An Entry into Obtaining Pyrazole-, Chromone-, or Oxadiazole-Substituted 1H-Pyrazoles *via* 2,3-Furandiones

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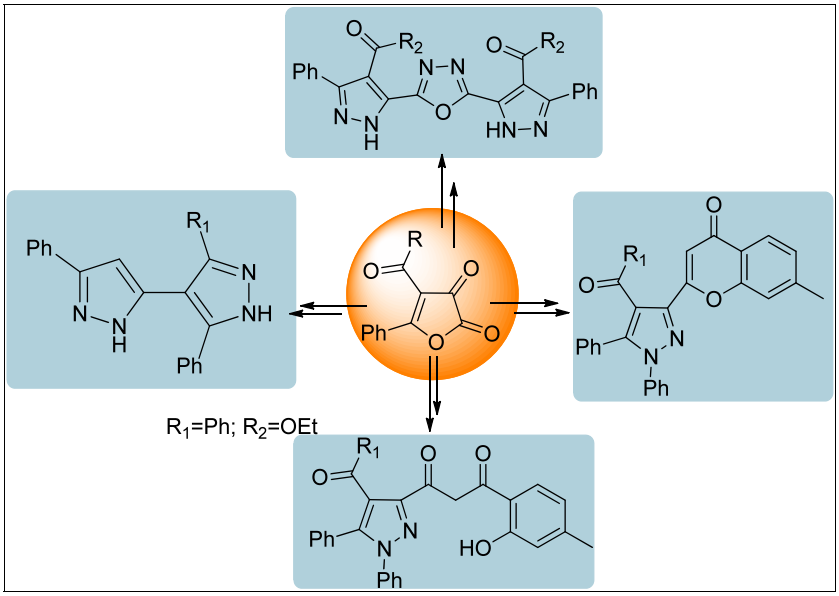

Some new pyrazole-, chromone-, or oxadiazole-substituted 1H-pyrazoles were obtained *via* 2,3-furandiones. Also, we have presented their plausible mechanisms based on rearrangement; one of these rearrangements is Baker–Venkataraman.

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INTRODUCTION

2,3-Furandiones (Fig. 1) are very susceptible to attacking of nucleophiles and are very important synthon materials for lots of heterocyclic compounds [1], one of which is pyrazole derivatives.

Pyrazole derivatives are an important class of double nitrogen-containing heterocyclic compounds. Pyrazoles also occupy a unique position in the design and synthesis of novel biologically active agents that exert remarkable anticancer activities. In fact, pyrazoles have been studied for a long time as an important class of heterocyclic compounds and continue to attract considerable attention due to the broad range of biological activities such as antibacterial–antifungal, tumor–necrosis inhibitor, antimicrobial, hypoglycemic, hypolipidemic, and anti-inflammatory [2–12]. A number of pyrazole-containing compounds such as the blockbuster drugs Viagra [13] (Sildenafil) and Celebrex [14] (Celecoxib) have been successfully commercialized. Moreover, some pyrazole-containing compounds are used as α-Helix mimetic [15] and applied as ligands for the transition-metal-catalyzed cross-coupling reactions [16, 17] (Fig. 2). Furthermore, 1,3,4-tri- or 1,3,4,5-tetra-substituted pyrazoles are pharmaceutically important and less represented in the literature, probably due to their synthetic difficulties. However, the difficulty in generating and handling fully substituted or heterocyclic ring-substituted pyrazoles often limit their synthetic utility. Therefore, a more convenient method that can be used more commonly is highly desirable. Although there are lots of methods both using 2,3-Furandiones and not using 2,3-Furandiones for synthesizing pyrazoles, we envisaged that we might reveal a useful method to construct a different type of substituted pyrazole compounds, containing pyrazole, chromone [18], or oxadiazole [19] in their structure.

RESULTS AND DISCUSSION

So far, we have developed new routes in heterocyclic synthesis [20–22], and herein, we report our experimental results and present the plausible reaction mechanisms involved in the ring-opening/recyclizations. These reactions consist of 1-(pyrazole-3-yl)-3-(2-hydroxy-4-methylphenyl)-1,3-propandione (6), 1H-pyrazole-3-chromone

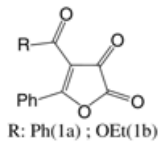


Figure 1. A generic structure of 2,3-furandiones.

(7), 1H-pyrazole-3-(3 or 4-acetyl-phenyl-carboxylate) (10, 11), 1H-pyrazole-3-carboxyhydrazide (13), 2,5-pyrazole-3yl-oxadiazole (14), and bis-1H-pyrazole (15) (Fig. 3). These new heterocyclic compounds were furnished by the reaction between the derivatives of 2,3-furandione (**1a**, **1b**), and miscellaneous reagents. The 2,3-furandiones, **1a** and **1b**, and their derivatives, 1H-pyrazole-3-carboxylic acid chloride 2 and 3,5-dibenzoyl-2,6-diphenyl-4-pyrone 3, were prepared following the procedures given in the literature [23–25].

Compound **2** was reacted with 4-methyl-2-hydroxy-acethophenone in pyridine solution at rt. The ester **12** was formed as an intermediate, and it was underwent Baker–Venkataraman [26] with KOH in one-pot as an instance of domino reaction to obtain 1,3-diketone compound **6**. Moreover, compound **6** was stirred in concentrated sulfuric acid at rt and gave the desired heterocyclic compound **7**. The mechanistic details of rearrangement reaction are displayed in Scheme 1.

After ester compound **12** is formed as an intermediate, the base takes a proton from the ester acyl group to form a carbanion (I). This anion has two kinds of resonance form. The double bond of resonance form, (II) negatively charged on oxygen atom, attacks to the ester carbonyl carbon to take place chromone derivative as an intermediate (III). After moving some pairs of electron, compound **6** forms. In addition, in pyridine at rt., compound **2** was treated not only with 3-hydroxy-acethophenone 8 but also 4-hydroxyacethophenone 9 to give acetyl-phenyl-pyrazole carboxylate 10, 11 (Scheme 2).

Although we have synthesized three acetyl-phenyl-pyrazole carboxylate 10, 11, and 12, only one of them, 12, which has acetyl group at C-2 position of phenyl ring, has undergone Baker–Venkataraman rearrangement. Having acetyl group on ortho-position of phenyl ring is a key feature to synthesize 1,3-diketone compound. Hence, if acyl group is not at ortho-position of phenyl ring, this rearrangement does not take place even if it is related to the Claisen Condensation. We have experienced this outcome when compounds **10** and **11** were refluxed with KOH. Ester compounds **10** and **11** have hydrolyzed when reacted with KOH, and therefore, we could not observe any diketone compound. The finding results have been proved by literature and by our investigations.

The other important point for this rearrangement is that when para- and ortho-positions of phenyl ring are closed with any substituent, the yield of the reaction may increase and side reactions may not have observed. A new study to prove these results is still being conducted.

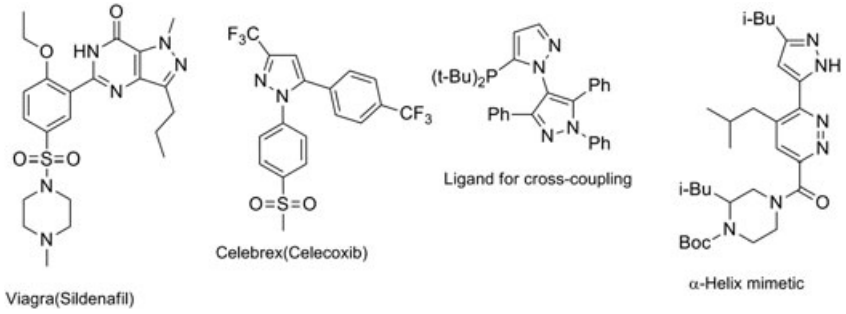


Figure 2. A series of important substituted pyrazoles.

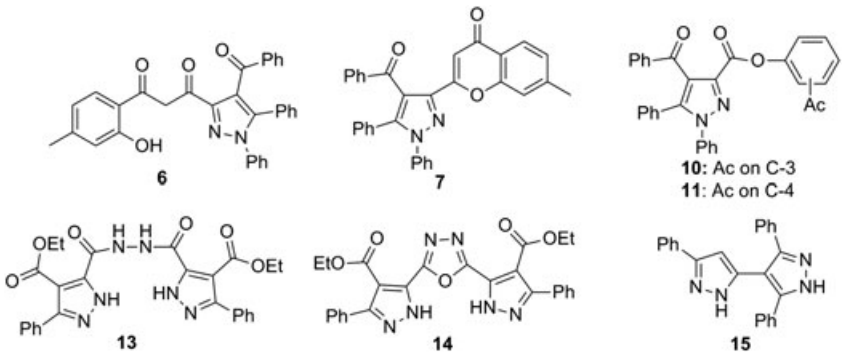
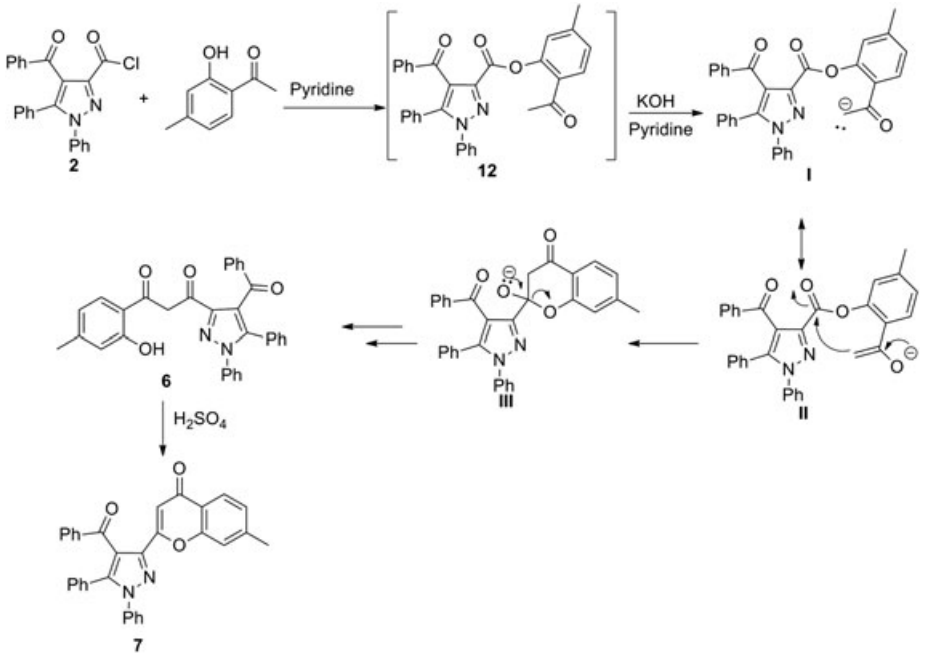
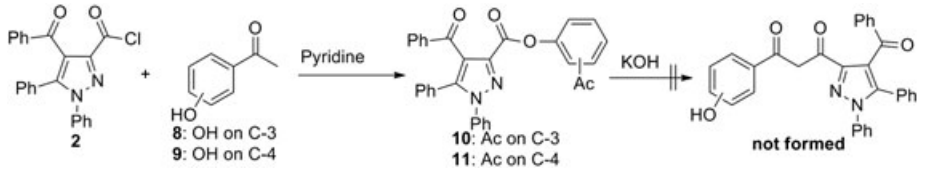


Figure 3. The target molecules.

Scheme 1. The plausible mechanism of compound **6**.



Scheme 2. The obtaining of compounds **10** and **11**.



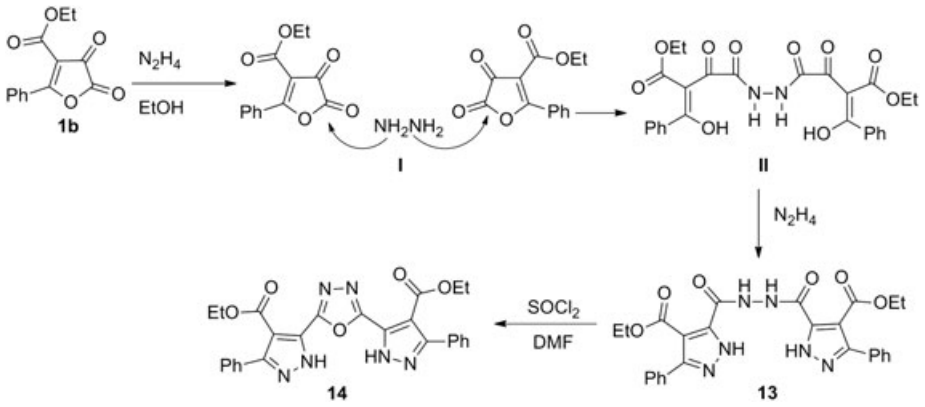
In addition, compound **1b** was reacted with anhydrous hydrazine in acetic acid to give 1H-pyrazole 3-carboxyhydrazide **13**. The plausible mechanism is displayed in Scheme 3.

In this reaction, we used anhydrous hydrazine 2, 5-fold excess molar. Theoretically, 0.5 mol anhydrous hydrazine attacks to C-2 position of two molecules of furan-2,3-dione, 1b (I). This attack leads to the ring opening of furan-2,3-dione (II) and the intermediate undergoes recyclization with the other remaining of anhydrous hydrazine to furnish compound **13**. In the current study, compound **13** was underwent cyclization to obtain compound **14** after removing one of the molecule of H_2O using the mixture of DMF and $SOCl_2$. To obtain the last target compound **15**, compound **3** was reacted with excess molar hydrazine monohydrate. The plausible reaction mechanism of this compound is illustrated in Scheme 4.

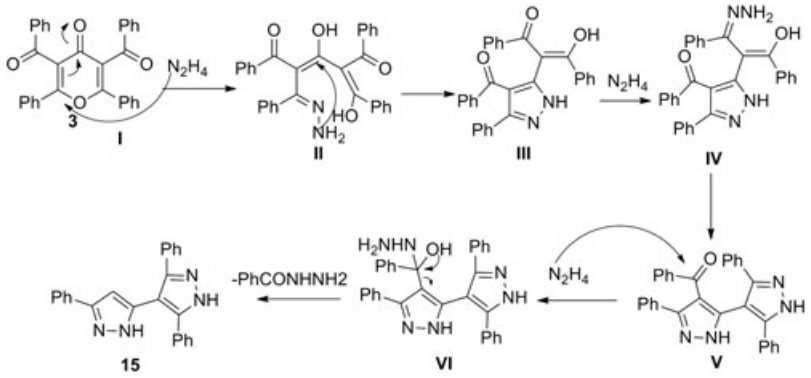
In our study, first, compound **3** was obtained *via* **1a**. A nitrogen atom of hydrazine molecule attacks to the C-2 position of pyran ring 3 (I) and pyran ring undergoes ring opening (II). Attacking of the other nitrogen atom leads to forming pyrazole ring (III). Another hydrazine molecule forms hydrazone molecule with benzoyl group (IV). After forming the hydrazone, a new pyrazole ring takes place (V). For furnishing of compound **15**, last step is that benzoyl group is attacked by hydrazine, and a hydrazide group leaves from structure to give compound **15** (VI), probably owing to the usage of excess hydrazine monohydrate.

Consequently, although there are many reactions that 2,3-furandiones treated with substituted hydrazine, we have developed a reusable method through 2,3-furandiones to construct new heterocyclic compounds with pyrazole scaffold including important rings. Our method gives an access to pyrazole with a variety of heterocyclic rings that are pyrazole, chromone, or oxadiazole. In addition, we have displayed their rearrangement mechanisms, one of which is Baker–Venkataraman rearrangement. We have also synthesized a new style of 1,3-diketone compound including either phenol ring or pyrazole ring. Because of the importance of having phenol ring, we assume that this compound **6** may use plenty of new scientific areas as a starting material in further application. Moreover, all of our synthesized products have two important rings, and we think that these derivatives may have a vital place in pharmaceutical fields.

Scheme 3. The plausible mechanism of obtaining of compound **13**.



Scheme 4. The reasonable mechanism for obtaining **15**.



EXPERIMENTAL

The ^{1}H-NMR and ^{13}C-NMR whose magnetic fields are 300 and 75 MHZ, respectively, spectra were recorded on a ASR 18 YUICH spectrometer using $Si(CH_4)_4$ as the reference. Elemental analyses were performed on Carlo Erba EAGER 200. Melting points were determined on an Electrothermal Gallenkamp apparatus. All reagents and solvents were of reagent grade quality and were obtained from commercial suppliers. All solvents were dried by refluxing with appropriate drying agents and distilled before use. The homogeneity of the products was tested in each step by TLC (SiO_2).

1-(4-Benzoyl-1,5-diphenyl-1H-pyrazol-3-yl)-3-(2-hydroxy-5-ethylphenyl)propane-1,3-dione (6). To a solution of compound **2** (0.386 g, 1 mmol) in pyridine (5 mL), the 2-hydroxy-4-methyl-acethophenone 0.150 g (1 mmol) was added and refluxed for 1 h. KOH (0.56 g, 10 mmol) was added to the reaction pot and refluxed for one more hour. During second period of refluxing, the product was precipitated. After finishing the reaction, 3*M* HCl 20 (mL) was added to the cooled solution for neutralizing. The formed precipitated product in brown was filtered and recrystallized from cyclohexane to give 0.225 g (45%) **6**.

Mp: 156–158°C (white crystal); ^{1}H-NMR (300 MHz, d_6-DMSO): δ = 13.01 (br, s 0.6H of enolform, OH), 7.99–7.01 (m,18H, Ar-H), 6.60 (s, 1H, C═CH), 4.01 (s, 1H, Ar-OH), 3.2 (s, 0.4H of ketoform, CH_2) 2.2 ppm (s, 3H, CH_3); ^{13}C-NMR (75 MHz, d_6-DMSO): δ = 203.2, 193.2, 190.4, 188.1, 146.8, 143.9, 140.4, 138.6, 137.9, 136.8, 136.0, 135.4, 134.9, 134.2, 133.2, 132.4, 131.1, 130.4, 129.3, 128.3, 124.5, 121.1, 115.5, 31.0, 20.41 ppm; IR (KBr): $\bar{\nu}$ = 3400, 3045, 2914, 1675, 1660, 1620, 1595 cm^{-1}; Anal. Calcd. for $C_{32}H_{24}N_2O_4$ (500.17): C, 76.78; H,4.83; N, 5.60%; Found: C, 76.84; H, 4.86; N, 5.69%.

2-(4-Benzoyl-1,5-diphenyl-1H-pyrazol-3-yl)-6-methyl-4H-chromen-4-one (7). To a solution of compound **6** (0.500 g, 1 mmol) was dissolved in concentrated H_2SO_4 (2 mL). The reaction was stirred for 4 h at rt. After TLC monitoring, water (10 mL) was added partly to the mixture on ice-bath. The formed precipitated product was filtered and recrystallized from ethanol to give 0.193 g (40%) **7**.

Mp: 210–212°C. (white crystal); ^{1}H-NMR (300 MHz, d_6-DMSO): δ 7.94–7.18 (m, 18H, Ar-H), 6.77 (s, 1H, C═CH), 2.34 ppm (s, 3H, CH_3); ^{13}C-NMR (75 MHz, d_6-DMSO): δ 191.0, 176.7, 157.5, 156.1, 147.9, 144.5, 138.9, 137.8, 136.4, 134.2, 131.1, 130.4, 129.3, 128.7, 127.1, 126.8, 126.1, 125.4, 122.4, 120.2, 117.1, 107.8, 20.4 ppm; IR (KBr): $\bar{\nu}$ = 2930, 1710, 1680, 1630, 1595 cm^{-1}; Anal. Calcd. for $C_{32}H_{22}N_2O_3$ (482.16): C, 79.65; H, 4.60; N, 5.81%; Found: C, 79.71; H, 4.69, N, 5.85%.

3-Acetylphenyl 4-benzoyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (10). Appropriate amounts of compound **2** (0.386 g, 1 mmol) and 0.136 g of 3-hydroxyacethophenone **8** (1 mmol) were dissolved in pyridine (5 mL) and refluxed for 1 h. The solution was cooled to rt. and neutralized with 3*M* HCl (20 mL). The formed precipitated product was filtered off and recrystallized from ethanol to give 0.330 g (68%) **10**.

Mp: 147–148°C (white crystal); ^{1}H-NMR(300 MHz, $CDCl_3$): δ 7.98–7.25 (m, 19H, Ar-H), 2.53 (s, 3H, CH_3) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 196.8, 190.8, 159.5, 150.2, 148.1, 143.2, 141.5, 138.4, 136.1, 133.4, 132.2, 130.1, 129.1, 128.3, 124.8, 121.3, 26.7 ppm; IR (KBr): $\bar{\nu}$ = 3050, 2930, 1780, 1690, 1645, 1609 cm^{-1}; Anal. Calcd. for $C_{31}H_{22}N_2O_4$ (486.16): C, 76.53; H, 4.56; N, 5.76%; Found: C, 76.66; H, 4.51; N, 5.82%.

4-Acetylphenyl 4-benzoyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (11). Same procedure of 10 with appropriate reactant was used 0.345 g (71%) **11**. Mp: 155–156°C (white crystal); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.92–7.08 (m, 19H, Ar-H) 2.27 ppm (s, 3H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.9, 190.8, 161.3, 158.5, 153.2, 146.1, 141.2, 139.9, 138.1, 136.1, 133.7, 133.1, 130.4, 128.2, 123.5, 120.4, 117.6, 26.5 ppm; IR (KBr): $\bar{\nu}$ = 3010, 2970, 1770, 1690, 1636, 1601 cm^{-1}; Anal. Calcd. for C_{31} $H_{22}N_2O_4$ (486.16): C, 76.53; H, 4.56; N, 5.76%; Found: C, 76.64; H, 4.50; N, 5.80%.

Diethyl 5,5′-hydrazinedicarbonylbis(3-phenyl-1H-pyrazole-4-carboxylate) (13). To a solution of compound **1b** (0.246 g, 1 mmol) in glacial AcOH (10 mL) was added anhydrous hydrazine (2.5 mmol). The reaction was refluxed for 3 h. After completing the reaction, the mixture was cooled to rt. The formed precipitated product was crystallized from methanol to give 0.221 g (43%) **13**.

Mp: 293–295°C.(white crystal); ^{1}H-NMR(300 MHz, $CDCl_3$): δ 13.99 (s, 2H, NH), 10.22 (s, 2H, NH), 7.62–7.43 (m, 10H, Ar-H), 4.21–4.05 (q, 2H, *J* = 7.2 Hz, OCH_2), 1.92–1.76 ppm (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C-NMR(75 MHz, d_6-DMSO): δ 164.3, 160.7, 145.9, 133.0, 129.0, 128.7, 127.8, 111.6, 61.0, 14.18 ppm; IR (KBr): $\bar{\nu}$ = 3150, 2900, 1710, 1620 cm^{-1}; Anal Calcd. for $C_{26}H_{24}N_6O_6$ (516.18): C, 60.46; H, 4.68; N, 16.27%; Found: C, 60.51; 4.70; N, 16.24%.

Diethyl 5,5′-(1,3,4-oxadiazole-2,5-diyl)bis(3-phenyl-1H-pyrazole-4-carboxylate) (14). A solution of compound **13** (0.516 g, 1mmol) in the mixtured solution (0.75 mL DMF plus 0.15 mL $SOCl_2$) was stirred overnight at 0°C. Water (15 mL) was added to the solution, and the formed precipitated product was filtered off and crystallized from toluene to give 0.274 g (55%) **14**.

Mp: 127–129°C. (white crystal); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.73-7.53 (m, 10H, Ar-H), (NH not observed), 4.18–4.11 (q, 2H, OCH_2, *J* = 7.2), 1.11–1.06 ppm (t, 3H, CH_3, *J* = 7.2); ^{13}C-NMR (75 MHz, d_6-DMSO): δ = 162.4, 159.2, 146.5, 137.2, 130.1, 129,5, 128.7, 127.1, 113.4, 61.3, 14.4 ppm; IR (KBr): $\bar{\nu}$ = 3162, 2981, 1722, 1592, 1564 cm^{-1}; Anal. Calcd. for $C_{26}H_{22}N_6O_5$ (498.17): C, 62.64; H, 4.45; N, 16.86%; Found: C, 62.71; H, 4.47; N, 16.89%.

3′,5,5′-Triphenyl-1H,1′H-3,4′-bispyrazole (15). To a solution of compound **3** (0.456 g, 1 mmol) in pyridine (20 mL) was added hydrazine monohydrate (10 mmol). The solution was refluxed for 8 h. After TLC monitoring, the solution was permitted to reach to rt. water (30 mL) was added to this solution and was neutralized with 3*M* HCl (20 mL) solution. The precipitated product was filtered and crystallized from methanol to give 0.181 g (50%) **15**.

Mp: 221–223°C.(white crystal); ^{1}H-NMR(300 MHz, d_6-DMSO): δ = 12.97 (s, 2H, NH), 7.85–7.19 (m, 15H, Ar-H), 6.77 ppm (s, 1H, C═CH); ^{13}C-NMR (75 MHz, d_6-DMSO): δ = 151.3, 145.8, 143.0, 136.3, 134.1, 129.4, 128.5, 127.8, 125.5, 105.5, 104.5 ppm; IR (KBr): $\bar{\nu}$ = 3050, 2930, 1610 cm^{-1}; Anal. Calcd. for $C_{24}H_{18}N_4$ (362.15): C, 79.54; H, 5.01; N, 15.46%; Found: C, 79.65; H, 4.96; N, 15.54%.

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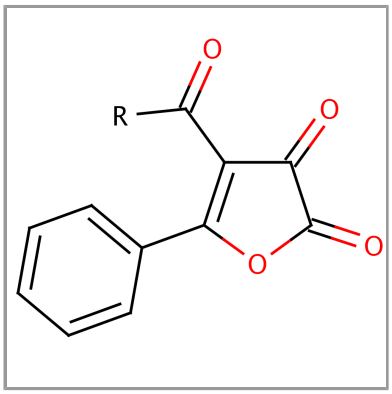

Compound Details Structure Search

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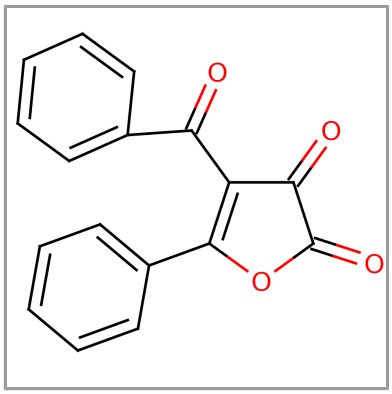

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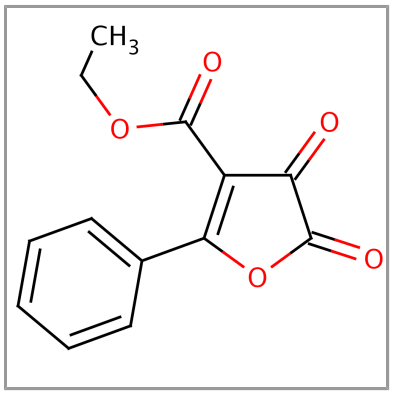

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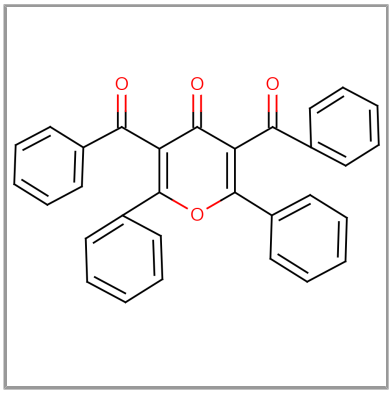
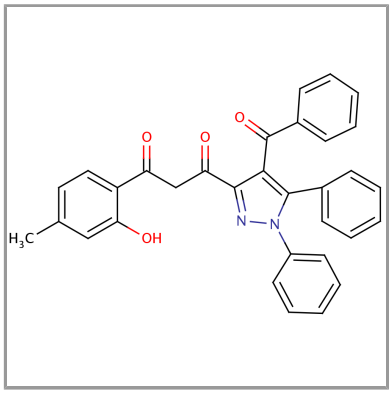


Compound Details Structure Search

6



Compound Details Structure Search

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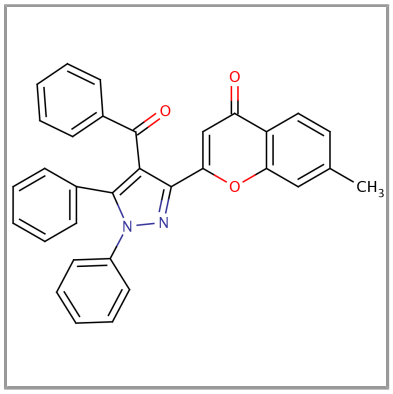

Compound Details Structure Search

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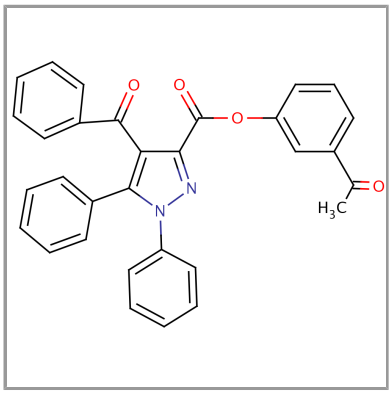

Compound Details Structure Search

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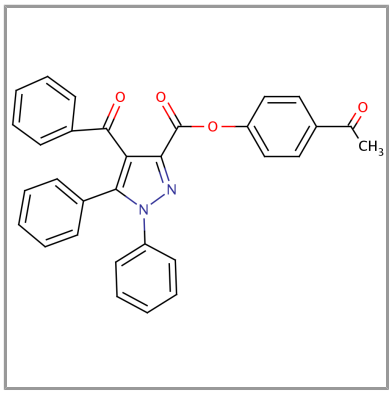

Compound Details Structure Search

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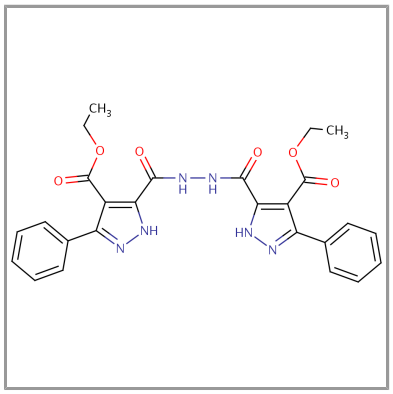

Compound Details Structure Search

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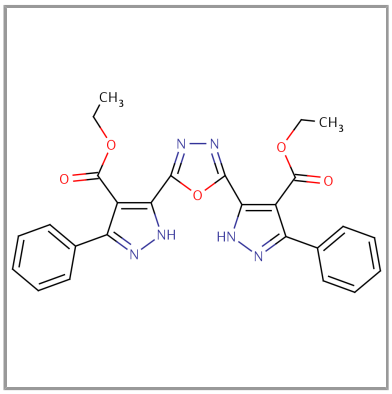

Compound Details Structure Search

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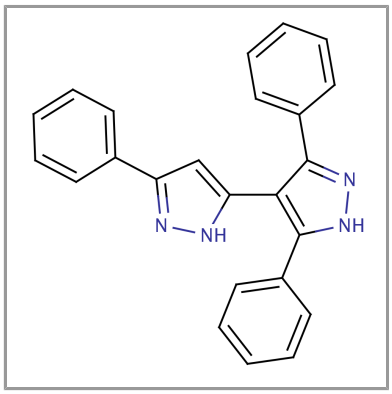

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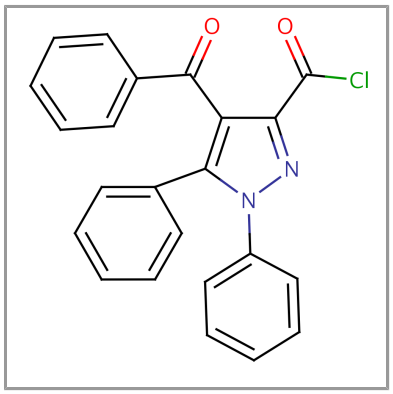

Compound Details Structure Search

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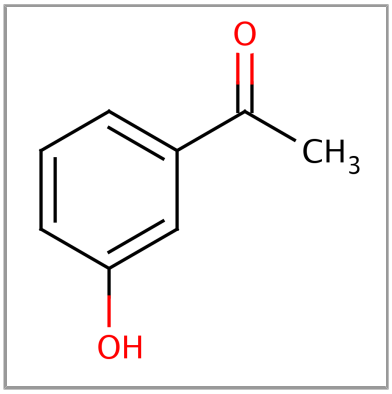

Compound Details Structure Search

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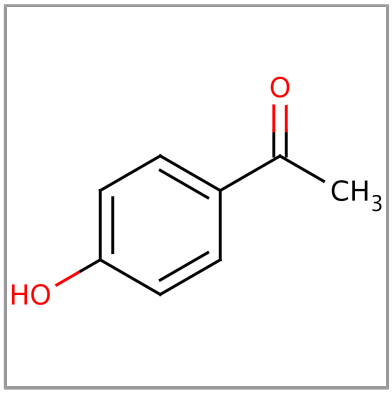

Compound Details Structure Search