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Synthesis and structure of some novel dicoumarinamines

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The present paper reports the synthesis and characterization of novel dicoumarinamines (7) as potential bioisostere compounds of dicoumarols (4). 3,3'-Methylenebis(4-amino-2H-chromen-2-one) (7a) was obtained in high yield in a reaction of 4-aminocoumarine (5) with aqueous formaldehyde. Best results in reactions of 5 with aldehydes 6 (b-h) were obtained when reactions were performed in acidified ethanol as a solvent. The structure and relative stability of the possible rotamers were studied by DFT methods at B3LYP/6-31+G** level with regard to their potential biological activity.

Key words: aminocoumarins, bioisostere, dicoumarols, anticoagulant, DFT.

1. INTRODUCTION

Currently, the chemistry and bioactivity of coumarins are of remarkable interest to medicinal chemists. Large number of compounds with coumarin scaffold are known to possess a wide range of pharmacological properties including antibacterial [1-2], antifungal [3-4], antioxidant [5-6], anticancer [7-8], antituberculosis [9-10], anti-HIV [11-12], antimalarial [13-14], anti-inflammatory [15], anti-allergic [16], and many other activities.

Probably, the most well-known bioactive coumarins are anticoagulants. Over six decades, warfarin (1) is the mainly prescribed oral anticoagulant drug. In last 20 years, related compounds, such as phenprocoumon (2) and acenocoumarol (3) are used as oral anticoagulation therapy worldwide (Figure 1). Nowadays, new or modified coumarins with same pharmacological activity are still in the focus of many research groups [17-20]. All these compounds are analogues and inspired of dicoumarol (4a) as a prototype. Anticoagulant activity of 4a is known for nearly one century and even before discovering of its structure in 1940. Dicoumarols (4) and similar [21] compounds nevertheless attract intense interest because of their activity (Figure 1) [22-26].

The different substituents in the coumarin derivatives have considerable influence on their biological activity. So, the identification of crucial structural characteristic is essential for the development of new analogues with improved efficacy and lower side-effects. The design and synthesis of new derivatives with high specific activity for known and other pharmacological targets is a nowadays challenge. The present paper reports the synthesis and characterization of novel dicoumarinamines (7) as potential bioisosteric compounds of 4. Also, density functional theory (DFT) was employed to interpret the observed NMR spectra of the studied species. These results were used to investigate the preferred conformation of the compounds and the molecular properties with regard to their potential biological activity

EXPERIMENTAL

Aldehydes 6 were purchased commercially and used without further purification.

Melting points were determined on a Reichert hot-stage apparatus.

The FTIR spectra (4000-400 cm^{-1}) were recorded at ambient temperature with 16 scans on Perkin-Elmer System 2000 with the resolution of 4 cm^{-1} using KBr pellets. The data for strong (s) and very strong (vs) bands are given.

The NMR spectra were run on a Bruker 250 DRX Spectrometer using standard Bruker Topspin software. DMSO-d_6 was used as a solvent and the chemical shifts were referenced to the residual solvent signal (2.5 ppm for ^1H and 39.5 ppm for ^{13}C spectra). The signals were assigned with the aid of 1D and 2D ^1H, ^{13}C, DEPT, COSY, HMQC and HMBC spectra. The digital resolution of the 1D-spectra was 0.12 Hz/Pt for ^1H and 1.4 Hz/Pt for ^{13}C.

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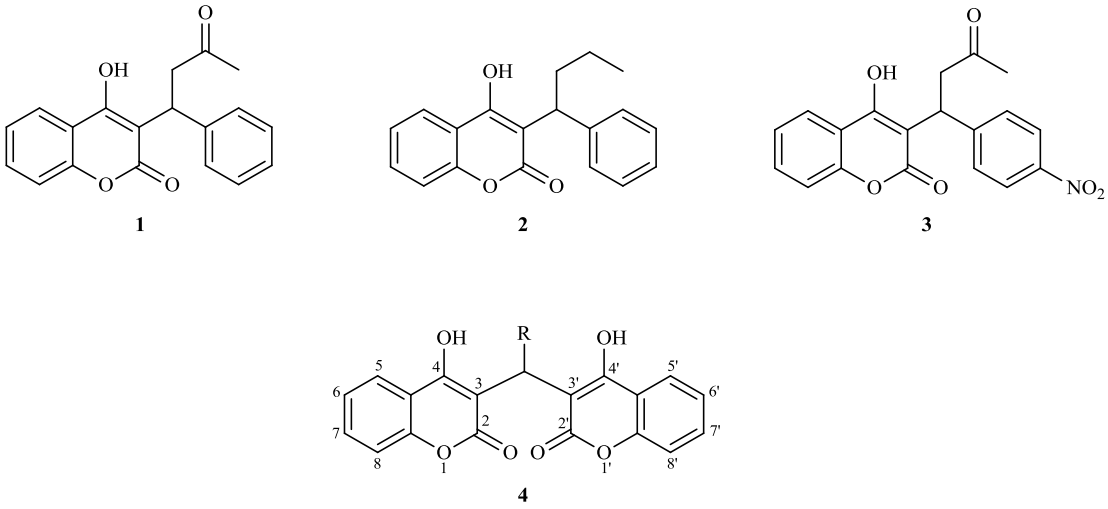


Fig. 1. Structures of well-known anticoagulants

The HR-ESI mass spectra were recorded on a QTof premiere conjugated with HPLC system.

The quantum chemical calculations were performed using the Gaussian 09 program package [27] running on MADARA grid. The geometries of possible conformational isomers of compound 7h were fully optimized using density functional theory (DFT). We employed B3LYP functional and standard 6-311+G** basis set. The stationary points found on the molecular potential energy hypersurfaces were characterized using standard analytical harmonic vibrational analyses.

4-Amino-2H-chromen-2-one (5) is not commercially available and it was synthesized as described previously [28].

3,3'-Methylenebis(4-amino-2H-chromen-2-one) (7a, $C_{19}H_{14}N_2O_4$).

To an aqueous (37%) formaldehyde solution (50 cm^3), well powdered 5 (1.012 g; 6.28 mmol) was added. The reaction mixture was stirred and heated up to 60 °C. After 2 h, the dense mixture was left to cool at room temperature. The crystals of the product 7a were collected by simple vacuum filtration. The typical yield of crude product was about 80%. For additional 10%, filtrate was cooled in ice bath. The purification was performed by dissolving the product in DMSO and precipitation with ethanol. Dirty white crystals, Mp: >300 °C (decomp.); FTIR(KBr)/cm^{-1}: 3391(s), 3213(s), 1669(s), 1645(vs), 1614(vs), 1600(vs), 1551(s), 748 (s); ^{1}H-NMR (250.13 MHz; DMSO-d_6) δ: 8.04 (br d, 2H, ^3J = 8.0 Hz, H-5), 7.83 (br s, 4H, NH_2), 7.62 (td, 2H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, H-7), 7.35 (overl, 4H, H-6, H-8), 3.65 (s, 2H, CH_2); ^{13}C-NMR (62.8 MHz; DMSO-d_6) δ: 164.8 (C2), 93.6 (C3), 153.5 (C4), 114.4 (C4a), 123.1 (C5), 124.0 (C6), 132.2 (C7), 116.9 (C8), 152.0 (C8a), 21.1 (CH_2); ESI TOF-MS (positive ions) (m/z): calcd. for $[M+H]^+$: 335.1032; found: 335.1034.

3,3'-Ethylidenebis(4-amino-2H-chromen-2-one)(7b, $C_{20}H_{16}N_2O_4$).

To ethanol (40 cm^3), acetaldehyde (6b) (0.9 cm^3; 16.10 mmol), well powdered 5 (1.997 g; 12.39 mmol) and 8 drops of "HCl" were added. Reaction mixture was refluxed for 2 h. After cooling, water was added (drop by drop) to precipitate the product. The typical yield of the crude product was about 90%. The purification was performed by dissolving the product in ethanol and precipitation with water. Pale ocher crystals, Mp: 202 °C (decomp.); FTIR(KBr)/cm^{-1}: 3370(s), 3221(s), 1648(vs), 1610(vs), 1546(vs), 754(s); ^{1}H-NMR (250.13 MHz; DMSO-d_6) δ: 8.03 (br d, 2H, ^3J = 8.0 Hz, H-5), 7.79 (br s, 4H, NH_2), 7.62 (td, 2H, ^3J = 8.0 Hz, ^4J= 2.0 Hz, H-7), 7.35 (overl, 4H, H-6, H-8), 4.58 (q, 1H,^3J = 7.5 Hz, CH), 1.66 (d, 3H, ^3J = 7.5 Hz, CH_3); ^{13}C-NMR (62.8 MHz; DMSO-d_6) δ: 164.2 (C2), 97.1 (C3), 153.2 (C4), 114.7 (C4a), 123.1 (C5), 124.0 (C6), 132.2 (C7), 116.8 (C8), 152.0 (C8a), 27.8 (CH), 15.6 (CH_3); ESI TOF-MS (m/z): calcd. for $[M+Na]^+$: 371.1008; found: 371.1007.

3,3'-Prophylidenebis(4-amino-2H-chromen-2-one)(7c, $C_{22}H_{20}N_2O_4$).

To ethanol (40 cm^3), butyraldehyde (6c) (1.4 cm^3; 15.53 mmol), well powdered 5 (2.007 g; 12.45 mmol) and 8 drops of "HCl" were added. Reaction mixture was refluxed for 1 h. After cooling, the crystals of the product were collected by simple vacuum filtration. The typical yield of the crude product was about 80%. The purification was performed by recrystallization from ethanol. Colorless crystals, Mp: 262-264 °C; FTIR(KBr)/cm-

[1]: 3389(s), 3212(s), 1630(vs), 1609(vs), 1546(vs), 1435(s), 756(s); ^{1}H-NMR (250.13 MHz; DMSO-d_6) δ: 8.02 (br d, 2H, ^3J = 8.0 Hz, H-5), 7.80 (br s, 4H, NH_2), 7.53 (td, 2H, ^3J = 8.0 Hz, ^4J= 2.0 Hz, H-7), 7.25 (overl, 4H, H-6, H-8), 4.40 (br t, 1H, ^3J = 7.5 Hz, CH), 2.20 (m, 2H, CH_2-*a*), 1.22 (m, 2H, CH_2-*b*), 0.85 (t, 3H, ^3J = 7.5 Hz, CH_3); ^{13}C-NMR (62.8 MHz; DMSO-d_6) δ: 164.4 (C2), 96.1 (C3), 153.8 (C4), 114.6 (C4a), 123.0 (C5), 123.8 (C6), 132.0 (C7), 116.6 (C8), 151.9 (C8a), 33.3 (CH), 31.0 (CH_2*a*), 21.4(CH_2*b*), 13.9 (CH_3); ESI TOF-MS (m/z): calcd. for $[M+H]^+$: 377.1501 found: 377.1500.

3,3'-Furfurylidenebis(4-amino-2H-chromen-2-one)(7d, $C_{23}H_{16}N_2O_5$).

To ethanol (40 cm^3), furfural (6c) (1.2 cm^3; 14.49 mmol), well powdered 5 (1.857 g; 11.52 mmol) and 8 drops of "HCl" were added. Reaction mixture was refluxed for 90 min. After cooling, the crystals of the product were collected by simple vacuum filtration. The typical yield of the crude product was about 80%. The purification was performed by dissolving the product in DMSO and precipitation with ethanol with several drops of water. Ocher crystals, Mp: 300-301 °C; FTIR(KBr)/cm^{-1}: 3452(s), 3358(s), 3221(s), 1645(vs), 1626(vs), 1608(vs), 1598(vs), 1548(vs), 1533(s), 1438(s), 756(s); ^{1}H-NMR (250.13 MHz; DMSO-d_6) δ: 8.08 (br d, 2H, ^3J = 7.5 Hz, H-5), 7.81 (br s, 4H, NH_2), 7.65 (td, 2H, ^3J = 8.0 Hz, ^4J= 2.0 Hz, H-7), 7.50 (br s, 1H, H-4´), 7.40 (overl, 4H, H-6, H-8), 6.33 (dd, 1H, ^3J = 3.0, 2.0 Hz, H-4´), 6.02 (br s, 1H, H-3´), 5.77 (s, 1H, CH); ^{13}C-NMR (62.8 MHz; DMSO-d_6) δ: 163.6 (C2), 93.6 (C3), 153.6 (C4), 114.4 (C4a), 123.2 (C5), 123.9 (C6), 132.4 (C7), 116.8 (C8), 153.6 (C8a), 33.2 (CH), 151.6 (C1-furanyl), 105.6 (C2-furanyl), 110.2 (C3-furanyl), 141.6 (C4-furanyl); ESI TOF-MS (m/z): calcd. for $[M+H]^+$: 401.1137; found: 401.1140.

3,3'-Benzilidenebis(4-amino-2H-chromen-2-one) (7e, $C_{25}H_{18}N_2O_4$).

Synthesis and purification as 7d. The typical yield was about 85%. Colorless crystals, Mp: 328-330 °C (decomp.); FTIR(KBr)/cm^{-1}: 3375(s), 3207(s), 1667(s), 1638(vs), 1622(vs), 1609(vs), 1593(vs), 1543(vs), 1520(s), 1436(s), 752(s); ^{1}H-NMR(250.13 MHz; DMSO-d_6) δ: 8.07 (d, 2H, ^3J = 7.5 Hz, H-5), 7.78 (br s, 4H, NH_2), 7.65 (td, 2H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, H-7), 7.40 (overl, 4H, H-6, H-8), 7.20 (overl. 2H, H-*m*), 7.10 (overl. 3H, H-*o*, H-*p*) 5.92 (s, 1H, CH); ^{13}C-NMR(62.8 MHz; DMSO-d_6) δ: 164.0 (C2), 94.5 (C3), 154.1 (C4), 114.5 (C4a), 123.2 (C5), 123.8 (C6), 132.2 (C7), 116.7 (C8), 152.1 (C8a), 37.4 (CH), 138.0 (C*i*), 126.5 (C*o*), 128.0 (C*m*), 125.4 (C*p*). ESI TOF-MS (m/z): calcd. for $[M+H]^+$: 411.1345; found: 411.1336.

3,3'-(4-Chlorobenzilidene)bis(4-amino-2H-chromen-2-one)(7f, $C_{25}H_{17}ClN_2O_4$).

Synthesis and purification as 7d. The typical yield was about 90%. Colorless crystals, Mp: 315-317 °C; FTIR(KBr)/cm^{-1}: 3403(s), 3216(s), 1637(vs), 1627(vs), 1611(vs), 1545(s), 1437(s), 758(s); ^{1}H-NMR(250.13 MHz; DMSO-d_6) δ: 8.08 (br d, 2H, ^3J = 7.5 Hz, H-5), 7.80 (br s, 4H, NH_2), 7.65 (td, 2H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, H-7), 7.40 (overl, 4H, H-6, H-8), 7.29 (d, 2H, ^3J = 8.0 Hz, H-*m*), 7.12 (d, 2H, ^3J = 8.0, H-*o*) 5.89 (s, 1H, CH); ^{13}C-NMR(62.8 MHz; DMSO-d_6) δ: 163.9 (C2), 94.1 (C3), 154.2 (C4), 114.4 (C4a), 123.2 (C5), 123.9 (C6), 132.4 (C7), 116.7 (C8), 152.1 (C8a), 37.0 (CH), 137.2 (C*i*), 128.5 (C*o*), 127.9 (C*m*), 130.0 (C*p*). ESI TOF-MS (m/z): calcd. for $[M+Na]^+$: 467.0775; found: 467.0777.

3,3'-(4-Nitrobenzilidene)bis(4-amino-2H-chromen-2-one)(7g, $C_{25}H_{17}N_3O_6$).

Synthesis and purification as 7d. The typical yield was about 80%. Dirty white crystals, Mp: >235 °C decomp.; FTIR(KBr)/cm^{-1}: 3441(s), 3354(s), 3207(s), 1634(vs), 1609(vs), 1547(s), 1528(vs), 1439(s), 1350(s), 758(s); ^{1}H-NMR (250.13 MHz; DMSO-d_6) *δ:* 8.12 (d, 2H, ^3J = 7.5 Hz, H-o), 8.11 (br d, 2H, ^3J = 7.5 Hz, H-5), 7.84 (br s, 4H, NH_2), 7.65 (td, 2H, ^3J = 8.0 Hz, ^{4}J= 2.0 Hz, H-7), 7.40 (overl, 4H, H-6, H-8), 7.40 (d, 1H, ^3J = 8.5, H-m) 6.04 (s, 1H, CH); ^{13}C-NMR (62.8 MHz; $CDCl_3$, DMSO-d_6) δ: 164.0 (C2), 93.5 (C3), 154.4 (C4), 114.4 (C4a), 123.3 (C5), 124.0 (C6), 132.5 (C7), 116.7 (C8), 152.1 (C8a), 37.3 (CH), 141.3 (C*i*), 129.6 (C*o*), 116.7 (C*m*), 148.0 (C*p*); ESI TOF-MS (m/z): calcd. for $[M+Na]^+$: 478.1015; found: 478.1022.

3,3'-(4-Methoxybenzilidene)bis(4-amino-2H-chromen-2-one) (7h, $C_{26}H_{20}N_2O_5$).

Synthesis and purification as 7d. The typical yield was about 80%. Colorless crystals, Mp: 278-280 °C; FTIR(KBr)/cm^{-1}: 3435(s), 3382(s), 3220(s), 1644(vs), 1624(vs), 1607(vs), 1593(vs), 1546(vs), 1509(s), 1434(s), 753(s); ^{1}H-NMR(250.13 MHz; DMSO-d_6) *δ:* 8.08 (br d, 2H, ^3J= 7.5 Hz, H-5), 7.78 (br s, 4H, NH_2), 7.63 (td, 2H, ^3J= 8.0 Hz, ^4J= 1.2 Hz, H-7), 7.56 (d, 2H, ^3J= 8.0, H-*o*), 7.40 (overl, 4H, H-6, H-8), 6.81 (d, 2H, ^3J= 8.0, H-*m*), 5.87 (s, 1H, CH), 3.71 (s, 3H, CH_3); ^{1}H-NMR(250 MHz; $CDCl_3$) *δ:* 7.61 (br d, 2H, ^3J= 8.0 Hz, H-5), 7.56 (td, 2H, ^3J= 8.0 Hz, ^4J= 1.2 Hz, H-7), 7.30 (overl, 4H, H-6, H-8), 7.13 (d, 2H, ^3J= 8.0, H-*o*), 7.00 (br s, 4H, NH_2), 6.78 (d, 2H, ^3J= 8.0, H-*m*), 6.13 (s, 1H, CH), 3.74 (s, 3H, CH_3); ^{13}C-NMR(62.8 MHz; DMSO-d_6) *δ:*

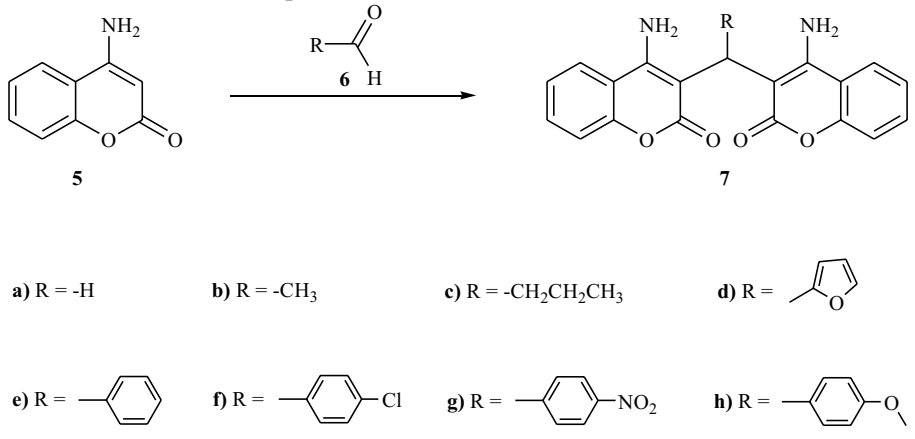
163.9 (C2), 94.7 (C3), 154.0 (C4), 114.5 (C4a), 123.2 (C5), 123.5 (C6), 132.2 (C7), 116.7 (C8), 152.1 (C8a), 36.7 (CH), 129.7 (C*i*), 127.5 (C*o*), 113.4 (C*m*), 157.8 (C*p*), 54.9 (OCH_3); ^{13}C-NMR(62.8 MHz; $CDCl_3$) *δ:* 165.3 (br, C2), 96.9 (br, C3), 153.9 (br, C4), 114.6 (C4a), 121.5 (C5), 123.9 (C6), 132.0 (C7), 117.5 (C8), 152.7 (C8a), 37.2 (CH), 129.7 (C*i*), 127.8 (C*o*), 113.6 (C*m*), 157.2 (C*p*), 55.2 (OCH_3); ESI TOF-MS (m/z): calcd. for $[M+Na]^+$: 463.1270; found: 463.1275.

RESULTS AND DISSCUSSON

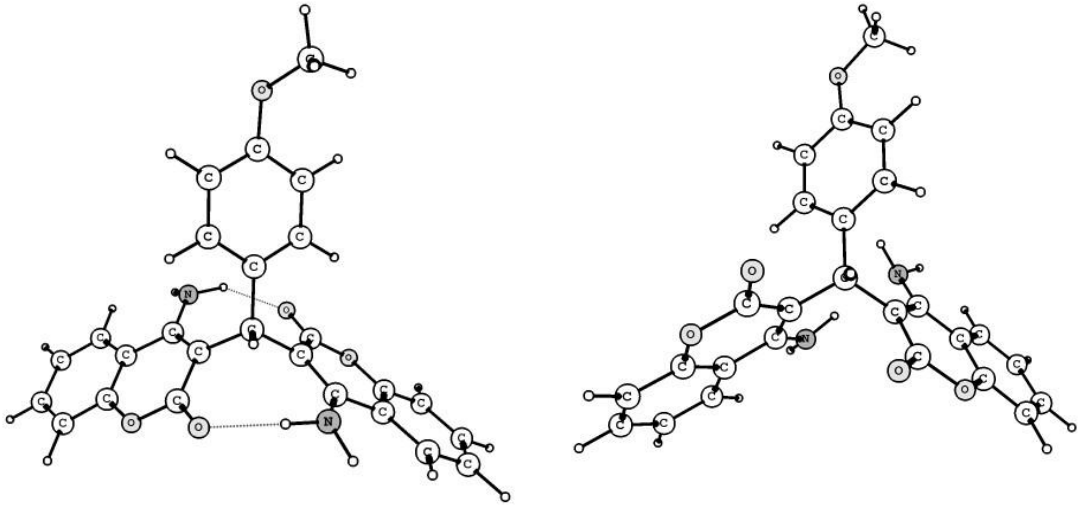
Not many reactions in which 4-aminocoumarin (**5**) is involved have been studied so far, although some of its derivatives possess biological activity [29-31]. In our previous work we had shown that the C-N bond distance at **5** indicates a considerable degree of double bond character [28]. The conjugation of NH_2 with coumarine moiety is most probably the reason for very low nucleophility of the nitrogen atom in molecule. Knowing this, we were almost sure that aldehydes in reaction of **5** would not give nucleophilic addition product or Mannich reaction products. As we predicted, reactions of **5** with some aliphatic and aromatic aldehydes (**6**) led to corresponding dicoumarinamines (**7**) as products (Reaction Scheme 1).

Compound **5** is not soluble in water at room temperature, but soluble in aqueous solution of formaldehyde (**6a**) from where (after several minutes) crystals of dicoumaroamine **7a** were formed. Higher yield was obtained when reaction mixture was heated up to 60 °C. Reactions with other aldehydes **6** can be performed in aqueous mixture acidified with HCl, especially with alkyl aldehydes **6b** and **6c**. However, the best results were obtained when reactions were performed refluxing acidified mixture of **5** and **6** in ethanol as a solvent.

It has been shown that the dicoumarol derivatives substituted at the bridge carbon exhibit a double hindered rotation around the bonds connecting this carbon. The restricted rotation is due to intramolecular hydrogen bonds [32-33]. The presence of hydrogen bonded structure for dicoumarols was confirmed with DFT, AIM [34] and X-ray studies [35]. The formation of these intramolecular hydrogen bonds may hold the structures in a suitable configuration for binding to an enzyme and hence may be an important factor for the biological activity. That is why we considered that is interesting to gain information on a similar process for diaminocoumarines. The most of the investigated compounds were insoluble in $CDCl_3$. Their NMR spectra were measured in DMSO-d_6. It is known that the intramolecular hydrogen bond is broken by the molecules of the solvent DMSO by competitive intermolecular bonding. From all investigated compounds only **7h** was dissolvable in $CDCl_3$ to obtain spectra in a solvent permitting formation of intermolecular hydrogen bonds. The comparison of the ^{1}H spectra in DMSO-d_6 and $CDCl_3$ showed differences in the chemical shifts, mostly of H-5 (0.46 ppm), C<u>H</u> (-0.26 ppm) and H-*o* (0.43 ppm), indicating different conformational behavior. The ^{1}H spectrum didn't exhibit doubling or broadening of signals but the signals for C-2, C-3 and C-4 in the ^{13}C spectrum were broad indicating a dynamic process. Due to the low concentration, variable temperature measurements were not possible. B3LYP/6-311+G(d,p) calculations showed presence of only two stable rotamers C1 and C2 (**Figure 2**) with an energy difference ΔE = 9.8 kcal/mol.



Reaction Scheme 1.



C1 C2

Fig. 2. Structures of the rotamers of **7h** molecule optimized by B3LYP/6-311+G** calculations.

The preferred rotamer (C1) is stabilized with an intramolecular hydrogen bond in analogy to the dicoumarols. The other is sterically favored. The hydrogen bonding $NH_2\cdots O=$ is less strong compared to the $OH\cdots O=$ and the gain of steric energy could stabilize a rotamer without hydrogen bonding.

As a conclusion, 4-aminocoumarine reacts with aldehydes leading to the corresponding dicoumarinamines as products. In this way, eight compounds have been prepared and characterized for the first time. The preferred rotamer of the compound **7h** is stabilized with an intramolecular hydrogen bond in analogy to the dicoumarols. The novel dicoumarinamines might be potential bioisostere compounds of dicoumarols.

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СИНТЕЗА И СТРУКТУРА НА НЯКОИ НОВИ ДИКУМАРИН-АМИНИ

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(Резюме)

В настоящата работа се съобщава за синтезата и охарактеризирането на нови дикумарин-амини (7) като потенциално био-изостерни съединения на дикумаролите (4). 3,3'-метилен-бис(4-амино-2H-хромен-2-он) (7a) е получен с висок добив в реакцията на 4-аминокумарин (5) с формалдехид във вода. Най-добри резултати на реакцията на 5 с алдехиди 6 (b-h) са постигнати когато реакцията се извършва в подкислен етанл като разтворител. Структурата и относителната стабилност на възможните ротамери са изследвани с DFT-метода на ниво B3LYP/6-31+G** с оглед тяхната биологична активност.