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ANALYSIS

SPECTROSCOPIC STUDY OF HEXAHYDROQUINOLINE DERIVATIVES – A POTENTIAL GROUP OF CALCIUM ANTAGONISTS

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Abstract: Spectral properties of 2, 6, 6-trimethyl-3-carbmethoxy-4-phenyl-5-oxo -1,4,5,6,7,8-hexahydroquinoline derivatives (HHQ) with different substituents in the phenyl ring (-Cl, $-NO_2$, $-CF_3$, $-CH_3$, $-OCH_3$) have been studied. Their emission and absorption spectra have been analyzed and quantum yields of emission were determined. The quantum yield of emission was found to depend on the kind, number, and position of substituents in the phenyl ring: it was the highest for the chlorine derivatives of HHQ, and the lowest for the compounds containing $-NO_2$ group.

Keywords: calcium channel blockers, dihydropyridine derivatives, photodegradation, emission, light.

Problems with the circulatory system such as hypertension and ischaemia of the cardiac muscle have become a pressing social issue and studies on development of effective treatment are continued. The search for therapeutic substances is carried out along two lines: synthesis of compounds of the structure similar to that of already recognized drugs and pharmacological tests of new substances. One of the groups of drugs applied in the treatment of the circulatory system disturbances is that of calcium channel antagonists (1-3).

The calcium channel antagonists have also been found effective in the treatment of other diseases in nephrology, gynaecology, gastroenterology or central nervous system and others. A new group of calcium antagonists has been synthesized by C. Safak group (4-8) – they are derivatives of hexahydroquinoline (HHQ) and reveal structural resemblance to derivatives of 1,4-dihydropyridine. A common element of structure of these two groups is the dihydropyridine ring, substituted phenyl ring, and ester substituents at the C_3 position of the DHP ring (9-11). These structural elements are necessary for the compound to act as calcium antagonist. The HHQ derivatives meet all conditions for potential calcium channel blockers. The pharmacological study has shown that the activity of HHQ derivatives as calcium channel blockers depends on the kind and position of a substituent in the phenyl ring. This paper reports results of a study of spectral properties of HHQ derivatives.

EXPERIMENTAL

Materials

The compounds of 2,6,6-trimethyl-3-carbethoxy-4-(aryl)-5-oxo-1,4,5,6,7,8- hexahydroquinoline (HHQ) with different substituents at different positions in the phenyl ring were prepared by R. Şimşek and C. Şafak, the Hacettepe University, Ankara, Turkey (see Table 1).

RESULTS AND DISCUSSION

HHQ derivatives were subjected to spectroscopic studies in order to determine their absorption and emission properties.

Solutions of HHQ derivatives listed in Table 1 were prepared and their UV spectra were recorded on a Shimadzu spectrophotometer. The values of molar absorption coefficients determined for the derivatives are presented in Table 2.

It is known that the bands corresponding to the electronic transitions bring the information on the changes in the valency electron distribution caused by the intramolecular interactions. The UV spectra of the HHQ derivatives studied revealed the influence of the kind of substituents, their mutual positions and electron coupling with the chromophore. All the absorption spectra were composed of three bands: two of them with the maxima at 205-222 and 239-246 nm were assigned to the $\pi \rightarrow \pi^*$ transitions in the aromatic ring. The third band, with a maxi-

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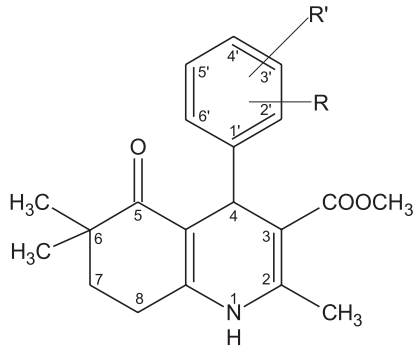
Table 1. Hexahydroquinoline derivatives (HHQ).



	HHQ derivative	Formula	R	R'	Substituent
1	2-Cl	$C_{20}H_{22}O_3NCl$	-Cl	-H	R=2'
2	3-Cl	$C_{20}H_{22}O_3NCl$	-H	-Cl	R=3'
3	2-Cl 3-Cl	$C_{20}H_{21}O_3NCl_2$	-Cl	-Cl	R=2' R'=3'
4	2-Cl 4-Cl	$C_{20}H_{21}O_3NCl_2$	-Cl	-Cl	R=2' R'=4'
5	2-Cl -Cl	$C_{20}H_{21}O_3NCl_2$	-Cl	-Cl	R=2' R'=6'
6	3-Cl 4-Cl	$C_{20}H_{21}O_3NCl_2$	-Cl	-Cl	R=3' R'=4'
7	2-NO_2	$C_{20}H_{22}O_5N_2$	-NO_2	-H	R=2'
8	3-NO_2	$C_{20}H_{22}O_5N_2$	-H	-NO_2	R=3'
9	2-CF_3	$C_{21}H_{22}O_3NF_3$	-CF_3	-H	R=2''
10	3-CF_3	$C_{21}H_{22}O_3NF_3$	-H	-CF_3	R=3'
11	2-CH_3	$C_{21}H_{25}O_3N$	-CH_3	-H	R=2''
12	3-CH_3	$C_{21}H_{25}O_3N$	-H	-CH_3	R=3'
13	2-OCH_3	$C_{21}H_{25}O_4N$	-OCH_3	-H	R=2''
14	3-OCH_3	$C_{21}H_{25}O_4N$	-H	-OCH_3	R=3'

Table 2. Analytical wavelengths and molar absorption coefficients of hexahydroquinoline derivatives.

HHQ derivative	λ [nm]	ε [$dm^3 \cdot mol^{-1} \cdot cm^{-1} \cdot 10^3$]	λ [nm]	ε [$dm^3 \cdot mol^{-1} \cdot cm^{-1} \cdot 10^4$]	λ [nm]	ε [$dm^3 \cdot mol^{-1} \cdot cm^{-1} \cdot 10^4$]
2-NO_2	366	5.393	241	2.025	212	1.585
3-NO_2	360	7.072	240	2.356	210	1.461
2-CF_3	365	7.324	241	1.663	207	1.254
3-CF_3	361	7.426	240	1.842	208	1.184
2-CH_3	365	8.300	246	1.458	212	1.315
3-CH_3	362	8.214	242	1.617	211	1.392
2-OCH_3	370	8.344	244	1.713	222	1.497
3-OCH_3	360	8.558	239	1.748	205	1.272
2-Cl	367	7.729	242	1.671	212	1.372
3-Cl	362	7.844	240	1.802	214	1.424
2-Cl 3-Cl	367	8.550	240	2.027	213	2.049
2-Cl 4-Cl	368	7.543	242	1.924	210	1.896
3-Cl 4-Cl	362	8.116	241	2.042	207	1.916
2-Cl 6-Cl	375	8.177	239	1.828	210	1.982

Table 3. Emission quantum yield [φ] of hexahydroquinoline derivatives (HHQ).

HHQ derivative	Concentration [mol/dm^3·10^5]	Emission intensity	Emission quantum yield
2-Cl	4.68	9812.31	$1.37 \cdot 10^{-2}$
3-Cl	4.37	5198.00	$0.79 \cdot 10^{-2}$
2-Cl 3-Cl	3.30	239.27	$2.17 \cdot 10^{-2}$
2-Cl 4-Cl	3.75	316.10	$2.86 \cdot 10^{-2}$
2-Cl 6-Cl	3.12	1066.93	$10.41 \cdot 10^{-2}$
3-Cl 4-Cl	5.73	175.38	$1.62 \cdot 10^{-2}$
2-NO_2	6.53	290.65	$4.23 \cdot 10^{-4}$
3-NO_2	4.87	5.51	$8.28 \cdot 10^{-6}$
2-CF_3	4.93	4872.35	$6.84 \cdot 10^{-3}$
3-CF_3	4.92	9194.40	$1.27 \cdot 10^{-2}$
2-CH_3	3.16	106.87	$1.02 \cdot 10^{-2}$
3-CH_3	3.70	179.43	$1.54 \cdot 10^{-2}$
2-OCH_3	3.60	173.79	$1.58 \cdot 10^{-2}$
3-OCH_3	6.46	107.99	$9.62 \cdot 10^{-3}$

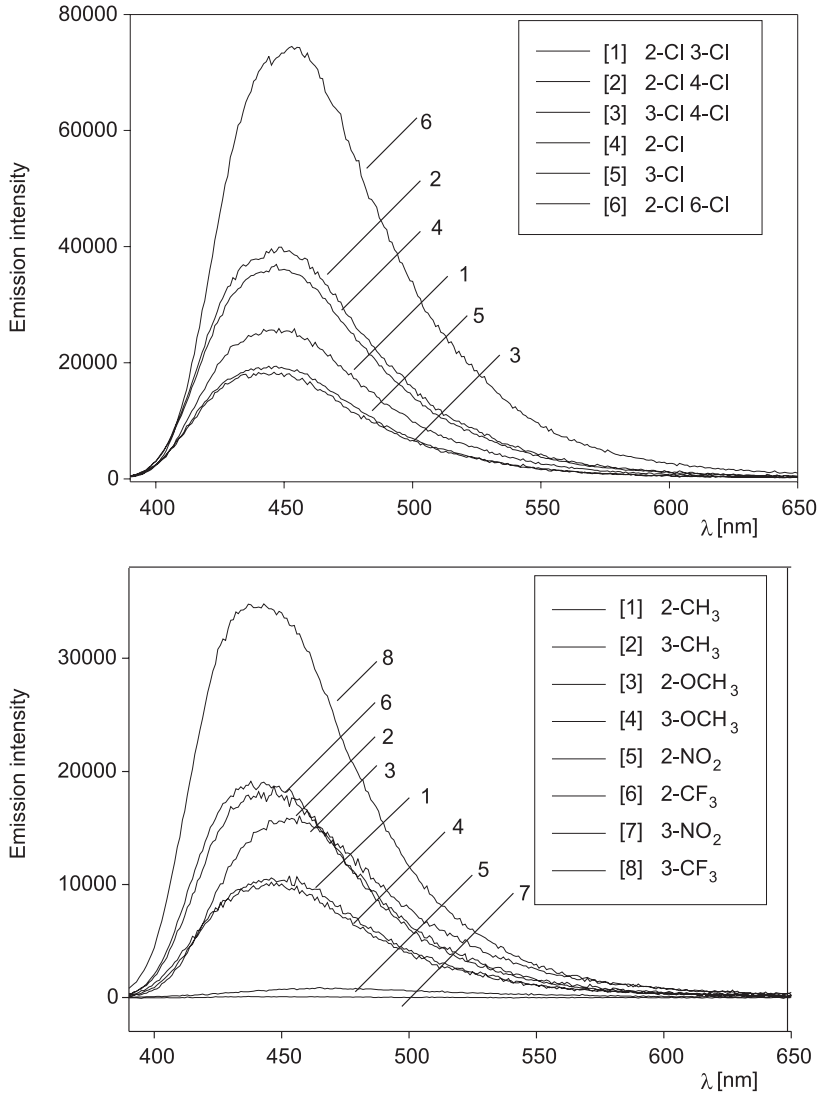


Figure 1A and 1B. Emission spectra of hexahydroquinoline derivatives.

mum at 360-375 nm was interpreted as corresponding to the $\pi \rightarrow \pi^*$ type transitions occurring in the six-membered heterocyclic DHP ring containing a nitrogen atom with a free electron pair.

The presence of substituents in the phenyl ring of both mono- and disubstituted HHQ was responsible for a shift of the benzene absorption band towards longer wavelength, and the batochromic effect was stronger for the compounds with a substituent at the *ortho* position. As follows from Table 2, the maxima of absorption of particular bands in the spectra of all the *ortho*-derivatives of HHQ occurred at longer wavelengths than those of the *meta* isomers. The character of the absorption spectra also reveals the influence of substituents coupling and interaction with π electrons from the aromatic ring, manifested as hypochromic effects. The increase in the bands' intensity was observed in particular in the short-wavelength part of the spectrum. Introduction of alkyl substituents (CH_3-) to a molecule of the HHQ derivatives studied was found to cause a small hypochromic effect. The effect caused by substituents with multiple bonds or free electron pairs was much greater, especially on the intensity of the absorption band at 235-242 nm. The substituents whose interactions with the π-electrons from the aromatic ring were the strongest were the nitro group and trifluoromethyl group ($-CF_3$).

For the emission studies, solutions of the HHQ derivatives in methanol were prepared at the concentrations given in Table 3.

The spectra were recorded in the range 388-700 nm on a spectrofluorimeter Perkin Elmer MPF-3, working at the wavelength λ_{exe} = 365 nm. The solutions were placed in measuring cells of the layer thickness l = 1 cm, and the apparatus slit width was 5/16. The emission spectra are presented in Figures 1A and 1B.

The quantum yield of emission was determined by the relative method, comparing the intensity of the emission of a sample studied with that of the standard. The standard was a solution of quinine sulfate (φ = 0.52) in sulfuric acid of a concentration of 0.05 mol/dm^3. The quantum yield values were calculated from the equation:

$$\varphi = S_{WZ} \cdot \varphi_{WZ} \cdot (1\text{-}10^{-AWZ}) / (1\text{-}10^{-APR}) \cdot S_{PR} \cdot I_{2WZ} / I_{2PR}$$

where:

A_{PR} – is the sample absorbance at λ_{exe} = 365 nm,

φ = 0.52 is a literature value,

S_{WZ} – the area of the standard fluorescence band,

S_{PR} – the area of the sample fluorescence band,

I_{2WZ}, I_{2PR} – relative intensities of the radiation incident on the standard and the sample.

The results are given in Table 3.

It has been established that the chemical structure of a molecule is related to the possibility of its absorption of electromagnetic radiation, which can be used to help predict the absorption properties of compounds. Unfortunately, no such relations have been found between the chemical structure and emission properties. The results obtained in this study indicate that for the compounds containing the dihydropyridine ring the presence of the nitro substituent in the phenyl ring significantly reduces the quantum yield of emission, in particular when the substituent is in the *meta* position. The highest values of quantum yield of emission were obtained for the HHQ derivatives containing chlorine atoms in the phenyl ring, especially when in *ortho* position. Moreover, it was found that the intensity of emission increases with the number of chlorine atoms in the aromatic ring, e.g. the emission of the 2-Cl,6-Cl derivative was 15-times more intense than that of 3-Cl one.

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