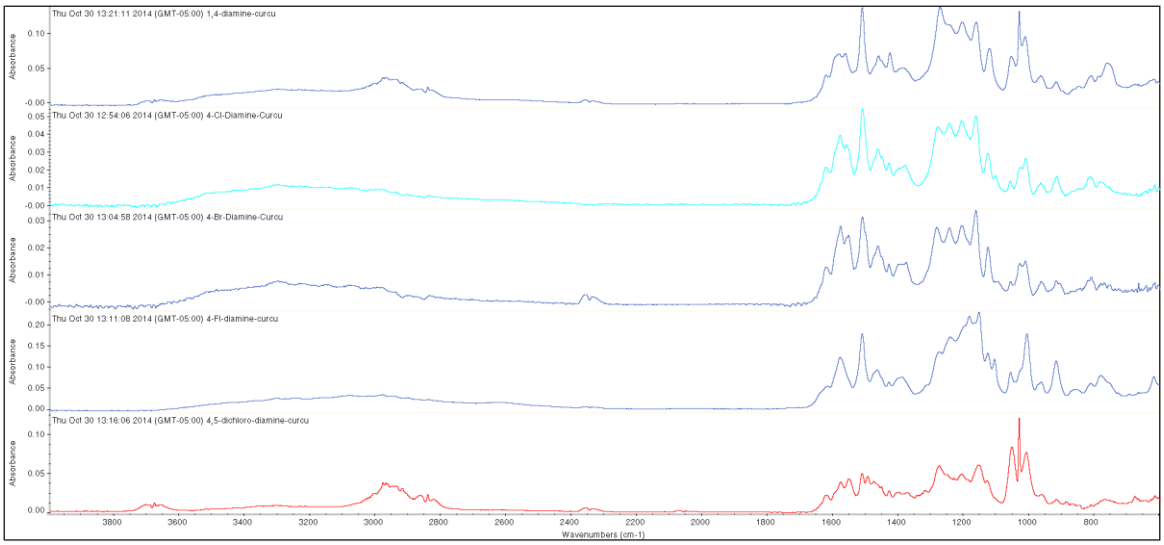


Figure3.8: Overlaid FT-IR spectra of curcumin Based Diazepines (18)

3.3.3 NMR of Tetrahydrocurcuminoids (THC) Based Diazepines (18)

The NMR of all curcumin based diazepines showed almost similar ^{1}H NMR spectra expect for the none halogenated compounds and the dihalogenated compounds. The aromatic rings protons in the region δ 6.9-7.9 ppm, which appeared as multiplets. The most de-shielded protons among all other aromatic protons one at the para position from the N of the diazipenring.A singlet signal attributed to OCH_3 attached to the ring appeared at δ 3.70, the aliphatic protons of C1, C2, C4, C-6, and C-7 appeared in the range of δ 1.8 and C-4 proton appeared at δ 2.7. The ^{1}H NMR spectrum of the bromodiazepine 4,4'-(1E,1'E)-(7-bromo-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (18C) is shown in the appendix

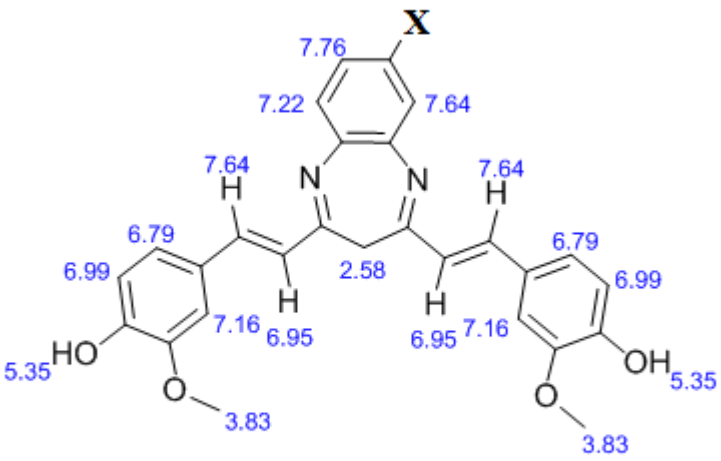


Figure 3.9: The figure shows the chemical shifts of the diazepines based THC in proton NMR spectroscopy.

The compounds showed similarities in their ^{13}C NMR spectra. Imine carbon (-C=N) appeared at about 164 ppm. The aromatic carbon bond to halogen (=C-X) appear at about 121 ppm. The other aromatic carbons on the diazepines ring showed in the range (125.0 to 143.0 ppm), =C-N carbon of the diazepine ring showed the lowest frequency (143 ppm) among the other aromatic rings. While the carbon of the curcumin aromatic moiety and the vinylic carbons showed up in the range of 113 to 147 ppm, the most de-shielded one is the one bonded to the methoxy groups. The carbon of the methoxy group appear at about 56.0 ppm in all compounds. The ^{13}CNMR spectrum of the bromodiazepine 4,4'-(1E,1'E)-(7-bromo-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) **18D** is shown in Figure 10 in the appendix

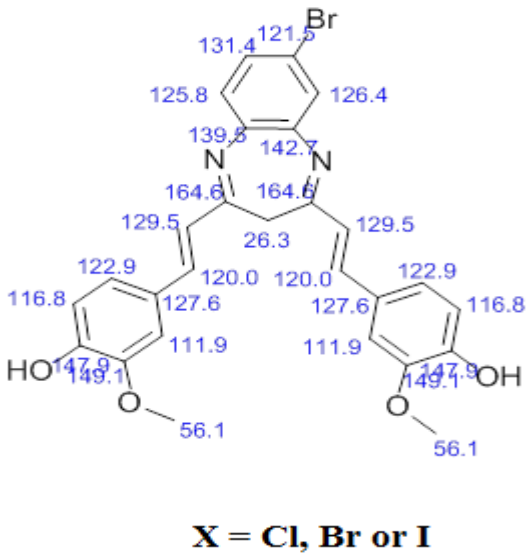


Figure 3.10: The figure shows the chemical shifts of the curcumin based diazepines in the C-13 NMR spectroscopy.

Cosey 2D NMR was obtained on 4,4'-((1E,1'E)-(7-bromo-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) **17D**, the spectrum is shown in Figure 3.11, As shown in the 2D spectrum the coupling is shown only in the aromatic and the vinylic regions.

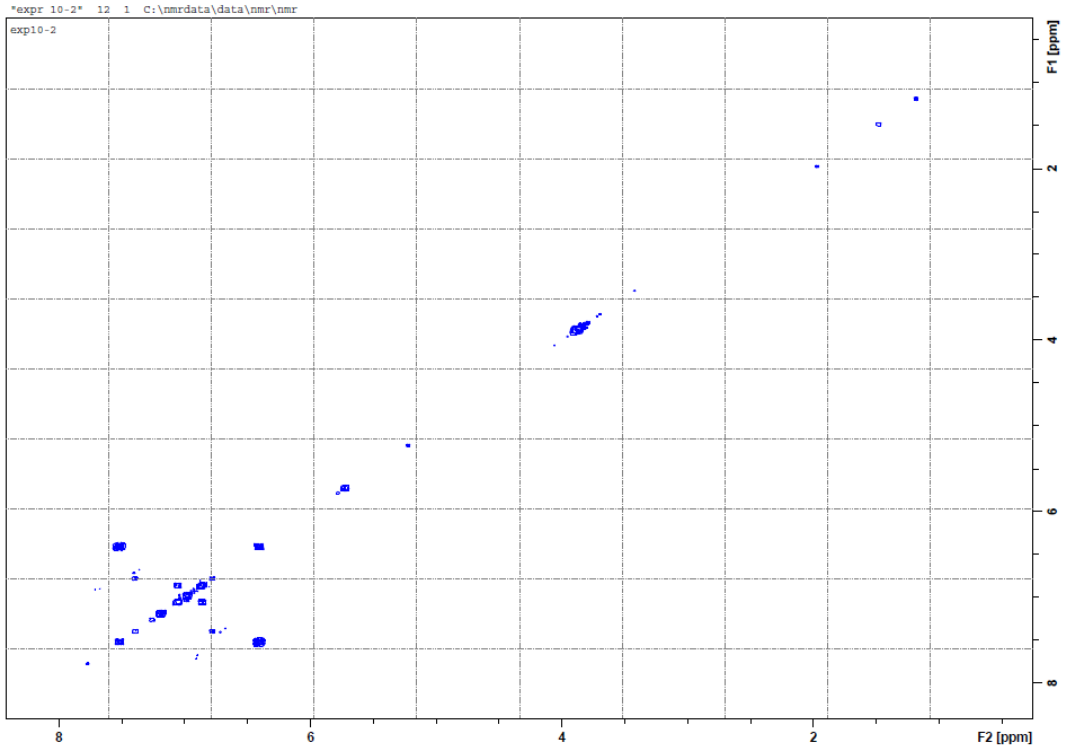


Figure 3.11: Cosey 2D NMR of 4,4'-((1E,1'E)-(7-bromo-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (17D)

3.3.4 Mass spectroscopy of Curcumin based diazepines

Mass spectroscopy was performed on all samples as shown before. All MS spectra are shown in the experimental part. As shown in the MS Figures (2.1 - 2.11) shown in the experimental part all compounds showed in addition to the molecular ion a base peak that represent a stable fragment in the MS detector. The fragmentation in the curcumin based diazepines is different from that shown by THC based diazepines. Since curucmine

based diazepines have longer conjugation system which doesn't present in the THC based diazepines. 4,4'-((1E,1'E)-(3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) **18B**shows a base peak at m/z 268. Compound 4,4'-((1E,1'E)-(7-chloro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) **18C** showed a base peak at m/z 302. Diazepine 4,4'-((1E,1'E)-(7-bromo-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) **18D** shows a base peak at about m/z 346. Compound 4,4'-((7-flouro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethane-2,1-diyl))bis(2-methoxyphenol) **18E** shows a base peak ta about m/z 286, and compound 4,4'-((1E,1'E)-(7,8-dichloro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) **21** showed a base peak of m/z 335. A shown in Figure 3.12, all diazepines based curcumin have same structure for the base peak considering different halogens on the aromatic rings. The fragment that represents the base peak has long chain of conjugation in addition to aromatic ring which could be the reason for its stability.

Figure 3.12: Structure of fragments represent the base peaks in MS spectra of curcumin based diazepines (18B to D).

Figure3.13: Structure of fragments represent the base peaks in MS spectra of curcumin based diazepines (18E and 21).

3.3.5 3D structures of Curcumin and THC based diazepines (17 and 18)

As shown in Figure 3.14 THC based diazepines **17** have flexible structures not rigid. The rotation is free of the aromatic ring and the aliphatic chain attached to it. However, the curcumin based diazepines have a rigid structure, the presence of the double bonds in the chain restrict the rotation of the aromatic rings. Which makes chiral molecule. While the THC-

based diazepines are achiral. For this reason curcumin based diazepines are expected to have much higher bioactivity than THC based diazepines.

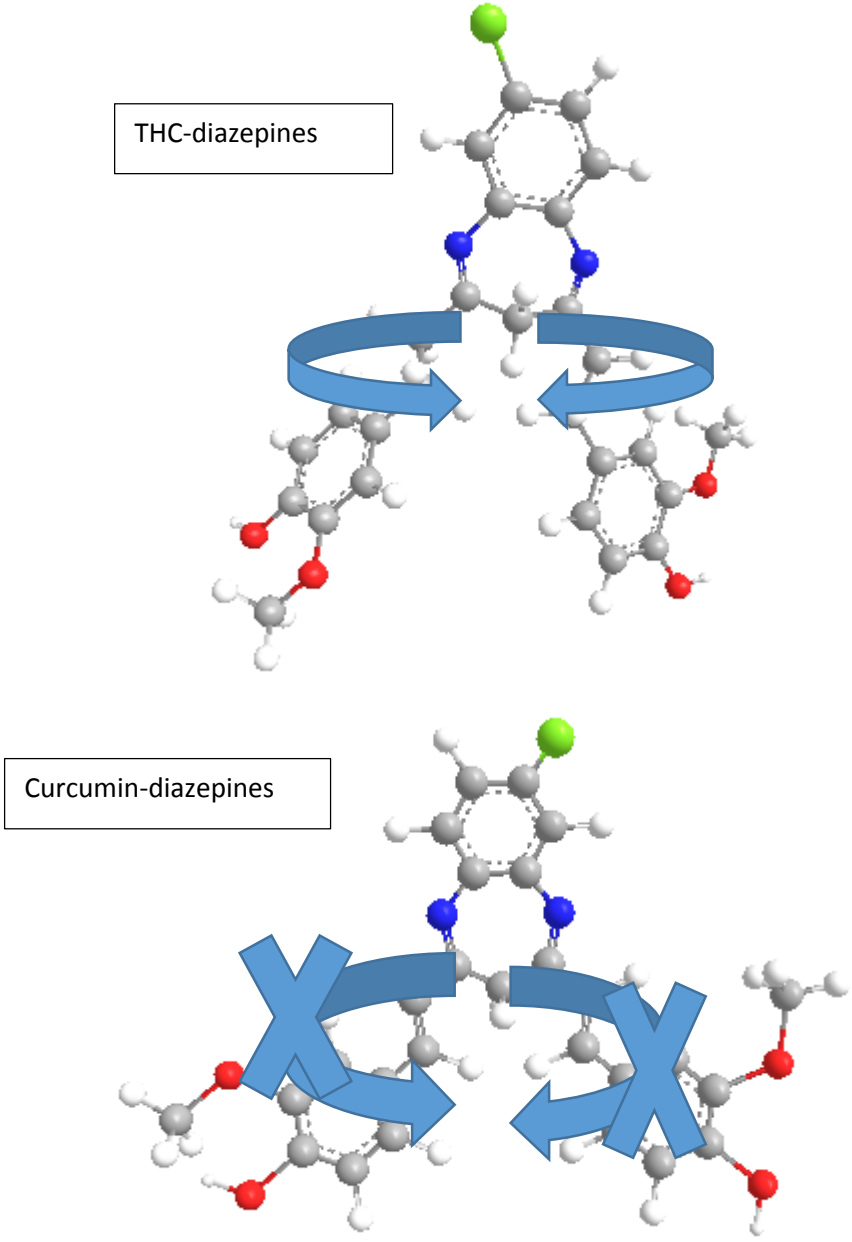


Figure 3.14: 3D structure of curcumin (18) and THC based diazepines (17)

Conclusion And Future Work

Conclusion:

1. A new series of curcumin and tetrahydrocurcumin (THC) based diazepines were synthesized.
2. Tetrahydrocurcumin was prepared by hydrogenation of curcumin using Pd/C as a catalyst.
3. Synthesis of the diazepines was carried out by a new method, in this method curcumin or tetrahydrocuccumin are dissolved in ethanol then reacted with various aromatic diamino compounds in presence of catalytic amount of concentrated sulfuric acid.
4. All prepared compounds were characterized by various spectroscopic techniques such as MS, FT-IR, ^{13}C and ^{1}H NMR spectroscopy.
5. The prepared diazepines are expected to have excellent antibacterial activity since in a previous study it has been shown that diazepine (figure below) made from curcumin and ethylene diamine exhibited a remarkable potency against Gram positive bacteria *S. aureus.* The antibacterial activityof the prepared diazepines against four different types of bacteria *Staphylococcus aureus*, *Escherichia coli*, *Proteus mirabilis* and *Pseudomonas aeruginosa* will be evaluated in a future work.

Future Work

The antibacterial activity of the prepared curcumin and tetrahydrocurcumin based heterocycles will be evaluated against Gram positive and Gram negative bacteria.

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Appendix

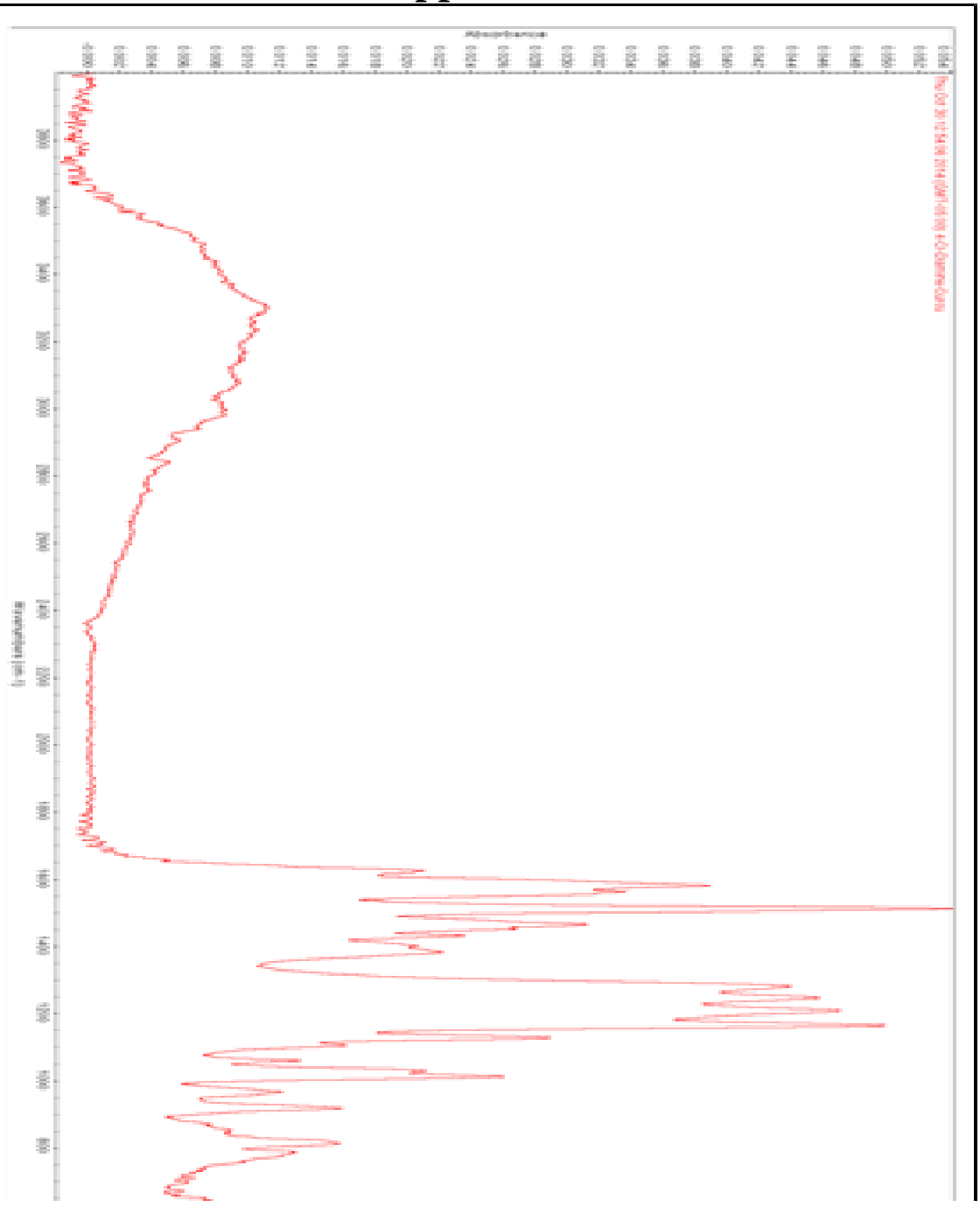

Figure 1: IR spectrum of 4,4'-((1*E*,1'*E*)-(7-chloro-3*H*-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 18C

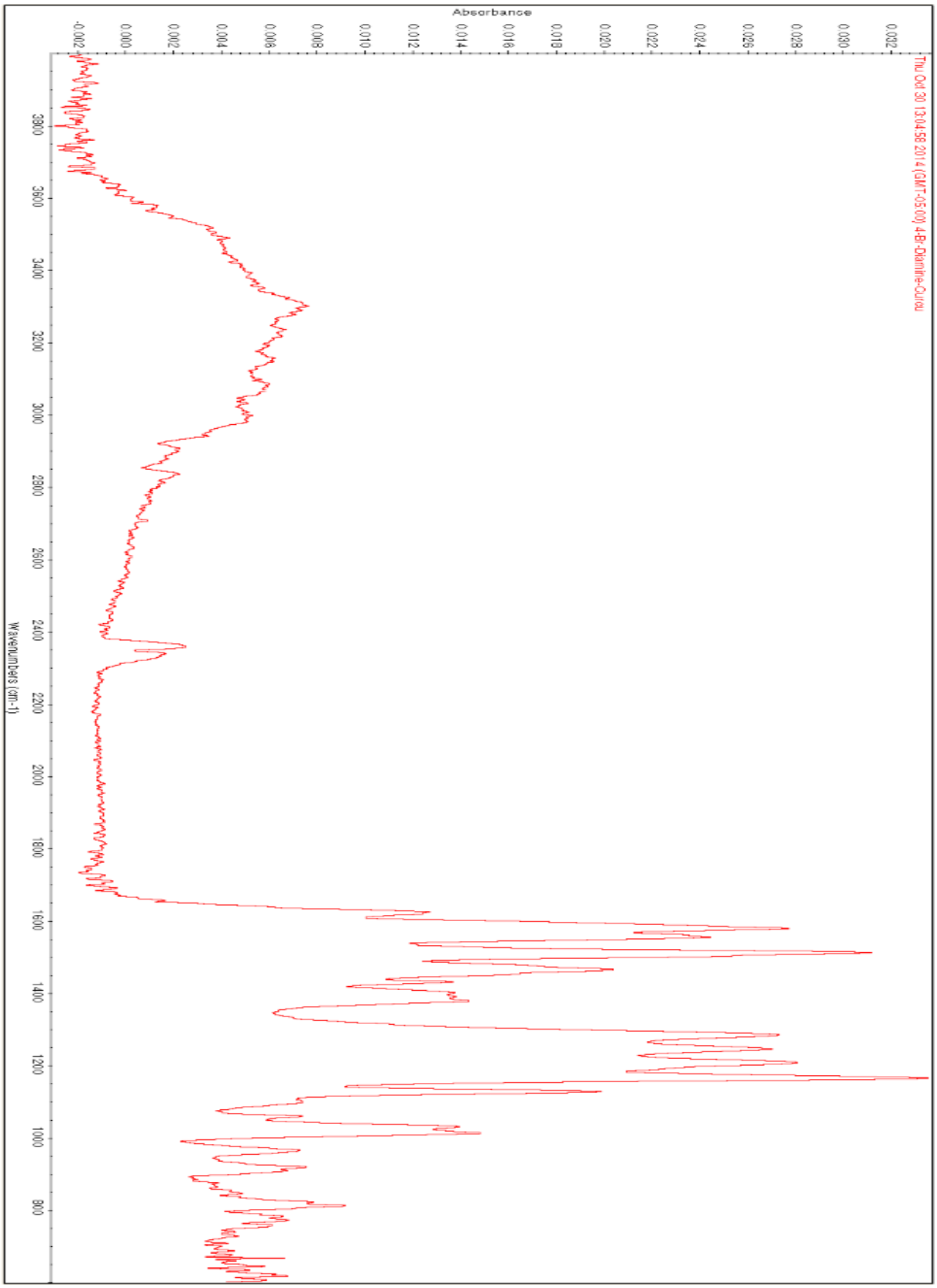

Figure 2: IR spectrum of 4,4'-((1*E*,1'*E*)-(7-bromo-3*H*-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 18D

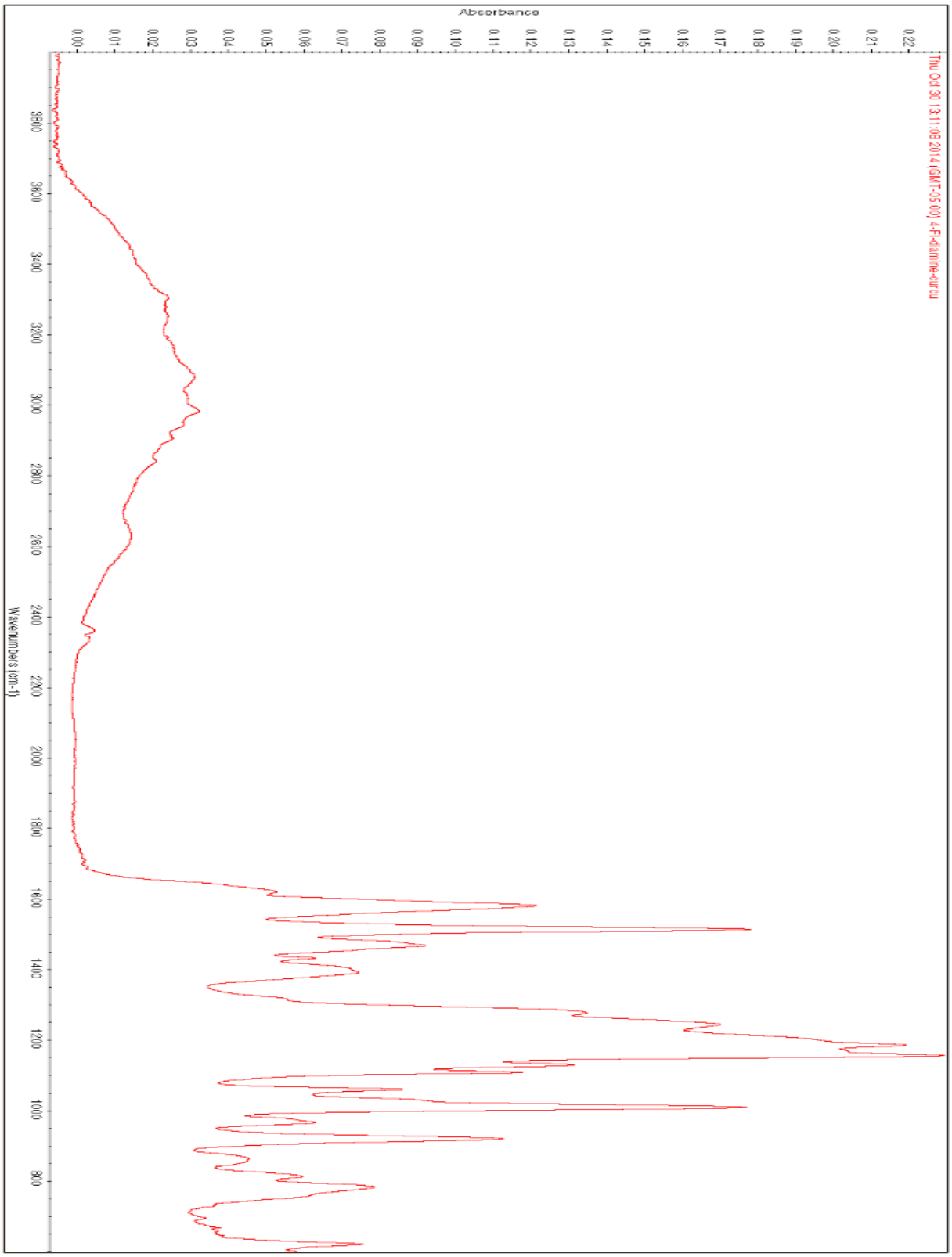

Figure 3: IR spectrum of 4,4'-((7-flouro-3*H*-benzo[b][1,4-diazepine-2,4-diyl)bis(ethane-2,1-diyl))bis(2-methoxyphenol) 17E

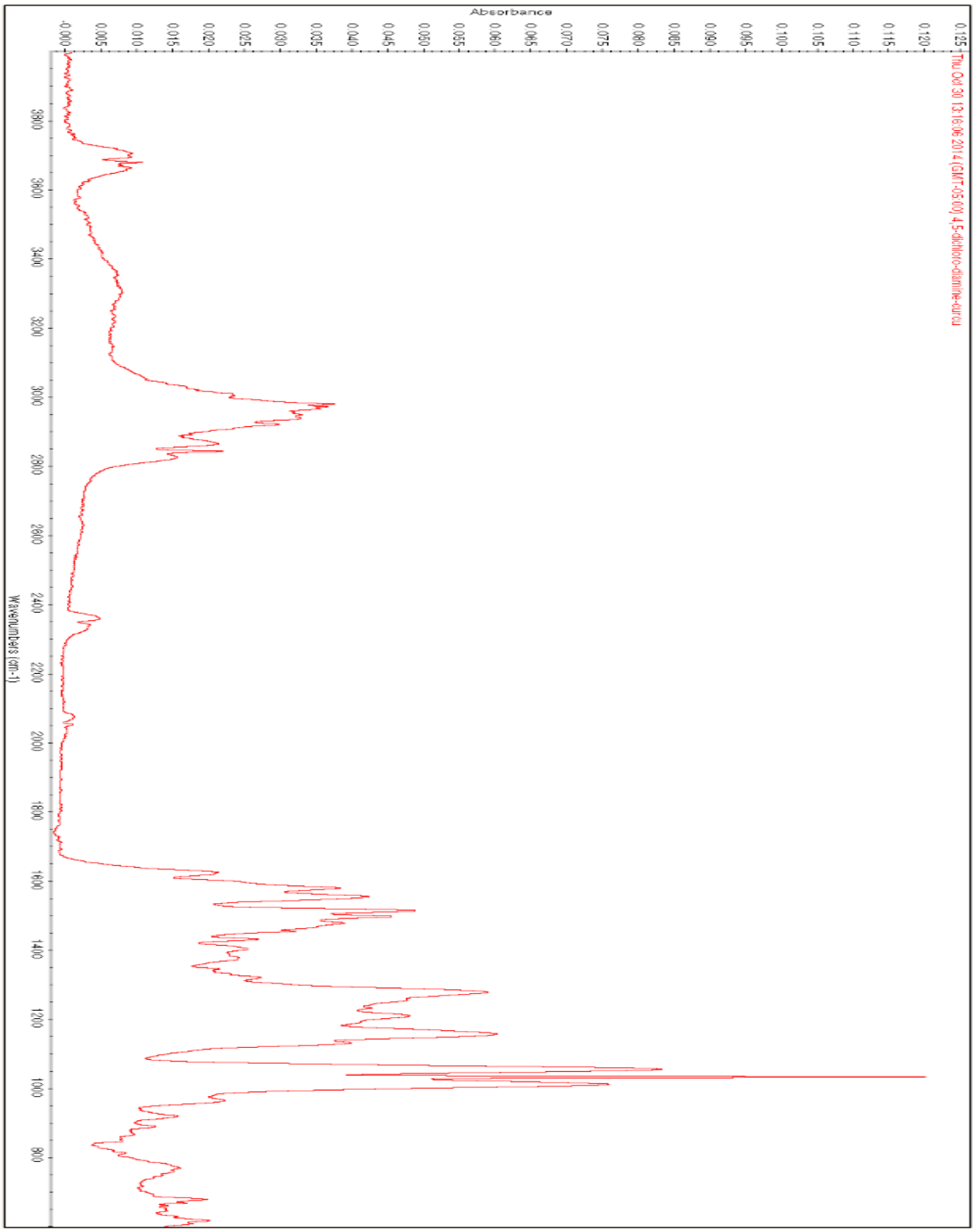

Figure 4: IR spectrum of 4,4'-((1*E*,1'*E*)-(7,8-dichloro-3*H*-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 19

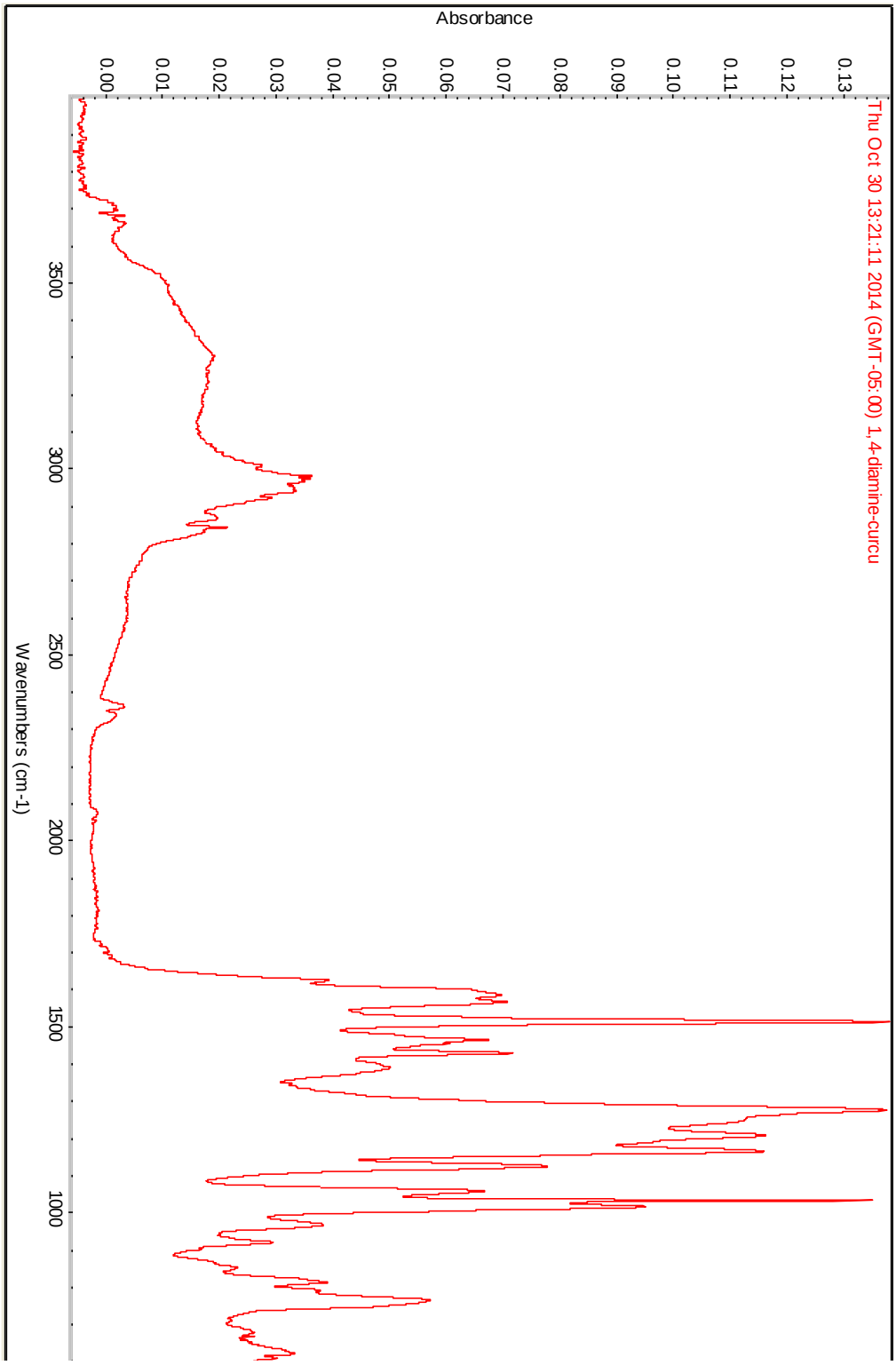

Figure 5: IR spectrum of 4,4'-((1*E*,1'*E*)-(3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 18B

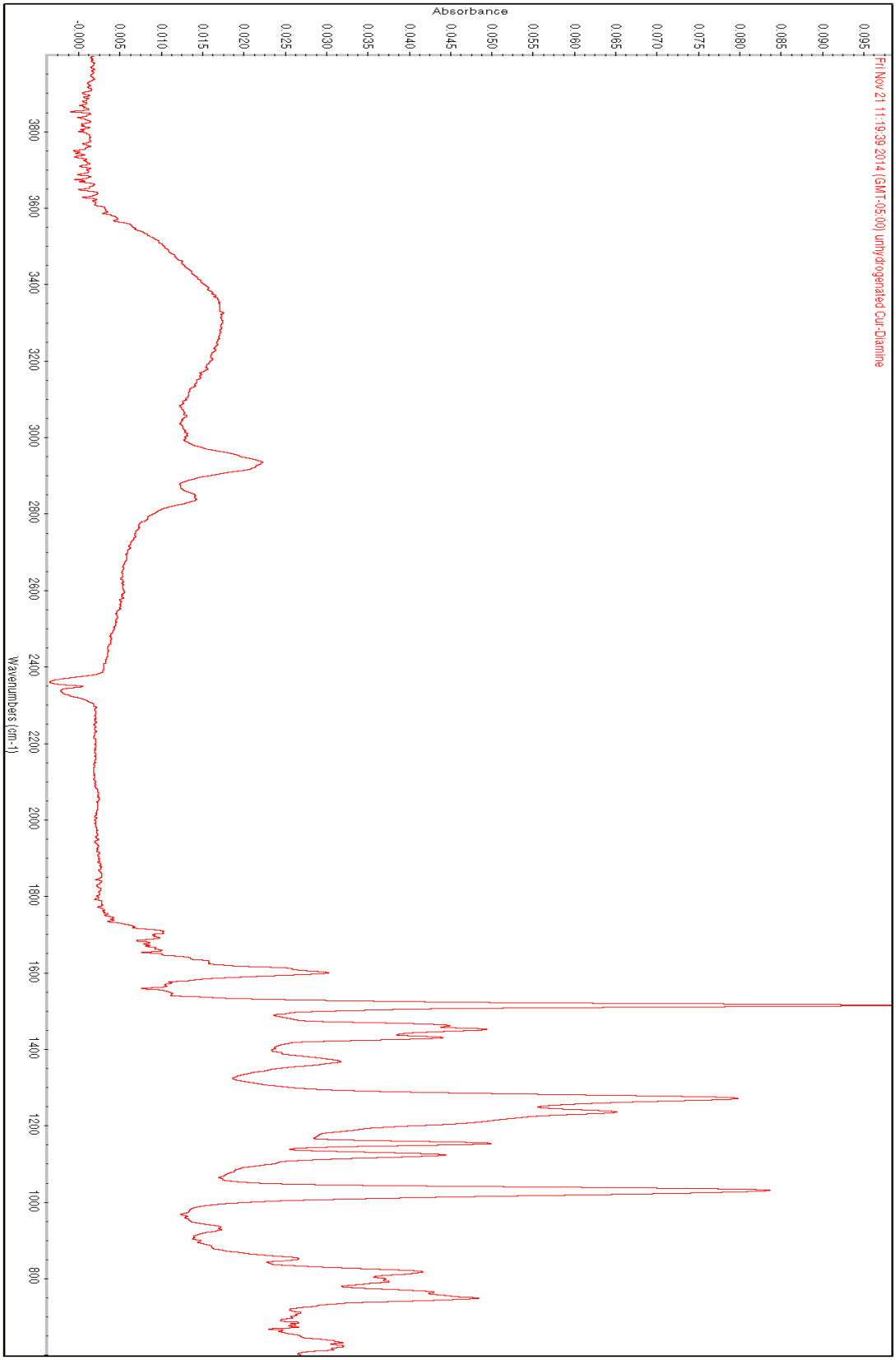

Figure 6: IR spectrum of 4,4'-((3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethane-2,1-diyl))bis(2-methoxyphenol) 16B

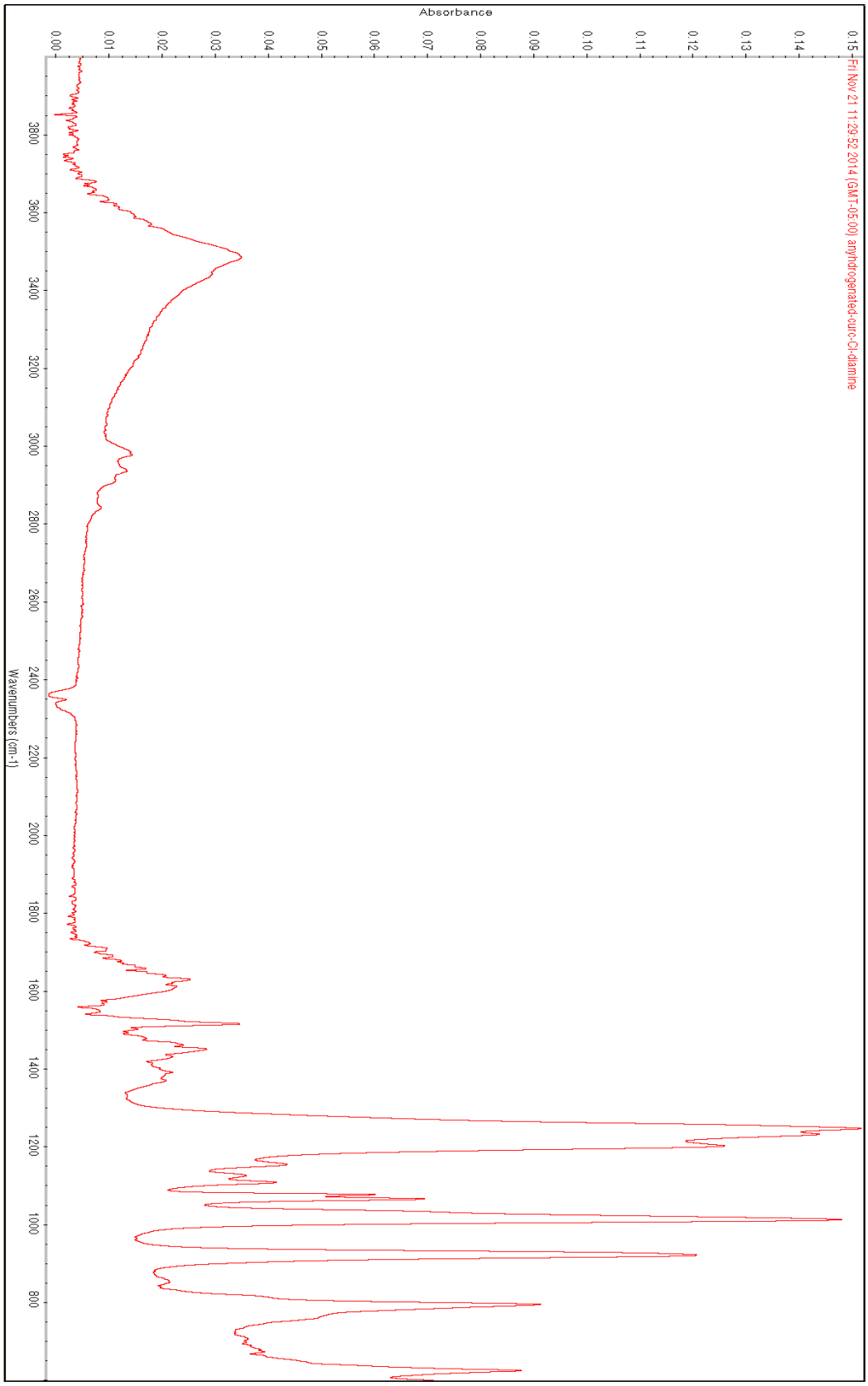

Figure 7: IR spectrum of ,4'-((1E,1'E)-(7-chloro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 18C

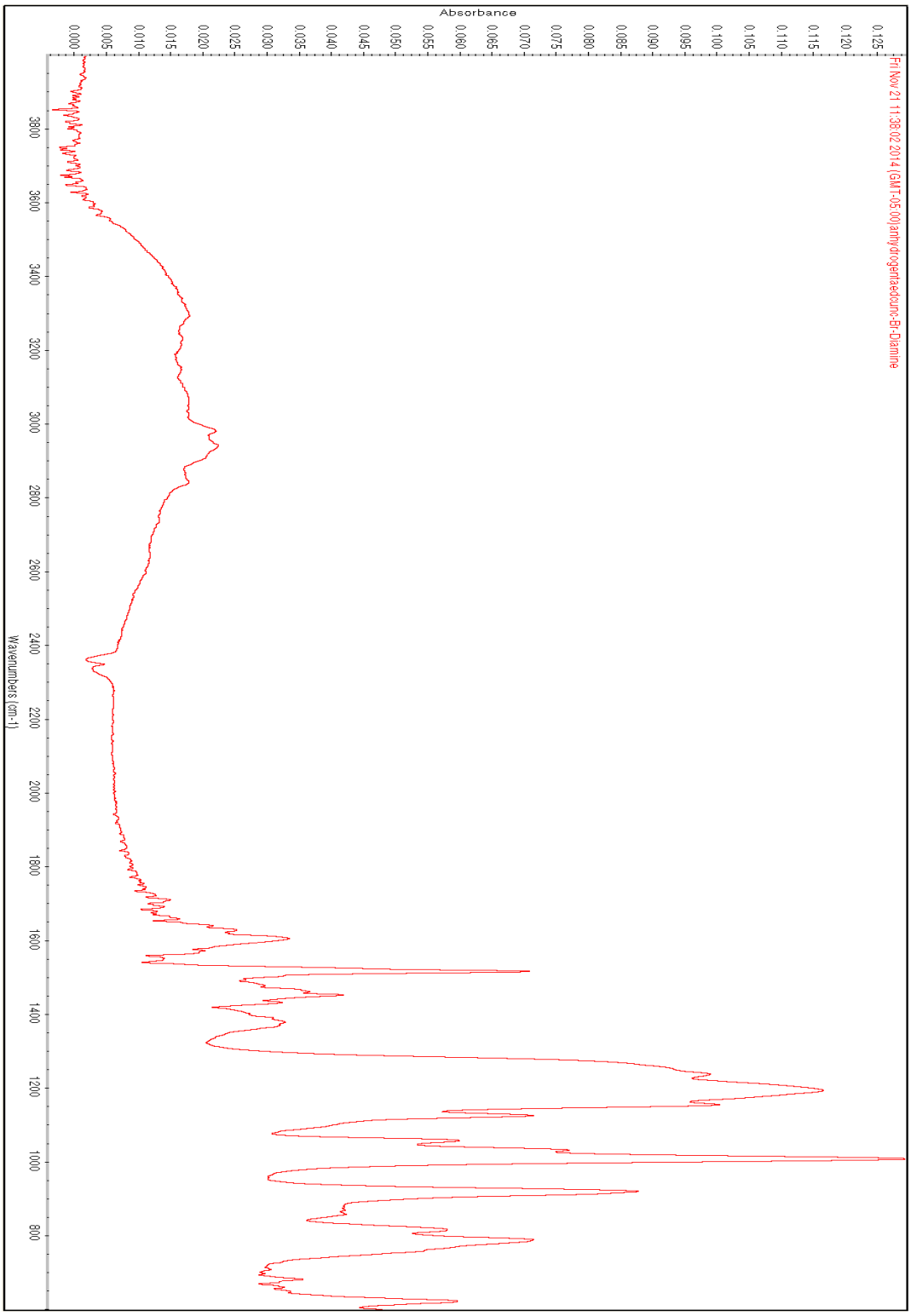

Figure 8: IR spectrum of 4,4'-((1E,1'E)-(7-bromo-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 18D

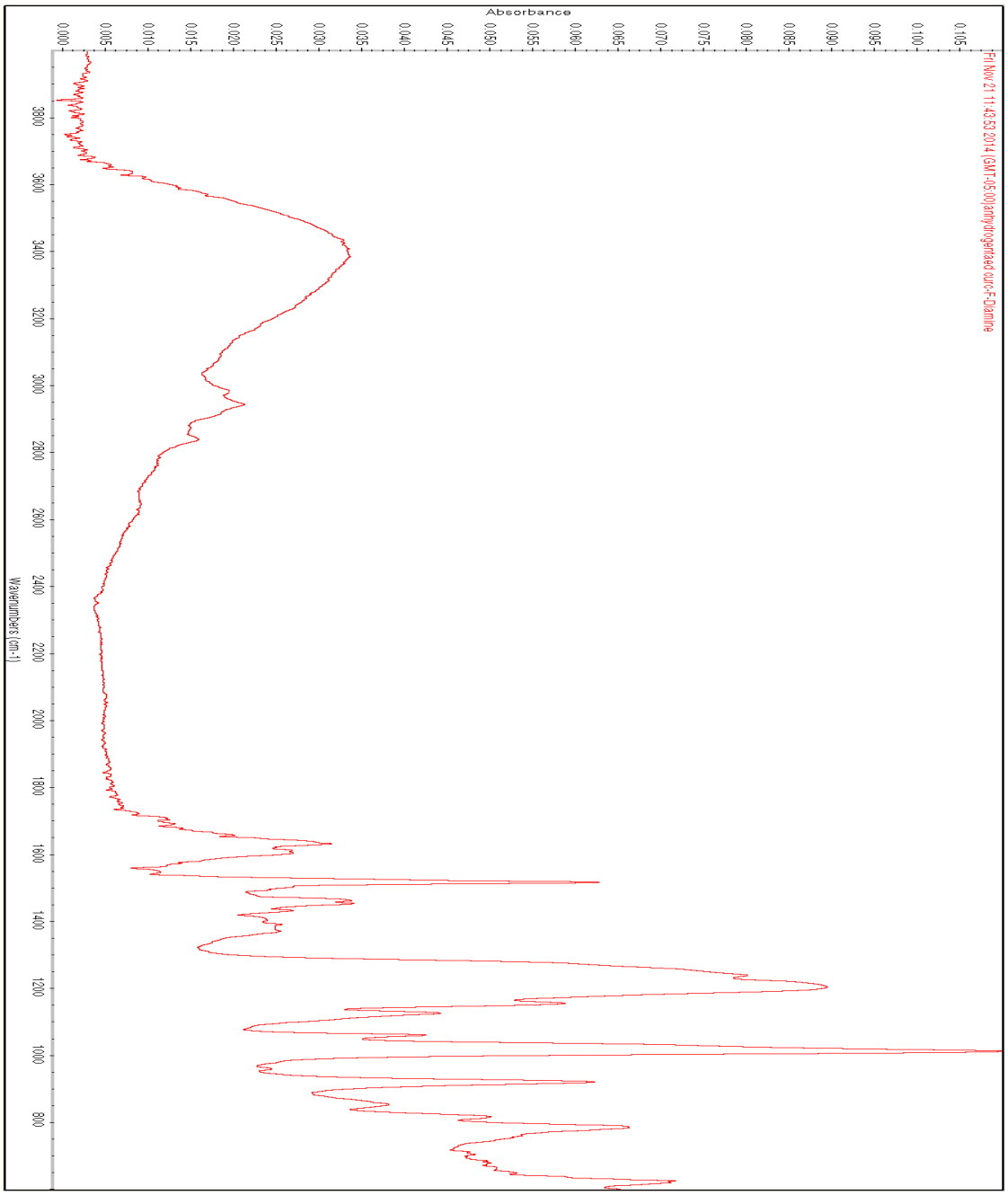

Figure 9: IR spectrum of 4,4'-((7-flouro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethane-2,1-diyl))bis(2-methoxyphenol) 17E

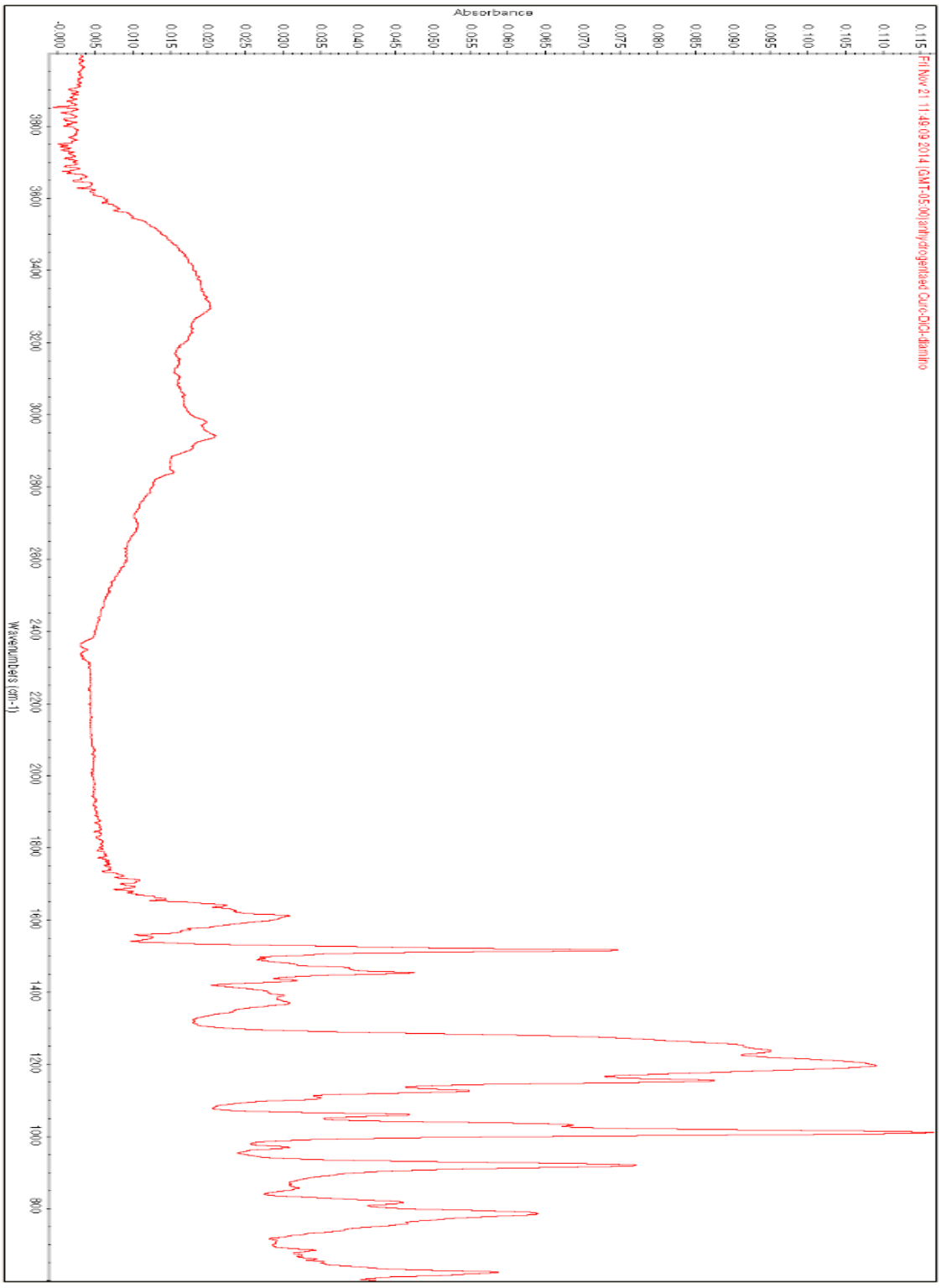

Figure 10: IR spectrum of 4,4'-((1E,1'E)-(7,8-dichloro-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 20

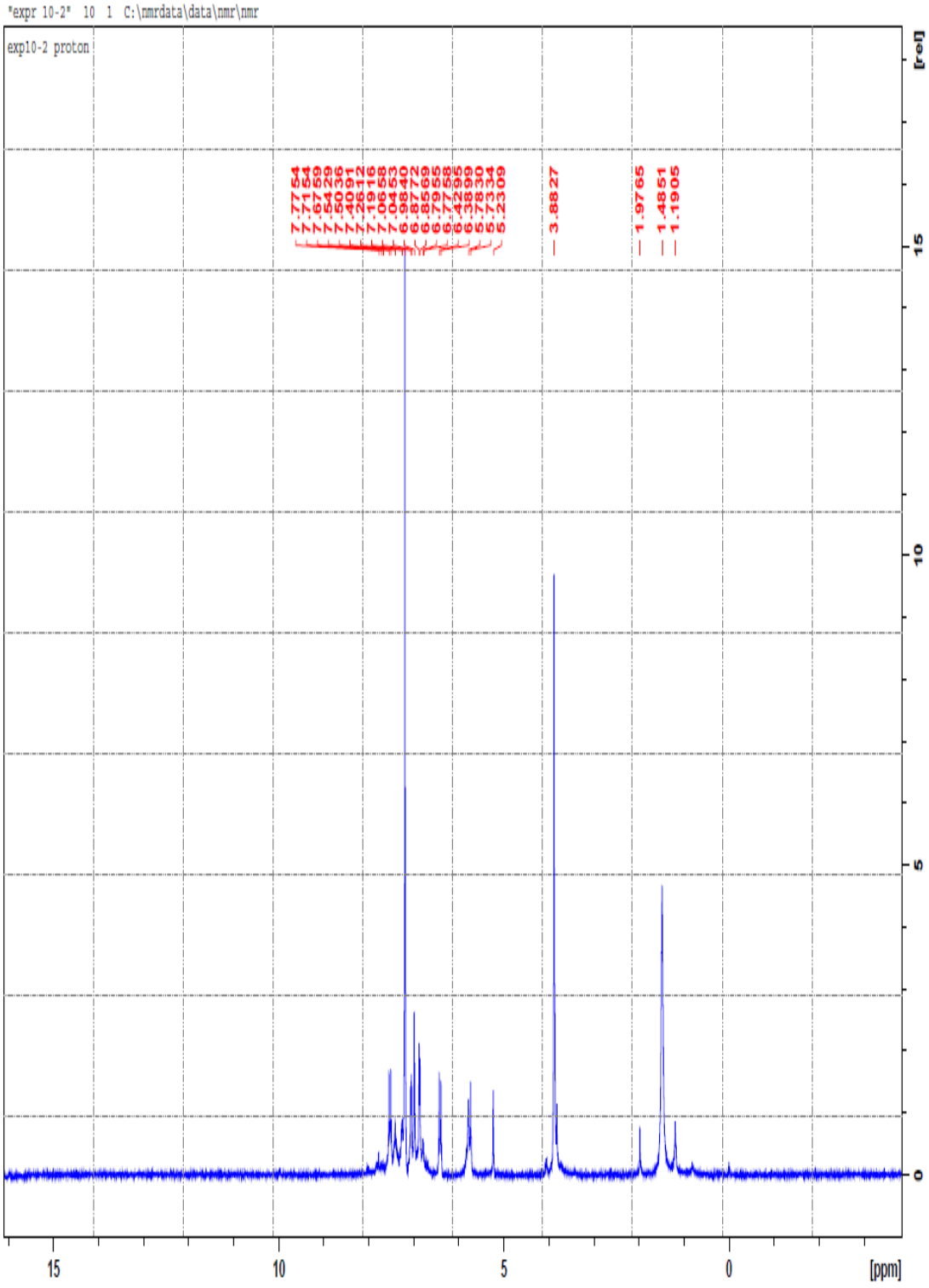

Figure 11: ^{1}H NMR spectrum of 4,4'-((1E,1'E)-(7-bromo-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 18D

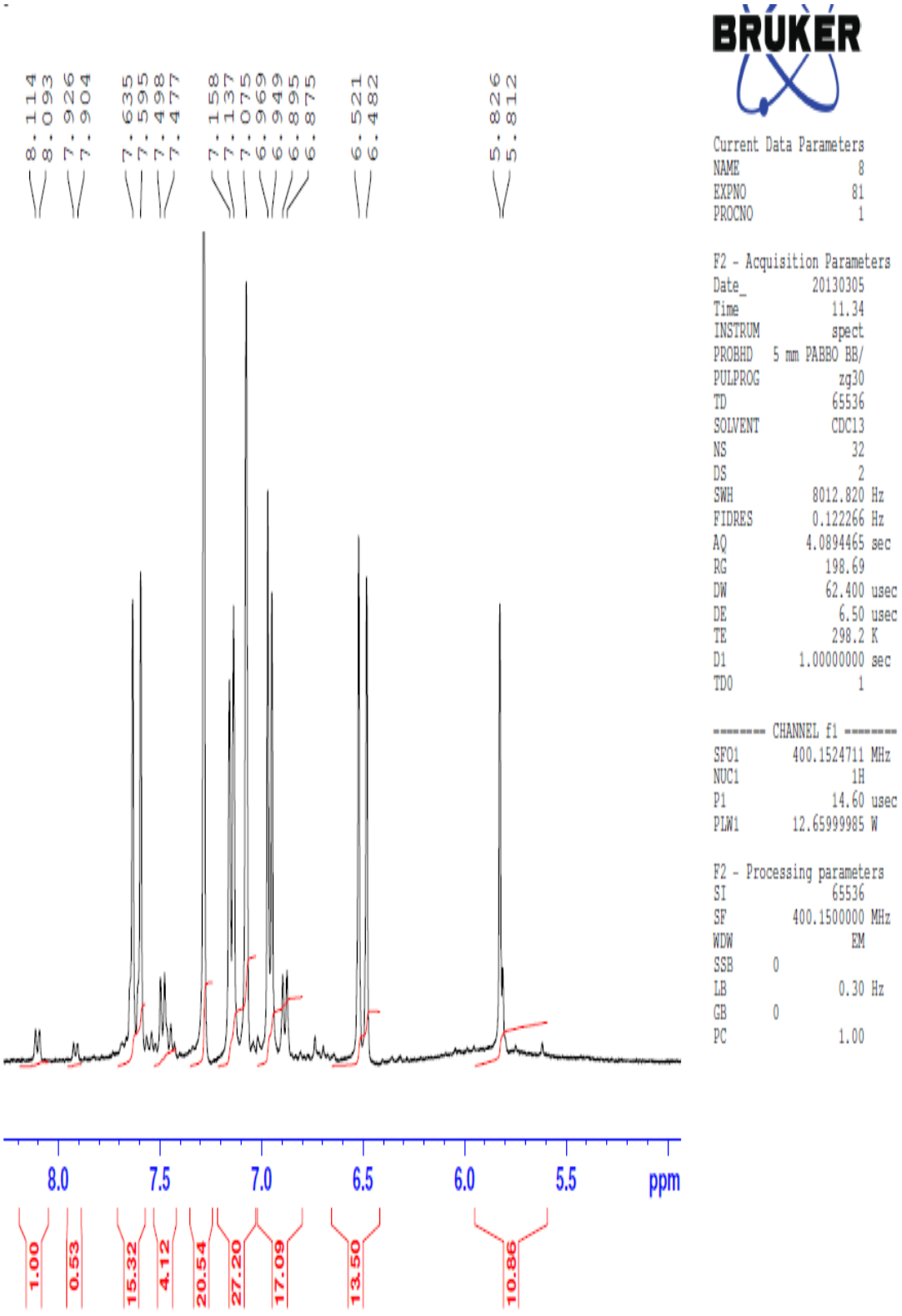

Figure 12: Expanded ^{1}H NMR spectrum of 4,4'-((1E,1'E)-(7-bromo-3H-benzo[b][1,4-diazepine-2,4-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 18D.

جامعة النجاح الوطنية

كلية الدراسات العليا

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قدمت هذه الرسالة استكمالاً لمتطلبات الحصول على درجة الماجستير في الكيمياء بكلية الدراسات العليا في جامعة النجاح الوطنية في نابلس، فلسطين.

2015م

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الملخص

سلسلة جديدة من المركبات من مشتقات الكركم و الكركم رباعي الهيدروجين من الديازيبين تم حضيرها. الكركم رباعي الهيدروجين تم تحضيره بهدرجة الكركم باستخدام البلاديوم/الكربون كعامل مساعد للتفاعل. تحضير الديازيبين تم بطريقة جديدة، في هذه الطريقة تم إذابة الكركم أو الكركم رباعي الهيدروجين في الإيثانول ومن ثم مفاعلته مع العديد من المركبات الأروماتية ثنائية الأمين بوجود كمية قليلة من حمض السلفوريك أسيد المركز كعامل مساعد.

مركبات الديازيبين التي تم تحضيرها تم تنقيتها باستخدام الفلاش كروماتوجرافي أو إعادة التبلور في محلول من الماء والإيثانول، ثم تم التأكد من أشكالها باستخدام عدة تقنيات طيفية مثل مطياف الكتلة و الأشعة تحت الحمراء و أطياف الرنين المغناطيسي .

مركبات الديازيبين التي تم تحضيرها سوف يتم فحص فاعليتها في دراسات قادمة ضد أربعة أنواع من البكتيريا وهي: ستافيلوكوكس أوريس، ايشيريشيا كولاي، بروتيس ميرابيلس و بسودومونس اريجنوزا. هذه المركبات متوقع أن يكون لها فاعلية ممتازة ضد البكتيريا، لأنه في دراسة سابقة أظهرت أن الديازيبين الموضح في الصورة أسفل الصفحة الذي تم تحضيره من تفاعل الكركم مع الإيثيلين ثنائي الأمين أظهر فعالية ملحوظة ضد ستافيلوكوكس اوريوس.

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