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Original Article

Molecular and crystal structure of 1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone]

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ABSTRACT

Background and Aims: The main purpose of this study is to determine the molecular structure and isomers of the new 1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone] (**5**) and to prove the 3Z-conformer of the compound **5**.
Methods: The molecular structure of E- and Z-isomer mixture **5** was confirmed by analytical and spectral data (UV, IR, ^{1}H NMR, HSQC-2D and MS). The Z-conformer of compound **5** was characterized by NMR spectroscopy and X-ray single crystal diffraction analysis method (SC-XRD).
Results: The compound **5** was synthesized by condensation of 1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione (**2**) with 4-(4-methoxyphenyl)thiosemicarbazide (**4**). The compound **5** was obtained in two separate forms, crystal and amorphous. It was proved by NMR data and X-ray diffraction findings that the crystal form is the *Z*-isomer and the amorphous form is a mixture of the *E*- and *Z*-isomers. The *E*- and *Z*-isomer ratios were determined by ^{1}H NMR spectroscopy. The crystal structure and molecular interactions of the *Z*-conformer were determined by X-ray single crystal diffraction analysis.
Conclusion: In the crystal, three intramolecular N–H···N, N–H···O and C–H···S hydrogen bonds provided isomer formation. Also, molecular packing was stabilized by intermolecular C–H···O hydrogen bonds, the π-π stacking interactions and weak CO···π (ring) contacts.

Keywords: Synthesis, molecular structure, isomerism, crystal structure, hydrogen bond, π-π stacking interaction

INTRODUCTION

1*H*-Indole-2,3-dione (isatin) is a natural product and important class of heterocyclic compounds. Isatin and its derivatives are in the spotlight of organic and medicinal chemistry as a consequence of having a wide range of biological and pharmacological activities especially as antiviral (Sadler, 1965), anti-inflammatory (Swathi & Sarangapani, 2014; Matheus, DeAlmeida Violante, Garden, Pinto, & Fernandes, 2007), antituberculosis (Pandeya, Sriram, Yogeeswari, & Ananthan, 2001), antibacterial (Pandeya & Sriram, 1998) and anticancer activity (Ma *et al.*, 2015; Vine, Matesic, Locke, Ranson, & Skropeta, 2009). *N*-Methylisatin-3-thiosemicarbazone

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(methisazone) was one of the Food and Drug Administration (FDA) approved first antiviral compounds used in clinical practice. This drug plays an important role as a prophylactic agent against several viral diseases. Also, *N*-methylisatin-3-(4,4-diethylthiosemicarbazone) inhibits reverse transcriptase (Ronen, Sherman, Bar-Nun, & Teitz, 1987). Isatin 3-thiosemicarbazone derivatives, which have anti-human immunodeficiency virus (HIV) effects, are used against smallpox and vaccinia viruses as prophylaxis (Hall *et al.*, 2009; Bal, Anand, Yogeeswari, & Sriram, 2005). Anticancer activity has been observed significantly for *N*-substituted isatin 3-thiosemicarbazone derivatives in many studies (Pape *et al.*, 2016; Priyanka, Manasa, & Sammaiah, 2014; Hall *et al.*, 2011; Sabet, Mohammadpour, Sadeghi, & Fassihi, 2010]. According to structure-activity relationship in 3-substituted 2-indolinone derivatives, it has been revealed that 3-thiosemicarbazone formation on the isatin moiety, aromatic/hydrophobic properties at the N_4 position of the thiosemicarbazone and introduction of electron-withdrawing groups on position 5 and alkylation on position 1 of isatin are required for anticancer activity (Hall *et al.*, 2011; Pervez, Saira, Iqbal, Yaqub, & Khan, 2011; Pervez *et al.*, 2010; Sabet *et al.*, 2010; Hall *et al.*, 2009; Güzel, Karalı, & Salman, 2008; Matesic *et al.*, 2008; Karalı *et al.*, 2007; Vine, Locke, Ranson, Pyne, & Bremner, 2007a; Vine, Locke, Ranson, Pyne, & Bremner, 2007b; Karalı, 2002). Additional studies infer that N_4-phenyl substituted thiosemicarbazone derivatives have significantly higher activity than N_4-alkyl, N_4-cycloalkyl and N_4-nonsubstitue thiosemicarbazone derivatives (Hall *et al.*, 2011; Hall *et al.*, 2009). The type and position of varied substituents on the phenyl ring linked to the N_4 position of the thiosemicarbazone part is much more important for activity (Pape *et al.*, 2016; Pervez, Chohan, Ramzan, Nasim, & Khan, 2009; Pervez *et al.*, 2008; Karalı *et al.*, 2007).

In studies in which isomer structures of isatin 3-thiosemicarbazone derivatives are examined, it has been noted that an intramolecular hydrogen bond may be formed between thioamide N_2 hydrogen and lactam oxygen of the indole ring, as well as between thioamide N_4 hydrogen and N_1 (Haribabu *et al.*, 2016; Muralisankar, Sujith, Bhuvanesh, & Sreekanth, 2016; Jakusová *et al.*, 2013; Kaynak, Özbey, & Karalı, 2013). There may be mention of the existence of intermolecular hydrogen bonds between the N—H···O, N—H···S and N—H···N (Haribabu *et al.*, 2016; Jakusová *et al.*, 2013; Kaynak *et al.*, 2013; Bain *et al.*, 1997; Sadler, 1961). The proton acceptor OCF_3, F, SO_3Na and NO_2 groups in the indole ring can form hydrogen bonds with the proton donor indole and thioamide N-H groups (Sakai *et al.*, 1998; Howard, Hoy, O'Hagan, & Smith, 1996; O'Sullivan, & Sadler, 1956). In a study examining the crystal structure and molecular interactions of 5-trifluoromethoxy-1*H*-indole-2,3-dione 3-(4-ethylthiosemicarbazone) derivative, the intramolecular and intermolecular interactions of proton donor groups are illuminated by dimer structure of the compound (Figure 1) (Kaynak *et al.*, 2013).

Anti (*E*) and sin (*Z*) isomers of 1*H*-indole-2,3-dione 3-thiosemicarbazone derivatives caused by $C=N_1$ bond were investigated in the aqueous solution. Theoretical and experimental studies have shown that *Z*-isomers are preferred and found at a higher rate compared to the *E*-isomers. It was determined that only the *Z*-configuration allowed the formation of the intramolecular hydrogen bond between the N_2-H of the thioamide group and the lactam oxygen of the indole ring. In these studies, the presence of two isomers formed by rotation around the thioamide N_2-C bond of isatin-3-thiosemicarbazones have been reported. Geometric isomers have been reported to occur if free rotation around the thioamide N_2-C bond is prevented (Figure 2) (DeSilva & Albu, 2007; Bain *et al.*, 1997).

In this study, the new (1-methyl-5-(trifluoromethoxy)-1*H*-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone] (**5**) was synthesized. The compound **5** was obtained in two separate forms, crystal (*3Z*-isomer) and amorphous (mixture of 3*E*- and 3*Z*-isomers). The structures of the 3*E* and 3*Z* isomers were determined by NMR data and X-ray diffraction findings.

MATERIALS AND METHODS

Synthesis

All the chemicals and reagents were purchased from Merck-Schuchardt and Sigma-Aldrich. The processes of the reactions

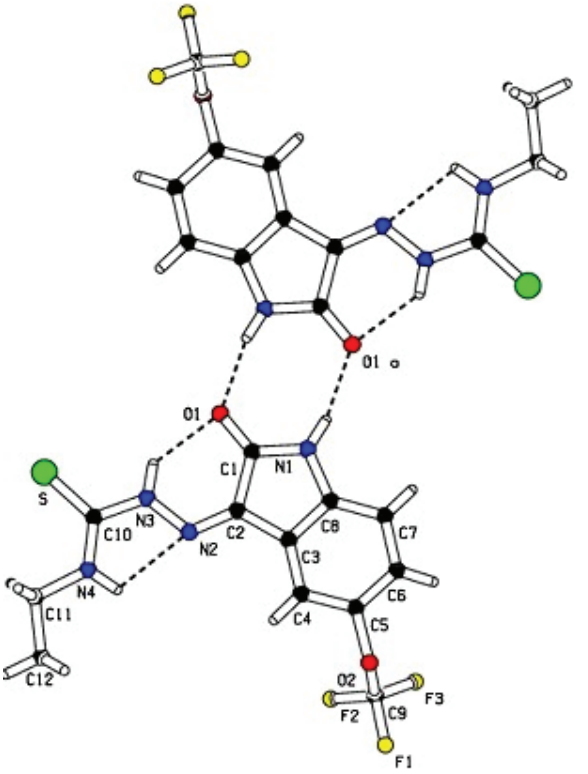


Figure 1. Crystal structure of 5-trifluoromethoxy-1*H*-indole-2,3-dione 3-(4-ethylthiosemicarbazone) (Kaynak *et al.*, 2013).

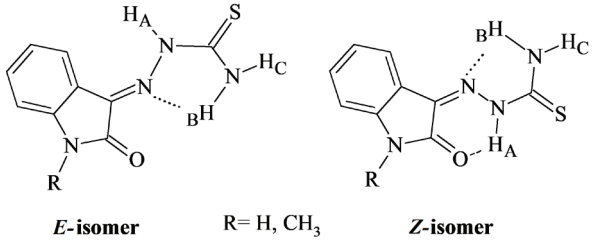


Figure 2. Possible *E*- and *Z*-conformers of 1*H*-indole-2,3-dione 3-thiosemicarbazone derivatives.

were monitored using thin layer chromatography (TLC). Silica gel 60 HF254 was used as the adsorbent and the solvent system was composed of ethylacetate:cyclohexane (50:50, v/v) for TLC. A UV lamp (Mineralight Lamp UVGL-58) was used at 254 nm for monitoring stains on the TLC plates after TLC was done.

The melting points of the compounds were estimated with a Buchi B-540 melting point apparatus in open capillary and was uncorrected. The UV spectra were obtained on Shimadzu UV-1800 spectrophotometer. The infrared (IR) spectra were recorded on a KBr disc, using a Shimadzu IR Affinity-1 FTIR spectrophotometer. ^{1}H Nuclear Magnetic Resonance (NMR) and Heteronuclear Single Quantum Coherence (HSQC-2D) spectra were procured on Varian UNITY INOVA 500 MHz, Varian Mercury (Agilent) 400 MHz and Oxford Pulsar 60 MHz NMR spectrophotometers dissolved in DMSO-d_6. The mass spectroscopy (MS) analysis was obtained on a Waters 2695 Alliance Micromass ZQ LC/MS spectrophotometer. The elemental analysis was performed on a Leco CHNS-932 elemental analyzer.

The synthesis of 1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione (2)

Potassium carbonate (7 mmol) was added to a solution of 5-trifluoromethoxy-1*H*-indole-2,3-dione (**1**) (5 mmol) in dimethylformamide (5 mL), and stirred for 1 hour at room temperature. After the addition of iodomethane (15 mmol) and potassium iodide (1 mmol), the reaction mixture was refluxed for 3 h at 50-60°C. It was firstly evaporated to dryness under reduced pressure to obtain a crude product, which was poured into iced water and then filtered (Güzel *et al.*, 2008).

Red powder (yield 90%), M.p.: 110-112 °C. UV λ (250 mL EtOH+0.5 mL DMSO)$_{max}$ nm (ε): 246.5 (42338), 252.3 (38906), 268.7 (13115), 295.0 (5270). IR (KBr) ν_{max} (cm^{-1}): 3064, 3043 (aromatic C-H), 2951, 2889 (aliphatic C-H), 1737, 1716, 1687 (C=O), 1616, 1489, 1473 (C=C). ^{1}H NMR (60 MHz) (DMSO-d_6/TMS) d (ppm): 3.31 (3H, s, indole N-CH_3), 7.34-7.61 (3H, m, indole $C_{4,6,7}$-H).

The synthesis of 4-(4-methoxyphenyl)thiosemicarbazide (4)

A suspension of 4-(methoxy)phenylisothiocyanate (**3**) (5 mmol) in ethanol (10 mL) was added dropwise with vigorous stirring to a solution of hydrazine hydrate (5 mmol) in ethanol (10 mL), and cooled in an ice bath. The mixture was allowed to stand overnight. The crystals formed were filtered off and recrystallized from ethanol (Tisler, 1956).

White powder (yield 70%), M.p.: 154 °C. UV λ (250 mL EtOH+0.5 mL DMSO)$_{max}$ nm (ε): 242.5 (14084), 268.2 (9566). IR (KBr) ν_{max} (cm^{-1}): 3319, 3273, 3163 (NH), 3045 (aromatic C-H), 2958, 2837 (aliphatic C-H), 1635, 1610, 1527, 1508 (C=C). ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.73 (3H, s, OCH_3), 4.68 (2H, s, NH_2), 6.85 (2H, d, *J*: 9.0 Hz, phenyl $C_{3,5}$-H), 7.44 (2H, d, *J*: 9.0 Hz, phenyl $C_{2,6}$-H), 8.89 (1H, s, N_4-H), 9.42 (1H, s, N_2-H). ^{13}C NMR (75 MHz) (DMSO-d_6/TMS) d (ppm): 56.40 (OCH_3), 114.43 (phenyl $C_{3,5}$), 126.87 (phenyl $C_{2,6}$), 133.42 (phenyl C_1), 157.38 (phenyl C_4), 181.00 (C=S) (Huang *et al.*, 2010).

The synthesis of 1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone] (5)

A solution of 4-(4-methoxyphenyl)thiosemicarbazide (**4**) (2.5 mmol) in ethanol (10 mL) was added to a solution of 1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione (**2**) (2.5 mmol) in ethanol (20 mL). Then 5-10 drops from trace amounts of concentrated sulfuric acid in ethanol (100 mL) were added to catalyze the reaction. The precipitated product was filtered after cooling and was washed with ethanol, and finally the isomer mixture of the compound **5** was obtained. Yellow-orange powder (yield 93%), M.p.: 185 °C (Karalı *et al.*, 2020)

The *Z*-isomer was obtained by crystallizing the isomer mixture from ethanol.

The amorphous form (mixture of 3*E* and 3*Z* isomers) of 1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone] (5): UV λ (250 mL EtOH+0.5 mL DMSO)$_{max}$ nm (ε): 229.5 (26779), 259.0 (18800), 365.0 (30641). IR (KBr) ν_{max} (cm^{-1}): 3307, 3219 (NH), 1693 (C=O), 1620, 1597, 1548, 1510 (C=N, C=C), 1163 (C=S). MS (ESI (+)) m/z (%): 425 ([M+H]$^+$; 100); 260 (18); 302 (1). Anal. calcd. for $C_{18}H_{15}F_3N_4O_3S$: C, 50.94; H, 3.56; N, 13.20; S, 7.56(%) Found: C, 51.10; H, 3.94; N, 13.65; S, 9.25(%).

3*Z*-isomer, ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.24 (3H, s, indole N-CH_3), 3.77 (3H, s, OCH_3), 6.98 (2H, d, *J*: 9.0 Hz, phenyl $C_{3,5}$-H), 7.25 (1H, d, *J*: 8.6 Hz, indole C_7-H), 7.44 (2H, d, *J*: 9.0 Hz, phenyl $C_{2,6}$-H), 7.44-7.47 (1H, m, indole C_6-H), 7.81 (1H, s, indole C_4-H), 10.81 (1H, s, N_4-H), 12.53 (1H, s, N_2-H) (The *E*/*Z* isomer ratio is 1:2) (Figure 3). ^{13}C NMR (HSQC-2D) (125 MHz) (DMSO-d_6/TMS) δ (ppm): 26.40 (indole N-CH_3), 55.76 (OCH_3), 111.50 (indole C_7), 114.14 (phenyl $C_{3,5}$), 114.60 (indole C_4), 120.68 (q, *J*: 256.2 Hz, OCF_3), 121.26 (indole C_{3a}), 124.42 (indole C_6), 127.86 (phenyl $C_{2,6}$), 130.54 (indole C_3), 131.53 (phenyl C_1), 142.95 (indole C_{7a}), 144.46 (d, *J*: 1.9 Hz, indole C_5), 158.03 (phenyl C_4), 161.37 (indole C_2), 177.05 (C=S) (Figures 4-6).

3*E*-isomer, ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.24 (3H, s, indole N-CH_3), 3.73 (3H, s, OCH_3), 6.88 (2H, d, *J*: 9.0 Hz, phenyl $C_{3,5}$-H), 7.25 (1H, d, *J*: 8.6 Hz, indole C_7-H), 7.35 (2H, d, *J*: 8.6 Hz, phenyl $C_{2,6}$-H), 7.44-7.47 (1H, m, indole C_6-H), 7.81 (1H, s, indole C_4-H), 9.52 (1H, s, N_4-H), 9.69 (1H, s, N_2-H) (The *E*/*Z* isomer ratio is 1:2) (Figure 3). ^{13}C NMR (HSQC-2D) (125 MHz) (DM-

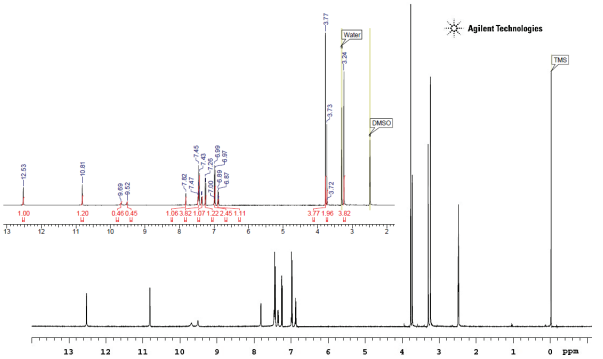


Figure 3. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of *E*- and *Z*-isomer mixture of the compound **5**.

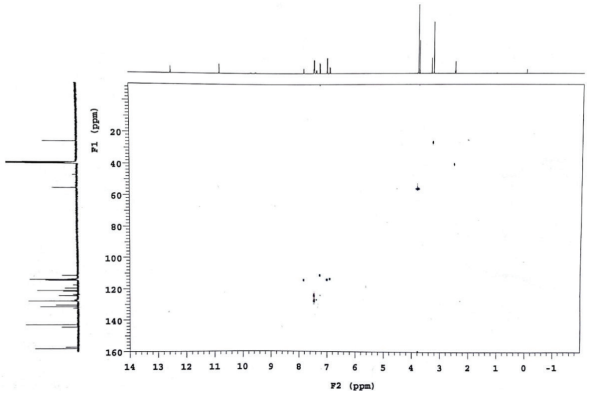


Figure 4. HSQC-2D NMR (500 MHz, DMSO-d_6) spectra of *E*- and *Z*-isomer mixture of the compound **5**.

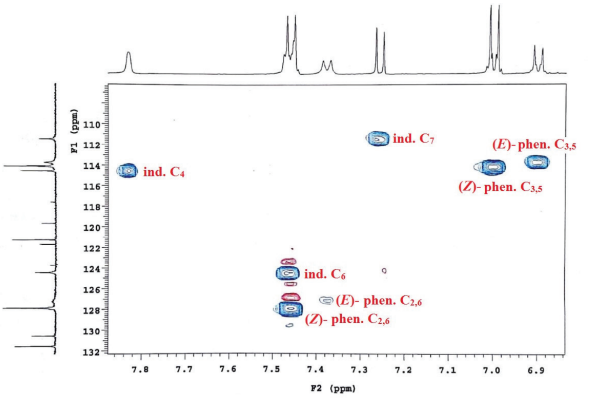


Figure 5. HSQC-2D NMR spectra of *E*- and *Z*-isomer mixture of the compound **5** (106-132 ppm).

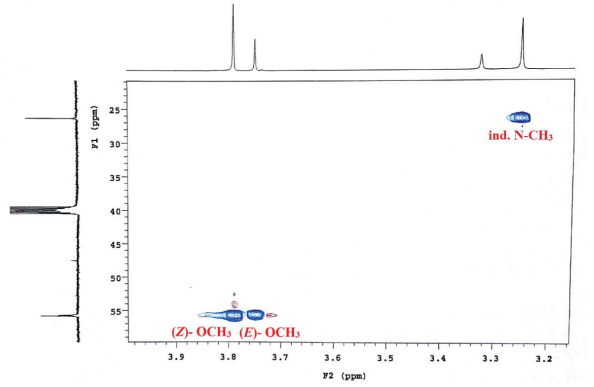


Figure 6. HSQC-2D NMR spectra of *E*- and *Z*-isomer mixture of the compound **5** (20-60 ppm).

SO-d_6/TMS) δ (ppm): 26.40 (indole N-CH_3), 55.66 (OCH_3), 111.50 (indole C_7), 113.78 (phenyl $C_{3,5}$), 114.60 (indole C_4), 120.68 (q, *J*: 256.2 Hz, OCF_3), 121.26 (indole C_{3a}), 124.42 (indole C_6), 127.21 (phenyl $C_{2,6}$), 130.54 (indole C_3), 131.53 (phenyl C_1), 142.95 (indole C_{7a}), 144.46 (d, *J*: 1.9 Hz, indole C_5), 157.15 (phenyl C_4), 161.37 (indole C_2), 177.05 (C=S) (Figures 4-6).

(3*Z*)-1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione 3-[4-(4-methoxyphenyl) thiosemicarbazone] (5): UV λ (250 mL EtOH+0.5 mL DMSO)$_{max}$ nm (ε): 228.0 (63192), 258.5 (13580), 365.0 (20837). IR (KBr) ν_{max} (cm^{-1}): 3307, 3223 (NH), 1693 (C=O), 1620, 1597, 1548, 1510 (C=N, C=C), 1161 (C=S). ^{1}H NMR (400 MHz) (DMSO-d_6/TMS) d (ppm): 3.24 (3H, s, indole N-CH_3), 3.77 (3H, s, OCH_3), 6.98 (2H, d, *J*: 9.1 Hz, phenyl $C_{3,5}$-H), 7.24 (1H, d, *J*: 8.6 Hz, indole C_7-H), 7.44 (2H, d, *J*: 9.1 Hz, phenyl $C_{2,6}$-H), 7,44-7,47 (1H, m, indole C_6-H), 7.81 (1H, s, indole C_4-H), 10.82 (1H, s, N_4-H), 12.52 (1H, s, N_2-H) (Figure 7).

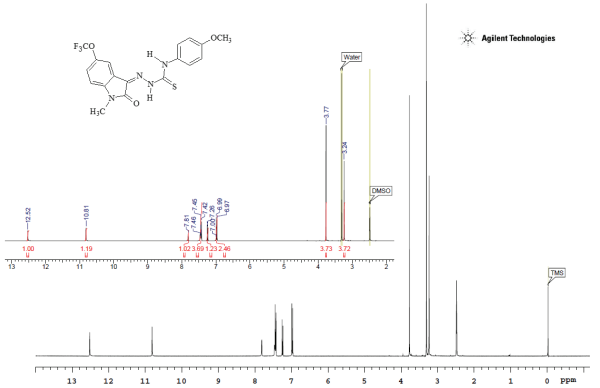


Figure 7. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of *Z*-isomer of the compound **5**.

X-ray single crystal diffraction analysis (SC-XRD)

Crystal data, data collection and structure refinement details for 3*Z*-izomer of the compound **5** are summarized in Table 1.

RESULTS AND DISCUSSION

In this study, 1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione (**2**) was reacted by 4-(4-methoxyphenyl)thiosemicarbazide (**4**) in ethanol to give 1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone] (**5**) (Scheme 1). The compound **5** was obtained in two separate forms, crystal and amorphous. It was proved by spectral and X-ray findings that the crystal form is the *Z*-isomer and the amorphous form are a mixture of the *E*- and *Z*-isomers. The mixture containing structures of *E*- and *Z*-isomers of the compound **5** were verified by elemental analysis and spectral data (UV, IR, ^{1}H NMR, HSQC-2D and MS). The 3*Z*-conformer of the compound **5** was further characterized by X-ray single crystal diffraction analysis method.

The ^{1}H NMR spectra of 3*Z*- and 3*E*-isomers of the compound **5** displayed OCH_3 (C18) protons at δ 3.77 and 3.73 ppm as singlets, respectively. The N_2 (N3) and N_4 (N4) protons of the thiosemicarbazone moiety showed an enormous change in the chemical shift of +2.83 and +1.30 ppm as a result of the intramolecular N3—H···O1 and N4—H···N2 hydrogen bonds in the 3*Z*-isomer. The phenyl protons of the thiosemicarbazone moiety of 3*Z*-isomer showed a change in the chemical shift of approximately +0.10 ppm. The spectra of 3*Z*- and 3*E*- isomers of the compound **5** showed the proton chemical shifts of a newer indole ring and N-CH_3 (C9). The carbon chemical shift values of 3*Z*- and 3*E*- isomers were established by HSQC-2D data of the compound **5**. The ortho (C13 and C17), meta (C14 and C16) and para (C15) carbons of phenyl were determined as changes in the chemical shift values of +0.65, +0.46 and +0.88 ppm, respectively. The change in the chemical shift value for OCH_3 (C18) was +0.10 ppm in 3*Z*-isomer. The chemical shifts of the other carbons were constant for the 3*Z*- and 3*E*- isomers.

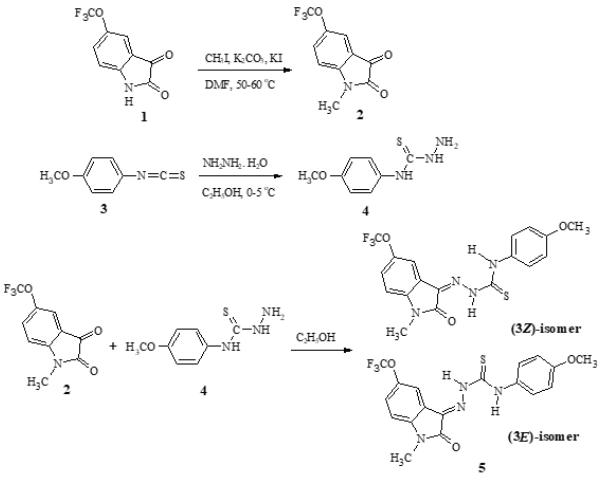
Table 1. Experimental details of the 3Z-conformer of the compound 5.

Chemical formula	$C_{18}H_{15}F_3N_4O_3S$
M_r	424.40
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	296
***a*, *b*, *c* (Å)**	13.266 (2), 7.8433 (19), 18.667 (4)
β (°)	102.524 (7)
***V* (Å³)**	1896.1 (7)
Z	4
Radiation type	Mo *K*α
μ (mm⁻¹)	0.23
Crystal size (mm)	0.09 × 0.07 × 0.06
Diffractometer	Bruker *APEX*-II CCD diffractometer
Absorption correction	Multi-scan (*SADABS*; Bruker, 2007)
T_{min}, T_{max}	0.536, 0.746
No. Of measured, independent and observed [$I > 2\sigma(I)$] reflections	54669, 4595, 3268
R_{int}	0.067
$(\sin\theta/\lambda)_{max}$ (Å⁻¹)	0.670
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.075, 0.154, 1.18
No. of reflections	4595
No. of parameters	271
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å⁻³)	0.30, −0.26

Computer programs: APEX2 and SAINT (Bruker, APEX2, SAINT and SADABS, Bruker AXS Inc., Madison, Wisconsin, USA), SHELXS97 (Sheldrick, 2008), SHELXL2014 (Sheldrick, 2015), WinGX (Farrugia, 2012) and PLATON (Spek, 2009).

The 3*E*/3*Z* isomer ratio obtained from integral values was assigned as 1:2 in DMSO-d_6 at room temperature (Figure 3).

NMR studies were performed in order to better understand the molecular properties of the 1*H*-indole-2,3-dion 3-thiosemicarbazone derivatives. The calculated and experimental signals of the thiosemicarbazone residue NH protons were compared. It was determined that the thioamide N_2 (H_A) proton made the most prominent hydrogen bond with the lactam oxygen, and it was recorded that it was monitored over a wide chemical shift range (d 12.4-14.2 ppm) due to this strong hydrogen bond. The thioamide NH signals of *Z*-isomers were observed at a lower area of about 1.00 ppm than the signals of the *E*-isomers. It has been determined that indole C_2, indole C_3 and C=S carbon resonances of *Z*-isomers give signals at a lower area than the *E*-isomers' resonances. The indole C_2 and C=S carbon resonances of (*Z*)-1*H*-indole-2,3-dion 3-(4,4'-dimethyl)thiosemicarbazone were observed at d 162.86 and 182.12 ppm, respectively. Whereas, the indole C_2 and C=S carbon signals of the *E*-isomer were determined at d 162.66 and 178.99 ppm, respectively (DeSilva & Albu, 2007). N_2 and N_4 proton signals of 1*H*-indole-2,3-dione 3-thiosemicarbazone derivatives, which have been proven to be in the form of *Z*-isomers, showed at d 12.25-12.81 and 9.30-11.09 ppm, respectively (Haribabu *et al.*, 2016; Zhang *et al.*, 2015; Ali *et al.*, 2014; Kaynak *et al.*, 2013). In the study where the crystal structure and spectral findings of (*Z*)-5-fluoro-1-methyl-1*H*-indole-2,3-dione 3-[4-(methylthio) phenyl]thiosemicarbazone were determined, NCH_3, phenyl $C_{3,5}$, phenyl $C_{2,6}$, thiosemicarbazone N_4 and N_2 protons were recorded at d 3.21, 7.30, 7.55, 10.81 and 12.56 ppm, respectively (Atioğlu, Sevinçli, Karalı, Akkurt, & Ersanlı, 2017a). The NMR findings of 1*H*-indole-2,3-dion 3-thiosemicarbazone derivatives given in the cited literatures confirmed the data of the compound **5.**



Scheme 1. Synthesis of (3*E*/3*Z*)-1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone] (**5**).

Figure 8 shows the molecular conformation of the 3*Z*-isomer of the compound **5**. A planar indole fused-ring (N1/C1–C8) [r.m.s deviation = 0.003 Å] made a dihedral angle of 4.13 (11)° with the benzene ring (C12–C17). The N—N—C S and N—N—C(S)—N torsion angles were -170.76(19) and 8.0 (3)°, respectively. All bond lengths and angles were within normal ranges and were in agreement with those reported for 2-(5-fluoro-1-methyl-2-oxoindolin-3-ylidene)-*N*-[4-(methylsulfanyl) phenyl]hydrazine-1-carbothioamide (Atioğlu, *et al.*, 2017a), (*Z*)-2-(6-fluoro-3-methyl-2-oxo-2,3-dihydro-1*H*-inden-1-ylidene)-*N*-(3-fluorophenyl)hydrazine-1-carbothioamide (Atioğlu, Sevinçli, Karalı, Akkurt, & Ersanlı, 2017b), (3*E*)-3-[(4-butylphenyl)imino]-1,3-dihydro-2*H*-indol-2-one (Akkurt, Öztürk, Erçağ, Özgür, & Heinemann, 2003), *N*'-[(2*Z*)-3-allyl-4-oxo-1,3-thiazolidin-2-ylidene]-5-fluoro-3-phenyl-1*H*-indole-2-carbohydrazide (Akkurt, Karaca, Cihan, Çapan, & Büyükgüngör, 2009) and 5-trifluoromethoxy-1*H*-indole-2,3-dione 3-thiosemicarbazone derivatives (Kaynak *et al.*, 2013).

As shown in Figure 8, in the crystal of (3*Z*)-1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone] (**5**), three intramolecular N—H···N, N—H···O

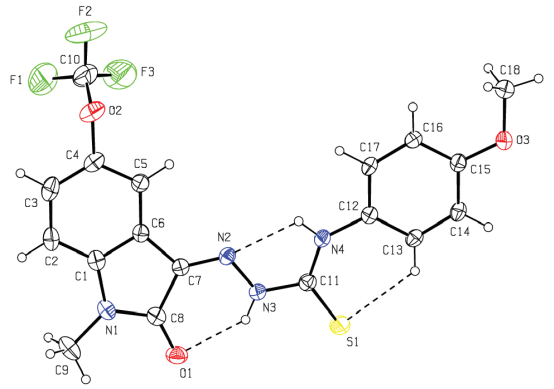


Figure 8. View of 3*Z*-isomer of the compound **5** with the atom numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 30% probability level.

and C—H···S hydrogen bonds generated S(5), S(6) and S(6) ring motifs, respectively (Table 2) (Bernstein, Davis, Shimoni, & Chang, 1995). H atoms attached to N atoms were localized in the difference Fourier map and refined freely with U_{iso}(H) = 1.2U_{eq}(N). All C-bound H-atoms were included in the geometrically determined positions and refined using a riding model with C—H = 0.93 and 0.96 Å and U_{iso}(H) = 1.2 or 1.5 U_{eq}(C). In the crystal, the molecular packing was stabilized by intermolecular C—H···O hydrogen bonds (Figure 9; Table 2), the *π*-*π* stacking interactions [*Cg*1···*Cg*3(1 - *x*, 1 - *y*, 1 - *z*) = 3.6021 (18) Å and *Cg*2···*Cg*2(2 - *x*, 1 - *y*, 1 - *z*) = 3.7250 (19) Å; where *Cg*1, *Cg*2 and *Cg*3 are the centroids of the five-membered (N1/C1/C6–C8) and six-membered (C1–C6) of the 1,3-dihydro-2*H*-indol-2-one ring system, and the methoxyphenyl ring (C12–C17), respectively]. In addition, weak C O···*π*(ring) contacts between the molecules contributed to the stabilization of the crystal structure (Table 2). Figure 9a and 9c show the views of the hydrogen bonding, along the a, b and c axes of the crystal packing of the compound **5**, respectively.

Table 2. Hydrogen-bond geometry (Å, °) of the 3Z-conformer of the compound 5.

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N3–H3N···O1	0.86 (3)	2.08 (3)	2.749 (3)	134 (2)
N4–H4N···N2	0.86 (3)	2.14 (3)	2.611 (3)	114 (2)
C3–H3···O3^{i}	0.9300	2.4200	3.307 (4)	158.00
C13–H13···S1	0.9300	2.6100	3.262 (3)	128
C8–O1···Cg3^{ii}	1.223 (3)	3.675 (3)	3.424 (3)	68.62 (15)

Symmetry codes: (i) *x*+1, *y*+1, *z*; (ii) −*x*+1, −*y*+1, −*z*+1.

CONCLUSION

The structures of the *E*- and *Z*- isomers of the new 1-methyl-5-trifluoromethoxy-1*H*-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone] (**5**) were characterized by NMR data. The *Z*-conformer of the compound **5** was further confirmed by X-ray single crystal diffraction analysis technique. The intramolecular hydrogen bonds in the 3*Z*-isomer resulted in strong downfield shifts for the N_2-H and N_4-H protons of the thiosemicarbazone moiety. The conformation of the 3*Z*-isomer of the compound **5** was stabilized by three intramolecular N—H···N, N—H···O and C—H···S hydrogen bonds. Intermolecular C—H···O hydrogen bonds, *π*-*π* stacking interactions and weak C O···*π*(ring) contacts contributed to the stabilization of the crystal structure.

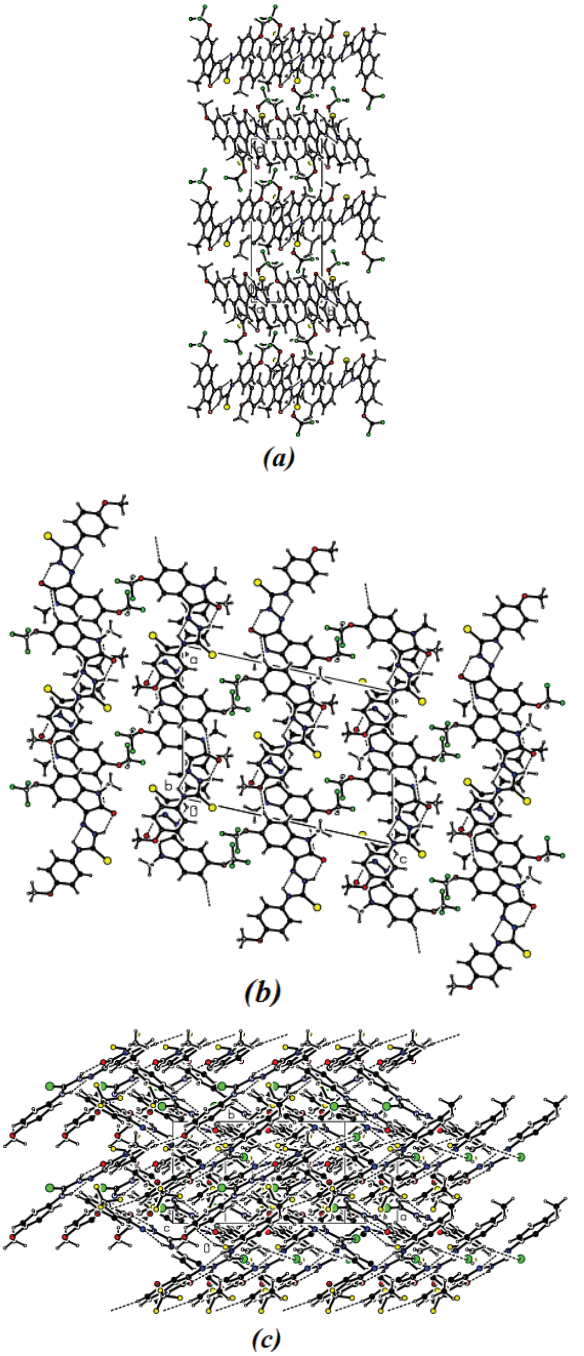


Figure 9. A view along the a axis **(a)**, b axis **(b)**, c axis **(c)** of the crystal packing and hydrogen bonding of 3*Z*-isomer of the compound **5**.

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Conflict of Interest: The authors have no conflict of interest to declare.

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