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

Özge Soylu Eter1,2, Zeliha Atioğlu3, Mehmet Akkurt4, Cem Cüneyt Ersanlı5, Nilgün Karalı1

1Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Istanbul, Turkey
2Istanbul University, Institute of Health Sciences, Istanbul, Turkey
3Cappadocia University, The Medical Imaging Techniques Program, Ilke Education and Health Foundation, Nevşehir, Turkey
4Erciyes University, Faculty of Sciences, Department of Physics, Kayseri, Turkey
5Sinop University, Faculty of Arts and Sciences, Department of Physics, Sinop, Turkey

ORCID IDs of the authors: Ö.S. 0000-0001-8875-3522; Z.A. 0000-0002-1141-5151; M.A. 0000-0003-2421-0929; C.C.E. 0000-0002-8113-5091; N.K. 0000-0002-6916-122X

Cite this article as: Soylu Eter, O., Atioglu, Z., Akkurt, M., Ersanli, C. C., & Karali, N. (2021). Molecular and crystal structure of 1-methyl-5-trifluoromethoxy-1H-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone]. Istanbul Journal of Pharmacy, 51(1), 59-66.

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-1H-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, 1H 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-1H-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone] (2) with 4-[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 1H 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

1H-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), antituberculous (Pandeya, Srim, Yogeeshwari, & Ananthan, 2001), antibacterial (Pandeya & Srim, 1998) and anticancer activity (Ma et al., 2015; Vine, Matesic, Locke, Ranson, & Skropeta, 2009). N-Methylisatin-3-thiosemicarbazone

Address for Correspondence: Özge SOYLU ETER, e-mail: ozge.soylu@istanbul.edu.tr

This work is licensed under a Creative Commons Attribution 4.0 International License.

Submitted: 12.08.2020
Revision Requested: 11.09.2020
Last Revision Received: 21.11.2020
Accepted: 04.12.2020
(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-diethythiosemicarbazone) 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 N2 position of the thiosemicarbazone and introduction of electron-withdrawing groups on the phenyl ring linked to the N4 position of the thiosemicarbazone derivatives have significantly higher activity than N4-alkyl, N4-cycloalkyl and N4-nonsubstitue thiosemicarbazone derivatives (Hall et al., 2011; Hall et al., 2009). The type and position of various substituents on the phenyl ring linked to the N2 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; Karali, 2007).

In this study, the new (1-methyl-5-(trifluoromethoxy)-1H-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 3E- and 3Z-isomers). The structures of the 3E and 3Z 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 and the lactam oxygen of the indole ring. In these studies, the presence of two isomers formed by rotation around the thioamide N2-C bond of isatin-3-thiosemicarbazones have been reported. Geometric isomers have been reported to occur if free rotation around the thioamide N2-C bond is prevented (Figure 2) (DeSilva & Albu, 2007; Bain et al., 1997).

In this study, the new (1-methyl-5-(trifluoromethoxy)-1H-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 3E- and 3Z-isomers). The structures of the 3E and 3Z 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 and the lactam oxygen of the indole ring. In these studies, the presence of two isomers formed by rotation around the thioamide N2-C bond of isatin-3-thiosemicarbazones have been reported. Geometric isomers have been reported to occur if free rotation around the thioamide N2-C bond is prevented (Figure 2) (DeSilva & Albu, 2007; Bain et al., 1997).

In this study, the new (1-methyl-5-(trifluoromethoxy)-1H-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 3E- and 3Z-isomers). The structures of the 3E and 3Z 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 and the lactam oxygen of the indole ring. In these studies, the presence of two isomers formed by rotation around the thioamide N2-C bond of isatin-3-thiosemicarbazones have been reported. Geometric isomers have been reported to occur if free rotation around the thioamide N2-C bond is prevented (Figure 2) (DeSilva & Albu, 2007; Bain et al., 1997).

In this study, the new (1-methyl-5-(trifluoromethoxy)-1H-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 3E- and 3Z-isomers). The structures of the 3E and 3Z 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 and the lactam oxygen of the indole ring. In these studies, the presence of two isomers formed by rotation around the thioamide N2-C bond of isatin-3-thiosemicarbazones have been reported. Geometric isomers have been reported to occur if free rotation around the thioamide N2-C bond is prevented (Figure 2) (DeSilva & Albu, 2007; Bain et al., 1997).
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 a Shimadzu UV-1800 spectrophotometer. The infrared (IR) spectra were recorded on a KBr disc, using a Shimadzu IR Affinity-1 FTIR spectrophotometer. ¹H 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 spectrometers dissolved in DMSO-d₆.

The synthesis of 1-methyl-5-trifluoromethoxy-1H-indole-2,3-dione (2)
Potassium carbonate (7 mmol) was added to a solution of 5-trifluoromethoxy-1H-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): 242.5 (14084), 268.2 (9566). IR (KBr) νmax (cm⁻¹): 3064, 3043 (aromatic C-H), 2951, 2889 (aliphatic C-H), 1737, 1716, 1687 (C=O) (C=C), 1614, 1489, 1473 (C=C). ¹H NMR (60 MHz) (DMSO-d₆) δ (ppm): 3.31 (3H, s, indole N-CH₃), 7.34-7.61 (3H, m, indole C₆-H), 8.89 (1H, s, N4-H), 9.42 (1H, s, N2-H). ¹³C NMR (75 MHz) (DMSO-d₆) δ (ppm): 121.26 (indole C₃a), 124.42 (indole C1), 126.40 (C₆-TMS), 130.54 (indole C3), 131.53 (phenyl C1), 142.95 (indole C₅), 144.46 (C₄), 158.03 (phenyl C2), 161.37 (indole C₄), 177.05 (C=S) (Figures 4-6). Mass spectroscopy (MS) analysis was obtained on a Waters Alliance Micromass ZQ LC/MS spectrophotometer. The elemental analysis was performed on a Leco CHNS-932 elemental analyzer.

The synthesis of 4-(4-methoxyphenyl)thiosemicarbazone (3)
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) was added to a solution of 1-methyl-5-trifluoromethoxy-1H-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 (Karali et al., 2020). The Z-isomer was obtained by crystallizing the isomer mixture from ethanol.

3Z-isomer, ¹H NMR (400 MHz) (DMSO-d₆/TMS) δ (ppm): 3.24 (3H, s, indole N-CH₃), 3.77 (3H, s, OCH₃), 6.98 (2H, d, J: 9.0 Hz, phenyl C₃,5-H), 7.25 (1H, d, J: 8.6 Hz, indole C₆-H), 7.44 (2H, d, J: 9.0 Hz, phenyl C₂,6-H), 7.44-7.47 (1H, m, indole C₇-H), 7.81 (1H, s, indole C₄-H), 10.81 (1H, s, N₄-H), 12.53 (1H, s, N₂-H) (The E/Z isomer ratio is 1:2) (Figure 3). ¹³C NMR (HSQC-2D) (125 MHz) (DMSO-d₆/TMS) δ (ppm): 26.40 (indole N-CH₃), 55.76 (OCH₃), 111.50 (indole C₄), 114.14 (phenyl C₃), 114.60 (indole C₄), 120.68 (C₆-TMS), 121.26 (indole C₇), 124.42 (indole C₈), 127.86 (phenyl C₉), 130.54 (indole C₉), 131.53 (phenyl C₁), 142.95 (indole C₅), 144.46 (C₄), 159.03 (phenyl C₂), 161.37 (indole C₄), 177.05 (C=S) (Figures 4-6).

3E-isomer, ¹H NMR (400 MHz) (DMSO-d₆/TMS) δ (ppm): 3.24 (3H, s, indole N-CH₃), 3.73 (3H, s, OCH₃), 6.88 (2H, d, J: 9.0 Hz, phenyl C₃,5-H), 7.25 (1H, d, J: 8.6 Hz, indole C₇-H), 7.35 (2H, d, J: 8.6 Hz, phenyl C₂,6-H), 7.44-7.47 (1H, m, indole C₇-H), 7.81 (1H, s, indole C₄-H), 9.52 (1H, s, N₄-H), 9.69 (1H, s, N₂-H) (The E/Z isomer ratio is 1:2) (Figure 3). ¹³C NMR (HSQC-2D) (125 MHz) (DM-
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 (phenyl C$_2$), 177.05 (C=S) (Figures 4-6).

3-(Z)-1-methyl-5-trifluoromethoxy-1H-indole-2,3-dione (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).

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).

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 3Z-isomer of the compound 5 are summarized in Table 1.

RESULTS AND DISCUSSION

In this study, 1-methyl-5-trifluoromethoxy-1H-indole-2,3-dione (2) was reacted by 4-(4-methoxyphenyl)thiosemicarbazide (4) in ethanol to give 1-methyl-5-trifluoromethoxy-1H-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 3Z-conformer of the compound 5 was further characterized by X-ray single crystal diffraction analysis method.

The $^1$H NMR spectra of 3Z- and 3E-isomers of the compound 5 displayed OCH$_3$ (C18) protons at δ 3.77 and 3.73 ppm as singlets, respectively. The N$_3$ (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 N$_3$—H···O1 and N$_4$—H···N2 hydrogen bonds in the 3Z-isomer. The phenyl protons of the thiosemicarbazone moiety of 3Z-isomer showed a change in the chemical shift of approximately +0.10 ppm. The spectra of 3Z- and 3E-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 3Z- and 3E-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 3Z-isomer. The chemical shifts of the other carbons were constant for the 3Z- and 3E-isomers.
The $3E/3Z$ 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 1H-indole-2,3-dione 3-thiosemicarbazone derivatives. The calculated and experimental signals of the thiosemicarbazone residue NH protons were compared. It was determined that the thioamide N$_2$ (HA) proton made the thiosemicarbazone residue NH protons were compared. The calculated and experimental signals of the 1H-indole-2,3-dione 3-thiosemicarbazone derivatives. The calculated and experimental signals of the 1H-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 (2)-5-fluoro-1-methyl-1H-indole-2,3-dione 3-(4-methoxyphenyl)phenyllithiumsemicarbazone were determined, NCH$_3$, phenyl C$_{15}$, phenyl C$_{26}$, thiocarbazone N$_2$ and N$_3$ protons were recorded at $d$ 3.21, 7.30, 7.55, 10.81 and 12.56 ppm, respectively (Atioğlu, Sevinçli, Karali, Akkurt, & Ersanlı, 2017a). The NMR findings of 1H-indole-2,3-dione 3-thiosemicarbazone derivatives given in the cited literatures confirmed the data of the compound 5.

Figure 8 shows the molecular conformation of the 3Z-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 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-(methylsulfonyl)phenyll]hydrazine-1-carbothioamide (Atioğlu, et al., 2017a), (Z)-2-(5-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-inden-1-ylidene)-N-(3-fluorophenyll)hydrazine-1-carbothioamide (Atioğlu, Sevinçli, Karali, Akkurt, & Ersanlı, 2017b), (3Z)-3-[4-(4-butylyphenylimino)-1,3-dihydro-2H-indol-2-one (Akkurt, Öztürk, Erçağ, Özgür, & Heinemann, 2003), N'-(3E)-3-allyl-4-oxo-1,3-thiazolidin-2-ylidene]-5-fluoro-3-phenyl-1H-indole-2-carboxhydrazide (Akkurt, Karaca, Cihan, Çapan, & Büyükşengoğlu, 2009) and 5-trifluoromethoxy-1H-indole-2,3-dione 3-thiosemicarbazone derivatives (Kaynak et al., 2013).

As shown in Figure 8, in the crystal of (3E)-1-methyl-5-trifluoromethoxy-1H-indole-2,3-dione 3-[4-(4-methoxyphenyl)thiosemicarbazone] (5), three intramolecular N—H···N, N—H···O hydrogen bonds 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$_3$ proton signals of 1H-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-1H-indole-2,3-dione 3-(4-methylthio) phenyllithiumsemicarbazone were determined, NCH$_3$, phenyl C$_{15}$, phenyl C$_{26}$, thiocarbazone N$_2$ and N$_3$ protons were recorded at $d$ 3.21, 7.30, 7.55, 10.81 and 12.56 ppm, respectively (Atioğlu, Sevinçli, Karali, Akkurt, & Ersanlı, 2017a). The NMR findings of 1H-indole-2,3-dione 3-thiosemicarbazone derivatives given in the cited literatures confirmed the data of the compound 5.

$$\text{Compounds: APEX2 and SAINT (Bruker, APEX2, SAINT and SADABBS, Bruker AXS Inc., Madison, Wisconsin, USA), SHELEX97 (Sheldrick, 2008), SHELX2014 (Sheldrick, 2015), WinGX (Farrugia, 2012) and PLATON (Spek, 2009).}$$
and C—H···S hydrogen bonds generated S(5), S(6) and S(6) ring motifs, respectively (Table 2) (Bernstein, Davis, Shimon, & Chang, 1995). H atoms attached to N atoms were localized in the difference Fourier map and refined freely with Uiso(H) = 1.2Ueq(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 Uiso(H) = 1.2 or 1.5 Ueq(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-2H-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···O3i | 0.9300 | 2.4200 | 3.307 (4) | 158.00 |
| C13—H13···S1 | 0.9300 | 2.6100 | 3.262 (3) | 128 |
| C8—O1···Cg3ii | 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-1H-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 3Z-isomer resulted in strong downfield shifts for the N2-H and N4-H protons of the thiosemicarbazone moiety. The conformation of the 3Z-isomer of the compound 5 was stabilized by three intramolecular N—H···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.
REFERENCES

- Akkurt, M., Karaca, S., Cihan, G., Çağan, G., & Büyükgüngör, O. (2009). N'-[2-(4-oxo-1,3-thiazolidin-2-ylidene)-5-fluoro-3-phenyl-1H-indol-2-carboxazide. Acta Crystallographica Section E, 65, o1009-o1010. https://doi.org/10.1107/S1603588609021677
- Akkurt, M., Öztürk, S., Erçağ, A., Özgür, M. U., & Heinemann, F.W. (2003). (33S)-3-(4-Butylphenyl)iminido-1,3-di-hydro-2H-indol-2-one. Acta Crystallographica Section E, 59, o780-o782. https://doi.org/10.1107/S160358860300953X
- Ali, A. Q., Teoh, S. G., Salhin, A., Eltayeb, N. E., Ahamed, M. B. K., & Majid, A. A. (2014). Synthesis of isatin thiosemicarbazones derivatives: in vitro anti-cancer, DNA binding and cleavage activities. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 125, 440-448. https://doi.org/10.1016/j.saa.2014.01.086
- Atışoğlu, Z., Sevinçli, Z. Ş., Karalı, N., Akkurt, M., & Ersanlı, C. C. (2017a). 2-(5-Fluoro-1-methyl-2-oxoindolin-3-ylidene)-N-(4-methylsulfonyl)phenyl)hydrazine-1-carbothioamide. IUCrData, 2, x170671. https://doi.org/10.1107/S2414314617009002
- Atışoğlu, Z., Sevinçli, Z. Ş., Karalı, N., Akkurt, M., & Ersanlı, C. C. (2017b). (Z2)-2-(5-Fluoro-1-methyl-2-oxoindolin-3-ylidene)-N-(3-fluorophenyl)hydrazine-1-carbothioamide. IUCrData, 2, x170900. https://doi.org/10.1107/S2414314617009002
- Bain, G. A., West, D. X., Krejci, J., Valdés-Martínez, J., Hernández-Ortega, S., & Toscano, R. A. (1997). Synthetic and spectroscopic investigations of N(4)-substituted isatin thiosemicarbazones and their copper (II) complexes. Polyhedron, 16(5), 815-862. https://doi.org/10.1016/S0277-5387(96)00323-3
- Bal, T. R., Anand, B., Yogeeswar, P., & Srinam, D. (2005). Synthesis and evaluation of anti-HIV activity of isatin beta-thiosemicarbazone derivatives. Bioorganic & Medicinal Chemistry Letters, 15(20), 4451-4455. https://doi.org/10.1016/j.bmcl.2005.07.046
- Bernstein, J., Davis, R. E., Shimoni, L., & Chang, N. L. (1995). Patterns in hydrogen bonding: functionality and graph set analysis in crystals. Angewandte Chemie International Edition in English, 34, 1555-1573. http://doi.org/10.1002/anie.199515551
- DeSilva, N. W. S. V. N., & Albu, T. V. (2007). A theoretical investigation on the isomerism and the NMR properties of thiosemicarbazones. Central European Journal of Chemistry, 5(2), 396-419. https://doi.org/10.2478/s11532-007-0012-1
- Farrugia, L. J. (2012). WinGX and ORTEP for Windows: an update. Journal of Applied Crystallography, 45, 849-854. https://doi.org/10.1107/S0021889812029111
- Güzel, Ö., Karalı, N., & Salman, A. (2008). Synthesis and antituberculosis activity of 5-methyl/trifluoromethoxy-1H-indole-2,3-dione 3-thiosemicarbazone derivatives. Bioorganic & Medicinal Chemistry, 16(19), 8976-8987. https://doi.org/10.1016/j.bmc.2008.08.050
- Hall, M.D., Brimacombe, K.R., Varonka, M.S., Pluchino, K.M., Manda, J.K., Li, J. … Gottesman, M.M. (2011). Synthesis and structure-activity evaluation of isatin-β-thiosemicarbazones with improved selective activity towards multidrug-resistant cells expressing P-glycoprotein. Journal of Medicinal Chemistry, 54(16), 5878-5889. http://doi.org/10.1021/jm2006047
- Hall, M.D., Salam, N.K., Hellawell, J.L., Fales, H.M., Knsler, C.B., Ludwig, J.A. … Gottesman, M.M. (2009). Synthesis, activity, and pharmacophore development for isatin-β-thiosemicarbazones with selective activity toward multidrug-resistant cells. Journal of Medicinal Chemistry, 52(10), 3191-3204. http://doi.org/10.1021/jmc800861c
- Haribabu, J., Subhashree, G., Saranya, S., Gomathi, K., Karvembu, R., & Gayathri, D. (2016). Isatin based thiosemicarbazone derivatives as potential bioactive agents: Anti-oxidant and molecular docking studies. Journal of Molecular Structure, 1110, 185-195. https://doi.org/10.1016/j.molstruc.2016.01.044
- Howard, J.A.K., Hoy,V.I., O'Hagan, D., & Smith,G.T. (1996). How good is fluorine as a hydrogen bond acceptor? Tetrahedron, 52(38), 12613-12622. https://doi.org/10.1016/S0040-4020(96)00749-1
- Huang, H., Chen, Q., Xu, X., Meng, L., Lin, L., Wang, X. … Liu, H. (2010). A Series of α-Heterocyclic Carboxaldehyde Thiosemicarbazones Inhibit Topoisomerase IIA Catalytic Activity. Journal of Medicinal Chemistry, 53(8), 3048-3064. http://doi.org/10.1021/jm1004394
- Jakusová, K., Gáplovský, M., Donovalová, J., cigáří, M., Stančíková, H. … Antov, G. (2013). Effect of reactants’ concentration on the ratio and yield of E, Z isomers of isatin-3-(4-phenyl)semicarbazone and N-methylisatin-3-(4-phenyl)semicarbazone. Chemical Papers, 67(1), 117-126. https://doi.org/10.2478/11696-012-0248-x
- Karalı, N. (2002). Synthesis and primary cytotoxicity evaluation of new 5-nitroindole-2,3-dione derivatives. European Journal of Medicinal Chemistry, 37(11), 909-918. https://doi.org/10.1016/S0223-5234(02)01416-2
- Karalı, N., Gürsoy, A., Kandemirli, F., Shvets, N., Kaynak, F.B., Özbeş, S. … Dimoglo, A. (2007). Synthesis and structure-antituberculosis activity relationship of 1H-indole-2,3-dione derivatives. Bioorganic & Medicinal Chemistry, 15(17), 5888-5904. https://doi.org/10.1016/j.bmc.2007.05.063
- Karalı, N., Soylu, Ọ., Gul, A., Ozer, H., Erman, B., Hasanusta, B., Ersoy, B., 5-Fluoro(trifluoromethyl)-2-indolindone derivatives. 11.02.2020 PCT/TR 2020/050401
- Kaynak, F.B., Özbeş, S., & Karalı, N. (2013). Three Novel Compounds Of 5-Trifluoromethyl-1H-indole-2,3-Dione 3-Thiosemicarbazone: Synthesis, Crystal Structures And Molecular Interactions. Journal of Molecular Structure, 1049, 157-164. https://doi.org/10.1016/j.molstruc.2013.06.039
- Ma, J., Bao, G., Wang, L., Li, W., Xu, B., Du, B. … Gong, P. (2015). Design, synthesis, biological evaluation and preliminary mechanism study of novel benzothiazole derivatives bearing indole-based moiety as potent antitumor agents. European Journal of Medicinal Chemistry, 96, 173-186. http://doi.org/10.1016/j.ejmech.2015.04.018
- Mateisic, L., Locke, J., Bremner, J.B., Pyne, S.G., Skrepoa, D., Ransom, M., & Vine, K.L. (2008). N-phenethyl and N-naphthylethyl isatins and analogues as in vitro cytotoxic agents. Bioorganic & Medicinal Chemistry, 16(6), 3118-3124. https://doi.org/10.1016/j.bmc.2007.12.026
- Matheus, M.E., DeAlmeida Volante, F., Garden, S.J., Pinto, A.C., & Fernandes, P.D. (2007). Isatins inhibit cyclooxygenase-2 and inducible nitric oxide synthase in a mouse macrophage cell line. European Journal of Pharmacology, 556(1-3), 200-206. https://doi.org/10.1016/j.ejphar.2006.10.057
