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Synthesis of New Hybrid Structures Based on 3*H*-Furanone and 1*H*-Pyrazole †

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Abstract: A series of new hybrid systems containing furan-2(3*H*)-one and 1*H*-pyrazole fragments were synthesized for the first time and characterized by elemental analysis, IR, NMR (^{1}H, ^{13}C, NOESY1D) spectroscopy. The implementation of the reaction of (*E*)-3-((2-oxo-5-arylfuran-3(2*H*)-ylidene)methyl)-4*H*-chromen-4-ones with hydrazine monohydrate at only one reaction center, namely, at the chromen-4-one fragment, is shown. Based on NMR spectroscopy data, it was shown that the resulting compounds—(*E*)-3-((5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)methylene)-5-arylfuran-2(3*H*)-ones exist in the form of *E*-isomers.

Keywords: hybrid structures; synthesis; furan-2(3*H*)-ones; 1*H*-pyrazole; physicochemical methods; spectroscopy; (*E*)-3-((5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)methylene)-5-arylfuran-2(3*H*)-ones

1. Introduction

The most developing area of research at present is hybrid systems containing several pharmacophore fragments and possessing a broad spectrum of biological action [1–5]. From this point of view, hybrid systems containing furan-2(3*H*)-one and chromen-4(4*H*)-one fragments are promising for research [6], their modification will further expand the spectrum of biological activity of new hybrid structures including the 1*H*-pyrazole fragment.

Thus, this work is devoted to searching for optimal synthesis conditions and establishing the structure of hybrid structures—(*E*)-3-((5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)methylene)-5-arylfuran-2(3*H*)-ones.

2. Materials and Methods

2.1. Physical Measurements

Melting points were determined on a Stuart™ SMP10 melting point apparatus (Cole-Parmer, Beacon Road, Stone, Staffordshire, ST15 OSA, UK). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured for solutions in acetone-d_6 on a Varian (Agilent) 400 spectrometer (Agilent Technologies, Santa Clara, CA, USA). FTIR spectra were collected on an FSM-1201 Fourier spectrometer (Infraspek, St. Petersburg, Russia) in the range 4000–400 cm^{-1} with a spectral resolution of 4 cm^{-1}. Samples were mixed with ground KBr (FTIR grade, Sigma–Aldrich, Saint Louis, MO, USA) and pressed into pellets by removing water and air traces under reduced pressure. Elemental analysis was done on an Elementar Vario MICRO cube CHNS analyzer (Elementar Analysensysteme GmbH, Hanau, Germany). The progress of the reaction and the purity of the synthesized compounds were monitored by TLC on ALUGRAM® SIL G UV254 plates (Macherey-Nagel, Düren, Germany), with hexane–ethyl acetate–acetone (3:1:1) as the eluent.

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2.2. Synthesis and Characterization of Compounds **2a–d**

In a round-bottomed flask equipped with a reflux condenser, 2 mmol of the corresponding (*E*)-3-((2-oxo-5-arylfuran-3(2*H*)-ylidene)methyl)-4*H*-chromen-4-one (**1a–d**), 2 mmol of hydrazine monohydrate, 5 mL of ethanol are placed and the reaction mixture is boiled from 15 to 60 min. Then the reaction mixture is evaporated on a rotary evaporator and the residue is triturated in water, the precipitated powder is filtered, washed with a large amount of water and dried.

(E)-3-((5-(2-hydroxyphenyl)-1H-pyrazol-4-yl)methylene)-5-phenylfuran-2(3H)-one **2a**

Yellow crystals. Yield—0.40 g (61%). mp 175–177 °C; FTIR (KBr), ν, cm^{-1}: 3435 (OH), 3332 (NH), 1742 (O–C=O), 1625 (C=N), 1211 (C–N); ^{1}H NMR (400 MHz, acetone-d_6): δ 7.02–7.09 (m, 2H, Ar–H), 7.32–7.37 (m, 2H, 1H Ar–H and C–H$_{Furanone}$), 7.43–7.55 (m, 5H, 4H Ar–H and =CH–), 7.82–7.88 (m, 2H, Ar–H), 8.59 (s, 1H, C–H$_{Pyrazole}$), 9.56 (br. s, 1H, OH), 12.71 (br. s, 1H, NH); ^{13}C NMR (100 MHz, acetone -d_6): δ 100.89 (C–H$_{Furanone}$), 116.58, 119.74, 122.41, 125.02, 125.09, 126.62 (=CH–), 126.90, 128.66, 128.76, 128.85, 129.99, 130.24, 130.41, 130.49, 143.82 (C–H$_{Pyrazole}$), 154.68, 154.72, 155.60, 168.71 (C=O). Anal. Calcd. For $C_{20}H_{14}N_2O_3$: C: 72.72%; H: 4.27%; N: 8.48%; Found: C: 72.51%; H: 4.32%; N: 8.20%.

(E)-3-((5-(2-hydroxyphenyl)-1H-pyrazol-4-yl)methylene)-5-(p-tolyl)furan-2(3H)-one **2b**

Yellow crystals. Yield—0.34 g (50%). mp 134–135 °C; FTIR (KBr), ν, cm^{-1}: 3500 (OH), 3404 (NH), 1750 (O–C=O), 1627 (C=N), 1245 (C–N); ^{1}H NMR (400 MHz, acetone-d_6): δ 2.39 (s, 3H, CH$_3$), 6.99–7.10 (m, 2H, Ar–H), 7.28–7.44 (m, 5H, 3H, Ar–H + 1H, =CH– + 1H, C–H$_{Furanone}$), 7.47–7.59 (m, 1H, Ar–H), 7.75 (d, J = 7.9 Hz, 2H, Ar–H), 8.58 (s, 1H, C–H$_{Pyrazole}$), 9.57 (br. s, 1H, OH), 12.87 (br. s, 1H, NH); ^{13}C NMR (100 MHz, acetone -d_6): δ 20.61 (CH$_3$), 100.08 (C–H$_{Furanone}$), 116.54, 119.76, 122.55, 125.11, 125.18, 125.96 (=CH–), 128.25, 129.26, 129.31, 129.53, 130.26, 130.38, 140.38, 141.61, 143.92 (C–H$_{Pyrazole}$), 149.95, 154.94, 155.55, 168.82 (C=O). Anal. Calcd. For $C_{21}H_{16}N_2O_3$: C: 73.24%; H: 4.68%; N: 8.13%; Found: C: 73.32%; H: 4.54%; N: 8.01%.

(E)-5-(3,4-dimethylphenyl)-3-((5-(2-hydroxyphenyl)-1H-pyrazol-4-yl)methylene)furan-2(3H)-one **2c**

Yellow crystals. Yield—0.37 g (52%). mp 166–168 °C; FTIR (KBr), ν, cm^{-1}: 3503 (OH), 3433 (NH), 1752 (O–C=O), 1629 (C=N), 1247 (C–N); ^{1}H NMR (400 MHz, acetone-d_6): δ 2.32 (unres. s, 6H, 2CH$_3$), 6.99–7.10 (m, 2H, Ar–H), 7.26 (s, 1H, =CH–), 7.28 (s, 1H, C–H$_{Furanone}$), 7.31–7.43 (m, 2H, Ar–H), 7.50 (d, J = 7.7 Hz, 1H, Ar–H), 7.59 (d, J = 8.0 Hz, 1H, Ar–H), 7.64 (s, 1H, Ar–H), 8.57 (s, 1H, C–H$_{Pyrazole}$), 9.54 (br. s, 1H, OH), 12.87 (br. s, 1H, NH); ^{13}C NMR (100 MHz, acetone -d_6): δ 18.88 (CH$_3$), 18.92 (CH$_3$), 99.90 (C–H$_{Furanone}$), 116.53, 119.76, 122.70, 126.06, 125.67, 128.24, 129.31, 129.39, 129.60, 130.05 (=CH–), 130.33, 137.17, 139.13, 139.16, 143.89 (C–H$_{Pyrazole}$), 149.92, 154.91, 155.12, 168.86 (C=O). Anal. Calcd. For $C_{22}H_{18}N_2O_3$: C: 73.73%; H: 5.06%; N: 7.82%; Found: C: 73.70%; H: 4.92%; N: 7.97%.

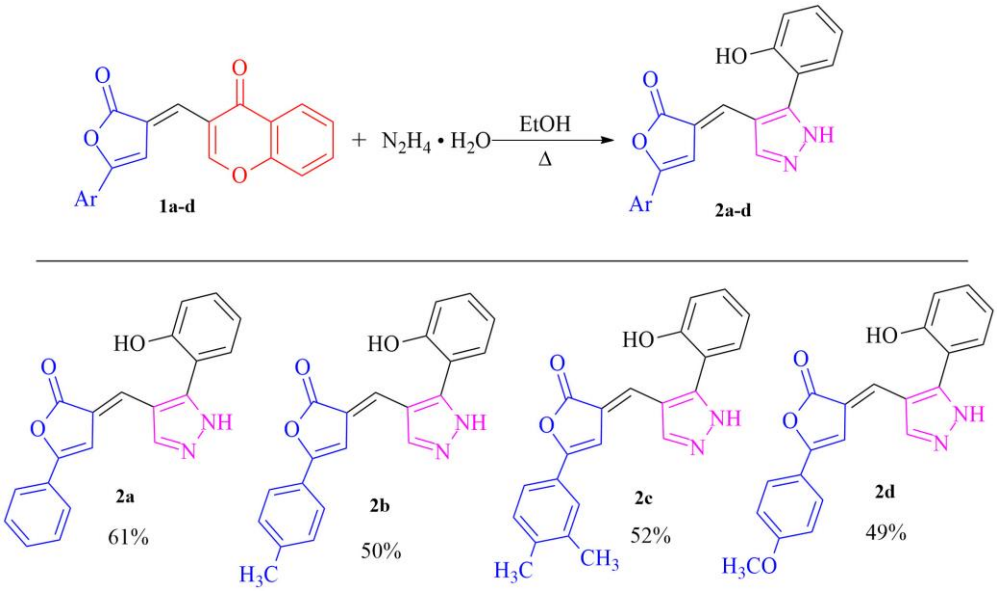
(E)-3-((5-(2-hydroxyphenyl)-1H-pyrazol-4-yl)methylene)-5-(4-methoxyphenyl)furan-2(3H)-one **2d**

Yellow crystals. Yield—0.35 g (49%). mp 120–122 °C; FTIR (KBr), ν, cm^{-1}: 3499 (OH), 3421 (NH), 1751 (O–C=O), 1628 (C=N), 1240 (C–N); ^{1}H NMR (400 MHz, acetone-d_6): δ 3.87 (s, 3H, OCH$_3$), 7.01–7.08 (m, 4H, Ar–H), 7.17 (s, 1H, C–H$_{Furanone}$), 7.30–7.41 (m, 2H, Ar–H + =CH–), 7.52 (d, J = 8.2 Hz, 1H, Ar–H), 7.80 (d, J = 8.6 Hz, 2H, Ar–H), 8.55 (s, 1H, C–H$_{Pyrazole}$), 9.59 (br. s, 1H, OH), 12.86 (br. s, 1H, NH); ^{13}C NMR (100 MHz, acetone -d_6): δ 54.96 (OCH$_3$), 98.88 (C–H$_{Furanone}$), 116.46, 119.68, 122.88, 124.88, 124.95 (=CH–), 126.78, 128.38, 129.30, 129.73, 130.10, 130.22, 130.44, 131.97, 141.48, 143.91 (C–H$_{Pyrazole}$), 154.95, 155.60, 161.40, 168.88 (C=O). Anal. Calcd. For $C_{21}H_{16}N_2O_4$: C: 69.99%; H: 4.48%; N: 7.77%; Found: C: 69.74%; H: 4.51%; N: 7.72%.

3. Results and Discussion

In this work, we present a new efficient method for the synthesis of hybrid structures—(*E*)-3-((5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)methylene)-5-arylfuran-2(3*H*)-ones

(**2a–d**), which is based on the interaction of equimolar amounts of (*E*)-3-((2-oxo-5-arylfuran-3(2*H*)-ylidene)methyl)-4*H*-chromen-4-ones (**1a–d**) with hydrazine monohydrate in ethanol without the use a catalyst, with thermal activation of the reaction mixture with various yields (Scheme 1).



Scheme 1. Synthesis of hybrid structures—(*E*)-3-((5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)methylene)-5-arylfuran-2(3*H*)-ones **2a–d**.

Taking into account the structure of reaction products **2a–d**, it can be assumed that there is an attack of hydrazine on the C_2-O bond of the chromen-4-one fragment, accompanied by opening of the ring with the formation of an enamine fragment, and a further attack of the amino group on the C=O group of the initial chromen-4-one leads to the formation of a pyrazole ring in the final reaction products.

The structure of hybrid structures **2a–d** was confirmed by IR, ^{1}H, ^{13}C NMR spectroscopy data. The key signals (*E*)-3-((5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)methylene)-5-arylfuran-2(3*H*)-ones **2a–d**, registered in acetone-d_6, are the signals of the furanone ring were observed in the range of 7.17–7.37 ppm; protons belonging to the exocyclic double bond C=C appeared at 7.26–7.46 ppm; protons singlets of the pyrazole ring were observed in the range of 8.55–8.59 ppm; broadened singlets of OH and NH protons were observed in the range of 9.54–9.59 ppm and 12.71–12.87 ppm respectively. The ^{13}C NMR spectrums of compounds **2a–d**, showed signals from the lactone carbon atom at 168.71–168.88 ppm. Based on NMR spectroscopy, it was shown that the resulting compounds **2a–d** exist in the form of *E*-isomers. The proof absence of the duplication of signals in the ^{1}H NMR spectra as well as the presence of a cross-peaks in the NOESY1D spectrums of compounds **2a–d**, corresponding the spatial proximity of the protons of the furanone and pyrazole rings (Figure 1).

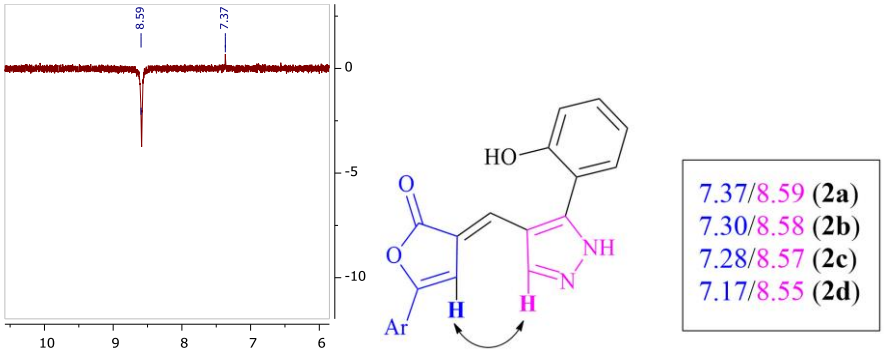


Figure 1. NOESY1D spectrum (*E*)-3-((5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)methylene)-5-phenylfuran-2(3*H*)-one **2a**.

4. Conclusions

In this work, we developed new method for obtaining hybrid structures (*E*)-3-((5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)methylene)-5-arylfuran-2(3*H*)-ones. The implementation of the reaction of (*E*)-3-((2-oxo-5-arylfuran-3(2*H*)-ylidene)methyl)-4*H*-chromen-4-ones with hydrazine monohydrate at only one reaction center, namely, at the chromen-4-one fragment, is shown. The structure of the (*E*)-3-((5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)methylene)-5-arylfuran-2(3*H*)-ones was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy data. According to NMR spectroscopy data, it was found that the target compounds **2a–d** exist in the form of *E*-isomers.

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