Synthesis of new coumarin based acetohydrazones and their correspounding oxadiazoles and oxadiazolines and the investigation of their keto-enol and/or amide–iminol tautomerization

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Article

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Abstract

Here we report the synthesis, structural identification and tautomeric behavior of new series of coumarin based hydrazide-hydrazones and their 1,3,4-oxadiazole and oxadiazoline derivatives. In fact The synthesis of 1,3,4-oxadiazoles and oxadiazoline bearing coumarin ring was intended for deducing the isomerization-tautomerization of their hydrazone precursors.

Convectional synthesis of several coumarin-oxadiazole derivatives from starting compound, 4-Methylcoumarinyl-7-yl-oxymethyl acetic acid hydrazide has been accomplished. Both types of hydrogens: the hydrazone N-H and methylene protons can take part to tautomeric isomerization equilibria. According to the nmr investigation we found that the keto-enol tautomerization is more favored than amide-iminol.

This concept was further established by converting the hydrazones to the corresponding 1,3,4-oxadiazoles and oxadiazolines according to the modified procedures.

Introduction

Aryl hydrazones and oxadiazoles are important classes of organic compounds. Coumarin based hydrazone and oxadiazole derivatives have found a lot of interest because of their bioactivities[1-4].

Oxadiazoles are the five-membered heterocyclic compounds containing one oxygen and two nitrogen atoms. Depending on the position of nitrogen atoms, oxadiazoles may occur in the form of four different isomers: 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole [Figure 1]:

compounds containing 1,3,4-oxadiazole unit exhibit a wide range of biological activities such as anticancer, antiparasitic, antifungal, antibacterial, antidepressant, anti-tubercular and anti-inflammatory[5-8]. Complex 1,3,4-oxadiazole derivatives are valuable compounds in this respect. These molecules are widely used in the production of many biopharmaceutical substances, showing a wide range of biological activities[9]. Oxadiazole heterocycles are therefore important structural motifs in the design of novel drugs[10-14].

Also oxadiazole molecules have many properties that are used in various industries. The oxadiazole moieties also have valuable optical properties. The 1,2-diazole fragment present in the molecule acts as an electron withdrawing group, so it is widely used in various types of conducting systems[15]. It is therefore possible to increase the quantum yield of fluorescence and improve the stability of the molecule. For this reason, oxadiazole derivatives are used as organic light emitting diodes, laser dyes, optical brighteners and scintillators[15-17]. These molecules can be also found in materials such as thermal insulation polymers.

Organic acid hydrazides include the vast group of organic derivatives. Hydrazides and their derivatives could be transformed into various heterocyclic compounds either by cyclisation or cyclo-addition with

numerous reagents. These acid hydrazides and their derivatives were found to be useful synthons for the synthesis of various heterocyclic five, six or seven-membered rings including one or more heteroatoms with versatile applications and properties[18-34].

Acid hydrazones are important bidentate ligands, which show keto-enol (amido-iminol) tautomerism. They usually exist in the keto form in the solid-state while it retains an equilibrium between keto and enol, when in a solution state [Figure 2]:

Nowaday, hydrazides and hydrazones have many technical and commercial importance due to their broad utilization as pharmaceutical in medicine. isocarboxazide, iproniazide, isoniazid, nifuroxazide, rifampisin as example drugs[35].

Imidazole bearing hydrazones, were demonstrated good antibacterial activities[27, 36-50].

Many organic substances containing the azomethine functional group (-NHN=CH-) have been synthesized[51-58]. Also synthesis of organic compounds containing the hydrazone group have been attended and reported such species to exhibit antibacterial activities. Hydrazones are the most important drugs against some microorganism cultures, Gram positive and negative bacteria and fungi. The acyl- and aroyl hydrazones are very important as chelating agents and also as versatile ligands in coordination chemistry[52].

Furthermore, Numerous representatives of the 1,3,4-oxadiazole and 1,3,4-oxadiazoline ring system exhibit remarkable physical, chemical or biological properties[1-4]. The Five membered heterocyclic compounds substituted 1,3,4- oxadiazoles derived from hydrazones also display a wide spectrum of activities. Overviewing at the importance of oxadiazole molecules, it was thought that it would be valuable to synthesize new oxadiazole derivatives. Their synthesis has increased attention in recent years and select them for potential biological activities. Owing to their various biological properties, such as antimalarial[59], antibacterial[60], antifungal[61], anti-inflammatory[62] and anticonvulsant[63].

An important aspect of the chemical structure of hydrazones is illustrated by the existence of prototropic tautomerism. So their structural characterization is an important feature in organic chemistry.

Some types of tautomerism is shown in the following examples [Figure 3, 4]:

In this article the synthesis of 1,3,4-oxadiazoles and oxadiazoline bearing coumarin ring was intended for deducing the isomerization-tautomerization of their hydrazone precursors Convectional and modified synthesis of several coumarin-oxadiazole derivatives from starting compound, 4-Methylcoumarinyl-7-oxyacetic acid hydrazide has been accomplished. Both hydrogens, the hydrazone N-H and methylene protons can take part to tautomeric isomerization equilibria [Figure 5 and 6]:

Experimental

General Information

Melting points were determined on Barnstead Electrothermal-9100 and are uncorrected. IR spectra were recorded on a Bruker IR spectrophotometer (Tensor model) as KBr pellets. The ^{1}H-NMR spectra were recorded on a Bruker Nuclear Magnetic Resonance (NMR) (300MHz) using DMSO-d or CDCl as solvents and TMS as internal standard. Thin layer chromatography (TLC) was attempted on silica gel plates using appropriate solvents as mobile phase. The ChemDrew- software was used for drawing and naming the synthesized compounds.

General procedure for the synthesis of 4-methylcoumarin-7-yl-oxymethyl-arylaldehyde acetohydrazone (1-3)

A (50 ml) round bottomed flask equipped with a magnet bar and magnetic stirrer was used as a reaction vessel and 15 ml glacial acetic acid was used as a solvent. 0.033 mole aryl aldehyde and (1 gm) 4-methylcoumarin-7-yl-oxymethyl acetohydrazide were added to the reaction vessel respectively. The reaction mixture was stirred at room temperature for 48 hours. The progress of the reaction was monitored by thin layer chromatography (TLC) on silica-gel as the stationary phase, and (CHCl - MeOH 2:1) was used as the mobile phase. After completion of the reaction, the mixture was poured on (150 gm) crushed ice. The crude product was formed as precipitate and purified by recrystallization by acetone. The melting points of products were determined and the structures were characterized by IR and NMR spectroscopy.

Synthesis of 4-methyl coumarin-7-yl-oxymethyl-p-methylbenzaldehyde acetohydrazone (3) as a typical procedure:

A (50 ml) round bottomed flask with a magnet bar was used as a reaction vessel, the vessel equipped with a magnetic stirrer. (15 ml) glacial acetic acid as a solvent, (0.4 gm) p-methyl benzaldehyde, and (1 gm) 4-methylcoumarin-7-yl-oxymethyl acetohydrazide were added to the reaction vessel respectively. The reaction mixture was stirred at room temperature for (48 hours). The progress of the reaction was monitored by thin layer chromatography (TLC) on silica-gel as the stationary phase, and (CHCl - MeOH 2:1) was used as the mobile phase. After completion of the reaction, the mixture was poured on (150 gr) crushed ice. The crude product was formed as precipitate and purified by recrystallization by acetone (Mp: 264-266 ºC).

General procedure for the synthesis of of 4-methyl-2-[(coumarin-7-yl-oxymethyl)]-4-acetyl-5-aryl-1, 3, 4-oxadiazolines (4,5)

A (50 ml) round bottomed flask with a magnet bar is used as a reaction vessel, the vessel equipped with a condenser and heater stirrer. (5 ml) dry acetic anhydride as a solvent and appropriate amounts of methylcoumarin-7-yl-oxymethyl arylaldehyde aceto hydrazone were added to the reaction vessel and refluxed for (6 hours). The progress of the reaction was monitored by thin layer chromatography (TLC) on silica-gel as the stationary phase, and (CHCl - MeOH 2:1) was used as the mobile phase. After completion

of the reaction, the mixture was poured on (100 gm) crushed ice. The crude product was formed as precipitate and purified by recrystallization from acetone The melting points of products were determined and the structures were characterized by IR and NMR spectroscopy.

Synthesis of 4-methyl-2-[(coumarin-7-yl-oxymethyl)]-4-acetyl-5-(4-methylphenyl)-1,3,4-oxadiazolines (4) as a typical procedure:

A (50 ml) round bottomed flask with a magnet bar used as a reaction vessel, the vessel equipped with a condenser and heater stirrer. (5 ml) dry acetic anhydride as a solvent and (0.2 gm) 4-methylcoumarin-7-yl-oxymethyl p-methylbenzaldehyde aceto hydrazone were added to the reaction vessel and refluxed for (6 hours). The progress of the reaction was monitored by thin layer chromatography (TLC) on silica-gel as the stationary phase, and (CHCl -MeOH 2:1) was used as the mobile phase. After completion of the reaction, the mixture was poured on (100 gm) crushed ice. The crude product was formed as precipitate and purified by recrystallization by acetone (Mp:168-170 ºC).

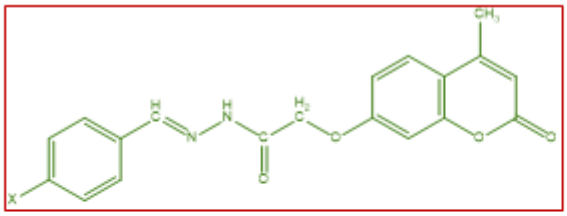
General procedure for the synthesis of 4-methyl-2-[(coumarin-7-yl-oxymethyl)]-5-aryl-1,3,4-oxadiazole (6-8)

A (50 ml) round bottomed flask with a magnet bar used as a reaction vessel, the vessel equipped with a condenser and magnetic heater stirrer. (7 ml) 1,4-dioxane used as a solvent and appropriate amount of 4-methylcoumarin-7-yl-oxymethyl arylaldehyde aceto hydrazone, (0.2 gm) potassium carbonate and (0.15 gm) iodine were added to the reaction vessel respectively and refluxed for (6 hours). The progress of the reaction was monitored by thin layer chromatography (TLC) on silica-gel as the stationary phase, and (CHCl - MeOH 2:1) was used as the mobile phase. After cooling the vessel, (20 ml) sodium thiosulfate (5%) was added to the reaction, mixture and extracted with (1:1) methanol-dichlromethane (3x15 ml). The crude extract was dried on anhydrous sodium sulfate and the solvent was evaporated and the solid product recrystallized from ethylacetate. The melting points of products were determined and the structures were characterized by IR and NMR spectroscopy.

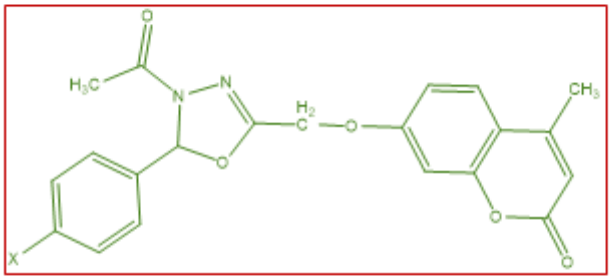
Synthesis of 4-methyl-2-[(coumarin-7-yl-oxymethyl)]-5-(4-methoxyphenyl)-1,3,4-oxadiazole (6) as a typical procedure:

A (50 ml) round bottomed flask with a magnet bar used as a reaction vessel, the vessel equipped with a condenser and magnetic heater stirrer. (7 ml) 1,4-dioxane used as a solvent and (0.18 gm) 4-methylcoumarin-7-yl-oxymethyl p-methoxy benzaldehyde aceto hydrazone, (0.2 gm) potassium carbonate and (0.15 gm) iodine were added to the reaction vessel respectively and refluxed for (6 hours). The progress of the reaction was monitored by thin layer chromatography (TLC) on silica-gel as the stationary phase, and (CHCl - MeOH 2:1) was used as the mobile phase. After cooling the vessel, (20 ml) sodium thiosulfate (5%) was added to the reaction, mixture and extracted with (1:1) methanol-dichlromethane (3x15 ml). The crude extract was dried on anhydrous sodium sulfate and the solvent was evaporated and the solid product recrystallized from ethylacetate (Mp:195-197 ºC).

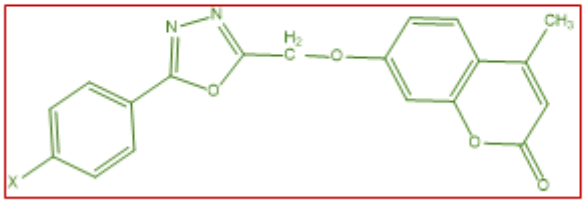
Results And Discussion



(1) X= H (2) X= OCH_3 (3) X= CH_3



(4) X= CH_3 (5) X= OCH_3



(6) X= OCH_3 (7) X= CH_3 (8) X= H

H-1 NMR, (300 MHz, DMSO), δ (ppm) (1):

2.37 (S) 1H, 4.7 – 5.2 (S) 2H, amide tautomeric forms; 6.1 – 6.2 (S) 1H, 6.9 – 7.7 (S) 5H, 7.4 (S) 3H, 8 – 8.3 (S) 1H, imine tautomeric forms; 11.6 (S) 1H.

IR, ῡ (Cm⁻¹) (1):

3300, 3150, 3000 – 3082, 2850 – 2924 – 2971, 1686, 1710, 1415 – 1615, 1353 – 1391, 1057 – 1270, 1057 – 1270, 687 – 882.

H-1 NMR, (300 MHz, DMSO), δ (ppm) (2):

2.37 (S) 1H, 4.77 (S) 3H, 4.7 – 5.2 (S) 2H, amide tautomeric forms; 6.1 (S) 1H, 6.99 (m) 4H, 7.6 (S) 3H, 7.9 – 8.2 (S) 1H, imine tautomeric forms; 11.49 (S) 1H.

IR, ῡ (Cm⁻¹) (2):

3311, 3000 – 3100, 3000 – 2850, 1690 – 1710, 1622 – 1400, 1390 – 1366, 1390 – 1366, 884 – 660.

H-1 NMR, (300 MHz, DMSO), δ (ppm) (3):

2.31 (S) 3H, 2.37 (S) 3H, 4.7 - 5.2 (S) 2H, amide tautomeric forms; 6.19 (d) 1H, 6.9 - 7.7 (m) 7H, overlapped signals; 7.9 - 8.2 (S) 1H, imine tautomeric forms; 11.5 (S) 1H.

IR, ῡ (Cm⁻¹) (3):

3300, 3150, 3000-3090, 2855-2969, 1684, 1710, 1616-1415, 1395.1, 1346.6, 1391-1353, 1269-1055, 882-687.

H-1 NMR, (300 MHz, DMSO), δ (ppm) (4):

2.37 (m) 9H, (Overlaped signals of Acetyl, Tolyl and Coumarin attached methyl groups; 5.3 (S), 4.8 (S) 2H, (CH Tautomers) 6.2 (S) 1H, (No.3-H of Coumarin) 6.9 – 7.17 (m) 7H, (Aromatic) 8.56 (S) 1H, (No.5-H of Oxadiazole ring) 12.8 (S) - broad, N-H (Tautomeric from of Oxadiazole ring).

C-13 NMR, (300 MHz, DMSO), δ (ppm) (4):

18, 21, 25, 68.3, 91.3, 101.5, 111, 112, 113, 126.2, 127.8, 129.5, 133.25, 140.07, 142.51, 153.3, 156.8, 160.06, 161.04, 165.96, 167.81, 170.79

IR, ῡ (Cm⁻¹) (4):

3079, 3065, 2924, 2854.7, 1724, 1712, 1615, 1560.64, 1509.79, 1390.17, 1281.31, 1190, 1153.83, 1073.06, 980.47, 951.08, 845.96, 810.28, 625.33, 585.36

Mass (4): MW= 394, Found: 394.2 (M+).

H-1 NMR, (300 MHz, DMSO), δ (PPM) (5):

2.36 (S) 3H, (Acetyl CH); 2.38 (S) 3H, (Coumarin attached CH); 3.85 (S) 3H, (OCH) 5.29 (S), 4.81 (S) 2H, (CH Tautomers); 6.19 (S) 1H, (No.3-H of Coumarin); 6.94 – 8.5 (m) 7H, (Aromatic); 8.50 (S) 1H, (No.5-H of Oxadiazole ring); 12.85 (S) broad, N-H (Tautomeric form of oxadiazole ring).

C-13 NMR, (300 MHz, DMSO), δ (ppm) (5):

18.1, 25.6, 55.5, 64.8, 68.3, 101.5, 103.3, 111.2, 112.2, 113.5, 114.5, 125.1, 126.3, 127.8, 130.4, 152, 153, 154, 160.7, 162.5, 167.7, 170.7

IR, ῡ (Cm⁻¹) (5):

3080, 3075, 2925, 2850, 1730, 1711.12, 1620.4, 1511.8, 1429, 1387.72, 1300.5, 1260, 1191.8, 1149.6, 1074.5, 1016.91, 951.36, 848.9, 829.41, 630

Mass (5): MW= 410, Found: 410.2 (M+).

H-1 NMR, (300 MHZ, DMSO), δ (ppm) (6):

2.39 (S) 3H, CH ; 3.83 (S) 3H, OCH ; 5.60 (S) 2H, CH ; 6.24 (S) 1H, (No.3-H of Coumarin; 6.97-7.95 (m) 7H, (Aromatic).

C-13 NMR, (300 MHz, DMSO), δ (ppm) (6):

18.1, 60.04, 101.94, 112.4, 114, 115, 126, 128, 153, 154, 160, 161, 162, 164, (some peaks are overlapped).

IR, ῡ (Cm⁻¹) (6):

3086, 3061.2, 2953.9, 2922, 1724, 1615, 1502.9, 1426, 1390.29, 1308.1, 1263.48, 1206.9, 1146.89, 1071.9, 1014.4, 851.26, 834, 740.65, 707.9, 634.42

Mass (6): MW= 367, Found: 367.1(M+).

H-1 NMR, (300 MHZ, DMSO), δ (ppm) (7):

2.34 (S) 3H, (Tolyl CH); 2.38 (S) 3H, (Coumarin attached CH); 5.60 (S) 2H, CH , 6.22 (S) 1H, (No.3-H of Coumarin); 7.07 – 7.89 (m) 7H, (Aromatic).

C-13 NMR, (300 MHz, DMSO), δ (ppm) (7):

18.4, 21.10, 60.04, 101.97, 111.90, 115, 114, 120, 126.70, 126.96, 131, 139, 142, 154, 160, 161, 164, (some peaks are overlapped).

IR, ῡ (Cm⁻¹) (7):

3088, 3061, 2954, 2923, 1714, 1688.25, 1612.76, 1561, 1500.7, 1415, 1390.32, 1272.28, 1196, 1156, 1138, 1068, 1019, 981, 834, 852, 733

Mass (7): MW= 351, Found: 351.2 (M+), 352.2 (M+1)

H-1 NMR, (300 MHz, DMSO), δ (PPM) (8):

2.3 (S) 3H, CH 5.63 (S) 2H, CH 6.24(S), 1H (No.3 H of coumarin) ; 7.09 – 8.02 (m) 8H Aromatic.

C-13 NMR, (300 MHz, DMSO), δ (ppm) (8):

18.17, 60, 66, 102, 111, 112, 114, 122, 126, 129, 132, 153, 154, 160, 162, 164, (some peaks are overlapped).

IR, ῡ (Cm⁻¹) (8):

3080, 3065, 2954.24, 1713.06, 1611.03, 1551.2, 1483.74, 1449.90, 1389.04, 1275.17, 1255, 1196, 1155.99, 1138.45, 1068, 1020, 981.52, 832.39, 775.18, 712.91, 692.02, 632.49

Mass (8): MW= 336, Found: 336.2 (M+), 337.2 (M+1)

Conclusions

In this study, different methods have been tried for the synthesis of novel, 4-methylcoumarin-7-yl-oxymethyl-arylaldehyde acetohydrazone (1–3). By converting these acetohydrazones to the novel 4-methyl-2-(coumarin-7-oxymethyl)-4-acetyl-5-aryl-1,3, 4-oxadiazolines (4,5) and 4-methyl-2-(coumarin-7-oxy methyl)-5-aryl-1,3,4-oxadiazole (6–8) we deduced that the hydrogens of methylene group in oxadiazoline (4,5) taken part to imine-enamin tautoumerism by the adjacent nitrogen of the oxadiazoline ring whereas in the oxadiaxoles (6–8) they didn't show any tautoumerism with the adjacent nitrogen because of the aromatic stability of the oxadiazole ring.

the best method was chosed, and the products was obtained, by extraction and purified by recrystallization method. The pure products was characterized by IR/HNMR/ and CNMR spectroscopy.

Declarations

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Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information files (Supplementary files IR1-IR8, NMR1-NMR8, MS4-MS8). Reasonable requests for additional data and techniques should be e-mail to the corresponding author.

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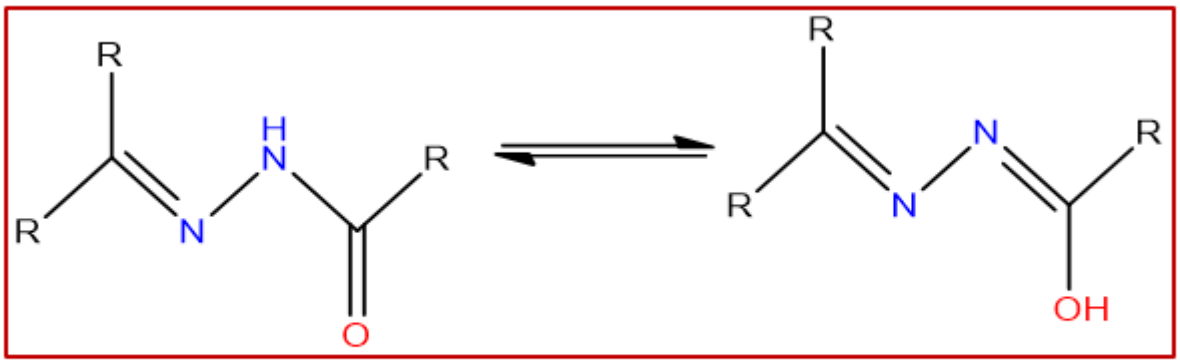
Figures

Figure 1

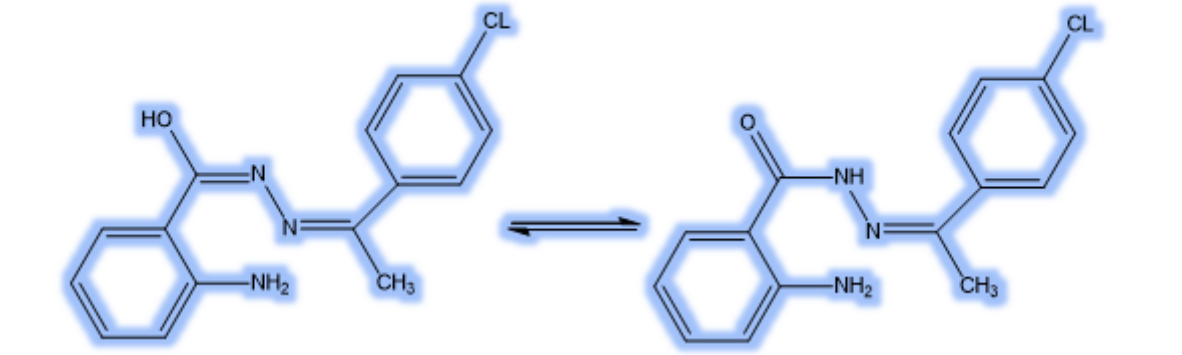
different oxadiazole isomers

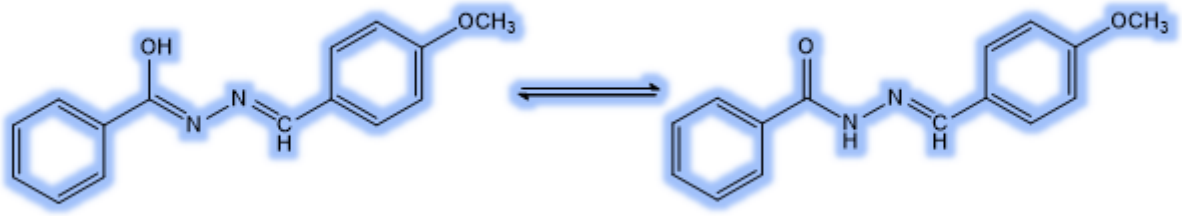


(keto form) (enol form)

Figure 2

Keto-enol froms of hydrazones





Amid Iminol

Figure 3

Amide-iminol tautomerism in the title compound

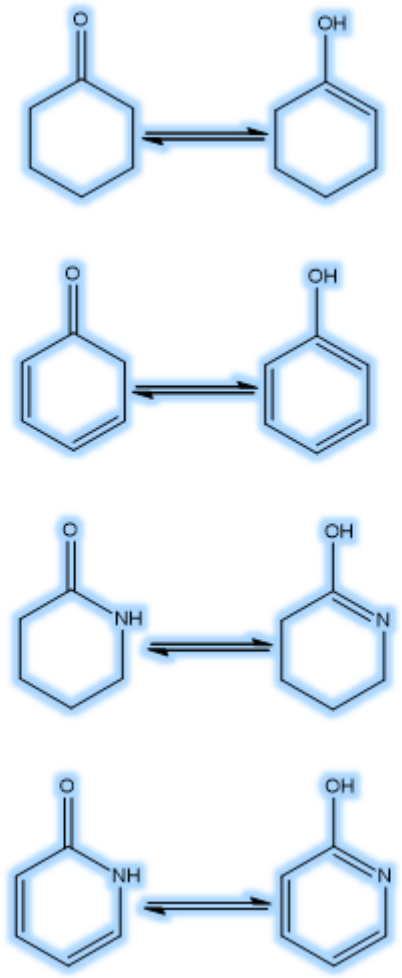


Figure 4

Tautomerism in some alicyclic and aromatic ketones and amides

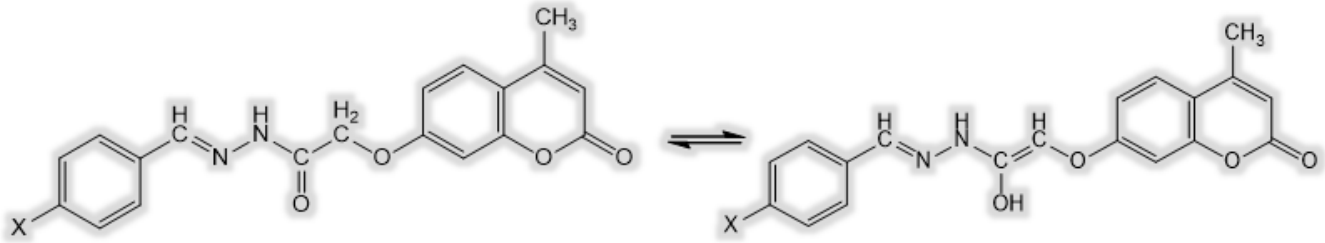


Figure 5

The keto-enol tautomerization

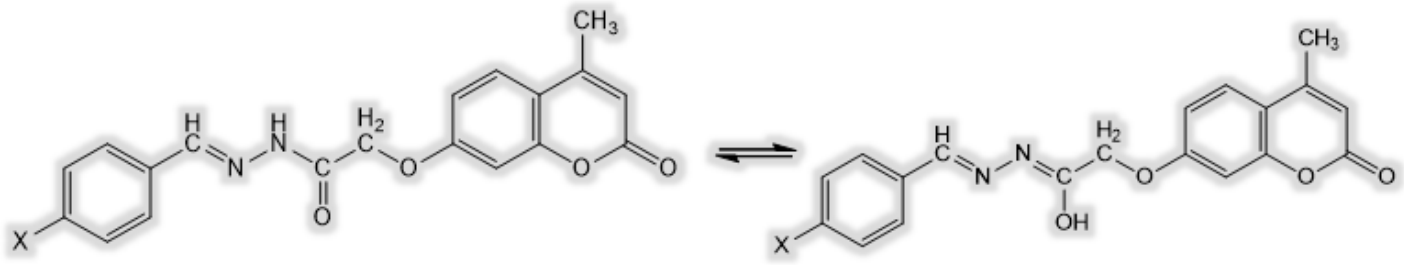
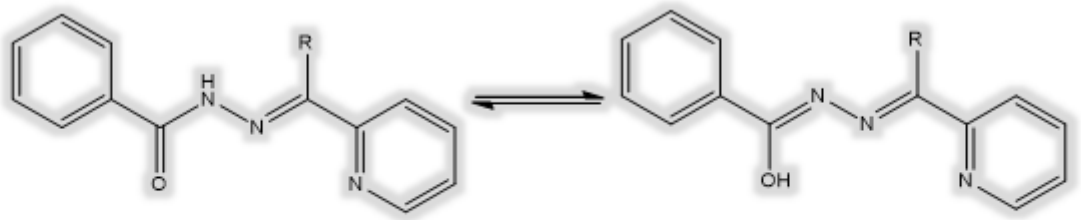


Figure 6

The amide-iminol tautomerization



amide form iminol from

Figure 7

amid-iminol tautomerism of hydrazone molecules

Supplementary Files

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- scheme1.png
- scheme2.png
- scheme3.png
- Graphicalabstract.png