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SPECTROPHOTOMETRIC DETERMINATION OF SOME PHARMACEUTICAL THIOLS USING 2,6-DICHLOROQUINONE -4-CHLORIMIDE*: PART II QUANTITATIVE RELATIONS BETWEEN MOLAR ABSORPTIVITIES AND MOLECULAR CONNECTIVITY INDEXES

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ABSTRACT: *Spectrophotometric determination of some pharmaceutical thiols using 2,6-dichloroquinone-4-chlorimide (DQC) at pH 7-8, has been previously reported. Correlation of ϵ_{max} or log ϵ_{max} with third-order valence molecular connectivity indexes of all the investigated compounds was found to be statistically highly significant. Correlation equations were used to predict the molar absorptivity of the interaction products of thiols with DQC.*

INTRODUCTION

In a previous communication we developed a simple spectrophotometric method for the determination of some thiol and thione compounds depending on their interaction with 2,6-dichloroquinone-4-chlorimide (DQC) and the molar absorptivities of the resulting interaction product(s) were calculated[1]. the mechanism of the reaction for three representative examples of the investigated compounds is outlined in scheme 1: thiosalicylic acid as a representative of aromatic thiols, dimercaprol as a representative of dithiols and aliphatic thiols, 2-thiobarbituric acid as a representative of heterocyclic thio-compounds.

It is well known that the molar absorptivity is governed by the size of the absorbing species. The relation was formulated by Braude[2,3] in the following expression:

$$\epsilon_{max} = 0.87 \; X \; 10^{29} \; a$$

where a is the effective area of the chromophore in square angstrom units. Since the surface area of the molecule depends on molecular structure, the conversion of structural formula into numerical values or indexes such as molecular connectivity indexes, which encode structural information like total number of atoms, number of different kinds of atoms and their linkage patterns, will be extremely helpful in correlation with physicochemical parameters[4-6]. Randic reported also the significance of molecular topographic descriptors of planar structures[7].

In the present investigation, we tried to correlate the experimentally measured ϵ_{max} value of the interaction products with first, second and third values connectivity indexes of the investigated compounds in order to find statistically significant relationships which may be useful in the prediction of the molar absorptivity of any thiol or thione compound. Similar correlations were previously reported for phenothiazines[8,9] and catecholamines[10], where highly significant relationships were obtained.

EXPERIMENTAL

Instruments:

a. Perkin-Elmer Lambda-3B, UV/VIS spectrophotometer connected with Perkin-Elmer R 100 A recorder (USA).
b. Copam Computer PC 88M (Taiwan).

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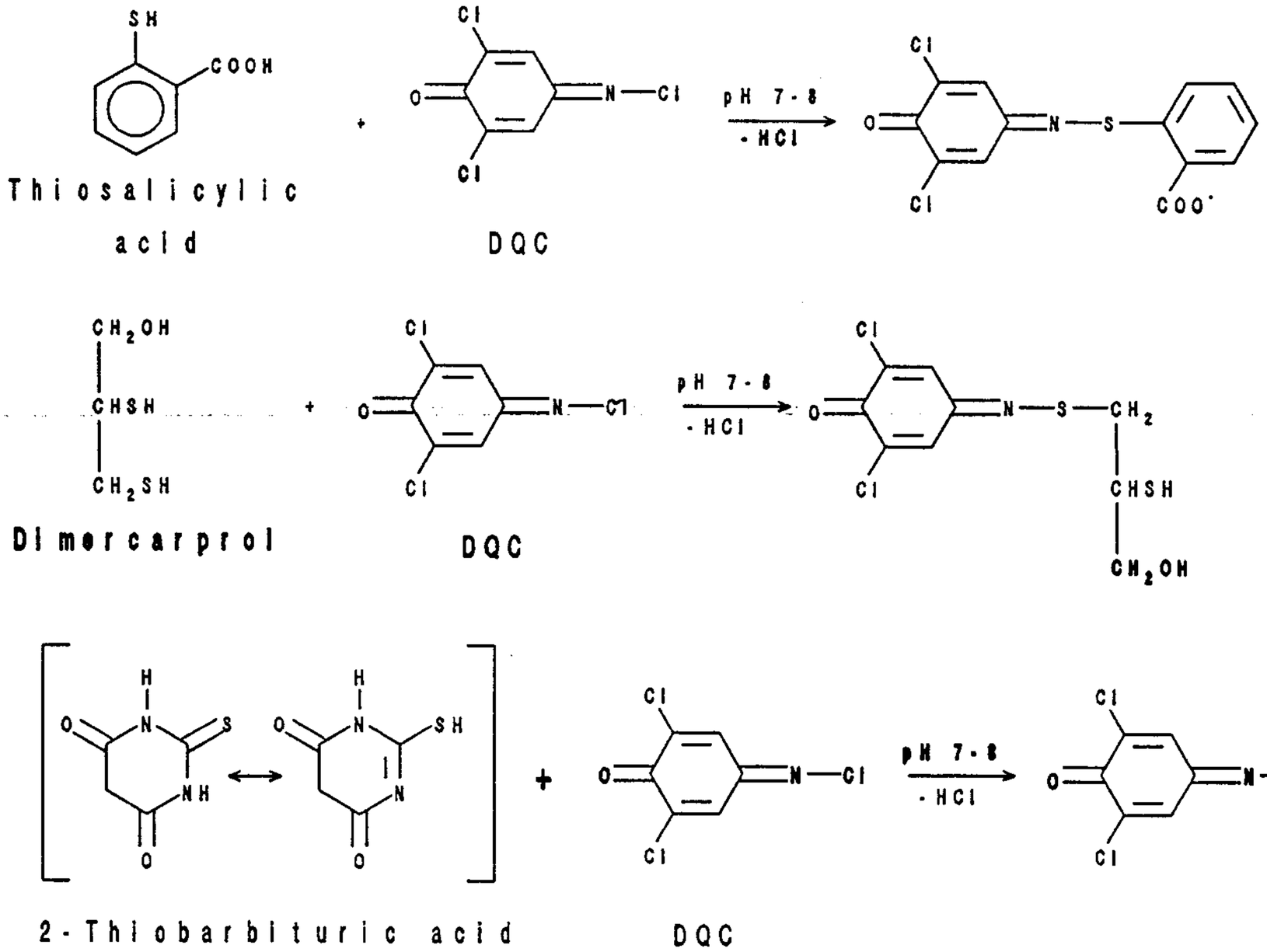
* Part 1 - Reference 1.



Scheme 1: Pathway of the reaction of thiols with DQC to form quinone sulfenimines.

Mathematical and Statistical Treatment of Data:

a. Molar absorptivities (ϵ_{max}) of the chromophores, resulting from the interaction of eight of the investigated thiols and thiones with DQC, were taken from published work[1] and their logarithm values were derived (log ϵ_{max}).

b. Calculation of the first, second and third order valence molecular connectivity indexes ($^1\chi^v$, $^2\chi^v$ and $^3\chi^v$) of thiol or thione (after tautomerism) compound, in the form RSH, was done according to the general rules of Hall and Kier[11]. The squares of the obtained values were also derived. The computed values are presented in Table 1. The calculations were made using a designed computer program named subroutine RLFOR from IMSL[12].

RESULTS AND DISCUSSION

To find a quantitative relationship between ϵ_{max} or log ϵ_{max} of the interaction products of thiols or thiones with DQC and the molecular connectivity indexes of the R group, almost all types of possible relationships were calculated. The relationships included were:

a. Linear curve fit. $Y = a + bX$

b. Logarithmic curve fit. $Y = a + b\ lnX$

c. Exponential curve fit. $Y = a\ e^{bX}$

d. Power curve fit. $Y = a\ X^b$

e. Polynomial (degree 2) $Y = a + bX + cX^2$

f. Polynomial (degree 3)

$$Y = a + bX + cX^2 + dX^3$$

g. Polynomial (degree 4)

$$Y = a + bX + cX^2 + dX^3 + eX^4$$

Table 1: Molecular connectivity indexes for the R group of the studied thiols and thiones and ϵ_{max} of their chromophores.

Compound	$^1\chi$	$^2\chi$	$^3\chi$	$^1\chi^2$	$^2\chi^2$	$^3\chi^2$	ϵ	log ϵ
Sulphathiourea	3.5709	2.1647	1.2484	12.751	4.686	1.559	12687.360	4.104
Tiopronin	2.3910	1.1784	0.6167	5.717	1.389	0.380	5574.080	3.55
Dimercaprol	1.9041	1.5621	0.3730	3.626	2.440	0.139	3734.881	3.572
Thioglycerol	1.3908	0.8361	0.2107	1.934	0.699	0.044	2195.648	3.342
Thiacetazone	4.1339	2.6659	1.5301	17.089	7.107	2.341	12051.300	4.08
Captopril	3.9561	3.0571	2.3703	15.651	9.346	5.618	2853.611	3.455
Thiobarbaturic Acid	3.9238	3.1189	1.7946	15.396	9.728	3.221	9682.075	3.986
Thiosalicylic Acid	2.5042	1.5809	0.8725	6.271	2.499	0.761	18117.325	4.25

h. Polynomial (degree 5)

$$Y = a + bX + cX^2 + dX^3 + eX^4 + fX^5$$

i. Polynomial (degree 6)

$$Y = a + bX + cX^2 + dX^3 + eX^4 + fX^5 + gX^6$$

where Y = ϵ_{max} or log ϵ_{max} and X = $^1\chi^v$, $^2\chi^v$, $^3\chi^v$ or their squares. The relationships obtained are presented in Tables 2-5. It is evident from the obtained 108 relations that:

a) The relationships of ϵ_{max} or log ϵ_{max} with $^1\chi$ and $^2\chi$ give relatively weaker correlations than $^3\chi$. This can be easily explained by the fact that the property of light absorption has a complex dependance on three dimensional structure of the molecule. A more satisfactory description of molecular structure requires the capability of expressing numerically relative structure in several dimensions or in terms of several kinds of fragments of the molecule[9]. This can be done by $^3\chi$ which dissects the molecule into three-bond fragments and thus better relate the physico-chemical parameter (ϵ_{max} or log ϵ_{max}) to molecular properties.

b) Regarding the type of regression equation the best curve fit, as estimated by correlation coefficient, standard deviation and significance of correlation indicated by F-test, is generally the polynomial regression of degree 6 (see Tables 2-5). The numbers of these equations are 27, 54, 81 and 108. Generally, extrapolation is forbidden and interpolation is done with precaution.

c) The most suitable equations for the prediction of ϵ_{max} of a thiol or a thione compound upon interaction with DQC are equations 54 and 108 (see Fig. 1 and 2).

$$\log Y = 3.481 - (1.530)X + (8.480)X^2 - (9.942)X^3 + (4.799)X^4 - (1.017)X^5 + (0.077)X^6$$

$$Y = 6004 - (65900)X + (261100)X^2 - (293680)X^3 + (140241)X^4 - (29624)X^5 + (2235)X^6$$

where Y = ϵ_{max}, x = $^3\chi^2$

The correlation coefficient of equations 54 and 108 are 0.9837 and 0.9709 respectively and the probability of correlation for both equations is 0.99. The latter equations were exploited for the calculation of ϵ_{max} of the thiol or thione compounds, Table 6.

In conclusion the present investigation resulted in finding statistically significant relationships which may be useful in the prediction of the molar absorptivity of the interaction product of thiol or thione compound with DQC, provided that there is no other group, in the compound, that may hinder or alter the proposed reaction.

Table 2: Regression analysis of ϵ_{max} of the chromophores versus molecular connectivity indexes.

Parameter	Type of eq.	No. of eq.	a x 10^{-3}	b x 10^{-3}	c x 10^{-3}	d x 10^{-3}	e x 10^{-3}	f x 10^{-3}	g x 10^{-3}	r	s x 10^{-3}	F	P
$^{1}\chi$	Linear	1	2.144	2.007						0.3605	5.906	2.32	0.81
	Log	2	1.901	6.060						0.4128	5.777	2.72	0.84
	Exp.	3	2.084	0.003						0.4899	6.300	2.96	0.85
	Power	4	2.066	0.001						0.5018	6.165	3.09	0.86
	Parab	5	-23.193	22.232	-3.545					0.5544	5.279	3.99	0.90
	Cubic	6	-12.567	8.464	1.956	-0.682				0.5573	5.267	4.03	0.90
	4th deg.	7	316.108	-540.754	325.959	-80.918	7.135			0.6841	4.575	5.69	0.94
	5th deg.	8	-469.891	1142.958	0.000	464.986	-96.473	7.590		0.7425	4.037	7.00	0.96
	6th deg.	9	29.698	-169.603	330.956	-293.101	128.814	-27.030	2.153	0.7687	4.055	7.21	0.96
$^{2}\chi$	Linear	10	5.057	1.511						0.2226	6.184	1.36	0.69
	Log	11	5.676	3.979						0.3210	6.007	2.03	0.78
	Exp.	12	3.262	0.0003						0.4294	6.606	2.47	0.83
	Power	13	3.914	0.0007						0.4669	6.452	2.75	0.84
	Parab	14	-19.010	29.394	-6.812					0.6438	4.853	5.04	0.93
	Cubic	15	-11.308	14.939	1.286	-1.376				0.6480	4.831	5.10	0.94
	4th deg.	16	62.046	-170.971	163.437	-59.718	7.397			0.6764	4.673	5.51	0.94
	5th deg.	17	68.138	-190.002	185.785	-72.141	10.685	0.333		0.6765	4.672	5.51	0.94
	6th deg.	18	63.493	-231.246	337.485	-254.36	111.309	-26.558	2.612	0.6751	4.646	5.53	0.94
$^{3}\chi$	Linear	19	6.626	1.318						0.1676	6.253	1.02	0.63
	Log	20	8.483	2.783						0.3935	5.831	2.57	0.83
	Exp.	21	4.621	0.0002						0.3912	6.683	2.23	0.80
	Power	22	6.624	0.0004						0.4811	6.339	2.89	0.83
	Parab	23	-3.972	26.411	-10.058					0.8322	3.517	9.01	0.97
	Cubic	24	-6.086	34.978	-18.080	2.052				0.8373	3.467	9.19	0.97
	4th deg.	25	3.672	-22.897	78.248	-56.557	11.632			0.8691	3.138	10.54	0.98
	5th deg.	26	25.467	-189.130	481.529	-469.433	197.693	-30.319		0.9065	2.681	12.87	0.98
	6th deg.	27	12.951	-68.900	78.308	152.188	-279.447	146.383	-25.063	0.9128	2.603	13.34	0.98

Table 3: Regression analysis of ϵ_{max} of the chromophores versus the squares of the molecular connectivity indexes.

Parameter	Type of eq.	No. of eq.	a x 10^{-3}	b x 10^{-3}	c x 10^{-3}	d x 10^{-3}	e x 10^{-3}	f x 10^{-3}	g x 10^{-3}	r	s x 10^{-3}	F	P
$^1\chi^2$	Linear	28	5.168	0.300						0.3094	6.031	1.95	0.78
	Log	29	1.901	2.030						0.4127	5.777	2.72	0.84
	Exp.	30	3.550	0.0006						0.4703	6.400	2.80	0.85
	Power	31	2.066	0.0005						0.5018	6.165	3.10	0.86
	Parab	32	-3.466	2.996	-0.138					0.5459	5.314	3.91	0.90
	Cubic	33	-9.157	5.889	-0.513	0.013				0.5868	5.136	4.35	0.91
	4th deg.	34	22.497	-17.954	4.701	-0.400	0.010			0.7638	4.095	7.10	0.96
	5th deg.	35	20.314	-16.001	4.432	-0.229	0.006	0.0001		0.7641	4.093	7.11	0.96
	6th deg.	36	-96.739	119.632	-51.965	10.398	-1.009	0.046	0.0008	0.7833	3.618	8.24	0.97
$^2\chi^2$	Linear	37	7.083	0.217						0.1322	6.287	0.80	0.50
	Log	38	5.676	1.989						0.3209	6.007	2.03	0.53
	Exp.	39	4.778	0.0005						0.3919	6.686	2.23	0.80
	Power	40	3.914	0.0003						0.4668	6.452	2.75	0.85
	Parab	41	-0.927	5.254	-0.741					0.6301	4.925	4.87	0.93
	Cubic	42	-4.853	9.426	-1.483	0.065				0.6616	4.756	5.29	0.94
	4th deg.	43	-0.578	2.475	1.585	-0.411	0.023			0.6777	4.664	5.53	0.94
	5th deg.	44	-10.099	22.486	-11.038	2.832	-0.336	0.014		0.7028	4.510	5.99	0.95
	6th deg.	45	18.155	-44.959	40.944	-14.99	2.675	-0.231	0.007	0.7644	4.063	7.16	0.96
$^3\chi^2$	Linear	46	8.327	-0.120						0.0393	6.338	0.24	0.13
	Log	47	8.485	1.391						0.3938	5.830	2.57	0.83
	Exp.	48	6.140	0.00001						0.3445	6.713	1.95	0.77
	Power	49	6.626	0.0002						0.4812	6.338	2.89	0.85
	Parab	50	4.327	6.766	-1.282					0.7124	4.451	6.09	0.95
	Cubic	51	1.183	19.475	-7.988	0.815				0.8517	3.324	9.76	0.97
	4th deg.	52	-0.592	31.750	-21.306	5.283	-0.440			0.8811	3.000	11.17	0.97
	5th deg.	53	0.075	24.464	-7.087	-4.112	1.988	-0.207		0.8842	2.962	11.36	0.98
	6th deg.	54	6.004	-65.900	261.100	-293.68	140.241	-29.624	2.235	0.9837	1.399	26.76	0.99

Table 4: Regression analysis of log ϵ_{max} of the chromophores versus molecular connectivity indexes.

Parameter	Type of eq.	No. of eq.	a x 10^{-3}	b x 10^{-3}	c x 10^{-3}	d x 10^{-3}	e x 10^{-3}	f x 10^{-3}	g x 10^{-3}	r	s x 10^{-3}	F	P
$^{1}\chi$	Linear	55	3.319	0.160						0.4813	0.331	3.29	0.87
	Log	56	3.315	0.467						0.5337	0.319	3.78	0.89
	Exp.	57	3.324	0.043						0.4902	0.333	3.34	0.88
	Power	58	3.321	0.126						0.5387	0.321	3.80	0.89
	Parab	59	1.811	1.363	-0.211					0.6392	0.291	4.99	0.93
	Cubic	60	2.005	1.111	-0.110	-0.012				0.6395	0.291	4.99	0.93
	4th deg.	61	16.309	-22.790	13.968	-3.504	0.311			0.7023	0.268	5.95	0.94
	5th deg.	62	-33.13	82.995	-72.859	30.719	-6.179	0.475		0.7566	0.230	7.48	0.96
	6th deg.	63	5.588	-18.268	33.840	-27.280	10.994	-2.155	0.163	0.7937	0.229	7.86	0.96
$^{2}\chi$	Linear	64	3.514	0.139						0.3425	0.355	2.18	0.80
	Log	65	3.593	0.328						0.4445	0.339	2.89	0.85
	Exp.	66	3.502	0.038						0.3558	0.356	2.26	0.81
	Power	67	3.579	0.089						0.4544	0.340	3.03	0.86
	Parab	68	2.015	1.875	-0.424					0.7183	0.263	6.20	0.95
	Cubic	69	2.425	1.106	0.007	-0.073				0.7213	0.262	6.25	0.95
	4th deg.	70	5.854	-7.586	7.588	-2.801	0.346			0.7371	0.255	6.55	0.96
	5th deg.	71	-3.192	20.758	-25.800	15.810	-4.593	0.502		0.7470	0.251	6.73	0.96
	6th deg.	72	-2.147	13.522	-9.892	-0.099	3.416	-1.475	0.190	0.7573	0.249	6.90	0.96
$^{3}\chi$	Linear	73	3.665	0.114						0.2441	0.367	1.51	0.72
	Log	74	3.821	0.204						0.4851	0.331	3.33	0.88
	Exp.	75	3.650	0.031						0.2550	0.368	1.57	0.73
	Power	76	3.808	0.055						0.4894	0.333	3.33	0.88
	Parab	77	3.979	1.739	-0.651					0.9188	0.149	13.96	0.99
	Cubic	78	2.953	1.842	-0.747	0.025				0.9189	0.149	13.98	0.99
	4th deg.	79	3.251	0.079	2.186	-1.760	0.354			0.9266	0.142	14.79	0.99
	5th deg.	80	3.961	-5.338	15.326	-15.212	6.416	-0.988		0.9373	0.132	16.13	0.99
	6th deg.	81	3.071	3.267	-13.713	29.780	-28.248	11.886	-1.830	0.9446	0.122	17.50	0.99

Table 5: Regression analysis of log ϵ_{max} of the chromophores versus the squares of the molecular connectivity indexes.

Parameter	Type of eq.	No. of eq.	a x 10^{-3}	b x 10^{-3}	c x 10^{-3}	d x 10^{-3}	e x 10^{-3}	f x 10^{-3}	g x 10^{-3}	r	s x 10^{-3}	F	P
$^{1}\chi^{2}$	Linear	82	3.550	0.025						0.4296	0.341	2.85	0.85
	Log	83	3.315	0.233						0.5337	0.320	3.79	0.89
	Exp.	84	3.539	0.006						0.4404	0.342	2.92	0.85
	Power	85	3.322	0.063						0.5387	0.321	3.80	0.89
	Parab	86	3.032	0.187	-0.008					0.6245	0.295	4.80	0.92
	Cubic	87	2.683	0.364	-0.031	0.001				0.6626	0.283	5.31	0.93
	4th deg.	88	4.258	-0.822	0.228	-0.020	0.0005			0.7782	0.237	7.43	0.96
	5th deg.	89	3.409	-0.063	0.007	0.008	-0.001	0.00003		0.7884	0.232	7.69	0.96
	6th deg.	90	-1.249	5.334	-2.224	0.435	-0.041	0.002	-0.00003	0.7954	0.220	8.20	0.96
$^{2}\chi^{2}$	Linear	91	3.679	0.024						0.2469	0.366	1.53	0.72
	Log	92	3.593	0.164						0.4445	0.339	2.98	0.86
	Exp.	93	3.662	0.006						0.2613	0.367	1.61	0.73
	Power	94	3.578	0.045						0.4543	0.341	3.03	0.86
	Parab	95	3.170	0.344	-0.030					0.7013	0.268	5.90	0.94
	Cubic	96	2.903	0.607	-0.094	0.004				0.7330	0.257	6.47	0.95
	4th deg.	97	3.225	0.117	0.123	-0.029	0.002			0.7534	0.249	6.87	0.95
	5th deg.	98	2.259	2.148	-1.159	0.300	-0.035	0.001		0.8177	0.217	8.53	0.97
	6th deg.	99	3.618	-1.100	1.348	-0.561	0.111	-0.010	0.0004	0.8551	0.194	9.99	0.98
$^{3}\chi^{2}$	Linear	100	3.788	0.003						0.0174	0.378	0.01	0.06
	Log	101	3.821	0.102						0.4855	0.330	3.33	0.88
	Exp.	102	3.772	0.001						0.0488	0.378	0.29	0.10
	Power	103	3.808	0.027						0.4898	0.333	3.34	0.88
	Parab	104	3.512	0.479	-0.089					0.8255	0.213	8.78	0.97
	Cubic	105	3.355	1.114	-0.424	0.041				0.9136	0.154	13.48	0.98
	4th deg.	106	3.256	1.792	-1.159	0.287	-0.024			0.9373	0.132	16.13	0.98
	5th deg.	107	3.277	1.568	-0.722	-0.001	0.050	-0.006		0.9380	0.131	16.24	0.98
	6th deg.	108	3.481	-1.530	8.480	-9.942	4.799	-1.017	0.077	0.9709	0.092	23.87	0.99

$Y = 6004-(65900)X+(261100)X^2-(293680)X^3+(140241)X^4-(29624)X^5+(2335)X^6$
where $Y = \epsilon$, $X = {}^3\chi^2$

$Y = 3.481-(1.530)X+(8.480)X^2+(9.942)X^3+(4.799)X^4-(1.017)X^5+(0.077)X^6$
where $Y = \log \epsilon$, $X = {}^3\chi^2$

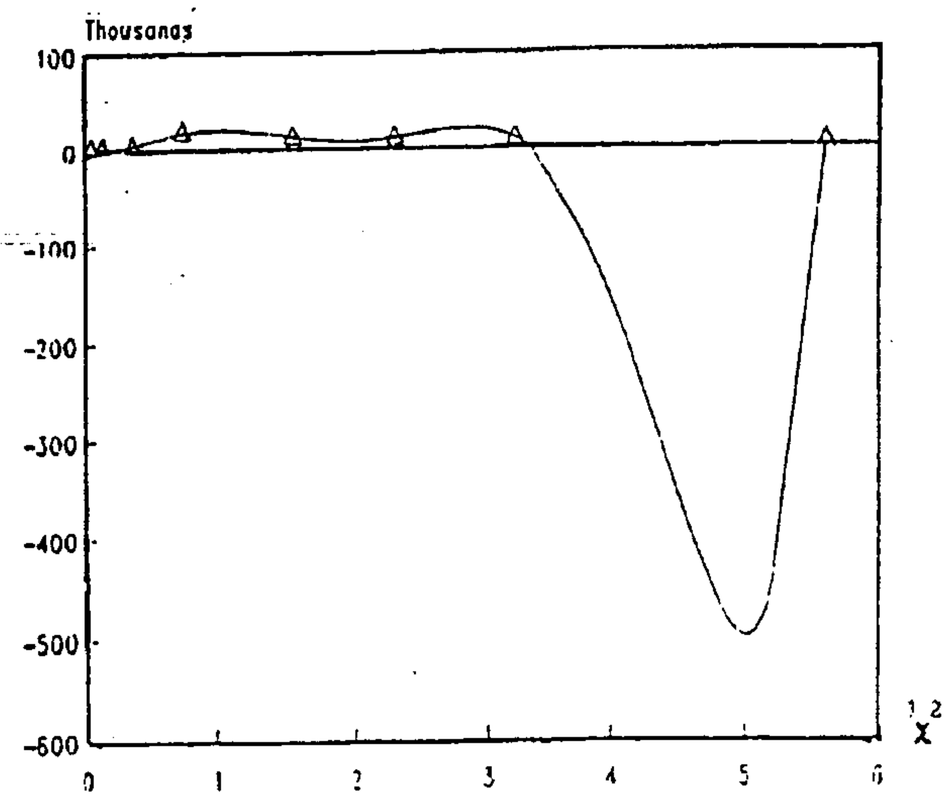


Fig. 1: ϵ_{max} as a function of ${}^3\chi^2$ (eq. 54).

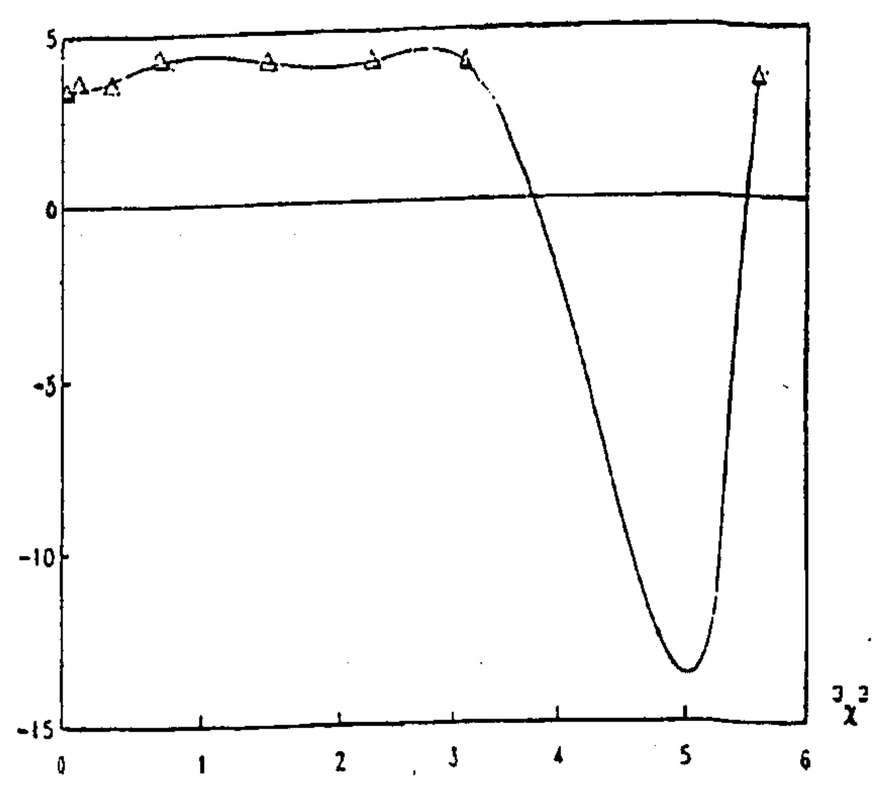


Fig. 2: log ϵ_{max} as a function of ${}^3\chi^2$ (eq. 108).

Table 6: Prediction of the molar absorptivity of the interaction products of thiols with DQC.

Compound	log ϵ_{max}		
	Calculated		Observed
	(54)*	(108)*	
Sulphathiourea	4.107	4.116	4.104
Tiopronin	3.720	3.670	3.553
Dimercaprol	3.061	3.407	3.572
Thioglycerol	3.555	3.429	3.342
Thiacetazone	4.080	4.077	4.081
Captopril	3.455	3.455	3.445
2-Thiobarbituric acid	3.986	3.987	3.986
Thiosalicylic acid	4.244	4.210	4.258

* No. of equation.

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التحليل الطيفى لبعض الثيولات الصيدلية بإستعمال ٢،٦-ثنائى كلوروكينون-٤-كلوريميد

٢- العلاقة الكمية بين شدة الامتصاص الجزيئى وعامل الترابط الجزيئى*.

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فى هذا البحث تم ربط شدة الامتصاص الجزيئى للون الناتج من تفاعل عدد ٨ مركبات من مشتقات الثيول أو الثيون ذات الأهمية الصيدلية مع ٢،٦-ثنائى كلوروكينون-٤-كلوريميد بمعامل الترابط الجزيئى للمركبات.

وقد أوضحت النتائج أن العلاقة بين لوغاريتم شدة الامتصاص الجزيئى من ناحية وعامل الترابط الجزيئى من ناحية أخرى ذات دلالة احصائية عالية.

ولقد تم اختيار افضل معادلتين من ١٠٨ علاقة رياضية استنبطت فى الدراسة وتم استخدامها فى التنبؤ بمعامل الامتصاص الجزيئى للثيولات بتفاعلها مع الكاشف المستخدم بدون اجراء تجارب معملية.

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