2.1. Materials and Methods:

2.1.1- Chemicals:

p-aminoacetophenone, anisaldehyde, benzylaldehyde,bromine, chloroform, ethanol, furfural,hydroxylamine hydrochloride, hydrochloric acid,methanol, nitric acid, petroleum ether, salicyaldehyde, sodium acetate, sodium hydroxide, were all obtained from LOBA company (India).

2.1.2- Solvents:

Chloroform ($CHCl_3$), ethanol (C_2H_5OH),Methanol (CH_3OH), and petroleum ether were obtained from LOBA (India). Ethanol was obtained from Elwatania, Sudan.

2.1.3- Reagents:

Concentrated hydrochloric acid (HCl), sodium hydroxide (NaOH), and sodium acetate (CH_3CO_2Na), were obtained from LOBA Company (India).

2.1.4- Thin Layer Chromatography (TLC) Plates.

Thin layer chromatography was carried out using precoated (250) Aluminium plates (Merck) with different mobile phases.

2.1.5. Database

In this QSAR studies, a total of 19 substituted 1, 4-benzoquinones derivatives were gathered from (Jaime *etal*., 2011). The vitro cytotoxicity of these compounds were reported against various human cell lines, (normal human lung fibroblasts MRC-5 and three human tumor cells: ASC gastric adenocarcinoma, Sk-MES-1 lung, and J82 bladder carcinoma. The target human cell line in this study is human lung cancer cells (SK-MES-1).Its biological activities were expressed as IC50 (the concentration of drug at which 50% of the target is inhibited) and were compared with Etoposide.

2.2. Softwares

2.2.1-ACD/ Labs Software

ACD/ ChemSketch, is a modelling program used to create and modify images of chemical structures. Also there is a software that allows molecules and molecular models displayed in two and three dimensions, to understand the structure of chemical bonds and the nature of chemical bonds and the of the functional group.

Using ACD/ChemSketch is primarily for educational use. With this program it is possible to write and perform chemical equations, diagrams laboratories and chemical structures of various entities.

2.2.2- Molecular Operating Environment(MOE) software

MOE is a molecular modelling program, which is specifically designed to handle large biological molecules. MOE is a drug discovery software platform that integrates visualization, modelling and simulations, as well as methodology development, in one package. It's scientific applications are used by biologists, medicinal chemists and computational chemists in pharmaceutical, biotechnology and academic research.

2.2.3- Statistical package for social sciences (SPSS) Software

SPSS is a package of programs for manipulating, analyzing, and presenting data; the package is widely used in the social and behavioural sciences

2.2.4- Spectroscopic Instruments.

2.2.4.1- (IR) spectrophotometers.

The infrared was recorded using KBr disk by using IR spectrophotometer; model Perkin Elmer FT IR (4000), USA.

2.2.4.2- Nuclear Magnetic Resonance (NMR) spectrometer.

Proton 1H nuclear magnetic resonance spectral data were obtained with NMR instrument model (Bruker, Germany) AMX(400 MGZ) spectrophotometer using DMSO as solvent as internal reference, 200ppm (performed in Cairo University, Egypt).

2.2.4.3- Mass Spectrometer (MS):

The mass spectra were run on a Shimadzu Qp-2010 Plus, 1000 mass spectrometer at 70ev (performed in Cairo University, Egypt).

2.2.4.4- General Instruments:

All glassware of pyrex type. Hot plate with magnetic stirrer. Electronic balance S, N,O.1296463, Japan, Melting point apparatus, Gallon Kamp.

2.3- Synthetic Methods:

2.3. 1-Preparation of2, 3, 5, 6-tertrabromo-1, 4-Benzoquinone (Bromanil). (I)

To a stirred solution of hydroquinone (6gm, 0.055 mole)in 60 ml glacial acetic acid was added 10 ml of concentrated nitric acid and the solution was further stirred for 30 minutes. Bromine (20ml, 62g, and 0.38mole) was added over a period of 30minutes. The mixture was stirred at room temperature for one hour. The precipitated product was filtered and washed with cold water. (Saeed *etal*., 2009)

2.3.2- Preparation of α, β unsaturated carbonyl compounds (II, III, IV,V)

(0.001 mole) of the required aldehyde and 0.135g (0.001 mole) of *p*-aminoacetophenone were dissolved in minimum amount of ethanol. Sodium hydroxide solution (0.02 moles) was added slowly and the molar mixture was stirred for 24 hours. The reaction product was poured in a 20 ml of cold distilled water.10% of HCl drops were added with stirring until,a precipitate obtained which was filtered, washed and recrystallized from ethanol. The completion of the reaction was monitored by TLC. (Kalirajan *etal*., 2009).

2.3.3- Preparation of isoxazoles derivatives (VI, VII, VIII, IX).

A mixture of α ,β unsaturated carbonyl compound (II,III,IV,V), (0.01 mole), hydroxylamine hydrochloride (0.01mole)and sodium acetate (0.1g,0.001mole) were dissolved in 20 ml of ethanol and refluxed for 6hours. The mixture was poured into ice-water and stirred using glass-rod until a precipitate was formed, 10% of HCl drops were added. The precipitate was filtered, washed and recrystallized from ethanol. The completion of the reaction was monitored by TLC.

2.3.4- Preparation of 2,5-dibromo-3,6-diisoxazolyl-1,4-benzoquinone derivatives (X, XI, XII,XIII).

A mixture of isoxazole derivative(VI,VII,VIII,IX) (0.001 mole) and bromanil (0.003) mole was dissolved in a minimum amount of ethanol (10 ml), galical acetic acid (10ml), distilled water (2ml) and (0.1g) of sodium acetate . The mixture was refluxed for 3hours. The reaction mixture was poured into ice-water and stirred using glass-rod until precipitate was formed, 10% of HCl drops were added. The precipitate was filtered, washed and recrystallized from ethanol. The completion of the reaction was monitored by TLC.

2.3.5-Preparationof 2,5-di (4-acetyl-aminobenzene)-aminoaryl-3,6-dibromo-1,4- Benzoquinone(XIV)

(0.003 mole) of Bromanil and (0.001 mole) of *p*-aminoacetophenone were dissolved in (10ml) of ethanol, (10ml) of glacial acetic acid, 2ml of water and (0.1g) of sodium acetate. The mixture was refluxed for 3hours.The mixture was poured into ice-water and stirred until precipitate was formed. The precipitate was filtered, washed and recrystallized from ethanol. The completion of the reaction was monitored by TLC.

2.3.6-Preparation ofquinonyl-α,β unsaturated carbonyl compounds derivatives (XV, XVI, XVII, XVIII).

(0.003 mole) Bromanil and (0.001) of α,β unsaturated carbonyl compounds (II, III, IV,V)) respectively, were dissolved in 10 ml of ethanol ,10ml of glacial acetic acid,(2ml) of H_2O and(0.1 g) of sodium acetate was added. The mixture was refluxed for 3 hours. It was poured into ice-water, 10% of HCl drops were added, and stirred until a precipitate was formed. The precipitate was filtered, washed and

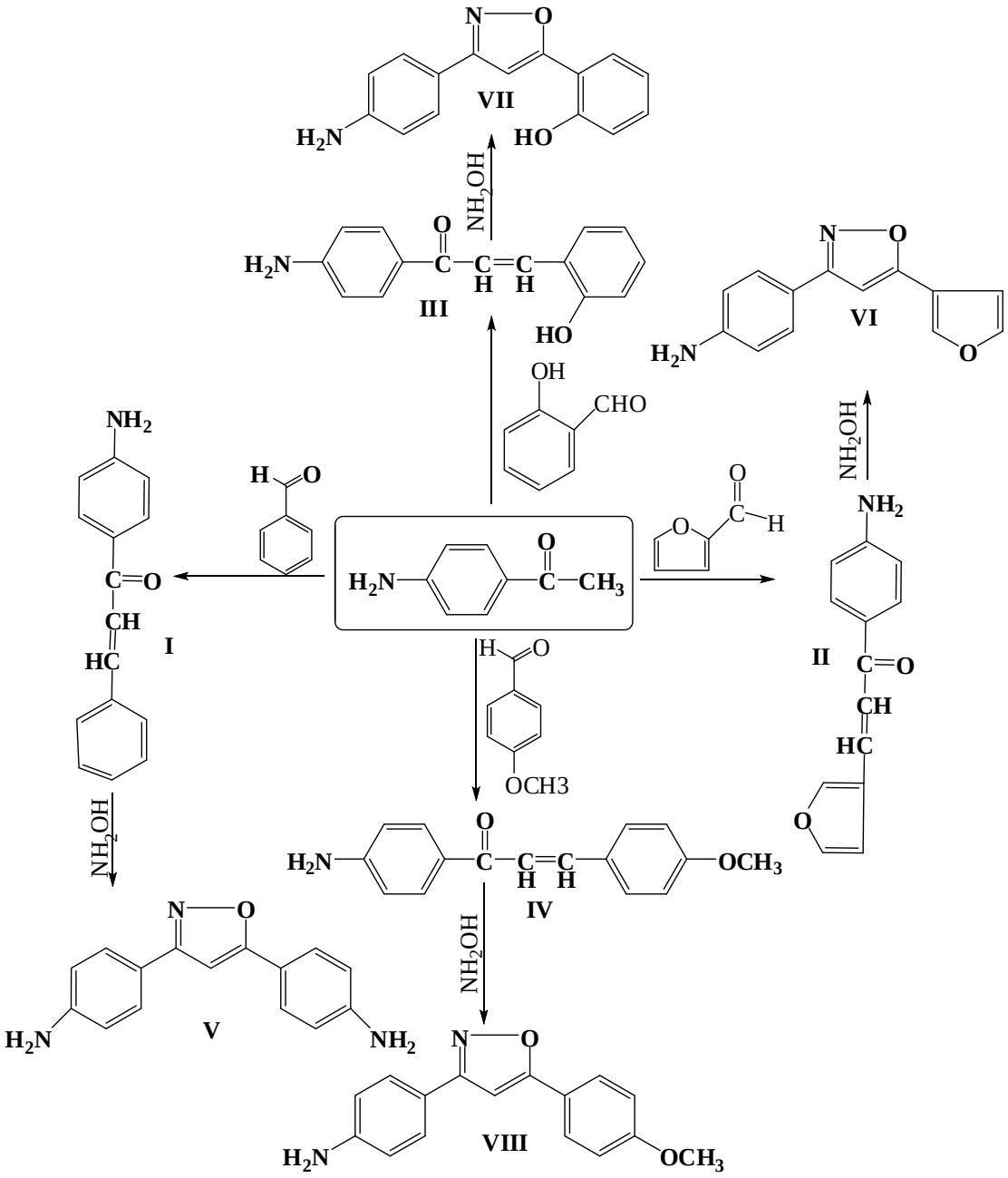
recrystallized from ethanol. The completion of the reaction was monitored by TLC.

2.3.7- Preparation of quinonyl α, β- unsaturated carbonyl compounds derivatives (XIX,XX,XXI,XXII) from compound (XIV)

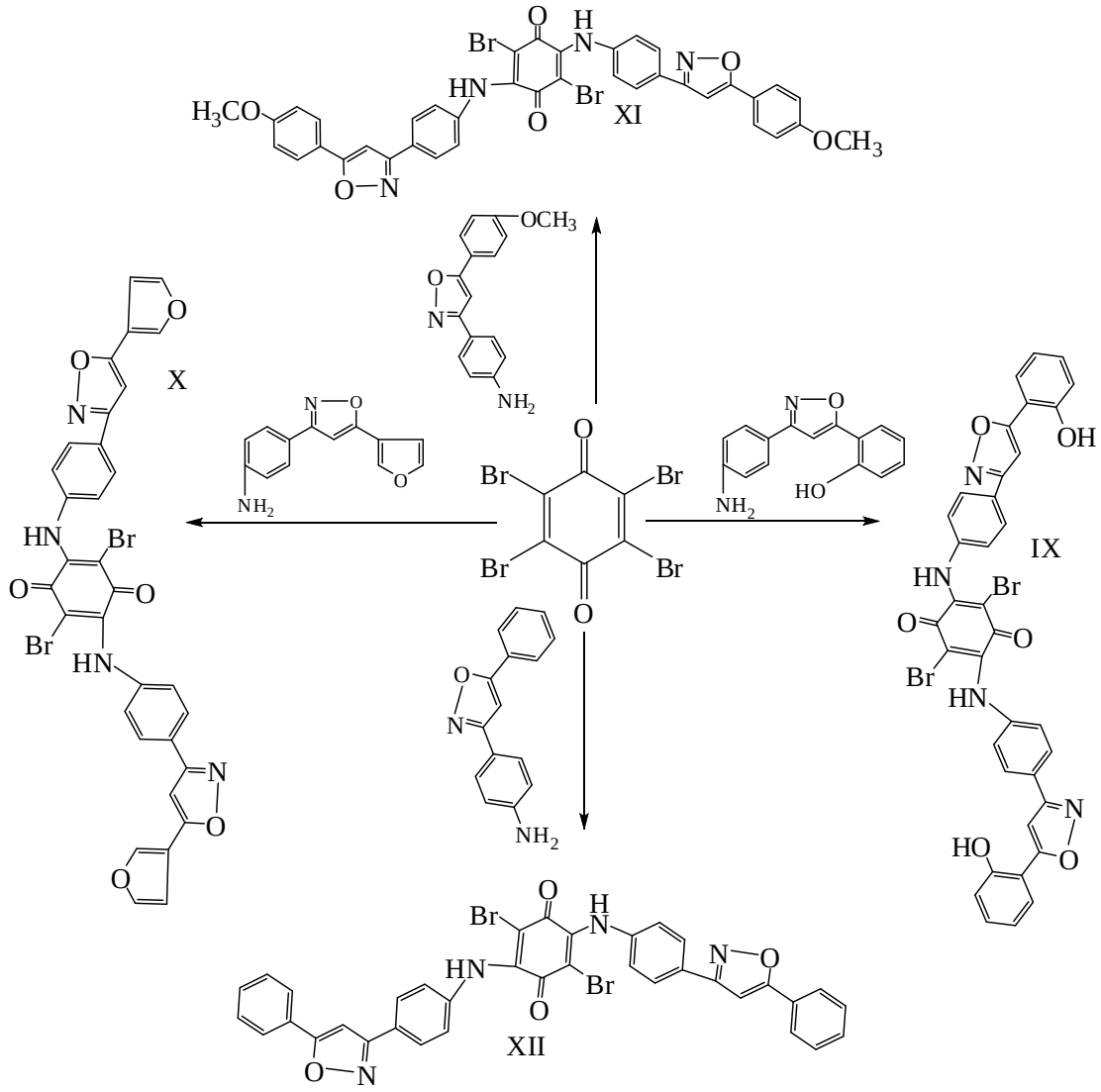
(0.001 mole) of compound (XIV) and (0.002 mole) of the required aldehyde, dissolved respectively in (20ml) ethanol. Sodium hydroxide solution (2M) was added slowly and the mixture was stirred for 24 hours. The mixture was poured into ice-water, 10% of HCl drops was added, and stirred until the precipitate was formed. . The precipitate was filtered, washed and recrystallized from ethanol. The completion of the reaction was monitored by TLC.

2.3.8-Preparation of the *p*-quinones derivatives (VI, VII, VIII, IX)

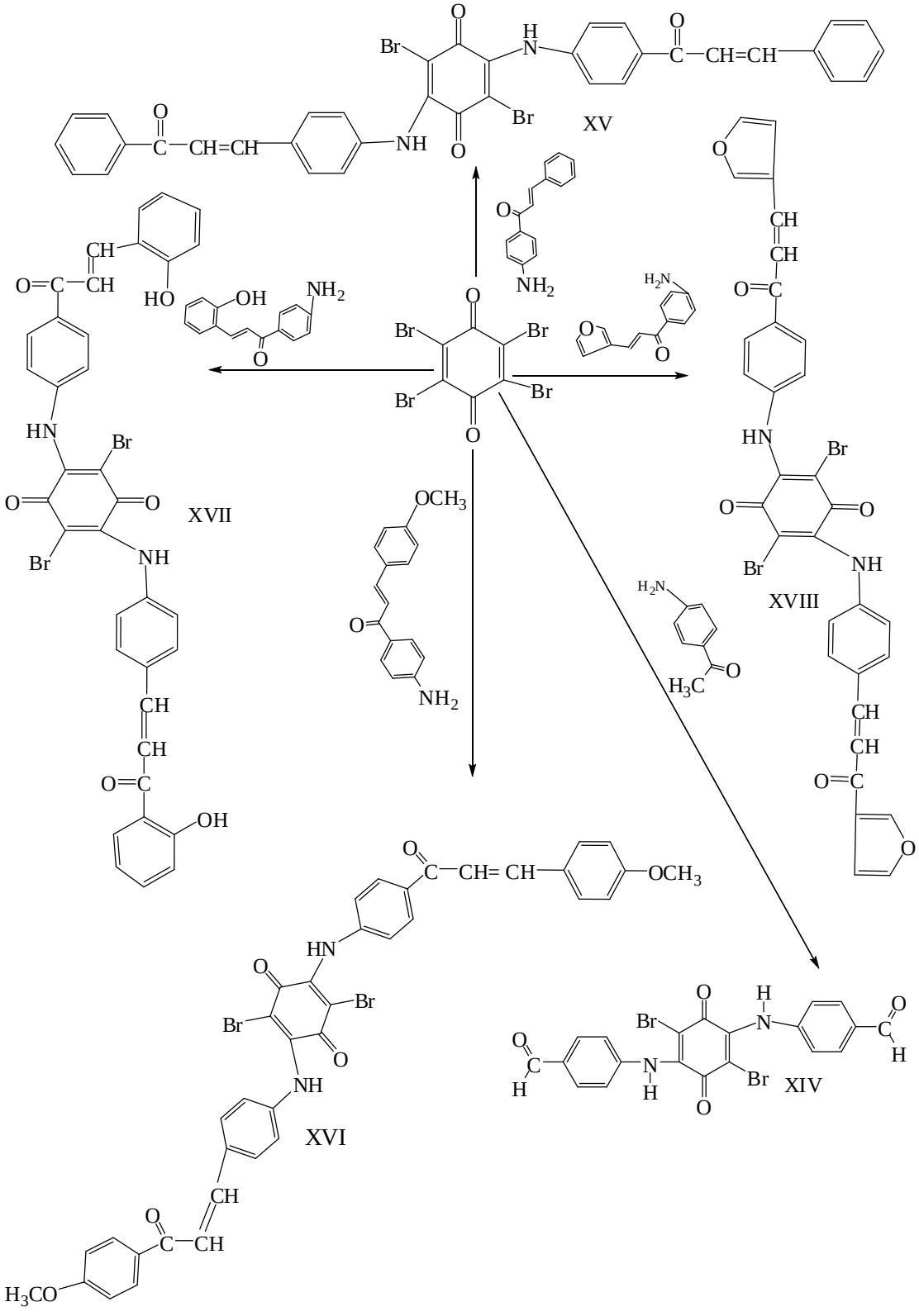
(0.001 mole)of quinonyl α,β -unsaturated carbonyl the derivatives of (XVIII, XIX, XX, XXI) and(0.002 mole) of hydroxylamine and sodium acetate (0.1g) were dissolved in (20ml) ethanol and refluxed for(6 hours).The mixture was poured into ice-water and stirred using glass rod until the precipitate was formed. The precipitate was filtered, washed and recrystallized from ethanol. The completion of the reaction was monitored by TLC.



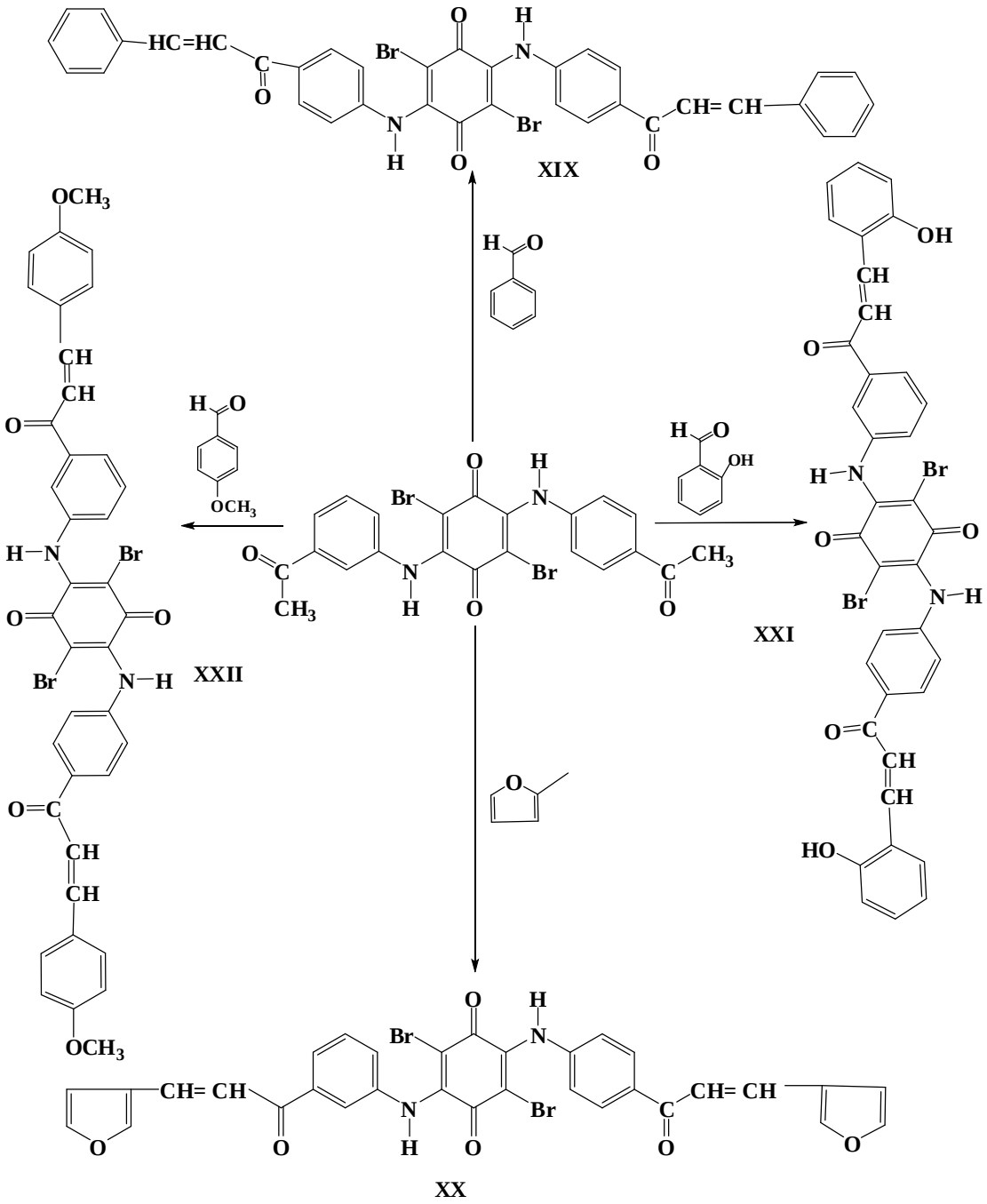
Scheme 2.1. Chemical structure of synthesized isoxazoles



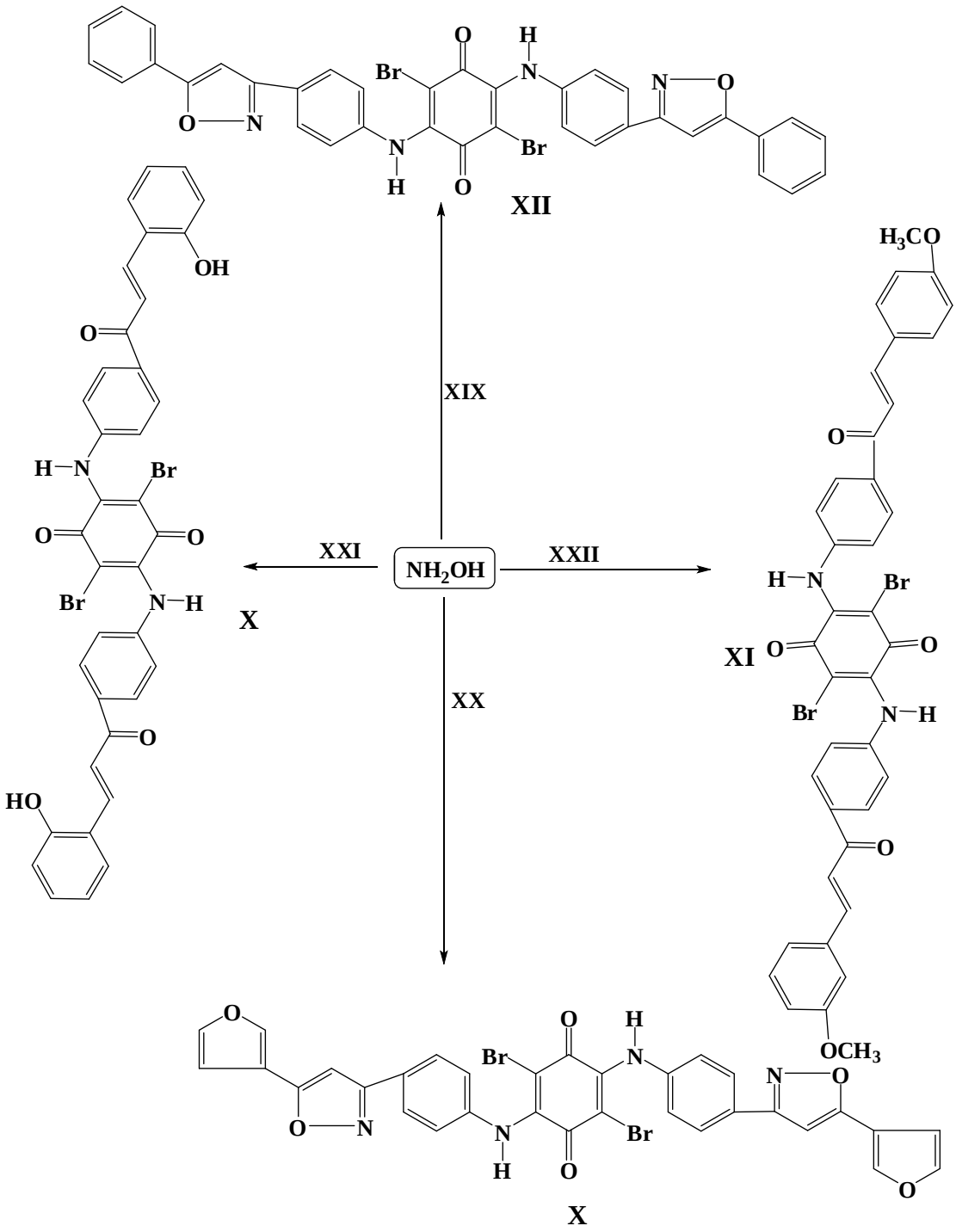
Scheme 2.2.Chemical structure of synthesized *p*-quinones derivatives



Scheme 2.3. Chemical structure of synthesized α,β-unsaturated carbonyl compounds



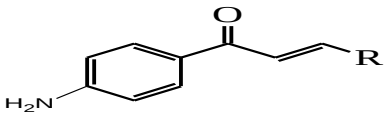
Scheme 2.4. Chemical structure of synthesized α,β-unsaturated carbonyl compounds derivatives.



Scheme 2.5.chemical structure of synthesized *p*-quinones derivatives

2.4. Chemical names of the synthesized compounds.

Table.(2.1): Chemical names for the synthesized α,β unsaturated carbonyl derivatives



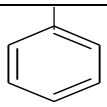
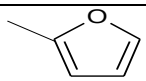
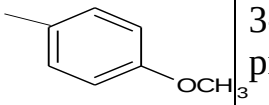
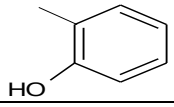
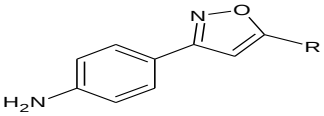
Compound No.	R	The chemical name
II		3-phenyl-1-(*p*-aminophenyl)-prop-2-en-1-one
III		3-fural-1-(*p*-aminophenyl)-prop-2-en- 1-one
IV		3-(4-methoxyphenyl)-1-(*p*–aminophenyl)-prop-2-en-1-one
V		3-(2-hydroxyphenyl)-1-(*p*- aminophenyl)-prop-2-en -1-one

Table.(2.2):Chemical names for isoxazolesderivatives.



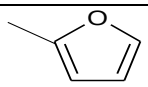
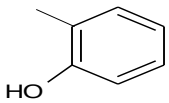
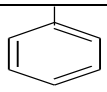
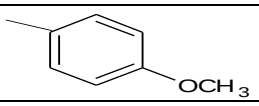
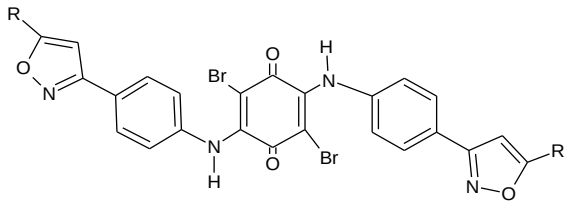
Compound No.	R	The chemical name
VI		5-fural-3(*p*-aminophenyl)-1,2-isoxazole.
VII		5-phenol-3(*p*-aminophenyl)-1,2-isoxazole.
VIII		5-phenyl-3(*p*-aminophenyl)-1,2-isoxazole.
IX		5-(4-methoxyphenyl-3(*p*-aminophenyl)-1,2-isoxazole.

Table (2.3): Chemical names for *p*-quinones derivatives.



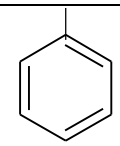
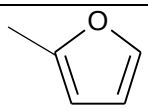
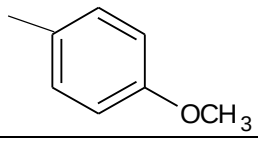
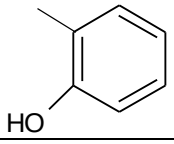
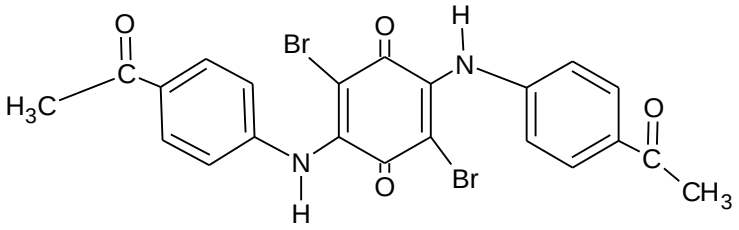
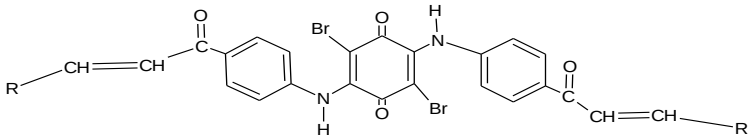
Compound No.	R	The chemical name
X		2, 5-dibromo-3, 6-di(4-(5-phenyl-3-diisoixazolyl-aminophenyl)-1,4-benzoquinone)
XI		2, 5-dibromo-3, 6-di(4-(5-fural-3-diisoixazolyl-amino phenyl)-1,4-benzoquinone)
XII		2, 5-dibromo--3, 6-di(4-(5-methoxy phenyl-3-diisoixazolyl-amino phenyl)-1,4-benzoquinone)
XIII		2, 5-dibromo-3, 6-di(4-(5-hydroxy phenyl-3-diisoixazolyl-amino phenyl)-1,4-benzoquinone)

Table (2.4): The chemical name for the synthesized compound (XIV).



Compound No.	**R**	The chemical name
XIV	-	2,5-dibromo -3,6-diamino-(*p*-diacetylphenyl)-1,4-dione.

Table (2.5): Thechemicalnames for the α,β unsaturated carbonyl compounds derivatives from the bromanil.XV, XVI, XVII, XVIII



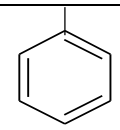
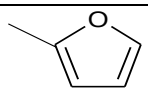
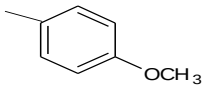
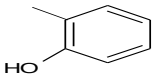
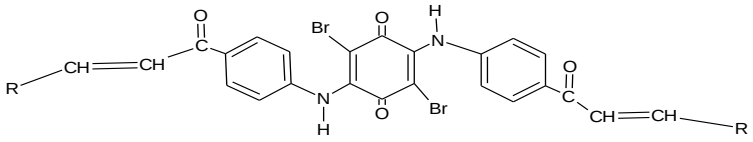
Compound No.	R	The chemical name
XV		3-diphenyl 2,5-diamino-3,6-di(*p*-aminophenyl)-(prop-2-en)-1-one
XVI		3-difural-2,5-diamino-3,6-di(*p*-aminophenyl)-(prop-2-en)-1-one
XVII		3-di-(4-methoxyphenyl)-2,5-diamino-3,6-di*(p*-aminophenyl)-(prop-2-en)-1-one
XVIII		3-di(2-hydroxyphenyl-2,5-diamino-3,6-di(*p*-aminophenyl)-(prop-2-en)-1-one

Table. (2.6): Chemical names for the α,β unsaturated carbonyl compounds derivatives from compound XIV. XIX, XX, XXI, XXII.



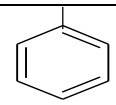
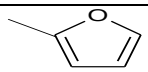
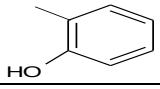
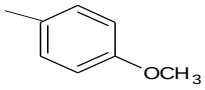
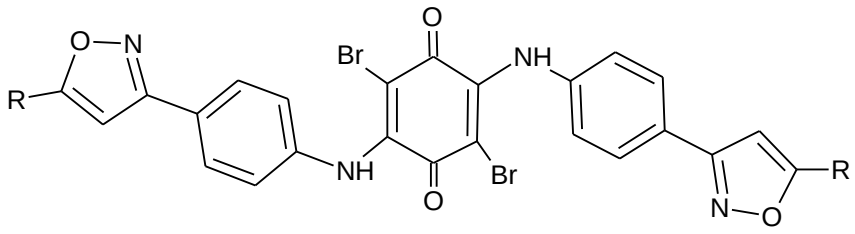
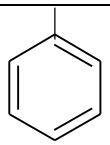
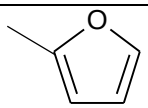
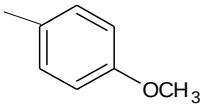
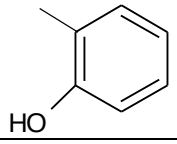
Compound No.	R	The chemical name
XIX		3-diphenyl 2,5-diamino-3,6-di(*p*-aminophenyl)-(prop-2-en)-1-one
XX		3-difural-2,5-diamino-3,6-di(*p*-aminophenyl)-(prop-2-en)-1-one
XXI		3-di(2-hydroxyphenyl-2,5-diamino-3,6-di(*p*-aminophenyl)-(prop-2-en)-1-one
XXII		3-di-(4-methoxyphenyl)-2,5-diamino-3,6-di(*p*-aminophenyl)-(prop-2-en)-1-one

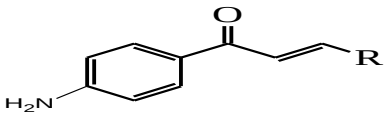
Table .(2.7):Chemical names for the *p*- quinones derivatives (X, XI, XII, XIII)



Compound No.	R	The chemical name
X		2, 5-dibromo-3, 6-di(4-(5-phenyl-3-diisoixazolyl-amino phenyl)-1,4-benzoquinone)
XI		2, 5-dibromo-3, 6-di(4-(5-fural-3-diisoixazolyl-amino phenyl)-1,4-benzoquinone)
XII		2, 5-dibromo--3, 6-di(4-(5-methoxy phenyl-3-diisoixazolyl-amino phenyl)-1,4-benzoquinone)
XIII		2, 5-dibromo-3, 6-di(4-(5-hydroxy phenyl-3-diisoixazolyl-amino phenyl)-1,4-benzoquinone)

2.4: The reaction conditions for the synthesized compounds

Table.(2.8):The reaction conditions of thesynthesized α,β unsaturated carbonyl compounds derivatives. II, III, IV, V



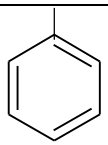
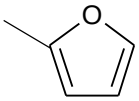
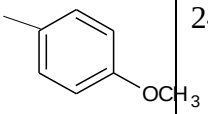
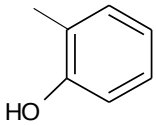
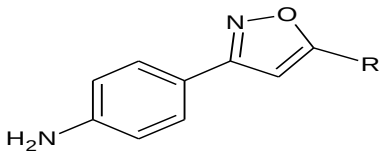
Com No.	R	Reaction Time	Temperature	Yield %	Recrystallization solvent	M.P
II		24 hours	Room Temperature	69.1%	Ethanol	139^0C-140^0C
III		24 hours	Room Temperature	72.9%	Ethanol	130^0C-131^0C
IV		24 hours	Room Temperature	39.1%	Ethanol	156^0C-157^0C
V		24 hours	Room Temperature	42.9%	Ethanol	152^0C-153^0C

Table. (2.9): The reactions conditions of isoxazoles (V, VI, VII, VIII).



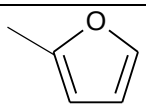
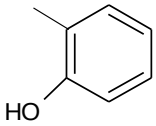
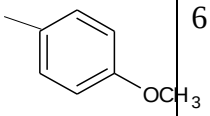
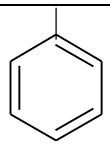
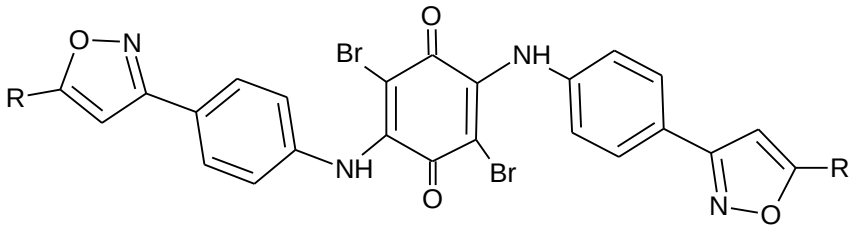
Com. No.	R	Reaction Time	Temperature	Yield %	Recrystallization solvent	M.P
VI		6 hours	Room Temperature	53.7%	Ethanol	197°C-199°C
VII		6 hours	Room Temperature	57.9%	Ethanol	189°C-191°C
VIII		6 hours	Room Temperature	69.2%	Ethanol	151°C-152°C
IX		6 hours	Room Temperature	64.3%	Ethanol	136°C-137°C

Table (2.10):The reaction conditions of *p*- quinones derivatives. X, XI, XII, XIII



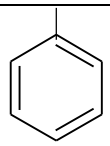
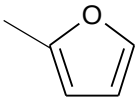
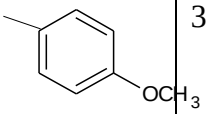
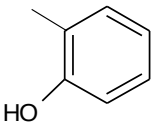
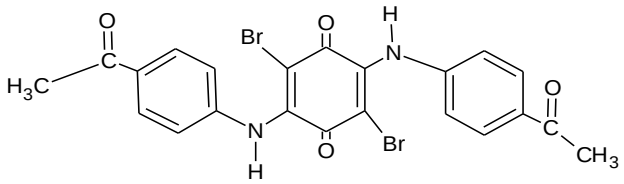
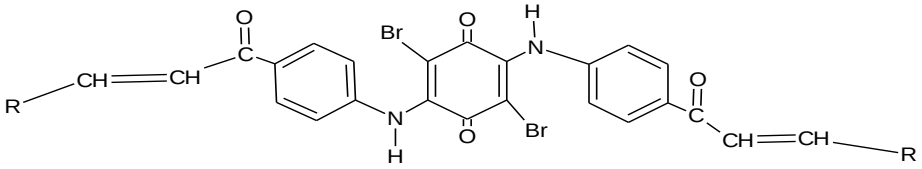
Com. No.	R	Reaction Time	Temperature	Yield%	Recrystallization solvent	M.P
X		3 hours	Room Temperature	61.7%	Ethanol	248^{o}C - 249^{o}C
XI		3 hours	Room Temperature	62.4%	Ethanol	253^{o}C - 254^{o}C
XII		3 hours	Room Temperature	59.9%	Ethanol	279^{o}C - 281^{o}C
XIII		3 hours	Room Temperature	52.5%	Ethanol	284^{o}C - 285^{o}C

Table (2.11):The reaction conditions of compound (XIV).



Com. No.	R	Reaction Time	Temperature	Yield%	Recrystallization Solvent	M.P
XIV	-	3hours	Room Temperature	67.3%	Ethanol	220°C-221°C

Table (2.12):the reaction conditions of compounds, (XV, XVI, XVII, XVIII).



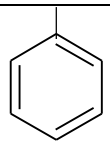
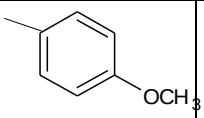
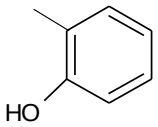
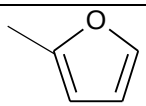
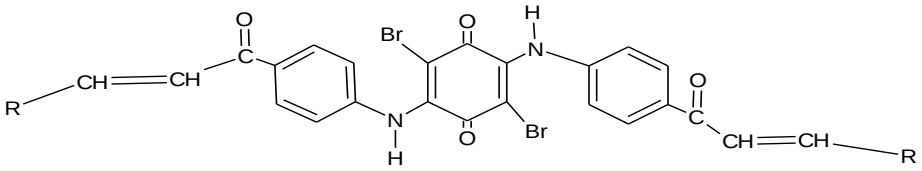
Com. No.	R	Reaction Time	Temperature	Yield%	Recrystallization Solvent	M.P
XV		3hours	Room Temperature	63.2%	Ethanol	247°C-248°C
XVI		3 hours	Room Temperature	52.9%	Ethanol	230°C-231°C
XVII		3 hours	Room Temperature	49.1%	Ethanol	244°C-245°C
XVIII		3 hours	Room Temperature	57.6%	Ethanol	240°C-241°C

Table (2.13):The reaction conditions of compounds (XIX, XX, XXI, XXII).



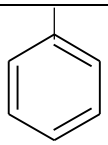
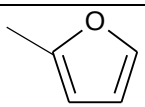
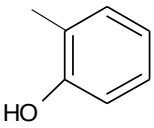
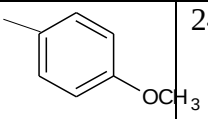
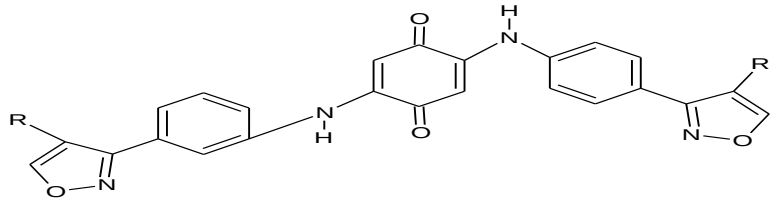
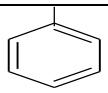
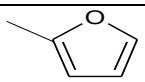
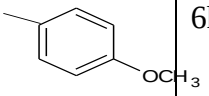
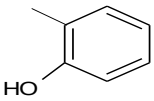
Com. No.	R	Reaction Time	Temperature	Yield%	Recrystallization solvent	M.P
XIX		24hours	Room Temperature	69.5%	Ethanol	241°C-242°C
XX		24hours	Room Temperature	54.3%	Ethanol	238°C-239°C
XXI		24hours	Room Temperature	63.4%	Ethanol	253°C-254°C
XXII		24hours	Room Temperature	51.2%	Ethanol	258°C-259°C

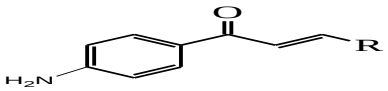
Table. (2.14):The reaction conditions of compounds (X, XI, XII, XIII).



Com. No.	R	Reaction Time	Temperature	Yield%	Recrystallization solvent	M.P
X		6hours	Room Temperature	54.7%	Ethanol	251°C-252°C
XI		6hours	Room Temperature	40.3%	Ethanol	259°C-260°C
XII		6hours	Room Temperature	43.5%	Ethanol	283°C-284°C
XIII		6hours	Room Temperature	62.8%	Ethanol	287°C-288°C

2.5: Infra-Red Spectrum bands of synthesized compounds

Table(2.15):Infra-red spectrum bands of α,β unsaturated carbonyl compounds derivatives. (II, III, IV, V).



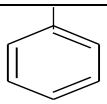
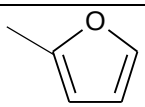
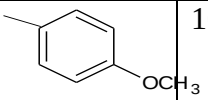
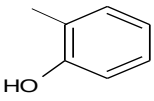
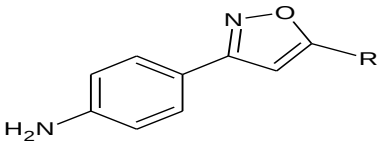
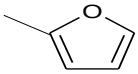
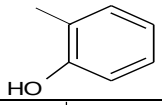
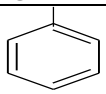
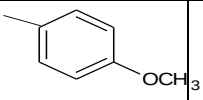
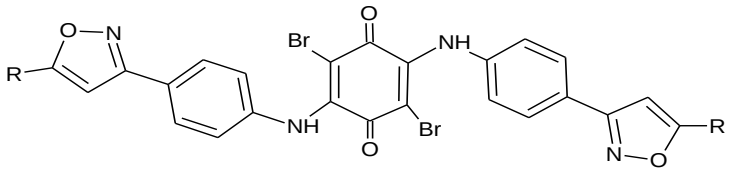
Com. No.	R	C=O st.vib cm^{-1}	C=C Olefinics t.vib cm^{-1}	C=Carom.st vib cm^{-1}	C-H st.vib cm^{-1}	C-H arom vib cm^{-1}	N-H	Other groups
II		1650.95	1629.74	1558.39	767.62	3342.41	3463.92	1336.58(C-N)
III		1637.45	1604.66	1585.38 1475.44	742.54	3328.91	3440.77	1336.58(C-N)
IV		1658.67	1596.95	1571.88	815.83	3336.32	3400	1292.22 (OCH_3) 1340,43(C-N)
V		1643.24	1595.02	1569.05	750.36	3247.90	3450	3247.64(O-H) 1342.36 (C-N)

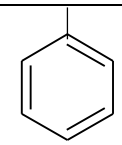
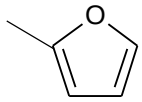
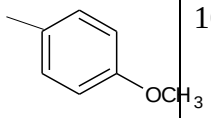
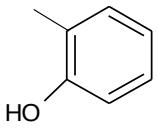
Table.(2.16):Infra-red spectrum bands of isoxazoles (VI,VII,VIII, IX).



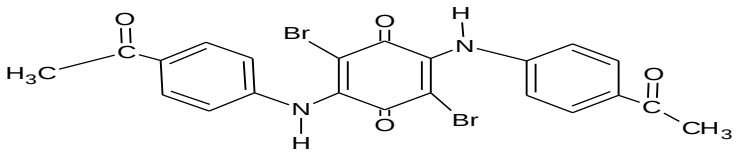
Com. No.	R	C=C Olefinic St-vib cm^{-1}	C=C (arom.) St-vib cm^{-1}	C-H St-vib cm^{-1}	C-H (arom.) vib cm^{-1}	C=N	NH_2
VI		1647.10	1591.16	805.98	3228.62	1564.16	3465.84
VII		1662.52	1512.09	678.90	3203.54	1583.45	3417.83
VIII		1564.16	1496.66	703.92	3348.19	1587.31	3743.57
IX		1645.17	1515.94	671.18	3000	1677.95	3336.62

Table(2.17):The infra-red spectrum of bands of compounds(X, XI,XII,XIII).



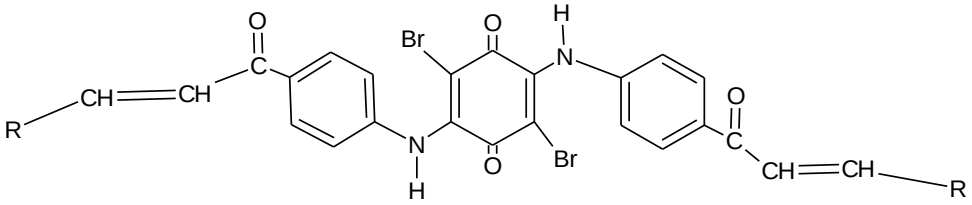
Com. No.	R	C=O	C=C (olefinic) st-vib cm^{-1}	C=C(arom.) St-vib cm^{-1}	C-H(olefinic) st-vib cm-1	C-H(arom	C=N	Other group
X		1672.17	1558.38	1541.02	3348.19	703.97	1458.08	867.91(C-Br)
XI		1672	1639	1541.02	3336.62	703.97	1488.94	867.91(C-Br)
XII		1672	1587.31	1564.16	3348.19	703.97	1496.66	867.91(C-Br)
XIII		1672.17	1639.38	1541.02	3336.62	703.19	1486.94	867.91(C-Br)

Table(2.18):Infra-Red spectrum bands of the synthesized compound (XIV)



Com. No.	C=O	C=C (olefinic) st-vib cm^{-1}	C=C(arom). st.vib cm^{-1}	C-H (olefinic) st-vib cm^{-1}	C-H (arom.) st-vib cm^{-1}	N-H	Other group
XIV	1627.81	1579.68	1521.73	3095.54	748.33	3404.13	867.91(C-Br)

Table.(2.19):The infra-Red spectrum bands of synthesized compounds (XV, XVI, XVII, XVIII).



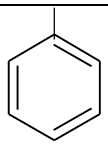
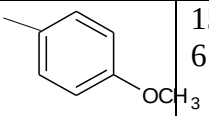
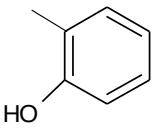
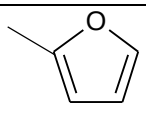
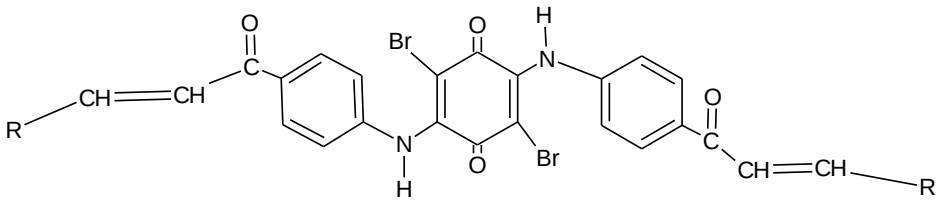
Com. No.	R	C=C olefin st.vib	C=C aroms t.vib	C=O st.vib	C-H St.vib	C-Haro mst.vib	N-H St.vib	Other groups
XV		1544.88	1473.51	1672.17	703.97	3336.6	3568.06	875.62 (C-Br)
XVI		1564.16	1419.51	1672.17	703.97	3336.62	3735.86	1338.51 (OCH_3) 867.91(C-Br)
XVII		1587.31	1498.66	1672.17	703.97	3203.54	3743.57	3348.19(OH) 867.19 (C-Br)
XVIII		1544.88	13338.51	1679.88	.703.96	3311.55	3735.86	867.19(C-Br)

Table 2.20:The infra Red spectrum bands of the synthesized compounds (XIX, XX,XXI,XXII)



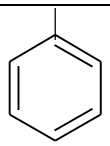
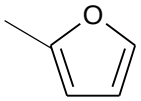
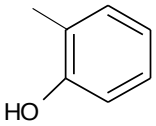
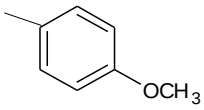
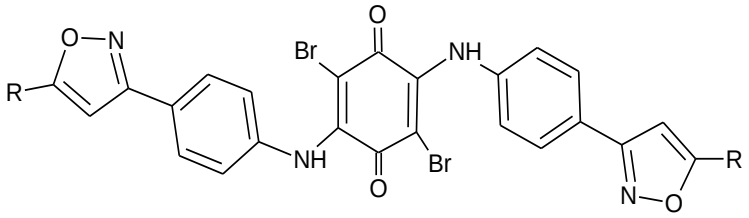
Compound No.	R	C=C olefin st.vib	C=C aromst.vib	C=O st.vib.	C-H aromst.vib	C-H st.Vib	N-H st.vib	Other group
XIX		1508.23	1338.51	1672.17	3336.62	703.97	3735.86	867.91(C-Br)
XX		1554.88	1338.51	1679.88	3311.35	703.97	3735.86	867.19(C-Br)
XXI		1541.02	1326.93	1647.10	3419.56	752.19	3853.51	3286.48(OH) 823.56(Br)
XXII		1539.09	1419.51	1645.17	3336.62	852.48	3743.7	1217(OCH_3) 852.48 (C-Br)

Table (2.21):The infra Red spectrum bands of the synthesized *p*-quinones derivatives(X, XI, XII, XIII).



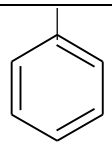
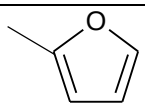
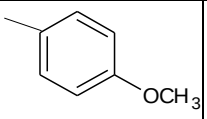
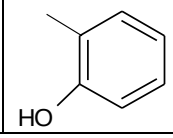
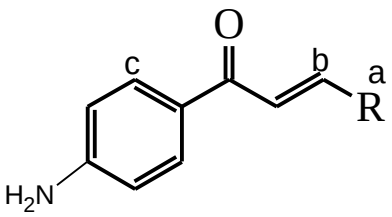
Com. No.	R	C=C olefin st.vib	C=C aromst .vib	C=O st.vib.	C-H aromst .vib	C-H st.vib	N-H st.vib	Other group
X		1564.16	1338.51	1672.17	3348.19	703.97	3735.60	(C-Br) 867.91
XI		1544.88	1338.51	1679.88	3311.55	703.97	3735.60	(C-Br) 867.91
XII		1541.02	1338.51	1672.17	3348.19	703.97	3749.36	(C-Br) 867.91
XIII		1544.88	1338.51	1672.17	3336.62	703.97	3751.29	(C-Br) 867.91

Table.(2.22): Proton Magnetic Resonance Spectrum bands of the synthesized compounds (^{1}H- NMR),(II,III,IV,V)



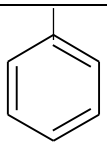
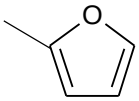
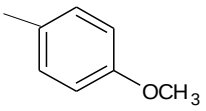
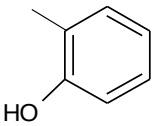
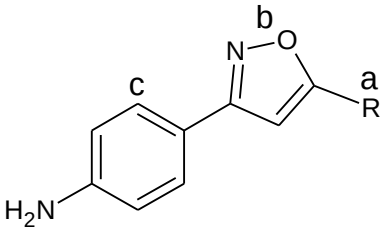
Com. No	R	Solvent	Chemical shift		
			a	B	c
II		DMSO	7.16-7.18 ppm(m,Ar-H)	2.38-2.50 ppm(d,2H)	7.89-7.92 ppm (m,Ar-H) 3.46-3.87(3.46-3.87) ppm(s,2H-NH_2
III		DMSO	6.12ppm (s,1H-furan	2.48-2.50ppm (d,2H)	7.46-7.84ppm (m,Ar-H) 3.32ppm (s,2H-NH_2)
IV		DMSO	7.78-7.97ppm (m,4Ar-H) 4.27ppm (s,3H-OCH_3)	2.39-2.40 ppm(d,2H)	7.63-7.95 ppm (m,4Ar-H) 3.80-3.86ppm (s,2H-NH_2)
V		DMSO	7.95-8.35ppm (m,4Ar-H) 4.59ppm (s,1H-OH)	2.38-2.59ppm (d,2H)	7.51-7.89ppm(m,4Ar-H) 3.45-3.56ppm (s,2H-NH_2

Table (2.23): Proton Magnetic Resonance Spectrum bands of the synthesized compounds (^{1}H- NMR),(VI,VII,VIII,IX)



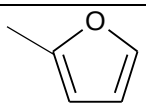
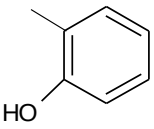
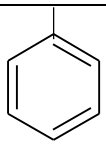
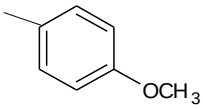
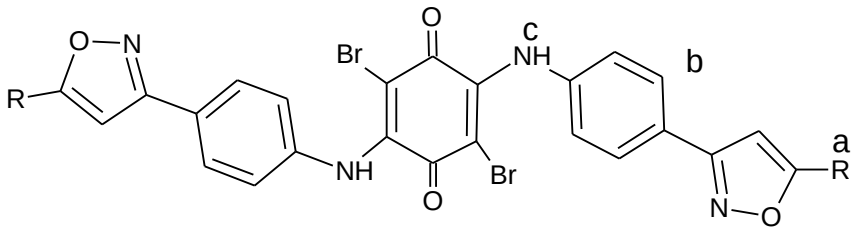
Com No.	R	Solvent	Chemical Shift		
			a	B	C
VI		DMSO	6.00 ppm (d,1H-furan	6.54-6.57 ppm(s,1H-isoxazole)	7.64-7.67ppm(m,4 Ar-H) 3.37ppm(s,2H -NH_2)
VII		DMSO	7.90-7.93 ppm (m,4Ar-H) 3.65ppm(s,1H -OH)	6.58-6.61ppm (s,1H-isoxazole)	7.66-7.68 ppm(m,4Ar-H 3.45 ppm (s,2H-NH_2)
VIII		DMSO	8.07-8.01ppm (m,5Ar-H)	7.39-7.43 ppm(s,1H-isoxazole)	8.66-8.67ppm(m,4 Ar-H) 3.61ppm(s,2H -NH_2)
IX		DMSO	6.50ppm(m,4 Ar-H) 4.18ppm(s,3H -OCH_3)	6.40 ppm(s,1H-isoxazole)	7.60 ppm(m,4Ar-H) 3.22-3.26 ppm(s,2H-NH_2)

Table (2.24): Proton Magnetic Resonance Spectrum bands of the synthesized compounds (^{1}H- NMR),(X,XI,XII,XIII)



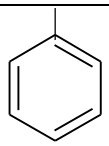
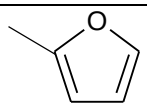
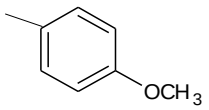
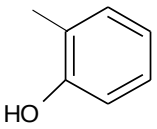
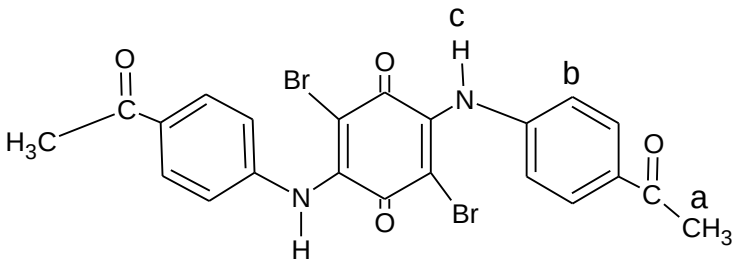
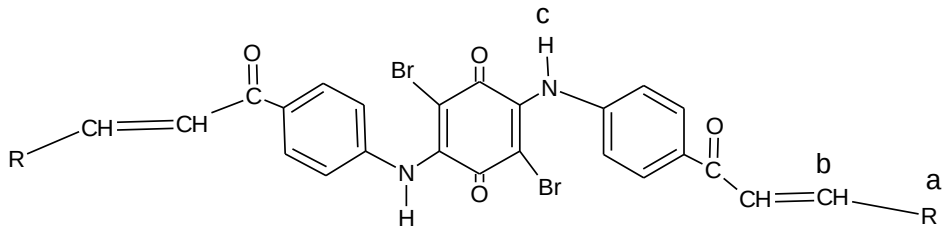
Com. No.	R	Solvent	Chemical shift		
X		DMSO	a	B	C
			7.78 ppm(m,8Ar-H)	6.40 ppm(s,2H-2 isoxazoles)	2.50 ppm(s,2H-2NH
XI		DMSO	6.90 ppm(s,1H-furan)	6.50 ppm(s,2H-2isoxazoles) 8.77ppm(m,8Ar-H).	2.49(s-2H-2NH)
XII		DMSO	7.80 ppm(m,8Ar-H 2 rings) 2.78 ppm (s,3H-OCH_3)	7.19 ppm (m,8Ar-H) 6.55ppm(s,2H-2 isoxazoles)	2.50(s,2H-2NH)
XIII		DMSO	7.80 ppm(m,8Ar-H 2 rings) 2.51ppm (s,2H-2-OH)	6.80 ppm(s,2H-2 isoxazoles).7.90 ppm (m,8Ar-H)	2.49-2.51 ppm(s,2H-2NH)

Table (2.25): Proton Magnetic Resonance Spectrum bands of the synthesized compound (^{1}H- NMR),(XIV)



Compound No.	R	solvent	Chemical Shift		
			a	B	C
XIV	-	DMSO	2.08 ppm (s,6H-2CH_3)	7.57-7.89 ppm (m,8Ar-H 2 rings)	2.49-2.50 ppm (s,2H-2NH)

Table(2.26) :Proton Magnetic Resonance Spectrum bands of the synthesized compounds (^{1}H- NMR.(XV,XVI,XVII,XVIII).



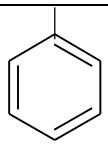
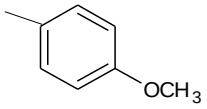
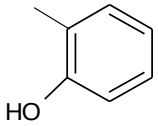
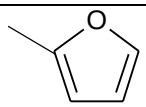
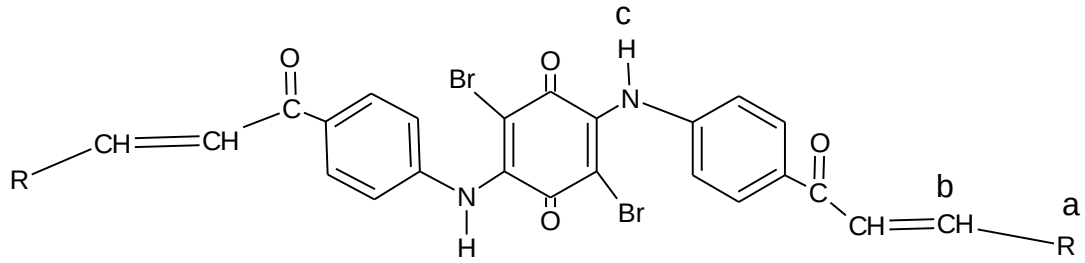
Com. No.	R	Solvent	Chemical shift		
			a	b	C
XV		DMSO	7.39 ppm(10Ar-H 2 rings)	2.08-2.09 ppm(d,4H)	2.49-2.50 ppm(s,2H-2NH)
XVI		DMSO	8.12-8.15 ppm(m,8Ar-H) 4.61 ppm (s,6H-2OCH_3)	2.08ppm (d,4H) 7.74-7.87 ppm (m,8Ar-H) 2 rings	3.82 ppm (s,2H-2NH)
XVII		DMSO	8.00 ppm(m,8Ar-H) 2 rings 4.49 ppm (s,2H-2OH)	2.00- 2.30) ppm (d,4H) 7.39 ppm (m,8Ar-H)	3.60 ppm (s,2H-2NH)
XVIII		DMSO	7.21 ppm (m,6Ar-H) 2 furan	2.25-2.27 ppm (d,4H) 7.80 ppm (m,8Ar-H)	3.60-3.90 ppm (s,2H-2NH)

Table (2.27): Proton Magnetic Resonance Spectrum bands of the synthesized compounds (^{1}H- NMR.(XIX,XX,XXI,XXII)



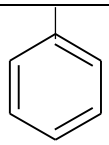
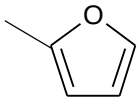
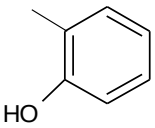
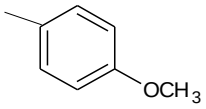
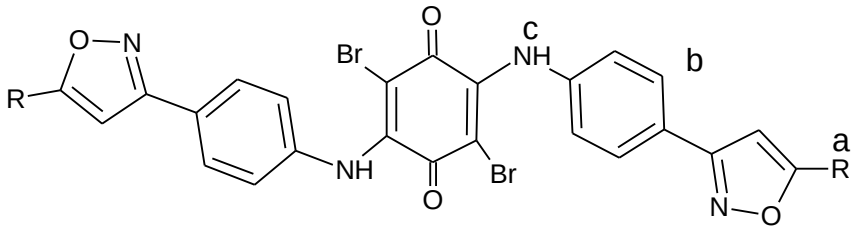
Com. No.	R	Solvent	Chemical Shift		
			a	b	C
XIX		DMSO	7.22-7.47 ppm(m,8Ar-H) 2 rings	7.90-7.96 ppm (m,8Ar-H) 2.50-2.55 ppm (d,4H-2CH=CH)	4.76 ppm(s,2H-2NH)
XX		DMSO	6.89 ppm (m,6Ar-H) 2 furan.	7.80-8.05 ppm(m,8Ar-H) 2.08-2.55 ppm(d,4H-2CH=CH)	4.76 ppm (s,2H-2NH)
XXI		DMSO	6.90-7.93 ppm(m,8Ar-H) 5.39-5.47 ppm(s,2H-2OH)	7.22-7.28 ppm(m,8Ar-H) 2.08-2.55ppm(d,4H-2CH=CH)	4.76-5.05 ppm(s,2H-2NH)
XXII		DMSO	6.90-7.93 ppm(m,8Ar-H)	7.87-7.93 ppm(m,8Ar-H) 2.08-2.55 ppm(d,4H-2CH=CH)	4.15-4.76 ppm(s-2H-2NH)

Table (2.28): Proton Magnetic Resonance Spectrum bands of the synthesized compounds (^{1}H- NMR.(X,XI,XII,XIII)



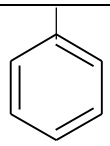
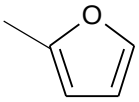
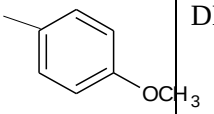
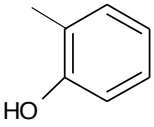
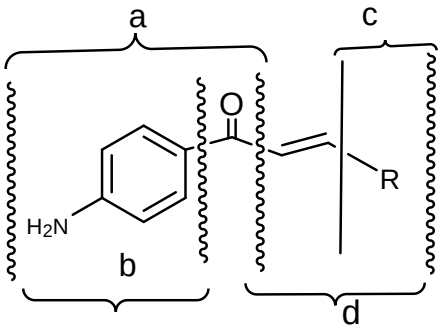
Com. No.	R	Solvent	Chemical shift		
			a	b	c
X		DMSO	7.89-7.91ppm (m, 8Ar-H)	7.11ppm(s,1H,isoxazole)	2.54ppm(s,1H, NH)
XI		DMSO	7.18ppm(d, 1H furan) 7.35-7.52ppm(m, 8Ar-H)	6.14ppm(s,1H,isoxazole)	2.50 ppm(s,1H,NH)
XII		DMSO	7.20-7.80ppm(m-8Ar-H).2.08(s,3H-OCH_3)	6.55ppm(s,1H-isoxazole)	2.50(s,1H,NH)
XIII		DMSO	7.20-7.80ppm(m, 8Ar-H 2.08(s,3H-OCH_3)	6.80ppm(s,1H-isoxazole	2.06(s,1H-NH)

Table (2.29): Mass spectrum bands of some synthesized α,β-unsaturated carbonyl compounds derivatives .II,III,IV,V.



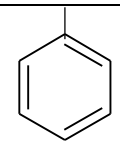
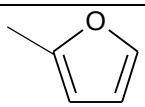
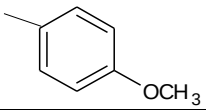
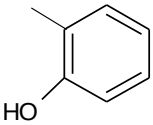
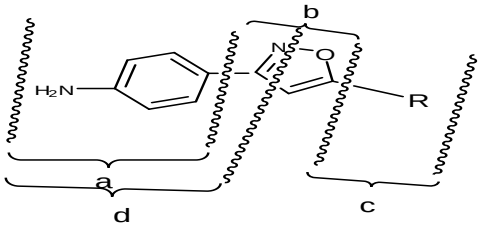
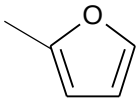
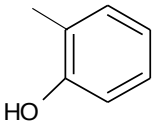
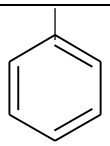
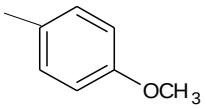
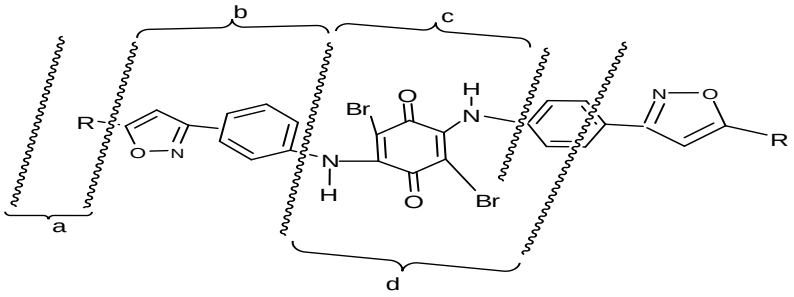
Com. No.	R	Molecular formula	MW (calculated)	MW(absorbed)	Z/M Relative. Abundance%			
					a	b	c	d
II		$C_{15}H_{13}NO$	223	223(44.07)	120(100)	92(44.31)	77(39.32)	135(21.46)
III		$C_{13}H_{11}N\ O_2$	213	213(100)	120(91)	92(45.98)	65(59.32)	91(4.36)
IV		$C_{16}H_{15}NO_2$	253	253(100)	120(65.79)	92(37.13)	105(1.22)	145(0.30)
V		$C_{15}H_{13}NO_2$	239	239(14.05)	120(100)	92(28.22)	93(60.96)	109(0.20)

Table (2.30): Mass spectrum of the synthesized isoxazoles(VI, VII, VIII,IX).



Compound No.	R	Molecular formula	MW (calculated)	M.W. Absorbed	Z/M Relative. Abundance%			
					a	b	c	d
VI		$C_{13}H_{10}N_2O_2$	226	226(0.96)	92 (40.80)	120(79.18)	55(18.24)	149 (3.00)
VII		$C_{16}H_{12}N_2O_2$	252	252(54.61)	92 (17.25)	118(23.81)	93(2.42)	94(0.40)
VIII		$C_{15}H_{13}N_2O$	236	237(3.56)	92 (54.68)	122 (73.17)	80(9 .90)	77(1 1.67)
IX		$C_{16}H_{14}N_2O_2$	266	266(2.20)	92 3.23)	120 (5. 18	110(3.54)	107(3.54)

Table(2.31):The mass spectrum bands of the synthesized *p*- quinones derivatives (X,XI,XII,XIII)



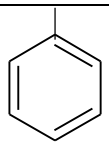
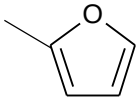
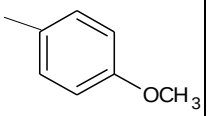
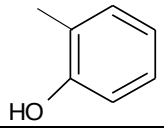
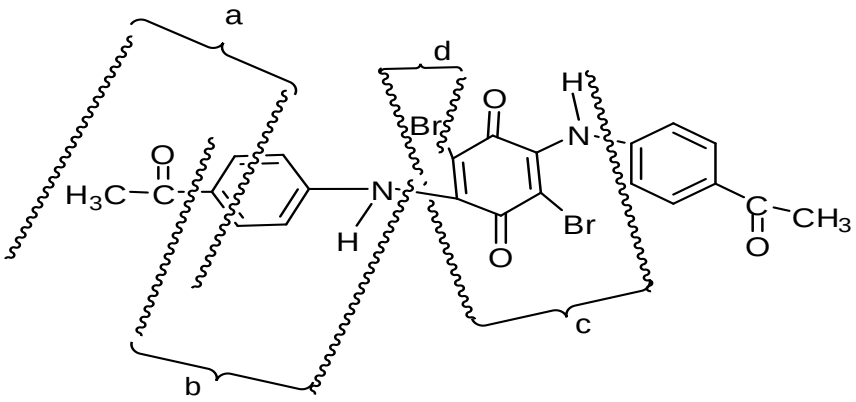
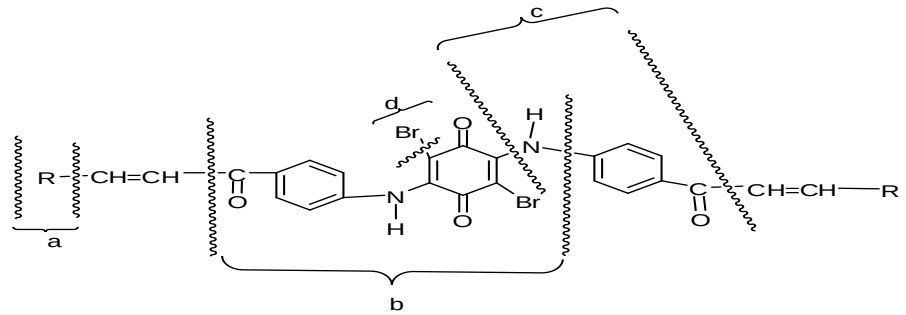
Compound No.	R	Molecular formula	M.W(calculated)	M.W(absorbed)	Z/M Relative. Abundance%			
					a	b	C	d
X		$C_{36}H_{22}N_4O_4Br_2$	734	733(4.71)	77 (20.30)	131 (12.18)	290(5.41)	343 (4.66)
XI		$C_{32}H_{18}N_4O_6Br_2$	714	714(0.23)	67 (0.82)	131 (100)	290(2.49)	343 (4.91)
XII		$C_{36}H_{26}N_4O_6Br_2$	794	795.80(0.29)	105(11.43)	131 (100)	290(2.52)	343 (54.94)
XIII		$C_{36}H_{22}N_4O_6Br_2$	766	766(0.12)	91 (9.01)	131 (100)	290(2.68)	343 (4.97)

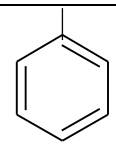
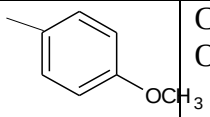
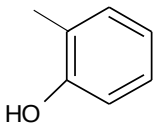
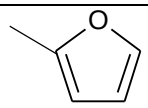
Table (2.32): The mass spectrum bands of the synthesized compound (XIV).



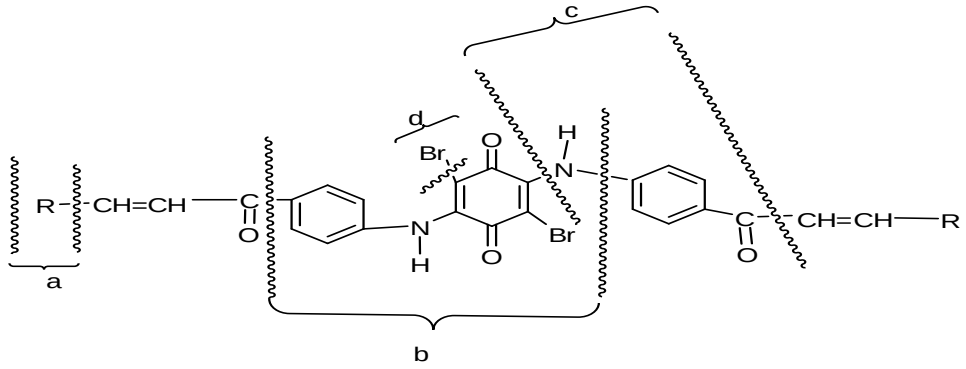
Com. No.	R	Molecular formula	M.W(calculated)	M.W(absorbed)	Z/M Relative. Abundance%			
					a	b	c	d
XIV	-	$C_{22}H_{16}N_2O_4Br_2$	532	532(76.84)	64(85.30)	91(86.82)	186(100.00)	80(81.04)

Table (2.33):The mass spectrum bands of the synthesized compound (XV, XVI, XVII, and XVIII).



Com. No.	R	Molecular formula	M.W(calculated)	M.W(absorbed)	Z/M Relative. Abundance%			
					a	b	C	d
XV		$C_{36}H_{24}N_2O_4Br_2$	708	708(5.12)	77(52.69)	367(13.06)	119(16.21)	80(100)
XVI		$C_{38}H_{28}N_2O_6Br_2$	768	768(0.20)	107(0.26)	369(0.15)	119(0.42)	80(100)
XVII		$C_{34}H_{26}N_2O_4Br_2$	740	740(2.26)	91(70.56)	367(19.24)	119(17.16)	80(100)
XVIII		$C_{32}H_{20}N_2O_6Br_2$	688	689(5.41)	64(55.03)	367(25.30)	119(20.54)	80(92.43)

Table(2.34): The mass spectrum bands of the synthesized compound (XIX, XX, XXI, XXII).



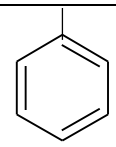
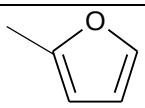
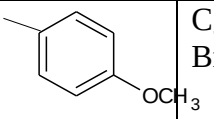
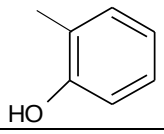
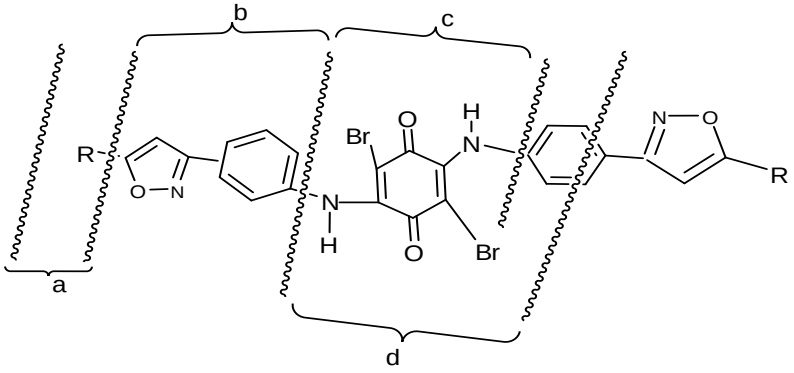
Com No.	R	Molecular formula	M.W (calculated)	M.W(absorbed)	Z/M Relative. Abundance%			
					a	b	C	d
XIX		$C_{36}H_{24}N_2O_4Br_2$	708	708(5.12)	77(52.69)	367(13.06)	119(16.21)	80(100)
XX		$C_{32}H_{20}N_2O_6Br_2$	688	689(5.41)	64(55.03)	367(25.30)	119(20.54)	80(92.43)
XXI		$C_{34}H_{26}N_2O_4Br_2$	740	740(2.26)	91(70.56)	367(19.24)	119(17.16)	80(100)
XXII		$C_{38}H_{28}N_2O_6Br_2$	768	768(0.20)	107(0.26)	369(0.15)	119(0.42)	80(100)

Table (2.35):The mass spectrum bands of the synthesized compound (X,XI, XII, XIII)



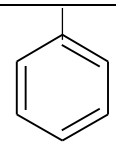
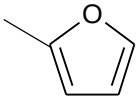
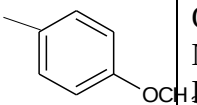
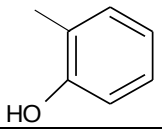
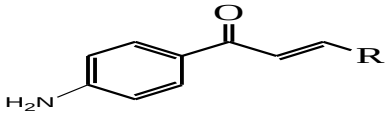
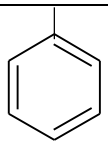
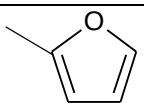
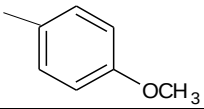
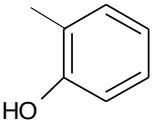
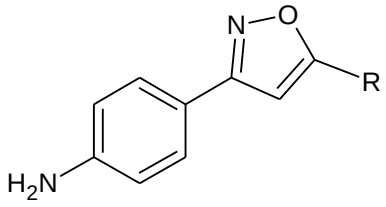
Com No	R	Molecular formula	M.W (calculated)	M.W(absorbed)	Z/M Relative. Abundance%			
					a	b	c	d
X		$C_{36}H_{22}N_4O_4Br_2$	734	734(1.43)	80(40.60)	131(2.91	289(1.90)	343(0.87)
XI		$C_{32}H_{18}N_4O_6Br_2$	714	714(5.18)	67(24.91)	131	294(4.23)	344(2.87)
XII		$C_{36}H_{26}N_4O_6Br_2$	794	794(4.25)	105(8.26)	135(13.75)	290(3.78)	347(2.01)
XIII		$C_{36}H_{22}N_4O_6Br_2$	766	794(4.25)	91(9.01)	131(100)	290(2.68)	343(4.97)

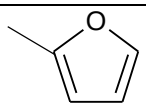
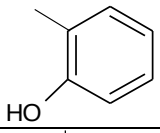
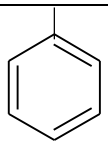
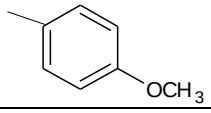
Table (2.36):TLC data of the α-β unsaturated carbonyl compounds(II, III, IV, V).



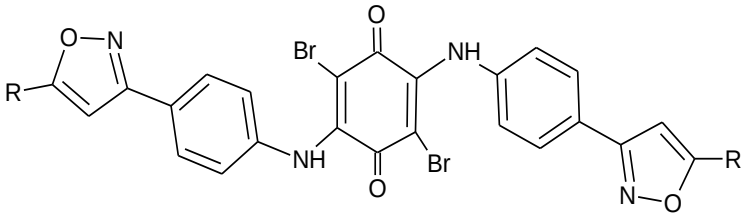
Compound No.	R	Solvent used	Rf value
II		Chloroform 9.8:0.2 methanol	0.97
III		Chloroform 9.8:0.2 methanol	0.85
IV		Chloroform 9.8:0.2 methanol	0.87
V		Chloroform 9.8:0.2 methanol	0.83

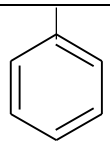
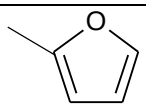
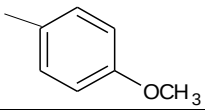
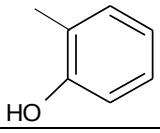
Table(2.37): TLC data of isoxazoles derivatives(VI,VII,VIII,IX).



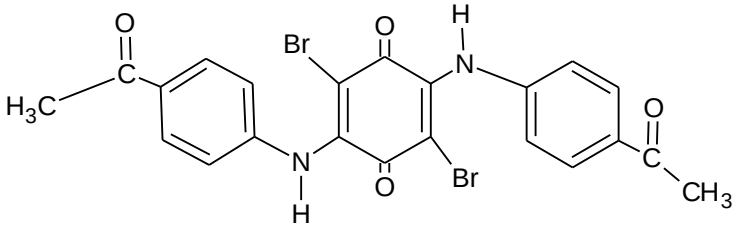
Compound No.	R	Solvent used	Rf value
VI		Chloroform 9.8:0.2 methanol	0.87
VII		Chloroform 9.8:0.2 methanol	0.83
VIII		Chloroform 9.8:0.2 methanol	0.76
IX		Chloroform 9.8:0.2 methanol	0.78

Table(2.38):TLC data of *p*- quinones derivatives compounds (X,XI,XII,XIII).



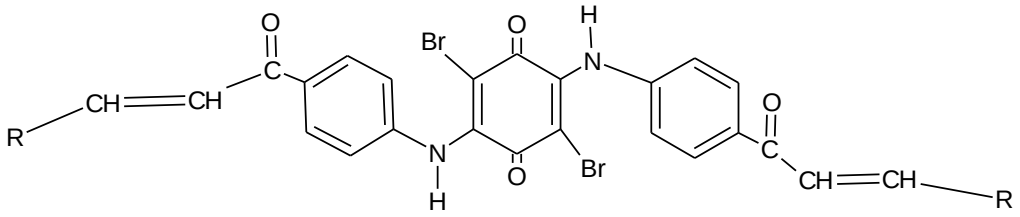
Compound No.	R	Solvent used	Rf. value
X		Chloroform 9.8:0.2 methanol	0.70
XI		Chloroform 9.8:0.2 methanol	0.78
XII		Chloroform 9.8:0.2 methanol	0.74
XIII		Chloroform 9.8:0.2 methanol	0.79

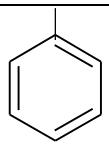
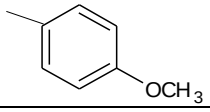
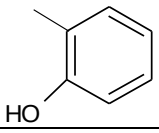
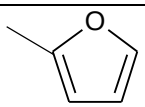
Table(2.39):TLC data of the synthesized compound (XIV).



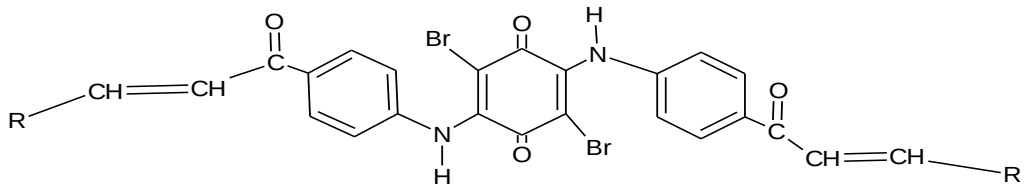
Compound No.	R	Solvent used	Rf value
XIV	-	Chloroform 9.8:0.2 methanol	0.72

Table (2.40): TLC data of the α,β- unsaturated carbonyl compounds derivatives XV,XVI,XVII,XVIII.



Compound No.	R	Solvent used	Rf value
XV		Chloroform 9.8:0.2 methanol	0.82
XVI		Chloroform 9.8:0.2 methanol	0.79
XVII		Chloroform 9.8:0.2 methanol	0.77
XVIII		Chloroform 9.8:0.2 methanol	0.78

Table(2.41):TLC data of the synthesized compounds(XIX,XX, XXI,XXII).



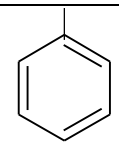
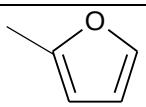
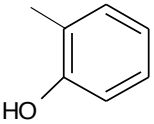
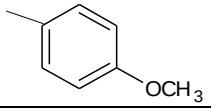
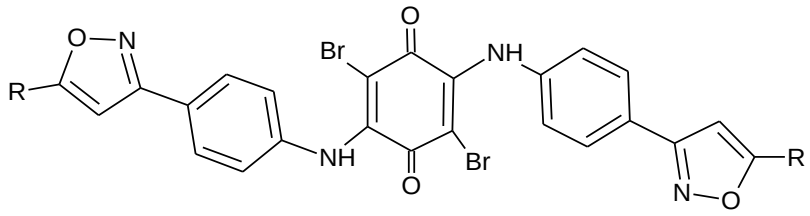
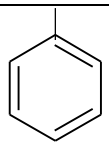
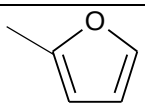
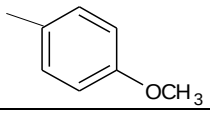
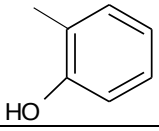
Compound No.	R	Solvent used	Rf value
XIX		Chloroform 9.9:0.1 methanol	0.84
XX		Chloroform 9.9:0.1 methanol	0.88
XXI		Chloroform 9.9:0.1 methanol	0.81
XXII		Chloroform 9.9:0.1 methanol	0.87

Table (2.42): TLC data of *p*- quinones derivatives(X, XI, XII, XIII).



Compound No.	R	Solvent used	Rf value
X		Chloroform 9.9:0.1 methanol	0.93
XI		Chloroform 9.9:0.1 methanol	0.38
XII		Chloroform 9.9:0.1 methanol	0.92
XIII		Chloroform 9.9:0.1 methanol	0.84

Chapter Three

Discussion

In this work, two procedures were carried out for the reactions of the synthesis of p-quinones derivatives (i.e.the target compounds). In the First one, the synthesis of α, β- unsaturated carbonyl compounds was carried out by the reaction of *p*- amino-acetophenone with different aromatic aldehydes in presence of NaOH. The characterization and identification of α,β- unsaturated carbonyl derivatives was carried out by determining physical properties(TLC, M.p, IR, ^{1}HMR, Ms).Then it was followed by the cyclization reaction of the hydroxylamine hydrochloride with the resulted α,β- unsaturated carbonyl derivatives to produce the target compounds. The second procedure was carried out by the reaction of tetrabromo-1,4-benzoquinone (bromanil) with *p*-amino-acetophenone whic gave the intermediate (2,5-dibromo-3,6-diamino-(*p*-diacetylphenyl)-1,4-dione).This was reacted with the required aldehydes to give the α,β-unsaturated carbonyl derivatives, which upon cyclization with hydroxylamine to yield the *p*-quinones derivatives.

3.1.Retrosynthetic analysis of α,β- unsaturated carbonyl compounds, isoxazoles, *p*-quinone derivatives.

Retrosynthetic analysis is used to describe a problem-solving approach that "works backward". An organic synthesis typically involves a series of steps to transform "starting materials" – the molecules that begun with – into the "target" molecule – the molecule that was made.
The synthetic strategies followed in courses of this work have been constructed from the appropriate retrosynthetic analysis of the target molecules.

The, β- unsaturated carbonyl compounds can be disconnected at-C=C-bond.The basic of ring of isoxazole derivatives can be disconnected at C-O, and C-N bonds through ring opening. The target molecules i.e. *p*-quinone derivatives were disconnected at C-N bond.

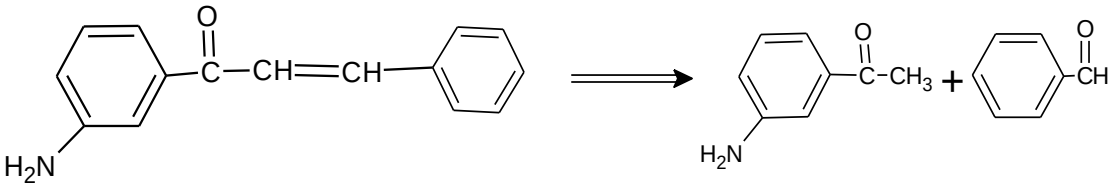


Fig. 3.1.Retrosynthesis analysis of α,β- unsaturated carbonyl compounds

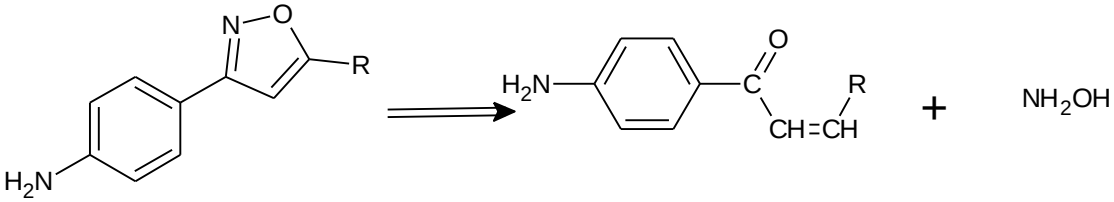


Fig.3.2.Retrosynthesis analysis of isxozoles derivatives

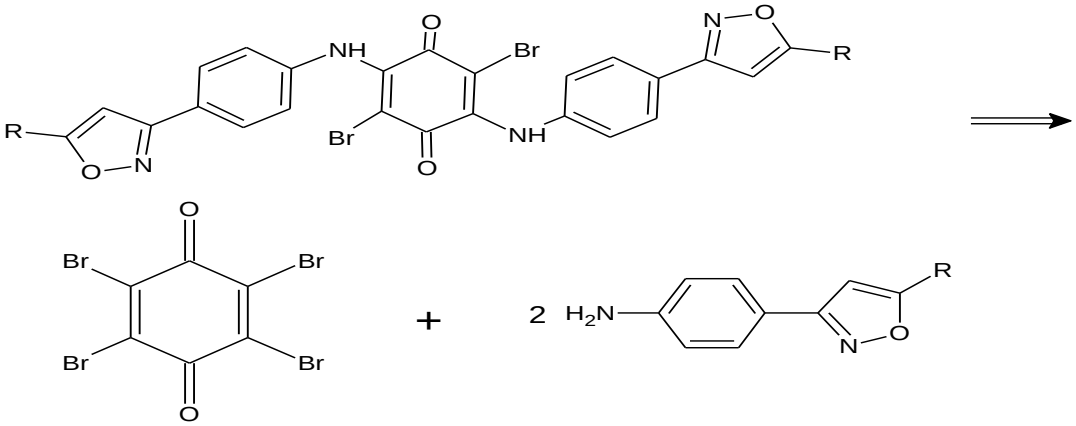


Fig.3.3.Retrosynthesis analysis of *p*- quinones derivatives

3.2. Reactions mechanism

3.2.1. The mechanism of the Base catalyzed reaction

The main method for the synthesis of the, β -unsaturated carbonyl compounds is the classical Claisen – Schmidt condensation in presence of aqueous alkaline bases.(Chetana *etal*., 2009).

Step 1

The nucleophilic addition of carbanion derived from the methyl group of the ketone, to the carbonyl carbon of the aromatic aldehyde.

Step 2

The dehydration of the β- hydroxyl ketone to form the conjugated compound, i.e. the,α, β-unsaturated carbonyl compound.

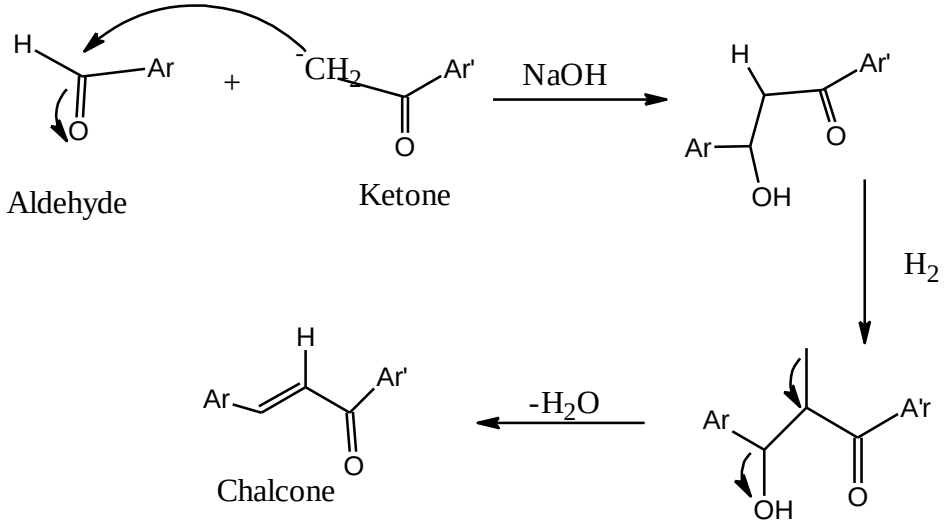


Fig.3.4.The mechanism of the base catalyzed reaction of formation ofthe α, β – unsaturated carbonyl compound.

3.2.2. The mechanism of Acid catalyzed reaction:-

The reaction is initiated by the protonation of the aromatic ketone or aldehyde followed by the nucleophilic addition of carbanian derived from the methyl ketone or aldehyde to the carbonyl carbon, and finally the dehydration of the β- hydroxyl ketone to form the conjugated compound, i.e. theα, β -unsaturated carbonyl compound.

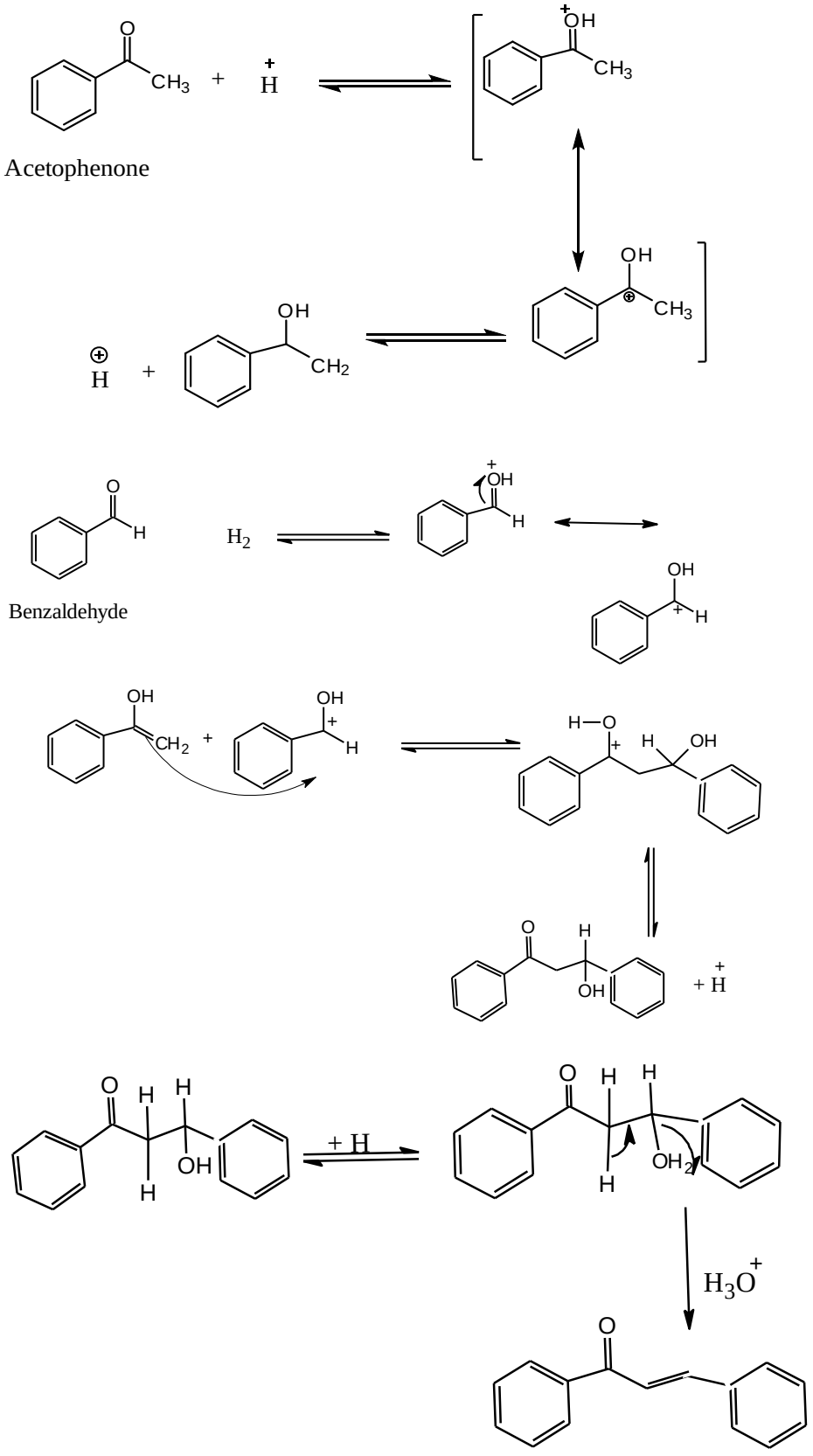


Fig.3.5. Reaction mechanism of the acidcatalyzed reaction of formation of , α, β – unsaturated carbonyl compound derivatives.

3. 2.3. Reaction mechanism of formation of isoxazole derivatives

Isoxazole is five membered heterocyclic compound containing oxygen and nitrogen in 1,2-position. It was prepared by condensation and cyclization of α,β-unsaturated carbonyl compounds with hydroxylamine hydrochloride in presence of a base and alcohol.

Step I. is the reaction by nucleophilic attack of nitrogen of hydroxylamine to carbon- carbonyl group.

Step II. nucleophilic attack by oxygen of hydroxyl to electrophilic β-carbon of conjugated α, β-unsaturated compound and protonated the oxygen of carbonyl group.

Step III. condensation of the product II.

Step IV. elimination reaction losing two molecule of water lead to the formation of isoxazole derivatives.

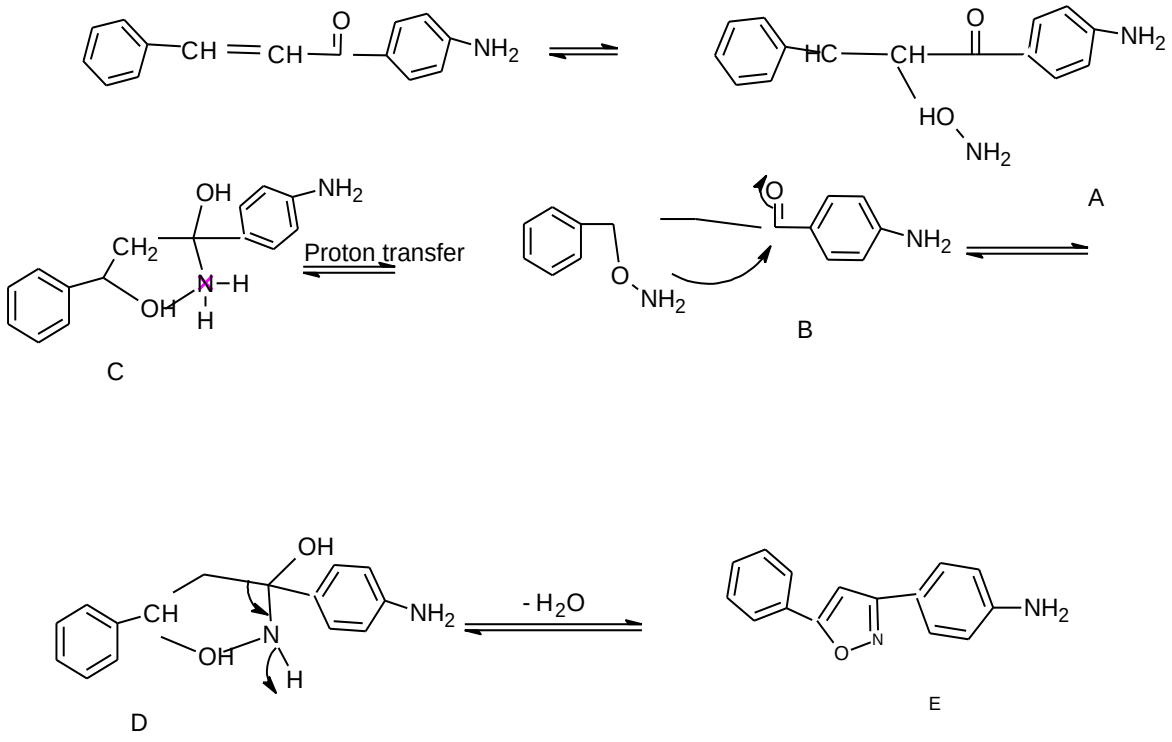
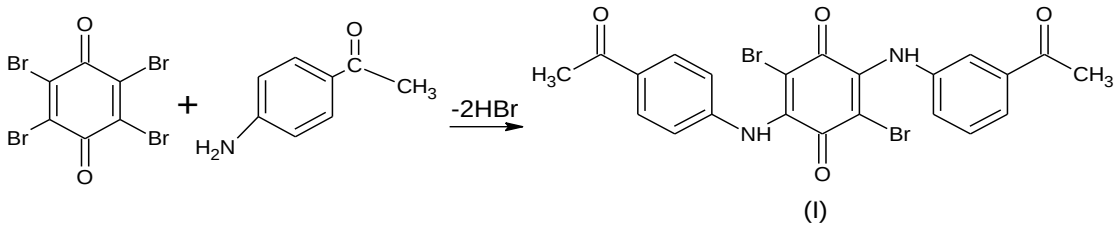


Fig.3.6.The mechanism of the reaction formation of isoxazole derivatives.

3. 2.4. Reaction mechanism of formation of *p*-quinones derivatives:

The initial step for the reaction of these,α,β- unsaturated cyclic diketone (i.e. *p*-quinones) is the elimination of 2HBr from the reactants.

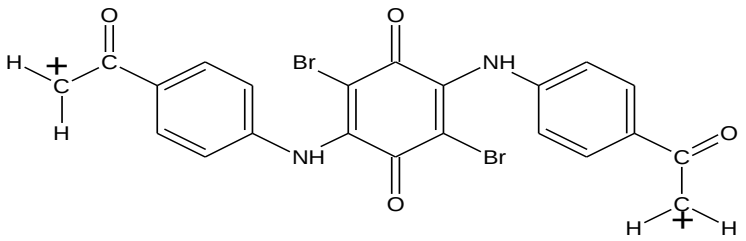
Step I



(I)

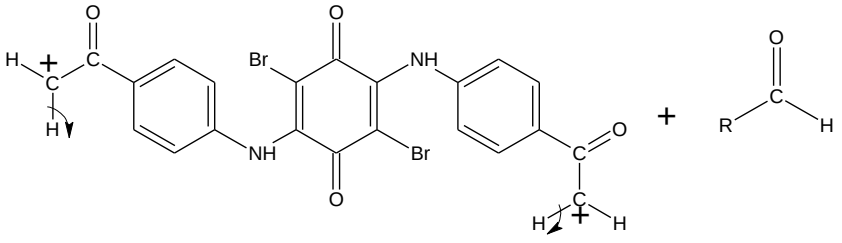
Step II

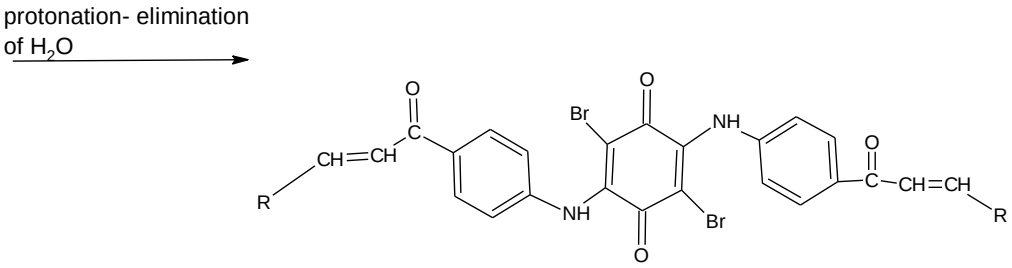
Removal of α-hydrogen from diketones to form the carbocations which react as nucelophiles in presence of a strong base.



Step III

Carbocation reacts with aromatic aldehyde derivatives under basic condition forming the α,β- unsaturated carbonyl compound.





Step IV. Compound (III) reacts with hydroxylamine in catalysis via intermediate compound form subsequently on cyclizative-dehydration lead to the formation of *p*-quinones derivatives.

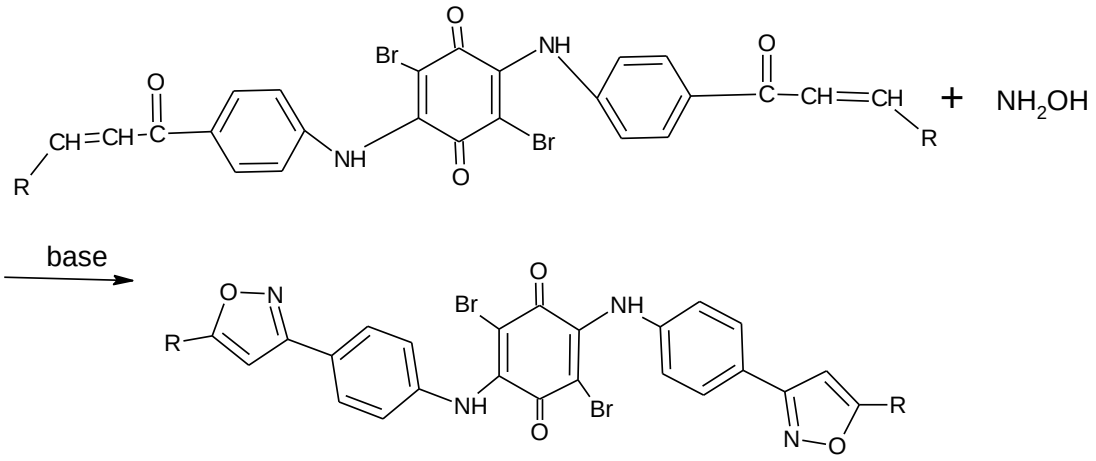


Fig.(3.7). The reaction mechanism of formation of *p*-quinones derivatives.

3.3. Spectroscopic analysis:

In this work, the identification and characterization of the synthetic compounds was carried out by determining their physical properties using (TLC, MP., IR,1HNMR and Ms) techniques.

The IR, spectrum bands of the synthesized compounds II,III,IV, V. exhibited characteristics of (C=O) st.vib which appear at (1658.67-1600.81) cm^{-1}arom (C=C) st.vib absorption bands appeared at (1585.38-1569.05) cm^{-1} · The absorption bands of olefinic (C=C)st.vib range at (1629.74-1595,02) cm^{-1}.

The synthesized compound (IV) which contained the methoxy group in the para position, its st.vib absorption bands appear at 1172.64 cm^{-1}. due to C-N .The absorption bands of IR for the synthesized the α,β-unsaturated carbonyl compound were presented in Table(2.15).

The synthesized isoxazoles derivatives in this work were prepared to give the *p*- quinones derivatives compound by the cyclization reaction of the α,β- unsaturated carbonyl compounds and hydroxylamine hydrochloric in presence of sodium acetate as a catalyst in ethanol, the mixture was refluxed for 6 hours.

The IR spectra of the synthesized isoxazoles (VII,VIII,IX,X) showed st-vib. of olefinic C=C at (1662.52- 1645.17) $cm^{-1}$and the arom. C= C st-vib bands showed at (1591.16-1512.09)cm^{-1}

The C=N absorption band were indicated at (1677.95-1564.16) cm^{-1}. The absorption bands showed at (805.48-671.18)$cm^{-1}$was C-H st.vib and the range (3348.15-3000) cm^{-1} appear due to the C-H arom. The absorption band in the range (3336.62-3465.84) cm^{-1} showed the NH_2 group of the synthesized isoxazoles. The absorption bands of IR for the synthesized isoxazoles were presented in Table(2.16).

The I.R. spectrum band of the synthesized *p*- quinones derivatives (X, XI, XII,XIII) showed the C=Ost.vib at the region 1672.17 cm^{-1} and arom C=C at the range (1564.18-1541.02) cm^{-1} and the olefinic C=C at (1639.38-1558.38)$cm^{-1}$and the arom C-H at 703.97cm^{-1} and C=N in the range (1496,66-1488.94) cm^{-1} and C-Br at the region 867.91cm^{-1}. The resulted *p*- quinones derivatives were synthesized by the reaction of the isoxazole derivatives with the reaction of the oxazoles derivatives with the bromanil in ethanolic sodium acetate and the mixture was refluxed for 3 hours.The absorption bands of IR for the synthesized p- quinones derivatives were presented in Table(2.17).

The IR spectrum of the prepared compound (XIV) showed C=O at 1627.81 cm^{-1} and arom C=C at (1521.73) cm^{-1} and the olefinic C=C was absorbed at (1579.68) cm^{-1} and the C- Hst.vib absorption bands showed at 3095.54 cm^{-1} and the C-H arom at 748.33cm^{-1} and the N-H at the region 3404.13 cm^{-1} and C-Br at 838.98 cm^{-1}.

This compound (XIV)was prepared by the reaction of bromanil (2,3,5,6-tetrabromo-1,4- Benzophenone) in sodium acetate in ethanol. The mixture was refluxed for 3 hours and left over- night at room temperature; the product was recrystallized from ethanol.The absorption bands of IR for the synthesized compound (XIV) werepresented in Table(2.18).

The synthesized compounds (XV,XVI,XVII,XVIII) were prepared by the reaction of bromonil with the four α,β- unsaturated carbonyl compounds (II,III,IV,V) in ethanolic sodium. The mixture was refluxed for three hours and the product was recrystallized from ethanol.

The IR spectrum band of these derivatives showed st.vib absorption bands in the range (1564.18-1544.88) cm^{-1} indicated the presence of (C=C) olefinic group and the range (1498.66-1338.51)cm^{-1} showed the presence of arom(C=C) group. The absorption at(1679.88-1672.17)cm^{-1} showed the (C=O) group, the st.vib absorption bands showed in the region(3336.62-3203.54)cm^{-1} indicated the st.vib C-H group and the region 703.97 cm^{-1}showed the arom(C-H) .

The st.vib bands showed in the region (3735.86-3568.06) cm^{-1} indicated the (N-H) group. The absorption bands of IR for the synthesized compounds (XV,XVI,XVII,XVIII) were presented in Table(2.19).

The IR spectra of the α,β- unsaturated carbonyl compounds (XIX,XX,XXI,XXII)st.vib bands in the range (1554.88-1539.09)cm^{-1} indicated the (C=C) olefinic group and the range(1338.51-1419.51) cm^{-1}indicated the arom (C=C),the absorption at (1679.88-1645.17) cm^{-1}indicated the (C=O) group.The region(852.48-703.97) showed the presence of C-H st-vib, and arom C-H appeared in the region (3419.56-3311.35)cm^{-1} and the(C-Br)group at 867.91 cm^{-1}.The absorption bands ofIR for the synthesized compounds (XIX, XX, XXI, XXII), were presented in Table(2.20).

The newly *p*-quinones derivatives (XXIII, XXIV, XXV,XXVI)were prepared in this work as final compounds by the cyclization of the α ,β-unsaturated carbonyl derivatives (XIX,XX,XXI,XXII) with the hydroxylamine hydrochloride in basic media and ethanol under reflux condition.

The IR spectrum bands of these derivatives showed st.vib. absorption bands in the range (1564.16-1541.02) cm^{-1} indicated the(C=C) olefinic and the region (1338.51) cm^{-1}showed the arom (C=C).The (C=O) group appeared at the range (1679.88-1672.17)cm^{-1}. The st.vib absorption bands in the range (3348.19-3311.55) cm^{-1} indicated the presence of C-H and at the region 703.97 cm^{-1}showedthearom. C-H. The st .Vib. absorption bands showed in the range (3751.29-3735.60) cm^{-1} indicate the presence of (N-H) group and at the region 867.91 cm^{-1} showed the (C-Br). The absorption bands of IR for the synthesized *p*-quinones derivatives compounds were presented in Table (2.21). ^{1}HNMR is a powerful spectroscopic technique used in structural determination of the unknown

molecules. It gives information about the accurate number, and the magnetic environment of each proton found in the unknown molecule. The results were in δ value (ppm) ,on which the resonance of the protons in TMS is 0.00 ppm. The^{1}HNMRof the synthesized α ,β- unsaturated carbonyl compounds (II,III,IV,V) their aromatic protons appeared as multiplied signals at 7.89-7.92ppm and the conjugated the α ,β-unsaturated carbonyl compounds protons appeared as two doublet signals at the range δ(2.38-2.50) ppm due to the two protons of the α ,β-unsaturated carbonyl compounds.

The four synthesized compounds have the same structure but differ in the substituent(R) i.e. aromatic aldehydes. In compound(II), the^{1} HNMR multiplet signal δ(7.16-7.18) ppm appear due to the five protons of the aromatic ring.

Compound (III) contain furan a single singlet appeared at δ 6.12ppm due to presence of one proton of furan and multiplet signal was appearad at δ (7.64-7.84)ppm due to protons of the ring.

Compound (IV) contain the methoxy group located at para position the multiplet signal appear at δ(7.78-7.97) ppm due to the four proton, and the methyl group show the three protons appeared at δ4.27 ppm.

The compound (V) contain the hydroxyl group located at ortho position, the multiplicity of benzene ring appear at the range δ (7.95-8.35) ppm due to the four protons of the benzene ring and the proton of hydroxyl group appear as singlet signal at δ 4.59ppm due to the effect of the lone pair of oxygen atom.The ^{1}H-NMR of synthesized α, β- unsaturated carbonyl derivatives were presented in Table (2.22).

The synthesized compounds of the isoxazole derivatives (VI, VII, VIII, XIX), in this work they were formed by the cyclization reaction of some synthesized α ,β- unsaturated carbonyl compounds .The presence of heteroatom influences the rate of substitution in the isoxazole ring, because of the electron withdrawing nature of nitrogen atom,the electrophilic attack is retarded. The ^{1}HNMR of these compounds, the singlet signal appeared at the range δ(6.00-7.40)ppm due to the proton of the isoxazole ring, and it also appeared at δ (3.22-3.61) ppm due to the two protons of (NH_2) because of the effect of the lone pair electrons of

the nitrogen atom. The multiplet signal of the benzene ring appears at δ (8.60-7.67) ppm due to the presence of the four electrons of the ring.

The compound (VI) contains furan as a substituent was resonated as a doublet signal at δ6.00 ppm due to the attached oxygen atom.

Compound (VII) contain the hydroxyl group attached to the benzene ring at ortho position the multiplicity appear at δ (7.90-7.93) ppm due to four protons of benzene ring and at δ(3.65) ppm appear as singlet signal due to the proton of the hydroxyl group.

The synthesized compound (VIII) contain the benzyl group which appear at the range δ(8.01-8.07) ppm i.e due to the five protons of the benzene ring. The compound (IX) contain the methoxy group at p-position the protons resonating as multiplet at δ 7.60 due to the four protons of benzene ring, and appear at δ 4.18ppm due to the 3 protons of methyl group attached to oxygen atom.The ^{1}H-NMR of synthesized the isoxazole derivatives were tabulate in Table (2.7.2).^{1}HNMR of the synthesized *p*- quinones derivatives compounds (X,XI,XII,XIII) , is displayed as a singlet signal of one proton intensity of isoxazole at δ(6.40-6.80) assigned to the proton isoxazoles rings and the protons of the aromatic rings that appeared as multiplied intensity at δ (7.19-8.77) ppm. Compound (X) contain the hydroxyl group located at the ortho position of aldehydic ring which showed at δ 2.51ppm, due to hydrogen bonding with the greater downfield shift higher δvalue of its resonance. Compound (XI) contain the furan showed doublet signal at δ 6.90ppm, and a singlet signal at δ(6.71) ppm due to the proton of the isoxazole ring.

The compound (XII) contain the methoxy group at para position of the aldehydic aryl ring was displayed singlets of the 3 proton of the methyl group intensity at δ(2.78) ppm due to the lone pair effect of oxygen atom.

Compound (XIII) contain the benzyl group which appeared as multiplet signal at δ(7.78) ppm due to the presence of the 5 protons of the benzene ring, another singlet signal atδ 6.40ppm and asinglet signal also appear at δ(2.50) ppm due to the proton attached to nitrogen atom of the amino group.The ^{1}H-NMR of synthesized *p*- quinones derivatives compounds were tabulated in Table (2.23).

^{1}HNMR spectrum of the synthesized compound (XIV) which contains two methyl groups attached to the carbonyl groups. It displays a singlet signal of six protons intensity at δ2.08 ppm due to the methyl groups, and a multiplet signals of the two aromatic rings at the rangeδ (7.59-7.89) ppm.The ^{1}H-NMR of synthesized compound (XIV) was tabulated in Table(2.24).^{1}HNMR of the synthesized compounds(XV, XVI, XVII,XVIII), displayed a signal of one proton intensity at δ(3.90-2.50) ppm due to the protons attached to the nitrogen atom of the amino group. These compounds also displayed doublet signal of the two protons intensity at δ(2.08-2.27)ppm due to the two proton of α, β-unsaturated carbonyl compounds.The synthesized compound (XV) contains the benzyl group which appear at δ (7.39) ppm,and a doublet signal at the range (2.08-2.09)ppm due to the two proton of α, β-unsaturated carbonyl compounds, and a singlet signal atδ (2.49-2.50) ppm due to the two protons of the amino group, compound (XVI) contain the methoxy group which display a singlet signal at the range δ (4.61),due to the three protons of the methyl group, and a doublet signal at the range δ 2.08ppm due to the two proton of α, β-unsaturated carbonyl compounds, and a multiplet signal atδ (8.12-8.15) ppm. Compound (XVII) contain hydroxyl group located at ortho position, a singlet signal showed as sharp signal at δ 4.49ppm, this is due to the deshielding that can be rationalized on the basis of the lone pair of oxygen, and a doublet signal at the range (2.30-2.50)ppm due to the two proton of α, β-unsaturated carbonyl compounds, a singlet signal at δ 3.60ppm due to the two protons of the amino group, and multiplet signal at δ 8.00 ppm. The synthesized compound (XVIII) contain the furan with its aromatic protons(multiplied) which appear at δ (7.21) ppm, and a doublet signal at the range δ (2.25-2.27) ppm due to the two proton of α, β-unsaturated carbonyl compounds, a singlet signal at δ(3.60-3.90)ppm due to the two protons of the amino group, and multiplet signal atδ (7.80) ppm.The ^{1}H-NMR of synthesized compounds (XV, XVI, XVII, and XVIII)was presented in Table (2.25).^{1}HNMR of the synthesized compound (XIX) contains the benzene ring which show multiplet signal at the range δ (7.22-7.47) ppm, and a singlet signal at δ (4.76) ppm due to the two protons of the amino group, and multiplet signal at δ (7.90-7.96)ppm of the aromatic ring.The ^{1}H-NMR of synthesized compounds (XIX, XX, XXI, XXII) was presented in Table (2.26).The ^{1}HNMR of the newly synthesized *p*- quinones derivatives

compounds (XXIII, XXIV,XXV and XXVI), their aromatic protons appear at δ(7.89-7.20)ppm , the intensity of protons resonating as a multiplied, and the isoxazole of these compounds was displayed as a singlet signal of one proton intensity at δ(6.14-7.11) ppm assigned to the proton of isoxazole ring. A singlet signal also appeared at δ2.49 due to the lone pair effect of nitrogen atom of the amino group.The ^{1}H-NMR of synthesized compounds was presented in Table (XXIII, XXIV, XXV and XXVI), werepresented in Table(2.27).

The mass spectrum of the synthesis of α,β-unsaturated carbonyl compounds, isoxazoles and *p*- quinones derivatives showed similar cleavage pattern. Cleavages of the chain of C-C and C-N bond .The molecular weights of all synthesized compounds are determined by mass spectra. Their details showed at M, M+1, M+2,M+3,M-1,M-2.The MS spectra of α, β-unsaturated carbonyl compounds derivatives, isoxazole derivatives and the *p*- quinones derivatives were presented in Tables (2.28), (2.29) ,(2.30).(2.31),(2.32),(2.33) respectively.

3.4. Biological activity

3.4.1:Antibacterial activity:

The target compounds were screened for their antimicrobial activity using a disc diffusion method. The disc diffusion method was used to screen the antibacterial activity of some para- quinones derivatives compounds and performed by using Mueller Hinton agar (MHA).

The experiment was carried out according to the National Committee for clinical Laboratory Standards Guidelines. [NCCLS, 1990.].

3.4.2: The Method:

Bacterial suspension was diluted with sterile physiological solution to 10^{8}

Cfu/ml (turbidity = McFarland Standard 0.5). One hundred microliters of bacterial suspension were swabbed uniformly on surface of MHA and the inoculums were allowed to dry for 5 minutes. Sterilized filter paper discs were placed on the surface of the MHA and soaked with 20ul of the solution of each compound. The inoculated plates were incubated at 37^{0}C for 24 hour in the inverted position. The diameters (mm) of the inhibition zones were measured.

The average of the diameters of the growth inhibition zones are shown in the table (3.1). The results were interpreted in terms of the commonly used terms (sensitive, intermediate and assistant).

12-18 mm growth inhibition zones is considered to be active, more than 18mm is very active, values 9-12 are partially active, Values less than 9mm is less reactive.

Table (2.52): Antibacterial Activity of Synthesized Compound.

Compound No.	**Conc.(uL)**	**E.c.**	**P.S.**	**S.a.**	**B.S.**	**C.a.**
IIIa	20	-	13	22	9	12
IIIb	20	-	12	17	-	16
IIIc	20	-	14	15	-	16
IIId	20	-	- -	14	-	-
IIIa	20	-	20	15	-	9
IIIb	20	-	11	18	-	9
IIIc	20	-	13	14	-	10
IIId	20	-	12	16	-	9

.

• E.C.: Escherichia coli

• P.S.: Pseudomonas aeruginosa

• S.a.: Staphylococcus aureus

• B.S.: Bacillus subtilis

• C.a.: Candida albicans

M.D.I.Z: diameter or growth inhibition zone (mm)

It was observed in the above table, the comparison between the synthesized compounds, that the electron-donating effect of the amino

group decreases the biological effect probably by lowering the oxidant capacity of the *p*- quinones system.

2.5. QSAR Modelling:

The term (IC_{50}) is the concentration of an inhibitor that is necessary for 50-percent inhibition of an enzyme in vitro. The (IC_{50}) which were gathered in (microgram per milliliter) were converted to (- log) concentration in moles (anticancer potential pIC_{50}), which is expressed by pIC_{50}

$1\mu M = 10^{-6} M$

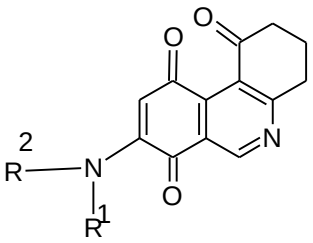
$pIC_{50} = \log 1/IC_{50}$

$pIC_{50} = -\log 10\ (IC_{50} x 10^{-6})$

ChemSketch/ACD lab software was used for drawing the studied compounds in table (3.2), table 3.3) and table (3.4).

The collected data set of the 1,4-benzoquinones derivatives were divided into a training set (14 compounds) and a test set of (3 compounds) by random selection.

Table (3.2): Structures, IC50 and pIC50 of the training set compounds (Jaime *etal*.,2011).



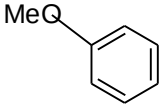
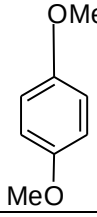
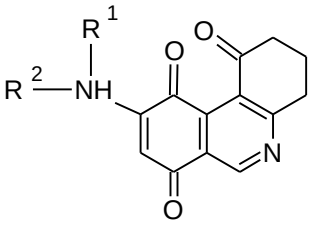
Compound No.	R^1	R^2	IC_{50}	pIC_{50}
1	H		2.0	7.70
2	H		1.8	5.74
3	Me		4.7	5.97
4	Et		11.7	5.93

Table (3.3): Structures, IC_{50} and pIC_{50} of the training set compounds (Jaime *etal*., 2011).



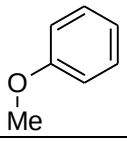
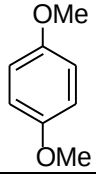
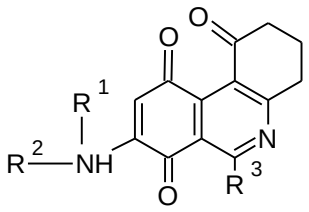
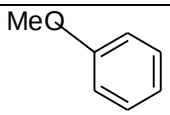
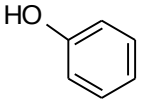
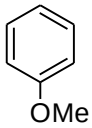
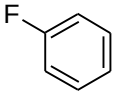
Compound No.	R^1	R^2	IC_{50}	pIC_{50}
5	H		3.7	6.43
6	H		21.3	5.67
7	Me		8.7	6.06
8	Et		17.7	5.75

Table (3.4): Structures, IC_{50} and pIC_{50} of the training set compounds (Jaime *etal*., 2011).



Compound No.	R^1	R^2	R^3	IC_{50}	IC_{50}
9	H		Me	4.1	6.39
10	H		Me	3.2	6.49
11	H		Me	4.3	6.37
12	H		Me	3.3	6.48
13	H			2.8	6.55
14	H			3.1	6.51
15	H			2.9	6.54
Etoposide	-	-	-	2.8	6.55

3.5.1:Molecular modelling parameters

Total number of 12molecular descriptors listed in table (2.45) were calculated for each compound in the training set using MOE programme for the 3D descriptors and log P(o/w) descriptor, and ACD/ lab was used to calculate the 2D descriptors e.g. (InR, ST, MV).

Eleven molecular descriptors namely, logP (octanol/water) (logP (o/w), number of H-bond donor atoms (a-don), number of H-bond acceptor atoms (a-acc), Topological polar surface area (TPSA), Potential energy

(E), Van der waals energy (E-vdw), Heat of formation (AMI-HF), Water accessible surface area (ASA), Atomic conductivity index order 0(Chio), Absolute difference in surface area (DASA), Molar refractivity (mr). These descriptors were calculated for each compound in the training set using MOE and ACD/lab programmes and were listed in table (3.2), (3.3), and(3.4).

Table 3.5: List of chemical descriptors with details used in QSAR modelling.

No.	Descriptor	Description
1.	logP (octanol/water) (logP (o/w)	Is a measure of the chemical compound hydrophilicity. (Jacek*etal*. , 2012)
2.	number of H-bond donor atoms (a-don)	In hydrogen bond, the electr-onegative atom not covalently attached to the hydrogen is named proton acceptor.
3.	number of H-bond acceptor atoms (a-acc)	In hydrogen bond, the electro-negative atom covalently attached to the hydrogen is named proton acceptor.
4.	Topological polar surface area (TPSA)	Is defined as the surface sum over all polar atoms, primarily oxygen and nitrogen, also including their attached hydrogen atoms.
5.	Potential energy (E)	Is the energy of an object or a system due to the position of the body or the arrangement of the particles of the system.
6.	Van der waals energy (E-vdw	The interaction of intermolecular forces between molecules.
7.	Heat of formation (AMI-HF)	Is the amount of heat absorbed or evolved at 25^0C and 1atmosphere
8.	Water accessible surface area (ASA)	Is the surface area of biomolecule that is accessible to the solvent.
9.	Atomic conductivity index order (Chi0)	Is the property of a material to conduct heat.
10.	Absolute difference in surface area	Is the number of pixels inside the surface region boundaries

	(DASA)	
11.	Molar refractivity (mr)	Is the measure of the total polarizability of a mole of a substance and its dependent on the temperature ,index of refraction and temperature.

Table 3.6:Values of chemical descriptors with details used in QSAR Modelling of the training set.

	mol	plC50	logP(o/w)	a_don	a_acc	TPSA	E	E_vdw	AM1_HF	ASA	chi0	DASA	mr
1		5.7400	1.9470	1.0000	6.0000	94.5900	95.0784	63.4552	-84.5937	627.9598	19.8361	94.5240	10.2134
2		5.9700	2.3330	0.0000	4.0000	67.3400	86.3905	58.3929	0.8140	556.9366	17.5517	41.1983	9.3930
3		5.9300	2.6740	0.0000	4.0000	67.3400	87.4296	58.6632	-4.4881	577.6579	18.2588	41.6308	9.8716
4		6.4300	1.9560	1.0000	5.0000	85.3600	81.8227	56.8987	-48.0106	582.8821	18.2588	61.7907	9.5719
5		5.6700	1.9470	1.0000	6.0000	94.5900	94.9621	63.2716	-84.8788	622.3205	19.8361	84.8601	10.2134
6		6.0600	2.3330	0.0000	4.0000	67.3400	87.8787	56.7356	0.7645	535.5406	17.5517	53.8083	9.3930
7		5.7500	2.3330	0.0000	4.0000	67.3400	84.2317	56.4865	-11.4511	607.9833	17.5517	57.0232	10.0554
8		6.3900	2.2140	1.0000	5.0000	85.3600	86.6039	59.6063	-47.0735	601.7169	19.1290	60.8516	10.0266
9		6.3700	2.2120	1.0000	5.0000	85.3600	92.7595	60.4734	-50.6141	603.2532	19.1290	66.0820	10.0303
10		6.4800	2.4110	1.0000	4.0000	76.1300	75.9636	53.8190	-58.3112	564.8865	18.4219	17.0073	9.4531
11		6.5500	3.9200	1.0000	4.0000	76.1300	110.6535	64.4453	30.5277	626.8151	20.6646	40.3148	11.4204
12		6.5100	2.6350	1.0000	4.0000	89.2700	95.4644	52.0949	15.2579	610.6581	19.9575	2.8346	10.7200
13		6.5400	3.5700	1.0000	4.0000	76.1300	87.8422	53.2258	28.0334	637.0912	19.9575	18.0258	11.2898
14		5.6600	2.2050	1.0000	6.0000	94.5900	100.3939	66.6742	-66.3807	653.2288	20.7064	88.2287	10.6680

3.5.2. Selection of subset descriptors.

One of the fundamental problems in developing (QSAR) models is to select the relevant chemical descriptors or features that describe the relationship between the compound and its activity.(Debojyoti*etal*., 2007). The number of molecular descriptors has hugely increased over time and nowadays thousands of descriptors, able to describe different aspects of a molecule, can be calculated by means of dedicated software.

The descriptors were selected by the ratio 5:1 i.e. from each five compounds in the training set one descriptor was selected. The correlation matrix was used to select the best sub-set of physicochemical properties from MOE programme.

	1	2	3	4	5	6	7	8	9	10	11	12
1. pIC50	100	53	41	-51	-12	-9	-52	46	-13	12	-70	23
2. logP(o/w)	53	100	7	-58	-37	41	-14	79	24	36	-58	71
3. a_don	41	7	100	50	81	31	19	-38	61	77	9	49
4. a_acc	-51	-58	50	100	85	29	70	-85	52	46	85	5
5. TPSA	-12	-37	81	85	100	38	44	-66	64	71	48	30
6. E	-9	41	31	29	38	100	66	14	61	76	25	72
7. E_vdw	-52	-14	19	70	44	66	100	-46	46	47	80	21
8. AM1_HF	46	79	-38	-85	-66	14	-46	100	-17	-11	-73	35
9. ASA	-13	24	61	52	64	61	46	-17	100	85	29	82
10. chi0	12	36	77	46	71	76	47	-11	85	100	14	84
11. DASA	-70	-58	9	85	48	25	80	-73	29	14	100	-14
12. mr	23	71	49	5	30	72	21	35	82	84	-14	100

Close

Fig. (3.8): Correlation Matrix for chemical descriptors in the training set.

About 20 regression equation was employed for Human lung cancer cell line (2.), using multiple linear regression method. QSAR model equation with high square of the correlation coefficient (r^2) was selected.

Table (3.7): The QSAR models between descriptors and biological activity of 1,4- Benzoquinones derivatives for Human lung cancer cell line.(Training set).

No.	Removed descriptors	QSAR Equations	r^2	RSMSE
1	logP(o/w), TPSA, E	Pc = 5.8629+0.614*logP(o/w)+0.01745 +TPSA-0.02922*E	0.54194	0.23039
2	logP(o/w), E,E_vdw	Pc = 7.65220-0.04131*E_vdw+0.25890*logP(o/w)+0.00315*E	0.49212	0.24259
3	logP(o/w), E-vdw,AMI_HF	Pc =7.78491-0,05032*E_vdw-0.00410*AMI_HF+0.48942*logP(o/w)	0.5454	0.22949
4	logP(o/w), E,AMI-HF	Pc = 6.4541+0.4469*logP(o/w)-0.0158*E-0.00058*AMI_HF	0.39782	0.26415
5	logP(o/w), a_acc,E	Pc= 6.5294+0.3957*logP(o/w)-0.01345*a_acc-0.01437*E	0.39666	0.26441
6	logP(o/w), a_acc,TPSA	Pc= 5.67805+0.09777*logP(o/w)-0.54488*a_acc+0.03424*TPSA	0.62985	0.20710
7	logP(o/w), TPSA,E_vdw	Pc = 7.16004+0.35094*logP(o/w)+0.01187*TPSA-0.04821*E_vdw	0.54242	0.21997
8	logP(o/w), a_don,ASA	Pc= 9.82998+0.40093*logP(o/w)+0.64560*a_don-0.00855*ASA	0.80287	0.15114
9	logP(o/w), a_don,Chiθ	10.98996+0.51805*logP(o/w)+0.96228*a_don-0.35622*Chiθ	0.82448	0.14261
10	logP(o/w), a_don, E	Pc= 6.83037+0.43485*logP(o/w)+0.39839*a_don -0.022660* E	0.64777	0.20202
11	logP(o/w), E,ASA	Pc = 6.89470+0.41092*logP(o/w)-0.01276*E- 0.00102*ASA	0.40209	0.26322
12	logP(o/w),	Pc= 7.74581+0.28916*logP(o/w)	0.49128	0.24279

	E_vdw,ASA	– 0.00039*ASA – 0.03536*E_vdw		
13	logP(o/w), AMI_HF, ASA	Pc = 7.11747+0.46423*logP(o/w) - 0.00361+ ASA-0.00176*AMI_HF	0.35911	0.27251
14	logP(o/w), a_acc,AMI_HF	Pc= 6.34767+0.34686*logP(o/w)-0,00441*AMI_HF- 0.25429*a_acc	0.38467	0.26702
15	logP(o/w), a_don,AMI_HF	Pc= 6.5288- 0.23315*logP(o/w) +0.00962*AMI_HF +0.64367*a_don	0.04897	0.20168
16	logP(o/w), a_don,a_acc	Pc= 8.02373- 0.10363*logP(o/w) +0.73043*a_don – 0.46142*a_acc	0.86835	0.12351
17	logP(o/w), a_acc,mr	Pc= 6.2562+0.2212*logP(o/w)-0.12616*a_acc- 0.00710*mr	0.34641	0.27520
18	logP(o/w), a_acc, DASA	Pc= 5.65891+ 0.14046*logP(o/w)+ 0.15793*a_acc – 0.01142*DASA	0.55025	0.22829
19	logP(o/w), DASA,mr	Pc= 6.08343+0.08433*logP(o/w) – 0.00769*DASA+ 0.02600*mr	0.51403	0.23730
20	logP(o/w), mr,a_don	Pc= 9.53025+ 0.72935*logP(o/w)+ 0.62402*a_don- 0.55449*mr	0.73884	0.17396

r^2: Squared correlation coefficient RMSE: Root mean square error

Equation No.16 was the best QSAR model equation, where (r^2 = 0.86835),represents the highest value of the squared correlation coefficient and the lowest value for the root mean square error (RMSE= 0.12351).

Pc= 8.02373- 0.10363*logP(o/w) +0.73043*a_don – 0.46142*a_acc

3.5.3. Calculation of statistical parameters

The calculation of statistical parameters i.e. the correlation coefficient (r), squared correlation coefficient (r^2), the root mean square error (RMSE), standard value of estimate (s) and F test value (ratio between the variances of observed and calculated activities. (F) was carried out by using statistical programme SPSS version 11.5, Table (3.8).

Small S, large F, Very small p-value, as well as r^2 and q^2 values close to one indicate a good promising QSAR model.

Table (3.8): Statistical parameters used for statistical quality of model.

Model No.	r	r^2	RSME	Q^2	S	F	P value
I	0.932	0.868	0.1235	0.7623	0.146	21.98	0.0001

3.5. 4.: Validation of quantitative structure-activity relationship model.

Validation is a crucial aspect of any QSAR modelling. It is the process by which the reliability and relevance of a procedure are established for a specific purpose of development at many times. (Ravichandran, 2011).

The internal stability and the predictive ability of the derived QSAR models was tested and validated by the internal validation and external validation test methods as follows:

a) Internal validation by training set compounds:

The most commonly employed internal metrics is Leave-one-out (LOO).

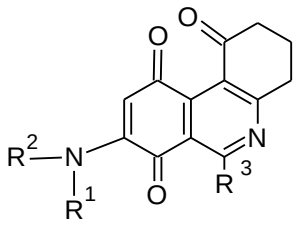
The training set is primarily modified by eliminating one compound from the set. The QSAR model is then rebuilt based on the remaining molecules of the training set using the descriptor combination originally selected, and the activity of the deleted compound is computed based on the resulting QSAR equation.

b) External validation by test set compounds:

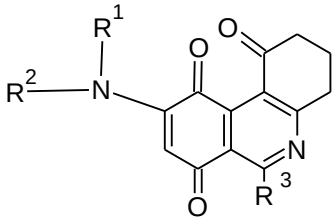
The activity of each compound in the test set was predicated by using the derived models developed from the training set compounds in table (3.2), (3.3), and (3.4).

The training set is used to derive a model, and a model is used to predict the activities of the test set members.

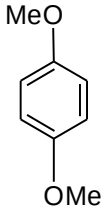
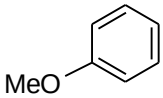
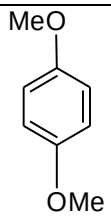
Table3.9: Experimental and predicted activities of training data set compounds and cross validation against the human lung cell line.



7a, 8a, 9a, 11,12,13,14,16,17,18



6b, 7b, 8b, 9b

Comp. No	R^1	R^2	R^3	Experimental pIC_{50}	Predicted pIC_{50}(M)	Residuals	Predicted CV	Residuals
7a	-H		-H	5.74	5.783919	-0.04392	5.800811	-0.06081
8a	-Me		-H	5.97	5.936334	0.033666	5.924913	0.045087
9a	-Et		-H	5.93	5.900998	0.029002	5.889726	0.040274
6b	-H		-H	6.43	6.244407	0.185593	6.194919	0.235081
7b	-H		-H	5.67	5.783919	-0.11392	5.827733	-0.15773

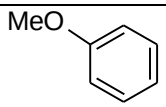
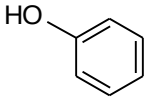
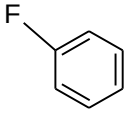
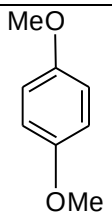
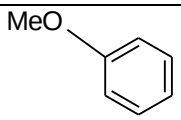
8b	-Me		-H	6.06	5.936334	0.123666	5.894379	0.165621
9b	-Et		-H	5.75	5.936334	-0.18633	5.99955	-0.24955
11	-H		-Me	6.39	6.217671	0.172329	6.192884	0.197116
13	-H		-Me	6.37	6.217878	0.152121	6.195913	0.174087
14	-H		-Me	6.48	6.658677	-0.17868	6.770065	-0.29007
15	-H			5.66	5.757184	-0.09718	5.80404	-0.14404
16	-H			6.55	6.502306	0.047695	6.433256	0.116744
17	-H			6.51	6.635465	-0.12546	6.68507	-0.17507
18	-H			6.54	6.538575	0.001425	6.537779	0.002221

Table (3.10): Predicated biological activity values of the test set.

Comp. No	R^1	R^2	R^3	Experimental pIC_{50}	Predicted pIC_{50}(M)	Residuals
6a	-H		-H	7.70	5.783919	-0.06081
4b	-H		-H	5.12	5.936334	0.045087
10	-H		-Me	6.24	5.900998	0.040274

3.6: Molecular Docking Study.

Molecular docking is well-established and widely used methodology in drug design. It is also consider to be one of the most frequently used methods in Structure-Based Drug Design (SBDD), because of its ability to predict, with a substantial degree of accuracy, the conformation of small-molecule ligands within appropriate target binding site. The identification of the most likely binding conformations requires two steps: (i) exploration of a large conformational space representing various potential binding modes. (ii) Accurate prediction of the interaction energy associated with each of the predicted binding conformations. (Leonardo *etal*., 2015).

3.6.1: Molecular Docking Procedure:

1) Receptor building: The receptor was downloaded from PDB.

2) After downloading the PDB format of the protein, the water molecules were removed by editing the TEXT of the protein.

3) Optimizing the protein by the parameters available in the software.The binding site was prepared.

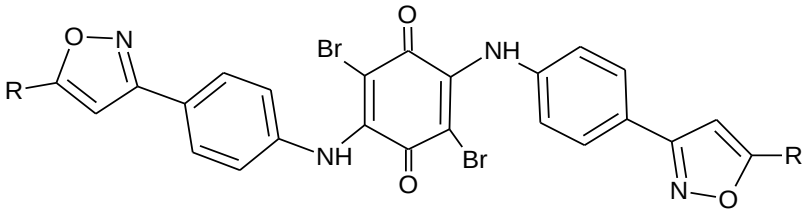
4) The active site was predicted and the ligand was uploaded later. All of the parameters were arranged such as a pose to be obtained and score and then start the docking.

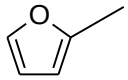
5) The score was calculated and even the fitness was displayed. Then the data was analyzed and the most optimum ligand with its pose was selected.

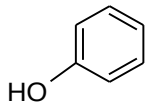
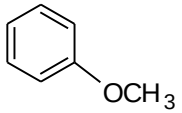
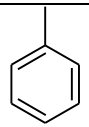
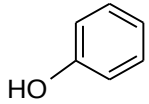
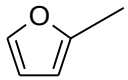
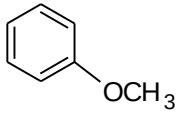
6) The complex was viewed and checked for the orientation of the ligand with the receptor.

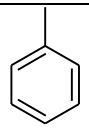
All the synthesized compounds (1, 4-Benzoquinones derivatives) were subjected to docking to examine their binding mechanism with 4LB9 protein, which was downloaded from protein data bank (PDB),and the results were presented in table (3.10).

Table 3.10: Docking results of the synthesized 1,4-Benzoquinones derivatives with 4LB9 using MOE software version 10.2009.



Compound No.	R	S(Kcal/mol)	Amino Acids	Interacting groups	Type of interaction	Length
Epotoside Validation	_	-19.338	Ser193 Arg197	OH group (1,3)dioxin (1,3)dioxole	H-bond H-bond H-bond	3.27 3.13 2.22
Xa		-32.102	Glu100 His247 His146	OH group Phenyl Isoxazole Phenyl	H-bond π-interaction π-interaction π-interaction	2.16

XIa		-23.6128	His146 His146	Isoxazole Isoxazole	H-bond π-interaction	2.30
XIIa		No interaction				
XIIIa		-29.0154	His247	Phenyl group Isoxazole group	π-interaction π-interaction	- -
Xb		-35.6960	Asp108	OH group	H-bond	2.12
XIb		-25.4727	His247 Lys190	Furfuryl group Isoxazole group Furfuryl group	π-interaction π-interaction π-interaction	- - -
XIIb			Arg114 His146 Arg197	Methoxy group Carbonyl of Benzoquinone moiety	H-bond H-bond H-bond	2.27 2.12 2.18

			Arg197	Phenyl group	π-interaction	-
XIIIb		-29.603	His247 His146	Isoxazole group Phenyl group Phenyl group	π-interaction π-interaction π-interaction	- - -

The molecular docking was carried out to study the interactions of the novel compounds with different amino acids, because most of these synthesized benzoquinones derivatives exhibit biological activity against human lung cancer SK-MES-.1.Listed in table (3.10)

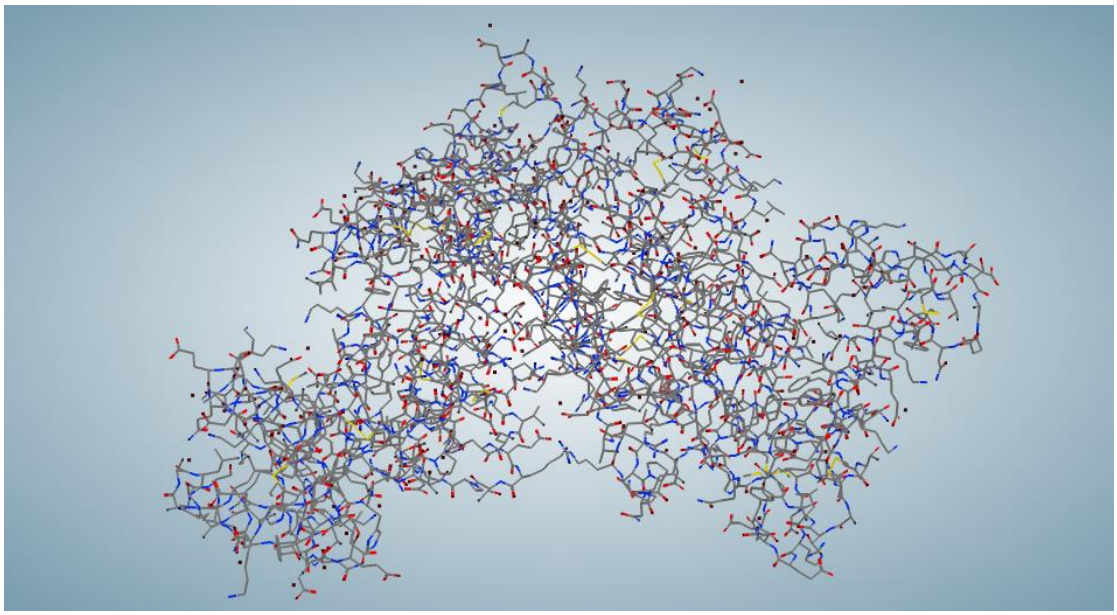


Fig. (3.9): Structure of Albumin 4L69 which was imported from PDB

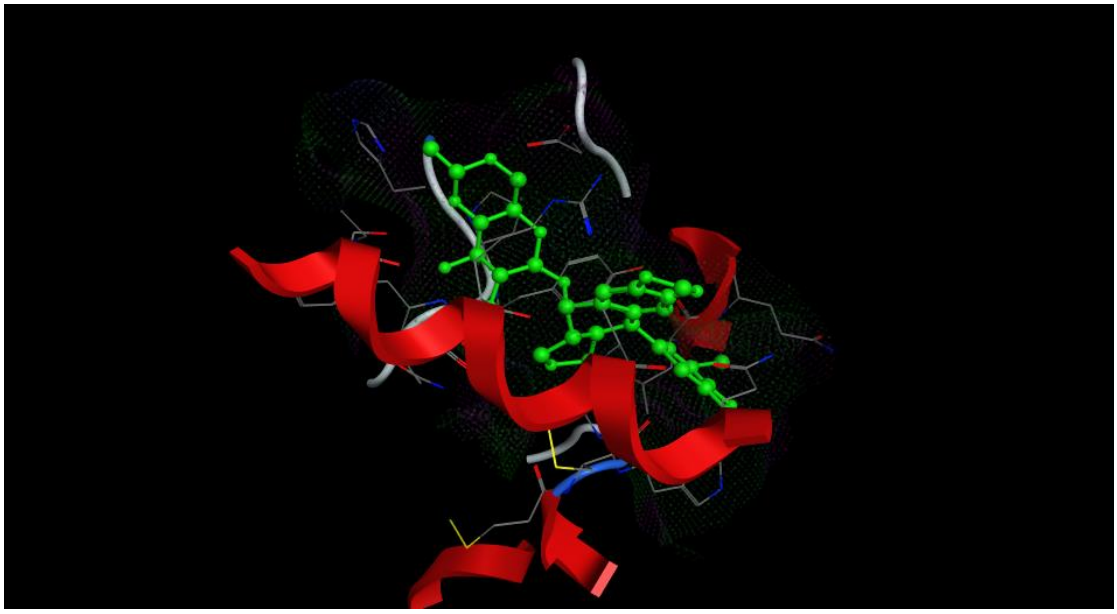


Fig. (3.10): Structure of Albumin 4L69 protein

All docking was done using MOE SOFTWARE. It was observed that all the synthesized compounds had shown excellent docking scores that range between (-23.6128), and (- 35.6960).

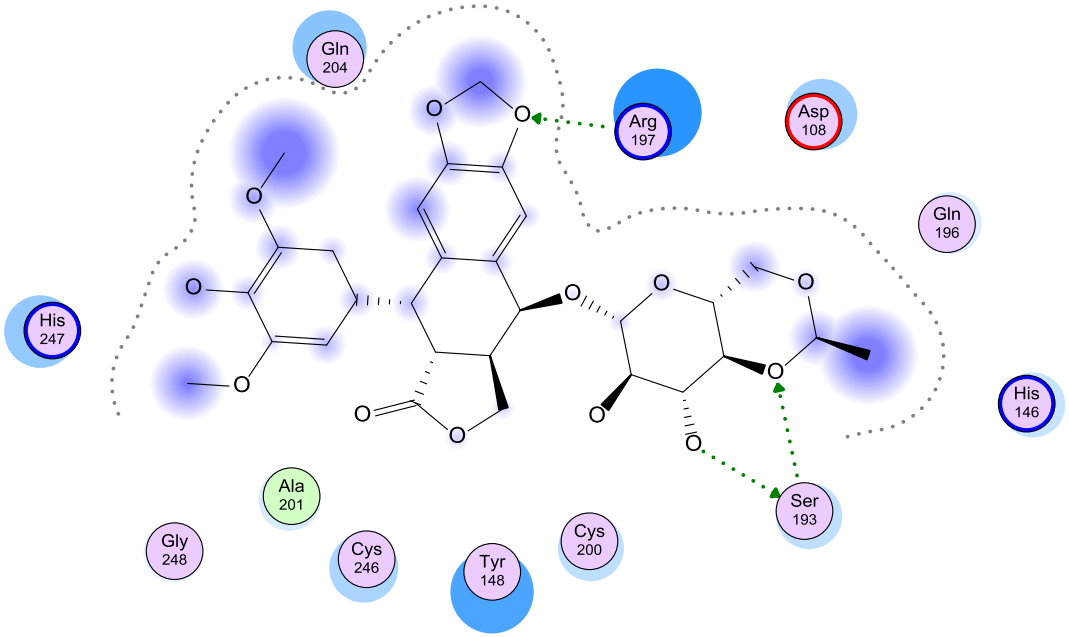


Fig. (3.11): 2D binding interaction of Etoposide inside the active side of 4L69 protein

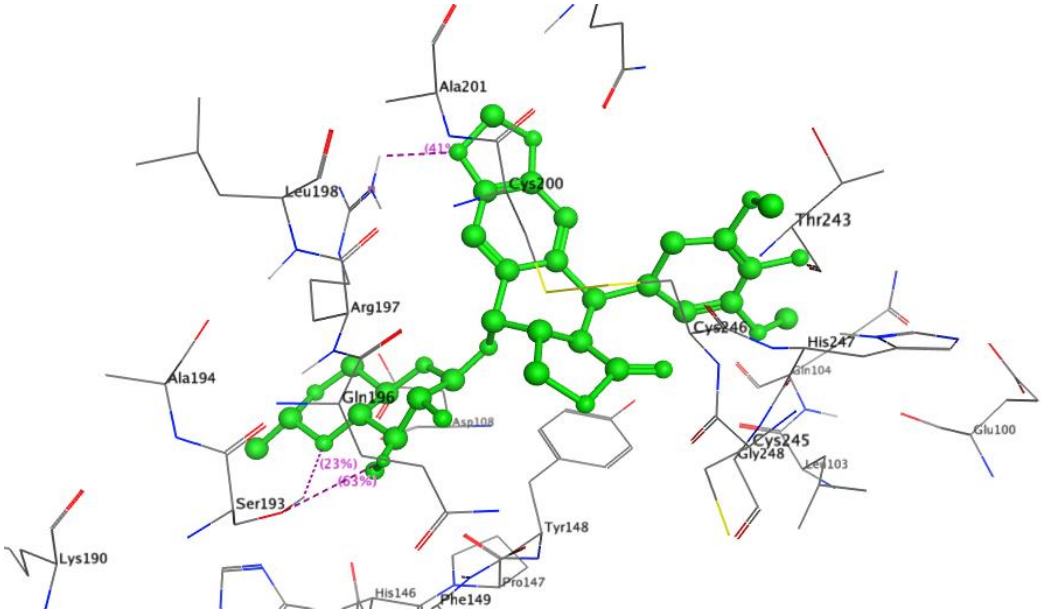


Fig. (3.12): 3D binding interaction of Etoposide inside the active side of 4L69 protein

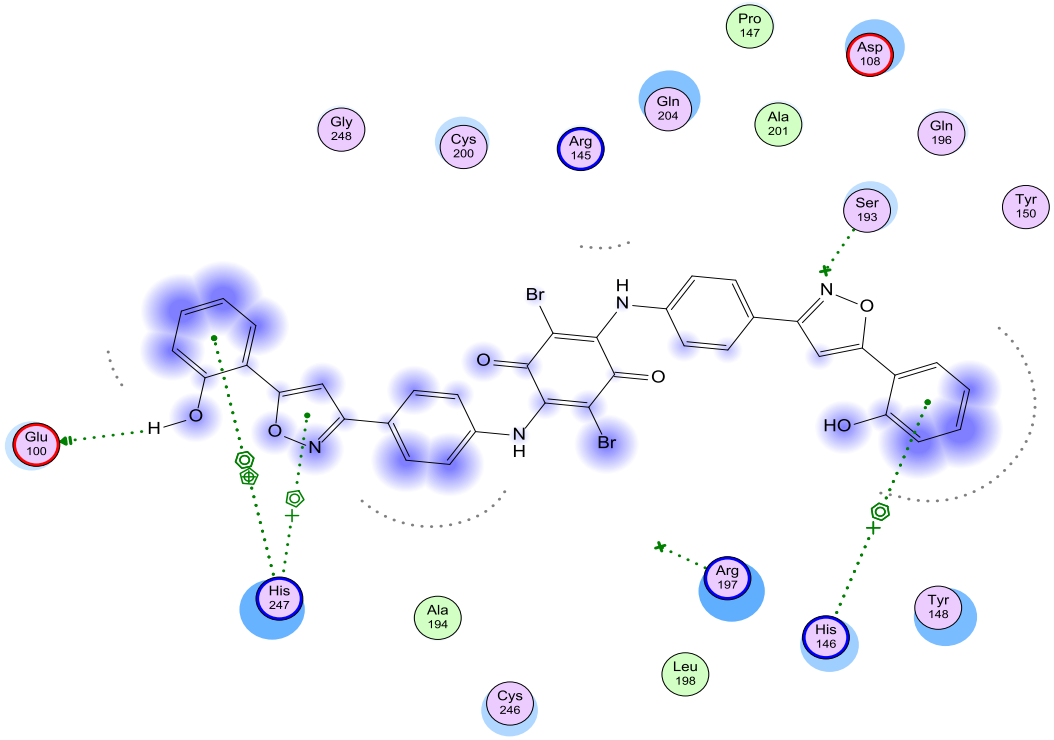


Fig. (3.13): 2D binding interaction of compound (Xa) inside the active side of 4L69 protein

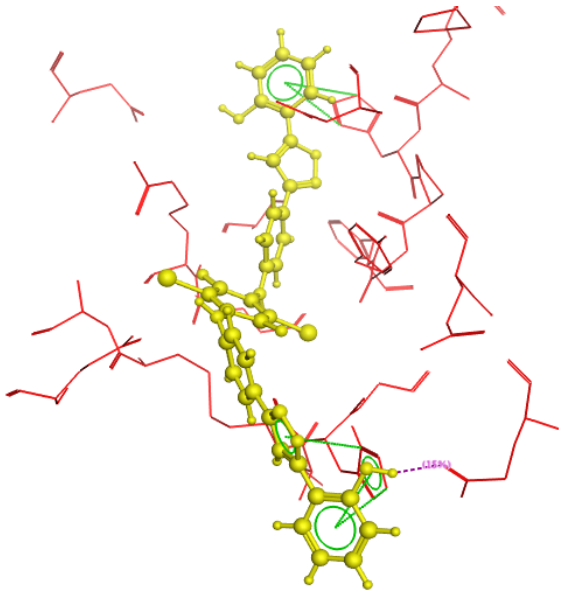


Fig. (3.14): 3D binding interaction of compound (Xa) inside the active side of 4L69 protein

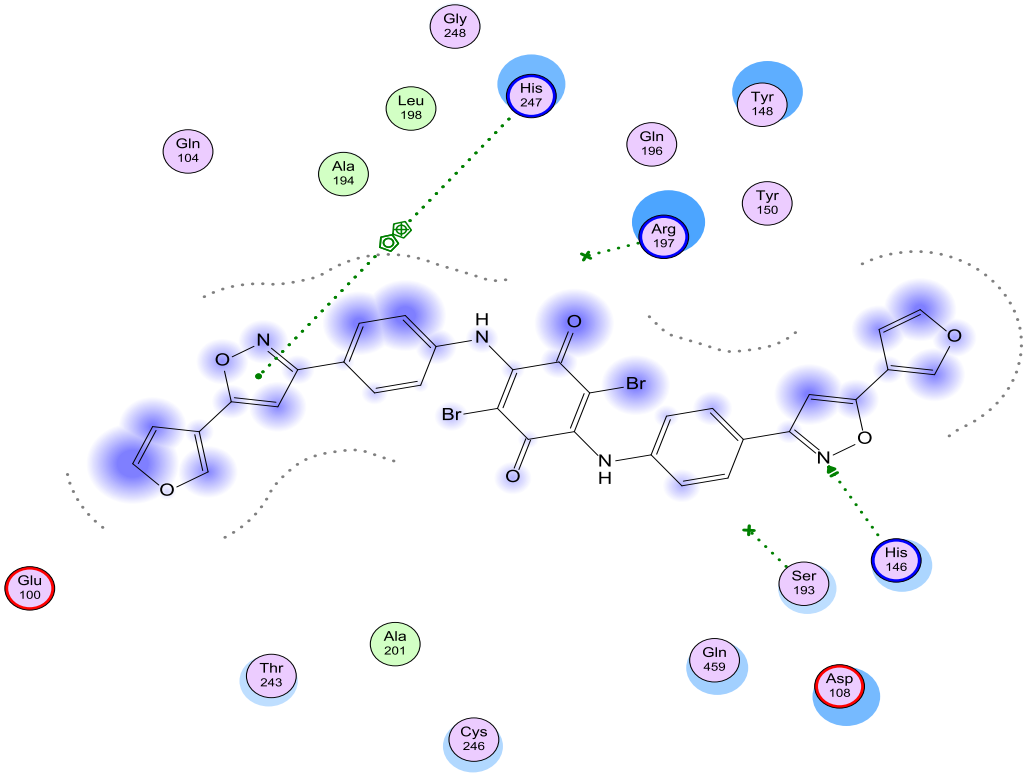


Fig. (3.15): 2D binding interaction of compound (XIa) inside the active of 4L69 protein

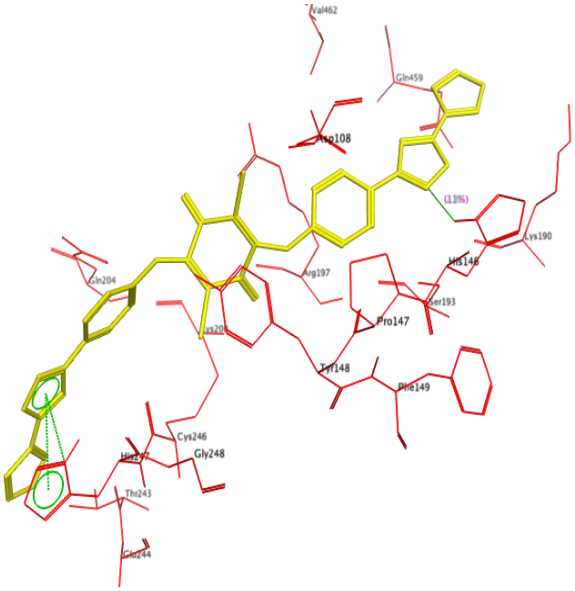


Fig. (3.16): 3D binding interaction of compound (XIa) inside the active of 4L69 protein

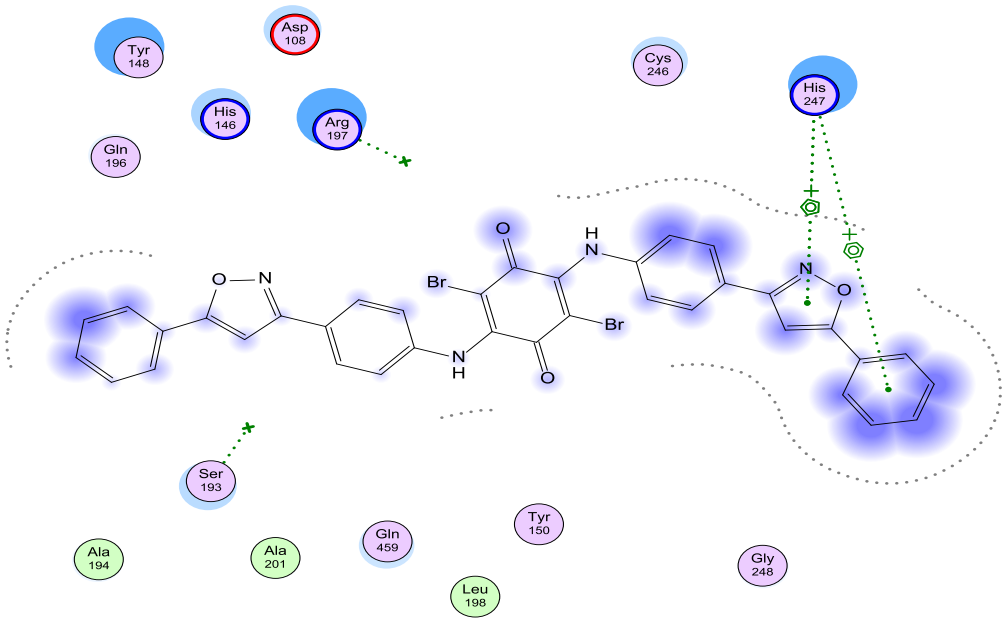


Fig. (3.17): 2D binding interaction of compound (XIIIa) inside the active of 4L69 protein

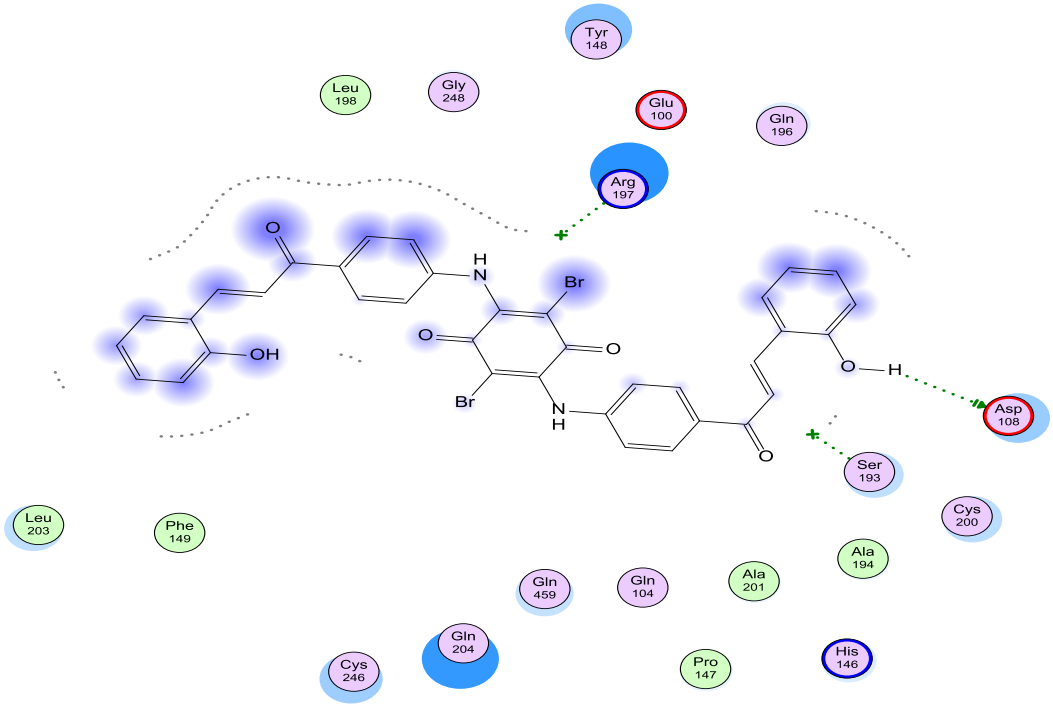


Fig. (3.18): 2D binding interaction of compound (Xb) inside the active of 4L69 protein

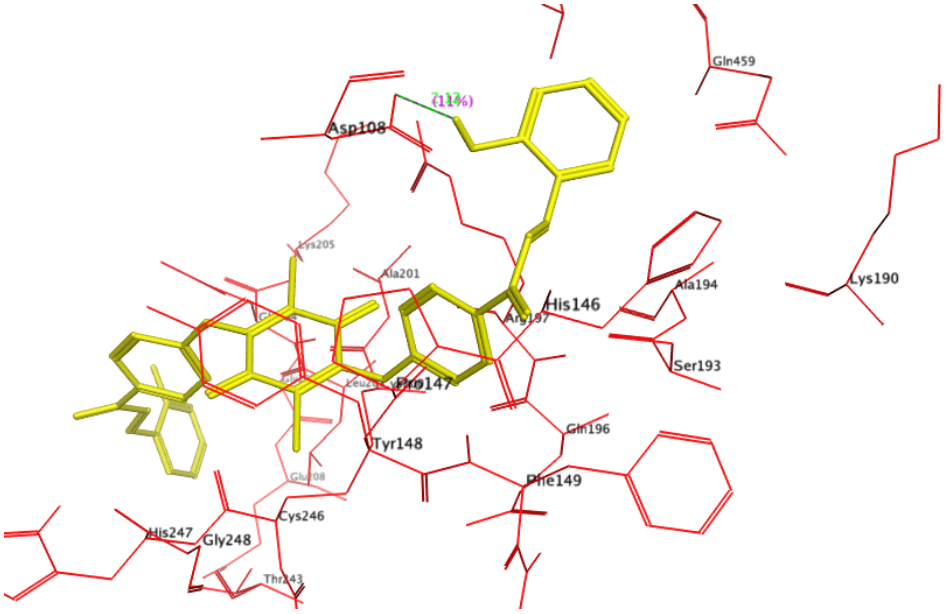


Fig. (3.19): 3D binding interaction of compound (Xb) inside the active of 4L69 protein.

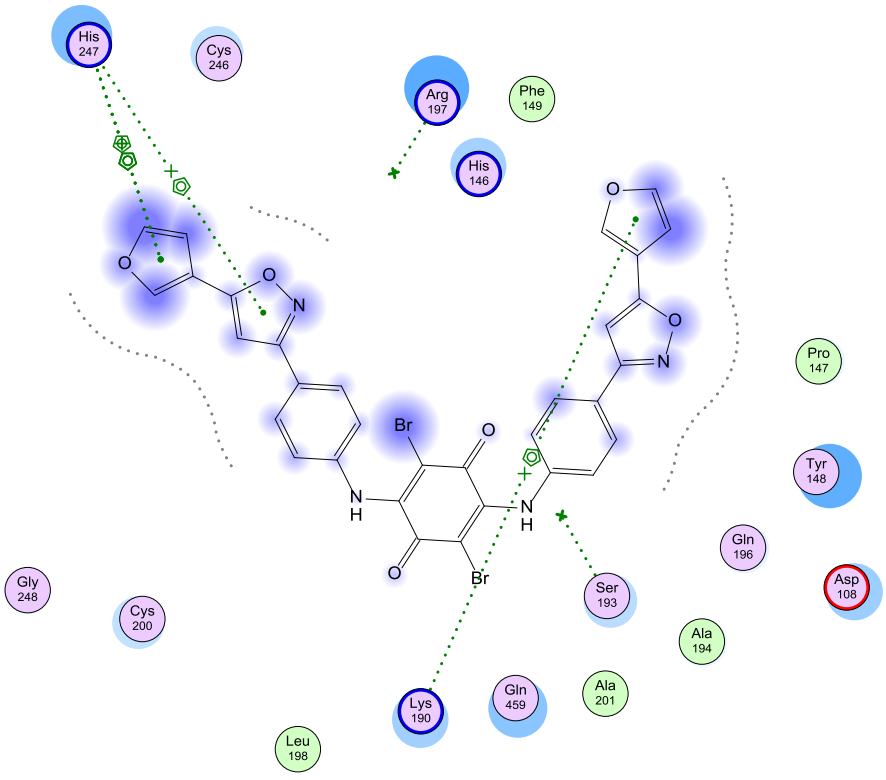


Fig. (3.20): 2D binding interaction of compound (XIb) inside the active of 4L69 protein

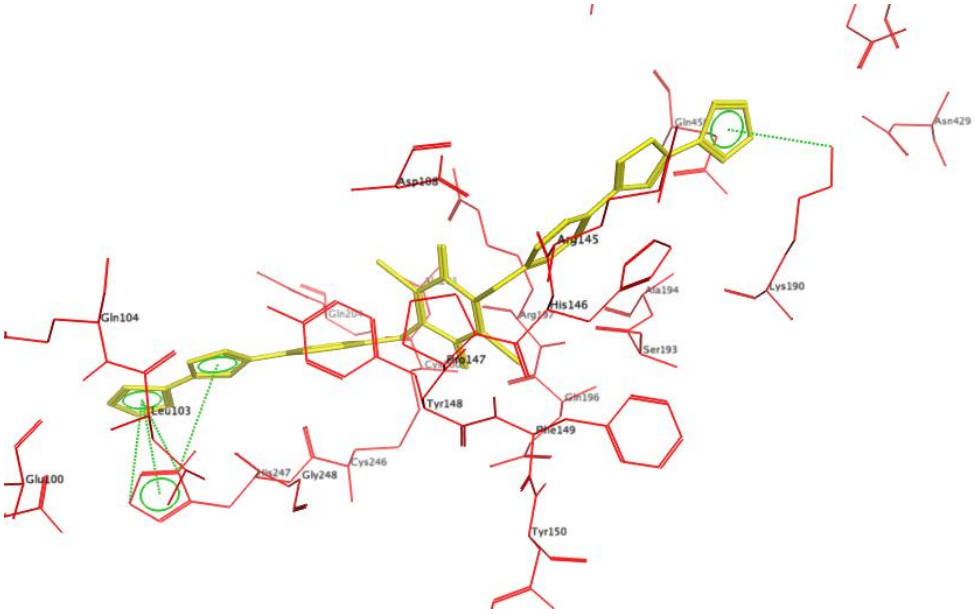


Fig. (3.21): 3D binding interaction of compound (XIb) inside the active of 4L69 protein.

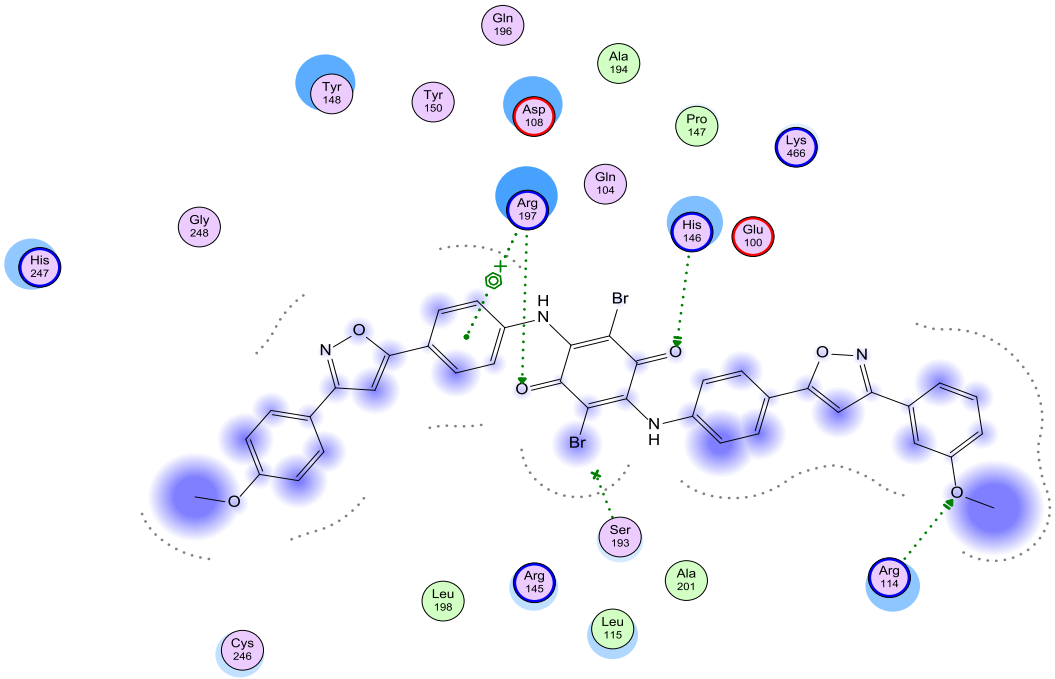


Fig. (3.22): 2D binding interaction of compound (XIIb) inside the active of 4L69 protein

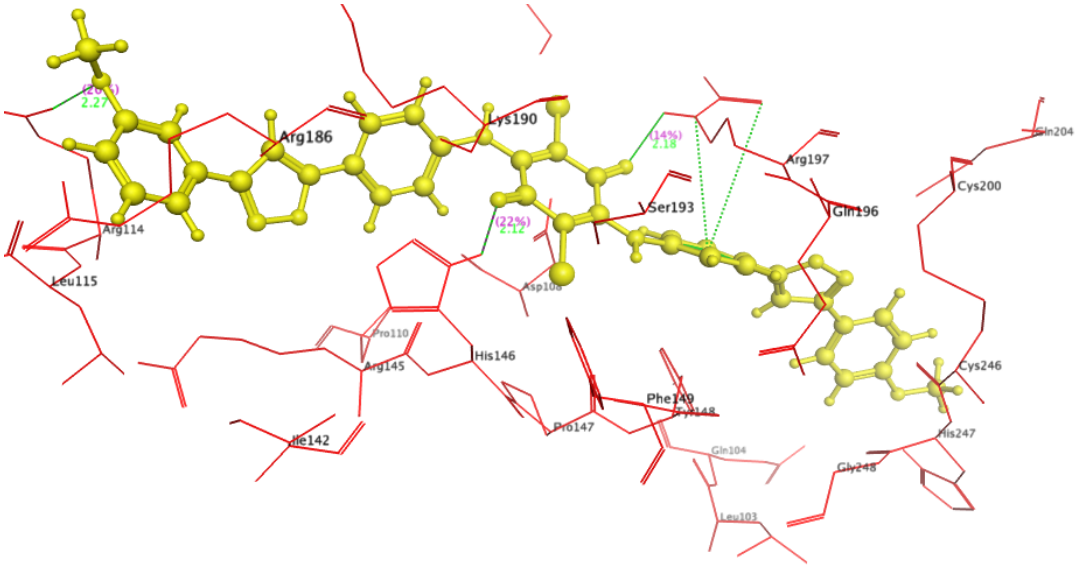


Fig. (3.23): 3D binding interaction of compound (XIIb) inside the active of 4L69 protein

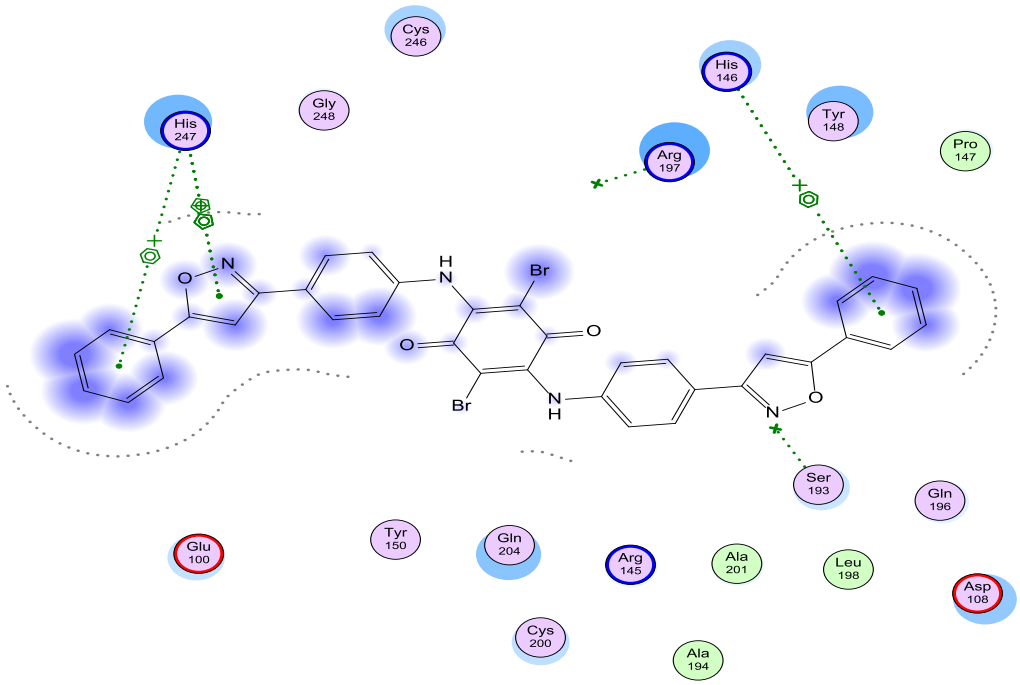


Fig. (3.24): 2D binding interaction of compound (XIIIb) inside the active of 4L69 protein

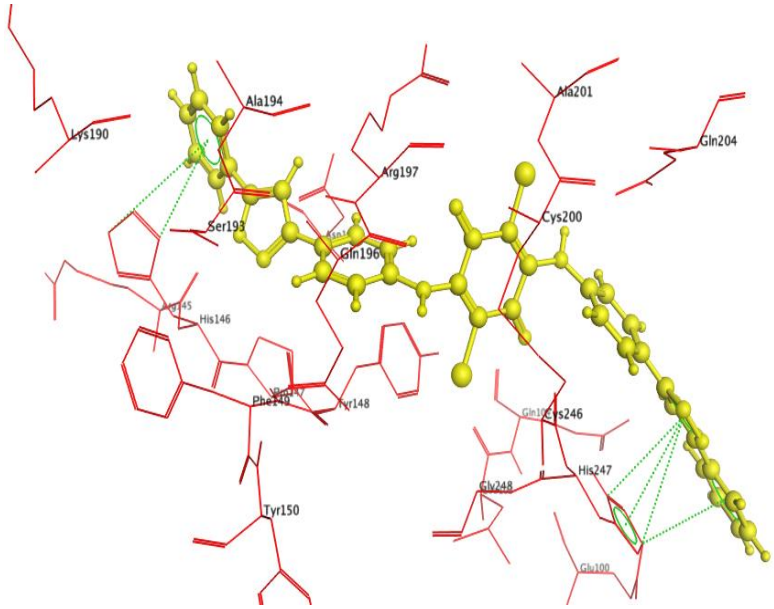


Fig. (3.25): 3D binding interaction of compound (XIIIb) inside the active of 4L69 protein

3.7: QSAR STUDY ANALYSIS.

Cancer is a diseasein which a group of abnormal cells grow. Cells are constantly subject to signals that dictate whether the cell should divide, differentiate into anothercell or die. Studies showed that is mostly deadly disease, and difficult to cure. The multiplication of subtly modified normal human cells**.**Most of the drugs usedfor the treatment of cancer are cytotoxic drugs, that work by interfering in some way with the operation of the cell's DNA.(Anita *etal*.,2013).

Lung cancer is markedly leading cause of cancer related mortality worldwide, with over 228,000 new cases and more than 1159,000 death reported in 2014 in the United States. Approximately 85% of lung cancer patients can be histologically classified as non-small cell lung cancer (NSCLC). The high prevalence and mortality rate are mainly due to the difficulty of early diagnosis. At present treatments for lung cancer include surgery, radiation therapy, chemotherapy, and targeted therapies. (Qiefi *etal*., 2016).

Quantitative structure activity relationship (QSAR) models may be considered data mining applications. These methods are used to predict physico-chemical properties and biological activities of compounds, or to classify molecules based on structural features. Beside their usefulness in

compound screening. QSAR modelsare also used due to their ability to explain action mechanics for the investigated compounds. (Sorana *etal*., 2009).

QSAR was carried out for the present work to define the structural determinants required to anti-lung cancer activity by means of MOE and ACD/lab programmes, for a disubstituted 1,4-Benzoquinones. Starting from the data collection from the literature (Jaime *etal*., 2011), from which (15) compounds were selected tables (3.2),(3.3),(3.4). Then were divided into two subsets, The training data set containing (14) compounds and the test set containing (3) compounds.

Total number of (11) molecular descriptors were calculated for the training set, and only (3) were calculated for the test set.

The selection of the test set should show the ratio of 5: 1 with the training set compounds, i.e. three descriptors are chosen for 15 compounds in the training set . Suitable statistical methods are deployed to derive a robust mathematical correlation involving small to large number of variables.

The activity of these compounds was investigated by means of multiple linear regression (MLR).The best QSAR model equation obtained was in equation No.16, table (3.7) where ($r^2 = 0.86835$),represents the highest value of the squared correlation coefficient and the lowest value for the root mean square error (RMSE= 0.12351).

$$Pc= 8.02373- 0.10363*logP(o/w) +0.73043*a\_don – 0.46142*a\_acc$$

This equation showed a relationship between the biological activity and correlated descriptors i.e. (logP, a_don, a_acc).

The statistical parameters used for the QSAR models, as shown in tables (3.2), (3.3) and (3.4) are: the correlation coefficient (r), square correlation coefficient (r^2), the root mean square error (RMSE), standard

value of estimate (s) and F test value (ratio between the variances of observed and calculated activities. (F).

Validation is a process by which the reliability and relevance of a procedure are established for a specific purpose; for QSAR models validation must be mainly for robustness, prediction. Performances and applicability domain of the models.

For validation of QSAR models; usually various strategies are adopted:

1. Internal validation or cross-validation. (While extracting data, Cross-validation is a measure of model robustness, the more a model is robust (higher Q^2) the data extraction perturb the original model.

2. External validation by splitting the available data set into training set for model development and predication set for model predictivity check.

To validate a QSAR model, Leave-One- Out (LOO) procedure was applied. The outcome from this procedure is a cross-validated correlation coefficient R^2 (Q^2). Frequently, Q^2 is used as a criterion of both robustness and predictive ability of a model. Many authors consider high (For instance, $Q^2>0.5$) as an indicator or even as the ultimate proof of high predictive power of, the QSAR model.(Ravichandran*etal*., 2011). In this study the robustness of the QSAR models was found to be with high Q^2 and acceptable statistical values.

r = 0.932 r^2 = 0.868 RSME = 0.1235 Q^2= 0.7623

S= 0.146 P value= 0.0001

The biological activity values of the test set in table (3.10) were calculated with the derived QSAR models and were compared with the experimental PIC_{50} in table (2.). It was observed from data in table (3.9),

there is a coincidence in the experimental and the predicted PIC_{50} values with a small residual values with the range (-0.061081- 0.235081). Figures (3.26), (3.27), and (3.28) respectively show, the plots of the linear regression predicted versus the experimental values of the biological activity of the training set, cross validation and test set compounds against lung cancer. The plots for QSAR model show a good fit with (r^2 =0.8684; and r = 0.9319) for the training set, and (r^2=0.7623; and r =0. 8731), and a very good fit with (r^2 = 0.8618 and r = 0.9283).

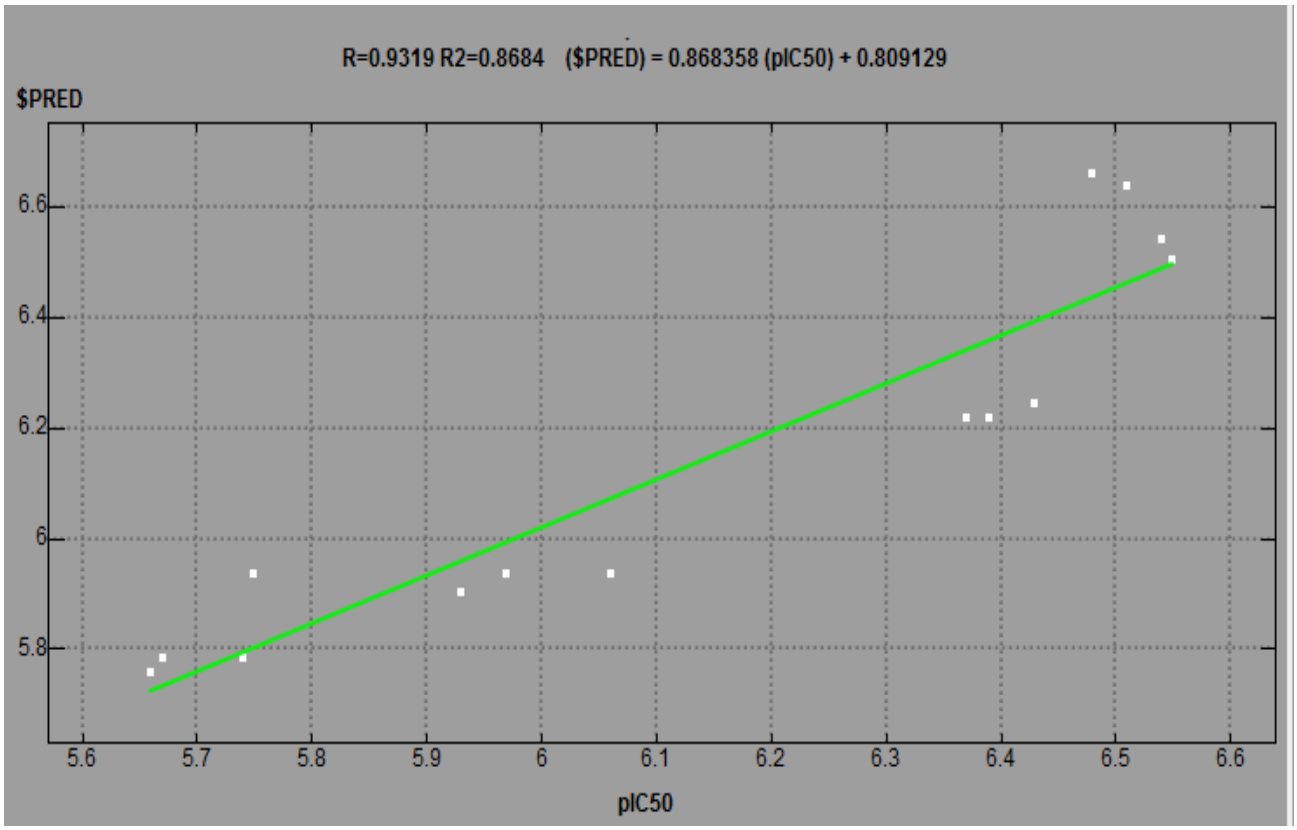


Fig. (3.26): Plots of predicted versus experimentally observed log IC_{50} oftraining set compounds against human lung cancer.

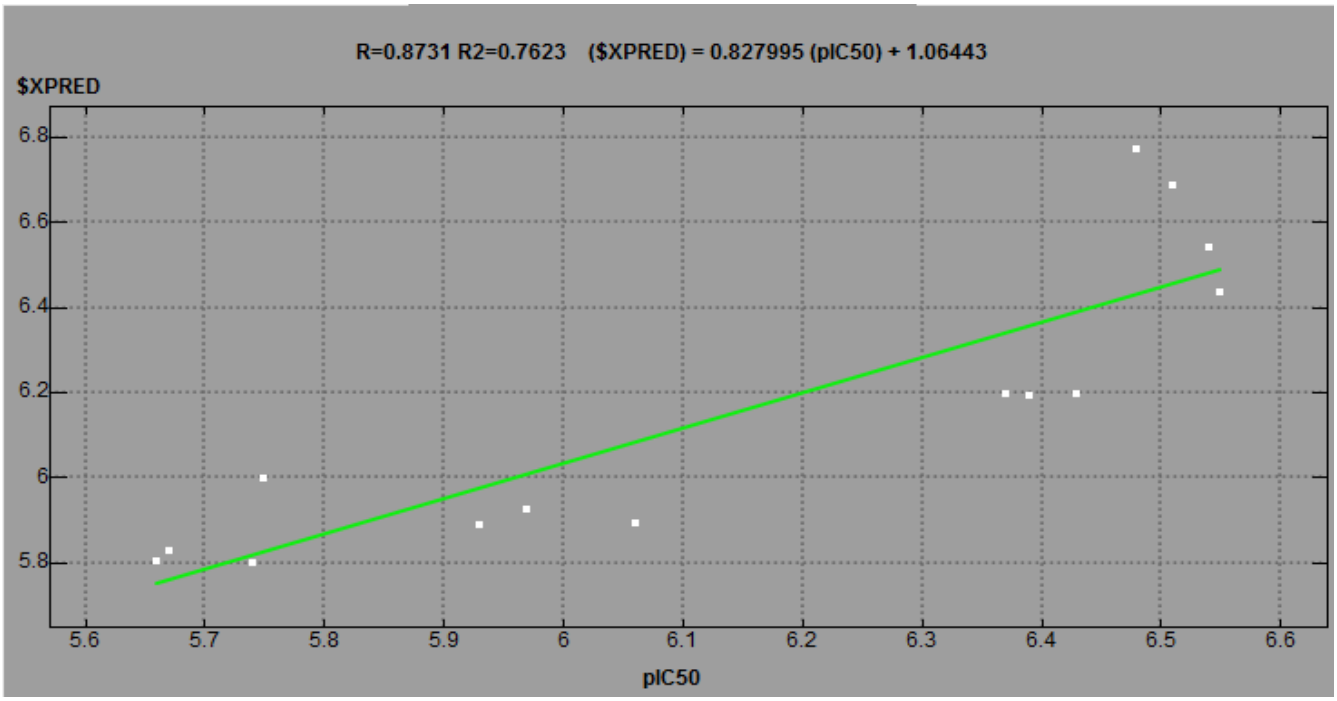


Fig. (3.27): Plots of predicted versus experimentally observed log IC_{50} of cross validation against human lung cancer.

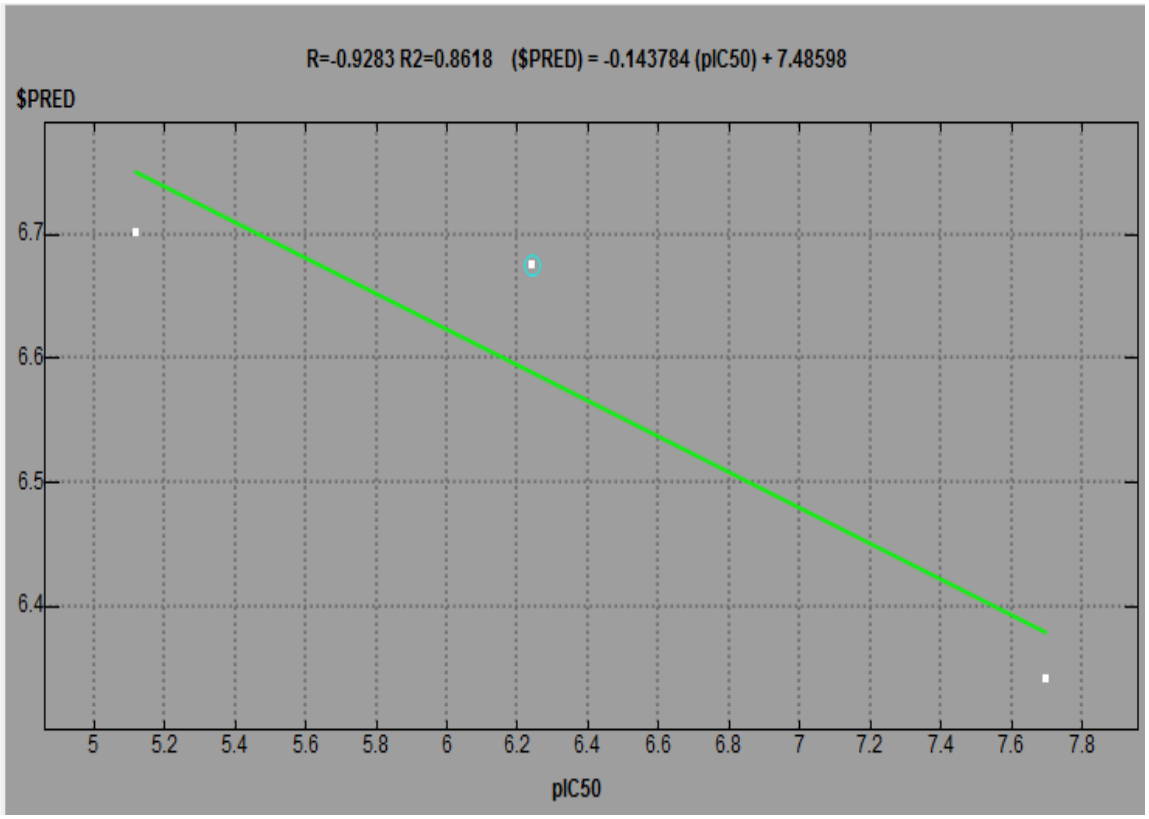


Fig.(3.28): Plots of predicated versus experimentally observed log IC_{50} of test compounds against human lung cancer.

Conclusion and recommendations:

The following points may be concluded from the results of this work:

I-The α,β-unsaturated carbonyl compounds were used as starting materials in the synthesis of a series of heterocyclic compounds like isoxazoles, quinones etc.

II- The condensation of p-amino acetophenone with some aromatic aldehydes (anisaldehyde, benzaldehyde, salicaldehyde, furfuraldehyde),

using (Claisen-Schmidt reaction) lead to the formation of α,β-unsaturated carbonyl compounds which on cyclization with hydroxylamine hydrochloride in sodium acetate furnish the isoxazoles.(Michael reaction).The reaction of synthesized isoxazoles derivativeswith 2, 3, 5, 6-tetrabromo-1,4-benzoquinone (bromonil) lead to the formation of the target compounds (*p*-quinones derivatives).

III-The synthesized compounds were characterized by TLC,melting points, ^{1}HNMR and Ms.

VI- The target compounds were evaluated for their antimicrobial activity.

V- QSAR study has been carried out for establishing a correlation between the structural properties of the synthesized compounds, (*p* - quinones derivatives) and their anti- lung cancer activities.

VI- Molecular Docking study was employed to find out the binding affinity of the synthesized compounds with the target protein.

VII- Further examination and investigation of the activity of the newly synthesized compounds i.e ,(*p*- quinones derivatives) can be carried out against the wide spread diseases such as malaria and cancer is recommended.

Chapter Four

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