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Spectroscopic Determination of Acid Dissociation Constants of *N*-Substituted-6-acylbenzothiazolone Derivatives

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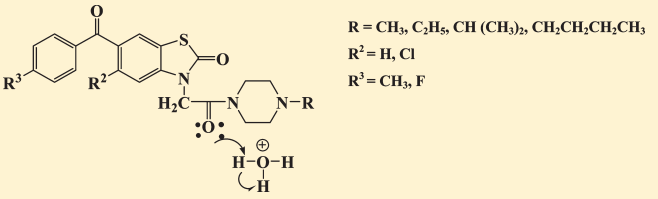
ABSTRACT: The acid dissociation constants of twelve novel drug precursor *N*-substituted-6-acylbenzothiazolone derivatives were determined by using the UV−vis spectroscopic technique. The protonation and deprotonation behaviors of the investigated molecules were researched from the super basic to super acid regions (i.e., 8 mol·L^{-1} KOH to 98% H_2SO_4) including the pH region. It is observed that all of the molecules are protonated in the super acidic region. The calculated relative stability values of possible tautomer structures indicate that the keto form of investigated molecules is favored over the enol form. It was predicted that protonation occurs at the amide (oxo) group found in the keto form.



INTRODUCTION

Benzothiazolone derivatives are considered as one of the candidate groups of nonsteroidal anti-inflammatory (NSAI) drugs due to their analgesic activities. These derivatives are known as antibacterial, anticonvulsive, diuretic, antihistaminic, antiarrhythmic and analgesic reagents and have a wide spectrum of biological activity, and they belong to the family of heterocyclic ring systems.[1−9] NSAI drugs have important side effect such as gastrointestinal lesions, kidney functional disorders and hematological activities.[10] Some 2-substituted benzothiazole derivatives have been used particularly in breast cancer treatment.[11] Some benzothiazole derivatives have found application in the development and preparation of anti-inflammatory drugs and analgesics.[12] Early studies had indicated that analgesic activity of 6-benzoyl-2-benzothiazolinone resembled that of novalgine.[13] Among the other 2-benzothiazolinone derivatives, tiaramide, which has the ring system 1-[2-(5-chloro-2-benzothiazolinone-3-yl) acetyl]-4-hydroxyethyl piperazine, shows strong anti-inflammatory activity by preventing prostaglandin synthesis.[13] It is an example of a nonacidic NSAI drug, but, unfortunately, it shows side effects in the gastrointestinal channel.[13] In addition, tiaramide is proven to have antihistaminic activity with low incidence of mild side effects.[14,15] Doğruer et al. had reported that 2-benzothiazolinon-3-yl-acetamides[16] and 6-acyl derivatives of these acetamides[17] alleviate induced pain and suppress induced inflammation with no observed toxicity.

The piperazine moiety has been classified as a privileged structure which is frequently found in biologically active compounds. Therefore, the piperazine moiety has been used intensively in many therapeutic areas such as antifungal, antidepressants, antiviral, and serotonin receptor (CS-HT) antagonist/agonist binding.[18−20] Piperazines and substituted piperazines are important pharmacophores that can be found in many marketed drugs, such as the Merck HIV protease inhibitor.[21−23] Several compounds that contain the piperazine moiety in their molecule bind to serotonin receptors.[24] Although as a group piperazine-like compounds cannot be considered as selective compounds for serotonin receptors, they may be more site selective with the appropriate substituents.[25]

The acidity constant (pK_a) of a compound is an important property in both the life sciences and chemistry since the propensity of a compound to donate or accept a proton is fundamental to understanding many chemical and biochemical processes.[26−28] The knowledge of acidity constant is a key parameter for understanding the chemical interactions between the compound of interest and its pharmacological target. Relationships between acid−base dissociation constant, pK_a, and structure may prove useful information in drug design studies and in explaining the biopharmaceutical properties of substances like benzoxazolinone or benzothiazolinone.[29,30] The results of early research indicate that compounds containing benzothiazolone and piperazine moieties can be considered as promising drug molecules. The important and useful use of these derivatives has made the compounds attractive to work on. In this work, we aim to determine the acid dissociation constant, pK_a values, of a series of twelve new drug precursor *N*-Substituted-6-acylbenzothiazolone derivatives using the UV−vis spectrophotometric method.

EXPERIMENTAL SECTION

Materials and Solutions. The studied compounds (Table 1) were of spectroscopic grade, and the procedures of synthesis are described in ref 31. Methanol (99.9%), ethanol (99.5%),

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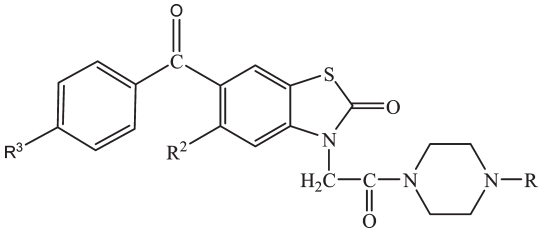
Table 1. IUPAC Nomenclature of the Studied Molecules 1 to 12



molecule	R	R^2	R^3	IUPAC name
1	CH_3	H	CH_3	6-(4-methylbenzoyl)-3-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)benzo[*d*]thiazol-2(3*H*)-one
2	C_2H_5	H	CH_3	3-(2-(4-ethylpiperazin-1-yl)-2-oxoethyl)-6-(4-methylbenzoyl)benzo[*d*]thiazol-2(3*H*)-one
3	C_3H_7	H	CH_3	3-(2-(4-isopropylpiperazin-1-yl)-2-oxoethyl)-6-(4-methylbenzoyl)benzo[*d*]thiazol-2(3*H*)-one
4	C_4H_9	H	CH_3	3-(2-(4-butylpiperazin-1-yl)-2-oxoethyl)-6-(4-methylbenzoyl)benzo[*d*]thiazol-2(3*H*)-one
5	CH_3	H	F	6-(4-fluorobenzoyl)-3-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)benzo[*d*]thiazol-2(3*H*)-one
6	C_2H_5	H	F	3-(2-(4-ethylpiperazin-1-yl)-2-oxoethyl)-6-(4-fluorobenzoyl)benzo[*d*]thiazol-2(3*H*)-one
7	C_3H_7	H	F	6-(4-fluorobenzoyl)-3-(2-(4-isopropylpiperazin-1-yl)-2-oxoethyl)benzo[*d*]thiazol-2(3*H*)-one
8	C_4H_9	H	F	3-(2-(4-butylpiperazin-1-yl)-2-oxoethyl)-6-(4-fluorobenzoyl)benzo[*d*]thiazol-2(3*H*)-one
9	CH_3	Cl	F	5-chloro-6-(4-fluorobenzoyl)-3-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)benzo[*d*]thiazol-2(3*H*)-one
10	C_2H_5	Cl	F	5-chloro-3-(2-(4-ethylpiperazin-1-yl)-2-oxoethyl)-6-(4-fluorobenzoyl)benzo[*d*]thiazol-2(3*H*)-one
11	C_3H_7	Cl	F	5-chloro-6-(4-fluorobenzoyl)-3-(2-(4-isopropylpiperazin-1-yl)-2-oxoethyl)benzo[*d*]thiazol-2(3*H*)-one
12	C_4H_9	Cl	F	3-(2-(4-butylpiperazin-1-yl)-2-oxoethyl)-5-chloro-6-(4-fluorobenzoyl)benzo[*d*]thiazol-2(3*H*)-one

glycine (98.5%), KOH (90%), H_2SO_4 (95.0−98.0%), HC1 (37%), CH_3COOH (99.99%), CH_3COONa (99.0%), NaOH (98.0%), KH_2PO_4 (99.99%), Na_2CO_3 (99.0%), $NaHCO_3$ (99.5%), NaCl (99.5%), methyl orange indicator, phenolphthalein indicator, and standard buffer solutions were used without further purification and were obtained from Sigma-Aldrich.

Apparatus. pH measurements were performed using a glass electrode. Standard buffer solutions of pH values of 4, 7, and 9 were used in the calibration of the Hanna instruments HI 221 pH meter; UV-2550 Shimadzu UV−vis spectrophotometer was used for measurements. Measurements were made at (25 ± 0.1) °C.

Procedure. Acid, KOH and pH solutions were prepared by using methods described in the literature.[32−35] Buffer solutions were prepared using Perrin's descriptions.[32] The potentiometric measurements were performed by measuring the hydrogen ion concentration under nitrogen atmosphere at 25 ± 0.1 °C, and ionic strengths of the media were maintained at 0.1 M using NaCl.[27,32]

Spectrometry is an ideal method[33] when a substance is not soluble enough for potentiometry or when its pK_a value is particularly low or high (i.e., less than 2 or more than 11). This method directly depends on determination of the ratio of the molecular species concentration, that is, the neutral molecules corresponding to the ionized species in a series of nonabsorbing buffer solutions for which pH values are either known or measured.[28] For determining the acid dissociation constants of very weak bases, solutions of known H_0 (designed for H_2SO_4) take the place of the buffer solutions mentioned above. This method takes into account any effect of the medium on the wavelength of the maximum UV absorption and the corresponding extinction coefficient. This effect is particularly at high acidities. The protonation of a substance can be defined as follows:

$$HX + SH \rightleftharpoons X^- + SH_2^+ \qquad (1)$$

where SH is the solvent. Then, the equilibrium constant might be expressed in terms of activity (eq 2):

$$K_a = \frac{a_{x^-} \cdot a_{SH_2^+}}{a_{HX}} \qquad (2)$$

By inserting the equivalence of a in eq 2 (where $a = c\gamma$; a, activity; γ, activity coefficient; c, concentration), we can derive eq 3:

$$K_a = \frac{[X^-]}{[HX]} \cdot \frac{\gamma_{X^-}}{\gamma_{HX}} \cdot a_{SH_2^+} = h_X \frac{[X^-]}{[HX]} \qquad (3)$$

and bearing in mind that

$$h_X = \frac{\gamma_{X^-}}{\gamma_{HX}} \cdot a_{SH_2^+} \qquad (4)$$

When we insert the h_X value in eq 3, we obtain eq 5.

$$H_X = -\log h_X = pK_a - \log[HX]/[X^-] \qquad (5)$$

where H_X is an acidity function. The H_0 scale is defined such that for the uncharged primary aniline indicators used a plot of log I (i.e., log ([HX]/[X^-])) against H_0 has unit slope. It was observed from work on bases other than the Hammett-type that the slopes of the plots of log I against H, shown by m, were not always unit. Thus, a series of structurally similar bases, like triarylmethanols, primary amides, and tertiary aromatic amines, defined individual acidity functions, H_R, H_A, and H, which have a linear relationship to H_0.

An experimental plot of log I against H_0 does not yield the pK_a at log $I = 0$, unless it is a Hammett base, but rather the H_0 at half-protonation ($H^{1/2}$). The general eq 3 may therefore be applied. By rearranging eq 5, we can get eq 6,

$$pK_a = H^{1/2} + \log I \qquad (6)$$

and mathematically it can be expressed as a straight line ($y = mx + n$) with a slope of m so it becomes as follows (eq 7):

$$pK_a = mH^{1/2} + \log I \qquad (7)$$

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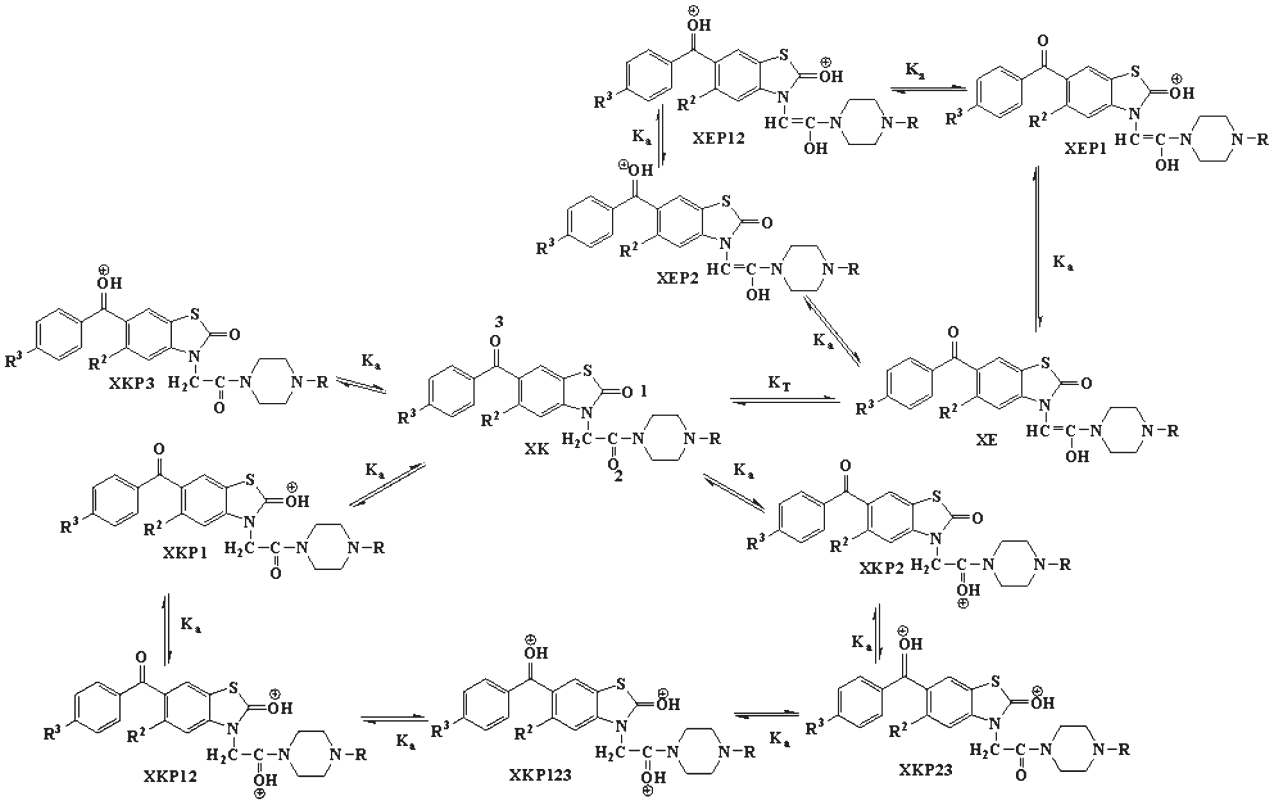

$R = CH_3, C_2H_5, CH(CH_3)_2, CH_2CH_2CH_2CH_3$
$R^2 = H, Cl$
$R^3 = CH_3, F$

Figure 1. Possible protonation patterns and tautomeric forms for the studied molecules.

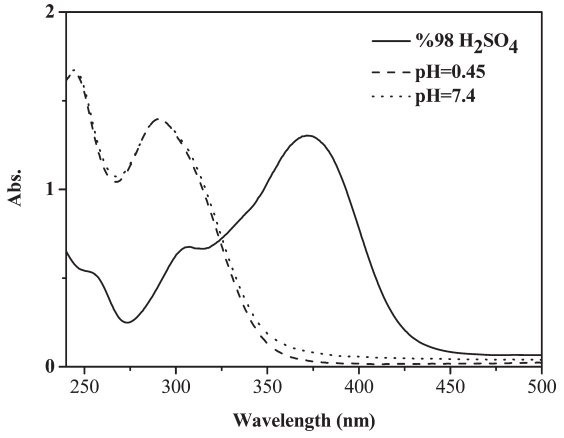

Figure 2. UV−visible spectrum of the investigated molecule **8**.

Since at the half-protonation point log I will be equal to zero, we will end up with eq 8.

$$pK_a = mH^{1/2} \quad (8)$$

where $H_{1/2}$ describes the half-protonation value.

The general procedure applied was as follows: A stock solution of the compound under investigation was prepared by dissolving the compound (∼10−20 mg) in water or sulfuric acid of known strength (25 mL) in a volumetric flask. Aliquots (1 mL) of this solution were transferred into 10 mL volumetric flasks and diluted to the mark with sulfuric acid solutions of various strengths or buffers of various pH values. The total mass of solution in each flask was measured, and the mass percent of sulfuric acid in each solution was than calculated from the known mass of sulfuric acid added and the total mass of the final solution. In the case of buffer solutions, the pH was measured before and after addition of the new solution. The optical density of each solution was then measured in 1 cm cells, against solvent blanks, using a constant temperature cell-holder of UV-2550 Shimadzu UV−vis spectrophotometer. The wavelengths were chosen such that the fully protonated form of the substrate had a much greater or a much smaller extinction coefficient than the neutral form. The analytical wavelengths, the half-protonation values, and the UV absorption maxima for each substrate studied are given in Table 3.

Calculations of half-protonation values were carried out as follows: The sigmoid curve of optical density or extinction coefficients at the analytical wavelength (OD, λ) was first obtained (Figure 2). The optical density of the fully protonated molecule (OD_{ca}, optical density of conjugated acid) and the pure base (OD_{fb}, optical density of free base) at an acidity were then calculated by linear extrapolation of the arms of the curve. Equation 3 gives the ionization ratio where the OD_{obsd} (the observed optical density) was converted into molar extinction

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ϵ_{obsd} using Beer's law of OD = ϵbc, (b = cell width (cm); c = concentration (mol·dm^{-3}).

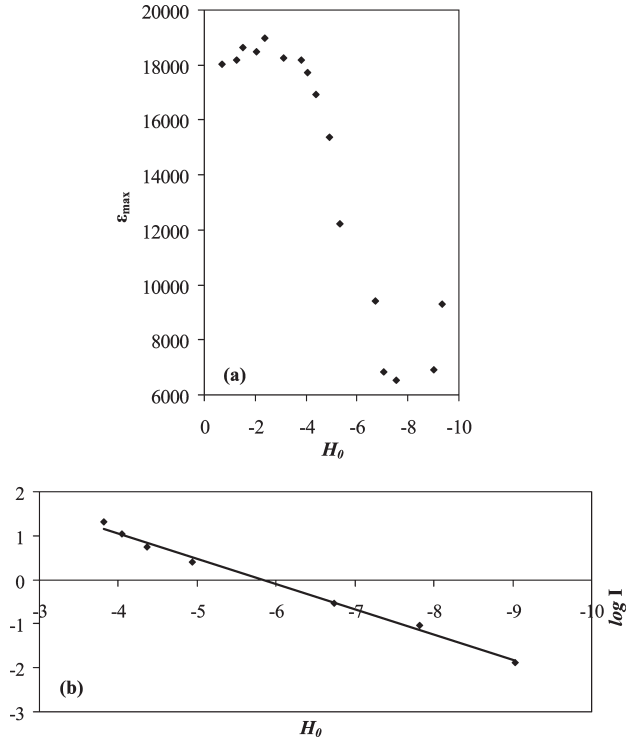


Figure 3. (a) ε_{max} as a function of $-H_0$ (obtained from the % H_2SO_4 vs $-H_0$ table of ref 33] (at 290 nm) plot for the protonation of molecule **1**. (b) H_0 as a function of log I (at 290 nm) plot for the protonation of molecule **1** ($y = 0.5766x + 3.3628$, $R^2 = 0.9933$).

$$I = \frac{[BH^+]}{[B]} = \frac{(OD_{obsd} - OD_{fb})}{(OD_{ca}\text{-}OD_{obsd})} = \frac{(\epsilon_{obsd} - \epsilon_{fb})}{(\epsilon_{ca} - \epsilon_{obsd})}$$

The linear plot of log I against H_0, using the values $-1.0 < \log I < 1.0$, had slope m, yielding the half-protonation value as $H^{1/2}$ at log $I = 0$ (Figure 3).

Method of Theoretical Calculation. Relative stability of investigated molecules was calculated in the aqueous phase by the semiempirical molecular orbital (AM1, PM3 and PM5) theory. The calculations were done by using CAChe6.1 software.[36]

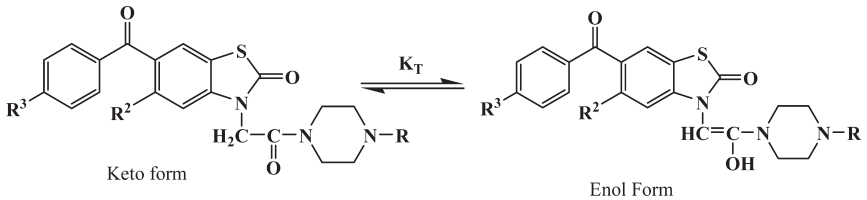
RESULT AND DISCUSSION

Nomenclature of investigated molecules **1** to **12** is depicted Table 1.

Tautomerism. Aqueous phase relative stability values for the studied molecules and the equilibrium between keto (K) and enol (E) forms are depicted in Table 2. The AM1, PM3 and PM5 calculated relative stability values indicate that the keto form is predominant and more stable than the enol form for all of the molecules.

Protonation Process. UV−visible spectroscopic data related to protonation processes are depicted in Table 3. Possible protonation patterns and tautomeric form are represented in Figure 1. The measured UV spectrum 98% H_2SO_4, pH = 0.45 and pH = 7.4 of molecule **8** is shown in Figure 2. The spectral characteristics of all molecules were used for determining acidity constant. As can be seen from Figure 2, the absorption spectrum of molecule **8** in 98% H_2SO_4 solution yielded one absorption band centered at 371.5 nm while this absorption band shifted from 371.5 to 290.5 nm in the pH = 7.4 and spectra overlaid shows one isosbestic point. The absorption spectra of the other molecules show similar behaviors.

Table 2. Values of Calculated Relative Stabilities (RS) of Investigated Molecules



Keto form Enol Form

	AM1			PM3			PM5		
prototautomeric equilibrium	$\Delta H_{f(K)}$	$\Delta H_{f(E)}$	RS[a,b]	$\Delta H_{f(K)}$	$\Delta H_{f(E)}$	RS[a,b]	$\Delta H_{f(K)}$	$\Delta H_{f(E)}$	RS[a,b]
1K−1E	−35.44	−24.41	11.03	−66.21	−57.18	9.03	−77.37	−63.46	13.90
2K−2E	−41.03	−24.42	16.61	−70.37	−57.18	13.20	−82.45	−62.45	20.01
3K−3E	−45.01	−26.89	18.12	−77.87	−64.07	13.80	−88.73	−69.35	19.37
4K−4E	−55.04	−38.12	16.93	−82.03	−69.48	12.55	−93.62	−74.50	19.12
5K−5E	−73.34	−57.38	15.95	−100.97	−86.85	14.12	−114.83	−97.38	17.45
6K−6E	−78.42	−78.38	0.03	−106.02	−92.09	13.93	−119.67	−94.20	25.47
7K−7E	−82.46	−64.93	17.53	−113.29	−100.24	13.04	−125.78	−106.54	19.25
8K−8E	−93.16	−76.28	16.88	−103.00	−92.95	10.05	−131.76	−105.18	26.58
9K−9E	−77.58	−60.03	17.55	−157.93	−60.18	97.75	−125.50	−105.77	19.73
10K−10E	−82.62	−65.40	17.22	−164.20	−147.41	16.79	−130.40	−110.65	19.75
11K−11E	−84.63	−67.39	17.24	−168.83	−151.92	16.91	−133.95	−114.95	19.00
12K−12E	−96.32	−80.50	15.82	−174.41	−159.91	14.50	−141.29	−124.00	17.29

[a] RS = $\Delta H_{f(E)} - \Delta H_{f(K)}$. [b] The plus sign of RS values indicates the stability of keto form (RS > 0).

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Table 3. UV−Vis Spectral Data, Acidity Constants, and pK_a Values of the Studied Compounds for the Protonation

	spectral maximum λ /nm					acidity measurements			
compd	neutral species[a]	(log ϵ_{max})	monocation[b]	(log ϵ_{max})	λ_{max}[c]/nm	$H^{1/2}$[d]	m[e]	pK_a[f]	correl coeff[g]
1	292.5	4.26	323	7.29	290	−5.8321 ± 0.069	0.5766	−3.3628	0.99
			381	7.36					
2	292	4.25	320	7.28	290	−5.6071 ± 0.082	0.4508	−2.5277	0.99
			382	7.36					
3	293	4.19	321	7.28	382	−6.2581 ± 0.183	0.5978	−3.7411	0.99
			382.5	7.36					
4	291	4.26	316	7.28	375	−6.5444 ± 0.068	0.4331	−2.8343	0.99
			384	7.36					
5	291	4.18	325.5	7.29	370	−6.6994 ± 0.072	0.5301	−3.7078	0.99
			370.5	7.35					
6	292	4.13	325	7.29	367	−7.8285 ± 0.101	0.4181	−3.2731	0.99
			372.5	7.35					
7	292	4.18	304	7.26	372	−7.2050 ± 0.076	0.5306	−3.8230	0.99
			372.8	7.35					
8	291	4.17	304	7.26	371	−7.3472 ± 0.056	0.5425	−3.9869	0.99
			371.5	7.35					
9	254	4.34	310.8	7.27	309	−5.1437 ± 0.083	0.4917	−2.5292	0.99
			351	7.32					
10	254	4.34	309.4	7.27	351	−4.7146 ± 0.116	0.6817	−3.2139	0.99
			346.8	7.32					
11	254	4.36	258.6	7.19	281	−3.8293 ± 0.136	0.4396	−1.6834	0.99
			316.2	7.28					
12	254	4.31	309.4	7.27	310	−4.7648 ± 0.057	0.6982	−3.3267	0.99
			343	7.31					

[a] Measured in 0.3 mol·L^{-1} H_2SO_4. [b] Measured in 98% H_2SO_4. [c] The analytic wavelength for pK_a determination. [d] Half-protonation values and ± uncertainties for standart errors for the protonation. [e] Slopes of the log $I-H_0$ plot. [f] Acidity constant values. [g] Correlations coefficients for log I against H_0 graph.

Chart 1

Molecule	**2**	**1**	**3**	**4**
Half protonation($H^{1/2}$)	-5.60	-5.83	-6.25	-6.54
pK_a	-2.52	-3.36	-3.74	-2.83
R(Substituent)	Ethyl	methyl	isopropyl	butyl
Molecule	**5**	**7**	**8**	**6**
Half protonation ($H^{1/2}$)	-6.69	-7.20	-7.34	-7.82
pK_a	-3.70	-3.82	-3.98	-3.27
R(Substituent)	Methyl	isopropyl	butyl	ethyl
Compound	**11**	**10**	**12**	**9**
Half protonation ($H^{1/2}$)	-3.82	-4.71	-4.76	-5.14
pK_a	-1.68	-3.21	-3.32	-2.52
R(Substituent)	Isopropyl	ethyl	butyl	methyl

Increasing acidity →

All of molecules show the trend depicted in Chart 1 with the increasing of their half-protonation, $H^{1/2}$, values. It seems that there is no correlation between the substituent size linked to piperazine moiety (methyl, ethyl, isopropyl and butyl) and half-protonation values of the studied molecules. Similar behavior was observed for 6-acyl benzothiazolone derivatives containing Cl substituent at the 5-position.[37]

The m values given in Table 3 which are about 0.5 suggest the oxo-protonation of the amide moiety for all of the studied molecules. The possible protonation pattern (KP2 protonation) was depicted in Figure 1. The pK_a value for oxo-protonation of acetamide supports this result.[38,39] In addition, the half-protonation values of the same groups of the studied molecules (**1**−**4**, **5**−**8** and **9**−**12**) are closer to each other, and we can say that they are protonated with the same mechanism.

Half-protonation values indicated that molecules **9**, **10**, **11** and **12** have larger basicity than those of molecules **1**, **2**, **3** and **4**. A Cl substituent located at R^2 and F substituent located at R^3 let the global electron density on **9**, **10**, **11** and **12** molecules increase which, in turn, increased the basicity.

Molecules **5**, **6**, **7** and **8** have relatively more acidity character than molecules **1**, **2**, **3** and **4**. It seems that the *p*-CH_3 (R^3 substituent) group on the phenyl ring makes **1**, **2**, **3** and **4** molecules, via inductive effect, more basic or less acidic than **5**, **6**, **7** and **8** molecules.

According to half-protonation ($H^{1/2}$), the fluoride atom (R^3 substituent) at the phenyl ring in the **5**, **6**, **7** and **8** molecules (i.e., Hammett constant for *p*-F atom is 0.06[40]) withdraws electrons from the ring and reduces electron density on the **5**, **6**, **7** and **8** molecules. Consequently, the basicity decreases.

CONCLUSIONS

In the present study, the acid dissociation constants of a new series of substitutive derivatives of *N*-substituted-6-acylbenzothiazolone derivatives have been carried out by using

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ultraviolet visible absorption spectroscopy in all regions (super acidic, super basic and pH regions). The protonation mechanism and molecular structure of investigated compounds were determined with the half-protonation values and acid dissociation constants. It is observed that all investigated compounds for first protonation are protonated from oxo 1 position of the keto form. Although there are the second protonation (oxo 2) and third protonation (oxo 3) which are located at the benzothiazolone and 6-acyl moieties, second protonation and third protonation values are not observed because absorption spectra born out from these centers overlaps with the first protonation absorption spectra. Moreover, acid dissociation constants were not found in super basic and pH regions.

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This work is dedicated to the memory of our colleague Professor Cemil Öğretir, who died on January 19, 2011. Professor Cemil Öğretir's primary contributions have been in determining acidity constants of novel biologically active compounds and in developing novel drugs. Professor Öğretir has been very involved in graduate student education. He has also been involved in international activities and is known with the worthy contributions in these areas. We are grateful to Turkish Scientific Council (TÜBİTAK) for the financial support to this work via the Research Project with the number of 108T192. We would like to thank Associated Professor Doctor Ahmet Çabuk and his PhD student Serap Gedikli for support with the UV-2550 Shimadzu UV−vis spectrophotometer.

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