بسم الله الرحمن الرحيم

Sudan University of Science and Technology
College of Graduate Studies

Quantitative Structure Activity Relationship, Molecular Docking Study and Synthesis of Some Quinoline Derivatives

العلاقة الكمية بين البنية التركيبية والنشاط ودراسة الالتحام الجزيئي وتخليق بعض مشتقات الكينولين

A Thesis Submitted in Fulfillment for the Requirement of the Ph.D. Degree in Chemistry

By

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قَالَ تَعَالَىٰ:

﴿ يَٰٓأَيُّهَا ٱلَّذِينَ ءَامَنُوٓاْ إِذَا قِيلَ لَكُمۡ تَفَسَّحُواْ فِي ٱلۡمَجَٰلِسِ فَٱفۡسَحُواْ يَفۡسَحِ ٱللَّهُ لَكُمۡۖ وَإِذَا قِيلَ ٱنشُزُواْ فَٱنشُزُواْ يَرۡفَعِ ٱللَّهُ ٱلَّذِينَ ءَامَنُواْ مِنكُمۡ وَٱلَّذِينَ أُوتُواْ ٱلۡعِلۡمَ دَرَجَٰتٖۚ وَٱللَّهُ بِمَا تَعۡمَلُونَ خَبِيرٞ ١١ ﴾

Dedication

I dedicate this work:

to my parents, to my wife, daughter, brothers, sisters and to my friend Emam Abdelgadir for their support and encouragement.

Mohammed Musa

Acknowledgement

I am grateful to Almighty Allah for the will and blessings in completing this research. I would like to express my thanks to my ***supervisor Professor Ahmed Elsadig Mohammed Saeed.***

My special thanks to university of kassala for giving me this chance. I wish to record my deep gratefulness to the staff of laboratory techniques, college of science, University of Sudan of Science and Technology their help and facilities kindly provided.

My special and deepest thanks to all colleagues in the researchers Laboratories College of Science, Sudan University of Science and Technology.

Finally, I express my sincere thanks and gratitude to my family to hold them precious odds and all these who contributed in the completion of this work with special thanks to my all friends.

List of Abbreviation

abbreviation	meaning
r.t	Room temperature
EtOH	Ethanol
R	Alkyl group
ES	Electrophilic Substitution
EtONa	Sodium eatho oxide
HMDA	Hexa methylene diamine
QSAR	Quantative structure activity relationships
QSTR	Quantitative structure toxicity relationships
QSPR	Quantitative structure property relationship
LOO	Leave one out
LMO	Leave more out
ANN	Article neural network
LR	Linear regression
MLR	Multiple linear regressions
PLS	Partial least square
PCA	Principle component analysis
PCR	Principle component regression
r^2	Square of the correlation coefficient
r	Correlation coefficient
Q^2	Cross validation regression coefficient
CV	Cross validation
ACD	Advance Chemistry Development
PIC_{50}	Potential Inhibitory concentration
IC_{50}	Fifty present inhibition concentration

logP(o/w)	Logarithm of octanol-water partition coefficient
MOE	Molecular Operating Environment
SPSS	Statistical package for social science
UV	Ultra violet Spectroscopy
IR	Infra-Red spectrophotometer.
FT-IR	Fourier Transformation Infra-Red
NMR	Nuclear Magnetic Resonance
GC-MS	Gas Chromatography Mass Spectrometer
TLC	Thin layer Chromatography
RF	Retardation Factor
m.p	Melting point
TB	Mycobacterial Tuberculosis
E-Ele	Electrostatic Energy
E-nb	Non-bonded Energy
DCASA	Absolute different in charge-weighted areas
DASA	Absolute different in surface areas
CSP	Calculation of statistical parameters
RMSE	Root mean square error
S	Standard error of estimate
D	Density
PDB	Protein Data Bank
H-B	Hydrogen Bond
WHO	World Health Organization
DOTS	Directly observed treatment, short-course
HIV	Human Immunodeficiency Virus
AIDS	Acquired immunodeficiency syndrome

MDR-TB	Multi drug resistant TB
XDR-TB	Extremely drug resistant TB
AMBER	Assisted Model Building with Energy Refinement
MM	Molecular Modeling
DD	Drug Design
MMP	Molecular Modeling Parameter

Abstract

Several quinoline derivatives have an important role in the biological activities field. This importance leads to investigate of newly designed and synthesized of quinoline derivatives against mycobacterium tuberculosis (TB). Chapter one of this thesis deals basically with chemistry of quinoline moiety and deals also with quinoline compounds together with review of their biological properties, in addition, a short concise synthesized quinoline methods was conducted.

In the present study the quantitative structure activity relationship (QSAR) studies were carried out to get model that can be used to predict the anti-mycobacterium tuberculosis activity for designed compounds. Data set compounds composed of quinoline derivatives were collected and their anti-mycobacterium tuberculosis (TB) activity with physiochemical descriptors using multiple linear regression methods was correlated. The model obtained was estimated by internal and external predictivity methods. The results of QSAR study showed very good predictive and statistically significant descriptors model (r^2 = 0.8231, r = 0.9071 for training set, Q^2 = 0.8015 for cross validation and r^2= 0.9792, r = 0.9896 for test set), and all statistical parameter were found in acceptable range (RMSE= 0.1236, S = 0.1646, F = 37.173, P = 0.0001. The obtained model showed positive correlated with logP (o/w) partition coefficient and (DCASA) Absolute different in charge-weighted areas. This model was used to predict the biological activity of designed 34 quinoline derivatives and this result compared with rifamycin. Drug ability of designed compounds was evaluated using Lipinski's rule of five to select compounds for synthesis. Therefore, 8 out of 34 compounds were selected for synthesis. The selected compounds for the synthesis were found to have less ant-mycobacterium tuberculosis (TB) than rifampicin.

Molecular docking study also was carried out to find out the binding affinity of target compounds with mycobacterium tuberculosis (TB) protein that was obtained

from protein data bank (PDB). The docking scores were calculated, fewness energy indicated the force binding adjective of ligand and receptor. Compounds (C9, C10, C30, C6, C20, C25 and C17) have showed excellent docking score (-21.8094, -21.3433, -21.3289, -20.7235, -19.6866, -19.3230 and -19.1307 kcal/mol respectively) comparing with rifampicin as references drug (-25.2369 kcal/mol). 6KGH protein was selected for docking study of quinoline derivatives and rifampicin as reference drug. The result study from this study showed that some of compounds were capable of forming interaction with amino acid in mycobacterium tuberculosis cells and their docking score ranged between (-21.8094 to -15.7230) kcal/mol.

In synthetic work, different aromatic aryl amine derivatives were react with sodium nitrite and hydrochloric acid and sodium acetate as electrophile in the presence of water as solvent to give amine salt and its react with acetyl acetone in low temperature to give diazonium salt as first intermediate, in the second step the coupling diazonium salt (first intermediate) was condensate with various aryl amine derivative to give the second intermediate and cyclization obtained result in the presence of concentrated sulphuric acid to shift water and give the final quinoline derivatives (target compounds). The structures of all synthesized compounds obtained from first and second step (I – XIV) were characterized by thin layer chromatography (TLC), melting point and FT-IR, but the structures of newly synthesized disubstituted quinoline derivatives (XIV-XXII) were established on the basis of TLC, melting point, FT-IR, UV, ^{1}H-NMR and MS spectroscopies analysis. This work achieved by two side study, the first theoretical study achieved on silico by ACD/lab and MOE software programs and the second practical study achieved by the researcher in laboratory for synthesis of the selected compounds.

ملخص البحث

العديد من مشتقات الكينولين لها دور مهم في مجال الأنشطة البيولوجية. هذه الأهمية تقود إلى الكشف عن النشاط المضاد لمشتقات الكينولين المصممة والمُخلقة حديثًا ضد البكتريا المتفطرة السُلِية (TB). الفصل الأول من هذا البحث يتناول كيمياء جزئ الكينولين وخصائصه البيولوجية، كما يعطي دراسة عن الطرق التي أجريت لتخليق الكينولين.

في هذه الدراسة تم إجراء دراسات كمية توضح العلاقة بين البنية التركيبية والنشاط (QSAR) للحصول على نموذج يمكن استخدامه للتنبؤ بنشاط مكافحة البكتريا المتفطرة السلية للمركبات المصممة. وللوصول لذلك، تم جمع مجموعة بيانات مكونة من مشتقات الكينولين وربط نشاطها المضاد للبكتيريا المتفطرة السُلِية بالوصف الفيزيوكيميائية باستخدام علاقة الإنحدار الخطي المتعدد. تم تقدير مقدرة النموذج المتحصل عليه عن التنبؤ باستخدام طرق التنبؤ الداخلية والخارجية. حيث أظهرت نتائج دراسة QSAR عن نموذج تنبؤي ودلالات إحصائية جيدة جدًا ($r = 0.8231$، $r = 0.9071$ لعينة التدريب ، $Q^2 = 0.8015$ و $r^2 = 0.9792$، $r = 0.9896$ للعينة الاختبارية)، كما أن كل الدلالات الإحصائية المتحصل عليها كانت في المدى المقبول $S = 0.1646$, RMSE= 0.1236، $F = 37.173$، $P = 0.0001$. كما أظهر النموذج المتحصل عليه ارتباطًا إيجابيًا مع معامل التجزئة (logP (o / w) و (DCASA). تم استخدام هذا النموذج للتنبؤ بالنشاط البيولوجي لعدد ٣٤ من مشتقات الكينولين المصممة وتمت مقارنة النتائج بالريفامبيسين كعقار مرجعي. تم تقييم الفعالية الدوائية والعلاجية للمركبات المصممة باستخدام قاعدة الخامسة للبينسكي لاختيار مركبات للتخليق. تم اختيار ٨ مركبات للتخليق ووجد أن المركبات المختارة للتخليق أقل من ريفامبيسين ضد البكتريا السُلِية المتفطرة (TB).

كما أجريت أيضاً دراسة الإلتحام الجزيئي لجميع المركبات المستهدفة لتقدير إلفة الإرتباط وتطابقها مع بروتين البكتريا المتفطرة السُلِية المتحصل عليه من بنك بيانات البروتين (PDB). تم حساب نتائج الإلتحام وعرضها في جدول، قيم الطاقة الأقل إشارة إلي قوة الإلتحام الجزيئي بين المعقد والمستقبل. أظهرت بعض المركبات (C9 و C10 و C30 و C6 و C20 و C25 و C17) قيم إلتحام ممتازة (-٢١.٨٠٩٤ ، -٢١.٣٤٣٣ ، -٢١.٣٢٨٩ ، -٢٠.٧٢٣٥ ، -١٩.٦٨٦٦ ، -١٩.٣٢٣٠ و -١٩.١٣٠٧ كيلو كالوري/ مول) على التوالي مقارنة مع ريفامبيسين كعقارمرجعي (-٢٥.٢٣٦٩ كيلو كالوري / مول). تم إختيار البروتين (6KGH) لدراسة الإلتحام الجزيئي لمشتقات الكينولين والريفامبيسين (Rifampicin) كعقار مرجعي. وأظهرت نتائج

الدراسة أن بعض المركبات قادرة علي تكوين ترابط مع الأحماض الأمينية لخلية البكتريا المتفطرة السُلِية وتتراوح قيم الإلتحام ما بين (-٢١.٨٠٩٤ إلى -١٥.٧٢٣٠) كيلو كالوري/ مول.

خلال عمل التخليق ، تفاعلت مشتقات الأريل امين العطرية المختلفة مع نتريت الصوديوم وحمض الهيدروكلوريك وخلات الصوديوم كباحث عن الإلكترون في وجود الماء كمذيب لإعطاء ملح أمين يمكن أن يقترن مع أسيتيل أسيتون في درجة حرارة منخفضة لإعطاء ملح الديازونيوم كوسيط اول ، الخطوة الثانية يتم اقتران ملح الديازونيوم (الوسيط الأول) بمشتقات أخرى من الأريل امين العطرية ليعطي وسيط ثاني الذي يتفاعل مع حمض الكبريتيك المركز لازاحة الماء واعطاء مشتقات الكينولين (المركبات المستهدفة) وللتأكد من أشكال المركبات التي تم الحصول عليها من الخطوة الاولى والثانية (I-XIV) تم وصفها باستخدام كروماتغرافيا الطبقة الرقيقة (TLC) ونقطة الانصهار وطيف الأشعة تحت الحمراء ، ولكن مستبدلات مشتقات الكينولين المخلقة الجديدة (XV-XXII) تم وصفها على أساس كروماتغرافيا الطبقة الرقيقة (TLC)، نقطة الانصهار، طيف الأشعة تحت الحمراء، الأشعة فوق البنفسجية، الرنين النووي المغنطيسي ومطياف الكتلة. تم إنجاز هذا العمل من خلال دراستين، الدراسة الأولى أجريت نظريا علي الكمبيوتر بواسطة برنامج ACD / lab و MOE soft ، والثانية أجريت عمليا بواسطة الباحث في المختبر لتخليق المركبات المختارة.

LIST OF PUBLICATIONS

Published Papers:

- Mohammed Musa Ahmed Mohammed[1], and Ahmed Elsadig Mohamed Saeed[2]. QSAR modeling and molecular docking studies of 3,7-disubstituted quinoline derivatives against mycobacterium tuberculosis (TB). *International Journal of Multidisciplinary Research and Development*, year (2022) Volume 9, Issue 2, page 106-116.
- Mohammed Musa Ahmed Mohammed[1], and Ahmed Elsadig Mohamed Saeed[2]. Synthesis of new 6-substituted-3-(4-substitutedphenyl)diazenyl)-2, 4-dimethyl quinoline derivatives. *International Journal of Multidisciplinary Research and Development*, year (2022) Volume 9, Issue 2, page 98-105.

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Chapter One
Introduction and literature review

1. Introduction

Organic chemistry is that branch of chemistry that deals with the structure, properties, and reactions of compounds that contain carbon (Finar 1975).

Organic compounds can have a variety of structures. These structures can be acyclic or cyclic. The cyclic systems containing only carbon atoms and are called carbocyclic, and the cyclic systems containing carbons and at least one other element are called heterocyclic. Though a number of heteroatoms are known to be part of the heterocyclic rings, the most common heteroatoms are nitrogen, oxygen or Sulphur. A heterocyclic ring may contain one or more heteroatoms which may or may not be same. Also, the rings may be saturated or unsaturated. Nearly half of the known organic compounds contain at least one heterocyclic ring. Many heterocyclic compounds occur naturally and are actively involved in biology. The study of heterocyclic chemistry is a vast and expanding area of chemistry because of their applications in medicine, agriculture, photodiodes and other fields (Abdel-Rahman and Bawazir 2018).

Chemical synthesis is the artificial execution of useful chemical reactions to obtain one or several products. This occurs by physical and chemical manipulations usually involving one or more reactions. In modern laboratory uses, the process is reproducible, reliable, and established to work the same in multiple laboratories. A chemical synthesis involves one or more compounds known as reagents or reactants that will undergo a transformation when subjected to certain conditions. Various reaction types can be applied to formulate a desired product. This requires mixing the compounds in a reaction vessel, such as a chemical reactor or a simple round bottom flask. Many reactions require some form of workup or purification procedure to isolate the final product (Furniss *et al*., 1996, Vogel 1996).

Synthetic Organic Chemistry is related to the chemical science involving in the construction of specific chemical compounds from simple compounds. The process permits synthesis of naturally occurring compounds with actual structure or once needed with structural variation to enhance desired characteristics (Mason 1997).

The term synthesis means in Greek "put together" Synthetic organic chemistry is the "art" of building-up complex molecular structures of organic compounds putting together smaller, or Synthetic organic chemistry is the art of building-up organic compounds from smaller entities. This science has found application in the production of organic compounds of commercial interest, in the construction of new, potentially bioactive molecules derived from rational design, in the challenge to synthesize very complex natural products, in finding new methods and strategies to render this science efficient (Nicotra 1998).

1.1 Quinoline Chemistry

1.1.1 Definition of Quinoline

Quinoline is a heterocyclic aromatic organic compound with chemical formula C_9H_7N. It is colorless hygroscopic liquid with strong odder. Aged sample, exposed to light, become yellow and latter brown. Quinoline is only slightly soluble in cold water but dissolves readily in hot water and most organic solvent. Quinoline itself has few applications, but many it's derivatives are useful in divers' applications (Campbell 1964).

Quinoline ring is an aromatic heterocyclic compound containing nitrogen hetero atom in its moiety, quinoline structure is obtained by ortho-condensation of benzene ring with pyridine molecules, and it's also called 1-benzo [b] pyridine or 1-azanapthaline or benzazine (Bano *et al*., 2017).

It was first isolated from coal tar in 1834, it has a molecular formula C_7H_9N and its molecular weight 129.16, and it is colorless liquid with strong odor and nontoxic to humans on oral absorption and inhalation. It's a weak tertiary base and shows both

electrophilic and nucleophilic substitution reactions, the numbering of quinoline commences from the nitrogen atom which is assigned position-1 and rotated right the nitrogen atom see figure1.1 (Marella *et al*., 2013).

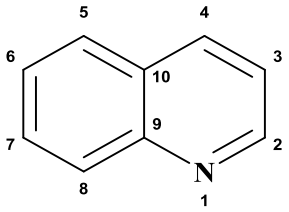


Figure (1.1): Numbering of quinoline structure

Quinoline was also recognized as a pyrolytic degradation product of cinchonamine, an alkaloid closely related to quinine, the word quinoline in fact is derived from the word quinine, which in turn is derived from quina, a Spanish version of a local South American name for the bark of quinine containing Cinchona species (Joule and Mills 2010).

Quinoline play part role in fundamental metabolism, and they occur relatively rarely in plants as secondary metabolites (alkaloids), quinine being much the best known. An important role played by quinoline compounds was that of providing the first photographic film sensitizers, such as the cyanine dye ‘ethyl red’ which extended photography from the blue into the green and then in 1994, with pinacyanol, into the red. Since that time, hundreds of sensitizing dyes have been made and investigated, and the quinoline nucleus has been pushed aside by other more efficient systems (Bergstrom 1944).

1.1.2 Physical and spectroscopies properties of quinoline

Quinoline is a colorless hygroscopic liquid, boiling point 237^{o}C and has a characteristic small resembling that of pyridine. On exposure to air, it develops a yellow color. Quinoline is miscible with organic solvent and is soluble in water to extent of 0.7 %. Quinoline is high aromatic and has resonance energy of 47.3 kcal/mole, dipole moment is 2.10 D and is weakly basic *pKa* 4.94 (Ellis 2009).

1.1.3 Synthesis of Quinoline

Quinoline synthesis and its derivatives has been prevalent in biomedical studies and attracted both synthetic and biological chemist because of its diverse chemical and pharmacological properties and synthetic methods as well as the relative low-cost production of these compounds. Apart from classical method for the synthesis of quinoline ring available like Skraup, Doebner-Miller, Friedländer, Pfitzinger, Conrad-Limpach, Combs syntheses (Kumar *et al*. 2009). There are several known methods that have been used for preparation of quinoline and its derivatives such as:

1.1.3.1 The Skraup Synthesis

In this extraordinary reaction, quinoline is produced when aniline, concentrated sulfuric acid, glycerol and a mild oxidizing agent are heated together. The reaction has been shown to proceed *via* dehydration of the glycerol to acrolein, to which aniline then adds in a conjugate fashion. Acid catalyzed cyclization produces 1,2-dihydroquinoline, finally dehydrogenated by the oxidizing agent the corresponding nitrobenzene or arsenic acid have been used classically. The Skraup synthesis is best for the ring synthesis of quinolines unsubstituted on the hetero ring (Manske and Kulka 2004).

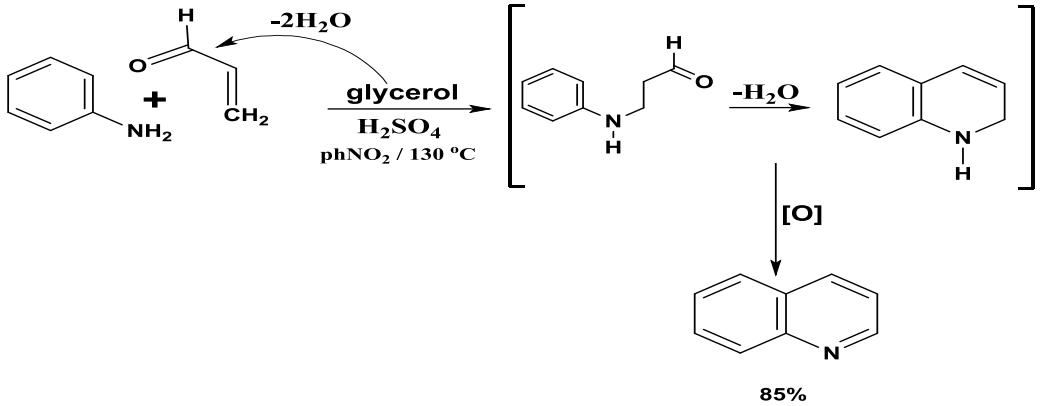


Figure (1.2): The Skraup quinoline synthesis

1.1.3.2 The Knorr quinoline synthesis

Is a reaction that converting a β-ketoanilide to 2-hydroxyquinoline using sulfuric acid, Knorr observed that in higher temperature (approximately 140°C) the anilide actually attack the ester group of the β-ketoester, leading to the thermodynamically preferred β-ketoacidanilides product (Heindel *et al*. 1966).

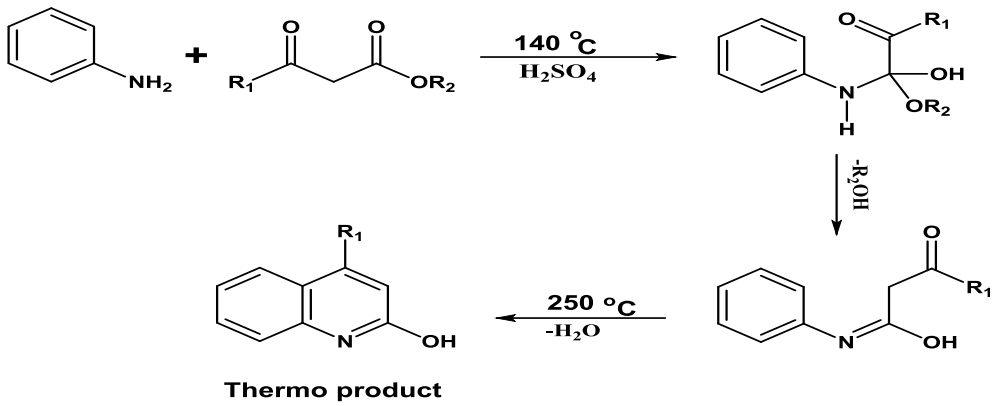


Figure (1.3): The Knorr quinoline synthesis

1.1.3.3 Conrad-Limpach-Knorr Reaction

If the 1,3-dicarbonyl component is at the 1,3-keto acid oxidation level, then the product is a quinoline. Anilines and β-ketoesters react at lower temperatures to give the kinetic product, a β-aminoacrylate, cyclization of which gives a 4-quinolone. At higher temperatures, β-ketoacidanilides are formed and cyclization of these affords 2-quinolones (Campbell 1964).

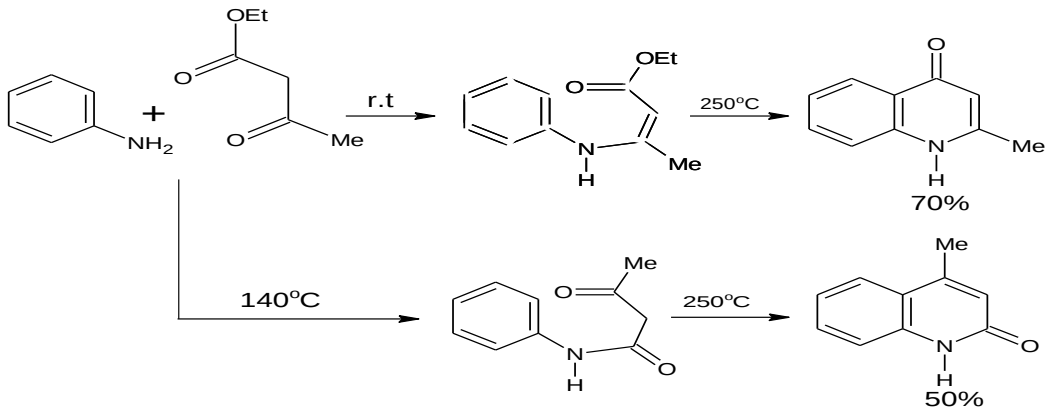


Figure (1.4): Conrad-Limpach quinoline synthesis

1.1.3.4 The Doebner-Millar Synthesis

The interaction of the aniline amino group with the carbonyl group is not the first step, and this variation is known as the Doebner-Miller synthesis (Matsugi *et al*. 2000).

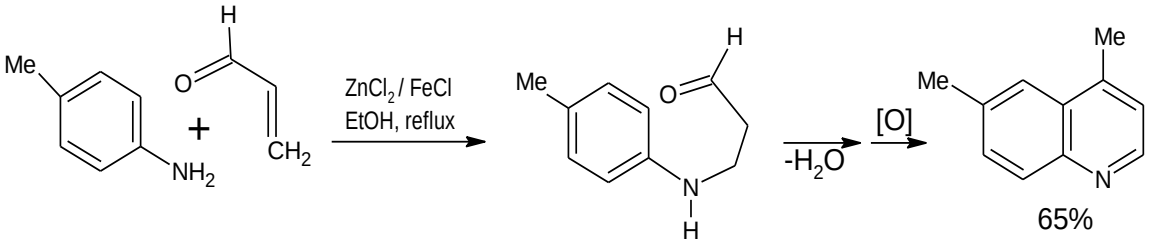


Figure (1.5): The Doebner-Millar quinoline synthesis

1.1.3.5 The Friedlander Synthesis

This route has been used extensively for the synthesis of substituted quinolines (Mcnaughton and Miller 2003, Shao *et al.*, 2019). In the original sequence, an orthoacylarylamine (Okabe and Sun 1995), is condensed with a ketone or aldehyde (which must contain an α-methylene group) by base or acid catalysis to yield the quinoline. The orientation of condensation depends on the regioselectivity of enolate or enol formation (Fehnel 1966). Control of regiochemistry can be obtained by using a removable phosphonate, to direct enolisation, as in $RCOCH_2P(O)(OMe)_2$. 2-Substituted quinolines can be obtained regioselectively

from methyl ketones using pyrrolidine as catalyst (Dormer 2003, Marco *et al*., 2009).

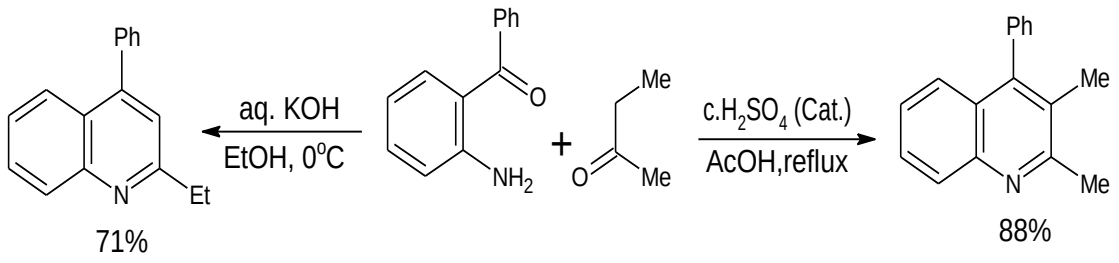


Figure (1.6): The Friedlander quinoline synthesis.

1.1.3.6 The Pfitzinger Synthesis

The requisite ortho amino benzaldehydes are often not easy to obtain, and this modification of the Friedlander approach uses substituted isatins, which as relatively easily synthesized. Alkali opens isatins to ortho amino phenyl glyoxylate anion. Condensation of which with appropriate ketones then gives quinoline-4-carboxylic acids. Many such compounds have been prepared for transformation in to derivatives for pharmacological testing because of their structural similarity to quinine. If not required the 4-carboxyl group can be eliminated by pyrolysis with calcium oxide (Calaway and Henze 1939).

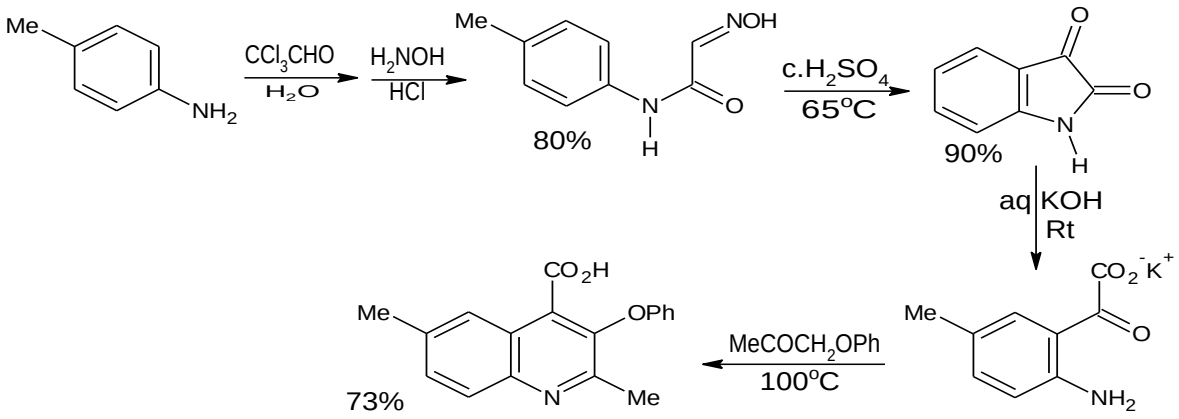


Figure (1.7): The Pfitzinger quinoline synthesis

1.1.3.7 The Camps Synthesis

It is also known as Camps cyclization and is a chemical reaction whereby an o-acyl aminoacetophenone is transformed into two different hydroxyquinoline using hydroxide ion (Camps 1901). The relative proportions of hydroxyquinoline (a) and (b) product are dependent upon the reaction and structure of starting material.

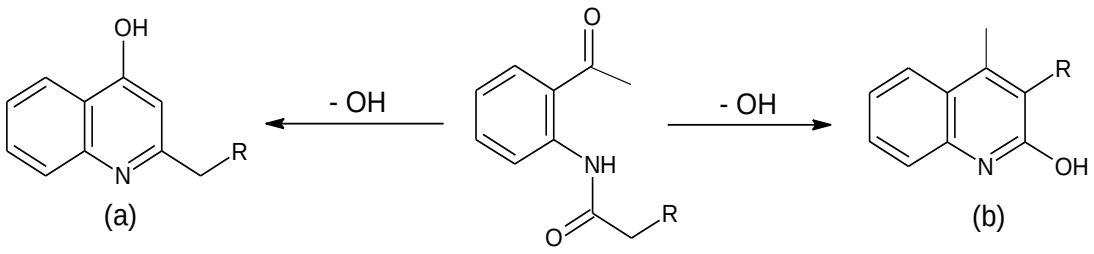


Figure (1.8): The Camps quinoline synthesis.

1.1.3.8 The Nimentowski Synthesis

In 1984, Nimentowski reported that 2-phenyl-4-hydroxyquinoline was formed when anthranilic acid and acetophenone were heated to 120 - 130°C. He later found that at higher heat 200°C, anthranilic acid and heptaldehyde formed minimal yields of 4-hydroxy-3-phenylquinoline derivatives (Manske 1942).

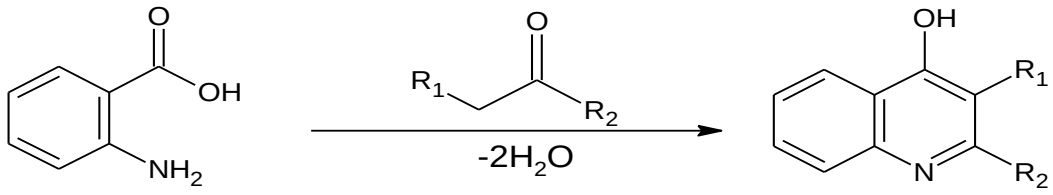


Figure (1.9): The Nimentowski synthesis.

1.1.3.9 The Pictet Synthesis

According to this procedure, *N*-ethylacetamide is heated with zinc chloride to yield 2-methylquinoline. Pictet found that *N*-ethylacetamide afforded a mixture of quinoline and toluidine. He therefore, proposed that the ethyl group migrated to the

ortho position first to produce *o*-ethylacetamide which then cyclized to methylquinoline. Reinvestigated this reaction using (acetyl)-*N*-methylacetamide and heated it at 290°C for 6 hr and obtained quinoline in 6.5 % yield in which quinoline was enriched at C-4. On this basis he suggested a modified mechanism for this reaction (Manske 1942).

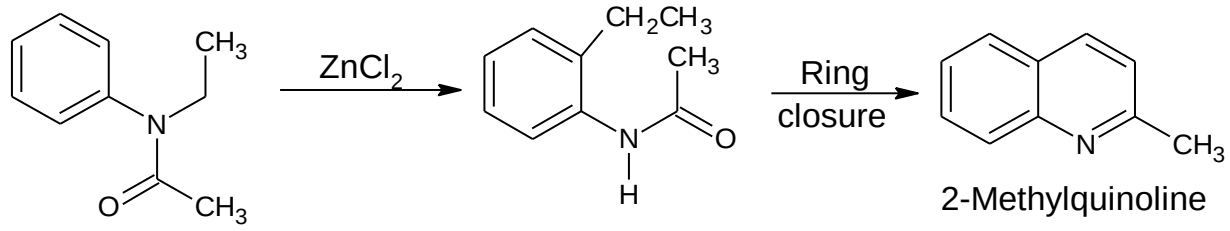


Figure (1.10): The Pictet quinolinesynthesis.

1.1.3.10 The Gould - Jacobs's Synthesis:

Gould-Jacobs reaction is sequence of the following: (1) Condensation of an aryl amine1 with either alkoxymethylenemalonicester 2 provided the anilido methylene malonic ester3. (2) Cyclization of 3 to the 4-hydroxy-3-carboxy quinoline to give4; (3) Saponification to form acid 5, and (4) decarboxylation to give the 4-hydroxyquinoline 6 (Lengyel *et al.*, 2015).

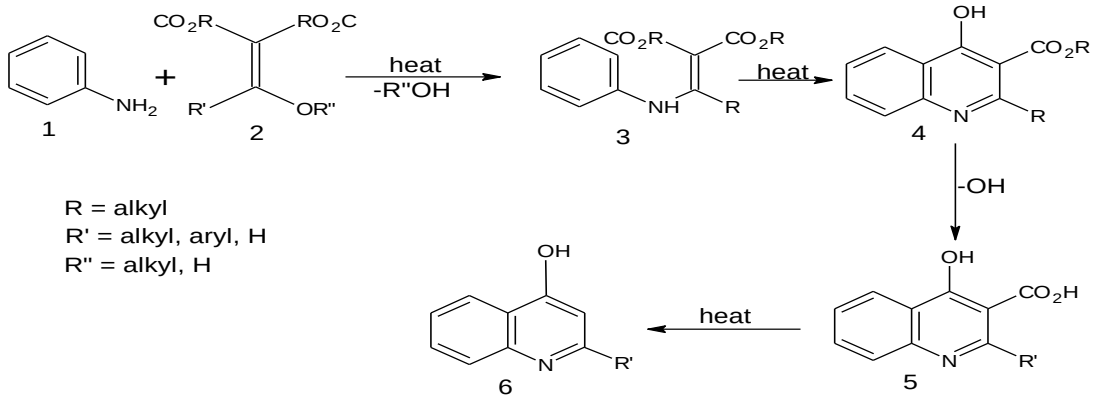


Figure (1.11): The Gould - Jacobs's quinoline synthesis

1.1.3.11 Miscellaneous Method:

Substituted quinolines have been prepared recently by Ruthenium-catalyzed oxidative coupling of alcohols. This is illustrated by the example.

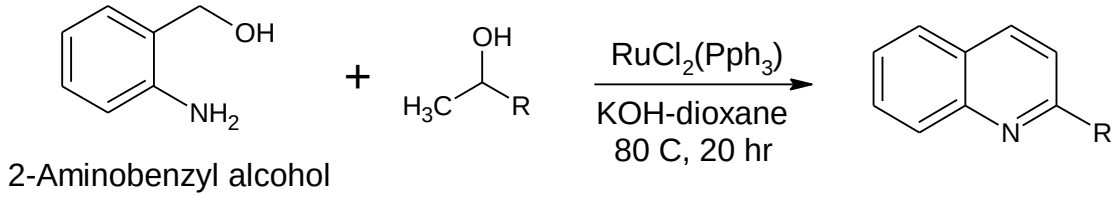


Figure (1.12): Miscellaneous quinoline synthesis

2,3-Dimethylindole reacts in a familiar manner with chloroform and sodium hydroxide in the presence of tetralkylammonium salt to give 2,4-dimethyl-3-chloroquinoline (Thummel and Kohli 1977).

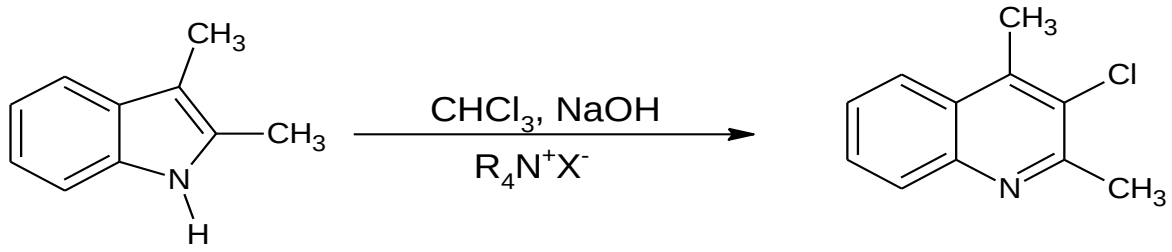


Figure (1.13): quinoline synthesis from 2,3-Dimethylindole.

Photocyclization of the following compound gives a thietane via an allowed (2+2) cycloaddition process. A subsequent cleavage yield a thiol which eliminate hydrogen sulfide to give 2,3-dimethylquinoline (De Mayo *et al*., 1980).

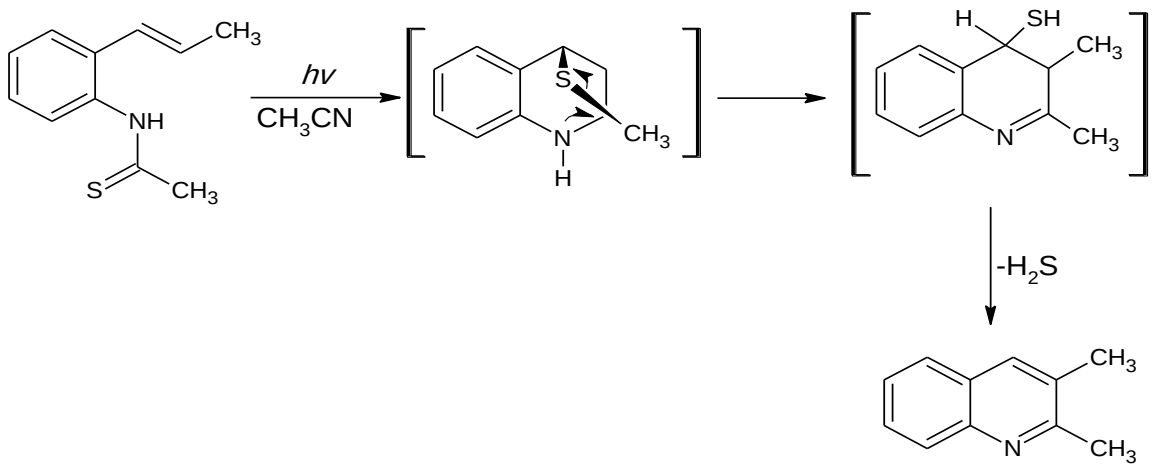


Figure (1.14): quinoline synthesis by Photocyclization

Quinolines have also been obtained by the photolysis of *o*-vinylthioanilides. Reactions of two compounds in which one or both contain annucleophilic center condense in the presence of base to give quinoline. The Friedlander quinoline synthesis is an example of this type of reaction (Bures and Jorgensen 1988).

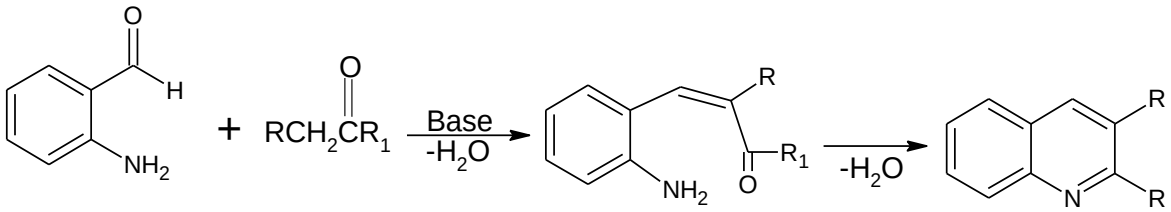


Figure (1.15): quinoline synthesis by photolysis of o-vinylthioanilides

Substituted quinolines have also been prepared from an aromatic amine and an excess of 2-ethylacrolein in 70 % H_2SO_4 at 110°C in the presence of catalytic amount of iodine. The catalyst enables the oxidation of the intermediate dihydroquinoline by sulfuric acid used as solvent.

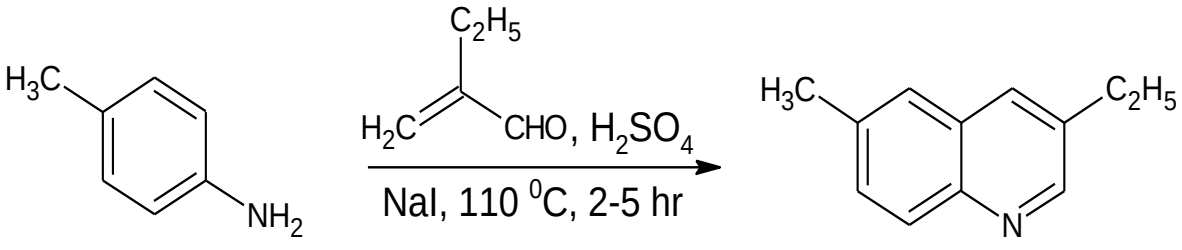


Figure (1.16): quinoline synthesis from aromatic amine and 2-ethylacrolein.

1.1.3.12 The Povarov Reaction

Is an organic reaction described as a formal cycloaddition between an aromatic imine and an alkene. The imine in this organic reaction is a condensation reaction product from an aniline type compound and a benzaldehyde type compound (Worth and Elslager 1970). The alkene must be electron rich which means that functional groups attached to the alkene must be able to donate electrons. Such alkenes are enol ethers and enamines. The reaction product in the original Povarov reaction is a quinoline. Because the reactions can be carried out with the three components premixed in one reactor it is an example of a multi-component reaction (Joh and Hagihara 1967, Silva and Frenhe 2011).

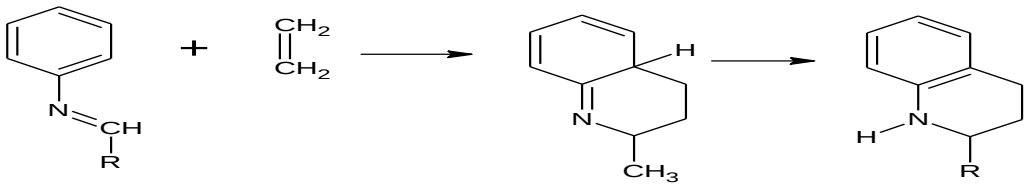


Figure (1.17): The Povarov reaction for quinoline synthesis

1.1.3.13 The Combes synthesis

The combes quinoline synthesis is the chemical reaction involving the condensation of unsubstituted aniline with β-diketones to form substituted quinoline after an acid catalyzed ring clouser of an intermediate.

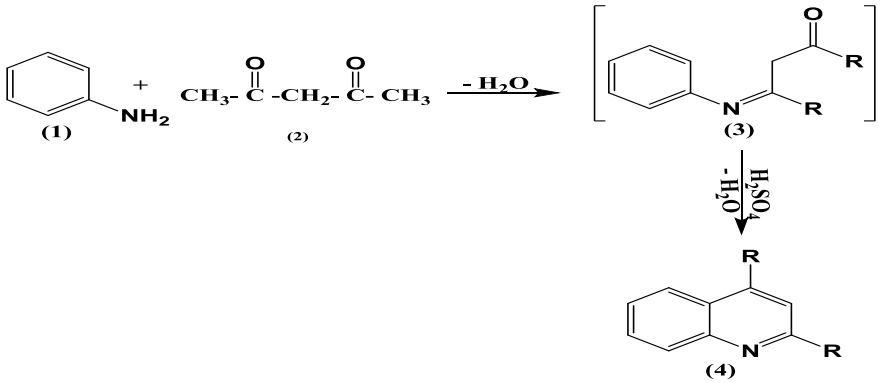


Figure (1.18): The Combs quinoline synthesis

Condensation of a 1, 3-dicarbonyl compound with an aryl amine gives a high yield of the β-amino-enone, which can then be cyclized with concentrated acid. The cyclization step is an electrophilic substitution by the mesomeric *o*-protonated amino-enone followed by loss of water to give the aromatic quinoline (Broeckx *et al*., 1971, Amarasekara 1999).

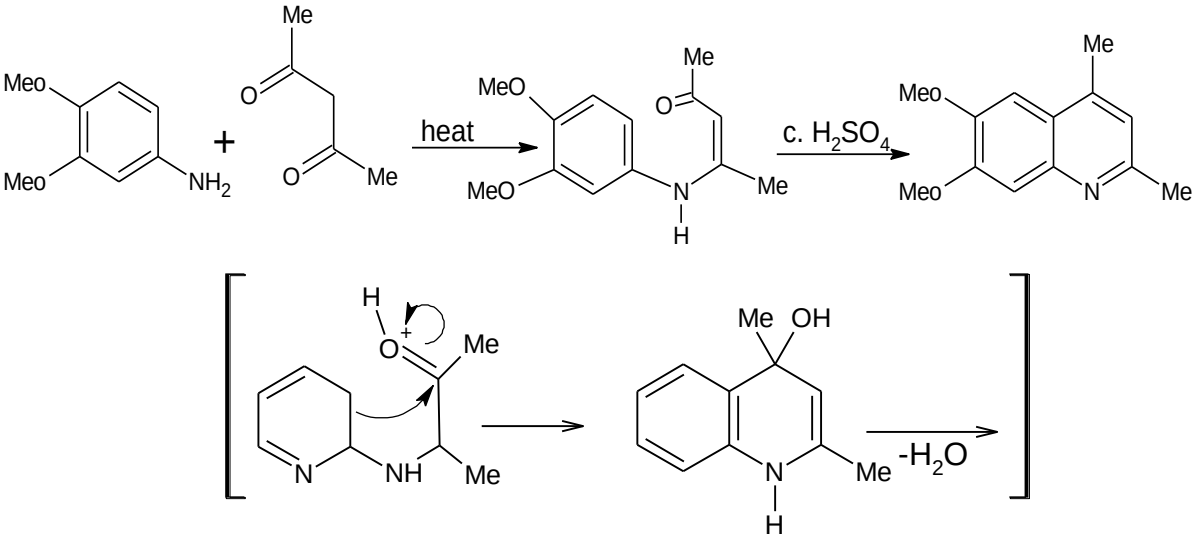


Figure (1.19): The Combes quinoline synthesis in presence H_2SO_4 cyclization.

In order to access 4 - unsubstituted quinolines, a 1,3- ketoaldehyde, in protected form, guarantees the required regioselectivity; the example below produces a 1,8-naphthyridine (Litvinov 2006). (Pyrido [2,3 - *b*]pyridine) (Nakatani *et al*., 1999).

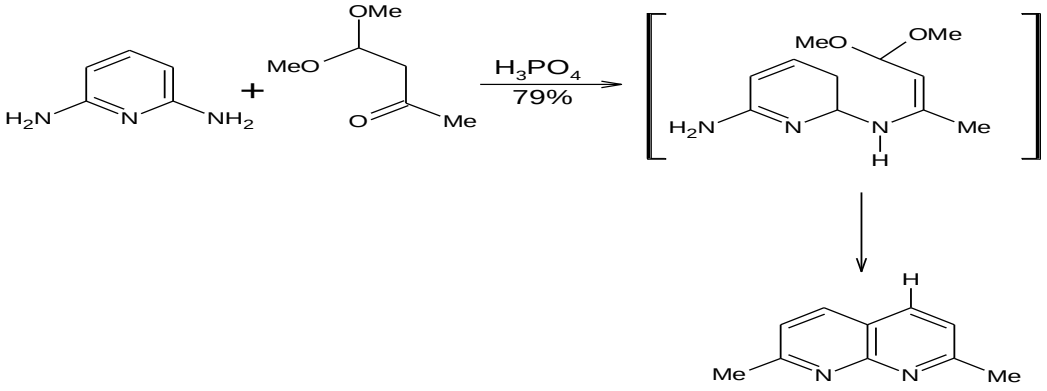


Figure (1.20): The Combs quinoline synthesis in presence H_3PO_4 cyclization.

1.1.4 The quinoline chemical reactions

Quinoline displays chemical properties associated with tertiary amine. In addition because of the fusion of a benzene ring, properties of both benzonoid and pyridinoid compounds frequently manifest them selves.

1.1.4.1 Reaction With acids

Quinoline is a week base and thus protonated on the ring nitrogen mineral acids to form water soluble salt.

1.1.4.2 Electrophilic Substitution (E S)

The electron-rich nitrogen atom of quinoline is main center for attack by electrophilic. The hetero atom has considerable deactivating effect on the ring towards electrophiles attack. In this respect the electrophilic reaction of quinoline may be compared with the 1-nitronaphthalene just as that of pyridine with the nitrobenzene. Therefore, electrophilic substitution on quinoline nucleus requires severe conditions though less than those in the case of pyridine. The attack in the protonated quinoline takes place in the carbocyclic ring at C-5 and C-8 position because the corresponding (c) and (d) can be represented resonance structure in which the aromaticity of the heterocyclic ring is the still preserved.

(c) (d)

Figure (1.21): electrophilic substitution best position on quinoline nucleus.

As a π-electron deficient heterocycle, quinoline is less reactive than benzene particularly in acid solution.

1.1.4.2.1 Proton Exchange

Benzene ring C-protonation, and then exchange, via *N*-protonated quinoline, requires strong sulfuric acid and occurs fastest at C-8, then at C-5 and C-6; comparable exchange in isoquinoline takes place somewhat faster at C - 5 than at C-8. At lower acid strengths each system undergoes exchange α to nitrogen, at C-2 for quinoline and C-1 for isoquinoline. These processes involve a zwitterions produced by deprotonation of the *N*-protonated heterocycle.

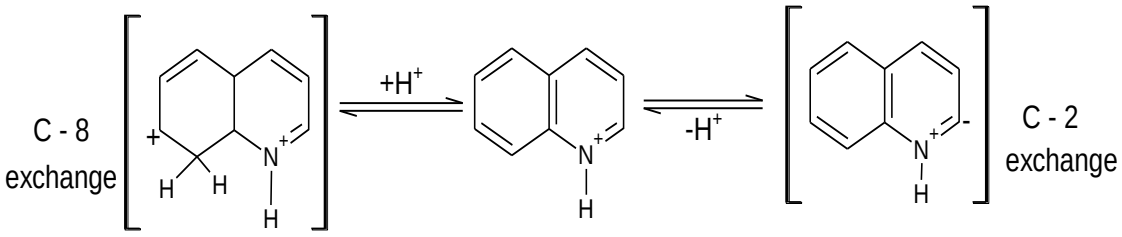


Figure (1.22): Proton Exchangeon quinoline nucleus

1.1.4.2.2 Halogenations

Attack by halogen depends on the nature of the reagent employed for halogenations. Chlorination (SO_2Cl_2) of quinoline for instance, yields 3-chloroquinoline while bromination (Br_2 , CCl_4) yields 3-bromoquinoline. The product is obtained by the following addition- elimination mechanism. Orientation in the presence of strong acids (Br_2, Ag_2SO_4) proceeds to give a mixture of 5-and 8-bromoquinolines, the reacting species being quinolinium cation (De la Mare *et al.*, 1960, De la Mare 1974).

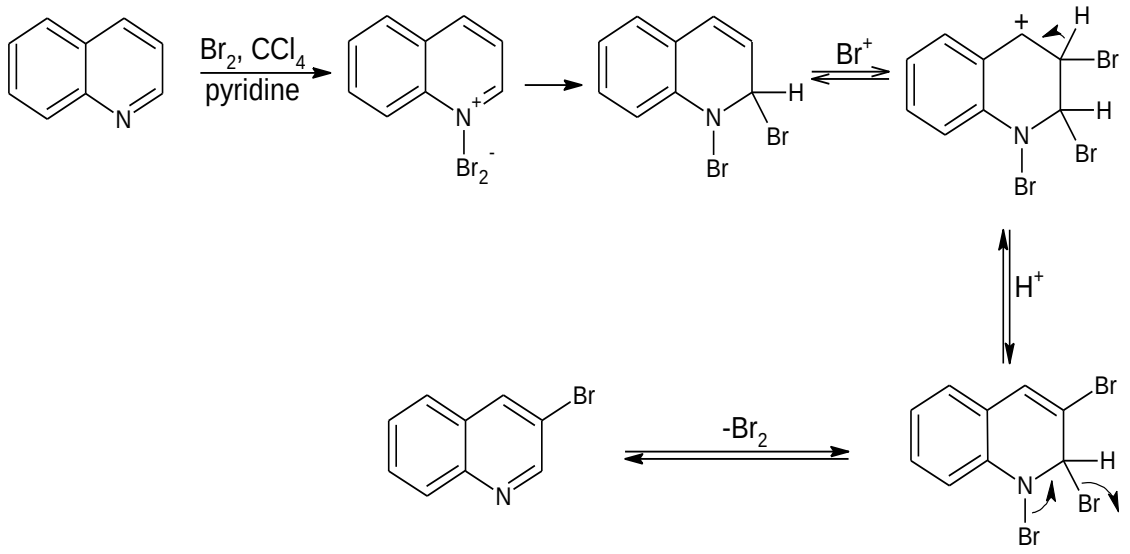


Figure (1.23): Halogenations of quinoline nucleus.

1.1.4.2.3 Nitration

The nitration and sulfonation of quinoline can be carried out under conditions which are less strenuous than those in the case of pyridine. The pyridine ring is already π-electron deficient and becomes more so by protonation of the ring nitrogen atom. Acidic electrophilic reagents thus show a strong preference for attack in the benzene ring. Nitration (HNO_3, H_2SO_4 $0^{\circ}C$) of quinoline gives a mixture of 5- and 8-nitroquinolines. In equal amounts. In acetic anhydride as solvent or with dinitrogen tetra oxide as nitrating agent, the nitration proceeds in a totally different manner and very inefficiently. After the reaction much quinoline is recovered unchanged 3-nitroquinoline in a yield of 6% along with a small quantity and 8-nitroquinoline.

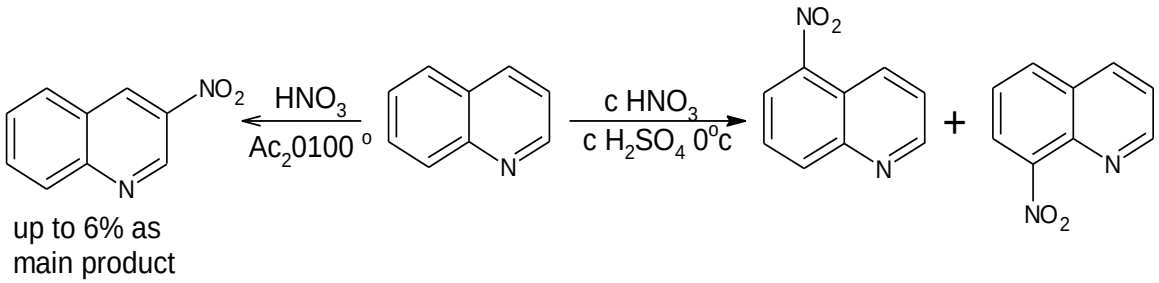


Figure (1.24): Nitration of quinoline nucleus.

1.1.4.2.4 Sulfonation

The products of sulfonation vary with the experimental conditions. In conc. Sulfuric acid quinoline almost entirely is converted into quinolinium cation. Sulfonation at 220° C results in attack at the benzene ring to give largely quinoline 8-sulfonic acid. At a very high temperature (300° C), 6-quinolinesulfonic acid is obtained because the 5- and 8-isomers rearrange to the 6-isomer which is thermodynamically more stable.

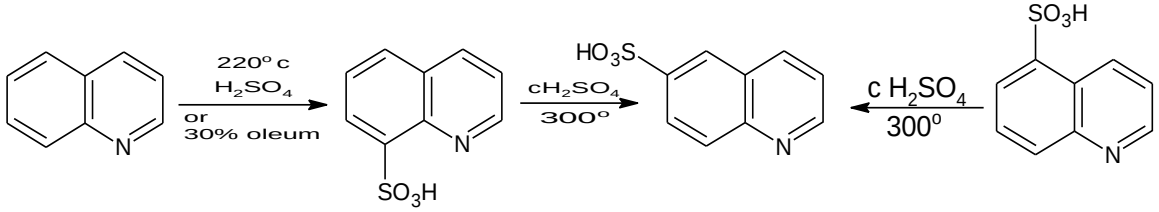


Figure (1.25): Sulfonation of quinoline nucleus.

1.1.4.2.5 Mercuration

With mercuric acetate, quinoline forms quaternary n-mercuriacetate at room temperature. At 160°C further substitution occurs and treatment with sodium chloride gives a mixture of 3- and 8- mercurichlorides.

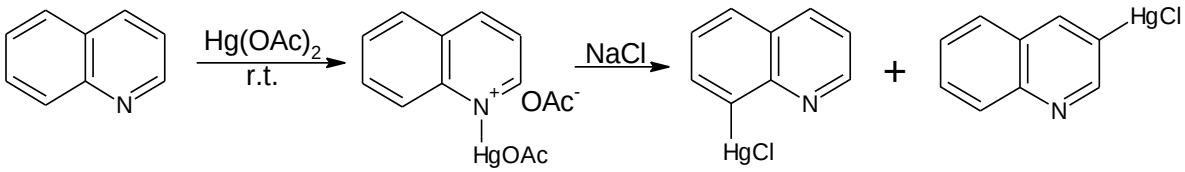


Figure (1.26): Mercurationof quinoline nucleus.

Reactions of quinoline with the free radicals are often unselective and form complex mixture of products. Thus phenylation of quinoline with benzoyl peroxide gives all seven phenylquinolines (Dewar *et al.*, 1956).

1.1.4.2.6 The Friedel-Crafts Reaction

This reaction is rare in quinoline series because of the deactivation of the ring by the nitrogen atom. However, the Friedel-Crafts acylation of 8-methoxyquinoline occurs at the 5-position but not at position-7 (Li Chang *et al.*, 2008).

1.1.4.3. Reaction with Nucleophilic

Attack by nucleophile occurs in the pyridine ring of quinoline and position-2 is preferred site for such an attack (Frenna *et al.*, 2014).

1.1.4.3.1 Amination

Quinoline reacts rapidly with NaH_2in liquid $NH_3$to givea 3:1 mixture of α- and γ-adducts. At RT, reaction goes further to give 2-aminoquinoline: the nature of the cation influence the yield, which is highest (80 percent) when $Ba(NH_2)_2$ is used. That 4-aminoquinoline is not formed in this reaction suggests that the reversibly formed γ-adduct suffers hydride loss much less readily under these conditions;

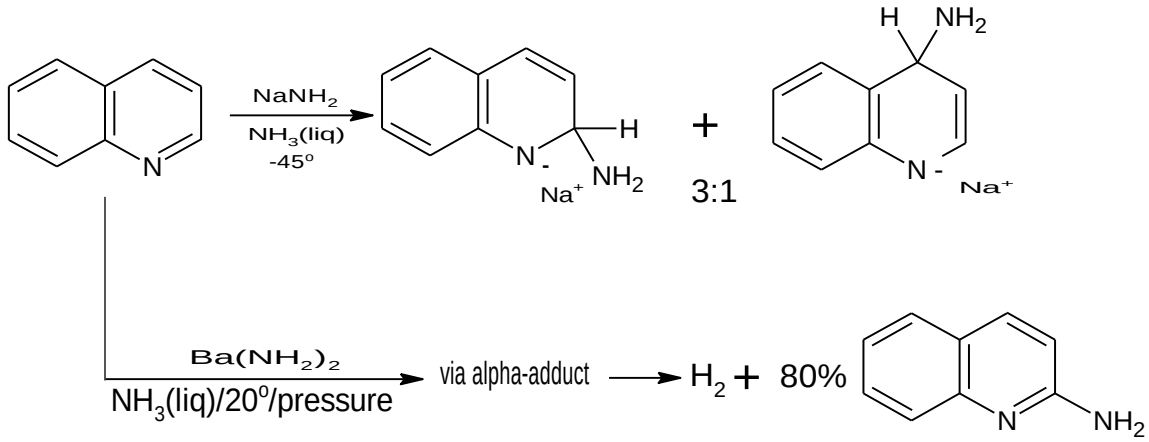


Figure (1.27): Amination of quinoline nucleus.

However, up to 10 per cent 4-aminoquinoline may be obtained in the presence of $NaNO_3$ as hydride acceptor. When substitution cannot occur at C2, as 2-phenylquinoline, the 4-amino derivative is product (Joule and Smith 1978).

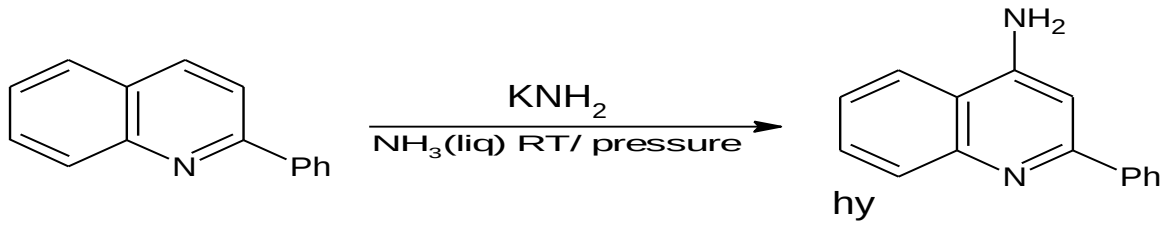


Figure (1.28): Amination of 2-phenylquinoline.

1.1.4.3.2 Arylation with lithium compounds

The addition of organolithium reagents to quinoline in a 1,2-fashion is well established and the resultant 1,2-dihydroquinoline can be manipulated oxidation leads to 2-alkylquinoline while reduction with Na/C_2H_5OH or metal hydrides to 2-substituted 1,2,3,4-tetrahydraquinoline (Shrinivas *et al.*, 2016).

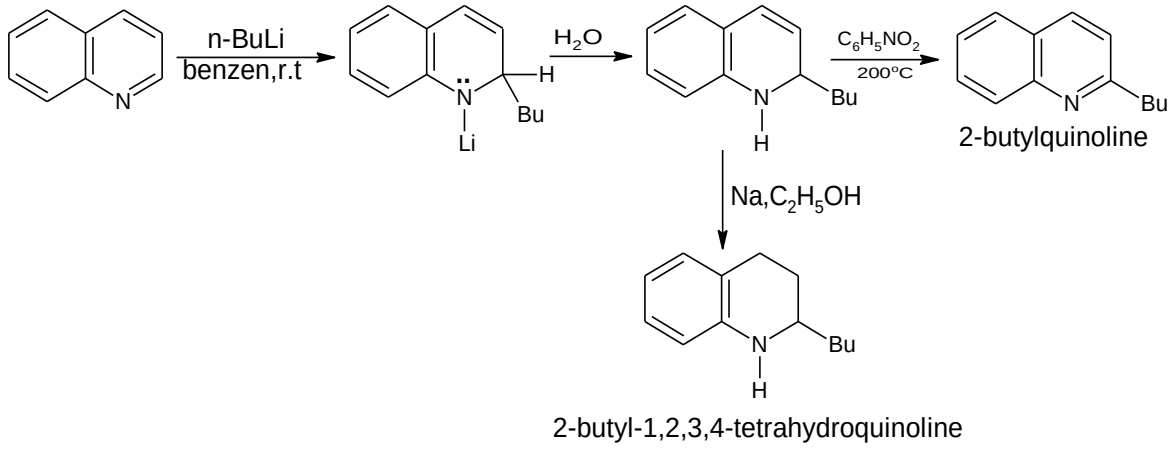


Figure (1.29): Quinoline Arylation with lithium compounds

Quaternization at the nitrogen atom reinforces the ability to react with nucleophilic reagents. With sodium hydroxide, carbinolamine is formed but the actual product isolated is dimeric carbinolamine ether. Even weak nucleophile attack readily on the 1-alkylquinoline cation (Yamato *et al.*, 1987)

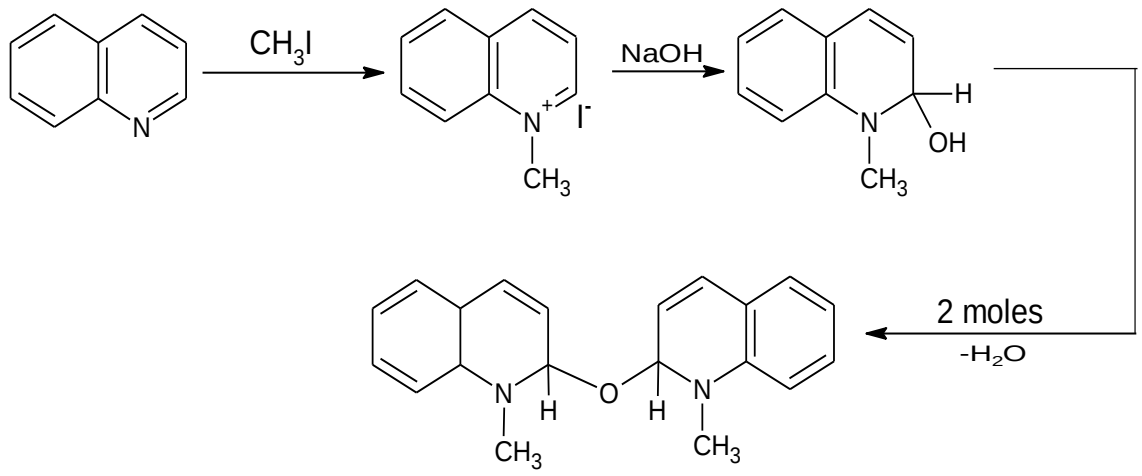


Figure (1.30): Carbinolamine formed from quinoline

This behavior is illustrated by the attack of Grignard reagent and the resultant formation of 1-methyl-2-phenyl-1, 2-dihydroquinoline known as Reissert compounds (Popp *et al*., 1968).

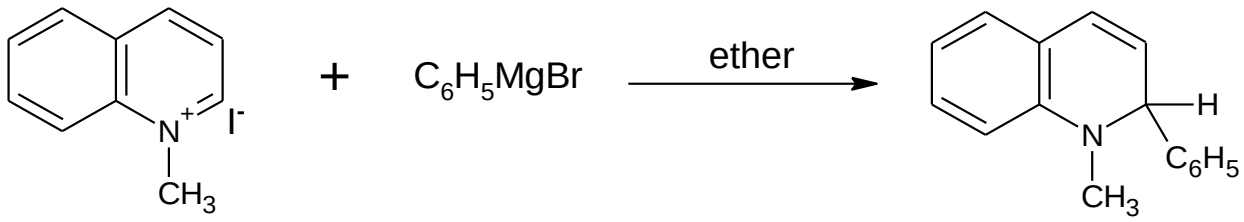


Figure (1.31): quinoline reaction with Grignard reagent.

1.1.4.3.3 Quinoline Hydroxylation:

When the quinoline is heated with the KOH or NaOH-KOH, 2-quinoline is produce together with a nearly-quantitative yield of hydrogen. As with Amination, the cation is importance, for reaction with sodium hydroxide occurs only at about 300^{o} and is much less efficient.

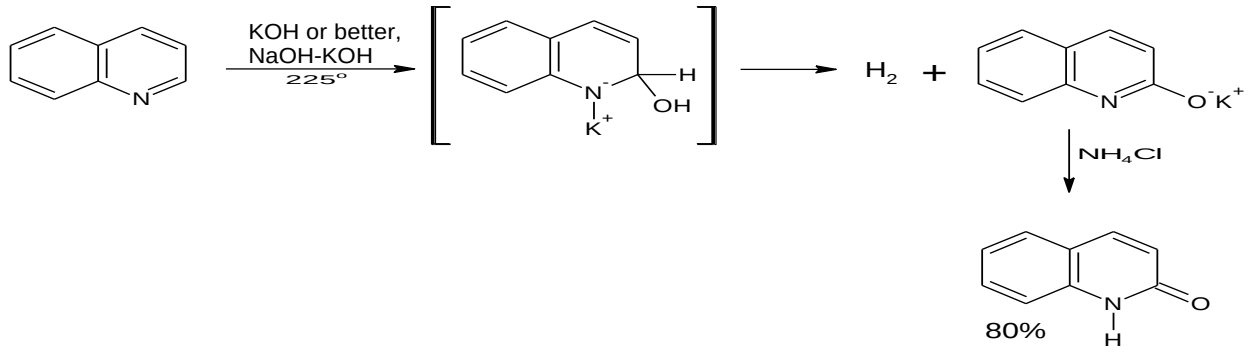


Figure (1.32): Quinoline Hydroxylation.

1.1.4.3.4 Substitution with displacement of halides:

Quinolines with halogen at C3, C5, C6, C7, and C8 have normal halo benzene type reactivity that is resistance to substitution by nucleophilic reagent. 2- and 4-haloquinolines, however, react easily by substitution, as the following examples show.

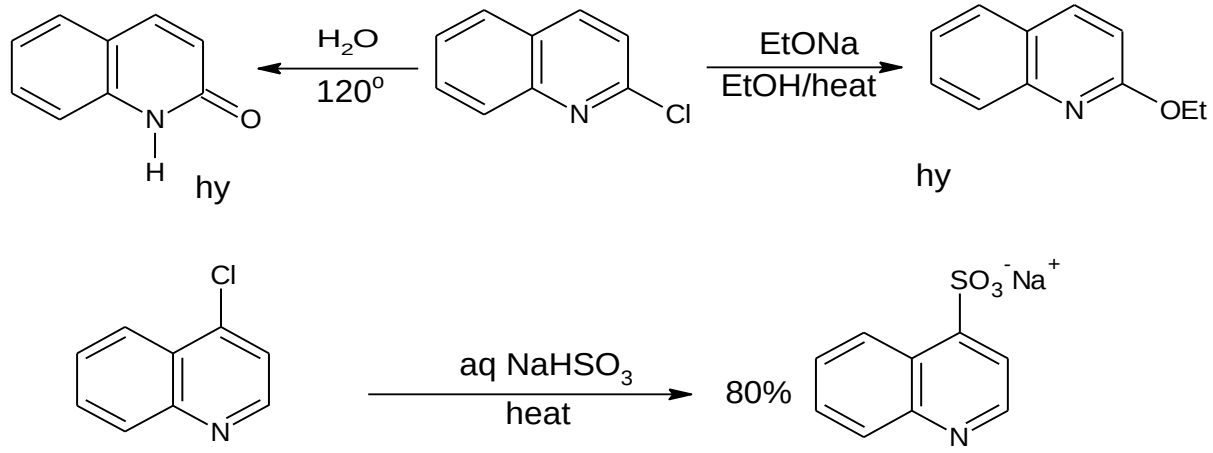


Figure (1.33): Substitution with displacement of halides

None of the four bromo- and chloroquinolines appears to have been made to react with magnesium or lithium; however, lithio derivatives can be obtained from both homo- and hetero-ring bromides by reaction with two moles of butyl lithium at a temperature low enough (-70^{o}C) to suppress addition.

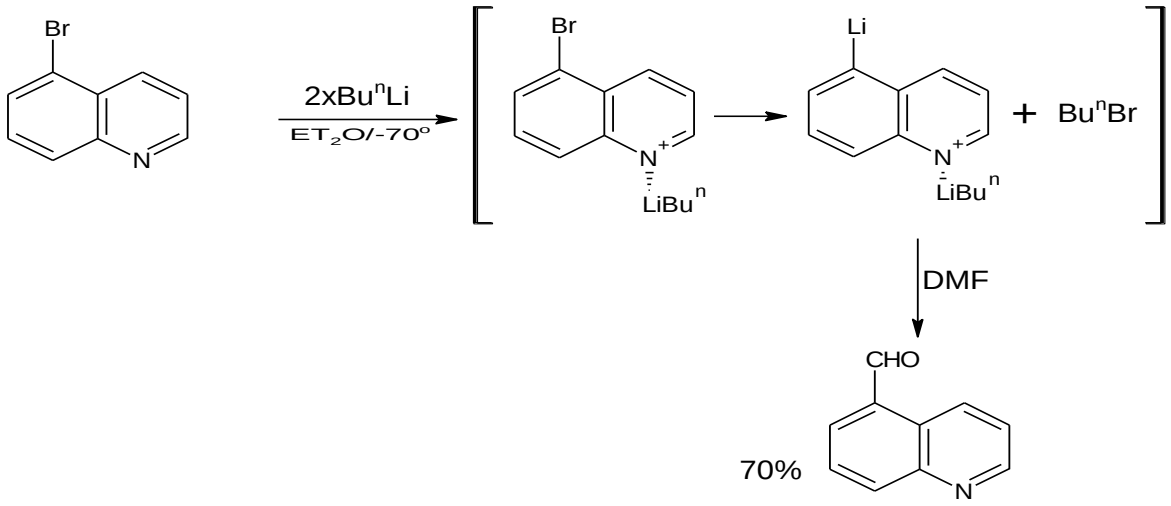


Figure (1.34): quinoline halides react with lithium.

Halo derivatives of quinoline on reaction with potassium amide in liquid ammonia give rise to product of amination viz the "hetaryne" type intermediate. For instance, 2-amino-3-bromoquinoline forms 2, 3-diaminoquinoline under these conditions (Joshi *et al*., 2016).

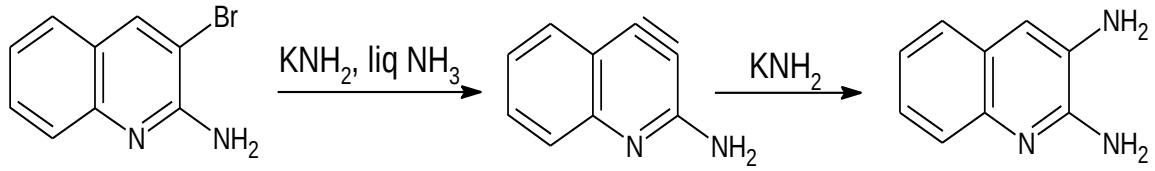


Figure (1.35): quinoline halides amine react with potassium amide.

Besides halo derivatives of quinoline, undergo rapid nucleophilic substitution with nucleophiles like alkoxides and thiolate ions. The reaction is accomplished using microwave irradiation (Cherng 2002).

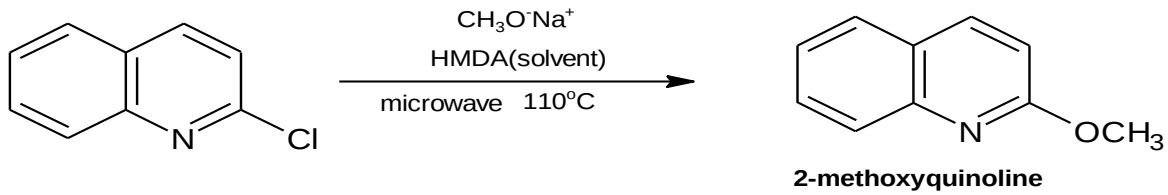


Figure (1.36): quinoline halides react with alkoxides and thiolate.

1.1.4.4 Reaction with Free Radicals

Quinoline is attacked by phenyl radicals generated by decomposition of benzoyl peroxide. All seven monosubstitution products are formed with 8-phenylquinoline predominating.

Substitution position	2	3	4	5	6	7	8
% of product	6	14	20	12	8	8	30

A much greater degree of specificity occurs when the quinoline cation is attacked, and by less reactive radicals. Carboxamide and acetyl radicals have been introduced into quinoline 2- and 4-position in this way (Mahmoud *et al.*, 2014).

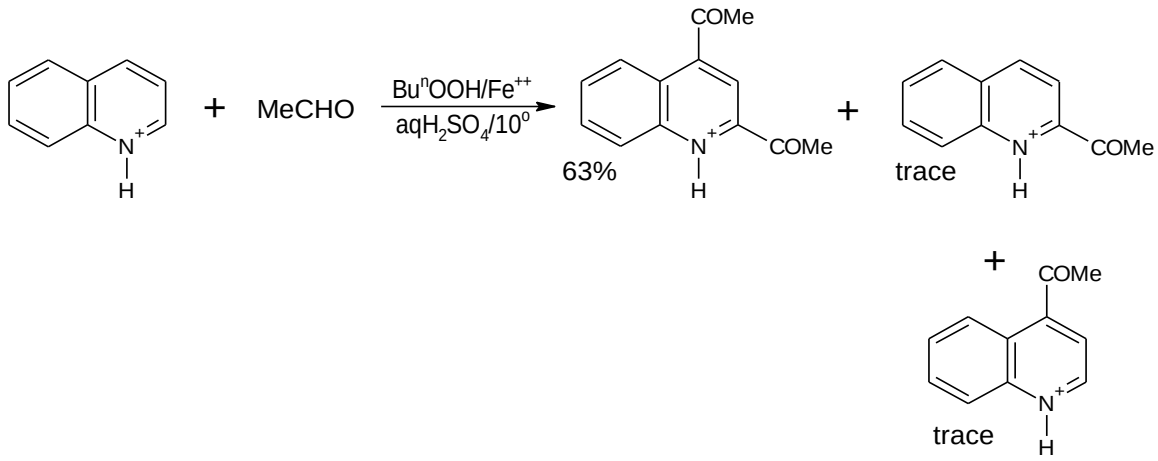


Figure (1.37): quinoline reaction with Free Radicals.

1.1.4.5 Reaction with Reducing Agents

Quinoline is more readily reducing than naphthalene just as pyridine is easily reducing than benzene. Therefore, many types' reagents reduce the hetero cyclic ring. Reducing of quinoline to 1, 2, 3, 4-tetrahydroquinoline is best achieved with Raney nickel or PtO_2, H_2, or ammonium carbonate, Pd/C (Sharpless and Young 1975). In acid media the benzo group can be selectively reduced (Van Buren *et al*. 1982). Hydrogenation to decahydroquinoline is difficult (Vierhapper *et al.*,1974) ring rupture takes place when quinoline is reducing over night at 260-380°c.

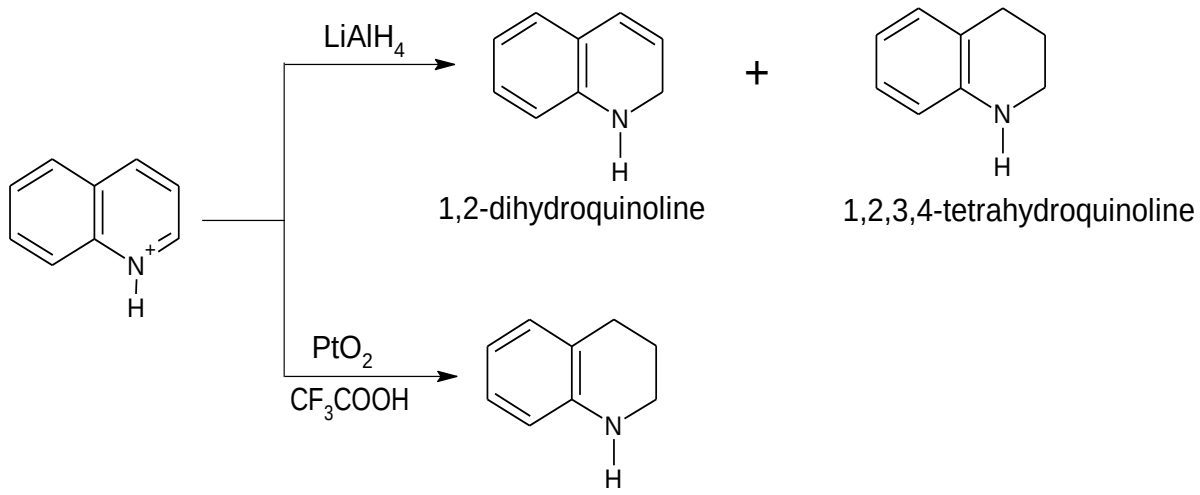


Figure (1.38): quinoline reaction with reducing Agents.

Reducing to the isomeric 5,6,7,8-tetrahydroquinoline can be achieve by Pt/H_2 reduction in concentrated HCl, which with longer reaction times leads to the *cis*- and trans-decahydroquinoline. 1,2,3,4-tetrahydroquinoline is very easily de hydrogenated to quinoline (Katritzky and Johnson 1967).

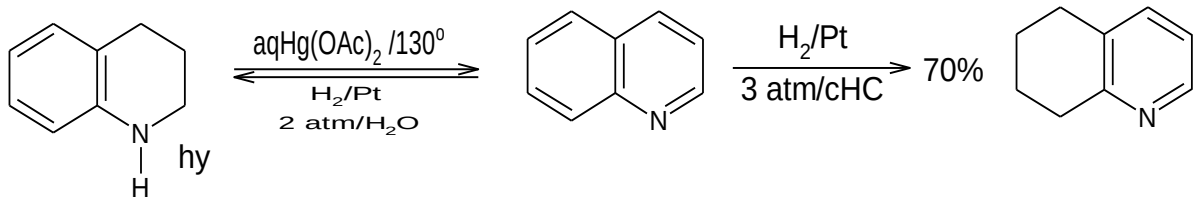


Figure (1.39): reducing quinoline to the isomeric 5,6,7,8-tetrahydroquinoline.

1.1.4.6 Reaction with Oxidizing Agents

The course of derivative oxidation of quinoline and its derivatives complex an either ring may be opened. The pyridine ring is π-deficient and oxidation is independent of electron availability. The pyridine ring thus remains intact while the benzene ring is destroyed on treatment with alkaline potassium permanganate (Theodoridis and Malamas 1991).

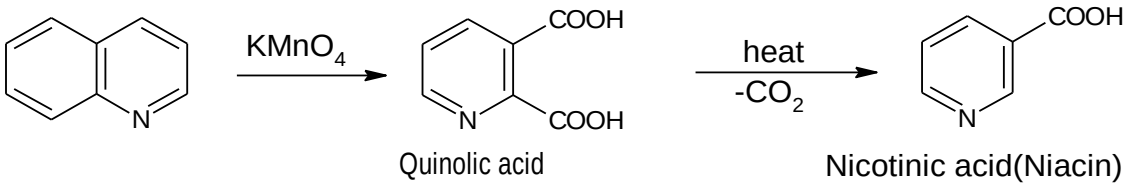


Figure (1.40): oxidation quinoline.

Ozonolysis of quinoline gives glyoxal and pyridine-2,3-dicarboxaldehyde,as equation blow.

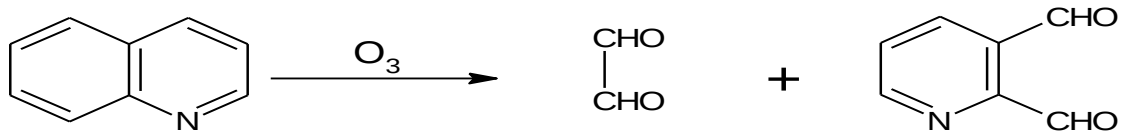


Figure (1.41): Ozonolysis of quinoline.

Oxidation of quinolines with peracids leads to quinoline N-oxides in excellent yields. In substituted quinolines the yield depends on the nature and location of the substituent (Stermitz *et al*., 1970).

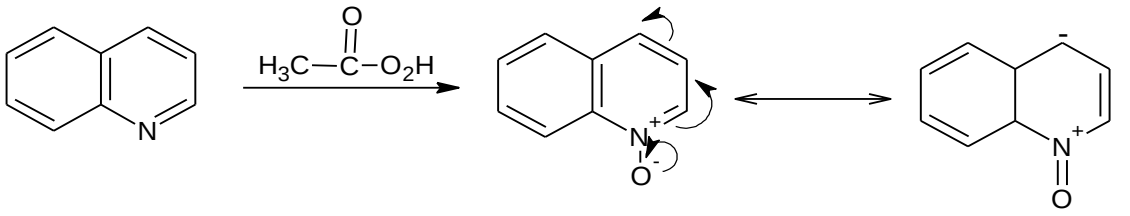


Figure (1.42): oxidation quinoline with acid

The ring activation by *N*-oxide group of quinoline is analogous to that or pyridine *N*-oxide. The electrophilic attack in quinoline *N*-oxide takes place at C4 to give 4 nitroquinoline *N*-oxide while at low temperature 5- and 8-isomers are also obtained.

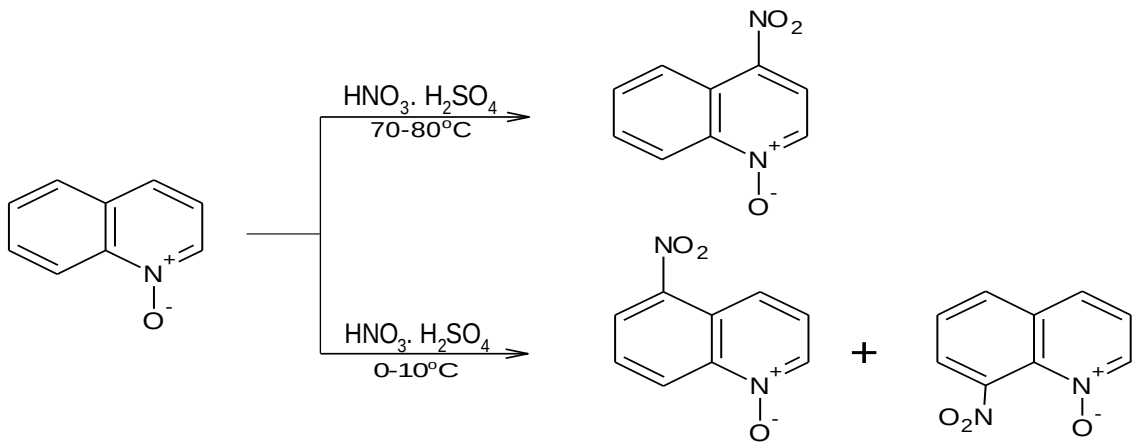


Figure (1.43): *N*-oxide group of quinoline reaction.

1.1.5 Biological Properties of Quinoline:

Quinoline and its derivatves have been attracted considerable interest because a large number of natural products and drugs contain this heterocyclic moiety. Further, these compounds are used as building blocks of various other compounds (Hajalsiddig and Saeed 2019). Quinoline and its derivatives are well known for their antimalarial drugs, such as chloroquine,quinine and mefloquine are mainstays of chemotherapy against malaria (Zibaseresht *et al*., 2013). Quinoline is a heterocyclic scaffold of paramount importance to human race. Several quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use (Chevalier *et al*., 2001).

Indeed quinoline derivatives are some of the oldest compounds which have been utilized for the treatment of a variety of diseases. The bark of Cinchona plant (also known as Jesuit's or Cardinal's bark) containing quinine was utilized to treat palpitations, fevers and tertians since more than 200 years ago. Quinoline, a distereoisomer of quinine was in the early 20th century acknowledged as the most potent of the antiarrhythmic compounds isolated from the Cinchona plant (Chen *et al*., 2001).

Compounds containing quinoline motif are most widely used as antimalarial, antibacterial, antifungals and anticancer agents (Dassonneville *et al*., 2000). Additionally, quinoline derivatives find use in the synthesis of fungicides, viruses, biocides, alkaloids, rubber chemicals and flavoring agents. They are also used as polymers, catalysts, corrosion inhibitors, preservatives, and as solvent for resins and terpenes. Furthermore, these compounds find applications in chemistry of transition metal catalyst for uniform polymerization and luminescence chemistry. Quinoline derivatives also act as antifoaming agent in refineries. Owing to such significance, the synthesis of substituted quinolines has been a subject of great focus in organic chemistry (Musiol *et al*., 2006).

Quinoline and its derivatives also have important roles in other biological compounds that are involved in cardiovascular, anticancer, and anti-inflammatory activities (Baba *et al.,* 1996). Additionally, researchers, such as Luo Zai-gang et al., looked at the synthesis and use of quinoline derivatives as HIV-1 integrase inhibitors (Zai *et al*., 2010). They also looked at how the substituent placement on the quinoline derivatives affected the primary anti-HIV-1 inhibitory activity (Luo *et al*., 2009).

Quinoline is used in the manufacture of dyes, the preparation of hydroxyl quinoline sulfate and niacin. It has also used as a solvent for resins and terpenes. Quinoline is mainly used as a feedstock in the production of other chemicals. Approximately 4 tonnes are produced annually according to a report published in 2005. Its principal use is as a precursor to 8-hydroxyquinoline, which is a versatile chelating agent and precursor to pesticides. Its 2- and 4-methyl derivatives are precursors to cyanine dyes'.Oxidation of quinoline affords quinolinic acid (pyridine-2, 3-dicarboxylic acid), a precursor to the herbicide sold under the name "Assert"(Joule and mills 2013).

1.2 Molecular modeling (MM) and drug design (DD)

Molecular modeling (MM) is general term used to describe the use of computer to construct molecules and perform a variety of calculation on these molecules in order to predict their chemical characteristics and behavior. Molecular modelling encompasses all theoretical methods and computational techniques used to mimic and study the structure and behaviour of molecules, ranging from small chemical systems to large biological molecules and material assemblies. Molecular modeling is a collection of (computer based) techniques for deriving, representing and manipulating the structures and reactions of molecules, and those properties that are dependent on these three-dimensional structures (Dutta *et al*., 2007). Molecular modeling is an important tool to aid the understanding of the fundamental concepts of structure activity relationships, and to elucidate the mechanism of action of drugs (drug-receptor interaction), used in the teaching-research-extension (Patel *et al.*, 2014).

Drug design is the process which is deriving by technological breakthrough implying advanced experimental and computational methods. Drug design, often referred to as rational drug design or simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target (Mukesh and Rakesh 2011). The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the bimolecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modeling techniques (Yadav *et al.*, 2017). Drug discovery is the process through which potential new therapeutic entities are identified, using a

combination of computational, experimental, translational, and clinical models (Nandi and Bagchi 2010).

1.3 Quantative structure activity realationships (QSAR)

1.3.1 Definition of QSAR

QSAR has been traditionally perceived as a means of establishing correlations between trends in chemical structure modifications and respective changes of biological activity (Katritzky *et al*., 1995). QSAR is a widely accepted predictive and diagnostic process used for finding associations between chemical structures and biological activity. QSAR has emerged and has evolved trying to fulfill the medicinal chemist's need and desire to predict biological response. Quantitative structure-activity relationships (QSAR) represent an attempt to correlate structural or property descriptors of compounds with activities. These physicochemical descriptors, which include parameters to account for hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods. Activities used in QSAR include chemical measurements and biological assays. QSAR currently are being applied in many disciplines, with many pertaining to drug design and environmental risk assessment (Borman 1990).

Quantitative structure relationship (QSAR) is the name usually applied to methods which correlate molecular structure to some kind of *in vitro* or *in vivo* biological property. When this approach is applied to modeling toxicological data, it is termed quantitative structure toxicity relationships (QSTR). When applied to modeling physiochemical properties it is called quantitative structure property relationship (QSPR) (Ghosh *et al*., 2006).

Quantitative structure-activity relationship (QSAR) and quantitative structure property relationship (QSPR) makes it possible to predict the activities/properties of a given compound as a function of its molecular substituent. Essentially, new

and untested compounds possessing similar molecular features as compounds used in the development of QSAR/QSPR models are likewise assumed to also possess similar activities/properties (Isarankura *et al*., 2009).

The QSAR (quantitative structure relationship) referred to statistical analysis of the potential relationships between chemical structure and biological activity. QSAR is essentially a computerized statistical method which tries to explain the observed variance in the biological effect of certain class of compounds as a functional of molecular changes caused by the substituents. These physiochemical descriptors which included parameters to account hydrophobicity, electronic properties and structure effect, are determined empirically or more recently by computational methods (Sahu *et al*., 2013).

QSPR/ QSAR models represent mathematical equations correlating the response of chemicals (activity/property) with their structural and physicochemical information in the form of numerical quantities (Roy *et al*., 2015).

In addition, the quantitative structure activity relationship are mathematical models that seek to predict complicated physicochemical /biological properties of chemicals from their simpler experimental or calculated properties. QSAR enables the investigator to establishes a reliable quantitative relationship between structure and activity which will be used to derive an insilicon model to predict the activity of novel molecules prior to their synthesis. The past few decades have witnessed much advances in the development of computational models for the prediction of a wide span of biological and chemical activities that are beneficial for screening promising compounds with robust properties (Muhammad *et al*., 2018).

Also the (QSAR) is widely accepted predictive and diagnostic process used for finding associations between chemical structures and biological activity. QSAR has emerged and has evolved trying to fulfill the medicinal chemist's need and desire to predict biological response. It found its way into the practice of agro

chemistry, pharmaceutical chemistry, and eventually most facts of chemistry (Cantor 2001).

Quantitative structure activity relationships are based on the assumption that the structure of a molecule (i.e. its geometric, steric and electronic properties) must contain the features responsible for its physical, chemical, and biological properties, and on the ability to represent the chemical by one, or more, numerical descriptor(s) (Gramatica 2008).

QSAR is the final result of computational processes that start with a suitable description of molecular structure and ends with some inference, hypothesis, and predictions on the behavior of molecules in environmental, physicochemical and biological system under analysis (Eriksson *et al*., 2003).

Quantitative structure activity relationship (QSAR) modeling pertains to the construction of predictive models of biological activities as a function of structural and molecular information of a compound library. The concept of QSAR has typically been used for drug discovery and development and has gained wide application for correlating molecular information with not only biological activities but also with other physicochemical properties, which has therefore been termed quantitative structure-property relationship (QSPR). QSAR is widely accepted predictive and diagnostic process used for finding associations between chemical structures and biological activity. The QSAR models are useful for various purposes including the prediction of activities of untested chemicals. It helps in the rational design of drugs by computer aided tools via molecular modeling, simulation and virtual screening of promising candidates prior to synthesis (Muhammad *et al.*, 2018).

1.3.2 History of QSAR

Proposed a relationship which existed between the toxicity of primary aliphatic alcohols with their water solubility. In 1868 Crum-Brown and Fraser published an

equation which is considerable to be the first generation formulation of a quantitative structure activity relationship, in their investigations of different alkaloids (Muhammad *et al*., 2018). Systematic QSAR began with the work of on the narcotic activity of various drugs (Pohorille *et al*., 1998). Hammett introduced a method to account for substituent effects on reaction mechanism (Hammett 1935). Taking Hammetts model into account, Taft proposed in 1956 an approach for separating polar, steric, and resonance effects of substituents in aliphatic compounds (Taft 1956). Classical approach to QSAR/QSPR was led by the pioneering works of Hansch in the development of linear Hansch equation (Fujita *et al.*,1964).

1.3.3 Objectives of QSAR

QSAR attempts to correlate structural, chemical, statistical and physical properties with biological activity by various approaches (Verma *et al*., 2010). And models are scientific credible tools for predicting and classifying biological activities of untested chemicals, also is an essential tool for lead development (optimization), a growing trend is to used early in drug discovery process as a screening and enrichment tool to eliminate from further development those chemicals lacking "drug like" properties or those chemicals predicted to elicit a toxic response (Perkins *et al*., 2003).

1.3.4 Purpose of QSAR

There are many practical purposes of a QSAR, these techniques are utilized widely in many situations includes the following:

a. To correlate quantitatively and recapitulate the relationships between trends in chemical structure alteration and respective change in biological end point comprehending which chemical properties are most likely determinants for their biological activities.

b. To predict biological activity and physicochemical properties by rational means (Consonni and Todeschini 2010).
c. To comprehend and rationalize the mechanisms of action within a series of chemical.
d. Saving in the cost of product development.
e. Prediction could reduce the requirement for lengthy and expensive animal tests.
f. Reduction of animal tests, thus reducing animal use and obviously pain and discomfort to animal.
g. Other areas of promoting green and greener chemistry to increase efficiency and eliminate waste by not following leads unlikely to be successful (Alexander *et al.*, 2015).

1.3.5 Classification of QSAR Methodologies

There are different types of computational methods in QSAR depends upon the data complexity those are:

1- Based on dimensional compounds:

- (1D-QSAR) correlation activity with global molecular properties such as logP, pKa etc.
- (2D-QSAR) correlation activity with structural patterns such as two side pharmacophores, connectivity, also 2D-QSAR is insensitive to the conformational arrangements of atoms in space (Livingstone 2004).
- (3D-QSAR) needs information on the position of the atoms in three spatial dimensions like correlation activity with non-covalent interaction field surrounding molecule (Albuquerque *et al*., 1998).
- (4D-QSAR) for each molecule, a set of automatically docked orientations and conformations are developed by genetic algorithms like ligand configuration in 3D-QSAR (Ravi *et al*., 2001).

- (5QSAR) Induced-fit scenarios of ligands upon binding to the active site as the fifth (protein flexibility).
- (6-DQSAR) further solvation models can be thought of and sixth entropy dimensions (Dong *et al*., 2003).

2- Based on the type of chemometric methods:

Sometimes QSAR methods are classifieds depending on type of correlation technique employed establish a relationship between structural and biological activity.

- Linear methods including linear regression (LR), multiple linear regression (MLR), partial least square (PLS), and principle component analysis, principle component regression (PCA/PCR).
- Non-linear methods consist of artificial neural network (ANN), and Bayesian neural net, k-nearest neighbor.

1.3.6 Steps of quantitative structure activity relationships (QSAR)

The process of QSAR model development can be generally divided into three stages: data preparation, data analysis, and model validation.

(a) The first stage includes selection of a molecular dataset for QSAR studies, calculation of molecular descriptors, and selection of a QSAR (statistical analysis and correlation) method. These steps represent a standard practice of any QSAR modeling, and their specific details are generally determined by the researchers' interests and software availability

(b) Second part of QSAR model development consists of an application of statistical approaches for QSAR model development. Many different algorithms and computer software are available for this purpose. Most are based on linear (multiple linear) regression with variable selection, partial least squares (PLS, etc.) as well as non-linear (genetic algorithms, artificial neural networks, etc.) methods.

In all approaches, descriptors serve as independent variables, and biological activities as dependent variables (Wold 1978).

(c) The last stage most important part of QSAR model development is the model validation. Most of the QSAR modeling methods implement the leave-one-out (or leave-some-out) cross-validation procedure. The outcome from the cross-validation procedure across-validated R^2 (q^2), which is used as a criterion of both robustness and predictive ability of the model. Many authors consider high q^2 (for instance, $q^2 > 0.5$) as an indicator or even as the ultimate proof that the model is highly predictive (Hoffman *et al*., 1999).

1.3.7 Validation types of quantitative structure activity relationship model

To test the internal stability and predictive ability of the derived QSAR model, it was validated or cross-checked by the internal validation and external validation test procedure as follow:

a. Internal validation by training set compounds:

Internal validation of a QSAR model is performed based on the molecules used in the model development. It involves activity prediction of the studied molecules followed by estimation of parameters for detecting the precision of predictions (Wold 1978).

Internal validation of the derived QSAR model was carried out by using leave more out (LMO) validation methods. For calculating cross validation regression coefficient (Q^2), each molecule in the training set was eliminate once, and the activity of eliminated molecule was predicted by using the QSAR developed by the remaining molecules.

b. External validation by test set compounds: for external validation of QSAR model. The active of each molecule in the test set was predicted by using the derived QSAR model developed by the training set compounds. The predictive accuracy of the derived QSAR model for external test refers by

correlation coefficient (r) and square of the correlation coefficient (r^2). (Yadav and Gaur 2014).

Thus, for external validation, the available data set is usually divided into training and test sets, then subsequently a model is developed with the training set, and then the constructed model is employed to check the external validation employing the test set molecules which are not utilized in the model development process. The external validation ensures the predictability and applicability of the developed QSAR model for the prediction of untested molecules (Gramatica 2007).

1.3.8 Molecular Descriptors

Molecular descriptors can be defined as numerical values that characterize properties of molecule (Mansouri *et al.,* 2013). Also, it can be defined as essential information of a molecule in terms of its physiochemical properties such as constitutional, electronic, geometrical, hydrophobic, lipophilicity, solubility, steric, quantum chemical, and topological. From a practical view point, molecular descriptors are chemical formation that is encoded within the molecular structure for which numerous sets of algorithms are available for such transformation (Isarankura *et al*., 2009). Molecular descriptors have now become some of the most importance variable used in molecular modeling, and, consequently, managed by statistics, chemometric and chemoinformatic (Consonni and Todeschini 2010).

1.3.8.1 Classification of Molecular Descriptors

Molecular descriptors are divided into main classes: a) Experimental measurement: such as logP, molecular reactivity, dipole moment, Polarizability, and, in general physiochemical properties. b) Theoretical molecular descriptors: theoretical descriptors derived from physiochemical theories show some natural overlap with experimental measurement. Several quantum chemical descriptors, surface areas and volume descriptors also having an experimental counterpart. With respect to experimental measurement. The greatest recognized advantages of the theoretical

descriptors are usually but not always in terms of cost time and availability. The fundamental difference between theoretical descriptors and experimentally measured ones is that theoretical descriptors contain no statistical error due to experimental noise, as opposed to experimental measurement (Karelson *et al*., 1996).

1.3.8.2 Descriptors Selection Methods

Descriptor's selection is an important step for several reasons, because of using a few descriptors increases interpretability and understanding of resulting models. It can reduce the risk over fitting from noisy redundant molecular descriptors; it can provide faster and cost-effective model and it remove the activity cliff. However, noisy, redundant, or irrelevant descriptors should be removed in a way that the dimension of the input space is reduced without any loss of significant information. To remove irrelevant descriptors, a selection criterion is required that can measure the relevance of each selected descriptors with the output of any classifier. Depict the procedure that can be used for the selection an obvious requirement in develop of the robust QSAR models. The interpretability and generality of the models obtained by these methods are highly dependent on the statistical relation among the descriptors and target properties. Thus, expert knowledge in the selection process is required to again user confidence in the selected set of descriptors (Khan 2016).

1.3.9 Application of QSAR

The application of QSAR models depends on statistical significance and predictive ability of the models (Todeschini and Consonni, 2008). There are a large number of applications of these models within industry, academia and governmental (regulatory) agencies, such as estimation of physiochemical properties, biological activities and understanding the physicochemical features behind a biological response in drug design, the rational design of numerous other products such as (surface active agents, perfumes, dyes, and fine chemicals), The

prediction of a variety of physiochemical properties of molecules, The prediction of fate of molecules which are released into the environment and the identification of hazardous compounds at early stages of product development the prediction of toxicity to humans and environment (Youan 2004).

1.4 Molecular Docking

1.4.1 Definition and aims of Molecular Docking

Molecular modeling methods are of very importance in the planning and design of new drugs. Molecular docking is one of the largely acclaimed structure-based approaches, widely used for the study of molecular recognition, which aims to predict the binding mode and binding affinity of a complex formed by two or more constituent molecules with known structures (Koes *et al.,* 2012).

The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes (McConkey *et al.,* 2002).

Molecular docking is the computer-aided prediction of the bound geometry of two or more molecules. Molecules may be docked manually with the aid of computer graphics or automatically by using computer algorithms (Schleinkofer *et al*., 2006). Molecular docking has become an important common component of the drug discovery toolbox, and its relative low-cost implications and perceived simplicity of use has stimulated an ever-increasing popularity within academic communities. The inherent "garbage-in-garbage-out" defect of molecular docking, however, leads a lot of researchers to dedicate countless hours to the identification of hit compounds that later prove to be inactive. Several considerations that can greatly improve the success and enrichment of true bioactive hit compounds are commonly overlooked at the initial stages of a molecular docking study (Berry *et al*., 2015).

Docking is frequently used to predict the binding orientation of drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs (Mukesh and Rakesh 2011).

The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand so that the free energy of the overall system is minimized. Molecular recognition plays a key role in promoting fundamental bimolecular events such as enzyme substrate, drug-protein and drug-nucleic acid interactions. Detailed understanding of the general principles that govern the nature of the interactions (van der Waals, hydrogen bonding, electrostatic) between the ligands and their protein or nucleic acid targets may provide a framework for designing the desired potency and specificity of potential drug leads for a given therapeutic target. Practical application of this knowledge requires structural data for the target of interest and a procedure for evaluating candidate ligands (Brooijmans and Kuntz 2003).

1.4.2 Application of molecular docking

A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may result in agonist or antagonism. Docking is most commonly used in the field of drug design. Most drugs are organic molecules, and docking may be applied for:

a) *Hit identification*: docking combined with a scoring function can be used to quickly screen large databases of potential drugs an Insilco to identify molecules that are likely to bind to protein target of interest.
b) *Lead optimization*: docking can be used to predict in where and in which relative orientation a ligand binds to a protein (i.e., binding mode or pose).

This information may in turn be used to design more potent and selective analogs.

c) *Bio remodulation*: Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes (Suresh *et al*., 2008).

1.4.3 Mechanism of Docking

To perform a docking screen, the first requirement is a structure of the protein of interest. Usually the structure has been determined using a biophysical technique such as X-ray crystallography, or less often, NMR spectroscopy. This protein structure and a database of ligands serve as inputs to a docking program. The success of a docking program depends on two components such as search algorithm and scoring function.

1- *Search algorithm (searching conformational space)*: The search space consists of all possible orientations and conformations of the protein paired with ligand. With present computing resources, it is impossible to exhaustively explore the search space this would enumerating all possible distortions of each molecule and all possible rotational and translational orientations of the ligand relative to the protein at a given level of granularity. Most docking programs in use account for flexible ligand, and several are attempting to model a flexible protein receptor. Each "snapshot" of the pair is referred as a pose.

2- *Scoring functions:*The scoring function takes a pose as input and returns a number indicating the likelihood that the pose represents a favorable binding interaction. Most scoring functions are physics based molecular mechanics force fields that estimate the energy of the pose; a low (negative) energy indicates stable system and thus a likely binding interaction. An alternative approach is to derive a statistical potential for interactions from a large database of protein-ligand complexes, such as the Protein Data Bank, and evaluate the fit of the pose according to this inferred potential (Muegge and Martin 1999).

Aims and Objectives of the Present Study

There was always been and will continue to be need for new and novel chemical entities with diverse biological activities. The present work deals with the:

- Design new disubstituted quinoline derivatives expecting to possess anti-mycotubercular activity.
- Generate QSAR models that can be used to predict anti-mycotubercular activity against mycobacterium tuberculosis (TB) by using compounds collected from literature.
- Study the useful QSAR models in the prediction of the antimycotubercular activity of designed disubstituted quinoline derivatives against mycobacterium tuberculosis (TB).
- Evaluation the pharmacological value of designed compounds by using Lipinski's rule, QSAR model validation of pIC_{50} values and interaction molecular docking with amino acid in the receptor.
- Selection of synthesized compounds in this work based on QSAR model validation of pIC_{50} values, interaction molecular docking result, and "Lipinski's rule of five".
- Synthesize selected disubstituted quinoline derivatives.
- Characterize these compounds for structure elucidation using spectroscopic techniques as FT-IR, UV, GC-MS, ^{1}HNMR spectral studies.
- Prediction of the ligand receptor complex structure through molecular docking studies of the synthesized compounds.

Chapter Two
Materials and Methods

2. Material and Methods

2.1 materials, soft wares and instrument:

2.1.1 Chemicals

Aniline, *p*.toluidine, *p*.chloroaniline, *p*.aminoacetophenone, Sulfanilamide, *p*.aminobenzoicacid, acetyl acetone %, ethanol %, Acetone, *n*.hexane, Chloroform, diethyl ether, Calcium Chloride, Calcium Sulphate, Sodium Nitrate, Sodium Carbonate, Sodium acetate, petroleum ether, Concentrated Hydrochloric acid and Sulfuric acid, all Chemicals in this work were obtained from LOBA Company (India).

2.1.2 Soft Wares

2.1.2.1 ACD/lab software

ACD/Chemo Sketch version 2016.2 (freeware) is a drawing package that allows drawing chemical molecules structures including organics, organometallics, polymers and naming structures (fewer than 50 atoms and 3 rings). It also includes calculation molecular properties such as (molecular weight, density etc.), 2D and 3D structure cleaning and prediction logP. The freeware version of Chemo Sketch was used Copyright 1998-2016, ACD/ Labs 2016.2

2.1.2.2 ChemDraw professional (CDP) Software

Chemo Draw professional (version 16.0.0.82) designed for scientists, students, and scientific authors, ChemDraw is a powerful, yet easy-to use, tool for producing chemical and biological drawings. ChemDraw strives to be a vital and preferred tool for illustrating chemical and biological concepts. Copyright 1998 – 2016 PerkinElmer Informatics, Inc.

2.1.2.3: Molecular Operating Environment (MOE) software

MOE, chemical computing groups Molecular operating Environmental is an interactive, windows-based chemical computing and molecular modeling tool with abroad base of scientific application: bioinformatics, chemo informatics, structure,

based design, protein modeling, high throughput discovery, molecular modeling and simulation, and methodology development. Molecular operating environment (MOE) 2010. 10; chemical computing group Inc., 1010 Sherbrook St. West, Suite 910, Montreal, QC, Canada H3A2R7, 2010.

2.1.2.4 Statistical package for social science (SPSS) Software

SPSS for windows version 22.0 program provides powerful statistical analysis and data management system in a graphical environment, using descriptive menus and simple dialog boxes to do most of the work for work.

2.1.4 Spectroscopy Instrument

2.1.4.1 Ultra violet Spectroscopy (UV)

UV-visible data was carried out using (UV.3101PC. Shimadzu, Jaban).

2.1.4.2 Infrared Spectrophotometer (IR)

The infrared spectral data were recorded using KBr disk by using infrared spectrophotometer, Model FTIR-84005 Shimadzu, Japan.

2.1.4.3 Nuclear Magnetic Resonance Spectrophotometer (NMR)

The proton nuclear magnetic resonance spectral data were obtained with NMR instrument Model ultrashield-300 plus Instrument (NMR Vario) Germany using DMSO as solvent and operating at 300 MHZ. Employing 5 mm high resonances broad-band TMS.

2.1.4.4 Gas Chromatography Mass spectrometer (GC-MS)

The mass spectral recorded on (GC-MS) Shimadzu Qp-1000 EX. Japan.

2.1.5 General Instrument

- Melting point apparatus: Made in UK Bibby Sterilin ltd. Stone Staffordshire, ST 150SA.UK.
- Magnetic stirrer: ISO 9001, Model LMS-1003, Scott Science, UK.
-Water bath: Fisher scientific England.
- Sensitive balance Sartorius-BI2105 model

2.1.6 Thin layer Chromatography (TLC)

The progress and purity of all synthesized disubstituted quinoline were carried out on aluminum coated plates with different mobile phases and visualizing the spots using Iodine crystalised.

2.1.7 Glassware

All glassware used were of Pyrex type

2.2 QSAR modeling

2.2.1 Dataset

In QSAR studies, a total of 15 disubstituted quinoline derivatives were gathered from De Souza *et al.,* 2009. The reported evaluation for their *Invitro* anti-mycobacteria activity mentioned compounds against mycobacterium tuberculosis $H_{33}Rv$. The biological activity in this compounds group expressed as the IC_{50} (concentration of compounds inhibitory concentration (MIC) in µg/ml) of cell for human mycobacterium tuberculosis (TB) and were compared with proposing compounds study.

2.2.2 Methods

The activity in conditions of IC_{50} of the series studying compounds in microgram per milliliter were converted to negative logarithm concentration in moles (anti-mycobacterial potential pIC_{50}) order to obtain higher mathematical values when the structures are biologically activity very efficient (Rollinger *et al*., 2006).

The anti-mycobacterial tuberculosis (TB) activity which is expressed by the anti-mycobacterium potential (pIC_{50}) is defined by equation (2.1).

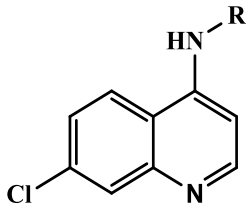
$1Mm = 10^{-6}$ M

$pIC_{50} = \log 1/IC_{50}$

$pIC_{50} = {}^{-}\log_{10} (IC_{50} \text{ X } 10^{-6})$ (eq.2.1)

Chemo Sketch, ACD/lab was used for drawing of the study compounds table (2.1). After that the data set of study compounds was divided into training set of **15** and a test set of **3** compounds by random selection.

Table (2.1): structure, $IC_{50}$and pIC_{50} of a series of quinoline derivative reported by (De Souza *et al*., 2009).



Compound No	R	IC_{50}(µM)	pIC_{50}
1	$-CH_2CH_2Cl$	12.50	4.900
2	$-CH_2CH_2N_3$ (LO)	50.00	4.300
3	$-CH_2CH_2NHBN$ [T]	50.00	4.300
4	$-(CH_2)_6NH_2$	25.00	4.600
5	$-(CH_2)_8NH_2$ [T]	6.250	5.200
6	$-(CH_2)_{10}NH_2$	3.120	5.500
7	$-CH_2CH_2NH$i-Pr	100.0	4.000
8	$-CH_2CH_2CH_2CH_3$	12.50	4.900
9	$-CH_2CH_2CH_2Cl$ (LO)	50.00	4.300
10	-H	100.0	4.000
11	$-CH_2CH_2NH$Cyclohexyle	100.0	4.000
12	-Propyl	50.00	4.300
13	-i-Propyl	50.00	4.300
14	$-CH_3$	100.0	4.000
15	$-SCH_2CH(C_2H_5)\ CH_2Cl$ [T]	50.00	4.300

*T = test set. *LO = leave out.

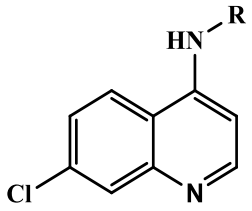
2.2.3 Molecular Modeling Parameters (MMP)

Total of **9** molecular descriptor listed in table (2.2) was initially calculated for each compound in training set see table (2.1) using MOE program (version 2010.10 chemical computing group Inc.). Table (2.3) illustrated values of descriptors that calculated by MOE program for training set. Nine molecular descriptors were calculated is including log octanole/water partition (logP o/w), dipole moment (MNDO - dipole), electrostatic energy (E-ele), Absolute different in surface areas (DASA), Absolute different in charge-weighted areas (DCASA), potential energy (E), Non-bonded Energy (E-nb), Dipole moment (AM1-dipole), Dipole moment (MP3-dipole),

Table (2.2) List of some descriptors used in the QSAR optimization model

No	Descriptor's symbol	Name of descriptor(s)	Class
1	log (o/w)	Log octanol/water partition coefficient	2D
2	E-ele	Electrostatic Energy	3D
3	DCASA	Absolute different in charge-weighted areas	3D
4	PM3-dipole	Dipole moment	3D
5	E	Potential Energy	3D
6	AM1-dipole	Dipole moment	3D
7	DASA	Absolute different in surface areas	3D
8	MNDO-dipole	Dipole moment	3D
9	E-nb	Non-bonded Energy	3D

Table (2.3): the values of descriptors used in QSAR of training set compounds.



Com.No	logP ($_{o/w}$)	E-ele	DCASA	PM3-dipole	E	AM1-dipole	DASA	MNDO dipole	E-nb
1	3.34	-7.05	27.36	3.77	37.92	4.68	12.07	4.49	26.4
2	1.57	28.81	85.56	2.54	19.37	3.26	26.28	2.92	2.21
3	1.58	28.81	102.27	2.55	19.37	3.27	31.41	2.47	2.20
4	3.39	-7.11	25.50	3.73	42.00	4.59	11.25	4.68	26.90
5	3.78	-7.05	25.61	3.67	37.71	4.73	11.30	4.50	27.52
6	2.06	-7.24	42.53	3.36	37.50	4.09	18.52	3.94	20.52
7	3.97	3.82	14.08	4.17	49.00	5.10	4.45	4.41	47.27
8	2.95	3.89	26.11	3.72	45.50	4.72	8.25	4.42	41.40
9	3.34	-7.04	28.19	3.77	37.92	4.65	12.44	4.50	26.39
10	2.38	-7.06	45.12	3.50	39.96	4.30	19.91	4.37	24.09

2.2.4 Selection of subset descriptors:

The ratio of the compounds to physiochemical descriptors used the correlation is usually **5:1** (Jain *et al.*, 2012). To select the best sub-set of physiochemical properties in training and test set, highly correlated chemical descriptors was excluded through co-variance analysis using correlation matrix figure (2.1).

Figure (2.1): details of correlation matrix for chemical descriptors in training set.

	1	2	3	4	5	6	7	8	9
1. logP(o/w)	100	77	-89	91	79	94	-92	83	83
2. E_ele	77	100	-93	94	99	94	-92	88	97
3. DCASA	-89	-93	100	-98	-94	-98	96	-97	-91
4. PM3_dipole	91	94	-98	100	96	99	-95	93	94
5. E	79	99	-94	96	100	94	-92	90	96
6. AM1_dipole	94	94	-98	99	94	100	-97	93	94
7. DASA	-92	-92	96	-95	-92	-97	100	-89	-95
8. MNDO_dipole	83	88	-97	93	90	93	-89	100	82
9. E_nb	83	97	-91	94	96	94	-95	82	100

The correlation matrix in figure (2.1) showed that pm3-dipole, MNDO-dipole and AM1-dipole are correlated to each other and are highly correlated to E, also, MNDO-dipole and AM1-dipole Correlated to logP (o/w). So, pm3-dipole, MNDO-dipole, AM1-dipole, E, E-nb, and E-ele are excluded from study.

About **34** regression equation was employed for **(**ATCC27294**)**mycobacterial tuberculosis(TB)in training set table (2.4). using multiple linear regression method. Lastly, a QSAR model equation with High Square of the correlation coefficient (r^2) was selected.

Table (2.4): the QSAR model between descriptors and biological activity of some a serise quinoline derivatives for mycobacterial tuberculosis (TB) training set.

No.	Calculated descriptors	QSAR equation	R^2*	RMSE*
1	logP(o/w), PM3-dipole	pIC_{50} = 8.47913 + 0.84771× logP(o/w) - 1.86089 × PM3-dipole	0.80553	0.20538
2	E-ele , logP (o/w)	pIC_{50} = 2.9534 + 0.33673 × logP (o/w) - 0.05284 × E-ele	0.70129	0.25454
3	logP(o/w), GCUT-SMR-0	pIC_{50} =1.41144-0.43515 × logP(o/w) -8.42001 × GCUT-SMR-0	0.35769	0.37325
4	logP(o/w), E-stb.	pIC_{50} = 4.29980 + 0.19175 × logP (o/w) -3.39473 × E-stb.	0.33921	0.37858
5	logP(o/w), dipoleX.	pIC_{50} = 4.97444 + 0.23868 × logP (o/w) -2.44941 × dipole.	0.53550	0.31741
6	logP(o/w), dipole	pIC_{50} =7.70814 + 0.41647 × logP (o/w) -4.28546 × dipole	0.62676	0.28453
7	logP(o/w), BCUT-PEOE-2	pIC_{50} = -7.61723 + 0.24422 × logP (o/w) +18.40808 × BCUT-PEOE-2	0.42787	0.35227
8	logP(o/w), DCASA	pIC_{50} = 0.95860 + 0.74495 × logP (o/w) + 0.03159 × DCASA	0.82282	0.19604
9	logP (o/w), E	pIC_{50} = 5.66640 + 0.37358 × logP (o/w) -0.06356 × E	0.73759	0.23857
10	logP(o/w), AM1-dipole	pIC_{50} = 9.45543 + 1.06520 × logP (o/w) -1.85912 × AM1-dipole	0.75192	0.23197

11	logP(o/w), DASA	pIC_{50} = 0.28740 + 0.82155 × logP (o/w) +0.11482 × DASA	0.72059	0.24618
12	logP(o/w), MNDOdipole	pIC_{50} = 6.60787 + 0.40040 × logP (o/w) - 0.82208 × MNDO-dipole	0.61720	0.28815
13	logP(o/w), E-nb	pIC_{50} = 4.33749 + 0.38995 × logP (o/w) -0.04268 × E-nb	0.59486	0.29644
14	logP(o/w), vsurf-ID2	pIC_{50} = 5.19342 - 0.49476 × logP (o/w) + 0.12130 × vsurf-ID2	0.37068	0.36946
15	logP(o/w),BCUT-PEOE-1	pIC_{50} = -7.35598 + 0.24191 × logP (o/w) -18.97746 × BCUT-PEOE-1	0.47551	0.33729

***r^2**= Squared correlation coefficient ***RMSE** = Root mean square error

The QSAR model equation with high square of the correlation coefficient (r^2 = 0.82282) and low root mean square erorr (RMSE = 0.19604) was QSAR equation No. 8:

pIC_{50} = 0.95860 + 0.74495 × logP (o/w) + 0.03159 × DCASA

2.2.5 Calculation of statistical parameters (CSP)

The statistical quality of model was justified by statistical parameters such as root mean square error (RMSE), correlation coefficient (r), squared correlation coefficient (r^2), standard error of estimate (s) and F- test values (ratio between the variance of observed and calculated activities, F). Calculation of statistical parameters was carried out by using statistical program SPSS version 24.00 table (2.5).

Table (2.5) statistical parameters used for statistical quality of model.

Model	r	r^2	RMSE	Q^2	S	F	P value
values	0.907	0.823	0.219	0.801	0.164	37.43	0.0001

2.2.6 Validation of quantitative structure activity relationship model

For the validation of the predictive power of a QSAR model, two basic principles (internal validation and external validation) used in this study to Developed QSAR models by the following procedure (Yadav *et al.*, 2014).

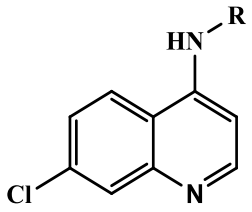
(a) Internal validation by training set compounds

Internal validation of the derived QSAR models was carried out by using leave more out (LMO) validation method to calculate cross validation regression coefficient (Q^2) and the result were illustrated in table (2.6) for training.

(b) External validation by test set compounds:

For external validation of QSAR models, the activity of each compound in the test set was predicted by using the derived models developed by the training set compounds in table (2.7)

Table (2.6): experimental and predicted activity of training data set compounds and cross validation against the (**ATCC27294)** mycobacterial tuberculosis (TB) for training set.



No	R	$IC_{50}(\mu M)_{(Exp)}$	$pIC_{50(Exp)}$	$pIC_{50(predict)}$	Residual
1	CH_2CH_2Cl	12.50	4.900	4.3088	-0.0088
2	$CH_2CH_2N_3$ (LO)	50.00	4.300	……	……
3	CH_2CH_2NHBN **T**	50.00	4.300	4.232	0.0679
4	$(CH_2)_6NH_2$	25.00	4.600	4.8357	-0.2357
5	$(CH_2)_8NH_2$ **T**	6.250	5.200	5.1875	0.0125
6	$(CH_2)_{10}NH_2$	3.120	5.500	5.3636	0.1364
7	CH_2CH_2NHi-Pr	100.0	4.000	4.1370	0.1630
8	$CH_2CH_2CH_2CH_3$	12.50	4.900	4.5858	0.3172
9	$CH_2CH_2CH_2Cl$ (LO)	50.00	4.300	……	……
10	H	100.0	4.000	3.8393	0.1607
11	CH_2CH_2NHCyclohexyl	100.0	4.000	4.3608	0.3608
12	Propyl	50.00	4.300	3.9782	0.0218
13	i-Propyl	50.00	4.300	4.3353	-0.0353
14	CH_3	100.0	4.000	4.1585	-0.1585
15	$SCH_2CH(C_2H_5)$-CH_2Cl **T**	50.00	4.300	4.3803	-0.0803

*T = test set. *LO = leave out.

Table (2.7): predicted biological activity values of test set:

No.	R	Experimental pIC_{50} M	Predicted pIC_{50} M	Residuals
3	CH_2CH_2NHBN	4.300	4.2321	0.0679
5	$CH_2)_8NH_2$	5.200	5.1875	0.0125
15	$SCH_2CH(C_2H_5)CH_2Cl$	4.300	4.3803	-0.0803

2.2.7 Modeling of quinoline derivatives

The quinoline nucleus is an important class of heterocyclic compounds found in many synthetic and natural products with a wide range of pharmacological activities, such as antiviral, anticancer, antibacterial, antifungal, anti-obesity, anti-inflammatory, and tuberculosis, which can be well illustrated by the large number of drugs in the market containing this heterocyclic class. However, spite of its wide range of pharmacological activities, few studies described against cancer in comparison with other classes (De Souza *et al*., 2009). Furthermore, the use of the combination of the different pharmacological compounds in the design of new drugs may lead finding novel drugs with interesting biological activity. In view of this points, about 34 disubstituted quinoline derivatives were modeled and designed as anticancer. The new designed compounds were made by linking 2,4-pentadione with different primary aromatic amine to produce some quinoline substituent in position 3 and 7 see figure (2.2).

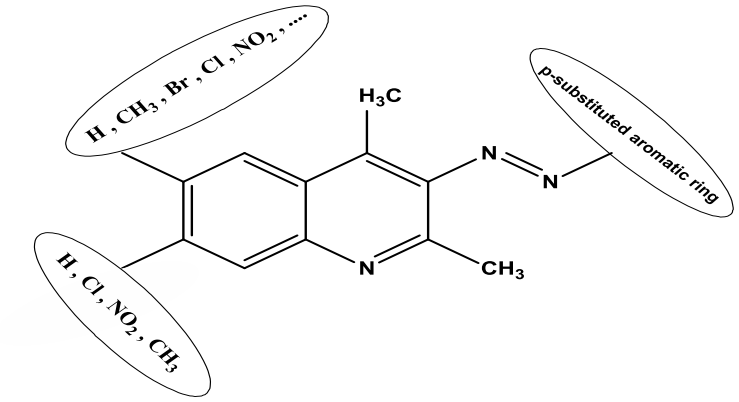
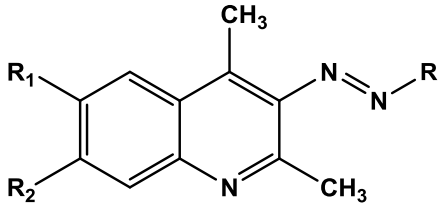
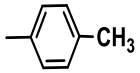
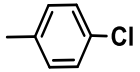
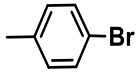
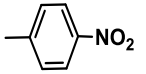
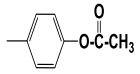
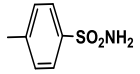


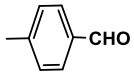
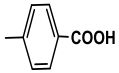
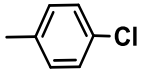
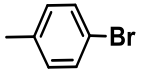
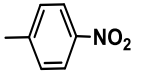
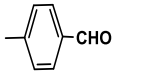
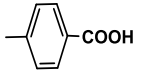
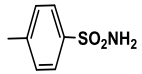
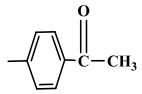
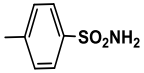
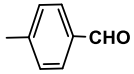
Figure (2.2): designing of target compounds

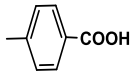
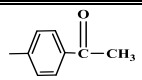
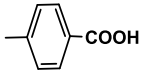
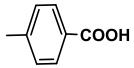
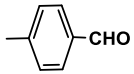
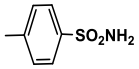
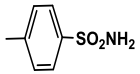
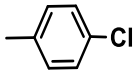
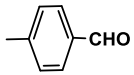
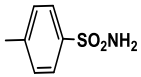
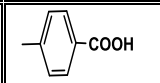
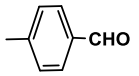
The quinoline derivatives are interesting target class of compound which are extensively investigated due to their biological activities, including anti-inflammatory, antitumor, anti-invasive, anti-fungal, anti-malarial, anticancer and antibacterial properties. They are regarded as promising antibacterial against mycobacterial tuberculosis (TB). Some quinoline derivatives were modeled and designed as antibacterial agent against mycobacterial tuberculosis (TB) table (2.8).

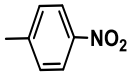
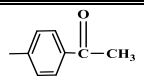
Table (2.8): design of some 3.7-disubstituted quinoline derivatives:



Comp. No:	R	R_1	R_2	Molecular weight	Density	logP (o/w)	IP	HB donors	HB acceptors	Predicted pIC_{50}
1		$-CH_3$	-H	289.38	0.675	5.298	8.902	0	3	9.715
2		- Cl	-H	330.22	0.802	5.886	9.091	0	3	13.120
3		-Br	-H	419.12	0.957	6.298	9.226	0	3	16.904
4		$-NO_2$	-H	261.37	0.646	5.936	8.916	0	1	12.239
5		-H	-H	233.31	0.656	4.961	9.036	0	1	9.158
6		CH_3COO^-	-H	377.40	0.753	4.568	9.324	0	5	9.773
7		$-SO_2NH_2$	-H	363.42	0.879	3.995	9.732	2	5	4.785

8		-CHO	-H	261.28	0.729	3.495	9.422	0	3	11.077
9		-COOH	-H	293.28	0.782	5.592	9.519	4	5	11.653
10		$-CH_3$	-H	309.80	0.737	5.798	8.978	0	3	6.792
11		$-CH_3$	-H	354.25	0.818	5.298	9.009	0	3	8.208
12		$-CH_3$	-H	289.38	0.675	4.927	8.897	0	3	9.185
13		$-CH_3$	-H	303.37	0.706	4.927	9.051	0	4	10.204
14		$-CH_3$	-H	319.36	0.728	4.677	9.068	2	5	9.658
15		$-CH_3$	-H	354.43	0.775	3.428	9.133	1	5	7.233
16		-Cl	-H	317.39	0.699	4.853	9.016	0	4	8.520
17		-Cl	-H	374.85	0.835	3.722	9.232	1	5	12.297
18		-Cl	-H	295.73	0.794	4.706	9.364	0	4	4.850

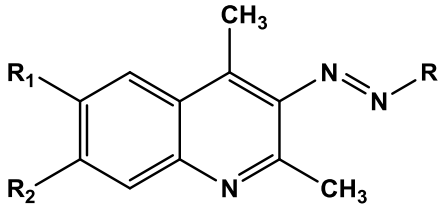
19		-Cl	-H	339.78	0.791	4.971	9.177	2	5	8.606
20		-Cl	-H	333.35	0.758	5.147	9.178	0	4	7.921
21		-CHO	-H	384.47	0.759	4.306	9.331	2	6	10.097
22		$-SO_2NH_2$	-H	368.47	0.823	2.807	9.443	3	7	5.140
23		$-SO_2NH_2$	-H	382.44	0.803	3.057	9.419	1	6	7,509
24		$-COCH_3$	-H	419.30	0.792	2.983	9.369	1	6	4.791
25		-Br	-H	330.22	0.908	3.928	9.349	1	5	14.981
26		-H	-Cl	317.35	0.8.2	5.886	9.013	0	3	12.580
27		-H	-CHO	374.85	0.736	4.556	9.307	0	5	11.448
28		-H	-Cl	349.35	0.835	3.722	9.171	1	5	11.410
29		-H	-COOH	333.25	0.780	4.056	9.367	4	7	8.761
30		-H	-COOH	289.32	0.759	4.306	9.353	2	6	11.066

31		-H	$-NO_2$	289.32	0.675	5.298	8.871	0	3	10.004
32		CH_3CO-	-H	275.35	1.0737	5.000	9.061	0	3	8.6064
33		$-CH_3$	-H	303.36	0.7060	4.555	9.110	0	4	8.6067
34		-COOH	-H	345.26	0.7200	4.408	9.264	0	5	7.5305

2.2.8 Predicting the biological activity of designed compounds

The model QSAR was selected to predict the biological activity of designed disubstituted quinoline derivatives (1-34) against mycobacterial tuberculosis (TB) and pharmacological was evaluated using Lipinski "rule of five" in order to select compounds for synthesis. According to Lipinski rule of five, most drug-like molecules have logP ≤ 5, number of hydrogen bonding acceptor ≤ 10, molecular weight ≤ 500, and number of hydrogen bond donors ≤ 5. Molecular violating one or more of this rule may have problems with bioavailability (Hoffman *et al.*, 1999). Therefore, 8 out of 34 compounds were selected for synthesis in the next step. Descriptors of selected Compounds, predicted pIC_{50} and Lipinski rule parameters of designed compounds and training were listed in table (2.9) and table (2.10) respectively.

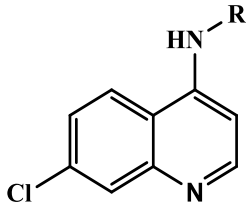
Table (2.9): predicted descriptors, predicted activity against mycobacterial tuberculosis (TB) and Lipinski's parameters of selected design of some 3,7-disubstituted quinolines.



Comp. No	MW	D	logP (o/w)	IP	HB donors	HB acceptors	Predicted pIC_{50}
1	289.38	0.675	5.298	8.902	0	3	9.715
2	330.22	0.802	5.886	9.091	0	3	13.120
3	419.12	0.957	6.298	9.226	0	3	16.904
4	261.37	0.646	5.936	8.916	0	1	12.239
5	233.31	0.656	4.961	9.036	0	1	9.158
6	377.40	0.753	4.568	9.324	0	5	9.773
7	363.42	0.879	3.995	9.732	2	5	4.785
8	261.28	0.729	3.495	9.422	0	3	11.077
9	293.28	0.782	5.592	9.519	4	5	11.653
10	309.80	0.737	5.798	8.978	0	3	6.792
11	354.25	0.818	5.298	9.009	0	3	8.208
12	289.38	0.675	4.927	8.897	0	3	9.185
13	303.37	0.706	4.927	9.051	0	4	10.204
14	319.36	0.728	4.677	9.068	2	5	9.658
15	354.43	0.775	3.428	9.133	1	5	7.233
16	317.39	0.699	4.853	9.016	0	4	8.520
17	374.85	0.835	3.722	9.232	1	5	12.297

18	295.73	0.794	4.706	9.364	0	4	4.850
19	339.78	0.791	4.971	9.177	2	5	8.606
20	333.35	0.758	5.147	9.178	0	4	7.921
21	384.47	0.759	4.306	9.331	2	6	10.097
22	368.47	0.823	2.807	9.443	3	7	5.140
23	382.44	0.803	3.057	9.419	1	6	7,509
24	419.30	0.792	2.983	9.369	1	6	4.791
25	330.22	0.908	3.928	9.349	1	5	14.981
26	317.35	0.8.2	5.886	9.013	0	3	12.580
27	374.85	0.736	4.556	9.307	0	5	11.448
28	349.35	0.835	3.722	9.171	1	5	11.410
29	333.25	0.780	4.056	9.367	4	7	8.761
30	289.32	0.759	4.306	9.353	2	6	11.066
31	289.32	0.675	5.298	8.871	0	3	10.004
32	275.35	1.0737	5.000	9.061	0	3	8.6064
33	303.36	0.7060	4.555	9.110	0	4	8.6067
34	345.26	0.7200	4.408	9.264	0	5	7.5305

Table (2.10): predicted descriptors and activity against mycobacterium tuberculosis (TB) and Lipinski's parameters selected of training set.



Compound No.	MW	logP (o/w)	D	H-bond donors	H-bond acceptors	Predicted pIC_{50}
1	220.70	3.337	1.015	1	1	4.3088
2	207.66	1.576	1.089	2	2	4.8357
3	207.66	1.576	1.091	2	2	5.3636
4	220.70	3.158	1.029	1	1	4.1370
5	234.73	3.779	0.995	1	1	4.5828
6	178.62	2.063	1.103	1	1	3.8395
7	303.83	3.970	0.999	2	2	4.3608
8	263.77	2.946	1.002	2	2	3.9782
9	220.70	3.337	1.015	1	1	4.3353
10	192.65	2.382	1.072	1	1	4.1585

2.3 Docking Study

Molecular docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex (Lengauer and Rarey 1996). Molecular docking is a computational procedure that aims to predict the favored orientation of a ligand to its macromolecular target (receptor), when these are bound to each other to form a stable complex (Perez and Tvaroška 2014).

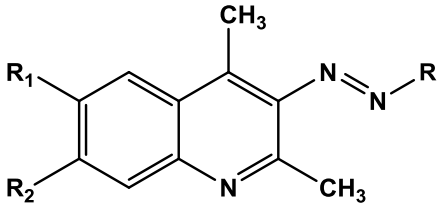
Molecular docking softwares are mainly used in drug devolopment. The most importance application of docking softwares is virtual screening. In virtual screening the most intersting and promising molecule are selected from existing database for further research (Mukesh and Rakesh 2011).

2.3.1 Molecular Docking Ssteps

1. Get the complex coordinates from the PDB.
2. Clean the complex (delete all the water and the solvent molecules and all noninteracting ions).
3. Add the missing hydrogens/side chain atoms and minimized the complex (AMBER Program).
4. Clean the minimized complex (delete all the water and the solvent molecules and all non-interacting ions).
5. Separate the minimized in macromolecule and ligand.
6. Prepare the docking suitable files (pdbqt files).
7. Prepare all the needing files for docking (grid parameter file, map files, docking parameter files).
8. Run the docking.
9. Analyze the docking results.

All synthesized of 6-substituted-3-((4-substituted phenyl) diazenyl) -2,4-dimethyl quinoline (XV – XXII) were subjected to docking study to investigate their bindind mechanim with (6KGH) protein wich dawnloaded from (PDB). The protein file selected for this purpose and he result was puted in table (2.22).

Table (2.11): docking result of the designed compounds (1-34)



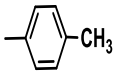
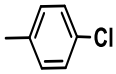
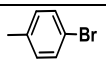
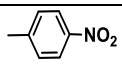
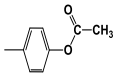
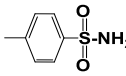
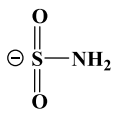
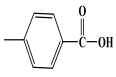
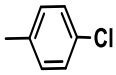
C.No	R	R_1	R_2	binding energy.s	Amino acid	Interaction group	type of interaction	length (A°)
C1		$-CH_3$	-H	-17.8167	Thr433	N.deiazenyl	H-bond	-
C2		-Cl	-H	-19.6877	Arg564	phenyl	π-π	-
C3		-Br	-H	-17.7075	Thr433	N.deiazenyl	H-bond	-
C4		$-NO_2$	-H	-19.0964	No interaction			
C5		-H	-H	-15.7230	Thr433	N.deiazenyl	H-bond	-
C6			-H	-20.7435	Gln575	C=O	H-bond	2.21
C7			-H	-18.5165	Thr433 Gln575 Pro431 Arg564	NH_2 SO_2 NH_2 SO_2	H-bond H-bond H-bond H-bond	2.68 2.58 1.95 2.04
C8			-H	-17.036	No interaction			
C9		-COOH	-H	-21.3433	Arg564	C=O	H-bond	2.26
C10		$-CH_3$	-H	-21.3433	Arg564	C=O	H-bond	2.91

Table (2.23): continued

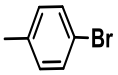
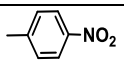
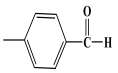
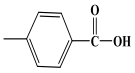
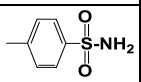
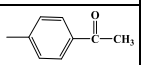
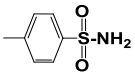
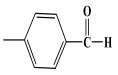
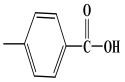
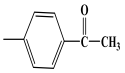
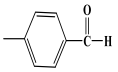
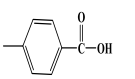
C11		-CH_3	-H	-18.3209	Thr433	phenyl	π-π	-
C12		-CH_3	-H	-17.1306	Thr433	N.deiazenyl	H-bond	2.96
C13		-CH_3	-H	-18.5967	Thr433	N.deiazenyl	H-bond	2.24
C14		-CH_3	-H	-17.999	Arg564 Arg564	C=O phenyl	H-bond π-π	2.84 -
C15		-CH_3	-H	-18.5967	Gln575 Thr433	NH_2 SO_2	H-bond H-bond	2.68 2.91
C16		-CH_3	-H	-16.5463	Thr433 Arg564	N.phenyl N.deiazenyl	H-bond H-bond	- -
C17		-Cl	-H	-19.1307	Gln575 Arg564 Pro431 Thr433	SO_2 phenyl NH_2 NH_2	H-bond π-π H-bond H-bond	1.96 - 2.02 1.99
C18		-Cl	-H	-17.2369	Thr433	phenyl	π-π	-
C19		-Cl	-H	-16.1915	Arg564 Thr433	C=O phenyl	H-bond π-π	3.04 -
C20		-Cl	-H	-19.6866	Arg564	phenyl	π-π	-
C21		-CHO	-H	-17.7461	No interaction			
C22			-H	-17.4285	Pro431 Thr433 Arg564	NH_2 NH_2 C=O	H-bond H-bond H-bond	1.98 2.35 2.03

Table (2.23): continued

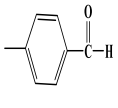
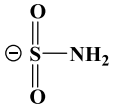
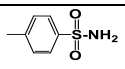
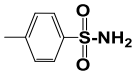
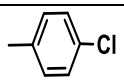
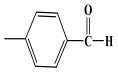
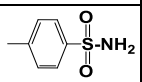
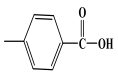
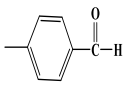
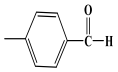
C23			-H	-17.2346	Thr433 Gln575	N.deiazenyl NH_2	H-bond H-bond	2.15 1.97
C24		$-OCH_3$	-H	-17.8389	Thr433 Thr435 Gln575 Pro431	N.deiazenyl NH_2 SO_2 NH_2	H-bond H-bond H-bond H-bond	2.88 2.59 2.31 2.52
C25		-Br	-H	-19.3230	Gln561 Thr435 Arg564 Pro431 Gln575 Ala555	NH_2 N.phenyl phenyl NH_2 NH_2 NH_2	H-bond H-bond π-π H-bond H-bond H-bond	2.09 - - 1.98 2.07 2.05
C26		-Cl	-H	-18.9608	Thr433	N.phenyl	H-bond	-
C27		-CHO	-H	-17.8260	Thr433 Gln575 Pro431	NH_2 SO_2 NH_2	H-bond H-bond H-bond	2.60 2.02 1.94
C28		-Cl	-H	-18.3328	Arg564 Arg564 Gln575 Pro431	phenyl SO_2 SO_2 NH_2	π-π H-bond H-bond H-bond	- 2.97 2.99 2.88
C29		-COOH	-H	-18.9448	Thr433 Arg564	N.phenyl C=O	H-bond H-bond	1.87 2.11
C30		-COOH	-H	-21.5289	Thr433 Arg564	N.deiazenyl C=O	H-bond H-bond	2.16 2.89
C31		$-NO_2$	-H	-18.7960	Thr433	N.deiazenyl	H-bond	2.13
C32		$-CH_3$	-H	-16.9094	Thr433	N.deiazenyl	H-bond	2.54

Table (2.23): continued

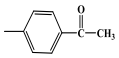
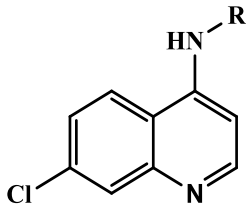
C33		CH_3CO-	-H	-18.4047	Thr433	CH_3CO-	H-bond	3.11
C34		CH_3CO-	-H	-19.1323	Gln575	N.deiazenyl	H-bond	3.72
Reference drug (Rafampicin)				-25.236	Gin575 Thr433 Pro431	C-O C=O NH_2	H-bond H-bond H-bond	1.89 2.09 1.83

Table (2.12): Docking result of the training and test set compounds of a series quinoline derivative reported by (De Souza *et al.*, 2009).



C.N	R	s- energy	amino acid	interaction group	type of interaction	length (A^o)
1	$-CH_2CH_2Cl$	-15.57695	Th433	-NH	H-bond	2.87
2	$-CH_2CH_2NHBN$ [T]	-20.26943	Tyr574	phenyl	π-π	-
3	$-(CH_2)_6NH_2$	-14.89765	Pro431	-NH	H-bond	1.94
4	$-(CH_2)_8NH_2$ [T]	-19.64986	Lys440	-NH	H-bond	2.49
5	$-(CH_2)_{10}NH_2$	-19.22596	Arg569	$-NH_2$	H-bond	2.54
6	$-CH_2CH_2NH$i-Pr	-13.83842	no interaction			
7	$-CH_2CH_2CH_2CH_3$	-16.83704	no interaction			
8	-H	-13.82262	no interaction			
9	$-CH_2CH_2NH$ Cyclohexene	-15.50278	GIn575 Pro431 Th433	$-NH_2$ $-NH_2$ -NH	H-bond H-bond H-bond	1.76 1.84 2.31
10	Propyl	-13.72923	Pro431 Gin575 GIn575	$-NH_2$ $-NH_2$ $-NH_2$	H-bond H-bond H-bond	1.87 1.82 1.91
11	$-CH_3$	-14.02032	no interaction			
12	$-SCH_2CH(C_2H_5)CH_2Cl$ [T]	-19.37063	GIn575	-NH	H-bond	2.35

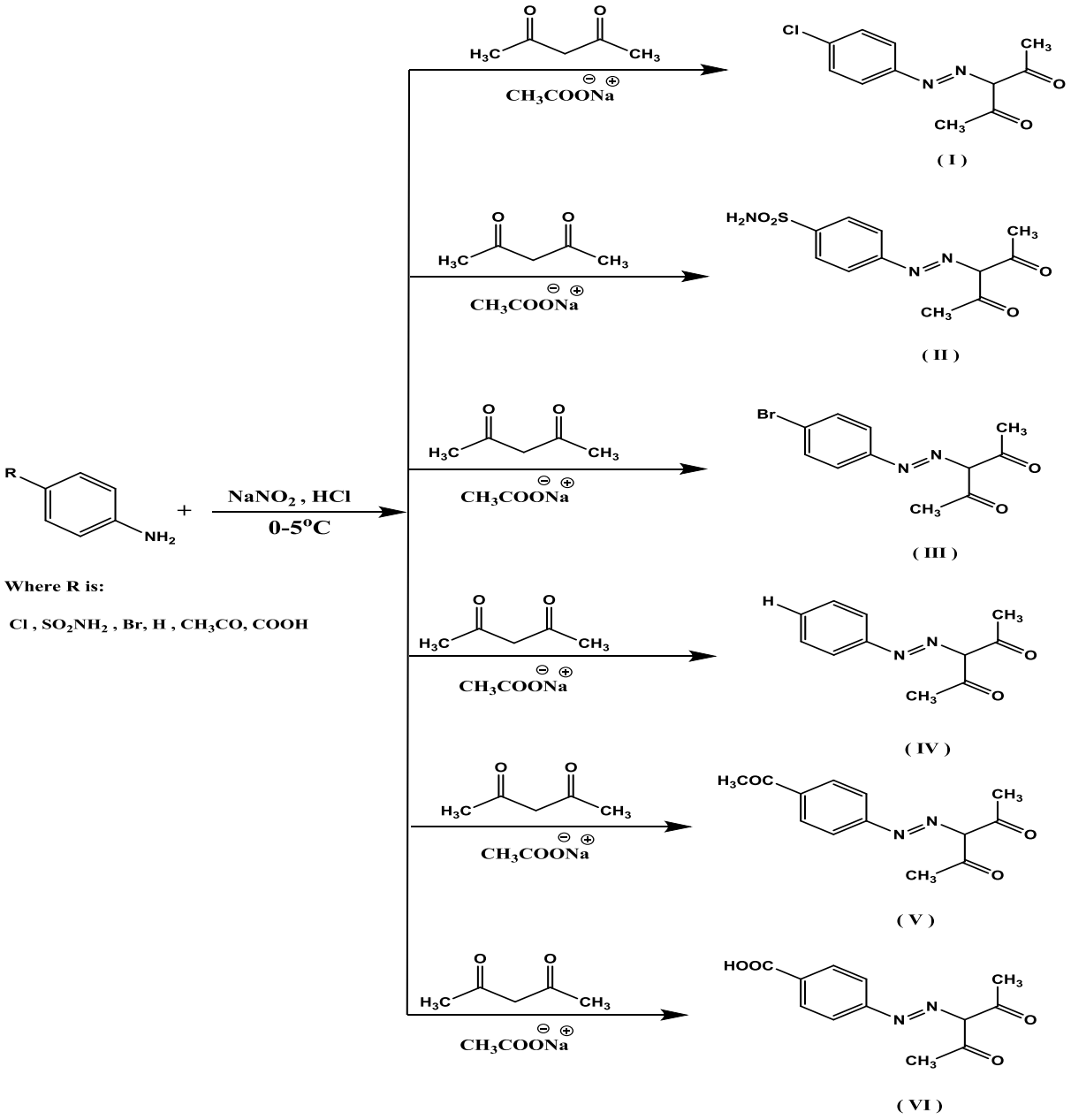
T*: test set.

2.4 Synthesis Methods

2.4.1 General Procedures for the Synthesis Compounds

2.4.1.1 General Method for Synthesis of (*E*)-3-((4-substituted phenyl)diazenyl pentane-2, 4-dione (I-VI)

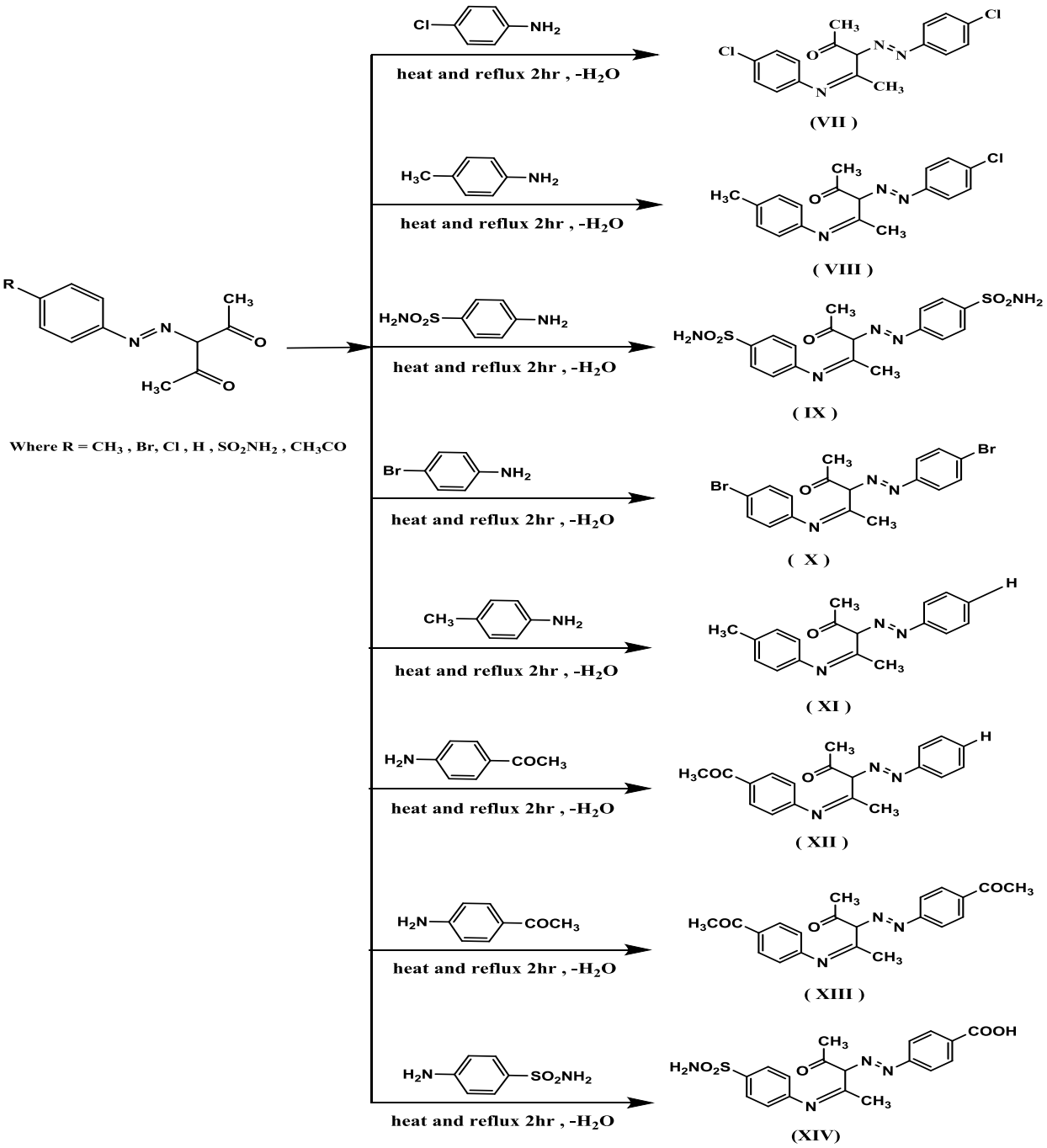
p-substituted aniline (0.01mole) was dissolved in a mixture of concentrated HCl (8 ml) and water (6 mL) and cooled to 0-5 ^{o}C on ice bath. A cold aqueous solution of sodium nitrite (0.02mole) was added. The cold diazonium salt solution was filtered into a cooled solution of acetylacetone (6 ml) in presence of sodium nitrite (0.01mole) and sodium acetate (0.05mole) in aqueous ethanol (20 ml) and stirred for 2 hours and resulting solid was filtered, dried and purified by recrystallization from ethanol to afford compounds (I – VI) intermediate (1) see scheme (2.1). Chemical name, physiochemical properties and Infra-red spectral data were tabulated in table (2.13), (2.16) and table (2.19) respectively.



Scheme (2.1): chemical structure of (*E*)-3-((4-substitutedphenyl)diazenylpentane-2, 4-dione (I-VI)

2.4.1.2 General Method for Synthesis of (*Z*)-3-((*E*)-(4-substitutedphenyl) diazenyl)-4-((4-substitutedphenyl)imino)pentan-2-one derivatives (VII–XIV).

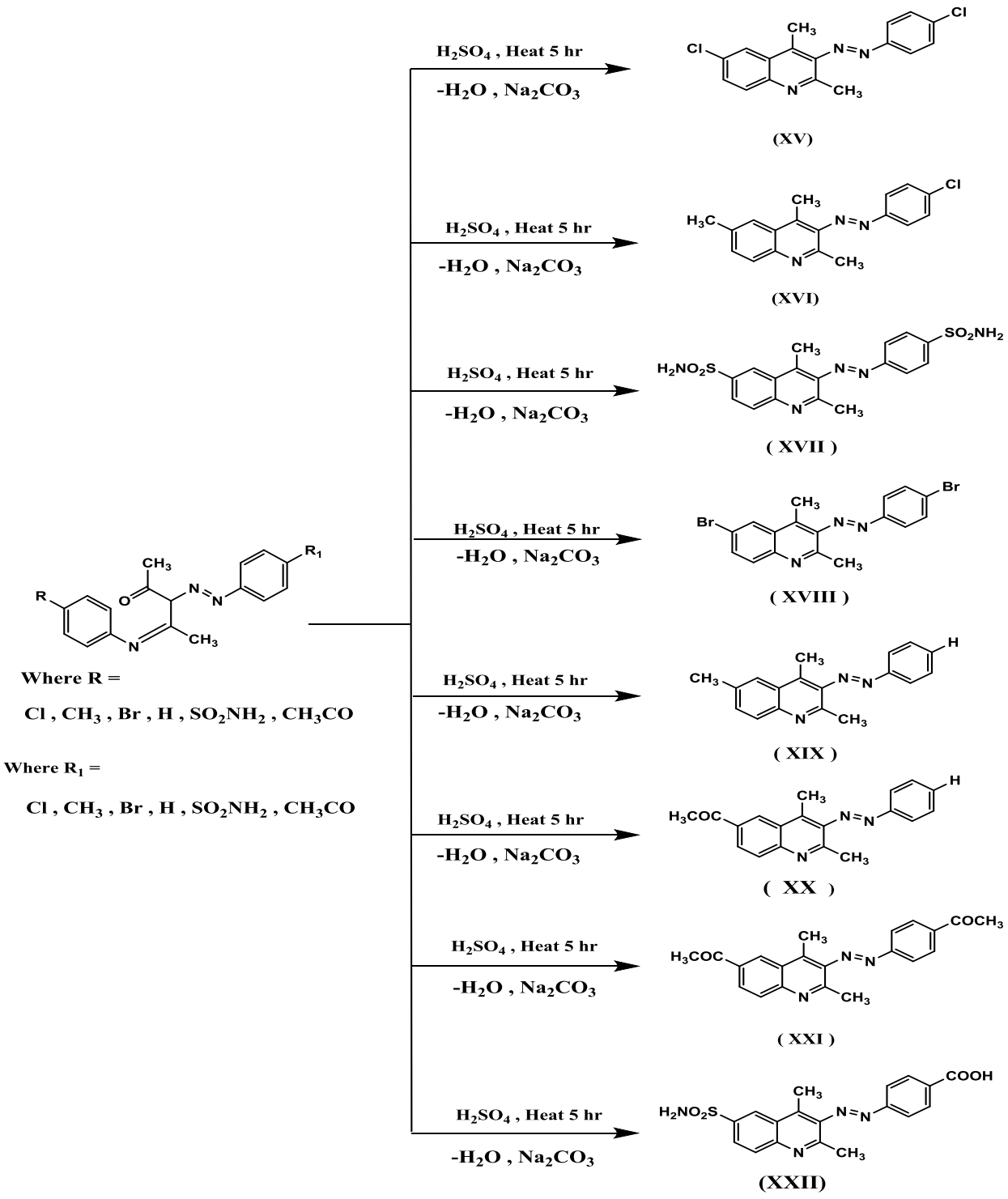
Added 10g of granular anhydrous calcium sulphate to a mixture of 5.32g (0.05 mole) of aniline *p*.substituent and 5.1g (0.05mole) of (*E*)-3-((4-substitutedphenyl) diazenylpentane-2, 4-dione (I - VI) contained in a 100 ml round bottomed flask, attached an air condenser fitted with calcium chloride guard-tube to the flask and heated the mixture on the steam bath for 1 hour, with occasional shaking. Cooled, and added 40 ml of ether to the reaction mixture and filter. Washed the calcium sulphate in the filter funnel with 40 ml ether and evaporated the combined ether filtrates. Dry and recrystallization the solid obtained from hexane to afford compounds (VII – XIV) intermediate (2) see scheme (2.2). Chemical name and physiochemical properties Infra-red spectral data were tabulated in table (2.14), (2.17) and table (2.20) respectively.



Scheme (2.2): chemical structure of (Z)-3-((E)-(4-substituted phenyl) diazenyl)-4-((4-substitutedphenyl)imino)pentan-2-one (VII – XIV)

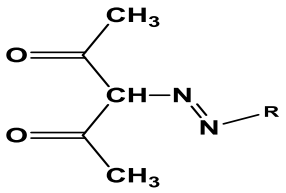
2.4.1.3 General Method for Synthesis (E)-6-substituted-3-((4-substituted phenyl)diazenyl)-2,4-dimethylquinoline (XV-XXII)

added 6g (0.032mole) of above (*Z*)-3-((*E*)-(4-substituted phenyl)diazenyl)-4-((4-substitutedphenyl)imino)pentan-2-one (VII - XIV) in portions to 25 ml of concentrated sulphuric acid (*d*1.84) contained in a 250 ml conical flask, stirred the mixture occasionally to ensure through mixed. The first portion of the enamine dissolved rather slowly but solution occurs more rapidly with later portions as the temperature of the mixture increased to 60 – 70 ^{0}C. When addition is completed, heated the mixture on water-bath at 100^{o} for 5 hr, then cooled the brown solution at room temperature and cautiously poured into ice-water (200 ml) in 1-liter baker. Basify the resulting solution by added solid sodium carbonate, and filtered off then, cooled the mixture in an ice-water bath until the precipitated product from 60 % aqueous ethanol to afford compounds (XV - XXII) see scheme (2.3). Chemical name, physiochemical properties, Infra-red spectral data, UV spectral data, ^{1}HNMR data and mass spectroscopy were tabulated in table (2.15), (2.18), (2.21), (2.22), (2.23) and table (2.24) respectively.



Scheme (2.3): chemical structure of (*E*)-6-substituted-3-((4-substitutedphenyl) diazenyl)-2,4-dimethylquinoline derivatives (XV – XXII)

Table (2-13) Chemical names of synthesised (*E*)-3-((4-substitutedphenyl)diazenyl pentane-2,4-dione (I-VI).



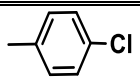
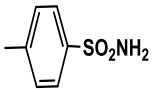
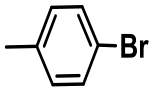
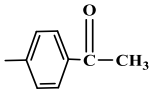
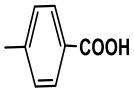
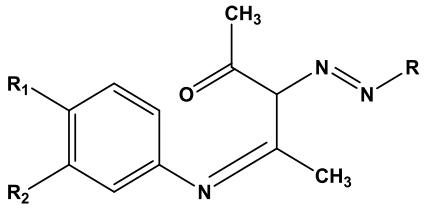
Comp. No.	R	Chemical Name
I		(*E*)-3-((4-Chlorophenl) diazenyl)pentane-2,4-dione
II		(*E*)-4-((2,4-dioxopentan-3-yl)diazenyl)benzene sulfonamide
III		(*E*)-3-((4-bromophenyl)diazenyl)pentane-2,4-dione
IV		(*E*)-3-(phenyldiazenyl) pentane-2,4-dione
V		(*E*)-3-((4-acetylphenyl)diazenyl)pentane-2,4-dione
V1		**(***E*)-4-(2-(2,4-dioxopentan-3-yl)diazenyl)benzoic acid

Table (2.14): Chemical Name of synthesized (Z)-4-((4-substitutedphenyl) imino)-3-((E)-4-substituted) diazenyl) pentan-2-one (VII – XIV).



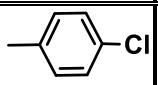
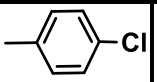
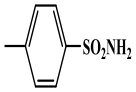
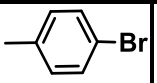
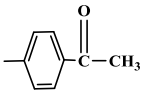
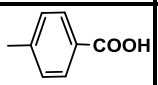
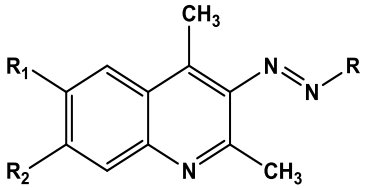
Comp No	R	R_1	R_2	Chemical Name
VII		-Cl	-H	(Z)-3-(E)-(4-chlorophenyl)diazenyl)-4-((4-chloro phenyl)imino)pentan-2-one.
VIII		$-CH_3$	-H	(Z)-3-((E)-(4-chlorophenyl)diazenyl)-4-(p-tolyl imino)pentan-2-one.
IX		$-SO_2NH_2$	-H	4-(Z)-4-oxo-3-((E)-(4-sulfamoyophenyl) diazenyl) pentan-2-ylidene)amino)benzene sulfone amide.
X		-Br	-H	(Z)-((E)-(4-bromophenyl)diazenyl)-4-((4-bromo phenyl)imino)pentane-2-one
XI		$-CH_3$	-H	(Z)-3-((E)-phenyldiazenyl)-4-(p-tolylimino) pentane-2-one
XII		$-COCH_3$	-H	(Z)-4-((4-acetylphenyl)imino)-3-((E)-phenyl diazenyl)pentan-2-one
XIII		$-COCH_3$	-H	(Z)-3-((E)-(4-acetylphenyl)diazenyl)-4-((4-acetyl phenyl)imino)pentane-2-one
XIV		$-SO_2NH_2$	-H	4-((E)-((Z)-2-oxo-4-((4-sulfamoylphenyl)imino) pentan-3-yl)diazenyl)benzoicacid.

Table (2.15): Chemical Name of synthesized (E)-6-substituted-3-((4-substituted phenyl)diazenyl) -2,4-dimethylquinoline (XV – XXII).



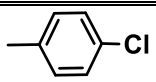
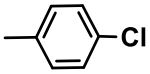
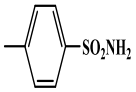
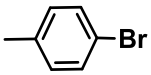
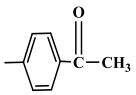
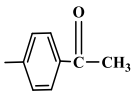
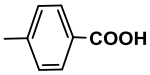
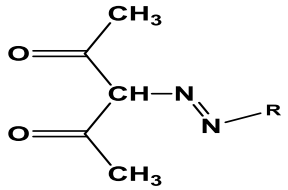
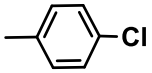
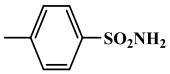
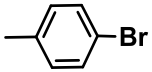
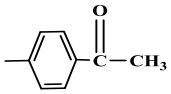
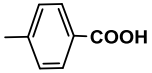
C. No	R	R_1	R_2	Chemical Name
XV		-Cl	-H	(E)-6-chloro-3-((4-chlorophenyl)diazenyl)-2,4-dimethylquinoline.
XVI		$-CH_3$	-H	(E)-3-((4-chlorophenyl)diazenyl)-2,4,6-trimethyl quinoline.
XVII		$-SO_2NH_2$	-H	(E)-2,4-dimethyl-3-((4-sulfamoylphenyl) diazenyl) quinoline-6-sulfonamide.
XVIII		-Br	-H	(E)-6-bromo-3-((4-bromophenyl)diazenyl)-2,4-dimethylquinoline.
XIX		$-CH_3$	-H	(E)-2,4,6-trimethyl-3-(phenyldiazenyl)quinoline.
XX		$-COCH_3$	-H	(E)-1-(2,4-dimethyl-3-(phenyldiazenyl) quinoline-6-yl)ethan-1-one.
XXI		$-COCH_3$	-H	((E)-1-(-4-((6-acetyl-2,4-dimethylquinoline-3-yl) diazenyl)phenyl)ethan-1-one.
XXI		$-COCH_3$	-H	((E)-1-(-4-((6-acetyl-2,4-dimethylquinoline-3-yl) diazenyl)phenyl)ethan-1-one.
XXII		$-SO_2NH_2$	-H	(E)-4-((2,4-dimethyl-6-sulfamoylquinoline-3-yl) diazenyl)benzoic acid.

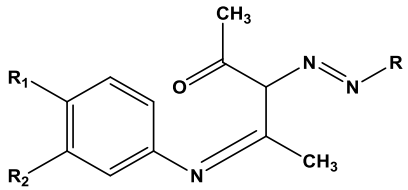
Table (2.16): Physiochemical data of synthesized (*E*)-3-((4-substitutedphenyl)diazenyl pentane-2,4-dione (I-VI).

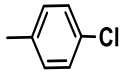
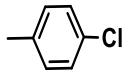
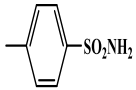
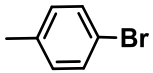


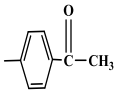
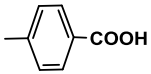
Comp.No.	R	Color	MF	MW	m.p. (ºc)	Yield %	R_f value*
I		yellow	$C_{11}H_{11}Cl_2N_2O_2$	238.67	133-135	94	0.84
II		yellow	$C_{11}H_{13}N_3O_4S$	283.30	217-219	45	0.82
III		deep yellow	$C_{11}H_{11}BrN_2O_2$	283.13	99-103	90	0.75
IV		yellow	$C_{11}H_{12}N_2O_2$	204.23	85-87	53	0.72
V		brown	$C_{13}H_{14}N_2O_3$	246.27	145-147	78	0.76
VI		yellow	$C_{12}H_{12}N_2O_4$	248.24	272-274	88	0.86

Eluting Solvent: Ethanol

Table (2.17): Physiochemical data of synthesized (Z)-4-((4-substitutedphenyl) imino)-3-((E)-4-substituted) diazenyl) pentan-2-one (VII – XIV)

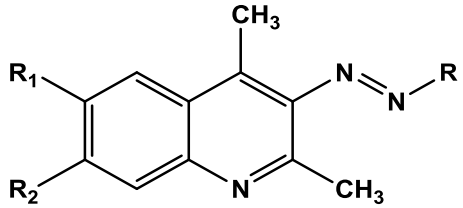


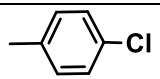
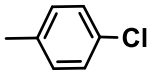
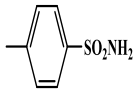
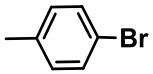
Comp.No.	R	R_1	R_2	Color	MF	MW	m.p. (°c)	Yield %	R_f value*
VII		-Cl	-H	yellow	$C_{17}H_{15}Cl_2N_3O$	347.23	139-142	68	0.84
VIII		$-CH_3$	-H	yellow	$C_{18}H_{18}ClN_3O$	327.81	102-104	69	0.69
IX		$-SO_2NH_2$	-H	yellow	$C_{17}H_{19}N_5O_5S_2$	437.08	154-156	95	0.81
X		-Br	-H	brown	$C_{17}H_{15}Br_2N_3O$	437.14	78-80	73	0.79
XI		$-CH_3$	-H	yellow	$C_{18}H_{19}N_3O$	293.37	91-92	82	0.83
XII		$-COCH_3$	-H	green yellow	$C_{19}H_{19}N_3O_2$	321.38	101-103	35	0.66

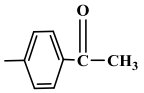
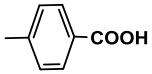
XIII		$-COCH_3$	-H	brown	$C_{21}H_{21}N_3O_3$	363.42	138-140	79	0.78
XIV		$-SO_2NH_2$	-H	yellow	$C_{18}H_{18}N_4O_5S$	402.43	227-229	91	0.80

Eluting Solvent: n. hexane

Table (2.18): Physiochemical data of synthesized (E)-6-substituted-3-((4-substitutedphenyl) diazenyl)-2,4-dimethyl quinoline (XV – XXII).

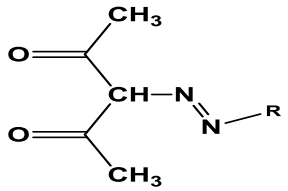


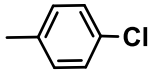
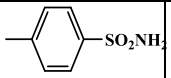
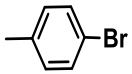
Comp No.	R	R_1	R_2	Color	MF	MW	m.p. (°c)	Yield %	R_f value*
XV		-Cl	-H	yellow	$C_{17}H_{13}Cl_2N_3$	330.21	113-115	86	0.81
XVI		$-CH_3$	-H	yellow	$C_{18}H_{16}ClN_3$	309.80	97-99	42	0.79
XVII		$-SO_2NH_2$	-H	Orange	$C_{17}H_{17}N_5O_4S_2$	419.37	222-224	51	0.69
XVIII		-Br	-H	dark brown	$C_{17}H_{13}Br_2N_3$	419.12	163-165	90	0.82
XIX		$-CH_3$	-H	yellow	$C_{18}H_{17}N_3$	275.63	261-263	78	0.66
XX		$-COCH_3$	-H	green yellow	$C_{19}H_{17}N_3O$	303.37	117-119	84	0.75

XXI		$-COCH_3$	-H	brown	$C_{21}H_{19}N_3O_2$	345.40	141-143	62	0.83
XXII		$-SO_2NH_2$	-H	2997	$C_{18}H_{16}N_4O_4S$	384.41	170-173	89	0.78

Eluting Solvent: 60 % Ethanol

Table (2.19): Infra-red spectral data (KBr) cm^{-1} of synthesized (*E*)-3-((4-substitutedphenyl)diazenylpentane-2,4-dione (I-VI).



Compound No.	R	ArC-H st.vib	C=O st.vib	-N=N- st.vib	C=C st.vib	ArC-N st.sib	C-N st.vib	N-H st.vib	C-CH_3 st.vib	Other
I		3095	1668	1623	1510	1188	1303	3431	1417	769 (C-Cl)
II		3022	1679	1633	1504	1147	1321	3114	1417	3352(asym. -NH_2) 3257(sym. -NH_2) 1263 (asym. -SO_2) 1147 (sym. -SO_2)
III		3085	1668	1625	1504	1182	1315	3533	1421	624 (C-Br)
IV		3093	1674	1623	1510	1188	1309	3533	1417	3006 (aliphatic C-H st. vib)

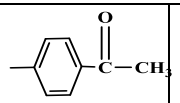
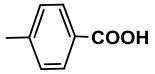
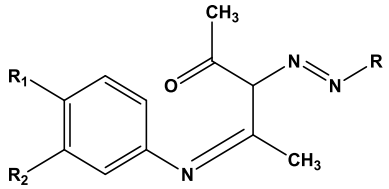
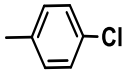
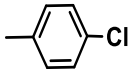
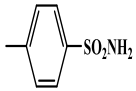
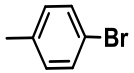
V		3051	1674 1600	1600	1506	1155	1309	3446	1419	2995 (aliphatic C-H st. vib)
VI		2663	1679 1596	1614	1510	1166	1301	2977	1423	3477 - 3726 (O-H)

Table (2.20): Infra-red spectral data (KBr) cm^{-1} of synthesized (Z)-4-((4-substitutedphenyl) imino)-3-((E)-4-substituted)diazenyl) pentan-2-one (VII – XIV).



Comp No.	R	R_1	R_2	ArC-H st.vib	C=O st.vib	-N=N- st.vib	C=C st.vib	ArC-N st.vib	C-N st.vib	-C-CH_3 st.vib	Other
VII		-Cl	-H	3078	1668	1625	1519	1188	1305	1417	769 (C-Cl
VIII		-CH_3	-H	3058	1652	1589	1519	1174	1280	1433	769 (C-Cl 3396 (N-H)
IX		-SO_2NH_2	-H	2354	1679	1591	1502	1147	1309	1425	3352 (asym.NH_2) 3257 (sym. NH_2) 1303(asym.-SO_2) 1159 (sym. -SO_2)
X		-Br	-H	3087	1668	1625	1506	1182	1315	1417	626 (C-Br)

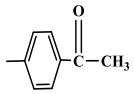
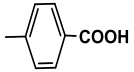
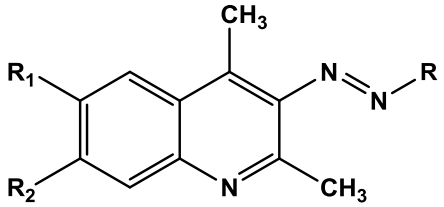
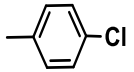
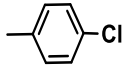
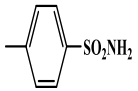
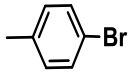
XI		$-CH_3$	-H	3095	1674	1623	1519	1188	1309	1415	3006 (C-H)
XII		$-COCH_3$	-H	3324	1647	1589	1433	1170	1272	1359	3394 (O-H)
XIII		$-COCH_3$	-H	3089	1674 1617	1596	1504	1153	1303	1357	2995 (C-H)
XIV		$-SO_2NH_2$	-H	2977	1677 1625	1596	1508	1159	1303	1423	2661 (C-H) 3317 (asym.NH_2) 3242 (sym. NH_2) 1303(asym.-SO_2) 1159 (sym. -SO_2) 3477-3726 (O-H)

Table (2.21): Infra-red spectral data (KBr) cm^{-1} of synthesized (E)-6-substituted-3-((4-substitutedphenyl) diazenyl)-2,4-dimethyl quinoline (XV – XXII).



Comp No.	R	R_1	R_2	ArC-H st.vib	-N=N- st.vib	C=C st.vib	ArC-N st.vib	C-N st.vib	$-C-CH_3$ st.vib	Other
XV		-Cl	-H	3078	1666	1521	1184	1307	1415	769 (C-Cl
XVI		$-CH_3$	-H	3058	1650	1589	1172	1274	1431	769 (C-Cl
XVII		$-SO_2NH_2$	-H	925	1677	1514	1149	1101	1423	3342 (asym.NH_2) 3257 (sym. NH_2) 1317 (asym.-SO_2) 1149 (sym. -SO_2)
XVIII		-Br	-H	3033	1618	1489	1186	1236	1417	626 (C-Br) 2918 (C-H)
XIX		$-CH_3$	-H	3056	1637	1517	1190	1315	1438	2356 (C-H)
XX		$-COCH_3$	-H	3226	1589	1519	1176	1272	1433	1645 (C=O)

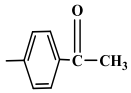
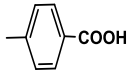
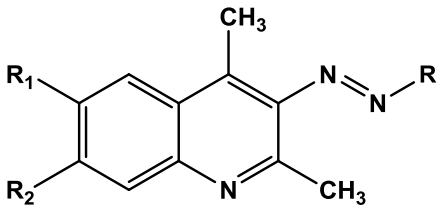
XXI		$-COCH_3$	-H	3103	1596	1504	1153	1261	1357	2997 (asym. C-H_3) 2929 (sym. C-H_3) 1674 (C=O)
XXII		$-SO_2NH_2$	-H	2997	1552	1512	1151	1309	1392	3369 (asym.NH_2) 3269 (sym. NH_2) 1151(asym.-SO_2) 1095 (sym. -SO_2) C=O (1600) 3461 - 3787 (O-H)

Table (2.22): UV specteral data of synthesized (E)-6-substituted-3-((4-substituted phenyl)diazenyl) -2,4-dimethylquinoline (XV – XXII).



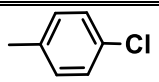
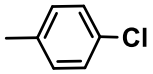
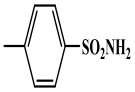
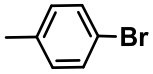
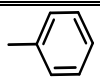
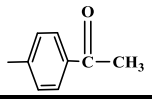
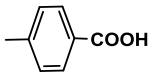
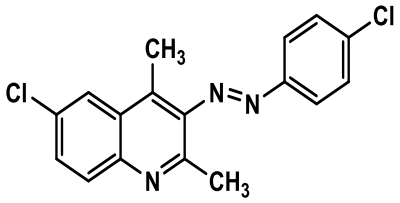
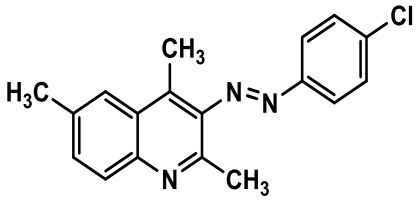
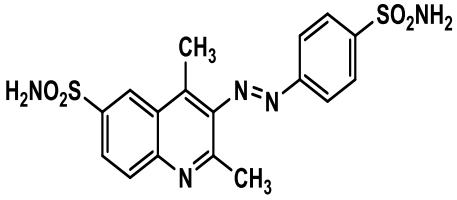
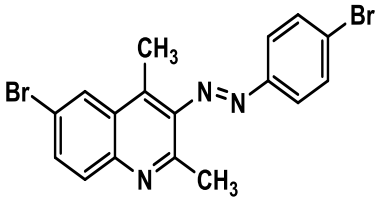
Comp No	R	R_1	R_2	λ_{max} (EtOH 60 %)
XV		-Cl	-H	203, 241, 310, 357
XVI		$-CH_3$	-H	205, 234, 334
XVII		$-SO_2NH_2$	-H	209, 257, 363
XVIII		-Br	-H	206, 236
XIX		$-CH_3$	-H	203, 247, 363
XX		$-COCH_3$	-H	204, 235, 320
XXI		$-COCH_3$	-H	241, 271, 369
XXII		$-SO_2NH_2$	-H	209, 260, 366

Table (2.23): ^{1}HNMR data of synthesized (E)-6-substituted-3-((4-substituted phenyl)diazenyl)-2,4-dimethylquinoline (XV – XXII).

compounds No.	Structure of compoud	Chemical shift (ppm)
XV		2.43 (S, 3H, CH_3), 3.35 (s, 3H, CH_3), 7.15 (d, 2H, H-Ar), 7.18 (d, 2H, H-Ar), 7.22 (s, 1H, CH quinoline), 7.47 (d, 1H, CH quinoline), 7.60 (d, 1H, CH quinoline).
XVI		2.36 (t, 6H, CH_3), 2.48 (s, 3H, CH_3), 7.17 (d, 2H, H-Ar), 7.18 (d, 2H, H-Ar), 7.40 – 7.43 (m, 3H, H -Ar), 7.52 (t, 1H, H-Ar), 7.68 (d, 1H, H-Ar).
XVII		2.45 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 6.85 (s, 4H, 2NH_2**s**ulfonamide), 7.73-7.79 (m, 4H, H-Ar), 7.68 (d, 1H, CH quinoline),7.71(d, 1H, CH quinoline), 7.85 (s, 1H, CH quinoline).
XVIII		2.37 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 7.23 (q, 2H, H-Ar), 7.87 (q, 2H, H-Ar), 8.13-8.41 (q, 2H, CH quinoline), 9.14 (s, 1H, CH quinoline).

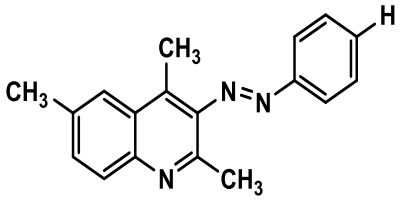
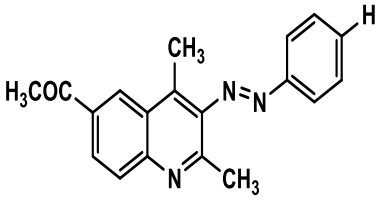
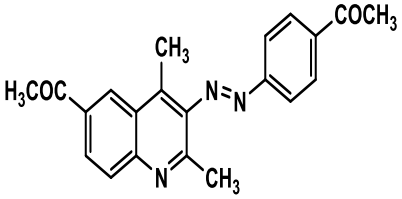
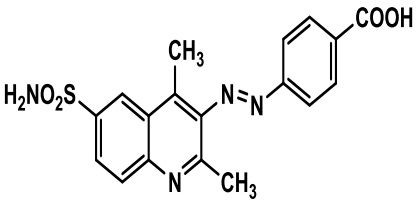
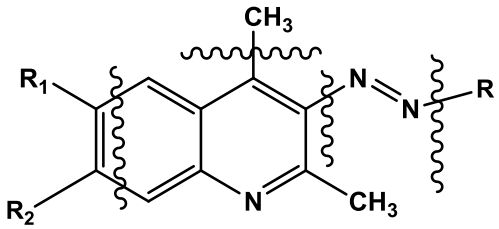
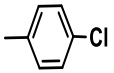
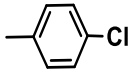
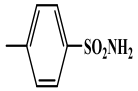
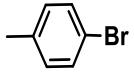
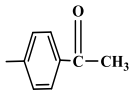
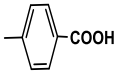
XIX		2.31 (t, 6H, CH_3), 2.43 (s, 3H, CH_3), 7.03 (t, H, H-Ar), 7.49 (d, 2H, H-Ar), 7.25 (t, 2H, H -Ar), 7.51(m, 1H, 1H, CH quinoline), 7.58 (m, 1H, 1H, CH quinoline),7.66 (t, 1H, 1H, CH quinoline).
XX		2.31 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.48 (s, 3H, -OCH_3), 7.48 (q, 2H, H-Ar), 7.50 (q, 2H, H-Ar), 7.63 (m, 2H, H-Ar), 7.64 (d, 1H, CH quinoline), 7.66 (d, 1H, CH quinoline),7.68 (s, 1H, CH quinoline).
XXI		2.31 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.48 (s, 3H, -OCH_3), 7.59 (q, 2H, H-Ar), 7.64 (q, 2H, H-Ar), 7.95 (d, 1H, CH quinoline), 7.99 (d, 1H, CH quinoline), 8.00 (s, 1H, CH quinoline).
XXII		2.31(s, 3H, CH_3), 2.43 (s, 3H, CH_3), 5.78 (s, 2H, NH_2), 7.73-7.09 (d, 2H, H-Ar), 7.27 (d, 2H, H-Ar), 7.44 (d, 1H, CH quinoline), 7.48 (d, 1H, CH quinoline), 7.84 (s, 1H, CH quinoline),8.94 (s, 1H, COOH)

Table (2.24): Mass specteral of synthesized (E)-6-substituted-3-((4-substituted phenyl)diazenyl) -2,4-dimethylquinoline (XV – XXII).



Co. No	R	R_1	R_2	MW (calculate)	MW (M^+) (found)	M+1	M+2	M+4	M/Z:Relative aboundance %
XV		-Cl	-H	330.21	325.00 (14.20)	326 (4.46)	-	329.00 (16.25)	325.90 (4.46), 313 (4.44), 120 (100), 91 (69.06), 205 (15.21).
XVI		$-CH_3$	-H	309.80	305.95 (0.48)	-	307.95 (.32)	-	279 (.80), 236 (2.17), 120 (100), 198 (4.69), 92 (49.79). 256 (.45).
XVII		$-SO_2NH_2$	-H	419.07	418.00	419.00 (1.48)	420.00 (1.48)	-	402(1.52), 265 (4.17), 250 (2.41), 64 (100), 171 (36.46),184 (7.49), 155 (46.03).
XVIII		-Br	-H	419.12	420.00 (2.64)	-	422.00 (1.99)	423.00 (1.76)	415 (1.81), 401 (1.71), 313 (5.22), 237 (3.68), 186 (1.67), 262 (2.49), 57 (4.59), 64 (8.98).

XIX		$-CH_3$	-H	275.36	276.10	277.10 (1.25)	278.10 (1.89)	279.10 (1.30)	262 (6.86),247 (5.07), 200 (20.03), 224 (2.71), 144 (11.41), 131 (4.68), 106 (12.55), 65 (14.94).
XX		$-COCH_3$	-H	303.37	304.00	305.00 (1.07)	306.00 (1.07)	-	281 (2.52), 251 (3.73), 237 (1.41), 185 (2.48), 163 (3.76), 146 (1.21), 120 (100), 68(8.68), 52 (10.38).
XXI		$-COCH_3$	-H	345.40	344.00	345.00 (3.68)	346.00 (3.04)	347.00 (3.88)	320 (3.59), 294 (10.23), 251 (6.55), 247 (13.01), 207 (7.22), 160 (9.33), 106 (3.83), 68 (13.28), 57 (100).
XXII		$-SO_2NH_2$	-H	384.41	384.09	385.09 (19.5	386.09 (4.50)	-	346 (34.12), 316(2.54), 307(1.39), 289 (1.16), 263 (1.33), 231(3.06), 189 (11.36),122 (3.21), 55 (11.24).

Chapter Three
Results and Discussion

3. Discussion

3.1 QSAR Study

Tuberculosis (TB) is one of the leading worldwide health problems which cause the death of millions of people each year. The disease is caused by an infectious bacillus called Mycobacterium tuberculosis and is the second largest killer disease after HIV/AIDS among various diseases caused by a single infectious agent. World Health Organization (WHO) has recommended standard strategy for the treatment of the tuberculosis by a program called DOTS (Directly observed treatment, short-course), which include six-month regimen of four first-line TB-drugs, Isoniazid, Rifampicin, Ethambutol and Pyrazinamide (two months course of all four drugs followed by four months course of Isoniazid and Rifampicin) (Nayak *et al*., 2016).

In spite of the availability of these drugs, rapidly increasing multi drug resistant TB (MDR-TB) has resulted enormous difficulty in fighting against TB. In addition, the weak or no activity of the current drugs against extremely drug resistant TB (XDR-TB), particularly in HIV infected patients is a serious problem in TB control (Corbett *et al.,* 2003). However, due to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis, this poses a big challenge towards the successful treatment of tuberculosis (Lamichhane *et al.,* 2011). This led to development of new therapeutics against diverse strains of mycobacterium tuberculosis due to high impact of MDR and recently XDR in TB treatment; its need new drugs and strategies to treat this disease efficiently (Organization 2017).

Quinoline moiety is of great importance to chemists as well as biologists as it is found in a large variety of naturally occurring compounds and also chemically useful molecules having diverse biological activities (Eswaran *et al*., 2010).

Quinoline synthesis and its derivatives has been prevalent in biomedical studies and attracted both synthetic and biological chemist because of its diverse chemical

and pharmacological properties and synthetic methods as well as the relative low-cost production of these compounds (Kumar *et al*., 2009). Quinolines and its derivatives have been attracted considerable interest because a large number of natural products and drugs contain this heterocyclic moiety. Further, these compounds are used to building blocks of various other compounds (Hajalsiddig and Saeed 2019). Quinoline and its derivatives are known historically to possess antimalarial and biological activities (Ilango *et al*., 2015).

Quantitative structure-activity relationship (QSAR) is an essential tool in modern chemistry that is used to find a correlation between biological activities measured for a panel of compounds and molecular descriptors (Hadaji *et al*., 2017). It is used in many areas of science to reduce the excessive number of experiments, sometimes long expensive and harmful for environment properties (N, Guessan *et al.,* 2017). The key success of the QSAR method is the possibility to predict the properties of new chemical compounds without the need to synthesize and test them. The QSAR technique is broadly utilized for the prediction of physicochemical properties in the chemical, industrial, pharmaceutical, biological, and environmental spheres (Wong *et al*., 2014). Molecular descriptors can be defined as the essential information of a molecule in terms of its physicochemical properties such as constitutional, electronic, geometrical, hydrophobic, lipophilicity, solubility, steric, quantum chemical, and topological descriptor (Isarankura *et al.,* 2009).

Structural properties expressed in terms of descriptors. Molecular descriptors play fundamental role in developing models for chemistry. Molecular descriptors can be calculated from the chemical formula (1D descriptor), the 2D structure (2D descriptors), and the 3D conformation (3D descriptors) using multiple methods based on atom types, molecular fragments and the three-dimensional structure (Nandi and Bagchi 2010).

In this context, QSAR study was carried out for a group of quinoline derivatives with biological activity reported by (De Souza *et al.*, 2009) to obtain models, which were used to predict the biological activity against TB. Consist of 15 compounds showed in table (2.6) which split in to two sub set. Training set containing 13 compounds and test set of two compounds.

Total of 9 molecular descriptors were calculated and depended of high correlation matrix between them and logP. Nine molecular descriptors were calculated is including log octanole/water partition (logP o/w), dipole moment (MNDO - dipole), electrostatic energy (E-ele), Absolute different in surface areas (DASA), Absolute different in charge-weighted areas (DCASA), potential energy (E), Non-bonded Energy (E-nb), Dipole moment (AM1-dipole), Dipole moment (MP3-dipole), were calculated for each compound in training and test set of the material. All descriptors were calculated by using MOE and ACD/lab programs and listed in table (2.2) and table (2.3) respectively.

For a statistically relation between the number of compounds and number of descriptors should bear a ratio at least **5:1**. Thus, only two descriptors are required for 11 compounds in training set to develop statistically credible QSAR model in this study. To selection the best sub-set of fitting descriptors from large number of them, using correlation matrix for selected descriptors by using MEO software see figure (2.1). The analysis of this matrix shows select nine descriptors in training set. Multiple linear regressions (MLR) are commonly used method in QSAR due to its simplicity, transparency, reproducibility, and easy interpretability (Roy *et al.*, 2015). QSAR model referred during MLR analysis with two descriptors and the best equation No (10) which showed high squared correlation coefficient (r^2) and low root mean square error (RMSE), was considered as the best model with logP (o/w) and DCASA descriptors.

$$Pc = 0.95860 + 0.74495 \times \log P\ (o/w) + 0.03159 \times DCASA \quad \text{..... Model}$$

The above equation showed that there is positive correlation between the biological activity, Absolute different in charge-weighted areas (DCASA) and logP octanol/water partition coefficient (logP (o/w).

Validation of the predictive power of a QSAR model carried out by internal validation by training set compounds (cross validation) and external validation by test set compounds. The statistical fit of QSAR can be determined by the several statistical tests to obtain quality models such as r, r^2, Q^2, RMSE, S, F, and P value depicted in table (2.5).

The QSAR in this work are acceptable because have good internal, external predictive abilities and all values of statistical measured are found in acceptable range (the r^2 more than 0.60).

r = 0.9071, **r^2** = 0.8231, **RMSE** = 0.1236, **Q^2** = 0.8015, **s** = 0.1646

F = 37.173 **P** = 0.0001

The predictive power is very important characteristics of a QSAR model to build ability of a model to predict accurately the biological activity of compounds that were not used for model development (external validation). External validation methods (test set compounds) only way used to determine the true predictive power of a QSAR model not used to for the model development.

The predictive of regression model were estimated by comparing the predict and observed values of pIC_{50} against Mycobacterium tuberculosis (TB) of training set and cross validation, the residual calculated and tabulated in table (2.6), (2.7) for training and test set respectively.

The presented data in table (2.6) and (2.7) shown the agreement between experimental and predicted pIC_{50} values and the residual values are small this indicates good predictability of the established model (Roy *et al.*, 2016).

Figure (3.1), (3.2), (3.3) shows the plots of linear regression predicted versus experimental values of the biological activity of training set, cross validation and

test set compounds against Mycobacterium tuberculosis (TB) respectively. The plots for QSAR model show good fitted with r^2 = 0.8243; r = 0.9071 for training set, r^2 = 0.9792; r = 0.9896 for cross validation and very good fit with the r^2 = 0.8534; r = 0.9234 for test set.

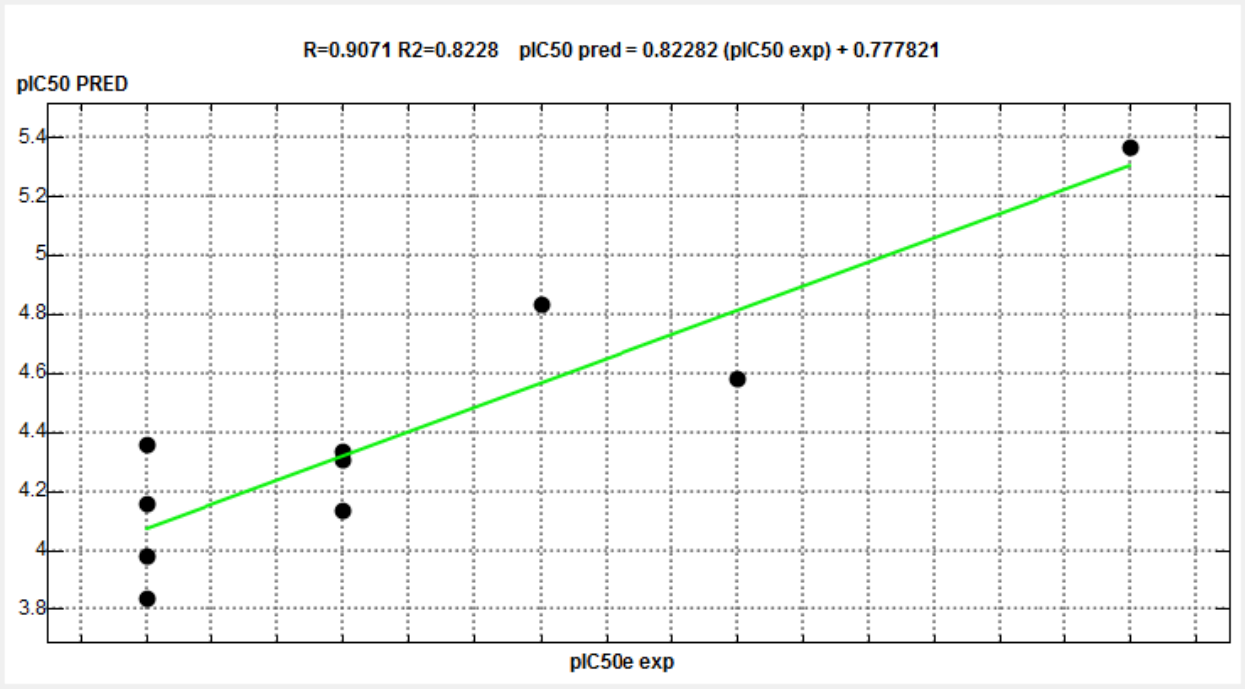


Figure (3.1): plots of predicted training set versus experimental p IC_{50} values against mycobacterium tuberculosis (TB).

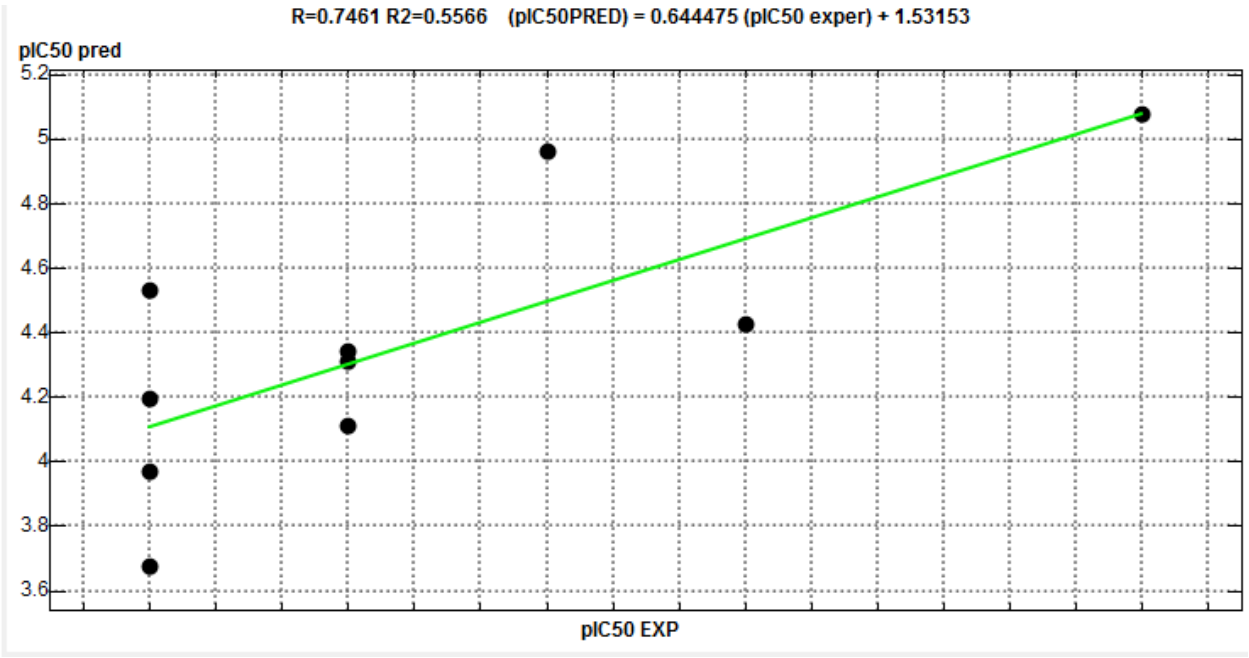


Figure (3.2): plots of cross validation prediction versus experimental pIC_{50} values against mycobacterium tuberculosis (TB).

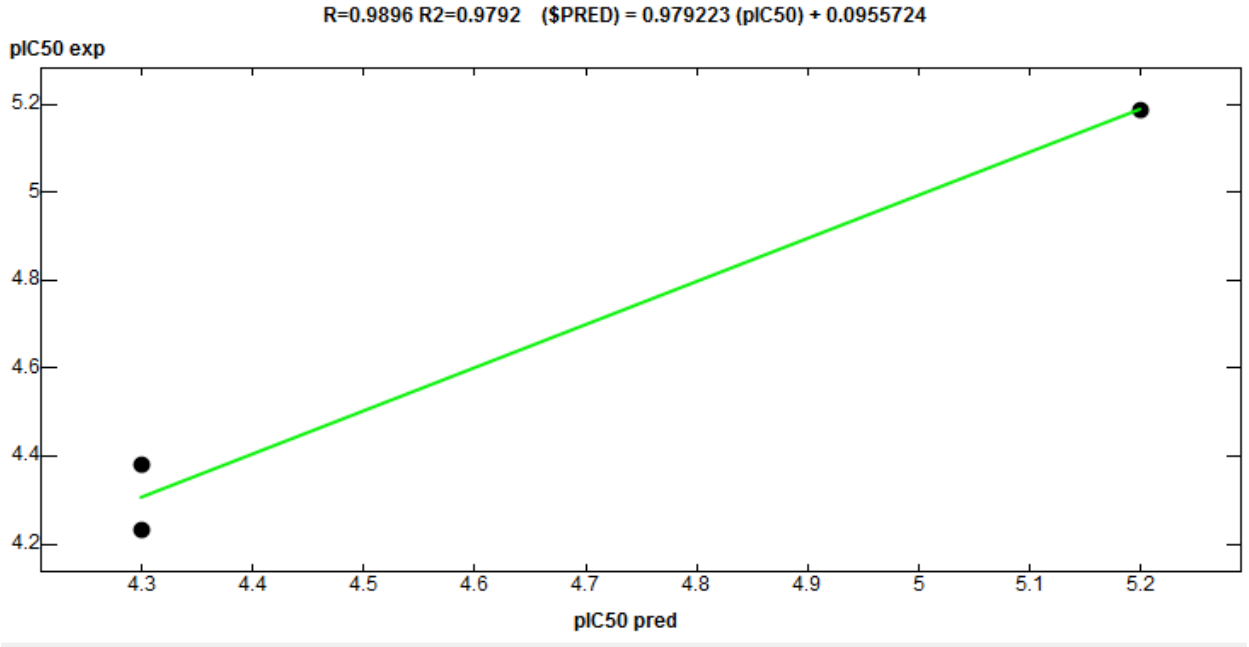


Figure (3.3): plots of predicted test set versus experimentally pIC_{50} values against mycobacterium tuberculosis (TB).

3.2 Designing of disubstituted quinoline derivatives

Quinoline synthesis and its derivatives has been prevalent in biomedical studies and attracted both synthetic and biological chemist because of its diverse chemical and pharmacological properties and synthetic methods as well as the relative low-cost production of these compounds (Kumar *et al.*, 2009). Further, the quinoline compounds and derivatives are used to building blocks of various other compounds. Quinoline and its derivatives are known historically to possess antimalarial and biological activities (Hajalsiddig and Saeed 2019). In order to synthesize quinoline derivatives expecting to possess biological activity against mycobacterium tuberculosis about 34 compounds were designed as anti-mycobacteria tuberculosis (TB) and their structure illustrated in table (2.8).

The proposed model has all condition to be considered as predicted. It has correlation coefficient of cross validation (Q^2) over 0.5, prediction the (r^2) higher than 0.6 and very good prediction in external validation (r^2= 0.82). Consequence, this model was used to predict the *in-vitro* biological activity of designed quinoline derivatives (1-34) against mycobacterium tuberculosis (TB), predicted biological activity of these compounds along with predicted chemical descriptors were listed in table (2.8).

To select compounds for synthesis from designed compounds potency, the drugability of these compounds were evaluated through "Lipinski's rule of five" which proposes that molecule with poor permeation and oral absorption have logP > 5, molecular weight > 500, more than 5 hydrogen bond donor and acceptor group more than 10.

LogP is the logarithm of the partition coefficient in the biphasic system (e.g., *n*-octanol/water), defined as the ratio of a compound concentration in phase 1 and phase 2. A value of logP is determined for the uncharged species of the drug (Musiol *et al.*, 2007). Lipophilicity is a property that has a major effect on

absorption, distribution, metabolism, excretion, toxicity properties as well as pharmacological activity, because drugs cross biological membranes through the passive transport, which depends on their lipophilicity. LogP one of the lipophilicity descriptors are used for structure activity relations description and prediction (Cieslik *et al.*, 2012).

So, the logP value very important descriptors because indicates the lipophilicity and hydrophobicity of a compound. The problem is that compounds excessively lipophilic has difficult to dissolve in the water of the organism, and then it will to be absorbed. The molecular weight describes the molecular size. Big molecules will have difficult to be absorbed, because the passage through biological membranes is unfavorable (De la Fuente and Gimenez-Llort 2010). The compounds that not passed in this criterion were 1, 2, 3, 4, 9, 20, and 31 see table (2.9). The hydrogen bonds (HB) donor and acceptor groups correlate to the capacity of intermolecular interactions, mainly with water molecules. The passage through cellular membrane becomes thermodynamically unfavorable with the increase of HB count groups because desolvatation is needed to enter in the lipidic environment (Veber *et al*., 2002). All the designed quinoline derivatives have acceptable number of hydrogen bond donor and acceptor group see table (2.8).

3.3 Docking Study

Molecular docking is a computational method used to determine the binding strength between the active site residues and specific molecule(s) (Lill and Danielson 2011). Molecular docking is expedient tool used in the drug discovery field to investigate the binding compatibility of molecules (ligands) to target receptor (Hawkins *et al.*, 2007). Molecular docking in this study was carried out in order to elucidate which of a series quinoline derivative has the best binding affinity against mycobacterium tuberculosis H_{37}Rv strain (ATCC27294, susceptible both to rifampin and isoniazid). The structure of ATCC 27294 used in

the study was obtained from protein data bank (PDB) with code 6KGH. All docking procedures were achieved by MOE (Molecular Operating Environment) software 2010.10. The prepared ligand and receptor were shown in Figure (3.7) and 2D biding and active side of the receptor see figure (3.8). The optimized structures of quinoline derivatives initially saved as PDB files using (MOE). Molecular docking suggested that all of the designed quinoline derivatives were capable of forming a hydrogen bond with the amino acids and energy score (s) and the result of docking studies of all designed compounds conformations with active sites are tabulated in table (2.11).

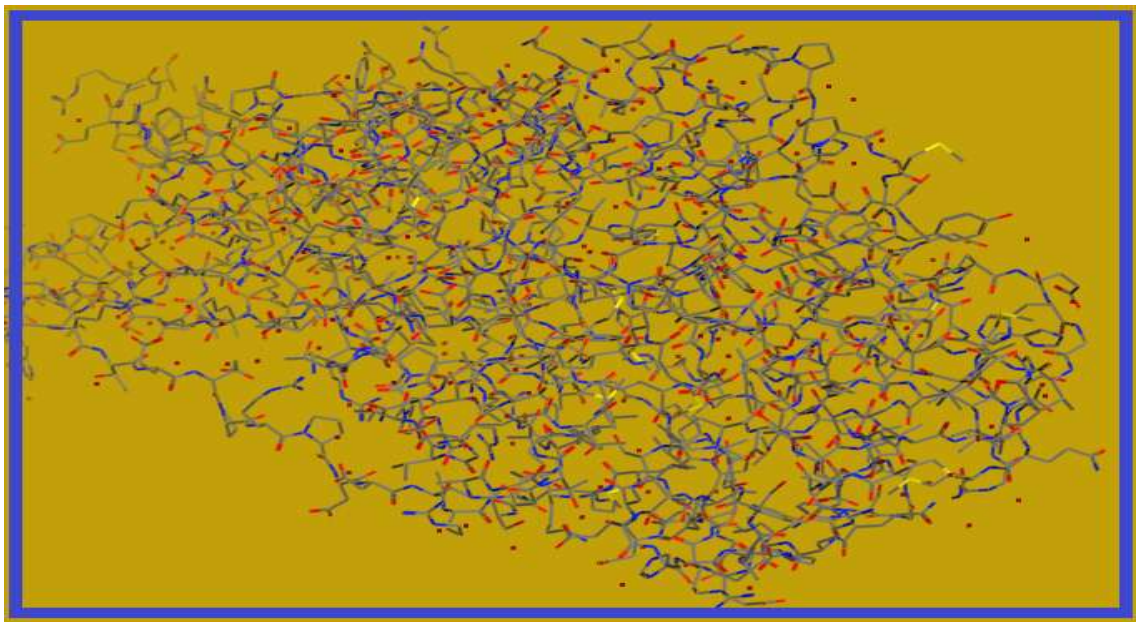


Figure (3.4): structure of 6KGH was load from PDB.

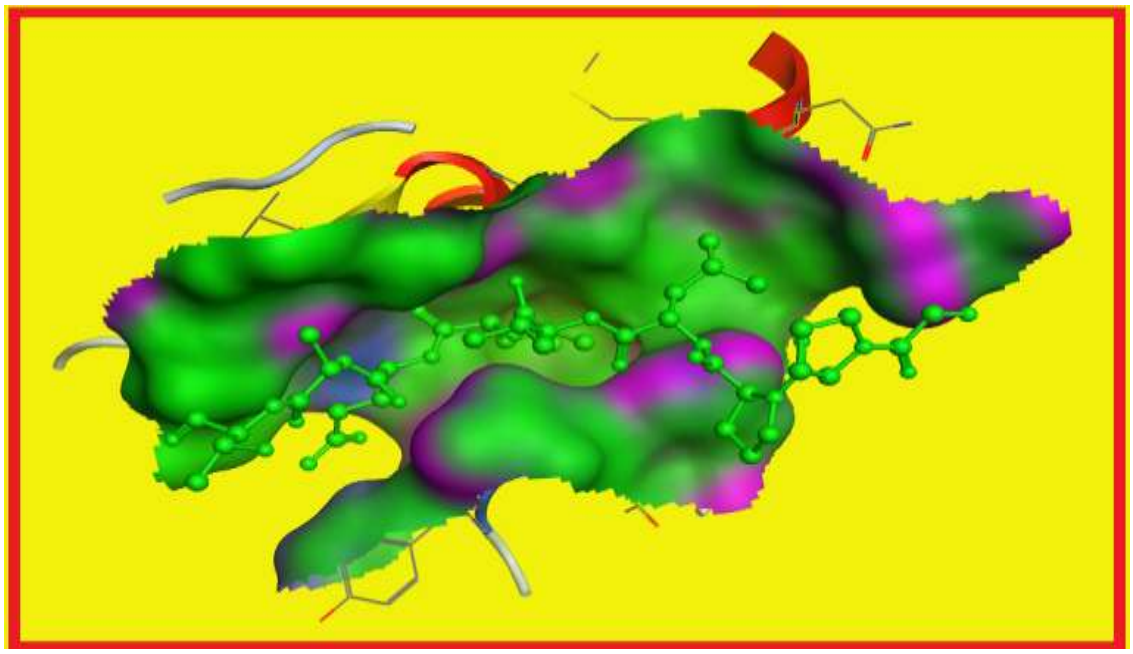


Figure (3.5): structure of receptor surface and maps.

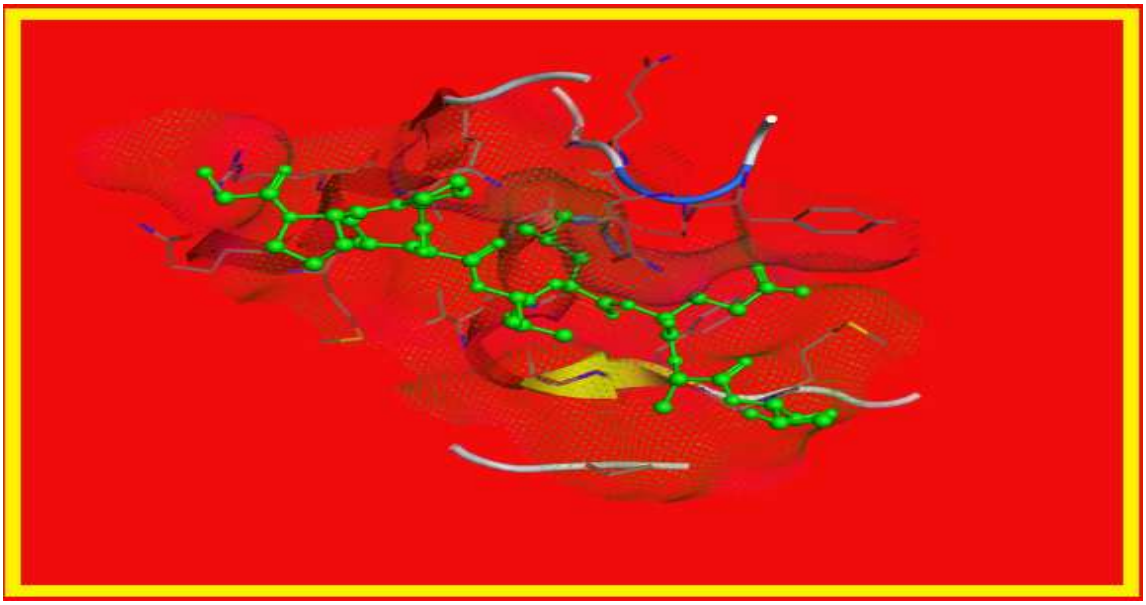


Figure (3.6): structure of 6KGH pocked and ligand

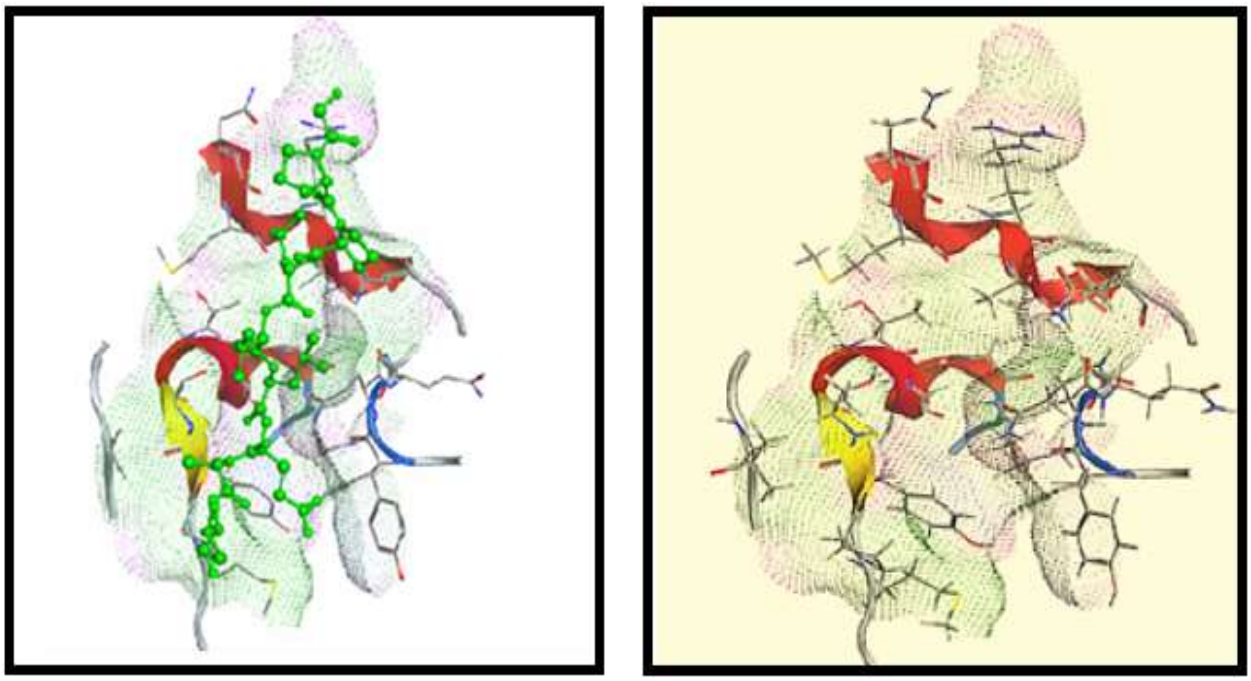


Figure (3.7): structure of the receptor and ligand preparation after load from PDB.

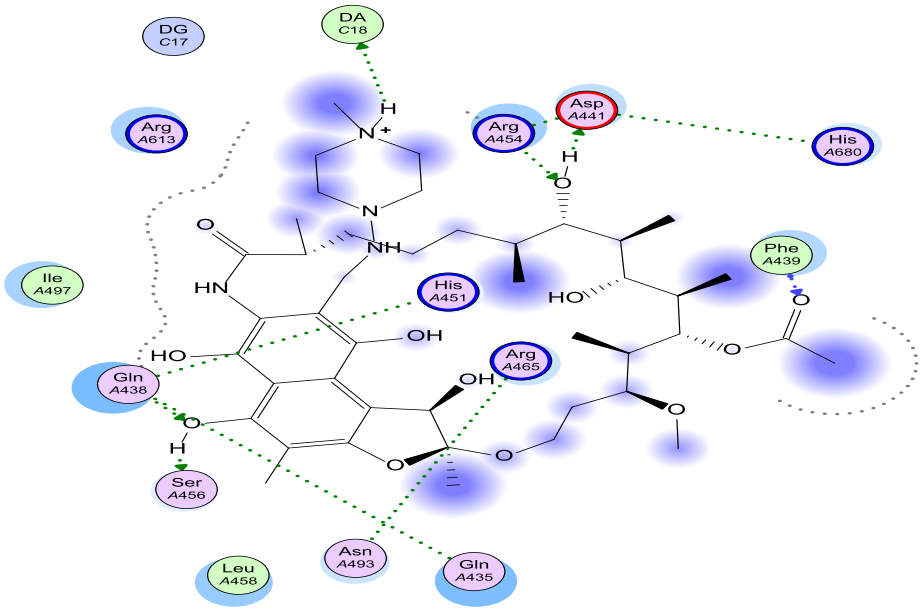


Figure (3.8): 2D binding interaction and active side the receptor

In a further, it can be observed that more active newly synthesized compounds such as (C9, C10, C30, C25, C28, C24, C27, C22, C17) have showing excellent docking score (-21.8094, -21.3433, -21.6289, -19.2330, -18.3328, -17.8389, -17.8260, -17.4285 and -17,23461307 respectively) see table (2.22), also these compounds were capable of forming bonds with amino acid (Arg564, Thr433, Gln575, Pro431, Ala555). Amino acid interactions of most active compounds towards the receptor are illustrated in figure (3.7), (3.8) and (3.9), the rest of figures can find in the appendix C.

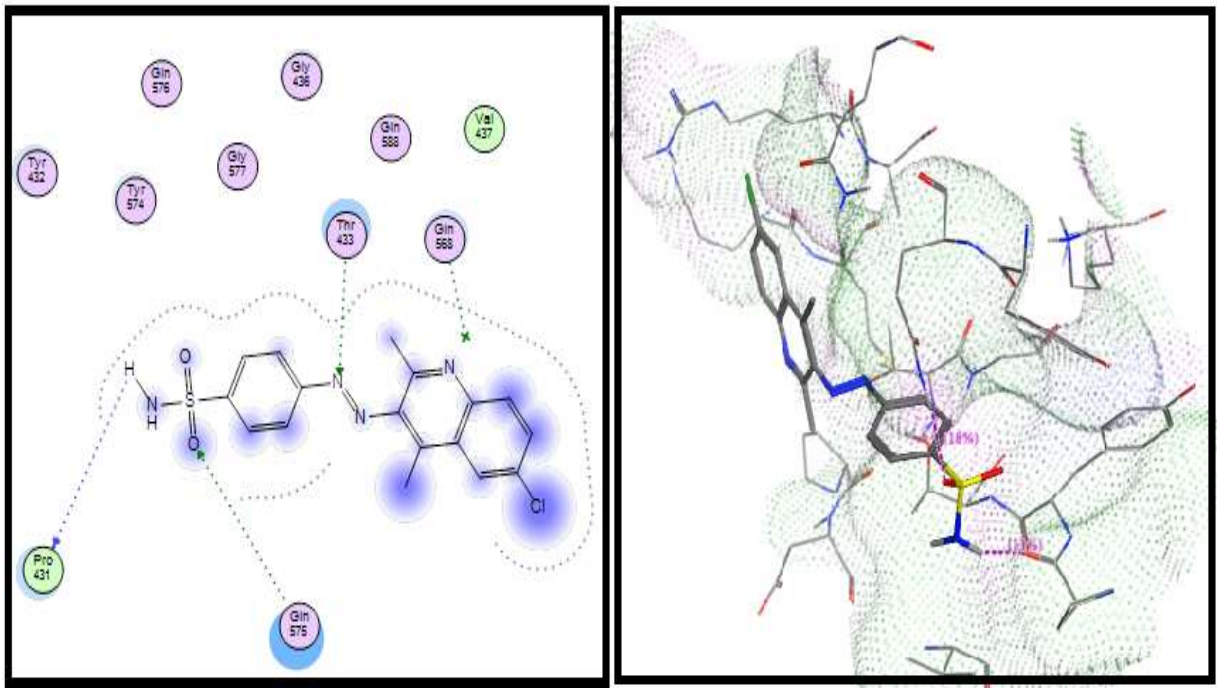


Figure (3.9): 2D Binding interaction and 3D structure of C17 active site.

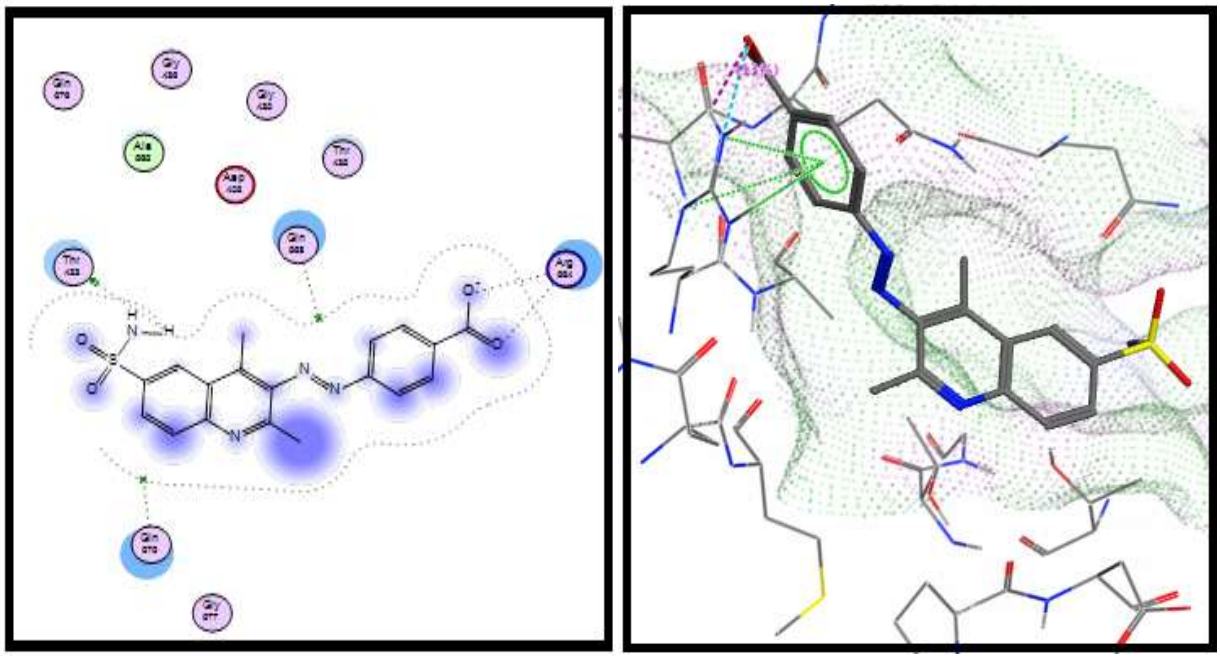


Figure (3.10): 2D Binding interaction and 3D structure of C22 active site.

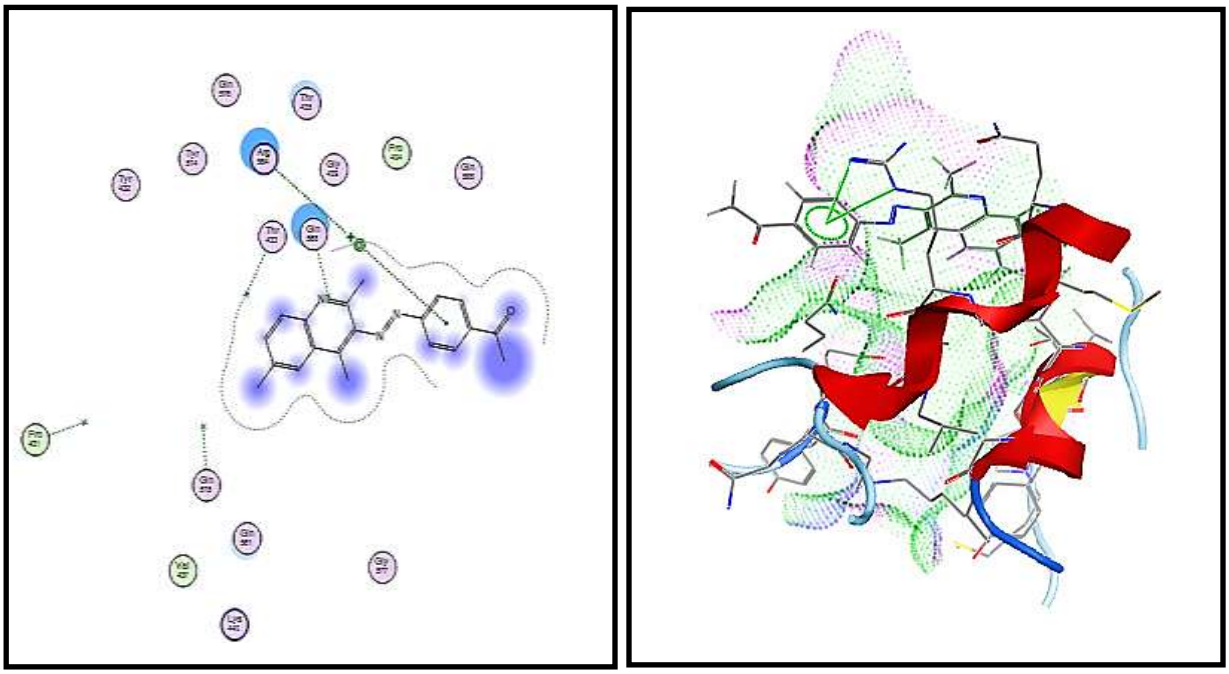


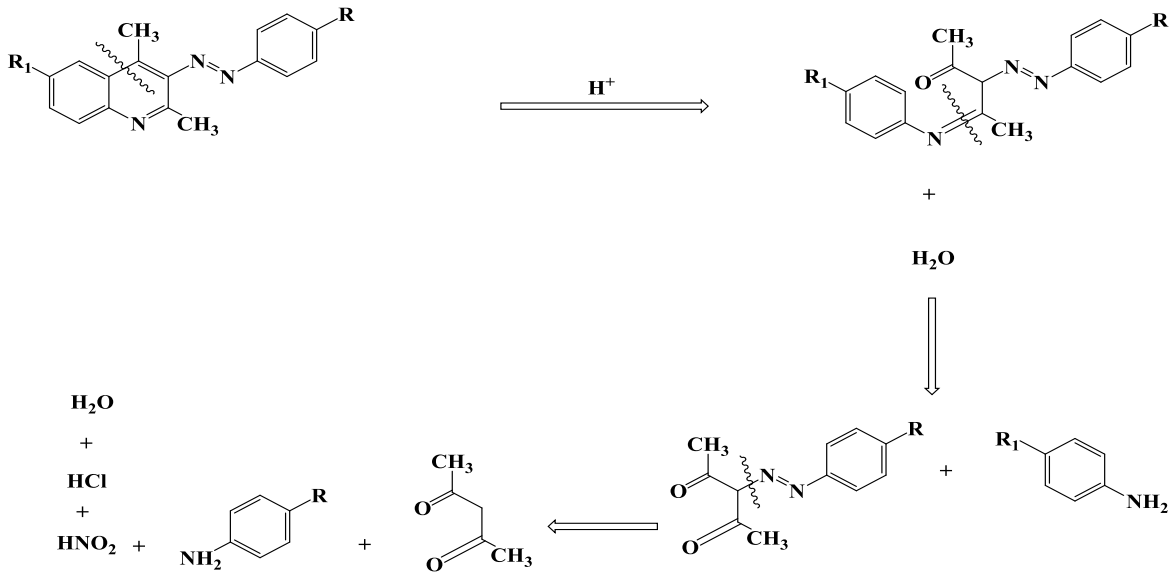
Figure (3.11): 2D Binding interaction and 3D structure of C16 active site.

3.4 Organic synthesis

Selection of synthesized compounds in this work based on QSAR model validation of pIC_{50} values and interaction molecular docking with amino acid in the receptor, also some of synthesized compounds were evaluated through "Lipinski's rule of five".

3.4.1 Synthetic design

The synthetic design and strategies of the compounds in this work have been constructed from the appropriate retrosynthetic analysis of the target quinolines.

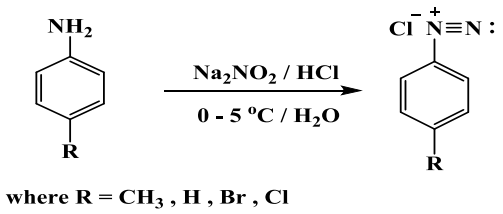


Scheme (3.1): Retrosynthetic analysis of target compounds

3.4.2 Step (I): preparation of Diazonium salt

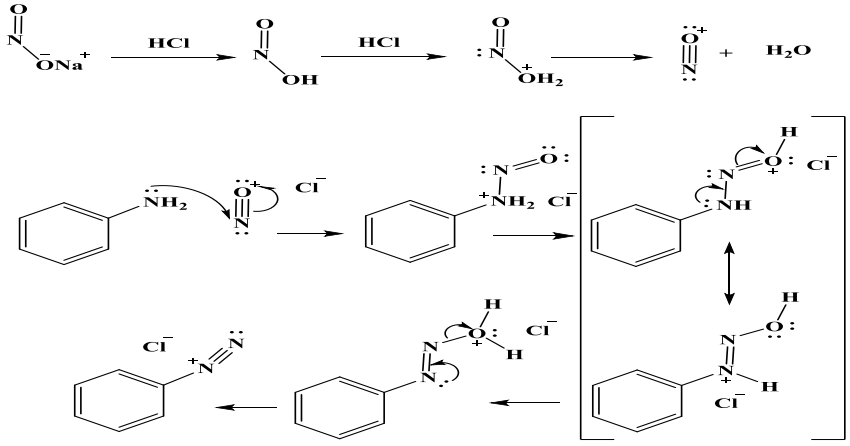
A diazo compound is an aliphatic, aromatic, or heterocyclic compound in which a --N_2 group is attached to a carbon atom. The most important aromatic diazonium compounds are the diazonium salt such as aryldiazonium ions. Aromatic diazonium salts, represented by the general formula, Ar-N_2^+X, are highly reactive compounds and serves as intermediate in the synthesis of a wide variety of organic aromatic compounds. There are many chemical reactions like reduction, oxidation,

condensation, hydrolysis, complexation and coupling etc. (Patil *et al.*, 2015). In the present piece of work, we have the aryldiazonium salt preparation.



Scheme (3.2): general reaction of diazonium salt

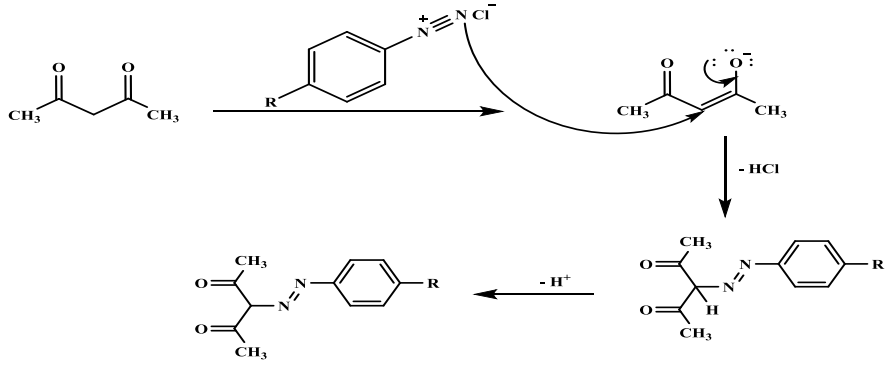
In the above reaction the mechanisms start by protonated sodium nitrite by HCl to give nitrous acid and nitrosonium ion. And the next step is formation of the diazonium ion from the reaction between aromatic primary amine and nitrosonium ion.



Scheme (3.3): mechanism formation of diazonium salt

3.4.3 Step (II): synthesis of 3(4-Substitutedphenylazo)-pentane-2, 4-dione (I-VI)

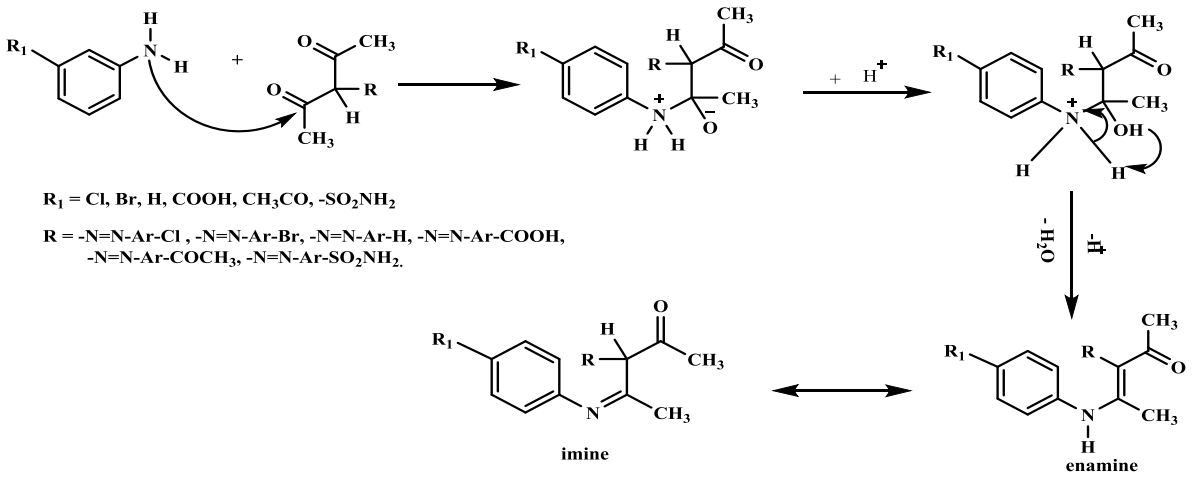
Aniline and substituted anilines are used for the preparation of diazonium salt then they are coupling upon with Acetyl acetone to give (Phenyldiazenyl)-acetyl acetone (I-VI). Thereof, these compounds will be useful as building block for organic researchers in past time and the near future (Patil *et al.*, 2015).



Scheme (3.4): mechanism of synthesis of 3(4-Substitutedphenylazo)-pentane-2, 4-dione (I-VI).

3.4.4 Step (III): 4(4-substituted phenyl)imino)-3(4-substituted) diazenyl) pentan-2-one (VII-XIV)

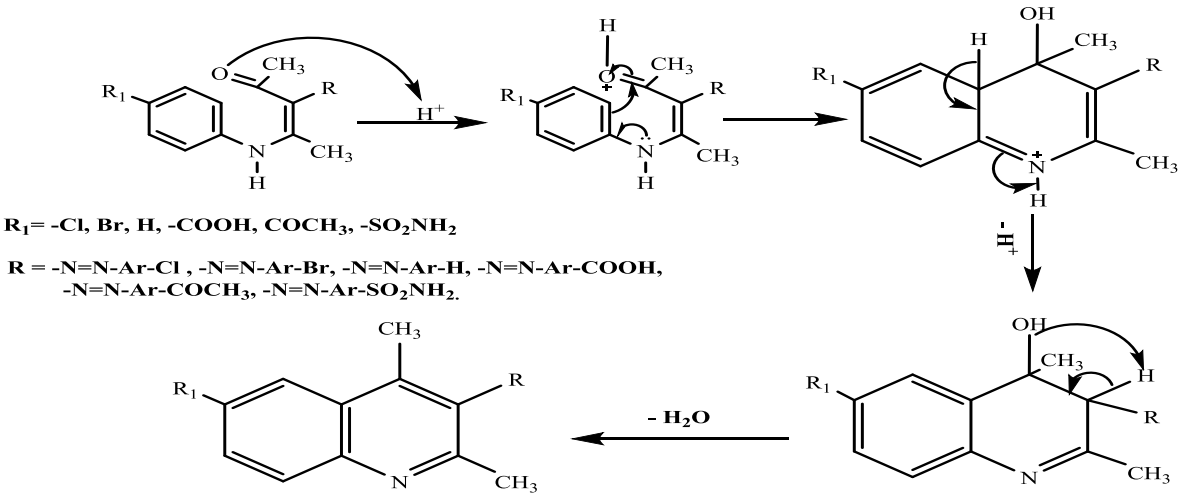
Condensation reactions are important for useful intermediate compounds in organic syntheses and the creation of many important biological molecules, such as quinoline and their derivatives. This steps the reaction involves a condensation between *p*.substituted aniline and 3(4-Substitutedphenylazo)-pentane-2, 4-dione to form imine and enamine of 4(4-substitutedphenyl)imino)-3(4-substituted)diazenyl) pentan-2-one the suggested mechanism for this step illustrated below.



Scheme (3.5): Proposed mechanism of coupling (Phenylhydrazono)-acetyl acetone with p. substituted primary aromatic amine (VII-XIV)

3.4.5 Step (IV): Synthesis of 6-substituted-3-((4-substituted phenyl) diazinyl) -2,4-dimethylquinoline (XV – XXII).

Eight compounds of 6-substituted-3(4-substitutedphenyl)diazinyl)-2,4-dimethyl quinoline (XV-XXII) were synthesized by cyclization of 4(4-substituted phenyl) imino)-3(4-substituted)diazinyl)pentan-2-one. This step achieved by heating stem on the water bath after dissolve in sulphuric acid in medium base to give target compounds in this step. Scheme (3.6) shows the mechanism of this reaction.



Scheme (3.6): Proposed mechanism of synthesized of 6-substituted-3(4-substituted phenyl) diazinyl) -2,4-dimethylquinoline (XV – XXII).

3.5 Spectroscopy analysis

Spectroscopy is the study of the interaction between matter and electromagnetic radiation (EMR). Spectroscopy it is an instrumental technique of analysis and structural elucidation of compounds by measured with the little or no sample loss. Organic chemists use spectroscopy as a necessary tool for structure determination (Pant *et al.,* 2011).

3.5.1 Infrared spectroscopy analysis (FT-IR)

Infrared spectroscopy is a technique based on the vibrations of the atoms of a molecule. The IR absorption bands can be attributed to the vibration of individual

bonds, and these bands are the most diagnostically useful since they help in the identification of the functional groups present in the molecule (Fernández *et al.*, 2012).

3.5.1.1 Synthesis of 3(4-Substitutedphenylazo)pentane-2, 4-dione (I-VI)

These compounds showed several characteristic sharp bands in the IR spectra, where the bands in the range between 1668-1667 cm^{-1} indicated the appearance of the carbonyl C=O st.vib groups of acetylacetone molecule. The absorption bands for C=N st.vib and Ar-C-N of all st.vib of compounds appeared at 1301-1321 cm^{-1} and 1147-1188 cm^{-1}, respectively.

Absorption bands at 1625 -1589 cm^{-1} and 2977 – 3533 cm^{-1} due the N=N and N-H group respectively in all compounds. Compounds I and III showed absorption bands at 769 cm-1 and 624 cm^{-1}indicated the presence halogen groups C-Cl and C-Br respectively. Compounds VI showed absorption bands at 3776 cm^{-1} referring of the presence of O-H in carboxylic acid group. Compounds IV and V are containing aliphatic C-H group which was absorbed between 3006 - 2995 cm^{-1}. Compounds II showed absorption bands at 3352 - 3257 cm^{-1} due to asymmetry and symmetry stretching NH_2. The C-CH_3 group in all compounds absorbed bands between 1417-1423 cm^{-1} were observed. Aromatic C-H stretch also observed at 2663-3095 cm^{-1}in all intermediates (I-VI).

3.5.1.2 4 (4-substituted phenyl) imino)-3(4-substituted)diazinyl) pentan-2-one (VII-XIV)

The IR spectra of these compounds show the disappearance of conjugated system (-N=N-) of the intermediate one derivative (I-VI), and appearance (Ar-C-N) also disappearance of the -NH due to loss one molecule of water and one group of carbonyl group from acetylacetone structure and this's indicator to form structure of compounds (VII-XIV).

3.5.1.3 Synthesis of 6-substituted-3-((4-substitutedphenyl)diazenyl)-2,4-dimethylquinoline (XV – XXII).

All these derivatives have disappearance of (C=O) groups due to closure of ring and disapearance of (-NH) st.vib group. C=C stretching band of aromatic rings appeared at 1489-1519 cm^{-1}. The absorption bands at 1589 -1677 cm^{-1}, 1149 -1190 cm^{-1} were attributed to the (-N=N-) and (C-N) stretching vibrations, these confirms the formation of the quinoline ring and diazenyl group in all the compounds (XV-XXII). Compounds XVII-XXII which contain NH_2 group show two stretching vibration absorption bands at range 3342-3257 $cm^{-1}$and 3369-3269 cm^{-1}.

3.5.2 Ultra Violet Spectroscopy Analysis (UV)

Ultra violet spectroscopy is the technique provides information about compounds with conjugated double bonds. UV spectroscopy was an important technique and was used to identify the key chromophore of an unknown molecule. Ultraviolet (UV) and visible (VIS) spectroscopy deals with the recording of the absorption of radiations in the ultraviolet and visible regions of the electromagnetic spectrum, the regions where wavelengths range from 200 nm to 800 nm (Pavia *et al.*, 2001). The UV-Vis spectra of Synthesis of 6-substituted-3-((4-substitutedphenyl) diazenyl)-2,4-dimethylquinoline (XV – XXII) recorded in 60 % ethanol. The λ max values are summarized in table (2.22). The absorption band positions broadly lie between 234-369 nm assignable to π -π* transitions due to the conjugated in quinoline moiety.

3.5.3 Nuclear magnetic resonance spectroscopy analysis (^{1}HNMR)

Nuclear magnetic resonance (NMR) is a spectroscopy method that its very important to the organic chemist than infrared spectroscopy because NMR gives information about the number of magnetically distict atoms of the type being studied, but the infrared spectroscopy deals the type of funtional groups find in a molecule, Whereas. (Pavia *et al.*, 2001).

^{1}HNMR tool of the NMR technique used in structure determination of the unknown molecules. It give information abuot the number, and the megantic environment of the each protone found the unknown molecule. The results were in δvalue (ppm), on which the resonance of the protone in DMSO, all compounds have the same structure but defferent in the substetuent (R, R_1). The ^{1}HNMR spectera of the synthesized quinoline derivatives (XV-XXII). All synthesized compounds (XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII) have three protone of methyl group (-CH_3) appeared as single (s) peak at the 2.31 – 2.87 ppm, and their aromatic protone in defferent invironmentwere apeared at exepted region and the bound of them was tabulated in table (2.23).

Compounds (XV, XVII, XVIII, XIX, XX, XXI, XXII)appeared CH-quinoline protoneas single, doupled, multiplied between range (7.99 – 9.14) ppm.

XX, XXI compounds exhibid two single (s) peak at 2.53 ppm and 2.51 ppm charasterctic of acetyl group (CH_3CO-link with aromatic ring.Six protone of three amino group (3NH_2) attached to XVII and XXII obsorbed as single peak at 5.78 - 6. 85 ppm.Compound XVII have one protone of carboxilic acid group (-COOH) which is appeared as single (s) peak at 8.94 ppm.

3.5.4 Mass Spectroscopy Analysis (MS)

Mass spectrometry is a powerful analytical technique used to quantify known materials, to identify unknown compounds within a sample, and to elucidate the structure and chemical properties of different molecules (Lapthorn *et al.,* 2013). Mass spectroscopy (MS) was used to detrmine the molecular wiegths of disubstetuted quinoline (XV-XXII). Amolecular ion peaks (M^+) was observed for all synthesized compounds in their respective mass spectra. Details of all synthesized compounds showed at [M^+], [M^++1], [M^++2] and [M^++4] the results were tabulated in table (2.24).

The M+1 and M+2 isotops peaks was obsorved in compounds (XVII - XXII). M+1 occur due to the presence of isotops ^{2}H, ^{13}C. M+2 (307.95) the isotope peak of one halogen atom (Cl) in compounds (XVI). Compounds XV, XVIII showing M+4 (329.00), (423.00) isotops peak due to this compounds have two halogen atom (Cl or Br) respectivly.

3.5. Conclusion and recommendation

The following points can be concluded from this study:

- ✓ QSAR model developed, and were statistically significant and predictive, and could be used for the design and synthesis of new antibacterial molecules against mycrobaterium tuberculosis (TB).
- ✓ Model showed that the anti-mycrobacterium tuberculosis (TB) activity was positivly correlated with charge-weighted areas (DCASA) and Log octanole/water partition coefficient (logP (o/w).
- ✓ The model obtained was used to predict the anti-mycrobacterim tuberculosis activity of designed 34 quinoline derivatives.
- ✓ 8 of 34 compounds selected for synthesized in synthetic part, including the intermediates. After the passing to Lipinsk's "rule of five".
- ✓ Molecular docking studies was carried out to investigate interaction between anti-mycrobacterim tuberculosis protein and synthesized disubstituted quinoline derivatives.
- ✓ The target compounds showed a good correlation between QSAR and docking results.
- ✓ The aromatic amine and acetyle acetone compounds were used as starting materials in the synthesis of the quinoline derivatives as target compounds.
- ✓ To synthesized of disubstituted quinoline derivatives (target compounds) were used combs quinoline reaction.
- ✓ The reaction of synthesized disubstituted quinoline derivatives were followed by TLC, melting point and their structure were characterized using spectroscopy analysis such as IR, UV, ^{1}HNMR and GC-MS.
- ✓ The target compounds were evaluated for their antimacrobial activity.
- ✓ The optained results were agreed well with the optained designed and synthised compounds results.

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Appendixes

APPENDIXES

Appendix A: Spectroscopic analysis figures:

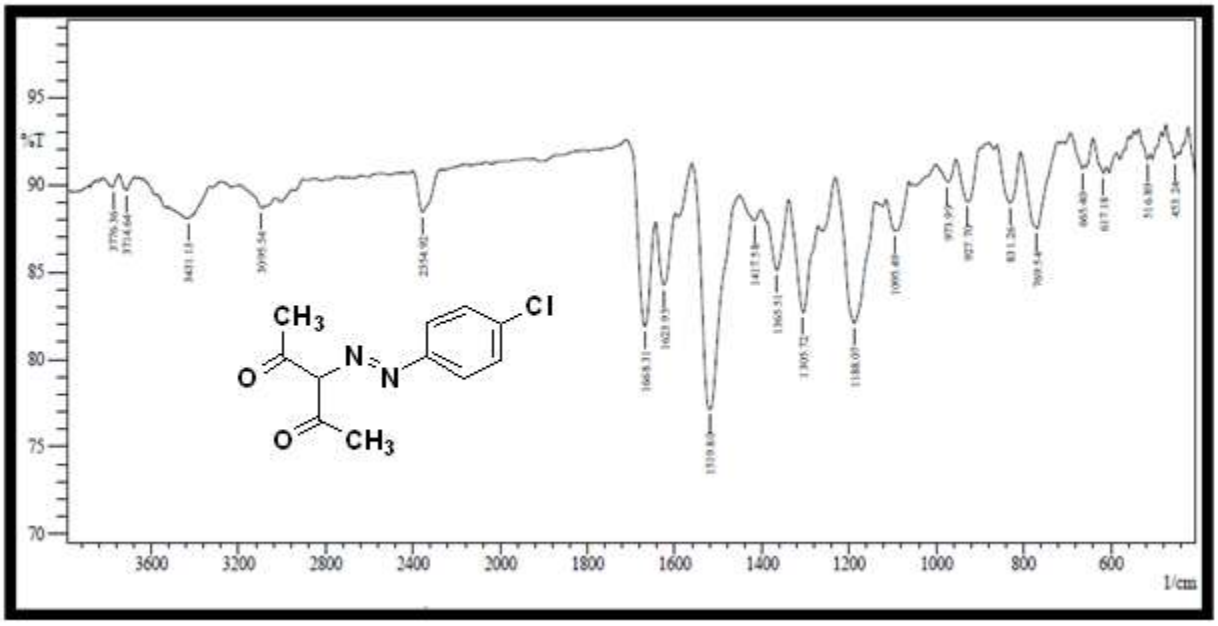

Figure (4.1): IR Spectrum of (*E*)-3-((4-Chlorophenl)diazenyl)pentane-2,4-dione (I).

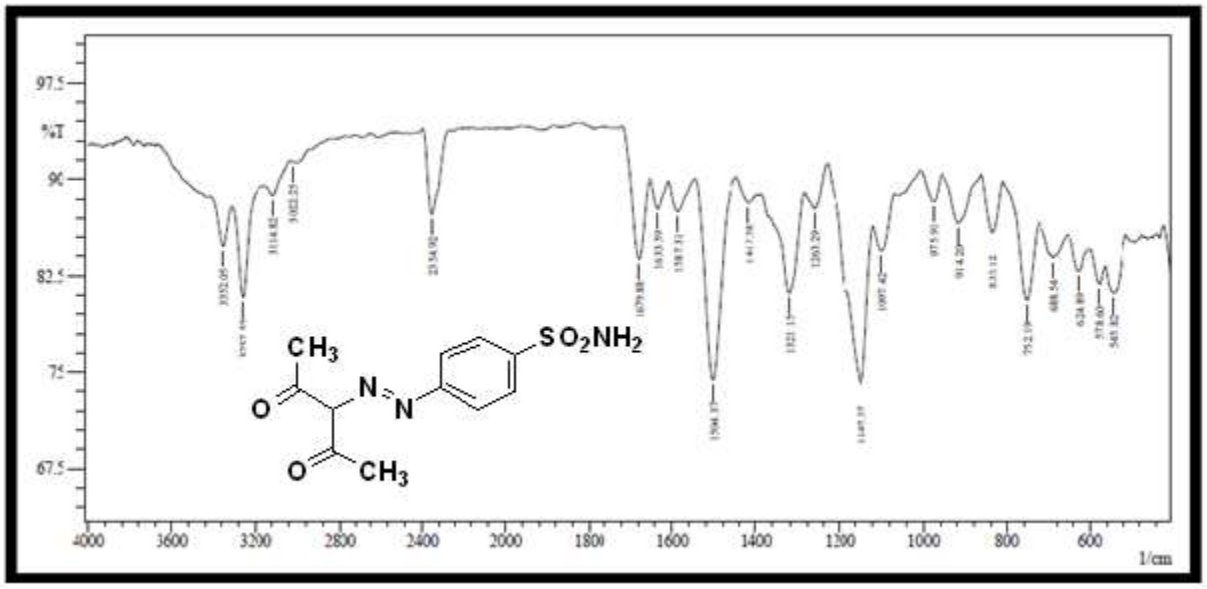

Figure (4.2): IR Spectrum of (*E*)-4-((2,4-dioxopentan-3-yl)diazenyl)benzene sulfonamide (II).

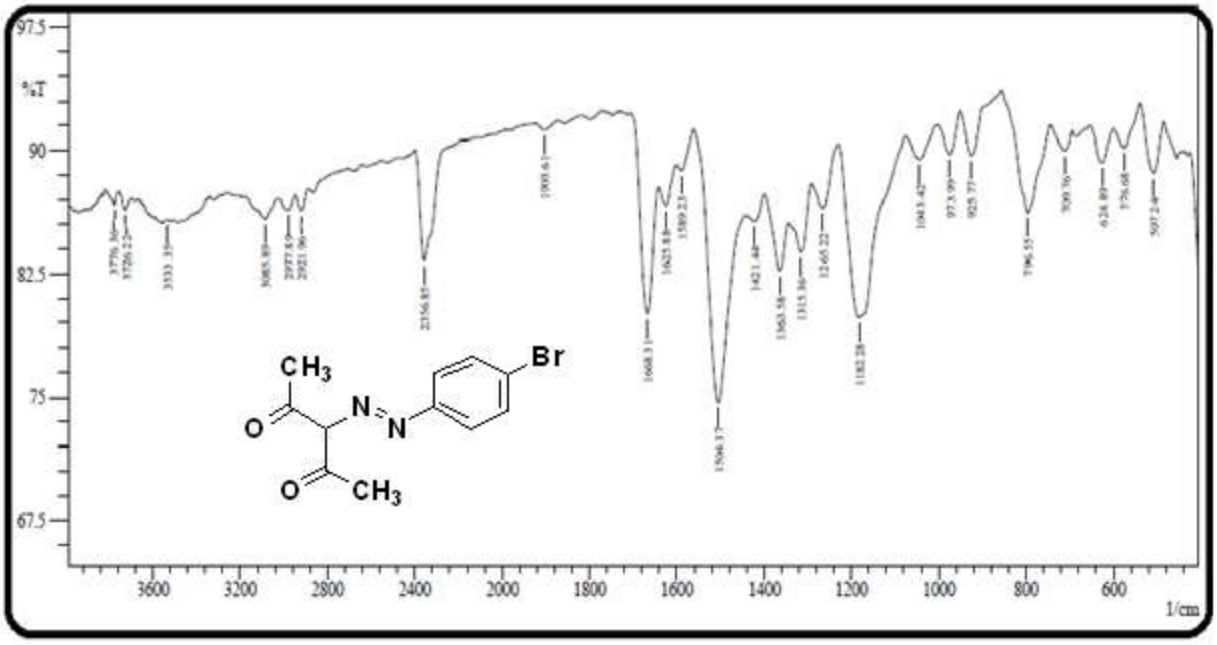

Figure (4.3): IR Spectrum of (*E*)-3-((4-bromophenyl)diazenyl)pentane-2,4-dione (III).

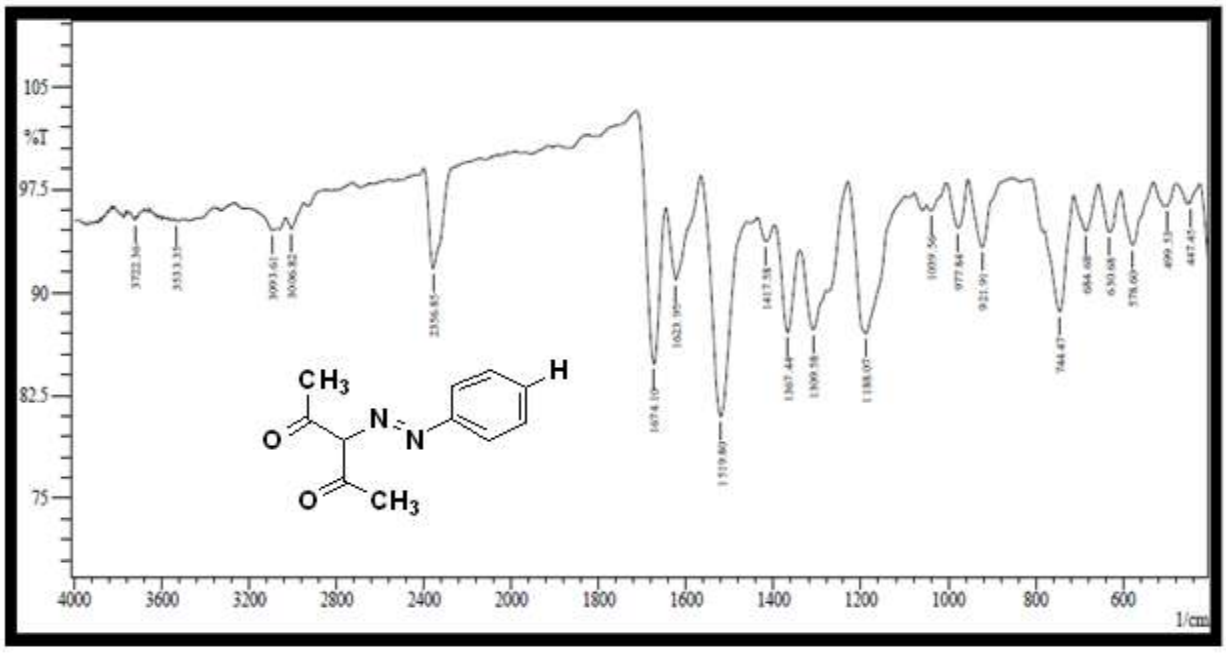

Figure (4.4): IR Spectrum of (*E*)-3-(phenyldiazenyl)pentane-2,4-dione (IV).

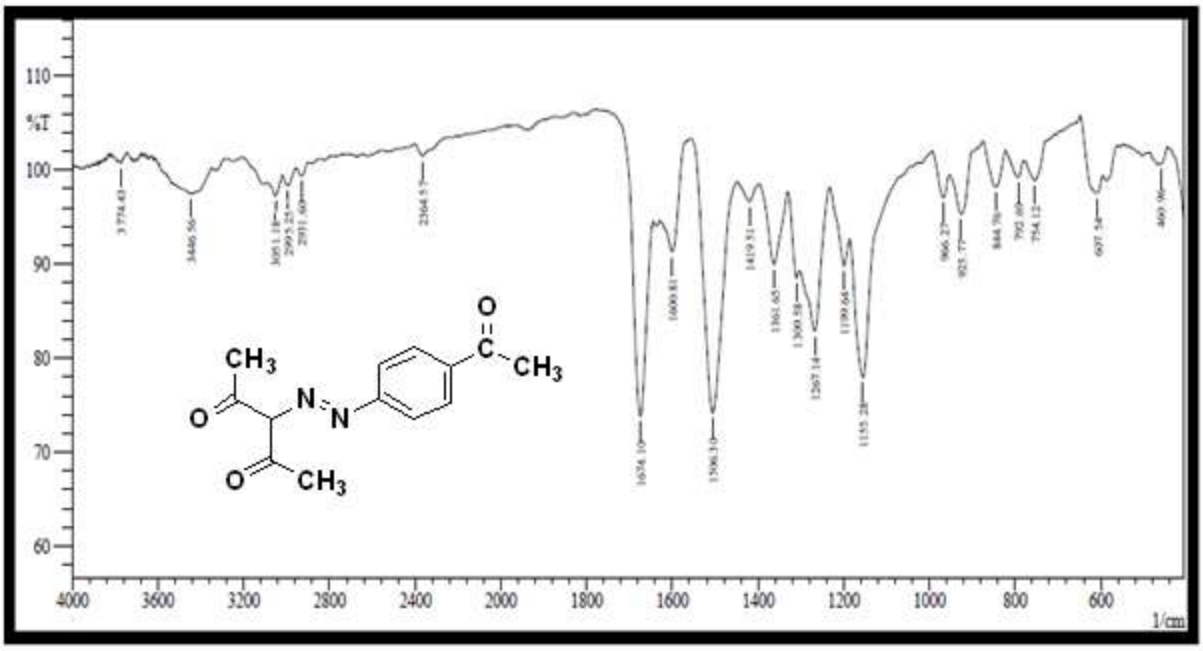

Figure (4.5): IR Spectrum of (*E*)-3-((4-acetylphenyl)diazenyl)pentane-2,4-dione (V).

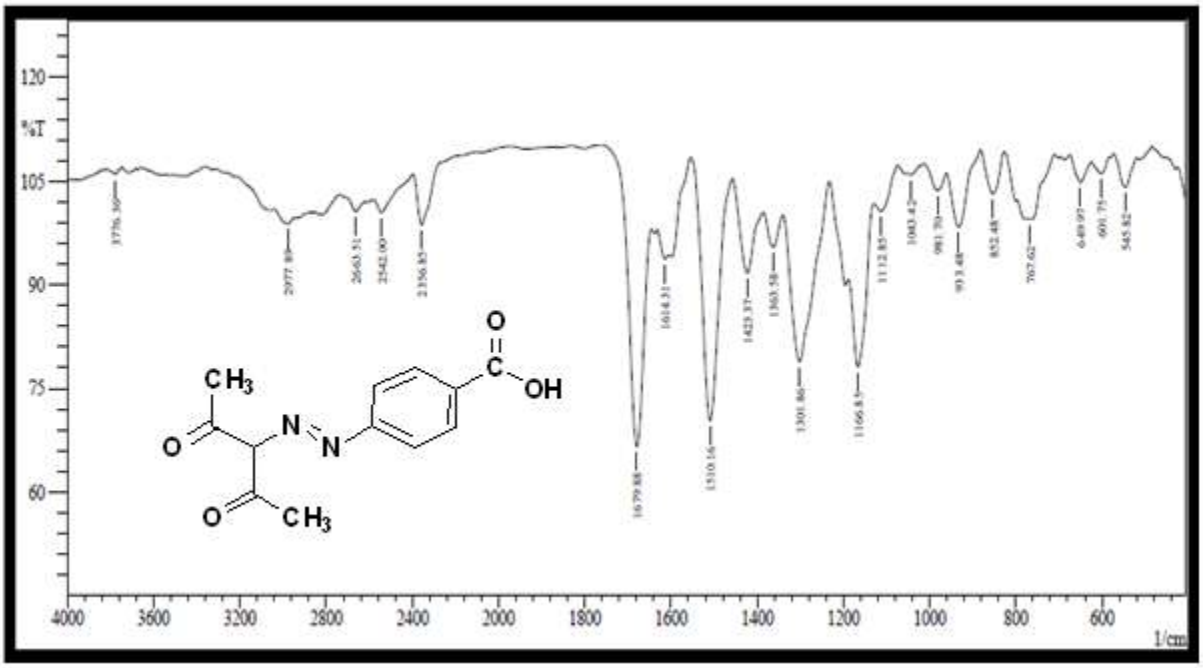

Figure (4.6): IR Spectrum of (*E*)-4-(2-(2,4-dioxopentan-3-yl)diazenyl)benzoic acid (VI).

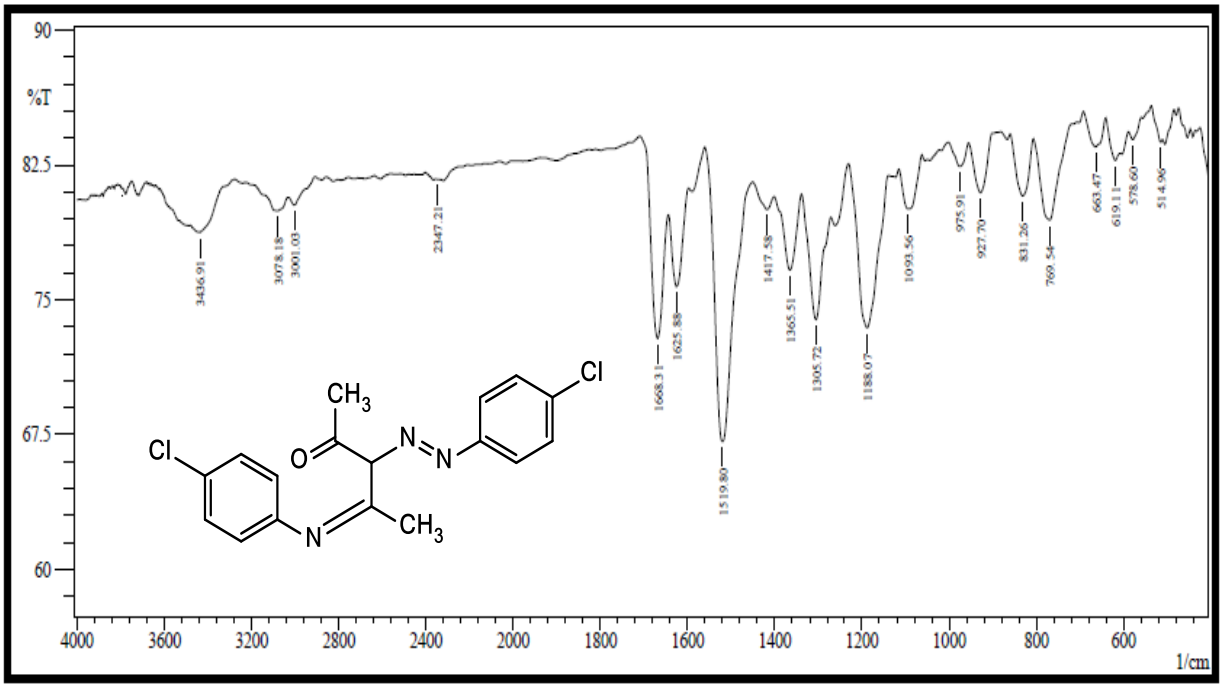

Figure (4.7): IR Spectrum of (Z)-3-(E) -(4-chlorophenyl)diazinyl)-4-((4-chlorophenyl) imino) pentan-2-one (VII).

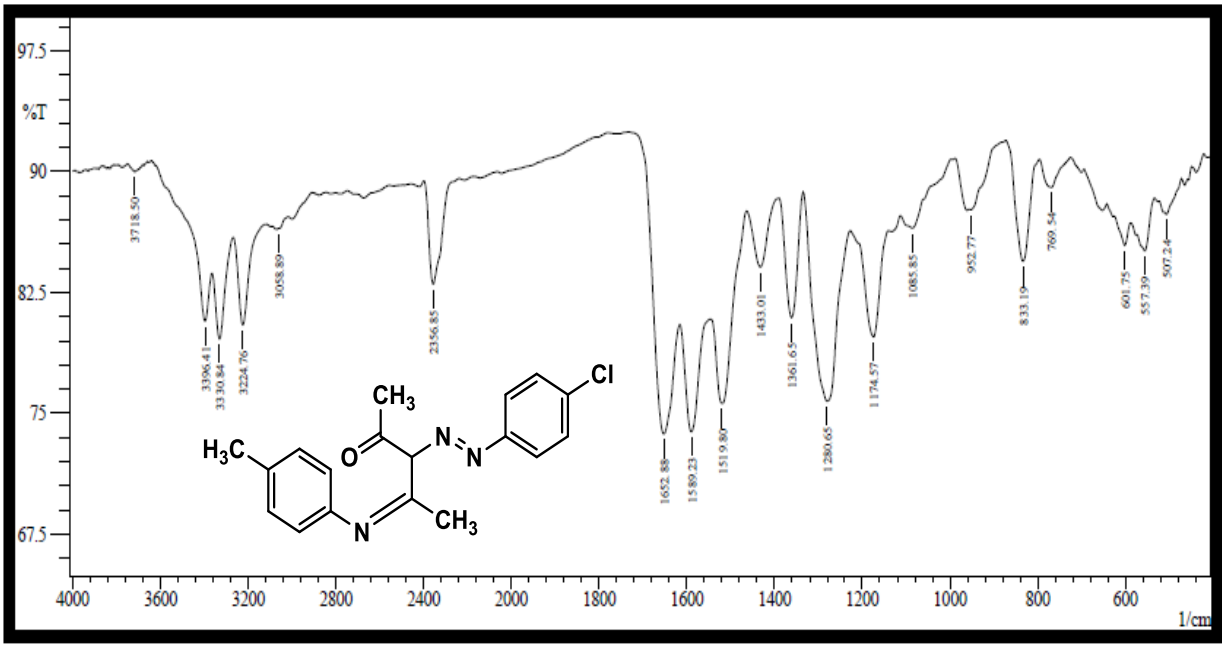

Figure (4.8): IR Spectrum of (Z)-3-((E)-(4-chlorophenyl) diazinyl)-4-(p-tolylimino) pentan-2-one (VIII)

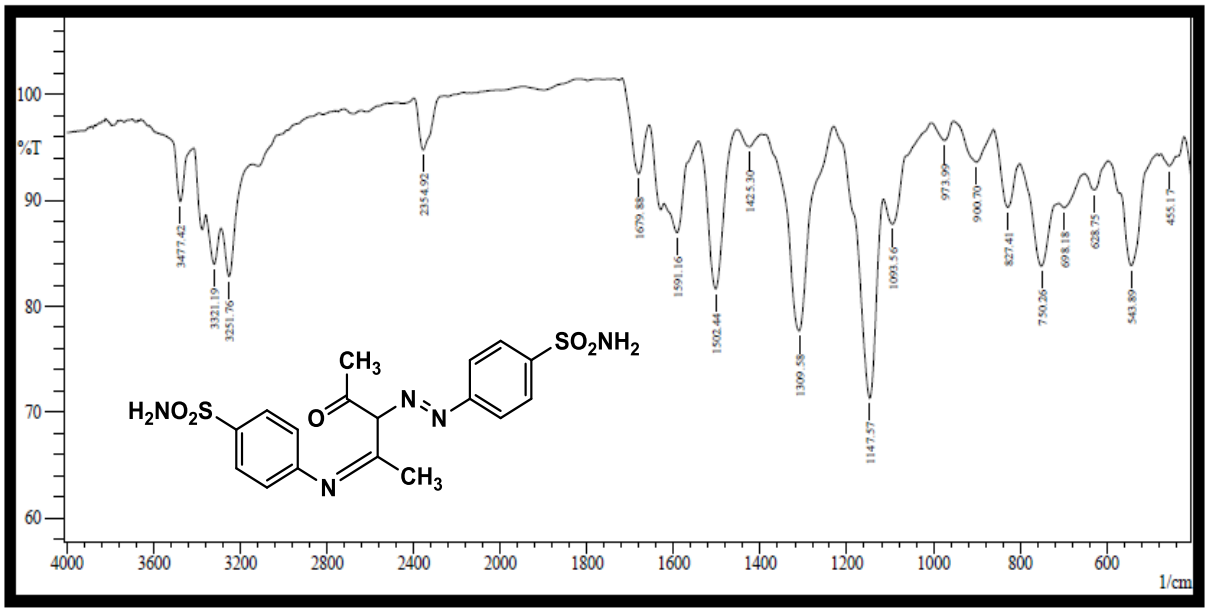

Figure (4.9): IR Spectrumof4-(((Z)-4-oxo-3-((E)-(4-sulfamoyophenyl)diazenyl) pentan-2-ylidene) amino) benzene sulfonamide (IX).

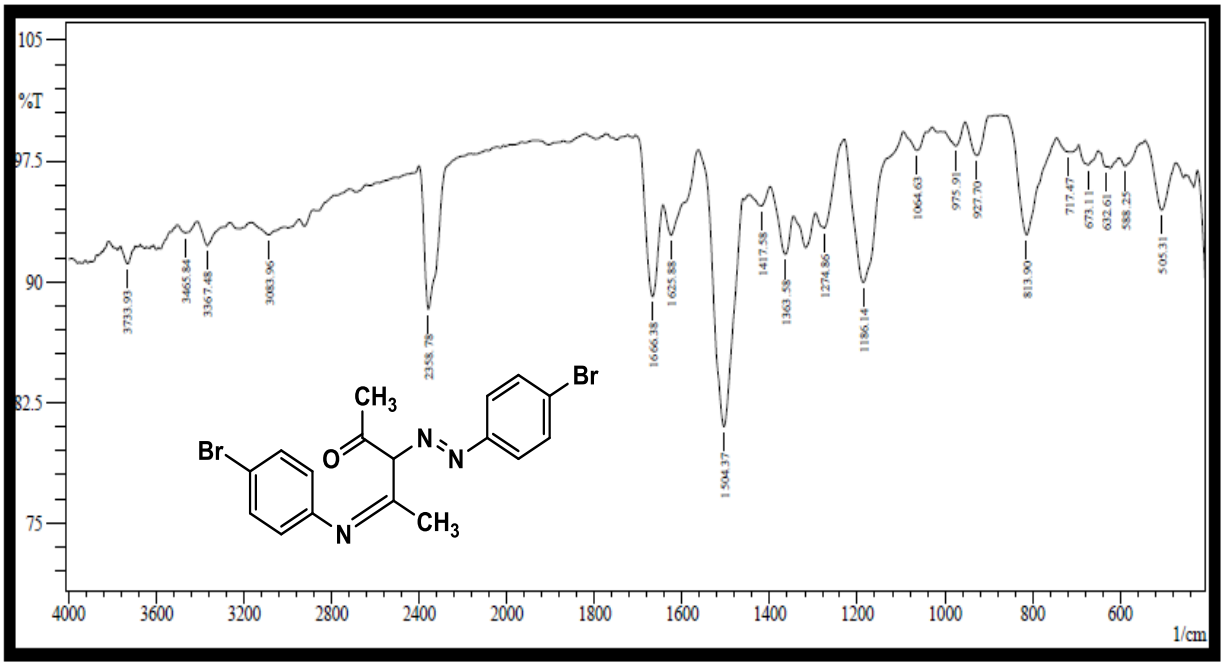

Figure (4.10): IR Spectrum of (Z)-((E)-(4-bromophenyl) diazenyl)-4-((4-bromophenyl) imino) pentane-2-one (X).

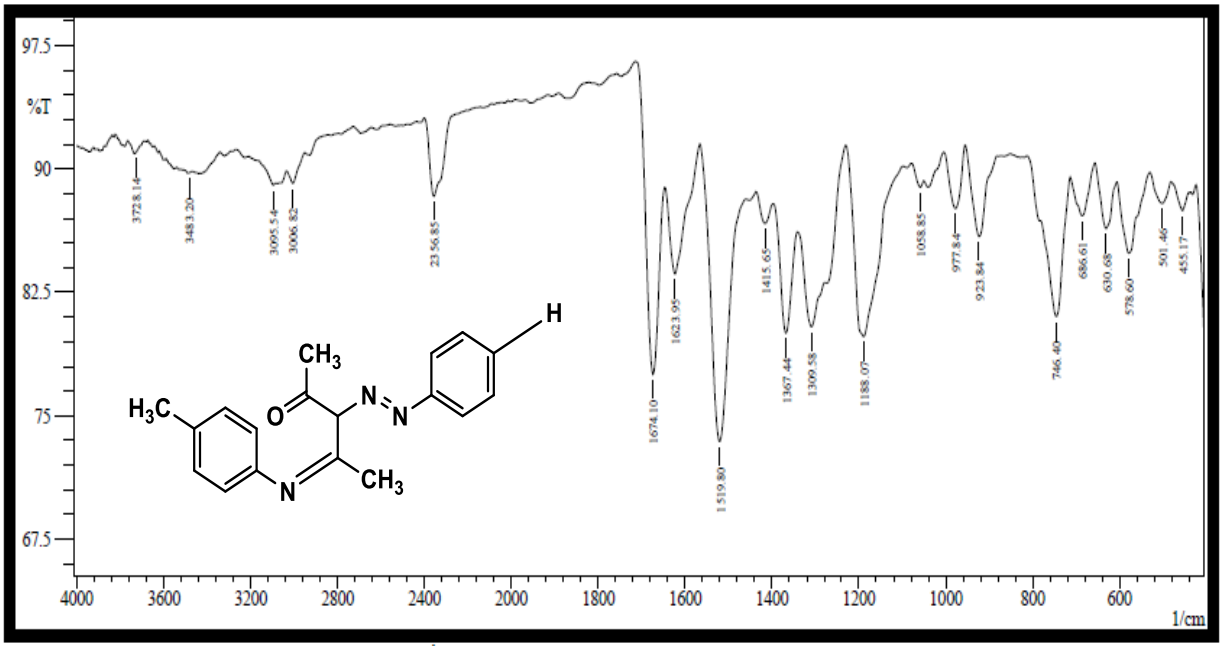

Figure (4.11): IR Spectrum of (Z)-3-((E)-phenyldiazenyl)-4-(p-tolylimino) pentane-2-one (XI)

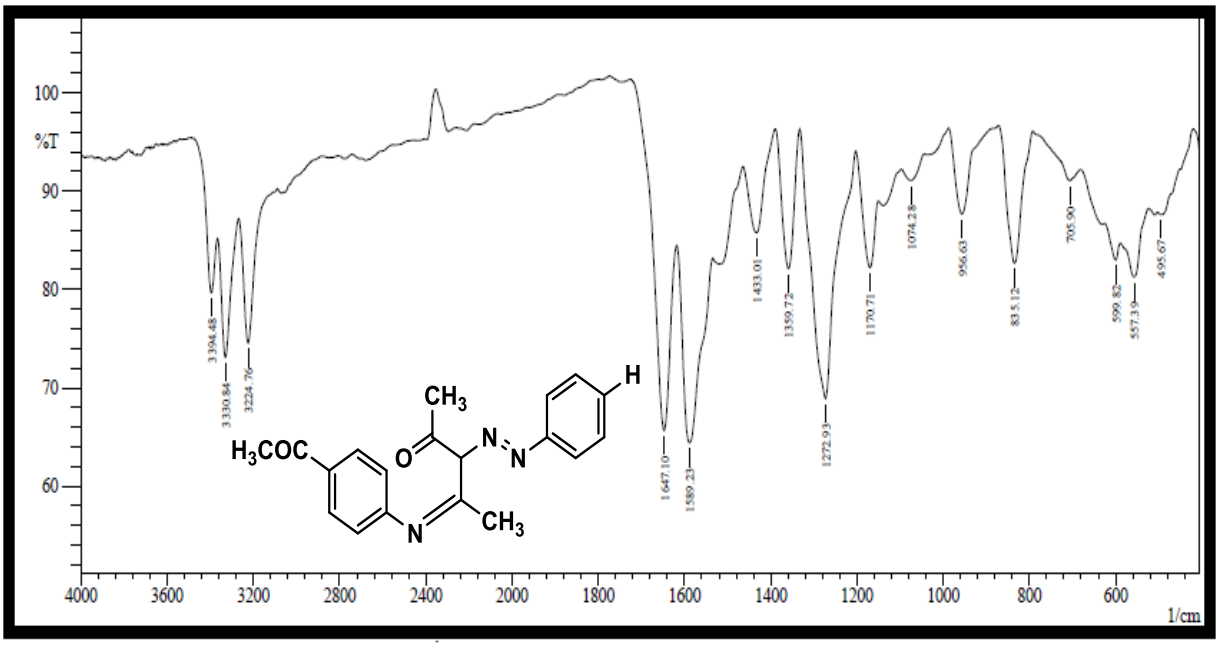

Figure (4.12): IR Spectrum of(Z)-4-((4-acetylphenyl) imino)-3-((E)-phenyldiazenyl) pentan-2-one (XII)

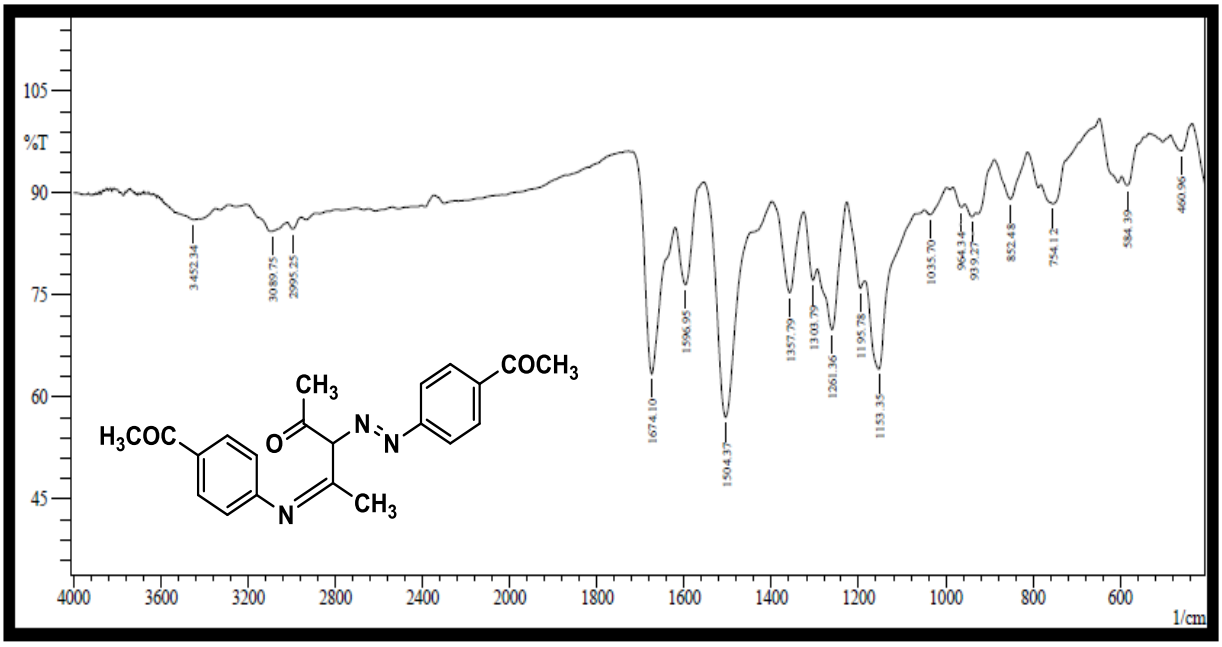

Figure (4.13): IR Spectrum of(Z)-3-((E)-(4-acetylphenyl) diazenyl)-4-((4-acetylphenyl) imino) pentane-2-one (XIII)

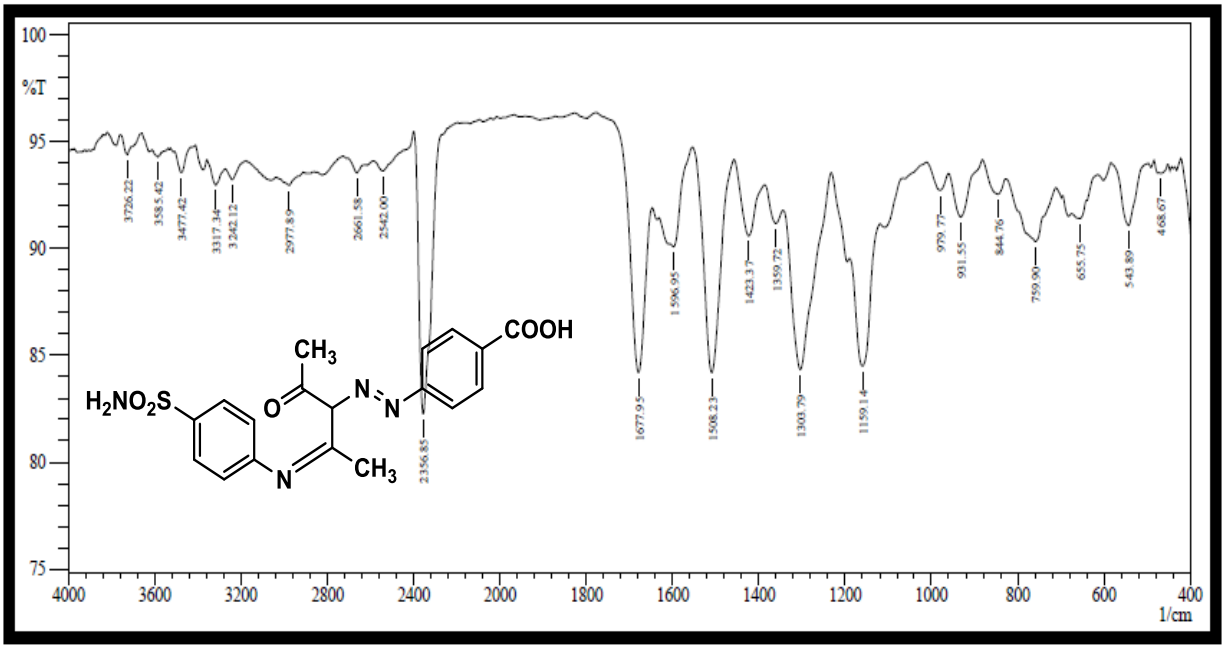

Figure (4.14): IR Spectrum of4-((E)-((Z)-2-oxo-4-((4-sulfamoylphenyl) imino) pentan-3-yl) diazenyl) benzoic acid (XIV).

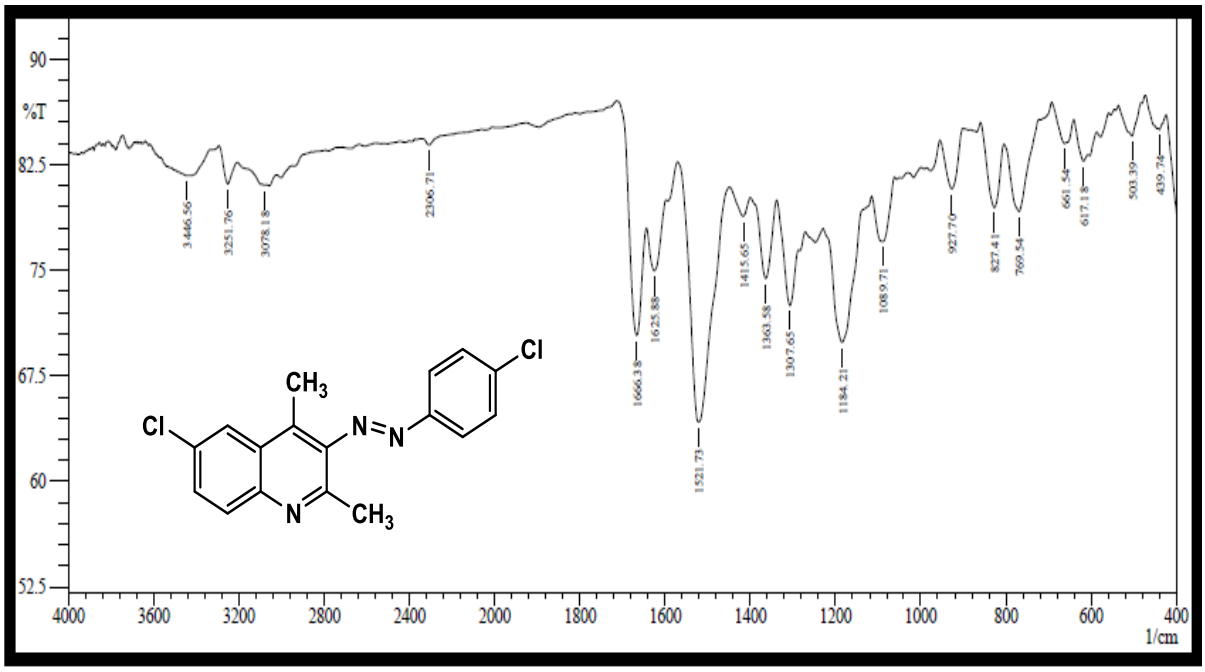

Figure (4.15): IR Spectrum of (E)-6-chloro-3-((4-chlorophenyl) diazenyl)-2,4-dimethyl quinoline (XV)

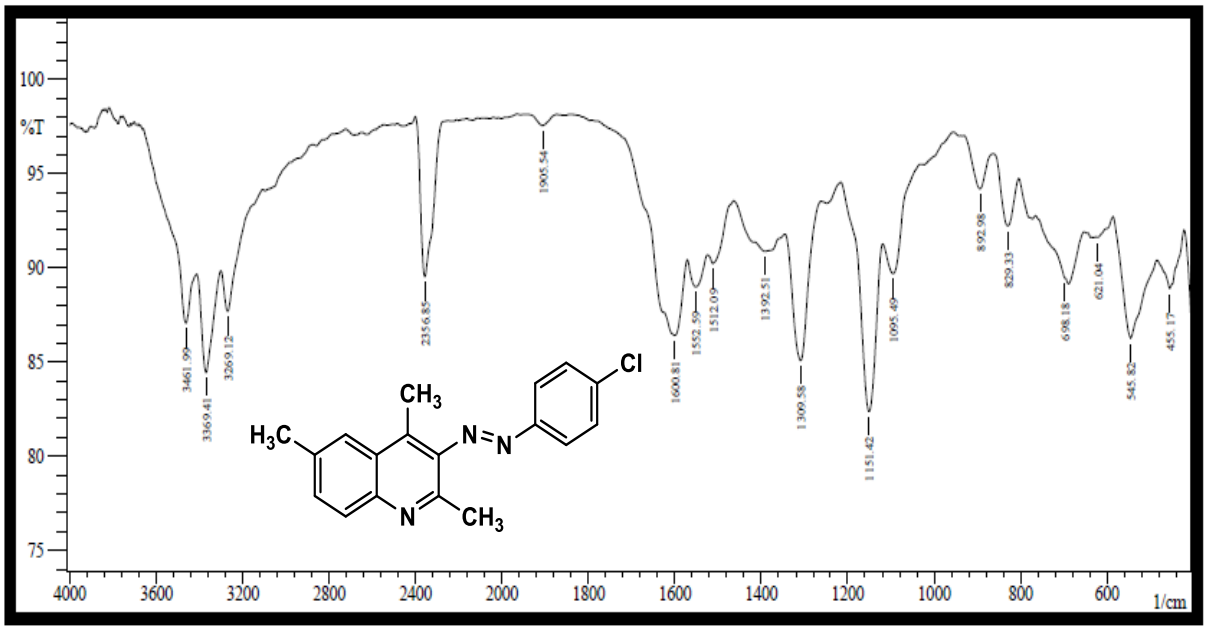

Figure (4.16): IR Spectrum of (E)-3-((4-chlorophenyl) diazenyl)-2,4,6-trimethylquinoline (XVI)

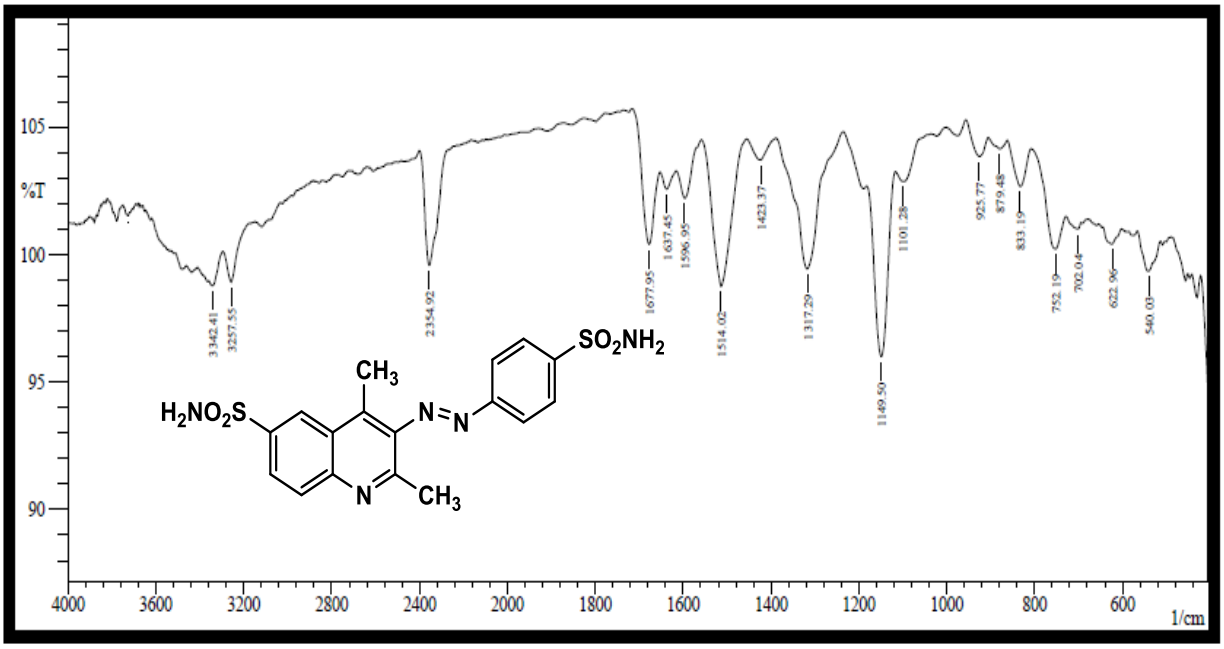

Figure (4.17): IR Spectrum of (E)-2,4-dimethyl-3-((4-sulfamoylphenyl) diazenyl) quinoline-6-sulfonamide (XVII)

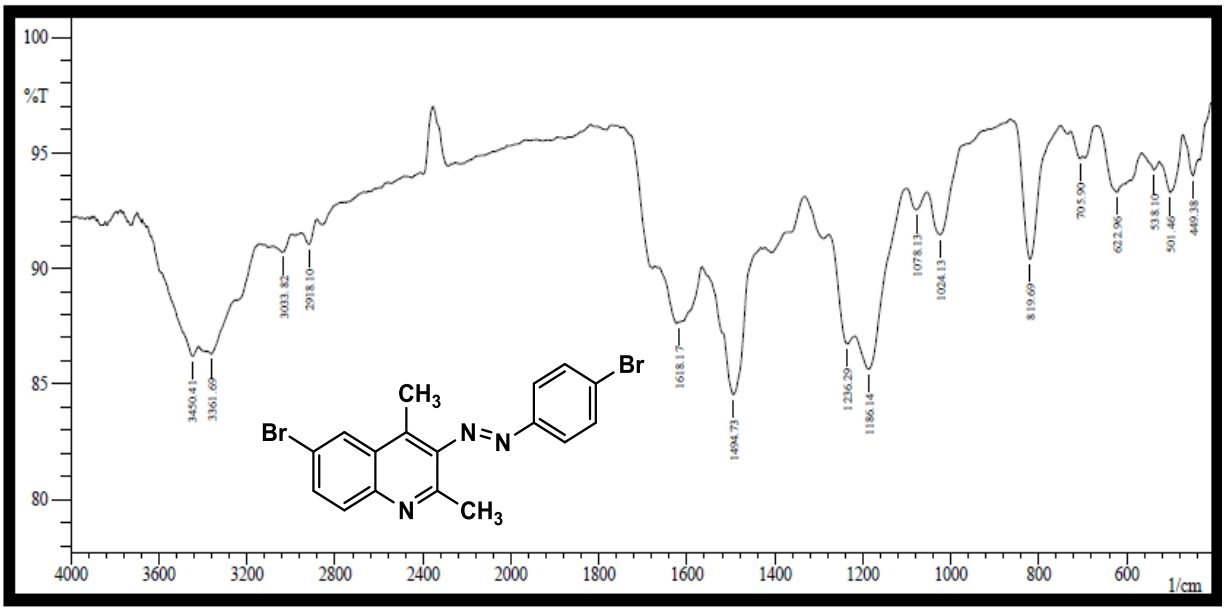

Figure (4.18): IR Spectrum of (E)-6-bromo-3-((4-bromophenyl) diazenyl)-2,4-dimethylquinoline (XVIII)

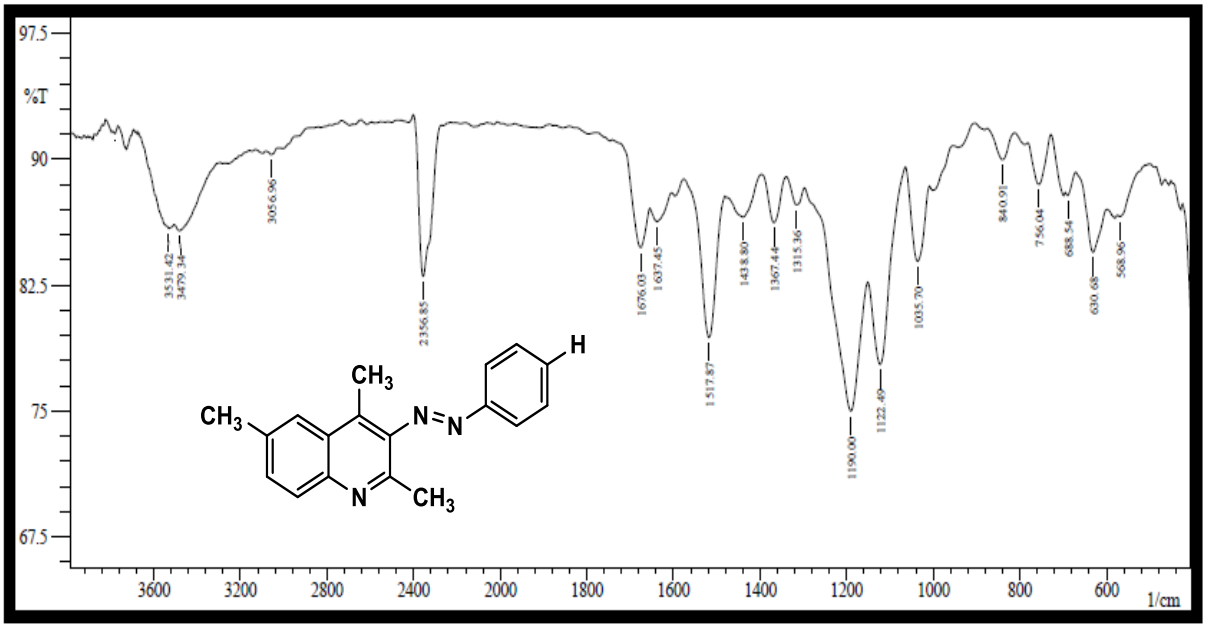

Figure (4.19): IR Spectrum of (E)-2,4,6-trimethyl-3-(phenyldiazenyl) quinoline (XIX)

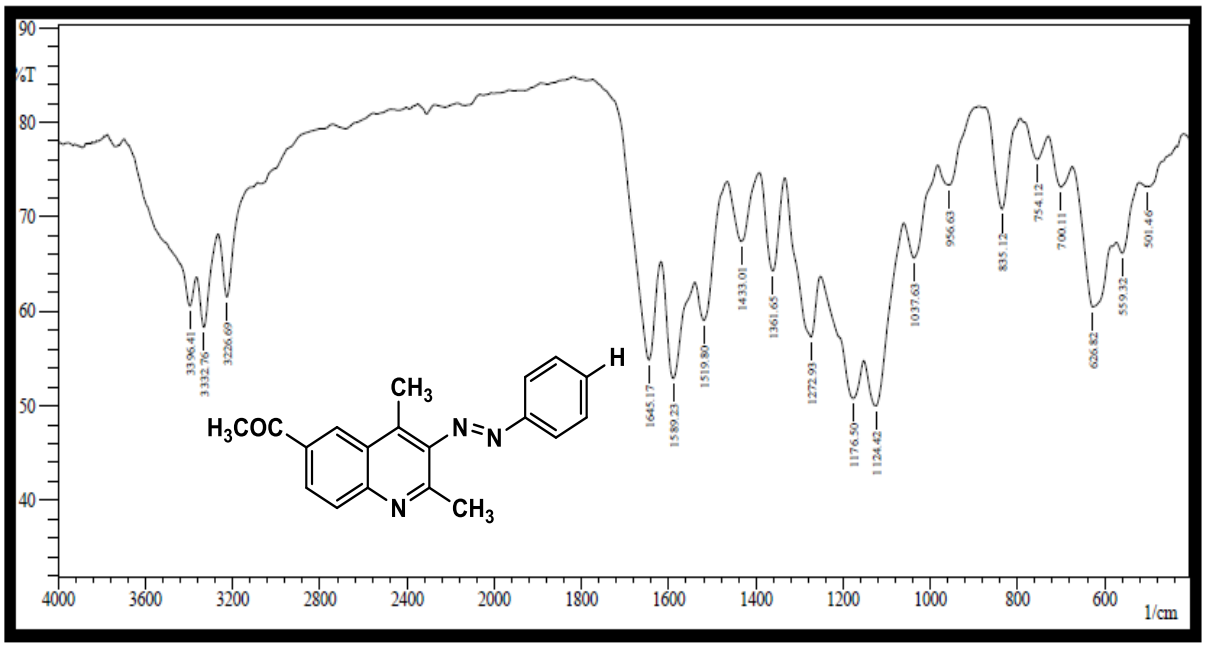

Figure (4.20): IR Spectrum of (E)-1-(2,4-dimethyl-3-(phenyldiazenyl) quinoline-6-yl) ethan-1-one (XX)

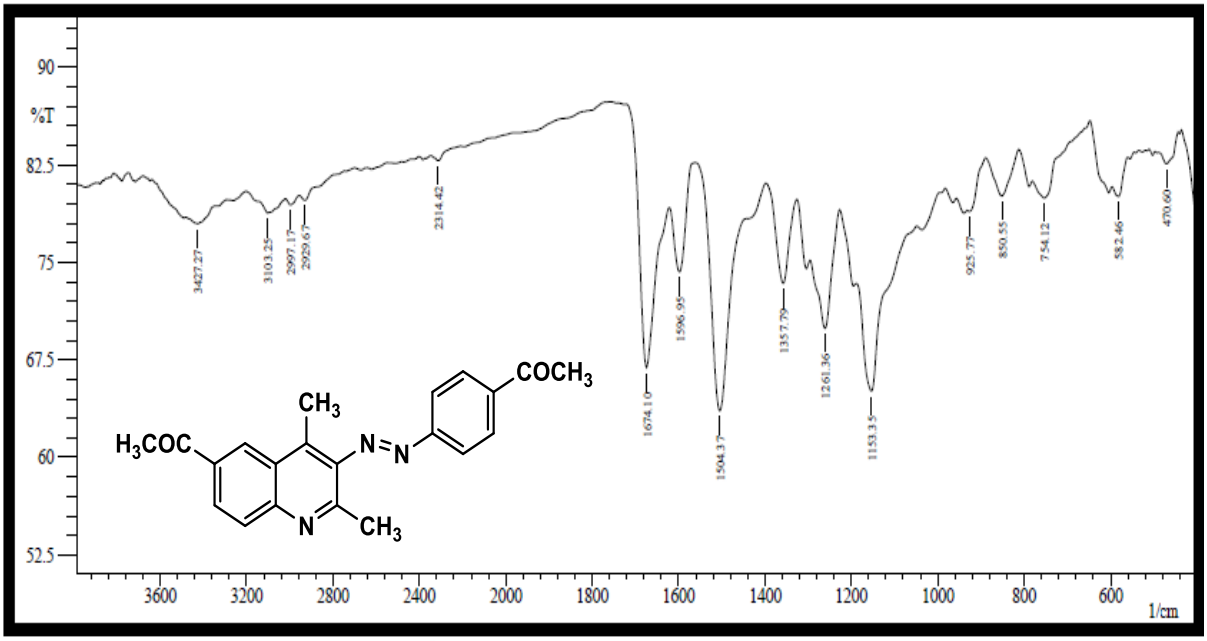

Figure (4.21): IR Spectrum of (E)-1-(-4-((6-acetyl-2,4-dimethylquinoline-3-yl) diazenyl) phenyl) ethan-1-one (XXI)

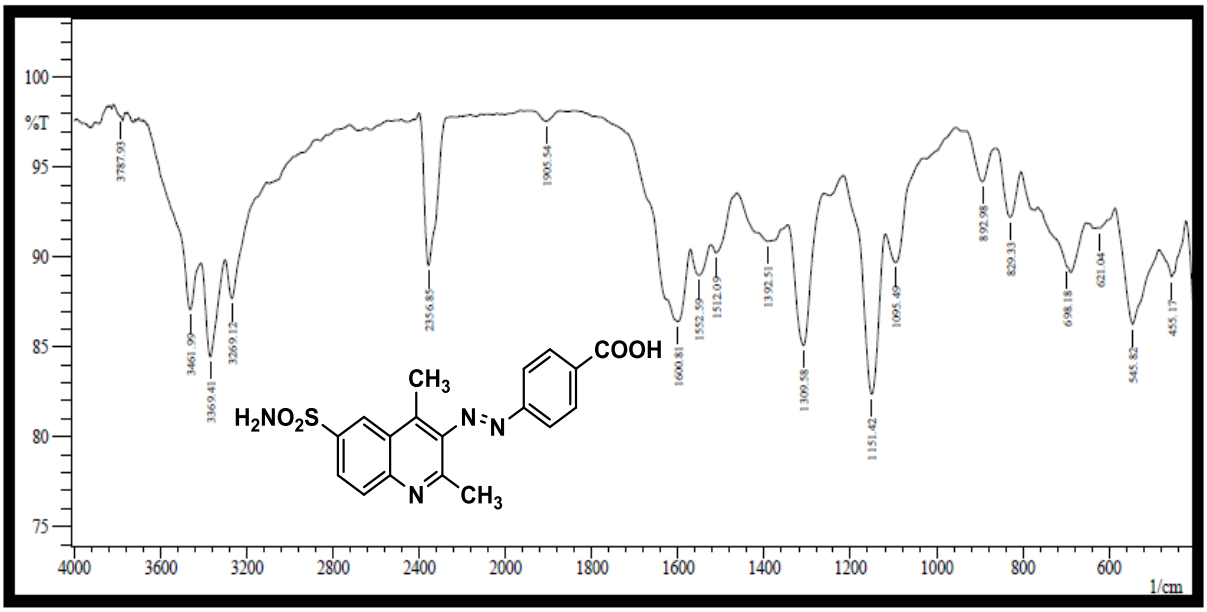

Figure (4.22): IR Spectrum of (E)-4-((2,4-dimethyl-6-sulfamoylquinoline-3-yl) diazenyl) benzoic acid (XXII)

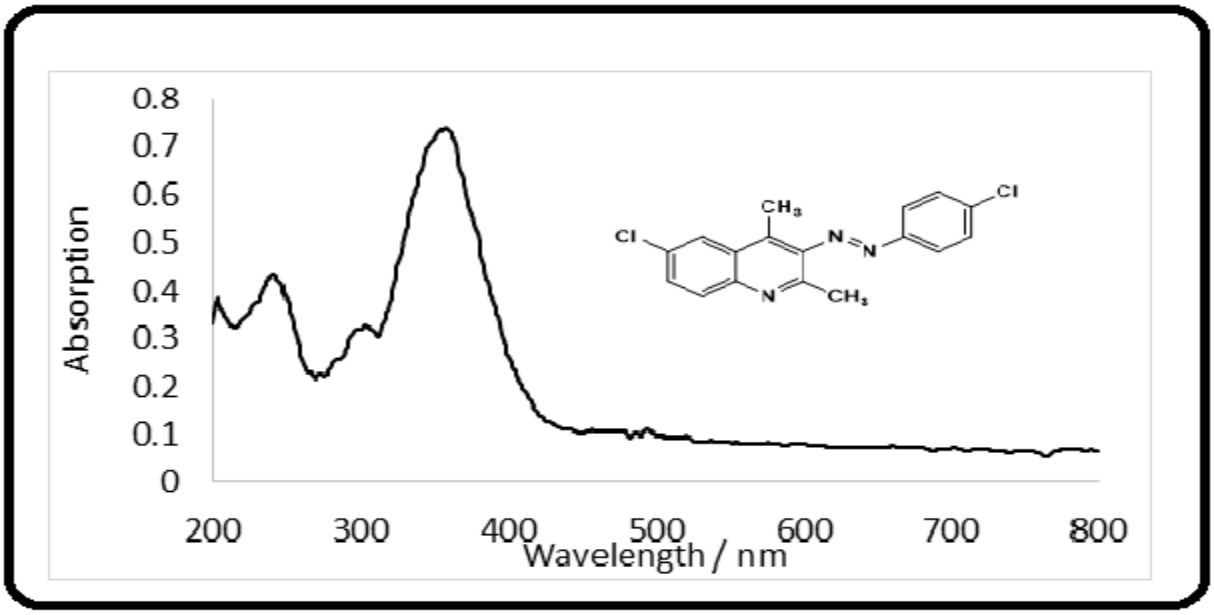

Figure (4.23): UV Spectrum of (E)-6-chloro-3-((4-chlorophenyl) diazenyl)-2,4-dimethylquinoline (XV).

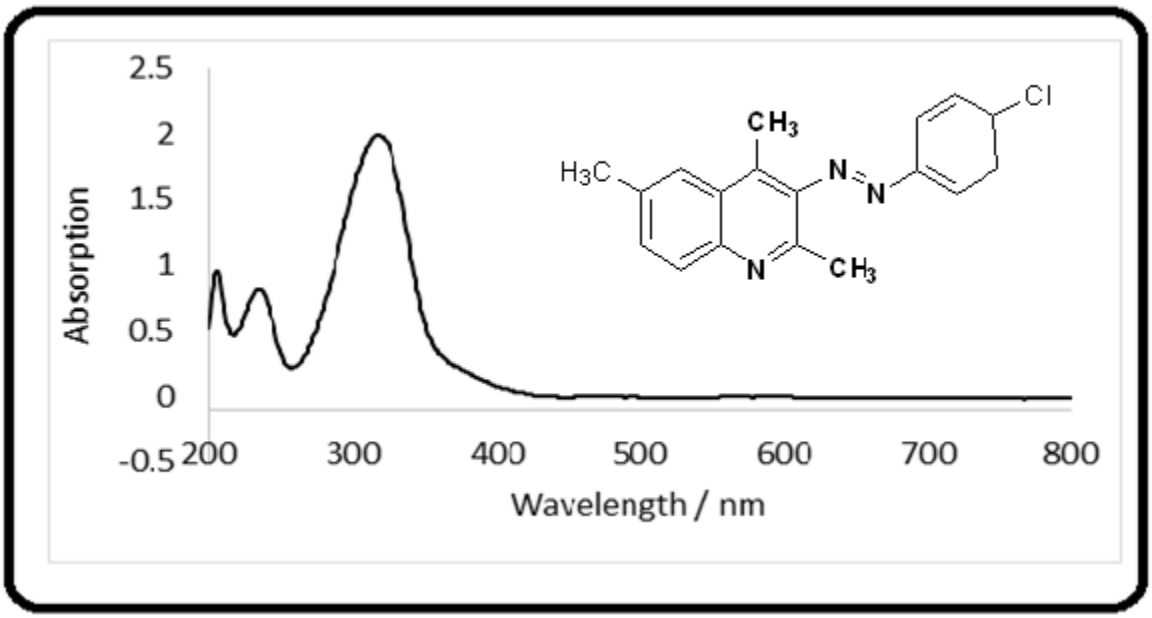

Figure (4.24): UV Spectrum of(E)-3-((4-chlorophenyl) diazenyl)-2,4,6-trimethylquinoline (XVI).

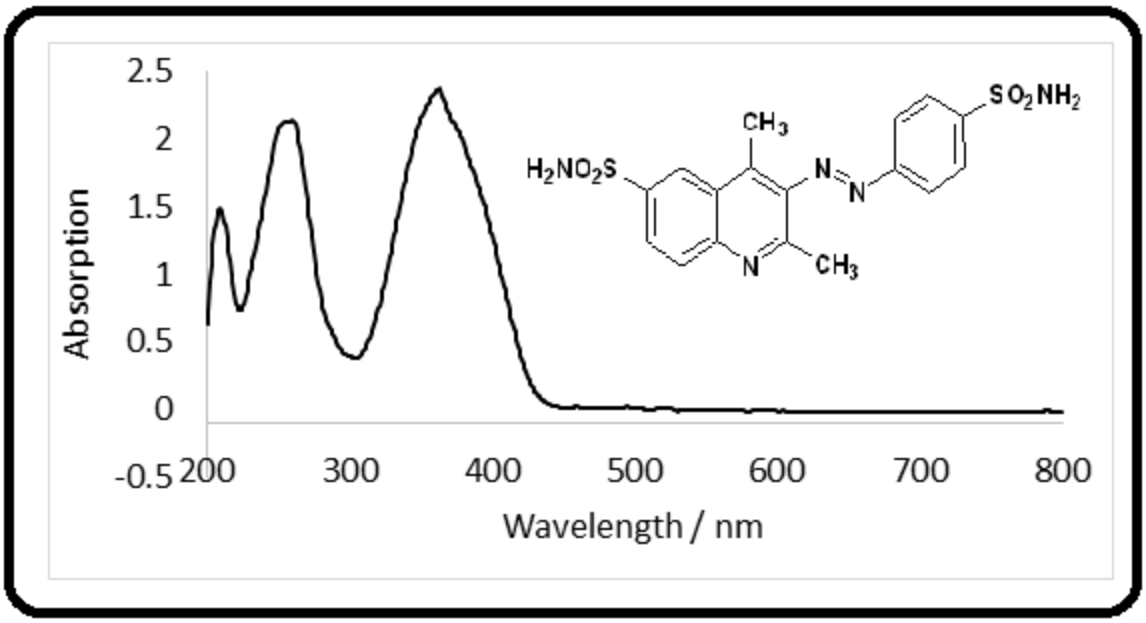

Figure (4.25): UV Spectrumof(E)-2,4-dimethyl-3-((4-sulfamoylphenyl) diazenyl) quinoline-6-sulfonamide (XVII)

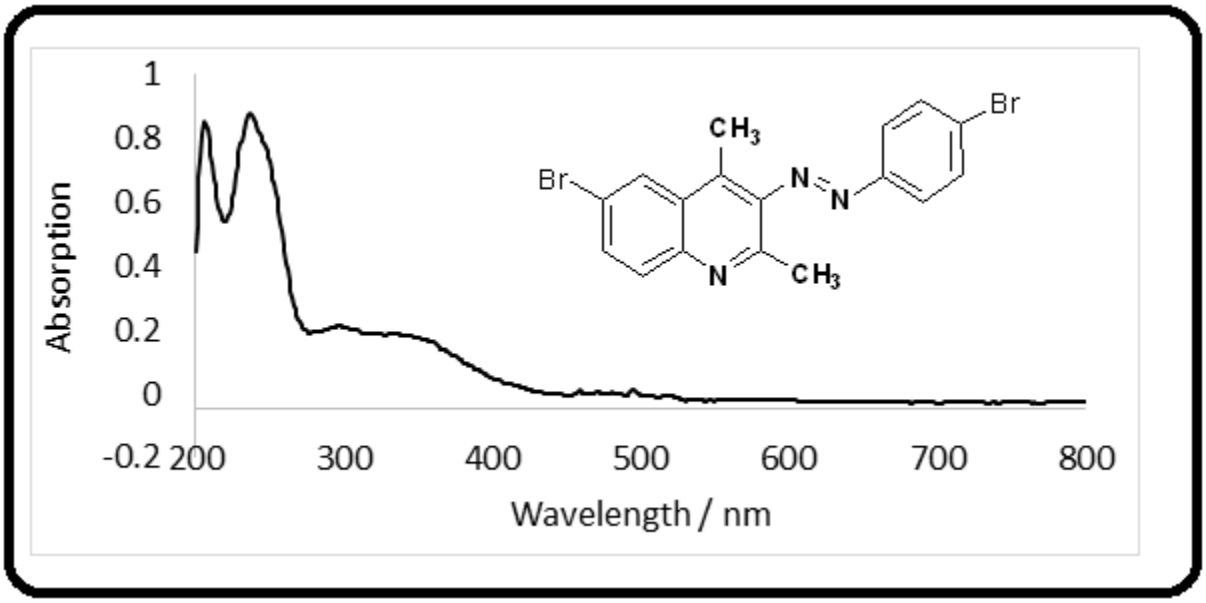

Figure (4.26): UVSpectrumof(E)-6-bromo-3-((4-bromophenyl) diazenyl)-2,4-dimethylquinoline (XVIII)

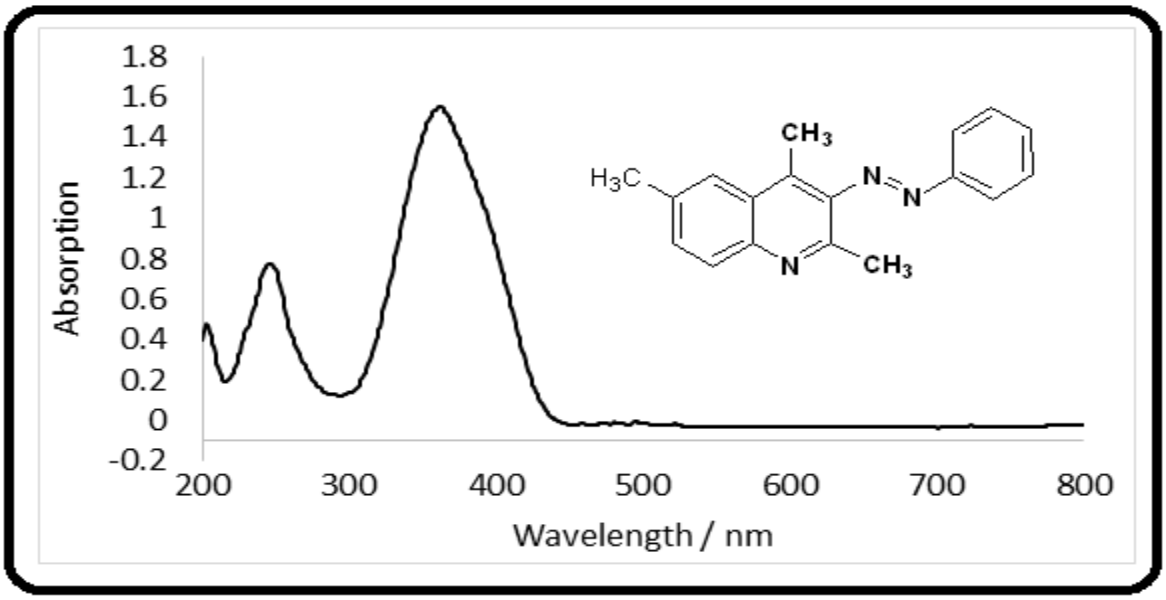

Figure (4.27): UV Spectrum of(E)-2,4,6-trimethyl-3(phenyldiazenyl)quinoline (XIX)

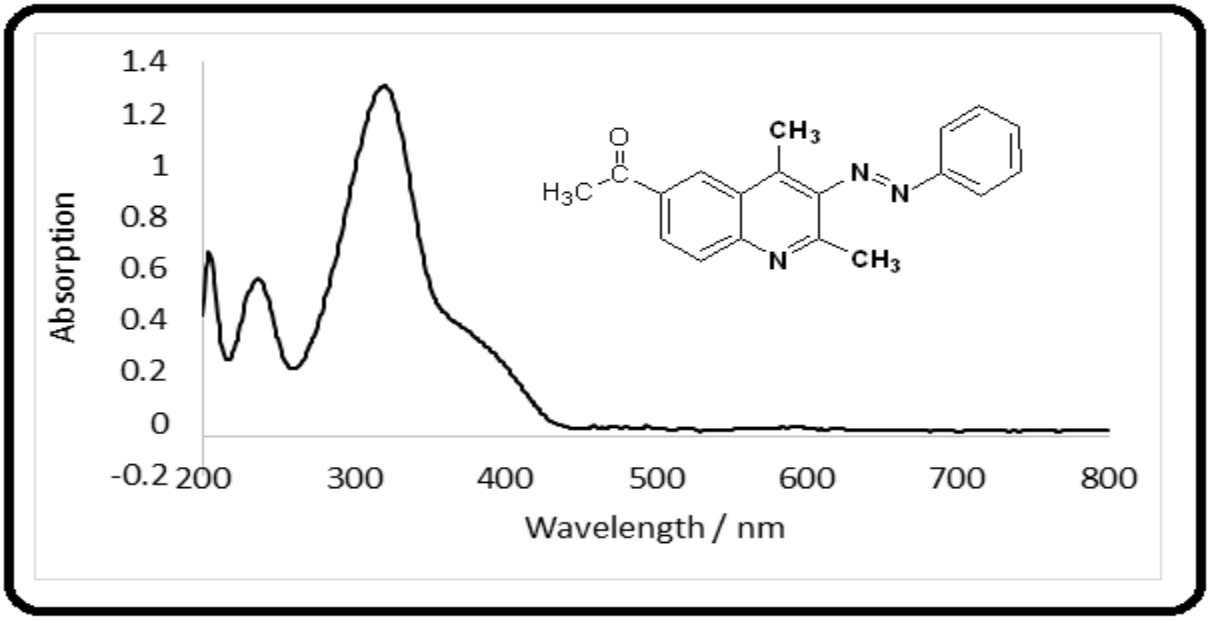

Figure (4.28): UV Spectrum of (E)-1-(2,4-dimethyl-3-(phenyldiazenyl)quinoline-6-yl) ethan-1-one (XX).

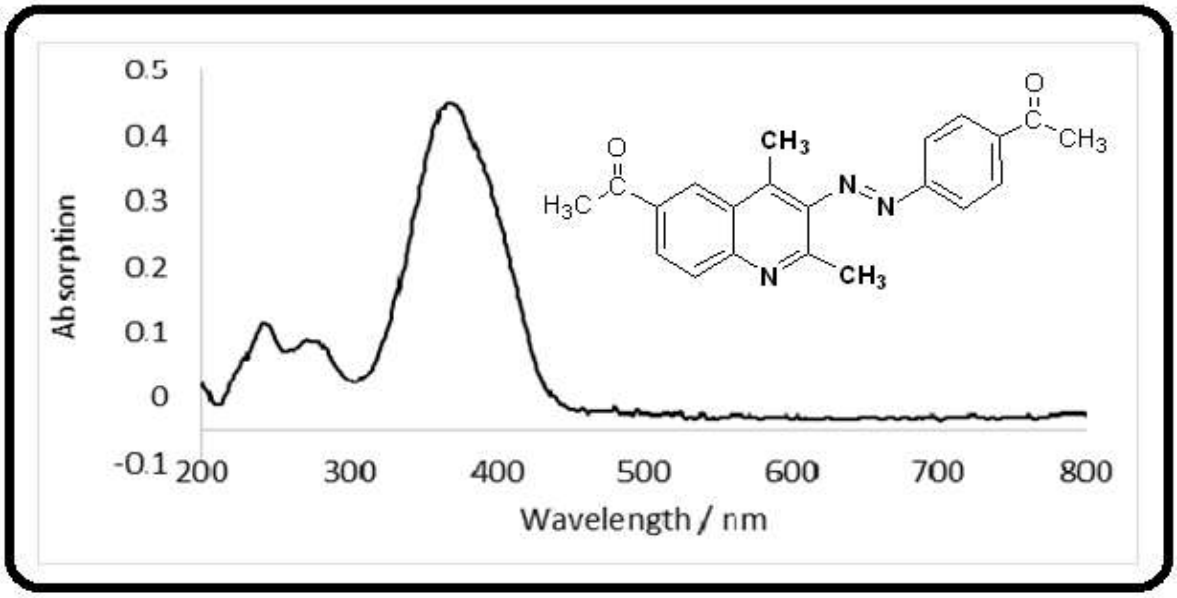

Figure (4.29): UV Spectrum of (E)-1-(-4-((6-acetyl-2,4-dimethylquinoline-3-yl) diazenyl) phenyl) ethan-1-one (XXI).

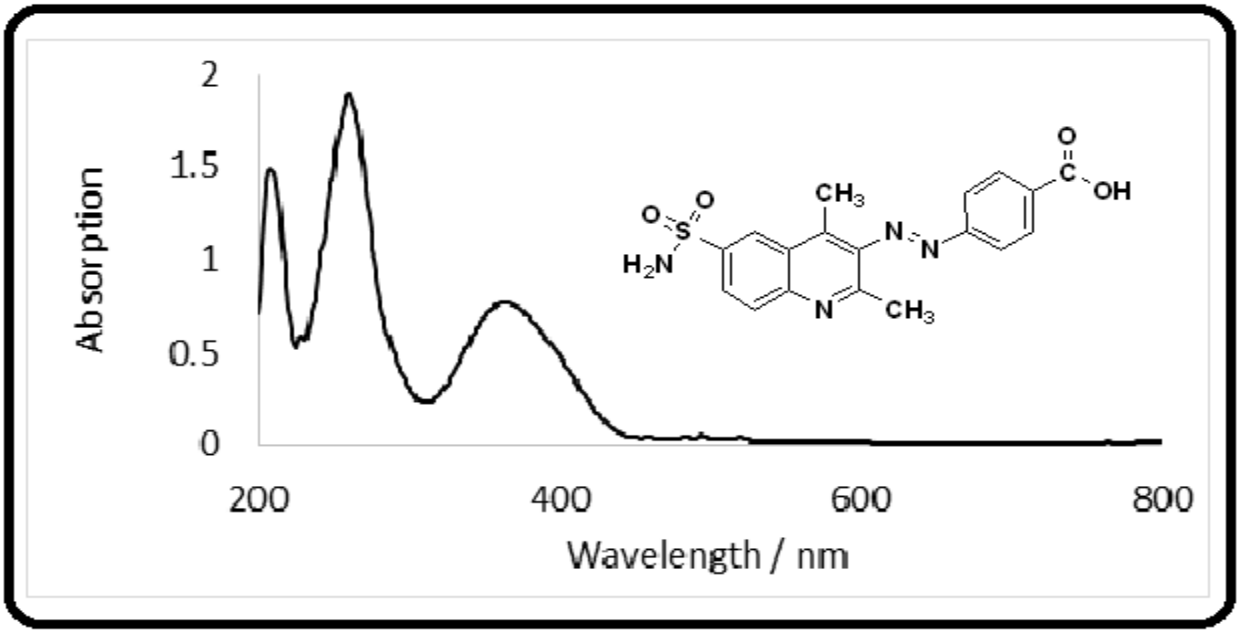

Figure (4.30): UV Spectrum of (E)-4-((2,4-dimethyl-6-sulfamoylquinoline-3-yl) diazenyl)benzoic acid (XXII).

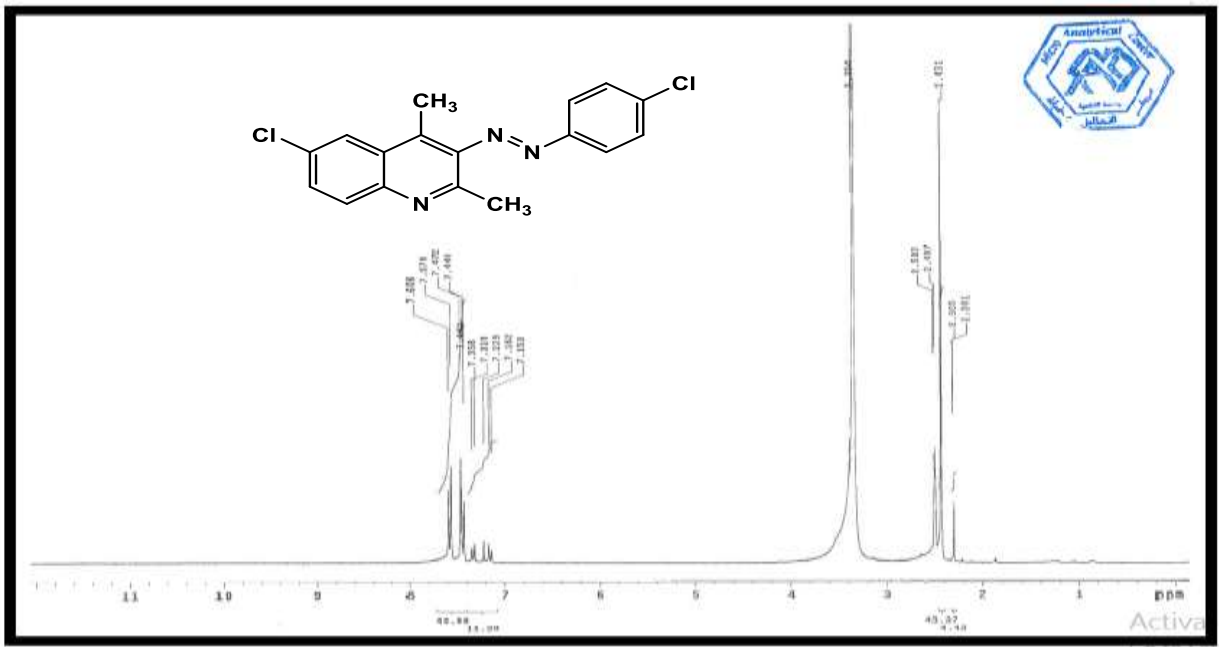

Figure (4.31): [1]HNMR Spectrum of (E)-6-chloro-3-((4-chlorophenyl) diazenyl)-2,4-dimethylquinoline (XV)

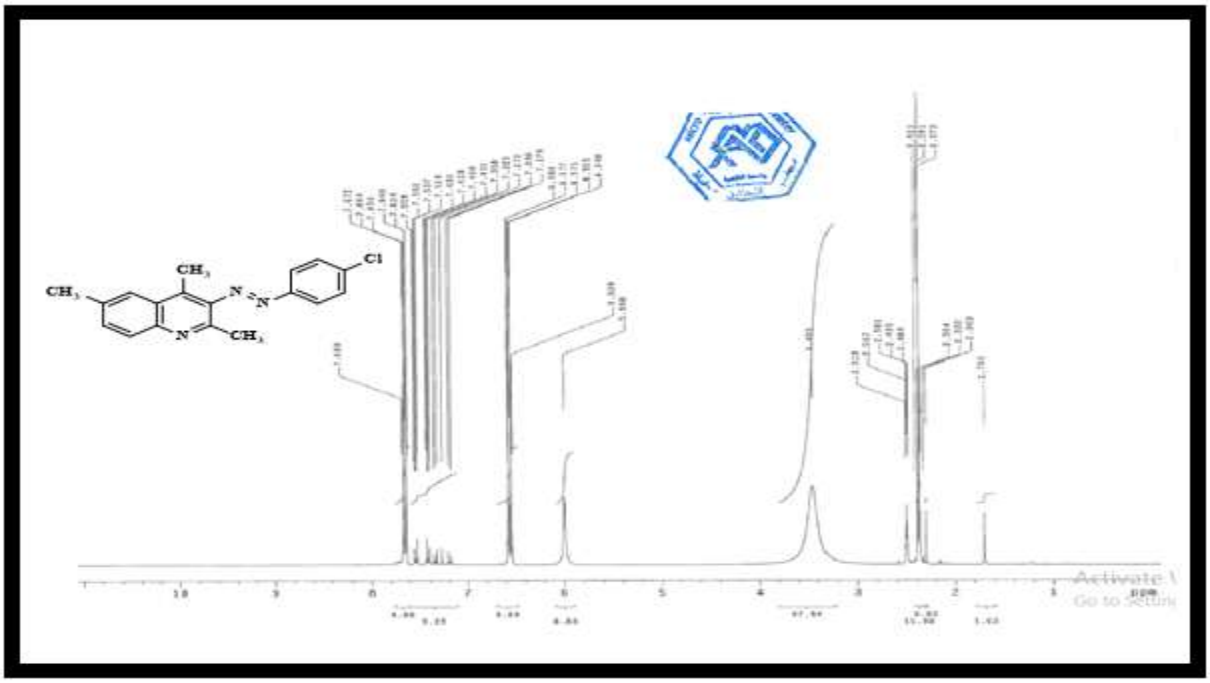

Figure (4.32): [1]HNMR Spectrum of (E)-3-((4-chlorophenyl) diazenyl)-2,4,6-trimethylquinoline (XVI)

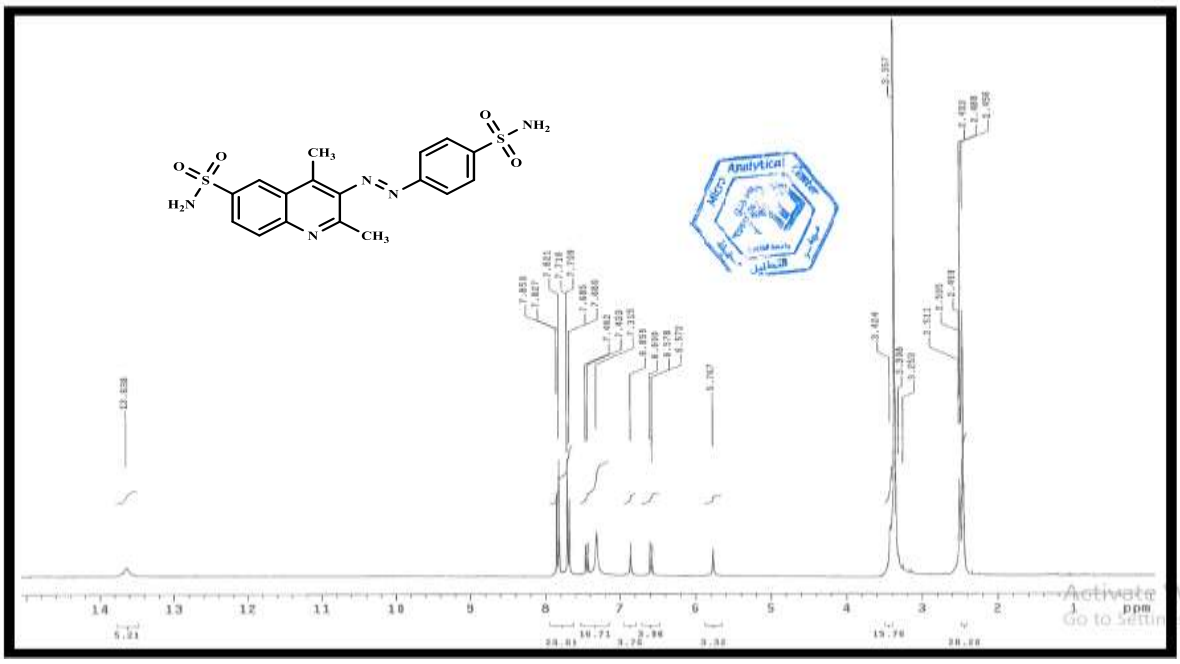

Figure (4.33): [1]HNMR Spectrum of (E)-2,4-dimethyl-3-((4-sulfamoylphenyl) diazenyl) quinoline-6-sulfonamide (XVII)

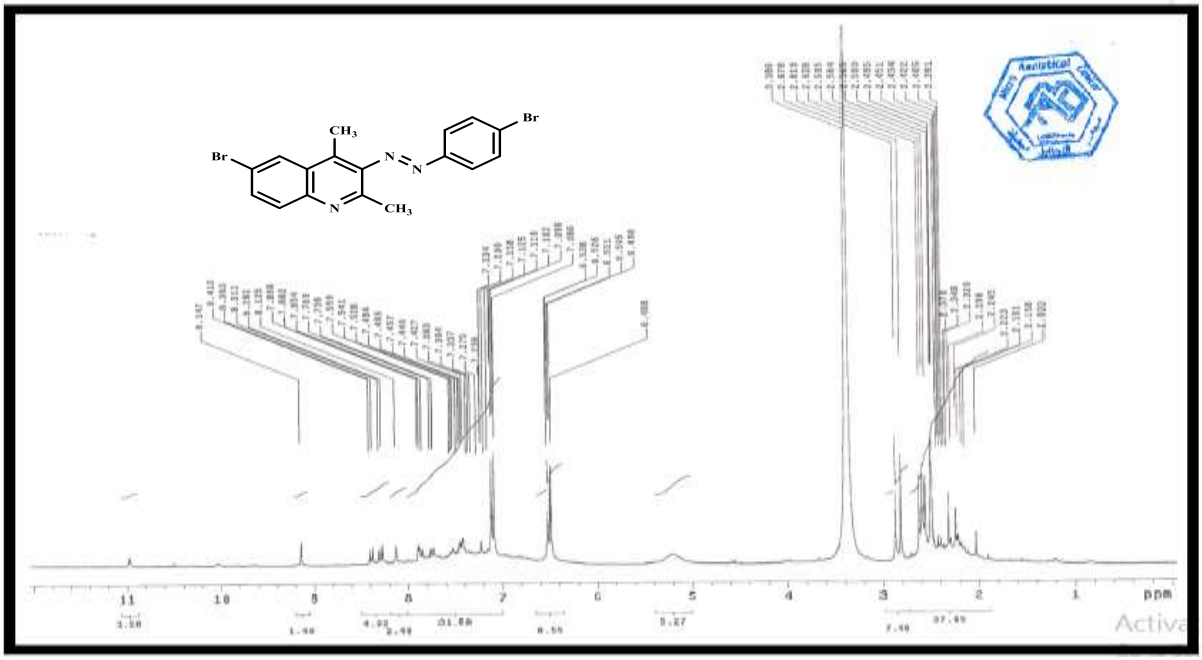

Figure (4.34): [1]HNMR Spectrum of (E)-6-bromo-3-((4-bromophenyl) diazenyl)-2,4-dimethylquinoline (XVIII)

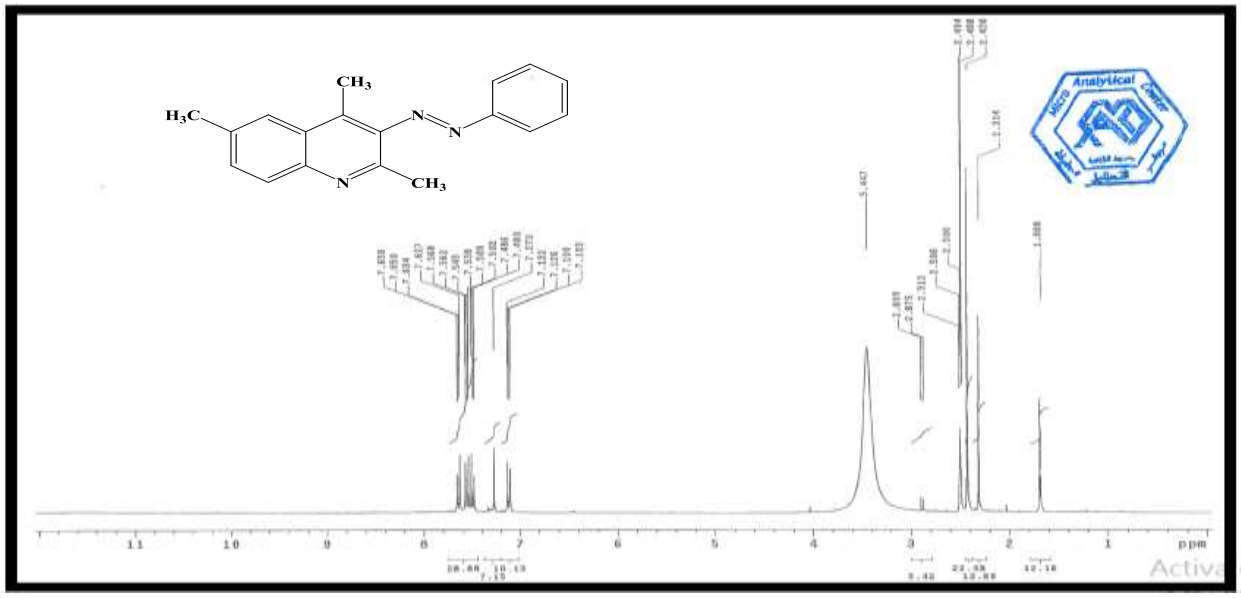

Figure (4.35): [1]HNMR Spectrum of (E)-2,4,6-trimethyl-3(phenyldiazenyl) quinoline (XIX)

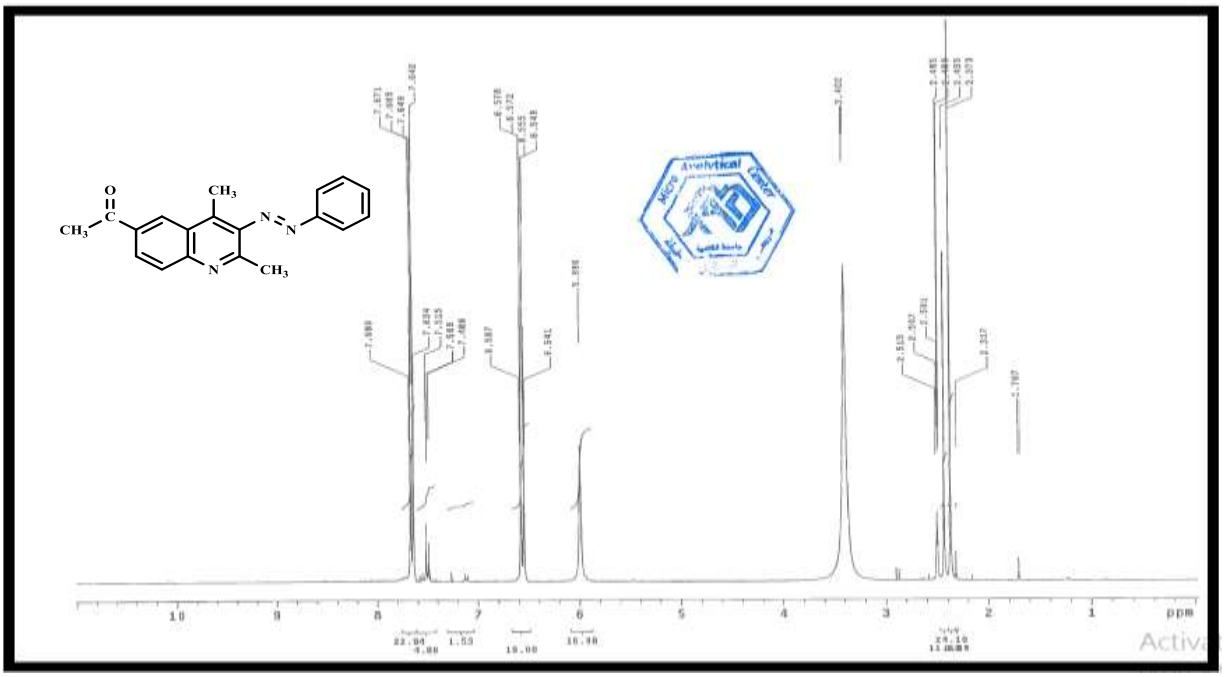

Figure (4.36): [1]HNMR Spectrum of (E)-1-(2,4-dimethyl-3-(phenyldiazenyl) quinoline-6-yl) ethan-1-one (XX)

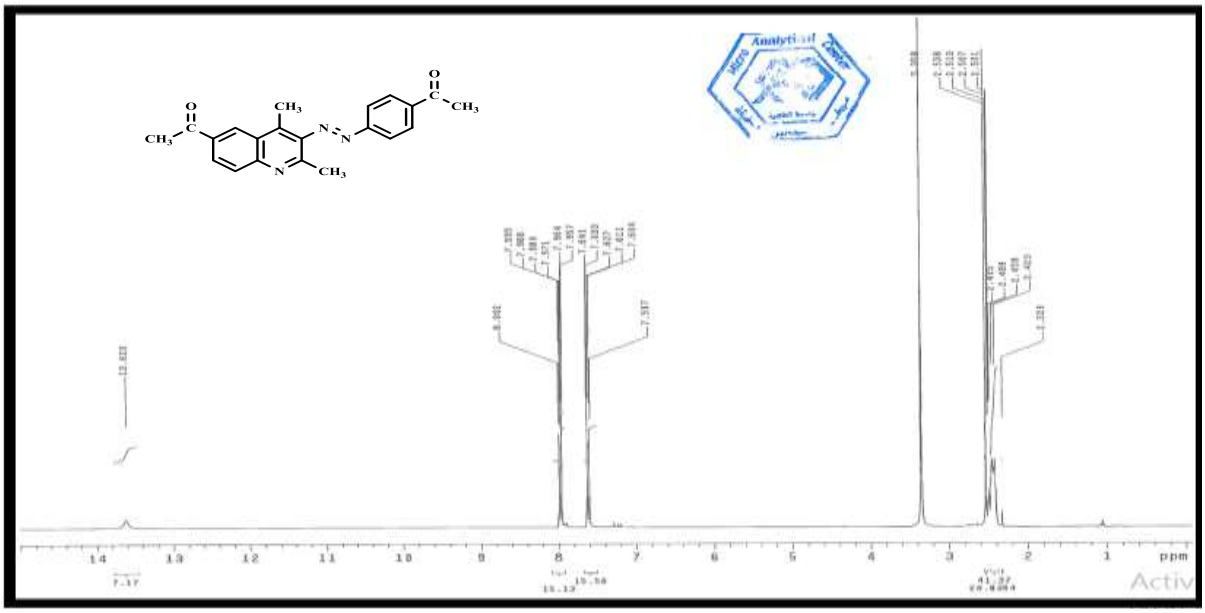

Figure (4.37): IR Spectrum of (E)-1-(-4-((6-acetyl-2,4-dimethylquinoline-3-yl) diazenyl) phenyl) ethan-1-one (XXI)

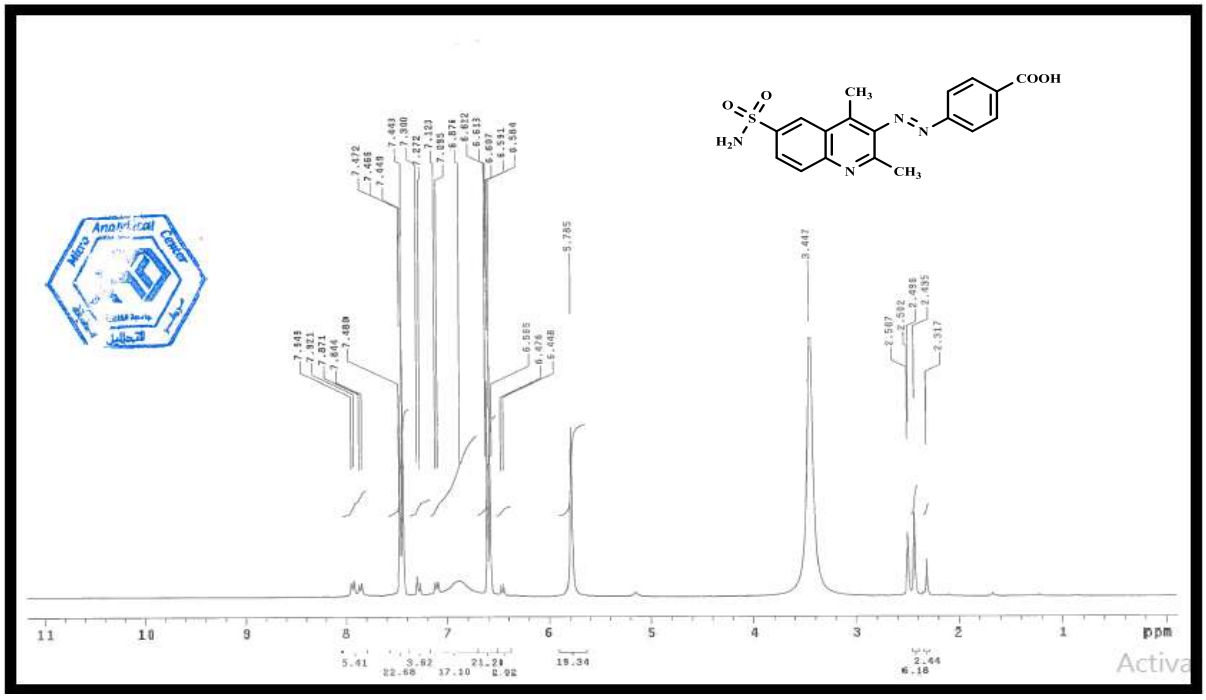

Figure (4.38): IR Spectrum of (E)-4-((2,4-dimethyl-6-sulfamoylquinoline-3-yl) diazenyl) benzoic acid (XXII).

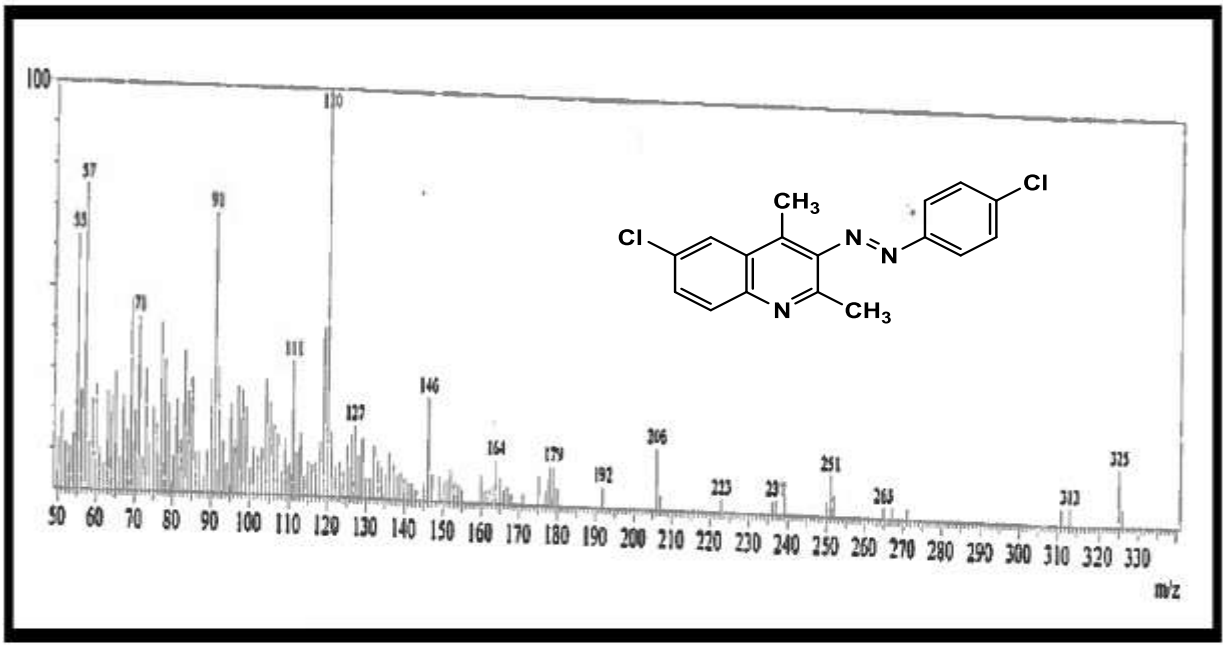

Figure (4.39): MS Spectrum of (E)-6-chloro-3-((4-chlorophenyl) diazenyl)-2,4-dimethylquinoline (XV).

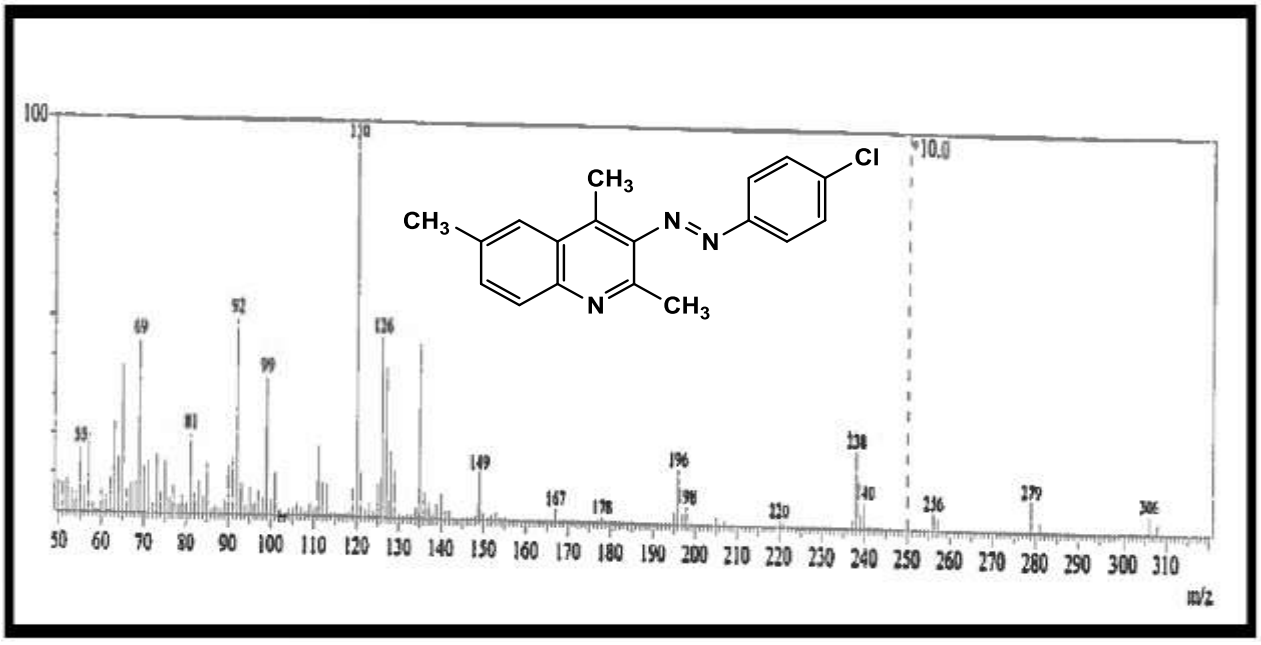

Figure (4.40): MS Spectrum of (E)-3-((4-chlorophenyl) diazenyl)-2,4,6-trimethylquinoline (XVI).

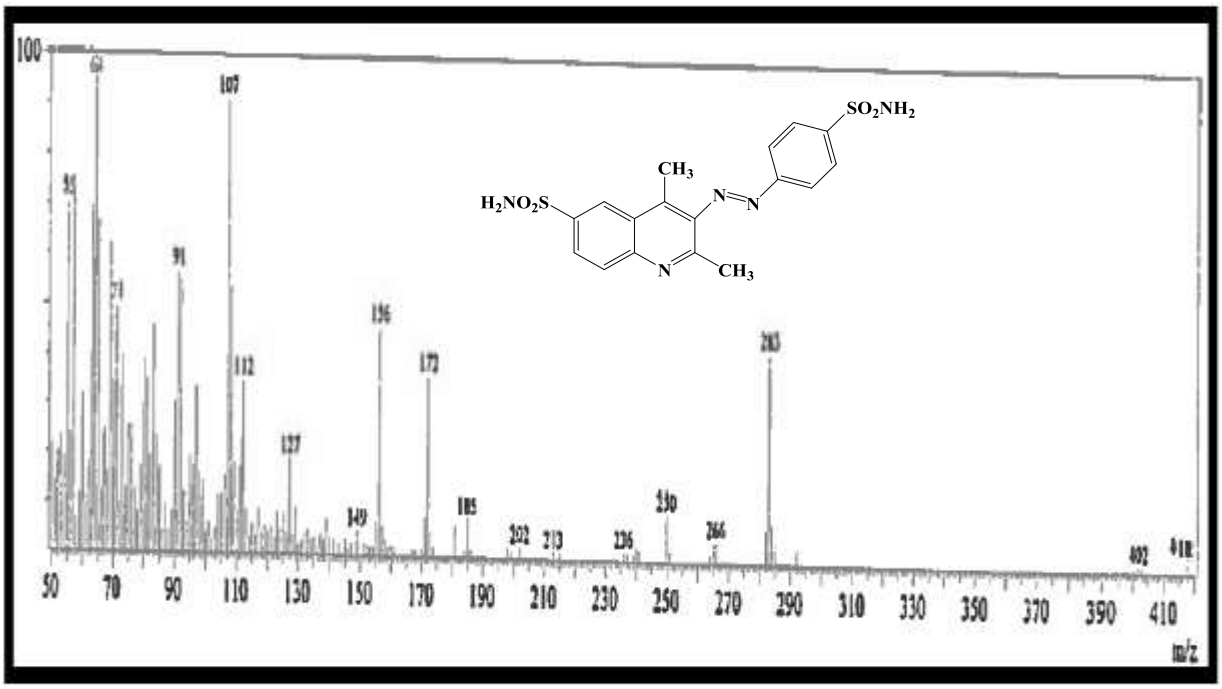

Figure (4.41): MS Spectrum of (E)-2,4-dimethyl-3-((4-sulfamoylphenyl) diazenyl) quinoline-6-sulfonamide (XVII).

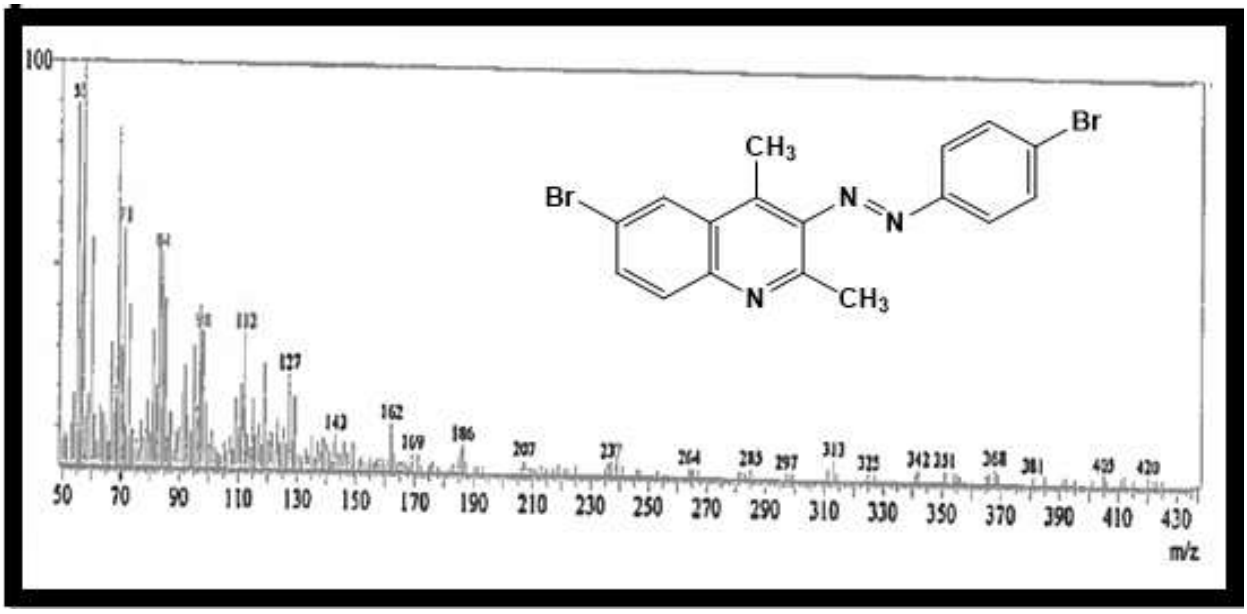

Figure (4.42): MS Spectrum of (E)-6-bromo-3-((4-bromophenyl) diazenyl)-2,4-dimethylquinoline (XVIII).

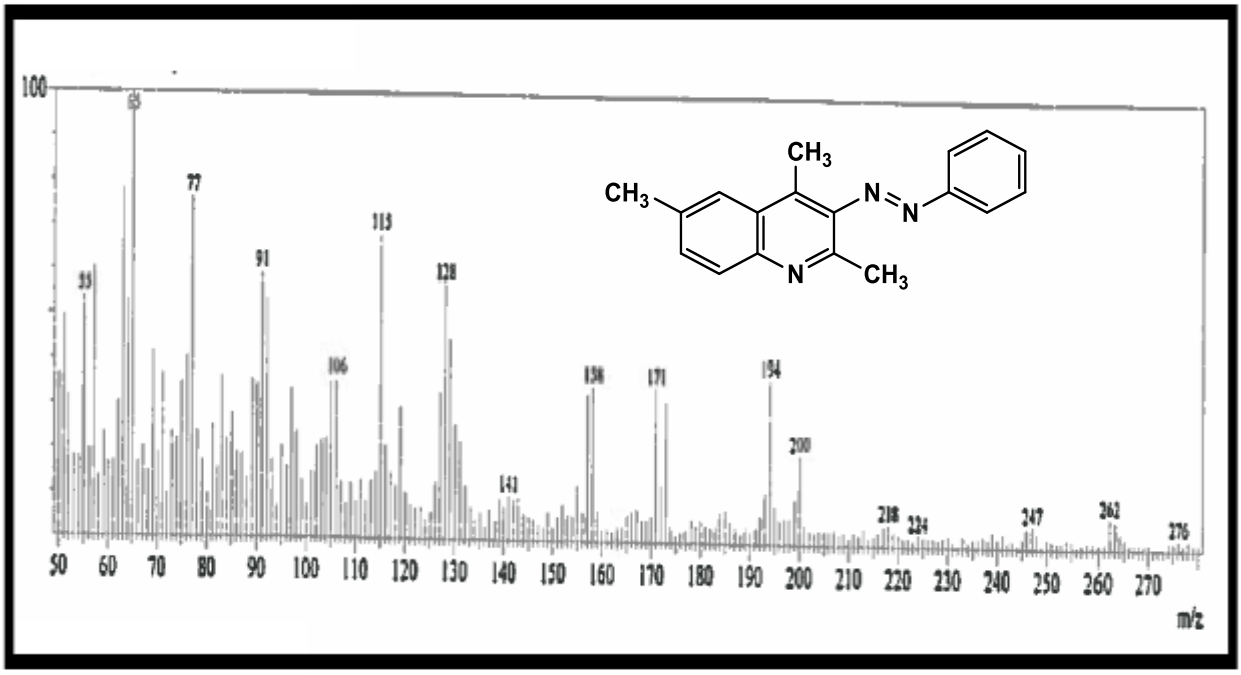

Figure (4.43): MS Spectrum of (E)-2,4,6-trimethyl-3(phenyldiazenyl) quinoline (XIX).

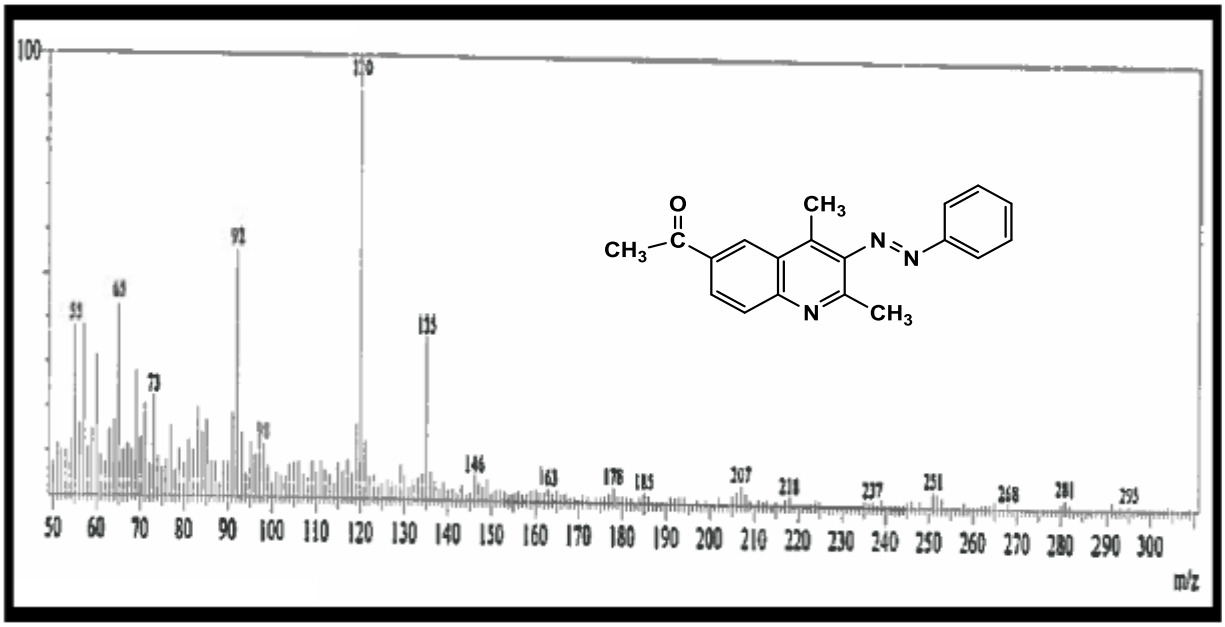

Figure (4.44): MS Spectrum of (E)-1-(2,4-dimethyl-3-(phenyldiazenyl) quinoline-6-yl) ethan-1-one (XX).

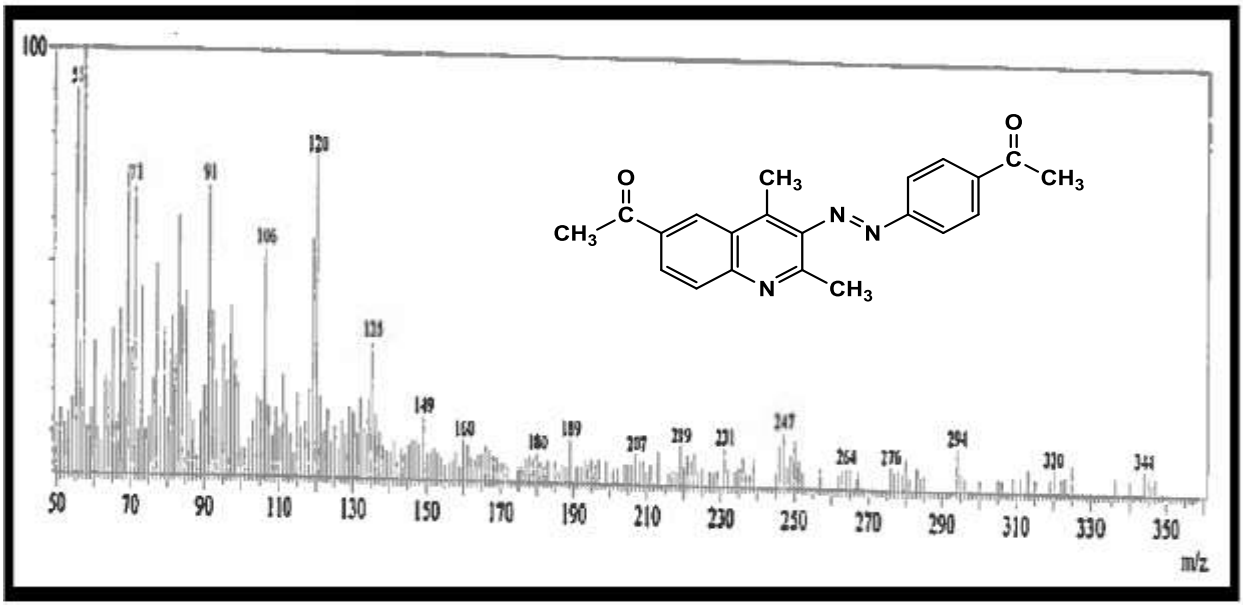

Figure (4.45): MS Spectrum of (E)-1-(-4-((6-acetyl-2,4-dimethylquinoline-3-yl) diazenyl) phenyl) ethan-1-one (XXI).

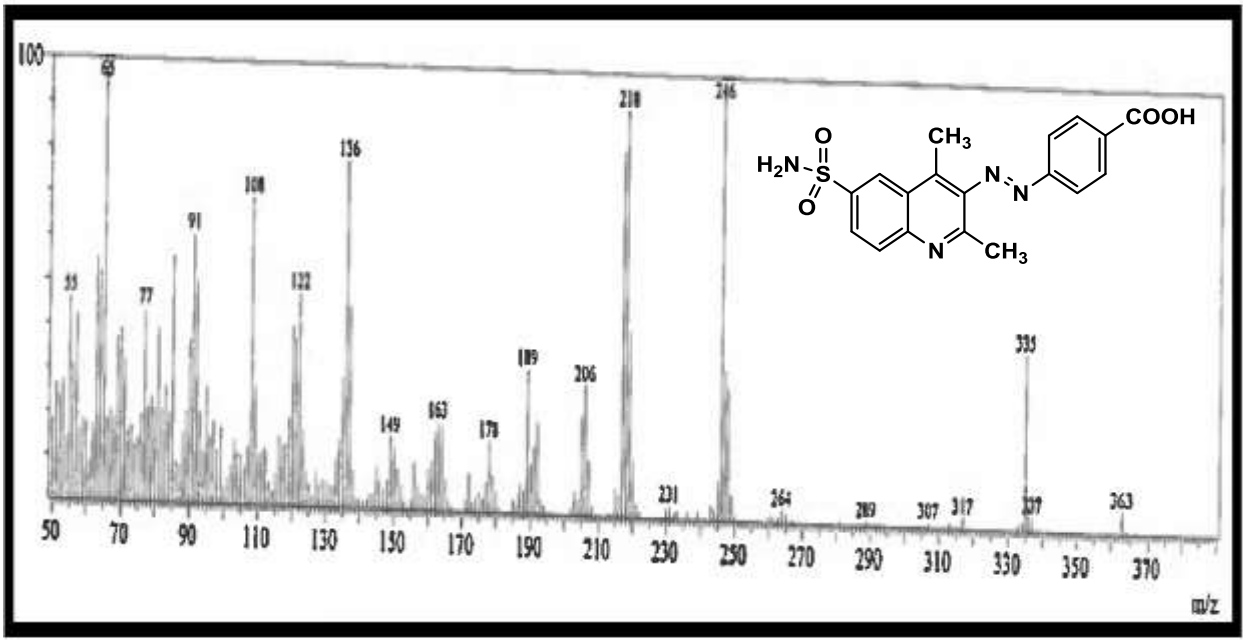

Figure (4.46): MS Spectrum of (E)-4-((2,4-dimethyl-6-sulfamoylquinoline-3-yl) diazenyl) benzoic acid (XXII).

Appendix B: Docking figures of some design synthesized compounds

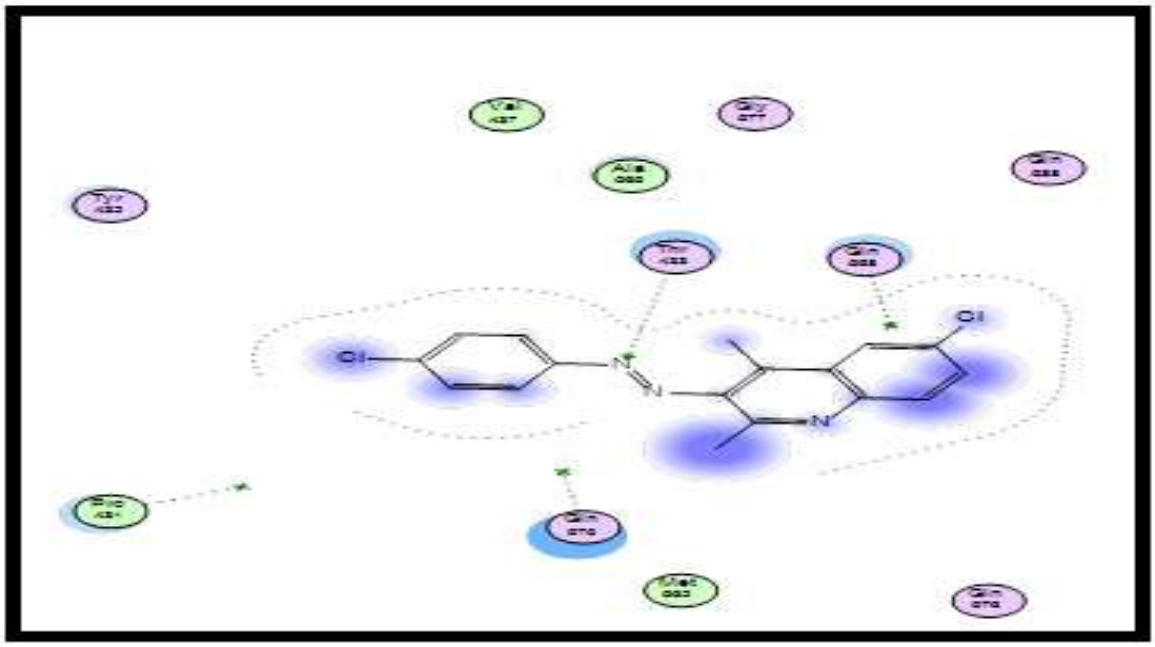

Figure (4.47): Compound XV showed interaction with the active site amino acid of 6kgh

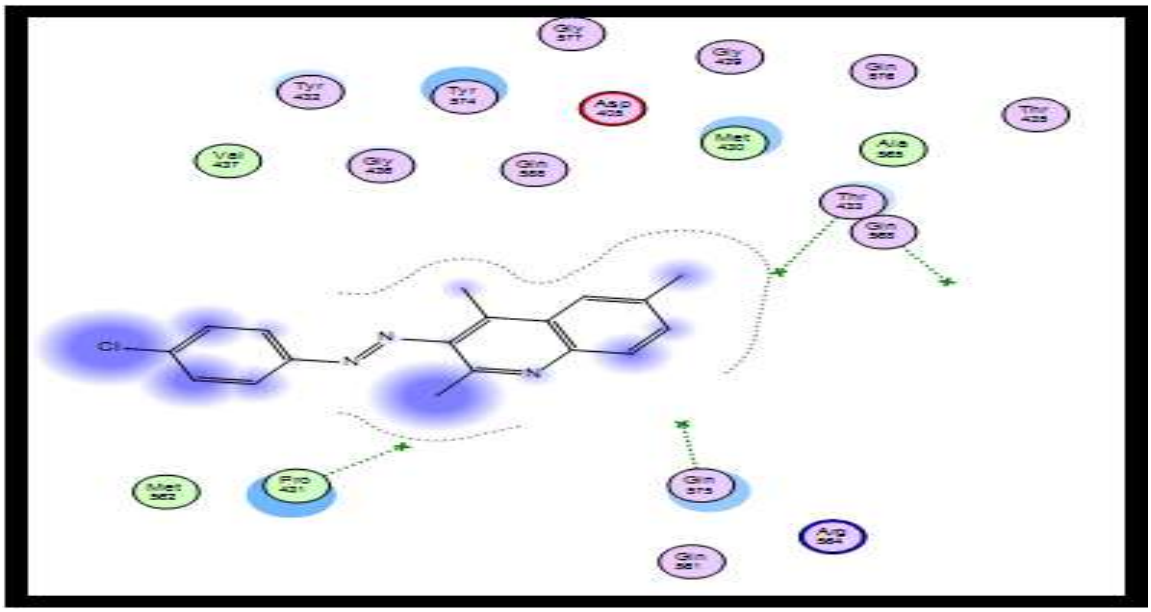

Figure (4.48): Compound **XVI** showed no interaction with the active site amino acid of 6kgh

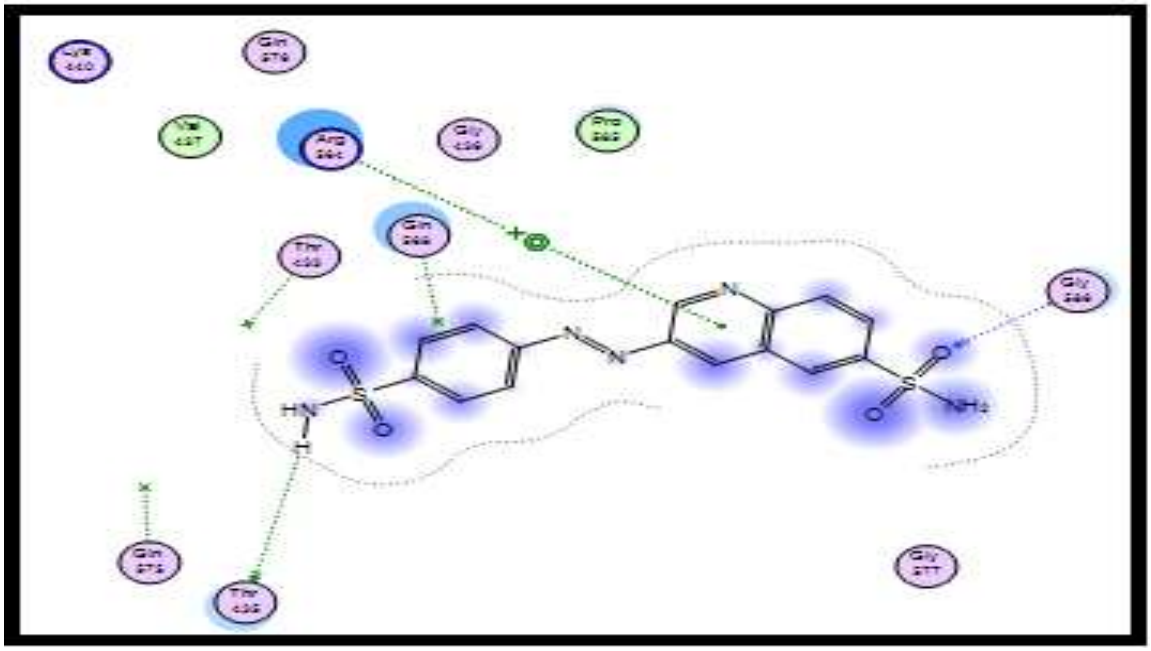

Figure (4.49): Compound **XVII** showed interaction with the active site amino acid of 6kgh

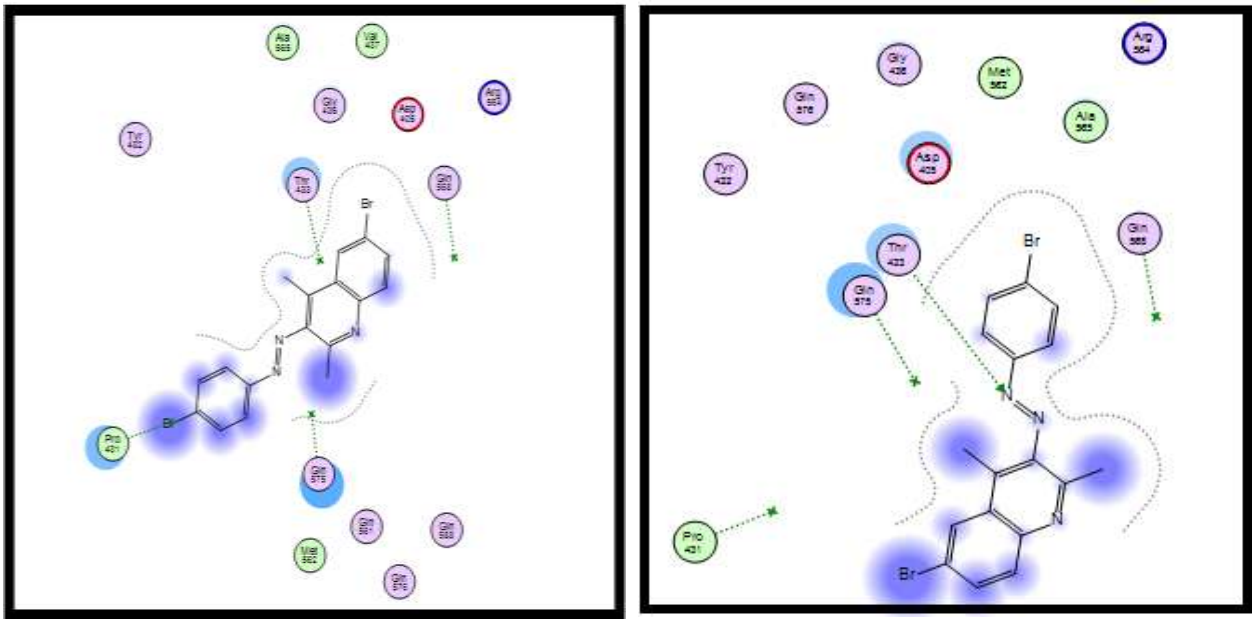

Figure (4.50): Compound **XVIII** showed different interaction with the active site amino acid of 6kgh

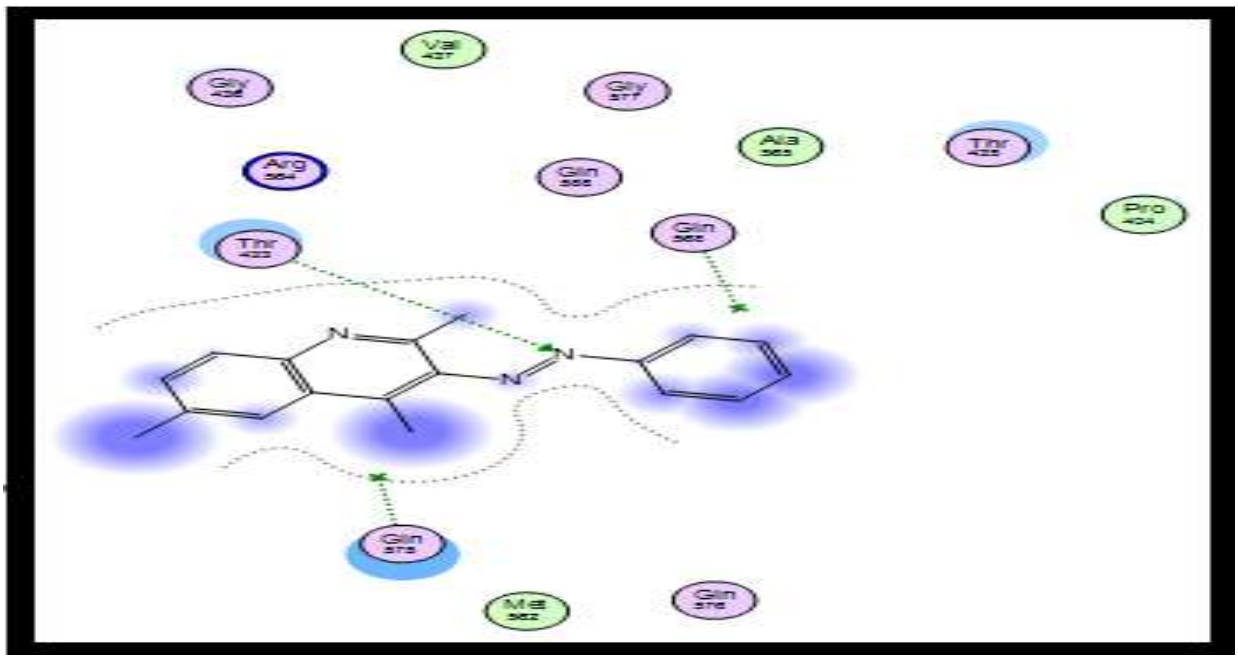

Figure (4.51): Compound **XIX** showed interaction with the active site amino acid of 6kgh

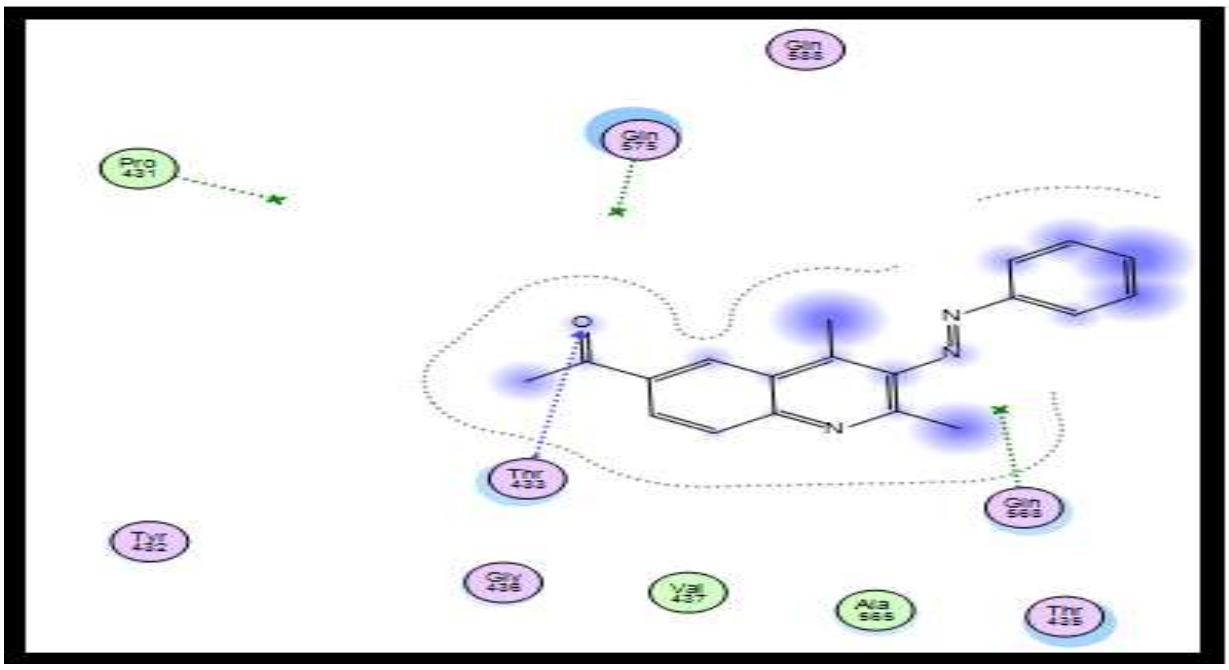

Figure (4.52): Compound **XX** showed interaction with the active site amino acid of 6kgh

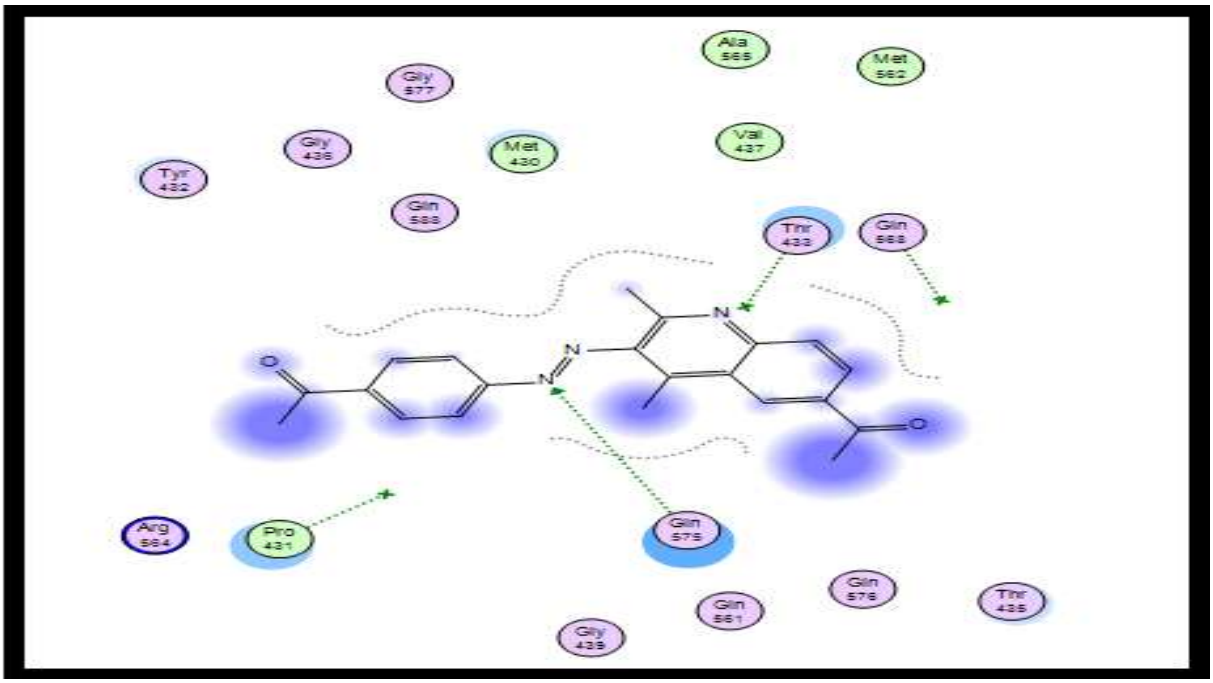

Figure (4.53): Compound **XXI** showed interaction with the active site amino acid of 6kgh

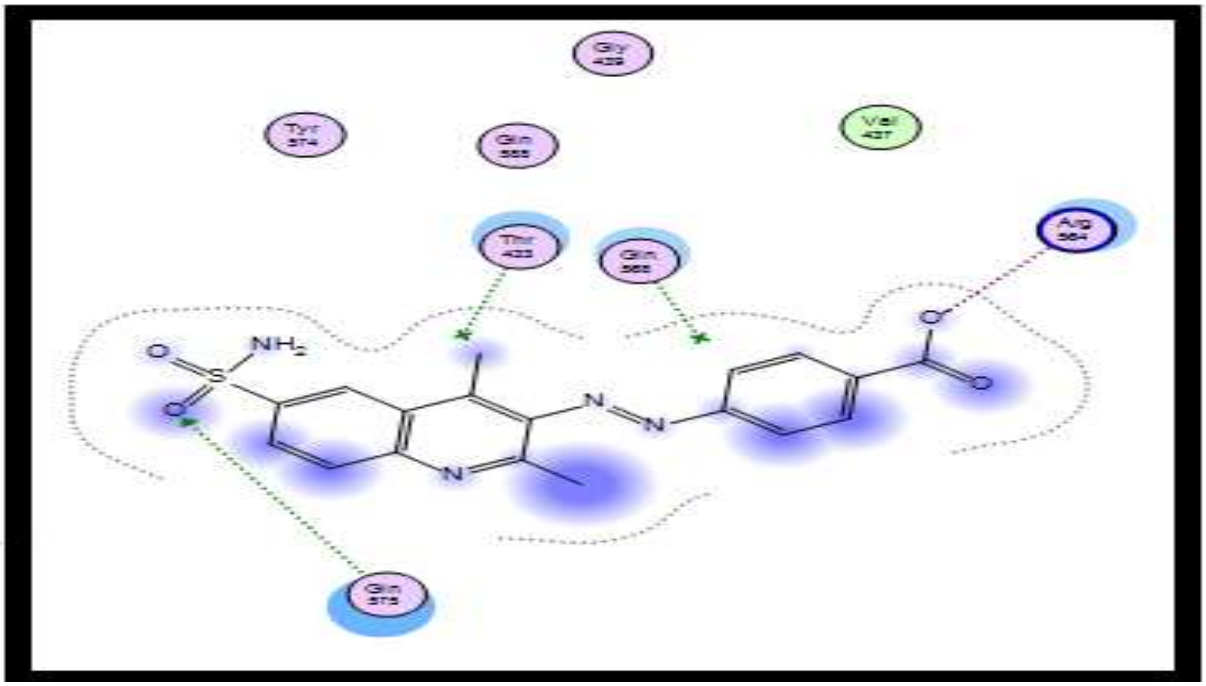

Figure (4.54): Compound **XXII** showed interaction with the active site amino acid of 6kgh