

Short Note

# (2Z,5Z)-5-((3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-((4-methoxyphenyl)imino)-3-phenylthiazolidin-4-one

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**Abstract:** The reaction of a 1:1 mixture of 3-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (1) and 2-((4-methoxyphenyl)imino)-3-phenylthiazolidin-4-one (2) in anhydrous ethanol containing piperidine as a catalyst under reflux for 4 h gave (2Z,5Z)-5-((3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-((4-methoxyphenyl)imino)-3-phenylthiazolidin-4-one (3), C<sub>34</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>F, in 82% yield. The structure of the newly synthesized heterocycle was confirmed via X-ray diffraction and spectral analyses.

**Keywords:** benzofuran; thiazolidine; pyrazole; X-ray diffraction; heterocycles; synthesis



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## 1. Introduction

Benzofurans form the core of many substances with medicinal applications. The design and synthesis of new heterocycles containing the benzofuran ring system are important due to the profound physiological and chemotherapeutic properties of the compounds [1]. 2-Substituted benzofurans are prevalent in nature, as exemplified by aianthoidol, which exhibits antiviral, antioxidant, and antifungal activities [2–4]. Heterocycles containing both benzofuran and nitrogen heterocyclic (e.g., pyrazole) moieties have a range of medical applications because they act as antibacterial, anti-inflammatory, antipyretic, anticonvulsant, hypotensive, and antidiabetic agents [5–9].

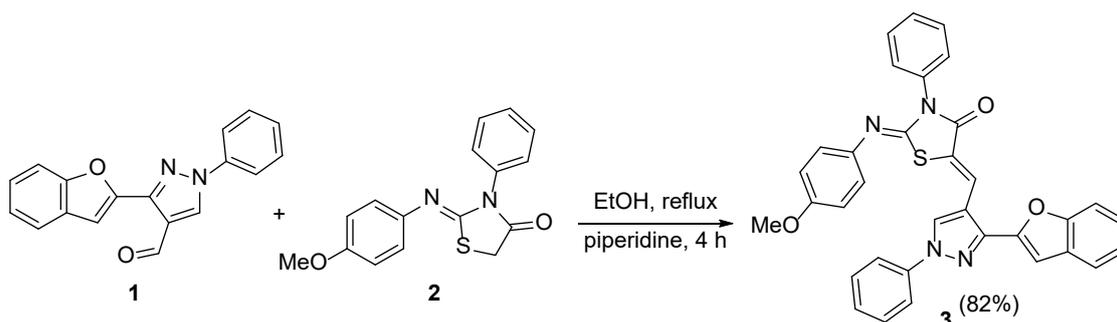
Thiazolidin-4-ones are scaffolds of importance in pharmacological and medicinal chemistry [10,11]. They display a range of biological activities, including acting as antifungal, antibacterial, anti-inflammatory, and antioxidant agents [12–17].

The current study reports the synthesis of a new heterocycle, containing benzofuran, thiazolidin-4-one, and pyrazole moieties, using a simple procedure. This is in continuation of the investigation into the synthesis and structure elucidation of a range of new heterocyclic compounds reported in recent years [18–22].

## 2. Results and Discussion

### 2.1. Synthesis of 3

The title heterocycle was synthesized based on a reported procedure [23]. The condensation of equimolar equivalents of 3-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (1) and 2-((4-methoxyphenyl)imino)-3-phenylthiazolidin-4-one (2) in anhydrous ethanol (EtOH) containing a catalytic amount of piperidine under reflux for 4 h gave (2Z,5Z)-5-((3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-((4-methoxyphenyl)imino)-3-phenylthiazolidin-4-one (3) (Scheme 1). The solid obtained was recrystallized from dimethylformamide (DMF) to give 3 in 82% yield.



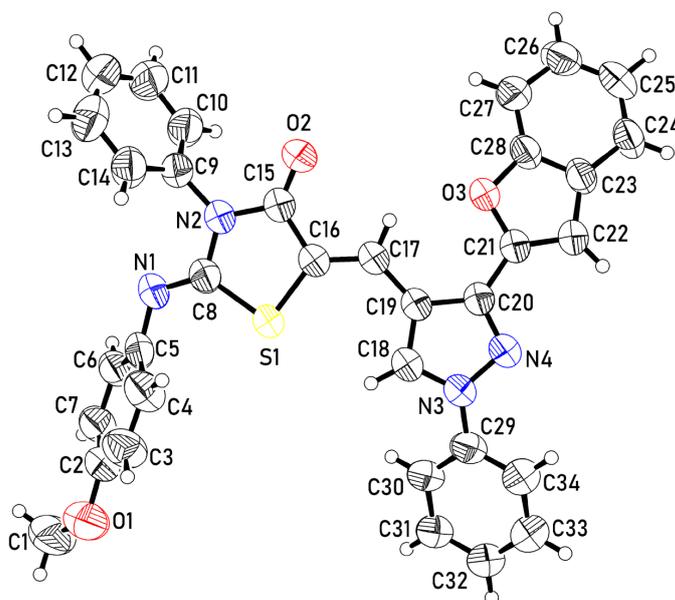
**Scheme 1.** Synthesis of title heterocycle 3.

### 2.2. IR and NMR Spectroscopy of 3

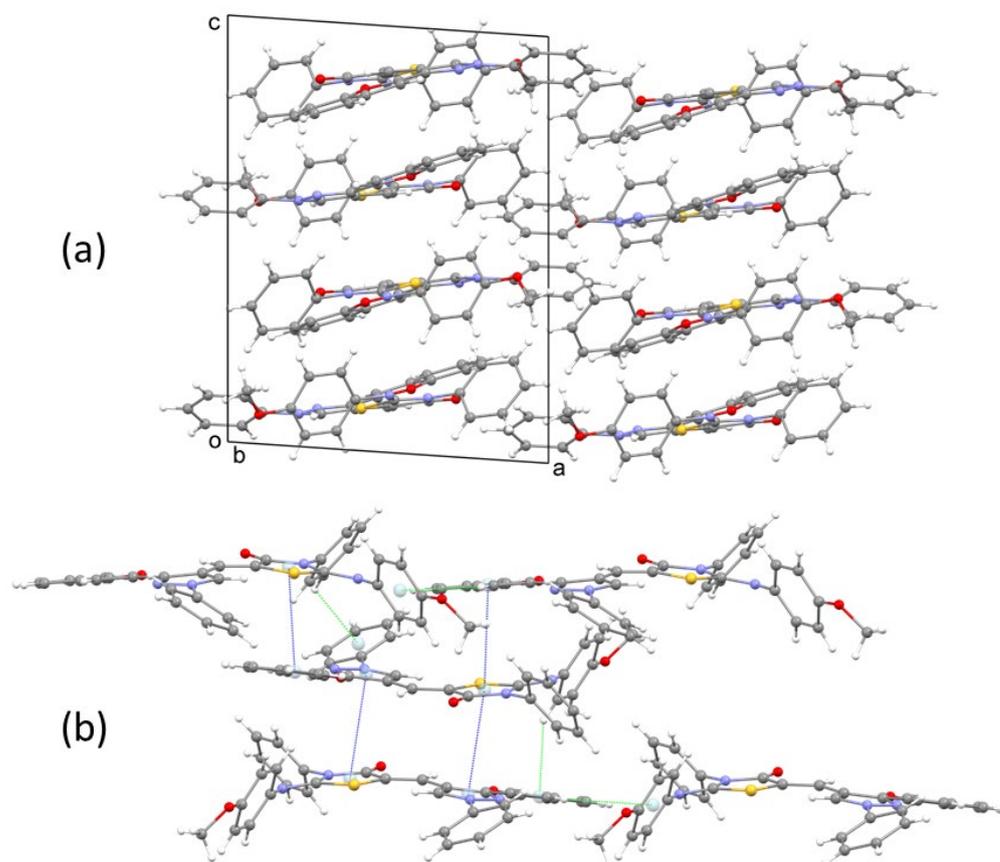
The IR spectrum of 3 showed a strong absorption band at  $1706\text{ cm}^{-1}$  due to the C=O group. The NMR spectra of 3 showed a mixture of two stereoisomers in unequal proportion. The spectra clearly showed the presence of extra signals and peak broadness in some signals in the  $^1\text{H}$ -NMR spectrum. For the major isomer, the  $^1\text{H}$ -NMR spectrum showed a singlet signal that appeared at a high field (3.71 ppm) due to the three protons of the methoxy group, while the pyrazolyl and the CH protons appeared as singlet signals at a very low field (8.59 and 8.06 ppm, respectively). In addition, the spectrum showed all the expected protons of the aromatic rings. The  $^{13}\text{C}$ -NMR spectrum showed that the carbonyl carbon of the thiazolidin-4-one ring and the C4 of the 4-methoxyphenyl group appeared at a very low field (165.8 and 157.1 ppm, respectively), for the major isomer. The carbon of the methoxy group appeared at high field (55.7 ppm). For the IR and NMR spectra, see the Supplementary Materials.

### 2.3. Crystal Structure of 3

For the major isomer, the molecule of the title compound  $\text{C}_{34}\text{H}_{24}\text{N}_4\text{O}_3$ , 3 (Figure 1) comprises methoxybenzene (A, C1–C7, O1), iminomethylthiazolidinone (B, C8, C15–C17, N1, N2, O2, S1), pyrazole (C, C18–C20, N3, N4), benzofuran (D, C21–C28, O3) groups, and two phenyl rings [(E, C9–C14), and (F, C29–C34)]. Groups B, C, and D are approximately co-planar, with twist angles B/C =  $10.0(1)^\circ$  and C/D =  $9.8(1)^\circ$ . The plane through groups B, C, and D is oriented close to the (001) crystallographic plane (Figure 2a).



**Figure 1.** An ortep representation of the asymmetric unit of 3 showing 50% probability atomic displacement parameters.



**Figure 2.** (a): The crystal structure of **3** viewed down the *b* axis. (b): A segment of the crystal structure showing  $\pi$ - $\pi$  interactions (blue dashed lines) and edge-to-face-contacts (green dashed lines). Atom colors are: carbon = grey, Nitrogen = blue, oxygen = red, sulfur = yellow, hydrogen = white.

In the crystal structure, intramolecular C-H ... (O,S) contacts occur between the groups in the planar fragment of the molecule, with geometry [C17 ... O3 = 2.934(4) Å, C17-H17 ... O3 = 124.9°] and [C18 ... S1 = 3.300(3) Å, C18-H18 ... S1 = 121.1°]. Groups **A**, **E** and **F** deviate from the **B**, **C**, and **D** plane as illustrated by the twist angles **A/B** = 61.2(1)°, **B/E** = 58.5(1)° and **C/F** = 33.2(3)°. Similarly to **3**, the [pyrazolyl-methylidene-thiazolidinone] group in the structure of (*Z*)-5-((3-(3,4-dichlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)thiazolidine-2,4-dione is planar, with the phenyl group attached to the pyrazole ring being twisted out of this plane [24].

In the crystal, contacts of  $\pi$ - $\pi$  type between benzofuran, thiazolidine and pyrazolidine ring systems occur, with centroid-to-centroid distances in the range of 3.93–3.95 Å (Figure 2b). Edge-to-face contacts with C-H ... centroid distances in the 2.9–3.4 Å range are also observed.

### 3. Materials and Methods

#### 3.1. General

Chemicals, reagents, and solvents were purchased from Merck and used as received. The IR spectrum of **3** was recorded on a Bruker Vertex 80 ATR-FTIR spectrometer (400–4000 cm<sup>-1</sup>) (Bruker, Billerica, MA, USA). The NMR spectra of **3**, at 500 MHz for the <sup>1</sup>H and 125 MHz for <sup>13</sup>C measurements, were recorded in deuterated dimethyl sulfoxide using a JEOLNMR spectrometer (JEOL, Akishima, Japan). The chemical shift ( $\delta$ ) was reported in ppm and the coupling constant (*J*) was measured in Hz. Compounds **1** [25] and **2** [26] were produced employing reported procedures.

### 3.2. Synthesis of **3**

A mixture of **1** (0.57 g, 2.0 mmol) and **2** (0.60 g, 2.0 mmol) in dry EtOH (15 mL) containing piperidine (0.1 mL) was refluxed for 4 h. The mixture was left to cool to 20 °C and the solid obtained was removed via filtration. The product was washed with EtOH, dried, and recrystallized from DMF to give **3** in 82% yield, m.p. 218–220 °C. IR (KBr): 3109 (CH), 1706 (C=O), 1612 (C=C)  $\text{cm}^{-1}$ . For the NMR spectral data, the signals reported are for the major isomer.  $^1\text{H-NMR}$ : 3.71 (s, 3H, OMe), 6.89–6.93 (m, 4H, Ar), 7.25–7.52 (m, 11H, Ar), 7.58 (d, 8.5 Hz, 1H, Ar), 7.68 (d, 7.7 Hz, 1H, Ar), 7.90 (d, 7.7 Hz, 2H, Ar), 8.06 (s, 1H, CH), 8.59 (s, 1H, pyrazolyl).  $^{13}\text{C-NMR}$ : 55.7, 106.3, 111.8, 114.8, 115.2, 116.7, 120.2, 120.7, 121.4, 122.2, 122.6, 124.1, 125.9, 128.2, 128.4, 128.7, 129.0, 129.5, 130.1, 135.8, 139.2, 141.2, 144.0, 149.2, 149.7, 154.9, 157.1, 165.8. Anal. Calcd. for  $\text{C}_{34}\text{H}_{24}\text{N}_4\text{O}_3\text{S}$  (568.65): C, 71.81; H, 4.25; N, 9.85. Found: C, 71.92; H, 4.33; N, 9.93%.

### 3.3. Crystal Structure Determination

An Agilent SuperNova Dual Atlas diffractometer using mirror monochromated  $\text{CuK}\alpha$  radiation was used to collect single crystal diffraction data. The structure of **3** was solved via direct methods using SHELXS [27] and refined via full-matrix least-squares methods on  $F^2$  with SHELXL [28]. The phenyl group linked to the pyrazole ring is disordered and was refined with two components of occupancy 0.47(2)/0.53(2).  $\text{C}_{34}\text{H}_{24}\text{N}_4\text{O}_3\text{F}$ , FW = 568.63, T = 293(2) K,  $\lambda = 1.54184 \text{ \AA}$ , monoclinic,  $\text{P2}_1/\text{c}$ , a = 12.0555(3)  $\text{ \AA}$ , b = 14.5178(3)  $\text{ \AA}$ , c = 16.1237(5)  $\text{ \AA}$ ,  $\beta = 93.871(3)^\circ$ , V = 2815.52(13)  $\text{ \AA}^3$ , Z = 4, calculated density = 1.341  $\text{g/cm}^3$ , absorption coefficient = 1.370  $\text{mm}^{-1}$ , F(000) = 1184, crystal size = 0.32 × 0.18 × 0.07  $\text{mm}^3$ , reflections collected = 20193, independent reflections = 5534, R(int) = 0.0339, parameters = 411, goodness-of-fit on  $F^2 = 1.101$ , R1 = 0.0734, wR2 = 0.2207 for (I > 2 $\sigma$ (I)), R1 = 0.0848, wR2 = 0.2331 for all data, largest difference peak and hole = 0.576 and  $-0.430 \text{ e. \AA}^{-3}$ . The X-ray crystallographic data for compound **3** have been deposited in the Cambridge Crystallographic Data Center with CCDC reference number 2265175.

## 4. Conclusions

A novel heterocycle containing benzofuran, pyrazole, and thiazolidin-4-one moieties has been synthesized. The procedure used was simple and the yield obtained was high. Nuclear magnetic resonance and X-ray diffraction were used to establish the structure of the newly synthesized heterocycle.

**Supplementary Materials:** The following supporting information are available online:  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra, CIFs, and checkcif reports for the title heterocycle **3**.

**Author Contributions:** Conceptualization: G.A.E.-H. and B.M.K.; methodology: B.F.A.-W., B.M.K. and G.A.E.-H.; X-ray crystal structures: B.M.K.; investigation: B.F.A.-W., H.A.M., B.M.K. and G.A.E.-H.; writing—original draft preparation: B.F.A.-W., H.A.M., B.M.K. and G.A.E.-H.; writing—review and editing: B.F.A.-W., H.A.M., B.M.K. and G.A.E.-H. All authors have read and agreed to the published version of the manuscript.

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**Sample Availability:** A sample of the title compound is available from the authors.

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