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Furan derivatives of substituted phenylthiourea: spectral studies, semi-empirical quantum-chemical calculations and X-ray structure analyses

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Abstract

Fifty new derivatives of 1-(furan-2-carbonyl)- and 1-(furan-3-carbonyl)-3-phenyl substituted thiourea have been synthesised and identified. Intramolecular hydrogen bonds were investigated in detail, using IR spectroscopy. The three-level Fermi resonance effect in the IR spectra was analysed after deconvolution and band separation. Semi-empirical quantum-chemical calculations (AM1 and PM3) support the results of the IR spectroscopic studies. X-ray single crystal diffraction analyses of four selected compounds, namely 1-(furan-3-carbonyl)-3-(2-trifluoromethyl-phenyl)-thiourea (1e), 1-(2-methyl-furan-3-carbonyl)-3-(2-trifluoromethyl-phenyl)-thiourea (2e), 1-(2,6-dichlorophenyl)-3-(2-methyl-furan-3-carbonyl)-thiourea (2n) and 1-(4-methoxyphenyl)-3-(3-methyl-2-furan-carbonyl)-thiourea (3e), corroborated the molecular and crystal structure of these compounds. Relatively strong intramolecular hydrogen bonds of the N–H…O=C type as well as intermolecular two-centred and bifurcated three-centred hydrogen bonds were observed, confirming the results of the IR spectral study and the semi-empirical quantum-chemical calculations. A variety of intermolecular interactions, yielding the supramolecular architectures in the four crystalline compounds, are discussed in detail.

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Keywords: Thiourea; Hydrogen bonds; Fermi resonance; AM1; PM3; X-ray structure analysis

1. Introduction

Their interesting biological properties, potential for practical application and availability have considerably stimulated structure investigation of derivatives of thiourea [1-3], especially, with respect to their capability of hydrogen bond formation [4]. Besides an interest in preparation and properties of individual molecules, an increasingly significant portion of up-to-date research in

organic chemistry concerns interactions among molecules. Such interactions are governed by intermolecular forces whose energetic and geometric properties are less well understood than those of covalent bonds. Conventional hydrogen bonds (i.e. O-H···O, N-H···O) play a dominating role among intermolecular interactions due to their strength and directionality. They are also known to influence properties and functions of biologically significant substances, e.g. saccharides, proteins and nucleic acids [5]; hence information about hydrogen bond interactions involving these molecules has proved to be essential for the understanding of biochemical processes of vital importance, such as enzyme-substrate, drug-receptor, and proteinligand interactions, among others. Nevertheless, because recognition as well as packing of molecules is determined by a sensitive balance of many different intermolecular

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forces, a substantial amount of chemical research today is directed toward increasing the understanding of the nature and character of weaker interaction forces than those of classical hydrogen bonds [6,7]. Interactions involving organic halogens have been discussed in the literature for some considerable time [8,9]. However, hydrogen bonds, differing from the conventional X–H···X (X=O, N) case, such as C-H···O and X-H··· π interactions (X=O, N, C) [10–15], anti-hydrogen bonds [16–18] and the 'dihydrogen bond' X–H···H–M (X=O, N; M=Ir, Re) [10] have been recognized as interactions of chemical relevance only during the last decade. Moreover, although sulphur, an important element in biochemistry, can be regarded as a conventional H-bond acceptor [19], the X-H...S bonds (X=O, N) are only of moderate strength [20] and together with the considerably weaker C-H···S interactions are demanding further evidence. In this connection, investigation of the conditions and requirements of formation of hydrogen bonds and related intermolecular interactions by various thiourea derivatives in the solid state may lead to valuable information about interaction modes between selected functional groups, on the one hand, and about the characteristics of this compound family, on the other.

Conventional hydrogen bonds can be detected by vibrational spectroscopy. In addition, very specific so-called resonance phenomena can also be observed in vibrational spectra, mainly Fermi resonance, which is very important for analysis of rotation–vibration spectra and correct interpretation of hydrogen bonds. We encounter it mainly in polyatomic molecules, if two or three vibrational levels exhibit the same symmetry and similar energies.

In accordance with the ideas mentioned above, the aim of the present investigation has been to contribute to the study of hydrogen bonds in four series of, mostly novel, 1-(furan-2-carbonyl)- and 1-(furan-3-carbonyl)-3-phenyl-substituted thiourea derivatives. These compounds seem to us to be good model compounds for such a study, because they contain various heteroatoms and functional groups accessible to formation of hydrogen bonds. We have therefore studied hydrogen bonding in this class of compounds, using IR spectroscopy, semi-empirical calculations and X-ray diffraction analysis.

2. Results and discussion

2.1. Syntheses

The derivatives of 1-(furan-2-carbonyl)- and 1-(furan-3carbonyl)-3-phenyl-substituted thiourea (1a–1n, 2a–2p, 3a–3n, 4a–4f) (Scheme 1) were prepared by reaction of corresponding furoylisothiocyanates with amines. The molecular structures of the newly synthesized compounds were established by IR and NMR spectral methods. The details are gathered in the experimental part.

2.2. IR spectroscopy

IR spectra of 1-(furan-2-carbonyl)- and 1-(furan-3-carbonyl)-3-phenyl thiourea derivatives are shown in Table 1.

In a detailed study of the IR spectra of these substances, we observed the absorption bands belonging to the free amidic NH group, which appear in the 3423-3385.1 cm⁻ region (Table 1). The spectra of all studied compounds exhibit absorption bands also in the $3238.3-3208.8 \text{ cm}^{-1}$ region, which we attribute to intramolecular hydrogen bonding between the hydrogen atom of the thioamidic NH group and the oxygen atom of the carbonyl group [4,21,22]. The concentration independence of the intensity ratio of those bands as well as the absence of another band of the free NH group at low concentrations also indicate that the compounds occur mostly in the conformation containing the closed, H-bonded six-membered ring. In addition to the hydrogen bond indication, we also observed anomalous splitting of the absorption bands of the thioamidic NH bond due to Fermi resonance [23,24], with the ν (C=C)_{ar} overtone and the $\nu(C=C)_{ar} + \delta(NH)$ combination vibration, so it gives the interaction for three vibrational levels (Table 1). It is also well known that Fermi resonance can play a major role not only in strong hydrogen bonds, but also in relatively weak hydrogen bonds [25,26]. This implies that, if we want to assess the hydrogen bond strength, we have to obtain the wave number of the absorption bands without the influence of Fermi resonance, because only such wave numbers will be dependent solely on the force constant [27]. For this reason, the relations based on the method of Langseth and Lord and improved by Nyquist et al. [28] have been applied in cases involving three-level interactions to enable the calculation of the wave numbers of the bands, corrected for Fermi resonance (Table 1). We found that the first band in the Fermi triplet is associated with the branch that, after elimination of the resonance, belongs to the bonded ν (NH) stretching vibration. The middle branch of the triplet can be assigned to the first overtone $\nu(C=C)_{ar}$ of the phenyl ring, and the other side branch of the triplet is connected with the ν (C=C)_{ar} + δ (NH) combination vibration. From the unperturbed wave number values we calculated the extent of interaction [28,29] between the absorption band pairs W_{AB} , $W_{\rm BC}$, $W_{\rm AC}$ (Table 1), and found that the $\nu(\rm NH\cdots O=C)$ ground stretching vibration interacts more with the $\nu(C=C)_{ar} + \delta(NH)$ combination vibration than with the $\nu(C=C)_{ar}$ overtone in almost all of the compounds. The very strong absorption bands of the carbonyl stretching vibrations lie within the 1699.6–1670 cm^{-1} range for all the compounds, but the wave numbers are also affected by the intramolecular NH \cdots O=C hydrogen bonds. The strength of those hydrogen bonds can be demonstrated by calculating their force constants [30] from the band positions corrected for Fermi resonance. For the NH····O=C hydrogen bonds, the force constants lie within the $(5.749-5.654) \times 10^2$ N m⁻ range. These results could be compared with previous data

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1		$\langle $	R			F	2
	R		R		R		R
1a 1b 1c 1d 1e 1f 1g	H 4-CH ₃ 2,4-(CH ₃) ₂ 4-C(CH ₃) ₃ 2-CF ₃ 3-CF ₃ 4-CF ₃	1h 1i 1j 1k 11 1m 1n	3,5-(CF ₃) ₂ 4-OCH ₃ 4-OCF ₃ 2-F 2,6-(Cl) ₂ 4-Br 4-I	- 2a 2b 2c 2d 2e 2f 2g . 2h	H 4-CH ₃ 2,4-(CH ₃) ₂ 4-C(CH ₃) ₃ 2-CF ₃ 3-CF ₃ 4-CF ₃ 4-CF ₃ 4-OCH ₃	2i 2j 2k 2l 2m 2n 20 2p	4-OCF ₃ 2-F 4-F 4-Cl 2,3-(Cl) ₂ 2,6-(Cl) ₂ 4-Br 4-I
		$-\langle$	R	H ₃ C			R
	R		R		R		
3a	4-CH ₃	3h	4 - F	- 4a	4-C(CH ₃) ₃		
3b	2,4-(CH ₃) ₂	3i	2,4-(F) ₂	4b	3-CF ₃		
3e	4-C(CH ₃) ₃	3j	4-C1	4c	2-F		
3d	4-CF ₃	3k	$2,6-(Cl)_2$	4d	4 - F		
3e 2f	4-0CH ₃	31 2m	3,4-(CI) ₂	4e	2,4-(F) ₂		
3g	4-0CF ₃ 2-F	3n	4- D г 4-I	4f	3,4-(Cl) ₂		

Scheme 1.

[31]. To find the influence of substituents on the hydrogen bond strength, we utilised the linear correlation between spectroscopic properties and Hammet's substituent constants σ_p [32]. We have taken into consideration the wave numbers of ν (NH)_{free}, ν (C=O) and the unperturbed ν_A^0 (NH···O=C) wave numbers, i.e. those corrected for Fermi resonance. Statistical results of this correlation are listed in Table 2.

The correlations for free NH groups are statistically most significant for all compounds. Similarly, the unperturbed wave numbers for bonded NH groups and ν (C=O) for 1a-**3n** also fit the correlation quite well. In the case of the **4a–4f** compounds, the correlations are less significant because of the very few substances available for investigation. The correlation includes also a few 2,4- and 3,4-disubstituted compounds, the σ values of which were calculated assuming additivity of $\sigma_{\rm p}$ and $\sigma_{\rm m}$ values. The relatively small effect of ortho and meta-substituents on the strength of intramolecular hydrogen bonding can be explained by the nonplanarity of the studied compounds and by the substituted phenyl ring being turned toward other parts of the molecule. The deviations in the mentioned dependencies can also be due to the presence of weak interactions between the solute molecule and the solvent.

2.3. Semi-empirical calculations

After spectroscopic verification of the existence of relatively strong intramolecular hydrogen bonds in the studied compounds, we tried to obtain more information about the most stable conformations of selected molecules. For such conformational studies, we used the semi-empirical methods AM1 and PM3. Geometries were completely optimised, whereupon we carried out the conformational study. The calculated bond distances and bond angles are presented in Table 3. (Supplementary Material) for 1-(furan-2-carbonyl)- and 1-(furan-3-carbonyl)-3-phenyl-thiourea derivatives. The lengths of hydrogen bonds are in the range of 1.81-1.84 Å for PM3 and 2.05-2.10 Å for AM1 calculations. The calculated angles N-H...O are more than 120° for all compounds. The observed deviation of phenyl ring is caused by presence of the substituents. The most significant deviation is recognized in derivatives containing two atoms of chlorine at 2,6 positions of phenyl ring. The calculated torsion angles for 2,6-dichloro-substituted compounds (11, 2n, 3k) are around 91.29°.

The results obtained from the calculations proved that the most stable conformation for all derivatives of thiourea

Table 1				
IR band	positions (cm	⁻¹) of	compounds	1a–4f

	$\nu(\text{NH})^{a}$ free	Fermi triplet para	ameters ^b after band s	eparation ^a	v(C=O) ^a	ν (NH···O=C),	$2\nu(C=C)_{ar}$		ν (C=C) _{ar} +	$-\delta(NH)$	$W_{AB}; W_{AC}; W_{BC}$
		Band I ^c	Band II ^c	Band III ^c		$v_{\rm A}^{0 c}$	$\nu_{\rm B}^{0\rm c}$	Sum ^d	$v_{\rm C}^{0\rm c}$	Sum ^d	-
1a	3415.3 (1.662)	3234.7 (1.114)	3185.0 (0.604)	3151.2 (1.226)	1677.7 (4.216)	3202.70	3186.00	3192	3182.20	3140	11.05; 22.48; 4.86
1b	3415.2 (1.800)	3234.5 (1.545)	3186.9 (0.624)	3156.2 (1.484)	1676.8 (5.179)	3205.90	3187.53	3192	3184.16	3144	10.32; 22.26; 4.17
1c	3416.0 (1.540)	3230.7 (1.953)	3187.3 (0.524)	3152.8 (1.857)	1676.4 (4.632)	3203.97	3185.39	3224	3181.44	3156	8.08; 22.87; 4.63
1d	3415.7 (1.885)	3234.0 (1.185)	3187.3 (0.646)	3154.5 (1.307)	1677.6 (4.897)	3203.64	3187.93	3192	3184.23	3140	10.41; 21.34; 4.82
1e	3415.5 (1.684)	3223.9 (0.509)	3187.0 (0.481)	3147.7 (1.464)	1681.3 (4.073)	3191.30	3184.91	3220	3182.40	3150	4.70; 16.12; 3.74
1f	3414.1 (1.483)	3234.3 (0.483)	3186.9 (0.449)	3151.3 (1.175)	1678.2 (4.098)	3197.69	3188.34	3200	3186.47	3152	7.21; 18.67; 2.77
1g	3413.0 (1.247)	3233.8 (0.240)	3165.9 (1.083)	3136.2 (0.204)	1679.7 (2.671)	3187.93	3180.10	3200	3167.87	3148	17.59; 11.33; 17.58
1h	3413.6 (1.578)	3228.7 (0.166)	3169.9 (0.653)	3146.8 (0.380)	1680.3 (3.752)	3186.84	3181.17	3248	3177.39	3172	12.01; 12.46; 7.30
1i	3415.7 (0.901)	3235.1 (1.899)	3183.8 (1.143)	3150.5 (1.637)	1677.0 (2.226)	3203.69	3185.36	3192	3180.35	3140	13.59; 22.32; 6.53
1j	3414.5 (1.606)	3237.7 (0.629)	3177.6 (1.158)	3143.4 (0.735)	1679.5 (3.818)	3196.22	3184.67	3208	3177.82	3148	16.45; 18.24; 10.59
1k	3415.0 (1.615)	3233.3 (0.762)	3184.5 (0.682)	3145.1 (1.272)	1680.3 (3.883)	3196.62	3184.98	3240	3181.31	3172	9.79; 20.87; 5.33
1 l	3415.7 (1.521)	3215.7 (1.343)	3164.1 (1.132)	3141.6 (0.821)	1680.0 (5.090)	3187.26	3169.90	3160	3164.24	3124	16.38; 17.29; 7.38
1m	3414.3 (1.629)	3229.5 (0.574)	3171.3 (1.002)	3147.0 (0.445)	1679.1 (3.532)	3193.50	3180.92	3192	3173.37	3140	17.61; 15.10; 10.66
1n	3413.6 (1.134)	3225.9 (0.382)	3168.7 (0.665)	3150.3 (0.221)	1678.3 (2.524)	3192.91	3179.95	3184	3172.04	3136	18.08; 12.74; 10.51
2a	3421.2 (1.292)	3226.1 (0.328)	3178.2 (0.324)	3150.2 (0.930)	1671.7 (3.692)	3190.85	3182.09	3184	3181.55	3144	6.70; 16.74; 0.81
2b	3421.5 (1.743)	3224.1 (1.215)	3171.7 (0.458)	3144.7 (1.306)	1671.4 (3.709)	3193.73	3174.30	3176	3172.48	3124	10.17; 23.06; 2.24
2c	3423.0 (1.682)	3224.5 (1.551)	3176.8 (0.583)	3145.9 (1.649)	1671.5 (4.069)	3195.32	3177.38	3192	3174.50	3132	9.40; 22.47; 3.54
2d	3422.2 (1.720)	3225.4 (0.949)	3175.8 (0.574)	3144.8 (1.343)	1672.3 (3.655)	3192.43	3177.98	3176	3175.58	3112	9.66; 21.14; 3.21
2e	3422.6 (1.662)	3215.1 (0.669)	3171.4 (0.440)	3136.0 (0.960)	1675.8 (3.801)	3183.60	3171.19	3176	3167.72	3124	8.76; 20.06; 4.71
2f	3420.9 (1.742)	3218.6 (0.424)	3166.4 (0.737)	3127.7 (0.362)	1673.3 (3.489)	3181.90	3170.07	3184	3160.74	3144	16.50; 17.02; 13.44
2g	3420.2 (1.690)	3218.7 (0.318)	3162.3 (0.710)	3125.1 (0.245)	1674.4 (3.180)	3179.82	3168.62	3184	3157.65	3140	17.80; 15.32; 15.53
2h	3422.3 (1.780)	3227.9 (1.253)	3169.0 (1.395)	3129.7 (0.501)	1671.8 (3.698)	3193.45	3173.24	3184	3159.92	3124	22.35; 18.08; 16.51
2i	3420.9 (1.555)	3224.1 (0.641)	3177.5 (0.486)	3138.3 (1.352)	1673.8 (3.213)	3187.82	3177.35	3192	3174.73	3148	7.29; 20.21; 3.69
2j	3420.2 (1.579)	3221.1 (0.313)	3165.8 (0.850)	3119.2 (0.257)	1673.4 (2.791)	3179.73	3169.71	3168	3156.67	3120	17.59; 15.72; 18.74
2k	3421.6 (1.812)	3227.9 (0.840)	3182.3 (0.538)	3146.0 (1.485)	1672.1 (3.836)	3194.16	3182.37	3192	3179.67	3140	7.69; 20.40; 3.66
21	3421.1 (2.051)	3220.6 (0.742)	3164.7 (0.943)	3128.4 (0.794)	1673.3 (3.817)	3182.40	3168.85	3176	3162.46	3124	15.59; 20.10; 9.39
2m	3421.1 (1.738)	3209.7 (0.267)	3163.8 (0.215)	3146.8 (0.757)	1675.7 (3.460)	3179.28	3169.98	3192	3171.05	3128	6.10; 14.75; 1.53
2n	3422.9 (1.509)	3208.8 (0.791)	3173.1 (0.225)	3148.8 (1.101)	1675.0 (4.209)	3185.71	3173.20	3192	3171.79	3128	5.10; 17.11; 1.67
20	3421.2 (1.970)	3219.9 (0.933)	3168.8 (1.021)	3126.7 (0.855)	1674.9 (4.001)	3184.04	3169.60	3232	3161.76	3168	15.41; 20.81; 11.07
2p	3420.5 (1.744)	3217.2 (0.439)	3167.2 (0.215)	3155.4 (0.877)	1672.9 (3.550)	3188.28	3174.63	3160	3176.90	3116	7.09; 16.94; 2.92
3a	3400.6 (2.255)	3232.1 (1.401)	3182.1 (0.617)	3151.4 (1.657)	1670.2 (4.052)	3200.86	3183.63	3208	3181.11	3140	9.75; 22.55; 3.17
3b	3401.8 (2.176)	3230.5 (1.899)	3183.7 (1.015)	3148.2 (1.358)	1699.6 (4.529)	3202.17	3183.22	3208	3177.01	3136	13.41; 21.77; 7.87
3c	3400.9 (1.945)	3226.7 (1.180)	3181.2 (0.418)	3154.0 (1.009)	1670.1 (3.771)	3200.95	3182.01	3184	3178.94	3120	10.04; 21.21; 3.72
3d	3398.2 (2.258)	3230.1 (0.437)	3184.9 (0.589)	3143.5 (1.042)	1672.2 (3.746)	3192.43	3184.64	3192	3181.43	3140	7.99; 18.01; 5.22
3e	3401.4 (2.129)	3231.2 (1.543)	3181.4 (0.815)	3149.4 (1.077)	1670.0 (4.013)	3202.56	3182.50	3200	3176.95	3132	14.14; 21.87; 7.01
3f	3407.6 (2.336)	3238.3 (0.955)	3183.4 (0.878)	3150.1 (0.866)	1671.3 (4.027)	3203.37	3187.15	3200	3181.28	3144	15.58; 21.00; 8.12
3g	3400.6 (2.332)	3231.0 (0.787)	3183.8 (0.808)	3143.0 (1.132)	1673.6 (3.949)	3195.20	3183.73	3200	3178.87	3148	10.99; 20.31; 7.18
3h	3400.3 (2.178)	3232.3 (1.083)	3183.0 (0.655)	3149.7 (1.126)	1670.8 (3.941)	3200.65	3184.25	3208	3180.10	3152	11.78; 21.83; 5.48
3i	3400.2 (2.214)	3230.3 (0.807)	3187.1 (0.742)	3144.8 (1.141)	1673.3 (4.109)	3196.52	3185.38	3208	3180.31	3152	9.94; 20.10; 7.33
3j	3400.1 (2.353)	3227.4 (0.775)	3185.4 (0.267)	3155.1 (1.172)	1671.6 (4.443)	3199.01	3185.39	3184	3183.51	3140	6.12; 19.94; 2.28
3k	3399.2 (1.948)	3216.6 (1.297)	3174.4 (0.697)	3145.6 (1.238)	1673.3 (6.246)	3190.19	3175.08	3200	3171.33	3132	10.23; 19.18; 4.84
31	3399.0 (2.172)	3221.2 (0.462)	3168.1 (0.506)	3149.4 (0.379)	1671.5 (3.654)	3190.54	3176.26	3200	3171.90	3144	15.38; 16.20; 6.06

3m	3399.9 (2.250)	3225.0 (0.773)	3176.9 (0.468)	3148.2 (0.864)	1671.3 (3.869)	3194.67	3179.25	3192	3176.18	3148	10.92; 20.44; 4.07
3n	3399.0 (2.608)	3221.3 (0.927)	3176.7 (0.420)	3151.5 (0.916)	1671.1 (4.667)	3194.94	3178.56	3184	3176.00	3124	9.85; 19.68; 3.23
4a	3399.8 (1.900)	3229.1 (1.106)	3179.9 (0.565)	3152.2 (0.866)	1671.2 (5.638)	3201.10	3182.09	3200	3178.01	3140	12.90; 21.08; 5.17
4b	3385.1 (2.097)	3220.3 (0.463)	3167.5 (0.754)	3136.6 (0.874)	1672.8 (4.274)	3181.94	3172.83	3200	3169.63	3136	11.33; 17.28; 5.30
4c	3398.4 (2.160)	3231.0 (0.776)	3180.2 (0.936)	3137.5 (0.739)	1674.2 (4.207)	3194.61	3181.04	3200	3173.05	3156	15.30; 20.32; 11.46
4d	3398.6 (2.182)	3236.0 (0.941)	3185.9 (0.971)	3149.0 (0.930)	1671.9 (4.958)	3201.69	3187.76	3200	3181.45	3144	14.22; 20.01; 8.95
4e	3398.9 (2.013)	3234.1 (0.667)	3191.1 (0.636)	3147.7 (0.833)	1673.7 (4.011)	3200.68	3189.06	3200	3183.15	3156	10.89; 20.17; 8.51
4f	3398.0 (1.329)	3222.2 (0.178)	3175.5 (0.462)	3141.8 (0.131)	1672.7 (2.500)	3189.10	3180.43	3200	3169.97	3136	14.84; 12.12; 14.64
^a Inte ^b Due	gral absorption inten to the interaction of	sities $(dm^3 cm^{-2} m)^{\nu}$ w(NH···O=C). 2ν (C	ol ⁻¹) are given in p ⁶ C=C) ^{3,*} and ν (C=C) ³	arentheses. , + ν (NH).							
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The values obtained by summing up the experimental wave numbers

Obtained by perturbation calculation.

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comprises a six-membered ring with perturbed planarity, closed via an intramolecular $N-H\cdots O=C$ bond. This result is in line with the conclusions drawn from the analyses of the IR spectra.

2.4. X-ray structure analysis

X-ray diffraction analyses of four selected carbonylthiourea derivatives, namely **1e**, **2e**, **2n**, and **3e** (Scheme 1), were carried out in order (1) to get information about the solid-state conformation of these molecules, (2) to obtain direct structural evidence for the assumed intramolecular hydrogen bonds in the present compound families, and (3) to learn about molecular interactions modes and their variation in four closely related crystalline compounds.

Moreover, our aim was also to compare the results of the X-ray structure analyses with those of the spectroscopic studies and quantum-chemical calculations. The selection of the four derivatives (i.e. **1e**, **2e**, **2n**, and **3e**) was mainly directed by the ability of the compounds to form crystals suitable for single-crystal X-ray diffraction study (Table 4).

2.4.1. Molecular conformations

The results of the X-ray structure analyses confirmed the important common feature of the investigated thiourea derivatives, that is the relatively strong intramolecular $(N-)H\cdots O(=C)$ hydrogen bond (Fig. 1(a)–(e), Table 5), which leads to the formation of a six-membered closed loop with the graph-set notation **S**(6) [33–35]. Creation of this (pseudo) ring is crucial for the molecular conformations, because it prevents free rotation within the central carbonyl-thiourea moiety and locks its atoms in a nearly planar arrangement (Table 6).

The 1-(furan-3-carbonyl)-thiourea derivatives, such as 1e, 2e (molecules A and B) and 2n (molecules A, B, C and D), exhibit similar conformations, as seen in Fig. 1(a)-(d). The plane defined by the O(6)-C(6)-N(7)-C(8)-S(8)-N(9)atoms [i.e. the non-hydrogen atoms of the carbonylthiourea moiety] (plane 1) is only slightly tilted with respect to the furan ring plane (plane 2), but roughly perpendicular to the plane of the phenyl ring (plane 3) in these compounds. Accordingly, the dihedral angles formed by the leastsquares (LS) planes 1 and 2 in compounds 1e, 2e and 2n (i.e. in seven crystallographically independent molecules) range between 11.1 and 18.6° with the mean value 14 [3]^{\circ} (the dispersion around the arithmetic average is given in angular brackets), and the dihedral angles between LS planes 1 and 3 have the mean value 82° [5]°, and vary from 75.5 to 87.8°. The conformation of molecule 3e (Fig. 1(e)) is different, however. The backbone of this molecule is somewhat curved, with the furan and the phenyl ring (LS) planes slightly tilted with respect to the central plane defined by the O(6)-C(6)-N(7)-C(8)-S(8)-N(9) atoms, thus, yielding the dihedral angles 5.2(2) and $16.7(2)^{\circ}$, respectively. The obvious reason for the observed differences in the orientation of the phenyl ring is the presence of

Table 2	
Linear correlations for compounds $1-4$ (y=a+	bx)

	у	x	n^{a}	r ^b	s ^c	а	b
1	$\nu(\text{NH})_{\text{free}}$	$\sigma_{ m p}$	9	0.951	0.34	3415.0	-3.15
	$v_A^0(NH \cdots O = C)$	$\sigma_{\rm p}$	9	0.940	2.32	3199.8	-19.31
	ν (C=O)	$\sigma_{\rm p}$	9	0.945	0.42	1677.8	3.67
2	$\nu(\text{NH})_{\text{free}}$	$\sigma_{\rm p}$	11	0.927	0.33	3421.6	-2.68
	$v_A^0(NH\cdots O=C)^d$	$\sigma_{\rm p}$	10	0.914	2.28	3189.8	-16.13
	ν (C=O) ^e	$\sigma_{\rm p}$	10	0.907	0.46	1672.4	3.20
3	$\nu(\text{NH})_{\text{free}}^{f}$	$\sigma_{\rm p}$	11	0.959	0.32	3400.4	-3.46
	$\nu_A^0 (NH \cdots O = C)^f$	$\sigma_{\rm p}$	11	0.921	1.70	3198.9	-12.78
	ν (C=O) ^g	$\sigma_{\rm p}$	11	0.970	0.21	1670.6	2.56
4	$\nu(\text{NH})_{\text{free}}$	$\sigma_{\rm p}$	4	0.948	0.29	3399.1	-2.62
	$v_A^0(NH\cdots O=C)$	$\sigma_{\rm p}$	4	0.860	3.78	3200.3	-19.14
	ν(C=O)	$\sigma_{ m p}$	4	0.588	1.07	1672.1	2.33

^a Number of compounds used in the correlation.

^b Correlation coefficient.

^c Standard deviation.

^d Compound 2k omitted.

^e Compound 20 omitted.

^f Compound **3f** omitted.

^g Compound **3i** omitted.

the *ortho*-phenyl substituent(s), such as CF_3 in 1e and 2e, and the two Cl substituents in each of the four molecules of **2n**, whose space requirements force the respective phenyl ring out of the plane of the thiourea moiety. The methoxy group linked to the phenyl ring in 3e, however, does not have the same effect because of its para position. In addition, the moderately twisted attachment of the phenyl ring to the thiourea moiety in the crystalline 3e derivative opens a possibility for an intramolecular approach between the aryl C(15)–H and the thio [S(=C)] group (Table 5). Although C-H···S bonds are supposed to be very weak, a comparison with the literature [36] suggests that this interaction may contribute to the stabilization of the solidstate conformation of the 3e molecule. The furan ring, on the other hand, seems to prefer an orientation roughly coplanar with the central carbonyl-thiourea moiety in all four studied compounds. The o-methyl substituent on the furan ring in compounds 2e, 2n and 3e does not counteract this conformation. On the contrary, the observed conformation is possibly stabilized by a $(C_{methyl})H\cdots O(=C)$ intramolecular bond from the o-methyl substituent of the furan ring to the exa-cyclic carbonyl oxygen in each molecule (Fig. 1(b)-(e); Table 5). Even if this latter interaction is certainly rather weak, the repeated appearance of the same interaction pattern in seven crystallographically independent molecules in three different crystal structures suggests that these bonds have chemical relevance and may contribute to the determination of the orientation of the furan ring in each of the derivatives 2e, 2n and 3e.

The solid-state conformations, deduced from the X-ray diffraction analyses, are generally in agreement with the results of the quantum-chemical calculations. However, in **1e** the torsion angle τ_1 , defined by atoms C(8)–N(9)–C(10)–C(15), has the observed (X-ray) value 74.85(3)°, whereas the calculations yielded 82.64° for the same angle.

The observed $[-3.75(4)^{\circ}]$ and calculated (-11.71°) values of τ_2 , defined by atoms N(7)–C(6)–C(3)–C(4), are also somewhat different in 1e. Such differences may be the consequence of crystal packing forces (see below). At the same time, according to the X-ray investigations, τ_1 has the values 83.8(2) and $80.1(2)^{\circ}$ for molecules A and B in 2e, and 92.1(4), -90.4(4), 92.2(4) and $-93.8(4)^{\circ}$ for molecules A, B, C, and D in **2n**. The calculated value of τ_1 for the latter compound is 91.29°, which agrees very well with 92 [1.4]°, the mean value of the dihedral angles from the X-ray study. The different orientation of the phenyl ring in **3e**, as compared with that in the previous three compounds, is obvious from both the X-ray structure analysis $[\tau_1 =$ 21.5(4)°] and the theoretical calculations ($\tau_1 = 26.65^\circ$), although the observed and calculated values of τ_1 differ somewhat.

The torsion angle τ_3 , defined by atoms C(2)–C(3)–C(6)– O(6) (Fig. 1(a)–(d)), gives information about the orientation of the furan ring in relation to the carbonyl group and the central carbonylthiourea moiety. According to the X-ray investigations, τ_3 , has the values $-9.9(3)^\circ$ in 1e, 5.3(3) and $-4.5(3)^{\circ}$ for molecules A and B in 2e, and -11.3(4), 2.2(5), 9.5(5), $-12.4(5)^{\circ}$ for molecules A, B, C, and D in **2n**, respectively. The corresponding angle in **3e** (τ_4), defined by C(3)–C(2)–C(6)–O(6) (Fig. 1(e)), has the value $3.1(4)^{\circ}$ according to the X-ray study, whereas the theoretical calculations yielded the value 1.61°. We can see from these results, and also from the comparison of the observations in crystallographically independent molecules (e.g. A and B in 2e, and A, B, C, and D in 2n), that crystal packing forces give rise to larger variations in the orientation of the furan ring than the presence or absence of the 2-methyl (in 2e and 2n) or 3-methyl substituent (in 3e) (see also the following discussion of intermolecular interactions).

Table 3 Geometrical parameters of hydrogen bonds computed by AM1 a PM3

	d(NH) (Å)	d (H···O) (Å)	d (N···O) (Å)	∠ (°)
1a	1.01	2.07	2.797	127.3
	1.01	1.82	2.630	133.9
1b	1.01	2.07	2.797	127.3
	1.01	1.82	2.631	133.9
1c	1.01	2.07	2.796	126.9
	1.01	1.83	2.637	134.5
1d	1.01	2.07	2.800	127.7
	1.01	1.82	2.631	133.9
1e	1.01	2.07	2.624	126.5
	1.01	1.82	2.796	133.3
lf	1.01	2.06	2.794	127.3
	1.02	1.82	2.625	133.7
Ig	1.01	2.05	2.794	128.5
11.	1.02	1.82	2.020	133.9
IN	1.01	2.00	2.788	127.1
1;	1.02	2.08	2.021	135.5
11	1.00	2.08	2.790	120.9
1;	1.01	2.06	2.030	133.9
IJ	1.01	1.82	2.771	127.0
1k	1.02	2.08	2.027	126.4
	1.01	1.82	2.631	134.2
11	1.00	2.10	2.786	123.6
	1.01	1.84	2.606	130.2
1m	1.01	2.06	2.796	127.7
	1.02	1.82	2.629	133.9
1n	1.01	2.06	2.796	128.0
	1.02	1.82	2.907	133.9
2a	1.01	2.06	2.792	127.5
	1.01	1.82	2.629	133.9
2b	1.00	2.06	2.789	127.6
	1.01	1.82	2.630	133.9
2c	1.00	2.07	2.791	126.9
	1.01	1.82	2.636	134.5
2d	1.01	2.06	2.792	128.4
	1.01	1.82	2.630	133.9
2e	1.01	2.07	2.694	126.8
•	1.01	1.84	2.794	127.5
2f	1.01	2.06	2.785	127.2
•	1.02	1.82	2.624	133.8
2g	1.01	2.05	2.787	128.3
2 L	1.02	1.82	2.025	133.9
211	1.01	2.07	2.790	127.1
2 i	1.01	2.06	2.029	133.8
21	1.01	2.00	2.788	127.7
2i	1.02	2.07	2.020	126.5
-J	1.01	1.82	2.630	134.3
2k	1.01	2.06	2.789	127.3
	1.02	1.82	2.627	133.9
21	1.01	2.06	2.789	127.6
	1.02	1.82	2.628	133.9
2m	1.01	2.07	2.789	126.4
	1.02	1.82	2.629	133.8
2n	1.00	2.09	2.610	131.2
	1.01	1.83	2.781	128.6
20	1.01	2.06	2.789	127.8
	1.02	1.82	2.628	133.9
2p	1.01	2.06	2.789	127.8
	1.02	1.82	2.628	133.9
3a	1.01	2.07	2.798	127.6
	1.01	1.82	2.624	133.6

Table	3 (continued)			
	d(NH) (Å)	d (H···O) (Å)	$d (\mathbf{N} \cdots \mathbf{O}) (\mathbf{\mathring{A}})$	∠ (°)
3b	1.01	2.07	2.799	127.2
	1.01	1.82	2.630	134.2
3c	1.01	2.07	2.798	127.6
	1.01	1.81	2.621	133.4
3d	1.01	2.05	2.794	128.4
	1.02	1.82	2.620	133.5
3e	1.01	2.07	2.796	127.1
	1.01	1.82	2.624	133.6
3f	1.01	2.06	2.793	127.9
	1.01	1.82	2.620	133.5
3g	1.01	2.07	2.795	126.6
-	1.01	1.82	2.624	133.9
3h	1.01	2.06	2.795	127.5
	1.01	1.82	2.622	133.5
3i	1.01	2.07	2.793	126.6
	1.01	1.81	2.621	133.7
3j	1.01	2.05	2.797	128.8
	1.01	1.81	2.620	133.4
3k	1.00	2.10	2.786	123.8
	1.01	1.84	2.606	130.2
31	1.01	2.06	2.793	127.7
	1.01	1.82	2.620	133.5
3m	1.00	2.05	2.797	128.8
	1.01	1.82	2.622	133.6
3n	1.01	2.05	2.798	128.8
	1.01	1.82	2.622	133.6
4a	1.01	2.07	2.803	127.6
	1.01	1.83	2.631	133.8
4b	1.01	2.07	2.797	127.4
	1.02	1.82	2.626	133.7
4c	1.01	2.08	2.800	126.5
	1.01	1.82	2.633	134.2
4d	1.01	2.07	2.799	127.5
	1.01	1.82	2.629	133.8
4e	1.01	2.06	2.803	128.4
	1.01	1.82	2.630	134.0
4f	1.01	2.07	2.798	127.7
	1.01	1.82	2.629	133.8

 $\begin{pmatrix} AM1 \\ PM3 \end{pmatrix}$

2.4.2. Intermolecular interactions and packing relations

The selected four carbonylthiourea derivatives, namely **1e**, **2e**, **2n** and **3e**, differ only in the type and position of the substituent(s) connected to the terminal phenyl and/or furan rings. Hence, the size and overall shape of the molecules in the studied crystals differ only slightly from each other. However, due to the presence of a number of polar groups in the molecules, the more or less directional intermolecular interactions rather than shape recognition have been expected to play the leading role in the crystallization processes. Indeed, the closely related derivatives were found to exhibit various molecular recognition modes, utilizing a wide variety of non-covalent interactions in the formation of endless supramolecules in their crystals.

Besides the intramolecular $(N-)H\cdots O(=C)$ bond in compound **1e** (Fig. 1(a)), there are also intermolecular interactions, although considerably weaker, involving

Table 4

Summary of crystal data, experimental parameters and selected details of the refinement calculations in the X-ray diffraction analysis of compounds 1e, 2e, 2
and 3e

	1e	2e	2n	3e
CCDC deposition number	240290	240,291	240,292	240,293
Empirical formula (sum)	$C_{13}H_9F_3N_2O_2S$	$C_{28}H_{22}F_6N_4O_4S_2$	C ₅₆ H ₅₂ Cl ₈ N ₈ O ₁₀ S ₄	$C_{14}H_{14}N_2O_3S$
Empirical formula (moiety)	$C_{13}H_9F_3N_2O_2S$	$2(C_{14}H_{11}F_3N_2O_2S)$	$\frac{4(C_{13}H_{10}Cl_2N_2O_2S)}{2(C_2H_6O)}$	$C_{14}H_{14}N_2O_3S$
Formula weight	314.28	656.62	1408.90	290.33
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic
Space group	P - 1	P-1	Cc	$P 2_1/c$
a (Å)	8.152(2)	8.1760(10)	27.266(3)	11.8480(10)
b (Å)	8.219(2)	11.838(2)	13.3150(10)	8.7450(10)
<i>c</i> (Å)	10.618(2)	15.314(3)	19.509(2)	13.5750(10)
α (°)	99.56(2)	95.50(2)	90	90
β (°)	105.74(2)	103.48(2)	110.482(12)	90.366(12)
γ (°)	95.91(2)	95.43(2)	90	90
Ζ	2	2	4	4
$V(Å^3)$	667.0(3)	1424.2(4)	6634.9(11)	1406.5(2)
$D_{\text{calc,X-ray}} (\text{mg m}^{-3})$	1.565	1.531	1.410	1.371
Radiation/wavelength (Å)	Mo K _α /0.71073	Mo K _α /0.71073	Mo K _α /0.71073	Mo K _α /0.71073
$\mu_{X-ray} (mm^{-1})$	0.284	0.269	0.525	0.238
F(000)	320	672	2896	608
Crystal size (mm)	$0.15 \times 0.30 \times 0.40$	$0.07 \times 0.25 \times 0.25$	0.25×0.30×0.33	$0.10 \times 0.14 \times 0.35$
Crystal shape/colour	Irregular/colourless	Plate/colourless	Plate/colourless	Needle/colourless
Index ranges h,k,l	-9 < h < 9, -10 < k < 10,	-10 < h < 10, -14 < k <	-33 < h < 33, -16 < k <	-14 < h < 13, -10 < k <
	-12 < l < 13	14, -18 < l < 18	16, -23 < l < 23	10, -16 < l < 15
Reflections collected	8657	19036	28,161	9636
Independent reflections	2375	4064	12,414	2676
R _{int}	0.043	0.053	0.048	0.066
Reflections with $F > 4\sigma(F)$	2009	3172	10195	1852
Parameters refined	199	421	845	197
R_1 for $F > 4\sigma(F)$	0.044	0.041	0.040	0.064
wR_2^a for all unique F^2	0.123	0.117	0.104	0.144
S (Goodness-of-fit on F^2)	1.082	1.090	1.006	1.053
Final shift/esd, mean/max	0.000/0.001	0.000/0.005	0.004/0.118	0.000/0.001
Residual electron density, max/min $(e^{-}/Å^3)$	0.37/-0.33	0.24/-0.22	0.58/-0.65	0.23/-0.39

^a The weights of the F^2 values were calculated as $[\sigma^2(F^2) + (c_1 \cdot P)^2 + c_2 \cdot P]^{-1}$ where $P = (F_0^2 + 2F_c^2)/3$, and the constants, c_1 and c_2 have the values 0.077 and 0.110 for **1e**, 0.066 and 0.250 for **2e**, 0.066 and 0.0 for **2n**, and 0.073 and 0.300 for **3e**.

the same imino and carbonyl groups of nearest neighbouring molecules (Table 5). As a consequence, each N(9)–H group functions as a donor group in a bifurcated hydrogen bond, and each O(6) carbonyl oxygen accepts two H-bonds, one intra- and one intermolecular. In this way, an unusual fourmembered closed loop is created through four non-covalent H…O interactions, which connects two adjacent, centrosymmetrically related molecules into dimers (Fig. 2). Formation of the closed loop leads also to a relatively short intermolecular contact distance of 2.954(3) Å between the two carbonyl oxygen atoms in the four-membered ring. A pair of $(C-)H\cdots S$ interactions [19,36] link the dimeric units of the 1e derivative into infinite, parallel ribbons along the crystallographic *c*-axis. The packing of the ribbons seems to be directed by the space requirement of the protruding CF₃ groups, besides the common van der Waals' forces (Table 5).

Crystals of the **2e** derivative contain two symmetry independent (i.e. crystallographically unique) molecules, molecules A and B (Fig. 1(b)), which exhibit slightly different conformations (Table 6), most probably due to anisotropic crystal packing forces. Inspection of the intermolecular contact distances indicates a non-covalent carbonyl-carbonyl (i.e. dipole-dipole) interaction between centrosymmetrically related A molecules $[C \cdots O =$ 3.443(3) Å], and a tendency to similar approach between corresponding B molecules $[C \cdots O = 3.754(3) \text{ Å}]$. In the course of a systematic database analysis of the geometries of carbonyl-carbonyl interactions, Allen et al. [37] identified three distinct $C=O\cdots C=O$ contact patterns in crystals: the antiparallel, the perpendicular, and the sheared parallel motifs. Geometries of the C=O···C=O connections in 2e conform to that of the most frequently occurring antiparallel motif. Because the interacting keto groups in 2e are related by a centre of symmetry, the $C=O\cdots C=O$ torsion angle is restricted to 0° in both interactions. The unique C=O···C (A_1) and $O \cdots C = O (A_2)$ angles, respectively, have the values 80.11(11) and 99.89(12)° in the A dimer, and 63.95(13) and 116.05(13)° in the dimer of B molecules. Our observations are in accordance with those of the database



Fig. 1. Perspective view of the 1e (a) derivative, the two independent molecules of 2e (b), the two unique H-bonded $2n \cdot \text{ethanol}$ (2:1) associates (c, d), and the 3e molecule (e), respectively. The atomic displacement ellipsoids of the non-hydrogen atoms and disorder sites, shown with crystallographic labelling, are drawn at 30% probability level. Broken lines represent possible hydrogen bond interactions.

analysis by Allen et al. [37], which indicated that interactions with longer C···O distance [d(C··O) > 3.6 Å]tend to have angle values that deviate considerably from the most probable values, namely 83.5° for A₁ and 96.5° for A₂. At the same time, ab initio molecular-orbital calculations indicated that the strength of the carbonyl dipole–dipole interaction is comparable to that of a medium-strength hydrogen bond, even at longer distances [37]. Consequently, it is reasonable to suggest that the observed C=O··· C=O interactions in **2e**, also that between the B molecules, may play an important role in the supramolecular recognition processes. The A···A and B···B associates, Table 5

Distances (Å) and angles (°) in possible intra- and intermolecular hydrogen bond interactions, and selected intermolecular contact distances, observed in compounds 1e, 2e, 2n and 3e

Atoms involved	Symmetry	Distance D…A (Å)	Distance D-H (Å)	Distance H · · A (Å)	Angle $\angle D - H \cdot \cdot A$ (°)
1e					
$N(9) - H(9N) \cdots O(6)$	x y z	2 634(2)	0.96	1 89	133
$N(9) - H(9N) \cdots O(6)$	-r+1 - v+1 - z+2	3.257(2)	0.96	2.44	143
$C(4) - H(4) \cdots S(8)$	-r - v + 1 - z + 1	3,539(3)	0.93	2.44	168
O(6)O(6)	-r+1 - v+1 - z+2	2.954(3)	0.75	2.02	100
E(1) = E(1)	-x+1, -y+1, -z+2	2.934(3) 2.020(4)			
$\mathbf{F}(1)\cdots\mathbf{F}(2)$	-x+1, -y, -z+2	3.029(4) 3.201(2)			
$F(1)\cdots F(3)$	-x+1, -y, -z+2	5.201(5)			
$F(1)\cdots O(6)$	-x+1, -y+1, -z+2	5.246(5) 2.211(4)			
$F(1)\cdots C(5)$	-x, -y+1, -z+2	3.311(4)			
$F(3)\cdots C(6)$	x, y = 1, z	3.254(3)			
2e					
$N(9A)-H(9NA)\cdots O(6A)$	<i>x</i> , <i>y</i> , <i>z</i>	2.623(2)	0.91	1.91	134
$N(9B)-H(9NB)\cdots O(6B)$	<i>x</i> , <i>y</i> , <i>z</i>	2.590(2)	0.92	1.83	139
$N(7A)-H(7NA)\cdots S(8B)$	x, y+1, z	3.373(2)	0.93	2.45	160
$N(7B)-H(7NB)\cdots S(8A)$	x, y = 1, z	3.493(2)	0.93	2.59	166
$C(21A)-H(2A2)\cdots O(6A)$	<i>x</i> , <i>y</i> , <i>z</i>	3.052(3)	0.96	2.39	126
$C(21B)-H(2B1)\cdots O(6B)$	<i>x</i> , <i>y</i> , <i>z</i>	2.995(3)	0.96	2.43	117
$C(6A) \cdots C(6A)$	-x+1, -y+1, -z	3.449(4)			
C(6A)…O(6A)	-x+1, -y+1, -z	3.443(3)			
C(6B)…C(6B)	-x+1, -y-1, -z+1	3.400(4)			
C(6B)O(6B)	-x+1, -y-1, -z+1	3.754(3)			
$F(1A)\cdots C(14A)$	-x+1, -y, -z	3.140(3)			
$F(1A)\cdots C(13A)$	-x+1, -y, -z	3.413(3)			
$F(3A)\cdots C(5A)$	x, y-1, z	3.315(3)			
$F(1B)\cdots C(14B)$	-x+1, $-y$, $-z+1$	3.136(3)			
$F(1B)\cdots C(13B)$	-x+1, $-y$, $-z+1$	3.354(3)			
$F(1B)\cdots F(2B)$	-x+2, -y, -z+1	2.840(2)			
2n	, ,, ,,				
$N(9A) - H(9NA) \cdots O(6A)$	r v 7	2 651(3)	0.96	1 0/	120
$N(0R) = H(0NR) \cdots O(6R)$	x, y, z	2.031(3) 2.626(3)	0.00	1.97	125
$N(9C) - H(9NC) \cdots O(6C)$	x, y, z	2.626(3)	0.97	1.02	125
N(9C) = H(9NC) = O(6C)	x, y, z	2.030(3) 2.623(4)	0.94	1.90	142
$N(9D) = H(9ND) \cdots O(0D)$ $N(0A) = H(0NA) \cdots O(6C)$	x, y, z	2.023(4) 2.102(4)	0.09	2.40	142
N(0R) = H(0NR) = O(6C)	<i>x</i> , <i>y</i> , <i>z</i>	2.103(4)	0.90	2.40	100
N(9B) = H(9NG) = O(6A)	<i>x</i> , <i>y</i> , <i>z</i>	3.000(3)	0.99	2.30	120
$N(9C) = \Pi(9NC) \cdots O(6A)$	<i>x</i> , <i>y</i> , <i>z</i>	2.995(5)	0.94	2.20	132
$N(9D) = H(9ND) \cdots O(0B)$	<i>x</i> , <i>y</i> , <i>z</i>	5.002(5)	0.89	2.40	120
N(7R) - H(7NR) - O(1E1)	<i>x</i> , <i>y</i> , <i>z</i>	2.888(0)	0.83	2.11	157
$N(7B) = H(7NB) \cdots O(1E2)$	<i>x</i> , <i>y</i> , <i>z</i>	2.991(8)	0.80	2.22	149
$N(B) = H(B) \cdots O(E)$	<i>x</i> , <i>y</i> , <i>z</i>	3.050(7)	0.86	2.32	143
$C(21A) = H(2A1) \cdots O(6A)$	<i>x</i> , <i>y</i> , <i>z</i>	3.030(4)	0.96	2.39	120
$C(21B) - H(2B1) \cdots O(6B)$	<i>x</i> , <i>y</i> , <i>z</i>	3.034(4)	0.96	2.38	125
$C(21C) = H(2C1) \cdots O(6C)$	<i>x</i> , <i>y</i> , <i>z</i>	3.025(4)	0.96	2.42	121
$C(2ID) = H(2DI) \cdots O(6D)$	<i>x</i> , <i>y</i> , <i>z</i>	3.028(4)	0.96	2.40	122
$O(6A)\cdots O(6C)$	<i>x</i> , <i>y</i> , <i>z</i>	3.076(3)			
$O(6A)\cdots CI(IC)$	<i>x</i> , <i>y</i> , <i>z</i>	3.518(2)			
$S(8A) \cdots O(1E1)$	<i>x</i> , <i>y</i> , <i>z</i>	3.315(7)			
$CI(1A)\cdots N(7C)$	<i>x</i> , <i>y</i> , <i>z</i>	3.588(3)			
$Cl(1A)\cdots Cl(1C)$	<i>x</i> , <i>y</i> , <i>z</i>	3.586(2)			
$O(1A) \cdots O(6B)$	x = 0.5, y = 0.5, z	3.292(3)			
$O(1A)\cdots N(7B)$	x = 0.5, y = 0.5, z	3.105(3)			
$O(1A)\cdots Cl(5A)$	x, -y+1, z+0.5	3.263(2)			
$O(1A)\cdots Cl(5B)$	x = 0.5, y = 0.5, z	3.421(3)			
$S(8A)\cdots Cl(1B)$	x, y = 1, z	3. 781(1)			
$O(6B) \cdots O(6D)$	<i>x</i> , <i>y</i> , <i>z</i>	3.145(3)			
S(8B)…O(1E")	<i>x</i> , <i>y</i> , <i>z</i>	3.159(7)			
S(8B)…O(1E2)	<i>x</i> , <i>y</i> , <i>z</i>	3.478(7)			
$S(8B)\cdots Cl(1A)$	<i>x</i> , <i>y</i> , <i>z</i>	3.745(1)			
$O(6B)\cdots Cl(1D)$	<i>x</i> , <i>y</i> , <i>z</i>	3.497(2)			
$Cl(1B)\cdots Cl(1D)$	<i>x</i> , <i>y</i> , <i>z</i>	3.605(2)			
O(1B)···O(6A)	x+0.5, -y+1.5, z+0.5	2.974(3)			
$O(1B) \cdots N(7A)$	x+0.5, -y+1.5, z+0.5	3.247(3)		(c	continued on next page)

Table 5 (continued)

Atoms involved	Symmetry	Distance D…A (Å)	Distance D–H (Å)	Distance H · · A (Å)	Angle $\angle D - H \cdot \cdot A$ (°)
O(1B)…Cl(5A)	x + 0.5, -y + 1.5, z + 0.5	3.317(3)			
$O(1B) \cdots Cl(5B)$	x, -y+2, z+0.5	3.275(2)			
S(8C)…O(1E2)	<i>x</i> , <i>y</i> , <i>z</i>	3.653(8)			
S(8C)…Cl(1D)	<i>x</i> , <i>y</i> , <i>z</i>	3.533(1)			
O(1C)…Cl(5C)	x, -y+2, z=0.5	3.416(3)			
$N(7D)\cdots Cl(1B)$	<i>x</i> , <i>y</i> , <i>z</i>	3.579(3)			
$O(1D)\cdots Cl(5D)$	x, -y+3, z=0.5	3.560(3)			
$S(8D)\cdots Cl(1C)$	x, y+1, z	3.559(1)			
3e					
N(9)–H(9N)····O(6)	<i>x</i> , <i>y</i> , <i>z</i>	2.658(3)	0.93	1.89	139
C(31)–H(31C)···O(6)	x, y, z	3.083(4)	0.96	2.43	125
C(15)–H(15)····S(8)	x, y, z	3.210(3)	0.93	2.59	124
$C(14)-H(14)\cdots S(8)$	-x+1, -y, -z+1	3.617(3)	0.96	2.80	148
O(1)····O(6)	-x+2, -y+1, -z+1	3.321(3)			
$C(2)\cdots C(2)$	-x+2, -y+1, -z+1	3.532(5)			
C(2)…C(6)	-x+2, -y+1, -z+1	3.402(3)			
C(2)···O(6)	-x+2, -y+1, -z+1	3.534(3)			
C(3)…C(6)	-x+2, -y+1, -z+1	3.452(3)			
C(3)…N(7)	-x+2, -y+1, -z+1	3.470(3)			
C(4)…O(6)	-x+2, -y+1, -z+1	3.592(3)			
C(4)…N(9)	-x+2, -y+1, -z+1	3.406(4)			
C(5)…O(6)	-x+2, -y+1, -z+1	3.348(3)			
N(7)…C(31)	-x+2, -y+1, -z+1	3.584(4)			
C(6)…C(13)	-x+1, -y+1, -z+1	3.585(4)			
C(6)…O(13)	-x+1, -y+1, -z+1	3.417(3)			
O(6)…C(13)	-x+1, -y+1, -z+1	3.554(3)			
O(6)…C(14)	-x+1, -y+1, -z+1	3.209(4)			
N(9)…C(10)	-x+1, -y+1, -z+1	3.544(3)			
N(9)…C(15)	-x+1, -y+1, -z+1	3.560(3)			
C(10)…C(10)	-x+1, -y+1, -z+1	3.422(5)			
O(6)…C(16)	-x+1, y+0.5, -z+0.5	3.462(4)			
C(5)…O(13)	x+1, -y+0.5, z+0.5	3.503(4)			
$C(31)\cdots C(31)$	-x+2, -y+2, -z+1	3.407(6)			

Esd's, where given, are in parentheses. The (N-)H atoms were located from difference electron density calculations, and were held riding on their respective parent N atom during the subsequent refinement calculations, whereas the carbon-bonded H atoms were given calculated positions. The rigid methyl groups, however, were allowed to rotate around the C/O–C(methyl) bond [48]. The distances/angles have been calculated without correction or normalization of the H positions.

formed through the carbonyl–carbonyl interactions, are joined by a pair of $(N-)H\cdots S$ bonds (Table 5), which link them into endless chains in the crystallographic *c*-direction (Fig. 3). The exposed position of the CF₃ group in **2e** gives rise to some shorter inter-chain contact distances, involving the fluoro substituents (Table 5), just as in **1e**.

In the crystals of the **2n** derivative, solvate molecules were found to be included with 2:1 thiourea–ethanol (i.e. host–guest) ratio. The host molecules are linked together two-by-two (i.e. pairs of A–C and B–D molecules; Fig. 1(c) and (d)) in the very same way as in compound **1e**, which in the case of **2n** also leads to relatively short distances between the two carbonyl oxygens in each closed loop of $(N-)H\cdots O(=C)$ interactions [3.076(3) Å in the A–C, and 3.145(3) Å in the B–D pair of molecules; Table 5]. An important difference is, however, that each dimer in **1e** contains two centrosymmetrically related molecules, whereas the A, B, C and D molecules in the **2n** derivative, which form the two independent pairs of molecules, are all crystallographically unique. Moreover, the H-bonded A–C and B-D units in 2n are also hydrogen-bonded to solvate molecules, thus 2:1 host-guest associates are created via conventional H-bond interactions (Table 5, Figs. 1(c) and (d) and 4). Two non-equivalent ethanol molecules (E1 and E2) have been revealed, both being disordered, but in different ways. Whereas in E1 only the α -carbon was found to distribute among distinct locations (Fig. 1(c)), the E2 molecule occupies two partly overlapping disorder sites with only one carbon position in common (Fig. 1(d)). Because of the inequality of the ethanol molecules, the two H-bonded host-guest associates, containing E1 and E2, respectively, also differ somewhat, thus leading to a asymmetric crystallographic unit of considerable size for compound 2n, comprising four independent host (A, B, C and D) and two guest molecules (E1 and E2). Formation of the hydrogen-bonded host-guest associates gives rise to a number relatively short host-host and host-guest contact distances within each 2:1 aggregate. For example, the N-H···O(ethanol) host-guest hydrogen bonds lead also to noticeably short S…O(ethanol) distances (Table 5).

Table 6 Selected geometric features of compounds 1e, 2e, 2n and 3e

Compound	1e	2e	2n	3e
The non-hydrogen ator	ns are co-pla	nar to within	n (Å)	
Carbonyl-thiourea	_			
moiety				
[O(6)-C(6)-N(7)-	0.060	0.099	0.155	0.047
C(8)–S(8)–N(9)]		0.086	0.102	
			0.117	
			0.069	
Furan ring	0.051	0.014	0.004	0.007
[O(1)–C(2)–C(3)– C(4)–C(5)]		0.014	0.012	
			0.003	
			0.016	
Phenyl ring	0.019	0.010	0.016	0.008
[C(10)-C(11)-		0.013	0.033	
C(12)-C(13)-			0.018	
C(14)-C(15)]			0.022	
Dihedral angles forme	d by the LS p	olanes (°)		
Carbonyl-thiourea	11.1(2)	16.	18.6(2)	5.2(2)
moiety and the		84(11)		
furan ring		11.	11.96(12)	
		32(11)	13.0(2)	
			13.2(2)	
Carbonyl-thiourea	76.62(6)	79.46(5)	87.84(10)	16.7(2)
moiety and the		75.53(6)	87.63(10)	
phenyl ring			84.83(9)	
			84.06(8)	
The furan and the	67.	88.20(8)	72.70(14)	19.8(2)
phenyl rings	59(13)	72.28(7)	82.16(13)	
			72.41(12)	
			72.17(13)	

Esd's where given, are in parentheses. The least square (LS) planes were calculated through the non-hydrogen atoms.

Moreover, besides shorter intra-aggregate Cl···Cl connections [with $d(Cl\cdots Cl) \approx 3.6$ Å, Table 5], the chloro substituents are also involved in relatively short S…Cl approaches between the H-bonded host-guest associates $[S(8C)\cdots Cl(1D) = 3.533(1), S(8D)\cdots Cl(1C)_{x, y+1, z} =$ 3.559(1) Å, Table 5]. Since organic halogens act rather through specific anisotropic electronic effects, halogen contacts with heteroatoms, such as N, O, S or other halogens, may control crystal packing to varying degrees, due to their directional character [38]. The Cl···Cl and Cl··· S interactions are assumed to have similar nature and angle characteristics, although the Cl...S contacts are suggested to be more energetically significant than those between chloro substituents. The S \cdots Cl approaches in **2n** follow the angular preferences predicted by the electrophile-nucleophile model of Ramasubbu et al. [39]. Accordingly, the $(C=)S\cdots Cl-C$ angle is $160.0(1)^{\circ}$ in both connections (cf. above), in agreement with the nucleophilic character of the S…Cl contact. The interactions between sulphur and chlorine link the H-bonded 2n·EtOH (2:1) associates so as to form infinite, one-dimensional supramolecules, which extend parallel with the crystallographic b-direction (Fig. 4). In addition, there are a few other noteworthy inter-aggregate connections, involving the furan oxygens [O(1A) or O(1B)] on the one hand, and various polar atoms/ groups [e.g. (C=)O, N or Cl-substituents] on the other (Table 5). These latter observations suggest an electrostatically favourable packing of the endless supramolecular chains in 2n.

It is apparent from Fig. 5, that the relatively flat 3a molecules stack upon each other along the crystallographic *a*-axis and, by virtue of the inversion symmetry, the neighbouring molecules within the stack have opposite



Fig. 2. Stereo packing illustration of the crystal structure of the **1e** derivative. H atoms are omitted for clarity. Solid and broken lines represent covalent and hydrogen bonds, respectively.



Fig. 3. Stereo packing illustration of the 2e derivative. H atoms are omitted for clarity. Broken lines indicate possible hydrogen bonds and the O···C contacts in the observed carbonyl-carbonyl interactions.

orientations. At the same time, inspection of the intermolecular connections reveals several distances between centrosymmetrically related **3e** molecules, which are considerably shorter than the sum of the van der Waals' radii of the connected non-hydrogen atoms (Table 5). Accordingly, the C(6)–O(6)–N(7) and N(9) atoms of the carbonylthiourea moiety (Fig. 5) form a number of close contacts with the furan ring atoms that belong to the molecule related by the -x+2, -y+1, -z+1 symmetry operation. Moreover, atoms of the central carbonylthiourea skeleton also make noticeably contacts with the phenyl carbons of the molecule generated by the -x+1, -y+1, -z+1 symmetry operation. The interplanar spacing within the stack is estimated to be between 3.35 and 3.41 Å. These observations, together with the fact that the relatively flat solid-state conformation of the **3a** derivative promotes delocalisation of π -electrons and formation of extended conjugated π -systems, suggest



Fig. 4. Stereo packing illustration of the 2n ethanol (2:1) inclusion crystal. The H atoms and the C(1E') ethanol disorder site are omitted for clarity. Broken lines indicate possible hydrogen bonds and the most probable S…Cl interactions [with d(S…Cl) < 3.6 Å].



Fig. 5. Stereo packingdiagram of the **3e** derivative. H atoms are omitted for clarity. Possible H-bond interactions are indicated by broken lines between the connected non-H atoms.

charge-transfer or $\pi \cdots \pi$ stacking interaction between molecules forming the stacks along the *a*-axis. In the crystal, these stacks of molecules are then linked through weak C–H···S hydrogen bonds [19,36] into infinite layers, which extend perpendicular to the crystallographic *c*-axis (Fig. 5).

Crystals of the present four compounds were grown from ethanol solutions under similar experimental conditions. The 1e, 2e and 3e derivatives were found to form stable crystals on their own. Calculations [40] indicate close packing and no solvent-accessible space in the crystals. The crystal packing indices obtained: 68.9% for both 1e and 2e, and 68.1% for the 3e derivative, are normal values for close-packed organic crystals [40,41]. Although, the 2n derivative, containing the 2,6-dichloro-substituted phenyl ring, was found to form similar hydrogen-bonded dimeric units as the 1e derivative, the dimeric entities of 2n, unlike those of 1e, turned out to co-crystallize with ethanol as guest. The included solvent molecules fill up the voids between the H-bonded host associates, and thus enhance the packing density and also the stability of the crystal. Nevertheless, the packing coefficient for 2n (65.3%) is lower than those previously cited, and the calculations indicate also 95 $Å^3$ solvent-accessible free space in each unit cell of the inclusion crystal. These observations suggest that the ethanol molecules are not big enough to fill up the space allotted to the guest molecules in the crystal, and this in turn makes disorder of the included alcohol molecules possible.

3. Experimental

Melting points were measured on a Kofler micro hotstage, and recorded as uncorrected values. Infrared spectra (wave numbers in cm⁻¹) were recorded on a PU 9800 FTIR Philips analytical spectrometer, calibrated with polystyrene foil, using chloroform as solvent. ¹H and ¹³C NMR spectra of CDCl₃ or DMSO-d₆ solutions were measured with a Varian VXR-300 apparatus (300 MHz for ¹H, 75 MHz for ¹³C) at 25 °C, with tetramethylsilane as internal standard.

3.1. Preparation of methyl-furoyl isothiocyanate

A solution of 33 g of the corresponding methyl-furoyl chloride (0.23 mol) in dry acetone (10 cm³) was added slowly to a vigorously stirred solution of 24 g of dry potassium thiocyanate (0.24 mol) in dry acetone (260 cm³) at room temperature during 15 min. The mixture was boiled for 30 min and then cooled to 0 °C. The precipitate of potassium chloride was filtered off and the mixture was evaporated under reduced pressure. The residue was poured into dry cyclohexane (100 cm³), and the solid was filtered off. Evaporation of the solvents in vacuo gave a yellow oil, which was purified by distillation.

2-Methyl-3-furoyl isothiocyanate: $C_7H_5NO_2S$ yield: 28.8 g (75%); b.p. 60–61 °C/0.05 kPa; IR (CHCl₃): $\nu = 1697 \text{ cm}^{-1}(CO), \nu = 1965 \text{ cm}^{-1}(NCS).$

3-Methyl-2-furoyl isothiocyanate: $C_7H_5NO_2S$ yield: 29.2 g (76%); b.p. 86–88 °C/0.16 kPa; IR (CHCl₃): $\nu = 1699 \text{ cm}^{-1}(CO), \nu = 1972 \text{ cm}^{-1}(NCS).$

5-Methyl-2-furoyl isothiocyanate: $C_7H_5NO_2S$ yield: 26.9 g (70%); b.p. 60–61 °C/0.26 kPa; IR (CHCl₃): $\nu = 1692 \text{ cm}^{-1}(CO), \nu = 1978 \text{ cm}^{-1}(NCS).$

3.2. Preparation of 1,3-disubstituted thioureas (1a–1n, 2a–2p, 3a–3n, 4a–4f)

A solution of the corresponding amine (0.01 mol) in dry ether (2 cm³) was added in one portion to a vigorously stirred solution of the corresponding furoyl isothiocyanate (0.01 mol) in dry cyclohexane (80 cm³). The mixture was stirred at 5–10 °C for 5 h. The precipitate was filtered off and washed with *n*-hexane (2×10 cm³). By this reaction, analytically pure compounds were obtained. Thioureas may be crystallized from a small amount of ethanol.

3.2.1. $1-(2,4-Dimethyl-phenyl)-3-(furan-3-carbonyl)-thiourea (1c, <math>C_{14}H_{14}N_2O_2S)$

Yield: 82%; m.p.: 172–173 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.25, (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 6.78 (d, d, J_{4-5} =1.82 Hz, J_{4-2} =0.89 Hz, 1H, 4-H_{fur}), 7.42 (d, d, 2H, J=2.16 Hz, J=8.66 Hz, H_{ar}), 7.57 (d, d, J_{5-4} = 1.82 Hz, J_{5-2} =0.84 Hz, 1H, 5-H_{fur}), 8.19 (bs, 1H, 2-H_{fur}), 8.38 (d, 1H, J=8.66 Hz, H_{ar}), 8.81 (br. s, 1H, NH), 12.61 (br. s, 1H, NH) ppm.

3.2.2. 1-(4-tert-Butyl-phenyl)-3-(furan-3-carbonyl)thiourea (1d, $C_{16}H_{18}N_2O_2S$)

Yield: 80%; m.p.: 134–135 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.32$ (s, 9H, CH₃, CH₃, CH₃), 6.75 (d, d, $J_{4-5} = 1.88$ Hz, $J_{4-2} = 0.92$ Hz, 1H, 4-H_{fur}), 7.42 (d, 2H, J =8.88 Hz, H_{ar}), 7.52 (bs, 1H, 5-H_{fur}), 7.62 (d, 2H, J =8.88 Hz, H_{ar}), 8.14 (d, 1H, $J_{2-5} = 0.92$ Hz, 2-H_{fur}), 8.74 (br. s, 1H, NH), 12.38 (br. s, 1H, NH) ppm.

3.2.3. 1-(Furan-3-carbonyl)-3-(2-trifluoromethyl-phenyl)thiourea (**1e**, $C_{13}H_9F_3N_2O_2S$)

Yield: 78%; m.p.: 142–143 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 6.78$ (d, d, $J_{4-5} = 1.87$ Hz, $J_{4-2} = 0.84$ Hz, 1H, 4-H_{fur}), 7.42–7.47 (m, 1H, H_{ar}), 7.53 (d, $J_{5-4} = 1.87$ Hz, 1H, 5-H_{fur}), 7.61–7.72 (t, J = 7.27 Hz, 1H, H_{ar}), 7.72–7.74 (d, J = 7.74 Hz, 1H, H_{ar}), 7.92–7.95 (d, J = 7.98 Hz, 1H, H_{ar}), 8.18 (d, $J_{2-4} = 1.87$ Hz, 1H, 2-H_{fur}), 8.98 (br. s, 1H, NH), 12.42 (br. s, 1H, NH) ppm; ¹³C NMR (CDCl₃, 75 MHz): $\delta = 108.2$ (C-4_{fur}), 120.1 (C_{ar}), 121.9 (C_{ar}), 125.2 (q, CF₃), 123.2 (C_{ar}), 127.6 (C_{ar}), 129.8 (C_{ar}), 132.2 (C_{ar}), 135.2 (C_{ar}), 144.3 (C-5_{fur}), 147.9 (C-2_{fur}), 162.2 (C=O), 180.6 (C=S) ppm.

3.2.4. 1-(Furan-3-carbonyl)-3-(3-trifluoromethyl-phenyl)thiourea (**1**f, $C_{13}H_9F_3N_2O_2S$)

Yield: 79%; m.p.: 117–118 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 6.77$ (d, d, $J_{4-5} = 1.87$ Hz, $J_{4-2} = 0.74$ Hz, 1H, 4-H_{fur}), 7.18–8.15 (m, 5H, 5-H_{fur}, H_{ar}), 8.19 (bs, 1H, 2-H_{fur}), 8.84 (br. s, 1H, NH), 12.6 (br. s, 1H, NH) ppm.

3.2.5. 1-(Furan-3-carbonyl)-3-(4-trifluoromethyl-phenyl)thiourea (1g, $C_{13}H_9F_3N_2O_2S$)

Yield: 72%; m.p.: 151-152 °C; ¹H NMR (CDCl₃, 300 MHz): δ =6.76 (d, d, J_{4-5} =1.81 Hz, J_{4-2} =0.84 Hz, 1H, 4-H_{fur}), 7.21-7.36 (m, 2H, H_{ar}), 7.56 (d, d, J_{5-4} = 1.80 Hz, J_{5-2} =0.84 Hz, 1H, 5-H_{fur}), 8.15 (br. s, 1H, 2-H_{fur}), 8.75 (br. s, 1H, NH), 12.56 (br. s, 1H, NH) ppm.

3.2.6. 1-(3,5-Bis-trifluoromethyl-phenyl)-3-(furan-3carbonyl)-thiourea (**1h**, $C_{14}H_8F_6N_2O_2S$)

Yield: 69%; m.p.: 112–113 °C; ¹H NMR (CDCl₃, 300 MHz): δ =6.78 (d, d, J_{4-5} =1.78 Hz, J_{4-2} =0.78 Hz, 1H, 4-H_{fur}), 7.57 (t, J=1.78 Hz, 1H, H_{ar}), 7.76 (bs, 1H, 3-H_{fur}), 8.21 (t, J=1.38 Hz, 1H, 2-H_{fur}), 8.28 (bs, 2H, H_{Ar}), 8.83 (br. s, 1H, NH), 12.85 (br. s, 1H, NH) ppm.

3.2.7. 1-(Furan-3-carbonyl)-3-(4-methoxy-phenyl)-thiourea (Ii, $C_{13}H_{12}N_2O_3S$)

Yield: 69%; m.p.: 135–136 °C; ¹H NMR (DMSO-d₆, 300 MHz): $\delta = 3.72$ (s, 3H, OCH₃), 6.94 (d, J = 9.02 Hz, 2H, H_{ar}), 7.05 (d, d, $J_{4-5} = 1.86$ Hz, $J_{4-2} = 0.94$ Hz, 1H, 4-H_{fur}), 7.52 (d, J = 9.02 Hz, 2H, H_{ar}), 7.56 (d, d, $J_{5-4} = 1.86$ Hz, $J_{5-2} = 0.84$ Hz, 1H, 5-H_{fur}), 8.72 (br. s, 1H, 2-H_{fur}), 11.39 (br. s, 1H, NH), 12.45 (br. s, 1H, NH) ppm.

3.2.8. 1-(Furan-3-carbonyl)-3-(4-trifluoromethoxy-phenyl)thiourea (Ij, $C_{13}H_9F_3N_2O_3S$)

Yield: 69%; m.p.: 122–123 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 6.76$ (d, d, $J_{4-5} = 1.79$ Hz, $J_{4-2} = 0.85$ Hz, 1H, 4-H_{fur}), 7.25 (d, J = 8.66 Hz, 2H, H_{ar}), 7.55 (bs, 1H, 5-H_{fur}), 7.76 (d, J = 8.66 Hz, 2H, H_{ar}), 8.15 (br. s, 1H, 2-H_{fur}), 8.75 (br. s, 1H, NH), 12.76 (br. s, 1H, NH) ppm.

3.2.9. 1-(2-Fluoro-phenyl)-3-(furan-3-carbonyl)-thiourea (1k, $C_{12}H_9FN_2O_2S$)

Yield: 81%; m.p.: 153–154 °C; ¹H NMR (CDCl₃, 300 MHz): δ =6.76 (d, d, J_{4-5} =1.87 Hz, J_{4-2} =0.94 Hz, 1H, 4-H_{fur}), 7.18–7.34 (d, J=8.86 Hz, 2H, H_{ar}), 7.55 (d, 1H, J_{5-4} =1.86 Hz, 5-H_{fur}), 8.16 (d, d, 1H, J_{2-5} =0.94 Hz, J_{2-4} =0.86 Hz, 2-H_{fur}), 8.16–8.44 (m, 2H, H_{ar}), 8.78 (br. s, 1H, NH), 12.54 (br. s, 1H, NH) ppm.

3.2.10. 1-(2,6-Dichloro-phenyl)-3-(furan-3-carbonyl)thiourea (II, $C_{12}H_8Cl_2N_2O_2S$)

Yield: 89%; m.p.: 192 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 6.77$ (d, d, $J_{4-5} = 1.92$ Hz, $J_{4-2} = 0.78$ Hz, 1H, 4-H_{fur}), 7.22–7.76 (m, 4H, 5-H_{fur}, H_{ar}), 8.18 (d, 1H, $J_{2-5} = 0.98$ Hz, 2-H_{fur}), 8.98 (br. s, 1H, NH), 11.89 (br. s, 1H, NH) ppm.

3.2.11. 1-(Furan-3-carbonyl)-3-(4-iodo-phenyl)-thiourea (In, $C_{12}H_9IN_2O_2S$)

Yield: 82%; m.p.: 177–178 °C; ¹H NMR (CDCl₃, 300 MHz): δ =6.75 (bs 1H, 4-H_{fur}), 7.48 (d, 2H, J= 8.86 Hz, H_{ar}), 7.50 (bs, 1H, 5-H_{fur}), 7.72 (d, 2H, J= 8.86 Hz, H_{ar}), 8.15 (d, 1H, J_{2–5}=0.82 Hz, 2-H_{fur}), 8.76 (br. s, 1H, NH), 12.46 (br. s, 1H, NH) ppm.

3.2.12. 1-(2-Methyl-furan-3-carbonyl)-3-phenyl-thiourea (2a, $C_{13}H_{12}N_2O_2S$)

Yield: 79%; m.p.: 159–160 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.65 (s, 3H, Fur-CH₃), 6.57 (d, *J*=1.96 Hz, 1H, 4-H_{fur}), 7.34 (d, *J*=1.96 Hz, 1H, 5-H_{fur}), 7.40–7.78 (m, 5H, H_{ar}), 8.61 (br. s, 1H, NH), 12.49 (br. s, 1H, NH) ppm.

3.2.13. 1-(2-Methyl-furan-3-carbonyl)-3-(4-methylphenyl)-thiourea (**2b**, $C_{14}H_{14}N_2O_2S$)

Yield: 77%; m.p.: 131–132 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.36$ (s, 3H, Ar-CH₃), 2.64 (s, 3H, Fur-CH₃), 6.56 (d, $J_{4-5} = 1.97$ Hz, 1H, 4-H_{fur}), 7.20 (d, J = 8.66 Hz, H_{ar}), 7.33 (d, $J_{5-4} = 1.96$ Hz, 1H, 5-H_{fur}), 7.55 (d, J = 8.66 Hz, H_{ar}), 8.62 (br. s, 1H, NH), 12.45 (br. s, 1H, NH) ppm.

3.2.14. 1-(2,4-Dimethyl-phenyl)-3-(2-methyl-furan-3carbonyl)-thiourea (2c, $C_{15}H_{16}N_2O_2S$)

Yield: 81%; m.p.: 144–145 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.27 (s, 6H, 2×Ar-CH₃), 2.65 (s, 3H, Fur-CH₃), 6.57 (d, J_{4-5} =2.16 Hz, 1H, 4-H_{fur}), 7.16 (d, J=7.98 Hz, H_{ar}), 7.37 (d, J_{5-4} =2.16 Hz, 1H, 5-H_{fur}), 7.32–7.49 (m, 2H, H_{ar}), 8.61 (br. s, 1H, NH), 12.41 (br. s, 1H, NH) ppm.

3.2.15. 1-(4-tert-Butyl-phenyl)-3-(2-methyl-furan-3carbonyl)-thiourea (2d, $C_{17}H_{20}N_2O_2S$)

Yield: 76%; m.p.: 139–140 °C; ¹H NMR (CDCl₃, 300 MHz): δ =1.35 (s, 9H, CH₃, CH₃, CH₃), 2.67 (s, 3H, Fur-CH₃), 6.58 (d, J_{4-5} =2.16 Hz, 1H, 4-H_{fur}), 7.35 (d, J_{5-4} =2.16 Hz, 1H, 5-H_{fur}), 7.42 (d, J=8.65 Hz, H_{ar}), 7.63 (d, J=8.65 Hz, H_{ar}), 8.62 (br. s, 1H, NH), 12.51 (br. s, 1H, NH) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ =14.6 (CH₃), 31.3 (t-But), 108.4 (C-4_{fur}), 113.8 (C-3_{fur}), 123.7 (C_{ar}), 125.7 (C_{ar}), 135.3 (C_{ar}), 148.1 (C_{ar}), 149.8 (C-5_{fur}), 159.2 (C-2_{fur}), 163.2 (C=O), 178.8 (C=S) ppm.

3.2.16. 1-(2-Methyl-furan-3-carbonyl)-3-(2-

trifluoromethyl-phenyl)-thiourea (2e, $C_{14}H_{11}F_3N_2O_2S$)

Yield: 79%; m.p.: 144–145 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.66$ (s, 3H, Fur-CH₃), 6.57 (d, $J_{4-5} =$ 1.98 Hz, 1H, 4-H_{fur}), 7.35 (d, $J_{5-4} = 1.98$ Hz, 1H, 5-H_{fur}), 7.46 (d, J = 8.02 Hz, 2H, H_{ar}), 7.61–7.79 (m, 2H, H_{ar}), 7.93 (d, J = 8.02 Hz, 2H, H_{ar}), 8.74 (br. s, 1H, NH), 12.48 (br. s, 1H, NH) ppm; ¹³C NMR (CDCl₃, 75 MHz): $\delta = 14.6$ (CH₃), 106.8 (C-4_{fur}), 114.9 (C-3_{fur}), 126.3 (CF₃), 126.9 (C_{ar}), 130.2 (C_{ar}), 131.9 (C_{ar}), 134.7 (C_{ar}), 137.1 (C_{ar}), 143.5 (C-5_{fur}), 157.2 (C-2_{fur}), 164.9 (C=O), 181.2 (C=S) ppm.

3.2.17. 1-(2-Methyl-furan-3-carbonyl)-3-(3-

trifluoromethyl-phenyl)-thiourea (**2f**, $C_{14}H_{11}F_3N_2O_2S$) Yield: 77%; m.p.: 143–144 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.68 (s, 3H, Fur-CH₃), 6.57 (d, J_{4-5} = 2.14 Hz, 1H, 4 H,), 7.35 (d, I_{4-5} = 1.08 Hz, 1H, 5 H,)

2.14 Hz, 1H, 4-H_{fur}), 7.35 (d, J_{5-4} =1.98 Hz, 1H, 5-H_{fur}), 7.49–7.60 (m, 2H, H_{ar}), 7.92–8.12 (m, 2H, H_{ar}), 8.64 (br. s, 1H, NH), 12.74 (br. s, 1H, NH) ppm.

3.2.18. 1-(2-Methyl-furan-3-carbonyl)-3-(4-

trifluoromethyl-phenyl)-thiourea (**2g**, $C_{14}H_{11}F_3N_2O_2S$) Yield: 79%; m.p.: 104 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.66 (s, 3H, Fur-CH₃), 6.56 (d, J_{4-5} =2.16 Hz, 1H, 4-H_{fur}), 7.35 (d, J_{5-4} =2.16 Hz, 1H, 5-H_{fur}), 7.64

(d, J = 8.86 Hz, H_{ar}), 7.91 (d, J = 8.86 Hz, H_{ar}), 8.63 (br. s, 1H, NH), 12.81 (br. s, 1H, NH) ppm.

3.2.19. 1-(4-Methoxy-phenyl)-3-(2-methyl-furan-3carbonyl)-thiourea (2h, $C_{14}H_{14}N_2O_3S$)

Yield: 85%; m.p.: 154–155 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.62 (s, 3H, Fur-CH₃), 3.78 (s, 3H, OCH₃), 6.57 (d, J_{4-5} =2.17 Hz, 1H, 4-H_{fur}), 7.24 (d, J=8.91 Hz, 2H, H_a), 7.35 (d, J_{5-4} =2.17 Hz, 1H, 5-H_{fur}), 7.78 (d,

J=8.91 Hz, 2H, H_{ar}), 8.63 (br. s, 1H, NH), 12.64 (br. s, 1H, NH) ppm.

3.2.20. 1-(2-Methyl-furan-3-carbonyl)-3-(4-

trifluoromethoxy-phenyl)-thiourea (2i, $C_{14}H_{11}F_3N_2O_3S$)

Yield: 76%; m.p.: 145 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.66 (s, 3H, Fur-CH₃), 6.56 (d, J_{4-5} =2.17 Hz, 1H, 4-H_{fur}), 7.24 (d, J=8.9 Hz, 2H, H_ar), 7.37 (d, J_{5-4} = 2.17 Hz, 1H, 5-H_{fur}), 7.79 (d, J=8.9 Hz, 2H, H_ar), 8.64 (br. s, 1H, NH), 12.62 (br. s, 1H, NH) ppm.

3.2.21. 1-(2-Fluoro-phenyl)-3-(2-methyl-furan-3carbonyl)-thiourea (2j, $C_{13}H_{11}FN_2O_2S$)

Yield: 72%; m.p.: 158 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.61$ (s, 3H, Fur-CH₃), 6.57 (d, $J_{4-5} = 1.97$ Hz, 1H, 4-H_{fur}), 7.12–7.36 (m, 3H, H_{ar}), 7.34 (d, $J_{5-4} = 1.97$ Hz, 1H, 5-H_{fur}), 8.24–8.39 (m, 1H, H_{ar}), 8.67 (br. s, 1H, NH), 12.61 (br. s, 1H, NH) ppm.

3.2.22. 1-(4-Fluoro-phenyl)-3-(2-methyl-furan-3carbonyl)-thiourea (2k, $C_{13}H_{11}FN_2O_2S$)

Yield: 81%; m.p.: 158–159 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.61 (s, 3H, Fur-CH₃), 6.57 (d, J_{4-5} = 2.16 Hz, 1H, 4-H_{fur}), 7.10 (d, J=4.81 Hz, 1H, H_{ar}), 7.24 (d, J=9.01 Hz, 1H, H_{ar}), 7.34 (d, J_{5-4} =2.16 Hz, 1H, 5-H_{fur}), 7.52 (d, J=4.81 Hz, 1H, H_{ar}), 7.68 (d, J=9.01 Hz, 1H, H_{ar}), 8.63 (br. s, 1H, NH), 12.49 (br. s, 1H, NH) ppm.

3.2.23. 1-(4-Chloro-phenyl)-3-(2-methyl-furan-3carbonyl)-thiourea (**2l**, $C_{13}H_{11}ClN_2O_2S$)

Yield: 92%; m.p.: 155 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.64$ (s, 3H, Fur-CH₃), 6.56 (d, $J_{4-5} = 2.16$ Hz, 1H, 4-H_{fur}), 7.34 (d, $J_{5-4} = 2.16$ Hz, 1H, 5-H_{fur}), 7.37 (d, J =8.86 Hz, 2H, H_{ar}), 7.66 (d, J = 8.86 Hz, 2H, H_{ar}), 8.62 (br. s, 1H, NH), 12.59 (br. s, 1H, NH) ppm.

3.2.24. 1-(2,3-Dichloro-phenyl)-3-(2-methyl-furan-3carbonyl)-thiourea (2m, $C_{13}H_{10}Cl_2N_2O_2S$)

Yield: 92%; m.p.: 160–161 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.60 (s, 3H, Fur-CH₃), 6.57 (d, J_{4-5} = 1.98 Hz, 1H, 4-H_{fur}), 7.36 (d, J_{5-4} =1.98 Hz, 1H, 5-H_{fur}), 7.38 (d, J=2.36 Hz, 1H, H_{ar}), 8.26 (d, d, J=2.36 Hz, J= 8.2 Hz, 2 H, H_{ar}), 8.69 (br. s, 1H, NH), 12.73 (br. s, 1H, NH) ppm.

3.2.25. 1-(2,6-Dichloro-phenyl)-3-(2-methyl-furan-3carbonyl)-thiourea (2n, $C_{13}H_{10}Cl_2N_2O_2S$)

Yield: 85%; m.p.: 153–154 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.65 (s, 3H, Fur-CH₃), 6.59 (d, J_{4-5} = 1.92 Hz, 1H, 4-H_{fur}), 7.22–7.48 (m, 4H, 4-H_{fur}, H_{ar}), 8.86 (br. s, 1H, NH), 12.01 (br. s, 1H, NH) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ =14.8 (CH₃), 106.2 (C-4_{fur}), 114.6 (C-3_{fur}), 127.1 (C_{ar}), 127.2 (C_{ar}), 129.2 (C_{ar}), 132.8 (C_{ar}), 135.6 (C_{ar}), 136.2 (C_{ar}), 142.3 (C-5_{fur}), 159.6 (C-2_{fur}), 163.8 (C=O), 180.8 (C=S) ppm. 3.2.26. 1-(4-Bromo-phenyl)-3-(2-methyl-furan-3-carbonyl)thiourea (**20**, $C_{13}H_{11}BrN_2O_2S$)

Yield: 89%; m.p.: 150 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.65$ (s, 3H, Fur-CH₃), 6.55 (d, $J_{4-5} = 1.97$ Hz, 1H, 4-H_{fur}), 7.35 (d, $J_{5-4} = 1.97$ Hz, 1H, 5-H_{fur}), 7.52 (d, J =8.88 Hz, 2H, H_{ar}), 7.64 (d, J = 8.88 Hz, 2H, H_{ar}), 8.62 (br. s, 1H, NH), 12.60 (br. s, 1H, NH) ppm.

3.2.27. 1-(4-Iodo-phenyl)-3-(2-methyl-furan-3-carbonyl)thiourea (2p, $C_{13}H_{11}IN_2O_2S$)

Yield: 93%; m.p.: 165–166 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.67 (s, 3H, Fur-CH₃), 6.55 (d, J_{4-5} = 2.16 Hz, 1H, 4-H_{fur}), 7.35 (d, J_{5-4} =2.17 Hz, 1H, 5-H_{fur}), 7.48 (d, J=8.84 Hz, 2H, H_{ar}), 7.74 (d, J=8.84 Hz, 2H, H_{ar}), 8.61 (br. s, 1H, NH), 12.61 (br. s, 1H, NH) ppm.

3.2.28. 1-(3-Methyl-furan-2-carbonyl)-3-(4-methylphenyl)-thiourea (3a, $C_{14}H_{14}N_2O_2S$)

Yield: 88%; m.p.: 130–131 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.34$ (s, 3H, Ar-CH₃), 2.44 (s, 3H, Fur-CH₃), 6.46 (d, $J_{4-5}=1.59$ Hz, 1H, 4-H_{fur}), 7.20 (d, J=8.36 Hz, 2H, H_{ar}), 7.48 (d, $J_{5-4}=1.59$ Hz, 1H, 5-H_{fur}), 7.55 (d, J= 8.36 Hz, 2H, H_{ar}), 9.24 (br. s, 1H, NH), 12.28 (br. s, 1H, NH) ppm.

3.2.29. 1-(3-Methyl-furan-2-carbonyl)-3-(2,4-dimethylphenyl)-thiourea (**3b**, $C_{15}H_{16}N_2O_2S$)

Yield: 86%; m.p.: 136–137 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.26$ (s, 6H, 2×Ar-CH₃), 2.44 (s, 3H, Fur-CH₃), 6.45 (d, $J_{4-5}=1.58$ Hz, 1H, 4-H_{fur}), 7.16 (d, J=8.46 Hz, 2H, H_{ar}), 7.42 (d, J= 8.46 Hz, 2H, H_{ar}), 7.45 (d, $J_{5-4}=1.59$ Hz, 1H, 5-H_{fur}), 9.15 (br. s, 1H, NH), 12.24 (br. s, 1H, NH) ppm.

3.2.30. 1-(4-tert-Butyl-phenyl)-3-(3-methyl-2-furancarbonyl)-thiourea (3c, $C_{17}H_{20}N_2O_2S$)

Yield: 75%; m.p.: 118–119 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.33$ (s, 9H, 3×CH₃), 2.46 (s, 3H, Fur-CH₃), 6.46 (d, $J_{4-5}=1.59$ Hz, 1H, 4-H_{fur}), 7.42 (d, J=8.75 Hz, H_{ar}), 7.53 (d, J=8.75 Hz, H_{ar}), 7.55 (d, $J_{5-4}=$ 1.59 Hz, 1H, 5-H_{fur}), 9.26 (br. s, 1H, NH), 12.48 (br. s, 1H, NH) ppm.

3.2.31. 1-(3-Methyl-furan-2-carbonyl)-3-(4-

trifluoromethyl-phenyl)-thiourea (3d, $C_{14}H_{11}F_3N_2O_2S$)

Yield: 79%; m.p.: 127–128 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.46 (s, 3H, Fur-CH₃), 6.48 (d, J_{4-5} = 1.58 Hz, 1H, 4-H_{fur}), 7.49 (d, J_{5-4} =1.58 Hz, 1H, 5-H_{fur}), 7.49 (d, J=8.92 Hz, 2H, H_{ar}), 7.91 (d, J=8.92 Hz, 2H, H_{ar}), 9.23 (br. s, 1H, NH), 12.60 (br. s, 1H, NH) ppm.

3.2.32. 1-(4-Methoxy-phenyl)-3-(3-methyl-2-furancarbonyl)-thiourea (3e, $C_{14}H_{14}N_2O_3S$)

Yield: 83%; m.p.: 124–125 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.44$ (s, 3H, Fur-CH₃), 3.82 (s, 3H, OCH₃), 6.46 (d, $J_{4-5}=1.60$ Hz, 1H, 4-H_{fur}), 6.93 (d, J=8.61 Hz,

2H, H_{ar}), 7.46 (d, J_{5-4} =1.60 Hz, 1H, 5-H_{fur}), 7.53 (d, J= 8.55 Hz, 2H, H_{ar}), 9.18 (br. s, 1H, NH), 12.22 (br. s, 1H, NH) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ =12.3 (CH₃), 55.3 (OCH₃), 114.2 (C_{ar}), 116.6 (C-4_{fur}), 125.6 (C_{ar}), 130.5 (C-3_{fur}), 134.2 (C_{ar}), 139.8 (C-2_{fur}), 145.0 (C-5_{fur}), 156.2 (C_{ar}), 157.8 (C=O), 178.2 (C=S) ppm.

3.2.33. 1-(3-Methyl-furan-2-carbonyl)-3-(4trifluoromethoxy-phenyl)-thiourea (3f, $C_{14}H_{11}F_3N_2O_3S$)

Yield: 73%; m.p.: 130–131 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta =2.48$ (s, 3H, Fur-CH₃), 6.47 (bs, 1H, 4-H_{fur}), 7.48 (bs, 1H, 5-H_{fur}), 7.64 (d, J=8.66 Hz, 2H, H_{ar}), 7.93 (d, J=8.66 Hz, 2H, H_{ar}), 9.21 (br. s, 1H, NH), 12.64 (br. s, 1H, NH) ppm.

3.2.34. 1-(2-Fluoro-phenyl)-3-(3-methyl-2-furancarbonyl)-thiourea (3g, $C_{13}H_{11}FN_2O_2S$)

Yield: 82%; m.p.: 150 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.46 (s, 3H, Fur-CH₃), 6.46 (bs, 1H, 4-H_{fur}), 7.06 (m, 3H, H_{ar}), 7.47 (bs, 1H, 5-H_{fur}), 8.21–8.52 (m, 1H, H_{ar}), 9.23 (br. s, 1H, NH), 12.48 (br. s, 1H, NH) ppm.

3.2.35. 1-(4-Fluoro-phenyl)-3-(3-methyl-2-furancarbonyl)-thiourea (3h, $C_{13}H_{11}FN_2O_2S$)

Yield: 78%; m.p.: 133–134 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.44 (s, 3H, Fur-CH₃), 6.47 (d, J_{4-5} = 1.61 Hz, 1H, 4-H_{fur}), 7.05 (d, J=8.84 Hz, 1H, H_{ar}), 7.23 (d, J=4.9 Hz, 1H, H_{ar}), 7.49 (d, J_{5-4} =1.61 Hz, 1H, 5-H_{fur}), 7.62 (d, J=8.84 Hz, 2H, H_{ar}), 7.69 (d, J=4.92 Hz, 2H, H_{ar}), 9.21 (br. s, 1H, NH), 12.32 (br. s, 1H, NH) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ =11.4 (CH₃), 115.6 (d, J=22.3 Hz, C_{ar}), 116.5 (C-4_{fur}), 126.1 (d, J=8.3 Hz, C_{ar}), 130.5 (C-3_{fur}), 133.7 (C_{ar}), 139.8 (C-2_{fur}), 146.1 (C-5_{fur}), 161.2 (d, J=254.2 Hz, C_{ar}), 155.6 (C=O), 178.7 (C=S) ppm.

3.2.36. 1-(2,4-Difluoro-phenyl)-3-(3-methyl-2-furancarbonyl)-thiourea (**3i** $, <math>C_{13}H_{10}F_2N_2O_2S$)

Yield: 80%; m.p.: 174–175 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.48 (s, 3H, Fur-CH₃), 6.47 (d, J_{4-5} = 1.59 Hz, 1H, 4-H_{fur}), 6.63–7.32 (m, 2H, H_{ar}), 7.47 (d, J_{5-4} = 1.59 Hz, 1H, 5-H_{fur}), 8.2–8.43 (m, 1H, H_{ar}), 9.24 (br. s, 1H, NH), 12.26 (br. s, 1H, NH) ppm.

3.2.37. 1-(4-Chloro-phenyl)-3-(3-methyl-2-furancarbonyl)-thiourea (3j, $C_{13}H_{11}ClN_2O_2S$)

Yield: 81%; m.p.: 153 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.44$ (s, 3H, Fur-CH₃), 6.47 (d, $J_{4-5} = 1.38$ Hz, 1H, 4-H_{fur}), 7.36 (d, J = 8.85 Hz, 2H, H_{ar}), 7.47 (d, $J_{5-4} = 1.38$ Hz, 1H, 5-H_{fur}), 7.73 (d, J = 8.85 Hz, 2H, H_{ar}), 9.19 (br. s, 1H, NH), 12.43 (br. s, 1H, NH) ppm.

3.2.38. 1-(2,6-Dichloro-phenyl)-3-(3-methyl-2-furan-

carbonyl)-thiourea (3k, $C_{13}H_{10}Cl_2N_2O_2S$)

Yield: 72%; m.p.: 194 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.46$ (s, 3H, Fur-CH₃), 6.47 (bs, 1H, 4-H_{fur}), 7.21–7.56

(m, 4H, 5-H_{fur}, H_{Ar}), 9.37 (br. s, 1H, NH), 11.92 (br. s, 1H, NH) ppm.

3.2.39. 1-(3,4-Dichloro-phenyl)-3-(3-methyl-2-furancarbonyl)-thiourea (**31**, $C_{13}H_{10}Cl_2N_2O_2S$)

Yield: 75%; m.p.: 150 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.44 (s, 3H, Fur-CH₃), 6.48 (d, J_{4-5} =1.52 Hz, 1H, 4-H_{fur}), 7.24–7.68 (m, 3H, 5-H_{fur}, H_{ar}), 7.95 (d, J=2.16 Hz, 1H, H_{Ar}), 9.21 (br. s, 1H, NH), 12.51 (br. s, 1H, NH) ppm.

3.2.40. 1-(4-Bromo-phenyl)-3-(3-methyl-2-furan-carbonyl)thiourea (3m, $C_{13}H_{11}BrN_2O_2S$)

Yield: 78%; m.p.: 154–155 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.44$ (s, 3H, Fur-CH₃), 6.46 (d, $J_{4-5} =$ 1.57 Hz, 1H, 4-H_{fur}), 7.47 (d, $J_{5-4} = 1.57$ Hz, 1H, 5-H_{fur}), 7.49 (d, J = 8.66 Hz, 2H, H_{ar}), 7.66 (d, J = 8.66 Hz, 2H, H_{ar}), 9.19 (br. s, 1H, NH), 12.43 (br. s, 1H, NH) ppm.

3.2.41. 1-(4-Iodo-phenyl)-3-(3-methyl-2-furan-carbonyl)thiourea (**3n**, $C_{13}H_{11}IN_2O_2S$)

Yield: 82%; m.p.: 176–177 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.41 (s, 3H, Fur-CH₃), 6.44 (d, J_{4-5} = 1.52 Hz, 1H, 4-H_{fur}), 7.44 (d, J_{5-4} =1.52 Hz, 1H, 5-H_{fur}), 7.47 (d, J=8.12 Hz, 2H, H_{ar}), 7.68 (d, J=8.12 Hz, 2H, H_{ar}), 9.15 (br. s, 1H, NH), 12.41 (br. s, 1H, NH) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ =12.3 (CH₃), 91.1 (C_{Ar}), 116.7 (C-4_{fur}), 125.8 (C_{ar}), 133.9 (C_{Ar}), 137.5 (C-3_{fur}), 138.3 (C_{Ar}), 139.8 (C-2_{fur}), 144.6 (C-5_{fur}), 155.6 (C=O), 178.7 (C=S) ppm.

3.2.42. 1-(4-tert-Butyl-phenyl)-3-(5-methyl-2-furancarbonyl)-thiourea (4a, $C_{17}H_{20}N_2O_2S$)

Yield: 89%; m.p.: 156–158 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 1.38$ (s, 9H, CH₃, CH₃, CH₃), 2.41 (s, 3H, Fur-CH₃), 6.23 (d, d, $J_{4-3}=3.41$ Hz, J=0.78 Hz, 1 H, 4-H_{fur}), 7.28 (d, $J_{3-4}=3.41$ Hz, 1H, 3-H_{fur}), 7.42 (d, J=8.72 Hz, 2H, H_{ar}), 7.63 (d, J=8.72 Hz, 2H, H_{ar}), 9.13 (br. s, 1H, NH), 12.32 (br. s, 1H, NH) ppm.

3.2.43. 1-(5-Methyl-2-furan-carbonyl)-3-(3-

trifluoromethyl-phenyl)-thiourea (**4b**, $C_{14}H_{11}F_3N_2O_2S$) Yield: 80%; m.p.: 156–158 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.44$ (s, 3H, Fur-CH₃), 6.25 (d, d, $J_{4-3} =$ 3.54 Hz, J = 0.98 Hz, 1 H, 4-H_{fur}), 7.29 (d, $J_{3-4} = 3.54$ Hz, 1H, 3-H_{fur}), 7.52 (d, J = 5.35 Hz, 2H, H_{ar}), 7.85–8.16 (m, 2H, H_{ar}), 9.17 (br. s, 1H, NH), 12.56 (br. s, 1H, NH) ppm.

3.2.44. 1-(2-Fluoro-phenyl)-3-(5-methyl-2-furancarbonyl)-thiourea (4c, $C_{13}H_{11}FN_2O_2S$)

Yield: 76%; m.p.: 128–129 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.43 (s, 3H, Fur-CH₃), 6.24 (d, d, J_{4-3} = 3.42 Hz, J=0.73 Hz, 1 H, 4-H_{fur}), 7.10–7.28 (m, 3H, H_{Ar}), 7.29 (d, J_{3-4} =3.42 Hz, 1H, 3-H_{fur}), 8.32–8.47 (m, 1H, H_{ar}), 9.52 (br. s, 1H, NH), 12.79 (br. s, 1H, NH) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ =13.7 (CH₃), 109.9 (C-4_{fur}), 115.3 (d, J=21.6 Hz, C_{ar}), 118.9 (C_{Ar}), 120.6 (C-3_{fur}), 123.7 (C_{Ar}), 125.1 (C_{Ar}), 127.4 (d, J=8.3 Hz, C_{ar}), 144.3 (d, J=251.6 Hz, C_{ar}), 153.2 (C-2_{fur}), 156.7 (C=O), 157.9 (C-5_{fur}), 178.3 (C=S) ppm.

3.2.45. 1-(4-Fluoro-phenyl)-3-(5-methyl-2-furancarbonyl)-thiourea (4d, $C_{13}H_{11}FN_2O_2S$)

Yield: 78%; m.p.: 148–149 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.43$ (s, 3H, Fur-CH₃), 6.24 (d, d, $J_{4-3} =$ 3.38 Hz, J = 0.98 Hz, 1 H, 4-H_{fur}), 7.28 (d, $J_{3-4} = 3.38$ Hz, 1H, 3-H_{fur}), 7.62 (dd, J = 8.86 Hz, J = 4.32 Hz, 2H, H_{ar}), 9.14 (br. s, 1H, NH), 12.31 (br. s, 1H, NH) ppm.

3.2.46. 1-(2,4-Difluoro-phenyl)-3-(5-methyl-2-furan $carbonyl)-thiourea (4e, <math>C_{13}H_{10}F_2N_2O_2S$)

Yield: 82%; m.p.: 175–176 °C; ¹H NMR (CDCl₃, 300 MHz): $\delta = 2.43$ (s, 3H, Fur-CH₃), 6.24 (d, d, $J_{4-3} =$ 3.45 Hz, J = 0.78 Hz, 1 H, 4-H_{fur}), 6.81–7.16 (m, 1H, H_{ar}), 7.32 (d, $J_{3-4} = 3.38$ Hz, 1H, 3-H_{fur}), 8.03–8.41 (m, 2H, H_{ar}), 9.22 (br. s, 1H, NH), 12.33 (br. s, 1H, NH) ppm.

3.2.47. 1-(2,4-Dichloro-phenyl)-3-(5-methyl-2-furancarbonyl)-thiourea (4f, $C_{13}H_{10}Cl_2N_2O_2S$)

Yield: 81%; m.p.: 202–203 °C; ¹H NMR (CDCl₃, 300 MHz): δ =2.41 (s, 3H, Fur-CH₃), 6.26 (d, d, J_{4–3}= 3.45 Hz, J=0.78 Hz, 1 H, 4-H_{fur}), 7.31 (d, J_{3–4}=3.54 Hz, 1H, 3-H_{fur}), 7.44–7.58 (m, 2H, H_{ar}), 7.98 (d, J=1.96 Hz, 1H, H_{ar}), 9.15 (br. s, 1H, NH), 12.47 (br. s, 1H, NH) ppm.

The preparation and some properties of the studied compounds **1a**, **1b**, **1m** have been described in the literature [42].

3.3. Spectroscopic methods

The IR spectra for hydrogen bond study were measured at room temperature in the region 4000–600 cm⁻¹, using a Zeiss Specord M 85 spectrometer. The measurements were carried out in CHCl₃ (Uvasol) employing NaCl cells of 0.05 cm thickness. The concentrations of the solutions were 5×10^{-2} mol dm⁻³. The absorption intensities of the Fermi triplet components were determined after mathematical deconvolution and separation of overlapping bands. Curve analysis was carried out with a digital curve-fitting routine.

3.4. Semi-empirical calculations

All semi-empirical calculations were performed by means of AM1 [43] and PM3 [44], using the program package MOPAC 6.0 [45]. The calculations were carried out as simulations at a temperature of 298 K and a pressure of 1 atm.

3.5. Crystallography

Single crystals, suitable for X-ray diffraction analysis, were grown from ethanol solutions. Intensity data were collected at room temperature $(293 \pm 2 \text{ K})$, using a STOE

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IPDS (Imaging Plate Detection System) instrument, equipped with a rotating anode and Mo K_{α} radiation (λ = 0.71073 Å). Data reduction calculations [46] included corrections for Lorentz and polarization effects, but not for absorption or extinction effects. In the refinement of the unit cell parameters, the most suitable 5000 reflections were selected and used [46].

Application of direct methods [47] yielded preliminary structure models, which were completed and refined using the sheLxL-97 programs [48]. The non-hydrogen atoms and disorder sites (e.g. in **2n**) were refined together with their anisotropic displacement parameters, whereas the hydrogen atom positions were treated isotropically. The (N–)H atoms and possible (O–)H disorder sites were located from difference electron density maps, and were held riding on their parent N/O atoms in the subsequent calculations, whereas the carbon-bonded hydrogens were given positions deduced from geometric evidence. The rigid methyl groups, on the other hand, were allowed to rotate around the respective C/O–C(methyl) bonds [48].

Although a preliminary structure model of the **2e** compound could easily be deduced from the collected X-ray data, all efforts to properly refine the structure failed. Careful inspection of the intensity data proved the crystals of **2e** to be twins (non-merohedral twins). The reflections, coming from the two crystal domains, could be resolved using programs available in the software supplied with the STOE IPDS diffractometer [46]. New data reduction calculations were carried out, one for each intensity data set. Then, the two sets of structure factors (F^2 values), one from each domain, were used in the refinement calculations, after appropriate scaling and merging [48–50].

The triclinic (P-1) crystals of 2e contain two symmetryindependent molecules (A and B) (Fig. 1(b)). The related 2n compound, on the other hand, crystallizes with monoclinic (Cc) space group symmetry, and with four unique 2n molecules (A, B, C and D) and two ethanol solvates (E1 and E2) in each asymmetric crystallographic unit (Fig. 1(c) and (d)). Both solvate molecules exhibit disorder, static as well as dynamic (indicated by partial site occupancy, and relatively high atomic displacement parameters, respectively), but in different ways. Two disorder sites could be realized for the α -carbon of E1, C(1E1) and C(1E'), with the site occupation factors 0.64 and 0.36, respectively [assuming full occupancy (=1.0) for the pair of corresponding un-primed/primed disorder sites together], whereas the E2 molecule occupies at least two, partly overlapping disorder sites, having only the C(2E2) position in common. The probabilities of the un-primed and doubleprimed sites in E2 refined to 47 and 53%, respectively. The partially occupied ethanol O and C positions had to be refined with simple distance constraints in order to yield acceptable geometry for the guest alcohol skeletons. Moreover, because of the high mobility of the solvate entities, the final structure model comprises neither minor H disorder sites for E1, nor H sites at all for the heavily

disordered E2 molecule. As a consequence, some rest electron density was observed in the final difference electron density map ($\Delta \rho_{max} = 0.58 \text{ e}^{-}/\text{Å}^{3}$), located in the vicinity of the ethanol molecules, and indicating the approximate character of the disorder models. Although neither the **2n** derivative nor the guest ethanol contain a molecular stereogenic centre, the realized packing arrangement lacks inversion symmetry (i.e. is non-centrosymmetric). In the last stage of the structure refinement the calculated absolute structure or Flack parameter [48] reached a value of 0.02(4), thus indicating that the handedness of the **2n** crystal is most likely that shown in Fig. 4.

Crystal data, together with details of the data reduction and structure refinement calculations are shown in Table 4.

Crystallographic data (including final atomic coordinates and geometric parameters, and excluding structure factors) for the structure analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 240290 for **1e**, 240291 for **2e**, 240292 for **2n** and 240293 for **3e**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. Code +44 1223 336 033; e-mail: deposit@ ccdc.cam.ac.uk).

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