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Structure and radical scavenging activity of isoxazolo- and thiazolohydrazinylidene-chroman-2,4-diones

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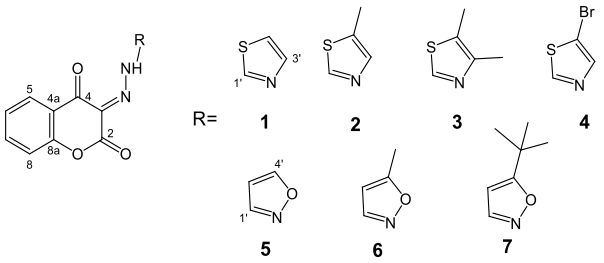
Dedicated to Acad. Ivan Juchnovski on the occasion of his 80th birthday

Quantum chemical calculations based on the density functional theory and NMR spectroscopy have been employed to perform structural analysis of four thiazolo- and three isoxazolohydrazinylidene-chroman-2,4-diones and to predict their relevant structural isomers. The scavenging capacities of the studied molecules towards nitric oxide ($NO^{\bullet}$), superoxide anion radical ($O_2^{\bullet-}$) and $DPPH^{\bullet}$ radicals were estimated. The compounds possessing a thiazolidine ring were 10-fold more active in the test with nitric oxide ($NO^{\bullet}$) than the rest of coumarins with isoxazolidine ring. A radical scavenging mechanism in aqueous medium was proposed to explain this activity.

Key words: hydrazinyldiene-chroman-2,4-diones, radical scavenging activity, structure, DFT, NMR

INTRODUCTION

Coumarins and related compounds are of remarkable interest to medicinal chemists due to their multiple pharmacological effects based on the antioxidative activity and modification of immune responses, cell proliferation and differentiation [1]. Coumarins and their derivatives are proved precursors in synthesis of a number of medical compounds and the heterocycles obtained from them are examined for their anticoagulant [2,3], anti-inflammatory and analgesic [4-6], antibacterial and antifungal [7-9], antiviral [10], antioxidant [11] and anticancer effect [12-18]. In a previous study [19], isoxazolo- and thiazolohydrazinylidene-chroman-2,4-diones that combine the coumarin core with five membered heterocycles (Scheme 1) have been synthesized and structurally characterized. In addition, their anticancer activity in vitro on different (metastatic) cancer cell lines was evaluated, when administered alone or in synergy with tamoxifen and doxorubicin [19-22]. In general, all synthesized compounds showed dose- and time-dependent effects, highlighting as the most potent the molecules containing a thiazole entity, with or without additional methyl groups bound to the carbons at positions 5 and/or 4 of the thiazole ring.



Scheme 1. Studied thiazolo- (**1-4**) and isoxazolo-hydrazinylidene-chroman-2,4-diones (**5-7**).

In continuation of the studies, here we present the RSA of isoxazolo- and thiazolohydrazinylidene-chroman-2,4-diones. Since the characterization of the most stable geometrical isomers of the studied molecules and the factors that contributed to their relative stability are essential to a complete understanding of their biological properties, we used Density Functional Theory (DFT) to perform structural analysis of the studied molecules and to predict the NMR spectra of their relevant structural isomers. The main goal of the present contribution

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is to evaluate the potential antioxidant activity of the synthesized compounds as well as to determine the preferred mechanism of this activity in polar environment, as a description of the processes taking place in the living organism.

EXPERIMENTAL

Synthesis and NMR spectroscopy

The compounds were prepared by derivatization of the appropriate heterocyclic amines which were used as electrophiles to attack the coumarine ring [19]. The NMR spectra were run on a Bruker-250 DRX Spectrometer in DMSO-d_6, as solvent using standard Bruker Topspin software. The chemical shifts were referenced to the residual solvent signal (2.5 ppm for the ^{1}H and 39.5 ppm for the ^{13}C spectra).

Nitric oxide radical scavenging micro-assay

For nitric oxide radical scavenging assay, the method of Harput *et al.* [23] was employed. Briefly, a strip plate, containing 100 µl of serial diluted compounds and 100 µl of freshly prepared 10 mM sodium nitroprusside in phosphate buffer (0.1 mM, pH 7.4), was irradiated with fluorescent light (36 W) for 15 minutes. Then, 100 µl of fresh Griess reagent were added and the absorption of the resulting mixture was measured at 560 nm.

Superoxide anion radical ($O_2^{\bullet-}$) scavenging assay

The superoxide anion radical scavenging capacity of the compounds was estimated in a riboflavin-light-NBT system, as described by Leelaprakash *et al.* [24]. The reaction mixture contained 75 µL riboflavin (0.04 mM), 75 µL phenazine methosulphate (1.0 mM) and 75 µL nitroblue tetrazolium (0.1 mM), prior to the addition of 75 µL sample. The reaction was started by illuminating the reaction mixture with the sample using a fluorescent lamp. After 20 min of incubation, the absorbance was measured at 560 nm.

DPPH radical micro-assay

The DPPH assay was performed using the method described by Nenadis and Tsimidou [25]. Briefly, an aliquot (296 µL) of a 0.1 mM ethanolic DPPH$^\bullet$ solution was mixed with 4 µL of each of the ethanolic sample solutions. The decrease of the absorption at 516 nm of the DPPH$^\bullet$ solution was measured 30 min after addition of each sample.

DFT calculations

The quantum chemical calculations were performed using the Gaussian 09 package [26]. The geometry optimizations of the structures investigated were done without symmetry restrictions, using DFT. We employed the B3LYP hybrid functional, which combines Becke's three-parameter nonlocal exchange with the correlation functional of Lee *et al*. [27,28], adopting 6-311++G**. The stationary points found on the molecular potential energy hypersurfaces were characterized using standard harmonic vibrational analysis. ^{1}H and ^{13}C-NMR chemical shifts of the studied compounds and of the solvent DMSO-d_6 were calculated by using the GIAO method [29] at the same level of theory (reference compound TMS was calculated at the same level).

The equations used for calculation of dissociation enthalpy (BDE) and ionization potential (IP) of the studied compounds are given below:

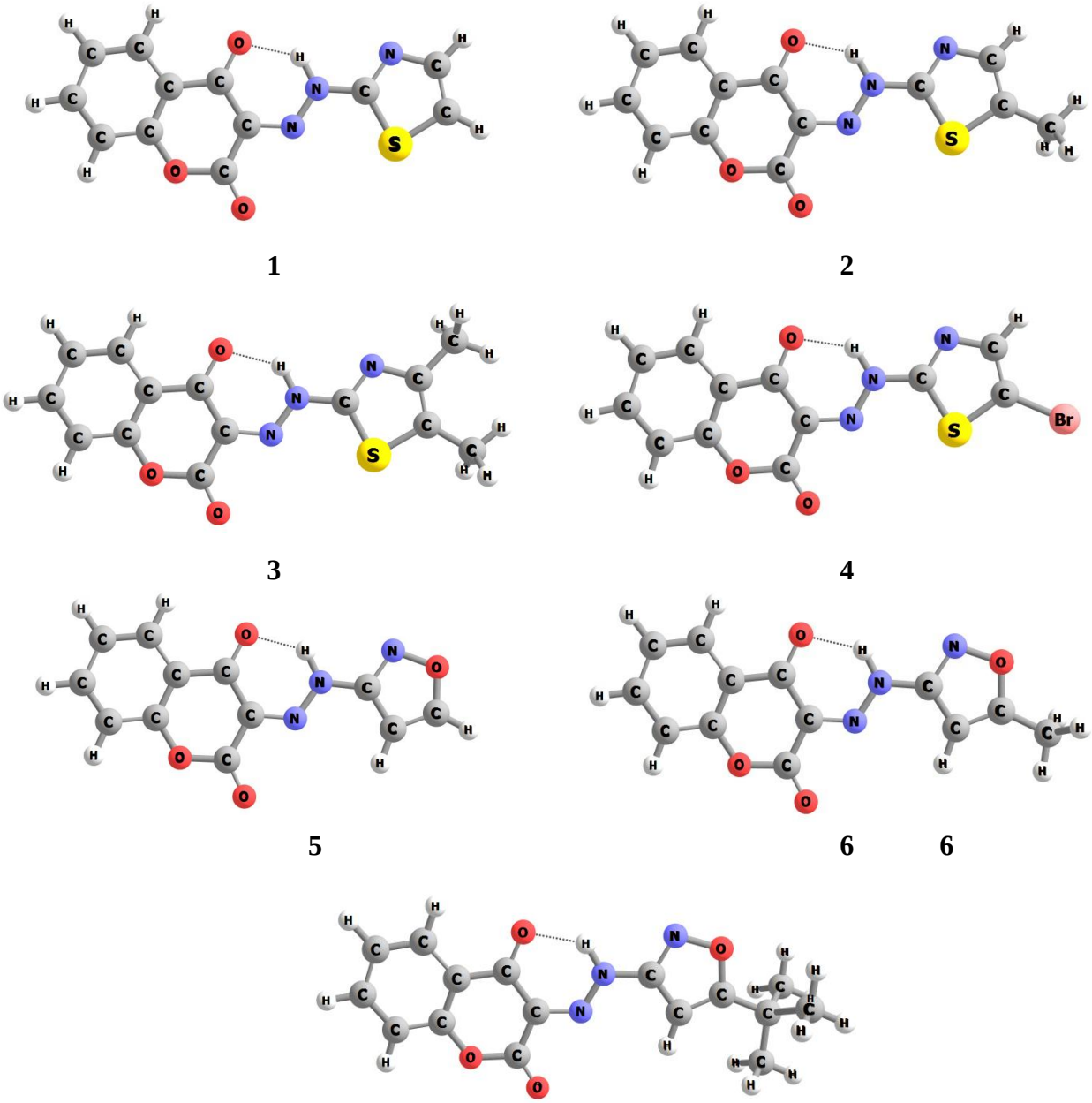
$$BDE = H(A^\cdot) + H(H^\cdot) - H(AH)$$

$$IP = H(AH^{+\cdot}) + H(e^-) - H(AH)$$

The enthalpy of the hydrogen atom, H(H) was obtained by the same method and basis set. All reaction enthalpies were calculated at 298 K. The enthalpies of proton H(H+), and electron, H(e^-), were taken from the literature – 6.197 kJ mol^{-1} and 3.145 kJ mol^{-1}, respectively [30]. Solvation enthalpies of proton H(H+), electron, H(e^-), in water, determined using IEF-PCM DFT/B3LYP/6-311++G** calculations, were used as reported [31].

RESULTS AND DISCUSSION

All of thiazolo- and isoxazolohydrazinylidene-chroman-2,4-diones studied (**1-7**) can exist in three different tautomeric forms (**A**, **B** and **C**; Scheme 2). The possible tautomeric forms of the thiazolo- and isoxazolohydrazinylidene-chroman-2,4-diones (**1-7**) were studied by quantum chemical calculations (B3LYP/6-311++G**). According to our calculations in gaseous phase the most stable is the diketo form **A**. The hydroxyl imines tautomeric forms **B** and **C** were found to be of no practical interest, because their energies are higher more than 20 kJ mol^{-1} for **B** and more than 40 kJ mol^{-1} for **C**. According to Minkin *et al.* [32], prototropic conversions are probable in case when the energy differences between the initial and the final structure do not exceed 20 kJ mol^{-1} with activation barrier not higher than105 kJ mol^{-1}.



Scheme 2. Geometry of the most stable forms of compounds **1-7.**

As it could be seen in Table 1, the energy differences are larger in the present case, and convince that only **A** should be expected to exist in real system. Different conformations resulting from internal rotation around the C3-N and N-R bonds are possible and should be taken into account. The energy differences of the respective conformations of tautomer **A** resulting from the rotation around C3-N fall in the interval between 1.0 and 1.5 kJmol^{-1}. The internal rotation around the N–R bond leads to energy differences from 4.5 to 5.4 kJ mol^{-1}. The most stable conformers for each studied compound (**1-7**) are represented in Scheme 2.

The most stable conformer for compound **7** corresponds to the structure which we have established by crystallographic analysis [33]. The calculated ^{13}C chemical shifts for the compounds **1-7** are in a good agreement with the experimental NMR data (Table 1). The only substantial difference between the experimental and calculated chemical shifts for C4' in compound **4** may be attributed to relativistic effects [34].

Table 1. Calculated and experimental ^{13}C chemical sifts (DMSO-d_6) for compounds **1 – 7.**

	1		**2**		**3**		**4**		**5**		**6**		**7**	
	calc.	exp.	calc.	exp.	calc.	exp.	calc.	exp.	calc.	exp.	calc.	exp.	calc.	exp.
2	155.0	157.3	155.1	157.3	155.2	157.3	154.8	157.2	155.5	157.6	155.5	157.6	159.4	157.6
3	123.5	125.0	123.3	124.6	123.2	124.0	124.0	125.3	124.6	126.0	124.2	125.7	122.7	125.7
4	179.9	177.9	179.8	177.6	179.3	177.2	180.6	177.3	179.7	178.6	179.7	178.4	174.3	178.3
4a	120.5	120.4	120.4	120.4	120.4	120.6	120.2	120.7	120.5	120.4	120.4	120.4	122.1	120.4
5	129.6	126.7	129.5	126.6	129.2	126.7	129.7	126.8	129.6	126.8	129.7	126.8	130.1	126.8
6	123.3	124.7	123.2	124.7	123.0	124.7	123.8	124.7	123.4	124.9	123.3	124.8	124.4	124.9
7	137.3	136.8	137.0	136.7	136.9	136.5	137.6	136.6	137.5	137.0	137.2	136.9	135.5	137.0
8	117.7	117.3	117.6	117.3	117.6	117.3	117.8	117.3	117.7	117.4	117.6	117.7	117.4	117.4
8a	158.7	154.1	158.2	153.9	159.0	153.9	157.5	154.0	159.2	154.1	158.6	154.1	157.0	154.1
1 '	170.8	166.3	169.3	164.5	166.7	163.9	169.7	163.1	166.2	162.2	166.6	162.7	166.4	162.4
3’	140.3	140.4	137.8	137.5	147.5	144.5	142.0	142.3						
4’	122.7	117.6	143.0	131.7	135.9	124.0	136.9	105.3	161.3	162.4	175.0	172	187.1	182.0
5’									96.0	97.3	93.1	94.1	89.6	91.2
C4-Me			9.2	11.9	9.5	11.2					8.6	12.3	34.8	32.9
C3-Me					12.8	14.0								
Me													23.7	28.2
Me													25.2	28.2
Me													25.2	28.2

The ^{13}C chemical shift of C4 is characteristic for C=O rather than C-OH and supports the predicted structure. No signals for OH and NH were observed in the ^{1}H spectrum [19] and this fact is also in accordance with the structure proposed by the quantum chemical calculations. The similarity of ^{1}H and ^{13}C chemical shifts of the coumarine moiety of compounds **1-7** reveals a similar electronic distribution. The different substituents do not influence it.

Having in mind the good NMR spectral descriptions obtained in this work and the relevance to the X-ray structural data of the compound 7 [33], we consider that the predictions of the structures of all studied compounds are reliable and the molecular structures of the compounds in solution are similar to their crystal structures. The scavenging capacities of the synthesized coumarin derivatives were estimated towards nitric oxide ($NO^{\bullet}$), superoxide anion radical ($O_2^{\bullet-}$) and 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radicals by classical methods adapted for a micro-scale on Elisa strip reader STATFAX 303+. Caffeic acid was used as a positive control. The absorbance of the negative control (A of control) was determined by replacing the sample with methanol. Seven concentrations of each compound (n = 3) were analyzed. The radical scavenging activities of the compounds (RSA) were calculated using the following formula:

$$RSA\ (\%) = (A_{\text{of control}} - A_{\text{of sample}}) / A_{\text{of control}} \times 100$$

The SC_{50} values (μg/mL) for each compound were calculated from the RSA = *f*(concentration) curves and were used in the structure–activity relationship study.

The seven compounds were less active than the caffeic acid (Table 2). The superoxide anion radical ($O_2^{\bullet-}$) and DPPH assays showed that the synthesized compounds were inactive in the concentration region between 0.5 and 7.2 mM. Under the same experimental conditions, the positive control caffeic acid was a strong scavenger, with concentration providing 50% inhibition (IC_{50}) of 61.1 μM (DPPH). However, some interesting correlations were observed between the title compounds and their RSA towards nitric oxide. The compounds were divided in two sets. The first one contained the most active compounds (**1-4**) with IC_{50} of 0.5 mM. All of them possess a thiazolidine ring and are 10-fold more active than the rest of coumarins, which form the second group.

Table 2. Radical scavenging capacities of compounds **1-7** towards nitric oxide (NO•) and calculated reaction enthalpies

	IC_{50} μM	BDE(Gas), kJ mol^{-1}	IP(Gas) kJ mol^{-1}	BDE(H_2O) kJ mol^{-1}	IP(H_2O) kJ mol^{-1}
1	454.4	370.8	773.9	359.6	370.2
2	525.2	367.4	749.0	354.6	353.5
3	492.2	366.6	724.6	350.9	339.3
4	488.6	368.2	764.3	360.2	366.7
5	5489.5	382.0	823.7	373.3	430.6
6	5276.2	381.4	806.1	372.4	422.5
7	3948.3	380.9	799.6	372.0	418.6

One possible mechanism by which the antioxidants can deactivate a free radical is H-atom abstraction (HAT mechanism) [30]:

$$A\text{-}H \rightarrow A^{\bullet} + H^{\bullet} \text{ (HAT)}$$

The efficacy of the antioxidant to react via HAT is characterized by the bond dissociation enthalpy (BDE). Higher stability of A *i.e.* lower BDE values correspond to good antioxidant capacity of A-H. Another possible mechanism is electron transfer (SET mechanism), in which the radical cation is first formed followed by deprotonation [31]:

$$A\text{-}H \rightarrow AH^{+\bullet} + e^{-} \text{ (SET)}$$

$$AH^{+\bullet} \rightarrow A^{\bullet} + H^{+}$$

For evaluation of reactivity via SET, the ionization potential (IP) is used. A lower IP implies an easier extraction of the electron. Based on calculation of the reaction enthalpies for each of the mechanisms, it is possible to suggest the most probable mechanism of action of a particular group of compounds [31].

The calculated reaction enthalpies, involved in the two mechanisms of antiradical activity of **1-7**, are presented in Table 2. We performed calculations of the respective values in nonpolar conditions (gas) and in polar medium (water). In the Table 2, the calculated reaction enthalpies are listed together with the experimentally found scavenging capacities of the coumarin derivatives towards nitric oxide (NO•).

As can be seen, in gas phase the BDEs of all studied compounds are almost the same and are considerably lower that the respective IPs, which indicates the HAT mechanism as the most favorable. BDEs are similar in water *i.e.* the energy requirements for HAT do not change much with the environment polarity. On the other hand, as a result of the greater stabilization in polar environment (water) the corresponding IPs are significantly lower than in gas phase. The calculated IP values in polar medium are substantially reduced compared to gas phase due to the fact that the electron and the radical cations are solvated and stabilized in polar medium. Furthermore, the IPs of the compounds possessing a thiazolidine ring are comparable or lower than their BDE values. The BDE values of the coumarins that do not possess a thiazolidine ring are still higher than the BDE values in all studied media. Therefore, it could be concluded that the SET mechanism would be competitive to the HAT one for compounds **1-4**, possessing a thiazolidine ring, in water. In this way, the superior activity of compounds **1-4** most probably could be explained by their capacity to deactivate free radicals simultaneously by two mechanisms (HAT and SET) in water.

The observed radical scavenging capacity towards nitric oxide (NO•) correlates with the results of a previous study about anticancer activity of the reported compounds [19-22]. The derivatives having sulphur in the five membered heterocycle showed a more potent effect on cancer cell viability. Nitric oxide (NO•) is a ubiquitous, water soluble, free radical gas, which plays key role in various physiological as well as pathological processes. Over the past decades, NO• has emerged as a 'Doubled-Edged Sword' in cancer. It is said to have both tumoracidal as well as tumor promoting effects which depends on its timing, location, and concentration. Interestingly, a statistically significant correlation was found between the measured in this study ability of the synthesized coumarin derivatives to scavenge NO• and their previously estimated growth-inhibition activity towards some cancer cell lines [35, 36]. This fact may be interpreted as a probable key role of the NO• molecule in the anticancer activity of the studied compounds.

CONCLUSION

The ability of four thiazolo- and three isoxazolohydrazinylidene-chroman-2,4-diones to scavenge superoxide ($O_2^{\bullet-}$) anion, nitric monooxide (NO•) radicals and 2,2-diphenyl-1-picrylhydrazyl free radical (DPPH•) was evaluated. The possible tautomeric forms of the thiazolo- and isoxazolo-hydrazinylidene-chroman-2,4-diones (**1-7**) were studied by quantum chemical calculations (B3LYP/6-311++G**) and in gaseous phase the most stable was the enamine structure **A** in

accordance with the crystallographic analysis and the NMR spectra. The compounds possessing a thiazolidine ring were 10-fold more active than the rest of coumarins possessing isoxazolidine ring towards nitric oxide ($NO^{\bullet}$). The observed radical scavenging capacity correlates with the results of a previous study about anticancer activity of the reported compounds. This superior activity could be explained by the ability of the thiazolo- derivatives to deactivate free radicals simultaneously by two mechanisms (HAT and SET) in water. The presented study is a complementation of the thorough investigation on various aspects of biological activities of this perspective class of compounds.

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СТРУКТУРА И РАДИКАЛ – УЛАВЯЩА АКТИВНОСТ НА ТИАЗОЛО- И ИЗОКСАЗОЛОХИДРАЗИНИЛИДЕН-ХРОМАН-2,4-ДИОНИ

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(Резюме)

Квантово-химични изчисления на базата на теорията на плътностния функционал (DFT/B3LYP/6-311++G**), както и ЯМР спектроскопия бяха приложени за структурен анализ и предсказване на енергетично изгодните изомери на четири тиазоло- и три изоксазоло-хидразинилиден-хроман-2,4-диони. Беше изследвана радикал – улавящата активност спрямо азотен оксид ($NO^{\bullet}$), супероксиден анион радикал ($O_2^{\bullet-}$) и 1,1,-дифенил-2-пикрил-хидразил радикал ($DPPH^{\bullet}$). Установено беше, че кумарините с тиазолов пръстен са 10 пъти по-активни спрямо азотен оксид ($NO^{\bullet}$) в сравнение с изоксазоловите производни. С цел обяснение на тази активност е предложен механизъм на процеса в полярна среда.