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Three novel compounds of 5-trifluoromethoxy-1*H*-indole-2,3-dione 3-thiosemicarbazone: Synthesis, crystal structures and molecular interactions

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HIGHLIGHTS

- 5-trifluoromethoxy-1H-indole-2,3-dione 3-thiosemicarbazone derivatives were synthesized.
- The structures were determined by analytical, spectral and single XRD methods.
- The molecules are linked into three dimensional framework structure by N—H···N and N—H···O hydrogen bonds.

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ABSTRACT

5-Trifluoromethoxy-1*H*-indole-2,3-dione 3-(*N*-ethyl/benzylthiosemicarbazone) (**2a**/**2b**) and 5-trifluoromethoxy-1-morpholinomethyl-1*H*-indole-2,3-dione 3-(*N*-ethylthiosemicarbazone) (**3a**) were synthesized. The structures of the compounds were confirmed by elemental analysis, spectral data and X-ray single crystal diffraction analysis. The morpholin ring which adopts chair conformation and ethylamino group of **3a** are disordered over two sets of sites with unequal occupancy. The indole heterocycle is nearly planar and the dihedral angle between the pyrrole and the adjacent phenyl ring is 2.09° (in **2a**), 4.61° (in **2b**) and 2.16° (in **3a**). In all three crystal structures, a strong N—H···O hydrogen bond links the flat conjugated H—N—N=C—C=O fragment into a six-membered ring. The molecules **2a**, **2b** and **3a** have potential groups of proton donors (thiosemicarbazone group) available for hydrogen bonding. The structures **2b** and **3a** consist of isolated molecules, while that of **2a** contains dimers formed by C—H···O hydrogen bonds. The molecules are linked into three dimensional framework structure by a combination of mainly N—H···N and N—H···O hydrogen bonds and weak C—F···π and π···π interactions.

1. Introduction

1*H*-indole-2,3-dione (isatin) is an endogenous compound identified in humans, and its effect has been studied in a variety of systems. Biological properties of isatin include a range of actions in the brain and offer protection against certain types of infections [1]. Isatin-3-thiosemicarbazone and its N-Mannich bases were active against various viruses [2–4]. *N*-methylisatin-3-thiosemicarbazone (methisazone) was one of the first antiviral compounds used in clinical practice. This drug plays an important role as a prophylactic agent against several viral diseases. Furthermore, inhibition of reverse transcriptase by *N*-methylisatin-3-(4′,4′-diethylthiosemicarbazone) has been reported by Ronen et al. [5–7]. This compound is known to be useful for the treatment of human and animal diseases caused by oncoviruses and foamy viruses [8]. Investigation of the structure–activity relationships in 3-substituted 2-indolinone derivatives revealed that 3-thiosemicarbazone formation of the isatin moiety are associated with increased activity against a range of human cancer cell lines and various viruses [9–13]. Hall and co-workers reported a new class of isatin-3-thiosemicarbazones with selective activity toward multidrug resistant (MDR) cells. Research on isatin-3-thiosemicarbazones showed that isatin-3-thiosemicarbazone moiety and aromatic/hydrophobic features at the N4 position of the thiosemicarbazone were essential for the MDR1-selective activity [13,14]. In the light of these findings, 5-trifluoromethoxy-1*H*-indole-2,3-dione 3-thiosemicarbazone derivatives were synthesized [12]. The structures of the synthesized compounds were determined by analytical, spectral (IR, ^{1}H NMR, and LCMS–APCI) and single crystal X-ray diffraction method.

This study focuses on the preferences of the molecular assembly by hydrogen bonding in the crystal structure. Our aim is to analyze the hydrogen bond packing of NH···N/NH···O/NH···S/CH···O and

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CH···S. It turned out that in all compounds the N3—H3···O1 and N4—H4···N2 bonds take parts in molecular stabilization via extensive intra-molecular hydrogen bonding.

2. Experimental

2.1. General procedure

Melting points were estimated with a Buchi 540 melting point apparatus in open capillaries and are uncorrected. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 elemental analyzer. IR spectra were recorded on KBr discs, using a Perkin–Elmer Model 1600 FT-IR spectrometer. ^{1}H NMR spectra was obtained on Bruker Avance DPX 400 and Varian^{UNITY} INOVA 500 spectrophotometers using DMSO-d_6. Mass spectra were determined on a Mass-AGILENT 1100 MSD instruments. All chemicals and solvents were purchased from Merck-Schuchardt, Aldrich and Fluka.

2.2. Synthesis

2.2.1. General method for the synthesis of N-substituted thiosemicarbazides

To a solution of hydrazine hydrate (5 mmol) in ethanol (10 mL), a suspension of an appropriate isothiocyanate (5 mmol) in ethanol (10 mL) was added dropwise with vigorous stirring and cooling in an ice bath. The mixture was allowed to stand overnight. The crystals formed were recrystallized from ethanol.

2.2.2. General method for the synthesis of 5-trifluoromethoxy-1H-indole-2,3-dione 3-thiosemicarbazones (**2a**, **2b**)

A solution of N-substituted thiosemicarbazides (3.5 mmol) in ethanol (10 mL) was added to a solution of 5-trifluoromethoxy-1*H*-indole-2,3-dione 1 (3.5 mmol) in ethanol (20 mL). After addition of a drop of concentrated sulfuric acid, the mixture was refluxed on a water bath for 5 h. The product formed after cooling was filtered and recrystallized from ethanol.

5-Trifluoromethoxy-1H-indole-2,3-dione 3-(N-ethylthiosemicarbazone) (2a)

Yellow crystals (67%): mp 235–236 °C; IR (KBr): υ 3324, 3182 (NH), 1696 (C=O), 1155 (C=S); ^{1}H NMR (DMSO-d6/400 MHz): δ 1.21 (t, J = 7.10 Hz, 3H, ethyl CH3), 3.65 (p, J = 7.0 Hz, 2H, ethyl CH2), 7.02 (d, J = 8.50, Hz, 1H, indole C7—H), 7.36 (dd, J = 8.50, 2.30 Hz, 1H, indole C6—H), 7.66 (d, J = 1.70 Hz, 1H, indole C4—H), 9.41 (t, J = 5.60 Hz, 1H, N4—H), 11.36 (s, 1H, indole NH), 12.43 (s, 1H, N2—H); LCMS–APCI (−/+): m/z (%) 333 (MH+, 100), 331 (MH−, 87), 230 (100). Anal. Calcd for C12H11F3N4O2S (332.30): C, 43.37; H, 3.34; N, 16.86. Found: C, 43.34; H, 2.81; N, 16.82.

5-Trifluoromethoxy-1H-indole-2,3-dione-3-(N-benzylthiosemicarbazone) (2b)

Orange crystals (90%): mp 215–216 °C; IR (KBr): υ 3221 (NH), 1702 (C=O), 1238 (C=S); 1H NMR (DMSO-d6/500 MHz): δ 4.88 (d, J = 4.10 Hz, 2H, benzyl CH2), 7.00 (d, J = 8.54 Hz, 1H, indole C7—H), 7.25 (t, J = 6.40 Hz, 1H, benzyl C4—H), 7.33–7.36 (m, 5H, indole C6—H, benzyl C2,3,5,6—H), 7.64 (d, J = 1.83 Hz, 1H, indole C4—H), 9.90 (t, J = 6.25 Hz, 1H, N4—H), 11.35 (s, 1H, indole NH), 12.53 (s, 1H, N2—H). Anal. Calcd for C17H13F3N4O2S·1/2H2O (403.38): C, 50.61; H, 3.49; N, 13.89. Found: C, 50.72; H, 3.36; N, 13.61.

2.2.3. The synthesis of 5-trifluoromethoxy-1-(morpholin-4-ylmethyl)-1H-indole-2,3-dione 3-(N-ethylthiosemicarbazone) (3a)

To a suspension of **2a** (2 mmol) in absolute ethanol (20 mL), 37% formaldehyde solution (0.5 mL) and morpholine (2 mmol) were added dropwise with vigorous stirring. After combining all reagents, the reaction mixture was stirred at room temperature for 10 h. The solid product was filtered and washed with petroleum ether.

Yellow crystals (78%): mp 205–207 °C; IR (KBr): υ 3260 (NH), 1695 (C=O), 1165 (C=S); ^{1}H NMR (DMSO/d_6, 400 MHz): δ 1.11 (t, J = 7.10 Hz, 3H, ethyl CH_3), 2.47 (br.t, J = 4.30 Hz, 4H, morph. $C_{3,5}$—H), 3.45 (br.t, J = 4.40 Hz, 4H, morph. $C_{2,6}$—H), 3.56 (p, J = 6.20 Hz, 2H, ethyl CH_2), 4.41 (s, 2H, N—CH_2—N), 7.28 (d, J = 8.60 Hz, 1H, indole C_7—H), 7.35 (dd, J = 8.60, 1.80 Hz, 1H, indole C_6—H), 7.62 (d, J = 1.40 Hz, 1H, indole C_4—H), 9.35 (t, J = 5.80 Hz, 1H, N_4—H), 12.25 (s, 1H, N_2—H); LCMS–APCI (−/+): m/z (%) 432 (MH^+, 14), 333 (100), 265 (99), 430 (MH^-, 8), 265 (100). Anal. Calcd for $C_{17}H_{20}F_3N_5O_3S$ (431.43): C, 47.33; H, 4.67; N, 16.23. Found: C, 47.48; H, 4.35; N, 16.27.

2.3. Single crystal X-ray structure determinations

The X-ray structure analysis was carried out for **2a**, **2b** and **3a**. Intensity data were collected on Enraf–Nonius CAD4 four circle diffractometer equipped with graphite monochromator Mo Kα radiation [15]. Structures were solved by direct methods using SHELXS-97 [16] and refined by full-matrix least squares on F^2 (SHELXL-97) [17]. All hydrogen atoms of the three compounds (except H1 for **2a**) were placed at calculated positions and refined by the riding model with Ueq(H) = 1.3Ueq(C), and fixed distances of C—H=0.93 Å (aromatic), C—H=0.96 Å (methyl) and C—H=0.97 Å (ethyl). The hydrogen atom of N1 was placed from difference Fourier map. The geometric calculations were performed using the program Platon [18]. The dihedral angles were calculated using the PARST program [19]. All crystallographic data and experimental details are listed in Table 1.

For compound **3a**, the obtained single crystals after the re-crystallization steps were not so good; the best suitable crystal was selected for X-ray data collection. During the refinement, a positional disorder was observed in the morpholin ring and ethylamino group. The occupancy factors of the disordered atoms are refined and then fixed to a ratio of 0.35:0.65. The disorder in the structure was resolved with occupancy factors of 0.65 for the sites C14—C17, O3 and N4, C11, C12 and of 0.35 for the sites C14′—C17′, O3′ and N4′, C11′, C12′. Non-hydrogen atom parameters except for disordered ones of the morpholin ring were refined anisotropically. Anisotropic refinement for the disordered atoms of the morpholin was also done but thermal vibrational parameters of the related atoms were increased to very high values. So, these atoms were refined isotropically. Due to the data quality, the resultant *R*-value is higher than the other two compounds.

Crystallographic data (with the exception of structure factors) for the structures in this paper were deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 829925, 829923 and 829924 for compounds **2a**, **2b** and **3a**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

3. Results and discussion

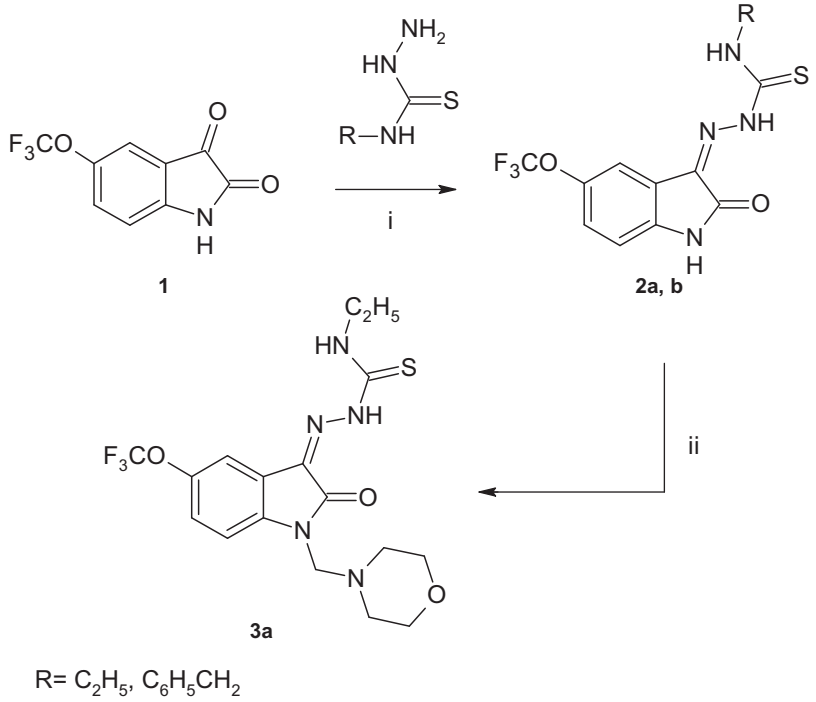
In this study, trifluoromethoxy-1*H*-indole-2,3-dione (**1**) reacted with N-substituted thiosemicarbazides in ethanol containing a catalytic amount of sulfuric acid, to give the corresponding 5-trifluoromethoxy-1*H*-indole-2,3-dione 3-thiosemicarbazones (**2a** and **2b**). 1-Morpholinomethyl-5-trifluoromethoxy-1*H*-indole-2,3-dione 3-(*N*-ethylthiosemicarbazone) **(3a)** were synthesized from the consecutive treatment of **2a** with formaldehyde solution and morpholine (Scheme 1) [12].

Table 1
Crystal data and details of the structure determination of the compounds **2a**, **2b** and **3a**.

	2a	**2b**	**3a**
Formula	$C_{12}H_{11}F_3N_4O_2S$	$C_{17}H_{13}F_3N_4O_2S$	$C_{17}H_{20}F_3N_5O_3S$
Formula weight	332.31	394.37	431.4
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1/a$	*Pcan*	*Pbca*
Cell constants			
a (Å)	7.811(6)	10.645(2)	11.2423(23)
b (Å)	16.420(2)	12.712(2)	18.4235(20)
c (Å)	11.2724(14)	25.831(8)	19.7649(23)
α (°)	90	90	90
β (°)	96.09(4)	90	90
γ (°)	90	90	90
V (Å^3)	1437.6(11)	3495.5(14)	4093.8(9)
Z; D_{calc} (g cm^{-3})	4; 1.535	8; 1.499	8; 1.40
μ (Mo Kα) (mm^{-1})	0.271	0.237	0.213
Crystal size (mm)	0.60 × 0.21 × 0.15	0.62 × 0.42 × 0.15	0.72 × 0.36 × 0.18
Radiation	Mo Kα (λ = 0.71073 Å)	Mo Kα (λ = 0.71073 Å)	Mo Kα (λ = 0.71073 Å)
Temp (K)	293(2)	293(2)	293(2)
θ limits (°)	2.2–26.29	2.5–23.55	2.4–23.5
Index ranges	$0 \leqslant h \geqslant 9$; $0 \leqslant k \geqslant 20$; $-13 \leqslant l \geqslant 14$	$0 \leqslant h \geqslant -11$; $0 \leqslant k \geqslant -14$; $0 \leqslant l \geqslant 29$	$-12 \leqslant h \geqslant 0$; $0 \leqslant k \geqslant 20$; $0 \leqslant l \geqslant 22$
Reflections collected	3127	2604	3046
Reflns. used in refinement	2909 [$I > 2\sigma(I)$]	2604 [$I > 2\sigma(I)$]	3045[$I > 2\sigma(I)$]
No. of refined parameters	204	244	270
R/R_w values	0.0559/0.1455	0.0638/0.2073	0.0735/0.2519
GOF	1.072	0.957	1.024
Final shift	0.0	0.0	0.0
Completeness	1.000	0.999	0.999
$(\Delta\rho)_{min}$, $(\Delta\rho)_{max}$ (e Å^{-3})	−0.528, 0.555	−0.272, 0.641	−0.470, 0.550

The structures of **2a**, **2b** and **3a** were confirmed by elemental analyses and spectral (IR, ^{1}H NMR and LCMS–APCI) data. The IR spectra of the compounds showed bands resulting from the indole and/or thioamide NH, lactam C=O and thioamide C=S functions in the 3324–3182, 1702–1695 and 1238–1155 cm^{-1} regions, respectively. The ^{1}H NMR spectra of **2a**, **2b** and **3a** displayed the NH protons of the thiosemicarbazone moiety (δ 9.35–9.90 and 12.25–12.53 ppm) as two separate signals. The indole NH protons were also observed as a singlet at δ 11.36 and 11.35 ppm in the spectra of **2a** and **2b**. Observation of only two NH signals assigned to the thiosemicarbazone moiety and of a singlet due to N—CH_2—N function (δ 4.41 ppm) and of signal attributed to morpholine in the ^{1}H NMR spectra of **3a** provided support for N-Mannich base formation. LCMS–APCI of **2a** and **3a** showed moleculer ions with different intensities which confirmed their molecular weights.

The conformations of 5-trifluoromethoxy-1*H*-indole-2,3-dione 3-(*N*-ethylthiosemicarbazone) (**2a**), 5-trifluoromethoxy-1*H*-indole-2,3-dione-3-(*N*-benzylthiosemicarbazone) (**2b**) and 5-triflu-



Scheme 1. Reagents and conditions: (i) EtOH, reflux, 5 h and (ii) morpholine, 37% HCHO, absolute EtOH, stir, room temperature, 10 h.

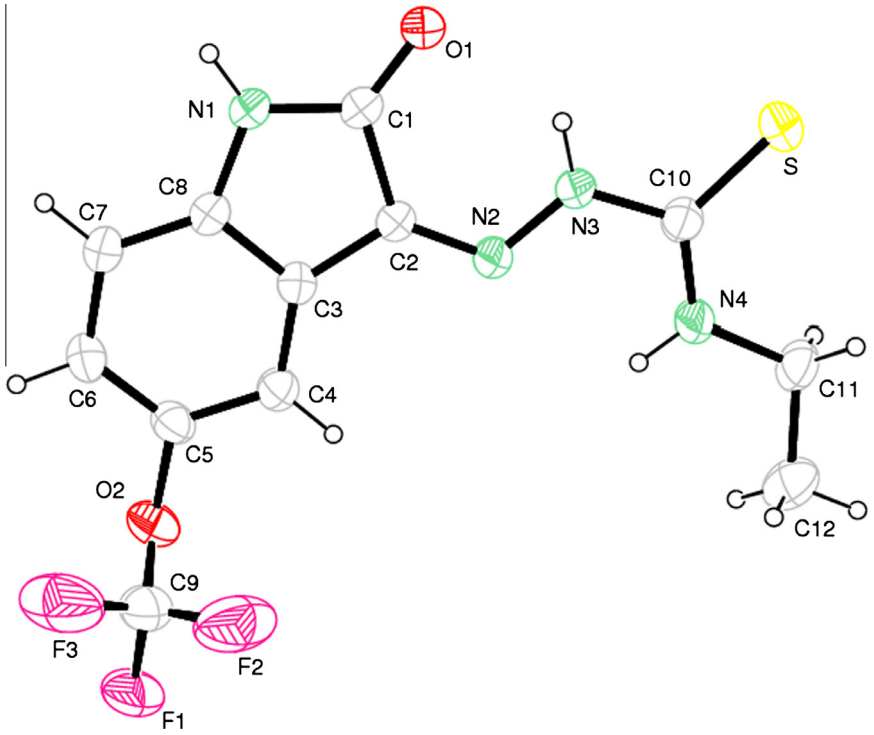


Fig. 1. ORTEP-3 view of the compound **2a**, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

oromethoxy-1-(morpholin-4-ylmethyl)-1*H*-indole-2,3-dione 3-(*N*-ethyl thiosemicarbazone) (**3a**) with the atom numbering are shown as Ortep diagrams in Figs. 1–3, respectively [20]. Selected geometric parameters for these compounds are given in Table 2 and the crystal packings are shown in Figs. 4–7.

In all compounds, the indole heterocycle is almost planar. The dihedral angles between the pyrrole and the phenyl ring are 2.09° and 2.16° for **2a** and **3a,** respectively while this value is observed as 4.61° in **2b**. The planarity of the indole ring of **2b** might have been affected by the C7—H7···O1 intermolecular hydrogen bond which is only exist in this molecule. The planarity of the indole system is usually observed [21–23]. The dihedral angles in the studied compounds are compared with the reported data by Kaynak et al. [24] which confirms that the dihedral angles between the pyrrole and the phenyl ring are 1.89(6)° and 0.81(9)°.

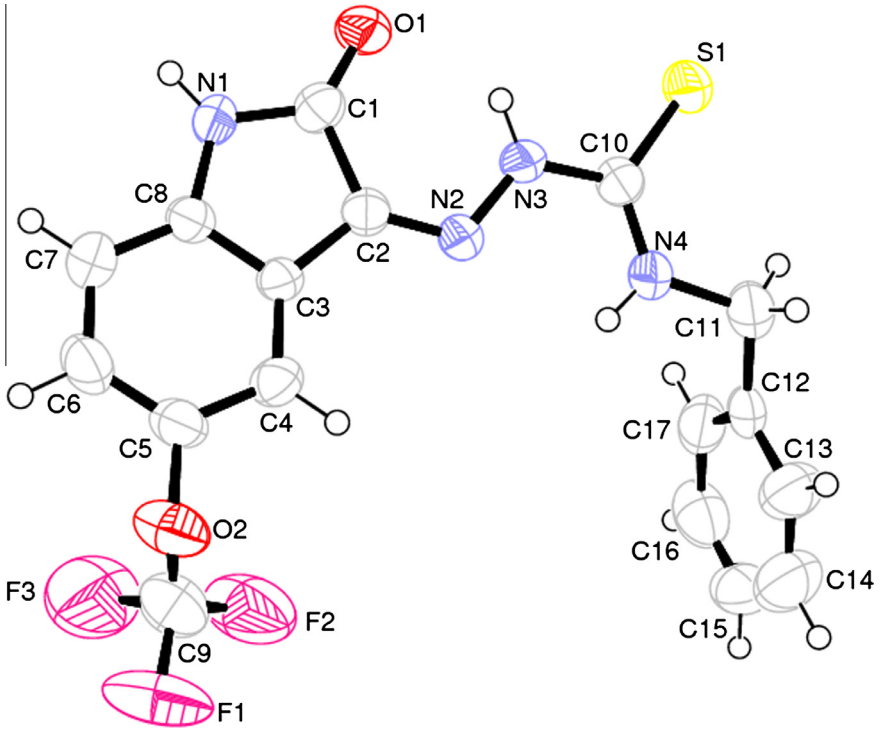


Fig. 2. ORTEP-3 view of the compound **2b**, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

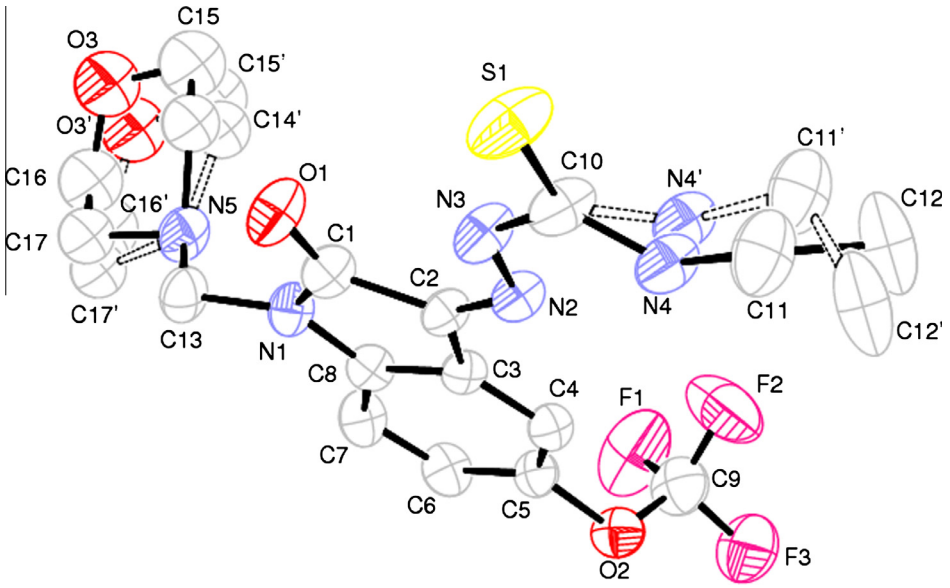


Fig. 3. (a) ORTEP-3 view of the compound **3a**, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 35% probability level. For the sake of clarity, H atoms have been omitted.

Table 2
Selected bond lengths (Å), bond angles (°) and main dihedral angles (°) of the compounds **2a**, **2b** and **3a** for the component with the occupancy factor of 0.65.

	2a	2b	3a
S1—C10	1.657(3)	1.671(6)	1.664(6)
N4—C10	1.318(3)	1.309(7)	1.320(12)
N4—C11	1.462(3)	1.461(8)	1.438(13)
C11—C12	1.495(4)	1.499(9)	1.487(9)
C10—N3	1.382(3)	1.362(7)	1.366(7)
N3—N2	1.339(3)	1.359(6)	1.349(6)
N2—C2	1.288(3)	1.287(7)	1.289(6)
C2—C1	1.505(3)	1.508(9)	1.499(8)
C1—O1	1.231(3)	1.216(7)	1.233(7)
C1—N1	1.355(3)	1.371(8)	1.362(7)
N1—C8	1.403(3)	1.388(7)	1.408(7)
C5—O2	1.420(3)	1.419(7)	1.427(7)
O2—C9	1.322(4)	1.275(9)	1.318(9)
F1—C9	1.311(3)	1.277(8)	1.319(9)
F2—C9	1.315(4)	1.276(9)	1.294(9)
F3—C9	1.305(3)	1.351(9)	1.305(8)
N1—C13	–	–	1.450(7)
C2—C3—C8	106.7(2)	106.3(5)	107.1(5)
C3—C8—N1	109.5(2)	110.8(5)	109.8(4)
C8—N1—C1	111.3(2)	111.1(5)	110.0(5)
N1—C1—C2	106.3(2)	105.5(5)	107.0(5)
C1—C2—C3	106.1(2)	106.1(5)	106.2(4)
C4—C3—C8	120.4(2)	121.2(5)	120.2(5)
C3—C4—C5	117.3(2)	117.7(6)	117.2(5)
C2—N2—N3	117.5(2)	115.6(5)	117.2(5)
N2—N3—C10	121.7(2)	120.7(5)	121.1(5)
N3—C10—N4	115.6(2)	116.7(5)	115.6(8)
C5—O2—C9	117.3(2)	117.7(6)	117.7(5)
C8—N1—C13	–	–	125.9(5)
N1—C13—N5	–	–	112.3(5)
C13—N5—C14	–	–	109.1(6)
N3—N2—C2—C1	−1.3(4)	1.7(9)	0.9(8)
C10—N3—N2—C2	−179.7(2)	−173.8(6)	−178.9(5)
S1—C10—N3—N2	179.3(2)	178.5(4)	−177.9(4)
N3—C10—N4—C11	175.7(2)	−177.6(6)	−174.6(10)
C3—C2—C1—N1	−1.1(3)	−4.1(7)	0.6(6)
C8—N1—C1—C2	2.4(3)	3.9(7)	0.5(6)
C12—C11—N4—C10	166.4(3)	−146.6(7)	−139.8(13)
C9—O2—C5—C6	−92.3(3)	101.5(8)	91.3(7)
N1—C13—N5—C14	–	–	−80.6(8)

In each of the three compounds, there are intra-molecular N—H···O and N—H···N hydrogen bonds and these interactions influence the molecular conformation (Table 3). So, the indole-thiosemicarbazone parts of the molecules are nearly planar. The overall conformation in each is defined by the first four torsion angles in Table 2.

In compound **2a**, the molecules are linked into centrosymmetric dimers by paired N—H···O hydrogen bonds, in which both the donor and the acceptor are parts of the pyrrole ring. The intermolec-

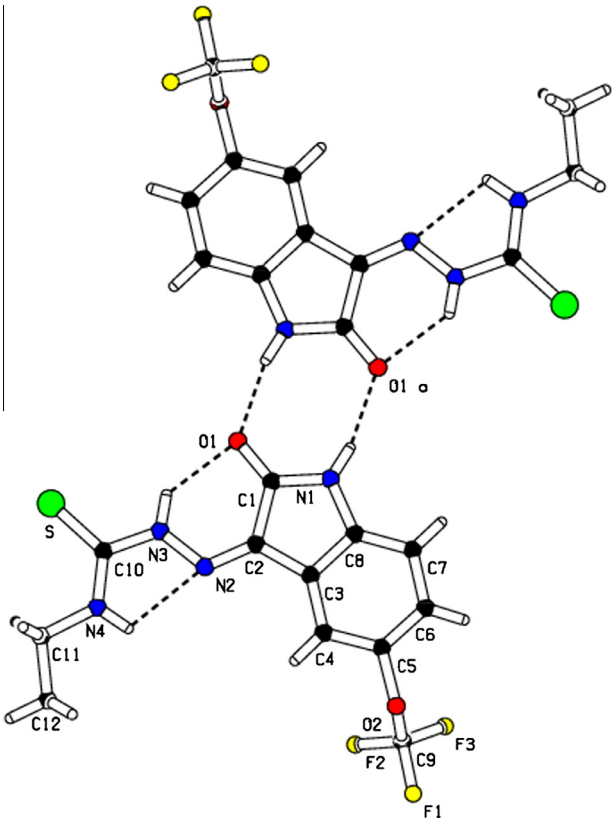


Fig. 4. Part of the crystal structure of compound **2a**, showing the formation of a centrocymmetric dimer. Hydrogen bonds are shown as dashed lines.

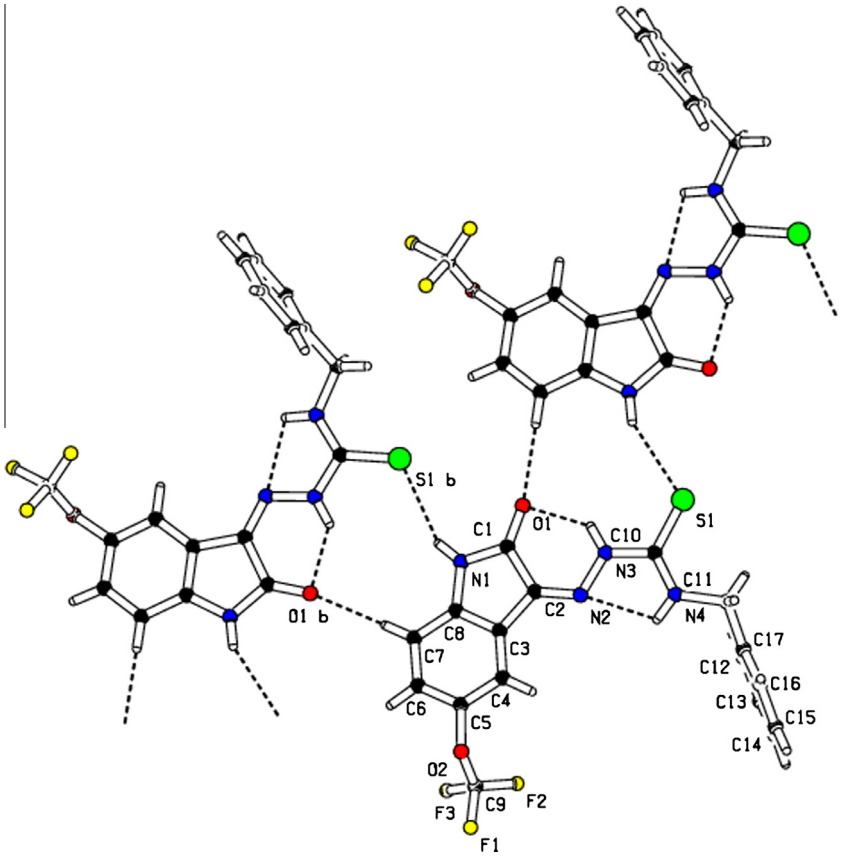


Fig. 5. Part of the crystal structure of compound **2b**. Hydrogen bonds are shown as dashed lines.

ular hydrogen bonds between the ketone O atom and the indole N—H group of neighboring molecules cause dimerization. It is clearly seen from the packing along *a*-axis, the molecules are in head-to-tail arrangement (Fig. 4). Furthermore, molecules are stacked in parallel layers onto the ac-plane to the [0.5,0,1] direction and the hydrogen bonded dimers are linked by a single aromatic π···π stacking interaction. In addition, there is a weak intermolecular C—F···π interaction between the F1 atom and pyrrole ring of a symmetry related molecule. The distance between F1 atom and the centroid of the pyrrole ring is 3.816(5) Å [symmetry code: $3/2-x$, $-1/2+y$, $-z$], whereas the C9—F1···centroid angle is 133°. For this compound we can observe an intermolecular π···π stacking involving the pyrrole and $(C3 \rightarrow C8)^{i}$ rings and the distance between the centroid of the indole ring and the centroid plane of the phenyl ring of a symmetry related molecule [symmetry code: (i) $-1/2+x$, $1/2-y$, z] is 3.454 Å with the dihedral angle between the planes is 7.24°.

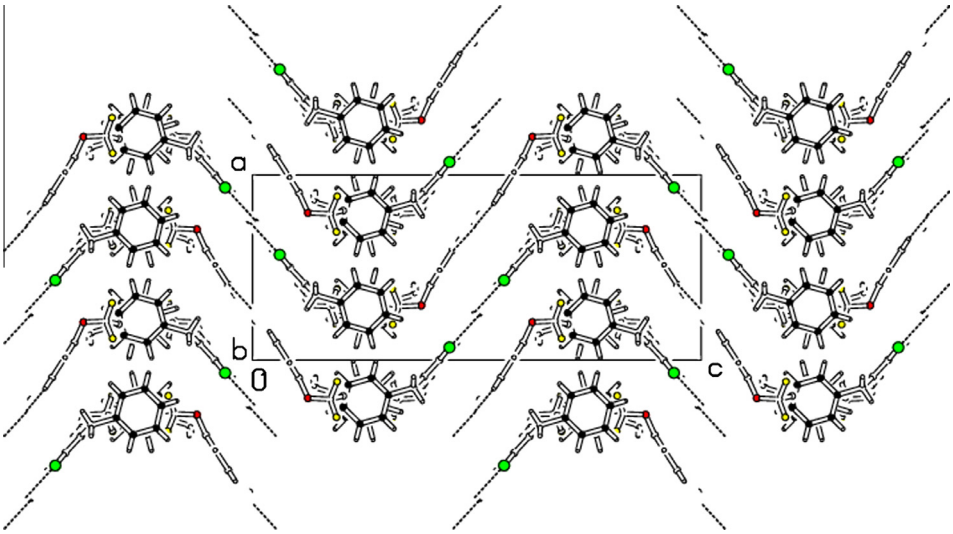


Fig. 6. The projection of the stacking interaction along *b*-axis of compound **2b**.

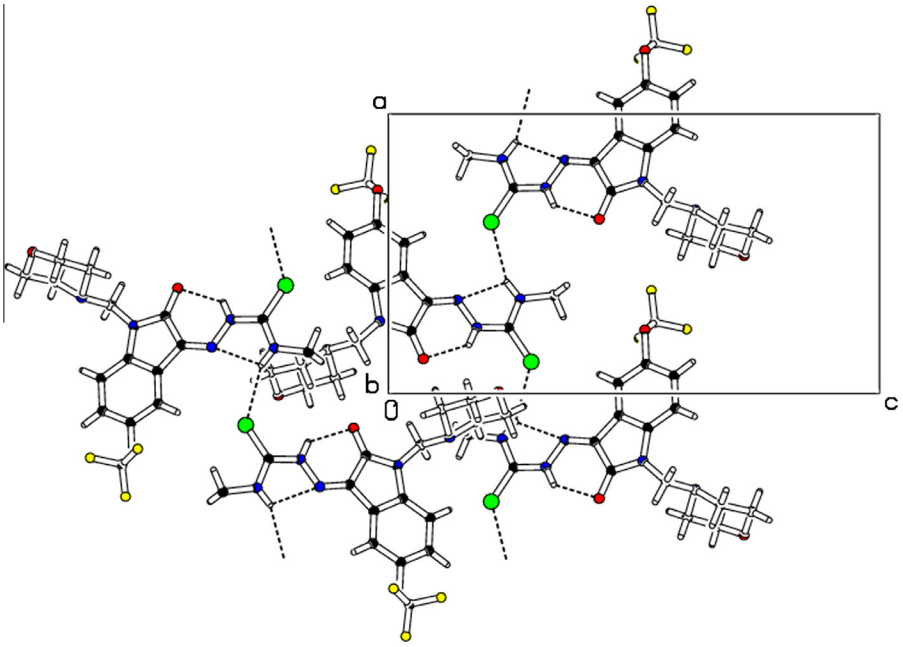


Fig. 7. Part of the crystal structure of compound **3a** showing the formation of a chain along [100]. Dotted lines represent the hydrogen interactions.

Table 3
Hydrogen bonds.

	D—H···A	Sym. operation	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (°)
2a	N1—H1···O1	$1-x, 1-y, -z$	0.88(3)	2.01(3)	2.874(4)	166(3)
	N3—H3···O1		0.86	2.06	2.753(4)	137
	N4—H4···N2		0.86	2.28	2.655(4)	107
2b	N1—H1···S1	$3/2-x, -1/2+y, -z$	0.86	2.62	3.4080	153
	N3—H3···O1		0.86	2.03	2.7184	137
	N4—H4A···N2		0.86	2.25	2.6428	108
	C7—H7···O1	$3/2-x, -1/2+y, -z$	0.93	2.31	3.2361	174
	C11—H11B···S1		0.97	2.72	3.1286	106
3a	N3—H3···O1		0.86	2.08	2.759(6)	136
	N4—H4···N2		0.86	2.27	2.641(14)	106
	N4—H4···S1	$1/2+x, y, 1/2-z$	0.86	2.59	3.372(14)	151
	C4—H4···S1	$1/2+x, y, 1/2-z$	0.93	2.82	3.613(6)	144
	C11—H11B···S1		0.97	2.57	3.039(13)	110
	C13—H13B···O1		0.97	2.53	2.915(7)	104
	C17—H17A···O1	$-x, 1-y, -z$	0.97	2.57	3.484(12)	157

In compound **2b**, benzyl group at C11 is nearly orthogonal to the indole moiety, as indicated by the dihedral angle 80.3°. The planar O1 atom takes part in two hydrogen bonding. N3—H3···O1 intra-molecular interaction can be regarded as one component; in the second component, atom C7 at (x,y,z) acts as hydrogen bond donor to atom O1 in the molecule at $(3/2-x,-1/2+y,-z)$. An interesting feature regarding the stacking interactions is clearly demonstrated in Figs. 5 and 6, which revealed that the molecule **2b** favoured to form chains along *b*-axis with NH···S and CH···O interactions. These hydrogen bonds connect the residues in the direction of the *b*-axis. These chains are not in the linear conformation. It is shown in the crystal packing represented onto ac-plane that these chains which are formed by NH···S and CH···O interactions are arranged in zig-zag formation. The weak fluor···π interaction is observed between F2 atom on C9 and benzyl group at C11 of symmetry related molecule; the distance between atom F2 and the centroid of the plane (C12 → C17)^{ii} is 3.5833 C [symmetry code: (i) $x, 1-y, 1/2-z$], whereas the C9—F2···centroid angle is 160°. The π···π stacking interaction involving the phenyl rings in the indole moiety [Cg(C12 → C17)···Cg(C12 → C17)^{iv} with symmetry code: $x, 1-y, 1/2-z$] also influences the packing arrangement of the molecule along *b*-axis. The distance between the centroids of the phenyl ring is 3.7739 Å and the dihedral angle between the planes is 1.54°.

For compound **3a**, as mentioned above the molecule is not planar entirely while the morpholin ring and the trifluoro groups are nearly perpendicular to the indole heterocyclic ring. The dihedral angle between the indole and the best plane of the morpholin ring is 89.8(4)°; the torsion angle of C9—O2—C5—C6 is 91.3(7)°. It is observed that the morpholin ring and ethylamino group are disordered over two positions with occupancy factors of 0.65 for the sites C14—C17, O3 and N4, C11, C12 and of 0.35 for the sites C14'—C17′, O3′ and N4′, C11′, C12′ (Fig. 3). The morpholin ring adopts chair conformation. The puckering parameters of this ring are $Q = 0.610(12)$ Å, $\theta = 168.6(10)°$, $\varphi = 11(7)°$, and atoms N5 and O3 are displaced from the C14/C15/C16/C17 mean plane by 0.795(5) and −0.571(10) Å, respectively. The molecular packing is stabilized by N—H···S, C—H···O and C—H···S intermolecular

hydrogen bonds. The molecules are linked through the N4—H4N···S1 hydrogen bond along the *a*-axis. For this compound two intermolecular π···π stacking are also observed. One of them is found between (N1 → C8) and (C3 → C8)^{i} rings and the other is observed between (C3 → C8) and (C3 → C8)^{i} rings; the distance between the centroid of the pyrrole and the centroid plane of the phenyl ring is 3.544 Å and the dihedral angle between the planes is 2.14°. The distance between the centroids of the phenyl rings is 3.642 Å [symmetry code: (i) $1-x$, $1-y$, $-z$].

4. Conclusions

Novel 5-trifluoromethoxy-1*H*-indole-2,3-dione 3-(*N*-ethyl/benzylthiosemi carbazone) (**2a**/**2b**) and 5-trifluoromethoxy-1-morpholinomethyl-1*H*-indole-2,3-dione 3-(*N*-ethylthiosemicarbazone) (**3a**) compounds were synthesized, their structures were confirmed by spectral data, elemental and single crystal X-ray diffraction analysis. Lactam and keton C=O stretching bands of 5-trifluoromethoxy-1*H*-indole-2,3-dione **1** absorbing as two separate bands absorbed as a single lactam C=O stretching band and a keton C=O stretching band disappeared in the IR spectra of **2a**, **2b** and **3a**. ^{1}H NMR spectra of the compounds supported the IR findings and displayed signals which were attributed to the NH protons of the thiosemicarbazone moiety. LCMS–APCI data of **2a** and **3a** were also determined in order to confirm the assigned thiosemicarbazone structure.

For three compounds, the geometric parameters obtained from X-ray crystal structure analysis are in the expected ranges. A positional disorder in the morpholin ring and ethylamino group in **3a** was resolved. The indole-thiosemicarbazone counterparts in the structures are nearly planar; the dihedral angles between the pyrrole and the adjacent phenyl rings are in the range of 2–5°. In all three crystal structures, a strong N—H···O hydrogen bond links the flat conjugated H—N—N=C—C=O fragment into a six-membered ring. The structures **2b** and **3a** consist of isolated molecules, while that of **2a** contains dimers formed by C—H···O hydrogen bonds. The molecules are linked into three dimensional framework structure by a combination of mainly N—H···N and N—H···O hydrogen bonds and weak C—F···π and π···π interactions.

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