August 2007 Volume 3 Issue 2

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 3(2), 2007 [51-59]

Determination And QSAR Study Of The Dissociation Constants Of Some 4,5-Disubsituted-2,4-Dihydro-3H-1,2,4-Triazoline-3-Thiones

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Received: 10th January, 2007 ; Accepted: 15th January, 2007

ABSTRACT

A number of 4,5-disubstituted-2, 4-dihydro-3H-1,2,4-triazoline-3-thiones were obtained by the cyclization of the appropriate thiosemicarbazides. The behavior of newly synthesized 1,2,4-triazole derivatives in aqueous NaOH solutions was studied at room temperature using the method of UV-VIS spectroscopy. The investigated compounds have two dissociation processes. The first process belongs to the dissociation of – SH proton; the second dissociation process is dissociation of phenolic –OH group. QSAR study on dissociation constant has been made using the Hansch and Free - Willson approach. The pKa values(dissociation of -SH and–OH group) were correlated with structure using various physicochemical(electronic, steric and hydrophobic) parameters.

KEYWORDS

Dissociation constants;
1,2,4-Triazole derivatives;
UV-VIS spectroscopy;
Hammett constants;
QSAR.

INTRODUCTION

The applications of pKa values are extremely diverse, ranging from the most fundamental ones, e.g. calculating the distribution functions in a given pH-interval, to exploring the transportation of substances through cell membrane. Therefore, the knowledge of the pKa value of a substance is essential for various investigations in pharmacology, physiology, in structural, environmental, preparative and analytical studies and for industrial purposes[1].

It is well know that the 1,2,4-triazole and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities. The 1,2,4 -triazole nucleus is associated with diverse pharmacological activities such as antibacterial, antifungal, hypoglycemic, antihypertensive and analgesic properties [2-6]. Triazole derivatives act as weak bases in acidic media[7]. Knowledge of the acidity constants of weakly basic substrates is of central importance to the study of reaction mechanisms taking place in acidic media [7,8].

It is also known that the dissociation constants pKa depends upon the polarity of molecule and directly or indirectly on the intra and intermolecular forces[9]. It was implicit that for maximum activity, the 1,2,4-triazoles should have a pKa that gives the proper equilibrium between the inherent activity and penetration, the half-dissociated status appears to present the best compromise between transport and activity[10]. The parameters accounted for the intra and intermolecular forces and steric effect definitely plays a significant role in the modeling of dissociation constants pKa. Physicochemical parameters taken into consideration in this QSAR study are electronic parameter of substituents σ hydrophobic parameters(logP and π) field effect as electronic influences(F), Verloop's STERIMOL parameter L for the steric interactions of the substituents R_2, and molar refractivity(MR) as steric parameter[11,12].

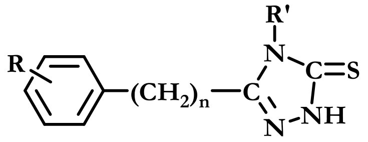
The aim of this work was to investigate the behaviors of some previously synthesize 4,5-disubstituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones[13,14], in sodium hydroxide solutions, at room temperature using the methods of UV/VIS spectroscopy in the 190-500 nm region. QSAR analysis of experimental pKa values was performed by the MVA (multi variable analysis), using different physicochemical (electronic, steric and hydrophobic)parameters.

EXPERIMENTAL

Materials

In our work we investigated the following compounds **(TABLE 1)** :

The newly synthesized compounds, reported elsewhere[13,14], were characterized by their melting points, IR and NMR spectra, as well by elemental analysis. Stock solutions of investigation compounds ($2x10^{-3}$mol/dm^3) were prepared by dissolving the required amounts of the substances in absolute ethanol. Those solutions were stable for long time; i.e. during two months there were no changes in their absorption spectra.



n=0, 1
R= 2-OH; 3-OH; 4-OH; 2-OH, 5-Cl; 3,4,5-CH_3O; 4-C_2H_5O
R'=C_6H_5-; n-C_4H_9-

TABLE 1: 4,5-Disubstituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones (P1-P7 and B1-B4) used in the present study

Comp. No.	R	R'	n	Mol. for. (mol. wt.)	Elem. analysis Cal./found [%] C	H	N
P1	2-OH	-C_6H_5	0	$C_{14}H_{11}N_3OS$ (269.318)	62.43/62.80	4.08/4.50	15.60/15.24
P2	3-OH	-C_6H_5	0	$C_{14}H_{11}N_3OS$ (269.318)	62.43/62.27	4.08/4.05	15.60/15.86
P3	4-OH	-C_6H_5	0	$C_{14}H_{11}N_3OS$ (269.318)	62.43/62.92	4.08/4.44	15.60/15.20
P4	2-OH, 5-Cl	-C_6H_5	0	$C_{14}H_{10}N_3OClS$ (303.763)	55.35/55.50	3.29/3.15	13.83/13.74
P5	4-OH	-C_6H_5	1	$C_{15}H_{13}N_3OS$ (285.345)	63.53/63.80	4.58/5.08	14.82/14.65
P6	4-OC_2H_5	-C_6H_5	1	$C_{17}H_{17}N_3OS$ (311.399)	65.57/65.86	5.50/5.43	13.49/14.00
P7	3,4,5-$(OCH_3)_3$	-C_6H_5	0	C17H17N3O3S (343.395)	59.46/59.05	4.99/5.40	12.23/11.84
B1	2-OH	n-C_4H_9	0	$C_{12}H_{15}N_3OS$ (249.328)	57.80/58.11	6.02/5.81	16.85/16.52
B2	3-OH	n-C_4H_9	0	$C_{12}H_{15}N_3OS$ (249.328)	57.80/58.11	6.02/5.81	16.85/16.30
B3	4-OH	n-C_4H_9	0	$C_{12}H_{15}N_3OS$ (249.328)	57.80/58.22	6.02/5.69	16.85/16.40
B4	4-OC_2H_5	n-C_4H_9	1	$C_{15}H_{21}N_3OS$ (291.409)	61.82/62.05	7.26/6.88	14.41/14.85

Spectral measurements

The spectrophotometric measurements where carried out on a Varian Cary 219 spectrophotometer in 1cm quartz cells, at 25^{0}C.

Alkaline solutions were prepared by dilution of a standard NaOH solution(0.1mol/dm^3 Titrival, Kemika). The pH values of the diluted aqueous solutions were measured on an Iskra MA-5704 pH meter after recording the spectra. The ionic strength (I=0.1mol/dm^3) of the diluted aqueous solutions was adjusted with $NaClO_4$(Kemika). All chemicals were of analytical grade(p.a.). Triply distilled water was used for the preparation of the aqueous solutions.

The concentration of the test solutions of the investigated compounds was $2x10^{-5}$mol/dm^3. The blanks had the same concentration as the test solutions and the same volume of ethanol was added instead of stock solutions of the investigated compounds. The ethanol content in all of the test solutions and the blanks was 1%.

QSAR analysis

The MVA (multi variable analysis) approach in QSAR analysis has been most widely and effectively used for theoretical drug design due to various physicochemical (electronic, steric and hydrophobic) parameters and structural indicator parameters used together, (Hansch and Free - Willson approach),[11,12].

The assumption can be formulated as given in Eqn.1, (Hansch approach):

$$pKa = A_1 x + A_2 y + A_3 z + B \qquad (1)$$

where x, y and z are molecular properties. From the values of linear slopes A_1, A_2, A_3 we can see the correlation of the particular molecular properties with the activity of the investigated compounds.

Applying the same chosen descriptors in Free - Willson analysis (Eqn.2) the activity contributions of phenyl-/butyl group and presence of - CH_2- group as a bridge between 1,2,4 -triazole and benzene ring, were determined from the correlation equation:

$$pKa = \Sigma\alpha_i I_i + \sum b_i x_i + B \qquad (2)$$

where I_i is the structural indicator parameter; x_i.

The variables used as descriptors in the analysis are electronic, steric and structural parameters (TABLES 2 and 3). Physicochemical parameters taken into consideration in QSAR study are σ electronic parameter of substituents, π hydrophobic parameter, F(field effect) as electronic influences, Verloop's STERIMOL parameter L for the steric interactions of the substituents R_2. L is defined as the length of a substituent along the axis of its substitution to the parent skeleton. Electronic effect of the substituents, expressed in term of F, is found to be important in determining the activity, as it is predictive in electrophilic reactions of bimolecules. The classical Hammett σ parameters and MR value were used(TABLE 2). For each compound the partition coefficient logP has been calculated[15], (TABLE 3).

TABLE 2: Physicochemical parameters of triazole derivatives studied

R	$(\Sigma)\sigma^{\alpha}$	$(\Sigma)\sigma_I^{c}$	$(\Sigma)\pi^{\alpha}$	$(\Sigma)MR^{\alpha}$	$(\Sigma)F^{\alpha}$	$(\Sigma)R^{\alpha}$
2-OH	-0.37^b	0.25	-0.67	2.85	0.29	-0.64
3-OH	0.12	0.25	-0.67	2.85	0.29	-0.64
4-OH	-0.37	0.25	-0.67	2.85	0.29	-0.64
2-OH, 5-Cl	0	0.72	0.04	3.18	0.70	-0.79
4-C_2H_5O	-0.24	0.27	0.38	12.41	0.22	-0.44
3,4,5-CH_3O-	-0.03	0.81	-0.06	23.61	0.78	-1.53

$^{\alpha}$Taken from Ref.[11]; (Σ) is for di- and three-substituted compounds; $^{\beta}$ Taken from Ref.[16]; ^{c}Taken from Ref.[17] ;

TABLE 4: Matrix for free Willson approach

	P1	P2	P3	P4	P5	P6	P7	B1	B2	B3	B4
I_{C6H5-}	1	1	1	1	1	1	1	0	0	0	0
I_{-CH2-}	1	1	1	1	0	0	1	1	1	1	0

Applying the Free -Willson analysis, the structural variable indicator I_{C6H5-} expresses the replacement of phenyl with butyl group. I_{C6H5-} is defined as 1 for the 4-phenyl-substituted1,2,4 -triazoline-3-tiones (P1-P7) and 0 for 4-butyl-substituted1,2,4-triazoline-3-tiones, (B1-B4).

In second step, the other indicator I_{-CH2-} is defined as 1 for compounds without - CH_2- group as a bridge between 1,2,4-triazole and benzene ring (P1-P4, P7, B1-B3), and 0 for compound with - CH_2- group as a bridge between 1,2,4-triazole and benzene ring (P5, P6 and B4), (TABLE 4).

RESULTS AND DISCUSSION

Absorption spectra

It is known that 1,2,4-triazole has pKa values of 2.19(as a base) and 10.26(as an acid)[18]. The dissociation of 1,2,4-triazolin-3-thiones, was investigated by spectrophotometric method, following the

TABLE 3: Calculated log P values for compounds (P1-P7, B1-B4)

Compounds	P1	P2	P3	P4	P5	P6	P7	B1	B2	B3	B4
log P^{α}	4.38	4.38	4.38	5.02	3.95	5.00	4.37	3.72	3.72	3.72	5.26

$^{\alpha}$Taken form Ref.[15]

TABLE 5 : Spectral characteristics of different ionic forms(λ_{max}, log ε_{max})for compaunds P1-P7 and B1-B4

Neutral form					
Compound	λ_{max}	ε_{max} x 10^{-3}	Compound	χ_{max}	ε_{max} x 10^{-3}
P1	258 282	19.20 10.85	B1	251 282	32.75 6.75
P2	258 281	22.10 15.10	B2	251 284	32.75 8.45
P3	255 268 293	21.95 22.00	B3	254 281	35.60 11.40
P4	254 298	20.15 8.75	B4	228 251 282	27.00 30.15 6.45
P5	223 255	22.60 20.47			
P6	228 254	23.50 21.30			
P7	258 264 283	30.36			

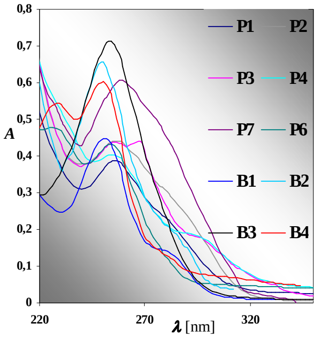


Figure 1 : Absorption spectra of some 4,5-disubsituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones in water (C= $2x10^{-5}$mol/dm^3)

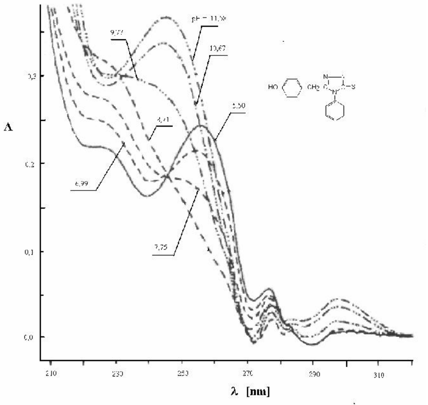


Figure 2 : UV spectra of 4-phenyl-5-(4-hydroxy-benzyl)-2,4-dihydro-3H-1,2,4-triazoline-3-tiones (P5) in water solution of NaOH with different pH

TABLE 6: Experimental data for calculation of the dissociation constants for sompound P5

pH	A(λ =253 nm)	log I	pK_{TH2}	log I	pK_{TH} -
5.50	0.345				
6.50	0.350				
6.58	0.350				
6.69	0.345	-1.3979	8.0879		
6.99	0.350	-0.699	7.6890		
7.15	0.355	-0.3786	7.5286		
7.35	0.360	-0.1347	7.4847		
7.58	0.360	-0.1347	7.7147		
7.75	0.365	0.0894	7.6606		
7.82	0.370	0.3263	7.4937		
8.10	0.372	0.4337	7.6663		
8.71	0.375	0.6232	8.0868		
8.87	0.380	1.1644	7.7056		
9.50	0.338			-1.4807	10.9807
9.59	0.340			-1.3802	10.9702
9.67	0.378			-0.6241	10.2941
9.77	0.403			-0.3847	10.1547
10.14	0.435			-0.1402	10.2802
10.20	0.445			-0.0696	10.2696
10.27	0.445			-0.0696	10.3396
10.40	0.465			0.0696	10.3304
10.67	0.505			0.368	10.3020
10.94	0.524			0.5396	10.4004
11.20	0.535			0.6585	10.5415
11.58	0.548			.8333	10.7467
11.75	0.560			1.0607	10.6893
12.20	0.575			1.6902	10.5098

A_{TH2}=0.3435 A_{TH}-=0.3825 A_T2-=0.5800

changes in the electronic absorption spectra of aqueous solution of investigated compounds in NaOH. The absorption spectra, recorded in neutral aqueous solutions are shown in figure. 1. The characteristic spectral data for neutral form of compounds P1-P7 and B1-B4 are given in TABLE 5.

The electronic absorption spectra of the investigated compounds(P1-P7 and B1-B4) in neutral media(water) are characterized by the presence of absorption maxima at about 223-228 nm, 251-264 nm and 281-298nm. The first band is ascribed to the excitation of π-electrons of the aromatic system; the second and the third absorption maxima are characteristic of electron transition in the 1,2,4 -triazoline-3-thione ring[19].

As in the case of other heterocyclic thiones[20,21], it is possible to consider that the 1,2,4-triazoline-3-thions may exist in thion-thiol tautomeric forms. Our chemical and spectral investigations showed that the thion structure dominates. The absorption maxima or shoulders at 251-264 and 281-298 nm, indicated that some of these compounds exist predominantly in the thion form in ethanolic solution, and absorption at 281-298 nm indicated the presence of a chromophoric C=S group[22,23].

Caculation of dissociation constants

Using the absorption spectra recorded in solutions of different pH(NaOH solutions), the dissociation processes of compounds P1-P7 and B1-B4 were investigated.

The increase of solution basity from 6.0-13.0, was accompanied by disappearance of absorption maxima at 258nm and appearance of new maximum at 303nm(compound P1 and P2). These changes were followed by appearance of the isosbestic points at 248 nm and 294nm(compound P1) and at 256 and 280nm(compound P2). The same changes can be seen in UV spectra of compounds 4-phenyl-5-(4-hydroxyphenyl)-2,4-dihydro-3H-1,2,4-triazoline-3-tiones P3 and 4-phenyl-5-(2'-hydroxy-5'-chloro phenyl)-2,4-dihydro-3H-1,2,4-triazoline-3-tiones P4.

In the basic media(pH 6.02-12.00) the absorption maxima at 223/228 nm, in the spectra of compounds P5 and P6, is shifted to shorter wavelength for about 2 nm, followed by hyperchromic effect, disappearance of maxima at 254/255 nm and decreasing of maxima at 275nm. The same changes can be seen in UV spectra of compound P7: two isosbestic points at 244 nm and 288 nm; disappearance of absorption maxima at 257 nm and hypochromic of absorption maxima at 283 nm while pH is changing from 5.76-3.0.

With increasing pH of solution (compound B1) from 6.16-7.90, the absorption spectra show hypsochromic shift of the absorption maxima at 250nm of about 3 nm. This hypsochromic shift of the absorption maxima was followed with decreasing absorption intensity at 250 nm and 276 nm. In the 8.38 - 9.90 pH range a new absorption maxima at 240 nm was formed, followed with increasing of maxima and hypsochromic effect(~3nm). A clear isosbestioc points at 240 nm and 250n m are formed. In the electronic absorption spectra of compounds B2 and B4, a clear isosbestic points at 241 nm and 271 nm (B2) and at 243nm(B4) appeared, followed with disappearance of absorption maximum at 251nm(B2) and at 248nm(B4) and appearance of new maximum at 241 nm. With increase pH of solution(compound B4) from 6.01-13.0, also increase the absorption intensity of maximum at 228nm.

The plots of absorbance on the chosen wavelengths against pH give sigmoid "S" curves(Figure. 3), which confirm two dissociation processes for compounds P1-P5 and B1-B3, and one for compounds: P6, P7 and B4.

The equilibrium constants of a weak organic acid TH , can be defined as follows:

$$\mathbf{TH \rightleftharpoons T^- + H^+}$$

The pK_{TH} can be calculated from equation:

$$\mathbf{pK_{TH} = \log I + m \cdot pH} \qquad (3)$$

where I is ionization ratio:

$$\mathbf{I = C_{TH}/C_{T-} = A - A_{T-}/A_{TH} - A}$$

where: A_{TH} is the absorbance of the neutral form, A_{T}- is the absorbance of the dissociated form, A is absorbance of the solution at given pH at same wave-

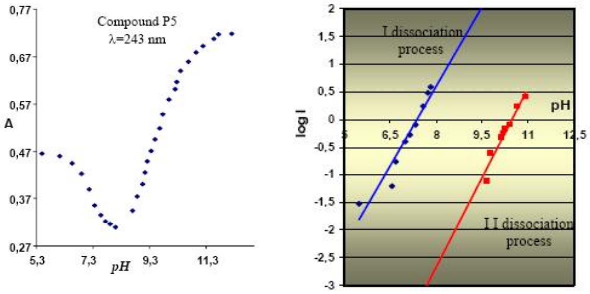


Figure 3 : (a) The absorption change as a function of the acidity of the solution; (b) Dependence of log I from pH value (compound P5)

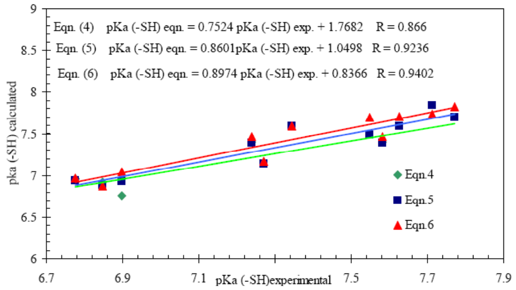


Figure 4 : Plot of experimental vc. calculated pKa (-SH) values of 4,5- disubstituted -1,2,4-triazoline -3- tiones (P1-P7 and B1 - B4) (Eqn.4, 5 and 6)

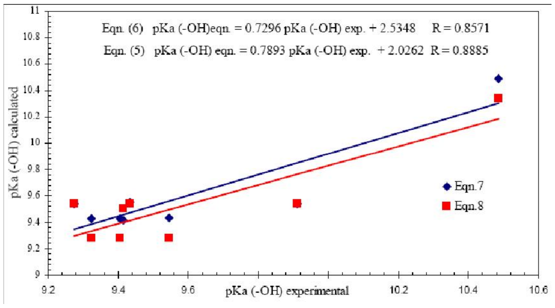


Figure 5: Plot of experimental vc. Calculated pKa (-OH) values of 4,5-disubstituted-1,2,4- triazoline-3-tiones (P1-P7 and B1-B4) (Eqn.7 and 8)

TABLE 7: Dissociation constants of compaunds P1-P7 and B1-B4

Compounds	Dissociation of -SH group		Dissociation of -OH group	
	pK_{TH2}* [pKa (-SH)]	m	pK_{TH-} [pKa (-OH)]	m
P1	7.5816	0.9569	9.2740	0.9861
P2	6.8983	0.9387	9.4345	0.9645
P3	7.2385	0.9797	9.9124	0.9622
P4	6.8466	0.9642	9.4145	0.9685
P5	7.7118	0.9689	10.4864	0.9792
P6	7.5492	0.9477	-	-
P7	6.7748	0.9757	-	-
B1	7.3452	0.9605	9.3242	0.9689
B2	7.2699	0.9861	9.5465	0.9802
B3	7.6257	0.9475	9.4063	0.9634
B4	7.7714	0.9436	-	-

***pK_{TH} for compound P6; P7 and B4**

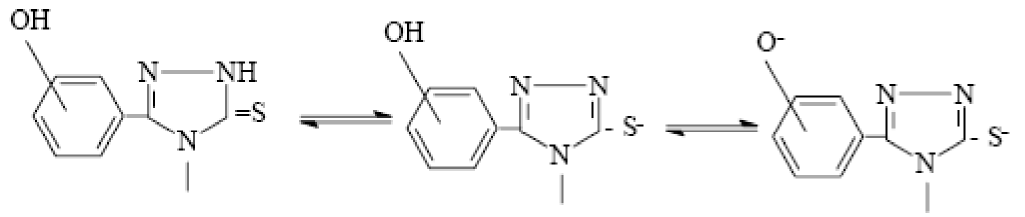
length λ TABLE 6, (Figure 3).

Since the concentrations of the investigated compound were very small, it is not necessary to correct the activity coefficients. The ionic strength is constant because the addition of salt to each sample, and the obtained pK_{TH} are thermodynamic values[24].

As we mentioned before, 1,2,4-triazoline-3-thions may exist in thion-thiol tautomeric forms, as in the case of other heterocyclic thiones[20,21], so the first dissociation equilibrium corresponds to the dissociation of - SH groups. The values of 6.77 to 7.77

According figure 3, the ionisation equilibria of 4,5-disupstituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones P1-P5 and B1-B3, shown in Scheme 1, are:

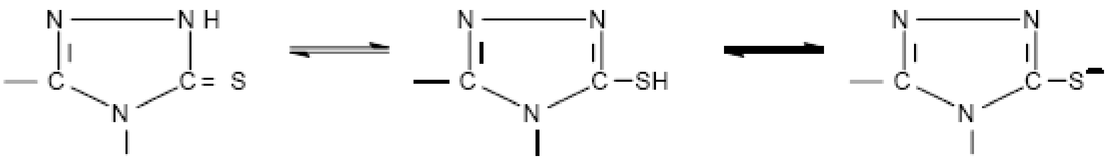
$$TH_2 \rightleftharpoons TH^- + H^+ \text{ (}pK_{TH2} \text{ or } pKa(\text{-SH})\text{)} \quad TH^- \rightleftharpoons T^2 \; + H^+ \text{(}pK_{TH}^- \text{ or } pKa(\text{-OH})\text{)}$$



SCHEME 1 : The dissociation process for compounds: P1-P5 and B1-B3

The dissociation process for compounds P6, P7 and B4, shown in Scheme 2, are

$$TH = TH^- + H^2 \text{ (pKTHor pKa (-SH))}$$



SCHEME 2 : The dissociation process for compounds: P6, P7 and B4

Using the equation (1), the dissociation constants were calculated (TABLE 7).

TABLE 8: Correlation matrix demonstrating correlation of the physicochemical parameters used and their correlation with the activity (pKa)

	pKa(-SH)	pKa(-OH)	σ	π	MR	σ_I	F	R	logP
pKa(-SH)	1.0000								
pKa(-OH)	0.3589	1.0000							
σ	0.7082	0.2606	1.0000						
π	0.0106	0.1833	0.1485	1.0000					
MR	0.2171	0.1833	0.1812	0.6669	1.0000				
σ_I	0.7043	0.1834	0.4221	0.4123	0.5816	1.0000			
F	0.7534	0.1833	0.4217	0.2407	0.4739	0.9833	1.0000		
R	0.6661	0.1833	0.3207	0.0231	0.6178	0.8201	0.8599	1.0000	
logP	0.0610	0.1361	0.1405	0.8505	0.4082	0.3084	0.1639	0.1199	1.0000

TABLE 9: Comparation of estimated pKa(-SH) and pKa(-OH) values of 4,5-disubsituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones (P1-P7, B1-B4), with those reported in TABLE 7. (Residue=difference between observed and estimated pKa)

Comp.	pKa (-SH) exp	Estimated pKa (-SH)					
		I		II		III	
		Eqn.4	Residue	Eqn.5	Residue	Eqn.6	Residue
P1	7.5816	7.3979	0.1836	7.3864	0.1951	7.4662	0.1154
P2	6.8983	6.7619	0.1363	6.9317	-0.0334	7.0438	-0.1455
P3	7.2385	7.3979	-0.1594	7.3864	-0.1479	7.4662	-0.2277
P4	6.8466	6.9177	-0.0711	6.8861	-0.0395	6.8727	-0.0261
P5	7.7118			7.8414	-0.1296	7.7352	-0.0234
P6	7.5492			7.4887	0.0605	7.6986	-0.1494
P7	6.7748	6.9566	-0.1818	6.9361	-0.1613	6.9677	-0.1929
B1	7.3452			7.5954	-0.2502	7.5932	-0.2480
B2	7.2699			7.1407	0.1292	7.1708	0.0990
B3	7.6257			7.5954	0.0303	7.7082	-0.0825
B4	7.7714			7.6977	0.0737	7.8256	-0.0542

Comp.	pKa (-OH) exp	Estimated pKa (-OH)			
		IV		V	
		Eqn.7	Residue	Eqn.8	Residue
P1	9.2740	9.5401	-0.2661	9.5411	-0.2671
P2	9.4345	9.5513	-0.1168	9.5411	-0.1066
P3	9.9124	9.5401	0.3722	9.5411	0.3712
P4	9.4145	9.4144	6E-05	9.5058	-0.0913
P5	10.4864	10.4891	-0.0027	10.3406	0.1457
B1	9.3242	9.4261	-0.1019	9.2796	0.0445
B2	9.5465	9.4373	0.1091	9.2796	0.2668
B3	9.4063	9.4261	-0.0198	9.2796	0.1266

are in good agreement with the literature data for the pK_{TH} values of the thiol-tion form of the pyrimidine-thione[21]. The second dissociation equilibrium of 4,5-disupstituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones P1-P5 and B1-B3 corresponds to the phenolic -OH group[24].

Correlation analysis of the pKa values of some 4,5-disubsituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones

The correlation of the used parameters and their correlation with the activity(pKa) are shown in TABLE 8.

Hammett approaches

In order to estimate the effect of substitution on pKa values of 1,2,4-triazoles studied, the correlation with Hammett σ constants[25] was performed. A good correlation is obtain when is used only the dissociation constants of -SH group (pK_{TH2}/ pK_{TH}). Plot of pK_{TH2}/ pK_{TH} values against the corresponding substituent σ constants is shown in figure 4.

The corresponding Hammett equation ($pKa = pKa^0 - r\sigma$)[26] obtained in this case is:

$$pKa\ (\text{-SH}) = 6.9177 - 1.298\sigma \qquad (4)$$

having the regression parameters R=0.8994 and SD=0.1716(SD-standard deviation).

As expected when correlation of equilibrium constants is concerned, ρ value is positive; meaning that extent of dissociation equilibrium is increased by electron-withdrawing substituents.

For 4,5-disubsituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones series ρ value of 1.298, showing that this reaction series is more sensitive to polar influence of substituents than dissociation of benzoic acid(ρ=1.00) [27]. This result is not surpassing even the reaction site(-SH group) is partially protected from the effect of substituent on aromatic nucleus, probably the effect is transmitted through the benzene and 1,2,4-triazole rings.

Hansch and Free-Willson approach

After the applying the Hansch approach, moderate linear collinearities exist between activity(pKa) and selected parameters(σ, σ_I, π, MR F, R and logP). This can be explained by the fact, that investigated 4,5-disubsituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones have significant structural modification (phenyl-/butyl group and presence of $\text{-}CH_2$-group as a bridge between 1,2,4-triazole and benzene ring).

The mono-parametric regression resulted into not statistically significant models, using the selected parameters.

The last step was applying the Free - Willson approach and the following correlations are obtained:

$$pKa(\text{-SH})=-0.928\sigma-0.221\pi-0.209I_{C6H5-} -0.455\, I_{-CH2-}+7.559 \qquad (5)$$

R=0.875 SD=0.238 n=11 F=4.877

$$pKa(\text{-SH})=- 0.862\sigma-0.004MR-0.694F-0.058R-0.127\, I_{C6H5-}-0.269\, I_{-CH2-} +7.696 \qquad (6)$$

R=0.903 SD=0.259 n=11 F=2.923

$$pKa(\text{-OH})=0.023\sigma\ 0.189\pi+0.114\, I_{C6H5-}-0.949I_{-CH2-}+10.257 \qquad (7)$$

R=0.889 SD=0.286 n=11 F=2.855

$$pKa(\text{-OH})=-0.312\sigma_I+0.174\, logP-1.021\, I_{-CH2-}+ 9.878 \qquad (8)$$

R=0.889 SD=0.247 n=11 F=5.005

where I_{C6H5-} is structural indicator parameter representing phenyl group as 1 and butyl group as 0. The other indicator I_{-CH2-} is defined as 1 for compounds without - CH_2- group as a bridge between 1,2,4-triazole and benzene ring(P1-P4, P7, B1-B3), and 0 for compound with - CH_2- group as a bridge between 1,2,4-triazole and benzene ring(P5, P6 and B4), (TABLE 4). In this correlations R is regression coefficient, SD is a standard deviation(standard error of estimation), n is number of data point and F is the F-ratio.

The equations(5) and(6) show that the physicochemical descriptors:σ, π MR, F, R and structural indicator parameter are negatively correlated with the pKa. The dissociation constant pKa(-SH) increases with the decrease of magnitude of these properties.

The equation(7) and (8) expressed that parameters π, σ_I and indicator parameter I_{-CH2-} have negative correlation with the activity, while the parameters: σ and logP showing positive correlation with the activity(pKa(-OH)).In order to confirm our findings, dissociation constants pKa(-SH) and pKa(-OH) predicted by Eqn.(4), (5), (6), (7) and (8) are compared with the pKa values reported in TABLE 7. Such comparison is showen in TABLE 9. Within experimental error, the values agree well.

Finally, a plot is obtained between the experimental and calculated pKa values as shown in figures 4 and 5, wherein all the four equation(4), (5), (6), (7) and (8) are used for calculated pKa respectly. R^2 values(0.8660, 0.9236, 0.9402, 0.8571 and 0.8885) obtained for each of those equations confirm our findings.

CONCLUSION

The 4,5-disubstituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones have two dissociation processes, and they may exist in thion-thiol tautomeric forms.

The first process belongs to the dissociation of –SH proton; the second dissociation process is dissociation of phenolic –OH group. The values of 6.77 to 7.77 and 9.2 to 10.4 are in good agreement with the literature data.

QSAR study on dissociation constant has been made using the Hansch and Free - Willson approach. The obtained pKa values were correlated with structure using various physicochemical parameters. For 4,5-disubsituted-2,4-dihydro-3H-1,2,4-triazoline-3-thiones series ρ value of 1.298, showing that this reaction series is sensitive to polar influence of substituents, because the reaction site(-SH group) is partially protected from the effect of substituent on aromatic nucleus, probably the effect is transmitted through the benzene and 1,2,4-triazole rings.

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