Sudan University of Science and Technology
College of Graduate Studies

# Quantitative Structure Activity Relationship (QSAR) Study of 1,4 – Naphthoquinone Derivatives as Anticancer Agents.

## دراسة كمية لعلاقة التركيب بالنشاطية لمشتقات 4,1-نافثوكوينون كعوامل مضادة للسرطان

**By**

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B. Sc. Chemistry, M. Sc. Chemistry

A thesis submitted in fulfillment of the requirements of the degree of doctor philosophy in chemistry

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**DEDICATION**

*To My Parents*

*(Sittana & Hassen)*

*To My Husband*

*(Mohamed Omer)*

*To My Daughters*

*(Saba & Juory)*

*& To My Sister (Eatmad)*

*& her Family*

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## ABSTRACT

The study presented quantitative structure activity relationship QSAR investigation on three groups of 11-12 bioactive naphthoquinone derivatives that have activity against certain cancer cell lines. These three groups are alkyl, amino and alkylamino naphthoquinones. Molecular descriptors: partition coefficient (logP), molar refractivity (MR), formula weight (FW), molar volume (MV), surface tension (ST), refractive index (RI) and density (D) were calculated. Several models for the prediction of biological activity have been drawn up by using simple and multiple regression technique.

The study indicated that QSAR of biological activity represented by $pED_{50}$ of 5,8-Dimethoxy-1,4-naphtha-quinone derivatives (DMNQ) against L1210 (Lymphocytic leukemia) and P388 (Lymphoid neoplasma) can be modeled using ClogP. These models are linear models with r2=0.856, 0.731 F=59.557, 24.492 و s=0.30422, 0.26445 and q2=0.856, 0.729 respectively. The inhibition of Lymphocytic leukemia and Lymphoid neoplasma are influenced mainly by hydrophobicity.

The biological activity of 2,3-Diyne-1,4-naphthoquinone derivatives against three cancer cell lines NCI-H358M, OVCAR-8 and PC-3M,can be modeled using partition coefficient as ClogP with r2=0.722, 0.656, and 0.867 F=20.790, 17.170 and 58.483 , s=0.08305, 0.12179 and 0.08404 and q2= 0.726, 0.661 and 0.869 respectively. All these three models suggest that an increase in the hydrophobicity should reduce the activity of 2,3-Diyne-1,4-naphthoquinone derivatives for all these three cancer cell lines.

The QSAR study of phenylaminonaphtoquinones for three cancer cell lines: DU145 (prostate), T24 (bladder) and MCF7 (breast) can be modeled using ClogP descriptor with good statistic values r2= 0.756, 0.889, 0.864, F=27.858, 72.027, 57.102, s=0.28937, 0.12594, 0.17294 and q2= 0.753,0.887 and 0.865. These show that the cytotoxic activities of phenylaminonaphtoquinones depend largely on their hydrophobicity. Also for DU145 (prostate)cancer cell line ST descriptor used to generate model with good statistical fit as evident from its r2=0.662, F=17.646, s=0.34033, q2= 0.5267 and the inhibition of human prostate carcinoma is influenced by, surface tension.

About 100 3- alkyl amino 2-hydroxy1,4-naphthoquinones and 3- alkyl amino-1,4-naphthoquinones were designed and their descriptors were calculated. Thirteen of 3- alkyl amino 2-hydroxy1,4-naphthoquinones were prepared using Mannich reaction between lawsone, aldehyde and amine. The reaction condition required dark room, stirring the reaction mixture for half day at room temperature. The reaction progress for all synthesized compounds was checked by TLC techniques. The structures of these compounds were confirmed spectroscopically using UV, IR and $^{1}$HNMR.

## الخلاصـــة


قدمت هذه الدراسة تقصي ل QSAR على ثلاث مجموعات من 11-12 من مشتقات النافثوكينون النشطة حيويا ضد بعض الخلايا السرطانية . هذه الثلاث مجموعات هي ألكيل و امينو والكيل امينو نافثوكينونات. تم حساب الواصفات الجزيئية: معامل التجزئة logP، الانكسارية المولارية MR، الوزن الصيغي FW، الحجم المولاري MV ، التوتر السطحي ST ، معامل الانكسار RI والكثافة D. وقد وضعت عدة نماذج للتنبؤ بالنشاط البيولوجي باستخدام تقنية الانحدار البسيط والمتعدد.

وأشارت الدراسة إلى أنه يمكن وضع نماذج QSAR للنشاط البيولوجي معبر عنها بـ $pED_{50}$ لمشتقات 5،8- ثنائي ميثوكسي - 1،4- نافثوكينون ضد سرطان الدم الليمفاوي (L1210) وP388 (الاورام اللمفاوية) باستخدام ClogP. هذه النماذج هي نماذج خطية لها r2=0.856, 0.731 ، F=59.557, 24.492، q2=0.856, 0.729 وs=0.30422, 0.26445 على التوالي. يتأثر تثبيط سرطان الدم الليمفاوي و الاورام اللمفاوية أساسا بالهيدروفوبية (كره الماء).

يمكن وضع نماذج QSAR للنشاط البيولوجي لمشتقات 2 ، 3- ثنائي- اين -1،4- نافثوكينون ضد ثلاثة خطوط خلايا سرطانية NCI-H358M، OVCAR-8 و PC-3M، باستخدام ClogP مع r2=0.722, 0.656, 0.867 F=20.790, q2= 0.726, 0.661, 0.869 ,0.08404 s=0.08305, 0.12179 , 58.483 , 17.170 على التوالي.النماذج الثلاثة هذه تقترح ان زيادة الهيدروفوبية يجب ان تختزل نشاطية مشتقات 2 ، 3- ثنائي- اين -1،4- نافثوكينون.

من خلال دراسة QSAR فينيل امينو نافثوكينونات لمجموعات الخلايا السرطانية الثلاثة: DU145 (البروستات)، T24 (المثانة) وMCF7 (الثدي) يمكن وضع نماذج باستخدام ClogP بقيم إحصائية جيدة r2= 0.756, 0.889, 0.864, F=27.858, 72.027, 57.102, s=0.28937, 0.12594, 0.17294, q2= 0.753, 0.887 and 0.865. هذه تدل على أن نشاطية سمية الخلايا لمشتقات فينيل امينو نافثوكينون تعتمد إلى حد كبير على الهيدروفوبية (كره الماء).

أيضا لخط الخلايا السرطانية DU145 (البروستات) يمكن استخدام ST لتوليد نموذج مع تناسب احصائي جيد واضحا r2=0.662, F=17.646, s=0.34033, q2= 0.5267 وتثبيط سرطان البروستاتا البشري يتأثر بالتوتر السطحي .

تم تصميم حوالي 100 3- ألكيل امينو 2- هيدروكسي - 1،4- نافثوكينونات و3- ألكيل أمينو- 1،4- نافثوكينونات وحسبت واصفاتها. تم تحضير ثلاثة عشر منهم باستخدام تفاعل Mannich بين اللوسون و ألدهيد وأمين. التفاعل يتطلب غرفة مظلمة وتحريك خليط التفاعل لمدة نصف يوم في درجة حرارة الغرفة. وتم التأكد من تقدم التفاعل لجميع المركبات المحضرة باستخدام تقنية الـ TLC. وتم التأكد من بنية هذه المركبات طيفيا باستخدام مطيافية الأشعة فوق البنفسجية و الاشعة تحت الحمراء و الرنين النووي المغناطيسي للبروتونات.

## List of Publications

**a) Published Papers:**

(1) **Ali, L. H. M.;** and Saeed, A. E. M. (2016). QSAR Study of 3-Phenylamino-1,4-naphtoquinones Anti-cancer Activities; *International Research Journal of Pure &Applied Chemistry*,13(3): 1-6.

(2) **Ali, L. H. M.;** and Saeed, A. E. M. (2016). QSAR Study of 2,3-Diyne-1,4-naphtoquinone Derivatives Anti-cancer Activities; *Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences*,2(4): 116-121.

(3) **Ali, L. H. M.;** and Saeed, A. E. M. (2016). QSAR Study of 5,8-Dimethoxy-1,4-naphtoquinones as Anti-cancer Agents; *Imperial Journal of International Research*, 2(12): 2170-2173.

(4) **Ali, L. H. M.;** and Saeed, A. E. M. (2017). Computer-Aided Design of Anticancer 1,4-Naphtoquinones; *Chemistry Science International Journal*, 18(4):1-11.

**b) Submitted Papers:**

**Ali, L. H. M.;** and Saeed, A. E. M. (2017). Synthesis of a Series of 2-Hydroxy-3- substituted-1,4-naphthoquinone Derivatives using Mannich Reaction.

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## List of Abbreviations

| | |
|---|---|
| Q | Quinone |
| DNA | Deoxyribonucleic acid |
| $Q^-$ | Semiquinone |
| $Q^{2-}$ | Hydroquinone |
| PPDK | Pyruvate phosphate dikinase |
| DMF | Dimethylformamide |
| CAN | Cerium ammonium nitrate |
| DMSO | Dimethylsulfoxide |
| DCM | Dichloromethane |
| FNQ13 | 2-Methyl-5(or 8)-hydroxynaphtho[2,3-b]furan-4,9-dione |
| FNQ | Naphtho[2,3-b]furan-4,9-dione (furanonaphthoquinone |
| LUMO | Lowest unoccupied molecular orbita |
| HOMO | Highest Occupied Molecular Orbital |
| DDQ | Dichlorodicyanoquinone |
| UV | Ultraviolet region |
| IR | Infrared region |
| NMR | Nuclear magnetic resonance |
| CD | Circular dichroism |
| $\pi$ | Hydrophobic constant |
| MR | Molar refractivity |
| logP | Partition coefficient |
| log $S_w$ | Molar aqueous solubility |
| D | Dimension |
| $IC_{50}$ | Inhibitory concentration, 50% |
| $LD_{50}$ | Lethal Dose, 50% |
| $ED_{90}$ | Effective dose , 90% |
| $ED_{50}$ | Effective dose, 50% |
| $EC_{50}$ | Effective concentration, 50% |
| QSAR | Quantitative Structure-Activity Relationship |
| CADD | Computer-Aided Drug Design |
| CAMD | Computer-Assisted Molecular Design |
| MD | Molecular dynamics |
| QSPR | Quantitative Structure-Property Relationship |
| QSTR | Quantitative Structure-Toxicity Relationship |
| MV | Molar volume |
| RI | Refraction index |
| FW | Formula weight |
| D | Density |
| ST | Surface tension |
| $r^2$ | Correlation coefficient |
| t | t-test statiatic |
| F | F-test statiatic |
| S | Standard deviation |
| sig. | Significant |
| DW | Durbin-Watson test |

| | |
|---|---|
| ACD | Advanced Chemistry Development |
| SPSS | Statistical Package for the Social Sciences |
| C | Concentration |
| LOO | Leave one out |
| CV | Cross validation |
| q2 | Square of cross-validated |
| $C_{obsrv.}$ | Observed concentration |
| $C_{pred.}$ | Predicted concentration |
| ΔpC | Difference concentrations |
| TLC | Thin Layer Chromatography |
| $R_f$ | Retardation factor |
| st. vib. | Stretching vibration |
| ben. | Bending |
| smy. | Symmetry |
| asym. | Asymmetry |
| $\lambda_{max}$ | The maximum wavelength |
| S | Singlet |
| D | Doublet |
| Dd | Double doublet |
| T | Triplet |
| M | Multiplet |
| L1220 | Lymphocytic leukemia |
| p338 | Lymphoid neoplasma |
| NCI-H358M | Human bronchoalveolar lung carcinoma |
| OVCAR-8 | Human ovarian adenocarcinoma |
| PC-3M DU145 | Human metastatic prostate cancer |
| DU145 | Prostate Cancerous |
| T24 | Bladder Cancerous |
| MCF7 | Breast Cancerous |
| VIS | Visible region |
| TMS | Tetramethylsilane |

# 1. Introduction

## 1.1. Quinones

### 1.1.1. Definition of Quinones

Quinones are alpha- beta – unsaturated cyclic diketones with both the oxygen atoms in simple or fused conjugated ring system (Saeed & Omer, 2009).

Also, quinones are defined as unsaturated cyclic diketones or tetraketones which derived from aromatic compounds by conversion of two or four CH groups into CO groups with any necessary rearrangement of double bonds which make them non-aromatic compounds although possessing a nucleus of six member ring of C-atoms (Rigaudy & Klesney,1979).

### 1.1.2. Nomenclature and Structure of Quinones

IUPAC employs the ending"-quinone" instead of" –dione" for a cyclic diketone that can be derived from a molecular-skeleton parent with the maximum number of noncumulative double bonds. In this case, two –CH= groups are formally replaced by two CO= with concomitant rearrangement of double bonds (Bunzli, 2007).

Quinones are named simply by indicating the position of the carbonyls numerically and adding quinone to the name of the parent phenol fig (1.1) (Kaplan, 2014).

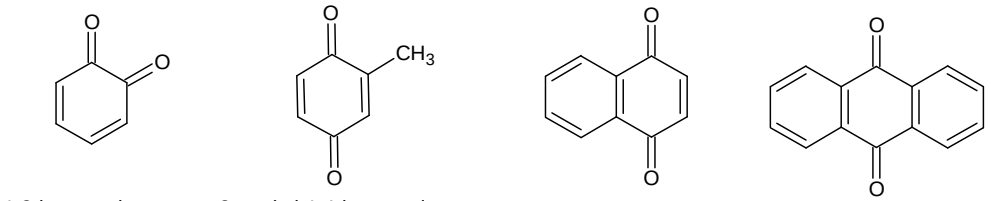



Figure (1.1): Chemical Structures of Simple Quinones.

### 1.1.3. Naturally Occurring Quinones

The quinones form the large group of natural pigments and are found mainly in plants, many of them have also been isolated from microorganisms such as fungi and lichens, and also from marine animals and certain insects. The natural quinones are divided as:

**a. Benzoquinones:** These occur mainly in fungi and insects fig (1.2). The most important benzoquinones produced by higher plants are the ubiquinones (coenzyme Q) and plastoquinones fig (1.2) (Ikan, 1991).

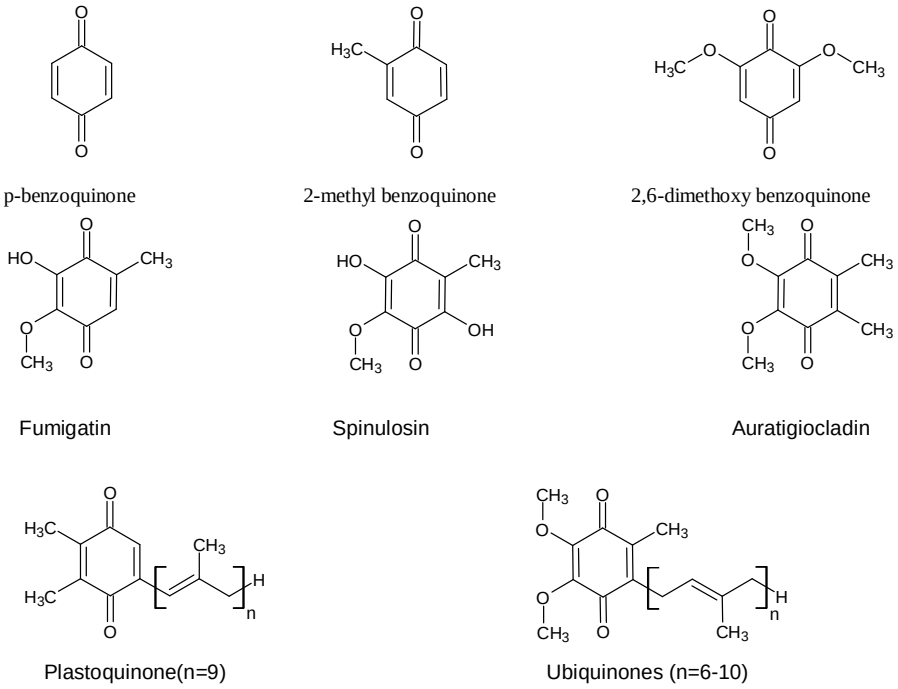



Figure (1.2): Structure of Some Natural Benzoquinones.

**b. 2, 5-Dihydroxy Benzoquinones:** These occur principally in the higher fungi. Some mold products are diquinones related to fumigation and spinulosin fig (1.3) (Ikan, 1991).

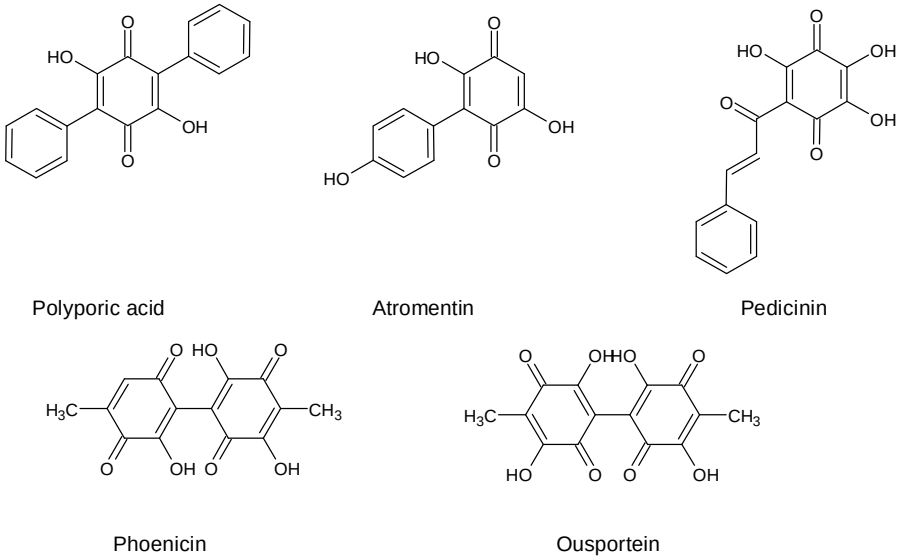



Figure (1.3): Structure of Some Natural Dihydroxybenzoquinones.

**c.Naphthoquinones:** These are mostly isolated from plants fig (1.4) and some from animal pigments fig (1.5) (Ikan, 1991).

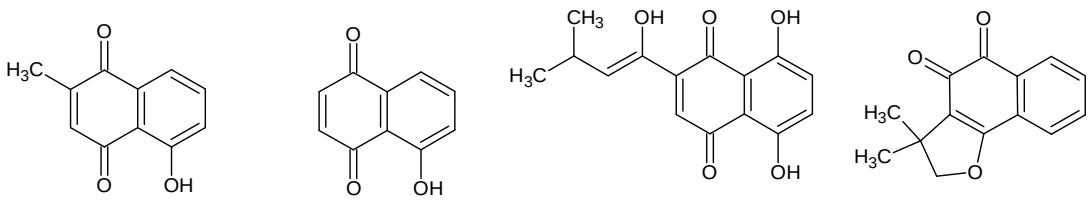



Figure (1.4): Structure of Some Natural Naphthoquinones Isolated from Plants.

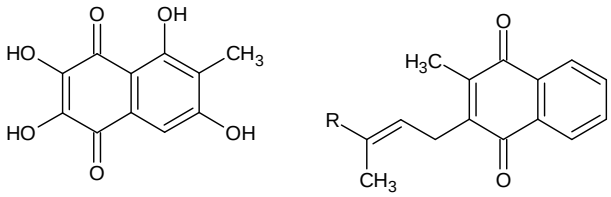



Figure (1.5): Structure of Some natural Naphhoquinones Isolated from Animal Pigments.

**d.Anthraquinones:** This group is largest. Many of these pigments occur in the Rubiaceae, polygonaceae, Rhamaceae, and Leguminosae fig (1.6).

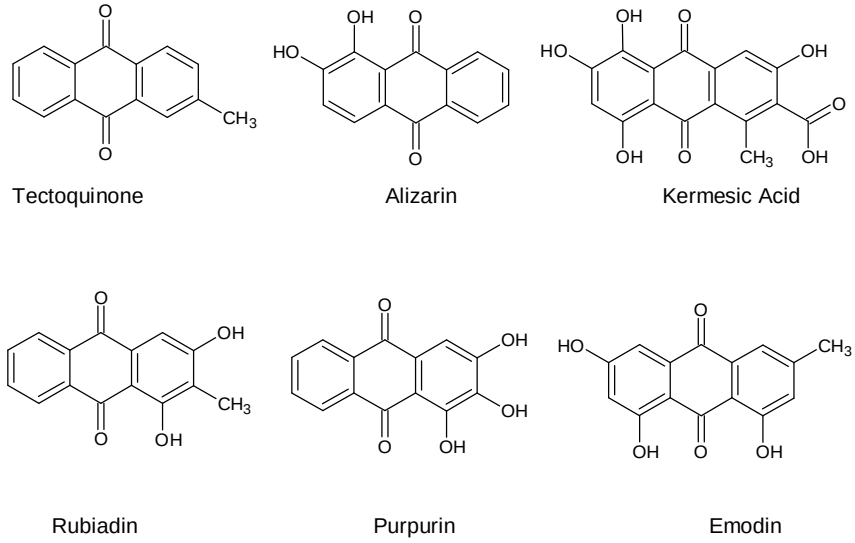



Figure (1.6): Structure of Some Natural Anthraquinones.

The best known insect pigments is carminic acid fig (1.7).A more complex, extended anthraquinone, closely related to emodin, is hypericin, which occurs in Hypericum species. It is formed by stepwise intramolecular coupling fig (1.8) (Ikan, 1991).

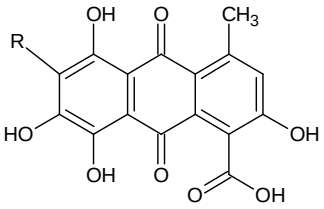



Figure (1.7): Structure of Carminic Acid.

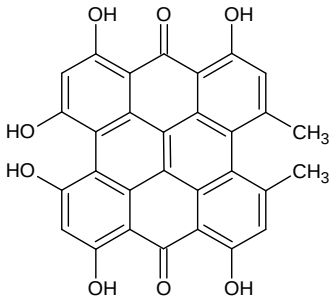



Figure (1.8): Structure of Hypericin.

### 1.1.4. Properties of Quinones

In general, quinones are yellow, red, orange, or brown in color, but when present as salts of hydroxyl quinones, their color are purple, blue, or green (Ikan, 1991). Most quinones are solids and form crystals; their solubility dependent on their structures. Quinones in free-state form easily dissolve in organic solvent such as ether and benzene. The quinones containing phenol, carboxylic, or glycosyl groups are water-soluble (dissolve in hot water), soluble in alkaline solution, methanol, ethanol, acetone, chloroform, benzene, DMSO and acetic acid. Hydroxyquinones usually acidic due to the existence of phenolic hydroxyl groups in structures thus can dissolve in basic aqueous solutions to form red or purple products. Quinone derivatives produce purple products. Benzoquinone and anthraquinone derivatives can turn the colorless ethanol solution of leucomethylene blue into blue. Carminic acid is soluble both in water and ethanol; kermesic acid is soluble only in water, while alizarin, plumbagin and juglone are slightly soluble in hot water and soluble in alkaline solutions and in ethanol. Almost all quinones are soluble in organic solvents. Ubiquinone, menaquinone, and plastoquinone are lipophilic compounds, soluble in lipids and organic solvents. The complex polycyclic quinones have poor solubilities both in water and organic solvents (Socaciu, 2007; Liu, 2011; Babula *et al*., 2009).

### 1.1.5. Mode of Action of Quinones

The cytotoxic effects of quinones are mainly due to the inhibition of DNA topoisomerase-II. Because of the complex structure of most antitumor quinonoid compounds it is often difficult to separate the contributions of chemical reactivity and the different pathways of metabolism to overall biological activity. The quinoid anticancer agents undergo enzymatic reduction via one or two

electrons to give the corresponding semiquinone($Q^-$) radical or hydroquinone($Q^{2-}$) fig(1.9). Under aerobic conditions the semiquinone radical anion can give its extra electron to molecular oxygen to

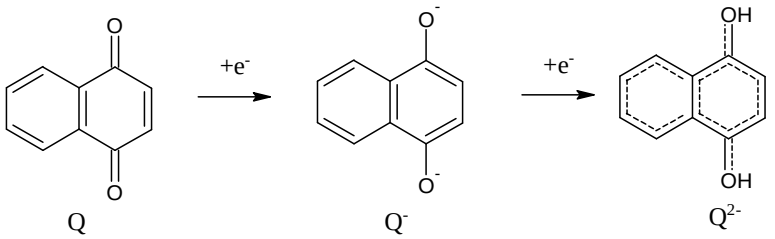



Figure (1.9): Redox Properties of Naphthoquinones.

give the parent quinone(Q) and superoxide radical anion. This reaction sequence, initiated by bioreduction of the quinone followed by oxidation with dioxygen of the radical anion intermediate, is known as redox-cycling, and it continues until the system becomes anaerobic. The hydroquinone formed via a two electron reduction, depending upon its stability, can be excreted by the organism in a detoxification pathway or can undergo a comproportionation reaction with the parent quinone to yield the semiquinone radical anion. Both the semiquinone and the superoxide radical anion can generate the hydroxyl radical, which is the cause of DNA strand breaks (Vásquez, 2010; Romos *et al*, 2015).

Naphthoquinones are widely distributed in nature and play important physiological roles in animals and plants. Quinone derivatives may be toxic to cells by a number of mechanisms including redox cycling, arylation, intercalation, induction of DNA strands breaks, generation of free radicals and alkylation *via* quinone methide formation (Kanaan *et al*, 2009).

### 1.1.6. Pharmacological Properties of Quinones

A number of 1,4-naphthoquinone derivatives have been found to possess powerful pharmacological effects such as antibacterial, antifungal, anti-inflammatory, antithrombotic, antiplatelet, antiviral, antiallergic, apoptotic, lipoxygenase inhibiting, radical scavenging and antiringworm activities ( Chung,2007; Romos *et al* , 2015).

The hydroxynaphthoquinones have been extensively investigated over the past 50 years for their anti-malarial activity and Hydrolapachol was the first hydroxynaphthoquinone discovered that possessed anti-malarial activity (Schuck *et al*., 2013).

Sesquiterpene quinol/quinone compounds have cytotoxic, antimicrobial, antiviral and anti-inflammatory activities. Insertion of a hydroxyquinone or a short hydroxide/alkoxide side-chain at C20 on several sesquiterpene compounds increases the inhibition of pyruvate phosphate dikinase (PPDK) at variance a large amine side-chain at the same position (Motti *et al.* 2007).

Riffle, *et al.*, 2002 demonstrated the antibacterial activity of a series of 1, 4-naphthoquinones and the most active one was 5-amino-8-hydroxy-1, 4-naphthoquinones and naphthazarin.

### 1.1.7. Synthesis of *p*-Quinones

*p*-Quinones were discovered in Liebig's laboratory from the oxidation of quinic acid with manganese dioxide and sulfuric acid fig (1.10) (Fieser & Fieser,1950).

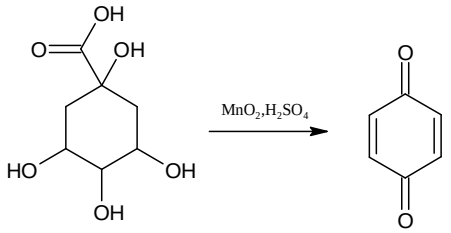



Figure (1.10): Synthesis of Quinone from Quinic Acid.

Quinones can be prepared by many methods, including oxidation of non-quinoid precursors, cyclization methods, condensation methods and annulations methods (Smith, 2011) which are described below.

#### 1.1.7.1. By Oxidation:

##### 1.1.7.1.1. Oxidation of Aromatic Hydrocarbons

Quinones may be prepared in some cases by the direct oxidation of aromatic hydrocarbons. Anthracene, naphthalene, and phenanthrene are oxidized to the corresponding quinones by chromic acid mixtures fig (1.11) (Cheroins, 1942).

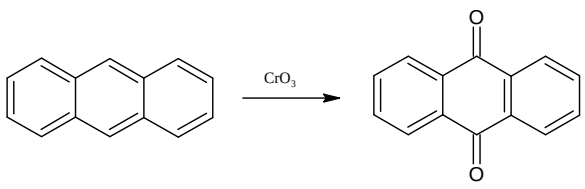



Figure (1.11): Synthesis of Quinones from Hydrocarbones.

### 1.1.7.1.2. Oxidation of Phenols

*p*-Quinones can be prepared directly by anodic oxidation of phenolic compounds fig(1.12) (Trost *et al*, 1991).

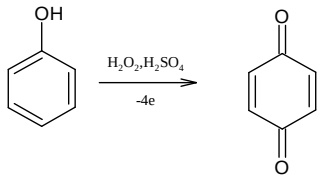



Figure (1.12): Synthesis of Quinones from Phenols Using Anodic Oxidation

Potassium nitrosodisulfonate (Fremy's salt) or disodium nitrosodisulfonate (Fremy's salt in solid state may decompose spontaneously but aqueous solution of it is stable) can be used for the oxidation of phenols or anilines (when there is no *para* substituents) to *p*-quinones fig (1.13).These reactions called Tuber Quinone Synthesis (Hassner & Namboothiri, 2011) and suitable to synthezied heterocyclic quinones when other oxidants fail (Abraham *et al*, 2011).

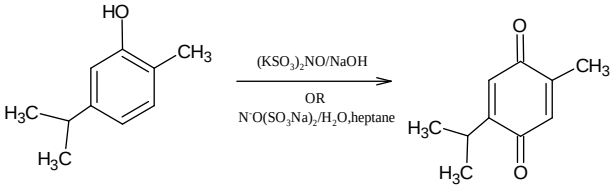



Figure (1.13): Synthesis of Quinones from Phenols Using Fremy's Salt.

Other method to the synthesis of *p*-benzoquinones carried out by oxygen sensitizers , molecular oxygen in the presence of catalytic system bis(acetylacetone)oxovanadium(IV) in dichloromethane, or aqueous hydrogen peroxide and mesoporous titanium-containing silicate materials as heterogeneous catalyst and the last one is green synthesis fig (1.14) ( Avendano *et al*, 2014).

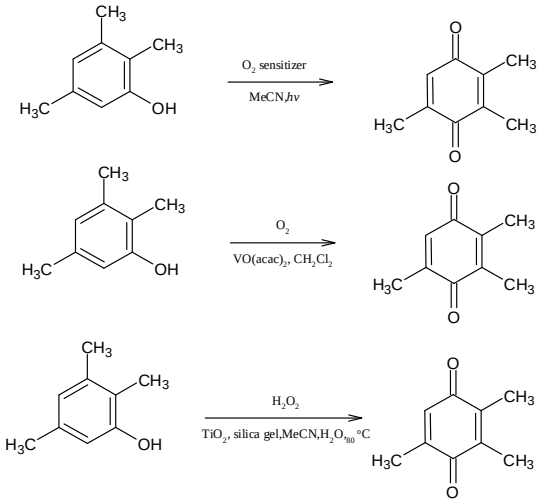



Figure (1.14): Synthesis of Quinones from Phenols Using Oxygen.

Reuthenium catalyst [$RuCl_2(PPh_3)_3$] was oxidized phenols with alkyl hydroperoxides(ROOH) to 2-substituted 1,4-benzoquinones followed by treatment with Lewis acid ($TiCl_4$) fig (1.15) (Avendano *et al*, 2014).

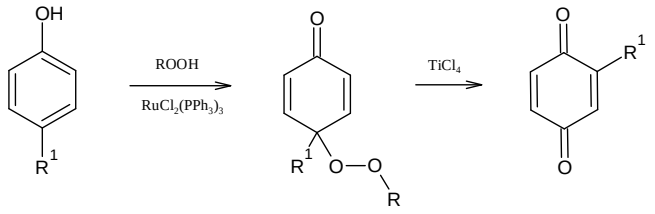



Figure (1.15): Synthesis of Quinones from *p*-Alkylphenols ($R_1$ = Me,iPr,Bn**).**

Ortho and para diols are easily oxidized to ortho- and para-quinones, respectively. The reaction has been successfully carried out with other groups para to OH; $NH_2$, halogen, OR, Me, t-Bu, and even H, although with the last yields are poor fig (1.16).

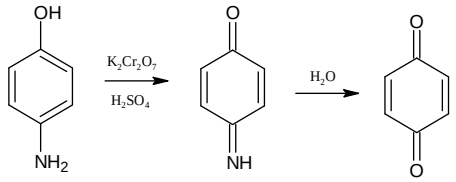



Figure (1.16): Synthesis of Quinones from *p*-Aminophenols.

Many oxidizing agents have been used: acid dichromate, silver oxide, silver carbonate, lead tetraacetate, $HIO_4$, $MnO_2$ on Bentonite with microwave irradiation, dimethyl dioxirane, and atmospheric oxygen, to name a few. Substituted phenols, such as 4-($CH_2CH_2CH_2COOH$) phenol, are oxidized with a polymer-bound hypervalent iodine reagent to give a quinone with a spirocyclic lactone unit at C-4. Oxidation has been done photochemically with $O_2$ and tetraphenylporphine. A particularly effective reagent for rings with only one OH or $NH_2$ group is $(KSO_3)_2N$-O. (dipotassium nitrosodisulfonate; Fremy's salt), which is a stable free radical. Phenols, even some whose para positions are unoccupied, can be oxidized to ortho-quinones with diphenylseleninic anhydride. Quinoid coupling products are obtained from substituted phenol treated with $O_2$, a dicopper complex, and mushroom tyrosinase (Smith & March, 2007).

Chromyl chloride reacts with halogen and alkyl substituted phenols to give brown amorphous solids which, in general, do not show a stoichiometric composition. The hydrolysis of these solids gives varying yields of quinones, diphenoquinone, and polymeric compounds. The reaction is performed

at room temperature in carbon tetrachloride using different substrate to oxidant ratios. Also, 2,6-dichlorophenol and 2,4,6-trichlorophenol give good yield of 2,6-dichloro-*p*-benzoquinone fig (1.17) (Caineli and Cardilo,2012).

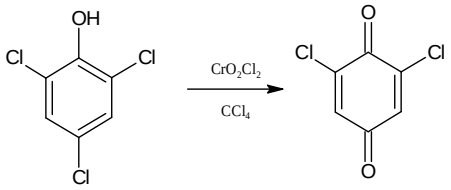



Figure (1.17): Synthesis of Quinones from *p*-Halophenols.

A variety of oxidants and conditions can be used for the conversion of 2-substituted hydroquinones into the corresponding benzoquinones. The most common ones are dichromate, iron(III) chloride, silver (I) oxide, hydrogen peroxide, ammonium cerium(IV) nitrate, 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone, and manganese (IV) oxide fig (1.18) (Brown *et al*, 2011; Griesbeck, 2014; Abraham *et al*, 2011).

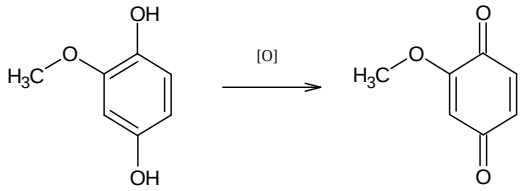



Figure (1.18): Synthesis of Quinones from Hydroquinones.

The oxidation of sulfur-substituted hydroquinone into the corresponding 1,4-benzoquinones can be occurred using sodium periodate coated on silica gel and polymer-supported (diacetoxyiodo)benzene fig (1.19) (Griesbeck, 2014).

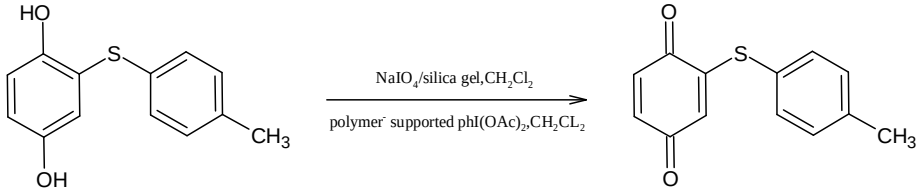



Figure (1.19): Synthesis of Quinones from Sulfur-Substituted Hydroquinones

A new green method of synthesis was developed for the synthesis of amino-naphthoquinones, which have anticancer activity, in a one-pot synthesis directly. For example, Nuclear monoamination of a 1,4-dihydroxy-2-naphthoic acid with primary aromatic amines was catalysed by the commercial laccase, Novozym 51003, from Novozymes (a non-hazardous oxidizing agent) to afford amino-

naphthoquinones (having the amine moiety in the ortho position to the ketone of the quinone ring). Succinate-lactate buffer and a co-solvent, dimethylformamide (DMF), under mild reaction conditions in a vessel open to air at pH 4.5 and pH 6.0 was used fig (1.20).

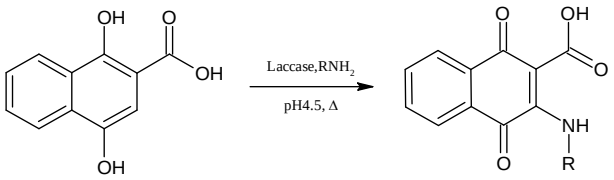



Figure (1.20).Synthesis of Aminonaphthoquinones (R=aryl).

The role of laccase is simply that of an oxidant, two laccase oxidations occur before the aminonaphthoquinone is formed.Novozymes has a few laccases available on the market in different preparation. Novozym 51003 is a robust, stable laccase used for lignin modification within pulps and effluents. It is produced by submerged fermentation of genetically modified Aspergillus sp with molecular weight of 56,000 Da (Wellington & Kolesnikova, 2012).

### 1.1.7.1.3. Oxidation of Phenol Ethers and Phenol Esters

*p*-Quinones can be obtained by oxidative demethylation of phenol ethers by [bis (trifluoroacetoxy) iodo] benzene or polymer supporting reagent fig (1.21) (Wirth ,2003).

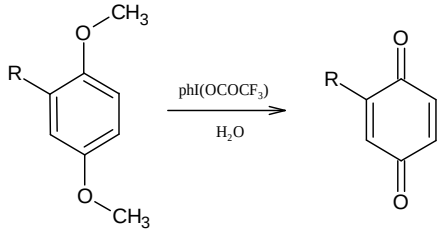



Figure (1.21): Synthesis of Quinones from Phenol Ether Using [Bis(trifluoro-acetoxy)iodo] benzene.

Electrochemical oxidation of substituted 1,4-dimethoxybenzenes has been applied to the synthesis of various benzoquinone derivatives. For example, the synthesis of 2-(chloromethyl)-1,4-benzoquinone from 2-(chloromethyl)-1,4-dimethoxybenzne using a platinum electrode and acetone-sulfuric acid fig (1.22) (Avendano *et al*, 2014).

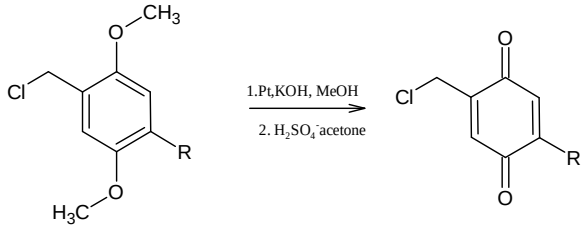



Figure (1.22): Synthesis of Quinones from Electrochemical Oxidation of Substituted 1,4-Dimethoxybenzenes.

The oxygenation of *m*-dimethoxybenzenes give *p*-dimethoxyphenol which followed by oxidation to *p*-benzoquinones using 2,6-disubstituted pyridine N-oxides with rethennium porphyrins (RuPor/N-oxide system) (Kadish *et al*, 2000). Retheium catalyst was used for oxidation of wide array of naphthalene derivatives and phenanthrene into quinones fig (1.23) (Fuchs, 2013).

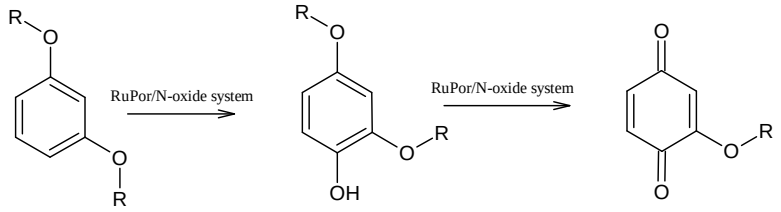



Figure (1.23): Synthesis of Quinones from Oxidation of Substituted 1,3-Dimethoxybenzenes.

Cerium ammonium nitrate (CAN), chromium(VI) oxide and nitric acid can be also used as oxidants for synthesis of *p*-benzoquinones from *p*-dimethoxy benzene fig (1.24) (Griesbeck, 2014; Chung *et al* , 2004).

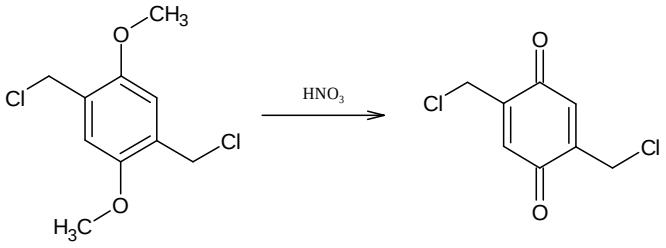



Figure (1.24): Synthesis of Quinones from Oxidation of Substituted 1,4-Dimethoxybenzenes Using Nitric Acid.

Dimethoxy groups in heterocyclic compounds were oxidized with ferric chloride in aqueous solution or with CAN in aqueous acetic acid to the quinones fig (1.25) (Garuti *et al*, 2001; Valderrama *et al*, 2002).

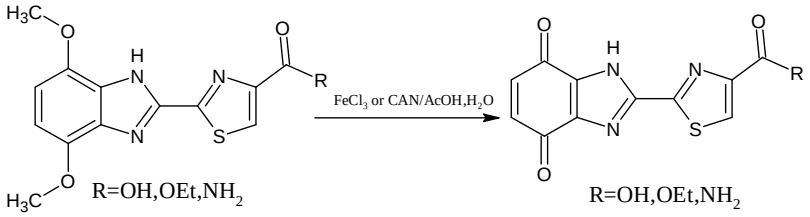



Figure (1.25) Synthesis of Thiazolylbenzimidazole-4,7-diones.

**1.1.7.1.4. Oxidation of Aromatic Amines (Aminoarenes and 1,4-Diaminoarenes)**

Aniline was oxidized to *p*-benzoquinone using dichromate fig (1.26) (Norman & Coxon, 1993). Ortho and *p*-diamines are easily oxidized to *o*- and *p*-quinones, respectively. Either or both $NH_2$ groups can be replaced by OH groups to give the same products (Smith & March, 2007).

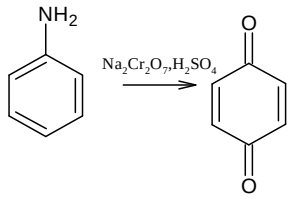



Figure (1.26): Synthesis of Quinones from Aromatic Amines.

### 1.1.7.2. Synthesis by Ring-Closure Reactions

#### 1.1.7.2.1. From 1,4-Benzoquinones and Dienes (Quinone Diels-Alder Reaction)

This reaction is useful synthetic pathway for natural compounds e.g. steroids cortisone and cholesterol (Witayakran, 2008)1,4-benzoquinone reacts readily with butadiene at room temperature to give a high yield of mono-adduct, tetrahydronaphthoquinone; under more vigorous conditions a bis-adduct is obtained which can be converted into anthraquinone by oxidation of an alkaline solution with atmospheric oxygen fig (1.27) ( Reader, 2000; Valderrama *et al*, 2002).

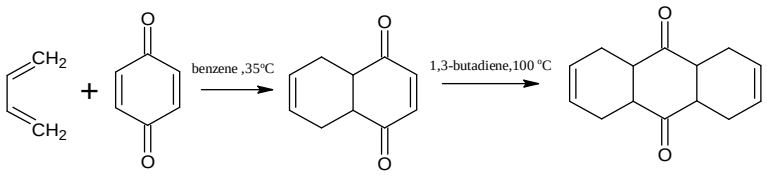



Figure (1.27): Synthesis of Quinones from **1**,4-Benzoquinones and Dienes.

#### 1.1.7.2.2. By Cycloalkylation and Cycloacylation Rreactions

An important use of the Friedel–Crafts acylation is to effect ring closure. This can be done if an acyl halide, anhydride, or carboxylic acid group is in the proper position. An example is the reaction in fig (1.28). Many fused-ring systems are made in this manner. If the bridging group is CO, the product is a quinone (Smith & March, 2007).

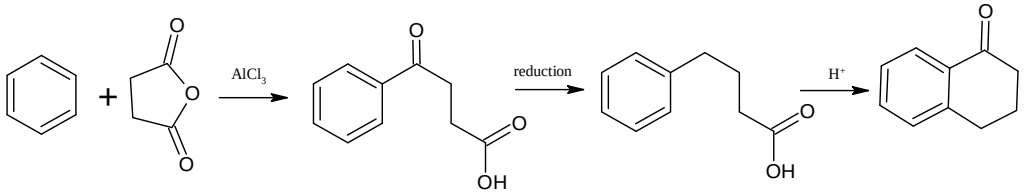



Figure (1.28): Friedel-Craft Acylation.

Thermal [2+2] cycloaddition reactions can be applied to quinones when photochemically excited fig (1.29) (Smith & March, 2007).

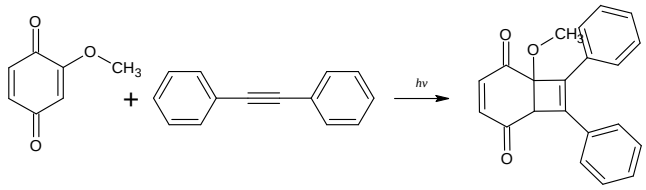


Figure (1.29): Thermal [2+2] Cycloaddition Reactions of Quinones.

[4+2]-cycloaddition adducts of 5-arylidene-4-thioxo-2-thiazolidinones and 1,4- Naphthoquinones can undergo the *hetero*-Diels-Alder reaction due to their ability naphthoquinone undergo spontaneous oxidation (dehydrogenation) due to the excess amount of 1,4-naphthoquinone in glacial acetic acid in the presence of a catalytic amount of fused sodium acetate Fig (1.30) (Atamanyuk *et al*, 2013).

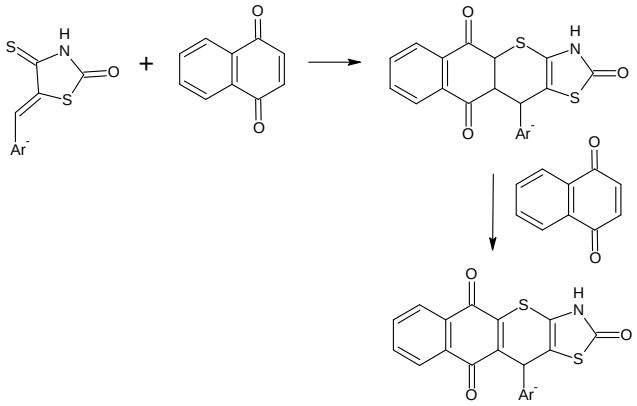


Figure (1.30): Synthesis of 3,11-Dihydro-2H-benzo[6,7] thiochromeno[2,3-d][1,3]thiazole-2,5,10-triones.

**1.1.7.2.3. From Acetylenes and Metalcarbonyls**

An oxidative addition of a transition-metal to a cyclobutenedione followed by coupling with an alkyne to produced quinones show in fig (1.31).

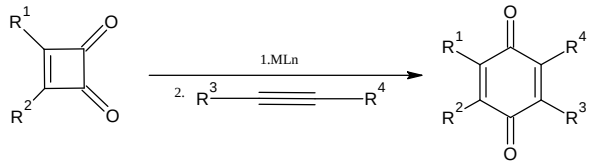


Figure (1.31): Synthesis of Quinone from Oxidation of 1,2-Diketones.

Also cyclobutenone can be used in the synthesis of quinones (Overman *et al*, 2008).

**1.1.7.3. From Other Quinones**

Two new 2-hydroxy-1,4-naphthoquinone derivatives were synthesized either by condensation (a Mannich reaction) of 2-hydroxy-1,4naphthoquinone with the corresponding aldehyde in the presence of butylamine or allyl amine in absolute ethanol fig (1.32) or by esterification reaction

between 2-hydroxy-1,4-naphthoquinone and piperic acid chloride and these derivatives showed pharmacological activities fig (1.33) ( Paengsir & Baramee, 2013).

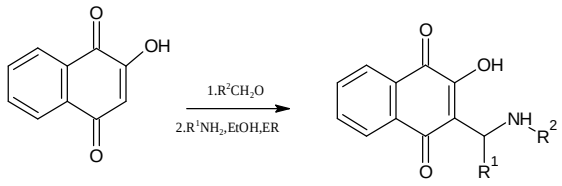



Figure (1.32): The Synthesis of 2-Hydroxy-1,4-naphthoquinone Derivatives by Condensation.

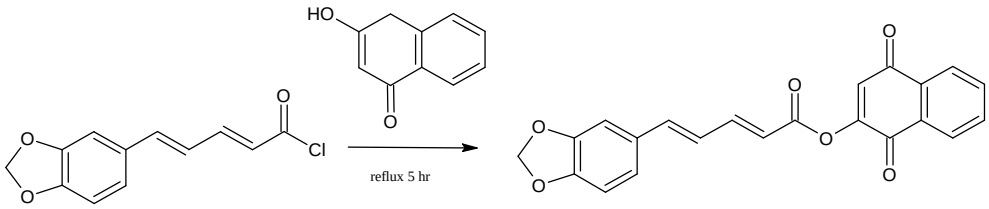



Figure (1.33) The Synthesis of 2-Hydroxy-1,4-naphthoquinone Derivatives by Esterification Reaction.

4-cycloalkylidineamino 1,2-naphthoquinone were synthesized by condensation of 4-amino-l, 2-naphthoquinone with cyclic ketones (cyclohexanone or cyclopentanone) in the presence of ethanol and concentrated sulphuric acid as catalyst fig (1.34) (Shukla *et al*, 2012).

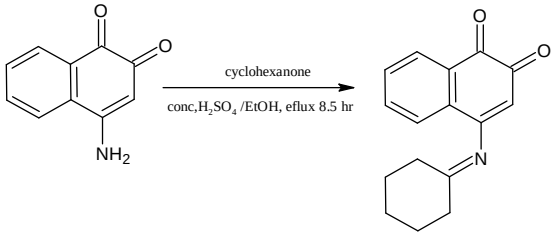



Figure (1.34) The Synthesis of 4-Cycloalkylidineamino 1,2-naphthoquinone.

2,3-diyne-1,4-naphthoquinone derivatives were synthesized employing Sonogashira cross-coupling reaction from 2,3-dibromo- 1,4-naphthoquinone and various functionalized terminal alkynes catalyzed by palladium complexe ($Pd(PPh_3)_2Cl_2$) and co-catalyzed by copper(I) iodide and triethylamine and solvents mixture were DMSO (dimethylsulfoxide) and DCM (dichloromethane). The products were acetylated using acetic anhydride and montmorillonite clay K-10 under ultrasound treatment producing new derivatives fig (1.35) (Silva *et al*, 2013).

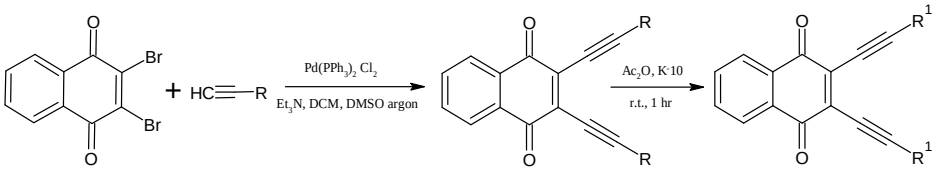



Figure (1.35): Synthesis of 2,3-Diyne-1,4-naphthoquinone derivatives$R^1$ = (R minus H) OAc.

### 1.1.7.4. Other Methods

Fedorov *et al*, 2011 reported that about 100 new *O*- or *S*- glycosides of 1,4-naphthoquinones and products of their intramolecular cyclisation were synthesized and have biological activities. Most of these compounds have a carbohydrate moiety attached to the quinone part of the molecule *via* sulfur atom (thioglycosyl group) fig (1.36).

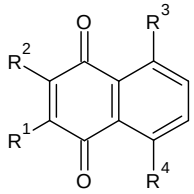



Figure (1.36): Structures of the 1,4-Naphthoquinone Glycosides
$R^1$and/or $R^2$=glycoside groups,H and $R^3$and/or $R^4$= H,alkyl,OH,OAc.OMe, $NH_2$ .

2-methyl-5(or8)-hydroxynaphtho[2,3-b]furan-4,9-dione (FNQ13) was synthesized by mixing 3-hydroxyphthalic anhydride, 2-acetyl-5-methylfuran, and aluminum chloride with nitrobenzene and heating to 100°C for 18 h. These naphtho[2,3-b]furan-4,9-dione (furanonaphthoquinone [FNQ]) analogues may be useful as another chemotherapeutic agent fig (1.37) and fig (1.38) (Nagata *et al*,1998).

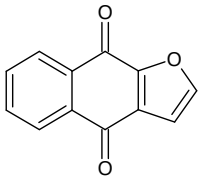



Figure (1.37): Chemical Structure of FNQ.

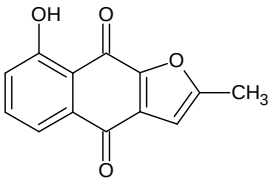



Figure (1.38): Chemical Structure of FNQ13.

Several diversely substituted 8-aminopyrimido[4,5-c]isoquinolinequinones were regioselectively synthesized by amination reaction of quinones with a variety of primary and secondary amines in ethanol in the presence of $CeCl_3.7H_2O$ under aerobic conditions. This nucleophilic substitution reaction takes place at room temperature. Variation in the structure of the nitrogen substituent

bonded to the 8-position of the pyrimidoisoquinolinequinone system led to a set of alkylamino-, phenylamino- and alkyphenylamino derivatives. Some of these compounds exhibited interesting antitumor activity fig (1.39) (Vásquez *et al*, 2010).

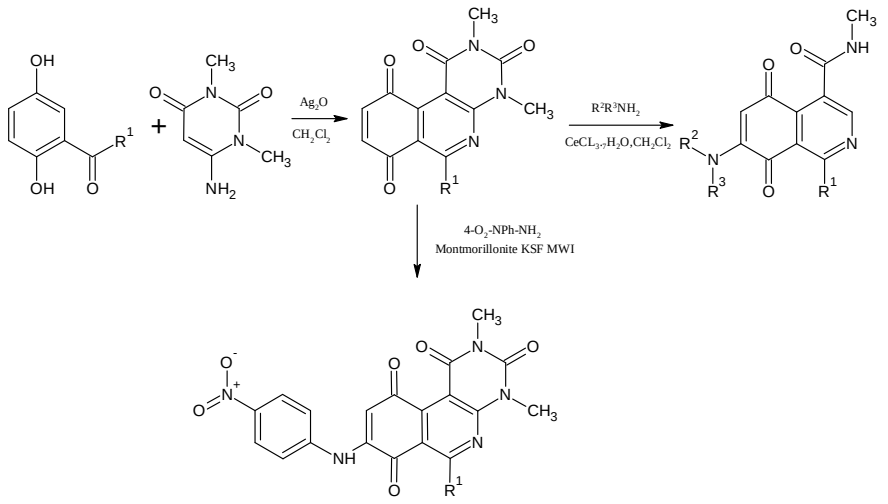



Figure (1.39): Synthesis of 8-Aminopyrimido[4,5-c]isoquinolinequinone Derivatives.$R^1$=H,Me

The oxidative coupling reaction reaction of (+)-euryfuran with highly electrophilic 1,4-benzoquinone; 1,4-naphthoquinone or 5-hydroxy-1,4-naphthoquinone (activated quinones) in acetic acid using palladium(II) acetate ( Hitahara's procedure) yields the corresponding euryfuryl-1,4-quinones which are antiprotozoal active fig (1.40).

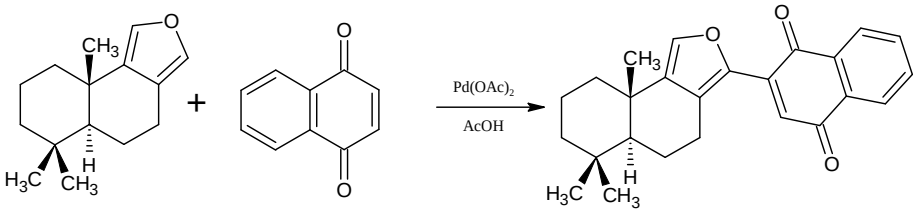



Figure (1.40): Synthesis of Euryfuryl-1,4-quinones Derivatives.

A regioselectivity of this reaction is controlled by the steric hindrance of the donor and protonation of the acceptor and this arylation method of 1,4-quinones proceeds cleanly and does not require an expensive catalyst, such as palladium(II) acetate, to promote the reaction.

The influence of the solvent to promote the Michael addition and the regioselectivity of the reaction with unsymmetrical quinones are important features that can be useful for the synthesis of new bioactive members of the euryfurylquinone series (Valderrama *et al.*, 2003).

The dimethylaminohydrazonofurylquinones were prepared by oxidative coupling reactions of 2-furaldehyde N,N-dimethylhydrazone with 1,4-naphthoquinone, 2-chloro-1,4-naphthoquinone and 2-methoxy-1,4-benzoquinone in acetic acid .The aldehydes were obtained by acid-induced hydrolysis of first product under mild conditions fig (1.41).

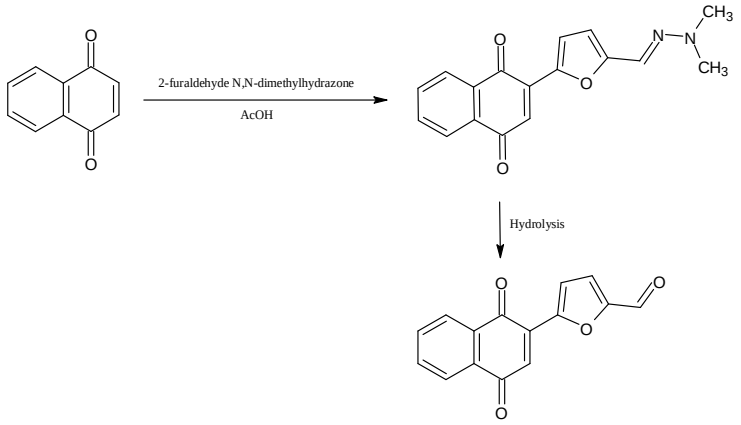



Figure (1.41): Synthesis of Dimethylaminohydrazonofurylquinones.

The cytotoxicity of furyl-1,4-quinones is dependent on the nature of the substituent linked to the quinone electroactive nucleus. The biological effect is apparently associated with the LUMO energies and the hydrophobic properties (Benites *et al* 2010).

Isoquinolinequinone was synthesized from 2,5-dihydroxybenzaldehyde, methyl aminocrotonate and silver (I) oxide fig (1.42) (Delgado *et al*, 2012).

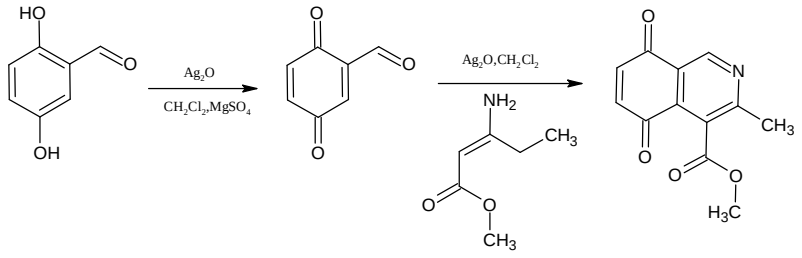



Figure (1.42): Synthesis and Reaction of Isoquinolinequinone with Methylamine.

The synthesis of the series of benzo[j]phenanthridine[4,5-c]isoquinolinequinones, containing phenyl and heteroaryl substituents at 6-position, was accomplished by reaction of acylnaphthohydroquinones, enaminones and silver (I) oxide in dichloromethane fig (1.43) (Iribarra *et al*, 2012).

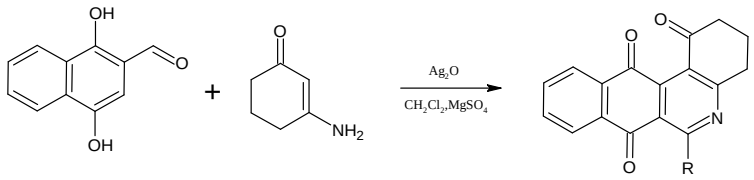



Figure (1.43): Synthesis of 6-Substituted Angular Quinones.

Halogenated naphthoquinones can be prepared from the corresponding alkyl derivatives using chlorine or bromine in acetic acid followed by dehydrohalogenation in concentrated sulphuric acid or sodium acetate respectively fig (1.44) (Ambrogi *et al* ,1970).

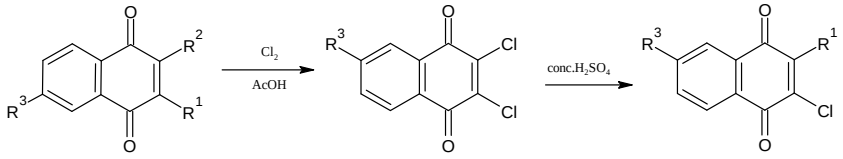



Figure (1.44): Synthesis of Halogenated Naphthoquinones.

Heterocyclisation of aminobezothiophenes to 6,9-dimethoxy-4*H*-[1]benzothieno[3,2-*d*][1,3]oxazin-4-one was attempted by reaction with sodium hydroxide, followed by reaction of the resulting sodium carboxylate with acetic anhydride. The treatment provided heterocycle and all attempts to obtain quinone by oxidative demethylation of with CAN were unsuccessful and the starting material was recovered in these experiments fig (1.45) (Valderrama *et al*, 2002)

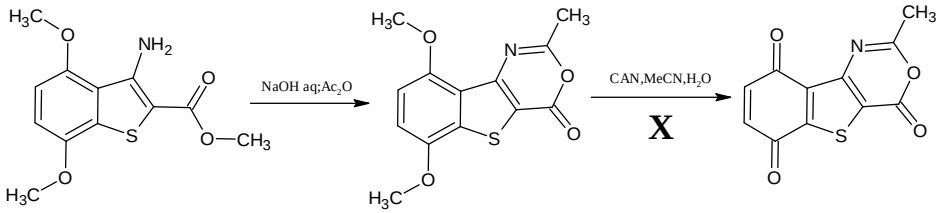



Figure (1.45): Heterocyclisation of 3,6-Dimethoxy-2-nitrobenzaldehyde.

### 1.1.8. Reactions of Quinones

Quinone (unsaturated diketone) can gain two electrons to form dianion of dihydrophenol fig (1.46).

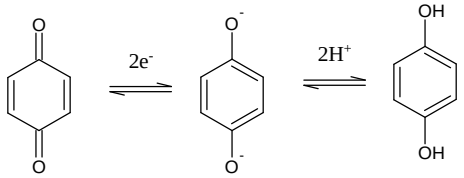



Figure (1.46): Reduction of Quinone

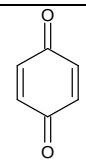
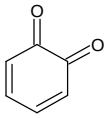
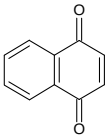
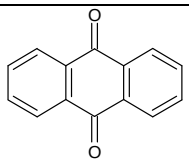
The electrode potential E of this system can be calculated as follows

$$E = E_o - 2R/2F \ln \frac{a_Q a_{H^+}^2}{a_{QH_2}}$$

where $E_o$ the standard electrode potential, a the activity of species X and F Faraday.

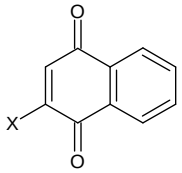
The standard electrode potential of some quinones given in table (1) which show $E_o$ for *o*-quinone is the largest value and this demonstated why *p*-quinone is more stable than *o*-quinone. Fused rings in

Table (1.1): The Standard Electrode Potential of Some Quinones

| Quinone structure |  |  |  |  |
|---|---|---|---|---|
| $E_o(H_2O)$/ volt | 0.699 | 0.792 | 0.470 | - |
| $E_o$(EtOH)/ volt | 0.715 | - | 0.484 | 0.154 |

naphthoquinone and anthraquinone make them less powerful oxidizing agents. Naphthoquinones with electron donating substituents have less value of $\Delta E_o$ than that with electron withdrawing substituents which make the later more powerful oxidizing agents table(2) (Tedder & Nechvatal, 1983).

Table (1.2): The Difference Standard Electrode Potential of Some Substituted Naphthoquinones with Naphthoquinone.

|  | X | $NHCH_3$ | $NH_2$ | OH | $OCH_3$ | $CH_3$ |
|---|---|---|---|---|---|---|
| | $\Delta E_o$(mV) | -253 | -210 | -128 | -131 | -76 |
| | X | $C_6H_5$ | $OCOCH_3$ | Cl | $SO_2Na$ | $SO_2C_6H_5CH_3$ |
| | $\Delta E_o$(mV) | -32 | -9 | +24 | +69 | +121 |

### 1.1.8.1. Reaction with Hydroxyl Amine

Quinone reacts as unsaturated ketone with hydroxyl amine to produce the momoxime then the dioxime fig (1.47) (Tedder & Nechvatal, 1983).

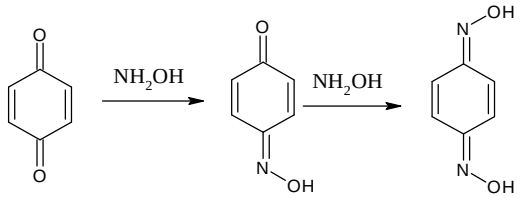



Figure (1.47): Reaction of Quinone with Hydroxyl Amine

### 1.1.8.2. Nucleophilic Addition

Quinone is reduced by phenyl hydrazine and the substituted phenyl hydrazine will react with carbonyl groups. Also cynide, bisulphate anion, diethyl malonate, ethyl cyano acetate enolate anione, Grinarad reagents and thiol anion react with quinoneas nucleophiles fig (1.48) (Tedder & Nechvatal, 1983).

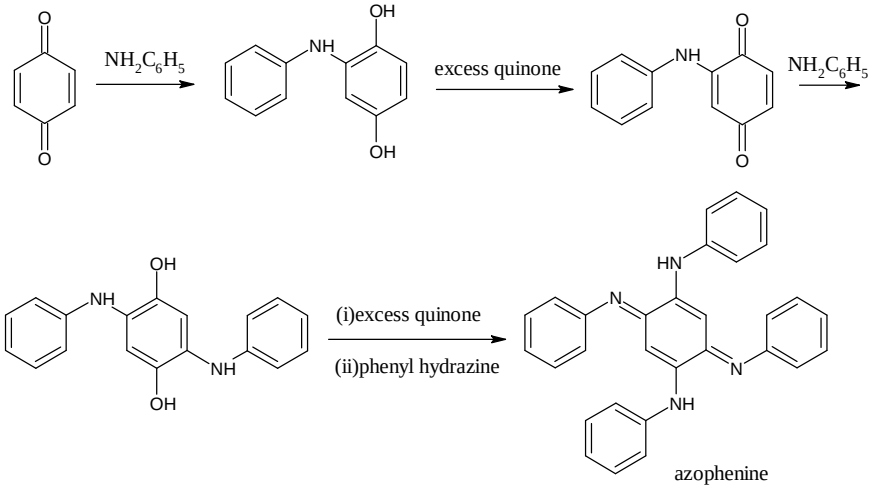



Figure (1.48): Reaction of Quinone with Phenyl Hydrazine

### 1.1.8.3. Electrophilic Addition

Hydrogen chloride reacts with quinone as follows

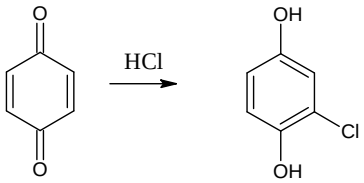



Figure (1.49): Reaction of Quinone with Hydrogen Chloride

Acetic anhydride and strong acid are common electrophiles that add to quinone (Tedder & Nechvatal, 1983).

### 1.1.8.4. Addition to Carbon-Carbon Double Bond

Quinone undergoes direct addition by bromine to give saturated tetrabromo-diketone fig (1.50).

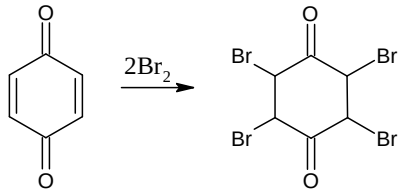



Figure (1.50): Reaction of Quinone with Bromine.

Also quinone undergoes Diels-Alder reaction with dienes fig (1.51).

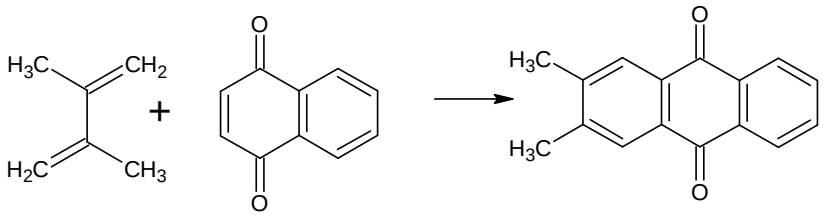



Figure (1.51): Diels-Alder Reaction of Quinone.

Diazomethane and methylazide react with quinone in the same manner. (Tedder & Nechvatal, 1983)

### 1.1.8.5. Conjugate Addition of Indole to *p*-Quinones

The condensation of indoles with quinones under acidic conditions usig bismuth triflate show fig (1.52) (Ollevier, 2012).

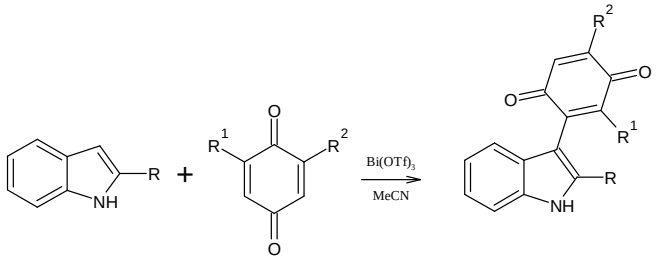



Figure (1.52): Condensation of Indoles with Quinones

### 1.1.8.6. Addition of a Ketene Acetals to Quinones (Formation of 2-Acyl-1,4-quinones)

The reaction between ketene acetals and quinones are useful in the synthesis of many natural occurring quinones fig (1.53). (Perlmutter, 2013)

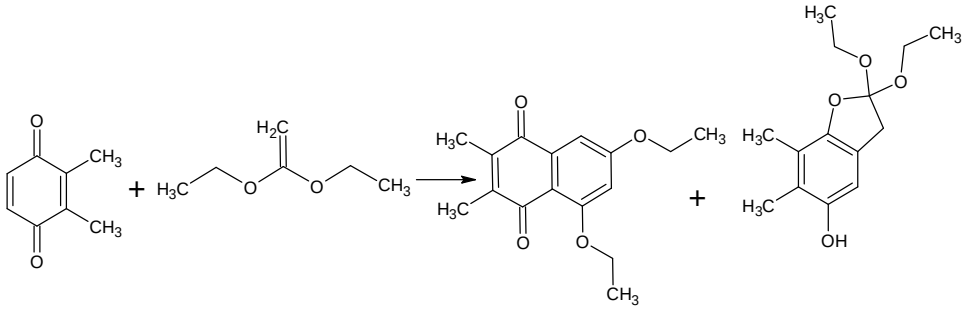


Figure (1.53): Addition of Ketene Acetals to Quinones

### 1.1.8.7. Electrophilic Aromatic Subistitution

The sulfonation of anthraquinone can be done using oleum ($SO_3$ in $H_2SO_4$ ) at 160 °C and the sulfonate group makes anthraquinone soluble in water fig (1.54) (Clayden *et al*, 2012).

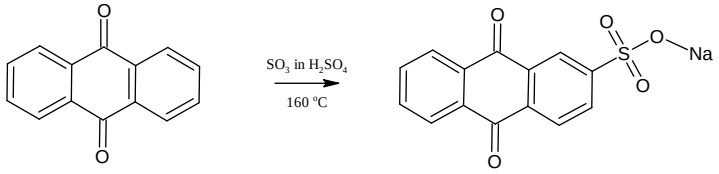


Figure (1.54):Electrophilic Aromatic Subistitution of Quinone.

### 1.1.8.8. Synthesis of Aromatic Heterocycles

Aromatic pyridines can be prepared by oxidation of the dihydropyridine using dichlorodicyanoquinone(DDQ) as oxidizing agent and these reaction belong to the Hantzsch pyridine synthesis fig (1.55) ( Clayden *et al*, , 2012).

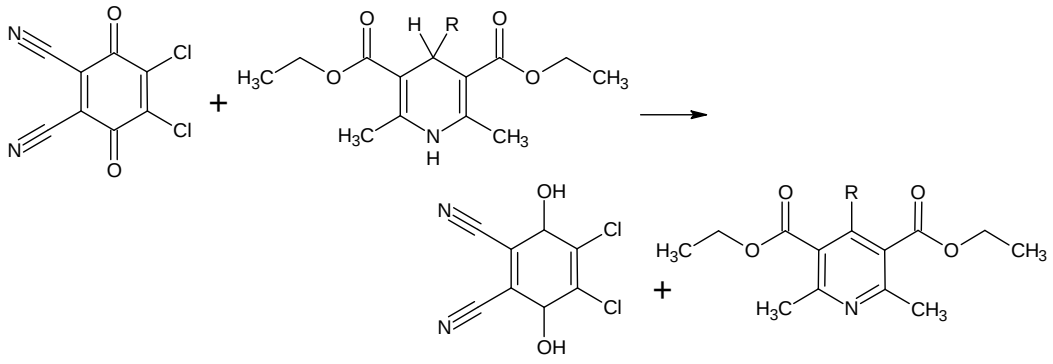


Figure (1.55): Synthesis of Aromatic Heterocycles from Quinone.

### 1.1.8.9. Synthesis of Cyclic Ethers and Amines

Cyclic ethers and amines can be formed from intramolecular cyclization of alcohols or amines using benzoquinone as oxidant and palladium acetate or palladium (II) complex as catalyst fig (1.56) (Clayden *et al*, 2012).

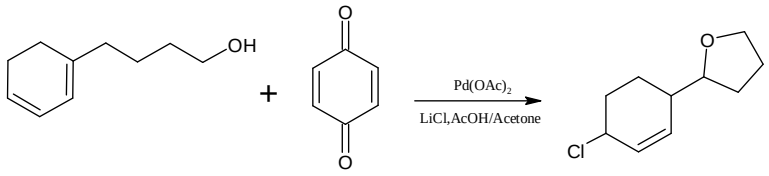



Figure (1.56): Synthesis of Cyclic Ethers and Amines.

One carbonyl group of quinones can be reduced with copper and sulfuric acid or with tin and HCl fig (1.57). (Smith & March, 2007)

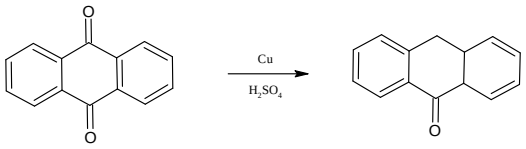



Figure (1.57): Reduction of Quinones

### 1.1.8.10. Nucleophilic Substitution Reaction

A mono-or di-halogenated derivative of 1, 4-naphthoquinone can be undergo nucleophilic substitution by the amine compound to prepare the corresponding amino derivatives fig (1.58) (Lopez *et al.*, 2014).

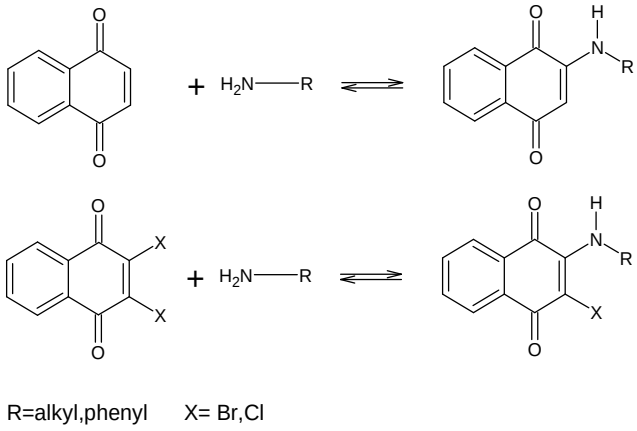



Figure (1.58): Alkyl/arylamino Naphthoquinone Synthesis by

a) Michael 1, 4-Addition and b) Nucleophilic Substitution.

Compounds containing the thiol (SH) and amino ($NH_2$) groups react readily with quinones. For example aryl amines react with 2,3,5,6-tertabromo-1,4- quinones fig (1.59) (Saeed and Omer, 2009).

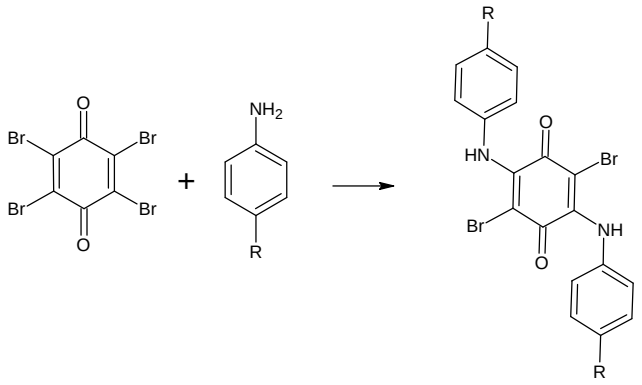



Figure (1.59): Synthesis of 2,5-Diaminoaryl-3,6-dibromo-1,4-benzoquinones.

**1.1.9. Hydroxyquinones (Lawsone)**

Lawsone (2-hydroxy-1,4- naphthoquinone ) is the principal active component of the henna plant and one of important derivatives of hydroxyl naphththoquinone. (e.g. alkyl and aminonaphthoquinones) which possesses chemical and pharmacological properties.

Lawsone is found as toutomeric forms:

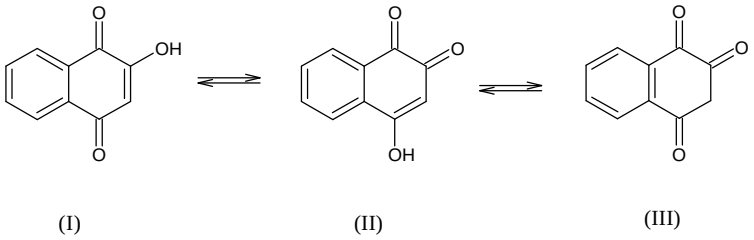



Figure (1.60): Toutomeric Forms of Lawsone

(I) 1,4-naphthoquinone structure, (II) 1,2-naphthoquinone structure and (III) 1,2,4-naphthotrione structure. [Stability (I) > (II) > (III)].

This stability is due to intramolecular hydrogen bond between carbonyl group (in C1) and hydroxyl grope (in C2) (Lopez *et al.*, 2014).

Lawsone is a weak acid and form soluble salts in alkaline solutions but the undiassociated form has a limited solubility in water fig (1.61) .Absorption in the visible region by lawsone solutions increase with increasing pH; the tautomer in excess in alkaline solutions is therefore more deeply colored than species associated with low pH value .

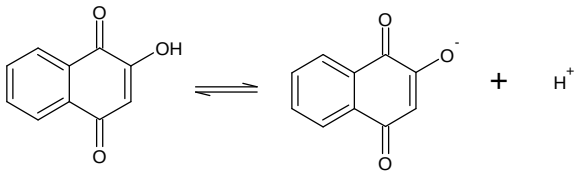


Figure (1.61): Dissociation of Lawsone

The visible region of the absorption spectra of the absorption of lawsone takes the form of a broad band around 450nm decreasing to zero absorption by 500nm. The absorption in red and yellow region of lawsone is equivalent at high pH values but as the pH falls, absorption in the red region decreases more rapidly than in the yellow (Amro *et al.,* 1994).

A Michael Reaction

2-amino-1, 4-naphthoquinones were synthesized from 2-hydroxy1, 4-naphthiquinone ring and the amino compound fig (1.62) (Lopez *et al.*, 2014).

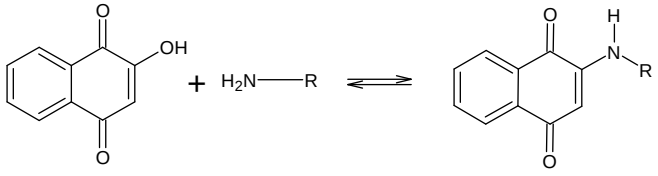


Figure (1.62): Amination of Lawsone

Lawsone reacts with benzal acetone in pyridine in two steps fig (1.63) (Zaugg, 1949).

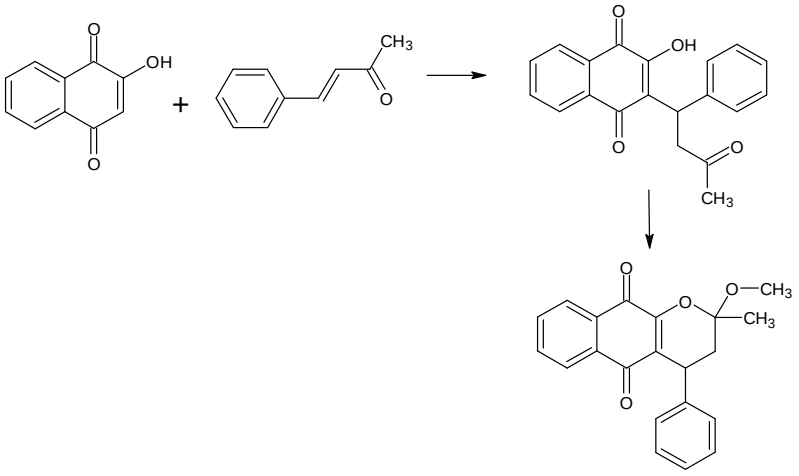


Figure (1.63): Benzylatin of Lawsone

**Bromination Reaction:**

Lawsone react with bromine and hydrogen peroxide in acidic medium fig (1.64) then the product (2-

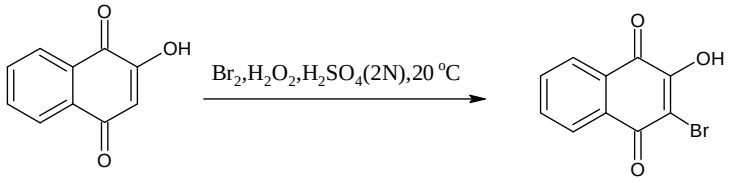



Figure (1.64): Bromination of Lawsone

hydroxy -3- bromo-1,4-naphthoquinone) methylated with dimethyl sulfate in acetone and potassium carbonate used as catalyst fig (1.65) (Tran *et al.*, 2009).

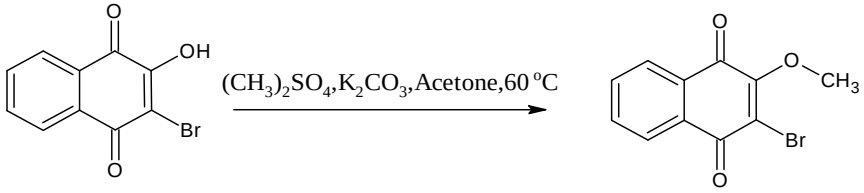



Figure (1.65): Methylation of Halogenated Lawsone

It was demonstrated that β-amino carbonyl lawsone derivatives (e.g. of Mannich base) were synthesized for the first time in 1948 from three components an amine, an aldehyde and enolizable ketone (Lopez *et al.*, 2014). Mannich bases can be easily and clean environmentally prepared from the reaction between lawsone, primary amines and benzaldehyde substitutent in ethanol at room temperature under stirring for an half day (Neves *et al.*, 2009).

The synthesis of lawsone Mannich bases under reflux heating for5-7 hr can be obtained easily in aqueous medium with high yield of the product and clean reaction from three –component reaction of lawsone , aromatic aldehyde and hetereocyclic or carbocyclic amines using $InCl_3$ as catalyst fig (1.66) (Dabiri *et al.*, 2011).

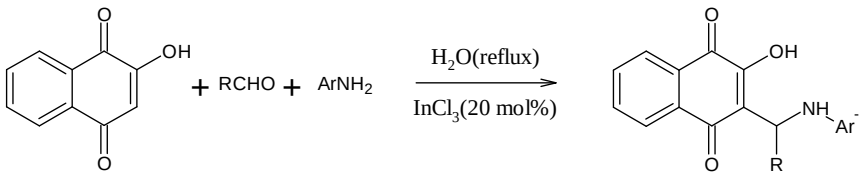



Figure (1.66): Synthesis of Mannich Bases from Lawsone

**Hooker Condensation:**

This is a classical method for the synthesis of 2-hydroxy-3-substituted naphthoquinones where Lawsone reacts with aldehyde to give poor yields and difficult purification of the product fig (1.67) (Perez *et al.*, 2007).

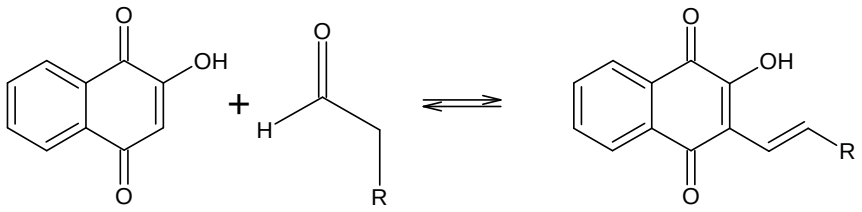



Figure (1.67): Alkylation of Lawsone

**Heck Reaction:**

Halogenated Quinones reacts with polar groups (e.g. unsaturated acid and amides) using palladium catalyst under refluxing for 2-7hr and the product easily purification fig (1.68) (Perez *et al.*, 2007).

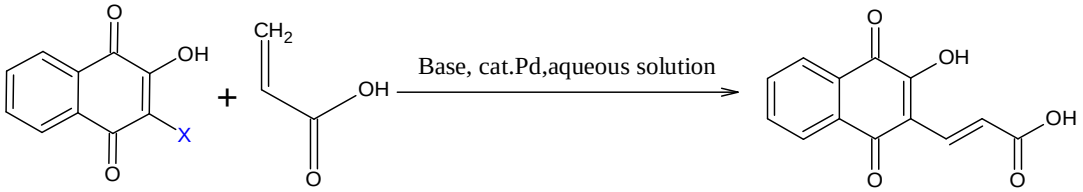



Figure (1.68): Heck Reaction of Lawsone.

Lawsone have a broad range of absorption wavelength in UV visible and near-IR regions between 650 nm and 700 nm due to presence of hydroxyl and carbonyl groups and lawsone structure attach well to the $TiO_2$ photoelectrode because the absorption band of the UV spectra shifted to higher energy compared to the absorption peak in the visible region (Safie *et al.*, 2015).

Two new 2-hydroxy-1,4-naphthoquinone derivatives were synthesized either by condensation (a Mannich reaction) of 2-hydroxy-1,4naphthoquinone with the corresponding aldehyde in the presence of butylamine or allyl amine in absolute ethanol fig (1.69) or by esterification reaction between 2-hydroxy-1,4naphthoquinone and piperic acid chloride and these derivatives showed pharmacological activities fig (1.70) ( Paengsir & Baramee, 2013) .

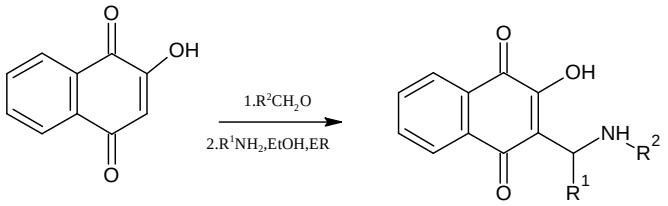



Figure (1.69): The Synthesis of 2-Hydroxy-1,4-naphthoquinone Derivatives by Condensation.

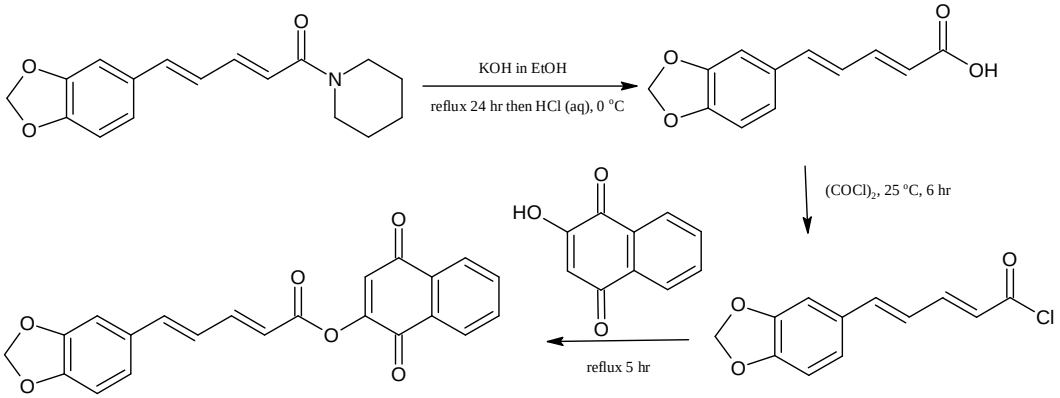



Figure (1.70) The Synthesis of 2-Hydroxy-1,4-naphthoquinone Derivatives by Esterification Reaction.

Hydroxyquinones form stable zwiterionic compounds of the general type fig (1.71). These compounds can be described as hybrids of 1,4 or 1,2- dipoles or as ylides, where Z is a moiety of the elements P, S, N or I. All these ylides exhibit significant stability, and hence low reactivity, with exception of iodonium ylides (Spyroudis, 2000).

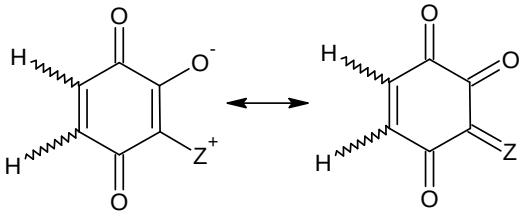



Figure (1.71): Formation of Ylides.

## 1.2. Quantitative Structure–Activity Relationships (QSARs)

### 1.2.1. Definition of Computational Chemistry

The term *computational chemistry* is generally used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer. Note that the words ``exact" and ``perfect" do not appear in these definitions. Very few aspects of chemistry can be computed exactly, but almost every aspect of chemistry has been described in a qualitative or approximately quantitative computational scheme. The biggest mistake a computational chemist can make is to assume that any computed number is exact. However, just as not all spectra are perfectly resolved, often a qualitative or approximate computation can give useful insight into chemistry if the researcher understands what it does and does not predict (Young, 2001).

*Computational chemistry* is an exciting and fast-emerging discipline which deals with the modeling and the computer simulation of systems such as biomolecules, polymers, drugs, inorganic and organic molecules, and so on. The major computational requirements are:

1. Molecular energies and structures.
2. Geometry optimization from an empirical input.
3. Energies and structures of transition states.
4. Bond energies.
5. Reaction energies and all thermodynamic properties.
6. Molecular orbitals.
7. Multipole moments.
8. Atomic charges and electrostatic potential.
9. Vibrational frequencies.
10. IR and Raman spectra.
11. NMR spectra.
12. CD spectra.
13. Magnetic properties.
14. Polarizabilities and hyperpolarize-abilities.
15. Reaction pathway.
16. Properties such as the ionization potential electron affinity proton affinity.
17. Modeling excited states.
18. Modeling surface properties and so on (Cronin, 2002).

### 1.2.2. Molecular Descriptor

#### 1.2.2.1. Definition of Molecular Descriptors

Molecular descriptors in simple definition are numerical values that characterize properties of molecules. For example, they may represent the physicochemical properties of a molecule or they

may be values that are derived by applying algorithmic techniques to the molecular structures (Leach and Gillet, 2007).

Also it can be defined as the final result of logical and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into useful number or the result of some standardized experiment (Todeschini and Consonni, 2008).

#### 1.2.2.1. Classification of Molecular Descriptors

The most important of properties used in QSAR are steric (e.g. shape and volume), electronic (e.g. electric charge and electrostatic potential), and lipophilic properties (how polar or non-polar the sections of the molecule are, usually exemplified by the log of the octanol-water partition coefficient, logP).

Molecular descriptors can be divided in two types: fragment descriptors which involve properties of sections of molecules such as hydrophobic constant $\pi$, molar refractivity MR, and whole molecule descriptors based on the properties of the intact molecule as molecular size, molecular weight and partition coefficient logP (Winkler, 2001).

Most of molecular discriptors can be classified as:
i) Descriptors related to size: molecular weight, calculated molecular refractivity, molecular volume.
ii) Descriptors related to hydrophobicity: the log of partition coefficient, hydrophobic constant, the log of the molar aqueous solubility (log $S_w$)
iii) Descriptors related to electronic effects: the estimated polarizibility, atomic charge.
iv) Hydrogen bonding descriptors that estimate basicity or acidity factors.
v) Topological descriptors derived from connectivity matrices (Oprea, 2002).
The majority of molecular descriptors can be classified according to their dimensionality", which refers to the representation of molecules from which descriptor values are computed.
Molecular descriptors obtained from the chemical formula can be called 0D descriptors which independent of molecular structure. Examples are the atom number, molecular weight, atom-type count, and, in general, constitutional descriptors and any function of the atomic properties such as atomic mass, atomic charge, covalent and van der Waals radii, atomic polarizability, and hydrophobic atomic constants.
1D descriptors which derived from a list of structural fragments of a molecule (a partial list of fragments, functional groups, or substituents of interest,) and not requiring a complete knowledge of

the molecule structure. These type of descriptors are typically used in substructural analysis and substructure searching with a common name of molecular fingerprints.

2D descriptors which are derived from a molecular graph (topological representation of the molecule) depend on the connectivity of atoms in the molecule in terms of the presence and nature of chemical bond. Examples of these descriptors are equilibrium interatomic distances between nuclei, bond angles, and torsion angles.

3D descriptors are derived from 3D representation which views the overall spatial configuration of the molecule such as the geometrical descriptors, several steric descriptors, and size descriptors ( Todeschini and Consonni, 2009 ).

However, 1D and 2D methods have a tendency to find mainly close chemical analogues to known active compounds but fail to predict activity differences between them. What is lacking from 1D and 2D methods is obviously 3D structural information of compounds and target proteins. Binding affinity between molecules and target proteins is governed by atomic interactions in the 3D space. Consequently, molecules that have similar 3D shape and properties could share biological activities, even while their 1D and 2D representations are not similar. Therefore, 3D methods have gained more attention recently because of their potential to overcome key limitations of 1D and 2D methods.However, a main challenge of 3D methods is how to treat ligand conformational flexibility. In addition, since multiple ligand conformations are considered, 3D methods require more storage space and computational time compared to 1D and 2D methods. Another important consideration is that a biologically active structure does not always match the lowest energy conformation of a molecule (Shin *et al*, 2015).

A 1D formula can give only 1D data (molecular mass, numbers of atoms, other scalars). A 2D formula produces 2D data (2D matrices of topological descriptors, etc.), and 3D representation enables the extraction of 3D data (volume or spatial distribution of some property in the form of 3D matrices,) (Kiralj, R. & Ferreira, 2003).

The 1D descriptors (sometimes called 0D descriptors in the literature) are calculated solely based on the molecular formula. The atom counts include numbers of different atoms and the total number of atoms in the molecule. Two physicochemical properties are molecular weight and average molecular weight. The 2D descriptors are calculated from the 2D structure of a molecule, though some of them such as logP and fragment counts are called 1D descriptors in the literature. The 2D descriptor's counts of atoms are different from those in the 1D descriptors since different types of atoms are counted. That is, all types of carbon atoms are considered as the same in 1D descriptors because a

1D molecular formula does not distinguish among them. Types of carbon atoms in the 2D descriptors are distinguished based on hybridization status, such as primary carbon, tertiary carbon on ring structure, unsubstituted aromatic carbon, and so on. The second type of 2D descriptors is related to the bond information such as numbers of single bonds, double bonds,aromatic bonds, rotatable bonds, and so on ( Hong *et al*, 2008) .

In the 1980s, the new era of the drug design process, named Computer-Aided/Assisted Drug Design (CADD) or Computer-Aided/Assisted Molecular Design (CAMD) came into being and QSAR methodology has became in a broad subfield of CADD. Since then, several QSAR methodologies have been proposed. Each of them can be characterized by having particular approaches for calculating and selecting the molecular descriptors, and specific statistical algorithms for constructing the resulting models. In analogy to the "direct" (i.e., receptor-based, or structure-based) and "indirect" (i.e., ligand-based) approaches currently used in the CADD process, QSAR studies can be grouped in two major groups: receptor-independent (RI) and receptor dependent (RD) QSAR analyses. In the first group either the geometry of the receptor is not available, or it is neglected in the QSAR analysis because of uncertainty in the receptor geometry and/or ligand binding mode. This group included the "classical" (zero-dimensional), one-dimensional (1D), two-dimensional (2D), three-dimensional (3D), and four-dimensional QSAR approaches. The calculated descriptors are recognizable molecular features, such as atom and molecular counts, molecular weight, sum of atomic properties (0D-QSAR); fragment counts (1D-QSAR); topological descriptors (2D-QSAR); geometrical, atomic coordinates, or energy grid descriptors (3D-QSAR); and the combination of atomic coordinates and sampling of conformations (RI-4D-QSAR). In the RD-QSAR analysis, models are derived from the 3D structure of the multiple ligand-receptor complex conformations. This approach provides an explicit simulation of the induced-fit process, using the structure of the ligand-receptor complex, where both ligand and receptor are allowed to be completely flexible by the use of molecular dynamics (MD) simulation. RD-QSAR is used to gather binding interaction energies, as descriptors, from the interaction between the analog molecules and the receptor (Andrade *et al*, 2010).

### 1.2.3. Structure-Property Relationships

Structure-property relationships are qualitatively or quantitatively empirically defined empirical relationships between molecular structure and observed properties. In some cases this may seem to duplicate statistical mechanical results; however, structure-property relationships need not be based on any rigorous theoretical principles.

The simplest case of structure-property relationships are qualitative thumb rules. For example, an experienced polymer chemist may be able to predict whether a polymer will be soft or brittle based on the geometry and bonding of the monomers.

When structure-property relationships are mentioned in the current literature, it usually implies a quantitative mathematical relationship. These relationships are most often derived by using curve fitting software to find the linear combination of molecular properties, which best reproduces the desired property. The molecular properties are usually obtained from molecular modeling computations. Other molecular descriptors, such as molecular weight or topological descriptions, are also used.

When the property being described is a physical property, such as the boiling point, this is referred to as a Quantitative Structure-Property Relationship (QSPR).When the property being described is a type of biological activity (such as a drug activity), this is referred to as a Quantitative Structure-Activity Relationship (QSAR) (Puzyn *et al*, 2010*)* and QSTR (Quantitative Structure-Toxicity Relationship) is the name applied to correlate molecular structure to the toxicological data (Winkler, 2001).

So, QSAR (Quantitative Structure Activity Relationships) have been applied for decades in the development of relationships between physicochemical properties of chemical substances and their biological activities to obtain a reliable mathematical and statistical model for prediction of the activities of new chemical entities ( Jhanwar *et al*,2011).

A QSAR generally takes the form:

$$\log (BR) = f(x_1, x_2, \ldots\ldots x_N)$$

where BR is biological response (e.g. $IC_{50}$, $LD_{50}$,$ED_{90}$,….), $f$ is usually an unknown, complex, non-linear function, and $x_1, \ldots..x_N$ are molecular descriptors (Winkler, 2001).

And building of this model involves three stages: data preparation which deals with selection of appropriate data set that is used in study, data analysis which deals with selection of appropriate technique for statistical analysis and correlation studies and model validation which is necessary to find out how predictive a model and the accuracy of the model to predict the activity of bioactive agent. (Veerasamy *et al*, 2011); ( Mahobia *et al*, 2010).

### 1.2.4. Quantitative Structure–Activity Relationships (QSARs)

#### 1.2.4.1. Purpose of QSAR

(QSAR) have helped the scientists in the development of mathematical relationships linking chemical structures and pharmacological activity in quantitative manner of series of compound. QSAR certainly decreases the number of compounds to be synthesized by facilitating the selection of the most promising candidates. This review seeks to provide a view of the different QSAR approaches employed within the current drug discovery process to construct predictive structure–activity relationships and also discusses the limitations that are fundamental to these approaches, as well as those that might be overcome with the improved strategies (Jhanwar *et al*, 2011).

There are many practical purposes of a QSAR and these techniques are utilized widely in many situations which include the following:

• To predict biological activity and physico-chemical properties by rational means.

• To comprehend and rationalize the mechanisms of action within a series of chemicals.

Underlying these aims, the reasons for wishing to develop these models include

• Savings in the cost of product development (e.g. in the pharmaceutical, pesticide, personal products, etc. areas).

• Predictions could reduce the requirement for lengthy and expensive animal tests.

• Reduction (and even, in some cases, replacement) of animal tests, thus reducing animal use and obviously pain and discomfort to animals.

• Other areas of promoting green and greener chemistry to increase efficiency and eliminate waste by not following leads unlikely to be successful (Puzyn *et al*, 2010).

#### 1.2.4.2. Applications of QSAR

Over the last 40 years, the glut in scientific information has resulted in the development of thousands of equations pertaining to structure-activity relationships in biological systems. In its original definition, the Hansch equation was defined to model drug-receptor interactions involving electronic, steric, and hydrophobic contributions. Nonlinear relationships helped refine this approach in cellular systems and organisms where pharmacokinetic constraints had to be considered and

tackled. They have also found increased utility in addressing the complex QSAR of some receptor - ligand interactions. In many cases the Kubinyi bilinear model has provided a sophisticated approach to delineation of steric effects in such interactions (Selassie, 2003).

The ability to predict a biological activity is valuable in any number of industries. Whilst some QSARs appear to be little more than academic studies, there are a large number of applications of these models within industry, academia and governmental (regulatory) agencies. A small number of potential uses are listed below:

• The rational identification of new leads with pharmacological, or pesticides activity.

• The optimization of pharmacological, biotical or pesticides activity.

• The rational design of numerous other products such as surface-active agents, perfumes, dyes, and fine chemicals.

• The identification of hazardous compounds at early stages of product development or the screening of inventories of existing compounds.

• The designing out of toxicity and side-effects in new compounds.

• The prediction of toxicity to humans through deliberate, occasional and occupational exposure.

• The prediction of toxicity to environmental species.

• The selection of compounds with optimal pharmacokinetic properties, whether it be stability or availability in biological systems.

• The prediction of a variety of physico-chemical properties of molecules (whether they be pharmaceuticals, pesticides, personal products, fine chemicals, etc.).

• The prediction of the fate of molecules which are released into the environment.

• The rationalization and prediction of the combined effects of molecules, whether it be in mixtures or formulations.

The key feature of the role of *in silico* technologies (conducted by means of computer modelling or computer simulation) in all of these areas is that predictions can be made from molecular structure alone (Puzyn *et al*, 2010).

### 1.2.4.3. QSAR Descriptors

The QSAR descriptors came to particular demand during last decades when the amounts of chemical information started to grow explosively. Nowadays, scientists routinely work with collections of hundreds of thousands of molecular structures which cannot be efficiently processed without use of diverse sets of QSAR parameters. Modern QSAR science uses a broad range of

atomic and molecular properties varying from merely empirical to quantum-chemical. The most commonly used QSAR arsenals can include up to hundreds and even thousands of descriptors readily computable for extensive molecular datasets. Such varieties of available descriptors in combination with numerous powerful statistical and machine learning techniques allow creating effective and sophisticated structure-bioactivity relationships (Cherkasov, 2005).

Molecular descriptors must then be computed. Any numerical value that describes the molecule could be used. Many descriptors are obtained from molecular mechanics or semiempirical calculations. Energies, population analysis, and vibrational frequency analysis with its associated thermodynamic quantities are often obtained this way table (1.1) (Young, 2001).

**Table (1.3): Common Molecular Descriptors** (Young, 2001).

| Molecular Descriptors | Examples |
|---|---|
| Constitutional Descriptors | Molecular weight, Number of atoms of various elements, Number of bonds of various orders, Number of rings |
| Topological Descriptors | Weiner index, Connectivity index |
| Electrostatic Descriptors | Partial charges, Polarity indices |
| Geometrical Descriptors | Moments of inertia, Molecular volume, Molecular surface areas |
| Quantum Chemical Descriptors | Net atomic charges, Bond orders, HOMO and LUMO energies, Refractivity, Total energy, Ionization potential, Electron affinity, Energy of protonation, Sum of the squared atomic charge densities, Sum of the absolute values of charges, Absolute hardness |
| Statistical Mechanical Descriptors | Vibrational frequencies, Rotational enthalpy and entropy, Vibrational enthalpy and entropy, Translational enthalpy and entropy |

### 1.2.4.4. Historical Development and Theories of QSAR

More than a century ago, Crum-Brown and Fraser expressed the idea that the physiological action of a substance was a function of its chemical composition and constitution. A few decades later, in 1893, Richet showed that the cytotoxicities of a diverse set of simple organic molecules were inversely related to their corresponding water solubilities. At the turn of the $20^{th}$ century, Meyer and Overton independently suggested that the narcotic (depressant) action of a group of organic compounds paralleled their olive oil/water partition coefficients. In 1939 Ferguson introduced a thermodynamic generalization to the correlation of depressant action with the relative saturation of

volatile compounds in the vehicle in which they were administered. The extensive work of Albert, and Bell and Roblin established the importance of ionization of bases and weak acids in bacteriostatic activity (Pattan *et al*, 2011).

Meanwhile on the physical organic front, great strides were being made in the delineation of substituent effects on organic reactions, led by the seminal work of Hammett, which gave rise to the "sigma-rho" culture. Taft devised a way for separating polar, steric, and resonance effects and introducing the first steric parameter, $E_S$ (Abraham, 2011). The contributions of Hammett and Taft together laid the mechanistic basis for the development of the QSAR paradigm by Hansch and Fujita. In 1962 Hansch and Muir published their brilliant study on the structure-activity relationships of plant growth regulators and their dependency on Hammett constants and hydrophobicity . Using the octanol/water system, a whole series of partition coefficients were measured, and thus a new hydrophobic scale was introduced .The parameter p, which is the relative hydrophobicity of a substituent, was defined in a manner analogous to the definition of sigma.

$$\pi_X = \log P_X - \log P_H$$

$P_X$ and $P_H$ represent the partition coefficients of a derivative and the parent molecule, respectively. Fujita and Hansch then combined these hydrophobic constants with Hammett's electronic constants to yield the linear Hansch equation and its many extended forms.

$$\text{Log } 1/C = a\sigma + b\pi + c\kappa$$

Hundreds of equations later, the failure of linear equations in cases with extended hydrophobicity ranges led to the development of the Hansch parabolic equation:

$$\text{Log } 1/C = a \log P - 2\, b(\log P)^2 + c\sigma + \kappa$$

The delineation of these models led to explosive development in QSAR analysis and related approaches. The Kubinyi bilinear model is a refinement of the parabolic model and, in many cases; it has proved to be superior

$$\text{Log } 1/C = a \log P - b \log (\beta P + 1) + \kappa$$

Besides the Hansch approach, other methodologies were also developed to tackle structure- activity questions (Selassie, 2003). Also in 1964, Free and Wilson derived a mathematical model that describes the presence and absence of certain structural features i.e. those groups that are chemical

modified, by values of 1 and 0 and correlates the resulting structural matrix with biological activity values

$$Log1/C = \Sigma a_i X_i + \mu$$

Logarithms of inverse molar concentration C that produce a certain biological effect, the values of ai are the biological activity groups contributing of the substituents X1, X2,……Xi in the different positions p of the first compound, the presence or absence of these substituents is coded by the values 1 and 0 respectively, and μ is the biological activity values of the reference compound.

The close theoretical relationship between Free-Wilson analysis and linear Hansch analysis can be used in one model, the so-called 'mixed approach' which combines the advantage of Hansch and Free Wilson analysis and widens the applicability of both methods (Sethi, 2012).

$$\log 1/C = a (\log P)^2 + b \log P + c\sigma + \ldots + \Sigma a_i + k$$

**1.2.4.5. General Scheme of a QSAR Study**

The chemoinformatics methods used in building QSAR models can be divided into three groups i.e. extracting descriptors from molecular structure, choosing those informative in the context of analyzed activity and finally using the values of the descriptors as independent variables to define a mapping that correlates them with the activity in question. (Sethi, 2012)

**1.2.3.6. Advantages and Disadvantages of QSAR**

The advantage of using QSAR over other modeling techniques is that it takes into account the full complexity of the biological system without requiring any information about the binding site. The disadvantage is that the method will not distinguish between the contribution of binding and transport properties in determining drug activity. QSAR is very useful for determining general criteria for activity, but it does not readily yield detailed structural predictions (Young, 2001).

**1.2.4.7. Assessing Applicability Domains of Toxicological QSARs**

For QSARs to be truly successful as predictive tools, their applicability domain must be known and understood. The applicability domain of a QSAR model is considered to be the response and chemical structure space in which the model makes predictions with a given reliability. Without directly stating so, this definition implies some form of classification by the mechanism of toxic action in addition to physicochemical and structural properties.

The use of an applicability domain assists in the greater comprehension and utilization of a QSAR. This will ultimately assist in the development of better predictive models as the selection of the training set will determine the structural and descriptor applicability domains of the QSAR. For instance, QSARs for which the training set is based on a congeneric series (e.g., methyl, ethyl, butyl, etc.) of a single parent compound often have excellent predictivity. However, since the chemical space of the training set is very narrow, it has a very limited applicability domain and thus is of limited practical use. In contrast, a QSAR where the training set is selected on a strategy based on structural (and possibly mechanistic) diversity may be more robust with an applicability domain extended in terms of its biological response and structural space. .

There are a number of issues relating to the use of QSARs to make predictions for regulatory purposes. These include their validation and the development of suitable tools to determine applicability domains. As with any assay being used to predict a toxicological (or fate) endpoint, a QSAR model must undergo an evaluation and characterization process that could ultimately lead to validation. The validation of a QSAR (or other computer model) can be defined as the process by which the reliability and relevance of the model are established for a particular purpose. While the reliability of a computer model (i.e., the reproducibility of its results) should not be an issue, the relevance of a proposed model (i.e., its ability to predict the biological effect of interest correctly) needs to be established, and evaluated according to stated criteria. The nature of these criteria for QSAR evaluation and validation has been under considerable debate and indicates the complexity of these processes. Despite the debate, there is likely to be a strong emphasis toward some form of external validation with predictions being made for compounds within the structural and descriptor spaces of, but excluded from, the set of training chemicals (Schultza *et al*., 2006).

#### 1.2.4.8. QSAR Data Analysis Approaches

There are two major approaches to analyze QSAR data:

i) The properties (or activity) of a series of compounds is expressed as a multiple linear regression (MLR) of descriptors.

ii) The non-linear regression method represents the properties (or activity) with artificial neural network (ANN). (Cho *et al*,2001)

### 1.2.5. Molecular Modeling

Molecular modeling is an investigation of molecular structures and properties using computational chemistry and graphical visualization technique to provide a three dimensional representation of the molecule under a given set of circumstances. (Santos *et al*, 2014)

### Aims and Objectives

Computational chemistry is a branch of science that produces information which supplements experimental data on the structures, properties and reactivety of substances. Utilizing computational chemistry programming it is possible to play out these calculations. In same manner, and with the extensive variety of biological activities in quinone nucleus of compounds, the main objectives of this work are to:

- ✓ Evaluation of the impact of quinones containing alkyl, amino, alkylamio groups upon biological activities and extent of napthoquinones based upon QSAR technique.
- ✓ Modeling the biological activity of some selected naphthoquinones.
- ✓ Highlight further experiences in chemical – biological interactions in drug research and in addition in the regions of toxicology.
- ✓ Enrich the potential utilization of QSAR models for screening of chemical information bases or virtual libraries before their synthesis.
- ✓ Selection of the most critical determinant of activity of quinones.
- ✓ Continuation of therapeutic advances in the group of quinone containing moieties.
- ✓ Design of models to limit the synthetic challenges keeping in mind the end goal to yield particular successful quinones.
- ✓ Synthesis of series of alkylamino 1,4-naphthoquinone derivatives using Mannich reaction a three component coupling of amines with an aromatic aldehyde and lawsone.
- ✓ Analyse these compounds, which expected to have important biological effects, such as antimicrobial, antimalarial and molluscicidal activities, using some spectral analysis (IR, UV, $^{1}$HNMR)
- ✓ Calculate of the physicochemical properties of these synthesized compounds and compare them with that used in QSAR modeling.

# 2. Material and Methods

## 2.1. QSAR Analysis

### 2.1.1. Collection of Dataset

The biological activities of three groups of naphthoquinone derivatives were collected from literatures (Chung *et al.*, 2004; Chung *et al.*, 2007; Silva *et al.*, 2013; Benites *et al*, 2010) and these groups classified as alkylaminonaphthoquinones, alkylnaphthoquinones, and aminonaphtho-quinones. The biological activities in these literatures express as $ED_{50}$, $IC_{50}$ and $EC_{50}$where $EC_{50}$: Clinical efficacy of a drug, reported as the drug concentration required to produce 50% of the maximum effect (may be inhibitory or stimulatory effect), $IC_{50}$: Concentration required to produce 50% inhibition (Figure 4). The amount of inhibitor required depends on various factors, such as substrate concentration, target accessibility, cell permeability, duration of incubation, type of cells used, etc. and $ED_{50}$ refers to the median effective dose (as opposed to concentration) at which 50% of individuals exhibit the specified quantal effect. It is a measure of reasonable expectance of a drug effect, but not necessarily equal to the prescribed dose (Mohan *et al*, 2013).

### 2.1.2. Software:

- ACD/ChemSketch Freeware version 12.01 is a drawing package that allows you to draw chemical structures including organics, organometallics, and polymers structures. It also includes features such as calculation of molecular properties (e.g., molecular weight, density, molar refractivity etc.), 2D and 3D structure cleaning and viewing, functionality for naming structures (fewer than 50 atoms and 3 rings), and prediction of logP. The freeware version of ChemSketch does not include all of the functionality of the commercial version such as ACD/Dictinory and search of files on personal computer by structures. This computer program in version 12 was used to sketch all the chemical structures in this research. Advanced Chemistry Development, Inc., (ACD/Labs) was established in 1994 in Toronto, Canada.
- IBM SPSS Statistics version 20 is a software package used for statistical analysis. The software name originally stood for Statistical Package for the Social Sciences (SPSS). The software was released in its first version in 1968 as the Statistical Package for the Social Sciences (SPSS) then it was acquired by IBM in 2009.This program can be used to perform data entry and analysis and to create tables and graphs. SPSS is capable of handling large

amounts of data and can perform all types of the analysis. SPSS can take data from any type of file and use them to generate tabulated reports, charts and plots of distributions and trends, descriptive statistics, and complex statistical analysis.

### 2.1.3. Calculation of Molecular Descriptors

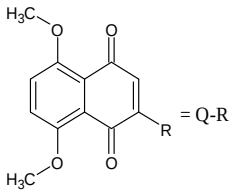
The structures of all alkylaminonaphthoquinone, alkylnaphthoquinone, and aminonaphthoquinone derivatives were sketched and all available molecular descriptors of these structures were calculated using ACD/ChemSketch program as shown tables (2.1), (2.2) and (2.3) respectively. The octanol/water partition coefficient (logP), molar volume (MV), refraction index (RI), molar refractivity (MR), the formula weight (FW), the density (D) and surface tension (ST) are the seven descriptors used in this study.

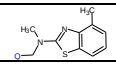
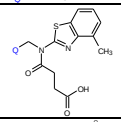
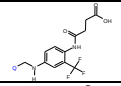
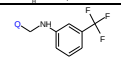
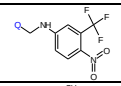
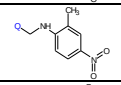
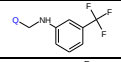
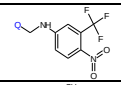
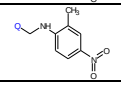
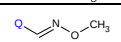
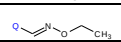
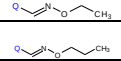
### 2.1.4. Calculation of Correlation Matrixes and QSAR Models

The correlation between activity of naphthoquinones and each descriptor were calculated in correlation matrix for the three groups of naphthoquinones table (2.4), (2.5) and (2.6).

About 50 regressions were employed for each cancer cell line for the three groups of naphthoquinone derivatives using multiple linear regression method and the correlation coefficient $r^2$, F-test, standard deviation s, significant and Durbin-Watson test were calculated for each regression using SPSS program.

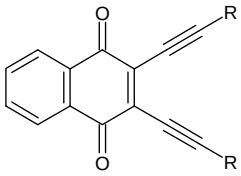
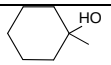
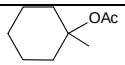
Table (2.1): Structures, Biological Activities (Chung *et al.*, 2004; Chung *et al.*, 2007) and Physicochemical Parameters of 5,8-Dimethoxy-1,4-naphthoquinone Derivatives for Two Cancer Cell Lines L1210 and P388.




| No. | R- | $(ED_{50})_{obsv}$ (µgmL$^{-1}$) | | Partition Coefficient (Log P) | Molar Refractivity (MR)/ cm$^3$ | Formula Weight (FW) | Molar Volume (MV) / cm$^3$ | Index of Refraction (RI) | Surface Tension(ST) /dyne cm$^{-1}$ | Density (D)/gcm$^{-3}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $C_1$ | $C_2$ | | | | | | | |
| | | L1220 | P388 | | | | | | | |
| **1** |  | 1.21 | 0.56 | 4.67 | 113.97 | 408.4702 | 305.0 | 1.670 | 59.6 | 1.338 |
| **2** |  | 4.76 | 4.19 | 4.09 | 129.47 | 494.51638 | 346.3 | 1.670 | 68.2 | 1.427 |
| **3** |  | 8.92 | 0.36 | 2.17 | 120.21 | 506.4279496 | 347.6 | 1.607 | 58.6 | 1.456 |
| **4*** |  | 0.45 | 0.60 | 3.00 | 94.22 | 393.3564296 | 290.9 | 1.560 | 45.1 | 1.35 |
| **5*** |  | 0.61 | 0.21 | 3.50 | 100.25 | 438.3539896 | 301.9 | 1.578 | 52.1 | 1.45 |
| **6*** |  | 0.16 | 0.91 | 2.55 | 99.88 | 384.3826 | 286.8 | 1.613 | 56.8 | 1.34 |
| **7** |  | .18 | 0.67 | 4.59 | 95.11 | 391.3405496 | 286.9 | 1.577 | 46.2 | 1.363 |
| **8** |  | 0.19 | 0.13 | 5.09 | 101.65 | 436.3381096 | 298.8 | 1.595 | 52.7 | 1.46 |
| **9** |  | 0.05 | 2.24 | 4.14 | 101.50 | 382.36672 | 281.5 | 1.640 | 59.3 | 1.357 |
| **10** |  | 4.97 | 2.29 | 2.39 | 70.33 | 275.25672 | 217.1 | 1.561 | 41.5 | 1.26 |
| **11** |  | 5.10 | 2.76 | 2.92 | 74.94 | 289.2833 | 233.2 | 1.555 | 40.9 | 1.24 |
| **12** |  | 5.28 | 0.56 | 3.46 | 79.55 | 303.30988 | 249.3 | 1.551 | 40.4 | 1.21 |

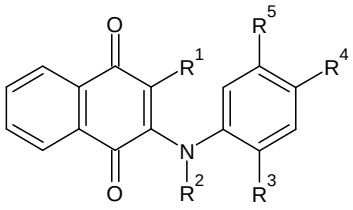
* R in C7 position of naphthoquinone ring and C is the concentration of compound.

Table (2.2): Structures, Biological Activities (Silva *et al.*, 2013) and Physicochemical Parameters of 2,3-Diyn
Derivatives for Three Cancer Cell Lines NCI-H358M, OVCAR-8 and PC-3M.

| | No. | R- | $IC_{50}$ / μM | | | Partition Coefficient (Log P) | Molar Refractivity(MR) / $cm^3$ | Formula Weight (FW) | Molar Volume(MV) / $cm^3$ | Index of Refraction |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $C_3$ | $C_4$ | $C_5$ | | | | | |
| | | | NCI-H358M | OVCAR-8 | PC-3M | | | | | |
|  | 13 | Ph- | 6.55 | 4.49 | 14.26 | 7.48 | 106.88 | 358.38816 | 274.4 | 1.7 |
| | 14 | 4-OMePh- | 4.57 | 3.90 | 9.03 | 7.31 | 119.61 | 418.44012 | 317.7 | 1.6 |
| | 15 | $-C(CH_3)_2OH$ | 2.98 | 2.28 | 4.28 | 4.12 | 88.32 | 322.35452 | 249.1 | 1.6 |
| | 16 | $-C(CH_3)_2OAc$ | 4.95 | 5.63 | 5.74 | 5.91 | 107.49 | 406.42788 | 324.9 | 1.5 |
| | 17 |  | 5.07 | 5.98 | 6.56 | 5.79 | 112.03 | 402.48224 | 308.5 | 1.6 |
| | 18 |  | 2.74 | 3.09 | 5.26 | 7.59 | 131.20 | 486.5556 | 384.0 | 1.5 |
| | 19 | $-(CH_2)_3CH_3$ | 6.23 | 6.56 | 8.94 | 7.16 | 94.50 | 318.40888 | 286.0 | 1.5 |
| | 20 | $-(CH_2)_3OAc$ | 5.48 | 7.40 | 6.92 | 4.94 | 107.48 | 406.42788 | 324.1 | 1.5 |
| | 21 | $-(CH_2)_2 CH_3$ | 8.03 | 9.01 | 9.17 | 6.10 | 85.24 | 290.35572 | 253.6 | 1.5 |
| | 22 | $-(CH_2)_5 CH_3$ | 6.42 | 9.70 | 20.23 | 9.29 | 113.02 | 374.5152 | 350.7 | 1.5 |
| | 23 | $-(CH_2)_7 CH_3$ | 3.99 | 7.53 | 17.70 | 11.41 | 131.55 | 430.62152 | 415.2 | 1.5 |

C is the concentration of compound.

Table (2.3): Structures, Biological Activities (2013; Benites *et al*, 2010) and Physicochemical Par
Phenylaminonaphtoquinone Derivatives for Three Cancer Cell Lines DU145 Cancerous, MCF7 Cancerous




| No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $EC_{50}$ / $\mu gmL^{-1}$ | | | **Partition Coefficient (Log P)** | **Molar Refractivity(MR) / $cm^3$** | **Formula Weight (FW)** | **Molar Volume(MV) / $cm^3$** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | $C_6$ | $C_7$ | $C_8$ | | | | |
| | | | | | | DU145 | MCF7 Cancerous | T24 Cancerous | | | | |
| 24 | H | H | H | H | H | 4 | 2.6 | 1.2 | 2.89 | 72.12 | 249.26404 | 185.4 |
| 25 | Cl | H | H | H | H | 66.8 | 6.3 | 14.8 | 3.08 | 76.10 | 283.7091 | 202.9 |
| 26 | H | H | Me | H | H | 7.7 | 0.8 | 7.7 | 3.35 | 76.95 | 263.29062 | 201.7 |
| 27 | Cl | H | Me | H | H | 25.8 | 4.9 | 9.3 | 3.54 | 80.72 | 297.73568 | 218.6 |
| 28 | H | H | H | OH | H | 0.9 | 0.8 | 2.3 | 2.15 | 74.00 | 265.26344 | 183.9 |
| 29 | Cl | H | H | OH | H | 1.9 | 2.8 | 0.6 | 2.34 | 77.63 | 299.7085 | 199.8 |
| 30 | H | H | H | OMe | H | 7.6 | 3.7 | 8.1 | 2.84 | 78.80 | 279.29002 | 209.4 |
| 31 | H | H | OMe | H | OMe | 35.2 | 1.2 | 10.9 | 3.10 | 85.48 | 309.316 | 233.4 |
| 32 | Cl | H | OMe | H | OMe | 6 | 4.6 | 2.4 | 3.29 | 88.83 | 343.76106 | 246.6 |
| 33 | H | Me | H | H | H | 20.9 | 7.8 | 8.4 | 3.03 | 76.83 | 263.29062 | 204.0 |
| 34 | Cl | Me | H | H | H | 6.7 | 1.2 | 6 | 3.22 | 80.96 | 297.73568 | 217.9 |

C is the concentration of compound.

Table (2.4): Correlation Matrix of the Physicochemical Parameters Used and the Activity of 5,8-Dimethoxy-1,4-naphthoquinone Derivatives.

| | $pC_1$ | $pC_2$ | logP | MR | FW | MV | RI | ST | D |
|---|---|---|---|---|---|---|---|---|---|
| $pC_1$ | 1.000 | | | | | | | | |
| $pC_2$ | 0.851 | 1.000 | | | | | | | |
| logP | 0.470 | 0.382 | 1.000 | | | | | | |
| MR | 0.072 | -0.162 | 0.305 | 1.000 | | | | | |
| FW | 0.099 | -0.233 | 0.242 | 0.938 | 1.000 | | | | |
| MV | 0.061 | -0.230 | 0.236 | 0.967 | 0.970 | 1.000 | | | |
| RI | 0.161 | 0.104 | 0.409 | 0.820 | 0.359 | 0.985 | 1.000 | | |
| ST | 0.170 | 0.007 | 0.279 | 0.927 | 0.359 | 0.600 | 0.931 | 1.000 | |
| D | 0.280 | -0.070 | 0.288 | 0.774 | 0.641 | 0.841 | 0.445 | 0.675 | 1.000 |

pC= -logC

Table (2.5): Correlation Matrix of the Physicochemical Parameters Used and the Activity of 2,3-Diyne-1,4-naphthoquinone Derivatives.

| | $pC_3$ | $pC_4$ | $pC_5$ | logP | MR | FW | MV | RI | ST | D |
|---|---|---|---|---|---|---|---|---|---|---|
| $pC_3$ | 1.000 | | | | | | | | | |
| $pC_4$ | 0.762 | 1.000 | | | | | | | | |
| $pC_5$ | 0.516 | 0.629 | 1.000 | | | | | | | |
| logP | -0.036 | -0.382 | -0.810 | 1.000 | | | | | | |
| MR | 0.448 | 0.043 | -0.269 | 0.653 | 1.000 | | | | | |
| FW | 0.576 | 0.197 | 0.071 | 0.344 | 0.927 | 1.000 | | | | |
| MV | 0.389 | -0.189 | -0.326 | 0.725 | 0.912 | 0.828 | 1.000 | | | |
| RI | 0.015 | 0.545 | 0.141 | -0.300 | -0.058 | -0.039 | -0.459 | 1.000 | | |
| ST | 0.255 | 0.665 | 0.475 | -0.543 | -0.039 | 0.112 | -0.410 | 0.900 | 1.000 | |
| D | 0.301 | 0.690 | 0.661 | -0.686 | -0.067 | 0.183 | -0.394 | 0.774 | 0.935 | 1.000 |

pC= -logC

Table (2.6): Correlation Matrix of the Physicochemical Parameters Used and the Activity of Phenylaminonaphtoquinone Derivatives.

| | $pC_6$ | $pC_7$ | $pC_8$ | logP | MR | FW | MV | RI | ST | D |
|---|---|---|---|---|---|---|---|---|---|---|
| $pC_6$ | 1.000 | | | | | | | | | |
| $pC_7$ | 0.476 | 1.000 | | | | | | | | |
| $pC_8$ | 0.812 | 0.137 | 1.000 | | | | | | | |
| logP | -0.699 | -0.244 | -0.390 | 1.000 | | | | | | |
| MR | -0.289 | -0.083 | -0.295 | 0.475 | 1.000 | | | | | |
| FW | -0.159 | -0.164 | -0.231 | 0.290 | 0.923 | 1.000 | | | | |
| MV | -0.420 | -0.184 | -0.370 | 0.588 | 0.986 | 0.896 | 1.000 | | | |
| RI | 0.691 | 0.399 | 0.512 | -0.785 | -0.839 | -0.728 | 0.918 | 1.000 | | |
| ST | 0.814 | 0.419 | 0.544 | -0.899 | -0.610 | -0.448 | -0.729 | 0.933 | 1.000 | |
| D | 0.554 | 0.070 | 0.291 | -0.643 | -0.048 | 0.305 | -0.148 | 0.366 | 0.594 | 1.000 |

pC= -logC

Table (2.7): The QSAR Models between Descriptors and Biological Activity of 5,8-Dimethoxy-1,4-naphthoquinone Derivatives for L1210 Cancer Cell Line.

| No. | Removed Parameters | QSAR Equation | $r^2$ | F | sd | sig. | DW |
|---|---|---|---|---|---|---|---|
| **1A** | logP,MR,FW | $pC_1$=-161.197-0.0172MV+10.427RI+-0.0252ST+8.720D | 0.260 | 0.616 | 0.82472 | 0.665 | 1.9464 |
| **2A** | logP,MR,MV | $pC_1$=-18.527-0.0158FW+7.763RI+-0.00292ST+13.653D | 0.337 | 0.890 | 0.78079 | 0.517 | 2.054 |
| **3A** | logP,MR,RI | $pC_1$=-78.343+-0.214FW+0.275MV+0.01446ST+65.361D | 0.878 | 12.664 | 0.33437 | 0.003 | 1.662 |
| **4A** | logP,MR,ST | $pC_1$=-80.139+-0.216FW+0.279MV+0.746RI+65.918D | 0.870 | 11.734 | 0.34547 | 0.003 | 1.793 |
| **5A** | logP,MR,D | $pC_1$=1.607+0.017231FW+-0.0354MV+4.638RI+0.00825ST | 0.112 | 0.220 | 0.90382 | 0.919 | 1.496 |
| **6A** | logP,FW,MV | $pC_1$=-27.073-0.0591MR+17.090RI+-0.0109ST+8.987D | 0.313 | 0.798 | 0.79470 | 0.563 | 2.030 |
| **7A** | logP,FW,RI | $pC_1$=-0.560-0.0549MR+-0.000531MV+0.0782ST+5.971D | 0.249 | 0.579 | 0.83121 | 0.688 | 1.963 |
| **8A** | logP,FW,ST | $pC_1$=-218.660-0.987MR+0.323MV+140.240RI+3.701D | 0.756 | 5.416 | 0.47390 | 0.026 | 2.786 |
| **9A** | logP,FW,D | $pC_1$=-222.543-1.090MR+0.359MV+143.421RI+0.0670ST | 0.747 | 5.161 | 0.48256 | 0.030 | 2.495 |
| **10A** | logP,MV,RI | $pC_1$=-13.920+0.0860MR+-0.0368FW+-0.0287ST+20.224D | 0.362 | 0.992 | 0.76616 | 0.471 | 2.022 |
| **11A** | logP,MV,ST | $pC_1$=71.939+0.683MR+-0.186FW+-90.193RI+61.987D | 0.682 | 1.524 | 0.70107 | 0.293 | 2.158 |
| **12A** | logP,MV,D | $pC_1$=-38.018-0.166MR+0.0278FW+31.101RI+-0.00524ST | 0.261 | 0.619 | 0.82422 | 0.663 | 1.913 |
| **13A** | logP.RI,ST | $pC_1$=-79.461+0.00374MR+-0.217FW+0.280MV+66.252D | 0.870 | 11.689 | 0.34605 | 0.003 | 1.806 |
| **14A** | logP.RI,D | $pC_1$=3.309-0.124MR+0.00410FW+0.0226MV+0.132ST | 0.167 | 0.351 | 0.87526 | 0.836 | 1.526 |
| **15A** | logP.ST,D | $pC_1$=-228.104-1.051MR+0.00966FW+0.333MV+148.977RI | 0.738 | 4.937 | 0.49057 | 0.033 | 2.691 |
| **16A** | FW,MV,RI | $pC_1$=-0.713+0.366logP+-0.0602MR+0.0788ST+5.377D | 0.442 | 1.385 | 0.71651 | 0.331 | 2.136 |
| **17A** | FW,MV,ST | $pC_1$=-17.282+0.269logP+-0.0500MR+10.930RI+7.244D | 0.400 | 1.168 | 0.74267 | 0.401 | 2.114 |
| **18A** | FW,MV,D | $pC_1$=32.758+0.558logP+-0.0518MR+-20.739RI+0.184ST | 0.426 | 1.298 | 0.72667 | 0.357 | 1.892 |

| | | | | | |
|---|---|---|---|---|---|
| **19A** | FW,RI,ST | $pC_1$=0.145+0.322logP+0.00568MR+-0.0142MV+6.085D | 0.345 | 0.924 | |
| **20A** | FW,RI,D | $pC_1$=-1.724+0.581logP+-0.262MR+0.0690MV+0.224ST | 0.575 | 2.371 | |
| **21A** | FW,ST,D | $pC_1$=-214.632+0.197logP+-1.002MR+0.336MV+139.025RI | 0.763 | 5.620 | |
| **22A** | MR,FW,MV | $pC_1$=19.291+0.440logP+-10.863RI+0.0496ST+-0.0271D | 0.262 | 0.621 | |
| **23A** | MR,FW,RI | $pC_1$=0.0419+0.309logP+-0.0164MV+0.0256ST+6.125D | 0.373 | 1.041 | |
| **24A** | MR,FW,ST | $pC_1$=-4.769+0.288logP+-0.0146MV+3.157RI+6.594D | 0.359 | 0.979 | |
| **25A** | MR,FW,D | $pC_1$=40.666+0.550logP+-0.0149MV+-25.569RI+0.165ST | 0.379 | 1.067 | |
| **26A** | MR,MV,RI | $pC_1$=-5.881+0.280logP+-0.015FW+0.032ST+11.079D | 0.434 | 1.342 | |
| **27A** | MR,MV,ST | $pC_1$=-11.726+0.253logP+-0.013FW+4.195RI+11.304D | 0.414 | 1.234 | |
| **28A** | MR,MV,D | $pC_1$=48.816+0.608logP+-0.00911FW+-32.364RI+0.200ST | 0.381 | 1.076 | |
| **29A** | MR,RI,ST | $pC_1$=-80.027-0.00287logP+-0.2184FW+0.284MV+66.570D | 0.869 | 11.646 | |
| **30A** | MR,RI,D | $pC_1$=6.834+0.351logP+0.0128FW+-0.0290MV+0.0244ST | 0.288 | 0.709 | |
| **31A** | MR,ST,D | $pC_1$=4.257+0.348logP+0.0133FW+-0.0268MV+1.872RI | 0.267 | 0.639 | |
| **32A** | MV,RI,ST | $pC_1$=-80.027-0.00287logP+0.284MR+-0.218FW+66.570D | 0.436 | 11.646 | |
| **33A** | MV,RI,D | $pC_1$=4.189+0.442logP+-0.110MR+0.0129FW+0.116ST | 0.288 | 1.350 | |
| **34A** | MV,ST,D | $pC_1$=-26.707+0.298logP+-0.136MR+0.0227FW+22.629RI | 0.373 | 1.040 | |
| **35A** | RI,ST,D | $pC_1$=6.349+0.381logP+-0.00579MR+0.0111FW-0.0190MV | 0.263 | 0.626 | |
| **36A** | MR,RI,ST,D | $pC_1$= 6.612+0.372logP+0.0118FW+-0.0228MV | 0.263 | 0.949 | |
| **37A** | MR,MV,ST,D | $pC_1$=5.813+0.383logP+6.902x$10^{-5}$FW+-0.736RI | 0.222 | 0.761 | |
| **38A** | MR,MV,RI,D | $pC_1$=4.616+0.364logP+-0.00131 FW+0.0121ST | 0.228 | 0.788 | |
| **39A** | MR,MV,RI,ST | $pC_1$= -4.075+0.316logP+-0.100FW+9.536D | 0.388 | 1.691 | |
| **40A** | MR,MV,FW,ST | $pC_1$=5.604+0.363 logP+-2.065RI+1.795D | 0.253 | 0.904 | |

| | | | | |
|---|---|---|---|---|
| **41A** | RI,ST,D,FW,MV | $pC_1$=4.973+0.390logP+-0.00338MR | 0.226 | 1.317 |
| **42A** | RI,ST,D,MV,MR | $pC_1$= 4.758+0.374logP+-0.000157FW | 0.221 | 1.277 |
| **43A** | RI,ST,D,FW,MR | $pC_1$= 4.964+0.381logP+-0.00102MV | 0.223 | 1.295 |
| **44A** | MV,ST,D,FW,MR | $pC_1$= 5.725+0.383logP+-0.664RI | 0.222 | 1.284 |
| **45A** | MV,RI,D,FW,MR | $pC_1$= 4.554-0.362logP+0.00359ST | 0.222 | 1.287 |
| **46A** | MV,RI,ST,FW,MR | $pC_1$= 2.907+0.335logP+1.423D | 0.244 | 1.450 |
| **47A** | logP,RI,ST,D ,MR | $pC_1$=7.528+0.0134FW+-0.0235MV | 0.054 | 0.257 |
| **48A** | logP,MV,ST,D ,MR | $pC_1$=1.467+4.109x$10^{-5}$FW+2.841RI | 0.026 | 0.120 |
| **49A** | logP,MV,RI,D ,MR | $pC_1$=5.329-0.00106FW+0.0214ST | 0.033 | 0.152 |
| **50A** | logP,MV,RI,ST,MR | $pC_1$=-4.790-0.0107FW+11.072D | 0.242 | 1.436 |
| **51A** | logP,MV,FW,ST,MR | $pC_1$= 1.550+0.816RI+2.341D | 0.080 | 0.392 |
| **52A** | MR,RI,ST,logP | $pC_1$=-79.861-0.2184FW+0.283MV+66.438D | 0.869 | 17.745 |
| **53A** | FW,ST,D,logP | $pC_1$=-235.038+-1.085MR+0.363MV+152.373RI | 0.715 | 6.693 |
| **54A** | MV,RI,ST,FW,MR,D | $pC_1$=6.714-0.0868ClogP | 0.856 | 59.557 |

Table (2.8): The QSAR Models between Descriptors and Biological Activity of 5,8-Dimethoxy-1,4-naphthoquin
Cancer Cell Line.

| No. | Removed Parameters | QSAR Equation | $r^2$ | F |
|---|---|---|---|---|
| **1B** | logP,MR,FW | $pC_2$=-13.287-0.0179MV+11.436RI+-0.0191ST+5.221D | 0.269 | 0.644 |
| **2B** | logP,MR,MV | $pC_2$=-15.759-0.0159FW+8.885RI+-0.00162ST+10.084D | 0.359 | 0.981 |
| **3B** | logP,MR,RI | $pC_2$=-66.710+-0.194FW+0.247MV+0.0284ST+56.371D | 0.918 | 19.720 |
| **4B** | logP,MR,ST | $pC_2$=-70.931+-0.192FW+0.246MV+3.340RI+56.156D | 0.896 | 15.037 |
| **5B** | logP,MR,D | $pC_2$=0.0991+0.006061FW-0.0217MV+5.613RI+0.0138ST | 0.182 | 0.391 |
| **6B** | logP,FW,MV | $pC_2$=-24.301-0.0590MR+18.256RI+-0.007157ST+5.350D | 0.323 | 0.836 |
| **7B** | logP,FW,RI | $pC_2$=4.047-0.0206MR+-0.0125MV+0.0632ST+3.135D | 0.235 | 0.536 |
| **8B** | logP,FW,ST | $pC_2$=-172.485-0.775MR+0.249MV+113.512RI+1.295D | 0.666 | 3.486 |
| **9B** | logP,FW,D | $pC_2$=-171.279-0.812MR+0.261MV+122.787RI+0.0372ST | 0.672 | 3.585 |
| **10B** | logP,MV,RI | $pC_2$=-10.547+0.0992MR+-0.0401FW+-0.0285ST+17.670D | 0.402 | 1.177 |
| **11B** | logP,MV,ST | $pC_2$=87.889+0.791MR+-0.213FW+-103.766RI+66.093D | 0.583 | 2.443 |
| **12B** | logP,MV,D | $pC_2$=-27.389-0.113MR+0.01468FW+24.136RI-0.00249ST | 0.281 | 0.685 |
| **13B** | logP.RI,ST | $pC_2$=-67.111+0.0241MR+-0.195FW+0.243MV+57.285D | 0.896 | 15.117 |
| **14B** | logP.RI,D | $pC_2$=4.611-0.0819MR+0.004061FW+0.0185MV+0.110ST | 0.208 | 0.460 |
| **15B** | logP.ST,D | $pC_2$=-177.585-0.806MR+0.000878FW+0.261MV+117.448RI | 0.660 | 3.390 |
| **16B** | FW,MV,RI | $pC_2$=-3.884+0.325logP+-0.0594MR+0.0888ST+1.592D | 0.446 | 1.297 |
| **17B** | FW,MV,ST | $pC_2$=-17.135+0.203logP+-0.0520MR+13.754RI+4.057D | 0.388 | 1.108 |
| **18B** | FW,MV,D | $pC_2$=13.200+0.379logP+-0.0566MR+-5.703RI+0.117ST | 0.422 | 1.278 |

| | | | | |
|---|---|---|---|---|
| **19B** | FW,RI,ST | $pC_2$=4.609+0.250logP+0.0291MR+-0.0239MV+3.284D | 0.308 | 0.780 |
| **20B** | FW,RI,D | $pC_2$=2.656+0.416logP+-0.152MR+0.0305MV+0.155ST | 0.479 | 1.608 |
| **21B** | FW,ST,D | $pC_2$=-164.574+0.132log*P*-0.245MR+0.245MV+108.833RI | 0.687 | 3.838 |
| **22B** | MR,FW,MV | $pC_2$=12.468+0.334logP+-3.492RI+0.0211ST+-2.380D | 0.184 | 0.395 |
| **23B** | MR,FW,RI | $pC_2$=4.442+0.266logP+-0.0175MV+0.0389ST+2.641D | 0.364 | 1.001 |
| **24B** | MR,FW,ST | $pC_2$=-4.621+0.220logP+-0.0159MV+5.923RI+3.605D | 0.343 | 0.914 |
| **25B** | MR,FW,D | $pC_2$=23.177+0.377logP+-0.0172MV+-11.900RI+0.104ST | 0.371 | 1.030 |
| **26B** | MR,MV,RI | $pC_2$=-1.632+0.237logP+-0.0152FW+0.045ST+7.667D | 0.440 | 1.374 |
| **27B** | MR,MV,ST | $pC_2$=-11.602+0.185logP+-0.0139FW+6.844RI+8.404D | 0.412 | 1.228 |
| **28B** | MR,MV,D | $pC_2$=34.260+0.453logP+-0.0111FW+-20.962RI+0.152ST | 0.395 | 1.142 |
| **29B** | MR,RI,ST | $pC_2$=-70.344-0.0114logP+-0.2044FW+0.266MV+59.004D | 0.873 | 12.080 |
| **30B** | MR,RI,D | $pC_2$=6.789+0.288logP+0.0137FW+-0.0151MV+0.0373ST | 0.333 | 0.874 |
| **31B** | MR,ST,D | $pC_2$=0.525+0.261logP+0.00378FW+-0.0157MV+4.709RI | 0.295 | 0.733 |
| **32B** | MV,RI,ST | $pC_2$=-6.153-0.162logP+0.0544MR+-0.0281FW+12.694D | 0.434 | 1.344 |
| **33B** | MV,RI,D | $pC_2$=5.362+0.345logP+-0.0694MR+0.00304FW+0.0965ST | 0.419 | 1.264 |
| **34B** | MV,ST,D | $pC_2$=-20.431+0.225log*P*-0.0914MR+0.01127FW+18.891RI | 0.363 | 0.999 |
| **35B** | RI,ST,D | $pC_2$=7.299+0.291logP+-0.0188MR+0.00214FW-0.0177MV | 0.267 | 0.639 |
| **36B** | MR,RI,ST,D | $pC_2$= 6.448+0.321logP+0.000107FW+-0.00558MV | 0.255 | 0.912 |
| **37B** | MR,MV,ST,D | $pC_2$= 1.438+0.282logP+-0.00402FW+3.178RI | 0.275 | 1.011 |
| **38B** | MR,MV,RI,D | $pC_2$=5.632+0.295logP+ -0.00591FW+0.0309ST | 0.312 | 1.209 |
| **39B** | MR,MV,RI,ST | $pC_2$= 0.880+0.288logP+-0.008763FW+5.521D | 0.324 | 1.280 |
| **40B** | MR,MV,FW,ST | $pC_2$= 6.637+0.301logP+0.256RI+-1.603D | 0.182 | 0.593 |

| | | | | |
|---|---|---|---|---|
| **41B** | RI,ST,D,FW,MV | $pC_2$=5.920+0.330logP+-0.0117MR | 0.232 | 1.356 |
| **42B** | RI,ST,D,MV,MR | $pC_2$= 5.994+0.321logP+-0.00304FW | 0.252 | 1.513 |
| **43B** | RI,ST,D,FW,MR | $pC_2$= 6.463+0.321logP+-0.00578MV | 0.255 | 1.539 |
| **44B** | MV,ST,D,FW,MR | $pC_2$= 6.529+0.283logP+-0.995RI | 0.150 | 0.791 |
| **45B** | MV,RI,D,FW,MR | $pC_2$= 5.347+0.286logP+-0.00811ST | 0.150 | 0.838 |
| **46B** | MV,RI,ST,FW,MR | $pC_2$= 6.971+0.305logP+-1.557D | 0.182 | 1.000 |
| **47B** | logP,RI,ST,D ,MR | $pC_2$=7.238+0.00123FW+-0.000619MV | 0.054 | 0.255 |
| **48B** | logP,MV,ST,D ,MR | $pC_2$=-1.758-0.00404FW+5.809RI | 0.137 | 0.717 |
| **49B** | logP,MV,RI,D ,MR | $pC_2$=6.211-0.00577FW+0.0385ST | 0.145 | 0.762 |
| **50B** | logP,MV,RI,ST,MR | $pC_2$=0.230-0.00933FW+6.919D | 0.167 | 0.903 |
| **51B** | logP,MV,FW,ST,MR | $pC_2$= 3.278+2.643RI+-1.151D | 0.028 | 0.128 |
| **52B** | logP,MR,RI,ST | $pC_2$=-69.685+-0.202FW+0.264MV+58.482D | 0.873 | 18.377 |
| **53B** | MV,RI,ST,FW,MR,D | $pC_2$=6.210-0.0228ClogP | 0.683 | 21.519 |
| **53B*** | MV,RI,ST,FW,MR,D | $pC_2$=6.490-0.0839ClogP | 0.756 | 24.841 |

*Outlier compound 3 and 9

Table (2.9): The QSAR Models between Descriptors and Biological Activity of 2,3-Diyne-1,4-naphthoquinone D
Cancer Cell Line.

| No. | Removed Parameters | QSAR Equation | $r^2$ | F |
|---|---|---|---|---|
| **1C** | logP,MR,FW | $pC_3$= 7.439+0.00139MV+-2.412RI+0.0203ST+0.118D | 0.502 | 1.511 |
| **2C** | logP,MR,MV | $pC_3$= 8.037+0.00113FW+ -2.479RI+0.0216ST+-0.345D | 0.485 | 1.412 |
| **3C** | logP,MR,RI | $pC_3$=0.683+ -0.00769FW+0.0107MV+ -0.00653ST+3.770D | 0.455 | 1.250 |
| **4C** | logP,MR,ST | $pC_3$= 2.227+-0.00862FW+0.0116MV+-1.389RI+ 4.090D | 0.524 | 1.648 |
| **5C** | logP,MR,D | $pC_3$= 7.703-0.000467FW+0.00191MV-2.632RI+0.0246ST | 0.503 | 1.519 |
| **6C** | logP,FW,MV | $pC_3$= 8.358+0.00410MR+ -2.962RI+0.0207ST+0.0672D | 0.494 | 1.463 |
| **7C** | logP,FW,RI | $pC_3$=3.430 +-0.0197MR+0.00793 MV+ $0.0201^{ST}$+0.297D | 0.526 | 1.665 |
| **8C** | logP,FW,ST | $pC_3$= -2.570+-0.0371MR+ 0.0138MV+3.663RI +1.359D | 0.480 | 1.384 |
| **9C** | logP,FW,D | $pC_3$= 2.998+-0.0235MR+ 0.00917MV+0.345RI+0.0246ST | 0.521 | 1.632 |
| **10C** | logP,MV,RI | $pC_3$= 5.806+-0.0148MR+0.00538FW+ 0.0193ST+-1.695D | 0.438 | 1.167 |
| **11C** | logP,MV,ST | $pC_3$= 12.320+0.0608MR+-0.0160FW+ -9.343RI+6.220D | 0.527 | 1.668 |
| **12C** | logP,MV,D | $pC_3$= 8.751+0.00527MR+-0.000349FW+ -3.251RI+ 0.0235ST | 0.494 | 1.467 |
| **13C** | logP.RI,ST | $pC_3$= 0.589+-0.0101MR+-0.00708FW+0.0131MV+ 3.609D | 0.517 | 1.607 |
| **14C** | logP.RI,D | $pC_3$= 3.625+-0.020571MR+0.000320FW+0.00783MV+ 0.0230ST | 0.522 | 1.638 |
| **15C** | logP.ST,D | $pC_3$= -4.921+-0.0545MR+0.00404FW+0.0149MV+6.156RI | 0.442 | 1.188 |
| **16C** | FW,MV,RI | $pC_3$=5.253+-0.0613logP+-0.00932MR+ 0.00479ST+-0.665D | 0.399 | 0.997 |
| **17C** | FW,MV,ST | $pC_3$= 6.588+0.0445logP+0.000771MR+ -2.548RI+ 1.998D | 0.435 | 1.155 |
| **18C** | FW,MV,D | $pC_3$= 9.764+0.0263logP+0.00178MR+ -4.125RI+0.0314ST | 0.505 | 1.532 |

| | | | | |
|---|---|---|---|---|
| **19C** | FW,RI,ST | $pC_3$= 2.290+0.0461logP+-0.0207MR+ 0.00709MV+2.225 D | 0.468 | 1.319 |
| **20C** | FW,RI,D | $pC_3$= 3.483+0.00391logP+-0.0223MR+ 0.00868MV+ 0.0259ST | 0.521 | 1.633 |
| **21C** | FW,ST,D | $pC_3$= -4.363+-0.0620logP+-0.0364MR+ 0.0153MV+5.740RI | 0.462 | 1.288 |
| **22C** | MR,FW,MV | $pC_3$= 9.613+0.544logP+ -4.587RI+0.0258ST+1.000D | 0.540 | 1.762 |
| **23C** | MR,FW,RI | $pC_3$= 4.652-0.0429logP+ 0.00266MV+ 0.102ST+-0387D | 0.456 | 1.256 |
| **24C** | MR,FW,ST | $pC_3$= 5.633+0.0190logP+ 0.00979MV+-1.590RI+1.475 D | 0.439 | 1.175 |
| **25C** | MR,FW,D | $pC_3$= 9.053+0.0212logP+ 0.000758MV+-3.631RI+0.0298ST | 0.508 | 1.548 |
| **26C** | MR,MV,RI | $pC_3$= 5.450-0.0371logP+ 0.00209FW +0.0103ST+-1.052D | 0.417 | 1.075 |
| **27C** | MR,MV,ST | $pC_3$= 7.317+0.0794logP+ -0.000632FW+ -3.671RI+ 2.953D | 0.438 | 1.167 |
| **28C** | MR,MV,D | $pC_3$= 9.514+0.0295logP+ 0.000467FW+ -3.934RI+0.030.ST | 0.510 | 1.563 |
| **29C** | MR,RI,ST | $pC_3$= 1.051-0.0370logP+ -0.00830FW+0.0122MV+3.158 D | 0.512 | 1.573 |
| **30C** | MR,RI,D | $pC_3$= 4.022-0.0540logP+ -0.00229FW+0.00559MV+ 0.0135ST | 0.479 | 1.378 |
| **31C** | MR,ST,D | $pC_3$= 1.302-0.0919logP+ -0.00268FW+0.00712MV+ 2.128RI | 0.437 | 1.166 |
| **32C** | MV,RI,ST | $pC_3$= 4.878-0.0338logP+0.00382MR+0.000946FW+ -0.0937D | 0.385 | 0.979 |
| **33C** | MV,RI,D | $pC_3$= 4.689+0.00809logP+-0.00689MR+0.00302FW+ $0.00271^{ST}$ | 0.398 | 0.991 |
| **34C** | MV,ST,D | $pC_3$= 5.430-0.0541logP+0.0111MR+-0.000657FW+ -0.436RI | 0.403 | 1.011 |
| **35C** | RI,ST,D | $pC_3$= 4.719-0.0684logP+0.0104MR+-0.00147FW+0.00156MV | 0.412 | 1.053 |
| **36C** | MR,MV,RI,D | $pC_3$= 4.992-0.0198logP+0.00169FW+-0.120RI | 0.396 | 1.527 |
| **37C** | MV.MR,RI,D | $pC_3$= 4.735-0.0160logP+0.00163FW+0.00105ST | 0.396 | 1.530 |
| **38C** | MV.MR,RI,D,ST | $pC_3$=4.794 -0.0188logP+ 0.00168FW | 0.394 | 2.599 |
| **39C** | MV.MR,RI,D,FW | $pC_3$= 5.304-0.00244logP+0.0119RI | 0.001 | 0.005 |
| **40C** | MV.MR,ST,D,FW | $pC_3$= 4.899+0.0103logP+0.00587ST | 0.080 | 0.347 |

| | | | | |
|---|---|---|---|---|
| **41C** | logP,MR,MV,ST,D | $pC_3$=4.582+0.00145FW+0.104RI | 0.333 | 1.999 |
| **42C** | logP,MR,MV,RI,,D | $pC_3$=4.578+0.00140FW+0.00339ST | 0.369 | 2.334 |
| **43C** | logP,MR,MV,RI,,ST | $pC_3$=4.447+0.00136FW+0.281D | 0.371 | 2.363 |
| **44C** | logP,MV,FW,ST,D | $pC_3$=4.661+0.114RI+0.00424MR | 0.202 | 1.014 |
| **45C** | logP,MR,FW,ST,D | $pC_3$=3.763+0.686RI+0.00139 MV | 0.198 | 0.988 |
| **46C** | logP,MV,FW,RI,D | $pC_3$=4.563+0.151ST+0.208MR | 0.275 | 1.515 |
| **47C** | logP,MR,FW,RI,D | $pC_3$=4.2840.00876ST+0.00165MV | 0.357 | 2.224 |
| **48C** | MV.MR,RI,D,FW,RI | $pC_3$=5.588-0.00775ClogP | 0.586 | 12.73 |
| **48C*** | MV.MR,RI,D,FW,RI | $pC_3$=-0.00857 ClogP + 5.602 | 0.714 | 17.49 |

* Outlier compounds 19 and 23

Table (2.10): The QSAR Models between Descriptors and Biological Activity of 2,3-Diyne-1,4-naphthoquinone Cancer Cell Line.

| No. | Removed Parameters | QSAR Equation | $r^2$ | F |
|---|---|---|---|---|
| **1D** | logP,MR,FW | $pC_4$= 3.886+0.000389MV+ -0.189RI+0.00636ST+0.987D | 0.489 | 1.438 |
| **2D** | logP,MR,MV | $pC_4$= 4.101+0.000273FW+-0.237 RI+0.00686ST+0.865D | 0.487 | 1.424 |
| **3D** | logP,MR,RI | $pC_4$=0.362+-0.00783 FW+0.009574MV+-0.00169 ST+4.101D | 0.522 | 1.639 |
| **4D** | logP,MR,ST | $pC_4$= 0.639+-0.00761FW+0.00932MV+-0.118RI+ 3.950D | 0.522 | 1.638 |
| **5D** | logP,MR,D | $pC_4$= 5.186+0.00138FW+-0.00127MV+-0.553RI+0.0147ST | 0.472 | 1.339 |
| **6D** | logP,FW,MV | $pC_4$= 4.162+0.00106MR+-0349RI+0.00655ST+0.968D | 0.488 | 1.430 |
| **7D** | logP,FW,RI | $pC_4$= 3.498+-0.00483MR+ 0.00195MV+ 0.00973ST+0.924D | 0.493 | 1.461 |
| **8D** | logP,FW,ST | $pC_4$= -5.273+-0.0409MR+0.0140 MV+5.357RI +1.600D | 0.514 | 1.584 |
| **9D** | logP,FW,D | $pC_4$= 2.042+-0.0172MR+ 0.00598MV+1.143RI+0.0238ST | 0.468 | 1.319 |
| **10D** | logP,MV,RI | $pC_4$= 3.602+-0.00174MR+-0.000178FW+ 0.00267ST+1.146D | 0.487 | 1.423 |
| **11D** | logP,MV,ST | $pC_4$= 7.652+0.0417MR+-0.0115FW+ -5.511RI+ 4.995D | 0.512 | 1.573 |
| **12D** | logP,MV,D | $pC_4$= 3.865-0.00630MR+0.00207FW+ 0.387RI+0.0117ST | 0.478 | 1.373 |
| **13D** | logP.RI,ST | $pC_4$= 0.495+-0.000903MR+-0.00745FW+0.00947MV+ 3.913D | 0.522 | 1.638 |
| **14D** | logP.RI,D | $pC_4$= 4.211+-0.00710MR+0.00144FW+0.000977MV+ 0.0169ST | 0.478 | 1.374 |
| **15D** | logP.ST,D | $pC_4$= -8.528+-0.0643MR+0.00493FW+0.0160MV+8.599RI | 0.498 | 1.489 |
| **16D** | FW,MV,RI | $pC_4$=3.204+0.0239 logP+-0.00779MR+ -0.000464ST+1.655D | 0.493 | 1.459 |
| **17D** | FW,MV,ST | $pC_4$= 5.377+0.148logP+-0.0109MR+ -3.346RI+ 4.474D | 0.532 | 1.703 |
| **18D** | FW,MV,D | $pC_4$= 5.151+-0.00903logP+0.00159MR+ -0.659RI +0.0186ST | 0.462 | 1.290 |

| | | | | |
|---|---|---|---|---|
| **19D** | FW,RI,ST | $pC_4$= 0.273+0.131 logP+-0.0332MR+ 0.00788MV+ 4.284D | 0.542 | 1.778 |
| **20D** | FW,RI,D | $pC_4$= 3.970-0.00617logP+-0.00638MR+0.00256 MV+ 0.0213ST | 0.467 | 1.314 |
| **21D** | FW,ST,D | $pC_4$= -6.299-0.0668logP+-0.0352MR+ 0.0139MV+7.124RI | 0.470 | 1.328 |
| **22D** | MR,FW,MV | $pC_4$= 4.522+0.0213logP+ -0.943RI+0.00801ST+1.364D | 0.500 | 1.503 |
| **23D** | MR,FW,RI | $pC_4$=3.357+0.0136 logP+ 9.620x$10^{-5}$MV+0.00145 ST+1.403D | 0.492 | 1.455 |
| **24D** | MR,FW,ST | $pC_2$= 7.199+0.135logP+ -0.00325MV+-4.247RI+ 4.109D | 0.521 | 1.633 |
| **25D** | MR,FW,D | $pC_4$= 4.416-0.0149logP+ 0.000723MV+-0.142RI+0.0166ST | 0.464 | 1.298 |
| **26D** | MR,MV,RI | $pC_4$= 3.276+0.0183logP+ 6.55x$10^{-5}$FW +0.000140ST+1.549D | 0.492 | 1.455 |
| **27D** | MR,MV,ST | $pC_4$= 7.046+0.167logP+ -0.00357FW+ -5.534RI+ 6.036D | 0.546 | 1.802 |
| **28D** | MR,MV,D | $pC_4$= 4.622-0.00989logP+0.000542 FW+ -0.241RI +0.0156ST | 0.468 | 1.318 |
| **29D** | MR,RI,ST | $pC_4$= 0.660+0.00631logP+-0.00700 FW+0.00848MV +3.764 D | 0.523 | 1.643 |
| **30D** | MR,RI,D | $pC_4$= 4.464-0.00548logP+ 0.00136FW+-0.00106MV+ 0.0114ST | 0.469 | 1.325 |
| **31D** | MR,ST,D | $pC_4$= 2.248-0.0342logP+ 0.00124FW+-0.000106MV+ 1.689RI | 0.451 | 1.234 |
| **32D** | MV,RI,ST | $pC_4$= 2.981+0.0798logP+-0.0163MR+0.00311FW+ 1.903D | 0.503 | 1.519 |
| **33D** | MV,RI,D | $pC_4$= 3.942+0.191logP+-0.0582MR+0.0123FW+ 0.0278ST | 0.534 | 1.721 |
| **34D** | MV,ST,D | $pC_4$= 1.401+0.0344logP+-0.0226MR+0.00594FW+ 2.365RI | 0.467 | 1.314 |
| **35D** | RI,ST,D. | $pC_4$= 5.119+0.0151logP+6.368x10-5MR+0.00429FW-0.00483`MV | 0.439 | 1.176 |
| **36D** | MR,MV,RI,D | $pC_4$= 2.293-0.0353logP+0.00117FW+1.723RI | 0.451 | 1.919 |
| **37D** | MV.MR,RI,D | $pC_4$=4.329-0.0127 logP+0.000613FW+0.0138ST | 0.467 | 2.048 |
| **38D** | MV.MR,RI,D,ST | $pC_4$= 5.116-0.0494logP+0.00128 FW | 0.268 | 1.467 |
| **39D** | MV.MR,RI,D,FW | $pC_4$=2.509-0.0232 logP+1.815RI | 0.350 | 2.151 |
| **40D** | MV.MR,ST,D,FW | $pC_4$= 4.391-0.00277logP+0.0156ST | 0.443 | 3.187 |

| | | | | |
|---|---|---|---|---|
| **41D** | logP,MR,MV,ST,D | $pC_4$=1.563+0.000753FW+2.123RI | 0.345 | 2.109 |
| **42D** | logP,MR,MV,RI,,D | $pC_4$=4.205+0.000428FW+0.0156ST | 0.458 | 3.382 |
| **43D** | logP,MR,MV,RI,,ST | $pC_4$=3.615+0.000252FW+1.282D | 0.481 | 3.713 |
| **44D** | logP,MV,FW,ST,D | $pC_4$=1.773+2.107RI+0.000960MR | 0.303 | 1.738 |
| **45D** | logP,MR,FW,ST,D | $pC_4$=1.590+2.227RI+0.000296 MV | 0.302 | 1.732 |
| **46D** | logP,MV,FW,RI,D | $pC_4$=4.251+0.0160ST+0.000882MR | 0.448 | 3.240 |
| **47D** | logP,MR,FW,RI,D | $pC_4$=4.171+0.0170ST+0.000385MV | 0.451 | 3.291 |
| **48D** | MV,RI,ST,FW,MR,D | $pC_4$=5.539 – 0.00639ClogP | 0.656 | 17.17 |
| **48D*** | MV,RI,ST,FW,MR,D | $pC_4$=5.761 -0.0136ClogP | 0.869 | 46.24 |

* Outlier compounds 22 and 23

Table (2.11): The QSAR Models between Descriptors and Biological Activity of 2,3-Diyne-1,4-naphthoquinon
H358M Cancer Cell Line.

| No. | Removed Parameters | QSAR Equation | $r^2$ | F |
|---|---|---|---|---|
| **1E** | logP,MR,FW | $pC_5$=10.665+-0.00119MV+-5.393RI+0.0142ST+2.169D | 0.850 | 8.498 |
| **2E** | logP,MR,MV | $pC_5$= 10.173+-0.000981FW+-5.347 RI+0.0131ST+2.566D | 0.846 | 8.266 |
| **3E** | logP,MR,RI | $pC_5$=3.291+0.00146 FW+-0.00229MV+-0.0304 ST+3.031D | 0.618 | 2.426 |
| **4E** | logP,MR,ST | $pC_5$= 9.386+0.00120FW+-0.00252MV+-4.306RI+ 2.423D | 0.837 | 7.697 |
| **5E** | logP,MR,D | $pC_5$=13.137+0.005263FW-0.007373MV-5.566RI+0.0208ST | 0.854 | 8.801 |
| **6E** | logP,FW,MV | $pC_5$= 9.880+-0.00349MR+ -4.923RI+0.0139ST+2.213D | 0.847 | 8.325 |
| **7E** | logP,FW,RI | $pC_5$= 1.890+-0.0356MR+0.0107 MV+0.00509 ST+2.767D | 0.803 | 6.132 |
| **8E** | logP,FW,ST | $pC_5$= 13.377+0.0213MR+-0.00820 MV+-7.019RI +2.678D | 0.842 | 8.009 |
| **9E** | logP,FW,D | $pC_5$= 25.193+0.0566MR+ -0.0202MV-13.900RI+0.0428ST | 0.793 | 5.755 |
| **10E** | logP,MV,RI | $pC_5$=6.210+-0.0413MR+0.0107FW+ 0.0198ST+-1.566D | 0.841 | 7.911 |
| **11E** | logP,MV,ST | $pC_5$= 9.037+-0.00336MR+-0.00189FW+ -4.870RI+ 3.478D | 0.835 | 7.577 |
| **12E** | logP,MV,D | $pC_5$= 8.095+-0.0248MR+0.00604FW+ -2.332RI+0.0193ST | 0.847 | 8.335 |
| **13E** | logP.RI,ST | $pC_5$= 4.260+-0.0318MR+0.00592FW+0.00255MV+ 0.976D | 0.821 | 6.860 |
| **14E** | logP.RI,D | $pC_5$=4.686-0.0394MR+0.00708FW+0.00368MV+ 0.0138ST | 0.838 | 7.742 |
| **15E** | logP.ST,D | $pC_5$= 7.638+-0.0195MR+0.00835FW+-0.00440MV-1.408RI | 0.818 | 6.727 |
| **16E** | FW,MV,RI | $pC_5$= 5.295-0.132logP+0.00758MR+ -0.00740ST+0.243D | 0.797 | 5.878 |
| **17E** | FW,MV,ST | $pC_5$= 8.296+0.000269log*P*-0.000332MR -3.954RI+ 2.873D | 0.834 | 7.544 |
| **18E** | FW,MV,D | $pC_5$= 8.148-0.101logP+0.00473MR+ -2.226RI+0.0119ST | 0.811 | 6.430 |
| **19E** | FW,RI,ST | $pC_5$= 3.513-0.0660logP+-0.0159MR+ 0.00599MV+1.520 D | 0.813 | 6.541 |

| | | | | |
|---|---|---|---|---|
| **20E** | FW,RI,D | $pC_5$=5.034-0.123log*P*-0.00189MR+0.00285MV+0.00331ST | 0.802 | 6.089 |
| **21E** | FW,ST,D | $pC_5$= 9.945-0.122logP+0.0231MR+-0.00551 MV+-2.989RI | 0.808 | 6.303 |
| **22E** | MR,FW,MV | $pC_5$= 8.851-0.0380logP+ -3.739RI+0.00968ST+1.596D | 0.838 | 7.752 |
| **23E** | MR,FW,RI | $pC_5$= 4.774-0.114logP+0.00206 MV+ -0.00387ST+0.543D | 0.806 | 6.216 |
| **24E** | MR,FW,ST | $pC_5$=9.547+0.0184logP+ -0.00162MV+-4.983RI+ 3.227D | 0.837 | 7.687 |
| **25E** | MR,FW,D | $pC_5$=7.290-0.100logP+ 0.00153MV+-1.703RI+0.0127ST | 0.808 | 6.292 |
| **26E** | MR,MV,RI | $pC_5$= 5.499-0.114logP+ 0.00175FW +-0.00246ST+-0.141D | 0.807 | 6.256 |
| **27E** | MR,MV,ST | $pC_5$= 8.718+0.00245logP+ -0.000995FW -4.491RI+ 3.242D | 0.835 | 7.569 |
| **28E** | MR,MV,D | $pC_5$= 7.811-0.0885logP+ 0.00111FW+ -1.981RI+0.0110ST | 0.819 | 6.791 |
| **29E** | MR,RI,ST | $pC_5$= 5.695-0.118logP+0.00196 FW-0.000141MV+ -0.425D | 0.806 | 6.233 |
| **30E** | MR,RI,D | $pC_5$=5.353-0.114logP+0.00141FW+0.000398MV-0.00282ST | 0.807 | 6.257 |
| **31E** | MR,ST,D | $pC_5$= 8.950-0.0520logP+ 0.00485FW+-0.00537MV -2.291RI | 0.823 | 6.969 |
| **32E** | MV,RI,ST | $pC_5$= 5.272-0.0372logP+-0.0216MR+0.00606FW+ 0.0625D | 0.821 | 6.900 |
| **33E** | MV,RI,D | $pC_5$= 5.172+0.0103log*P*-0.0348MR+0.00870FW+ 0.00469ST | 0.826 | 7.114 |
| **34E** | MV,ST,D | $pC_5$= 5.419-0.0481logP+-0.0188MR+0.00554FW+ -0.0564RI | 0.821 | 6.896 |
| **35E** | RI,ST,D | $pC_5$=5.335-0.0440log*P*-0.0201MR+0.00581FW-3.085x$10^{-6}$MV | 0.821 | 6.894 |
| **36E** | MR,MV,RI,D | $pC_5$= 6.166-0.106logP+0.001551FW+-0.594RI | 0.812 | 10.108 |
| **37E** | MV.MR,RI,D | $pC_5$=5.403-0.111 logP+0.00169FW+-0.00371$^{ST}$ | 0.806 | 9.721 |
| **38E** | MV.MR,RI,D,ST | $pC_5$= 5.192-0.102logP+0.00151 FW | 0.795 | 15.487 |
| **39E** | MV.MR,RI,D,FW | $pC_5$= 6.453-0.0905logP+-0.473RI | 0.667 | 8.017 |
| **40E** | MV.MR,ST,D,FW | $pC_5$=5.574-0.0840 logP+0.00131ST | 0.658 | 7.681 |
| **41E** | logP,MR,MV,ST,D | $pC_5$=3.962+0.000293FW+0.613RI | 0.026 | 0.106 |

| | | | | |
|---|---|---|---|---|
| **42E** | logP,MR,MV,RI,,D | $pC_5$=4.316+6.989X$10^{-5}$ FW+0.0126ST | 0.226 | 1.166 |
| **43E** | logP,MR,MV,RI,,ST | $pC_5$=3.432+0.000198FW+1.409D | 0.440 | 3.145 |
| **44E** | logP,MV,FW,ST,D | $pC_5$=4.605+0.536RI+-0.00373MR | 0.088 | 0.387 |
| **45E** | logP,MR,FW,ST,D | $pC_5$=5.572-0.0443RI+ -0.00139MV | 0.106 | 0.476 |
| **46E** | logP,MV,FW,RI,D | $pC_5$=4.743+0.0123ST+-0.00357MR | 0.288 | 1.619 |
| **47E** | logP,MR,FW,RI,D | $pC_5$=4.648+0.0109ST+-0.000665MV | 0.246 | 1.305 |
| **48E** | logP,FW,MV,MR,ST | $pC_5$= 7.877-3.933RI+2.894D | 0.781 | 14.257 |
| **49E** | logP,MV,RI,ST,D | $pC_5$=5.425-0.0341MR+0.00873FW | 0.807 | 16.738 |
| **50E** | MR,FW,MV,RI,ST,D | $pC_5$=5.669-0.0869logP | 0.656 | 17.153 |
| **51E** | MR, MV,ST,RI,D | $pC_5$= 5.192-0.102logP+0.00151FW | 0.795 | 15.487 |
| **52E** | MV,RI,ST,FW,MR,D | $pC_5$=5.308-0.00323ClogP | 0.867 | 58.483 |

Table (2.12): The QSAR Models between Descriptors and Biological Activity of Phenylaminonaphtoquin
DU145Cancer Cell Line.

| No. | Removed Parameters | QSAR Equation | $r^2$ | F |
|---|---|---|---|---|
| **1F** | logP,MR,FW | $pC_6$= -72.117+0.0393MV+41.235RI+-0.0164ST+0.524D | 0.744 | 4.355 |
| **2F** | logP,MR,MV | $pC_6$= -94.211+ 0.0398FW+60.903 RI+-0.0636ST+-7.632D | 0.773 | 5.105 |
| **3F** | logP,MR,RI | $pC_6$= 66.953+0.247FW+-0.319MV+0.166 ST+-55.934D | 0.821 | 6.899 |
| **4F** | logP,MR,ST | $pC_6$= -21.073+0.289FW+-0.335MV+59.177RI+-62.912 D | 0.870 | 10.061 |
| **5F** | logP,MR,D | $pC_6$= -82.178+0.00527FW+0.0361MV+48.004RI-0.0393ST | 0.747 | 4.432 |
| **6F** | logP,FW,MV | $pC_6$= -53.705+0.105MR +29.952RI+-0.00478ST+0.324D | 0.742 | 4.313 |
| **7F** | logP,FW,RI | $pC_6$= -3.989+0.230MR +-0.0575MV +0.0592ST+-0.583D | 0.732 | 4.106 |
| **8F** | logP,FW,ST | $pC_6$= -67.552+-0.0372MR +0.0490MV+38.638RI +0.297D | 0.744 | 4.349 |
| **9F** | logP,FW,D | $pC_6$= -66.253-0.0258MR +0.0455MV+37.918RI+0.00233ST | 0.743 | 4.336 |
| **10F** | logP,MV,RI | $pC_6$= 9.569+-0.141MR+0.0409FW+0.148 ST+-10.530D | 0.737 | 4.194 |
| **11F** | logP,MV,ST | $pC_6$= -96.313+-0.493MR+0.163FW+ 84.345RI+ -35.116D | 0.821 | 6.880 |
| **12F** | logP,MV,D | $pC_6$= -65.632+0.0991MR+0.00473FW+ 37.750RI-0.0301ST | 0.745 | 4.382 |
| **13F** | logP.RI,ST | $pC_6$= 69.998+0.780MR+0.273FW+-0.590MV+ -59.443D | 0.833 | 7.487 |
| **14F** | logP.RI,D | $pC_6$= -4.460+0.254MR-0.000691FW-0.0643MV+0.0504 ST | 0.731 | 4.076 |
| **15F** | logP.ST,D | $pC_6$= -66.771-0.0461MR+0.00270FW+0.0475MV+38.551RI | 0.745 | 4.390 |
| **16F** | FW,MV,RI | $pC_6$= -6.487+0.441logP+0.0418MR + 0.126ST+-0.702D | 0.744 | 4.362 |
| **17F** | FW,MV,ST | $pC_6$= -60.518+0.264logP+0.112MR +32.745RI+ 0.721D | 0.750 | 4.491 |
| **18F** | FW,MV,D | $pC_6$= -39.618+0.345logP+0.0858MR +20.030RI+0.0516ST | 0.751 | 4.536 |
| **19F** | FW,RI,ST | $pC_6$= -7.273+0.226logP+0.535MR+ -0.151MV+0.748 D | 0.726 | 3.969 |

| | | | | |
|---|---|---|---|---|
| **20F** | FW,RI,D | $pC_6$= -7.582+0.435logP+0.229MR+-0.0569 MV+0.0833 ST | 0.749 | 4.468 |
| **21F** | FW,ST,D | $pC_6$= -71.037+0.186logP+0.0201MR+ 0.0334MV+39.869RI | 0.744 | 4.439 |
| **22F** | MR,FW,MV | $pC_6$=20.560 +0.501logP + -15.951RI+0.180ST+-1.082D | 0.727 | 3.996 |
| **23F** | MR,FW,RI | $pC_6$= -6.212+0.443logP + 0.0123MV+ 0.134ST+-0.757D | 0.741 | 4.299 |
| **24F** | MR,FW,ST | $pC_6$= -72.819+0.250logP + 0.0389MV+40.478RI+ 0.734D | 0.750 | 4.511 |
| **25F** | MR,FW,D | $pC_6$= -51.178+0.318logP + 0.0308MV+27.336RI+0.0467ST | 0.751 | 4.525 |
| **26F** | MR,MV,RI | $pC_6$= -3.585+0.439logP +0.00969FW+ 0.138ST+-2.998D | 0.748 | 4.456 |
| **27F** | MR,MV,ST | $pC_6$= -70.784+0.251logP +0.0319FW+ 44.471RI+ -6.401D | 0.775 | 5.159 |
| **28F** | MR,MV,D | $pC_6$= 0.343+0.499logP +0.00398FW+ -3.524RI+0.128ST | 0.724 | 3.944 |
| **29F** | MR,RI,ST | $pC_6$= 9.317+-0.738logP +0.0139FW+-0.0209MV+ -1.221D | 0.508 | 1.549 |
| **30F** | MR,RI,D | $pC_6$= -6.984+0.458logP +-0.00191FW+0.0143MV+0.131 ST | 0.739 | 4.256 |
| **31F** | MR,ST,D | $pC_6$= -71.787+0.276logP +0.00481FW+0.0320MV+40.452RI | 0.754 | 4.593 |
| **32F** | MV,RI,ST | $pC_6$= -25.551+0.0744logP+0.355MR+-0.739FW +17.210D | 0.650 | 2.785 |
| **33F** | MV,RI,D | $pC_6$= -7.281+0.451logP+0.0499MR+-0.00210FW+0.122 ST | 0.743 | 4.332 |
| **34F** | MV,ST,D | $pC_6$= -61.674+0.289logP+0.0916MR+0.00486FW+34.089 RI | 0.753 | 4.579 |
| **35F** | RI,ST,D | $pC_6$= -6.262+0.250logP+0.534MR+0.00479FW+-0.157MV | 0.729 | 4.033 |
| **36F** | MR,MV,RI,ST,D | $pC_6$= 7.589+-0.945logP +0.00103FW | 0.491 | 3.852 |
| **37F** | FW,MV,RI,ST,D | $pC_6$= 7.404+-0.964logP+0.00679MR | 0.491 | 3.859 |
| **38F** | MR,MV,RI,ST,D,FW | $pC_6$= 7.827+-0.926logP | 0.488 | 8.589 |
| **39F** | logP,MV,RI,ST,D,FW | $pC_6$= 7.667-0.0330MR | 0.084 | 0.820 |
| **40F** | MR,MV,RI,ST,logP | $pC_6$= -1.209+-0.00713FW+6.088D | 0.416 | 2.849 |
| **41F** | MR,MV,RI,logP,D | $pC_6$= -1.416+0.00455FW+0.0826ST | 0.702 | 9.423 |

| | | | | |
|---|---|---|---|---|
| **42F** | FW,MV,RI,ST,logP | $pC_6$= 0.474+-0.0283MR+4.997D | 0.368 | 2.330 |
| **43F** | MR,MV,FW,ST,logP | $pC_6$= -17.815+3.002D+11.180RI | 0.563 | 5160 |
| **44F** | MR,MV,RI,FW,logP | $pC_6$= -0.184+0.608D+0.0705ST | 0.665 | 7.933 |
| **45F** | MR,FW,RI,ST,logP | $pC_6$= 0.801+-0.009701MV+4.607D | 0.421 | 2.801 |
| **46F** | MR,MV,RI,logP,D,FW | $pC_6$=0.412+0.0742ST | 0.662 | 17.646 |
| **47F** | MR,MV,logP,ST,D,FW | $pC_6$=-18.323+13.870RI | 0.478 | 8.241 |
| **48F** | MV,RI,ST,FW,MR,D | $pC_6$=5.470-0.000778ClogP | 0.756 | 27.858 |

Table (2.13): The QSAR Models between Descriptors and Biological Activity of Phenylaminonaphtoquinone Cancer Cell Line.

| No. | Removed Parameters | QSAR Equation | $r^2$ | F |
|---|---|---|---|---|
| **1G** | logP,MR,FW | $pC_7$= -198.890+ 0.0910MV+120.278RI+-0.290ST+1.183D | 0.774 | 5.139 |
| **2G** | logP,MR,MV | $pC_7$= -154.750+0.069573FW+ 123.519RI+-0.284ST+ -14.105D | 0.771 | 5.052 |
| **3G** | logP,MR,RI | $pC_7$= -10.006+-0.0488FW+MV+0.0582ST+7.355D | 0.363 | 0.853 |
| **4G** | logP,MR,ST | $pC_7$= -39.936+0.0260FW+-0.00130MV+30.008RI+-8.817 D | 0.516 | 1.600 |
| **5G** | logP,MR,D | $pC_7$=-199.0003+0.00565 FW+0.0840MV+121.282RI+-0.292ST | 0.775 | 5.171 |
| **6G** | logP,FW,MV | $pC_7$= -160.159+0.249MR +96.435RI+-0.271$^{ST}$+0.803D | 0.772 | 5.087 |
| **7G** | logP,FW,RI | $pC_7$=-0.871 +0.791 MR+-0.227 MV +-0.0947ST+-1.787D | 0.615 | 2.397 |
| **8G** | logP,FW,ST | $pC_7$=-2.853+0.363 MR +-0.0943MV+2.418RI +-3.290D | 0.540 | 1.760 |
| **9G** | logP,FW,D | $pC_7$=-159.451+ 0.157MR +0.0287MV+96.453RI+-0.246ST | 0.768 | 4.979 |
| **10G** | logP,MV,RI | $pC_7$= -28.728+0.502MR+-0.105FW+-0.0587ST+20.792D | 0.542 | 1.776 |
| **11G** | logP,MV,ST | $pC_7$=-30.288+ 0.140MR+-0.0127FW+ 17.315RI+-0.439 D | 0.527 | 1.668 |
| **12G** | logP,MV,D | $pC_7$= -163.812+0.236MR+0.004345FW+ 99.358RI+-0.277ST | 0.774 | 5.138 |
| **13G** | logP.RI,ST | $pC_7$=11.173+0.435 MR+0.0368FW+-0.167MV+ -11.338D | 0.545 | 1.793 |
| **14G** | logP.RI,D | $pC_7$=-3.092+ 0.788MR+-0.00793FW+-0.216MV+-0.0962ST | 0.617 | 2.383 |
| **15G** | logP.ST,D | $pC_7$= -5.959+0.352MR+-0.0148FW+-0.0718MV+1.810RI | 0.535 | 1.726 |
| **16G** | FW,MV,RI | $pC_7$= -1.949+0.652logP+0.0414MR +0.104 ST+-3.067D | 0.472 | 1.340 |
| **17G** | FW,MV,ST | $pC_7$=-56.673+0.667logP+0.116MR +32.076RI+ -2.022D | 0.644 | 2.711 |
| **18G** | FW,MV,D | $pC_7$= -141.703+0.252logP+0.227MR +84.447RI+-0.210ST | 0.780 | 5.312 |
| **19G** | FW,RI,ST | $pC_7$= -5.467+0.708logP+0.571MR+ -0.159MV+-2.059D | 0.671 | 3.059 |

| | | | | |
|---|---|---|---|---|
| **20G** | FW,RI,D | $pC_7$=-6.685+0.630logP+0.842MR+-0.244MV+-0.079ST | 0.670 | 3.004 |
| **21G** | FW,ST,D | $pC_7$=-16.355 +0.896logP+0.471MR+-0.128 MV+5.295RI | 0.614 | 2.389 |
| **22G** | MR,FW,MV | $pC_7$=16.510+0.667logP + -10.180RI+0.126ST+-2.2728D | 0.364 | 0.857 |
| **23G** | MR,FW,RI | $pC_7$= -1.482+0.650logP +0.0115 MV+ 0.109ST+-3.016D | 0.447 | 1.213 |
| **24G** | MR,FW,ST | $pC_7$= -67.955+0.641logP + 0.040MV+39.350RI+ -1.969D | 0.624 | 2.492 |
| **25G** | MR,FW,D | $pC_7$= -171.774+0.181logP + 0.0811MV+103.464RI+-0.222ST | 0.770 | 5.016 |
| **26G** | MR,MV,RI | $pC_7$= 0.999+0.642logP +0.00839FW+ 0.110ST+-4.847D | 0.442 | 1.187 |
| **27G** | MR,MV,ST | $pC_7$= -61.877+0.609logP +0.0302FW+ 40.936RI+ -8.606D | 0.617 | 2.421 |
| **28G** | MR,MV,D | $pC_7$= -12.807+0.694logP +0.00421FW+ 7.336RI+0.0447ST | 0.295 | 0.627 |
| **29G** | MR,RI,ST | $pC_7$= -51.608+0.183logP +-0.195FW+0.265MV+41.802 D | 0.261 | 0.529 |
| **30G** | MR,RI,D | $pC_7$= -5.437+0.657logP +-0.0140FW+0.0303MV+ 0.107ST | 0.455 | 1.250 |
| **31G** | MR,ST,D | $pC_7$= -69.616+0.648logP +-0.00898FW+0.0512MV+38.782RI | 0.625 | 2.500 |
| **32G** | MV,RI,ST | $pC_7$= -31.434+0.734logP+0.459MR+-0.0941FW +18.716D | 0.644 | 2.708 |
| **33G** | MV,RI,D | $pC_7$= -6.330+0.637logP+0.112MR+-0.0153FW+0.0893 ST | 0.515 | 1.593 |
| **34G** | MV,ST,D | $pC_7$= -54.451+0.672logP+0.152MR-0.00959FW+ 29.042RI | 0.649 | 2.777 |
| **35G** | RI,ST,D | $pC_7$= -6.330+0.637logP+0.112MR+-0.15FW+0.089MV | 0.671 | 3.061 |
| **36G** | MR,MV,RI,ST,D | $pC_7$=1.407+-0.183logP +-0.00135FW | 0.069 | 0.296 |
| **37G** | FW,MV,RI,ST,D | $pC_7$=6.018+-0.226logP +0.00321MR | 0.061 | 0.259 |
| **38G** | MR,MV,RI,ST,D,FW | $pC_7$=6.219 +-0.208logP | 0.059 | 0.569 |
| **39G** | logP,MV,RI,ST,D,FW | $pC_7$=6.080+-0.00613MR | 0.007 | 0.063 |
| **40G** | MR,MV,RI,ST,logP | $pC_7$=5.321 +0.762D+-0.00267FW | 0.042 | 0.174 |
| **41G** | MR,MV,RI,logP,D | $pC_7$=3.981+0.0249ST+0.000179FW | 0.175 | 0.851 |

| | | | | |
|---|---|---|---|---|
| **42G** | FW,MV,RI,ST,logP | $pC_7$=5.528+-0.00577MR+0.384D | 0.011 | 0.044 |
| **43G** | MR,MV,FW,ST,logP | $pC_7$=-3.175+5.797RI+-3.175D | 0.170 | 0.822 |
| **44G** | MR,MV,RI,FW,logP | $pC_7$=5.972 +-1.961D+0.0368ST | 0.239 | 1.254 |
| **45G** | MR,FW,RI,ST,logP | $pC_7$=5.995+0.224D+-0.00336MV | 0.035 | 0.146 |
| **46G** | logP,MR,FW,D | $pC_7$=-178.566+ 0.0843MV+108.3718RI+-0.247ST | 0.764 | 7.533 |
| **47G** | logP,FW,MV,D | $pC_7$= -148.566+0.237MR +89.703RI+-0.243ST | 0.767 | 7.689 |
| **48G** | logP,FW,D,MR,MV,RI | $pC_7$=4.053+ 0.0246ST | 0.175 | 1.912 |
| **49G** | logP.ST,D,MR,FW,MV | $pC_7$=-3.077+5.164RI | 0.159 | 1.703 |
| **50G** | FW,MV,ST,logP,D | $pC_7$=-22.246+0.0591MR +13.799RI | 0.358 | 2.235 |
| **51G** | FW,MV,D,ST,logP | $pC_7$=-22.246+0.0591MR +13.799RI | 0.358 | 2.235 |
| **52G** | FW,RI,ST,logP,D | $pC_7$=-0.0906+ 0.249MR+ -0.0668MV | 0.365 | 2.304 |
| **53G** | MR,FW,ST,logP,D | $pC_7$=-28.746+ 0.0205MV+17.896RI | 0.353 | 2.185 |
| **54G** | MR,MV,ST,logP,D | $pC_7$=-7.531+0.00311FW+ 7.286RI | 0.186 | 0.916 |
| **55G** | MV,RI,ST,logP | $pC_7$=-15.425+0.311MR+-0.061FW +10.124D | 0.509 | 2.420 |
| **56G** | MV,RI,ST,FW,MR,D | $pC_7$=6.052-0.0447ClogP | 0.889 | 72.027 |

Table (2.14): The QSAR Models between Descriptors and Biological Activity of Phenylaminonaphtoquinone De
Cell Line.

| No. | Removed Parameters | QSAR Equation | $r^2$ | F |
|---|---|---|---|---|
| **1H** | logP,MR,FW | $pC_8$= -110.563+0.048 MV+65.958RI+-0.119ST+1.663D | 0.336 | 0.8 |
| **2H** | logP,MR,MV | $pC_8$= -121.882+0.0436FW+ 79.881 RI-0.149ST-7.497D | 0.349 | 0.9 |
| **3H** | logP,MR,RI | $pC_8$= 41.275+0.144FW+-0.188MV+0.118ST+-33.223D | 0.321 | 0.8 |
| **4H** | logP,MR,ST | $pC_8$= -18.583+0.210FW+-0.244MV+46.362RI+ -46.240D | 0.362 | 0.9 |

| | | | | |
|---|---|---|---|---|
| **5H** | logP,MR,D | $pC_8$= -117.038+0.00971FW+0.0386MV+71.362RI+-0.135ST | 0.339 | 0.8 |
| **6H** | logP,FW,MV | $pC_8$= -85.573+0.127MR+50.724RI-0.100ST+1.346 | 0.332 | 0.8 |
| **7H** | logP,FW,RI | $pC_8$= -1.167+0.319MR -0.0916MV +0.0149ST+-0.126D | 0.312 | 0.7 |
| **8H** | logP,FW,ST | $pC_8$= -66.195-0.156MR +0.0796MV+40.099RI +-0.207D | 0.326 | 0.8 |
| **9H** | logP,FW,D | $pC_8$= -104.822-0.184MR +0.104MV+63.444RI+-0.0610ST | 0.333 | 0.8 |
| **10H** | logP,MV,RI | $pC_8$= 0.157+0.0224 MR+-0.00139FW+0.0790ST+-0.936D | 0.303 | 0.7 |
| **11H** | logP,MV,ST | $pC_8$= -76.606-0.408 MR +68.993RI+0.131FW+-28.845D | 0.352 | 0.9 |
| **12H** | logP,MV,D | $pC_8$= -98.208+0.104MR+0.00919FW+ 59.752RI+-0.124ST | 0.336 | 0.8 |
| **13H** | logP.RI,ST | $pC_8$= 50.494+0.595MR+0.189FW+-0.428MV+ -41.580D | 0.342 | 0.9 |
| **14H** | logP.RI,D | $pC_8$==-1.536+0.337 MR+-0.000632FW-0.096MV+0.00844ST | 0.312 | 0.7 |
| **15H** | logP.ST,D | $pC_8$= -66.150+-0.163MR +-5.741x$10^{-5}$FW+ 0.081MV+40.016RI | 0.326 | 0.8 |
| **16H** | FW,MV,RI | $pC_8$==-7.507+0.985logP+0.0199MR +0.136ST+ -0.247D | 0.356 | 0.9 |
| **17H** | FW,MV,ST | $pC_8$= -64.886+0.774logP+0.094MR +34.818RI+1.369D | 0.363 | 0.9 |
| **18H** | FW,MV,D | $pC_8$= -39.285+0.839logP+0.0655MR+ 19.537RI+0.0640ST | 0.362 | 0.9 |
| **19H** | FW,RI,ST | $pC_8$= -8.343+0.743logP+0.549MR+-0.162MV+1.375D | 0.348 | 0.72 |
| **20H** | FW,RI,D | $pC_8$= -8.156+0.936logP+0.218MR+ -0.0594MV+0.0931$^{ST}$ | 0.360 | 0.9 |
| **21H** | FW,ST,D | $pC_8$= -75.669+0.622logP +-0.00404 MR+0.0368MV+42.655RI | 0.358 | 0.9 |
| **22H** | MR,FW,MV | $pC_8$= 2.682+1.007logP +-5.810 RI+ 0.153ST+-0.228D | 0.351 | 0.9 |
| **23H** | MR,FW,RI | $pC_8$= -7.334+0.986logP + 0.00566MV+0.140 ST+-0.251D | 0.355 | 0.9 |
| **24H** | MR,FW,ST | $pC_8$= -75.433+0.764logP + 0.0329MV+ 41.433RI+1.375D | 0.364 | 1.0 |
| **25H** | MR,FW,D | $pC_8$= -47.889+0.819 logP + 0.023405MV+ 24.980RI+0.061$^{ST}$ | 0.361 | 0.9 |
| **26H** | MR,MV,RI | $pC_8$= -6.135 +0.986logP +0.00448FW+ 0.142ST+ -1.294D | 0.356 | 0.9 |

| | | | | |
|---|---|---|---|---|
| **27H** | MR,MV,ST | $pC_8$= -72.905+0.759logP +0.0266FW+ 44.323RI+-4.543D | 0.371 | 1.0 |
| **28H** | MR,MV,D | $pC_8$= -24.446+0.972logP +0.00700FW+ 11.398RI+0.0894ST | 0.355 | 0.9 |
| **29H** | MR,RI,ST | $pC_8$= -28.167+0.0593logP +-0.108FW+0.137MV+ 26.016D | 0.214 | 0.4 |
| **30H** | MR,RI,D | $pC_8$= -7.572+0.995logP +-0.000391FW+0.00591MV+ 0.139ST | 0.355 | 0.9 |
| **31H** | MR,ST,D | $pC_8$= -74.267+0.779logP +0.00709FW+0.0235MV+41.803RI | 0.366 | 1.0 |
| **32H** | MV,RI,ST | $pC_8$= -31.317+0.675logP+0.396MR+-0.0875FW +20.749D | 0.317 | 0.8 |
| **33H** | MV,RI,D | $pC_8$= -7.818+0.985logP+0.0240MR+-0.000971FW+ 0.135ST | 0.356 | 0.9 |
| **34H** | MV,ST,D | $pC_8$= -66.781+0.788logP+0.0667MR+0.00717FW+ 37.106RI | 0.365 | 1.0 |
| **35H** | RI,ST,D | $pC_8$= -6.583+0.756logP+0.554MR+0.00700FW+-0.173MV | 0.350 | 0.9 |
| **36H** | FW,MV,RI,ST,D | $pC_8$= 8.037+-0.627logP +-0.00342FW | 0.167 | 0.9 |
| **37H** | MR,MV,RI,ST,D,FW | $pC_8$= 8.575+-0.573logP+-0.0213MR | 0.167 | 0.9 |
| **38H** | MR,MV,RI,ST,D,FW | $pC_8$= 7.246+-0.693logP | 0.152 | 1.7 |
| **39H** | MR,MV,RI,ST,logP | $pC_8$= 8.677+-0.0442MR | 0.087 | 0.9 |
| **40H** | MR,MV,RI,logP,D | $pC_8$= 1.084+-0.00938FW+4.970D | 0.198 | 1.1 |
| **41H** | FW,MV,RI,ST,logP | $pC_8$= 0.921 +0.000421FW+0.0663ST | 0.296 | 1.8 |
| **42H** | MR,MV,FW,ST,logP | $pC_8$= 3.785+-0.042MR+3.641D | 0.164 | 2.1 |
| **43H** | MR,MV,RI,FW,logP | $pC_8$= -17.241+1.496D+12.143RI | 0.274 | 1.7 |
| **44H** | MR,FW,RI,ST,logP | $pC_8$= 1.707+-0.605D+0.0688ST | 0.297 | 1.9 |
| **45H** | logP,MR,RI,ST,D,FW | $pC_8$= 8.170+-0.014MV | 0.137 | 1.5 |
| **47H** | logP,MR,RI,ST,D,MV | $pC_8$= 6.948+-0.00614FW | 0.053 | 1.8 |
| **48H** | logP,MR,FW,ST,D,MV | $pC_8$= -17.110+13.284RI | 0.262 | 3.5 |
| **49H** | logP,MR,FW,RI,D,MV | $pC_8$= 1.096+0.0654ST | 0.296 | 4.1 |

| | | | | |
|---|---|---|---|---|
| **50H** | logP,MR,FW,RI,ST,MV | $pC_8$= 0.209+3.629D | 0.085 | 0.3 |
| **51H** | MV,RI,ST,FW,MR,D | $pC_8$= 5.922-0.0287ClogP | 0.864 | 57.1 |
| **51H*** | MV,RI,ST,FW,MR,D | $pC_8$=5.978-0.0326ClogP | 0.881 | 52.0 |

### 2.1.5. Cross Validation Method

The best possible QSAR models were selected on the basis of the highest correlation coefficients $r^2$ and F-ratio, as well as the lowest standard deviations s. The selected models were additionally validated using leave one out (LOO) method of cross validation (CV) to calculate the correlation coefficients $q^2$.

Table (2.15): Cross Validation of Model 54A

| No. | $pC_{obsrv.}$ | $pC_{pred.}$ | $\Delta pC$ |
|---|---|---|---|
| 1 | 5.92 | 6.25 | -0.33 |
| 2 | 5.32 | 4.92 | 0.40 |
| 3 | 5.05 | 5.03 | 0.02 |
| 4 | 6.35 | 6.64 | -0.29 |
| 5 | 6.21 | 6.58 | -0.37 |
| 6 | 6.80 | 6.65 | 0.15 |
| 7 | 6.74 | 6.62 | 0.12 |
| 8 | 6.72 | 6.61 | 0.11 |
| 9 | 7.30 | 6.58 | 0.73 |
| 10 | 5.30 | 5.73 | -0.43 |
| 11 | 5.29 | 5.44 | -0.15 |
| 12 | 5.28 | 5.08 | 0.20 |

Table (2.16): Cross Validation of Model 53B*

| No. | $pC_{obsrv.}$ | $pC_{pred.}$ | $\Delta pC$ |
|---|---|---|---|
| 1 | 6.25 | 6.20 | 0.05 |
| 2 | 5.38 | 4.41 | 0.97 |
| 3* | 4.39 | -0.12 | 4.51 |
| 4 | 6.44 | 6.29 | 0.15 |
| 5 | 6.22 | 6.24 | -0.02 |
| 6 | 6.68 | 6.27 | 0.41 |
| 7 | 6.04 | 6.09 | -0.05 |
| 8 | 6.17 | 6.14 | 0.03 |
| 9* | 6.89 | 6.35 | 0.54 |
| 10 | 5.65 | 6.03 | -0.38 |
| 11 | 5.64 | 5.93 | -0.29 |
| 12 | 5.56 | 5.71 | -0.15 |

*outlier points.

Table (2.17): Cross Validation of Model 48C*

| No. | $pC_{obsrv.}$ | $pC_{pred.}$ | $\Delta pC$ |
|---|---|---|---|
| 13 | 5.18 | 5.18 | -0.00 |
| 14 | 5.34 | 5.31 | 0.03 |
| 15 | 5.53 | 5.48 | 0.05 |
| 16 | 5.31 | 5.36 | -0.05 |
| 17 | 5.29 | 5.36 | -0.07 |
| 18 | 5.56 | 5.39 | 0.17 |
| 19* | 5.21 | 5.22 | -0.01 |
| 20 | 5.26 | 5.39 | -0.13 |
| 21 | 5.10 | 5.21 | -0.11 |
| 22 | 5.19 | 5.01 | 0.18 |
| 23* | 5.40 | 5.21 | 0.19 |

*outlier points.

Table (2.18): Cross Validation of Model 48D

| No. | $pC_{obsrv.}$ | $pC_{pred.}$ | $\Delta pC$ |
|---|---|---|---|
| 13 | 5.35 | 5.30 | 0.05 |
| 14 | 5.41 | 5.37 | 0.04 |
| 15 | 5.64 | 5.62 | 0.02 |
| 16 | 5.25 | 5.31 | -0.06 |
| 17 | 5.22 | 5.30 | -0.08 |
| 18 | 5.51 | 5.42 | 0.09 |
| 19 | 5.18 | 5.10 | 0.08 |
| 20 | 5.13 | 5.28 | -0.15 |
| 21 | 5.05 | 4.98 | 0.07 |
| 22 | 5.01 | 4.53 | 0.48 |
| 23 | 5.12 | 4.59 | 0.53 |

Table (2.19): Cross Validation of Model 52E

| No. | $pC_{obsrv.}$ | $pC_{pred.}$ | $\Delta pC$ |
|---|---|---|---|
| 13 | 4.85 | 4.98 | -0.13 |
| 14 | 5.04 | 5.10 | -0.06 |
| 15 | 5.37 | 5.23 | 0.14 |
| 16 | 5.24 | 5.19 | 0.05 |
| 17 | 5.18 | 5.19 | -0.01 |
| 18 | 5.28 | 5.16 | 0.12 |
| 19 | 5.05 | 5.10 | -0.06 |
| 20 | 5.16 | 5.20 | -0.04 |
| 21 | 5.04 | 5.14 | -0.10 |
| 22 | 4.69 | 4.71 | -0.02 |
| 23 | 4.75 | 4.56 | 0.19 |

Table (2.20): Cross Validation of Model 46F

| No. | $pC_{obsrv.}$ | $pC_{pred.}$ | ΔpC |
|---|---|---|---|
| 24 | 5.4 | 5.31 | 0.09 |
| 25 | 4.18 | 4.93 | -0.75 |
| 26 | 5.11 | 5.04 | 0.07 |
| 27 | 4.59 | 4.70 | -0.11 |
| 28 | 6.05 | 6.18 | -0.13 |
| 29 | 5.72 | 5.63 | 0.09 |
| 30 | 5.12 | 4.99 | 0.13 |
| 31 | 4.45 | 4.81 | -0.36 |
| 32 | 5.22 | 4.65 | 0.57 |
| 33 | 4.68 | 4.86 | -0.18 |
| 34 | 5.17 | 4.66 | 0.51 |

Table (2.21): Cross Validation of Model 48F

| No. | $pC_{obsrv.}$ | $pC_{pred.}$ | ΔpC |
|---|---|---|---|
| 24 | 5.4 | 5.46 | -0.06 |
| 25 | 4.18 | 5.31 | -1.13 |
| 26 | 5.11 | 5.45 | -0.33 |
| 27 | 4.59 | 5.40 | -0.81 |
| 28 | 6.05 | 5.47 | 0.58 |
| 29 | 5.72 | 5.47 | 0.25 |
| 30 | 5.12 | 5.45 | -0.33 |
| 31 | 4.45 | 5.39 | -0.94 |
| 32 | 5.22 | 5.45 | -0.23 |
| 33 | 4.68 | 5.42 | -0.74 |
| 34 | 5.17 | 5.45 | -0.28 |

Table (2.22): Cross Validation of Model 56G

| No. | $pC_{obsrv.}$ | $pC_{pred.}$ | ΔpC |
|---|---|---|---|
| 24 | 5.59 | 5.73 | -0.14 |
| 25 | 5.2 | 5.18 | 0.02 |
| 26 | 6.1 | 5.89 | 0.21 |
| 27 | 5.31 | 5.27 | 0.04 |
| 28 | 6.1 | 5.94 | 0.16 |
| 29 | 5.55 | 5.79 | -0.24 |
| 30 | 5.43 | 5.60 | -0.17 |
| 31 | 5.92 | 5.88 | 0.04 |
| 32 | 5.34 | 5.38 | -0.04 |
| 33 | 5.11 | 4.92 | 0.19 |
| 34 | 5.92 | 5.89 | 0.03 |

Table (2.23): Cross Validation of Model 51H*

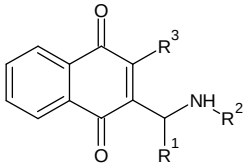
| No. | $pC_{obsrv.}$ | $pC_{pred.}$ | $\Delta pC$ |
|---|---|---|---|
| 24 | 5.92 | 5.85 | 0.07 |
| 25* | 4.83 | 4.49 | 0.34 |
| 26 | 5.11 | 5.14 | -0.03 |
| 27 | 5.03 | 4.84 | 0.19 |
| 28 | 5.64 | 5.87 | -0.23 |
| 29 | 6.22 | 5.81 | 0.41 |
| 30 | 5.09 | 5.25 | -0.16 |
| 31 | 4.96 | 4.83 | 0.13 |
| 32 | 5.62 | 5.74 | -0.12 |
| 33* | 5.08 | 5.15 | -0.07 |
| 34 | 5.22 | 5.85 | 0.07 |

*outlier points

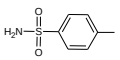
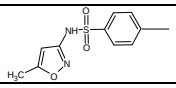
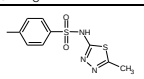
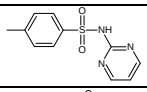
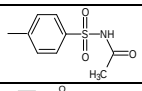
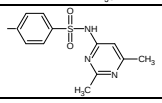
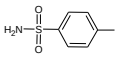
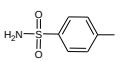
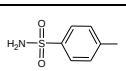
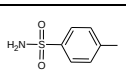
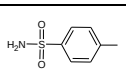
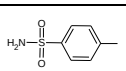
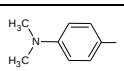
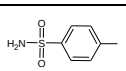
### 2.1.6. Modeling 1,4-Naphthoquinones

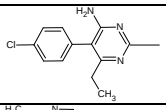
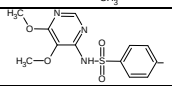
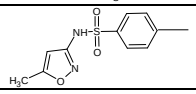
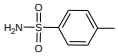
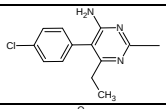
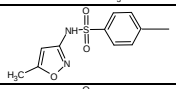
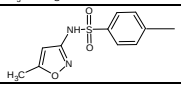
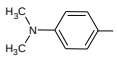
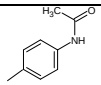
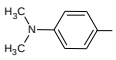
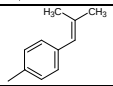
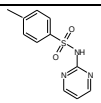
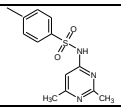
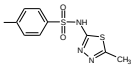
100 compounds were modeled and designed using ACD/ChemSketch program and all seven descriptors were calculated table (2.15).

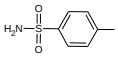
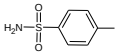
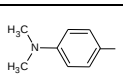
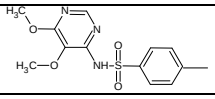
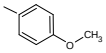
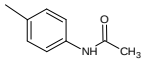
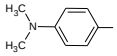
Table (2.24): Modeling 1,4- Naphthoquinone Compounds.



$R^3$=OH, H

| No. | $R^1$ | $R^2$ | Calculated Log P | Molar Refractivity ($cm^3$) | Formula Weight | Molar Volume ($cm^3$) | Index of Refraction | Surface Tension (dyne $cm^{-1}$) | Density ( $g/cm^3$) |
|---|---|---|---|---|---|---|---|---|---|
| **35** | $CH_3CH_2$- |  | 2.67 | 99.11 | 386.42162 | 260.4 | 1.686 | 75.6 | 1.483 |
| **36** | | | 2.72 | 97.80 | 370.42222 | 265.4 | 1.658 | 65.3 | 1.395 |
| **37** | $CH_3CH_2$- |  | 4.58 | 118.76 | 467.49434 | 312.8 | 1.683 | 77.8 | 1.494 |
| **38** | | | 4.63 | 117.45 | 451.49494 | 317.9 | 1.660 | 68.9 | 1.420 |
| **39** | $CH_3CH_2$- |  | 4.02 | 122.21 | 484.548 | 312.8 | 1.709 | 86.7 | 1.549 |
| **40** | | | 4.07 | 120.91 | 468.5486 | 317.8 | 1.685 | 76.9 | 1.474 |
| **41** | $CH_3CH_2$- |  | 3.51 | 119.45 | 464.4937 | 307.0 | 1.705 | 84.6 | 1.512 |
| **42** | | | 3.56 | 118.14 | 448.4943 | 312.0 | 1.681 | 74.9 | 1.437 |
| **43** | $CH_3CH_2$- |  | 2.75 | 108.52 | 428.4583 | 295.7 | 1.655 | 68.8 | 1.448 |
| **44** | | | 2.80 | 107.21 | 412.4589 | 300.7 | 1.631 | 60.4 | 1.371 |
| **45** | $CH_3CH_2$- |  | 3.27 | 128.69 | 492.54686 | 339.5 | 1.682 | 77.6 | 1.450 |
| **46** | | | 3.31 | 127.39 | 476.54746 | 344.39 | 1.661 | 69.4 | 1.382 |
| **47** |  |  | 2.44 | 127..58 | 491.51574 | 320.4 | 1.727 | 85.1 | 1.533 |
| **48** | | | 2.39 | 126.28 | 475.51634 | 325.4 | 1.703 | 75.7 | 1.461 |
| **49** |  |  | 3.49 | 120.93 | 464.4904 | 311.3 | 1.704 | 76.3 | 1.491 |
| **50** | | | 3.44 | 119.62 | 448.491 | 316.3 | 1.680 | 67.5 | 1.417 |
| **51** |  |  | 4.03 | 119.19 | 448.491 | 303.6 | 1.714 | 77.1 | 1.477 |
| **52** | | | 3.98 | 117.88 | 432.4916 | 308.6 | 1.689 | 68.1 | 1.401 |
| **53** |  |  | 2.91 | 125.67 | 492.5005 | 324.9 | 1.700 | 77.9 | 1.515 |
| **54** | | | 2.86 | 124.37 | 476.5011 | 330.0 | 1.677 | 69.3 | 1.443 |
| **55*** |  |  | 2.54 | 122.46 | 480.4898 | 309.8 | 1.720 | 83.1 | 1.555 |
| **56** | | | 2.49 | 121.15 | 464.4904 | 314.8 | 1.696 | 73.6 | 1.475 |
| **57** | $CH_3$- |  | 2.14 | 94.48 | 372.39504 | 243.9 | 1.710 | 79.3 | 1.526 |
| **58** | | | 2.19 | 93.17 | 356.39564 | 248.9 | 1.671 | 67.9 | 1.431 |
| **59*** |  |  | 3.68 | 127.70 | 477.5322 | 325.3 | 1.714 | 77.8 | 1.467 |
| **60** | | | 3.63 | 126.39 | 461.53282 | 330.3 | 1.690 | 69.2 | 1.396 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **61*** |  |  | 6.47 | 142.29 | 510.97092 | 357.2 | 1.728 | 77.7 | 1.430 |
| **62** | | | 6.31 | 140.70 | 494.97152 | 362.2 | 1.704 | 69.9 | 1.366 |
| **63*** |  |  | 4.94 | 147.63 | 572.58846 | 381.9 | 1.699 | 79.9 | 1.498 |
| **64** | | | 4.98 | 146.32 | 556.58906 | 387.0 | 1.680 | 72.4 | 1.438 |
| **65*** |  |  | 5.48 | 134.21 | 515.53714 | 339.8 | 1.719 | 82.1 | 1.517 |
| **66** | | | 5.43 | 132.90 | 499.53774 | 344.8 | 1.697 | 73.5 | 1.448 |
| **67*** |  |  | 2.83 | 116.09 | 450.46382 | 285.7 | 1.747 | 88.6 | 1.576 |
| **68** | | | 2.79 | 114.78 | 434.46442 | 290.8 | 1.719 | 77.7 | 1.493 |
| **69*** |  |  | 5.43 | 150.85 | 556.9963 | 379.6 | 1.725 | 79.7 | 1.467 |
| **70** | | | 5.28 | 149.26 | 540.9969 | 384.6 | 1.703 | 72.1 | 1.406 |
| **71*** |  |  | 5.59 | 147.34 | 558.60494 | 377.8 | 1.708 | 79.3 | 1.478 |
| **72** | | | 5.54 | 146.04 | 542.60554 | 3828 | 1.688 | 71.8 | 1.417 |
| **73*** |  |  | 4.45 | 142.10 | 561.56252 | 362.2 | 1.713 | 84.0 | 1.550 |
| **74** | | | 4.40 | 140.79 | 545.56312 | 367.2 | 1.692 | 75.7 | 1.485 |
| **75** | $CH_3$- |  | 3.79 | 97.21 | 336.38844 | 252.9 | 1.694 | 67.4 | 1.329 |
| **76** | | | 3.84 | 95.62 | 320.385 | 257.9 | 1.663 | 57.9 | 1.241 |
| **77** |  |  | 5.00 | 109.51 | 385.41196 | 282.4 | 1.702 | 68.5 | 1.364 |
| **78** | | | 4.95 | 107.92 | 369.41256 | 287.4 | 1.674 | 59.8 | 1.285 |
| **79** |  |  | 5.55 | 107.66 | 369.41256 | 274.6 | 1.712 | 69.2 | 1.344 |
| **80** | | | 5.50 | 106.07 | 353.41316 | 279.7 | 1.683 | 60.1 | 1.263 |
| **81** |  |  | 4.35 | 104.71 | 371.38538 | 256.8 | 1.750 | 80.4 | 1.445 |
| **82** | | | 4.30 | 103.13 | 355.38598 | 261.8 | 1.717 | 69.4 | 1.357 |
| **83** |  |  | 3.80 | 107.07 | 370.40062 | 260.7 | 1.758 | 80.9 | 1.420 |
| **84** | | | 3.76 | 105.48 | 354.40122 | 265.7 | 1.724 | 70.0 | 1.333 |
| **85** |  |  | 3.95 | 117.10 | 412.4373 | 291.5 | 1.736 | 77.8 | 1.414 |
| **86** | | | 3.90 | 115.52 | 396.4379 | 296.5 | 1.707 | 68.3 | 1.336 |
| **87** |  |  | 5.20 | 117.14 | 398.45378 | 296.4 | 1.720 | 70.4 | 1.344 |
| **88** | | | 5.15 | 115.56 | 382.45438 | 301.4 | 1.692 | 61.8 | 1.268 |
| **89** |  |  | 4.42 | 114.17 | 413.42206 | 296.0 | 1.698 | 70.5 | 1.396 |
| **90** | | | 4.37 | 112.59 | 397.42266 | 301.0 | 1.670 | 61.9 | 1.320 |
| **91** |  |  | 6.64 | 123.20 | 409.47642 | 315.7 | 1.708 | 65.0 | 1.297 |
| **92** | | | 6.59 | 121.61 | 393.47702 | 320.7 | 1.682 | 57.4 | 1.226 |
| **93** |  |  | 5.53 | 114.14 | 399.43854 | 298.9 | 1.689 | 66.2 | 1.336 |
| **94** | | | 5.48 | 112.56 | 383.43914 | 303.9 | 1.662 | 58.1 | 1.261 |
| **95** |  |  | 4.41 | 134.90 | 512.5365 | 333.9 | 1.741 | 88.7 | 1.534 |
| **96** | | | 4.36 | 133.59 | 496.5371 | 339.0 | 1.717 | 79.3 | 1.464 |
| **97** |  |  | 4.16 | 144.15 | 540.58966 | 366.5 | 1.715 | 81.6 | 1.474 |
| **98** | | | 4.12 | 142.84 | 524.59026 | 371.5 | 1.695 | 73.6 | 1.411 |
| **99** |  |  | 4.92 | 137.66 | 532.5908 | 339.7 | 1.744 | 90.6 | 1.567 |
| **100** | | | 4.87 | 136.36 | 516.5914 | 344.7 | 1.721 | 81.2 | 1.498 |
| **101** |  |  | 3.65 | 123.97 | 476.5011 | 322.6 | 1.694 | 73.7 | 1.476 |
| **102** | | | 3.60 | 122.66 | 460.5017 | 327.6 | 1.671 | 65.5 | 1.405 |
| **103** |  | $CH_3$- | 3.97 | 81.88 | 293.3166 | 219.8 | 1.667 | 63.3 | 1.333 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **104** | | | 3.81 | 80.29 | 277.3172 | 224.9 | 1.632 | 53.0 | 1.232 |
| **105** |  | $CH_3CH_2$- | 4.50 | 86.51 | 307.34318 | 236.4 | 1.652 | 60.8 | 1.300 |
| **106** | | | 4.34 | 84.92 | 291.34378 | 241.4 | 1.621 | 51.6 | 1.206 |
| **107** |  | $CH_3CH_2CH_2$- | 5.03 | 91.14 | 321.36976 | 252.9 | 1.640 | 58.8 | 1.270 |
| **108** | | | 4.87 | 89.56 | 305.37036 | 257.9 | 1.611 | 50.3 | 1.183 |
| **109** |  | $(CH_3)_2CH$- | 4.84 | 91.10 | 321.36976 | 253.2 | 1.638 | 57.8 | 1.268 |
| **110** | | | 4.69 | 89.52 | 305.37036 | 258.3 | 1.602 | 49.4 | 1.182 |
| **111** |  | $CH_3CH_2CH_2CH_2$- | 5.56 | 95.78 | 335.39634 | 269.78 | 1.629 | 57.0 | 1.244 |
| **112** | | | 5.40 | 94.19 | 319.39649 | 274.4 | 1.602 | 49.3 | 1.163 |
| **113*** |  |  | 3.57 | 114.56 | 434.46442 | 287.3 | 1.728 | 80.8 | 1.511 |
| **114** | | | 3.52 | 113.26 | 418.46502 | 292.3 | 1.702 | 70.8 | 1.431 |
| **115*** |  |  | 4.17 | 123.73 | 460.5017 | 312.7 | 1.721 | 77.9 | 1.472 |
| **116** | | | 4.15 | 122.43 | 444.5023 | 317.8 | 1.697 | 69.0 | 1.398 |
| **117*** |  | $CH_3$- | 2.93 | 90.44 | 339.34198 | 242.3 | 1.669 | 67.3 | 1.400 |
| **118** | | | 2.78 | 88.85 | 323.34258 | 247.3 | 1.637 | 57.4 | 1.307 |
| **119*** |  |  | 5.05 | 160.76 | 615.65626 | 419.9 | 1.691 | 77.7 | 1.465 |
| **120** | | | 5.00 | 159.46 | 599.65686 | 425.0 | 1673 | 71.0 | 1.410 |
| **121** |  | $CH(CH_3)_2CH_2$- | 5.38 | 95.74 | 335.39634 | 269.7 | 1.627 | 56.1 | 1.243 |
| **122** | | | 5.22 | 94.15 | 319.39649 | 274.8 | 1.601 | 48.4 | 1.162 |
| **123** | $CH_3$- |  | 4.12 | 87.72 | 307.34318 | 231.2 | 1.683 | 65.7 | 1.329 |
| **124** | | | 4.16 | 86.13 | 291.34378 | 236.2 | 1.649 | 55.6 | 1.233 |
| **125** | $CH_3$- |  | 3.47 | 89.57 | 323.34258 | 238.9 | 1.672 | 65.1 | 1.353 |
| **126** | | | 3.52 | 87.99 | 307.34318 | 243.9 | 1.640 | 55.3 | 1.259 |
| **127** | $CH_3$- |  | 2.91 | 84.77 | 309.316 | 213.4 | 1.725 | 78.6 | 1.449 |
| **128** | | | 2.96 | 83.19 | 293.3166 | 218.4 | 1.686 | 65.8 | 1.342 |
| **129** | $CH_3$- |  | 1.97 | 87.13 | 308.33124 | 217.2 | 1.734 | 79.2 | 1.419 |
| **130** | | | 2.02 | 85.54 | 292.33184 | 222.2 | 1.696 | 66.5 | 1.315 |
| **131** | $CH_3$- |  | 2.12 | 97.17 | 350.36792 | 248.0 | 1.712 | 75.8 | 1.412 |
| **132** | | | 2.17 | 95.58 | 334.36852 | 253.0 | 1.679 | 65.0 | 1.321 |
| **133** | $CH_3$- |  | 3.79 | 97.21 | 336.3844 | 252.9 | 1.694 | 67.4 | 1.329 |
| **134** | | | 3.84 | 95.62 | 320.385 | 257.9 | 1.663 | 57.9 | 1.241 |

55≡V, 59≡IV, 61≡VII, 63≡IX, 65≡VIII, 67≡III, 69≡XII, 71≡XI, 73≡XIII, 113≡I, 115≡II, 117≡VI and 119≡X.

## 2.2. Synthesis

### 2.2.1. Materials

- 4-(Dimethylamino) benzaldehyde,$C_9H_{11}NO$, Assay 98%, Loba chemie Pvt. Ltd, India.
- Absolute ethanol, $C_2H_6O$, Density 0.790 – 0.793g/cm$^3$, Assay 98%, BDH chemicals Ltd, England.
- Benzaldehyde, $C_7H_6O$, Density 1.044 - 1.047g/cm$^3$, Assay 98.5-100%, Alpha Chemika, India.
- Cinnmaldehyde, $C_9H_8O_2$, Density 1.050 –1.052g/cm$^3$, Assay >98%, Alpha Chemika, India.
- Diethylether,$C_2H_6O$, Density 0.790 – 0.793g/cm$^3$, Assay 99.5%
- Ethanol, $C_2H_6O$, Density 0.789g/cm$^3$, Assay 97%, Alwatania, Sudan.
- Lawsone (2-Hydroxy-1,4-naphthoquinone), $C_{10}H_6O_3$, Assay 97%, Sigma-Aldrich, England.
- Methanol, $CH_4O$, Density 0.790 – 0.793g/cm$^3$, Assay 99.5%, Loba chemie Pvt. Ltd, India.
- Methylamine,$CH_5N$, Density 0.893 – 0.897g/cm$^3$ ,Assay 40%, Loba chemie Pvt. Ltd, India.
- Pyrimethamine, $C_{12}H_{13}ClN_4$,Assay 99%,
- Salicalaldehyde, $C_7H_6O_2$, Density 1.164–1.167g/cm$^3$, Assay 99%, Loba chemie Pvt. Ltd, India.
- Sulfadoxin, $C_{12}H_{14}N_4O_4S$, Assay 99%,
- Sulfamethoxazole, $C_{10}H_{11}N_3O_3S$,Assay 99%,
- Sulphanilamide, $C_6H_4.SO_2.NH_2$, Assay 99%, Reagent, India.
- Vanillin, $CH_3O.C_6H_3$ (OH).CHO Assay 99%, Loba chemie Pvt. Ltd, India.

### 2.2.2. Instruments

#### 2.2.2.1. Infra-Red Spectroscopy

Infra-red spectroscopy (IR) was recorded on TF/IR -4100 Fourier transform (Shimadzu, Japan) using KBr disc.

#### 2.2.2.2. Ultraviolet Spectroscopy (UV)

Ultraviolet spectroscopy (UV) was recorded on UV-1800, double beam, wave length 190-1100nm-(Shimadzu, Japan)

### 2.2.2.3. $^{1}$H Nuclear Magnetic Resonance Spectroscopy

$^{1}$H Nuclear magnetic resonance spectroscopy ($^{1}$HNMR) was recorded on Ultrashield-500 plus instrument (BRUKER, Germany) using deuterated solvents and operating at 500.13MHz for protons. Employing a 5mm high-resolution broad-band TMS gradients probe. The zg30 pulse program was used. Spectra were recorded over a sweep width of (10330.57 Hz) at 293.4k temperature and time domain data points giving an acquisition time of 1.00 seconds.

### 2.2.3. Thin Layer Chromatography (TLC)

TLC was carried out using silica gel 60 GF 254 (Merck Germany) precoated plates with different mobile phases.

### 2.2.4. Apparatus and Equipments

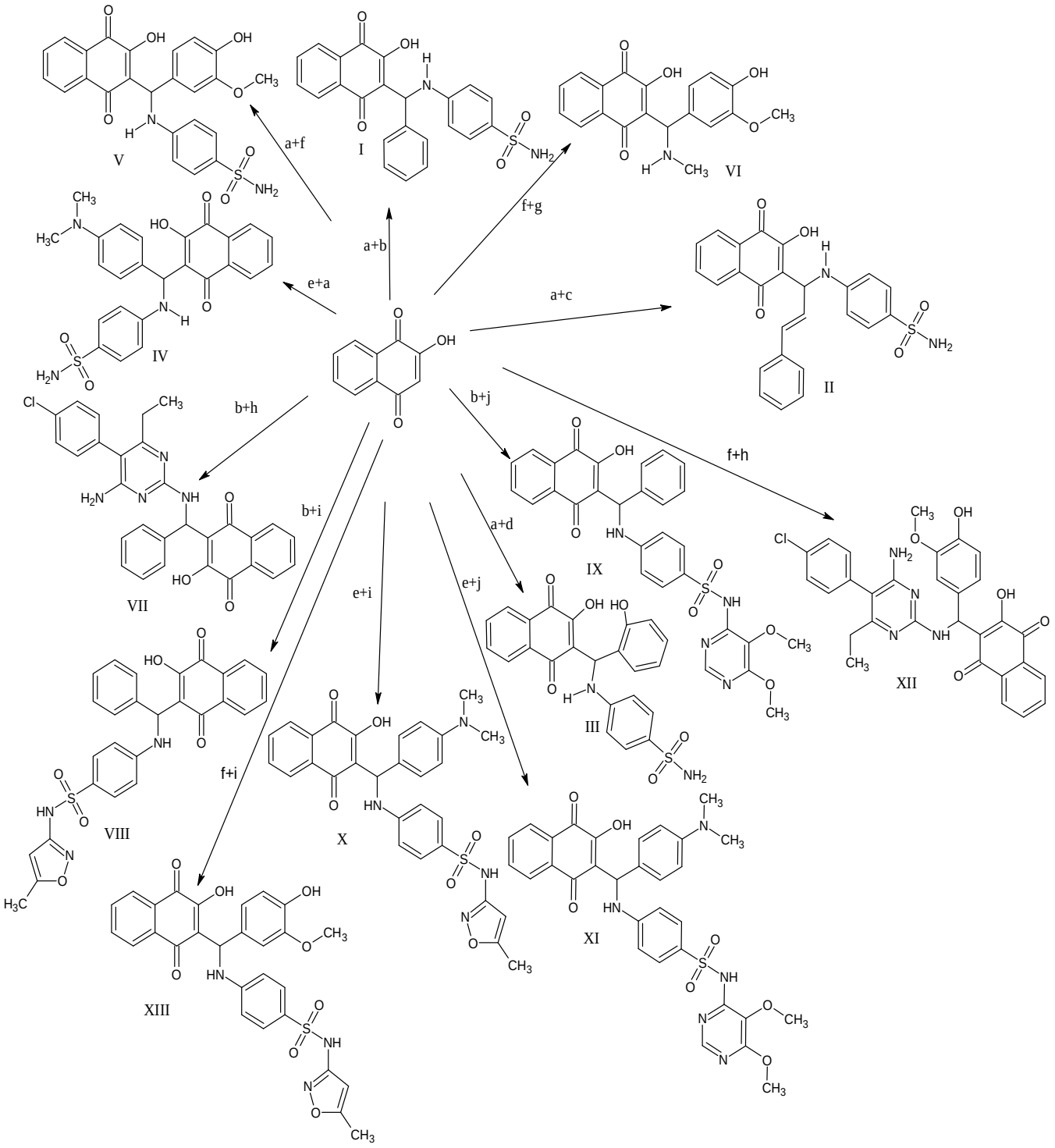
- Stirrer, Stuart, Bibby sterilin LTD, UK.
- Melting point apparatus, Gallenkamp, England.
- Sensitive balance, A&D-GR-120, Japan.

### 2.2.5. Glass Ware

- All glass wares were Pyrex type.

### 2.2.6. Synthesis of Lawsone Derivatives (I - XII):

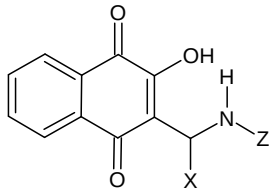
In 100 mL round bottom flask fitted with stopper glass movement over magnetic stirrer were placed 0.5 mmol(0.0870g) of lawsone and 1.5 mL of ethanol, the required amine (0.55 mmol) was added and the solution was stirred vigorously for 5 min. The required aldehyde (0.6mmol) was added and the mixture was stirred at room temperature for 12 h in the dark. The orange solid products were filtrated, washed, purified and dried under vacuum see scheme (2.1). Physical and chemical properties were tabulated (table 2.1).

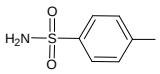
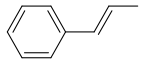
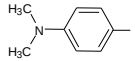
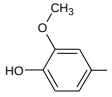
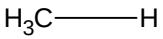
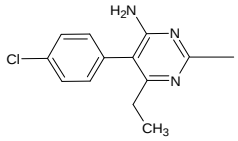
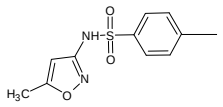
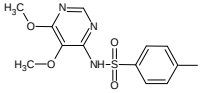



Scheme (2.1): Chemical Structures of Prepared Lawsone Derivatives

a:sulphanilamide,b:benzaldehyde,c:cinnamaldehyde,d: salicylaldehyde,e: 4-(dimethylamino) benzaldehyde, f:vanillin, g:methylamine, h:pyrimethamine, i:sulfamethoxazole,j:sulfadoxin

Table (2.25): Chemical Names of Prepared Lawsone Derivatives



| Compound no. | X | Z | Chemical Name |
|---|---|---|---|
| I |  |  | 2-hydroxy -3-[phenyl(*p*- sulfonamidophenylamino) methyl]-1,4-naphthaquinone |
| II |  | | 2-hydroxy -3-[( ethenylphenyl)( *p*- sulfonamidophenylamino) methyl] -1,4-naphthaquinone |
| III |  | | 2-hydroxy -3-[( 2-hydroxyphenyl)( *p*- sulfonamidophenylamino) methyl] -1,4-naphthaquinone |
| IV |  | | 2-hydroxy -3-[4-(dimethylamino) phenyl(*p*- sulfonamidophenylamino) methyl] -1,4-naphthaquinone |
| V |  | | 2-hydroxy -3-[(3-hydroxy -4- methoxyphenyl)(*p*- sulfonamideophenylamino) methyl] -1,4-naphthaquinone |
| VI |  |  | 2-hydroxy-3-[(4-hydroxy-3-methoxyphenyl) (methylamino) methyl] -1,4-naphthaquinone |
| VII |  |  | 2-hydroxy -3-[phenyl(5-(4-chlorophenyl) -6-ethylpyrimidine-4-amino) methyl] -1,4-naphthaquinone |
| VIII | |  | 2-hydroxy -3-[phenyl(4-amino-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfon-amido) methyl] -1,4-naphthaquinone |
| IX | |  | 2-hydroxy -3-[phenyl(4-amino-N-(5,6-dimethoxypyrimidin-4-yl) benzene-sulfonamido) methyl] -1,4-naphthaquinone |

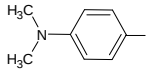
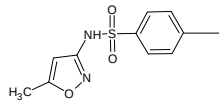
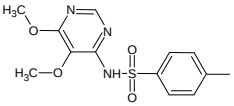
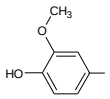
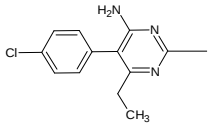
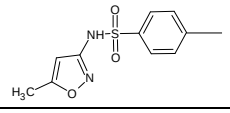
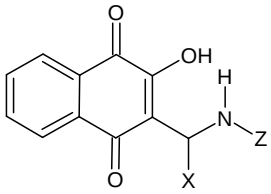
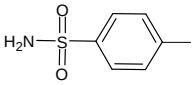
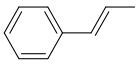
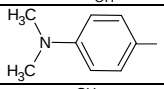
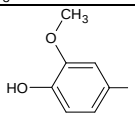
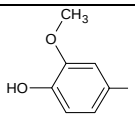
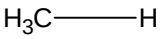
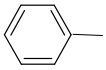
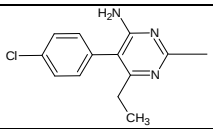
| | | | |
|---|---|---|---|
| X |  |  | 2-hydroxy -3-[4-(dimethylamino) phenyl (4-amino-<br>yl) benzenesulfonamido) methyl] -1,4-naphthaquin |
| XI | |  | 2-hydroxy -3-[4-(dimethylamino) phenyl (4-amino-<br>pyrimidin-4-yl)benzene sulfon amido) methyl] -1,4 |
| XII |  |  | 2-hydroxy -3-[(3-hydroxy -4- methoxyphenyl) (5-(<br>ethylpyrimidine-4-amino) methyl] -1,4-naphthaqui |
| XIII | |  | 2-hydroxy -3-[(3-hydroxy -4- methoxyphenyl) (4-a<br>oxazol-3-yl)benzenesulfon-amido) methyl] -1,4-na |

Table (2.26): Physicochemical Properties of Prepared Lawsone Derivatives



| Compound no. | X | Z | Color | Molecular weight | Recrystalization Solvent | Yield | Melting point (°C) |
|---|---|---|---|---|---|---|---|
| I |  |  | Orange powder | 434.46 | Ethanol-Diethyl ether | 75.3 | 209-213 |
| II |  | | Yellow orange powder | 460.50 | Ethanol-Diethyl ether | 66.4 | 210-215 |
| III |  | | Orange powder | 450 | Ethanol-Diethyl ether | 58.7 | 190-195 |
| IV |  | | Yellow powder | 477.53 | Ethanol-Diethyl ether | 88.7 | 198-202 |
| V |  | | Yellow orange powder | 480.49 | Ethanol-Diethyl ether | 58.6 | 198-202 |
| VI |  |  | Red violet powder | 339.34 | Ethanol-Diethyl ether | 61.30 | 197-201 |
| VII |  |  | Red orange powder | 510.97 | Ethanol-Diethyl ether | 81.02 | 189-193 |

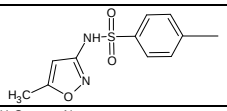
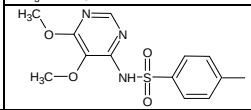
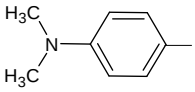
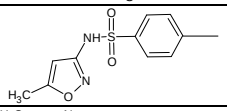
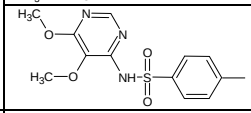
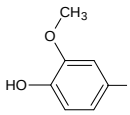
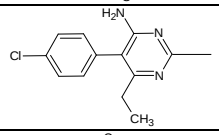
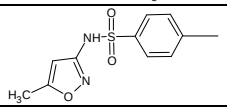
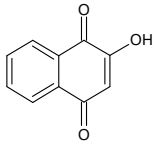
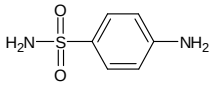
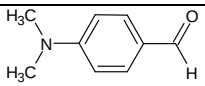
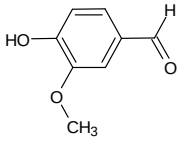
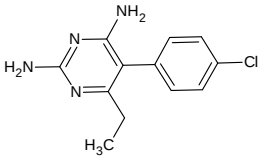
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| VIII | |  | Orange powder | 515.54 | Ethanol-Diethyl ether | 85.74 | 213-217 |
| IX | |  | Orange powder | 572.59 | Ethanol-Diethyl ether | 41.57 | 160-165 |
| X |  |  | Orange powder | 558.60 | Ethanol-Diethyl ether | 64.44 | 177-181 |
| XI | |  | Orange powder | 615.66 | Ethanol-Diethyl ether | 66.23 | 163-167 |
| XII |  |  | Red orange powder | 556.996 | Ethanol-Diethyl ether | 46.52 | 178-182 |
| XIII | |  | Red orange powder | 561.56 | Ethanol-Diethyl ether | 48.55 | 177-181 |

Table (2.27): $R_f$ Value of Starting Materials; Solvent System Chloroform: Methanol (9.5:0

| Starting Material | Lawson | Sulphanilamide | 4-(Dimethylamino) Benzaldehyde | Vanillin | Pyrimethamine | Sulfamet |
|---|---|---|---|---|---|---|
| $R_f$ value | 0.75 orange | 0.54 | 0.91 | 0.50 | 0.56 | 0. |

Table (2.28): Infrared Spectrum Bands of Starting Materials

| Structure of Starting Material | C=O st.vib. | O-H st.vib. | C-O st.vib. | C-H st.vib. (aliphatic) | C-H st.vib. (aromatic) | $CH_3$ st.vib. | C=C st.vib. (aromatic) | 1°N-H st.vib. | 2°N-H st.vib. | C-N st.vib. | $SO_2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  Lawson | 1680, 1640 | board 3600 - 3300 | 1210 | - | 3080 | - | 1600-1440 | - | - | | |
|  Sulphanilamide | - | - | - | 3060 | - | - | 1600-1460 | 3460, 3320, 3150, ben.1630, | - | 1290 | 11 |
|  4-(Dimethylamino) Benzaldehyde | 1610 | - | - | 2720 | - | - | 1600-1430 | - | | 1240 | |
|  Vanillin | 1640 | broad 3400 - 3000 | 1280 | 2925 | 3010 | 1380 | 1600-1440 | - | - | - | |
|  Pyrimethamine | - | - | - | - | - | 1380 | 1600-1440 1080 (C-C) aliphatic | 3460, 3320, 3150, ben.1630 | - | 1280 | |

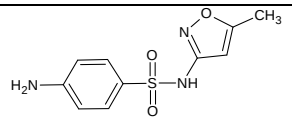
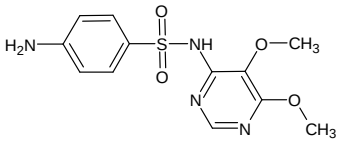
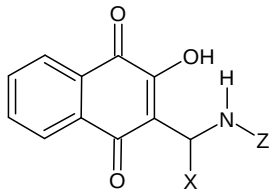
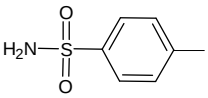
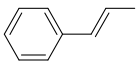
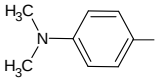
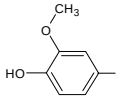
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  Sulfamethoxazole | - | - | 1160 | - | - | 1370 | 1600-1440 | 3470, 3380, 3300, ben.1620 | - | 1260 | 11 |
|  Sulfadoxin | - | - | 1190 | 2950 | 3050 | 1370 | 1600-1450 | 3470, 3380, 3270, ben.1650 (2º 3240) | - | 1220 | 11 |

Table (2.29): Infrared Spectrum Bands of Synthesized Compounds




| Compound no. | X | Z | C=O st.vib. | C=O st.vib. | C=C st.vib. (aromatic) | C-H st.vib. (Aromatic) | C-H st.vib. (aliphatic) | O-H st.vib. | C-O st.vib. | N-H st.vib. | C-N st.vib. | S=O st.vib. sym |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I |  |  | 1660 | 1640 | 1600 - 1440 | - | 2910 2850 | 3600-3200 broad | - | 3380, 3330, 3260, bend. 1550 | 1280 | 1150 |
| II |  | | 1605 | 1620 | 1600 - 1450 | 3040 | 2920 | 3600-3200 broad | - | 3350, 3460, 3370 | 1260 | 1150 |
| III |  | | 1620 | 1590 | 1600 - 1450 | 3080 | - | 3600-3200 broad | 1100 | 3340, 3240 | 1280 | 1160 |
| IV |  | | 1605 | 1580 | 1600 - 1430 | - | 2910 2810 | 3600-3200 broad | 1180 | 3280, 3320 | - | 1150 |
| V |  | | 1605 | 1630 | 1600 - 1430 | 3080 | 2960 | 3600-3200 broad | - | 3490, 3390, 3240 | 1270 | 1150 |

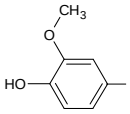
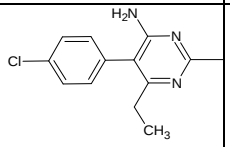
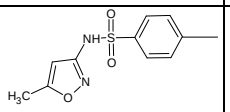
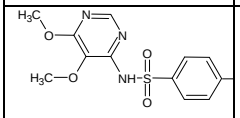
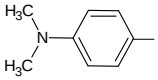
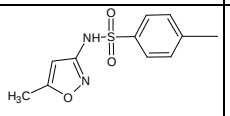
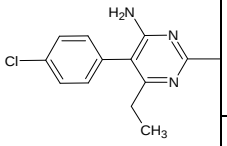
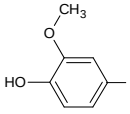
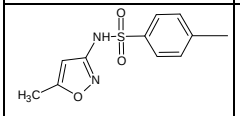
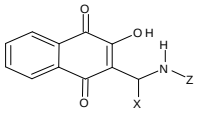
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VI |  |  | 1640 | - | 1600 - 1410 | 3005 | 2920 | 3600-3200 | - | 3280 | 1290 | 1140 |
| VII |  |  | 1640 | 1680 | 1600 - 1470 | - | 2980 | 3600-3100 | 1100 | 3460, 3290, 3100 | 1260 | - |
| VIII |  |  | 1620 | 1680 | 1600 - 1460 | 3070 | - | 3600-3200 | - | 3370, 3320, 3290 | 1260 | 1160 |
| IX | |  | 1670 | 1630 | 1600 - 1450 | 3070 | 2940 | 3600-3200 | - | 3360, 3320 | 1210 | 1160 |
| X |  |  | 1680 | 1650 | 1600 - 1450 | 3080 | 2950 | 3600-3200 | - | 3460, 3380, 3240 | 1280 | 1160 |
| XI | |  | 1680 | 1640 | 1600 - 1460 | 3080 | 2970 | 3600-3200 | - | - | 1280 | 1340 |
| XII |  | | - | - | - | - | - | 3600-3200 | - | - | - | - |
| XIII | |  | 1680 | 1650 | 1600 - 1450 | - | 2910 | 3600-3200 | - | - | - | - |

Table (2.30): Ultraviolet Spectra Data of Starting Materials

| **Compound no.** | **$\lambda_{max}$** |
|---|---|
| Lawson | 339.60, 268.80, 231.40, 216.00 |
| Sulphanilamide | 339.80,262.40 |
| 4-(Dimethylamino)benzaldehyde | 341.20,241.60 |
| Vanillin | 308.20,277.80, 230.40, 204.80 |
| Pyrimethamine | 341.20,285.20, 201.80 |
| Sulfamethoxazole | 341.20, 269.60 |
| Sulfadoxin | 342.00, 273.80 |

Table (2.31): Ultraviolet Spectra Data of Synthesized Compounds



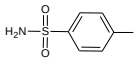
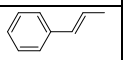
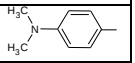
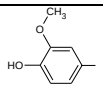
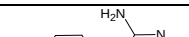
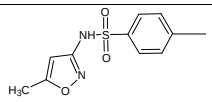
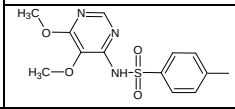
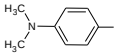
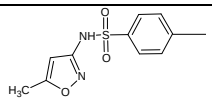
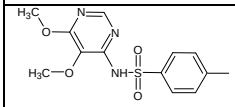
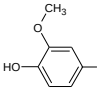
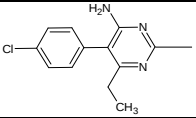
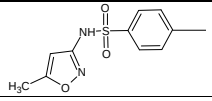
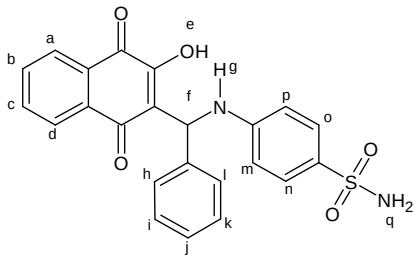
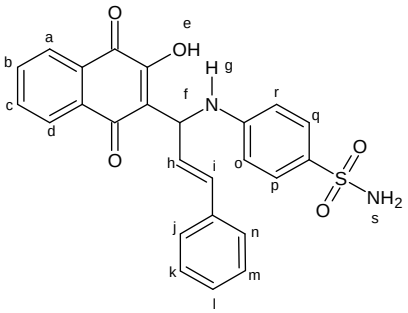
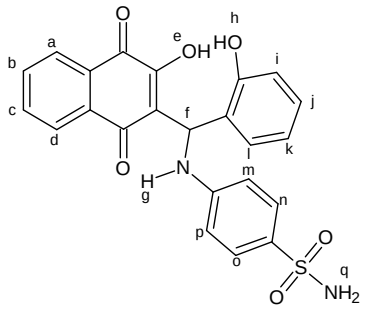
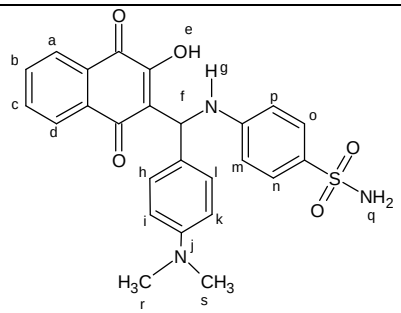
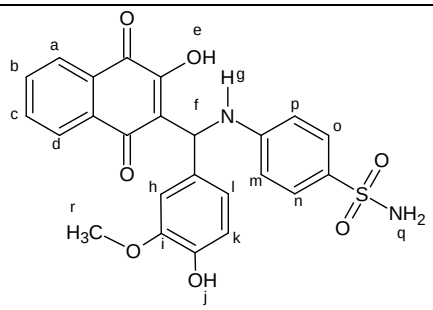
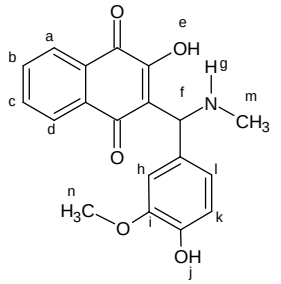
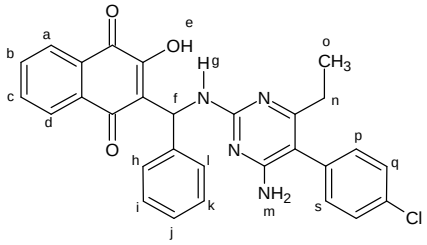
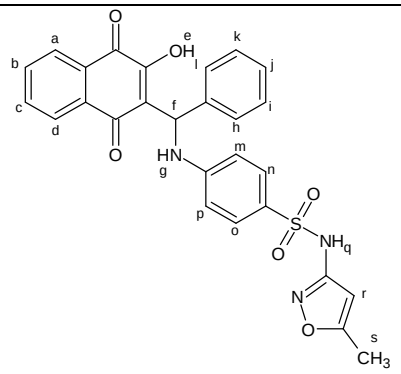
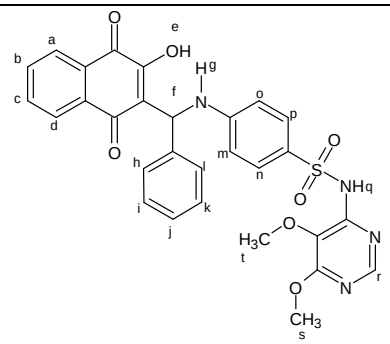
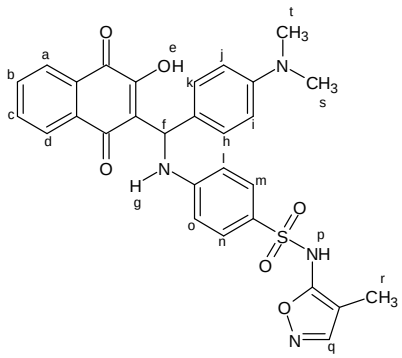
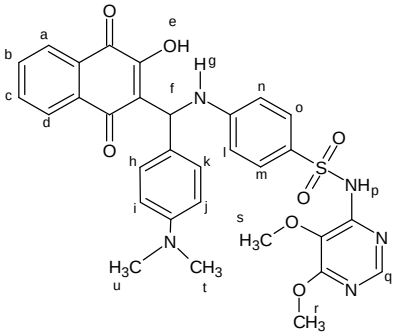
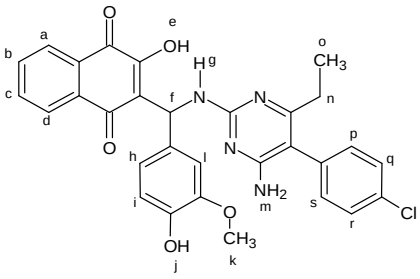
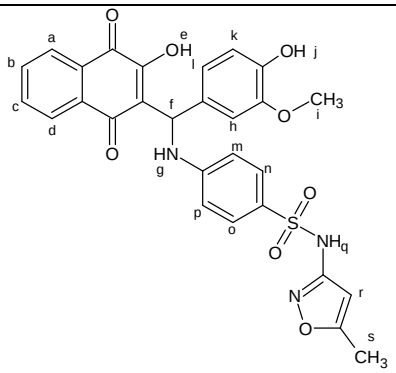
| Compound no. | X | Z | **$\lambda_{max}$** |
|---|---|---|---|
| I |  |  | 338.20,210.20 |
| II |  | | 310.80,230.20, 202.60 |
| III |  | | 339.60,274.20, 233.60,203.00 |
| IV |  | | 370.40,242.60,201.60 |
| V |  | | 331.00,264.00, 240.40,202.20 |
| VI |  |  | 274.20, 207.00 |
| VII |  |  | 273.40,217.40 |
| VIII | |  | 273.20, 231.00, 203.20 |
| IX | |  | 272.20,203.80 |
| X |  |  | 276.60, 252.20, 201.80 |
| XI | |  | 273.80,230.40,202.80 |
| XII |  |  | 274.20,203.40 |
| XIII | |  | 274.20,203.40 |

Table (2.32):[1]H NMR Data of Synthesized Compounds.

| No. | Structure of Compound | Chemical Shift (ppm) |
|---|---|---|
| I |  | q: 7.48 ppm, s, 1H, N-H (1º amino group)<br>f: 5.87 ppm, s, 1H, C-H bind to 2º amino group<br>g: 4.89 ppm, s, 1H, N-H (2º amino group)<br>a, d: 8.01ppm, dd, 2H, H-Ar<br>b, c, h, i, j, k, l, m, n, o, p: 7.58-7.56 ppm, m, 11H, H-Ar |
| II |  | f: 5.03 ppm, s, 1H, C-H bind to 2º amino group<br>g: 4.75 ppm, s, 1H, N-H (2º amino group)<br>a, d: 8.09-8.07 ppm, m, 2H, H-Ar<br>b, c, j, k, l, m, n, o, p, q, r: 7.86-7.47 ppm, m, 11H, H-Ar<br>h: 6.84ppm,t,1H, H-C=C<br>i: 6.82ppm,d,1H, H-C=C |
| III |  | h: 10.01ppm,s, 1H, O-H<br>q: 7.52 ppm, s, 1H, N-H (1º amino group)<br>a, d: 7.70-7.68 ppm, m, 2H, H-Ar<br>b, c, j, k, m, n, o, p: 7.58-7.53 ppm, m, 8H, H-Ar<br>i: 6.75ppm, t, 1H, H-Ar<br>l: 6.84ppm, t, 1H, H-Ar |
| IV |  | q: 7.51 ppm, s, 1H, N-H (1º amino group)<br>f: 5.87 ppm, s, 1H, C-H bind to 2º amino group<br>g: 4.89 ppm, s, 1H, N-H (2º amino group)<br>a, d: 7.90ppm, dd, 2H, H-Ar<br>b, c, i, k, m, n, o, p: 7.58-7.56 ppm, m, 8H, H-Ar<br>h, l: 6.78ppm, dd, 2H, H-Ar<br>r, s: 3.09 ppm, s, 6H, $CH_3$-N |

| | | |
|---|---|---|
| V |  | j: 9.65 ppm, s, 1H, O-H<br>q: 7.83 ppm, s, 1H, N-H (1º amino group)<br>f: 5.18ppm, s,1H, C-H bind to 2º amino group<br>g: 4.50 ppm, s, 1H, N-H (2º amino group)<br>a, b, c, d, h, k, l, m, n, o, p: 7.49-6.57 ppm, m, 11H, H-Ar<br>r: 3.75ppm, s, 3H, $CH_3$ |
| VI |  | m: 3.04ppm, d, 3H, $CH_3$-N<br>n: 2.77ppm, s, 3H, $CH_3$-O<br>f: 5.29 ppm, s, 1H, C-H bind to 2º amino group<br>g: 2.91-2.86 ppm, m, 1H, N-H (2º amino group)<br>a, b, c, d, h, k, l: 7.26-6.53 ppm, m, 7H, H-Ar |
| VII |  | f: 5.36 -5.33 ppm, s, 1H, C-H bind to 2º amino group<br>g: 4.61 ppm, s, 1H, N-H (2º amino group)<br>a, d: 8.09 ppm, m, 2H, H-Ar<br>b, c, h, i, j, k, l, p, q, r, s: 7.94-7.21 ppm, m, 11H, H-Ar<br>m: 6.78ppm, s, 2H, N-H (1º amino group)<br>n:1.25ppm, dd, 2H, -$CH_2$-<br>o:3.17-3.01ppm, m, 3H, $CH_3$- |
| VIII |  | q: 9.98 ppm, s, 1H, N-H (1º amino group) bind to heterocycle<br>f: 5.85 ppm, s, 1H, C-H bind to 2º amino group<br>g: 4.60 ppm, s, 1H, N-H (2º amino group)<br>a, d: 8.03 ppm, m, 2H, H-Ar<br>b, c, h, i, j, k, l, m, n, o, p: 7.91-7.20 ppm, m, 11H, H-Ar<br>r: 6.08ppm, s, 1H, -CH on heterocycle<br>s: 2.30ppm, s, 3H, -$CH_3$ on heterocycle |

| | | |
|---|---|---|
| IX |  | f: 5.66 ppm, s, 1H, C-H bind to 2º amino group<br>g: 4.48 ppm, s, 1H, N-H (2º amino group)<br>a, d: 8.17-8.02 ppm, m, 2H, H-Ar<br>b, c, h, i, j, k, l, m, n, o, p : 7.73-7.17 ppm, m, 11H,H-Ar<br>s:4.20ppm, s, 3H, $CH_3$- near from N on heterocycle<br>t: 3.09ppm, s, 3H, $CH_3$- far from N on heterocycle |
| X |  | q: 8.15 ppm, s, 1H, H-C=<br>f: 5.87 ppm, s, 1H, C-H bind to 2º amino group<br>g: 4.89 ppm, s, 1H, N-H (2º amino group)<br>a, d: 8.05ppm, d, 2H, H-Ar<br>b, c, i, j, l, m, n, o: 7.92-7.62 ppm, m, 8H, H-Ar<br>h, k: 6.66ppm. d, 2H,H-Ar<br>s,t: 3.01,s,6H, $CH_3$- |
| XI |  | q: 8.41 ppm, s, 1H, H-C= in heterocycle<br>f: 5.81 ppm, s, 1H, C-H bind to 2º amino group<br>g: 4.49 ppm, s, 1H, N-H (2º amino group)<br>a, d: 8.17-8.02 ppm, m, 2H, H-Ar<br>b, c, h, i, j, k, l, m, n, o: 7.91-7.24 ppm, m, 10H,H-Ar<br>r:4.20ppm, s, 3H, $CH_3$- near to N on heterocycle<br>s:3.44ppm, s, 3H, $CH_3$- far from N on heterocycle<br>u,t: 3.72ppm, 6H, $CH_3$- bind to 3º amino group |
| XII |  | j: 9.65ppm,s, 1H, O-H of benzene ring<br>f: 4.49 ppm, s, 1H, C-H bind to 2º amino group<br>a, b, c, d, p, q, r, s: 7.97-7.87 ppm, m, 8H, H-Ar<br>m: 7.62ppm, s, 2H, N-H (1º amino group)<br>h, i, l: 6.54ppm,s, 3H, H-Ar<br>k: 3.82ppm, s, 3H, $CH_3O$-<br>n:3.07ppm, s , 2H, -$CH_2$-<br>o: 1.06ppm, d, 3H, $CH_3$- |

| | | |
|---|---|---|
| XIII |  | j: 9.32 ppm, s, 1H, O-H bind to phenyl group<br>f: 5.66 ppm, s, 1H, C-H bind to 2º amino group<br>g: 4.85 ppm, s, 1H, N-H (2º amino group)<br>a, d: 8.03 ppm, m, 2H, H-Ar<br>a, b, c, d, h, i, j, k, l, m, n, o, p: 7.62-7.01 ppm, m, 13H, H-Ar<br>r: 6.2ppm, s, 1H, -CH in heterocycle<br>s: 2.73ppm, s, 3H, -$CH_3$ bind to heterocycle |

## 3. Discussion

### 3.1. QSAR Analysis

Cancer, a second reason for death in the world, is described by a deregulation of the cell cycle, which results in a progressive loss of the cell separation and a non-controlled cell growth. In spite of the advancement accomplished in drug amid century, cancer is still a main life undermining pathology. Along these lines, there is an expanding requirement for new treatments, particularly those that depend on current information of tumor science and in addition that exploiting the malignancy cells phenotype. Quinones which present in many drugs are used clinically in the therapy of solid cancers (Vasquez *et al*, 2010). There are several studies on 1,4-quinone derivatives which demonstrate that the cytotoxic activities of 1,4-quinones depend on redox capability and lipophilicity (Benites *et al*, 2010).

QSAR methodologies have the potential of decreasing substantially the time and effort required for the discovery of the new medicines. A major step in constructing the QSAR models is to find a set of molecular descriptors that represents variation of the structural properties of the molecules. The QSAR analysis employs statistical methods to drive quantitative mathematical relationships between chemical structure and biological activity. Thus, the use of the QSAR in the development of a theoretical model to predict the biological activity of a set of compounds is very important. The strategy used in the QSAR methodology includes the following steps:

(1) selection of a data set; (2) generation of the molecular structures; (3) optimization of the geometry of the molecular structures by appropriate method; (4) generation of several structural descriptors; (5) application of variable selection or/and methods data reduction of the calculated descriptors; (6) regression analysis; and finally (7) evaluation of the validity and predictability of the developed QSAR models (Motta *et al*, 2011).

On this basis, seven molecular descriptors were calculated for all compounds under the study using the computer software ChemSketch/ ACDlab program version 12.01 and they are described below. The octanol/water partition coefficient (logP) is the most frequently used measure of hydrophobicity (or lipophilicity) of chemicals, which, in turn, is a very important property in medicinal chemistry, toxicology, pharmaceutical and environmental sciences (Katritzky *et al*, 1999). Molar Volume (derived from liquid-density) MV= FW/D. Refraction Index (RI) of the medium is the ratio of the velocity of light in vacuum to the velocity of light in the medium and it is an important property of the structural arrangement of atom in molecule. The molar refractivity (MR) can be determined using Lorentz-Lorentz equation:

MR= $[(RI^2-1)/(RI^2+2)]$ (FW/D) where RI is the refractive index, FW is the formula weight, D is the density of the substance (Taleganonkar *et al.*, 2011;Verma, 2006). Surface Tension (ST) or Inter facial tension is the cumulative effect of the different intra and intermolecular forces of two different surfaces. $ST=(Pc/MV)^4$ (Thakur,2005). The influence of these descriptors on the cytotoxic effects on cancer cells where collected from literature as shown on Tables (2.1), (2.2) and (2.3).

The values of calculated logP of alkylamino1,4-naphthoquinones are displayed within the range 2.17-5.09 and 4.49-11.41 for alkyl 1,4-naphthoquinones and 3.54-2.15 for amino1,4-naphthoquinones .According to these data alkyl 1,4-naphthoquinones showed the lowest hydrophilicites and amino1,4-naphthoquinones the lowest hydrophobicites which confirm with the polarity of each substituent on them. Also the direct relationship appears between MV, FW, MR and D but these descriptors are inversely portion with RI and ST.

Validation of QSAR models is a very important aspect to understand reliability of the model for prediction of a new compound not present in the data set. If 1000 reported QSAR models were considered, out of which only 50 to 60 models are really, predictive but it's not sure that these 60 models have been obeyed all the conditions and validation parameters. There are two methods of validation internal validation and external validation. Even then, predictions by QSAR models remain as a risky procedure (Verma, 2006).

Validation methods are needed to establish the productiveness of a model on unseen data and to help determine the complexity of an equation that the amount of data justifies. Using the data that created the model (an internal method) or using a separate data set (an external method) can help validate the QSAR model.

A common method for internally validating a QSAR model is cross-validation (CV, $Q^2$ or $q^2$). CV process repeats the regression many times on subsets of data. Usually each molecule is left out once (only), in turn, and the R is computed using the predicted values of the missing molecule. A cross-validated $q^2$ is usually smaller than the overall $r^2$ for a QSAR equation (Difference between $r^2$ and $q^2$ should not be more than 0.3). It is used as a diagnostic tool to evaluate the predictive power of an equation.

The process of CV begins with the removal of one or a group of compounds, which becomes a temporary test set, from the training set. A CV model is created from the remaining data points using the descriptors from the original model, and tested on the removed molecules for its ability to correctly predict the bioactivities.

In the leave-one-out (LOO) method of CV, the process of removing a molecule, and creating and validating the model against the individual molecules is performed for the entire training set.

Once complete, the mean is taken of all the $q^2$ values and reported. The data utilized in obtaining $q^2$ is an augmented training set of the compounds (data points) used to determine $r^2$. The method of removing one molecule from the training set is considered to be an inconsistent method. Many authors consider high $q^2$ (for instance, $q^2 > 0.5$) as an indicator or even as the ultimate proof of the high predictive power of, the QSAR model. They do not test the models for their ability to predict the activity of compounds of an external test set (Veerasamy *et al*, 2011).

**3.1.1. Alkyl amino-1,4-naphthoquinones**

Regressions 2A, 3A, 4A, 8A, 13A, 15A and 29A have significant value < 0.05 but for one or more than one individual regression coefficients the significant value ≥ 0.05. Regressions 52A and 53A also have significant value < 0.05 for individual regression coefficients and for the whole regression but there is correlation between FW, MV, D and RI which cannot be used any two of them in the same regression. All other regressions are rejected because their significant value≥ 0.05.

The correlation matrix of the used parameters and their correlation with the biological activity for two cancer cell lines L1210 and P388 explain that the mono-parametric regression equations between logP, MR, FW ,MV ST, RI or D and activities for L1210 and P388 with small value of Pearson correlation which gave poor models. Also, this matrix show the relation between different parameters and it's clear that there is a satisfy relation between MV, FW and D which reject as QSAR models in regressions 52A and 52B and also between MV, FW and MR in regression 53A. The partition coefficient is affected on the biological activities for this cancer cell line with poor value of Pearson correlation of 0.221 and this direct relation between mono-parameter (logP) and activity (pC) needs modification to raise this value to be acceptable mono-parametric regression equation. More than 125 equations were employed between partition coefficient and biological activity for this cancer cell lines and about 52 multi-parametric regression equations also generated between selected parameters and biological activity to find satisfactory correlation. Between them two QSAR models with mono-parametric regression equations (Table 2.7 and 2.8) were produced for both L1210 and P388 cancer cell lines in this study with high $r^2$ value of 0.856 and 0.683 eq.53A and eq. 53B respectively and the overall significant level is better than 95% Tables (6.1) and (6.2). Model 53B* is modified by excluding compound 2 which has better statistic than that of model 53B. Also the standard deviation s of model 53A and 53B* are equal 0.30422 and 0.26445 which are less than standard deviation of the biological data 0.764993 and 0.671597 respectively. F values equal 59.557 and 24.492 indicate that overall significance level is better than 95% for 53A and 53B* models respectively Tables (6.1) and (6.3).

Both these models contain ClogP descriptor. In order to confirm these models the predicted activates were calculated for different compounds and plotted the later against observed activities using cross validation method to gave $q^2$ value 0.7995 and 0.5309 respectively (fig.2.1 and fig. 2.2). The standard deviation of residual activity was 0.344245and 0.385667for both models must be less than that of original data 0.765142 and 0.425233show in table 6.1 and 6.2 .These best-fitted mono-parametric equations 53A and eq.53B* indicate that partition coefficient plays major roles in the inhibiting activity against lymphoid leukemia L1210 and Lymphoid neoplasma P388. The negative coefficient of ClogP in eq.53A and eq.53B* suggests that lower hydrophobic compounds will increase the activities. These models 53A and eq.53B* were acceptable models Tables (6.1) and (6.3).

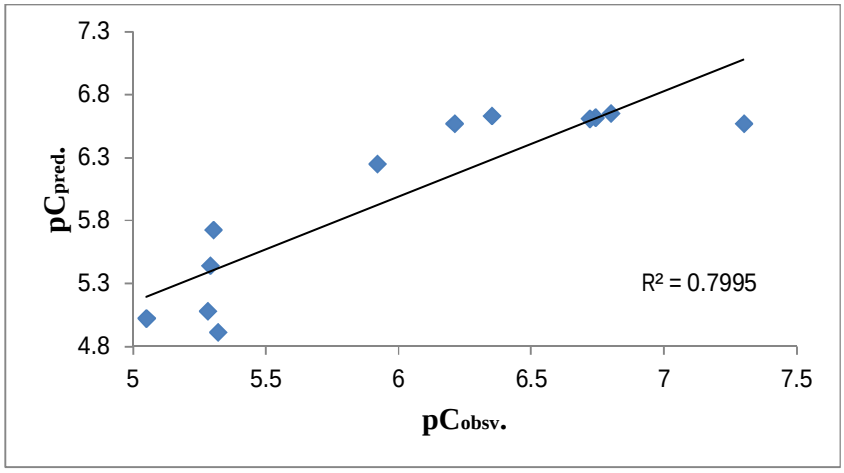



Figure (2.1): Cross Validation of Model 54A

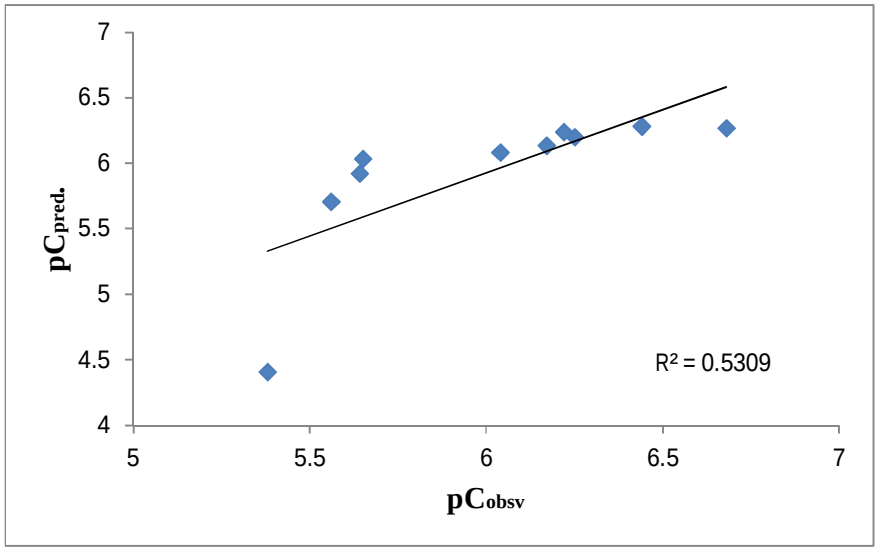



Figure (2.2): Cross Validation of Model 53B

### 3.1.2. Alkyl -1,4-naphthoquinones

For all regressions (1C-47C) and (1D-47D) significant value≥ 0.05 of both overall regressions and all individual regression coefficients were rejected shown in Table (2.9) and (2.10) except regression 48C and 48D which were satisfactory.

Regressions 3E, 41E and 43E-47E gave regression significant ≥ 0.05 so they are rejected. All other regressions gave one or more individual regression coefficients significant ≤ 0.05 when excluded them from regression that gave unsatisfied $r^2$ value except regressions 48E and 49E table (2.11)which are rejected due to good correlation between descriptors (RI and D) and (MR and FW) table (2.5).

The correlation matrix of the used parameters logP, MR, FW ,MV ST, RI , D and the biological activity for three cancer cell lines NCI-H358M, OVCAR-8 and PC-3M shown on table(2.5) which explain that there is a strong relation between logP, MR, MV and D which is same as relation between MR, FW, MV also as it between RI, D and ST with D. It appears also that the biological activity for OVCAR-8 cancer cell line ($pC_4$) has strong relation with ST and D same as the biological activity for PC-3M cancer cell line ($pC_5$) has strong relation with logP. These features confirm with rejection of models in eq.48E and eq.49E. More than 45 mono and multi-parametric regression equations generated between selected parameters and

biological activity for each cancer cell line to find satisfy correlation. Between the three QSAR models with mono-parametric regression equations (Tables 2.9, 2.10 and 2.11) were produced for NCI-H358M, OVCAR-8 and PC-3M cancer cell lines in this study with high $r^2$ value of 0.722, 0.656, 0.656 and 0.867 eq. 48C*, eq. 48D, eq. 50E, and eq. 51E respectively and the overall significant level and those of all individual regression coefficients is better than 95%Tables (6.5), (6.6), (6.7) and (6.8). All models contain partition coefficient with negative sign which suggests that the compound with highly hydrophobic effect will be less active. Model 50 E was rejected because the cross validation method did not give significant value of $q^2$ although one or two compounds were excluded. Notice that eq. 48C* was modified by removed compound no. 11 from eq.48C of the alkyl naphthoquinones set and this modification lead to better statistic values to model 48C* than model 48C tables (6.4) and (6.5).

In order to confirm these models the predicted activates of different compounds were plotted against observed activities using leave one out method and gave $q^2$value 0.5127, 0.8111, and 0.7926 respectively fig (2.3), (2.4) and (2.5). The value of residual activity was shown in tables (2.17), (2.18), and (2.19) and the standard deviation of all of them (0.11222,

0.083193and 0.097307) (Tables 6.3, 6.4 and 6.5) was less than that of observed activities 0.15411, 0.190007, and 0.218886 respectively. So, the models are acceptable.

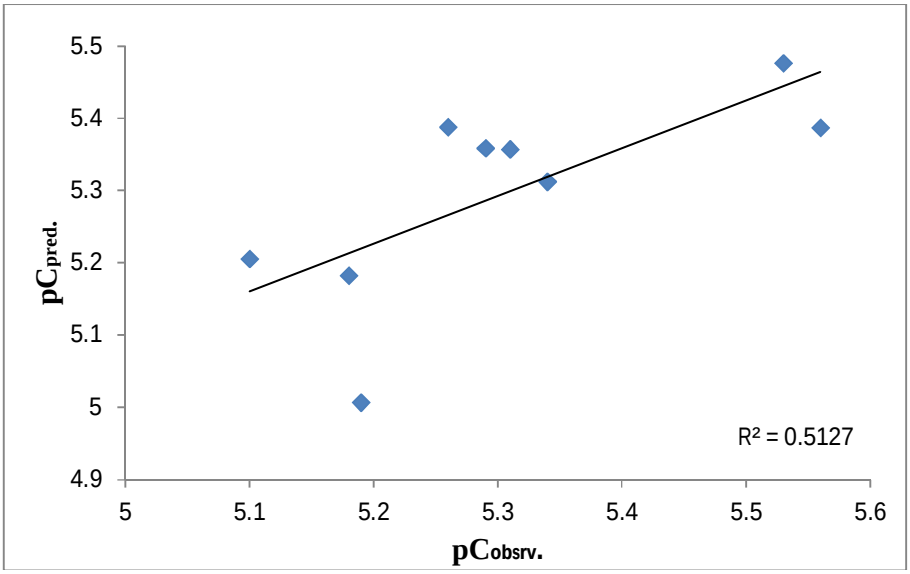



Figure (2.3): Cross Validation of Model 48C*

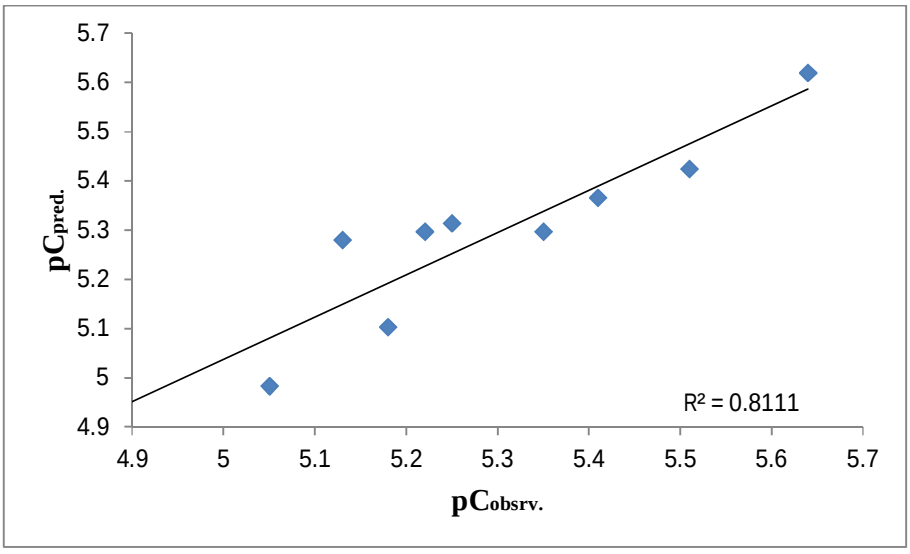



Figure (2.4): Cross Validation of Model 48D

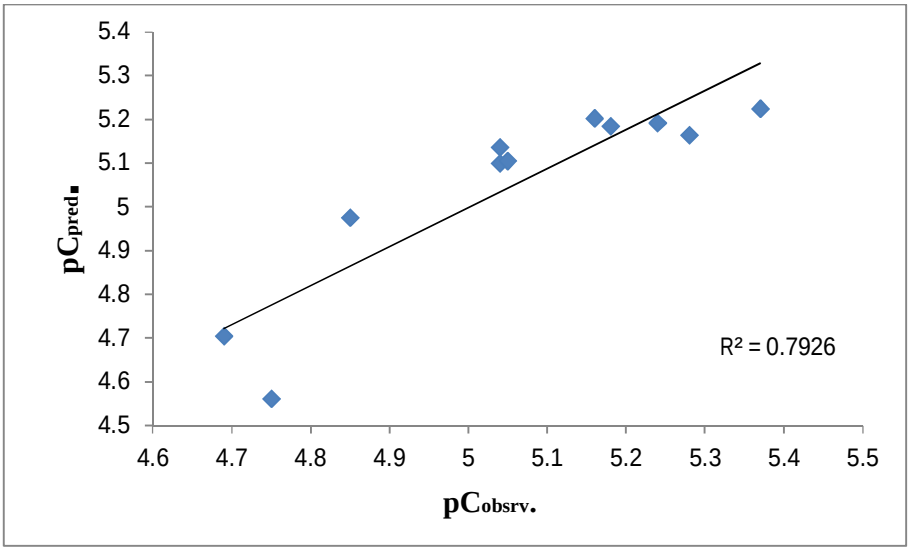



Figure (2.5): Cross Validation of Model 52E

The study indicated that QSAR of biological activity represented by $pIC_{50}$ of 2,3-Diyne-1,4-naphthoquinone derivatives against three cancer cell lines NCI-H358M, OVCAR-8 and PC-3M,can be modeled using molecular descriptors. The best model is mono-parametric regression equation for three tumor cell lines: human ovarian adenocarcinoma (OVCAR-8), human metastatic prostate cancer (PC-3M) and human bronchoalveolar lung carcinoma (NCI-H358M). These models involve ClogP with very good statistical fit as evident from their $r^2$=0.722, 0.656, and 0.867 F=20.790, 17.170 and 58.483 and sd=0.08305, 0.12179 and 0.08404 respectively. So the inhibition of these cancer cell lines is influenced mainly by, hydrophobicity. All these three models have negative coefficient of ClogP which suggest that an increase in the hydrophobicity should reduce the activity of 2,3-Diyne-1,4-naphthoquinone derivatives for all these three cancer cell lines.

### 3.1.3. Amino-1,4-naphthoquinones

The QSAR study of phenylaminonaphtoquinones involve three cancer cell lines: DU145 (prostate), T24 (bladder) and MCF7 (breast). All regressions for DU145 cancer cell line gave significant ≥ 0.05 except regressions 2F-4F, 11F, 13F, 27F, 38F, 41F, 43F and 44F. These excepted regressions were divided into two groups: first group 2F,11F,38F,41F gave t value ≥ 0.05 for all individual regression coefficients, second group gave one or more individual regression coefficients when excluded them from regression that gave unsatisfied $r^2$ value except that for 46F and 47F shown in table (2.12). Models 46F and 47F are mono-parametric regression involve surface tension and partition coefficient respectively with satisfied statistic values $r^2$= 0.662 and 0.756, F= 17.646 and 27.858, sd=0.34033 and 0.28937, the overall significant level is better than 95% and the predicted activity were calculated and plotted against

observed activity fig.(2.6) and fig.(2.7) . Cross validation of these two models gave $q^2$ = 0.5657 and 0.6799and the standard deviation of residual (0.371482 and 0.316304) less than that of observed of biological activity (0.55554) tables (6.8) and (6.9).

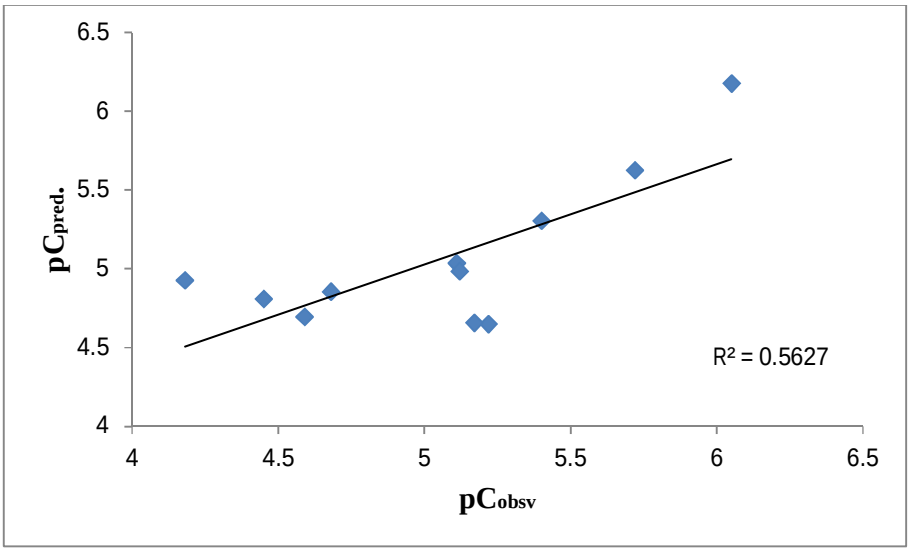



Figure (2.6): Cross Validation of Model 46F

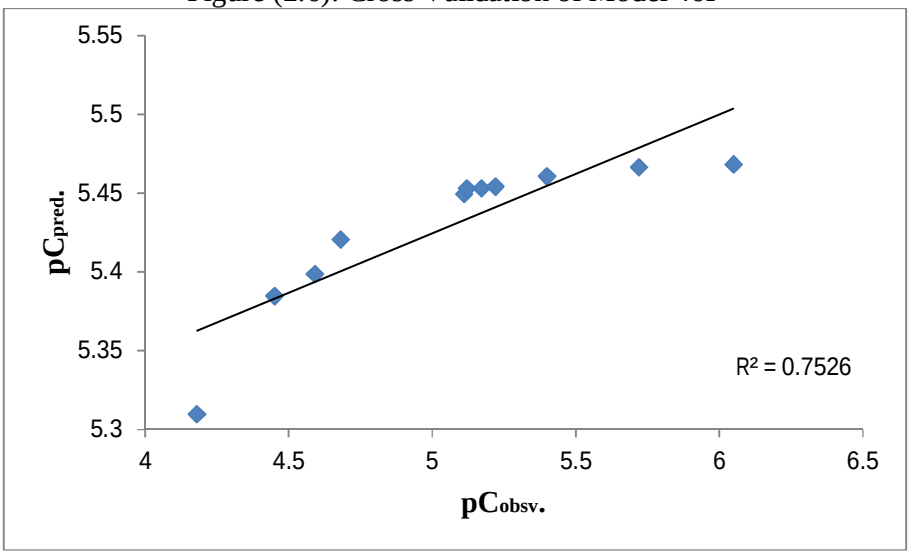



Figure (2.7): Cross Validation of Model 48F

For T24 cancer cell line significant value≥ 0.05 of both overall regressions and all individual regression coefficients (3G, 4G, 7G, 8G, 10G, 11G, 13G, 14G, 16G, 21G-23G, 26G, 28G-30G, 33G, and 36G -45G) were rejected. But regressions gave one or more (not all) individual regression coefficients with significant value≥ 0.05 and this (these) coefficient(s) was (were) excluded from regression (1G, 5G, 6G, 12G) to gave either satisfied individual regression coefficients with significant value≥ 0.05 (46G and 47G ) or (9G,15G, 17G-20G,24G,25G,27G, 31G-35G) gave other rejected regression (48G-55G). Show table (2.13). But 46G and 47G models are also rejected because the correlation between descriptors (MV/MR, RI and ST) table (2.6). Model 56G can be accepted according to $r^2$= 0.889, F=72.027 which indicate that overall

significance level is better than 95%, sd= 0.17290 and $q^2$= 0.8369 fig.(2.8) and table(2.23) and the standard deviation of the residuals (0.14635) less than that of original data(0.35889). This model show that compound with highly hydrophobic properties will be less active.

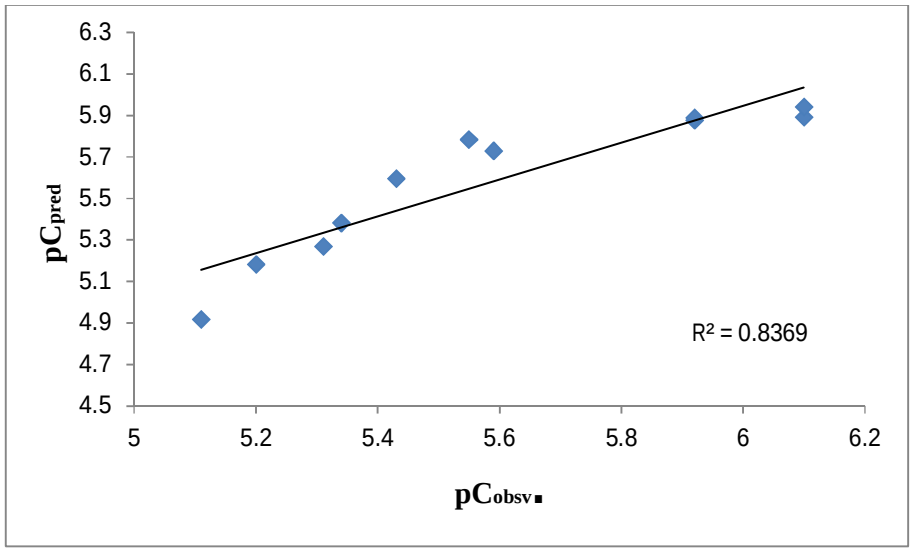



Figure (2.8): Cross Validation of Model 56G

For MCF7 cancer cell line all regressions (1H-50H) significant value≥ 0.05 of both overall regressions and all individual regression coefficients were rejected. Model 51H is accepted which involve ClogP .This model has best statistic values ($r^2$= 0.864, F=57.102, sd=0.17290 and sig.=0.000) table (2.14) . In order to validate model 51H the predicted activates of different compounds were plotted against observed activities (Table 2.23and fig (2.9)). The standard deviation of residual (0.204367) was less than that of observed activities (0.445393). Cross validation gave $q^2$ value 0.7928 for both models using leave one out method which suggest that the models are acceptable (Tables 6.11).

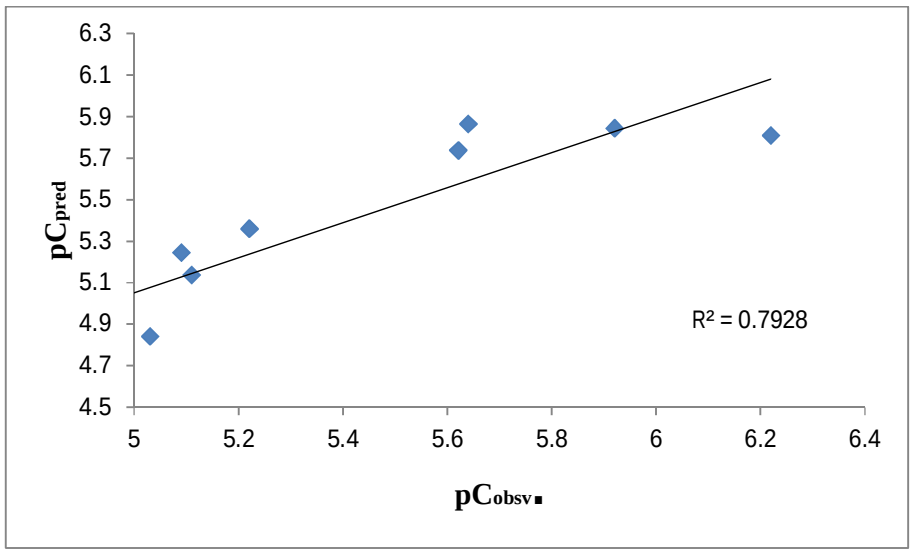



Figure (2.9): Cross Validation of Model 51H*

The correlation matrix of the used parameters logP, MR, FW ,MV ST, RI , D and the biological activity for three cancer cell lines DU145 , T24 , and MCF7 were shown on table(2.6) which explain that there is a strong relation between logP, ,MV,RI,ST and D same as relation between MR,FW,MV,RI and ST. Also as it between RI and ST with D. also it appears that the biological activity for DU145 cancer cell line ($pC_6$) has good relation with logP,RI, ST and D same as the biological activity for MCF7cancer cell line ($pC_8$) has good relation with logP. These features confirm with rejection of models in eq.46G and eq.47G.

More than 45 regression equations for three cancer cell lines DU145 (prostate), T24 (bladder) and MCF7 (breast) were generated between selected parameters and biological activity to find satisfactory correlation. Between them 4 QSAR models with mono-parametric regression equations were produced with high $r^2$ value and three of them involve ClogP descriptor and the fourth one include surface tension

These show that the cytotoxic activities of phenylaminonaphtoquinones depend largely on their hydrophobicity and the inhibition of human prostate carcinoma is influenced mainly by, surface tension.

Finally, all eight QSARs which obtained from cytotoxic activities of three different series of 1,4-naphthoquinones against different cancer cell lines (L1220, p338,NCI-H358M, OVCAR-8 ,PC-3M DU145 , T24 and MCF7 ) are linear equations and depend on the hydrophopicity of the compounds with negative coefficient and these lead to suggest these series of 1,4-naphthoquinones may target the same kind of receptor in each of these eight cancer cell lines.

### 3.1.4. Modeling 1,4- Naphthoquinone Compounds

Lipinski *et al.* in 1979 formulated the 'Rule of Five' to predict drug-likeness, which consists of four important properties, each related to the number 5. The rule is based on data in the literature for a large number of compounds, including all known drugs that correlate physical properties with oral bioavailability. Lipinski's 'Rule of Five': Poor absorption or permeation is more likely when:

- There are more than 5 H-bond donors (expressed as the sum of OHs and NHs)
- The molecular weight (MW) is over 500
- The Log P is over 5
- There are more than 10 H-bond acceptors (expressed as the sum of Ns and Os)

Compound classes that are substrates for biological transporters are exceptions to the rule.

About 100 compounds were sketched and kept the naphtjoquinone core at 50 ones and 2-hydroxynaphthoquinone core at others and the substituents at C3 were changed using different aldehydes and amines.

Compounds from 35, 37, 39, 41…… 133 are 2-hydroxy-1,4- naphthoquinone derivatives but compounds from 36, 38, 40……134 are 1,4- naphthoquinone derivatives analogous table (2.15). For all these compounds the difference in formula weight between two analogues is about 15.999 which indicate the presence or absence of OH group in C2. All other descriptors for these compounds gave the same difference between two analogous ΔlogP≈ 0.05 or 0.16, ΔMR≈1.3-1.59, ΔMV≈ -5, ΔRI≈0.02-0.039, ΔST≈12.8-6.7, ΔD≈0.18-0.06.

Compounds 69, 70, 71, 72, 73, 74, 95, 97, 98, 99, 100, 119 & 120 have FW> 500 so were excluded according to Lipinski's 'Rule of Five'.

When the $R^2$ substituent bound to amino group is simple alkyl such as methyl, ethyl, propyl, iso-propyl or n-butyl the difference in partition coefficient is equal ≈ 0.16(compounds no. 103,105, 107, 109,111, 117 and 121) and this large difference when OH group is inserted at C2 can be refer to conversion of polarity of compound which make them less hydrophobic. The same difference in partition coefficient appears for compound no. 61 and 69.

Compounds 61, 62, 65, 66, 69, 70, 71, 72, 77, 79, 80, 87, 88, 91, 92, 39, 80, 107, 111, 112, 119, 121 & 122 have logP> 5 and were excluded according to Lipinski's 'Rule of Five'.

When one or both substituents at C3 is/are nonpolar or medium in polarity the difference in molar refractivity raises from 1.3 to 1.58 or 1.59 and when OH group is inserted at C2 such as compound no. 61, 69, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 103, 105, 107, 109, 111,117,121, 123, 125, 127, 129, 131 and 133.

For all 100 compounds the difference in molar volume for two analogous is equal -5 when OH group is inserted at C2 which indicate the molar volume is not affected by the change in the polarity.

Compounds no. 57, 127 and 129 have the largest difference in the refractive index between two analogues (0.038-0.039). These compounds are similar to each other in methyl group as $R^1$ substituent and phenyl ring with simple *para*- substituent (such as $–NH_2$, -OH, $SO_2NH_2$) as $R^2$ group due to simple in the structural arrangement of atoms in the molecule. Also compounds 109 and 111 have difference in the refractive index between two analogues within range 0.036-0.034. These compounds are similar to each other in simple alkyl group as $R^1$ substituent (methyl,

isopropyl) and phenyl ring as $R^2$ group. These differences falls to 0.019 and 0.018 for compounds 63, 119 and their analogues due to steric effect of substituents $R^1$ and $R^2$.

Compounds 127, 129 and their analogues have the highest difference in the surface tension (12.8 and 12.7) and these are due to high intramolecular forces between acidic hydrogen of polar group ($NH_2$ and OH) on phenyl substituent as $R^2$ and carbonyl group of quinone nucleus. These differences fall to 6.7 for compound 119 and its analogue because there is poor intra or intermolecular forces of substituents $R^1$, $R^2$ and quinone nucleus.

Compounds 127, 129 and their analogues have the highest difference in the density (0.107 and 0.104). These differences fall to 0.055 for compound 119 and its analogue and this can be explain according to the formula weight which duplicated for compound 43(615.66) comparing to compounds 127 and 129 (309.32 and 308.33).

**3.2. Organic Synthesis**

All synthetic compound were identified using physical properties such as color and melting point, also spectroscopic techniques were used such as UV, IR, NMR spectroscopies and TLC technique.

**3.3. Synthetic Design**

Retrosynthesis of Mannich base suggests disconnection of the internal C-C and C-N bonds. By this disconnection σ-electron from C-C bond move to the α-C atom and from a C-N bond to the N atom. Two positive charges that formally appear on the central C-atom can be compensated by the double bond to the O atom; hence the third reagent is the aldehyde.

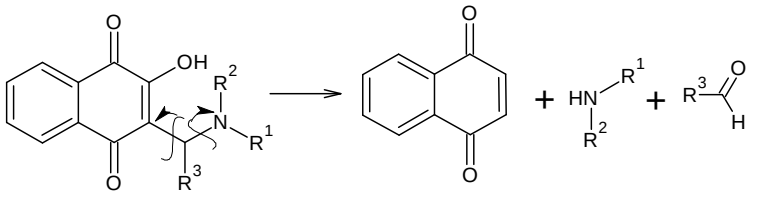
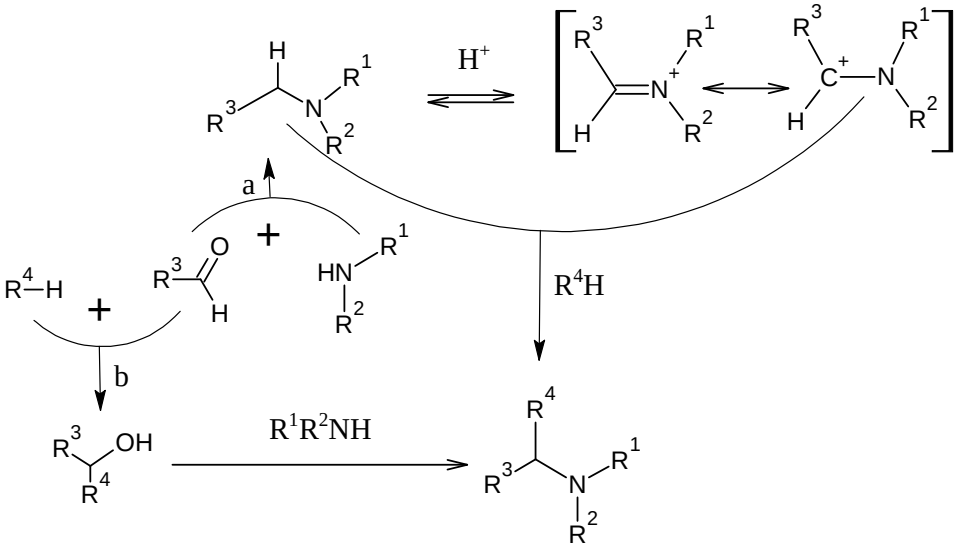



Fig (3.1): Retrosynthetic of Mannich Base.

**3.4. Reaction Mechanism**

Mannich reaction is a condensation reaction which involves three reactants: amine $R^1R^2$-NH, aldehyde R3-CHO and a substrate R4-H which is a compound containing an active hydrogen atom (such as –CH(R) C=O, -CHCHO, RC≡CH, -CHCOOH,-CHCOOOR, -$CHNO_2$, 2,4-dialkylphenol,pyrroles and furans),i.e. one that readily form a carbanion. (Bansal, 1998)

The reaction mechanism of Mannich base follows two pathways. Pathway **a** involves the iminium ion formation between the aldehyde and the amine and the substrate undergoes nucleophilic attack on the electrophilic iminium carbon. Alternatively pathway **b**, a hydroxymethyl derivative is generated,then reacts with amine to give Mannich base. (Kalsi, 2007) and (Tramontini and Angiolini, 1994)




Scheme (3.1): Mechanistic Route of Mannich Reaction

### 3.5. Spectroscopic Analysis

#### 3.5.1. IR Spectroschopic Analysis

IR spectroscopy is often used to identify structures because functional groups give rise to characteristic bands both in terms of intensity and position (frequency). The infrared spectrum can be used for molecules much as a fingerprint can be used for humans. By comparing the infrared spectra of two substances thought to be identical, you can establish whether they are, in fact, identical. A second and more important use of the infrared spectrum is to determine structural information about a molecule (Pavia *et al*, 2013).

All synthetic compounds show two different absorptions at 1680-1580 $cm^{-1}$ to both carbonyl groups ($C=O_{st.vib}$) in quinone nucleus also, aromatic $C=C_{st.vib}$ bands were observed at 1600-1410 $cm^{-1}$. The broad band at range 3600-3200 $cm^{-1}$ observed for $–OH_{st.vib}$ for all compounds. Compounds I-V and VII which contain $NH_2$ group show three stretching vibration absorption bands at range 3490-3370, 3390-3290 and 3350-3100 $cm^{-1}$. Other compounds show $–NH_{st.vib}$ for secondary amine. All synthetic compounds except VI and VII contain $SO_2$ group and two bands

at range 1140-1160 and 1300-1380 $cm^{-1}$ were observed. Also all prepared compounds absorbed at 800-840 $cm^{-1}$ which indicate a *para*-substituent on aromatic system.

### 3.5.2. UV Spectroscopic Analysis

Most organic molecules and functional groups are straightforward in the portions of the electromagnetic spectrum that are called the ultraviolet (UV) and visible (VIS) regions —that is, the regions where wavelengths range from 190 nm to 800 nm. It is often difficult to extract a great deal of information from a UV spectrum used by it. It should be clear by now that a UV spectrum is most useful when at least a general idea of the structure is already known.

However, in some cases useful information can be derived from these regions of the spectrum. That information, when combined with the details provided by infrared and nuclear magnetic resonance (NMR) spectra, can lead to valuable structural proposals (Pavia *et al*, 2013).

Molecules containing π-electrons or non-bonding electrons (n-electrons) can absorb the energy in the form of ultraviolet or visible light to excite these electrons to higher anti-bonding molecular orbitals. The more easily excited the electrons (i.e. lower energy gap between the HOMO and the LUMO), the longer the wavelength of light it can absorb.

In all synthetic compounds (except Compounds I-V) carbonyl groups show allowed π→π* transitions in the range 264.00-279.40 nm which is longer than the principle π→π* transition 190 nm for the carbonyl group and this due to the carbonyl group is part of a conjugated system of double bonds in quinone nucleus so that π→π* band is shifted to longer wavelength.

Compounds I-V show single band at wavelength in the range 310.80-370.40 nm for π→π* transition to carbonyl groups which is higher than that to other synthetic compounds (264.00-279.40) because to additional conjugation between lone pair on primary amino group of sulphanilamide and quinone nucleus.

All synthetic compounds show primary band 201.60-217.40 nm (for benzene at 184 and 202 nm)and secondary band 230.20-252.20 nm (for benzene at 255 nm)which indicate π→π* transitions in aromatic system. These bands were shifted to longer wavelength in the spectra due to polynuclear aromatic hydrocarbons.

### 3.5.3. $^{1}$HNMR Spectroscopic Analysis

The information about different type and number of protons present in compounds and the environment about the protons are elucidate by $^{1}$H nuclear magnetic resonance (1H-NMR) technique, the results were reported on δ value (ppm) scale with the signals appear to the left of TMS table (2.23).

Compound (I) showed (dd, 1Ha, 1Hd) and (m, 1Hb, 1Hc) for two protons of naphthoquinone ring at position five and eight at δ (8.01), (m, 1Hb, 1Hc) for two protons of naphthoquinone ring at position six and seven and (m, 9H) for nine protons of aromatic rings which linked with methylene group at position three in naphthoquinone ring at δ (7.58-7.56 ppm), (s,1Hg) and (s,1Hq) for a proton of secondary and primary amino groups observed at δ (4.89 ppm) and (7.48 ppm) respectively, the last signal was (s, 1H) for a protons of methylene group at δ(5.87 ppm) linked with secondary amino group fig(6.41).

Compound (II) showed multiplet at δ (8.09-8.07 ppm) which indicated a (1Ha, 1Hd) for two protons of naphthoquinone ring at C5 and C8 positions, two protons at C6 and C7 of naphthoquinone ring and nine protons of aromatic ring which linked with methylene group at position three in naphthoquinone ring observed at δ (7.86-7.47 ppm) as multiplet signal, (s,1Hf) and (s,1Hg) for a proton of methylene group and secondary amino group observed at δ (5.03 ppm) and (4.75 ppm) respectively, the last two signals were (t, 1H) and (d, 1H) for two protons of ethylene group geminal with methylene group and other with phenyl at δ(6.84 ppm) and (6.82ppm) respectively fig(6.42).

Compound (III) showed multiplet at δ (7.70-7.68 ppm) which indicated a (1Ha, 1Hd) for two protons of naphthoquinone ring, and (1Hb, 1Hc) for two protons at position six and seven in naphthoquinone ring and six protons of two aromatic rings which linked in position three in naphthoquinone ring at δ (7.58-7.53 ppm), two singlet signals observed for the first one at δ (10.01ppm) indicated the OH group of benzene ring, the second one at δ (7.52 ppm) for a proton in primary amino group, the last two triplet signals at δ (6.75ppm) and (6.84ppm) indicated a two protons of benzene ring one is near to OH group and the other one is near to methylene group respectively fig(6.43).

Compound (IV) showed, (dd,2H) at δ (7.90ppm) which indicated a (1Ha, 1Hd) for two protons of naphthoquinone ring at C5 and C8 positions, (m, 8H) at δ (7.58-7.56 ppm) which indicated a (1Ha, 1Hc) for two protons of naphthoquinone ring and six protons of aromatic rings which linked at position three in naphthoquinone ring, singlet signal observed at δ (3.09ppm) for six protons of two methyl groups which linked with nitrogen atom, three singlet signals observed (s,1Hg), (s,1Hq) and (s,1Hf) two protons of secondary and primary amino groups and the last one for methylene group at δ linked with secondary amino group observed at δ (4.89 ppm), (7.51 ppm) and (5.87 ppm) respectively, the last signal was (dd, 2H) for two nearer protons of phenyl group linked with methylene group at δ(6.68ppm) fig(6.44).

Compound (V) showed multiplet at δ (7.49-6.57 ppm) which indicated a (1Ha, 1Hd, 1Hb, 1Hc) for four protons at C8, C7, C6 and C5 of naphthoquinone ring, and seven protons of two aromatic rings which linked in position three in naphthoquinone ring, five singlet signals observed the first one at δ (9.65 1ppm) indicated an OH group of benzene ring, the second one at δ (7.83 ppm) for a proton in primary amino group, the last three singlet signals at δ (5.18,4.50 and 3.75ppm) indicated a five protons the first one for methylene group linked with secondary amino group and the second proton for secondary amino group and the last three protons for methyl group respectively fig(6.45).

Compound (VI) showed multiplet at δ (7.26-6.53 ppm) which indicated for four protons of naphthoquinone ring at C8, C7, C6 and C5, and three protons of the aromatic ring which linked in position three in naphthoquinone ring, three singlet signals observed the first one at δ (2.77ppm) indicated a methoxy group of benzene ring, the second one at δ (5.29 ppm) for a proton in mthylene group linked to secondary amino group, the last singlet signal at δ (2.91-2.86) indicated a protons of secondary amino group respectively and the last signal is doublet for three protons of methyl group linked with secondary amino group at δ (3.04ppm) fig(6.46).

Compound (VII) showed (m,1Ha, 1Hd) for two protons of naphthoquinone ring at δ (8.10ppm), (m,11H) two protons (1Ha, 1Hc) of naphthoquinone ring and nine protons of aromatic rings which linked at position three in naphthoquinone ring at δ (7.94-7.21 ppm), (d, 2H) two protons of -CH2- linked to methyl group observed as doublet signal at δ (1.25ppm), (m,3H) three protons of methyl linked to -CH2- observed as multiplet signal at δ (3.17-3.01ppm), three singlet signal observed the first one at δ (6.78ppm) indicated a primary amino group , the second one at δ (4.61 ppm) indicated a secondary amino group, the last one observed at δ (5.36 -5.33ppm) indicated a methylene linked to secondary amino group fig(6.47).

Compound (VIII) showed (m,1Ha, 1Hd) for two protons of naphthoquinone ring at δ (8.10ppm), (m,11H) for two protons (1Hb, 1Hc) of naphthoquinone ring and nine protons of aromatic rings at δ (7.91-7.20ppm), five singlet signals observed the first one at δ (9.98 ppm) indicated a HNSO2 group, the second one at δ (2.30ppm) indicated a three protons of methyl group linked to heterocyclic ring, the third one observed at δ (6.08ppm) indicated an only proton in heterocyclic ring, the last two singlet signals observed at δ (4.60 ppm) and (5.85 ppm) indicated a two protons of secondary amino group and methylene linked to this amino group respectively fig(6.48).

Compound (IX) showed, (m,2H) at δ (8.17-8.02 ppm) which indicated a (1Ha, 1Hd) for two protons of naphthoquinone ring at C5 and C8 positions, (m, 10H) at δ (7.73-7.17 ppm) which indicated a (1Ha, 1Hc) for two protons of naphthoquinone ring at C6 and C7 positions and eight

protons of two aromatic rings and heterocyclic ring which branched from position three in naphthoquinone ring, two singlet signals observed at δ (3.09 and 4.20ppm) for six protons of two methoxy groups which linked with heterocyclic ring one methoxy group near to N atom in heterocyclic ring and the other far from N atoms in this ring, two singlet signals observed (s,1Hg), and (s,1Hf) two protons of secondary amino group and methylene linked to this amino group at (5.66 and 4.48 ppm) respectively fig(6.49).

Compound (X) showed (d, 1Ha, 1Hd) at δ (8.05ppm) for two protons of naphthoquinone ring at position five and eight, (m, 1Hb, 1Hc) for two protons (1Hb, 1Hc) of naphthoquinone ring at position six and seven and (9H) for nine protons of aromatic rings which linked with methylene group at position three in naphthoquinone ring multiplet signal observed at δ (7.92-7.62ppm), (s,1Hg) and (s,1Hf) for a proton of secondary amino group and methylene linked to this amino group observed at δ (4.89 ppm) and (5.87 ppm) respectively, singlet signal observed at δ (3.01ppm) for six protons of two methyl group which linked with nitrogen atom, other singlet signal appeared at δ (8.15ppm) indicated an only proton in heterocyclic ring the last signal was (d, 2H) for two protons of phenyl group near to methylene group at δ(6.66ppm) linked with secondary amino group fig(6.50).

Compound (XI) showed (m, 1Ha, 1Hd), for two protons of C8 and C5 naphthoquinone ring at δ (8.17-8.02ppm), , (m, 10H) indicated a eight protons of two benzene rings, (1Hb, 1Hc) two protons of C7 and C6 of naphthoquinone ring observed at δ (7.91-7.24ppm), three singlet signals observed at δ (8.41 ppm), (4.20ppm) and (3.44ppm) for (1Hq)the only proton in heterocyclic ring and (3Hr, 3Hs) six protons of two methoxy groups which linked with heterocyclic ring, also other three singlet signals observed the first one at δ (5.81 ppm) for (1Hf) a proton of methylene group which linked at three position in naphthoquinone ring , the second signal at δ (4.49 ppm) for (1Hg) only proton of secondary amino group which linked with methylene group and the last signal for (3Hu,3Ht)six protons of two methyl groups which linked with N atom fig(6.51).

Compound (XII) showed (m,8H) for four protons(1Ha, 1Hd, 1Ha, 1Hc) of naphthoquinone ring and four protons of aromatic ring which linked to Cl atom and heterocyclic ring at δ (7.97-7.87 ppm), (s, 2H) two protons of -CH2- linked to methyl group observed as siglet signal at δ (3.07ppm), (m,3H) three protons of methyl linked to -CH2- observed as doublet signal at δ (1.06ppm), four singlet signal observed the first one at δ (7.62ppm) indicated a primary amino group , the second one at δ (4.49 ppm) indicated a methylene group linked with secondary amino group, the third one indicated a hydroxyl group at δ (9.65ppm) the last one observed at δ

(3.82ppm) indicated a methoxy group, Also three singlet signals appeared at δ (6.68ppm) indicated a three protons of benzene ring linked with methylene group fig(6.52).

Compound (XIII) showed (m, 13H) for four protons (1Ha ,1Hb, 1Hc, 1Hd) of naphthoquinone ring and (9H) for nine protons of aromatic rings which linked with methylene group at position three in naphthoquinone ring multiplet signal observed at δ (7.62-7.01ppm), (s,1Hg) and (s,1Hf) for a proton of secondary amino group and methylene linked to this amino group observed at δ (4.85ppm) and (5.66 ppm) respectively, singlet signal appeared at δ (6.2ppm) indicated an only proton in heterocyclic ring the other singlet signal for a proton of O-H group bind to phenyl group near to methylene group appeared at δ(9.32ppm) linked with secondary amino group and the last singlet signal at δ(2.73ppm) indicated a three protons of methyl group bind to heterocycle fig(6.50).

## 4. Conclusion and Recommendation

The following points can be concluded and recommended according to this study:

- The study indicated that QSAR of biological activity represented by $pED_{50}$ of 5,8-Dimethoxy-1,4-naphtha-quinone derivatives against L1210 (Lymphocytic leukemia) and P388 (Lymphoid neoplasma) show that the inhibition of cytotoxic activities of these compounds are influenced mainly by hydrophobicity.

- The study indicated that QSAR of biological activity represented by $pIC_{50}$ of 2,3-Diyne-1,4-naphthoquinone derivatives against three cancer cell lines human ovarian adenocarcinoma (OVCAR-8), human metastatic prostate cancer (PC-3M) and human bronchoalveolar lung carcinoma (NCI-H358M) can be modeled using molecular descriptors. The best models involve ClogP with very good statistic values. The inhibition of these cancer cell lines depend largly on their hydrophobicity.
- The relation between activity of human bronchoalveolar lung carcinoma (NCI-H358M) and partition coefficient of 2,3-Diyne-1,4-naphthoquinone derivatives also can be modeled directly .
- The QSAR study of phenylaminonaphtoquinones for three cancer cell lines: DU145 (prostate), T24 (bladder) and MCF7 (breast) can be modeled using ClogP descriptor with good statistic values. It also shows that the cytotoxic activities of phenylaminonaphtoquinones depend largely on their hydrophobicity.

- Also for DU145 (prostate) cancer cell line ST descriptor used to generate model with very good statistical fit as evident from its and the inhibition of human prostate carcinoma is influenced mainly by, surface tension.

- During this study about 100 compounds were modeled and their descriptors were calculated and the hydrophobicity of these compounds increase when removed hydroxyl group from C2 in naphthoquinone nucleus and then we suggest the cytotoxic activities of these compounds decrease.
- From these 100 compounds 13 compounds were synthesized and predicted compounds II has less biological activity against different cancer cell lines, and V have more active. Predicted Activity: II < IV < I < VI < III < V.

  Compounds VII, IX, VIII, XII, XI, XIII & X cannot be used as drug according to Lipinski's 'Rule of Five' (FW > 500 and/or logP > 5)

- Using Mannich reactions to synthesis the structure core of 2-hydroxy1,4-naphthoquinone with different substituent.
- Using different aliphatic and aromatic aldehydes and amines as a substituent in position three in 2-hydroxy1,4-naphthoquinone.
- All synthesized compounds in this study were purified using TLC techniques and their structures were characterized using spectroscopic analysis such as IR. UV and $^{1}$H-NMR.

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## 6. Appendix

### 6.1. Appendix A

**Table (6.1): Statistical Data of Model 54A**

**Model Summary**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | | Durbin-Watson |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F Change | |
| 1 | .925[a] | .856 | .842 | .30422 | .856 | 59.557 | 1 | 10 | .000 | 2.247 |

**ANOVA**

| Model | | Sum of Squares | Df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 5.512 | 1 | 5.512 | 59.557 | .000 |
| | Residual | .925 | 10 | .093 | | |
| | Total | 6.437 | 11 | | | |

**Coefficients**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| 1 | (Constant) | 6.714 | .125 | | 53.573 | .000 | 6.435 | 6.993 |
| | ClogP | -.087- | .011 | -.925- | -7.717- | .000 | -.112- | -.062- |

**Residuals Statistics**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 5.0244 | 6.6959 | 6.0239 | .70787 | 12 |
| Residual | -.37943- | .60510 | .00000 | .29006 | 12 |
| Std. Predicted Value | -1.412- | .949 | .000 | 1.000 | 12 |
| Std. Residual | -1.247- | 1.989 | .000 | .953 | 12 |

**Table (6.2): Statistical Data of Model 53B**

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .826[a] | .683 | .651 | .39675 | .683 | 21.519 | 1 | 10 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 3.387 | 1 | 3.387 | 21.519 | .001[b] |
| | Residual | 1.574 | 10 | .157 | | |
| | Total | 4.961 | 11 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 6.210 | .128 | | 48.440 | .000 | 5.925 | 6.49 |
| | ClogP | -.023- | .005 | -.826- | -4.639- | .001 | -.034- | -.01 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 4.2140 | 6.1981 | 5.9430 | .55492 | 12 |
| Residual | -.44237- | .68803 | .00000 | .37829 | 12 |
| Std. Predicted Value | -3.116- | .460 | .000 | 1.000 | 12 |
| Std. Residual | -1.115- | 1.734 | .000 | .953 | 12 |

**Table (6.3): Statistical Data of Model 53B***

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .870[a] | .756 | .726 | .22261 | .756 | 24.841 | 1 | 8 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 1.231 | 1 | 1.231 | 24.841 | .001[b] |
| | Residual | .396 | 8 | .050 | | |
| | Total | 1.627 | 9 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 6.394 | .105 | | 60.644 | .000 | 6.151 | 6.63 |
| | Clogp | -.074- | .015 | -.870- | -4.984- | .001 | -.109- | -.04 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 5.1207 | 6.3544 | 6.0030 | .36983 | 10 |
| Residual | -.34638- | .32555 | .00000 | .20988 | 10 |
| Std. Predicted Value | -2.386- | .950 | .000 | 1.000 | 10 |
| Std. Residual | -1.556- | 1.462 | .000 | .943 | 10 |

**Table (6.4): Statistical Data of Model 48C**

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .765[a] | .586 | .540 | .09783 | .586 | 12.738 | 1 | 9 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .122 | 1 | .122 | 12.738 | .006[b] |
| | Residual | .086 | 9 | .010 | | |
| | Total | .208 | 10 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 5.588 | .084 | | 66.308 | .000 | 5.397 | 5.77 |
| | C3logP | -.008- | .002 | -.765- | -3.569- | .006 | -.013- | -.00 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 5.1257 | 5.4928 | 5.3062 | .11041 | 11 |
| Residual | -.11454- | .16390 | .00000 | .09281 | 11 |
| Std. Predicted Value | -1.634- | 1.690 | .000 | 1.000 | 11 |
| Std. Residual | -1.171- | 1.675 | .000 | .949 | 11 |

**Table (6.5): Statistical Data of Model 48C***

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .845[a] | .714 | .673 | .08807 | .714 | 17.495 | 1 | 7 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .136 | 1 | .136 | 17.495 | .004[b] |
| | Residual | .054 | 7 | .008 | | |
| | Total | .190 | 8 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 5.602 | .076 | | 73.269 | .000 | 5.421 | 5.78 |
| | ClogP | -.009- | .002 | -.845- | -4.183- | .004 | -.013- | -.00 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 5.0903 | 5.4966 | 5.3067 | .13024 | 9 |
| Residual | -.10971- | .13646 | .00000 | .08238 | 9 |
| Std. Predicted Value | -1.661- | 1.458 | .000 | 1.000 | 9 |
| Std. Residual | -1.246- | 1.549 | .000 | .935 | 9 |

**Table (6.6): Statistical Data of Model 48D**

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .810[a] | .656 | .618 | .12179 | .656 | 17.170 | 1 | 9 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .255 | 1 | .255 | 17.170 | .003[b] |
| | Residual | .133 | 9 | .015 | | |
| | Total | .388 | 10 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 5.539 | .076 | | 72.554 | .000 | 5.366 | 5.71 |
| | ClogP | -.006- | .002 | -.810- | -4.144- | .003 | -.010- | -.00 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 4.9630 | 5.4789 | 5.2616 | .15958 | 11 |
| Residual | -.17450- | .16320 | .00000 | .11554 | 11 |
| Std. Predicted Value | -1.871- | 1.362 | .000 | 1.000 | 11 |
| Std. Residual | -1.433- | 1.340 | .000 | .949 | 11 |

**Table (6.7): Statistical Data of Model 48D***

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .932[a] | .869 | .850 | .07389 | .869 | 46.244 | 1 | 7 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .252 | 1 | .252 | 46.244 | .000[b] |
| | Residual | .038 | 7 | .005 | | |
| | Total | .291 | 8 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 5.761 | .071 | | 80.602 | .000 | 5.592 | 5.93 |
| | ClogP | -.014- | .002 | -.932- | -6.800- | .000 | -.018- | -.00 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 5.0118 | 5.6328 | 5.3045 | .17766 | 9 |
| Residual | -.13185- | .06887 | .00000 | .06912 | 9 |
| Std. Predicted Value | -1.648- | 1.848 | .000 | 1.000 | 9 |
| Std. Residual | -1.784- | .932 | .000 | .935 | 9 |

**Table (6.8): Statistical Data of Model 52E**

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .931[a] | .867 | .852 | .08404 | .867 | 58.483 | 1 | 9 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | .413 | 1 | .413 | 58.483 | .000[b] |
| | Residual | .064 | 9 | .007 | | |
| | Total | .477 | 10 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 5.308 | .041 | | 128.875 | .000 | 5.215 | 5.40 |
| | C5logP | -.003- | .000 | -.931- | -7.647- | .000 | -.004- | -.00 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 4.6559 | 5.2508 | 5.0595 | .20324 | 11 |
| Residual | -.11759- | .11771 | .00000 | .07973 | 11 |
| Std. Predicted Value | -1.986- | .942 | .000 | 1.000 | 11 |
| Std. Residual | -1.399- | 1.401 | .000 | .949 | 11 |

**Table (6.9): Statistical Data of Model 46F**

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .814[a] | .662 | .625 | .34033 | .662 | 17.646 | 1 | 9 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 2.044 | 1 | 2.044 | 17.646 | .002[b] |
| | Residual | 1.042 | 9 | .116 | | |
| | Total | 3.086 | 10 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | .412 | 1.112 | | .370 | .720 | -2.103- | 2.92 |
| | ST | .074 | .018 | .814 | 4.201 | .002 | .034 | .11 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 4.6795 | 6.0971 | 5.0628 | .45209 | 11 |
| Residual | -.66757- | .49039 | .00000 | .32287 | 11 |
| Std. Predicted Value | -.848- | 2.288 | .000 | 1.000 | 11 |
| Std. Residual | -1.962- | 1.441 | .000 | .949 | 11 |

**Table (6.10): Statistical Data of Model 48F**

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .869[a] | .756 | .729 | .28937 | .756 | 27.858 | 1 | 9 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 2.333 | 1 | 2.333 | 27.858 | .001[b] |
| | Residual | .754 | 9 | .084 | | |
| | Total | 3.086 | 10 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 5.470 | .116 | | 46.958 | .000 | 5.207 | 5.73 |
| | ClogP | -.008- | .001 | -.869- | -5.278- | .001 | -.011- | -.00 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 3.8698 | 5.4551 | 5.0628 | .48298 | 11 |
| Residual | -.29774- | .59064 | .00000 | .27452 | 11 |
| Std. Predicted Value | -2.470- | .812 | .000 | 1.000 | 11 |
| Std. Residual | -1.029- | 2.041 | .000 | .949 | 11 |

**Table (6.11): Statistical Data of Model 56G**

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .943[a] | .889 | .877 | .12594 | .889 | 72.027 | 1 | 9 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 1.142 | 1 | 1.142 | 72.027 | .000[b] |
| | Residual | .143 | 9 | .016 | | |
| | Total | 1.285 | 10 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 6.052 | .066 | | 92.060 | .000 | 5.903 | 6.20 |
| | ClogP | -.045- | .005 | -.943- | -8.487- | .000 | -.057- | -.03 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 4.9955 | 5.9750 | 5.5964 | .33800 | 11 |
| Residual | -.20614- | .16485 | .00000 | .11948 | 11 |
| Std. Predicted Value | -1.778- | 1.120 | .000 | 1.000 | 11 |
| Std. Residual | -1.637- | 1.309 | .000 | .949 | 11 |

**Table (6.12): Statistical Data of Model 51H**

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .929[a] | .864 | .849 | .17294 | .864 | 57.102 | 1 | 9 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 1.708 | 1 | 1.708 | 57.102 | .000[b] |
| | Residual | .269 | 9 | .030 | | |
| | Total | 1.977 | 10 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 5.922 | .093 | | 63.591 | .000 | 5.711 | 6.13 |
| | ClogP | -.029- | .004 | -.929- | -7.557- | .000 | -.037- | -.02 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 4.6143 | 5.8816 | 5.3388 | .41327 | 11 |
| Residual | -.17048- | .34025 | .00000 | .16407 | 11 |
| Std. Predicted Value | -1.753- | 1.313 | .000 | 1.000 | 11 |
| Std. Residual | -.986- | 1.967 | .000 | .949 | 11 |

**Table (6.13): Statistical Data of Model 51H***

**Model Summary[b]**

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F |
| 1 | .939[a] | .881 | .864 | .16374 | .881 | 52.022 | 1 | 7 | |

**ANOVA[a]**

| Model | | Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| 1 | Regression | 1.395 | 1 | 1.395 | 52.022 | .000[b] |
| | Residual | .188 | 7 | .027 | | |
| | Total | 1.582 | 8 | | | |

**Coefficients[a]**

| Model | | Unstandardized Coefficients | | Standardized Coefficients | T | Sig. | 95.0% Confidence Interval fo B | |
|---|---|---|---|---|---|---|---|---|
| | | B | Std. Error | Beta | | | Lower Bound | Upper Boun |
| 1 | (Constant) | 5.978 | .094 | | 63.494 | .000 | 5.755 | 6.20 |
| | ClogP | -.033- | .005 | -.939- | -7.213- | .000 | -.043- | -.02 |

**Residuals Statistics[a]**

| | Minimum | Maximum | Mean | Std. Deviation | N |
|---|---|---|---|---|---|
| Predicted Value | 4.8749 | 5.9321 | 5.4246 | .41754 | 9 |
| Residual | -.17825- | .28973 | .00000 | .15316 | 9 |
| Std. Predicted Value | -1.317- | 1.215 | .000 | 1.000 | 9 |
| Std. Residual | -1.089- | 1.769 | .000 | .935 | 9 |

## 6.2. Appendix B

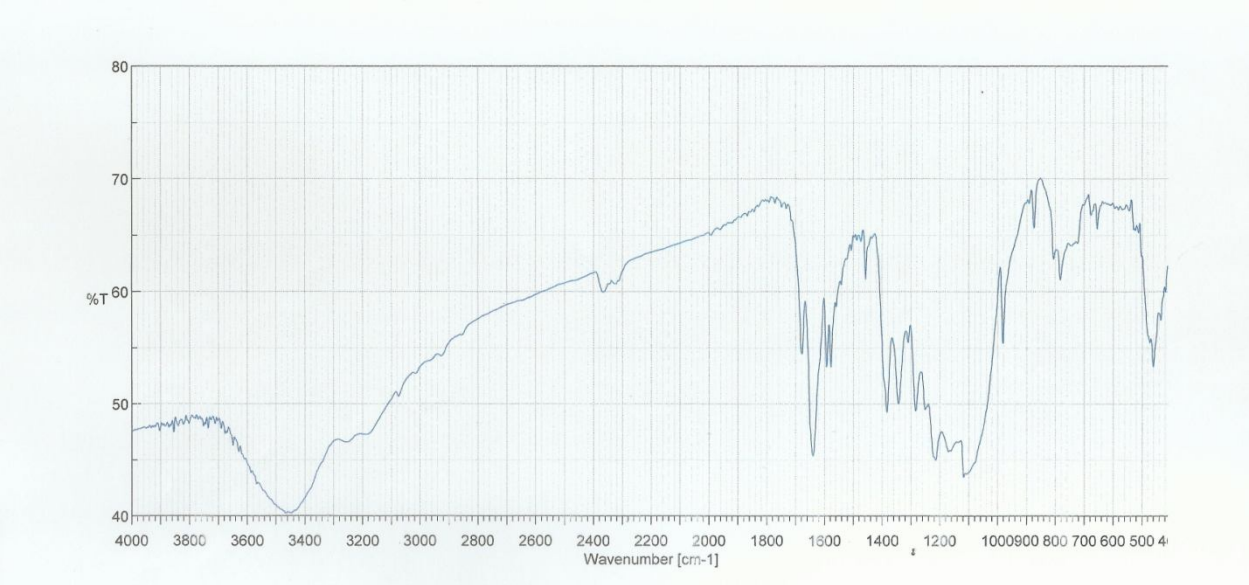


Figure (6.1): IR Spectrum of Lawsone

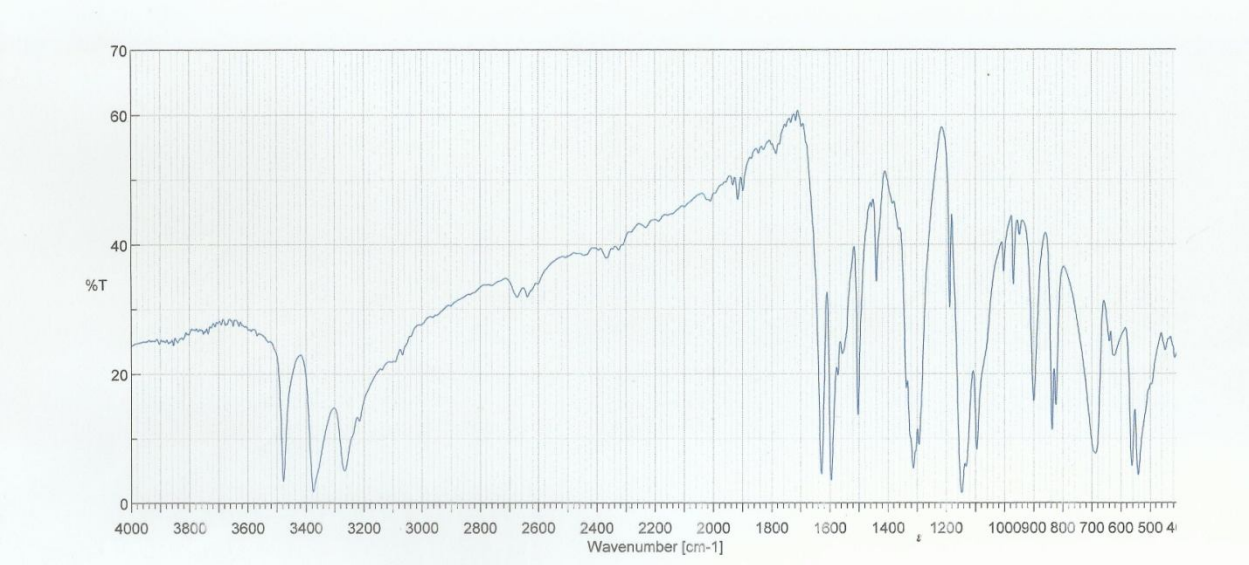


Figure (6.2): IR Spectrum of Sulphanilinamide

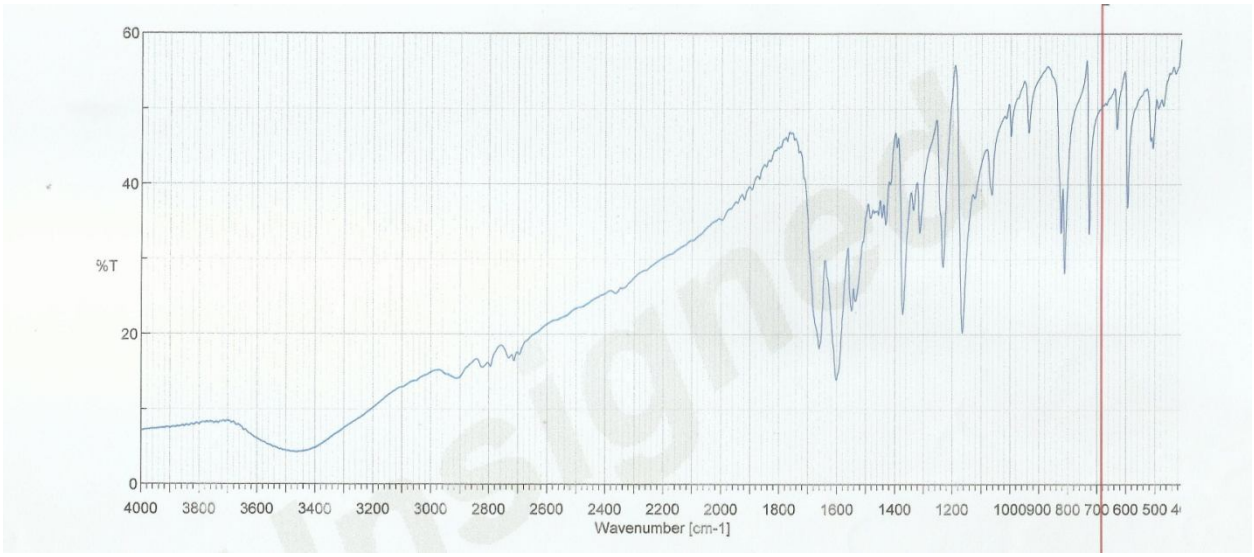


Figure (6.3): IR Spectrum of 4-(Dimethylamino)benzaldehyde

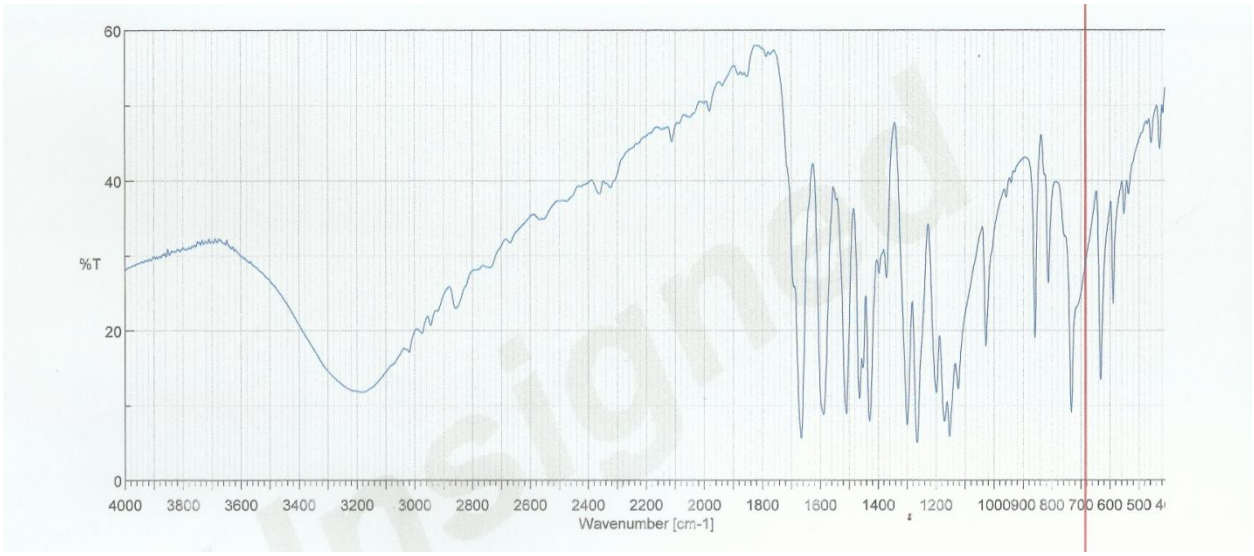


Figure (6.4): IR Spectrum of Vanillin

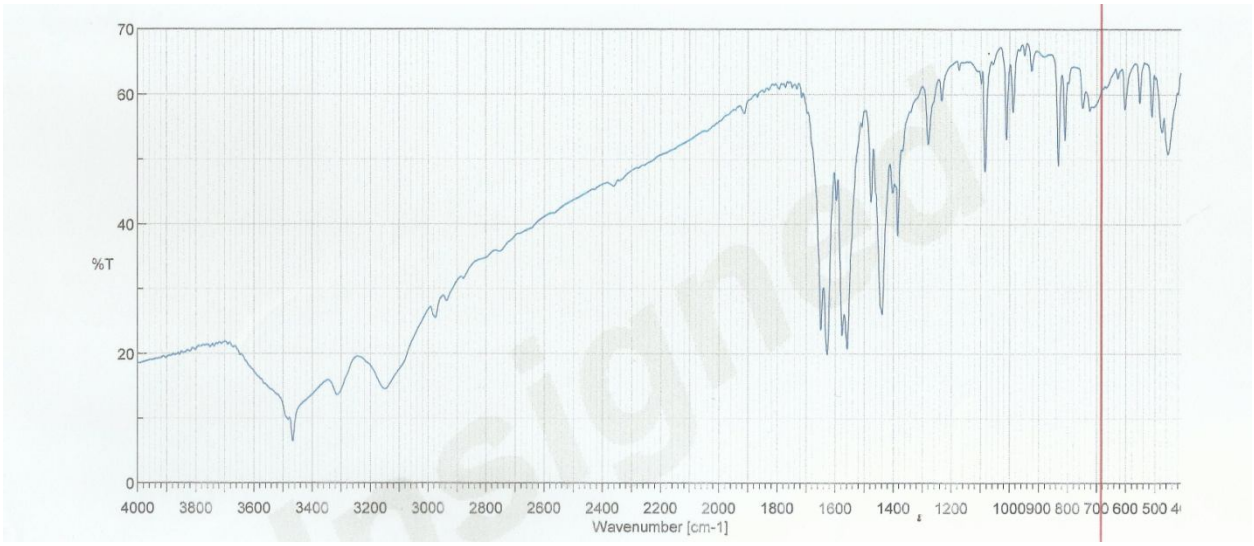


Figure (6.5): IR Spectrum of Pyrimethamine

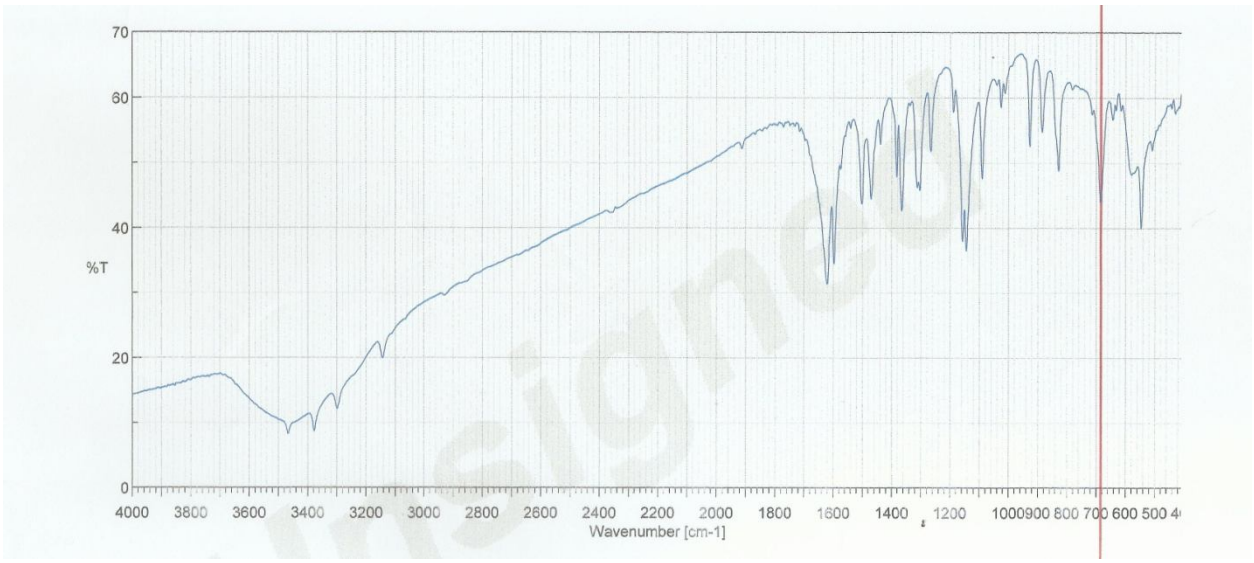


Figure (6.6): IR Spectrum of Sulfamethoxazole

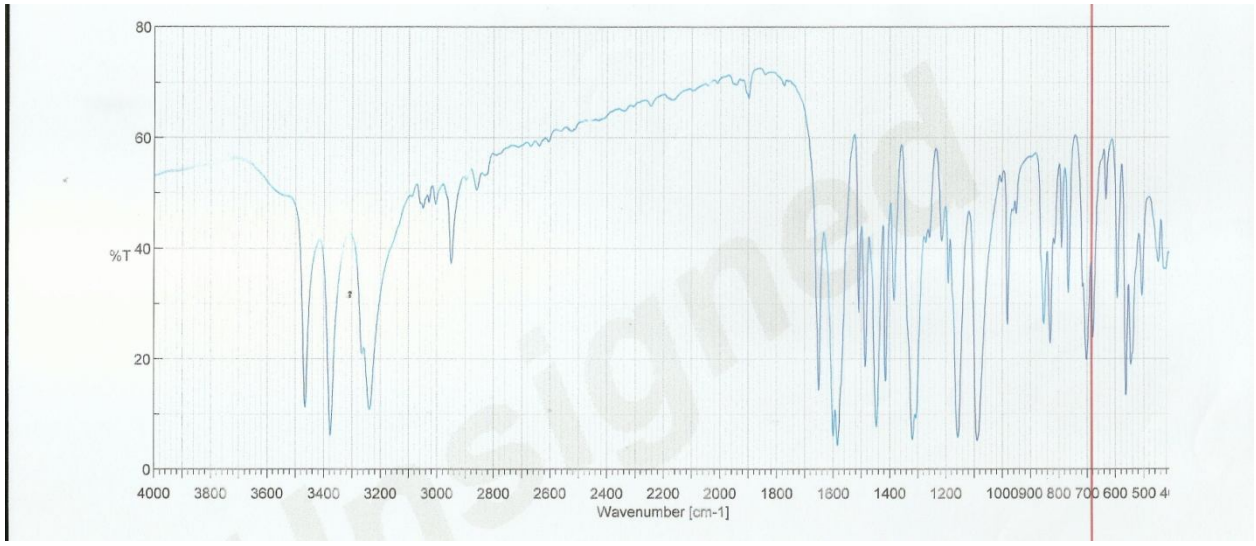


Figure (6.7): IR Spectrum of Sulfadoxin

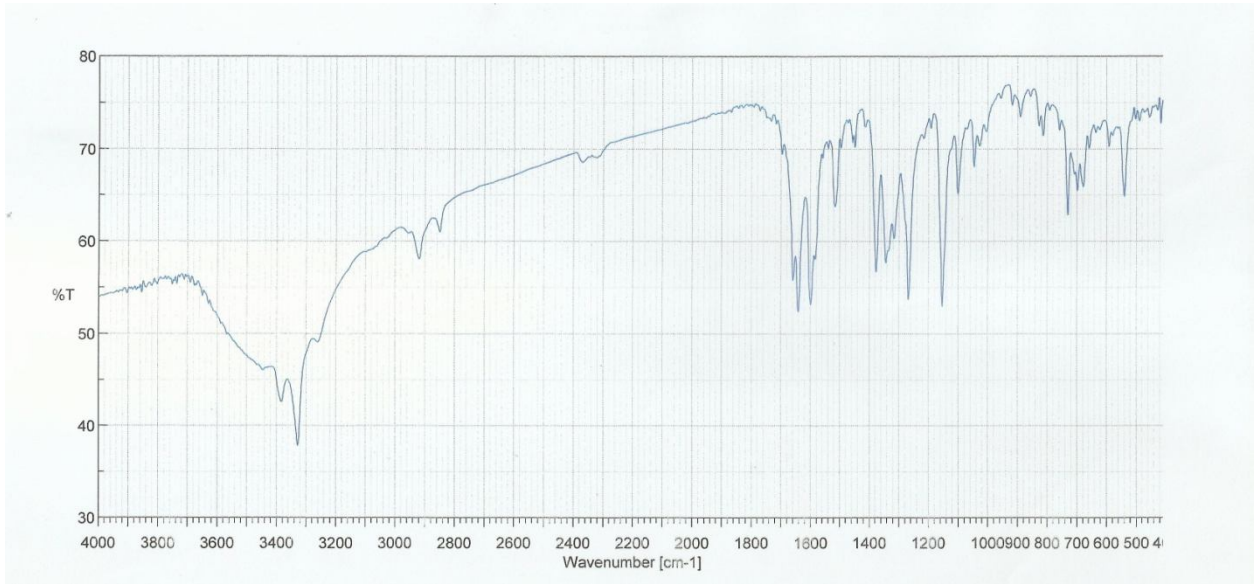


Figure (6.8): IR Spectrum of Compound I

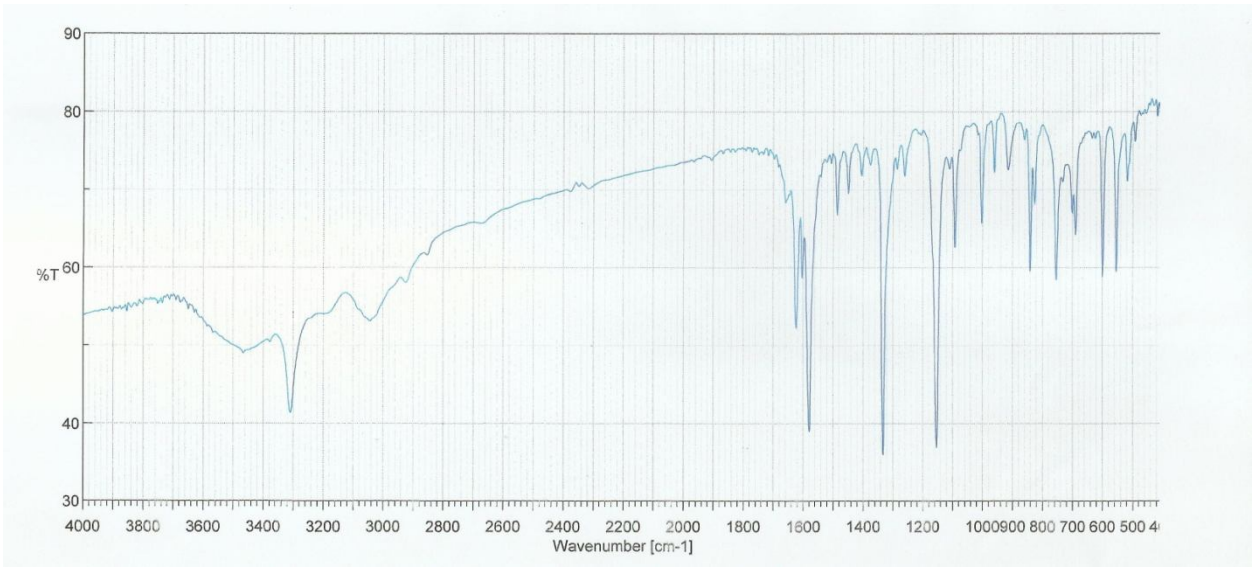


Figure (6.9): IR Spectrum of Compound II

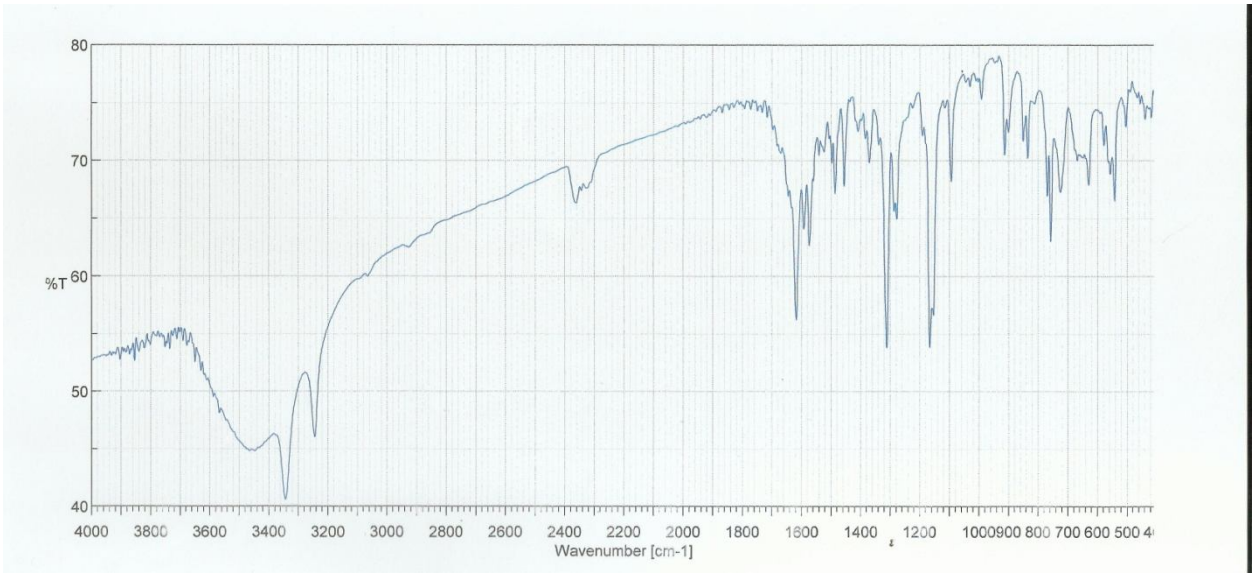


Figure (6.10): IR Spectrum of Compound III

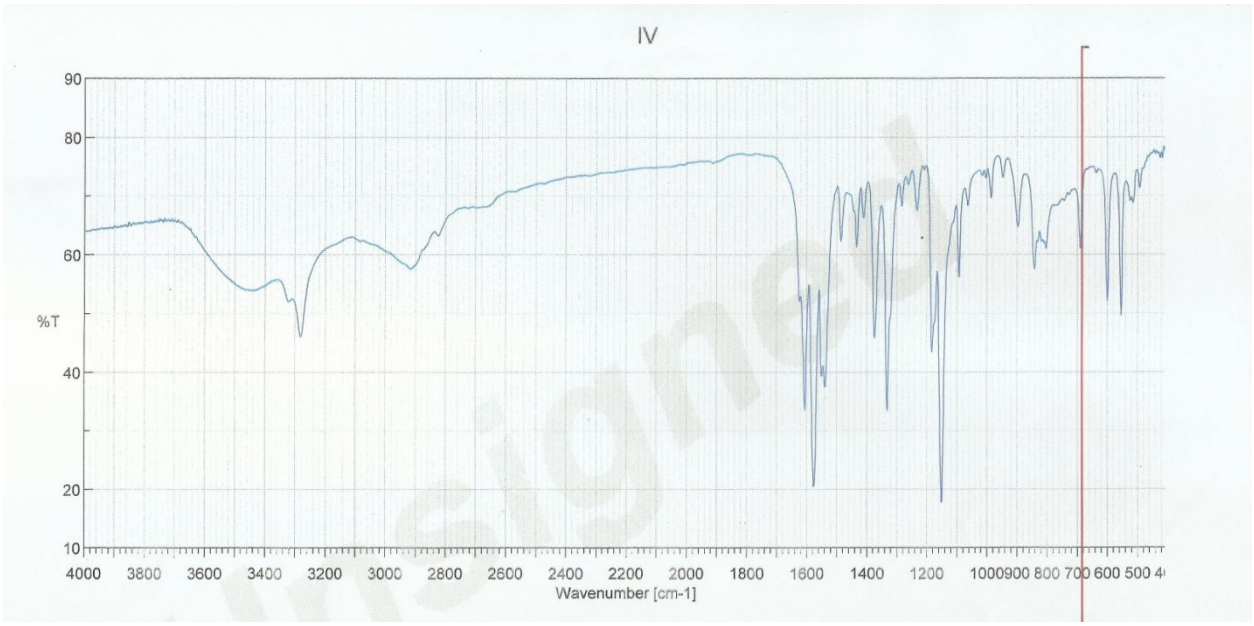


Figure (6.11): IR Spectrum of Compound IV

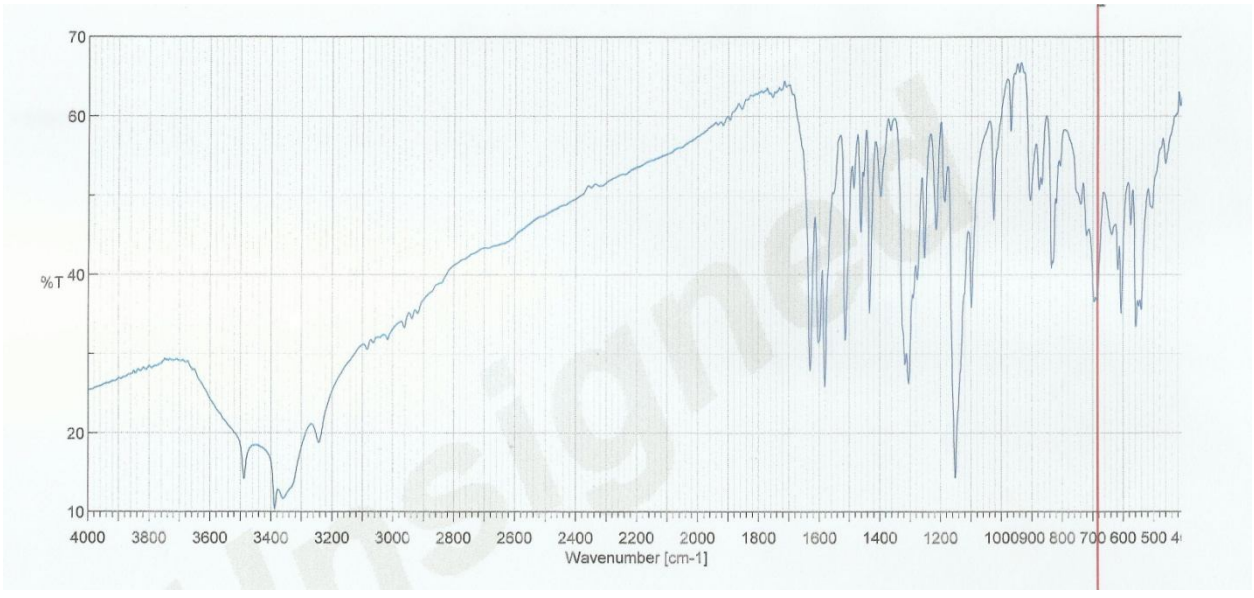


Figure (6.12): IR Spectrum of Compound V

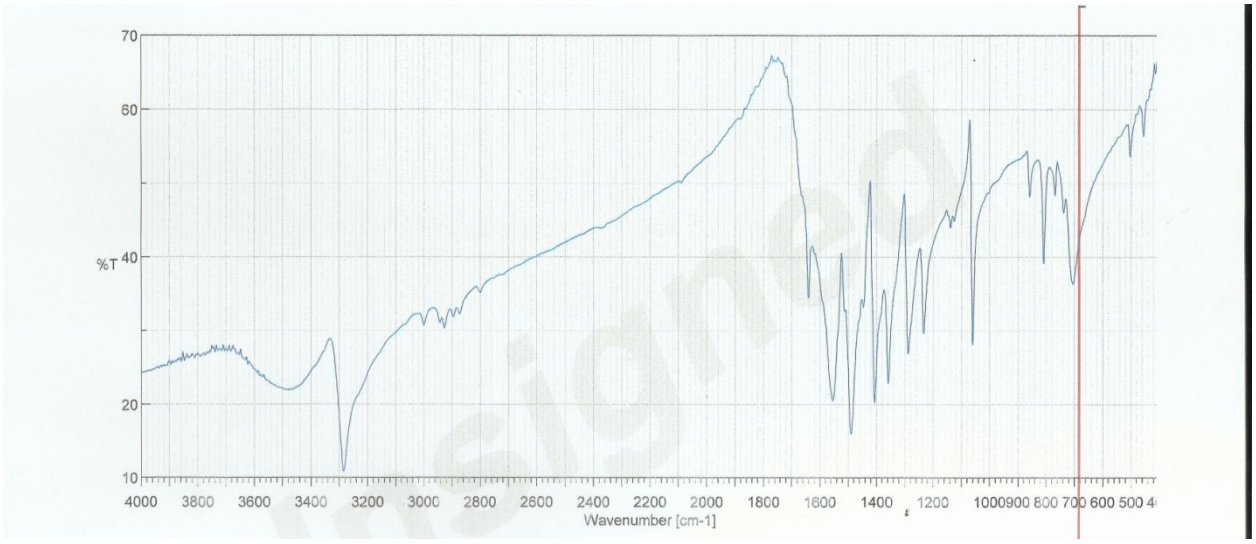


Figure (6.13): IR Spectrum of Compound VI

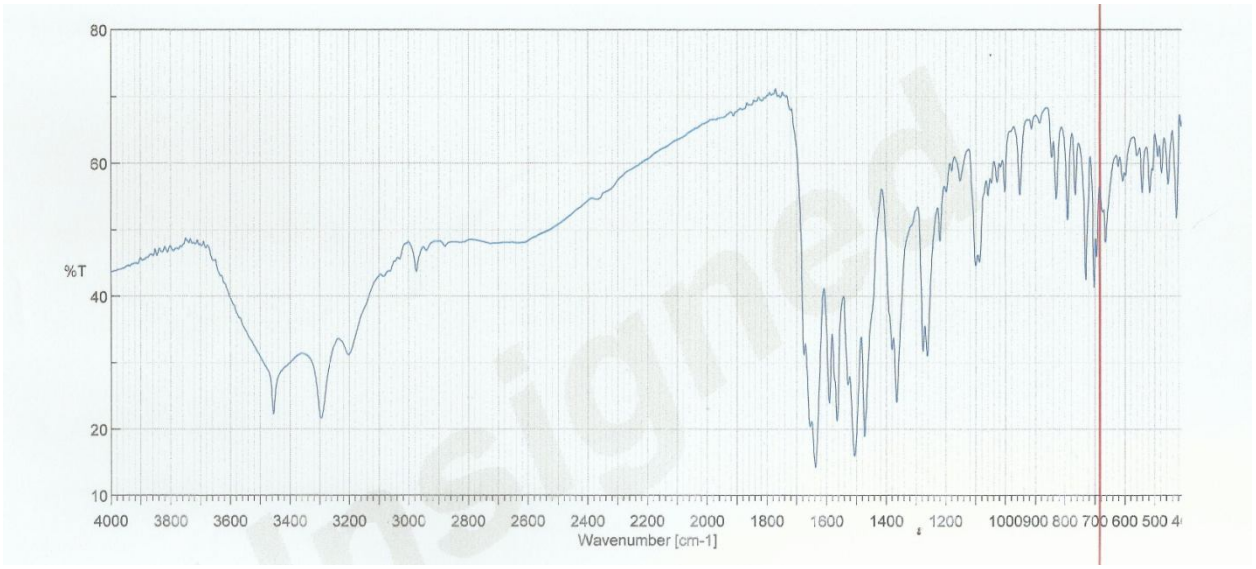


Figure (6.14): IR Spectrum of Compound VII

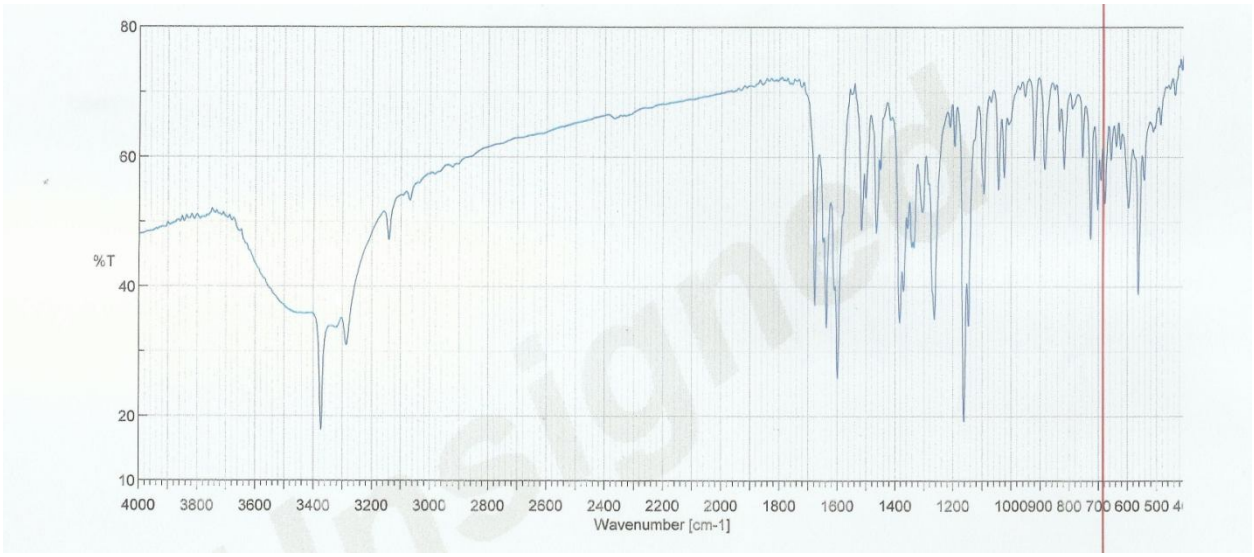


Figure (6.15): IR Spectrum of Compound VIII

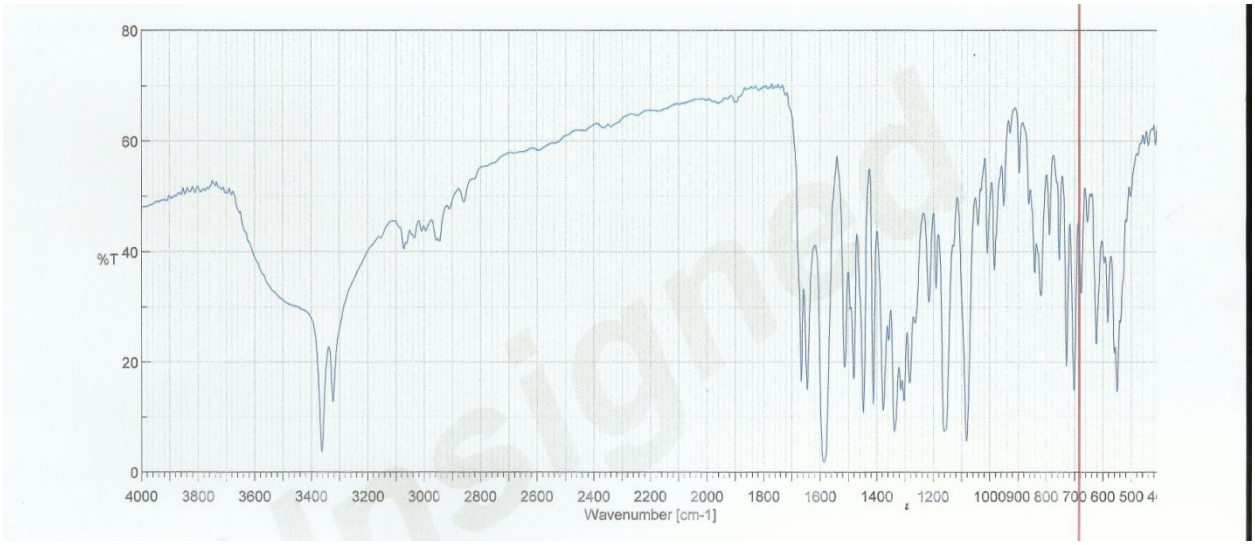


Figure (6.16): IR Spectrum of Compound IX

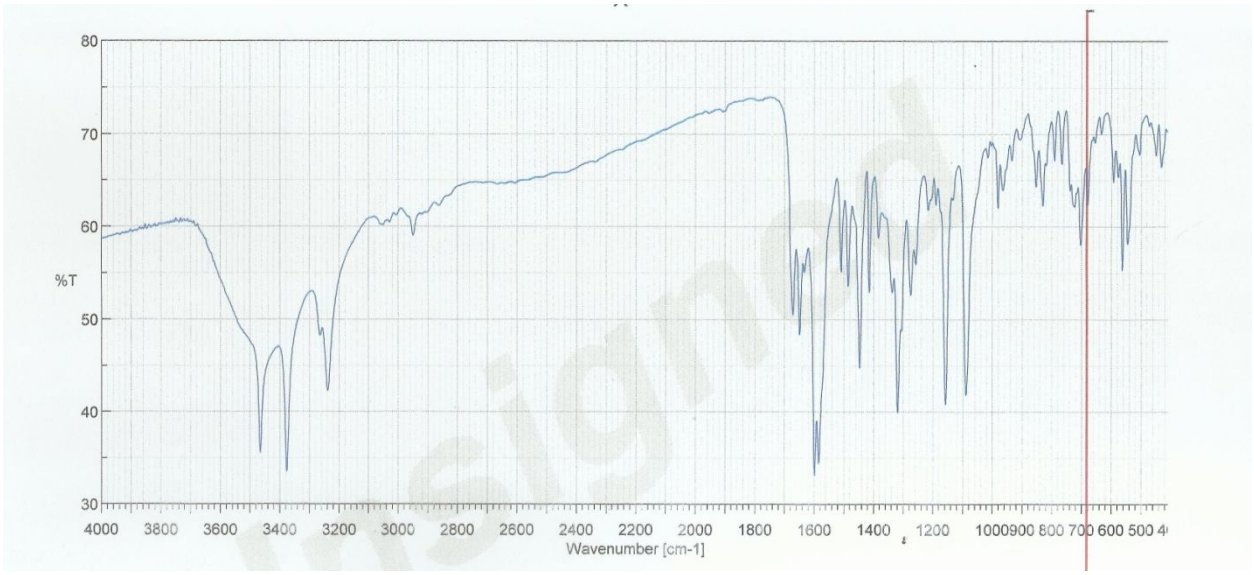


Figure (6.17): IR Spectrum of Compound X

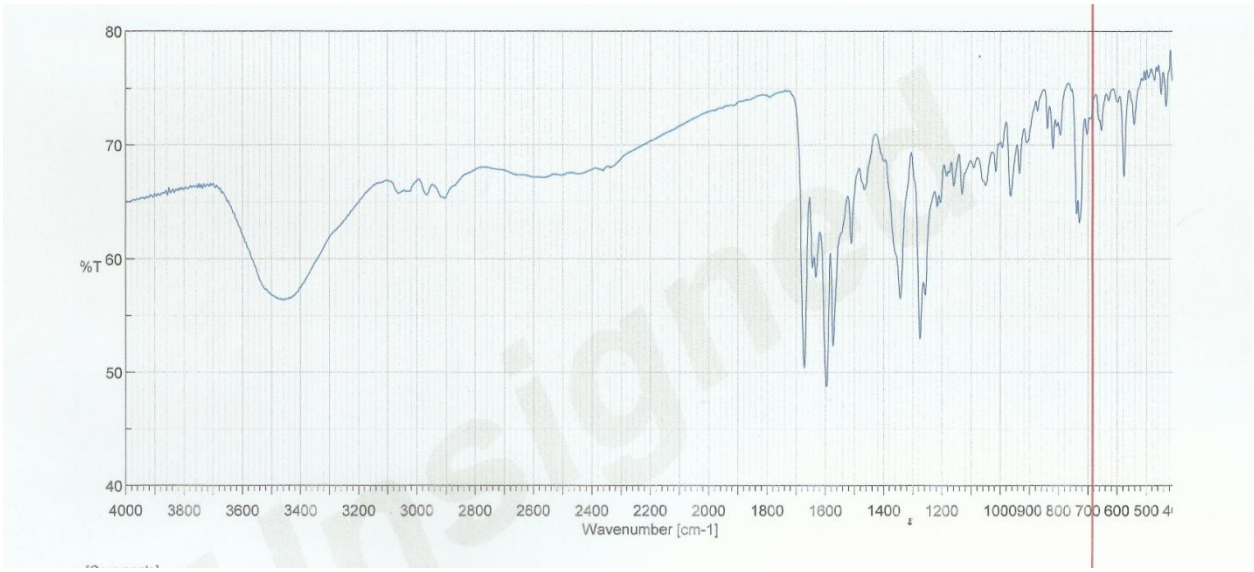


Figure (6.18): IR Spectrum of Compound XI

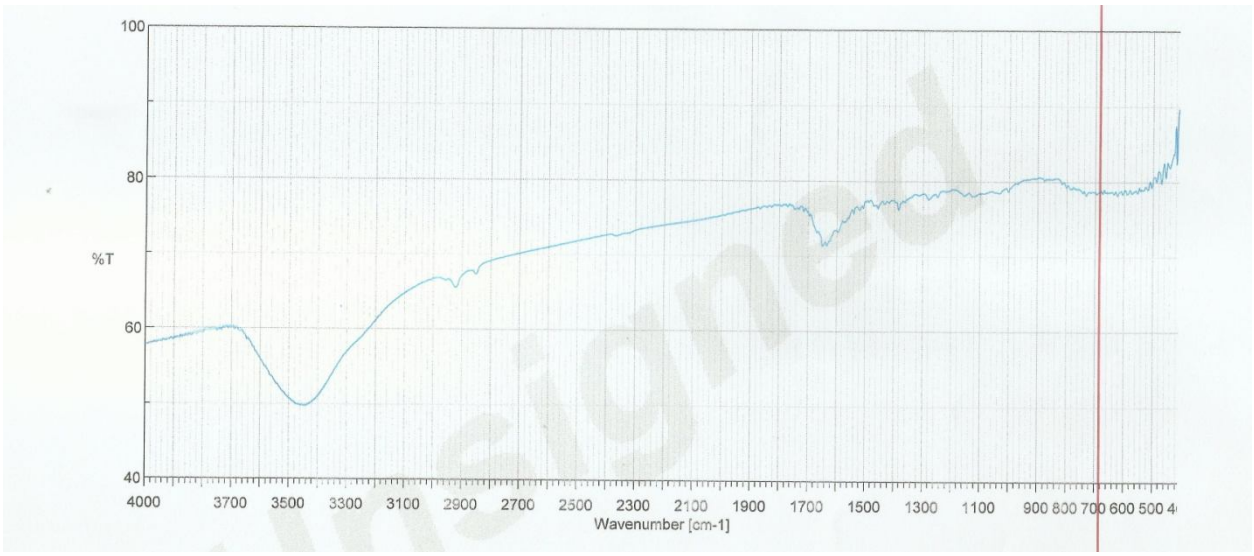


Figure (6.19): IR Spectrum of Compound XII

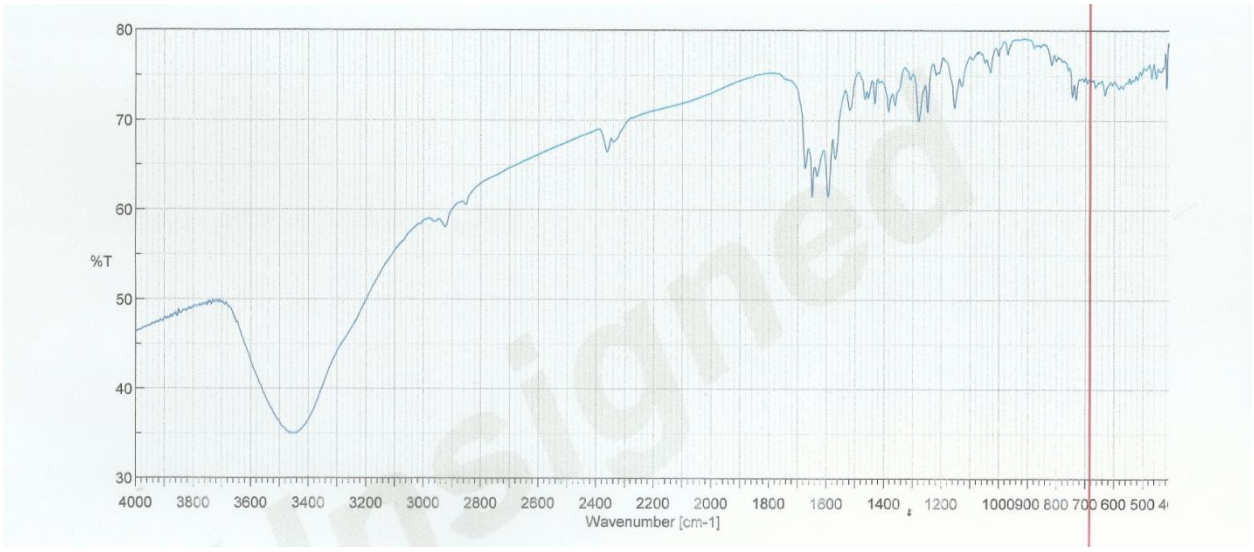


Figure (6.20): IR Spectrum of Compound XIII

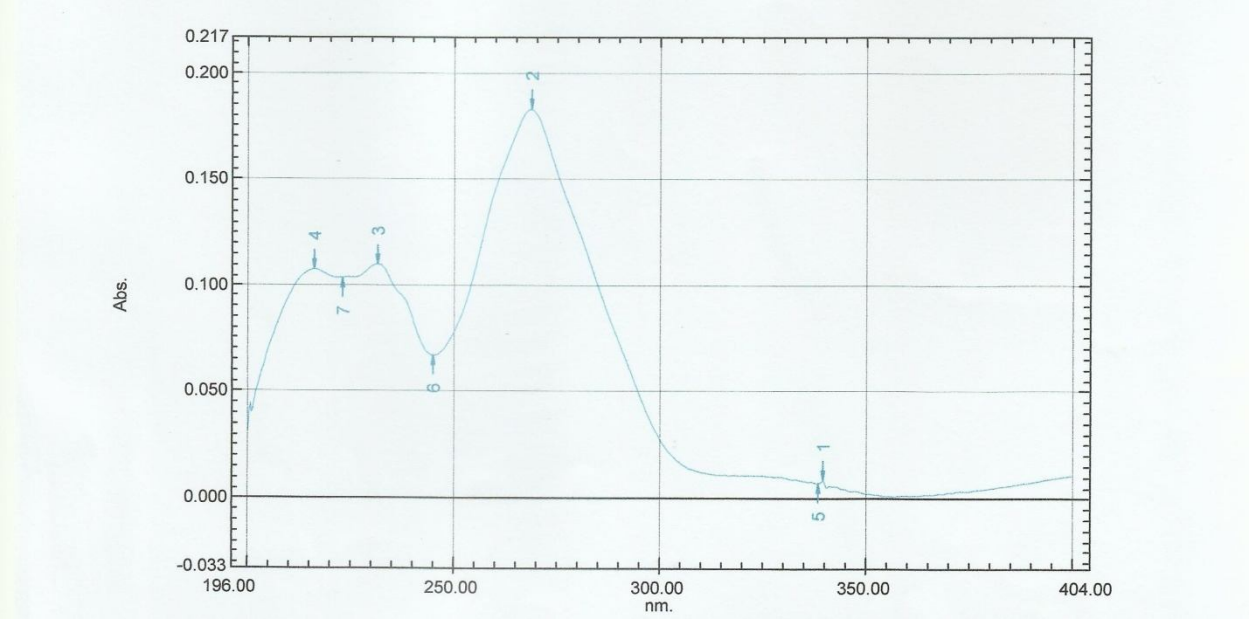


Figure (6.21): UV Spectrum of Lawsone.

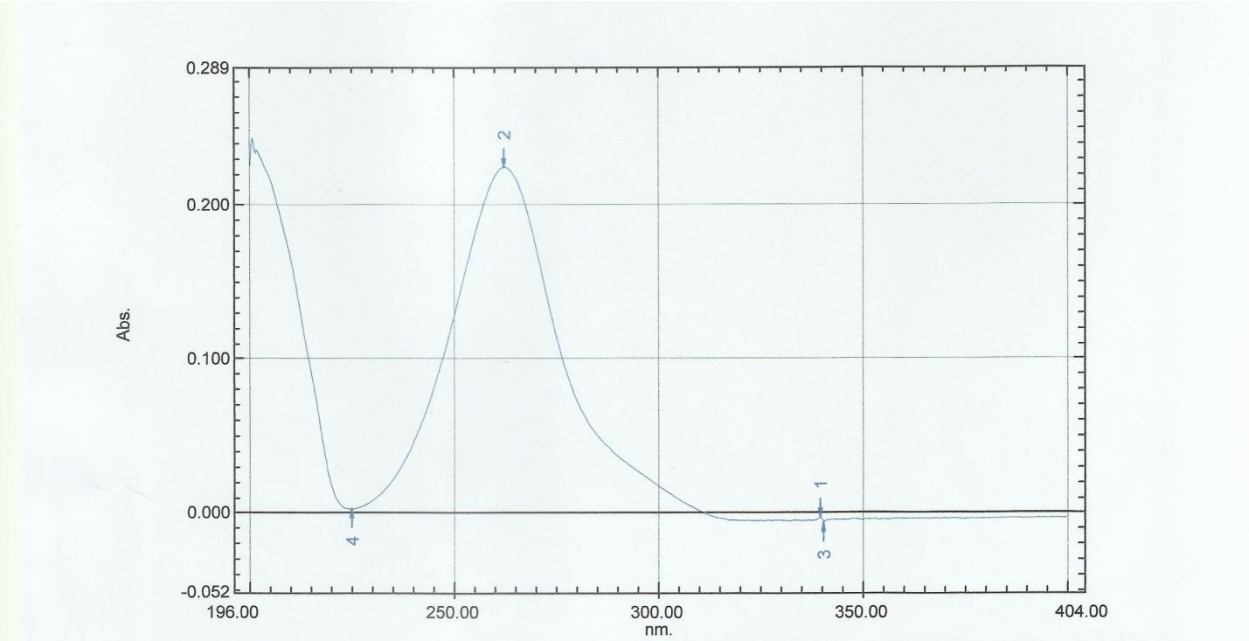


Figure (6.22): UV Spectrum of Sulphanilamide

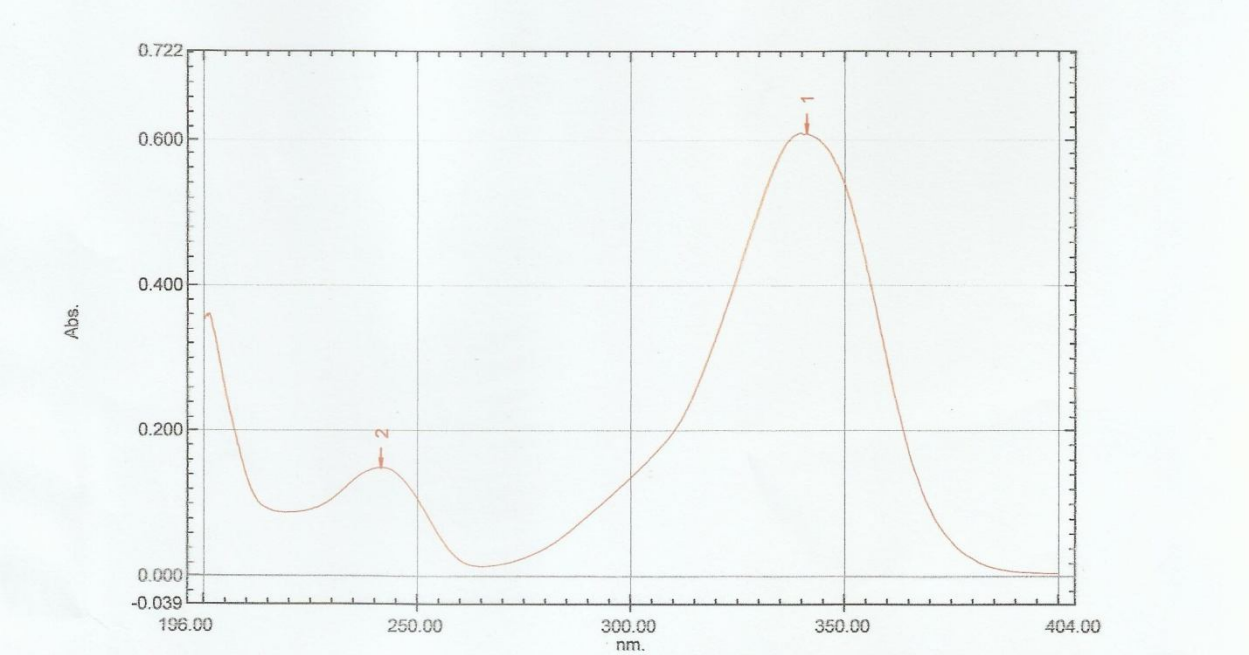


Figure (6.23): UV Spectrum of 4-(Dimethylamino)benzaldehyde

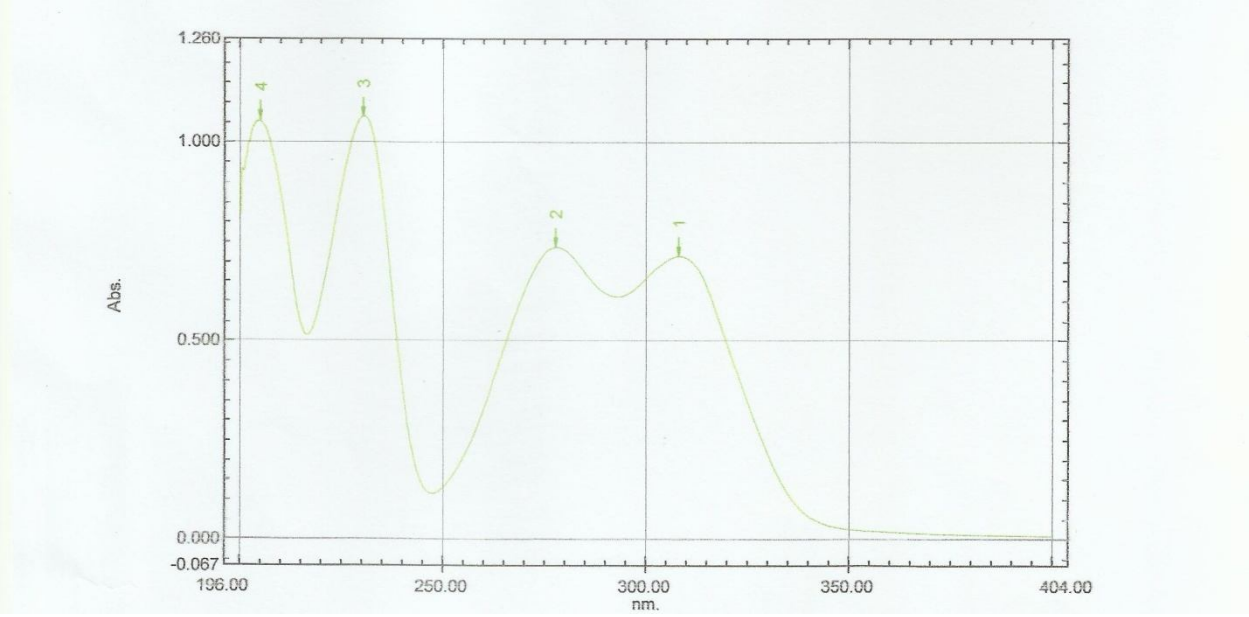


Figure (6.24): UV Spectrum of Vanillin

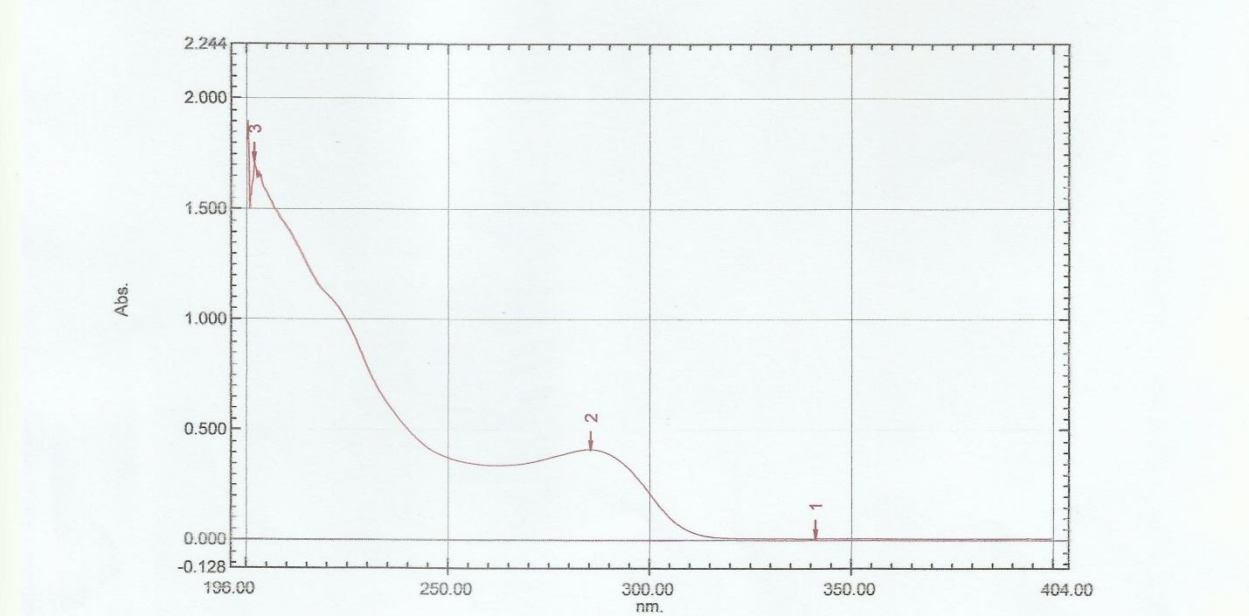


Figure (6.25): UV Spectrum of Pyrimethamine

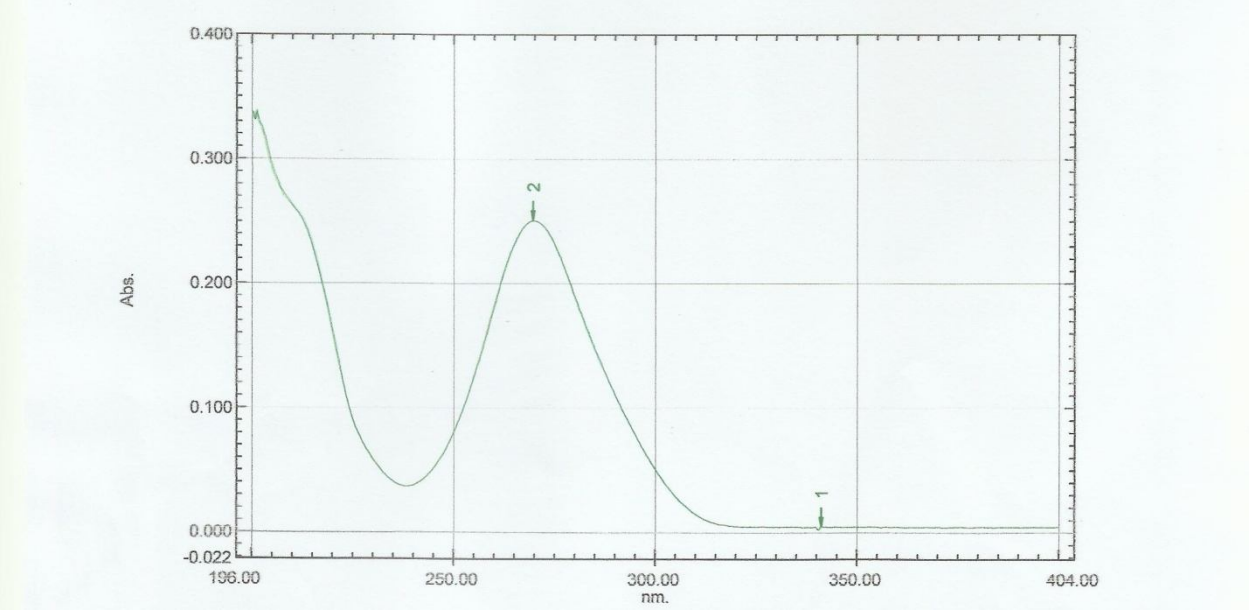


Figure (6.26): UV Spectrum of Sulfamethoxazole

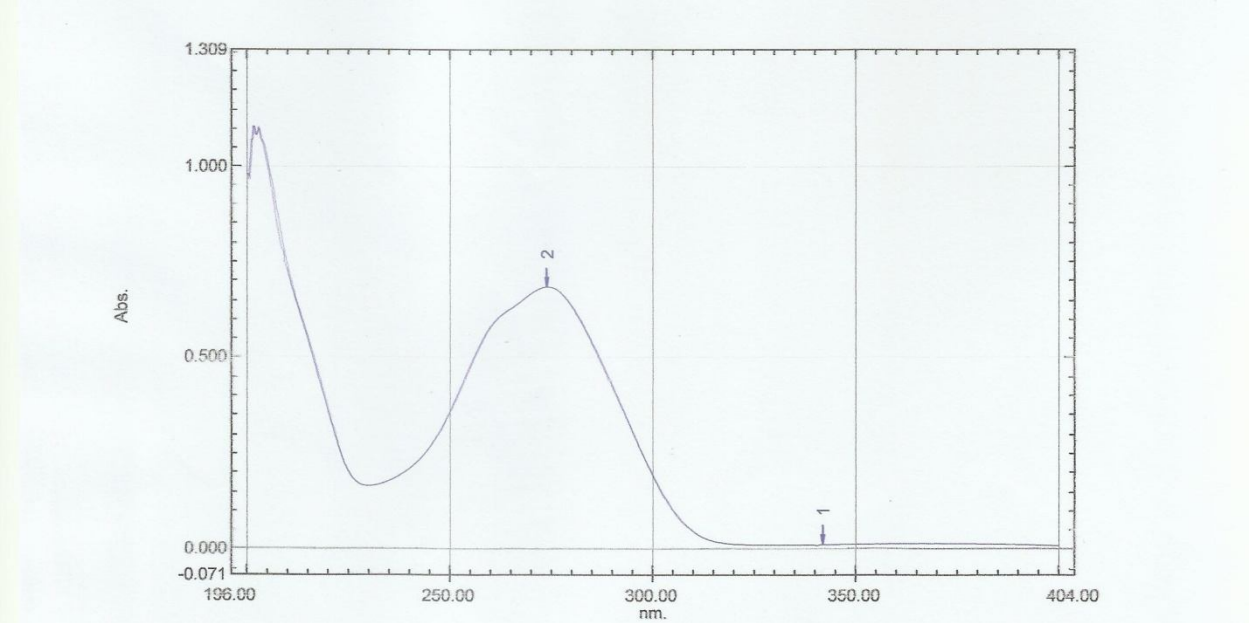


Figure (6.27): UV Spectrum of Sulfadoxin

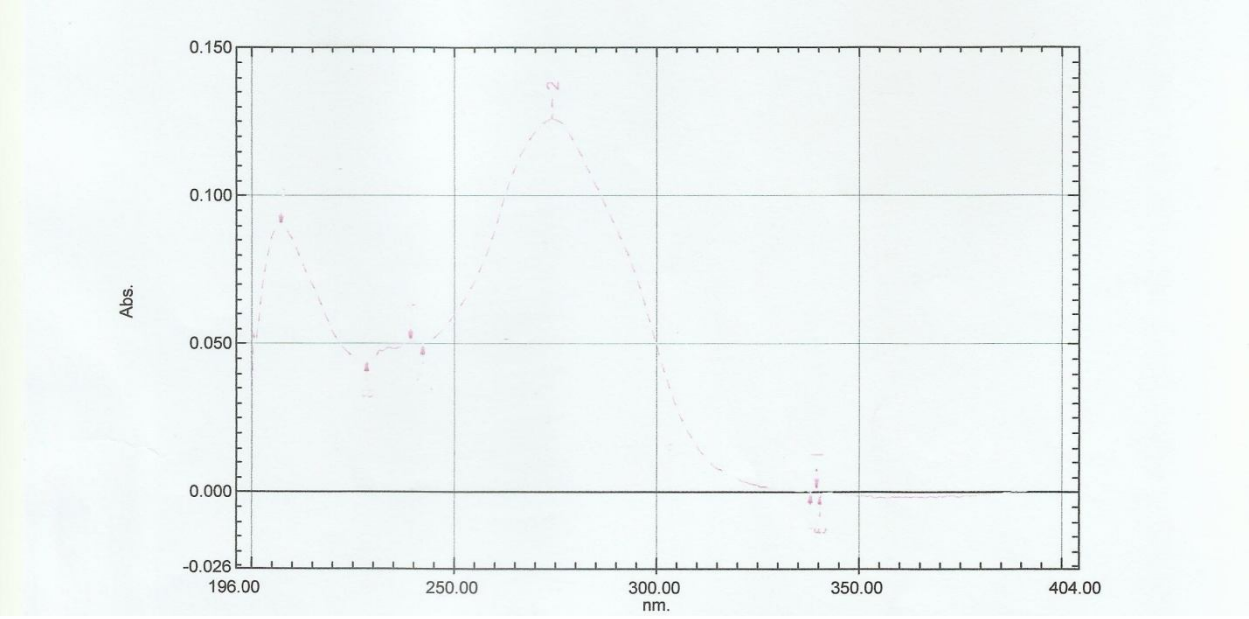


Figure (6.28): UV Spectrum of Compound I

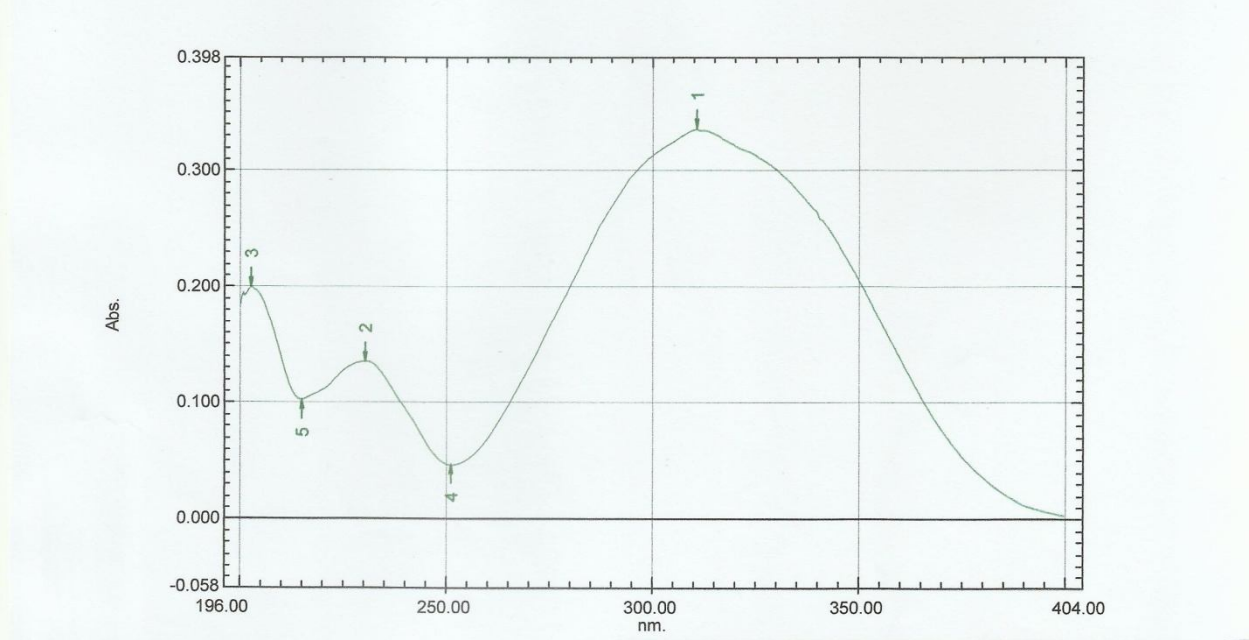


Figure (6.29): UV Spectrum of Compound II

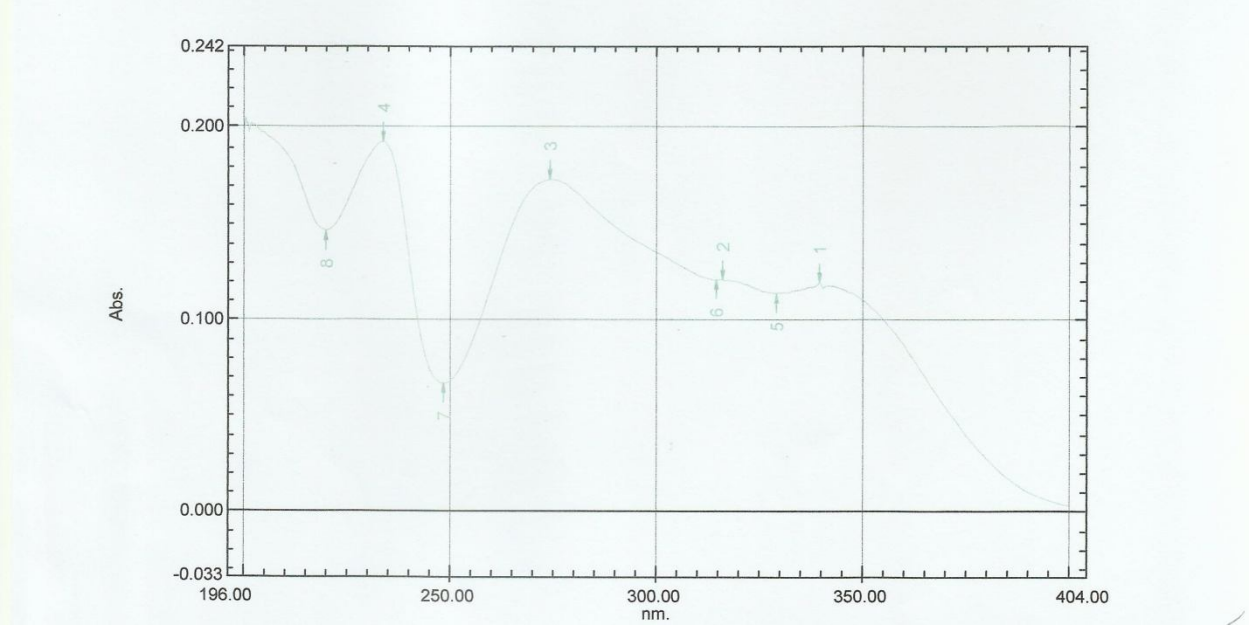


Figure (6.30): UV Spectrum of Compound III

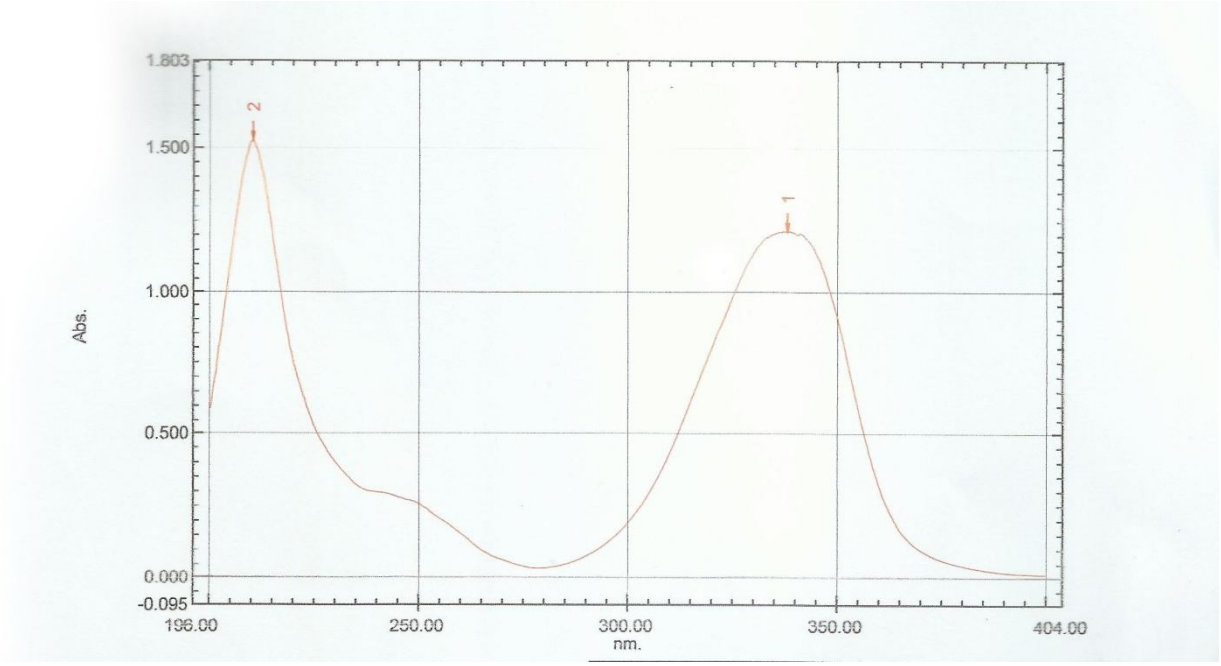


Figure (6.31): UV Spectrum of Compound IV

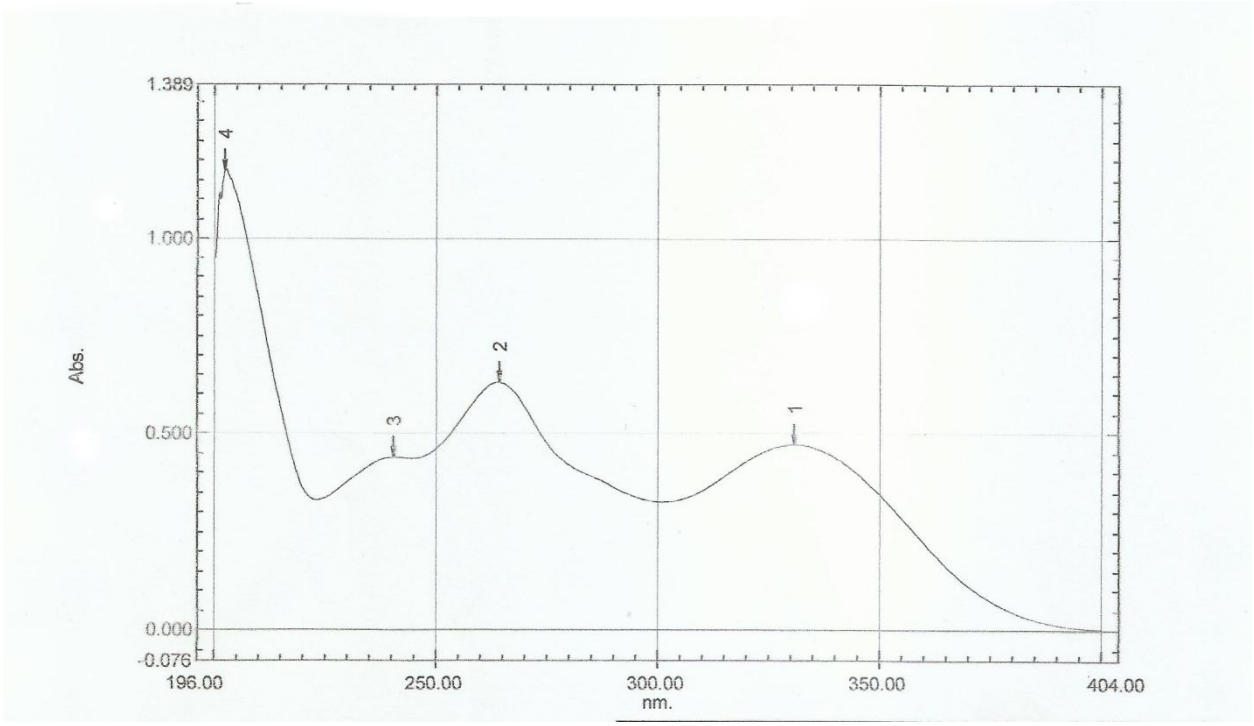


Figure (6.32): UV Spectrum of Compound V

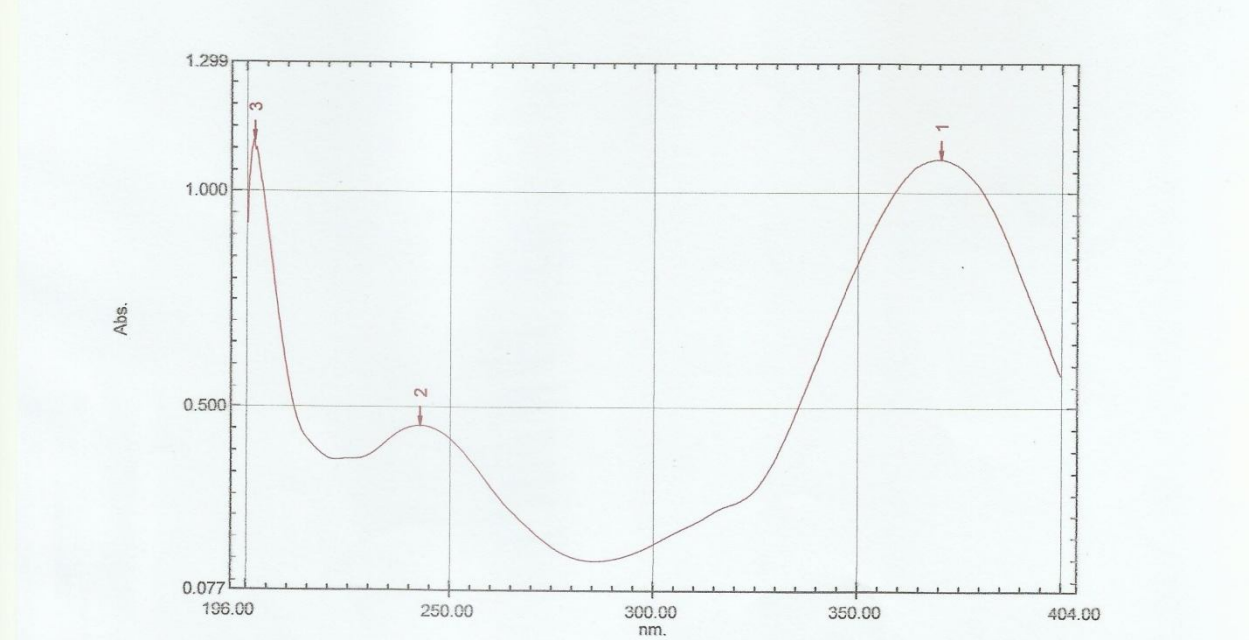


Figure (6.33): UV Spectrum of Compound VI

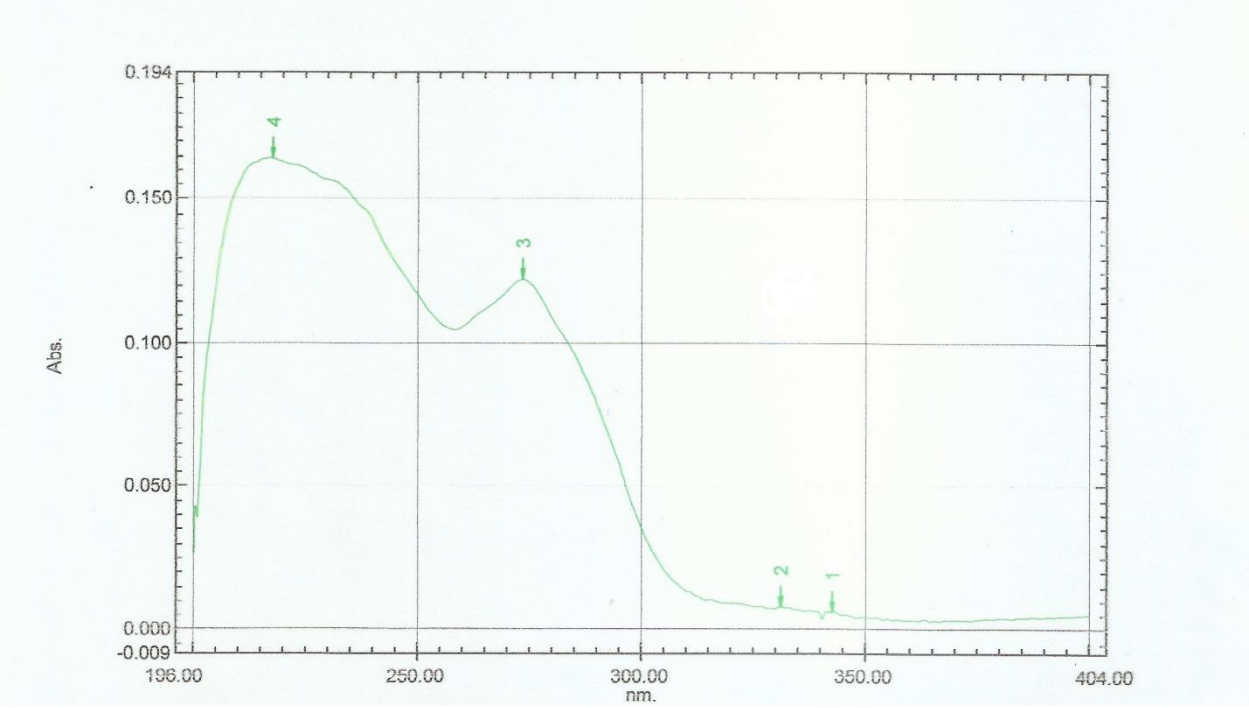


Figure (6.34): UV Spectrum of Compound VII

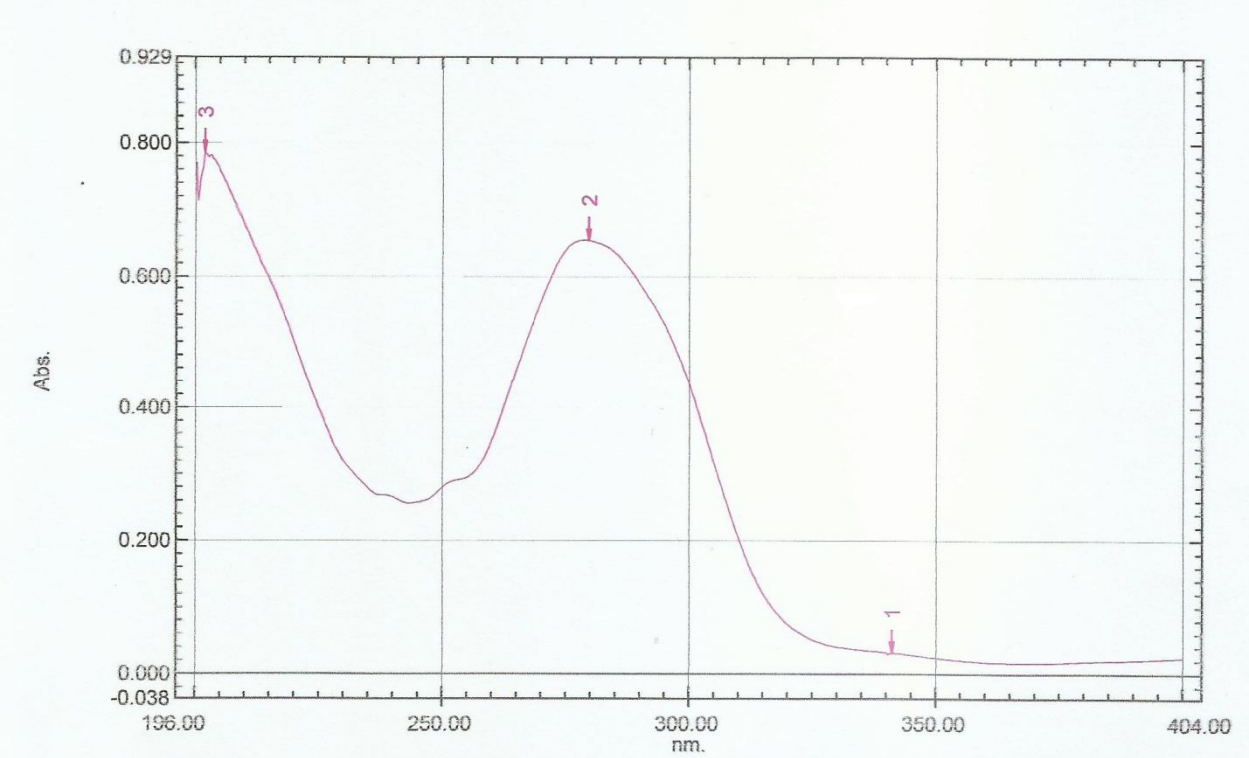


Figure (6.35): UV Spectrum of Compound VIII

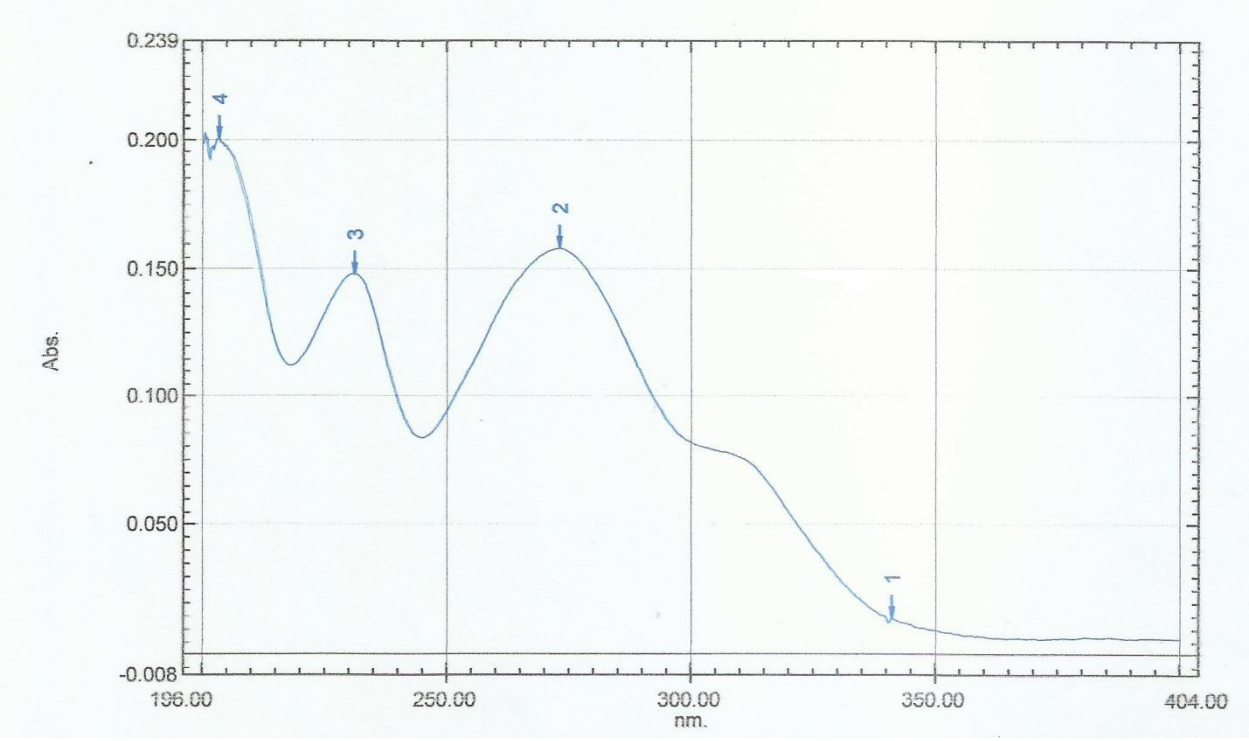


Figure (6.36): UV Spectrum of Compound IX

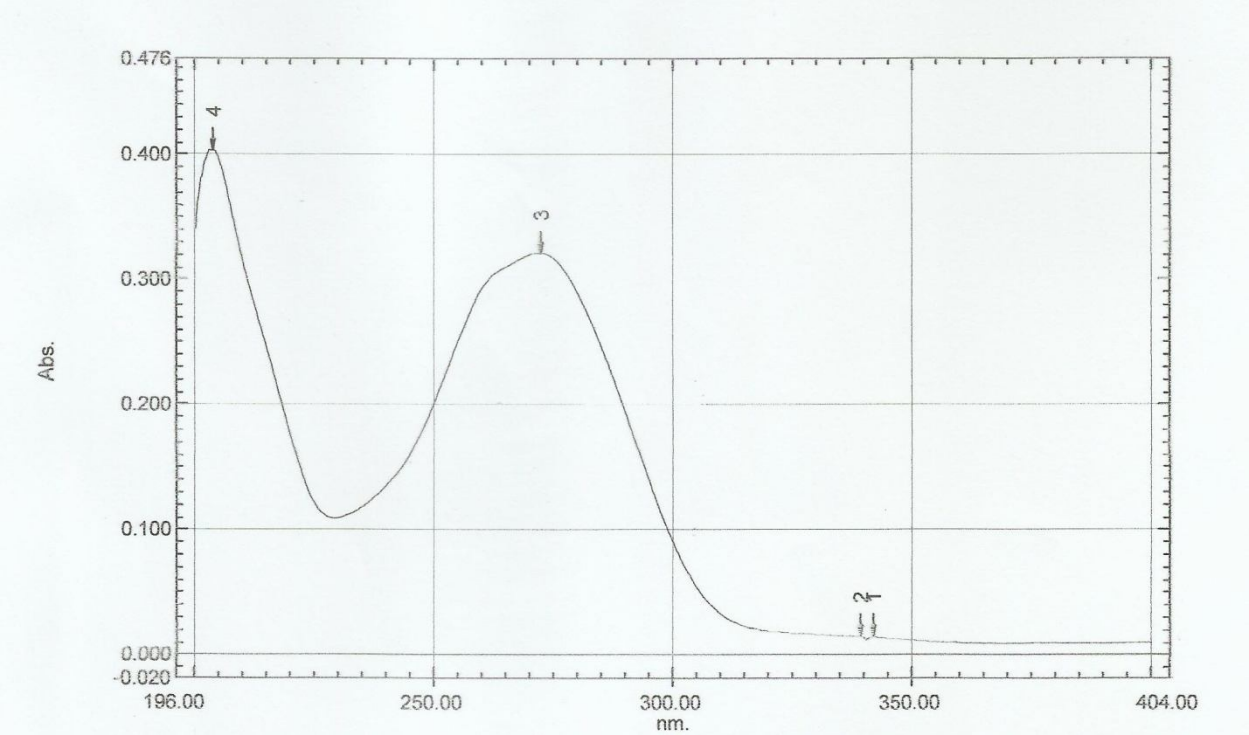


Figure (6.37): UV Spectrum of Compound X

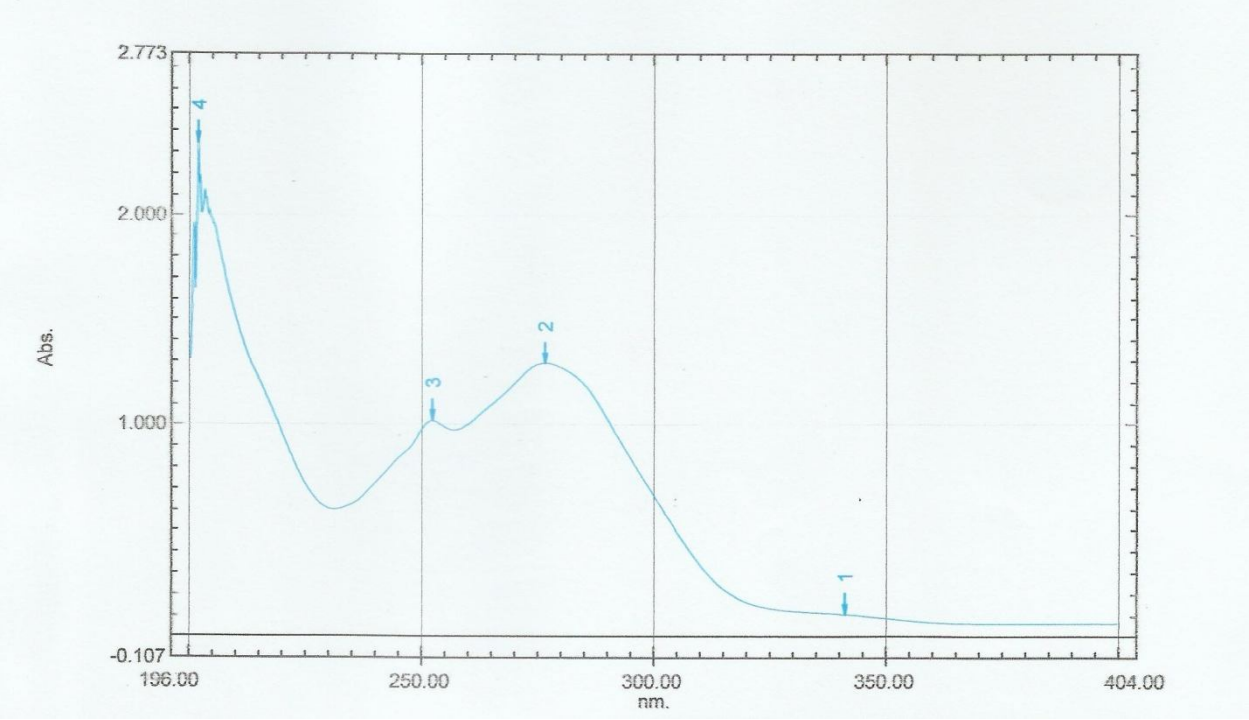


Figure (6.38): UV Spectrum of Compound XI

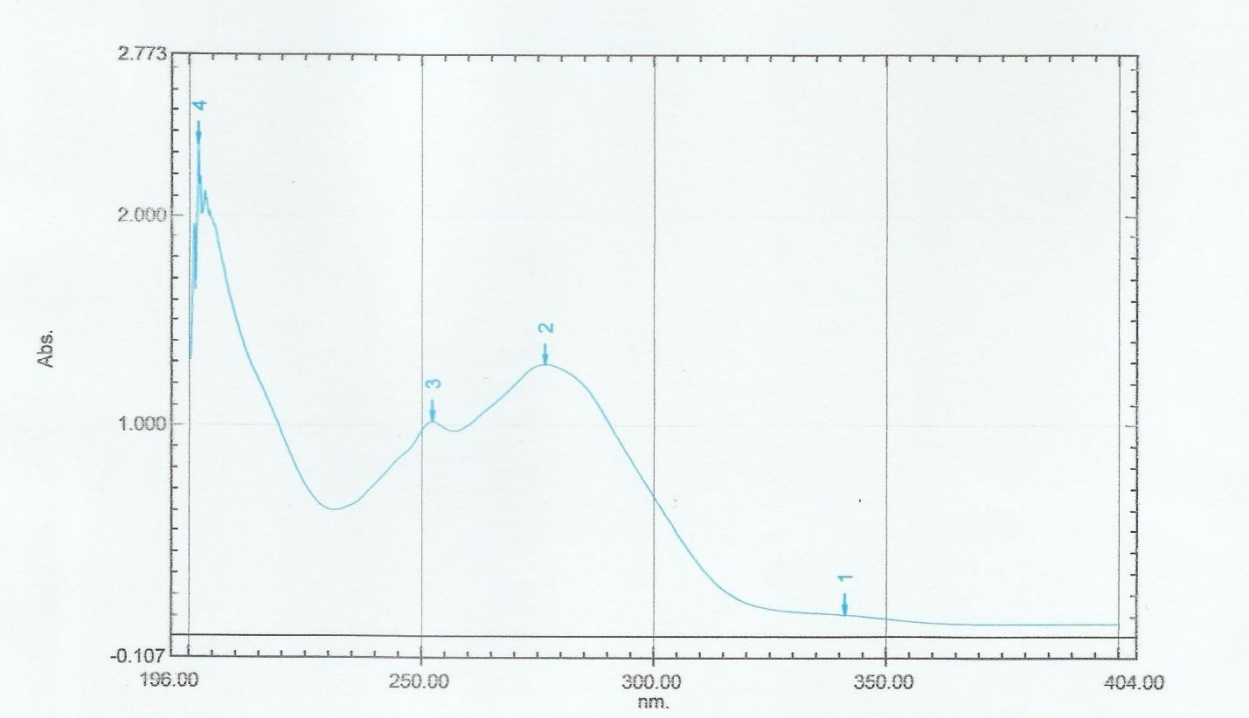


Figure (6.39): UV Spectrum of Compound XII

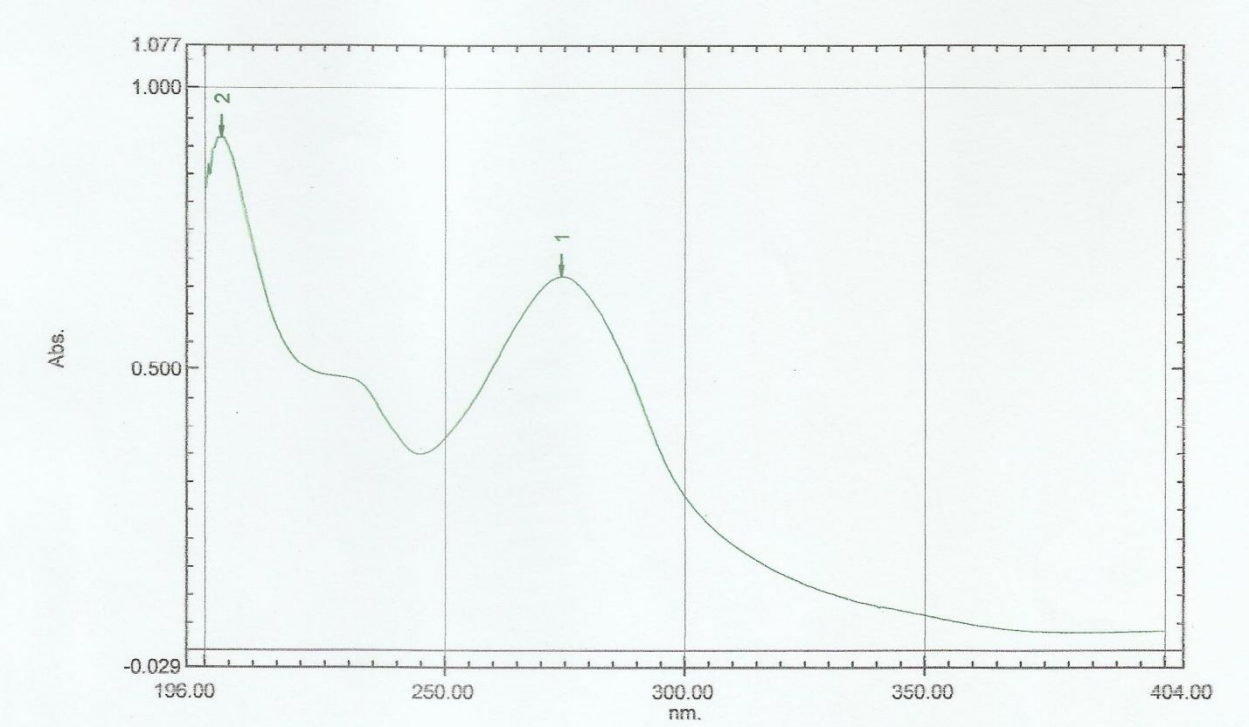


Figure (6.40): UV Spectrum of Compound XIII

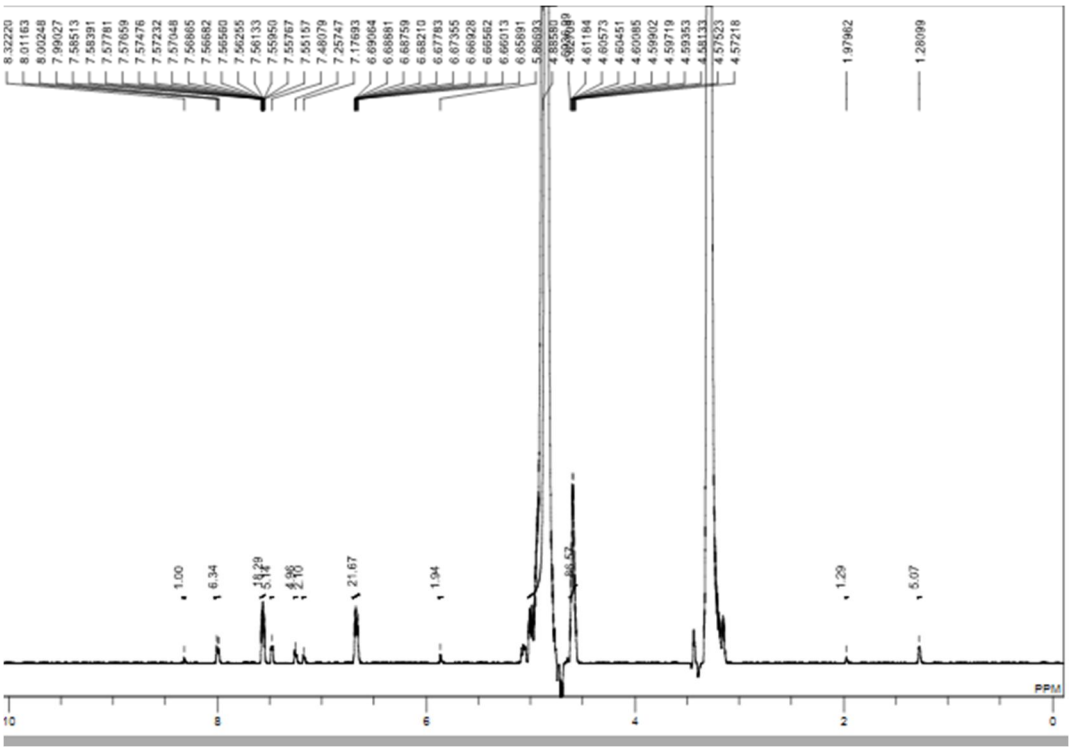


Figure (6.41): [1]HNMR Spectrum of Compound I

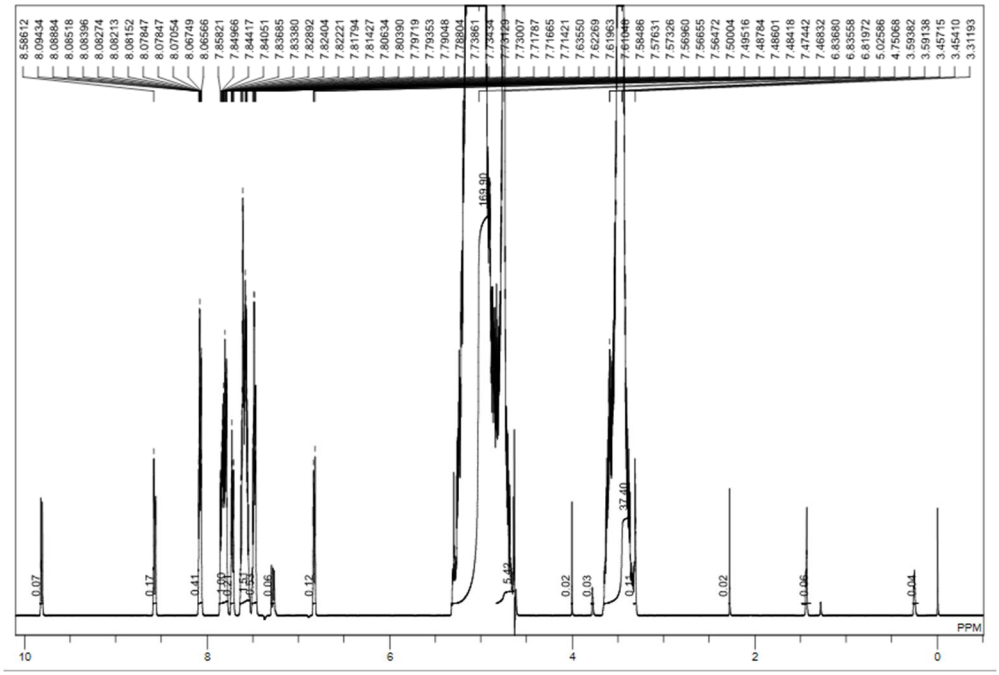


Figure (6.42): [1]HNMR Spectrum of Compound II

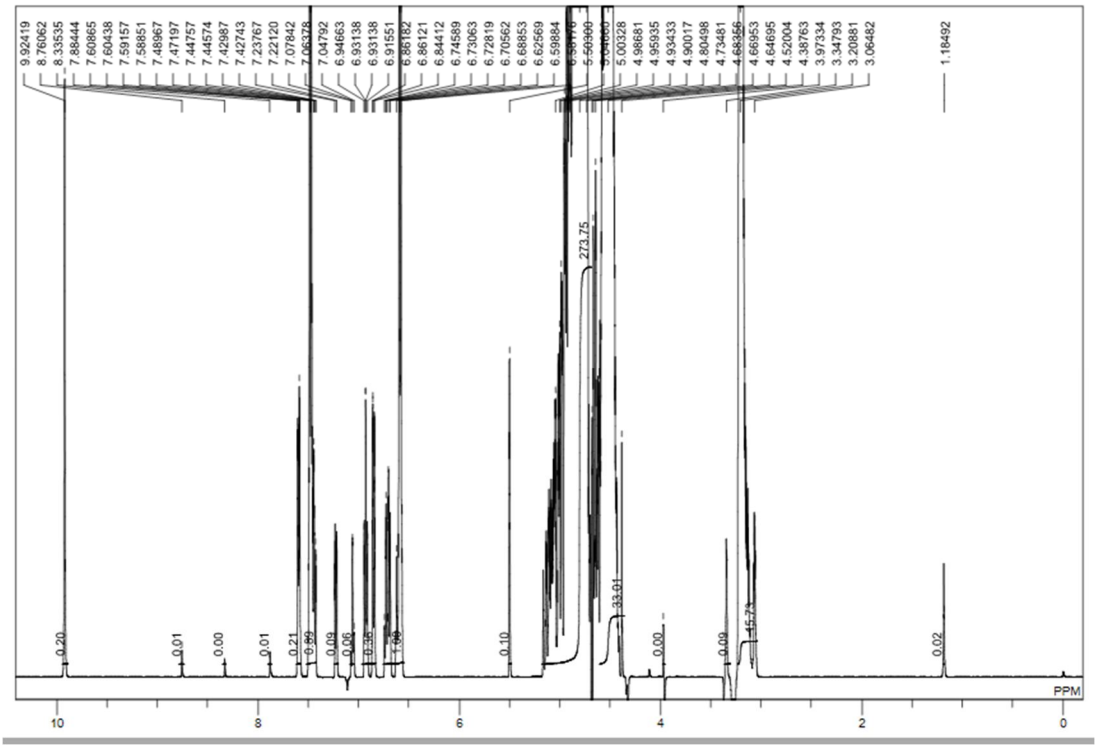


Figure (6.43): [1]HNMR Spectrum of Compound III

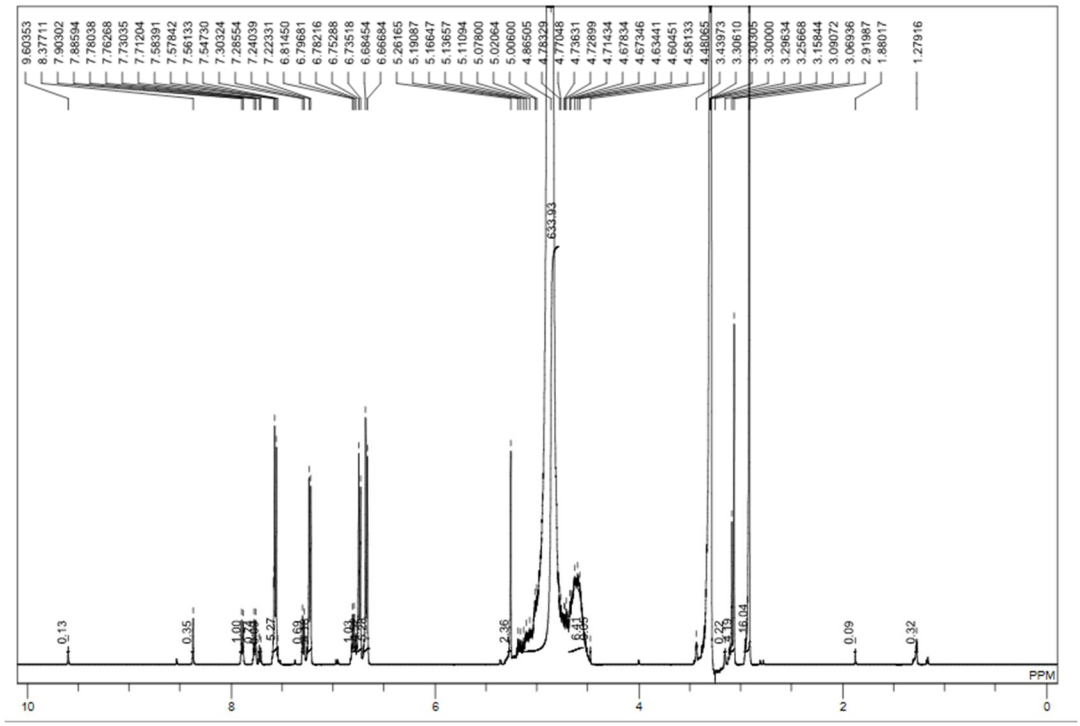


Figure (6.44): [1]HNMR Spectrum of Compound IV

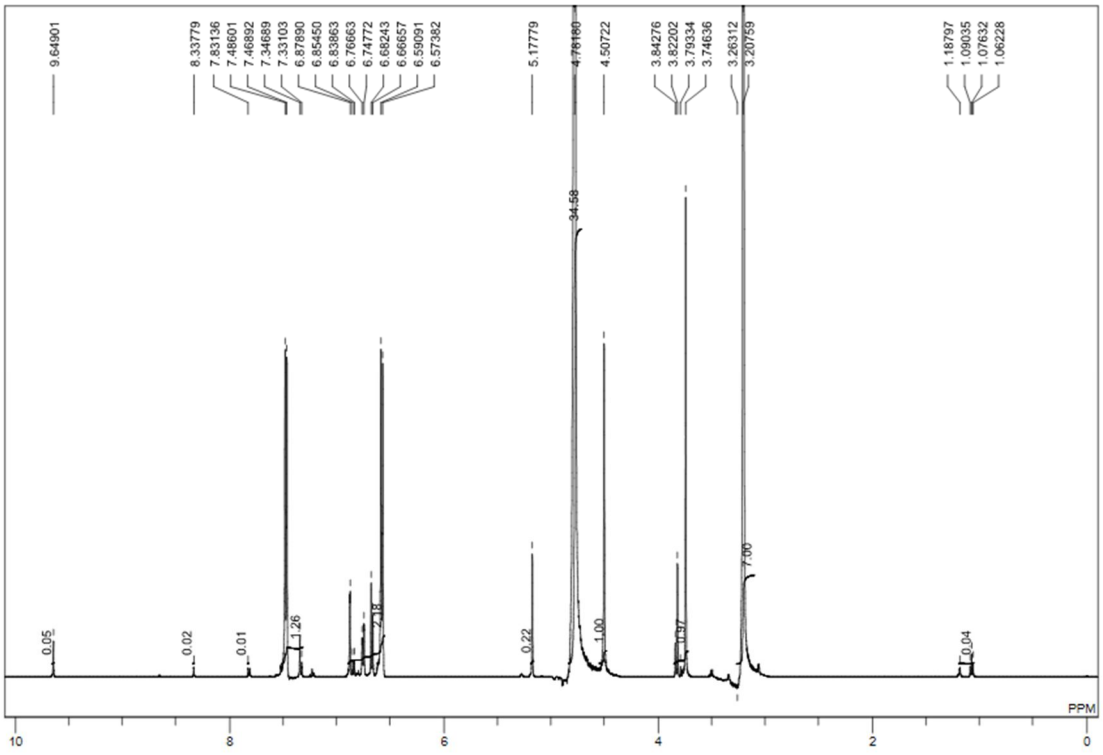


Figure (6.45): [1]HNMR Spectrum of Compound V

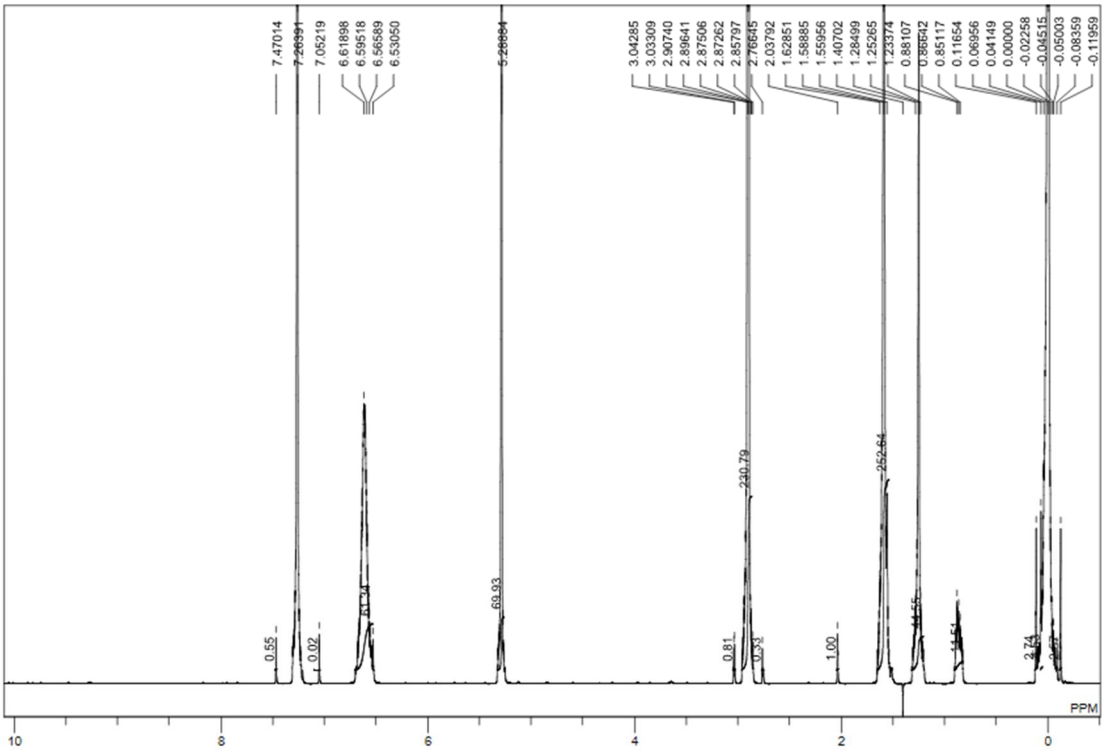


Figure (6.46): [1]HNMR Spectrum of Compound VI

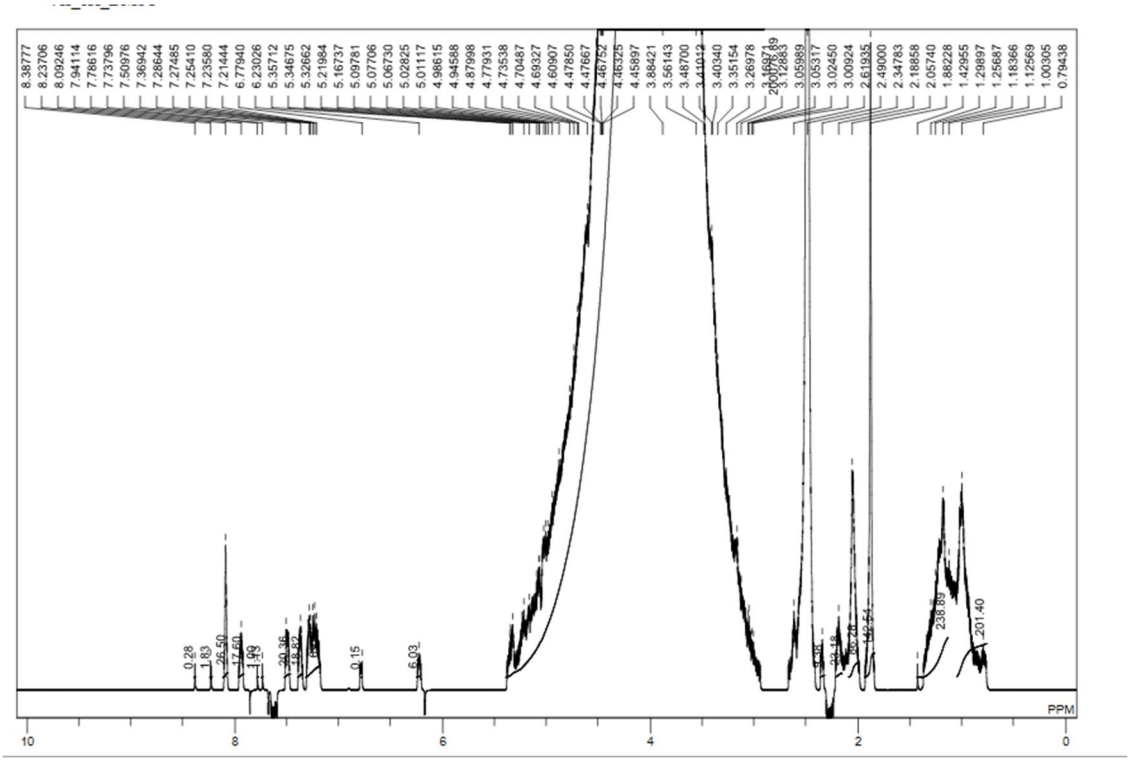

Figure (6.47): [1]HNMR Spectrum of Compound VII

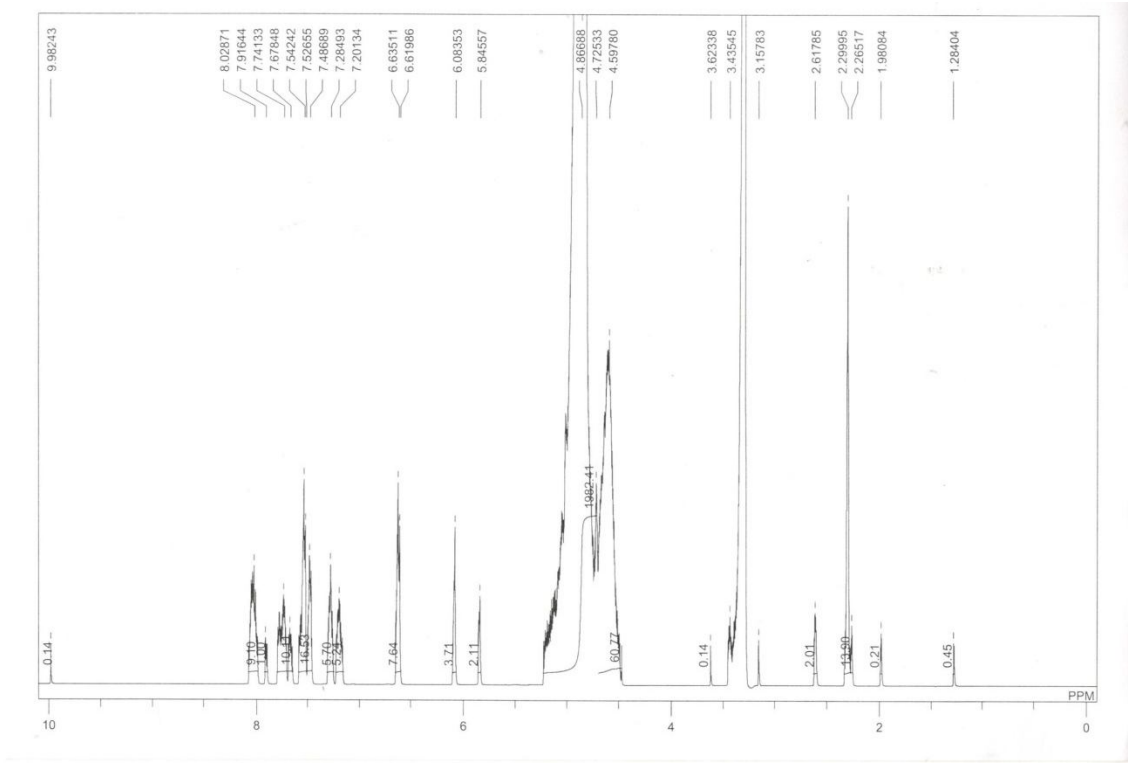

Figure (6.48): [1]HNMR Spectrum of Compound VIII

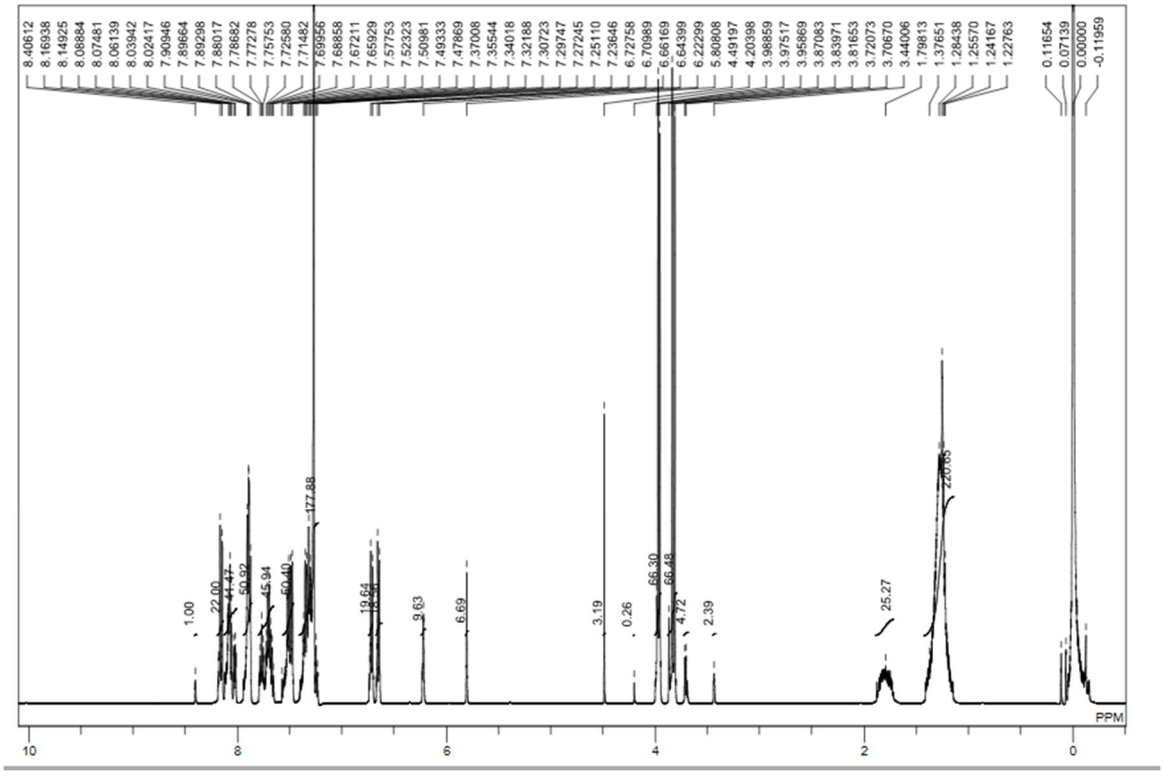

Figure (6.49): [1]HNMR Spectrum of Compound IX

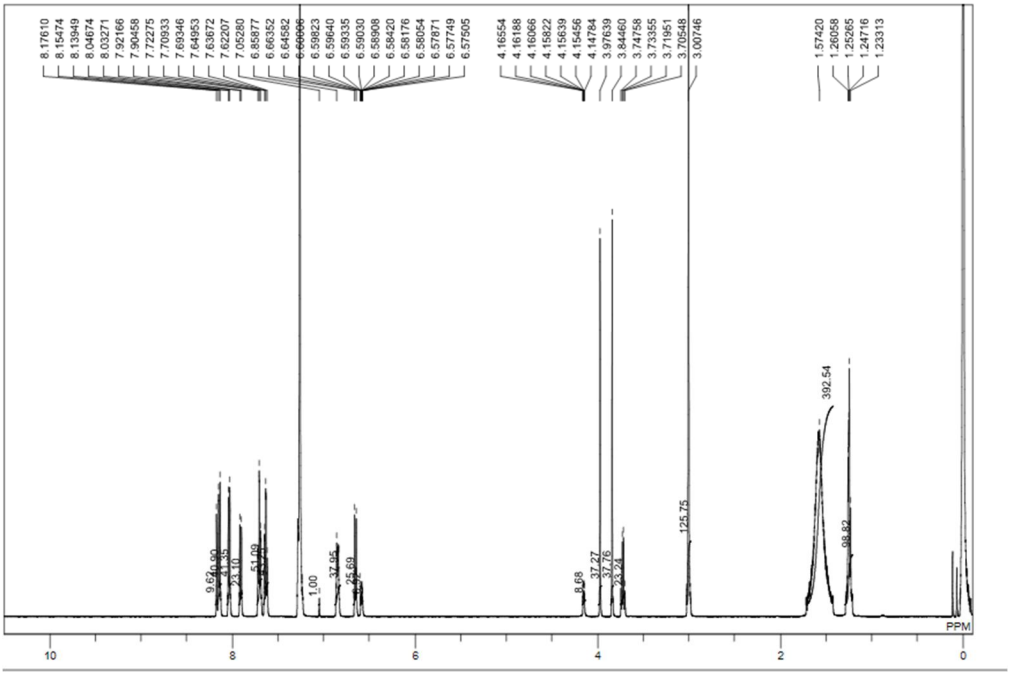

Figure (6.50): [1]HNMR Spectrum of Compound X

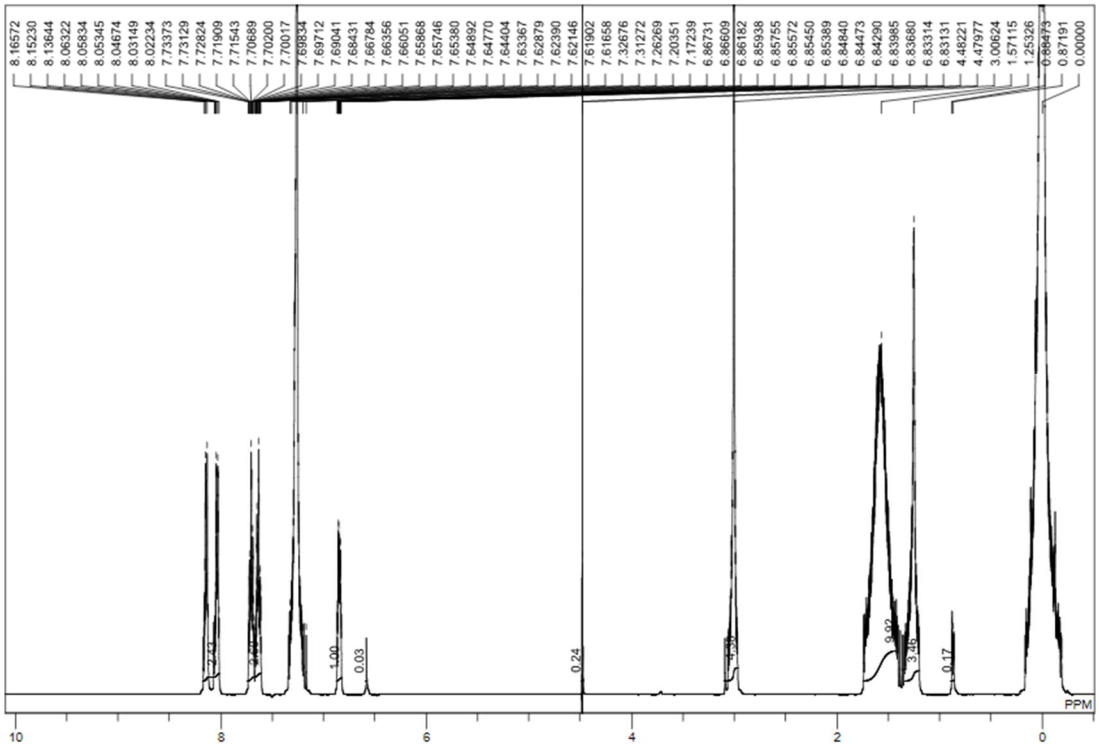

Figure (6.51): [1]HNMR Spectrum of Compound XI

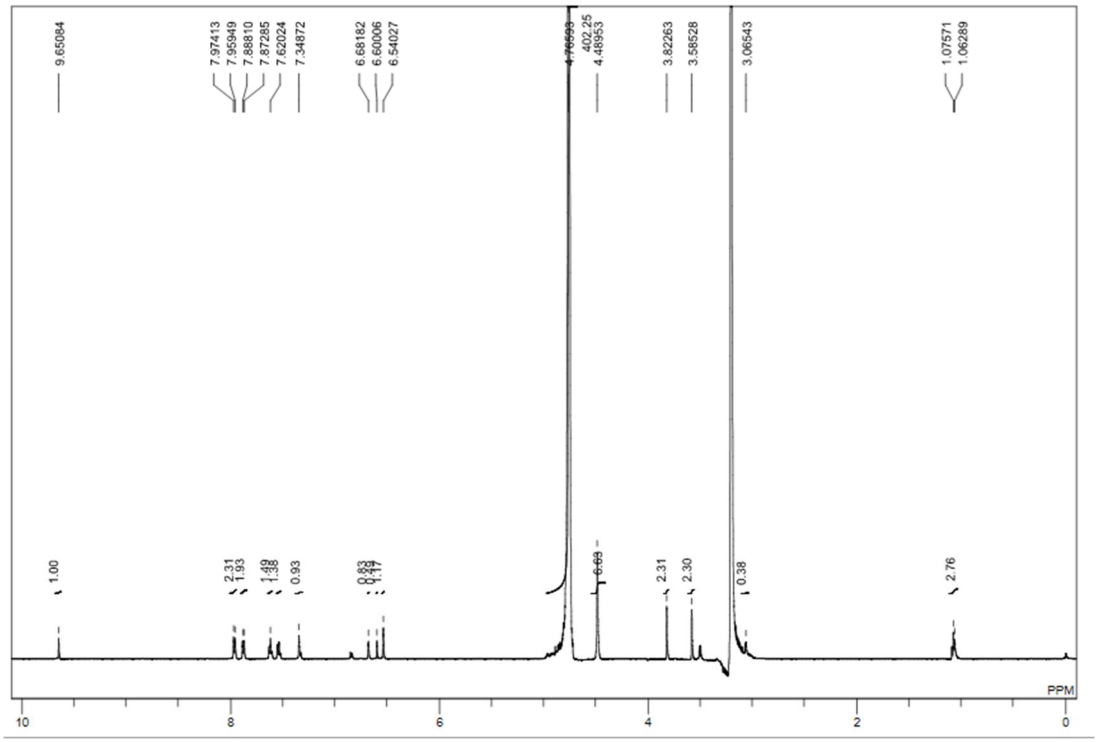

Figure (6.52): [1]HNMR Spectrum of Compound XII

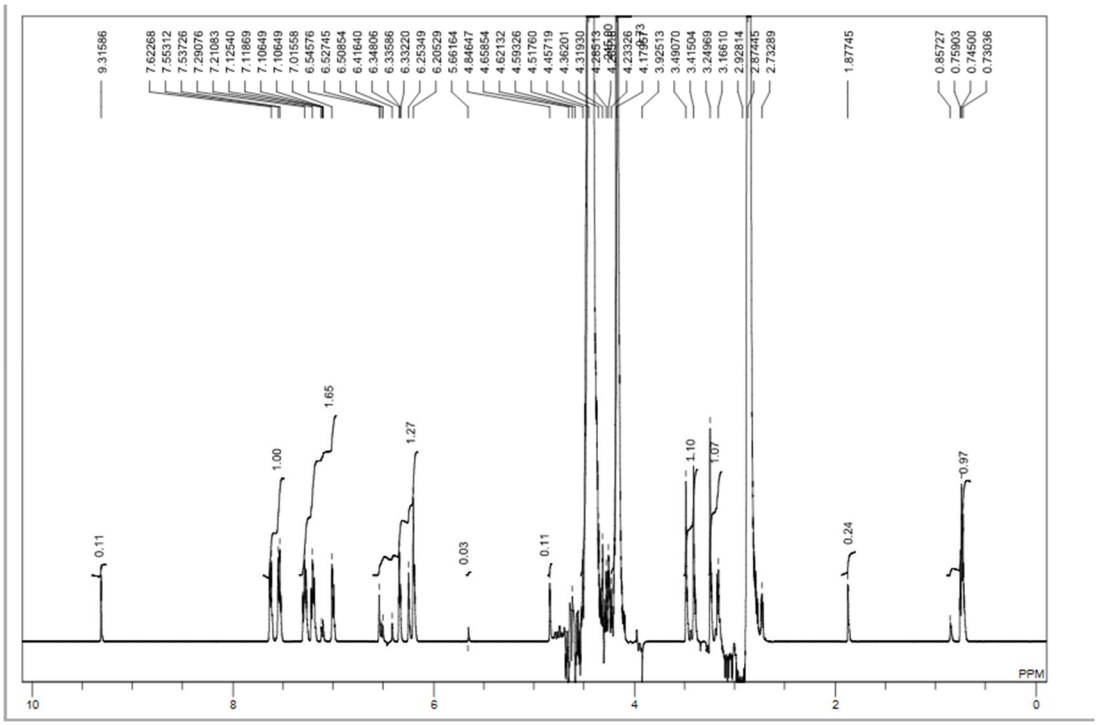


Figure (6.53): $^{1}$HNMR Spectrum of Compound XIII