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A Spectrophotometric and DFT study of the behavior of 6-bromoquercetin in aqueous solution

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Abstract

Acid-base activity, keto-enol tautomerism and complexing properties of 6-beomoquercetin are investigated in water media at different conditions. The constants of dissociation (pKa) have been determined in pH region at various ionic strength. The analysis of protonation process is conducted in strongly acidic solutions of HCl. The complexation were studied with trivalent lanthanides. The stability constant of monocomplex species ML (M(III) =Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Er, Tm, Yb, Lu) have been obtained. For interpretation and verification of received data the DFT calculations were implemented.

Keywords: DFT, Flavonoids, Lanthanide, Spectrophotometric.

Introduction

Being secondary metabolites, flavonoids exist ubiquitous in the plant world (Panche et al. 2016). Quercetin or 5,7,3′,4′-flavon-3-ol is the most known and studied ligand from this group of chemicals. The various qualities, such as anticancer (Le Marchand 2002), antibacterial (Cushnie and Lamb, 2005) and antidiabetic (Vinayagam and Xu 2015) activities demonstrate a multifaceted nature of quercetin. The numerous derivatives of quercetin are also show notable biochemical characteristics (Kessler et al 2003; Sotnikova et al 2013; Manach et al 1998). The complexes of flavonoids with all of groups of metals (Kasprzak et al. 2015; Samsonowicz and Regulska 2017) are described in literature primarily for solid-state conditions.

The flavonoids exhibit medical and biological properties in water. Nevertheless, the low solubility make them problematic objects for study of standard physical-chemical methods. The solubility of quercetin in H_2O at room temperature is about 10^{-4} M (Srinivas et al. 2010). In the same time, the necessary concentration for NMR-analysis or potentiometric study is 10^{-2}-10^{-1} M. In all works where the issue of flavonoids in solution has been discussed the water-ethanol mixtures or non-aqueous liquids were used as solvent. However, under such conditions the behaviour of flavonoids is fundamentally different from biological media. The spectrophotometric technique is one of the few methods that allow to research small amount of sparingly soluble compounds and determine all equilibrium parameters in pure water with concentration $<10^{-4}$ M.

The rare-earth elements (REEs) have the typical characteristics of trivalent metals in solution and suitable for consideration as the modelling systems. In addition, the data for linkages lanthanides with flavonoids can be used for extraction and separation of REEs. The goal of current research was to exploring of acid-base, keto-enol and metal bonding processes of 6-bromoquercetin and demonstrate that the halogen derivatives of flavonoids is also display the useful properties in solution.

Theoretical

The values of dissociation constant (pK_a) have been calculated using equation (Leggett 1985):

$$A_i = \frac{C_{HL}(\varepsilon_{L^-} \cdot K_a + \varepsilon_{HL}[H^+])}{K_a + [H^+]}, \quad (1)$$

with the Henderson-Hasselbach equation (Tiwari and Ghosh 2010):

$$\mathrm{pH} = pK_a + \log(\mathrm{IR}); \quad I\mathrm{R} = \frac{A_i - A_{HL}}{A_{L^-} - A_i}, \quad (2)$$

where IR - ionization ratio.

The non-linear Cox–Yates method (Cox 1983) based on the excess acidity function χ (Cox 1981) was used to determine the protonation constant (K_H) in strongly acidic solutions:

$$A_i = \frac{A_{HL} - A_{H_2L^+}}{1 + (\frac{C_{H^+}}{K_H})10^{(m*\chi)}} + A_{H_2L^+}; \quad (3)$$

where A_i, A_{HL} (ε_{HL}), A_{H2L+} (ε_{H2L+}), and A_{L-} (ε_{L-}) are the absorbances and molar extinction coefficients of the process solution, the free ligands, and its conjugate acid or base, respectively. Conditional stability constants (K') for monocomplex species were calculated from the equations 1-2 (Grebenyuk et al. 2015):

$$A^{\lambda}_{calc} = \varepsilon^{\lambda}_{HL}(C_{HL} - [ML]) + \varepsilon^{\lambda}_{M}(C_M - [ML]) + \varepsilon^{\lambda}_{ML}[ML], \quad (4)$$

$$[ML] = \tfrac{1}{2}\left[\left(\tfrac{1}{K'} + C_{HL} + C_M\right) + \sqrt{\left(\tfrac{1}{K'} + C_{HL} + C_M\right) - 4C_M C_{HL}}\right], \quad (5)$$

where A^{λ}_{calc} is an absorbance at a given wavelength and C_M and C_{HL} were analytical concentrations of lanthanides and ligand, respectively. The ε^{λ} is a value of molar extinction coefficient at single wavelength. The optimal values for K', K_a and K_H and ε^{λ} were found from the least squares analysis (Leggett 1985):

$$f(C_M, C_L, K', \varepsilon_i) = \sum_{i=1}^{n}(A_i^{\lambda} - A_i^{calc})^2 \xrightarrow{K,\varepsilon_i} \min . \quad (6)$$

Calculations of all equilibrium constants and molar extinction coefficients were performed using Wolfram Mathematica (http://www.wolfram.com/).

The quantum-chemical computations were performed using the GAMESS US (Schmidt 1993) program package on the cluster MVS-1000M of the Institute of computational modeling SB RAS. Geometry optimization was performed by density functional theory (DFT) with seven functionals: PBE0 (Adamo and Barone 1999) (under Grimme's empirical correction (Grimme et al. 2010)), revTPSS (Perdew et al. 2011), M06-2L; M06; M06-2X; M06-HF (Zhao and Truhlar 2008) and CAM-B3LYP (Yanai and Tew 2004). The cc-pVDZ (Dunning 1989) basis set functions was applied at C, H, O and Br atoms. The solvent effects were evaluated using the SMD solvation model (Marenich et al. 2009). The calculation of equilibrium constants were performed be following equation (Bryantsev et al. 2008):

$$\log K^{calc.} = -\Delta\Delta G^{solv.}/(2.303RT) \quad (7)$$

$$\Delta\Delta G^{solv.} = \Delta G^{gas} + \Delta G^{aq.} + \Delta E^{zpe} - E^{corr.} \quad (8)$$

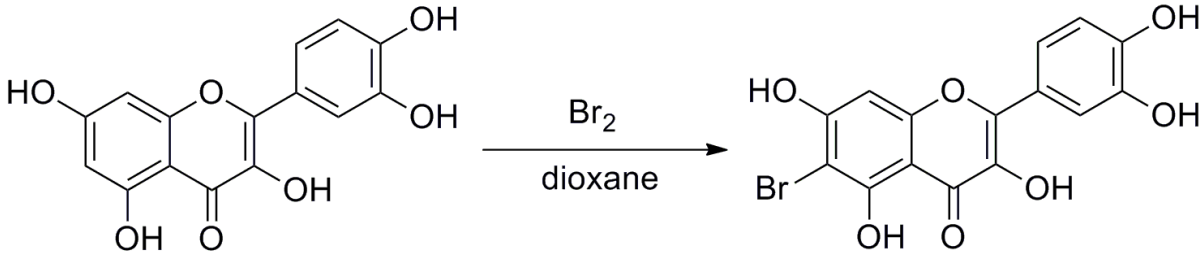
, where

$$E^{corr.} = RT\ln([H_2O]) = 9.964 \text{ kJ/mol.} \quad (9)$$

Here, $RT\ln([H_2O])$ is a free energy change associated with moving a solvent from a standard-state solution phase concentration of 1 M to a standard state of the pure liquid, 55.34 M (Vukovic et al. 2015). The change of Gibbs free energy in solid state and in solution (ΔG^{gas} and $\Delta G^{aq.}$). E^{zpe} is calculated harmonic vibrational frequencies to estimate the zero point energy correction.

Experimental

The UV-Vis spectra were measured with Leki SS2109-UV scanning spectrophotometer (Leki Instruments, Finland) using 1 cm quartz cells. Cell thermostating (±0.1 K) was performed with the Haake K15 thermostat connected to the Haake DC10 controller. All measurements were performed at 298 K. The synthesis of bromine derivative of quercetin was performed by the simple method described at (Nagimova et al. 1996): 1g of quercetin was brominated in dioxane at 298 K without stirring (Scheme 1). The precipitated orange crystals were washing with water and crystallize three times from ethanol. The test by paper chromatography have been demonstrate the absence of initial quercetin in the final products.



Scheme 1. The synthesis of 6-bromoquercetin.

Materials

Chemicals

All chemicals were of analytical grade: quercetin (Aldrich ≥95%, HPLC), CH_3COONa, CH_3COOH, citric acid, TRIS, Na_2HPO_4, glycine, Br_2, $NaClO_4$, HCl, $LnCl_3{\cdot}6H_2O$ (Ln= Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Er, Tm, Yb). All stock solutions were obtained by dissolution of dry salts and ligand weights. The solutions of bromquercetin were prepared from its ethanol concentrated solution ($C=6{\cdot}10^{-3}$ M). The concentration of ethanol did not exceed 1% in the final solution. Buffer solutions within the pH range from 1.80 to 3.60 were prepared with glycine and HCl, from 3.60 to 5.60 with CH_3COOH and CH_3COONa (for study of complexation), from 3.60 to 7.00 with citric acid and Na_2HPO_4 (for study of dissociation), from 7.00 to 8.60 with TRIS and HCl. The accurate desired pH values were obtained by adjusting the molarities of the buffer components in suitable amounts. The accurate concentration of Ln^{3+} has been establish by complexometric titration with EDTA.

Results and discussion

3.1 The study of acid-base properties

The various states of investigated flavonoid have the different shape of electronic spectra. Fig. 1 demonstrate the spectra of neutral, protonated and monoanionic forms of quercetin and 6-bromoqiercetin. In Table 1 represent the position of absorption maximum for bromoquercetin compared with pure quercetin. There is linear relationship between optical density and concentration for all forms of BQR. Thus, the formation of ionic associate or dimers are not taking place. The interaction between components of used buffers and ligand is not find.

It is seen that for BQR spectra all peaks are shifted in long-wave region with respect to peaks of quercetin.

Table 1. The values of wavelength (nm) of main absorbance peaks of BQR and quercetin

Form	6-Bromoquercetin		Quercetin	
	$\lambda^{max,\,1}$	$\lambda^{max,\,2}$	$\lambda^{max,\,1}$	$\lambda^{max,\,2}$
Neutral	256	373	255	367
Protonated	275	450	268	439
Monoanionic	281	393	272	383

The molar extinction coefficients is less for bromine derivative. At pH above 8.20 the destruction of BQR is observed. For this reason the acid-base properties of bromoquercetin were investigated in pH region from 2.0 to 7.3, where occurring only first step of dissociation. All raw spectroscopic data are given in the Supplementary Material (Tables S1-S6).

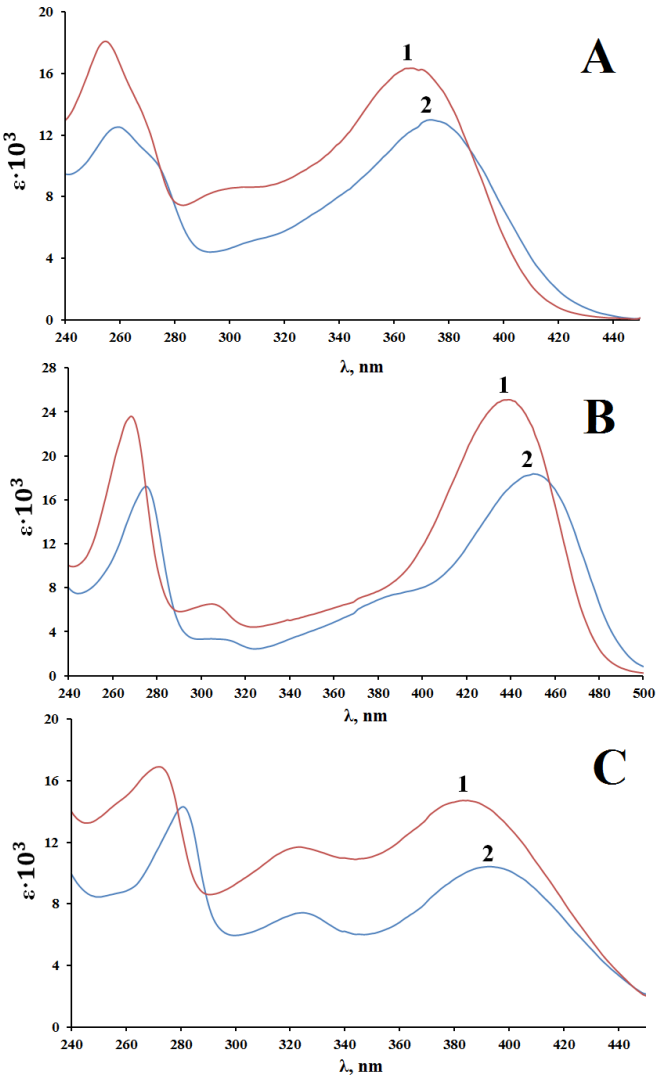


Fig. 1. The UV-vis spectra of different froms of quercetin(**1**) and 6-bromoquercetin(**2**): neutral at pH=1 (A), protonated at C(HCl)>10 M (B) and monoanionic (C) at pH=8.0.

As the derivative of quercetin, 6-bromoquercetin exhibit property of a weak acid. Fig. 2 provides the spectral change of BQR as function of pH. The presence of isosbestic points reflects the transformation only one form in single product. As a background electrolyte was utilized $NaClO_4$. The slight absorption of phosphate-citrate buffer was take into account in calculations of final values of pK_a. The obtained results of acid-base properties in pH region are given at Table 2. The constant of dissociation was determine at three values of ionic strength: 0.1, 0.5 and 1.0 M.

Table 2. The values of pK_a, extinctions of anionic and neutral form of BQR

I ($NaClO_4$)	0.1		0.5		1.0	
λ, nm	281	408	281	408	281	408
$pK_a \pm 0.02$	5.68	5.70	5.85	5.90	6.04	6.01
$\log(\varepsilon_{L-}) \pm 0.01$	4.16	3.96	4.14	3.94	4.14	3.93
$\log(\varepsilon_{HL}) \pm 0.01$	3.78	3.60	3.78	3.61	3.79	3.62

This has been done in order to use these data in various conditions. For three values of pK_a the analysis of log(IR)-pH relationship (eq. 2; Fig. S1) demonstrate the mono deprotonation character of during process. The founded values of pK_a of BQR lie from 5.68 to 6.04 logarithmic units. All these data characterize 6-bromoquercetin as more acidic ligand than quercetin (pKa = 7.20 (Kopacz 2003)). This fact can be explain by polarizing effect inducted by bromine atom: the appearance in molecular structure heavy halogen atom is increase of electrostatic tension and weaken of O-H bond.

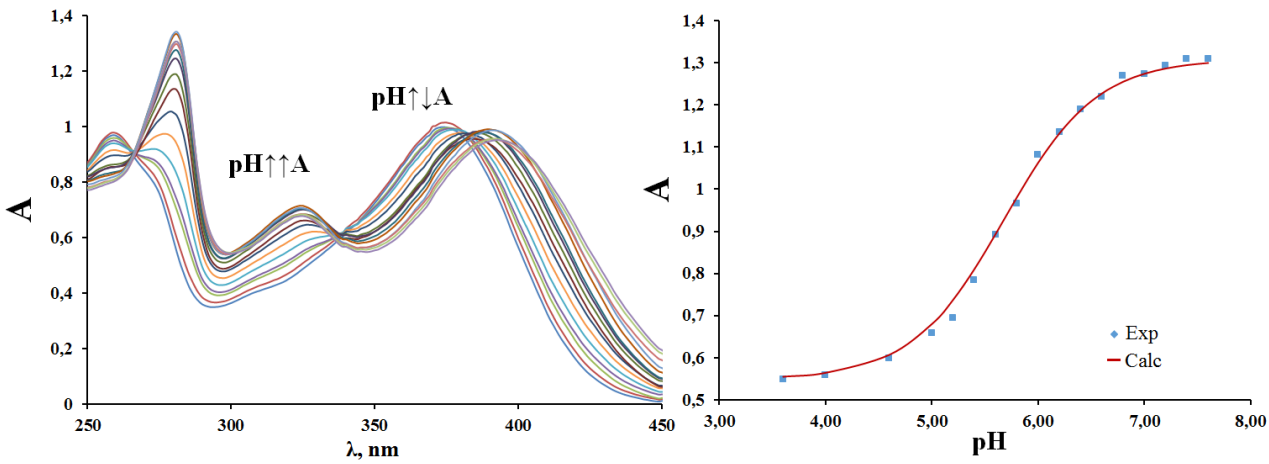


Fig. 2. The UV-Vis spectra and absorbance at 281 nm of 6-bromoquercetin at various values of pH; C(bromoquercetin) = $9.14 \cdot 10^{-5}$ M, I = 0.1 M.

The treatment of acid-base properties in acidic media was perform in concentrated hydrochloric solutions. Fig. 3 has shown a transformation of BQR spectra at increase of HCl concentration. The calculations of protonation constant (-pK_H) have been carried out for 2 wavelength – 450 and 375 nm. For both wavelength the assessment provides the equal values of -pK_H = 3.50±0.03 logarithmic units. An analogous value for quercetin is 2.30 log units (Kopacz 2003). Therefore, the reported value of -pK_H describes this flavonoid as a weaker base in acidic solution than quercetin. The m* parameter (from eq. 3) or solvation coefficien t (Hoyuelos et al. 2005) for this process is equal 0.97±0.04. This coefficient depend on the mechanism of protonation and nature of protonated atom. In this case (m*~1) it indicate that H_2L^+ form of BQR is small and not very polarizable molecule (Hoyuelos et al. 2005).

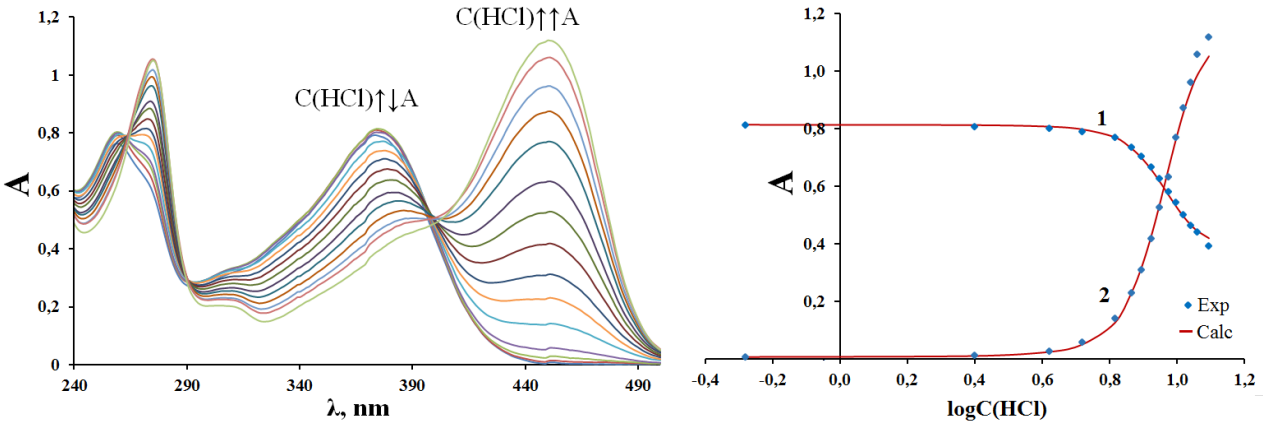
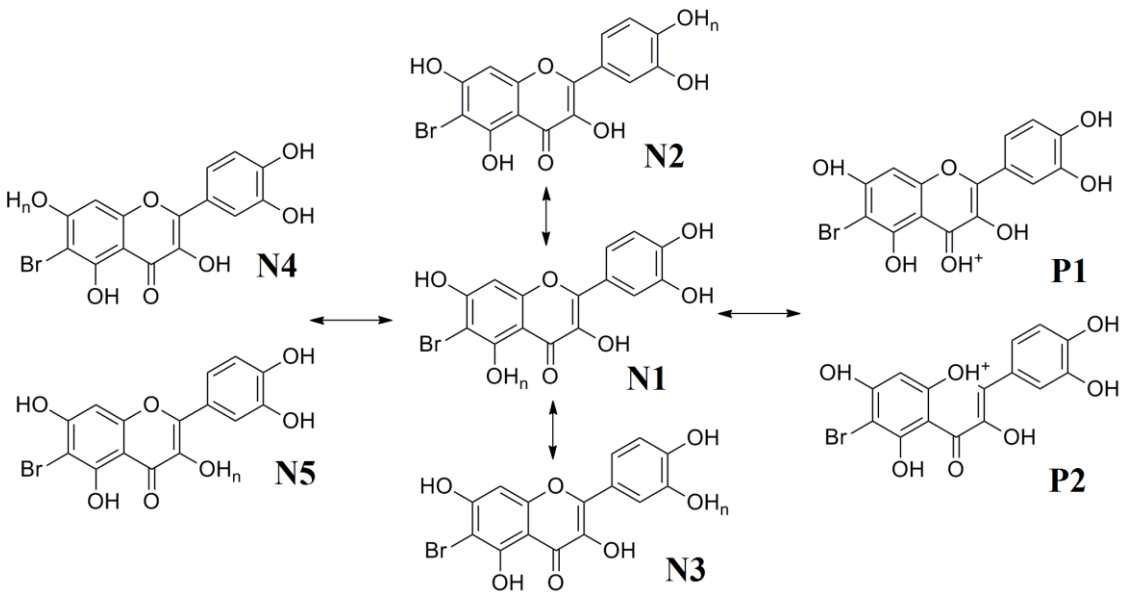


Fig. 1. The UV-vis scanning spectra of BQR obtained at various concentration of HCl and absorbance (1 – 375 nm; 2 – 450 nm) as a function of log(C(HCl)); C(bromoquercetin) = $6.09 \cdot 10^{-5}$ M.

3.1 The DFT study

The dissociation and protonation of neutral form of BQR can lead to the appearance of several tautomers. Each of OH group in this molecule can dissociate or be protonated. The all possible isomers of anionic and protonated forms are collected at Scheme 2.



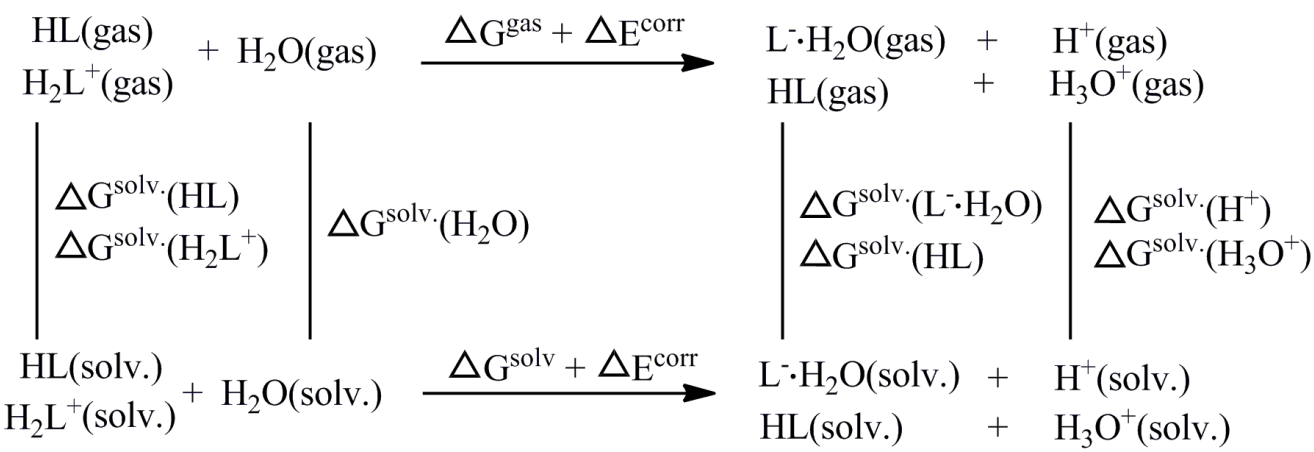
Scheme 2. The anionic (n=0) and protonated (n=2; P1 and P2) tautomers of BQR

The tautomers P1 and P2 are possible only for protonated form. For the estimate of thermodynamic stability of these structures the absolute and relative energies were calculated (Table 3) at level cc-pVDZ/DFT/PBE0/SMD. All assessments demonstrate that acid-base processes relate with 4-carbonyl and 5-hydroxyl groups. The most stable anionic form is the isomer with negative charge on the 5-hydroxyl position (N1). The domination form of protonated bromoquercetin is the cation P1 with one more proton atom on the 4-carbonyl group.

Table 3. The calculated absolute (a.u.) and relative (kJ·mol^{-1}) energies of BQR tautomers

	Protonated form (n=2)		Anionic form (n=0)	
Tautomer	Absolute energy	Relative energy	Absolute energy	Relative energy
N1	-3676.724254	92.19	-3675.946043	0.00
N2	-3676.740029	50.77	-3675.931125	39.17
N3	-3676.740148	50.46	-3675.931271	38.78
N4	-3676.747360	31.53	-3675.922961	60.60
N5	-3676.737160	58.31	-3675.937402	22.69
P1	-3676.759367	0.00		
P2	-3676.711874	124.69		

Now, the quantitative analysis of the Lowdin's charges can help to explain the difference of acid-base properties between quercetin and BQR. The charge of O-atom of 5-hydroxyl group is -0.304 and -0.272 for quercetin and bromoquercetin, respectively. The charge of hydrogen is the same for both cases. Thus, bromine to decrease of negative charge on oxygen atom and reinforces the repulsion between H and O that lead to high acidity. Analogous reasons suited to protonation activates: the charge of 4-carbonyl oxygen is high for BQR (-0.291) than for quercetin (-0.307) and electrostatic bonding O-H is durable for quercetin.



Scheme 3. The thermodynamic cycle for calculate $pK_a^{calc.}$ and $pK_H^{calc.}$

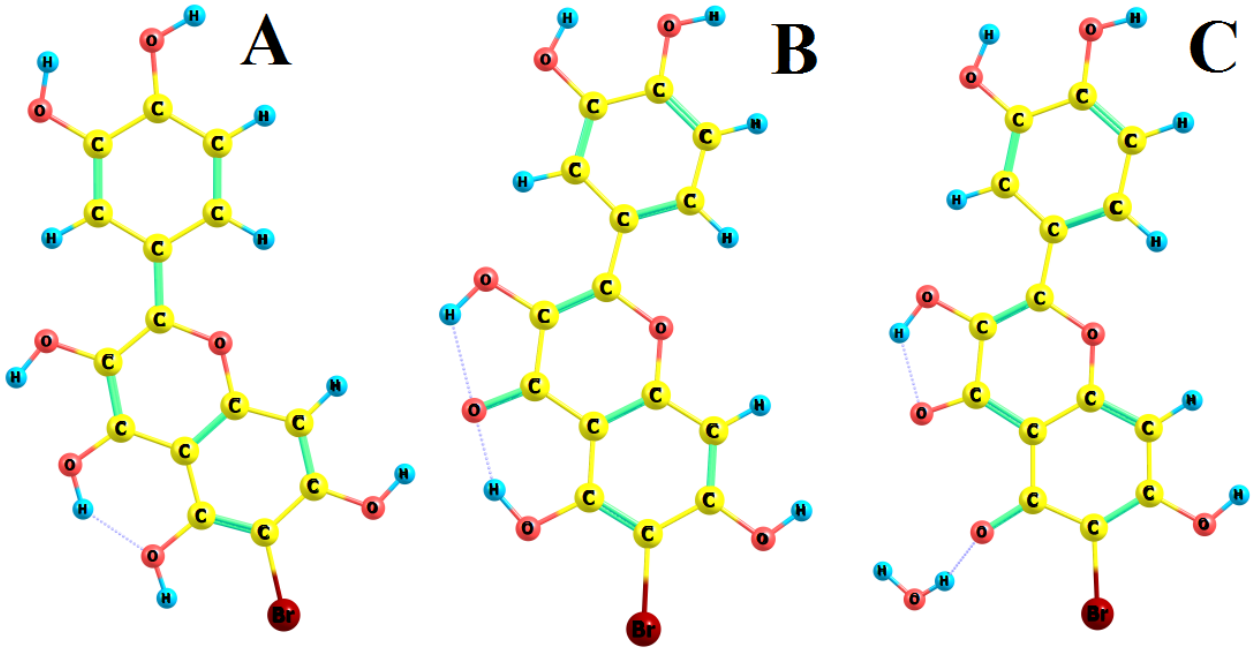


Fig. 4. The optimization geometry of protonated (**A**), neutral (**B**) and anionic (**C**) forms.

For search of optimal DFT method to describe thermodinamic results ab initio calculations have been produced. The thermodynamic cycle showed at Scheme 3 was used for computation protocol. The obtaining of $pK_a^{calc.}$ and $pK_H^{calc.}$ has been carried out at level cc-pVDZ/DFT/SMD with using seven density functional. The cc-pVDZ has established itself as usable for estimate of equilibrium processes of heterocyclic compounds (Lutoshkin and Kazachenko 2017). The functionals from minesota family, TPSS group and LYP-class were tested in this work. This choice was based on the wide using of these functionals for calculate of various equilibrium processes (Banerjee and Bhanja 2018). Guided by theoretical work (Bishnu and Schlegel 2016) the explicit water molecule was applied for compilation of $pKa^{calc.}$. The optimization geometry of studied species demonstrated at Fig. 4. The findings of estimation are given at Table 4. In our case, the better approximation (for dissociation process) provides functional M06-HF with 100% of Hartree-Fock exchange. PBE0 demonstrate the best approach for pK_a. All of other functionals gives grater discrepancy with experimental data.

Table 4. The results of quantum-chemical simulation.

Density Functional	Dissociation process			
	$\Delta G^{gas}+\Delta G^{solv.}$, kJ/mol	ΔE^{ZPE}	pK_a(calc)	pK_a(exp)
PBE0	91.23	-33.99	9.66	
revTPSS	104.79	-32.03	12.39	
M06-L	99.37	-34.05	11.08	
M06	82.97	-33.94	8.25	5.86
M06-2X	82.71	-34.30	8.12	
M06-HF	65.30	-33.86	5.15	
CAM-B3LYP	117.59	-33.56	9.74	
Density Functional	**Protonation process**			
	$\Delta G^{gas}+\Delta G^{solv.}$, kJ/mol	ΔE^{ZPE}	$-pK_H$(calc)	$-pK_H$(exp)
PBE0	-27.81	10.84	3.33	
revTPSS	-90.19	2.20	15.77	
M06-L	30.08	8.42	-6.39	
M06	31.35	7.70	-6.48	3.50
M06-2X	25.39	7.91	-5.47	
M06-HF	-81.32	7.83	13.23	
CAM-B3LYP	26.81	-12.60	-2.13	

3.3 Stability of Lanthanide complexes

Bromoquercetin, as well as quercetin, is effective complexing agent for trivalent lanthanides in solution. All measurements were completed in acetate buffer at ionic strength 0.5 M. The working pH range lie from 4.40 to 5.40. Due to the studied flavonoid has small aqueous solubility, the determination of stability constants has been performed at constant concentration of ligand in each series. The various concentration of lanthanides was taken in excess (C(M)>C(L)) for eliminating the possibility of the formation of poly-ligand complexes M_nL_m. In Fig. 5, the BQR spectra under different concentration of ytterbium(III) are shown. For BQR-Ln(III) system ΔA^{max} has a constant position at 430 nm (Fig. S2) and depends only from metal concentration. This facts, significant excess of Ln^{3+} and existence of a isopiestic points indicates about formation of one products – 1:1 complex ML. The similar reasons can be applied for all systems. The received data of equilibrium parameters for complexation are given at Table 3.

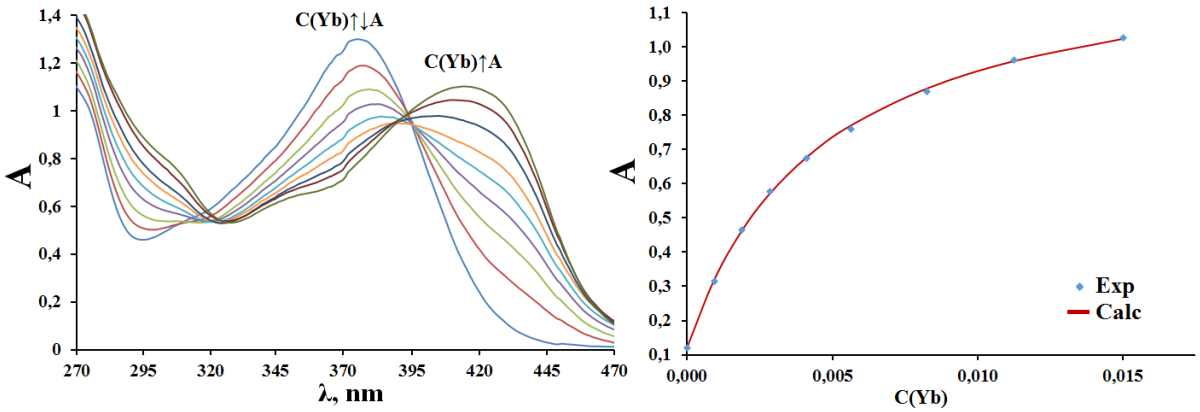


Fig. 5. The UV–Vis spectra and absorbance at single wavelength (429 nm) for Yb(III)-BQR system; C(bromoquercetin)= $9.14 \cdot 10^{-5}$ M; pH=4.4, I=0.5 M (NaClO4).

To confirm of chosen coordination model the stability constants for some of metals (Yb^{3+} and Er^{3+}) were obtain for three values of pH. The linear relationship of pH-logK and slope coefficient ≈1 testify to monodeprotonation of ligand upon complexation process. Furthermore, the formation of complexes with OH^- and acetate ions is typical for all rare earth metal. To take into account of side reactions the following equations were fitted:

$$K = \alpha_M \alpha_L K' \tag{10}$$

$$\alpha_M = 1 + \sum \beta_n [L]^n, \tag{11}$$

$$\alpha_L = 1 + \sum K_H [H^+], \tag{12}$$

where $K_H = 1/Ka$ was determine in pH region. The constants of adverse reaction (βn) for Ln(OAc)n and $Ln(OH)^{2+}$ was taken from previously work (Lutoshkin et al. 2018) and given at Table S7.

Table 5. Conditional (K'), "true" (K) stability constants and value of extinction at 429 nm for BQR-Ln(III) systems

Ln(III)	pH ± 0.01	logK'± 0.01	$\log\varepsilon^{429}$± 0.03	logK ± 0.05
Ce	5.20	2.18	4.14	4.04
Pr	5.20	2.31	4.14	4.83
Nd	5.20	2.13	4.17	4.27
Sm	5.20	2.59	4.12	4.91
Eu	5.40	2.72	4.13	4.83
Gd	5.20	2.64	4.14	4.82
Tb	4.60	2.43	4.15	5.50
Dy	4.60	2.24	4.16	5.27
	4.40	2.24	4.14	5.43
Er	4.60	2.40	4.18	5.40
	4.80	2.65	4.12	5.47
Tm	4.60	2.26	4.19	5.27
	4.20	2.12	4.14	6.40
Yb	4.40	2.34	4.15	6.42
	4.60	2.58	4.11	6.48
Lu	4.60	2.70	4.14	5.77

The obtained values of logK lie in region 4.0-6.5 logarithmic units. The stability constants follow the order: Ce<Nd<Gd≈Eu≈Pr<Sm<Dy≈Tm<Er<Tb<Lu<Yb. Fig. 6 (A) illustrate Ln(III)-logK relationship. This shape of logK-Ln(III) curve indicate about general ionic nature of the bonding (Choppin 1983).

The similarity of spectral changes and molecular structure quercetin and BQR allows to propose the same coordination of their lanthanides complexes (via 3-hydroxyl-4-carbonyl group (Woźnicka et al. 2017; Lutoshkin et al. 2018)). Fig. 6(A) demonstrate that lanthanides complexes of BQR by 1-2 order weaker than Ln(III)-quercetin complexes. Like in the case of dissociation, this can be attributed to general electrostatic of molecule: the bromine atom

decrease the electronic density on the of 3-hydroxyl group and increase of decoupling between O atom of chelate group and Ln^{3+}.

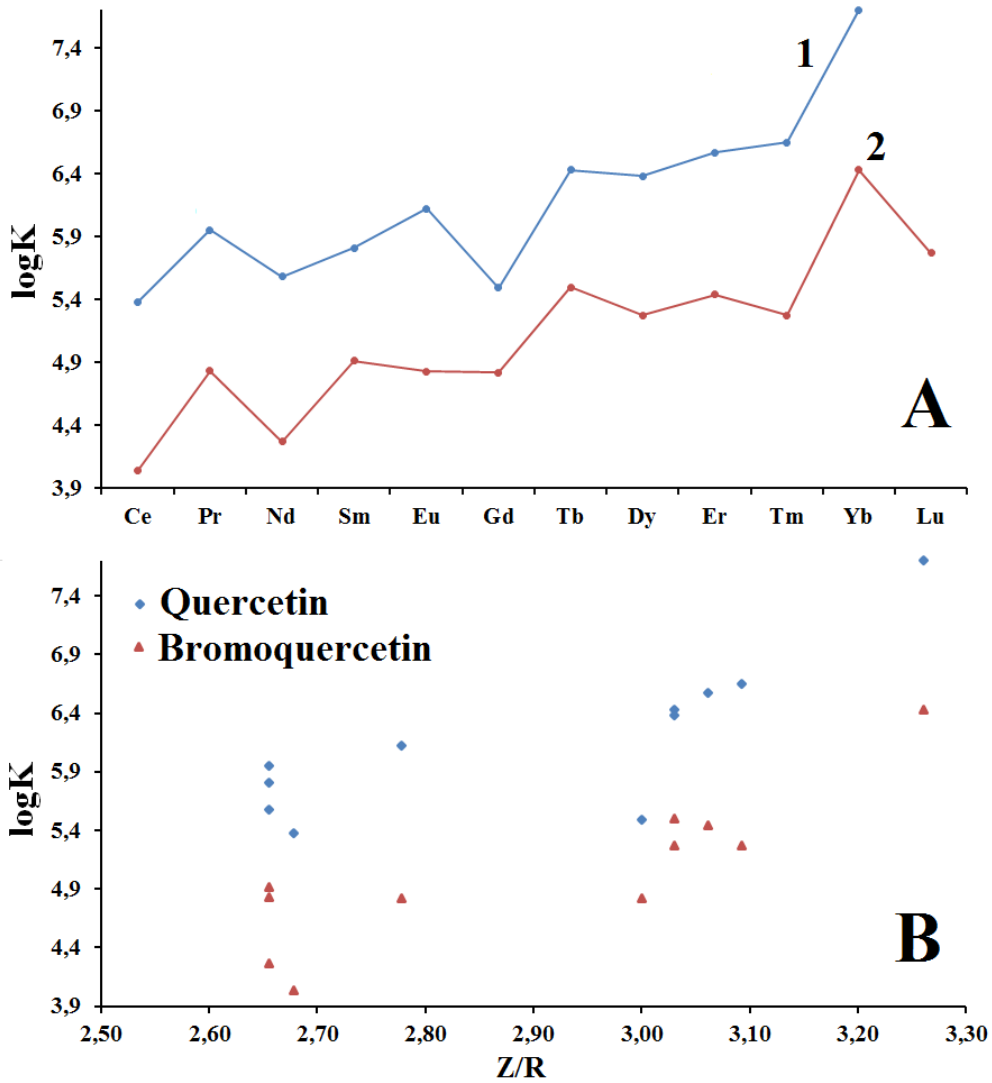


Fig. 6. The logK-Ln(III) curves (**A**) for quercetin (1) and bromoquercetin (2) and logK-Z/R points (**B**).

The distribution of points on the logK-Z/R plot is presented on Fig. 6 (B) has shown that (as in the case of quercetin) all metals separated by two group: Ce-Eu and Gd-Lu. The second group of lanthanides show a weak correlation with ionic potential. This suggests that electrostatic interaction for these metals a slightly stronger than for Ce-Eu group. Perhaps, the separation can be explained by the sharp rise of covalence contribution in Gd-Lu complexes and participation of the 6d and/or 7s orbitals rather than f orbitals in the bonding (Choppin and Rizkalla 1994).

Conclusions

The thermodynamic parameters of 6-bromoquercetin have been described in solution using electronic absorption spectroscopy. The spectral, acid-base and complexing properties were studied at various ionic strength and acidity. Bromoquercetin is a stronger acid (pK_a=5.68-6.04) and weak base (-pK_H=3.50) than quercetin.

At level cc-pVDZ/DFT/PBE0/SMD were suggests the dominated forms (neutral, monoanionic and protonated) of BQR and explain their acidity. Seven density functionals (PBE0, CAM-B3LYP, M06, M06-L, M06-2X, M06-HF and revTPSS) were tested for search an optimal theoretical pathways to describe of obtained data. M06-HF and PBE0 functionals provide the better approximation for dissociation and protonation processes, respectively. The computation protocol with explicit water and specific solvation has been allows to reproduce experimental values with discrepancies ± 0.5 logarithmic units.

The investigation of 1:1 complexes of bromoquercetin and 12 lanthanides has been perform at wide range of pH at constant ionic strength (I = 0.5 M). 16 conditionals and 12 “true” equilibrium stability constants were obtained. The received stability constants lie from 4.04 to 6.46 logarithmic units and increase in the following order: Ce<Nd<Gd≈Eu≈Pr<Sm<Dy≈Tm<Er<Tb<Lu<Yb. The low efficiency of BQR as complexation agent (compared to quercetin) was explain by the distribution of charges in optimization structure.

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Table 5. Conditional (K'), "true" (K) stability constants and value of extinction at 429 nm for BQR-Ln(III) systems

Ln(III)	pH ± 0.01	logK'± 0.01	$\log\varepsilon^{429}$± 0.03	logK ± 0.05
Ce	5.20	2.18	4.14	4.04
Pr	5.20	2.31	4.14	4.83
Nd	5.20	2.13	4.17	4.27
Sm	5.20	2.59	4.12	4.91
Eu	5.40	2.72	4.13	4.83
Gd	5.20	2.64	4.14	4.82
Tb	4.60	2.43	4.15	5.50
Dy	4.60	2.24	4.16	5.27
	4.40	2.24	4.14	5.43
Er	4.60	2.40	4.18	5.40
	4.80	2.65	4.12	5.47
Tm	4.60	2.26	4.19	5.27
	4.20	2.12	4.14	6.40
Yb	4.40	2.34	4.15	6.42
	4.60	2.58	4.11	6.48
Lu	4.60	2.70	4.14	5.77

Table 4. The results of quantum-chemical simulation.

Density Functional	Dissociation process			
	$\Delta G^{gas}+\Delta G^{solv.}$, kJ/mol	ΔE^{ZPE}	pK_a(calc)	pK_a(exp)
PBE0	91.23	-33.99	9.66	
revTPSS	104.79	-32.03	12.39	
M06-L	99.37	-34.05	11.08	
M06	82.97	-33.94	8.25	5.86
M06-2X	82.71	-34.30	8.12	
M06-HF	65.30	-33.86	5.15	
CAM-B3LYP	117.59	-33.56	9.74	
Density Functional	**Protonation process**			
	$\Delta G^{gas}+\Delta G^{solv.}$, kJ/mol	ΔE^{ZPE}	$-pK_H$(calc)	$-pK_H$(exp)
PBE0	-27.81	10.84	3.33	
revTPSS	-90.19	2.20	15.77	
M06-L	30.08	8.42	-6.39	
M06	31.35	7.70	-6.48	3.50
M06-2X	25.39	7.91	-5.47	
M06-HF	-81.32	7.83	13.23	
CAM-B3LYP	26.81	-12.60	-2.13	

Table 3. The calculated absolute (a.u.) and relative (kJ·mol^{-1}) energies of BQR tautomers

Tautomer	Protonated form (n=2)		Anionic form (n=0)	
	Absolute energy	Relative energy	Absolute energy	Relative energy
N1	-3676.724254	92.19	-3675.946043	0.00
N2	-3676.740029	50.77	-3675.931125	39.17
N3	-3676.740148	50.46	-3675.931271	38.78
N4	-3676.747360	31.53	-3675.922961	60.60
N5	-3676.737160	58.31	-3675.937402	22.69
P1	-3676.759367	0.00		
P2	-3676.711874	124.69		

Table 2. The values of pK_a, extinctions of anionic and neutral form of BQR

I ($NaClO_4$)	0.1		0.5		1.0	
λ, nm	281	408	281	408	281	408
$pK_a \pm 0.02$	5.68	5.70	5.85	5.90	6.04	6.01
$\log(\varepsilon_{L-}) \pm 0.01$	4.16	3.96	4.14	3.94	4.14	3.93
$\log(\varepsilon_{HL}) \pm 0.01$	3.78	3.60	3.78	3.61	3.79	3.62

Table 1. The values of wavelength (nm) of main absorbance peaks of BQR and quercetin

Form	6-Bromoquercetin		Quercetin	
	$\lambda^{max, 1}$	$\lambda^{max, 2}$	$\lambda^{max, 1}$	$\lambda^{max, 2}$
Neutral	256	373	255	367
Protonated	275	450	268	439
Monoanionic	281	393	272	383

Figure 1

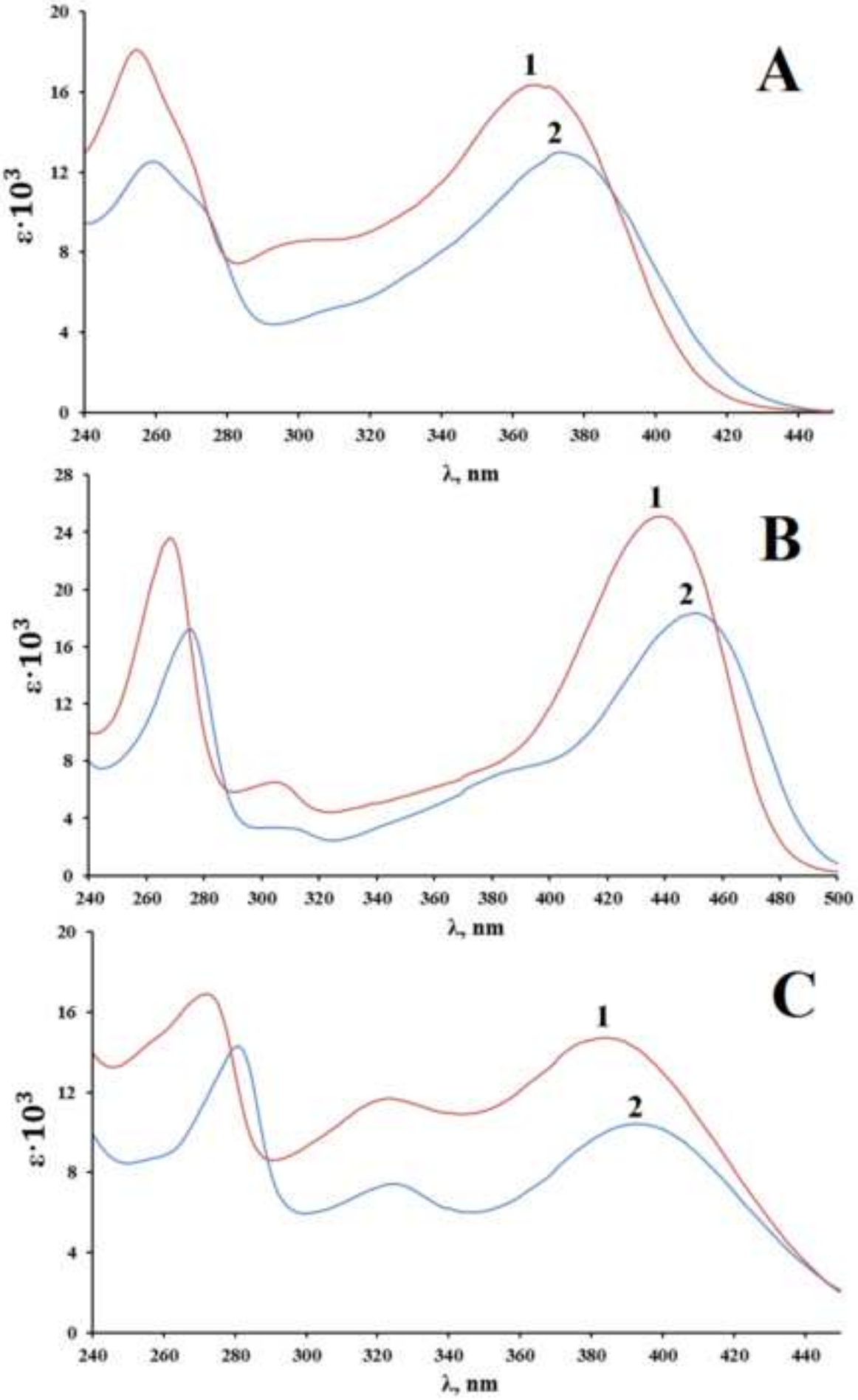


Figure 2

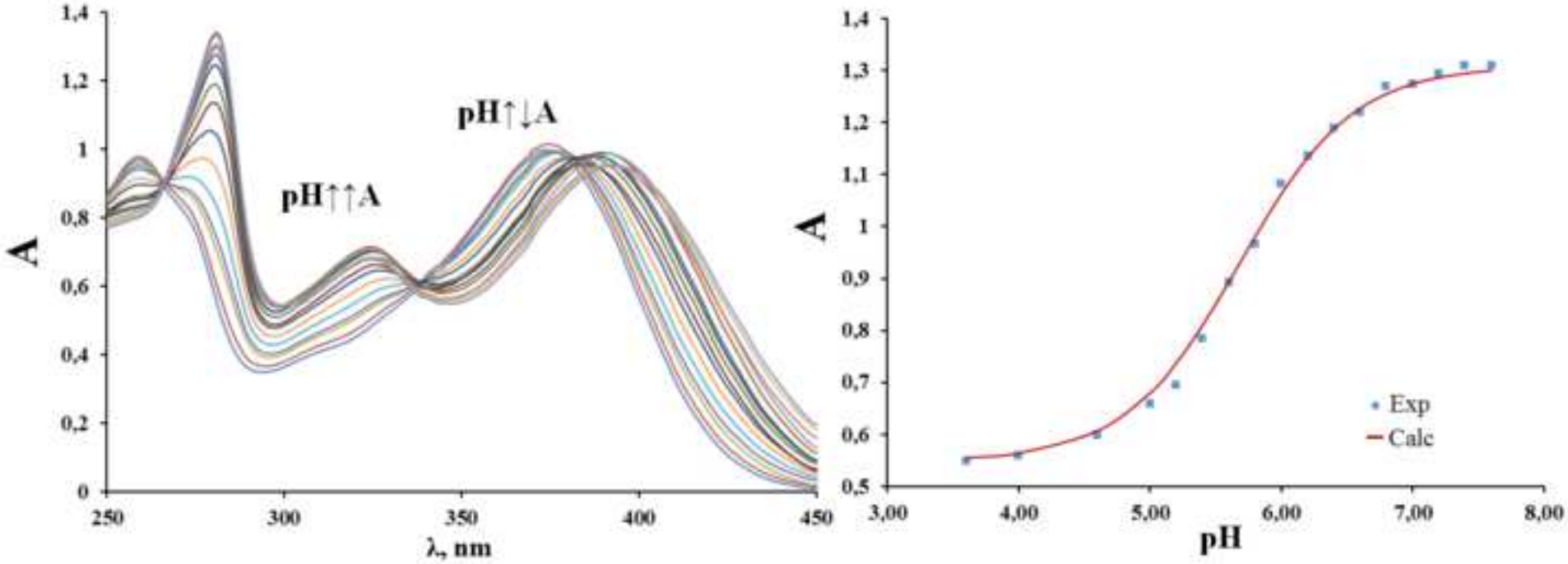


Figure 3

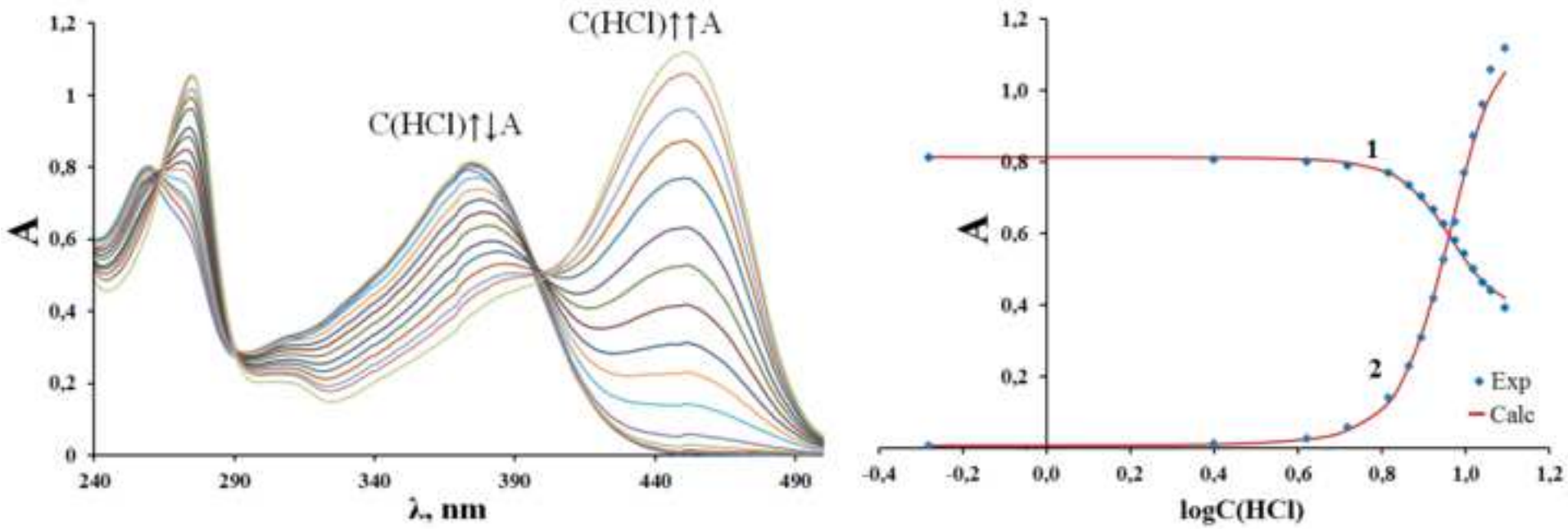


Figure 4

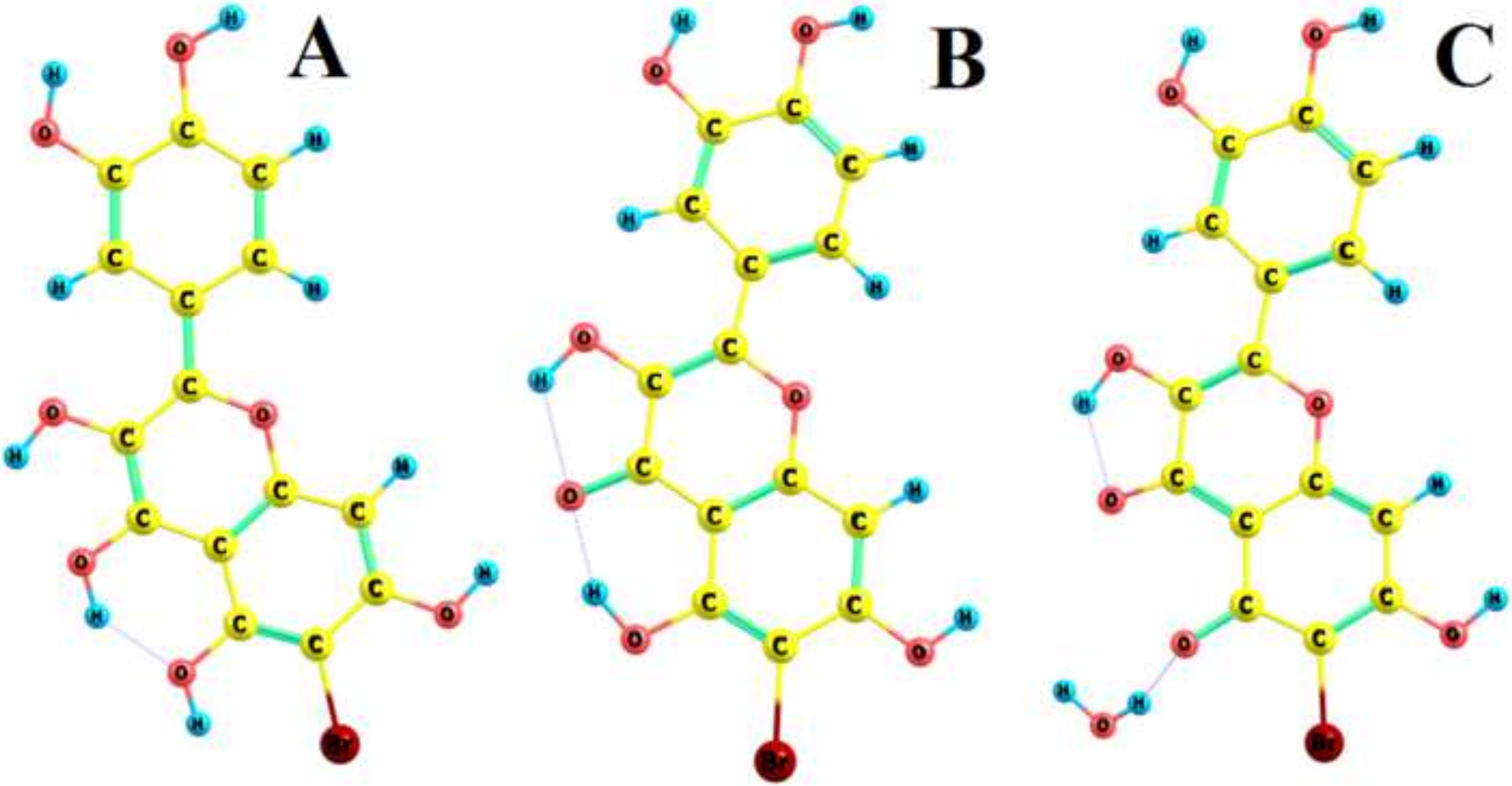


Figure 5

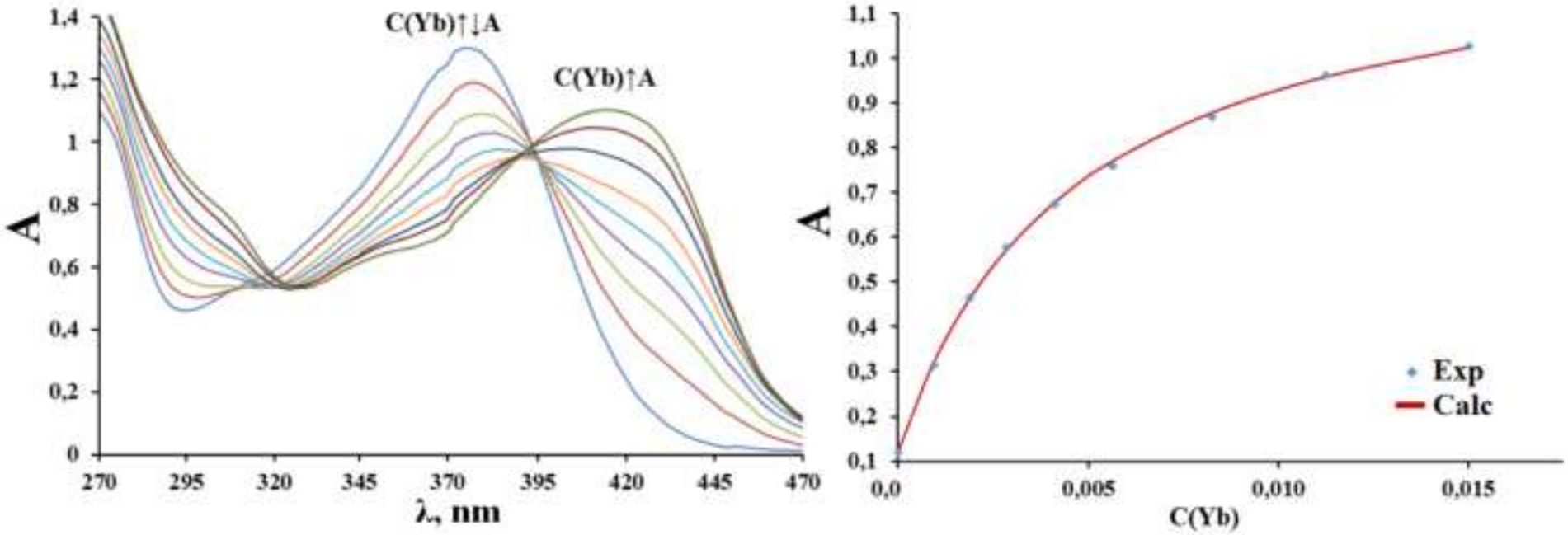
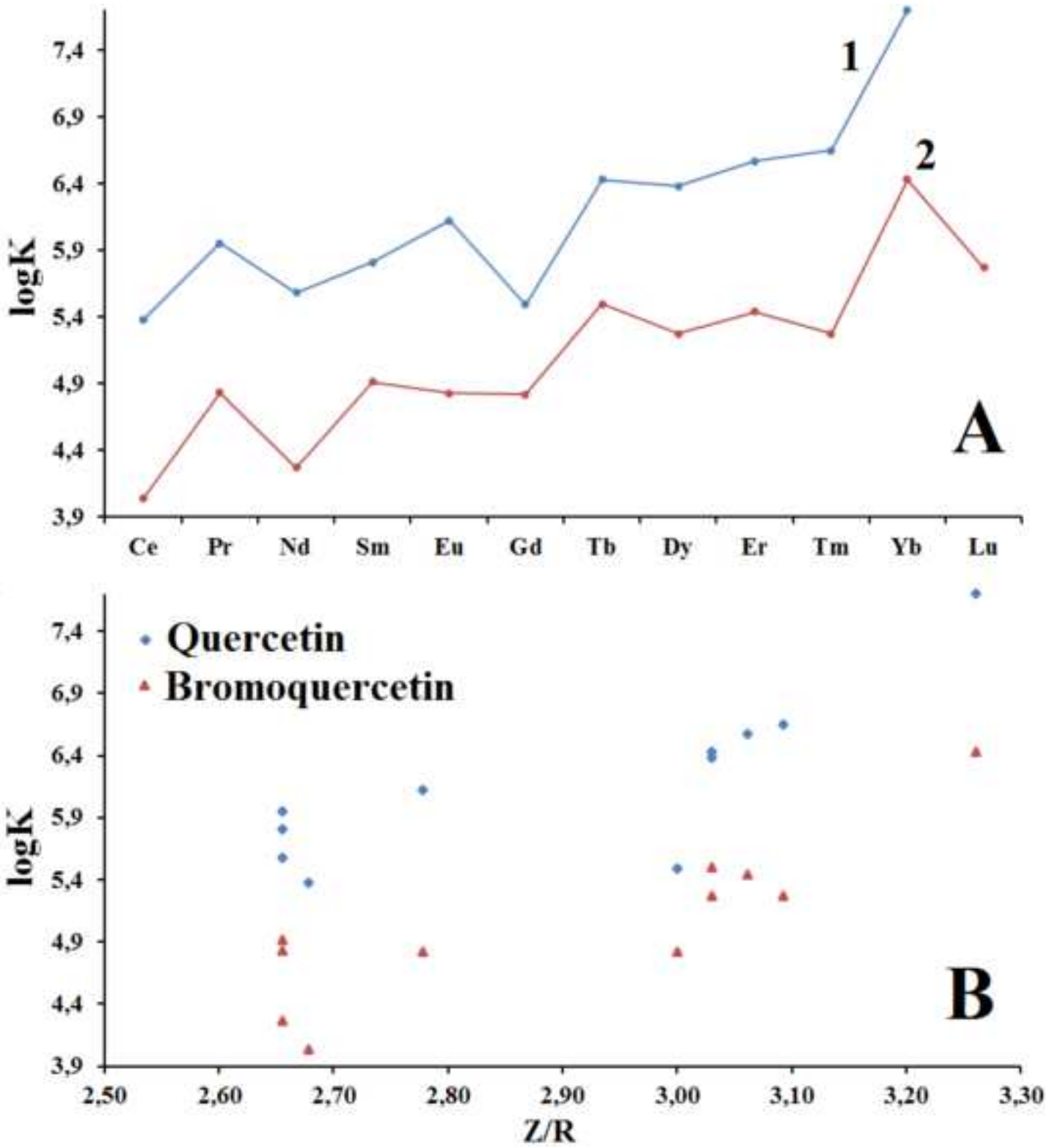
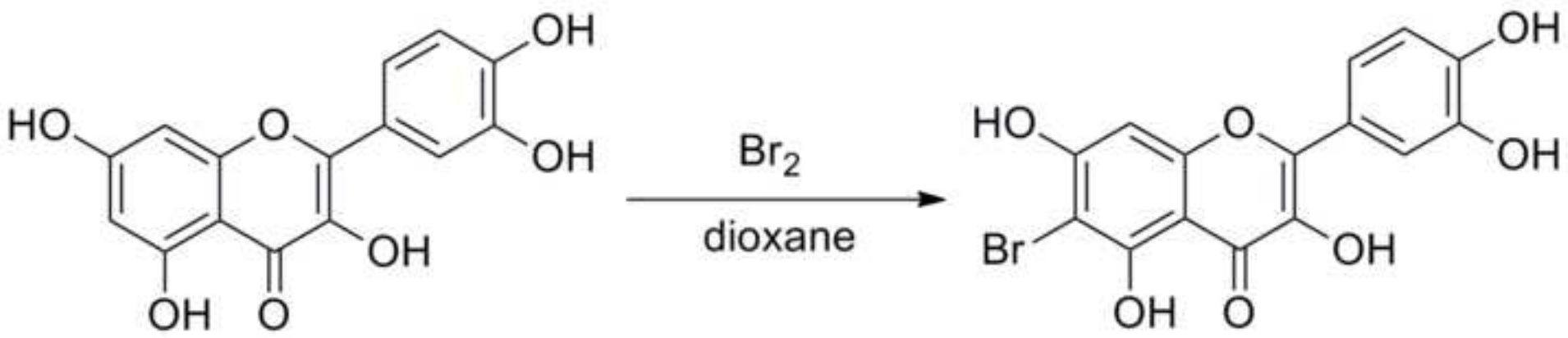


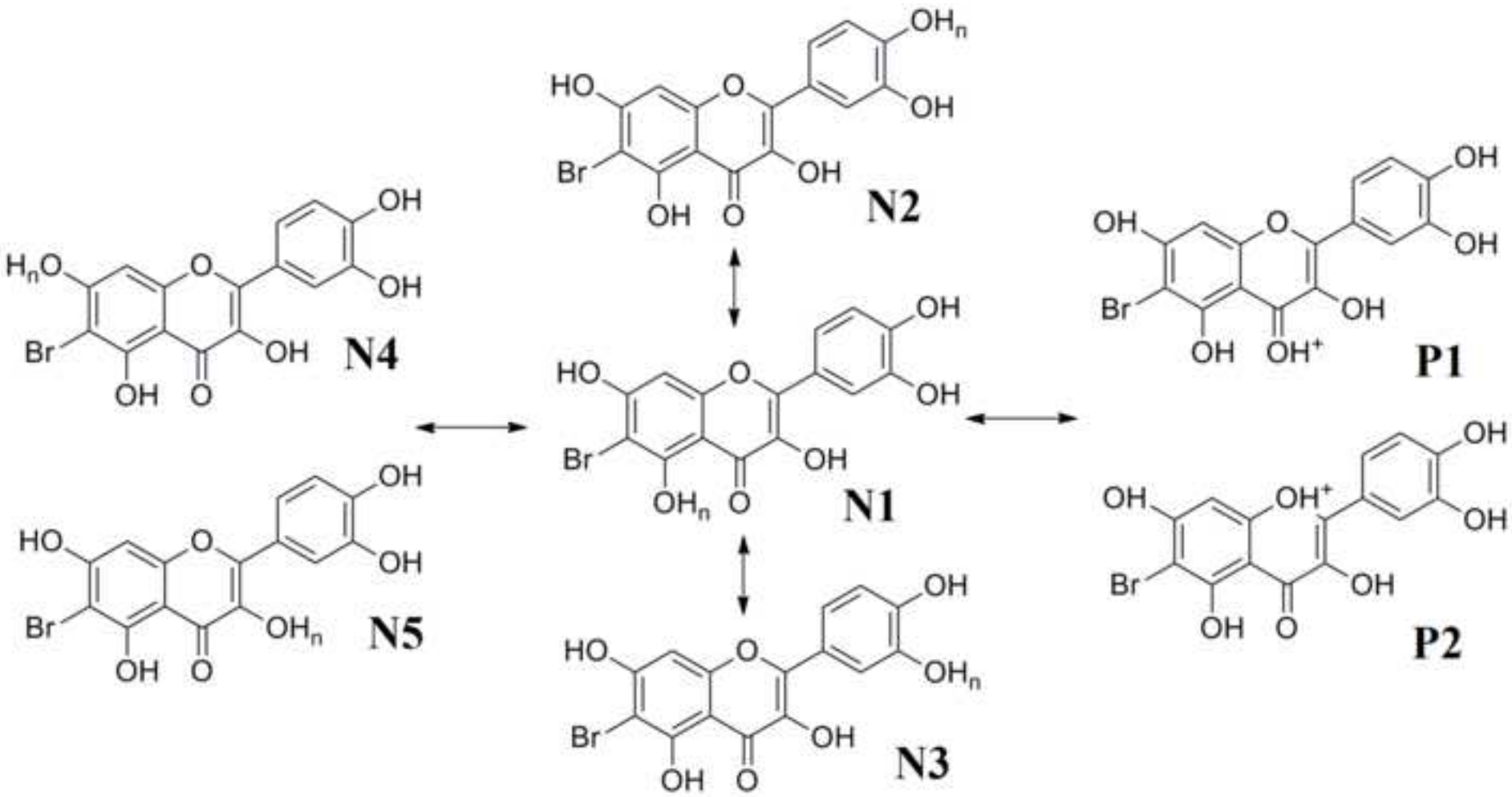
Figure 6



Scheme 1



Scheme 2



Scheme 3