Unexpected Configuration in Stereoselectively Synthesis of Some Novel (1*Z*)-1-(morpholin-1-yl)-N^2-Arylamidrazones

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Abstract: The nucleophilic substitution reaction of hydrazono-*N*-(aryl)-propanehydrazonyl chlorides **7** with piperidine or morpholine, under the same reaction conditions, resulted in the formation of 1-(piperdin-1-yl / morpholine-1-yl)-N^2-arylamidrazones **8a-k**, respectively. The X-ray diffraction of piperidin-1-yl-N^2-arylamidrazone (**8b**) confirmed its *1E*-configuration in agreement with the previously reported, whereas X-ray showed the unexpected *1Z*-configuration of their analogs, morpholin-1-yl-N^2-arylamidrazone (**8j**). This study established the role of hydrogen bond interaction in the stereochemistry of this class of amidrazones.

Keywords: Amidrazones, hydrogen bond interaction, stereoselectively, x-ray diffraction analyses.

INTRODUCTION

Open-chain or cyclic amidrazones have received much attention as shown by the numerous published studies due to their biological interests. Amidrazones are known to exhibit inhibitory activity against enzymes of arachidonic acid cascade which is responsible for the formation of important metabolites [1]. These substances are considered as potent mediators of inflammatory and allergic reaction in humans [2]. Amidrazones have been found to be effective towards cholinesterase, nucleoside hydrolase and glycosidase [3-5]. Consequently, the efficient construction of these molecules has received significant attention [6, 7]. In the light of pharmacological activity of amidrazones, several reports in the literature have focused on their configuration using X-ray diffraction analyses which revealed the role of hydrogen bond interaction in their stereochemistry [8-10].

Recently, we have been reported the synthesis of a new class of benzofuran-based (1Z)-*N*-arylpropanehydrazonoyl chlorides **1** with highly synthetic potency for stereoselective synthesis of (1*E*)-1-(piperdin-1-yl)-N^2-arylamidrazones **2** and **3** [9]. X-ray analyses of the latter amidrazones showed a conversion of configuration with respect to **1**. Moreover, Abdel-Aziz *et al*. have reported the (1*E*)-1-(piperidin-1-yl)-2-(benzathiazol-2-oyl)-N^2-arylamidrazones **4** with the same configuration of amidrazones **2** and **3** [10]. However, X-ray diffraction analyses of the latter piperidine-based amidrazones identified a different intra- and intermolecular hydrogen bond interaction.

In continuation of our interest in the synthesis of bioactive heterocycles [11-18], here, we deal with the syntheses of some morpholine-based amidrazones as structural analogs for (1*E*)-1-(piperdin-1-yl)-N^2-arylamidrazones **2-4**. Our latter studies prompted us to combine our present study with X-ray diffraction analysis to determine the configuration of the new 1-(morpholin-1-yl)-N^2-arylamidrazones.

Reaction of acid hydrazides **5** with 2-oxo-*N*-arylpropanehydrazonyl chlorides **6** yielded hydrazono]-*N*-(aryl)-propanehydrazonyl chlorides 7 [9, 10] (Fig. **1**). Next, heating each of the compounds **7**, in absolute ethanol, with piperidine or morpholine resulted in the formation of a precipitate, in each case during reflux. Single product was evidenced by TLC analysis of the product [19]. However, ^{1}H NMR and mass spectra were comparable with desired structures **8a-k** [20]. The IR spectra of the latter amidrazones exhibited, in each case, a band in the region of 1700-1680 cm^{-1} due to the carbonyl absorption, 1620-1590 cm^{-1} due to C=N stretching, whereas the absorption bands of 2 NH functions appeared in the region 3350-2980 cm^{-1}. Their ^{1}H NMR spectra were characterized by the two D_2O exchangeable signals of 2 NH groups in the region of δ 8.26-9.86 and δ 9.38-11.19. ^{1}H NMR spectra of piperidine-based amidrazones showed two signals of piperidine moiety in the regions δ 1.54-1.63 and δ 2.98-3.33, whereas, morpholine signals appeared in the region of δ 2.95-3.13 and δ 3.71-3.82 for morpholine-based amidrazones. The ^{13}C NMR spectra showed signals of sp^3 signals of piperidine carbons in the region δ 25.5-39.9 and morpholine carbons in the region δ 30-39.

The single crystal of **8b** was cultured from EtOH by slow evaporation at room temperature. The X-ray analysis of amidrazone **8b** showed its structure geometry as (1*E*,2*E*)-configuration (Fig. **2**) which confirms a conversion of configuration with respect to the geometry of their reactants hydrazonyl halides (1*E*,2*Z*) [10]. X-ray of the latter amidrazone confirmed both of the stereoselectivity of the reaction and the *E* configuration of amidrazone skeleton (1*E*

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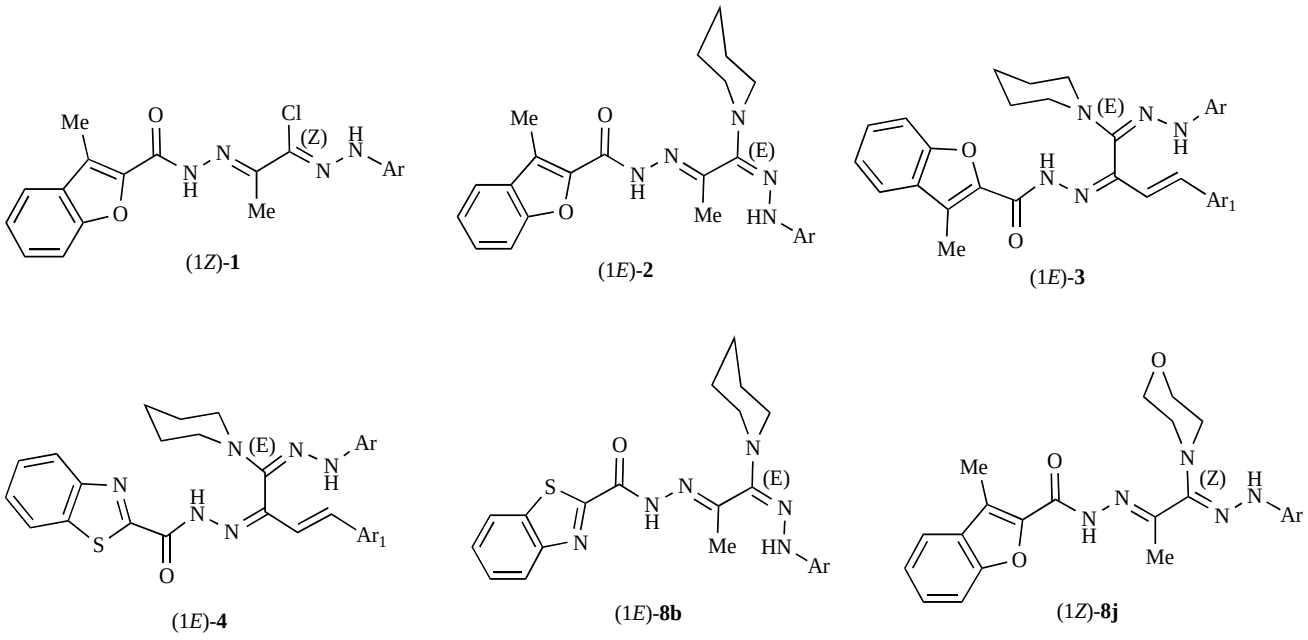
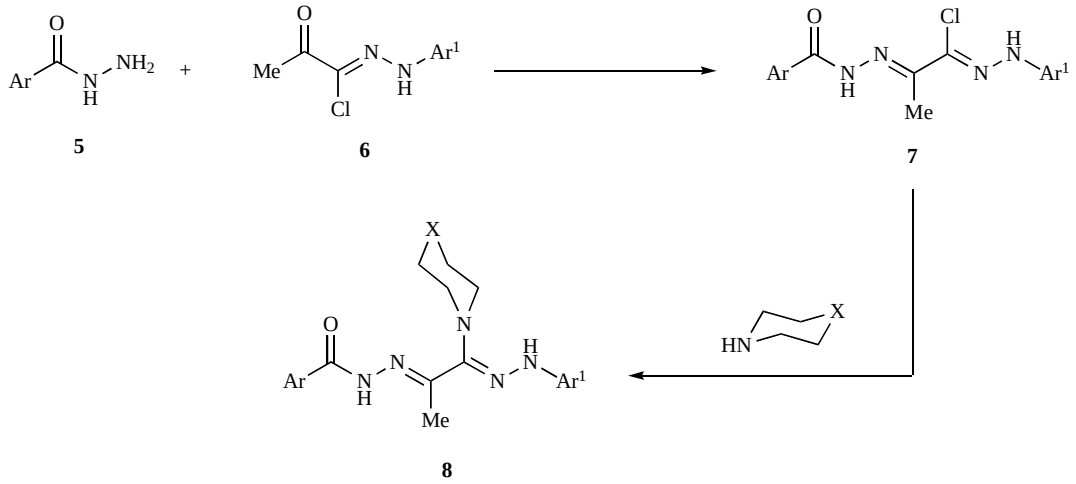
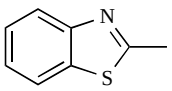
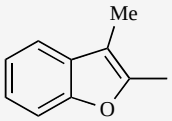


Fig. (1). Structure of hydrazonyl chloride **1** and amidrazones **2-4**, **8b**, and **8j**.



Comp.	Ar	Ar^1	X
8a		4-Me-C_6H_4-	CH_2
8b		4-Br-C_6H_4-	CH_2
8c		4-Me-C_6H_4-	O
8d		4-Br-C_6H_4-	O
8e		4-F-C_6H_4-	O
8f		4-NH_2SO_2-C_6H_4-	O
8g		2-Cl-C_6H_4-	CH_2
8h		3-Cl-C_6H_4-	CH_2
8i		4-NH_2SO_2-C_6H_4-	CH_2
8j		2-Cl-C_6H_4-	O
8k		4-NH_2SO_2-C_6H_4-	O

Scheme 1. Synthesis of compounds **8a-k**.

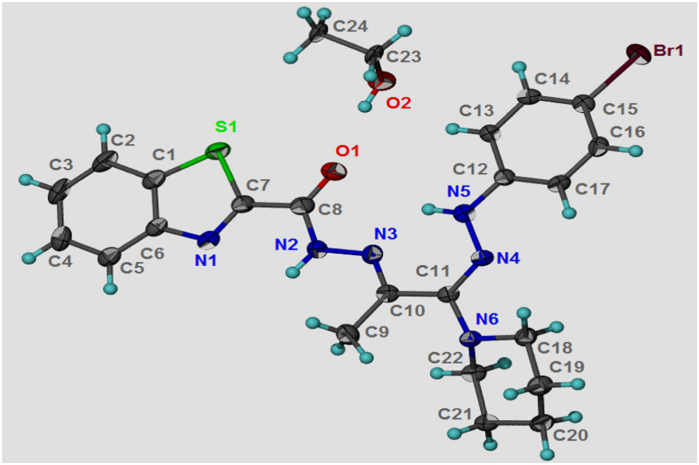
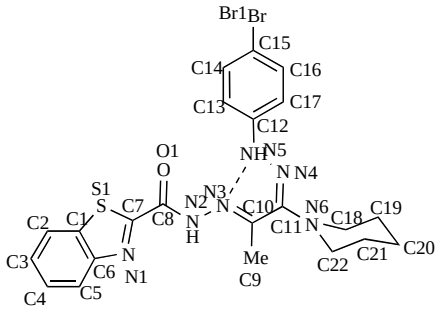


Fig. (2). X-ray structure of (1*E*,2*E*)-**8b** ethanol solvated.

Table 1. Characteristic Bond Lengths [Å], Torsion Angles [°] and Intramolecular H-bond of (1*E*,2*E*)-8b.

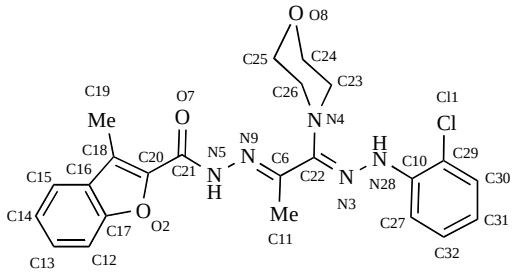


Bond Length [Å]					
Br1—C15	1.902 (1)	N6—C22	1.478 (1)	C15—C16	1.381
S1—C1	1.732 (1)	C1— C2	1.399	C16—C17	1.384
S1—C7	1.736 (1)	C1—C6	1.410	C18—C19	1.525 (1)
O1—C8	1.220 (2)	C2—C3	1.376	C19—C20	1.510 (1)
N1—C6	1.387	C3—C4	1.400	C20—C21	1.525 (1)
N1—C7	1.298	C4—C5	1.384	C21—C22	1.524 (1)
N2—N3	1.366	C5—C6	1.400	O2—C23	1.513 (1)
N2—C8	1.361	C7—C8	1.483	O2 —C24	1.478 (1)
N3—C10	1.294	C9—C10	1.505 (1)	C23—C24	1.497 (1)
N4—N5	1.354 (1)	C10—C11	1.479	C24—O2	1.478 (1)
N4—C11	1.301	C12—C13	1.398	C24—C24	1.176 (1)
N5—C12	1.392 (1)	C12—C17	1.391	O2—C23	1.513 (1)
N6—C11	1.412 (1)	C13—C14	1.380	C23—C24	1.497 (1)
N6—C18	1.469 (1)	C14—C15	1.391		
Torsion Angles [°]					
(1*E*) N6–C11–N4–N5			177.20		
(2*E*) C11–C10–N3–N2			178.99		
Intramolecular H-bond					
D—H----A		D—H	H----A	D----A	<(DHA)
N5—H5-----N6		0.961	1.870	2.578	128.27

The bond lengths [Å], torsion angles [°] and intramolecular H-bond of (1*E*,2*E*)-**8b** are well within the range that typically occurred in similar amidrazone derivatives [9,10].

= 177.20º and 2*E* = 178.99º) [21, 22]. The intramolecular hydrogen bond interaction N5—H5-----N3 played a crucial role in stabilizing the configuration of compound **8b** in solid state [8]. Selected bond distances, torsion angles [°] and intramolecular H-bond of bis-hydrazone **8b** are illustrated in Table **1**.

Table 2. Characteristic Bond Lengths [Å] and Torsion Angles [°] of (1*Z*,2*E*)-8j.



Bond length [Å]					
Cl1—C29	1.725 (5)	C6—C22	1.441 (5)	C27—C32	1.397 (7)
O2—C17	1.358 (5)	O8—C25	1.402 (5)	C27—C10	1.377 (6)
O2—C20	1.404 (4)	O8—C24	1.425 (5)	C25—C26	1.496 (5)
N3—N28	1.354 (4)	O7—C21	1.207 (4)	C32—C31	1.385 (11)
N3—C22	1.296 (4)	N28—C10	1.403 (5)	C29—C30	1.390 (9)
N4—C22	1.425 (4)	C16—C17	1.364 (5)	C29—C10	1.377 (6)
N4—C26	1.458 (4)	C16—C18	1.417 (6)	C14—C15	1.368 (6)
N4—C23	1.453 (5)	C16—C15	1.398 (6)	C14—C13	1.388 (7)
N5—N9	1.379 (4)	C17—C12	1.396 (6)	C31—C30	1.336 (11)
N5—C21	1.359 (5)	C20—C18	1.345 (5)	C12—C13	1.394 (6)
C6—N9	1.271 (4)	C20—C21	1.469 (5)	C23—C24	1.503 (5)
C6—C11	1.502 (5)	C18—C19	1.510 (5)		
Torsion angles [°]					
(1*Z*) N4–C22–N3–N28			-0.7(9)		
(2*E*) C22–C6–N9–N5			-178.0(15)		

The bond lengths [Å] and the torsion angles [°] of (1*Z*,2*E*)-**8j** are well within the range that typically occurred in similar amidrazone derivatives [9,10].

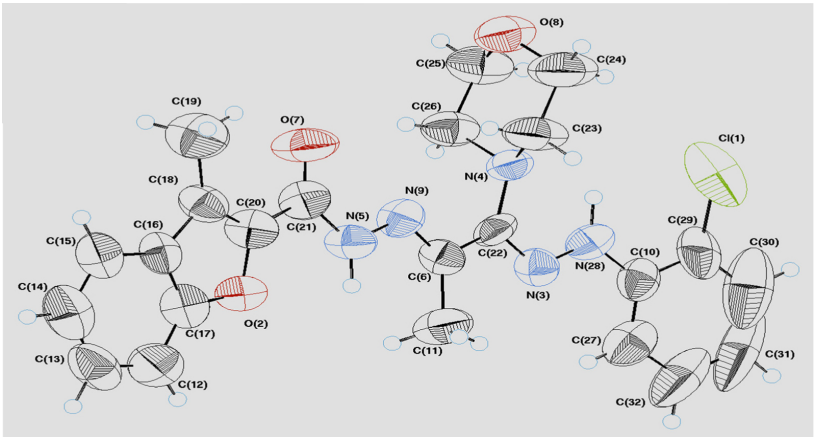


Fig. (3). X-ray structure of (1*Z*,2*E*)-**8j**.

Interestingly, the X-ray analysis of amidrazone **8j**, in contrast to that of compound **8b**, showed its structure geometry as (1*Z*,2*E*)-configuration (Fig. **3**) which confirms a retention of configuration with respect to the geometry of their reactants hydrazonyl chlorides (1*E*,2*Z*). Although, the single crystal of **8j** was cultured from the same solvent of crystal **8b**, EtOH, no intramolecular hydrogen bond interactions were detected in **8j**. Selected bond distances of **2** and torsion angles 1*Z* and 2*E* are illustrated in Table **2**.

In conclusion, we have uncovered an unexpected *1Z*-configuration of morpholin-1-yl-N^2-arylamidrazone with respect to that of their analogs, piperidin-1-yl-N^2-arylamidrazone with *1E*-configuration.

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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[19] *Synthesis of 1-(piperdin-1-yl / morpholine-1-yl)-N^2-arylamidrazones* ***8a-k***. To a solution of hydrazono-*N*-(aryl)-propanehydrazonyl chlorides 7 (1 mmol) in ethanol (50 mL), piperidine or morpholine (2 mmol) was added. The reaction mixture was heated 45 min at 100 °C then left to cool at room temperature overnight. The precipitated product was filtered off, washed with ethanol and dried, recrystallized from ethanol to afford the amidrazones **8a-k** in 65-78% yield.

[20] *(1E,2E)-1-(Piperidin-1-yl)-1-[(4-methylphenyl)hydrazono]-2-[benzothiazol-2-oyl)hydrazono]propane (**8a**). Mp 178-180 °C; IR (KBr) ν 3140, 3060* (2NH), 1700 (C=O), 1620 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.62 (s, 3CH_2, piperidino), 2.1 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 3.03 (s, 2CH_2, piperidino), 7.05- 7.16 (m, 8H, Ar-H), 9.30 (s, 1H, =NNH, D_2O exch.), 9.7 (s, 1H, CONH, D_2O exch.); ESI MS *m/z* 434.5 [M^+]. *(1E,2E)-1-(Piperidin-1-yl)-1-[(4-bromophenyl)hydrazono]-2-[benzothiazol-2-oyl)hydrazono]propane* (***8b***). Mp 148-150 °C; IR (KBr) ν 3350, 3000 (2NH), 1700 (C=O), 1590 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.59 (s, 3CH_2, piperidino), 2.26 (s, 3H, CH_3), 3.05 (s, 2CH_2, piperidino), 6.92- 8.27 (m, 8H, Ar-H), 9.41(s, 1H, =NNH, D_2O exch.), 10.80 (s, 1H, CONH, D_2O exch.); ^{13}C NMR (DMSO-d_6) δ 15.7, 18.4, 22.2, 23.9, 25.1, 25.5 (piperidine) 39.2, 39.9 (piperidine) 43.7, 48.9, 49.1, 56.0, 108.4, 113.8, 115.4, 122.9, 124.1, 127.1, 131.5, 136.0, 145.6, 146.3, 152.6; ESI MS *m/z* 499.2 [M^+]. *(1Z,2E)-1-(Morpholin-1-yl)-1-[(4-methylphenyl)hydrazono]-2-[benzothiazol-2-oyl)hydrazono]propane* (**8c**). Mp 238-240 °C; IR (KBr) ν 3000, 2900 (2NH), 1740 (C=O), 1640 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.0 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.09 (s, 2CH_2, morpholino), 3.79 (s, 2CH_2, morpholino), 7.00-7.20 (m, 8H, Ar-H), 9.57 (s, 1H, =NNH, D_2O exch.), 10.28 (s, 1H, CONH, D_2O exch.); ESI MS *m/z* (%) 436.9 [M^+]. *(1Z,2E)-1-(Morpholin-1-yl)-1-[(4-bromophenyl)hydrazono]-2-[benzothiazol-2-oyl)hydrazono]propane* (**8d**). Mp 188-190 °C; IR (KBr) ν 3000, 2960 (2NH), 1700 (C=O), 1600 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.3 (s, 3H, CH_3), 3.06 (s, 2CH_2, morpholino), 3.78 (s, 2CH_2, morpholino), 7.29-8.2 (m, 8H, Ar-H), 9.68 (s, 1H, =NNH, , D_2O exch.), 10.12 (s, 1H, CONH, D_2O exch.); ESI MS *m/z* 501.0 [M^+]. *(1Z,2E)-1-(Morpholin-1-yl)-1-[(4-flourophenyl)hydrazono]-2-[benzothiazol-2-oyl)hydrazono]propane* (**8e**). Mp 210-212 °C; IR (KBr) ν 3100, 3060 (2NH), 1710 (C=O), 1620 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.3 (s, 3H, CH_3), 2.95 (s, 2CH_2, morpholino), 3.71 (s, 2CH_2, morpholino), 7.02-8.27 (m, 8H, Ar-H), 9.60 (s, 1H, =NNH, D_2O exch.), 10.80 (s, 1H, CONH, D_2O exch.); ^{13}C NMR (DMSO-d_6) δ 30.64, 38.9, 39.9, 121.5, 147.3, 150.2, 167.6, 2.6.5; ESI MS *m/z* 440.9 [M^+]. *(1Z,2E)-1-(Mopholin-1-yl)-1-[(4-sulphonamidophenyl)hydrazono]-2-[benzothiazol-2-oyl)hydrazono]propane* (**8f**). *(1E,2E)-1-(Piperidin-1-yl)-1-[(2-chlorophenyl)hydrazono]-2-[3-methylbenzofuran-2-oyl)hydrazono]propane* (**8g**). Mp 195-197 °C; IR (KBr) ν 3300, 3000 (2NH), 1680 (C=O), 1590 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.63 (s, 3CH_2, piperidino), 2.29 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.98 (s, 2CH_2, piperidino), 7.31-7.80 (m, 8H, Ar-H), 9.37 (s, 1H, =NNH, D_2O exch.), 10.61 (s, 1H, CONH, D_2O exch.); ESI MS *m/z* 451.7 [M^+]. *(1E,2E)-1-(Piperidin-1-yl)-1-[(3-chlorophenyl)hydrazono]-2-[3-methylbenzofuran-2-oyl)hydrazono]propane* (**8h**). Mp 233-235°C; IR (KBr) ν 3020, 2980 (2NH), 1690 (C=O), 1600 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.54 (s, 3CH_2, piperidino), 2.24 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 3.33 (s, 2CH_2, piperidino), 6.66-7.83 (m, 8H, Ar-H), 8.91 (s, 1H, =NNH, D_2O exch.), 10.80 (s, 1H, CONH, D_2O exch.); ESI MS *m/z* 449.7 [M^+]. *(1E,2E)-1-(Piperidin-1-yl)-1-[(4-sulphonamidophenyl)hydrazono]-2-[3-methylbenzofuran-2-oyl)hydrazono]propane* (**8i**). Mp 220-222 °C; IR (KBr) ν 3040, 3000 (2NH), 1700 (C=O), 1590 (C=N) cm^{-1}; MS *m/z* 497.3 [M^++1]. Mp 228-230; °C; IR (KBr) ν 3300, 3100 (2NH), 1690 (C=O), 1600

(C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.36 (s, 3H, CH_3), 3.13 (s, $2CH_2$, morpholino), 3.82 (s, $2CH_2$, morpholino), 7.13 (s, 2H, SO_2NH_2), 7.42-8.30 (m, 8H, Ar-H), 9.86 (s, 1H, =NNH, , D_2O exch.), 11.19 (s, 1H, CONH, D_2O exch.); ESI MS *m/z* 501.7 [M^+]. *(1Z,2E)-1-(Morpholin-1-yl)-1-[2-chlorophenyl)hydrazono]-2-[3-methylbenzofuran-2-oyl)hydrazono]propane* (**8j**). Mp 222-225°C; IR (KBr) *v* 3360, 3280 (2NH), 1680 (C=O), 1590 (C=N) cm^{-1}; ESI MS *m/z* 453.9 [M^+]. *(1Z,2E)-1-(Morpholin-1-yl)-1-[4-sulphonamidophenyl)hydrazono]-2-[3-methylbenzofuran-2-oyl)hydrazono]propane* (**8k**). Mp 230-232 °C; IR (KBr) *v* 3400, 3280 (2NH), 1680 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.0 (s, 3H, CH_3), 3.0 (s, $2CH_2$, morpholino), 3.7 (s, $2CH_2$, morpholino), 6.52 (s, 2H, SO_2NH_2), 7.01-7.62 (m, 8H, Ar-H), 8.26 (s,1H, =NNH, D_2O exch.), 9.38 (s, 1H, CONH, D_2O exch.) ; ESI MS *m/z* 497.1 [M^+].

[21] The X-ray diffraction measurements of compound **8b** was made using Bruker (2009). APEX2 and SAINT (Bruker AXS Inc., Madison, Wisconsin, USA), at wavelength λ = 1.54184 Å. The X-ray diffraction measurements of compound **8j** was made using maXus (Bruker Nonius, Delft, The Netherlands and MacScience, Yokohama, Japan), at wavelength λ = 0.71073 Å.

[22] Crystallographic data for the structures **8b** and **8j** have been deposited with the Cambridge Crystallographic Data Center (CCDC) under the numbers 833322 and 835060, 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; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk].